



Current Oncological Abstract Service

COAS (Monthly)
November 2024, Volume 1, Issue 1



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Current Oncological Abstract Service (COAS)

Monthly

Aims of the Abstracts

The Current Oncological Abstract Service (COAS) aims to provide timely, curated abstracts from a broad spectrum of oncological literature. The objectives of the service are:

1. To deliver concise, up-to-date abstracts of recently published oncological research, covering various subfields such as medical oncology, radiation oncology, anesthesiology, surgical oncology, and hematology.
2. To assist healthcare professionals, researchers, and students in staying informed about the latest advances and trends in oncology.
3. To support clinical and research-based decision-making by providing quick access to relevant, high-impact studies.
4. To foster knowledge exchange across disciplines, promoting a broader understanding of cancer-related topics.

Scope of the Abstracts

1. COAS includes abstracts from areas such as cancer biology, genetics, epidemiology, clinical trials, and treatment modalities (e.g., chemotherapy, immunotherapy, and targeted therapies), as well as patient care practices.
2. Abstracts are sourced from global research publications, offering a comprehensive view of international advancements in oncology.
3. Priority is given to high-impact studies, systematic reviews, meta-analyses, and research with significant implications for clinical practice.
4. In addition to core oncology, abstracts may cover related fields such as molecular biology, pharmacology, palliative care, and psychological support in oncology, reflecting the interdisciplinary nature of cancer care.

Layout

The "Current Oncological Abstract Service" is designed as a targeted information resource that provides clinicians, researchers, and students in oncology with the latest research abstracts and developments in cancer-related fields. It offers a regularly updated collection of abstracts from recently published articles, journals, and reports in oncology to keep users informed about current research trends, treatments, diagnostic methods, and advancements in oncology. The service is delivered monthly via email and as a downloadable PDF available on the CNCI website.

Content Sections - The COAS includes summaries of:

- The latest and most impactful research papers.
- Updates on new treatments, drugs, and clinical trials.
- Abstracts on new diagnostic tools, biomarkers, and techniques.
- Insights into cancer prevention research and epidemiological studies.
- Information on palliative care, patient management, and supportive therapies.

Abstract Formatting Each entry in the Current Oncological Abstract Service (COAS) includes:

- The title of the article or study.
- Authors and publication details.
- A summary focused on key findings and relevance.
- Keywords for easier navigation.
- A direct link to the original source (if online access is available).

User Navigation

- An index organized by cancer types, treatment methods, and research areas to facilitate easy navigation.
- A searchable database on the web platform, allowing users to quickly locate relevant abstracts.

User Engagement

- **Feedback Mechanism:** Users can provide feedback on abstracts and suggest improvements.
- **Personalization:** Users can subscribe to specific categories or topics of interest.

Bibliographical Citation:

Title-The title of the paper is invariably given in English and non-English titles are translated into English.

Author-A maximum of ten author's names are given. In case of more than ten authors, names of first ten authors are given followed by et al.

Details-The title of the paper is followed by volume number, issue number (in parenthesis), pagination and the of publication. Late publication or late receipt of the journals (if any), language(s) and number of references cited in the publication are given in parenthesis.

Abstract-Abstracts are informative and comprehensive. New data or findings are specifically indicated.

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Compiler:

Sanmoy Chakraborty

Assistant Library & Information Officer

&

Ganesh Gorai

Assistant Library & Information Officer

Phone: 033 2475-9313, 033 3506-0600

Website: <https://www.cnci.ac.in/>

Email: cnci.library@gmail.com

DTP and Computer Processing:

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Anesthesiology**24COASNO1:****Title- The association between intraoperative low driving pressure ventilation and perioperative healthcare-associated costs: A retrospective multicenter cohort study,**

Luca J. Wachtendorf, Elena Ahrens, Aiman Suleiman, Dario von Wedel, Tim M. Tartler, Journal of Clinical Anesthesia, Volume 98,2024,111567, <https://doi.org/10.1016/j.jclinane.2024.111567>.

Abstract: Study objective: A low dynamic driving pressure during mechanical ventilation for general anesthesia has been associated with a lower risk of postoperative respiratory complications (PRC), a key driver of healthcare costs. It is, however, unclear whether maintaining low driving pressure is clinically relevant to measure and contain costs. We hypothesized that a lower dynamic driving pressure is associated with lower costs. Design: Multicenter retrospective cohort study. Setting: Two academic healthcare networks in New York and Massachusetts, USA. Patients: 46,715 adult surgical patients undergoing general anesthesia for non-ambulatory (inpatient and same-day admission) surgery between 2016 and 2021. Interventions: The primary exposure was the median intraoperative dynamic driving pressure. Measurements: The primary outcome was direct perioperative healthcare-associated costs, which were matched with data from the Healthcare Cost and Utilization Project-National Inpatient Sample (HCUP-NIS) to report absolute differences in total costs in United States Dollars (US\$). We assessed effect modification by patients' baseline risk of PRC (score for prediction of postoperative respiratory complications [SPORC] ≥ 7) and effect mediation by rates of PRC (including post-extubation saturation $< 90\%$, re-intubation or non-invasive ventilation within 7 days) and other major complications. Main results: The median intraoperative dynamic driving pressure was 17.2cmH₂O (IQR 14.0–21.3cmH₂O). In adjusted analyses, every 5cmH₂O reduction in dynamic driving pressure was associated with a decrease of -0.7% in direct perioperative healthcare-associated costs (95%CI -1.3 to -0.1% ; $p = 0.020$). When a dynamic driving pressure below 15cmH₂O was maintained, -US\$340 lower total perioperative healthcare-associated costs were observed (95%CI $-\text{US}\$546$ to $-\text{US}\$132$; $p = 0.001$). This association was limited to patients at high baseline risk of PRC ($n = 4059$; $-\text{US}\$1755$; 97.5%CI $-\text{US}\$2495$ to $-\text{US}\$986$; $p < 0.001$), where lower risks of PRC and other major complications mediated 10.7% and 7.2% of this association ($p < 0.001$ and $p = 0.015$, respectively). Conclusions: Intraoperative mechanical ventilation targeting low dynamic driving pressures could be a relevant measure to reduce perioperative healthcare-associated costs in high-risk patients.

Keywords: Lung-protective ventilation; Driving pressure; Healthcare costs; Postoperative respiratory complications

24COASNO2:**Title- Effectiveness of a delirium risk assessment and multidisciplinary care approach in reducing delirium incidence among surgical intensive care unit patients: A retrospective pre-post intervention study,**

Wei-Ling Hsiao, Pei-Yin Hsieh, Ling-Fang Hsu, Yeur-Hur Lai, Man-Ling Wang, Yu-Chang Yeh,

Journal of Clinical Anesthesia, Volume 98,2024,111566,

<https://doi.org/10.1016/j.jclinane.2024.111566>.

Abstract: Background: Delirium is a common complication in intensive care unit (ICU) patients. It can lead to various adverse events. In this study, we investigated the effectiveness of combining the use of the PREdiction of DELIRium (PRE-DELIRIC) model for delirium risk assessment and the use of a multicomponent care bundle for delirium assessment, prevention, and care in terms of reductions in the incidence of delirium among surgical ICU patients. Methods: This retrospective study included surgical ICU patients who had received PRE-DELIRIC-guided SMART/SmART care (SMART care: SmART bundle plus multidisciplinary team; SmART care: Sleep/sweet sense of home (creating a comforting and restful environment for patients), Assessment (regular and thorough evaluation of patient needs and conditions), Release (revised endotracheal tube care/removal, restraint device care, and immobility reduction for patient comfort), and Time (reorientation of time to optimize patient care schedules) in our hospital between May 2022 and March 2023 (intervention group) and individuals who had received usual care between January 2021 and April 2022 (historical control group). The SmART intervention involves providing care in the following domains: sleep/sweet sense of home, assessment, release, and time. Patients with a PRE-DELIRIC score of >30% received SMART care, which includes multidisciplinary (physicians, pharmacists, respiratory therapists, and physiotherapists) care in addition to SmART care. For the control group, usual care was provided following the guidelines for the prevention and management of pain, agitation, delirium, immobility, and sleep disruption. The primary outcome was delirium incidence during ICU stay, which was assessed using the Intensive Care Delirium Screening Checklist. The secondary outcomes were the duration of ICU stay, rate of unplanned self-extubation, and status of ICU discharge. Results: The intervention and control groups comprised 184 and 197 patients, respectively; their mean ages were 63.7 ± 18.4 years and 62.4 ± 19.5 years, respectively. The incidence of delirium was significantly lower ($p = 0.001$) in the intervention group (22.3%) than in the control group (47.7%). Conclusion: Our findings suggest that the PRE-DELIRIC-guided SMART/SmART care intervention is effective in preventing and managing delirium among surgical ICU patients.

Keywords: PRE-DELIRIC; Intensive care unit; Critically ill; Delirium; Risk assessment

24COASNO3:**Title- Huaxi integrated blood management reduces the red blood cell transfusion for on-pump cardiac surgery: A quasi-experimental study,**

Yishun Wang, Hao Yang, Kang Du, Xiali Liu, Jiyue Xiong, Xiang Yu, Zhong Wu, Yingqiang Guo, Lei Du,

Journal of Clinical Anesthesia, Volume 98,2024,111593,

<https://doi.org/10.1016/j.jclinane.2024.111593>.

Abstract: Objective: As many as half of patients undergoing on-pump cardiac surgery require red blood cell transfusion, emphasizing the need for effective strategies that can reduce this need. We conducted this analysis to assess the effectiveness of Huaxi Integrated Blood Management strategy at our medical center. Design: Before and after study. Participants: Patients who underwent on-pump cardiac surgery were included from January 2019 to December 2021. Two cohorts were compared, one before implementation of the strategy (1 January 2019 until 31 May 2020) and one after implementation (1 June 2020 until 31 December 2021). Measurements: We evaluated temporal trends in blood transfusion, safety, and efficacy of this strategy. Primary outcomes were the incidence and volume of intra- and postoperative blood transfusions of packed red blood cells. Secondary outcomes are intraoperative and postoperative transfusion of other blood products, all-cause mortality during hospitalization, and incidence of new-onset complications.

Main results: Our results demonstrated that this integrated strategy effectively decreased both the perioperative packed red blood cell transfusion volume and incidence for patients who underwent the on-pump cardiac surgery. Following the implementation, the incidence of packed red blood cell transfusions decreased by 8.1% during the intraoperative period and by 12.3% during the postoperative period. The mean volume of such transfusions decreased by 0.28 units during the intraoperative period and by 0.49 units during the postoperative period. Hemoglobin concentrations were significantly higher after implementation, and the maximal mean increase was 4.72 g/l on postoperative day 1. Similar benefit of the strategy was observed across subgroups of patients who underwent different types of surgery. Conclusions: The Huaxi Integrated Blood Management strategy may be effective at reducing the need for packed red blood cell transfusion and enhancing patient care.

Keywords: Packed red blood cell; Cardiac surgery; Cardiopulmonary bypass; Transfusion

24COASNO4:**Title- Impact of nitrous oxide use on parturient recall of neuraxial analgesia risks,**

Emily E. Sharpe, Lindsay L. Warner, Benjamin D. Brakke, Paul R. Davis, David M. Finkel, Christopher M. Burkle,

Journal of Clinical Anesthesia, Volume 98,2024,111579,

<https://doi.org/10.1016/j.jclinane.2024.111579>.

Abstract: Study objective: Nitrous oxide affects memory and recall. We aimed to determine if using nitrous oxide during labor affected patients' ability to learn and recall the risks and benefits of neuraxial analgesia. Design: Single-center, prospective cohort study. Setting: Labor and delivery unit in a large academic medical center. Patients: Nulliparous patients with spontaneous or planned induction of labor. Interventions: Parturients chose whether to

use nitrous oxide during labor. At the discussion for epidural consent, 4 risks were described: headache, infection, nerve damage, bleeding. Measurements: Labor pain score, time from nitrous oxide discontinuation, and cervical dilation were documented at the discussion of epidural risks. Patients were assessed for unprompted recall and prompted recall of epidural risks on postpartum day 1 and unprompted recall at postpartum week 6. The number and proportion of patients who indicated each true risk (unprompted and prompted recall) or distractor (prompted recall only) were summarized by treatment group and results compared using Pearson χ^2 tests. Main results: Of the 403 enrolled patients, 294 (73%) did not use nitrous oxide, and 109 (27%) did. The 2 groups were similar except women who used nitrous oxide were more likely to be cared for by midwives and had higher pain scores at their epidural request. Scores for unprompted or prompted recall of epidural risks were not different between women who received or did not receive nitrous oxide. All 4 risks were recalled unprompted by only 3% in the nitrous oxide group and by 6% in the group not receiving nitrous oxide ($P = .18$). Conclusions: The use of nitrous oxide for labor analgesia does not adversely influence a parturient's ability to recall the risks of epidural placement. Patients who receive nitrous oxide for labor analgesia should be considered eligible to provide consent for subsequent procedures.

Keywords: Epidural; Informed consent; Labor analgesia; Neuraxial analgesia; Nitrous oxide; Patient consent

24COASNO5:

Title- Effect of remimazolam versus propofol on hypotension after anesthetic induction in patients undergoing coronary artery bypass grafting: A randomized controlled trial,

Jae-Woo Ju, Dong Ju Lee, Jaeyeon Chung, Seohee Lee, Youn Joung Cho, Yunseok Jeon, Karam Nam,

Journal of Clinical Anesthesia, Volume 98, 2024, 111580,

<https://doi.org/10.1016/j.jclinane.2024.111580>.

Abstract: Study Objective: There is scarce evidence on the hemodynamic stability of remimazolam during anesthetic induction in patients with significant coronary artery disease. This study aims to compare the effects of remimazolam and propofol on post-induction hypotension in patients undergoing coronary artery bypass grafting (CABG). Design: Randomized controlled trial. Setting: Tertiary teaching hospital. Patients: Adult patients undergoing isolated CABG. Interventions: Patients were randomly allocated to received either remimazolam ($n = 50$) or propofol ($n = 50$) for anesthetic induction. The remimazolam group received an initial infusion at 6 mg/kg/h, which was later adjusted to 1–2 mg/kg/h to maintain a bispectral index of 40–60 after loss of consciousness. In the propofol group, a 1.5 mg/kg bolus of propofol was administered, followed by 1–1.5% sevoflurane inhalation as needed to achieve the target bispectral index. Measurements: The primary outcome was the area under the curve (AUC) below the baseline mean arterial pressure (MAP) during the first 10 min after anesthetic induction. Secondary outcomes included the AUC for MAP <65 mmHg and the requirement for vasopressors. Main Results: The remimazolam group demonstrated a significantly lower AUC under the baseline MAP compared to the propofol group (mean [SD], 169.8 [101.0] mmHg·min vs. 220.6 [102.4] mmHg·min; mean difference

[95% confidence interval], 50.8 [10.4–91.2] mmHg·min; $P = 0.014$). Additionally, the remimazolam group had a reduced AUC for MAP <65 mmHg (7.3 [10.3] mmHg·min vs. 13.9 [14.9] mmHg·min; $P = 0.007$) and a lower frequency of vasopressor use compared to the propofol group (60% vs. 88%, $P = 0.001$). Conclusions: Remimazolam may offer improved hemodynamic stability during anesthetic induction in patients undergoing CABG, suggesting its potential advantage over propofol for patients with significant coronary artery disease in terms of hemodynamic stability.

Keywords: Blood pressure; Coronary artery bypass; Hypotension; Propofol; Remimazolam

24COASN06:

Title- Comprehensive perioperative blood management in patients undergoing elective bypass cardiac surgery: Benefit effect of health care education and systematic correction of iron deficiency and anemia on red blood cell transfusion,

Hélène Charbonneau, Stéphanie Savy, Nicolas Savy, Marie Pasquié, Nicolas Mayeur, Olivier Angles, ...

Journal of Clinical Anesthesia, Volume 98, 2024, 111560,

<https://doi.org/10.1016/j.jclinane.2024.111560>.

Abstract: Study objective: The aim of this study was to investigate the efficacy of a two-step patient blood management (PBM) program in red blood cell (RBC) transfusion requirements among patients undergoing elective cardiopulmonary bypass (CPB) surgery. Design: Prospective, non-randomized, two-step protocol design. Setting: Cardiac surgery department of Clinique Pasteur, Toulouse, France. Patients: 897 patients undergoing for elective CPB surgery. Interventions: We conducted a two-steps protocol: PBMe and PBMc. PBMe involved a short quality improvement program for health care workers, while PBMc introduced a systematic approach to pre- and postoperative correction of deficiencies, incorporating iron injections, oral vitamins, and erythropoiesis-stimulating agents. Measurements: The PBM program's effectiveness was evaluated through comparison with a pre-PBM retrospective cohort after propensity score matching. The primary objective was the proportion of patients requiring RBC transfusions during their hospital stay. Secondary objectives were also analyzed. Main results: After matching, 343 patients were included in each group. Primary outcomes were observed in 35.7% (pre-PBM), 26.7% (PBMe), and 21.1% (PBMc) of patients, resulting in a significant reduction (40.6%) in the overall RBC transfusion rate. Both the PBMe and PBMc groups exhibited significantly lower risks of RBC transfusion compared to the pre-PBM group, with adjusted odds ratios of 0.59 [95% CI 0.44–0.79] and 0.44 [95% CI 0.32–0.60], respectively. Secondary endpoints included reductions in transfusions exceeding 2 units, total RBC units transfused, administration of allogeneic blood products, and total bleeding volume recorded on Day 1. There were no significant differences noted in mortality rates or the duration of hospital stays. Conclusions: This study suggests that health care education and systematic deficiency correction are associated with reduced RBC transfusion rates in elective CPB surgery. However, further randomized, controlled studies are needed to validate these findings and refine their clinical application.

Keywords: Red blood cell transfusion; Anemia; Iron deficiency; Erythropoiesis-stimulating agent; Elective cardiac surgery

24COASNO7:

Title- Desflurane versus sevoflurane anesthesia and postoperative recovery in older adults undergoing minor- to moderate-risk noncardiac surgery – A prospective, randomized, observer-blinded, clinical trial,

Alexander Taschner, Edith Fleischmann, Katharina Horvath, Nikolas Adamowitsch, David Emler,

Journal of Clinical Anesthesia, Volume 98, 2024, 111576,

<https://doi.org/10.1016/j.jclinane.2024.111576>.

Abstract: Study objective The effect of volatile anesthetics on postoperative recovery in older adults is still not entirely clear. Thus, we evaluated the effect of desflurane versus sevoflurane anesthesia on speed of postoperative recovery in older adults eligible for same-day discharge. We further evaluated the incidence of postoperative nausea and vomiting (PONV), bispectral index (BIS) values, and S100B concentrations. Design-Single-center, prospective, observer-blinded, randomized clinical trial. Setting-Operating room. Patients-190 patients ≥ 65 years of age and scheduled for minor- to moderate-risk noncardiac surgeries. Interventions- Goal-directed administration of desflurane versus sevoflurane for maintenance of anesthesia with an intraoperative goal of BIS 50 ± 5 . Measurements: The primary outcome was the time to anesthesia recovery, which was defined as the time between arrival at the post-anesthesia care unit (PACU) and reaching criteria for discharge from PACU, based on modified Aldrete score ≥ 12 points. Modified Aldrete scores were assessed at PACU arrival and thereafter in five-minute intervals. PONV was evaluated during PACU stay and the first three postoperative days, BIS values were recorded during PACU stay, and S100B values were measured before and after surgery, and on the second postoperative day. Main results: 95 patients were randomized to receive desflurane, and 95 patients to receive sevoflurane. We did not observe a significant difference in median duration of postoperative recovery between the groups (desflurane: 0 min [0;0]; sevoflurane: 0 min [0;0]; $p = 0.245$). 77 patients (81.1%) in the desflurane group and 84 patients (88.4%) in the sevoflurane group already had Aldrete scores ≥ 12 points upon arrival at PACU ($p = 0.277$). There was also no significant difference in the incidences of PONV ($p = 0.606$), postoperative BIS values ($p = 0.197$), and postoperative maximum S100B concentrations ($p = 0.821$) between the groups. Conclusions: Despite previous reports, we did not observe significant faster recovery times after desflurane anesthesia. Both volatile anesthetics may be appropriate for same-day discharge in older adults.

Keywords: Desflurane; Sevoflurane; Minor noncardiac surgery; Postoperative recovery; Neurocognitive recovery; Same-day surgery

24COASNO8:**Title- Enhancing Sepsis prognosis: Integrating social determinants and demographic variables into a comprehensive model for critically ill patients,**

Elie Sarraf, Alireza Vafaei Sadr, Vida Abedi, Anthony S. Bonavia,

Journal of Critical Care, Volume 83, 2024, 154857,

<https://doi.org/10.1016/j.jcrc.2024.154857>.

Abstract: Background: The Sequential Organ Failure Assessment (SOFA) score monitors organ failure and defines sepsis but may not fully capture factors influencing sepsis mortality. Socioeconomic and demographic impacts on sepsis outcomes have been highlighted recently. Objective: To evaluate the prognostic value of SOFA scores against demographic and social health determinants for predicting sepsis mortality in critically ill patients, and to assess if a combined model increases predictive accuracy. Methods: The study utilized retrospective data from the MIMIC-IV database and prospective external validation from the Penn State Health cohort. A Random Forest model incorporating SOFA scores, demographic/social data, and the Charlson Comorbidity Index was trained and validated. Findings: In the MIMIC-IV dataset of 32,970 sepsis patients, 6,824 (20.7%) died within 30 days. A model including demographic, socioeconomic, and comorbidity data with SOFA scores improved predictive accuracy beyond SOFA scores alone. Day 2 SOFA, age, weight, and comorbidities were significant predictors. External validation showed consistent performance, highlighting the importance of delta SOFA between days 1 and 3. Conclusion: Adding patient-specific demographic and socioeconomic information to clinical metrics significantly improves sepsis mortality prediction. This suggests a more comprehensive, multidimensional prognostic approach is needed for accurate sepsis outcome predictions.

Keywords: Sepsis; Machine learning; Sequential organ failure assessment score; MIMIC database; Mortality

24COASNO9:**Title- The interaction of net ultrafiltration rate with urine output and fluid balance after continuous renal replacement therapy initiation: A multi-Centre study.,**

Kyle White, Kevin B. Laupland, Rinaldo Bellomo, Ary Serpa-Neto,

Journal of Critical Care, Volume 83, 2024, 154835,

<https://doi.org/10.1016/j.jcrc.2024.154835>.

Abstract: Purpose: During continuous renal replacement therapy (CRRT), a high net ultrafiltration rate (NUF) may worsen the decrease in urine output (UO) associated with starting CRRT. However, fluid balance (FB) may modulate this association. We aimed to examine the relationship between NUF, UO and FB at the start of CRRT. Methods: A retrospective cohort study of 1030 CRRT-treated patients admitted to two tertiary ICUs. Results: Median age was 60 years (IQR, 48–70), median APACHE III was 94 (IQR, 76–114) and median NUF rate was 0.7 mL/kg/h. In the 24 h after CRRT started, the mean hourly UO decreased from 25.5 mL to 11.9 mL ($P < 0.001$). Moreover, after adjusting for multiple confounders on multivariable analysis, a higher NUF was not significantly associated with a lower UO (-1.5 mL/kg for every 1 mL/kg/h increase in NUF; 95% CI -3.1 to 0.04 ; $p = 0.064$). In addition, pre-CRRT FB did not modulate the above relationship between

higher NUF and lower UO. Conclusion: A higher NUF rate was not significantly associated with a greater immediate and sustained reduction in UO after CRRT commencement. FB before CRRT was also not associated with a greater reduction in UO. These findings do not provide evidence for an effect of NUF on renal function.

Keywords: Critical care; Acute kidney injury; Continuous renal replacement therapy; Net ultrafiltration

24COASNO10:

Title- Long-term survival of traumatic brain injury and intra-cerebral haemorrhage patients: A multicentric observational cohort,

E. Dantan, Y. Foucher, J. Simon-Pimmel, M. Léger, M. Campfort, S. Lasocki, K. Lakhal, M. Bouras, A. Roquilly, R. Cinotti,

Journal of Critical Care, Volume 83, 2024, 154843,

<https://doi.org/10.1016/j.jcrc.2024.154843>.

Abstract: Purpose: Mortality is often assessed during ICU stay and early after, but rarely at later stage. We aimed to compare the long-term mortality between TBI and ICH patients.

Materials and methods From an observational cohort, we studied 580 TBI patients and 435 ICH patients, admitted from January 2013 to February 2021 in 3 ICUs and alive at 7-days post-ICU discharge. We performed a Lasso-penalized Cox survival analysis. Results: We estimated 7-year survival rates at 72.8% (95%CI from 67.3% to 78.7%) for ICH patients and at 84.9% (95%CI from 80.9% to 89.1%) for TBI patients: ICH patients presenting a higher mortality risk than TBI patients. Additionally, we identified variables associated with higher mortality risk (age, ICU length of stay, tracheostomy, low GCS, absence of intracranial pressure monitoring). We also observed anisocoria related with the mortality risk in the early stage after ICU stay. Conclusions: In this ICU survivor population with a prolonged follow-up, we highlight an acute risk of death after ICU stay, which seems to last longer in ICH patients. Several variables characteristic of disease severity appeared associated with long-term mortality, raising the hypothesis that the most severe patients deserve closer follow-up after ICU stay.

Keywords: Traumatic brain injury; Intra-cerebral haemorrhage; Critical care; Long term mortality

24COASNO11:

Title- The ratio of parasternal intercostal muscle-thickening fraction-to-diaphragm thickening fraction for predicting weaning failure,

Li Peng, Hongshan Kang, Hairong Chang, Yue Sun, Yuanyuan Zhao, Heling Zhao,

Journal of Critical Care, Volume 83, 2024, 154847,

<https://doi.org/10.1016/j.jcrc.2024.154847>.

Abstract: Background: Diaphragm dysfunction is associated with weaning outcomes in mechanical ventilation patients, in the case of diaphragm dysfunction, the accessory respiratory muscles would be recruited. The main purpose of this study is to explore the performance of parasternal intercostal muscle thickening fraction in relation to diaphragmatic thickening fraction ratio (TFic1/TFdi2) for predicting weaning outcomes, and compare its

accuracy with D-RSBI in predicting weaning failure. Materials and methods: We prospectively enrolled consecutive patients from 7/2022–5/2023. We measured TFic, TFdi, and diaphragmatic excursion (DE3) by ultrasound and calculated the TFic/TFdi ratio and diaphragmatic rapid shallow breathing index (D-RSBI4). Receiver-operator characteristic (ROC5) curves evaluated the accuracy of the TFic/TFdi ratio and D-RSBI in predicting weaning failure. Results: 161 were included in the final analysis, 114 patients (70.8%) were successfully weaned from mechanical ventilation. The TFic/TFdi ratio (AUROC = 0.887 (95% CI: 0.821–0.953)) was superior to the D-RSBI (AUROC = 0.875 (95% CI: 0.807–0.944)) for predicting weaning failure. Conclusions: The TFic/TFdi ratio predicted weaning failure with high accuracy and outperformed the D-RSBI.

Keywords: Diaphragm ultrasound; Parasternal intercostal muscle ultrasound; Parasternal intercostal muscle-thickening fraction; Diaphragm thickening fraction; Extubation; Weaning

24COASNO12:

Title- High PEEP/low FiO2 ventilation is associated with lower mortality in COVID–19,

Robin L. Goossen, Relin van Vliet, Lieuwe D.J. Bos, Laura A. Buiteman-Kruizinga, Markus W. Hollman, Sheila N. Myatra, Ary Serpa Neto,...[et al.]

Journal of Critical Care, Volume 83, 2024, 154854,

<https://doi.org/10.1016/j.jcrc.2024.154854>.

Abstract: Rationale: The positive end–expiratory pressure (PEEP) strategy in patients with coronavirus 2019 (COVID–19) acute respiratory distress syndrome (ARDS) remains debated. Most studies originate from the initial waves of the pandemic. Here we aimed to assess the impact of high PEEP/low FiO2 ventilation on outcomes during the second wave in the Netherlands. Methods: Retrospective observational study of invasively ventilated COVID–19 patients during the second wave. Patients were categorized based on whether they received high PEEP or low PEEP ventilation according to the ARDS Network tables. The primary outcome was ICU mortality, and secondary outcomes included hospital and 90–day mortality, duration of ventilation and length of stay, and the occurrence of kidney injury. Propensity matching was performed to correct for factors with a known relationship to ICU mortality. Results: This analysis included 790 COVID–ARDS patients. At ICU discharge, 32 (22.5%) out of 142 high PEEP patients and 254 (39.2%) out of 848 low PEEP patients had died (HR 0.66 [0.46–0.96]; $P = 0.03$). High PEEP was linked to improved secondary outcomes. Matched analysis did not change findings. Conclusions: High PEEP ventilation was associated with improved ICU survival in patients with COVID–ARDS.

Keywords: Intensive care; Respiration; Artificial; Respiratory distress syndrome; Respiratory insufficiency; Pneumonia; Viral

24COASNO13:

Title- Phosphodiesterase 3 inhibitors do not influence lactate kinetics and clinical outcomes in patients with septic shock: A multicentre cohort study,

Sharon Tai-Passmann, Claire A.D. Slegers, Pleun Hemelaar, Nicole Waalders, Matty Koopmans,

Journal of Critical Care, Volume 83, 2024, 154827,

<https://doi.org/10.1016/j.jcrc.2024.154827>.

Abstract: Purpose: We investigated the association between the administration of phosphodiesterase 3 inhibitors (PDE3i) and lactate kinetics, resolution of organ failure, ICU and hospital length of stay (LOS) and hospital mortality in a retrospective cohort of patients with septic shock and persistently elevated lactate concentrations. Material and methods: Patients with septic shock and two arterial lactate concentrations ≥ 4 mmol/L with at least 4 h between measurements were eligible. Clinical data of the first four days of admission were collected in an online database. For each patient, the area between the actual lactate concentrations and 2.2 mmol/L (AUC_{lact2.2}), was calculated for three days. Results: Data on 229 patients from 10 hospitals were collected, of whom 123 received PDE3i (54%). First, a linear multivariate model was developed to predict AUC_{lact2.2} ($R^2 = 0.57$). Adding PDE3i as a cofactor did not affect R^2 . Second, 60 patients receiving PDE3i at any time between days 0 and 2 were compared to 60 propensity matched no-PDE3i patients. Third, 30 patients who received PDE3i from ICU admission to day 3 were compared to 30 propensity-matched no-PDE3i patients. These analyses showed no differences in AUC_{lact2.2}, SOFA scores, ICU or hospital LOS or hospital mortality between treatment groups. Conclusions: No association was found between the administration of PDE3i and lactate kinetics, resolution of organ failure, ICU or hospital LOS or hospital mortality.

Keywords: Sepsis; Lactate; Phosphodiesterase 3 inhibitors; Septic shock; Organ failure; Treatment

24COASNO14:

Title- Association between comorbidities at ICU admission and post-Sepsis physical impairment: A retrospective cohort study,

Seibi Kobara, Ryohei Yamamoto, Milad G. Rad, Jocelyn R. Grunwell, Nao Hikota, Yoshihiro Uzawa, Yoshiro Hayashi, Craig M. Coopernsmith, Rishikesan Kamaleswaran, Journal of Critical Care, Volume 83, 2024, 154833,

<https://doi.org/10.1016/j.jcrc.2024.154833>.

Abstract: Purpose: Few studies have measured the association between pre-existing comorbidities and post-sepsis physical impairment. The study aimed to estimate the risk of physical impairment at hospital discharge among sepsis patients, adjusting for pre-existing physical impairment prior to ICU admission and in-hospital mortality. Materials and methods: We analyzed all consecutive adult patients admitted to an ICU in a tertiary community hospital, Kameda Medical Center, with sepsis diagnosis from September 2014 to October 2020. Inverse probability attrition weighting using machine learning was employed to estimate the risk of physical impairment at hospital discharge for sepsis patients with and without pre-existing comorbidities at ICU admission. This estimation was adjusted for baseline covariates, pre-ICU physical impairment, and in-hospital mortality. Results: Of 889 sepsis patients analyzed, 668 [75.1%] had at least one comorbidity and 221 [24.9%] had no comorbidities at ICU admission. Upon adjusting for baseline covariates, pre-ICU physical impairment, and in-hospital mortality, pre-existing comorbidities were not associated with an elevated risk of physical impairment at hospital discharge (RR: 1.02, 95% CI: 0.92, 1.14). Conclusions: Pre-existing comorbidities prior to ICU admission were not associated with an

increased risk of physical impairment at hospital discharge among sepsis patients after adjusting for baseline covariates and in-hospital mortality.

Keywords: Physical conditioning; Comorbidity; Sepsis; Hospital mortality; Machine learning; Inverse probability attrition weighting

24COASNO15:

Title- Outcomes of extracorporeal blood purification with oXiris® membrane in critically ill patients: A systematic review and meta-analysis,

Li Ying Siew, Zheng-Yii Lee, Nor'azim Mohd Yunos, Rafidah Atan, Matthew Edward Cove, Nuttha Lumlertgul, Nattachai Srisawat, M. Shahnaz Hasan,

Journal of Critical Care, Volume 83, 2024, 154844,

<https://doi.org/10.1016/j.jcrc.2024.154844>.

Abstract: Purpose: To evaluate the efficacy of the novel oXiris® membrane in critically ill adult patients. Methods: We systematically searched MEDLINE, EMBASE, and CENTRAL from inception to 01/06/2023 for relevant randomised controlled trials (RCTs) and non-randomised studies of intervention (NRSI). The primary outcome was overall mortality. Random effect meta-analyses were conducted in RevMan 5.4.1. Study quality was evaluated using Cochrane's risk of bias tool. (PROSPERO: CRD42023389198). Results: Ten studies (2 RCTs and 8 NRSIs) with 481 patients were included. None had low risk of bias. Treatment using oXiris® was associated with reduced overall mortality (RR 0.78, 95%CI 0.62–0.98; $p = 0.03$; 6 NRSI). One RCT reported 28-day mortality, finding no significant difference between groups. Besides, pooled NRSIs results showed significant reductions in SOFA scores, norepinephrine dosage, and several inflammatory biomarkers (C-reactive protein [CRP], lactate, and interleukin-6 [IL-6]) post oXiris® treatment. However, other clinical outcomes (ICU and hospital length of stay, mechanical ventilation duration) were similar between groups. Conclusion: In critically ill patients, the use of oXiris® membrane was associated with reduced overall mortality, norepinephrine dosage, CRP, IL-6, lactate levels, along with improved organ function. However, the certainty of evidence was very low, necessitating high-quality RCTs to further evaluate its efficacy in this population.

Keywords: Critical illness; Cytokines; Endotoxins; Extracorporeal blood purification; Hemadsorption; oXiris®

24COASNO16:

Title- The effect of high-dose selenium on mortality and postoperative organ dysfunction in post-cardiotomy cardiogenic shock patients supported with mechanical circulatory support – A post-hoc analysis of the SUSTAIN CSX trial,

Sascha Ott, Ellen Dresen, Zheng Yii Lee, Lukas M. Müller-Wirtz, Livia Procopiuc, Elyad Ekrami,

Journal of Critical Care, Volume 83, 2024, 154853,

<https://doi.org/10.1016/j.jcrc.2024.154853>.

Abstract: Purpose: Cardiac surgery, post-cardiotomy cardiogenic shock (PCCS), and temporary mechanical circulatory support (tMCS) provoke substantial inflammation. We therefore investigated whether a selenium-based, anti-inflammatory strategy would benefit PCCS patients treated with tMCS in a post-hoc analysis of the sustain CSX trial. Methods:

Post-hoc analysis of patients receiving tMCS for PCCS in the Sustain CSX trial, which investigated the effects of high-dose selenium on postoperative organ dysfunction in cardiac surgery patients. Primary outcome: duration of tMCS therapy. Secondary outcomes: postoperative organ dysfunction and 30-day mortality. Results: Thirty-nine patients were treated with tMCS for PCCS. There was no difference in the median duration of tMCS between the selenium and the placebo group (3 days [IQR: 1–6] vs. 2 days [IQR: 1–7], $p = 0.52$). Median dialysis duration was longer in the selenium group (1.5 days [0–21.8] vs. 0 days [0–1.8], $p = 0.048$). There was no difference in 30-day mortality (53% vs. 41%, OR 1.44, 95% CI 0.32–6.47, $p = 0.62$). Conclusion: In this explorative study, a perioperative high-dose selenium-supplementation did not show beneficial effects on organ dysfunctions and mortality rates in patients with PCCS receiving tMCS.

Keywords: Antioxidants; Inflammation; Cardiac surgery; Post-cardiotomy cardiogenic shock; Mechanical circulatory support

24COASNO17:

Title- The impact of frailty on survival times up to one year among patients admitted to ICU with in-hospital cardiac arrest,

Ryo Ueno, Mallikarjuna Ponnappa Reddy, Daryl Jones, David Pilcher, Ashwin Subramaniam, Journal of Critical Care, Volume 83, 2024, 154842,

<https://doi.org/10.1016/j.jcrc.2024.154842>.

Abstract: Background: In-hospital cardiac arrest (IHCA) is a serious medical emergency. When IHCA occurs in patients with frailty, short-term survival is poor. However, the impact of frailty on long-term survival is unknown. Methods: We performed a retrospective multicentre study of all critically ill adult (age ≥ 16 years) patients admitted to Australian intensive care units (ICU) between 1st January 2018 to 31st March 2022. We included all patients who had an IHCA within the 24 h before ICU admission with a documented Clinical Frail Scale (CFS). The primary outcome was median survival up to one year following ICU admission. The effect of frailty on one-year survival was assessed using a Cox proportional hazards model, adjusting for age, sex, comorbidities, sequential organ failure assessment (SOFA) score, and hospital type. Results: We examined 3769 patients, of whom 30.8% ($n = 1160$) were frail (CFS ≥ 5). The median survival was significantly shorter for patients with frailty (median [IQR] days 19 [1–365] vs 302 [9–365]; $p < 0.001$). The overall one-year mortality was worse for the patients with frailty when compared to the non-frail group (64.8% [95%CI 61.9–67.5] vs 36.4% [95%CI 34.5–38.3], $p < 0.001$). Each unit increment in the CFS was associated with 22% worse survival outcome (adjusted Hazard ratio = 1.22, 95%-CI 1.19–1.26), after adjustment for confounders. The survival trend was similar among patients who survived the hospitalization. Conclusion: In this retrospective multicentre study, frailty was associated with poorer one-year survival in patients admitted to Australian ICUs following an IHCA.

Keywords: Frailty; ICU; Cardiac arrest

24COASNO18:**Title- Prevalence and prognostic relevance of invasive fungal disease during veno-arterial ECMO: A retrospective single-center study,**

Jens M. Poth, Mathias Schmandt, Jens-Christian Schewe, Felix Lehmann, Stefan Kreyer, Zaki Kohistani, Farhad Bakhtiary, Gunnar Hischebeth, Christian Putensen, Johannes Weller, ... [et al.]

Journal of Critical Care, Volume 83, 2024, 154831,

<https://doi.org/10.1016/j.jcrc.2024.154831>.

Abstract: Purpose: To assess the prevalence and relevance of invasive fungal disease (IFD) during veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO). Methods: Retrospective analysis from January 2013 to November 2023 of adult V-A ECMO cases at a German University Hospital. Parameters relating to IFD, demographics, length of stay (LoS), days on ECMO and mechanical ventilation, prognostic scores and survival were assessed. Multivariable logistic regression analyses with IFD and death as dependent variables were performed. Outcome was assessed after propensity score matching IFD-patients to non-IFD-controls. Results: 421 patients received V-A ECMO. 392 patients with full electronic datasets were included. The prevalence of IFD, invasive candidiasis and probable invasive pulmonary aspergillosis was 4.6%, 3.8% and 1.0%. Severity of acute disease, pre-existing moderate-to-severe renal disease and continuous kidney replacement therapy were predictive of IFD. In-hospital mortality (94% (17/18) compared to 67% (252/374) in non-IFD patients ($p = 0.0156$)) was predicted by female sex, SOFA score at admission, SAVE score and IFD (for IFD: OR: 8.31; CI: 1.60–153.18; $p: 0.044$). There was no difference in outcome after matching IFD-cases to non-IFD-controls. Conclusions: IFD are detected in about one in 20 patients on V-A ECMO, indicating mortality >90%. However, IFD do not contribute to prognosis in this population.

Keywords: Aspergillosis; Candidemia; Candidiasis; Extracorporeal membrane oxygenation (ECMO); Invasive fungal disease (IFD); Invasive fungal infection (IFI); Veno-arterial ECMO

24COASNO19:**Title- Echocardiography predictors of sustained sinus rhythm after cardioversion of supraventricular arrhythmia in patients with septic shock,**

M. Balik, P. Waldauf, M. Maly, T. Brozek, J. Rulisek, M. Porizka, R. Sachl, M. Otahal, P. Brestovansky, E. Svobodova, [et al.]

Journal of Critical Care, Volume 83, 2024, 154832,

<https://doi.org/10.1016/j.jcrc.2024.154832>.

Abstract: Purpose: The echocardiography parameters may predict the maintenance of sinus rhythm after cardioversion of a supraventricular arrhythmia (SVA). Materials and methods Patients in septic shock with onset of an SVA, normal to moderately reduced LV systolic function ($EF_{LV} \geq 35\%$) and on a continuous noradrenaline of $<1.0 \mu\text{g/kg.min}$ were included. Echocardiography was performed at the arrhythmia onset, 1 h and 4 h post cardioversion on an infusion of propafenone or amiodarone. Results: Cardioversion was achieved in 96% of the 209 patients within a median time of 6(1.8–15.6)h, 134(64.1%) patients experienced at least one SVA recurrence after cardioversion. At 4 h the left atrial emptying fraction (LA_{EF} ,

cut-off 38.4%, AUC 0.69, $p < 0.001$), and transmitral A wave velocity-time-integral (Avti, cut-off 6.8 cm, AUC 0.65, $p = 0.001$) showed as limited predictors of a single arrhythmia recurrence. The LA_EF 44(36,49)%, ($p = 0.005$) and the Avti 8.65(7.13,9.50)cm, ($p < 0.001$) were associated with sustained sinus rhythm and decreased proportionally to increasing numbers of arrhythmia recurrences ($p < 0.001$ and $p = 0.007$, respectively). The enlarged left atrial end-systolic diameter at the arrhythmia onset ($p = 0.04$) and elevated systolic pulmonary artery pressure at 4 h ($p = 0.007$) were weak predictors of multiple(>3) recurrences. Conclusion: The LA_EF and Avti are related to arrhythmia recurrences post-cardioversion suggesting potential guidance to the choice between rhythm and rate control strategies. Trial registration: ClinicalTrials.gov Identifier: NCT03029169, registered on 24th of January 2017.

Keywords: Atrial fibrillation; Left atrial end-systolic volume; Left-atrial end-systolic diameter; Left atrial emptying fraction; Trans-mitral a wave; A wave velocity-time-integral

24COASNO20:

Title- Behind the scenes: Key lessons learned from the RELIEVE-AKI clinical trial,

Nasrin Nikravangolsefid, Supawadee Suppadungsuk, Waryaam Singh, Paul M. Palevsky, Raghavan Murugan, Kianoush B. Kashani,

Journal of Critical Care, Volume 83, 2024, 154845,

<https://doi.org/10.1016/j.jcrc.2024.154845>.

Abstract: Continuous kidney replacement therapy (CKRT) is commonly used to manage critically ill patients with severe acute kidney injury. While recent trials focused on the correct dosing and timing of CKRT, our understanding regarding the optimum dose of net ultrafiltration is limited to retrospective data. The Restrictive versus Liberal Rate of Extracorporeal Volume Removal Evaluation in Acute Kidney Injury (RELIEVE-AKI) trial has been conducted to assess the feasibility of a prospective randomized trial in determining the optimum net ultrafiltration rate. This paper outlines the relevant challenges and solutions in implementing this complex ICU-based trial. Several difficulties were encountered, starting with clinical issues related to conducting a trial on patients with rapidly changing hemodynamics, low patient recruitment rates, increased nursing workload, and the enormous volume of data generated by patients undergoing prolonged CKRT. Following several brainstorming sessions, several points were highlighted to be considered, including the need to streamline the intervention, add more flexibility in the trial protocols, ensure comprehensive a priori planning, particularly regarding nursing roles and their compensation, and enhance data management systems. These insights are critical for guiding future ICU-based dynamically titrated intervention trials, leading to more efficient trial management, improved data quality, and enhanced patient safety.

Keywords: Continuous kidney replacement therapy; Acute kidney injury; Net ultrafiltration

24COASNO21:**Title- Prophylactic versus restrictive platelet transfusion strategy in patients with haematological malignancies in the ICU setting, a propensity-score analysis,**

Jean-Baptiste Berenger, Colombe Saillard, Antoine Sannini, Luca Servan, Frederic Gonzalez, Marion Faucher, Jean-Manuel de Guibert, Marie-Anne Hospital, Magali Bisbal, Laurent Chow-Chine, [et al.]

Journal of Critical Care, Volume 83, 2024, 154817,

<https://doi.org/10.1016/j.jcrc.2024.154817>.

Abstract: Purpose: Prophylactic platelet transfusions (PT) aim to reduce bleeding. We assessed whether restrictive PT compared to prophylactic strategy could apply in ICU. Material and methods: We conducted a retrospective monocentric study including patients >18 yo with haematological malignancy admitted to the ICU with thrombocytopenia <20 G/L between 2018 and 2021. Patients were classified in 2 groups according transfusion strategy applied during the first 3 days: prophylactic or restrictive transfusion. Results: 180 patients were included, 87 and 93 in the restrictive and prophylactic groups respectively. After propensity-score analysis, 2 groups of 54 matched patients were analyzed. Restrictive strategy led to a significant reduction in PT with incidence rate for 100-ICU-patients-days of 34.9 and 49.9, incidence rate ratio = 0.699 [0.5–0.9], $p = 0.006$, representing a 31% decrease. Decreased PT persisted until day 28 with platelet concentrates transfusions-free days at day 28 of 21 [13–25] and 16.5 [10.2–21] in the 2 groups ($p = 0.04$). Restrictive strategy did not result in higher grade ≥ 2 bleeding. Transfusion efficiency was low with similar number of days with platelet <10 or < 20 G/L regardless of strategy. Platelet transfusion strategy was not associated with 28-day mortality. Platelet nadir <5G/L was associated with day-28 mortality with HR = 1.882 [1.011–3.055], $p = 0.046$. Conclusion: A restrictive PT strategy appears feasible in the ICU.

Keywords: Severe thrombopenia; Bleeding; Platelet transfusion strategy; Restrictive transfusion; Haematology; Intensive care unit

24COASNO23:**Title- Effectiveness of early high-flow nasal oxygen therapy after extubation of patients in the intensive care unit,**

Atsushi Ishihara, Hideshi Okada, Teruki Mori, Takashi Yoshizane, Kentaro Morishita, Takuji Yamamoto, Izumi Toyoda, Toshiyuki Noda,

Journal of Critical Care, Volume 83, 2024, 154840,

<https://doi.org/10.1016/j.jcrc.2024.154840>.

Abstract: Purpose: This study aimed to evaluate the impact of early high-flow nasal oxygen (HFNO) therapy initiation using a pre-determined respiratory rate-oxygenation (ROX) index on reducing reintubation rates and duration of intensive care unit (ICU) stay in post-extubated patients. Materials and methods: We enrolled a total of 145 extubated patients (mean age: 67.1 ± 12.9 years; sex: 96 male and 49 female; acute physiology and chronic health evaluation II score: 18.4 ± 6.8 points) classified into two groups: 71 patients admitted to the ICU before establishing extubation criteria and 74 patients after criteria implementation, over a 6-month period. We compared the HFNO reintubation rates and ROX index at 2 h post-

extubation before and after implementing early HFNO criteria. Results: The utilization rate of HFNO pre- and post-establishment of early HFNO criteria did not differ significantly (19.7% vs. 17.6%). However, the reintubation rate significantly decreased (11.3% vs. 4.1%, $P < 0.05$) with early HFNO use. Additionally, significant differences were observed in the total intubation period (5.2 ± 7.0 vs. 2.5 ± 2.7 days, $P < 0.05$) and ICU duration (8.6 ± 9.7 vs. 5.8 ± 5.6 days, $P < 0.05$). Conclusions: Early initiation of HFNO guided by the ROX index threshold post-extubation in patients admitted to ICU is associated with reduced reintubation rates and shorter ICU stays.

Keywords: High-flow nasal oxygen; Intubation; Reintubation; ROX index

24COASNO24:

Title- Impact of AKI on metabolic compensation for respiratory acidosis in ICU patients with AECOPD,

Florian Marcy, Katharina Goettfried, Philipp Enghard, Sophie K. Piper, Julius Valentin Kunz, Tim Schroeder,

Journal of Critical Care, Volume 83, 2024, 154846,

<https://doi.org/10.1016/j.jcrc.2024.154846>.

Abstract: Purpose: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) can result in severe respiratory acidosis. Metabolic compensation is primarily achieved by renal retention of bicarbonate. The extent to which acute kidney injury (AKI) impairs the kidney's capacity to compensate for respiratory acidosis remains unclear. Materials and methods: This retrospective analysis covers clinical data between January 2009 and December 2021 for 498 ICU patients with AECOPD and need for respiratory support. Results: 278 patients (55.8%) presented with or developed AKI. Patients with AKI exhibited higher 30-day-mortality rates (14.5% vs. 4.5% $p = 0.001$), longer duration of mechanical ventilation (median 90 h vs. 14 h; $p = 0.001$) and more severe hypercapnic acidosis (pH 7.23 vs. 7.28; pCO₂ 68.5 mmHg vs. 61.8 mmHg). Patients with higher AKI stages exhibited lower HCO₃⁻/pCO₂ ratios and did not reach expected HCO₃⁻ levels. In a mixed model analysis with random intercept per patient we analyzed the association of pCO₂ (independent) and HCO₃⁻ (dependent variable). Lower estimates for averaged change in HCO₃⁻ were observed in patients with more severe AKI. Conclusion : AKI leads to poor outcomes and compromises metabolic compensation of respiratory acidosis in ICU patients with AECOPD. While buffering agents may aid compensation for severe AKI, their use should be approached with caution.

Keywords: COPD; Exacerbation; Acute kidney injury; AKI; Respiratory acidosis; Acid-base disorder

24COASNO25:**Title- Determinants of beta-lactam PK/PD target attainment in critically ill patients: A single center retrospective study,**

H. Gandéga, H. Poujol, M. Mezzarobba, L. Muller, J.C. Boyer, J.Y. Lefrant, G. Leguelinel, C. Roger,

Journal of Critical Care, Volume 83, 2024, 154828,

<https://doi.org/10.1016/j.jcrc.2024.154828>.

Abstract: Purpose: We aimed to identify factors associated with achieving target BL plasma concentrations and describe real world data for therapeutic drug monitoring (TDM). Methods: A retrospective single center study was conducted. We collected data from patients admitted to ICU with at least one BL TDM. We assessed the proportion of patients attaining the recommended plasma concentrations (i.e. $100\%fT > 4$ to 8 MIC). Univariate and multivariate analyses were performed to identify the determinants of BL target attainment. Results: 156 patients were included. At the first dosing, 34% achieved target BL plasma concentrations, 50% were overdosed, and 16% were underdosed. Median time for 1st TDM were 4 (SD = 2.9) days. Multivariate analysis revealed that CKD-EPI estimated glomerular filtration rate (OR = 1.02; CI [1.01; 1.03]; $p < 0.0001$) and total body weight (OR = 1.03; CI [1.01; 1.04]; $p = 0.0048$) were the main determinant of BL target attainment. Conversely, Continuous Renal Replacement Therapy (OR = 0.28; CI [0.09; 0.89]; $p = 0.0318$) and meropenem use (OR = 0.31; CI [0.14; 0.69]; $p = 0.0041$) were identified as risk factors for overdosing. No factor was associated with underdosing. Conclusion: Achieving target BL plasma concentrations remains challenging in ICUs. Identifying predictive factors of BL target attainment would favor implementing rapid dosing optimization strategies in both under and overdosing high risk patients.

Keywords: Beta-lactams; Therapeutic drug monitoring; Critically ill; ICU; Target attainment; Pharmacokinetics

24COASNO26:**Title- Propofol binds and inhibits skeletal muscle ryanodine receptor 1,**

Thomas T. Joseph, Weiming Bu, Omid Haji-Ghassemi, Yu S. Chen, Kellie Woll, Paul D. Allen, Grace Brannigan, Filip van Petegem, Roderic G. Eckenhoff,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1093-1100

<https://doi.org/10.1016/j.bja.2024.06.048>

Abstract: : Background: As the primary Ca^{2+} release channel in skeletal muscle sarcoplasmic reticulum (SR), mutations in type 1 ryanodine receptor (RyR1) or its binding partners underlie a constellation of muscle disorders, including malignant hyperthermia (MH). In patients with MH mutations, triggering agents including halogenated volatile anaesthetics bias RyR1 to an open state resulting in uncontrolled Ca^{2+} release, increased sarcomere tension, and heat production. Propofol does not trigger MH and is commonly used for patients at risk of MH. The atomic-level interactions of any anaesthetic with RyR1 are unknown. Methods: RyR1 opening was measured by [^3H]ryanodine binding in heavy SR vesicles (wild type) and single-channel recordings of MH mutant R615C RyR1 in planar lipid bilayers, each exposed to propofol or the photoaffinity ligand analogue m-azipropofol

(AziPm). Activator-mediated wild-type RyR1 opening as a function of propofol concentration was measured by Fura-2 Ca²⁺ imaging of human skeletal myotubes. AziPm binding sites, reflecting propofol binding, were identified on RyR1 using photoaffinity labelling. Propofol binding affinity to a photoadducted site was predicted using molecular dynamics (MD) simulation. Results: Both propofol and AziPm decreased RyR1 opening in planar lipid bilayers ($P < 0.01$) and heavy SR vesicles, and inhibited activator-induced Ca²⁺ release from human skeletal myotube SR. Several putative propofol binding sites on RyR1 were photoadducted by AziPm. MD simulation predicted propofol KD values of 55.8 μ M and 1.4 μ M in the V4828 pocket in open and closed RyR1, respectively. Conclusions: Propofol demonstrated direct binding and inhibition of RyR1 at clinically plausible concentrations, consistent with the hypothesis that propofol partially mitigates malignant hyperthermia by inhibition of induced Ca²⁺ flux through RyR1.

Keywords: free energy perturbation; malignant hyperthermia; photoaffinity labelling; propofol; ryanodine receptor 1; skeletal muscle

24COASNO27:

Title- Association between inspired oxygen fraction and development of postoperative pulmonary complications in thoracic surgery: a multicentre retrospective cohort study,

Nicholas J. Douville, Mark E. Smolkin, Bhiken I. Naik, Michael R. Mathis, Douglas A. Colquhoun, Sachin Kheterpal, Stephen R. Collins, Linda W. Martin,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1073-1084

<https://doi.org/10.1016/j.bja.2024.08.005>

Abstract: Background: Limited data exist to guide oxygen administration during one-lung ventilation for thoracic surgery. We hypothesised that high intraoperative inspired oxygen fraction during lung resection surgery requiring one-lung ventilation is independently associated with postoperative pulmonary complications (PPCs). Methods: We performed this retrospective multicentre study using two integrated perioperative databases (Multicenter Perioperative Outcomes Group and Society of Thoracic Surgeons General Thoracic Surgery Database) to study adult thoracic surgical procedures using one-lung ventilation. The primary outcome was a composite of PPCs (atelectasis, acute respiratory distress syndrome, pneumonia, respiratory failure, reintubation, and prolonged ventilation >48 h). The exposure of interest was high inspired oxygen fraction (FiO₂), defined by area under the curve of a FiO₂ threshold > 80%. Univariate analysis and logistic regression modelling assessed the association between intraoperative FiO₂ and PPCs. Results: Across four US medical centres, 141/2733 (5.2%) procedures conducted in 2716 patients (55% female; mean age 66 yr) resulted in PPCs. FiO₂ was univariately associated with PPCs (adjusted OR [aOR]: 1.17, 95% confidence interval [CI]: 1.04–1.33, $P=0.012$). Logistic regression modelling showed that duration of one-lung ventilation (aOR: 1.20, 95% CI: 1.03–1.41, $P=0.022$), but not the time-weighted average FiO₂ (aOR: 1.01, 95% CI: 1.00–1.02, $P=0.165$), was associated with PPCs. Conclusions: Our results do not support limiting the inspired oxygen fraction for the purpose of reducing postoperative pulmonary complications in thoracic surgery involving one-lung ventilation.

Keywords: hyperoxia; inspired oxygen fraction; lung resection; one-lung ventilation; postoperative pulmonary complications; protective ventilation; single-lung ventilation; thoracic surgery

24COASNO28:

Title- Preoperative neurologic comorbidity and unanticipated early postoperative reintubation: a multicentre cohort study,

Christian Mpody, Rachel C. Kidwell, Brittany L. Willer, Olubukola O. Nafiu, Joseph D. Tobias,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1085-1092

<https://doi.org/10.1016/j.bja.2024.08.006>

Abstract: Background: The risk of respiratory complications is highest in the first 72 h post-surgery. Postoperative respiratory events can exacerbate pre-existing respiratory compromise and lead to reintubation of the trachea, particularly in patients with neurologic disorders. This study examined the association between neurologic comorbidities and unanticipated early postoperative reintubation in children. Methods: This multicentre, 1:1 propensity score-matched study included 420 096 children who underwent inpatient, elective, noncardiac surgery at National Surgical Quality Improvement Program reporting hospitals in 2012–22. The primary outcome was unanticipated early postoperative reintubation within 72 h after surgery. The secondary outcome was prolonged postoperative mechanical ventilation, defined as ventilator use >72 h. We also evaluated 30-day mortality in patients requiring reintubation. Results: Cerebral palsy was associated with the highest risk of early reintubation (adjusted relative risk [RRadj]: 1.97, 95% confidence interval [CI]: 1.44–2.69; P<0.01), followed by seizure disorders (RRadj: 1.87, 95% CI: 1.50–2.34; P<0.01), neuromuscular disorders (RRadj: 1.76, 95% CI: 1.41–2.19; P<0.01), and structural central nervous system abnormalities (RRadj: 1.35, 95% CI: 1.13–1.61; P<0.01). Unanticipated early postoperative reintubation was associated with an eight-times increased risk of 30-day mortality (adjusted hazard ratio: 8.1, 95% CI: 6.0–11.1; P<0.01). Risk of prolonged postoperative mechanical ventilation was also increased with neurologic comorbidities, particularly seizure disorders (RRadj: 1.73, 95% CI: 1.55–1.93; P<0.01). Conclusions: Children with neurologic comorbidities have an increased risk of unanticipated early postoperative reintubation and prolonged mechanical ventilation. Given the high mortality risk associated with these outcomes, children with neurologic comorbidities require heightened monitoring and risk assessment.

Keywords: cerebral palsy; mechanical ventilation; neurologic comorbidity; NSQIP-Pediatric; paediatric surgery; postoperative complications; seizure disorders; unplanned reintubation

24COASNO29:

Title- From pain level to pain experience: redefining acute pain assessment to enhance understanding of chronic postsurgical pain,

Axel Maurice-Szamburski, Sophie Bringuier, Pascal Auquier, Xavier Capdevila,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1021-1027

<https://doi.org/10.1016/j.bja.2024.08.003>

Abstract: Background: Chronic postsurgical pain (CPSP) significantly impairs quality of life and poses a substantial healthcare burden, affecting up to a quarter of patients undergoing surgery. Although acute pain is recognised as a predictor for CPSP development, the role of patient experience remains underexplored. This study examines the predictive value of patient experience alongside traditional risk factors for CPSP after orthopaedic surgery. Methods: An exploratory analysis was conducted on 294 patients from a multicentre randomised clinical trial comparing continuous perineural analgesia and single-injection nerve block in ambulatory orthopaedic surgeries. Patient experience was assessed using the Evaluation du Vecu de l'Anesthésie Générale (EVAN-G) validated questionnaire. Factors associated with CPSP at 90 days after surgery were identified through univariate and multivariate analyses, incorporating patient-reported outcomes and classical variables. Results: Out of 219 patients with complete data, 63 (29%) developed CPSP at day 90. Multivariate analysis revealed a poor pain experience, as assessed by the pain dimension of EVAN-G on postoperative day 2, as an independent predictor of CPSP (odds ratio 6.45, 95% confidence interval 1.65–25.26, $P < 0.01$). Poor pain experience was associated with an augmented risk of CPSP. Conclusions: This study underscores the role of patient-reported outcomes, specifically the pain experience dimension captured by the EVAN-G scale, in prediction of CPSP 90 days after surgery. It suggests a shift from conventional assessments of pain intensity to a comprehensive understanding of pain experience, advocating for tailored pain management approaches that could reduce chronic pain, thereby improving patient quality of life and functional recovery.

Keywords: acute pain; ambulatory surgery; catastrophising; chronic postsurgical pain; orthopaedic surgery; patient experience; regional anaesthesia; rehabilitation; secondary analysis

24COASNO30:

Title- Effect of machine learning models on clinician prediction of postoperative complications: the Perioperative ORACLE randomised clinical trial,

Bradley A. Fritz, Christopher R. King, Mohamed Abdelhack, Yixin Chen, Alex Kronzer, Joanna Abraham,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1042-1050

<https://doi.org/10.1016/j.bja.2024.08.004>.

Abstract: Background: Anaesthesiologists might be able to mitigate risk if they know which patients are at greatest risk for postoperative complications. This trial examined the impact of machine learning models on clinician risk assessment. Methods: This single-centre, prospective, randomised clinical trial enrolled surgical patients aged ≥ 18 yr. Anaesthesiologists and nurse anaesthetists providing remote telemedicine support reviewed electronic health records with (assisted group) or without (unassisted group) reviewing machine learning predictions. Clinicians predicted the likelihood of postoperative 30-day all-cause mortality and postoperative acute kidney injury (AKI) within 7 days. The primary outcome was area under the receiver operating characteristic curve (AUROC) for clinician predictions of mortality and AKI, comparing AUROCs between assisted and unassisted

assessments. Results :We analysed 5071 patients (mean [range] age: 58 [18-100] yr; 52% female) assessed by 89 clinicians. Of these, 98 (2.2%) patients died within 30 days of surgery and 450 (11.1%) patients sustained AKI. Clinician predictions agreed with the models more strongly in the assisted vs unassisted group (weighted kappa 0.75 vs 0.62 for death, mean difference: 0.13 [95% CI 0.10–0.17]; and 0.79 vs 0.54 for AKI, mean difference: 0.25 [95% CI 0.21–0.29]). Clinical prediction of death was similar between the assisted (AUROC 0.793) and unassisted (AUROC 0.780) groups (mean difference: 0.013 [95% CI –0.070 to 0.097]; P=0.76). Prediction of AKI had an AUROC of 0.734 in the assisted group vs 0.688 in the unassisted group (difference 0.046 [95% CI –0.003 to 0.091]; P=0.06). Conclusions: Clinician performance was not improved by machine learning assistance. Further work is needed to clarify the role of machine learning in real-time perioperative risk stratification. Clinical trial registration NCT05042804.

Keywords: acute kidney injury; anaesthesiology risk assessment; artificial intelligence; clinical trial; machine learning; postoperative complications; postoperative death

24COASNO31:

Title- Trends in hip fracture surgery in the United States from 2016 to 2021: patient characteristics, clinical management, and outcomes,

Genewoo Hong, Haoyan Zhong, Alex Illescas, Lisa Reisinger, Crispiana Cozowicz, Jashvant Poeran, Jiabin Liu, Stavros G. Memtsoudis,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 955-964

<https://doi.org/10.1016/j.bja.2024.07.022>.

Abstract: Introduction: Hip fractures are a serious health concern and a major contributor to healthcare resource utilisation. We aimed to investigate nationwide trends in the USA in patient characteristics and outcomes in patients after hip fracture repair surgery. Methods: From the Premier Healthcare dataset, we extracted patient encounters for surgical hip fracture repair from 2016 to 2021. Patient characteristics, comorbidities, complications, and anaesthetic and surgical details were analysed. Cochran–Armitage trend tests and simple linear regression were used to determine trends. Results: We included 347 086 hip fracture repair encounters. Notable trends included the following: median patient age declined from 82 yr [interquartile range: 73–88 yr] to 81 yr [interquartile range: 73–88 yr], (P-value=0.002), the proportion of female patients decreased from 68% to 66.2% (P-value=0.019); internal fixation was the most common intervention initially, but with a declining percentage from 49.9% to 43.8% (P-value <0.001); in general, patients carried a greater comorbidity burden, with the proportion with three or more Elixhauser comorbidities increasing from 56.4% to 58.6% (P-value=0.006); general anaesthesia remained the most common anaesthetic technique, from 68.90% to 56.80% without a significant trend; per 1000 inpatient days, the most common complication remained acute renal failure; despite a higher comorbidity burden, no complication showed a statistically significant upward trend, and many showed downward trends. Conclusions: Over the 6-yr period from 2016 to 2021, a majority of hip fracture repairs continued to be performed under general anaesthesia but with that percentage declining over time. Notable trends included a lower percentage of female patients, an

increase in femoral neck fractures, a higher comorbidity burden among patients, and a decrease in complications.

Keywords: complications; COVID-19; hip fracture surgery; patient characteristics; trends; United States

24COASNO32:

Title- Efficacy and safety of intraoperative controlled hypotension: a systematic review and meta-analysis of randomised trials,

Leah Dauterman, Nabia Khan, Connor Tebbe, Jiangqiong Li, Yanhua Sun, David Gunderman, Ziyue Liu, David C. Adams, Daniel I. Sessler, Lingzhong Meng,

British Journal of Anaesthesia

Volume 133, Issue 5, November 2024, Pages 940-954

<https://doi.org/10.1016/j.bja.2024.06.008>.

Abstract: Background: Intraoperative controlled hypotension improves surgical field visibility by reducing blood loss (efficacy) but poses potential risks linked to organ hypoperfusion (safety). The use of controlled hypotension persists despite increasing evidence of associations between intraoperative inadvertent hypotension and adverse outcomes. Therefore, we tested the hypothesis that the focus and results of intraoperative controlled hypertension research differ across anaesthesia and surgery investigators because of differing priorities. Methods: We systematically reviewed randomised trials comparing controlled hypotension with usual care with trials categorised by investigators' affiliation. Results: We identified 48 eligible trials, of which 37 were conducted by anaesthesia investigators and 11 by surgery investigators. For the primary outcome, 54% of the anaesthesia-led trials focused on safety, whereas all (100%) surgery-led trials focused on efficacy ($P=0.004$). Compared with usual care, mean arterial pressure in controlled hypotension was 23% (95% confidence interval [CI] 17–29%) lower in anaesthesia trials and 30% (95% CI 14–37%) lower in surgery trials; estimated blood loss was 44% (95% CI 30–55%) less in anaesthesia trials and 38% (95% CI 30–49%) less in surgery trials. Overall, blood loss was reduced by 43% (95% CI 32–53%), and trial sequential analysis supported an efficacy conclusion. Mean arterial pressure and estimated blood loss reductions were associated ($R^2=0.41$, $P=0.002$). All trials were underpowered for safety outcomes, and none adequately evaluated myocardial or renal injury. Conclusions: Anaesthesia researchers prioritised safety outcomes, whereas surgery researchers emphasised efficacy in controlled hypotension trials. Controlled hypotension significantly reduces blood loss. In contrast, safety outcomes were poorly studied. Given increasing observational evidence linking inadvertent hypotension to myocardial and renal injury, the safety of controlled hypotension remains to be addressed.

Keywords: anaesthesia; controlled hypotension; efficacy; randomised trial; safety; surgery

24COASNO33:

Title- Lived experience of burnout and fatigue in perioperative healthcare professionals in Rwanda: a qualitative study,

M. Dylan Bould, Eugene Tuyishime, Charles Nkurunziza, Christophe Mpirimbanyi, Gedeon Mutabezi, Logan Wiwchar, Lydia Yilma, Christopher Charles, Christian Rangel, British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1051-1061
<https://doi.org/10.1016/j.bja.2024.07.018>.

Abstract: Background: There is a lack of qualitative data on the negative effects of workplace stressors on the well-being of healthcare professionals in hospitals in Africa. It is unclear how well research methods developed for high-income country contexts apply to different cultural, social, and economic contexts in the global south. Methods: We conducted a qualitative interview-based study including 64 perioperative healthcare professionals across all provinces of Rwanda. We used an iterative thematic analysis and aimed to explore the lived experience of Rwandan healthcare professionals and to consider to what extent the Maslach model aligns with these experiences. Results: We found mixed responses of the effects on individuals, including the denial of burnout and fatigue to the points of physical exhaustion. Responses aligned with Maslach's three-factor model of emotional exhaustion, decreased personal accomplishment, and depersonalisation, with downstream effects on the healthcare system. Other factors included strongly patriotic culture, goals framed by narratives of Rwanda's recovery after the genocide, and personal and collective investment in developing the Rwandan healthcare system. Conclusions: The Rwandan healthcare system presents many challenges which can become profoundly stressful for the workforce. Consideration of reduced personal and collective accomplishment, of moral injury, and its diverse downstream effects on the whole healthcare system may better represent the costs of burnout Rwanda. It is likely that improving the causes of work-based stress will require a significant investment in improving staffing and working conditions.

Keywords: burnout; fatigue; perioperative care; Rwanda; workforce

24COASNO34:

Title- Frailty and decisional regret after elective noncardiac surgery: a multicentre prospective cohort study,

Yonathan Agung, Emily Hladkowitz, Laura Boland, Husein Moloo, Luke T. Lavallée, Manoj M. Lalu, Daniel I. McIsaac,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 965-972

<https://doi.org/10.1016/j.bja.2024.08.001>.

Abstract: Background: Frailty is associated with morbidity and mortality after surgery. The association of frailty with decisional regret is poorly defined. Our objective was to estimate the association of preoperative frailty with decisional regret status in the year after surgery. Methods: We conducted a secondary analysis of a prospective, multicentre cohort study of patients aged ≥ 65 years who underwent elective noncardiac surgery. Decisional regret about having undergone surgery was ascertained at 30, 90, and 365 (primary time point) days after surgery using a 3-point ordinal scale. Bayesian ordinal logistic regression was used to estimate the association of frailty with decisional regret, adjusted for surgery type, age, sex, and mental health conditions. Subgroup and sensitivity analyses were conducted. Results: We identified 669 patients; 293 (43.8%) lived with frailty. At 365 days after surgery, the unadjusted odds ratio (OR) associating frailty with greater decisional regret was 2.21 (95%

credible interval [CrI] 0.98–5.09; $P(\text{OR}>1)=0.97$), which was attenuated after confounder adjustment (adjusted OR 1.68, 95% CrI 0.84–3.36; $P(\text{OR}>1)=0.93$). Similar results were estimated at 30 and 90 days. Additional adjustment for baseline comorbidities and disability score substantially altered the OR at 365 days (0.89, 95% CrI 0.37–2.12; $P(\text{OR}>1)=0.39$). There was a high probability that surgery type was an effect modifier (non-orthopaedic: OR 1.90, 95% CrI 1.00–3.59; $P(\text{OR}>1)=0.98$); orthopaedic: OR 0.87, 95% CrI 0.41–1.91; $P(\text{OR}>1)=0.36$). Conclusions: Among older surgical patients, there appears to be a complex association with frailty and decisional regret, with substantial heterogeneity based on assumed causal pathways and surgery type. Future studies are required to untangle the complex interplay between these factors.

Keywords: comorbidity; decisional regret; disability; epidemiology; frailty; postoperative complications; surgery

24COASNO35:

Title- Working conditions during pregnancy: a survey of 3590 European anaesthesiologists and intensivists,

Marko Zdravkovic, Barbara Kabon, Olivia Dow, Martina Klinecova, Federico Bilotta, Joana Berger-Estilita,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1062-1072

<https://doi.org/10.1016/j.bja.2024.08.002>.

Abstract: Background: Pregnancy adds challenges for healthcare professionals, regardless of gender. We investigated experiences during pregnancy, attitudes towards pregnant colleagues, family planning decisions, and awareness of regulations among European anaesthesiologists and intensivists. Methods: A cross-sectional online survey was conducted among 3590 anaesthesiologists and intensivists from 47 European countries. The survey, available for 12 weeks, collected data on demographics, working conditions, safety perceptions, and the impact of clinical practice and training demands on family planning. Quantitative data were analysed using descriptive statistics, whereas qualitative data underwent thematic content analysis. Results: Only 41.4% ($n=678$) of women were satisfied with their working conditions during pregnancy, and only 38.5% ($n=602$) considered their working environment safe. The proportion of women who changed their clinical practice during pregnancy and who took sick leave to avoid potentially harmful working conditions increased over time ($P<0.001$ for both). Men had children more often during residency than women ($P<0.001$). Pregnant colleagues' safety concerns influenced clinical practice, with women and men who had experience with their own and partner's pregnancy being more likely to modify their practices. Work and training demands discouraged plans to have children, particularly among women, leading to consideration of leaving training. Awareness of national regulations was limited, and respondents highlighted a need for better support and flexible working conditions. Conclusions: Improved support and working environments for pregnant colleagues and ability to express preferred clinical areas for work are needed. Department heads should commit to safety and family friendliness, and men transitioning to parenthood should not be neglected.

Keywords: anaesthesiology; gender; intensive care; pregnancy; survey; working conditions

24COASNO36:**Title- Sodium leak channels in the central amygdala modulate the analgesic potency of volatile anaesthetics in mice,**

Yaoxin Yang, Jingxuan Qiu, Jin Liu, Donghang Zhang, Mengchan Ou, Han Huang, Peng Liang, Tao Zhu, Cheng Zhou,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 983-997

<https://doi.org/10.1016/j.bja.2024.06.049>.

Abstract: Background: Analgesia is an important effect of volatile anaesthetics, for which the spinal cord is a critical neural target. However, how supraspinal mechanisms modulate analgesic potency of volatile anaesthetics is not clear. We investigated the contribution of the central amygdala (CeA) to the analgesic effects of isoflurane and sevoflurane. Methods: Analgesic potencies of volatile anaesthetics were tested during optogenetic and chemogenetic inhibition of CeA neurones. In vivo calcium imaging was used to measure neuronal activities of CeA neuronal subtypes under volatile anaesthesia. Contributions of the sodium leak channel (NALCN) in GABAergic CeA (CeAGABA) neurones to analgesic effects of volatile anaesthetics were explored by specific NALCN knockdown. Electrophysiological recordings on acute brain slices were applied to measure volatile anaesthetic modulation of CeA neuronal activity by NALCN. Results: Optogenetic or chemogenetic silencing CeA neurones reduced the analgesic effects of isoflurane or sevoflurane in vivo. The calcium signals of CeAGABA neurones increased during exposure to isoflurane or sevoflurane at analgesic concentrations. Knockdown of NALCN in CeAGABA neurones attenuated antinociceptive effects of isoflurane, sevoflurane, or both. For example, mean concentrations of isoflurane, sevoflurane, or both that induced immobility to tail-flick stimuli were significantly increased (isoflurane: 1.17 [0.05] vol% vs 1.24 [0.04] vol%, $P=0.01$; sevoflurane: 2.65 [0.07] vol% vs 2.81 [0.07] vol%; $P<0.001$). In brain slices, isoflurane, sevoflurane, or both at clinical concentrations increased NALCN-mediated holding currents and conductance in CeAGABA neurones, which increased excitability of CeAGABA neurones in an NALCN-dependent manner. Conclusions: The analgesic potencies of volatile anaesthetics are partially mediated by modulation of NALCN in CeAGABA neurones.

Keywords: analgesia; central amygdala; NALCN; sodium leak channel; supraspinal; volatile anaesthetic

24COASNO37:**Title- Characterisation of older patients that require, but do not undergo, emergency laparotomy: a multicentre cohort study,**

Angeline Price, Elizabeth McLennan, Stephen R. Knight, Nicola Reeves, Susan Chandler, Jemma Boyle, Lyndsay Pearce, Susan J. Moug, Rosalyn Shearer, Peter Mekhail, George Ramsay, Ashrafun Nessa, Rizwan Iqbal, Perry Maskell, ...

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 973-982

<https://doi.org/10.1016/j.bja.2024.07.009>.

Abstract: Background: Older adults (≥ 65 yr) account for the majority of emergency laparotomies in the UK and are well characterised with reported outcomes. In contrast, there is limited knowledge on those patients that require emergency laparotomy but do not undergo

surgery (NoLaps). Methods: A multicentre cohort study (n=64 UK surgical centres) recruited 750 consecutive NoLap patients (February 15th - November 15th 2021, inclusive of a 90-day follow up period). Each patient was admitted to hospital with a surgical condition treatable by an emergency laparotomy (defined by The National Emergency Laparotomy Audit (NELA) criteria), but a decision was made not to undergo surgery (NoLap). Results: NoLap patients were predominately female (452 patients, 60%), of advanced age (median age 83.0 yr, interquartile range 77.0–88.8), frail (523 patients, 70%), and had severe comorbidity (750 patients, 100%); 99% underwent CT scanning. The commonest diagnoses were perforation (26%), small bowel obstruction (17%), and ischaemic bowel (13%). The 90-day mortality was 79% and influencing factors were >80 yr, underweight BMI, elevated serum lactate or creatinine concentration. The majority of patients died in hospital (77%), with those with ischaemic bowel dying early. For the 21% of NoLap patients that survived to 90 days, 77% returned home with increased care requirements. Conclusions: This study reports that the NoLap patient population present significant medical challenges because of their extreme levels of comorbidity, frailty, and physiology. Despite these complexities a fifth remained alive at 90 days. Further work is underway to explore this high-risk decision-making process. Clinical trial registration ISRCTN14556210.

Keywords: cohort studies; emergency general surgery; futility; mortality; NoLap; older adults

24COASNO38:

Title- RNA-binding protein SYNCRIP contributes to neuropathic pain through stabilising CCR2 expression in primary sensory neurones,

Yang Zhang, Bing Wang, Xiaozhou Feng, Huixing Wang, Ju Gao, Xu Li, Xiaodong Huo, Bushra Yasin, Alex Bekker, Huijuan Hu, Yuan-Xiang Tao,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 1028-1041

<https://doi.org/10.1016/j.bja.2024.07.024>.

Abstract: Background: Nerve injury-induced changes in gene expression in the dorsal root ganglion (DRG) contribute to the genesis of neuropathic pain. SYNCRIP, an RNA-binding protein, is critical for the stabilisation of gene expression. Whether SYNCRIP participates in nerve injury-induced alterations in DRG gene expression and nociceptive hypersensitivity is unknown. Methods: The expression and distribution of SYNCRIP in mouse DRG after chronic constriction injury (CCI) of the unilateral sciatic nerve were assessed. Effect of microinjection of Syncrip small interfering RNA into the ipsilateral L3 and L4 DRGs on the CCI-induced upregulation of chemokine (C-C motif) receptor 2 (CCR2) and nociceptive hypersensitivity were examined. Additionally, effects of microinjection of adeno-associated virus 5 expressing full length Syncrip mRNA (AAV5-Syncrip) on basal DRG CCR2 expression and nociceptive thresholds were observed. Results: SYNCRIP is expressed predominantly in DRG neurones, where it co-exists with CCR2. Levels of Syncrip mRNA and SYNCRIP protein in injured DRG increased time-dependently on days 3–14 after CCI. Blocking this increase through microinjection of Syncrip small interfering RNA into injured DRG attenuated CCI-induced upregulation of DRG CCR2 and development and maintenance of nociceptive hypersensitivities. Mimicking this increase through DRG microinjection of

AAV5-Syncrip elevated CCR2 expression in microinjected DRGs, enhanced the responses to mechanical, heat, and cold stimuli, and induced ongoing pain in naive mice. Mechanistically, SYNCRIP bound to 3-UTR of Ccr2 mRNA and stabilised its expression in DRG neurones.

Conclusions: SYNCRIP contributes to the induction and maintenance of neuropathic pain likely through stabilising expression of CCR2 in injured DRG. SYNCRIP may be a potential target for treating this disorder.

Keywords: chemokine (C-C motif) receptor 2; dorsal root ganglion; neuropathic pain; peripheral nerve injury; SYNCRIP

24COASNO39:

Title- Effectiveness of pain medication tapering in chronic pain patients: a systematic review and meta-analysis,

Elke Wuyts, Lisa Goudman, Cleo L. Crunelle, Maria Merlano Gomez, Koen Putman, Frenn Bultinck, Julie G. Pilitsis, Maarten Moens,

British Journal of Anaesthesia Volume 133, Issue 5, November 2024, Pages 998-1020

<https://doi.org/10.1016/j.bja.2024.07.025>.

Abstract: Background: This systematic review and meta-analysis aimed to inventory all outcome measures that are affected by tapering in chronic noncancer pain and to investigate the effectiveness of tapering. Methods: A literature search was conducted from inception to April 2024 in MEDLINE via PubMed, Web of Science, SCOPUS, EMBASE, and PsycINFO. Results: The initial database search identified 3969 articles, which were screened by two independent reviewers. Studies evaluating pain medication tapering in adults with chronic noncancer pain were eligible for inclusion. In total, 57 and 34 articles were included in the systematic review and meta-analysis, respectively. Risk of bias assessment demonstrated poor, fair, and good quality in 30, 24, and three studies, respectively. Pain intensity was the most reported outcome measure, as reported in 28 studies. Furthermore, a random-effect three-level meta-analysis was performed. An overall effect size of 0.917 (95% confidence interval 0.61–1.22; $P < 0.001$) was found, indicating a beneficial effect of tapering. In addition, a statistically significant improvement was demonstrated after tapering for pain intensity, headache disability, the number of headache days per month, anxiety, depression, the number of pills consumed per month, the number of days with medication intake per month, pain catastrophising, and pain interference. No statistically significant effect was observed for physical functioning, mental health-related quality of life, opioid use, pain self-efficacy, and physical health-related quality of life. Conclusions: This systematic review revealed a broad range of outcome measures affected by tapering. Owing to the high risk of bias of the included articles, the results of this meta-analysis must be interpreted with caution. Systematic review protocol CRD42023416343 (PROSPERO).

Keywords: anti-migraine medication; chronic noncancer pain; gabapentinoids; opioids; pain medication tapering

24COASNO40:**Title- Association Between Arterial Pulse Waveform Analysis and Mortality in Patients With Septic Shock: A Retrospective Cohort Study Using Japanese Diagnosis Procedure Combination Data**

Koji Endo, MD, Kayoko Mizuno, MD, PhD [...], and Koji Kawakami, MD, PhD

Journal of Intensive Care Medicine 2024 Oct;39(10):939-948.

<https://doi.org/10.1177/08850666241246215>

Abstract: Purpose: Specialized pressure transducers for arterial pulse waveform analysis (S-APWA) devices are dedicated kits connected to an arterial pressure catheter that monitors hemodynamic parameters, such as cardiac output, pulse pressure variation, and stroke volume variation, less invasively. While the association between the use of S-APWA devices and clinical outcomes in perioperative patients has been previously evaluated, its assessment in patients with septic shock remains inadequate. Materials and Methods: This retrospective cohort study utilized a nationwide Diagnosis Procedure Combination database in Japan. Adult patients with septic shock admitted to the intensive care unit (ICU) with arterial pressure catheter placement on the admission day from August 2012 to February 2021 were included. Hospitalizations meeting the eligibility criteria were categorized into groups based on S-APWA device usage. The primary outcome, evaluated using Cox regression analysis, was 30-day all-cause mortality in the propensity score overlap-weighted population. Secondary outcomes included in-hospital mortality, ICU duration, and overall hospital stay. Results: Among 5130 eligible hospitalizations, 643 were in the S-APWA group and 4487 were in the conventional pressure transducer group. Cox regression analysis within the propensity score overlap-weighted population showed no significant difference in 30-day mortality (adjusted hazard ratio: 0.94; 95% confidence interval: 0.9-1.38; $P = .58$). Logistic regression analysis indicated no significant differences in the in-hospital mortality. While the S-APWA group had prolonged ICU stays, no significant difference in the overall hospital stay was observed according to linear regression analyses. Conclusions: Our study found no significant association between S-APWA use and 30-day mortality in patients with septic shock. These findings offer insights into optimizing monitoring systems in ICUs.

24COASNO41:**Title- What Are the Real Issues in Providing Extracorporeal Membrane Oxygenation (ECMO) Support: A Survey**

Lovkesh Arora, MBBS, MD, FASA, [...], and Raquel R. Bartz, MD, MMCI, MHA+5View all authors and affiliations

Journal of Intensive Care Medicine . 2024 Oct;39(10):949-957.

<https://doi.org/10.1177/08850666241245933>

Abstract: Introduction: By using a novel survey our study aimed to assess the challenges ECMO and Critical Care (CC) teams face when initiating and managing patient's ECMO support. Methods: A qualitative survey-based observational study was performed of members of 2 Critical Care Medicine organizations involved in decision-making around the practice of Extracorporeal Membrane Oxygenation (ECMO). The range of exploratory questions covered ethical principles of informed consent, autonomy and goals of care discussions,

beneficence, non-maleficence (offering life-sustaining treatments in end-of-life care), and justice (insurance-related limitations of treatment). Questions also covered pragmatic practice and quality improvement areas, such as exploring whether palliative care or ethics teams were involved in such decision-making. Results: 305 members received the survey links, and a total of 61 completed surveys were received, for an overall response rate of 20% among all eligible members. Only 70% of the participants who manage ECMO patients are involved in the ECMO initiation decision process. The majority do not involve Ethics or Palliative care at the initial ECMO initiation decision step. Of the ethical and moral dilemmas reported, the majority revolved around 1. Prognostication of patients receiving VV and VA ECMO support, 2. Lack of knowledge of patient's wishes and goals, 3. Disconnect between expectations of families and outcomes and 4. Staff moral distress around when to stop ECMO in case of futility. Conclusion: Our survey highlights areas of distress and dilemma which have been stressed before in the initiation, management, and outcomes of ECMO patients, however with the increasing use of this modality of cardiopulmonary mechanical support being offered, the survey results can offer a guidance using sound ethical principles.

24COASNO42:

Title- Association Between In-hospital Mortality and the Institutional Factors of Intensive Care Units with a Focus on the Intensivist-to-bed Ratio: A Retrospective Cohort Study

Hideki Endo, MD, MPH, PhD Hiroshi Okamoto, MD, MPH, [...], and Hiroaki Miyata, PhD
Journal of Intensive Care Medicine . 2024 Oct;39(10):958-964.

<https://doi.org/10.1177/08850666241245645>

Abstract: Purpose: To elucidate the relationship between in-hospital mortality and the institutional factors of intensive care units (ICUs), with a focus on the intensivist-to-bed ratio. Methods: A retrospective cohort study was conducted using a Japanese ICU database, including adult patients admitted between April 1, 2020 and March 31, 2021. We used a multilevel logistic regression model to investigate the associations between in-hospital mortality and the following institutional factors: the intensivist-to-bed ratios on weekdays or over weekends/holidays, different work shifts, hospital-to-ICU-bed ratio, annual-ICU-admission-to-bed ratio, type of hospital, and the presence of other medical staff. Results: The study population comprised 46 503 patients admitted to 65 ICUs. The in-hospital mortality rate was 8.1%. The median numbers of ICU beds and intensivists were 12 (interquartile range [IQR] 8-14) and 4 (IQR 2-9), respectively. In-hospital mortality decreased significantly as the intensivist-to-bed ratio at 10 am on weekdays increased: the average contrast indicated a 20% (95% confidence interval [CI]: 1%-38%) reduction when the ratio increased from 0 to 0.5, and a 38% (95% CI: 9%-67%) reduction when the ratio increased from 0 to 1. The other institutional factors did not present a significant effect. Conclusions: The intensivist-to-bed ratio at 10 am on weekdays had a significant effect on in-hospital mortality. Further investigation is needed to understand the processes leading to improved outcomes.

24COASNO43:**Title- Impact of Humidification Modality on Incidence of Endotracheal Tube Occlusion in COVID-19 Patients**

James Richard Mattson, MD, Kunal Dhiren Gada, MBBS, and Sahar Ahmad, MD,

Journal of Intensive Care Medicine . 2024 Oct;39(10):965-973.

<https://doi.org/10.1177/08850666241246969>

Abstract: Endotracheal tube (ETT) occlusion is reported at a higher frequency among coronavirus disease-2019 (COVID-19) patients. Prior to the COVID-19 pandemic, literature examining patient and ventilator characteristics, including humidification, as etiologies of ETT occlusion yielded mixed results. Our study examines the relationship of humidification modality with ETT occlusion in COVID-19 patients undergoing invasive mechanical ventilation (IMV). Methods: We conducted a retrospective chart review of COVID-19 patients requiring IMV at a tertiary care center in New York from April 2020 to April 2021. Teleflex Neptune heated wire heated humidification (HH) and hygroscopic Intersurgical FiltaTherm and Sunmed Ballard 1500 heat and moisture exchangers (HME) were used. Episodes of ETT occlusion were recorded. Univariate and multivariable logistic regression models were used to investigate the relationship between humidification modality and the occurrence of ETT occlusion. Findings: A total of 201 eligible patients were identified. Teleflex HH was utilized in 50.2% of the population and the others Intersurgical and Sunmed HME devices. Median age was 62 years and 78.6% of patients had at least one medical comorbidity. Precisely, 24% of patients experienced an ETT occlusion after a median of 12 days. The HME group was younger (58.5 vs 64 years), predominantly male (75% vs 59.4%), and experienced more total ventilator days than the HH group (24 vs 12). Those using the studied HME devices had significantly higher odds of ETT occlusion (OR 4.4, 95% CI 1.8-10.6, $P = .0011$). Three patients (6.1%) experienced cardiac arrest as a consequence of their occlusion. There were no deaths directly attributed to ETT occlusion. Conclusions: The studied HME devices were significantly associated with higher odds of ETT occlusion in COVID-19 patients requiring invasive mechanical ventilation. These events are not without significant clinical consequences. Prolonged use of under-performing HME devices remains suspect in the occurrence of ETT occlusions.

24COASNO45:**Title- A Proof-of-Concept Model for Implementing a “Smart-NICU” to Improve Infant Mortality**

Sidney Hilker, MD, Amundam Mancho, MD, [...], and Carl Britto, MD, PhD

Journal of Intensive Care Medicine . 2024 Apr 18:8850666241247532.

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Abstract: Low- and middle-income countries face limited critical care capacity due to constraints in staffing, resources, and technology. “Smart ICUs” that integrate telehealth to augment care delivery, communication, and data integration have the potential to bridge these gaps and reduce preventable morbidity and mortality. While their efficacy has been well validated in adult populations, applications of Smart-ICU services in the neonatal population have not been studied. Neonatal intensive care units (NICUs) in India using a common

Smart-NICU platform, developed by CloudPhysician, utilize a hub-and-spokes framework along with locally designed technology to facilitate remote patient care in collaboration with local health systems. In this article, we investigate the operational characteristics and performance outcomes for Smart-NICU deployment from the 18 NICUs and 214 beds deployed to date. These findings highlight the potential impact of Smart-NICUs and establish generalizable principles for implementation in low-resource settings.

24COASNO46:**Title- Pilot Study on the Impact of Early Subcutaneous Basal Insulin Administration in Diabetic Ketoacidosis**

Danielle S. Murray, PharmD, Brian W. Gilbert, PharmD, MBA, FCCM, FNCS, BCCCP, and Tessa R. Cox, PharmD, BCCCPView all authors and affiliations

Journal of Intensive Care Medicine . 2024 Oct;39(10):980-984.

<https://doi.org/10.1177/08850666241247516>

Abstract: Recent studies have shown improved outcomes with the initiation of earlier subcutaneous (SQ) basal insulin. The purpose of this study was to examine the effects of early SQ basal insulin administration on hospital length of stay in patients with mild to moderate diabetic ketoacidosis (DKA). Methods: This was a retrospective, single-center study from a large community teaching hospital that included patients 18 years or older with mild to moderate DKA, identified using ICD-10 codes, who received intravenous (IV) insulin. Patients who received SQ basal insulin prior to a documented anion gap ≤ 12 mmol/L were considered to have received early SQ basal insulin and were compared to patients who received SQ basal insulin after closure of their anion gap (AG). The primary outcome was hospital length of stay. Secondary outcomes included intensive care unit length of stay, duration of IV insulin, time to anion gap closure, and incidences of rebound hyperglycemia. Safety outcomes included incidences of hypoglycemia, and hypokalemia. Results: Of 301 patients screened, 108 patients were included in the final analysis. Forty patients received early SQ basal insulin and 68 did not. Median hospital length of stay in the nonearly group was 71 h, compared to 62 h in the early group ($P = .57$). Secondary and safety outcomes were similar between groups. Conclusions: In this study, there was no statistically significant difference in length of stay in patients that received early SQ basal insulin. Larger trials are needed to determine the significance of earlier SQ basal insulin in DKA.

24COASNO47:**Title- Transbronchial Lung Cryobiopsies, Transbronchial Forceps Lung Biopsies, and Surgical Lung Biopsies in Mechanically Ventilated Patients with Acute Hypoxemic Respiratory Failure: A Retrospective Cohort Study**

Qi Li, MD, Dominique Lafrance, MD, [...], and Michaël Chassé, MD, PhD +5View all authors and affiliations

Journal of Intensive Care Medicine . 2024 Oct;39(10):985-993.

<https://doi.org/10.1177/08850666241247145>

Abstract: Importance: Lung biopsies are sometimes performed in mechanically ventilated patients with acute hypoxemic respiratory failure (AHRF) of unknown etiology to guide

patient management. While surgical lung biopsies (SLB) offer high diagnostic rates, they may also cause significant complications. Transbronchial forceps lung biopsies (TBLB) are less invasive but often produce non-contributive specimens. Transbronchial lung cryobiopsies (TBLC) yield specimens of potentially better quality than TBLB, but due to their novel implementation in the intensive care unit (ICU), their accuracy and safety are still unclear. Objectives: Our main objective was to evaluate the risk of adverse events in patients with AHRF following the three biopsy techniques. Our secondary objectives were to assess the diagnostic yield and associated modifications of patient management of each technique. Design, Settings and Participants: We conducted a retrospective cohort study comparing TBLC, TBLB, and SLB in mechanically ventilated patients with AHRF. Main Outcomes and Measures: The primary outcome was the proportion of patients with at least one complication, and secondary outcomes included complication rates, diagnostic yields, treatment modifications, and mortality. Results: Of the 26 patients who underwent lung biopsies from 2018 to 2022, all TBLC and SLB patients and 60% of TBLB patients had at least one complication. TBLC patients had higher unadjusted numbers of total and severe complications, but also worse Sequential Organ Failure Assessment scores and P/F ratios. A total of 25 biopsies (25/26, 96%) provided histopathological diagnoses, 88% (22/25) of which contributed to patient management. ICU mortality was high for all modalities (63% for TBLC, 60% for TBLB and 50% for SLB). Conclusions and Relevance: All biopsy methods had high diagnostic yields and the great majority contributed to patient management; however, complication rates were elevated. Further research is needed to determine which patients may benefit from lung biopsies and to determine the best biopsy modality

24COASNO48:**Title- Hospital Outcomes in Patients Who Developed Acute Respiratory Distress Syndrome After Community-Acquired Pneumonia**

George Kasotakis, MD, MPH, Praruj Pant, BS, [...], and Tetsu Ohnuma, MD, MPH, PhD
+4View all authors and affiliations

Journal of Intensive Care Medicine . 2024 Oct;39(10):994-1001.

<https://doi.org/10.1177/08850666241248568>

Abstract: Purpose: To identify risk factors for and outcomes in acute respiratory distress syndrome (ARDS) in patients hospitalized with community-acquired pneumonia (CAP). Methods: This is a retrospective study using the Premier Healthcare Database between 2016 and 2020. Patients diagnosed with pneumonia, requiring mechanical ventilation (MV), antimicrobial therapy, and hospital admission ≥ 2 days were included. Multivariable regression models were used for outcomes including in-hospital mortality, hospital length of stay (LOS), intensive care unit (ICU) LOS, and days on MV. Results: 1924 (2.7%) of 72 107 patients with CAP developed ARDS. ARDS was associated with higher mortality (33.7% vs 18.9%; adjusted odds ratio 2.4; 95% confidence interval [CI] 2.16-2.66), longer hospital LOS (13 vs 9 days; adjusted incidence risk ratio (aIRR) 1.24; 95% CI 1.20-1.27), ICU LOS (9 vs 5 days; aIRR 1.51; 95% CI 1.46-1.56), more MV days (8 vs 5; aIRR 1.54; 95% CI 1.48-1.59), and increased hospitalization cost (\$46 459 vs \$29 441; aIRR 1.50; 95% CI 1.45-1.55). Conclusion: In CAP, ARDS was associated with worse in-patient

outcomes in terms of mortality, LOS, and hospitalization cost. Future studies are needed to explore outcomes in patients with CAP with ARDS and explore risk factors for development of ARDS after CAP.

24COASNO49:**Title- Delirium Associated with COVID-19 in Critically ill Children: An Observational Cohort Study**

Meghan C. Gray, MD, Chani Traube, MD, [...], and Andrew S. Geneslaw, MD, MS +1View all authors and affiliations

Journal of Intensive Care Medicine . 2024 Oct;39(10):1002-1011.

<https://doi.org/10.1177/08850666241249169>

Abstract: Objective: Delirium is an under-recognized problem in critically ill children. Although delirium is common in adults hospitalized with COVID-19, the relationship between pediatric COVID-19 and delirium has not been described. To address this gap, we characterized delirium in critically ill children with different manifestations of COVID-19 and investigated associations among demographic, disease, and treatment factors. We hypothesized that multisystem inflammatory syndrome in children (MIS-C) would be associated with a higher incidence of delirium given its underlying pathophysiology of hyperinflammation. Design: Retrospective, single-center cohort study. Setting: Quaternary-care pediatric intensive care unit (PICU). Patients Children less than 18 years of age hospitalized in the PICU between March 2020 and March 2023 with either active SARS-CoV-2 infection or serological evidence of prior infection. Measurements and main results: The cohort included 149 PICU hospitalizations among children with evidence of COVID-19. Patients were categorized by reason for PICU admission: 75 (50%) for COVID-19 respiratory disease, 36 (24%) MIS-C, and 38 (26%) any other primary reason with positive COVID-19 testing. Delirium was diagnosed in 43 (29%) patients. Delirium incidence was highest in patients requiring invasive mechanical ventilation (IMV) (56% vs 7.5% in patients who did not require IMV, $p < .001$). Patients who were exposed to opioids, dexmedetomidine, paralytics or benzodiazepines more frequently experienced delirium compared to those unexposed ($p < .001$, $p < .001$, $p < .001$ and $p = .001$, respectively). After multivariable adjustment, delirium was associated with IMV (HR 3 [95% CI 1.5–5.7]), female sex (HR 2.4 [1.2–4.7]), and developmental disability (HR 3.4 [95% CI 1–11.1]). There was no association between delirium and reason for PICU hospitalization. Conclusions: Delirium was common among children hospitalized with COVID-19. The overall incidence was much less than has been reported in adults with COVID-19. Delirium reduction efforts should focus on children with developmental disability and minimizing ongoing risks during IMV.

24COASNO50:**Title- Outcomes of High-Dose Versus Low-Dose Vitamin D on Prognosis of Sepsis Requiring Mechanical Ventilation: A Randomized Controlled Trial**

Tarek Mohamed Ashoor, MD, Abd Elmoniem Hassan Abd Elazim, MB BCh, [...], and Ibrahim Mamdouh Esmat, MD

Journal of Intensive Care Medicine . 2024 Oct;39(10):1012-1022.

<https://doi.org/10.1177/08850666241250319>

Abstract: Background: Critically ill patients with sepsis have a high incidence of vitamin D deficiency. Vitamin D promotes the synthesis of human cathelicidin antimicrobial peptide, a precursor of LL-37, which is a part of the innate immune system. This study investigated the effectiveness and safety of the early administration of high-dose enteral vitamin D₃ in comparison with low-dose vitamin D₃ in patients with sepsis requiring mechanical ventilation (MV). Methods: Eighty adult patients with sepsis requiring MV with known vitamin D deficiency were randomly assigned to receive either an enteral 50 000 IU (Group I) or 5000 IU (Group II) vitamin D supplementation. Clinical and laboratory parameters were evaluated at baseline and on days 4 and 7 between the study groups. The change in serum procalcitonin (PCT) levels on day 7 was the primary outcome, while the change in serum LL-37 levels on day 7, changes in sequential organ failure assessment (SOFA) score, and clinical pulmonary infection score on day 7, MV duration, and hospital length of stay (LOS) were the secondary outcomes. Results: The (day 7-day 0) change in serum PCT and LL-37 levels and SOFA score were significantly different in Group I ($P = .010$, $P < .001$, and $P < .001$, respectively). The SOFA score was significantly different on days 4 and 7 in Group I ($P < .001$ and $P < .001$, respectively). The incidence of early ventilator-associated pneumonia was significantly different between both treatment groups ($P = .025$). The hospital LOS was shorter in Group I ($P < .001$). No 25-hydroxyvitamin-D toxicity was observed in either group. Conclusions: Early enteral administration of high-dose vitamin D₃ in critically ill patients with sepsis requiring MV along with standard treatment for sepsis decreased serum procalcitonin levels, increased serum LL-37 levels, and ameliorated illness severity scores.

24COASNO51:

Title- Long-term Risk of Stroke After New-Onset Atrial Fibrillation in Sepsis Survivors: A 2-Year Follow-Up Study

Ahmed Ayaz, MBBS, Muhammad Ibrahim, and Ainan Arshad, MBBS, MRCP

Journal of Intensive Care Medicine . 2024 Oct;39(10):1023-1027.

<https://doi.org/10.1177/08850666241251755>

Abstract: Background: Cardiovascular complications such as new-onset atrial fibrillation (NOAF) are common in sepsis and are known to increase the risk of in-hospital mortality and stroke. However, only a handful of studies have evaluated the long-term risk of stroke after NOAF in sepsis survivors. As part of our efforts to address this issue, we conducted the first-ever follow-up study in a developing country evaluating the long-term risk of stroke for sepsis survivors following NOAF. Methods: This retrospective study evaluated all adult patients admitted at the Aga Khan University Hospital between July 2019 and December 2019 with the diagnosis of sepsis. Data was collected from medical records of the included patients. Outcome measures included in-hospital mortality and ischemic stroke within 2 years. Results: Seven hundred thirty patients were included in the study; 415 (57%) were males and 315 (43%) females; mean age was 59.4 ± 18 years. 59 (8%) patients developed NOAF. The risk of stroke within 2 years in sepsis survivors was 3.5%. Six out of 30 (20%) patients in the atrial fibrillation (AF) group developed stroke, whereas 11 out of 448 (2%) patients in the non-AF group developed stroke. NOAF was associated with an increased risk

of ischemic stroke within 2 years (OR = 6.6; 95% CI, 2.3-12.8; $P = <.001$). Conclusion: We conclude that AF occurred frequently in sepsis patients and was also associated with a 6-fold increase in the risk of ischemic stroke within 2 years. Reliable interventions for identifying high-risk patients for ischemic stroke are still poorly characterized, and this study may serve as a basis for more extensive multicenter studies to identify patients at high risk for ischemic stroke in the aftermath of septic AF and develop precise interventions for preventing it.

24COASNO52:**Title- Dual-Lumen Extracorporeal Membrane Oxygenation Cannulation Technique Using Only Transthoracic Echocardiography – A Case Series**

Lin Huang, MD, Li-li Wu, MD, [...], and Wai-Ching Sin, MD, PhD

Journal of Intensive Care Medicine . 2024 Oct;39(10):1028-1033.

<https://doi.org/10.1177/08850666241264231>

Abstract: Background: Bicaval dual lumen cannula (DLC) is gaining popularity in veno-venous extracorporeal membrane oxygenation (V-V ECMO) for having less recirculation and facilitating mobilization. It is usually inserted under fluoroscopic or transesophageal echocardiographic guidance to prevent potentially fatal complications. Thus, their utilization was limited during the COVID-19 outbreak due to stringent quarantine policy and manpower shortage, especially when emergency insertion was required. Purpose: To describe our experience on DLC insertion using transthoracic echocardiography alone during the pandemic, with a focus on safety considerations by using detail step-by-step procedural guide. Outcome: Four patients were performed V-V ECMO using the transthoracic echocardiographic-guided DLC cannulation technique during the fifth wave of the COVID-19 outbreak, with no cannulation-related complications. Conclusion: Transthoracic echocardiographic guidance for DLC insertion is feasible and probably safe with a detailed guide, which can be adopted as a supplementary tool during future endemic outbreaks.

24COASNO53:**Title- The effects of laryngeal mask versus endotracheal tube on atelectasis after general anesthesia induction assessed by lung ultrasound: A randomized controlled trial,**

Bin Liu, Yaxin Wang, Ling Li, Wei Xiong, Yifan Feng, Yan Liu, Xu Jin,

Journal of Clinical Anesthesia, Volume 98,2024,111564,

<https://doi.org/10.1016/j.jclinane.2024.111564>.

Abstract: This study aims to evaluate the impact of Supreme™ laryngeal masks versus endotracheal tubes on atelectasis during general anesthesia using lung ultrasound (LUS), and provide evidence for respiratory management. Design: A single-center, double-blind, randomized controlled trial was conducted. Setting: The study was conducted in both the operating room and the post-anesthesia care unit, with follow-up assessments performed in the ward. Patients: Enrollment included 180 cases undergoing non-laparoscopic surgeries in gynecology, urology, and orthopedic limb surgeries. Interventions: Patients were randomly assigned 1:1 to the endotracheal intubation or laryngeal mask group. Measurements: LUS scores were recorded across 12 lung regions at baseline, 15 min after airway establishment, at the end of surgery, and 30 min following airway removal. Outcome measures encompassed

the oxygenation index, dynamic lung compliance, incidence of postoperative pulmonary complications, throat pain, and other postoperative complications assessed at 24 and 48 h postoperatively. The primary outcome focused on the LUS score in all 12 lung regions at 15 min after airway establishment. Main results: Intention-to-treat analysis of 177 subjects revealed endotracheal intubation led to significantly higher LUS scores at 15 min { $P < 0.001$, mean difference 4.15 ± 0.60 , 95% CI [2.97, 5.33]}, end of surgery ($P < 0.001$, mean difference 3.37 ± 0.68 , 95% CI [2.02, 4.72]), and 30 min post-removal ($P < 0.001$, mean difference 2.63 ± 0.48 , 95% CI [1.68, 3.58]). No major complications occurred in the two groups. Conclusions: Compared to endotracheal intubation, laryngeal masks effectively reduce atelectasis formation and progression in gynecological, urological non-laparoscopic, and orthopedic limb surgeries. However, caution is warranted when generalizing these findings to surgeries with a higher risk of laryngeal mask leakage or obese patients. Additionally, the efficacy of laryngeal masks in reducing postoperative atelectasis remains uncertain when comprehensive monitoring of muscle relaxation and reversal therapy is employed.

Keywords: General anesthesia; Atelectasis; Endotracheal intubation; Laryngeal mask; Lung ultrasound score

24COASNO54:

Title- The evaluation of the performance of ChatGPT in the management of labor analgesia,

Nada Ismaiel, Teresa Phuongtram Nguyen, Nan Guo, Brendan Carvalho, Pervez Sultan, Anthony Chau,

Journal of Clinical Anesthesia, Volume 98, 2024, 111582,

<https://doi.org/10.1016/j.jclinane.2024.111582>.

Abstract: ChatGPT4 is a leading large language model (LLM) chatbot released by OpenAI in 2023. ChatGPT4 can respond to free-text queries, answer questions and make suggestions regarding virtually any topic. ChatGPT4 has successfully answered anesthesia and even obstetric anesthesia knowledge-based questions with reasonable accuracy. However, ChatGPT4 has yet to be challenged in obstetric anesthesia clinical decision-making. Study Objective: In this study, we evaluated the performance of ChatGPT4 in the management of clinical labor analgesia scenarios compared to expert obstetric anesthesiologists. Intervention: Eight clinical questions with progressively increasing medical complexity were posed to ChatGPT4. Measurements: The ChatGPT4 responses were rated by seven expert obstetric anesthesiologists based on safety, accuracy and completeness of each response using a five-point Likert rating scale. Main Results: ChatGPT4 was deemed safe in 73% of responses to the presented obstetric anesthesia clinical scenarios (27% of responses were deemed unsafe). None of the ChatGPT4 responses were unanimously deemed to be safe by all seven expert obstetric anesthesiologists. Moreover, ChatGPT4 responses were overall partly accurate (score 4 out of 5) and somewhat incomplete (score 3.5 out of 5). Conclusions: In summary, approximately one quarter of all responses by ChatGPT4 were deemed unsafe by expert obstetric anesthesiologists. These findings may suggest the need for more fine-tuning and training of LLMs such as ChatGPT4 specifically for clinical decision making in obstetric

anesthesia or other specialized medical fields. These LLMs may come to play an important future role in assisting obstetric anesthesiologists in clinical decision making and enhancing overall patient care.

Keywords: ChatGPT4; Chatbot; Anesthesiology; Obstetric; Safety; Analgesia

24COASN055:

Title- Recruitment-to-inflation ratio to assess response to PEEP during laparoscopic surgery: A physiologic study,

Marco Covotta, Claudia Claroni, Giulia Torregiani, Luca S. Menga, Emanuela Venti, Gaetano Gazzè,

Journal of Clinical Anesthesia, Volume 98, 2024, 111569,

<https://doi.org/10.1016/j.jclinane.2024.111569>.

Abstract: Study objective During laparoscopic surgery, the role of PEEP to improve outcome is controversial. Mechanistically, PEEP benefits depend on the extent of alveolar recruitment, which prevents ventilator-induced lung injury by reducing lung dynamic strain. The hypotheses of this study were that pneumoperitoneum-induced aeration loss and PEEP-induced recruitment are inter-individually variable, and that the recruitment-to-inflation ratio (R/I) can identify patients who benefit from PEEP in terms of strain reduction. Design: Sequential study. Setting: Operating room. Patients Seventeen ASA I-III patients receiving robot-assisted prostatectomy during Trendelenburg pneumoperitoneum. Interventions and measurements: Patients underwent end-expiratory lung volume (EELV) and respiratory/lung/chest wall mechanics (esophageal manometry and inspiratory/expiratory occlusions) assessment at PEEP = 0 cmH₂O before and after pneumoperitoneum, at PEEP = 4 and 12 cmH₂O during pneumoperitoneum. Pneumoperitoneum-induced derecruitment and PEEP-induced recruitment were assessed through a simplified method based on multiple pressure-volume curve. Dynamic and static strain changes were evaluated. R/I between 12 and 4 cmH₂O was assessed from EELV. Inter-individual variability was rated with the ratio of standard deviation to mean (CoV). Main results: Pneumoperitoneum reduced EELV by (median [IqR]) 410 mL [80–770] ($p < 0.001$) and increased dynamic strain by 0.04 [0.01–0.07] ($p < 0.001$), with high inter-individual variability (CoV = 70% and 88%, respectively). Compared to PEEP = 4 cmH₂O, PEEP = 12 cmH₂O yielded variable amount of recruitment (139 mL [96–366] CoV = 101%), causing different extent of dynamic strain reduction (median decrease 0.02 [0.01–0.04], $p = 0.002$; CoV = 86%) and static strain increases (median increase 0.05 [0.04–0.07], $p = 0.01$, CoV = 33%). R/I (1.73 [0.58–3.35]) estimated the decrease in dynamic strain ($p \leq 0.001$, $r = -0.90$) and the increase in static strain ($p = 0.009$, $r = -0.73$) induced by PEEP, while PEEP-induced changes in respiratory and lung mechanics did not. Conclusions: Trendelenburg pneumoperitoneum yields variable derecruitment: PEEP capability to revert these phenomena varies significantly among individuals. High R/I identifies patients in whom higher PEEP mostly reduces dynamic strain with limited static strain increases, potentially allowing individualized settings.

Keywords: Alveolar recruitment; Atelectasis; Laparoscopic surgery; PEEP; Recruitment-to-inflation ratio; Respiratory mechanics

24COASNO56:

Title- Effects of neuromuscular block reversal with neostigmine/glycopyrrolate versus sugammadex on bowel motility recovery after laparoscopic colorectal surgery: A randomized controlled trial,

Eun-Su Choi, Jiyoun Lee, Ji Hyeon Lee, Jin-Hee Kim, Sung-Hee Han, Jin-Woo Park,
Journal of Clinical Anesthesia, Volume 98, 2024, 111588,
<https://doi.org/10.1016/j.jclinane.2024.111588>.

Abstract: Study objective: To compare the effects of neostigmine/glycopyrrolate (a traditional agent) and sugammadex on bowel motility recovery and the occurrence of digestive system complications after colorectal surgery. Design Prospective, randomized controlled trial. Setting: A single tertiary center. Patients: 111 patients undergoing laparoscopic colorectal surgery. Interventions: Patients were randomized into two groups based on the block reversal agent: 1) a mixture of 50 µg.kg⁻¹ of neostigmine and 10 µg.kg⁻¹ of glycopyrrolate (neostigmine group) and 2) 2 mg.kg⁻¹ of sugammadex (sugammadex group). Measurements: The primary outcome was the time from the surgery's completion to the first flatus. The time to the first postoperative defecation, incidences of postoperative nausea or vomiting, ileus, and dry mouth, as well as postoperative length of stay, were also assessed. Main results: The time to the first flatus was significantly shorter in the sugammadex group than in the neostigmine group (59 [42–79] h vs 69 [53–90] h, $P = 0.027$). The time to the first defecation and the incidences of postoperative nausea or vomiting and ileus did not differ between the groups, nor did the postoperative length of stay. However, the incidence of postoperative dry mouth was significantly lower in the sugammadex group than in the neostigmine group (7 patients [13%] vs 39 patients [71%], $P < 0.001$). Conclusions: The time to the first flatus was shorter using 2 mg.kg⁻¹ sugammadex to reverse the neuromuscular block for laparoscopic colorectal surgery compared to reversal with conventional neostigmine/glycopyrrolate.

Keywords: Anesthesia; Anticholinergics; Bowel motility; Colorectal surgery; Laparoscopic surgery; Sugammadex

24COASNO57:

Title- Postoperative delirium risk in patients with hyperlipidemia: A prospective cohort study,

Yue Zhao, Ke Zhong, Yujie Zheng, Xiaoli Xia, Xue Lin, Ana Kowark, Xiaobin Wang, Daiying Zhang, Xiaoxia Duan,
Journal of Clinical Anesthesia, Volume 98, 2024, 111573,
<https://doi.org/10.1016/j.jclinane.2024.111573>.

Abstract: Study objective: Hyperlipidemia and postoperative delirium (POD) significantly affect patients' quality of life; however, the question of whether hyperlipidemia constitutes a risk factor for POD remain unclear. This study aimed to investigate whether patients with hyperlipidemia face elevated risks of developing POD and to identify potential causes for this increased risk. Design: A prospective cohort study. Setting: Operating room. Patients: Patients were adults scheduled for colorectal cancer surgery in 2023. Exposures: The exposure factor was hyperlipidemia, and the patients were divided into hyperlipidemia group

and non-hyperlipidemia group. Measurements: POD occurrence within three days post-surgery was assessed using the 3-Minute Diagnostic Interview for Confusion Assessment Method. Over one year, these patients were monitored through telephone to evaluate their survival and cognitive function. Logistic regression analysis was performed to evaluate the risk factors for POD development in patients with hyperlipidemia and to construct a clinical prediction model. Main results: This study included 555 patients. POD incidence was 21.6% in the hyperlipidemia group and 12.7% in the non-hyperlipidemia group. One year following surgery, patients with hyperlipidemia and POD exhibited significantly higher rates of mortality and cognitive decline than did those without POD ($p < 0.001$). A multifactorial logistic clinical prediction model was constructed from seven independent risk factors for POD development in patients with hyperlipidemia, including education, preoperative total cholesterol (TC), preoperative triglyceride (TG), diet, history of hypertension, Sedation-Agitation Scale, and postoperative trimethylamine N-oxide expression level, and it had the highest predictive value for POD development in patients with hyperlipidemia. Conclusions: Compared with those without hyperlipidemia, patients with hyperlipidemia had higher POD incidence. Elevated serum TC and TG levels are independent risk factors for POD in patients with hyperlipidemia. The study's findings could help develop strategies for improving POD and hyperlipidemia treatment.

Keywords: Cognitive decline; Diet structure; Hyperlipidemia; Postoperative delirium; Total cholesterol; Triglyceride

24COASNO58:

Title- A new video laryngoscope combined with flexible laryngeal mask insertion: A prospective randomized study,

Zhihao Zheng, Xiaodong Liang, Jinrui Li, Ying Li, Liwei Bi, Wei Sun, Zhanfei Hu, Jiannan Song, Qi Zhou, Haibo Li,

Journal of Clinical Anesthesia, Volume 98, 2024, 111590,

<https://doi.org/10.1016/j.jclinane.2024.111590>.

Abstract: The video laryngoscope (VLS) has been proven to be an effective insertion device for airway management. However, no laryngoscope has been specifically designed for the placement of the laryngeal mask airway (LMA). We improved the current VLS and developed a novel VLS method. This study aimed to evaluate the clinical efficacy of an improved VLS for inserting a flexible laryngeal mask airway (F-LMA) compared with the standard blind method. Methods: One hundred and fifty-seven patients who underwent F-LMA insertion under general anesthesia were randomly assigned to either the standard blind insertion technique (group B) or VLS -assisted insertion (group VL). First attempt success rates were recorded. Secondary outcomes included oropharyngeal leakage pressure (OLP), fiberoptic view, insertion time, position adjustment, reinsertion rate, and postoperative airway morbidity. Results: The first-attempt success rate was higher in group VL than that in group B (99% vs. 86%; $p = 0.002$). The OLP was significantly higher in the VLS-guided technique (26.4 ± 5.1 vs 23.8 ± 4.4 cmH₂O, $p = 0.002$). The fiberoptic view was significantly better in the group VL ($p < 0.001$) and required less readjustment and reinsertion to establish an effective airway ($p < 0.001$). The insertion time was shorter in the group B than that in group

VL (33.9 vs 41.3 s, $p < 0.001$). Hemodynamic stress responses and postoperative airway complications did not differ between the two groups. Conclusions: The new VLS-guided insertion technology has a high success rate, achieves greater OLP, and provides an ideal anatomical position with minimal adjustment, without increasing the risk of hemodynamic stress or adverse events. Trial registration: Chinese Clinical Trial Registry (registration number: ChiCTR2300075866; <https://www.chictr.org.cn>).

Keywords: Flexible laryngeal mask airway; Insertion technique; Video laryngoscope; Standard blind insertion; Anesthesia

24COASNO59:

Title- Impact of preoperative QTc interval prolongation on short-term postoperative outcomes: A retrospective study,

Chun-Ning Ho, Wei-Chu Chung, Chia-Li Kao, Chih-Wei Hsu, Kuo-Chuan Hung, Chia-Hung Yu, Jen-Yin Chen, I-Wen Chen,

Journal of Clinical Anesthesia, Volume 98, 2024, 111574,

<https://doi.org/10.1016/j.jclinane.2024.111574>.

Abstract: Although a prolonged heart rate-corrected QT interval (QTcI) is associated with an increased risk of mortality in the general population, its prognostic value in surgical patients remains unclear. We aimed to examine whether preoperative QTcI prolongation predicts short-term postoperative outcomes in elderly patients undergoing noncardiac surgery. Design: The study was a retrospective analysis using the TriNetX network database. Setting: Operating room. Intervention Assessment and categorization of preoperative QTcI. Patients: Data of patients aged ≥ 65 years who underwent non-cardiac surgery between 2010 and 2023 were analyzed. Measurements: Patients were categorized into four groups based on preoperative QTcI: long (500-600 ms), borderline (460-500 ms), high-normal (420-460 ms) and control (370-420 ms) groups. The groups were compared using a propensity score-matched analysis. The primary outcome was the all-cause 90-day mortality risk. The secondary outcomes included 90-day risks of postoperative new-onset atrial fibrillation (Af), ventricular arrhythmias (VAs), emergency visits, hospital readmissions, and pneumonia. Results: In total, data on 519,929 patients were collected in this study. Pairwise comparisons showed that all QTcI prolongation groups demonstrated a heightened incidence of postoperative mortality, arrhythmias, and other complications compared to the control group. Patients with a long QTcI had a 3-fold higher risk of mortality (hazard ratio [HR] = 3.124, $p < 0.001$), Af (HR = 3.059, $p < 0.001$), and VAs (HR = 3.617, $p < 0.001$) than controls. The risks of emergency visits (HR = 1.287, $p < 0.001$), hospital readmissions (HR = 1.591, $p < 0.001$), and pneumonia (HR = 1.672, $p < 0.001$) were also higher in the long QTcI group than in the control group. A dose-dependent response was evident between QTcI and mortality as well as arrhythmia risk. Conclusion: Preoperative QTcI screening effectively risk-stratifies elderly surgical patients, with a QTcI ≥ 500 ms being strongly predictive of short-term postoperative mortality and other complications. Incorporating QTcI assessment into the preoperative evaluation may guide perioperative monitoring and management.

Keywords: QT interval; Atrial fibrillation; Ventricular arrhythmias; Postoperative; Mortality; Pneumonia

Cancer Research

24COASN01:

Title- Tumor Dormancy Within the Lymphovascular Embolus Is Regulated by Multiple Metabolism-signaling Pathways

YIN YE, JUSTIN WANG, JORDAN DILLARD AND SANFORD H. BARSKY

Anticancer Research October 2024, 44 (10) 4165-4173;

DOI: <https://doi.org/10.21873/anticancerres.17247>

Abstract: Recently, we demonstrated that cancer dormancy is initiated within the lymphovascular tumor embolus and consists of decreased proliferation and lower mammalian target of rapamycin (mTOR) activity. In the present study, we investigated other intersecting metabolism-signaling pathways that may ultimately determine whether the lymphovascular tumor embolus remains dormant or undergoes cell death. **Materials and Methods:** The present study exploited a singular patient-derived xenograft (PDX) of inflammatory breast cancer (Mary-X) that spontaneously forms high density spheroids, the in vitro equivalent of emboli. The AMPK metabolic checkpoint pathway, the mTOR nutrient-responsive cell growth pathway, the P13K/Akt intracellular quiescence regulating pathway, and the calpain-mediated E-cadherin proteolytic pathway responsible for spontaneous spheroid-genesis were also investigated, to determine their relative contributions to dormancy. **Results:** The levels of phosphorylated AMPK proteins (AMPK α and β subunits) decreased gradually with the formation of MARY-X spheroids in vitro. Rapamycin down-regulated mTOR activity, yet dormancy persisted. LY294002, a PI3K/Akt inhibitor, completely abolished mTOR and induced spheroid disadherence and apoptosis. Compound C (AMPK inhibitor) up-regulated mTOR and induced spheroid disadherence and apoptosis. Increasing cellular metabolism led to cell death, even in enriched medium, whereas growing the spheroids in serum-free media (starvation) did not result in further mTOR inhibition, and dormancy was maintained. **Conclusion:** An increase in our understanding of dormancy from the standpoint of internal signaling pathways might ultimately provide clues to the external stimuli (starvation, hypoxia or other not yet understood phenomena) that act through these pathways to maintain or disrupt dormancy.

24COASN02:

Title- Antitumor Potential of Guttiferone E Combined With Carboplatin Against Osimertinib-resistant H1975 Lung Cancer Through Apoptosis

AAKASH NATHANI, ISLAUDDIN KHAN, MATHEUS HIKARU TANIMOTO,

Anticancer Research October 2024, 44 (10) 4175-4188;

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Abstract: Background/Aim: Low selectivity and high frequency of side-effects are the major problems of currently used chemotherapeutics. Among natural compounds, the polyphenylated acylphloroglucinol, guttiferone E, isolated from Brazilian red propolis, has attracted attention due to its marked anticancer properties and was evaluated here for its role against osimertinib-resistant H1975 cells (with double mutations of epidermal growth factor receptor: EGFR L858R/T790M). **Materials and Methods:** Guttiferone E was obtained from

red propolis using established extraction procedures. Guttiferone E was tested using the H1975 cell line in in vitro (2D and 3D) cell cultures and in vivo in BALB/c athymic nude mice. Live/dead assay was also performed to support the results. Tumor tissues obtained from in vivo studies were used for western blotting. Guttiferone E reduced H1975 cell viability in a concentration-dependent manner. The IC₅₀ values in 2D and 3D cell lines were 2.56±0.12 µM and 11.25±0.34 µM. Furthermore, at 10 mg/kg intraperitoneally, guttiferone E significantly reduced the tumor volume in tumor xenografts when used alone and in combination with carboplatin. Guttiferone E and carboplatin displayed synergistic inhibition of H1975 cells and animal tumors. Co-treatment of guttiferone E with carboplatin induced more prominent apoptosis than treatment with either drug alone. Guttiferone E treatment induced cleavage of poly-ADP ribose polymerase and induced apoptosis by significantly reducing levels of mammalian target of rapamycin, sirtuin 1, sirtuin 7, superoxide dismutase, programmed death-ligand 1, and programmed cell death 1 in tumor tissues. Conclusion: Our results show guttiferone E to be a promising, novel and potent antitumor drug candidate for osimertinib-resistant lung cancer with EGFR L858R/T790M mutations.

24COASNO3:

Title- Enhancing Retinoic Acid-mediated Effects Through Inhibition of CYP26A1, CYP26B1 and HGF Signaling in Neuroblastoma Cells

REEMA SAMI ISSA, MEIKE KAEHLER, NINA SOPHIE POMMERT, INGOLF CASCORBI and VICKI WAETZIG

Anticancer Research October 2024, 44 (10) 4189-4202;

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Abstract: Retinoic acid (RA) induces tumor cell differentiation in diseases like acute promyelocytic leukemia or high-risk neuroblastoma. However, the formation of resistant cells, which results from dysregulation of different signaling pathways, limits therapy success. The present study aimed to characterize basic regulatory processes induced by the application of RA in human neuroblastoma cells, to identify therapeutic targets independent of the often amplified oncogene MYCN. Materials and Methods: In MYCN-amplified Kelly and MYCN non-amplified SH-SY5Y cells, different assays were employed to quantify the viability and cytotoxicity, while RA-mediated expression changes were examined using genome-wide gene expression analysis followed by quantitative PCR. Enzyme-linked immunoabsorbent assays (ELISA) and western blots were used to determine the levels or activation of the examined proteins. Results: In Kelly cells, treatment with 5 µM RA for 3 days significantly reduced the cell number due to attenuated proliferation, while SH-SY5Y cells were less responsive. An up-regulation of the RA-metabolizing enzymes CYP26A1 and CYP26B1 was observed in both cell lines, and co-treatment with the selective CYP26 inhibitor talarozole markedly decreased cell viability. When RA and ketoconazole, which inhibits CYP26 as well as RA-degrading CYP3A enzymes, were co-administered, not only cell survival was impaired in both cell lines, but also the release of hepatocyte growth factor (HGF). Accordingly, co-application of the c-Met inhibitor tepotinib and RA or ketoconazole substantially decreased cell viability. Conclusion: Independent of MYCN amplification,

inhibitors of RA metabolism or HGF signaling might prevent the emergence of RA-resistant neuroblastoma cells when co-applied with RA.

24COASNO4:**Title- *TMPRSS2:ERG* Gene Fusion Might Predict Resistance to PARP Inhibitors in Metastatic Castration-resistant Prostate Cancer**

TIM SVENSTRUP POULSEN, ANDERS NYGAARD LØRUP, PER KONGSTED, RIKKE LØVENDAHL EEFSSEN, MARTIN HØJGAARD and ESTRID VILMA HØGDALL

Anticancer Research October 2024, 44 (10) 4203-4211;

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Abstract: The emergence of novel DNA damage repair (DDR) pathways in molecular-target therapy drugs (MTTD) has shown promising outcomes in treating patients with metastatic castration-resistant prostate cancer (mCRPC). About 25% of mCRPC patients have actionable deleterious aberrations in DDR genes, primarily in the homologous recombination (HR) pathway. However, the response rate in patients with BRCA1/2 or mutations in HRR-related genes is only 45%-55%, when exposed to poly ADP ribose polymerase (PARP) inhibitor-based therapy (PARPi). A frequent characteristic feature of prostate cancer (PC) is the occurrence of genomic rearrangement that affects the transmembrane protease serine 2 (TMPRSS2) and E26 transformation-specific (ETS)- transcription factor-related gene (ERG). **Materials and Methods:** In this study, a total of 114 patients with mCRPC had their RNA and DNA sequenced using next-generation sequencing. **Results:** Based on their genetic profile of deleterious gene alterations of BRCA1/2 or ATM, six patients were selected for PARPi. Patients with TMPRSS2:ERG gene fusion and homozygous alteration in ATM or BRCA2 (n=2) or heterozygous alterations (BRCA1 or BRCA2) and lack of TMPRSS2:ERG gene fusion (n=2) did not show clinical benefit from PARPi (treatment duration <16 weeks). In contrast, patients (n=2) without TMPRSS2:ERG gene fusion and homozygous deleterious alterations in ATM or BRCA2 all had clinical benefit from PARPi (treatment duration ≥16 weeks). **Conclusion:** The TMPRSS2:ERG transcript product might be used as a PARPi resistance biomarker.

24COASNO5:**Title- Loss of Malignancy of Super-Methotrexate-resistant Osteosarcoma Cells Is Associated With an Increase of Methylated Histone Marks H3K9me3 and H3K27me3**

YUSUKE AOKI, YUTARO KUBOTA, NORIYUKI MASAKI, KOYA OBARA, YASUNORI TOME, MICHAEL BOUVET, KOTARO NISHIDA and ROBERT M. HOFFMAN

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Abstract: Methotrexate (MTX) resistance in osteosarcoma results in a very poor patient prognosis. We previously reported that super MTX-resistant osteosarcoma (143B-MTX^{SR}) cells, selected from parental 143B osteosarcoma (143B-P) cells by culturing them with increasing concentrations of MTX, exhibited reduced malignancy, despite the over-expression of oncogenes. The present study explored the mechanism of reduced malignancy

in the super MTX-resistant osteosarcoma cells. **Materials and Methods:** Previously selected 143B-MTX^{SR} cells which are 5,500 times more MTX resistant than parental cells, were used for this study. The status of methylated histone H3K9me3 and H3K27me3 marks was examined with western immunoblotting and compared between 143B-MTX^{SR} and parental 143B-P cells. **Results:** Histone H3K9me3 and H3K27me3 marks were over-expressed in 143B-MTX^{SR} compared to 143B-P ($p < 0.05$, $p < 0.01$, respectively). **Conclusion:** Over-expression of histone H3K9me3 and H3K27me3 marks may be related to super-MTX resistance and to the loss of malignancy of super MTX-resistant osteosarcoma cells due to the fundamental relationship of methylation and cancer.

24COASNO6:

Title- Therapeutic Responses to Two New SN-38 Derivatives in Colorectal Cancer Patient-Derived Xenografts and Respective 3D *In Vitro* Cultures

KATARZYNA UNRUG-BIELAWSKA, DAVID EARNSHAW, MAGDALENA CYBULSKA-LUBAK, EWELINA KANIUGA, ZUZANNA SANDOWSKA-MARKIEWICZ,

Anticancer Research October 2024, 44 (10) 4219-4224;

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Abstract: SN-38, an active metabolite of irinotecan, exhibits toxicity to all proliferating cells, causing dose-limiting and potentially life-threatening side effects. Newly established water-soluble derivatives of SN-38, 7-ethyl-9-(N-morpholinyl)methyl-10-hydroxycamptothecin (BN-MOA) and 7-ethyl-9-(N-methylamino)methyl-10-hydroxycamptothecin (BN-NMe), exhibit a unique mechanism of spontaneous alkylation of aromatic bases in DNA and show greater *in vitro* activity on cancer cell lines than SN-38. The aim of this study was to compare the therapeutic responses to irinotecan, BN-MOA and BN-NMe *in vivo* and *in vitro* in 3D cultures using colorectal cancer (CRC) patient derived xenografts (PDX). **Materials and Methods:** Seven established PDX tissues were subcutaneously grown on the flanks of NSG or NSG-SGM3 mice and tumor diameters were measured with a caliper. Compounds were administrated intraperitoneally at 40 mg/kg every five days. 3D PDX cultures were performed on 96-well LifeGel plates and cell viability was determined with the CellTiter Glo 3D reagent. **Results:** Treatment with irinotecan significantly delayed or stopped the growth of 5 out of 7 PDXs, with a greater level of inhibition from BN-MOA compared to irinotecan and BN-NMe. *In vitro* studies exhibited the same trends in SN-38 and BN-NMe but not in BN-MOA. **Conclusion:** The new SN-38 derivatives, BN-MOA and BN-NMe, showed enhanced therapeutic effects compared to irinotecan in CRC models. BN-MOA demonstrated superior tumor inhibition *in vivo*, while BN-NMe had similar *in vitro* activity to SN-38. These findings highlight the potential of BN-MOA for greater antitumor efficacy *in vivo*, with BN-NMe showing comparable effectiveness to SN-38 *in vitro*. Future studies should optimize growth models to better predict anticancer drug responses.

24COASNO7:**Title- Impacts of Matrix Metalloproteinase-8 Genotypes, Smoking, Alcohol Drinking, and *Helicobacter Pylori* Infection on Gastric Cancer**

CHUN-KAI FU, WEI-CHING CHIEN, YING-JING CHEN, MEI-DUE YANG, JAW-CHYUN CHEN,

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Abstract: In gastric cancer (GCa) tissues, mRNA expression of matrix metalloproteinase-8 (MMP-8) is notably reduced compared to healthy tissues. Furthermore, abnormally low or elevated serum levels of MMP-8 have been linked to a significantly poor prognosis. The involvement of MMP-8 genotypes in susceptibility to GCa remains underexplored. We aimed to assess the influence of MMP-8 genotypes on GCa susceptibility and their potential interactions with smoking, alcohol consumption, and *Helicobacter pylori* (*H. pylori*) infection. Patients and Methods: The study utilized polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) to analyze MMP-8 rs11225395, rs34009635, and rs35866072 genotypes in 161 GCa patients and 483 controls. Results: No statistically significant difference was detected in the distribution of genotypic (p for trend=0.3635) or allelic (p =0.1954) frequencies of MMP-8 rs11225395. Under a dominant model, combined CT+TT genotypes showed no association with GCa risk [odds ratio (OR)=0.77, 95% confidence interval (95%CI)=0.54-1.10, p =0.1852]. Similarly, no association was observed for MMP-8 rs34009635 or rs35866072. Importantly, individuals with the MMP-8 rs11225395 CC genotype demonstrated a significant increase in GCa risk when exposed to smoking (OR=4.04, 95%CI=2.28-7.16, p =0.0001), alcohol consumption (OR=2.83, 95%CI=1.64-4.89, p =0.0002), and *H. pylori* infection (OR=3.53, 95%CI=2.12-5.90, p =0.0001). Conclusion: The findings indicate that individuals carrying the MMP-8 rs11225395 CC genotype have increased susceptibility to GCa, especially when combined with risk factors, such as smoking, alcohol consumption, and *H. pylori* infection. These results suggest that MMP-8 genotype-based preventive strategies, including lifestyle alterations and targeted infection treatments, may be valuable in mitigating GCa development.

24COASNO8:**Title- Identification of New Potential Targets for Pancreatic Ductal Adenocarcinoma by Integrated Bioinformatic Analysis**

RUJIA LI, TING YANG, KE REN, JUN LI, YUICHI NAGAKAWA, YUHAO ZENG, YUTARO NATSUYAMA and SHUANG-QIN YI

Anticancer Research October 2024, 44 (10) 4233-4250;

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Abstract: Pancreatic cancer is the fourth leading cause of cancer-related death in both men and women worldwide. The 5-year relative survival rate for pancreatic ductal adenocarcinoma (PDAC) is 10%, which is the lowest among all cancers. This study aimed to find more effective targets to improve the diagnosis, prognostic prediction, and treatment of PDAC. Materials and Methods: Three datasets were selected from the GEO database.

Correlation analysis was used to screen the datasets and samples. Differentially expressed genes were identified using GEO2R. Metascape was used to perform pathway and process enrichment analysis. Survival analysis using the GEPIA2 and Kaplan-Meier plotter databases was conducted to filter hub genes. Principal component analysis and LASSO regression analyses were used to further filter the key genes. Gene expression in PDAC and normal tissues and in different pathological stages was analyzed using the GEPIA2 database. Thereafter, gene expression was detected in three PDAC and HPDE cell lines using real-time polymerase chain reaction. Results: LPAR5, CYP2C18, SERPINH1, ACSL5, and HCAR3 exhibited higher transcription levels in PDAC tissues compared to matched normal tissues, whereas the PNLIP expression was lower. LPAR5, CYP2C18, SERPINH1 and ACSL5 were markedly upregulated in stage IV PDAC. LPAR5, CYP2C18, SERPINH1 and ACSL5 were upregulated in PDAC cell lines. Further verification suggested that the expression levels of these four genes were closely related to histological type, pathologic stage, therapeutic effects and prognosis of pancreatic cancer. Conclusion: LPAR5, CYP2C18, SERPINH1 and ACSL5 may serve as potential diagnostic, prognostic, and therapeutic targets for PDAC.

24COASN09:**Title- Sparing Effect on Cell Survival Under Normoxia Using Ultra-high Dose Rate Proton Beams from a Compact Superconducting AVF Cyclotron**

MASASHI YAGI, KAZUMASA MINAMI, KAZUKI FUJITA, SHINJI NOMURA, NAGAAKI KAMIGUCHI, KANA NAGATA, RYO HIDANI, DAIZO AMANO, KENZO SASAI, SHINICHI SHIMIZU and KAZUHIKO OGAWA

Anticancer Research October 2024, 44 (10) 4251-4260;

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Abstract: The purpose of this study was to evaluate whether the sparing effect on cell survival is observed under normoxia. **Materials and Methods:** A superconducting spiral sector-type azimuthally varying field (AVF) cyclotron produced 230 MeV proton beams at 250 Gy/s as ultra-high dose rate (uHDR) and 1 Gy/s as normal dose rate (NDR) to irradiate tumor and normal cell lines (HSGc-c5 and HDF up to 24 Gy at the center of spread-out Bragg peak (SOBP). The Advanced Markus chamber and Gafchromic film were used to measure the examined absolute dose and field sizes. Colony formation assay and immunofluorescence staining were conducted to evaluate the sparing effect. **Results:** A homogeneous field was achieved at the center of the SOBP for both uHDR and NDR scanned proton beams, and dose reproducibility and linearity were adequate for experiments. There were significant differences in cell surviving fractions of HSGc-C5 and HDF cells irradiated at uHDRs compared to NDRs at 20 Gy and 24 Gy. Increasing γ -H2AX foci were observed for both cell lines at NDR. **Conclusion:** The sparing effect on cell survival was first observed under normoxic conditions for tumor and normal cells with doses exceeding 20 Gy, using proton irradiation at 250 Gy/s extracted from a superconducting AVF cyclotron. This study marks a significant milestone in advancing our understanding of the underlying mechanism behind the sparing effect.

24COASNO10:**Title- Characterization of Molecular Subtypes of Rat Mammary Cancer and Their Association With Environmental Exposures**

YUKIKO NISHIMURA, DAISUKE IIZUKA, MASARU TAKABATAKE, KAZUHIRO DAINO,

Anticancer Research October 2024, 44 (10) 4261-4272;

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Abstract: Breast cancer is a heterogeneous disease with many subtypes, and the association between these subtypes and exposure to environmental factors such as radiation remains controversial. Although the rat is used widely for research into human breast cancer, the heterogeneity and subtype definitions are unclear. Here, we leveraged an archive of rat mammary cancer samples and gene expression microarray data to classify tumors and examine their association with exposures. **Materials and Methods:** Eighty-four mammary cancer and 12 normal mammary tissue samples were obtained from previous experiments in which rats were exposed to different types of radiation, chemical carcinogens, and diets. Tumors were then subjected to immunohistochemical (IHC) analysis of conventional biomarkers, as well as gene expression profiling; they were then classified by three approaches based on IHC results, the PAM50 classifier algorithm, and unsupervised clustering of gene expression profiles. **Results:** IHC identified four subtypes (luminal A-like, luminal B-like 1, luminal B-like 2, and triple-negative), while PAM50 identified six (luminal A, luminal B, basal-like, HER2-enriched, normal-like, and claudin-low). Unsupervised clustering divided the tumors into three large, statistically significant, groups (named “luminal A”, “luminal B”, and “non-luminal” clusters). The results of the three approaches were significantly associated with each other. Exposure to radiation and chemical carcinogens during post-pubertal development was significantly associated with an increased risk of developing luminal A tumors, whereas exposure to a high corn-oil diet was associated with a higher likelihood of luminal B tumors. **Conclusion:** Rat mammary cancer subtypes resemble those in humans and are related to environmental factors.

24COASNO12:**Title- Anticancer Effects of BAF312 (Siponimod) in Epithelial Ovarian Cancer**

HEE-EUN HA, JI-YOON RYU, SUIN YOON, YOUNG-JAE CHO, JUNG-JOO CHOI, JAE RYOUNG HWANG, JU-YEON CHOI, HEE DONG HAN and JEONG-WON LEE

Anticancer Research October 2024, 44 (10) 4273-4282;

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Abstract: Epithelial ovarian cancer (EOC) is a lethal disease that is the fifth leading cause of cancer-related death in women. BAF312 (siponimod) is a potent and selective sphingosine-1-phosphate (S1P) receptor modulator that has been approved as a treatment for multiple sclerosis. In addition to its immunomodulatory action, BAF312 shows preclinical antitumor effects in several cancer types. This study sought to determine whether BAF312 had anticancer properties against EOC using in vitro and in vivo models. **Materials and Methods:** EOC cell lines A2780, SKOV3ip1, A2780-CP20, and SKOV3-TR were treated with BAF312

and tested for cell proliferation, apoptosis, and migration using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, fluorescence-activated cell sorting, and migration assays. We investigated the expression of sphingosine-1-phosphate receptor 1 (S1PR1) in most EOC cell lines through western blot analysis. To investigate potential mechanisms, western blot analysis was used to assess the expression of AKT serine/threonine kinase 1 (AKT) and extracellular-regulated kinase (ERK) after BAF312 treatment. We also created poly(D,L-lactide-co-glycolide) nanoparticles encapsulating BAF312 (PLGA-NP-BAF312) for in vivo therapy. The average size and zeta potential of PLGA-NP-BAF312 were determined using dynamic light scattering. The therapeutic efficacy of PLGA-NP-BAF312 was tested in an A2780 tumor-bearing orthotopic mouse model of EOC. Results: S1PR1 was overexpressed in most EOC cell lines. BAF312 significantly reduced cell proliferation and migration while inducing significant apoptosis in all EOC cell lines. PLGA-NP-BAF312 treatment significantly reduced tumor weights in A2780 tumor-bearing mice. Furthermore, the anticancer effects of BAF312 were associated with reduced phosphorylation of ERK and AKT. Conclusion: Our findings show that BAF312 has significant anticancer effects in EOC cells by inhibiting the ERK and AKT pathways, and might potentially be used to treat EOCs.

24COASNO13:**Title- MiR-140-3p Improves Sensitivity to Docetaxel by Suppressing PD-L1/ABCG2/MVP Expression in Lung Adenocarcinoma**

MINJI KWON, DAYEON LIM, JAYEON PARK, WORLD GIL, JIWOO JUNG, SUYEON JUNG,

Anticancer Research October 2024, 44 (10) 4283-4299;

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Abstract: Lung adenocarcinoma (LUAD) or lung squamous cell carcinoma (LUSC) accounts for the majority of non-small cell lung cancer (NSCLC), and overexpression of programmed death ligand 1 (PD-L1) in these cells is known to induce tumor immune evasion or drug resistance. However, detailed studies are needed to determine whether microRNAs (miRNAs) that reduce PD-L1 expression can suppress drug resistance in NSCLC. Materials and Methods: Kaplan Meier plotter and Receiver Operating Characteristic plotter were used to determine the effect of specific miRNAs on survival and chemotherapy response in NSCLC patients. Cell viability, colony formation and invasion assays, and qPCR analyses were also performed. Results: The expression of miRNA-140-3p (miR-140-3p) was lower in LUAD patients, compared to the normal group, and low expression of miR-140-3p was associated with poor survival of LUAD patients, but not in LUSC. The miR-140-3p mimic inhibited proliferation, colony formation, and invasion of LUAD cells. Interestingly, the expression of miR-140-3p was significantly lower in the group of LUAD patients who did not respond to docetaxel. In LUAD cells, combined treatment with miR-140-3p and docetaxel significantly reduced cell viability as well as the expression of ABCG2 and MVP, genes associated with drug resistance, compared to either treatment alone. Additionally, combined injection of miR-140-3p mimic and docetaxel significantly inhibited tumor growth compared to treatment with docetaxel alone. Conclusion: These results suggest that the high

expression of miR-140-3p in LUAD is correlated with good patient prognosis and may contribute to the treatment of LUAD, especially by increasing responsiveness to docetaxel.

24COASNO14:**Title- Repurposing Valrubicin as a Potent Inhibitor of Ovarian Cancer Cell Growth**

JAE EUN LEE and KYUN HEO

Anticancer Research October 2024, 44 (10) 4301-4307;

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Abstract: Ovarian cancer (OC) is a leading cause of cancer-related mortality among women, and there remains a significant unmet need for new therapeutic agents to improve patient outcomes. This study aimed to explore drug repositioning by screening a library of Food and Drug Administration (FDA)-approved compounds to identify those with therapeutic potential against OC. We also aimed to elucidate the molecular mechanisms of action of such compounds to better understand how they inhibit cancer cell proliferation. **Materials and Methods:** Using the WST-1 assay, a library of 1710 FDA-approved drugs was screened to evaluate their effects on OC cell proliferation. The molecular mechanisms underlying the effects of selected compounds were assessed through terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay and immunoblot analysis. **Results:** Screening of FDA-approved libraries revealed valrubicin as a potent inhibitor of OVCAR8 cell proliferation and SKOV3 and A2780 cell growth. Furthermore, valrubicin treatment led to increased DNA fragmentation, as evidenced by the TUNEL assay, and activated apoptosis signaling through enhancement of cleaved caspase-3 and poly(ADP-ribose) polymerase levels. **Conclusion:** Valrubicin, through drug repositioning, can be applied as a new therapeutic agent for OC.

24COASNO15:**Title- Potential Anti-tumor Properties of PDIA4 in Lung Adenocarcinoma**

HYEON JI KIM and DO-YEON KIM

Anticancer Research October 2024, 44 (10) 4309-4315;

DOI: <https://doi.org/10.21873/anticancerres.17260>

Abstract: Given the high frequency and mortality rate of lung cancer, diverse molecular studies have been undertaken to understand cancer pathophysiology and develop novel treatment strategies. The PDIA4 gene, which is involved in protein assembly and endoplasmic reticulum homeostasis, is overexpressed in various lung cancer subtypes. However, its exact function in lung adenocarcinoma (LUAD) remains elusive. The study aimed to investigate the role of PDIA4 in LUAD and explore its role as double-agent gene. **Materials and Methods:** PDIA4 expression was knocked out in A549 and LA-4 lung adenoma cells using the Crispr/Cas9 technology. Cell growth, migration, and apoptosis were analyzed in control and PDIA4-deficient cells. **Results:** PDIA4 deficiency resulted in increased cell growth, enhanced migration capacity, and greater resistance to apoptosis in both A549 and LA-4 lung cancer cells. Mechanistically, up-regulation of oxidative stress followed by NF- κ B activation may contribute to tumor-promoting effects observed upon PDIA4 silencing. **Conclusion:** PDIA4 appears to function as a tumor suppressor in lung adenocarcinoma,

suggesting that PDIA4 may act as a double-agent gene, with roles both on tumor suppression and promotion depending on the context.

24COASNO16:**Title- Methyl Gallate Suppresses Canine Mammary Gland Tumors by Inducing Apoptosis and Anti-angiogenesis**

JAWUN CHOI, JI-YOUNG CHOI, HYUK JANG, YE-JI JANG, JUN SONG, GYU-MIN KIM and JAE-WON SEOL

Anticancer Research October 2024, 44 (10) 4317-4326;

DOI: <https://doi.org/10.21873/anticancer.17261>

Abstract: Methyl gallate (MG), a plant phenolic compound, has known anticancer properties. However, its effects on canine mammary gland tumors (CMTs) are unclear. This study evaluated the impact of MG on cell viability, migration, and apoptosis in two CMT cell lines. Materials and Methods: CMT-U27 and CF41.mg cells were used. In vitro experiments included MTT and scratch assays, Annexin-V/propidium iodide double staining, immunocytochemistry, and western blot analyses. An in vivo CMT xenograft mouse model was also used to observe the effects of MG on tumor growth and vasculature. Immunohistochemistry was performed to analyze vessel density and apoptosis in tumor tissues. Cell migration and tube formation assays with canine aortic endothelial cells assessed the anti-angiogenic effects of MG. Results: Data showed a significant decrease in cell viability and migration in both CMT cell lines after 24 h exposure to various MG concentrations. MG treatment induced dose-dependent apoptotic cell death and elevated cleaved caspase-3 expression. In vivo experiments confirmed tumor growth suppression 21 days post-treatment with 40 mg/kg MG. Tumor tissues displayed increased cleaved caspase-3 and reduced vessel density. MG also inhibited cell migration and disrupted tube formation in canine endothelial cells. Conclusion: MG has potential as an anticancer drug for CMTs by promoting apoptotic cell death and reducing angiogenesis, highlighting its therapeutic promise.

24COASNO17:**Title- Magnolol Induces Apoptosis and Suppresses Immune Evasion in Non-small Cell Lung Cancer Xenograft Models**

PO-JU LIN, YU-CHENG KUO, PO-WEI HU, WEI-LUNG CHEN, SHIH-CHIEH CHANG, FEI-TING HSU, JENG-YUAN WU and JIANN-HWA CHEN

Anticancer Research October 2024, 44 (10) 4327-4337;

DOI: <https://doi.org/10.21873/anticancer.17262>

Abstract: Non-small cell lung cancer is known for its rapid growth and immune evasion, demanding effective therapies targeting both tumor cells and the microenvironment. Magnolol has shown promising anti-tumor effects in various cancers. Materials and Methods: CL1-5-F4-bearing mice were divided into control, 40 mg/kg, and 60 mg/kg magnolol groups, once tumors reached 100 mm³. Tumor growth and body weight were monitored biweekly, and after 13 days, mice were euthanized for tumor and organ collection for subsequent

staining. Histopathology and serum biochemistry assessed organ toxicity. Results: Magnolol dose-dependently suppressed NSCLC progression, with no pathology alterations observed in normal organs. Magnolol-induced apoptosis and cell cycle arrest, evidenced by increased cleaved caspase-3 and decreased cyclin D1/CDK4 levels. It also down-regulated VEGF, FOXP3, and IDO-1 in tumors, implicating tumor microenvironment modulation. Conclusion: Magnolol exhibits significant antitumor effects in NSCLC by inducing apoptosis, inhibiting proliferation, and modulating the tumor microenvironment. These results support further investigation of magnolol as a therapeutic adjuvant to enhance NSCLC treatment outcomes.

24COASNO18:**Title- 5,10,15,20-Tetrakis(4-sulfonatophenyl)porphyrin Zinc and Chloro-aluminum Phthalocyanine Disulfonate in Photodynamic Therapy of Colorectal Adenocarcinoma *In Vitro***

JAKUB HOSIK, BARBORA HOSIKOVA, HANA KOLAROVA and ROBERT BAJGAR

Anticancer Research October 2024, 44 (10) 4339-4346;

DOI: <https://doi.org/10.21873/anticanres.17263>

Abstract: Colorectal cancer (CRC) is one of the most widespread malignancies. One of the alternative therapeutic methods appears to be photodynamic therapy (PDT). Materials and Methods: This study investigated the efficiency of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin zinc (ZnTPPS₄) and chloro-aluminum phthalocyanine disulfonate (ClAlPcS₂) with two commercial photosensitive compounds 5,10,15,20-tetrakis(1-methylpyridinium-4-yl)porphyrin (TMPyP) and tetramethylthionine chloride (methylene blue, MB) in PDT for CRC in vitro. In addition to the study of the photodynamic effect on the viability of the colorectal carcinoma cell line HT29, cellular uptake, ROS production, and DNA damage were investigated. Results: All photosensitizers showed good accumulation within HT29 cells, high efficiency in killing the cells, and a concentration-dependent increase in the production of ROS. Conclusion: PDT using ZnTPPS₄ and ClAlPcS₂ may be effective in the treatment of CRC, achieving a similar photocytotoxic effect at much lower concentrations compared to MB.

24COASNO19:**Title- Promising Approach for Optimizing *In Vivo* Fluorescence Imaging in a Tumor Mouse Model: Precision in Cancer Research**

YU-JEONG CHOI, SONNY C. RAMOS, HYUN BO SIM, JI YEON HAN, DAE-HAN PARK, SEUL-KI MUN, JU-BIN LEE, CHI-HO LEE, YONG-AN LEE and JONG-JIN KIM

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Abstract: Cancer remains a major global health concern due to its high mortality rates. Advanced diagnostic imaging, such as in vivo near-infrared (NIR) fluorescence imaging, enhances early detection by reducing autofluorescence and enabling deeper tissue penetration, addressing some limitations of conventional methods. Understanding the underlying causes of autofluorescence, even in mouse model fluorescence imaging, is crucial for accurate interpretation. This study investigated the origins of autofluorescence observed

in experimental animals under NIR wavelengths, achieving successful fluorescence imaging in a clinically relevant tumor mouse model. **Materials and Methods:** Both fasting and non-fasting groups were evaluated to assess the dietary impact on autofluorescence, with various feeds tested. Subcutaneous and lung tumor models were established in C57BL/6 and BALB/c nude mice using LL/2-iRFP cells. Cryo-sectioning and lung tissue imaging were conducted to confirm tumor presence and assess fluorescence signals. **Results:** It was found that autofluorescence, notably common in the abdomen, is attributed to dietary factors. By selecting feed that lacks autofluorescence, the impact of dietary fluorescence on imaging was evaluated, leading to the establishment of optimized imaging conditions suited to the presence or absence of autofluorescence. Subsequently, utilizing lung cancer cells expressing near-infrared proteins (LL/2-iRFP), intratracheal, and subcutaneous tumor mouse models were developed, and successful in vivo imaging was achieved using the optimized imaging protocols, effectively bypassing autofluorescence. **Conclusion:** This study emphasizes the importance of understanding and addressing autofluorescence in fluorescence imaging, presenting valuable insights for enhancing the reliability and accuracy of diagnostic imaging techniques in cancer research and clinical practice.

24COASNO20:

Title- Inhibition of Epithelial–Mesenchymal Transition and Migration in Cisplatin-resistant Cancer Through Combined Treatment With Cisplatin and SH003

HYEONG SIM CHOI, JEONG-KUI KU, SEONG-GYU KO and PIL-YOUNG YUN

Anticancer Research October 2024, 44 (10) 4359-4369;

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Abstract: This study investigated the synergistic effects of combining cisplatin and SH003 treatment on the viability, apoptosis, cytotoxicity, migration and epithelial–mesenchymal transition (EMT) in cisplatin-resistant cancer cell lines YD-8/CIS, YD-9/CIS and YD-38/CIS. **Materials and Methods:** The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to assess cell viability, while trypan blue exclusion assay was used to evaluate cytotoxicity. Flow cytometry and western blot analysis measured apoptotic cell death. Wound-healing assays evaluated cell migration and EMT markers. Combination index (CI) plots were used to evaluate the combinatory effects of the treatment. **Results:** Combination therapy significantly reduced cell viability more effectively than each agent alone, as demonstrated by the MTT assay, with CI plots confirming notable synergism. Trypan blue exclusion assays indicated increased cell death and cytotoxicity in combination treatment than in both monotherapies, although the increase was not significant. Flow cytometry and western blot analysis revealed no significant synergistic effect on apoptotic cell death. However, wound-healing assays revealed that the combination of cisplatin and SH003 significantly inhibited cell migration and regulated EMT markers, indicating the potential reversal of EMT. **Conclusion:** Combining cisplatin and SH003 therapy may potentially be a more effective strategy for treating cisplatin-resistant cancer by increasing cytotoxicity and inhibiting metastasis. Further research is required to elucidate the underlying mechanisms and evaluate the in vivo efficacy of this combination therapy.

24COASNO21:**Title- Nondysplastic Colon Crypts Intercalated in Tubular Adenomas Support Field Cancerization**

CARLOS A. RUBIO, MICHAEL VIETH and CORINNA LANG-SCHWARZ

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Abstract: Tubular adenomas of the colon (TA) are neoplastic polyps composed of dysplastic tube-like crypts. Nondysplastic crypts, mostly in asymmetric branching have been previously reported, both beneath and bordering TA. In the present article, intercalated nondysplastic crypts (INDC) amidst dysplastic crypts in TA are showcased. Patients and Methods: The occurrence of INDC was recorded in 139 TA. Results: Out of the 139 TA, 31% exhibited INDC; of these, 58% were in asymmetric branching (INDCAB), 35% were single intercalated crypts without branching (INDSNB), and 7% were in symmetric branching (INDCSB). Luminal dysplasia occurred in 53% out of the 43 TA: in 37% TA with INDCAB, in 16% TA with INDSNB, but in none of the TA with INDCSB. Thus, INDCAB predominated. Conclusion: The finding of INDC in TA domain contrasts with the infrequency of INDCSB and with the absence of INDCAB in the normal colorectal mucosa. Hence, INDC emerge as integral components in TA. Since only 1 or 2 sections were available per TA, the total number of INDC in the entire TA is likely higher. INDC in TA may be remnants of acquired nondysplastic mucosal cores of abnormal cryptogenesis that were subsequently replaced by top-down growing dysplastic epithelium. The present and previous findings support the concept of field cancerization in the human colorectum.

24COASNO22:**Title- Systemic Inflammation Indexes and Risk of Immune-related Adverse Events in Patients With Metastatic Urothelial Carcinoma Treated With Immunotherapy**

MICHELE DIONESE, DAVIDE BIMBATTI, FRANCESCO PIERANTONI, ELEONORA LAI,

Anticancer Research October 2024, 44 (10) 4379-4386;

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Abstract: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic urothelial carcinoma (mUC). However, they could be associated with immune-related adverse events (irAEs), which may be clinically significant. Identifying clinical characteristics that may be associated with a higher risk of irAEs is of great importance. Patients and Methods: We retrospectively collected data from all patients who received anti-PD1 or anti-PD-L1 for metastatic UC at our Institution from January 2017 to December 2022. Patients were dichotomized according to baseline neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and platelet-to-lymphocyte ratio (PLR) values. We performed univariate and multivariate logistic regression to determine the association between baseline characteristics and the development of irAEs. Results: A total of 119 patients were identified. At a median follow-up of 29.6 months, 96 patients progressed and 82 died. Forty-five patients developed irAEs of any grade, 8 patients developed grade 3

toxicities. In the univariate analysis PS of 0 ($p<0.01$), baseline NLR <3.52 , baseline PLR <194 ($p=0.04$) and baseline SII <906 ($p=0.01$) were significantly associated with a higher risk of developing irAEs, whereas in the multivariate analysis only PS=0 ($p<0.01$) and NLR <3.52 ($p=0.03$) maintained their correlation. Median progression-free survival (mPFS) and overall survival (mOS) were significantly longer in patients with NLR <3 (mPFS 3.8 vs. 2.6 months, $p=0.01$; mOS 15.3 vs. 5.6 months, $p=0.002$) and PS=0 (mPFS 4.8 vs. 2.1 months, $p<0.001$; mOS 15.3 vs. 3.8 months, $p<0.001$). Conclusion: Low baseline NLR, PLR, and SII and good PS are associated with a higher risk of developing irAEs in patients treated with ICIs for mUC.

24COASNO23:

Title- Identifying High Recurrence Risk in Breast Carcinoma Patients Through Spatial Transcriptomic Analysis

JINAH CHU, SUNG-IM DO and HYUN-SOO KIM

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Abstract

Background/Aim: Comparing gene expression profiles according to recurrence risk using spatially resolved transcriptomic analysis has not been reported. This study aimed to identify distinct genetic features of breast carcinoma associated with a high Oncotype DX Recurrence Score (ORS). Patients and Methods: Patients were categorized into two groups, ORS-high (ORS-H; two patients) and ORS-non-high (ORS-NH; five patients). We performed digital spatial profiling and bioinformatic analyses to investigate the spatial transcriptomic profiles. Results: Lysozyme (LYZ), complement C1q C chain (C1QC), and complement C1q B chain (C1QB) exhibited the highest fold changes in the stromal compartment of the ORS-H group. Gene ontology enrichment analysis of the ORS-H group revealed significant up-regulation of genes associated with immune response in the stromal compartment, including lymphocyte-mediated immunity, adaptive immune response related to the immunoglobulin superfamily, and leukocyte-mediated immunity. Gene set enrichment analysis showed significant positive enrichment of gene sets associated with interferon (IFN) response and complement pathways in the stromal compartment. Conclusion: This study highlights significant differences in gene expression profiles and spatially resolved transcriptional activities between ORS-H and ORS-NH breast carcinomas. The significant up-regulation of genes and pathways associated with cell-mediated immunity, IFN response, and complement C1q in the stromal compartment of the ORS-H group warrants further evaluation with larger population cohorts.

24COASNO24:

Title- Therapy Intensity Outweighs the Prognostic Importance of the Timing of Chemoradiotherapy in Newly Diagnosed Glioblastoma Patients

JAN LEPPERT, CLAUDIA DITZ, MAXIMILIAN GROHMANN, CHRISTIAN ZIEMANN,

Anticancer Research October 2024, 44 (10) 4403-4412;

DOI: <https://doi.org/10.21873/anticancerres.17269>

Abstract

Background/Aim: To investigate the significance of the timing of chemoradiotherapy together with clinical and laboratory features in newly diagnosed glioblastoma. **Patients and Methods:** Clinical and laboratory parameters of 209 patients with glioblastoma potentially influencing overall (OS) and progression-free (PFS) survival were analyzed in univariable and multivariable models. **Results:** On univariable analyses, Karnofsky performance status ($p<0.001$), recursive partitioning analysis (RPA) class ($p<0.001$), O⁶-methylguanine-DNA methyltransferase (MGMT)-status ($p<0.001$), extent of resection ($p<0.001$), radiotherapy dose ($p=0.01$), and the number of adjuvant temozolomide (TMZ) cycles ($p<0.001$) were significantly associated with OS. Additionally, MGMT-status ($p<0.001$), extent of resection ($p=0.03$), surgical site infections ($p=0.02$), and the number of adjuvant TMZ cycles ($p<0.001$) were significantly associated with PFS. Multivariable analysis identified radiotherapy dose as the only independent predictor ($p=0.049$) of OS. MGMT-status ($p=0.02$) and the number of adjuvant TMZ cycles ($p<0.001$) were independent predictors of PFS. **Conclusion:** The timing of chemoradiotherapy did not play a prognostic role. For OS, the radiotherapy dose, and for PFS, MGMT-status and the number of adjuvant TMZ cycles were identified as independent prognostic factors.

24COASNO25:

Title- Factors Limiting Ostomy Reversal After Cytoreductive Surgery for Ovarian Cancer: A Retrospective Study

BEATRIZ NAVARRO SANTANA, FREDERIC GUYON, OCTAVIO ARENCIBIA, GUILLAUME BABIN, EUDALDO TOMMASETTI, DANIEL GONZÁLEZ, SABRINA PIEDIMONTE and ALICIA MARTÍN MARTÍNEZ

Anticancer Research October 2024, 44 (10) 4413-4418;

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Abstract: **Background/Aim:** To investigate the factors related to non-reversal of ostomy after cytoreductive surgery in ovarian cancer. In many women with ovarian cancer, transitory ostomies are performed to limit the consequences of anastomotic leak. Although intended to be temporary, a proportion of these ostomies might never be reversed. **Patients and Methods:** This was a retrospective study of patients with 2014 International Federation of Obstetrics and Gynecology stage IIB-IVB ovarian cancer requiring a transitory ostomy during primary or secondary cytoreductive surgery at the Bergonie Institute, France, and the University Hospital of Las Palmas, Spain, between January 2012 and December 2022. Rate of ostomy reversal, its timing (weeks) and postoperative complications were assessed. Multivariate logistic regression analysis was performed to identify limiting factors for ostomy reversal. **Results:** During the study period, we reviewed data on 181 consecutive patients with ovarian cancer with transitory ostomy creation; 89 (49.2%) patients were not candidates for an ostomy reversal surgery because of disease progression ($n=65$), death ($n=16$), and patient's refusal of surgery ($n=8$). A total of 92 patients were candidates for reversal surgery and were therefore included in the final analysis. In total, 57 (62%) patients had their ostomy reversed.

The mean time from ostomy creation to ostomy closure was 47.7 (standard deviation=33.1) weeks. Hartmann's procedure (leaving a rectal stump of 5-6 cm) was identified as an independent predictive factor for non-reversal of ostomy (odds ratio=6.42, 95% confidence interval=1.61-25.53; $p=0.008$). Complications after ostomy reversal occurred in 32 patients (34.8%). Conclusion: Hartmann's procedure is a limiting factor for ostomy reversal in patients with ovarian cancer. We recommend avoiding Hartmann's procedure during cytoreductive surgery, even after colorectal anastomotic leak.

24COASNO26:**Title- Palliative Radiation Treatment in Patients Managed With Advanced/Interventional Pain Therapy such as Pump-delivered Continuous Opioids**

CARSTEN NIEDER, STINE M. JENSEN, SOLVEIG NILSEN and ELLINOR C. HAUKLAND

Anticancer Research October 2024, 44 (10) 4419-4425;

DOI: <https://doi.org/10.21873/anticanres.17271>

Abstract: Background/Aim: The study aim was to analyze the feasibility and efficacy of palliative radiotherapy in patients receiving advanced/interventional pain therapy, such as epidural or spinal anesthesia or subcutaneous pump delivery of opioids. Endpoints such as pain relief, treatment in the last month of life and survival were evaluated. Patients and Methods: Different baseline parameters including but not limited to age and Eastern Cooperative Oncology Group performance status (ECOG PS) were assessed. Outcomes were abstracted from electronic health records. The Edmonton Symptom Assessment System (ESAS) was utilized to score pain intensity. Results: The study included 48 patients, 44 of whom completed radiotherapy as prescribed. Device malfunction was not observed. Overall, 31 patients (65%) had journal notes available allowing for evaluation of pain relief. Twenty-six of 31 experienced pain relief (54% in the intention-to-treat population of 48 study patients). Twelve patients (25%) stopped interventional pain therapy and were converted to transdermal or oral drugs. Median survival was 1.6 months. Forty-four percent had received radiotherapy during the last month of life. Sixty-four percent of patients with ECOG PS 3-4 had received radiotherapy during the last month of life, compared to 22% of those with ECOG PS <3, $p=0.004$. Conclusion: Palliative radiotherapy was feasible in this setting, but given the short median survival and high likelihood of treatment during the last month of life, patient selection and choice of fractionation regimen should be optimized. The record review identified several patients who experienced worthwhile pain relief, sometimes leading to conversion of pain therapy back to non-invasive oral or transdermal application.

24COASNO27:**Title- Early Urinary Potassium Level Predicts High-dose Methotrexate Elimination Delay in Primary Central Nervous System Lymphoma**

VINCENT HARLAY, ALEXANDRE BERTUCCI, CÉLINE BOUCARD, GREGORIO PETRIRENA, CHANTAL CAMPELLO, MARYLINE BARRIÉ, DIDIER AUTRAN, OLIVIER CHINOT and EMELINE TABOURET

Anticancer Research October 2024, 44 (10) 4427-4433;

DOI: <https://doi.org/10.21873/anticancer.17272>

Abstract: Background/Aim: Treatment of primary central nervous system lymphoma (PCNSL) includes high dose methotrexate-based polychemotherapy (HD-MTX). This study aimed to identify early predictive factors of methotrexate (MTX) delayed elimination. Patients and Methods: We prospectively included all patients with newly-diagnosed PCNSL. Daily serum and urinary creatinine and ionogram were collected. We generated two independent cohorts: a training cohort (TC) and a confirmatory cohort (CC). Results: We included for analysis 64 cures of HD-MTX (20 patients) in the TC and 59 cures (22 patients) in the CC. Median elimination time of MTX was 95 h and 96 h in the TC and CC, respectively. In multivariate analysis, older age ($p=0.004$), low Karnofsky Performance Status ($p=0.036$) and high urinary K^+ ($p=0.001$) were associated with delayed MTX elimination. An optimal cutoff for urinary K^+ was defined. In the CC, we confirmed that high urinary K^+ ($p=0.004$) remained associated with delayed MTX elimination. Conclusion: High urinary K^+ may be predictive of delayed MTX elimination in primary central nervous system lymphoma. Its relevance as a decision-making factor needs to be validated in additional prospective studies.

24COASNO28:

Title- Predictive Biomarkers of Lymph Node Metastasis in Early Gastric Cancer: A Reference of Clinicopathological Characteristics, Protein Expression, Epstein-Barr Virus Status, and Microsatellite Instability

SUN-JU BYEON, MEE SOO CHANG, HYE EUN PARK, DOEHEE KANG, YUTING WANG,

Anticancer Research October 2024, 44 (10) 4435-4448;

DOI: <https://doi.org/10.21873/anticancer.17273>

Abstract: Background/Aim: Predicting lymph node metastasis (LNM) in early gastric cancer (EGC) is crucial for making treatment decisions. This study aimed to confirm risk factors for LNM and identify novel auxiliary biomarkers for predicting LNM in EGC. Patients and Methods: We established a training set, comprising 63 patients with LNM-EGC and 274 patients with non-LNM EGC, and a test set, comprising 19 patients with LNM-EGC and 146 non-LNM EGC. Immunohistochemistry for lymphangiogenic and related pathway components (VEGF-C, TGF- β 1, SMAD2/3, VEGF-D, pSTAT3, E-cadherin, CD44, c-MET, YAP, and HER2), in situ hybridization for Epstein-Barr virus-encoded small RNAs, and multiplex PCR for microsatellite instability were conducted. Results: In the training set, Lauren's diffuse/mixed classification, stromal desmoplasia, submucosal invasion ≥ 500 μ m, lymphatic invasion, and high VEGF-C and SMAD2/3 expression were independent risk factors for LNM ($p<0.05$). A large tumor size, mixed histology, submucosal invasion, perineural invasion, and ulceration were determined as risk factors using univariate analysis ($p<0.05$). The tumor cutoff size for predicting LNM was 2.65 cm, based on a ROC analysis. The test set study verified that stromal desmoplasia, submucosal invasion, and high VEGF-C expression were independent risk factors for LNM ($p<0.05$). Moreover, mixed histology,

lymphatic invasion, ulceration, and high SMAD 2/3 expression were identified as additional risk factors using univariate analysis ($p < 0.05$). Conclusion: Stromal desmoplasia, submucosal invasion, and high VEGF-C expression are potential biomarkers for LNM in EGC. VEGF-C expression might serve as an adjunct biomarker for predicting LNM on forceps-biopsy tissue at initial diagnosis.

24COASNO29:**Title- Intraoperative Bleeding Complications Leading to Blood Transfusions (BloTs) in 17,412 Cholecystectomies in Finland: A Study With Special Reference to Elderly Patients**

ANTTI KIVIVUORI, PEKKA LAMMI, MATTI ESKELINEN, TUOMO RANTANEN, HANNU PAAJANEN, JUKKA PULKKINEN and MIKA UKKONEN

Anticancer Research October 2024, 44 (10) 4449-4456;

DOI: <https://doi.org/10.21873/anticanres.17274>

Abstract: Background/Aim: Cholelithiasis (Chole) is one of the most common diseases needing operative management worldwide. However, there are few studies assessing the intraoperative bleeding (IOB) complications leading to blood transfusions (BloTs) in elderly patients with cholecystectomy (Ccy). Patients and Methods: Outcome after IOB complications and need for BloTs in a cohort of 17,412 patients with Ccys were assessed with special reference to elderly Ccy patients. Results: A total of 17,412 patients underwent Ccy and 11% of Ccy patients (1,856/17,412) were aged ≥ 75 years. The Ccy patients ≥ 75 years underwent more often emergency/open Ccys. Red blood cell BloTs were administered five times more often to Ccy patients ≥ 75 years versus Ccy patients < 75 years (13% versus 2.6%, $p < 0.001$). In Ccys by emergency surgery indications, the need for BloTs was four times higher in Ccy patients ≥ 75 years versus Ccy patients < 75 years (5.5% versus 1.3%, $p < 0.001$). Conclusion: The elderly Chole patients have a higher risk than younger Chole patients for perioperative IOB complications and thus are more likely to need BloTs.

24COASNO30:**Title- Changes in Bladder Volume During Radiotherapy for Prostate Cancer**

DIRK RADES, FLORIAN CREMERS, CHRISTIAN ZIEMANN, LAURA SPLETTSTÖSSER, CARLOS A. NARVAEZ-WOLF, AHMED AL-SALLOOL, MICHAEL VON STADEN, JAN-DIRK KÜTER, STEFAN JANSSEN and CARMEN TIMKE

Anticancer Research October 2024, 44 (10) 4457-4463;

DOI: <https://doi.org/10.21873/anticanres.17275>

Abstract: Background/Aim: Patients irradiated for prostate cancer may experience urinary toxicity, particularly if the bladder volume is small. A mobile application (app) that reminds the patients to drink water prior to each radiation fraction may help avoid small volumes. This study investigating bladder volumes during a radiotherapy course is a prerequisite for a prospective trial testing such a reminder app. Patients and Methods: Frequency of bladder volumes < 200 ml and seven potential risk factors were retrospectively evaluated in 72 patients receiving external beam radiotherapy for non-metastatic prostate cancer. Results:

The mean and median values of the numbers of radiation fractions with bladder volumes <200 ml were 17.8 (standard deviation=12.0) and 16.5 (interquartile range Q1-Q3=7.5-29.5) fractions, respectively. Higher numbers of fractions with volumes <200 ml were significantly associated with pre-radiotherapy bladder volumes <200 ml ($p<0.001$) and high-risk prostate cancer ($p=0.014$). Conclusion: The proportion of bladder volumes <200 ml during the radiotherapy course was high and needs to be decreased. Pre-radiotherapy bladder volume and risk level of prostate cancer were significant risk factors for higher numbers of fractions with volumes <200 ml. These results are important for designing a prospective trial.

24COASNO31:

Title- Hotspots of Anal Cancer Screening in a High-risk Population: A Clinical Study on Free Provision, Best Method, Self-sampling, and Independent Risk Factors

EDOARDO VIRGILIO, CARLO SALVEMINI, MARIA GRAZIA TREGLIA, ELENA THAI, EVA FRANCHI, SARA PANICO, LUIGI IPPOLITO, CLARA PAVLIDIS, ALFREDO ANNICCHIARICO, ENRICO MARIA SILINI and RENATO COSTI

Anticancer Research October 2024, 44 (10) 4465-4481;

DOI: <https://doi.org/10.21873/anticanres.17276>

Abstract: Background/Aim: As of 2024, anal cancer (AC) has been steadily increasing worldwide but, due to insufficient evidence, anal cancer screening (ACS) has yet to be standardized. Furthermore, most high-risk people in the world have no help paying for it. Therefore, our primary endpoint was to assess the best screening method for these subjects through a provision that was free of charge (all costs were covered by the Italian public health service). Awareness-raising campaign, determination of risk factors, education on anal self-examination, and sampling (ASS) were secondary objectives. Patients and Methods: Screening was on a voluntary basis. Engaging in receptive anal intercourse and having a history of cervical dysplasia were the main inclusion criteria. Level 1 ACS tools included digital ano-rectal examination, anoscopy, anal Pap, and anal human papillomavirus (HPV) DNA test (both through self- and proctologist- sampling); high-resolution anoscopy (HRA) with (HRAB) or without biopsy comprised level 2 screening. High-risk people were enrolled until the available funds were exhausted. Results: Fifty high-risk people (40 men who had sex with men -MSM-, 9 women, and 1 heterosexual man) were enrolled. AC was found in one HIV-seropositive MSM, high-grade squamous intraepithelial lesion in 10 (20%) MSM, low-grade squamous intraepithelial lesion LSIL in 13 cases (12 MSM and 1 woman). The combination of HRAB and Pap smear screening achieved the highest values for sensitivity, specificity, and accuracy. ASS HPV DNA test provided excellent results comparable to clinician retrieval. Overweight and college education were identified as independent factors for the risk of and prevention of AC, respectively. Conclusion: A free ACS not only appears justified but also recommended to people screened for AC. Excess weight represents a further risk for this population.

24COASNO32:**Title- Contribution of Immunoscore to Survival Prediction in Pancreatic Ductal Adenocarcinoma**

HARUKI MORI, TORU MIYAKE, HIROMITSU MAEHIRA, MASANORI SHIOHARA, HIROYA IIDA, NOBUHITO NITTA and MASAJI TANI

Anticancer Research October 2024, 44 (10) 4483-4492;

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Abstract: Background/Aim: The presence of tumor-infiltrating lymphocytes (TILs) has been demonstrated as a prognostic factor in colorectal cancer after surgical resection of malignancy, but knowledge on their role in pancreatic cancer is lacking. The Immunoscore (IS) assesses TILs at the core of the tumor (CT) and invasive margin (IM) and is being evaluated as a new concept in tumor immunity. The aim of this study was to evaluate the relationship between IS and prognosis in PDAC. Patients and Methods: The IS was analyzed by immunohistochemistry using surgical tissue blocks from 131 patients with pancreatic ductal adenocarcinoma (PDAC) who underwent surgery to investigate the relationship between immune cell infiltration into the tumor and prognosis in PDAC. Results: A high IS in both CT and IM of the tumor was significantly associated with prolonged overall survival (OS) ($p < 0.01$) and relapse-free survival (RFS) ($p < 0.01$). In multivariate logistic regression models adjusted for clinical pathology data, IS predicted survival and recurrence ($p < 0.01$ and $p < 0.01$, respectively). Moreover, in patients who received preoperative chemotherapy, a high IS was statistically significantly associated with longer OS and RFS ($p < 0.01$ and $p < 0.01$, respectively). Conclusion: The immunohistochemically assessed IS might be a useful prognostic marker for patients with PDAC who underwent primary tumor resection.

24COASNO32:**Title- Serum Inflammatory Dynamics as Novel Biomarkers for Immune Checkpoint Inhibitors in Non-small-cell Lung Cancer With Bone Metastases**

YOHEI ASANO, NORIO YAMAMOTO, KATSUHIRO HAYASHI, AKIHIKO TAKEUCHI,

Anticancer Research October 2024, 44 (10) 4493-4503;

DOI: <https://doi.org/10.21873/anticancer.17278>

Abstract: Background/Aim: The aim of the study was to develop a novel predictive scoring system based on the dynamics of serum inflammatory indicators in immune checkpoint inhibitor (ICI) treatment on non-small-cell lung cancer (NSCLC) with bone metastases. Patients and Methods: Sixty patients with NSCLC and bone metastases treated with ICIs between January 2016 and March 2021 were included in the development cohort. Serum neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) levels were assessed before (pre-value) and 6 weeks after (post-value) ICI treatment, and a novel predictive score was developed: pre-value $\geq$ post-value, 0 points; pre-value $<$ post-value, 1 point; total score: 0-2 points. The associations of these dynamics and the score with clinical outcomes, including overall survival (OS), progression-free survival (PFS), response rate (RR) of bone metastases, and disease control rate (DCR), were evaluated. Furthermore, cross-validation

was performed with 23 patients after April 2021 using the same inclusion criteria. Results: The patients with decreased serum inflammation levels had significantly better OS, PFS, and RR than those with increased levels. Applying the developed score to the development cohort, the patients with 0 points had significantly better OS, PFS, and RR than others. In multivariable analysis, the score independently predicted treatment response to ICI for bone metastasis and prognosis. Cross-validation showed that OS, PFS, and RR were significantly better in the patients in the 0-point group. Conclusion: The early NLR and CRP dynamics were associated with therapeutic responses to ICIs in NSCLC with bone metastases. Our novel scoring system based on these dynamics is simple and has a high predictive accuracy.

24COASNO33:**Title- PD-L1 as a Biomarker for the Efficacy of Durvalumab in Stage III EGFR Mutant NSCLC**

INSU KIM, SUN HA CHOI, SHIN YUP LEE, SEUNG SOO YOO, JI EUN PARK, KYEONG-CHEOL SHIN, JONG GEOL JANG, KYUNG SOO HONG,...

Anticancer Research October 2024, 44 (10) 4505-4516;

DOI: <https://doi.org/10.21873/anticancerres.17279>

Abstract: Background/Aim: Durvalumab consolidation is less effective in patients with epidermal growth factor receptor mutant (EGFR M+) NSCLC. Studies of durvalumab on EGFR M+ NSCLC as an expression of programmed death-ligand 1 (PD-L1) expression are limited. The purpose of this study was to determine the effect of durvalumab on PD-L1 expression in EGFR M+ patients. Patients and Methods: This study included 249 unresectable stage III NSCLC patients treated with durvalumab. The primary outcome was progression-free survival (PFS). Cox multivariate analysis was performed based on EGFR and PD-L1 statuses: EGFR M-, PD-L1 $\geq 50\%$ (cohort A); EGFR M-, PD-L1 $< 50\%$ (cohort B); EGFR M+, PD-L1 $\geq 50\%$ (cohort C); and EGFR M+, PD-L1 $< 50\%$ (cohort D). Results: Overall, 31 of 249 (12.4%) and 218 of the 249 (87.6%) patients had EGFR M+ and EGFR M- NSCLC, respectively. Median PFSs and OSs did not differ (PFS: 16.6 vs. 18.7 months, $p=0.591$; OS: 37.4 vs. 35.7 months, $p=0.271$). Median PFS of cohort A did not significantly differ from the median PFSs of cohorts B and C, but it was significantly longer than the median PFS of cohort D (23.7 vs. 15.2 months, $p=0.045$). Cox multivariate analysis revealed that cohort D exhibited a worse PFS (adjusted hazard ratio=2.27, 95% confidence interval=1.11-4.66, $p=0.025$) compared with cohort A. Median OSs were not different between the four cohorts. Conclusion: Durvalumab consolidation provided similar benefit in EGFR M+ patients with PD-L1 $\geq 50\%$ compared with EGFR M- patients. A therapeutic role of durvalumab in patients with EGFR M+, high PD-L1 unresectable stage III NSCLC should be considered.

24COASNO34:**Title- Safety and Efficacy of Durvalumab After Chemoradiotherapy in Antinuclear Antibody-positive Patients With Non-small Cell Lung Cancer**

AKIHIRO TSUKAGUCHI, AKIHIRO TAMIYA, SHOICHI FUKUDA, YUKI
IWAHASHI, KENSUKE KANAOKA, YUYA TANAKA, YUJI INAGAKI, YOSHIHIKO
TANIGUCHI, KEIKO NAKAO, TOMOKO KAGAWA, YOSHINOBU
MATSUDA and KYOICHI OKISHIO

Anticancer Research October 2024, 44 (10) 4517-4524;

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Abstract: Background/Aim: Pneumonitis during durvalumab consolidation therapy after chemoradiotherapy (CRT) is a major cause of treatment discontinuation. Although previous studies have revealed an association between antinuclear antibody (ANA) positivity and the safety and efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer (NSCLC), there are no reports on durvalumab consolidation therapy. This study investigated the safety and efficacy of durvalumab after CRT in ANA-positive patients. Patients and Methods: We retrospectively reviewed patients with unresectable NSCLC treated with durvalumab after CRT between August 2018 and July 2022 at our institution. We evaluated the association among ANA positivity, treatment-related adverse events (AEs), and survival outcomes. Results: Overall, 80 patients were enrolled, 39 of whom were ANA-positive. Although there were no significant differences in the incidence of each AE of any grade, ANA-positive patients tended to have a higher frequency of pneumonitis of grade 3 to 5 than ANA-negative patients (12.8% vs. 2.4%, $p=0.104$). ANA-positive patients had a significantly shorter median progression-free survival (PFS) and overall survival (OS) than ANA-negative patients [14.9 months vs. not reached (NR), $p=0.005$; NR vs. NR, $p=0.013$]. Multivariate analysis revealed that ANA positivity was an independent predictor of shorter PFS (HR=2.23; 95% CI=1.16-4.29; $p=0.016$) and OS (HR=2.28; 95% CI=1.01-5.12; $p=0.046$). Conclusion: ANA-positive patients receiving durvalumab after CRT tended to have a higher frequency of severe pneumonitis and significantly worse PFS and OS compared with ANA-negative patients.

24COASNO35:

Title- CD8-Positive T-Cells Are Key Immune Cells for Predicting the Therapeutic Effect of Neoadjuvant Chemotherapy in Triple-negative Breast Cancer

NATSUKI UENAKA, EIICHI SATO, YOSHIYA HORIMOTO, SAORI
KAWAI, MARIKO ASAOKA, HIROSHI KAISE, KIMITO YAMADA and TAKASHI
ISHIKAWA

Anticancer Research October 2024, 44 (10) 4525-4536;

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Abstract: Background/Aim: Patients with triple-negative breast cancer (TNBC) who obtain a pathological complete response (pCR) after neoadjuvant chemotherapy have an improved prognosis. Lymphocyte-predominant breast cancer is more likely to respond to neoadjuvant chemotherapy. Here, we investigated the correlation between tumor-infiltrating lymphocytes (TILs) in pre-treatment biopsy specimens from patients with TNBC in relation to response to NAC. Patients and Methods: The level of infiltration by immune cells expressing immune cell lineage surface markers (CD8, CD4, CD19, CD14, CD11c, and CD11b) in biopsy specimens from 52 patients with TNBC was examined using multispectral

immunofluorescent labelling. Results: The level of CD8-positive TILs was significantly higher in patients with a pCR ($p=0.045$). The Cox proportional hazard model confirmed that lymph node involvement was associated with poorer disease-free survival ($p=0.008$). A high level of CD8-positive TILs was related to significantly prolonged disease-free survival in patients with node-positive TNBC ($p=0.018$). Conclusion: Assessing infiltration by CD8-positive TILs in the primary tumor is a useful biomarker to predict pCR and improved outcome in patients with node-positive TNBC.

24COASNO36:**Title- Clinical Significance of Granzyme B Gene Expression in Pathological Stage II/III Gastric Cancer After Curative Gastrectomy**

TAKASHI OSHIMA, ITARU HASHIMOTO, YUKIHIKO HIROSHIMA, YAYOI
KIMURA, MIE TANABE, YUTA NAKAYAMA, SHINSUKE NAGASAWA, KYOHEI
KANEMATSU, TORU AOYAMA, TAKANOBU YAMADA, TAKASHI
OGATA and YOHEI MIYAGI

Anticancer Research October 2024, 44 (10) 4537-4542;

DOI: <https://doi.org/10.21873/anticancerres.17282>

Abstract

Background/Aim: Granzyme B (GZMB) is mainly produced by natural killer (NK) cells and activated CD8-positive T cells to induce tumor cell apoptosis. We analyzed the significance of GZMB expression in gastric cancer (GC) tissues from patients with pathological (p)Stage II/III GC after curative resection. Patients and Methods: Patients with pStage II/III GC who received curative resection ($n=253$) were included and the expression levels of GZMB in GC tissues and in the adjacent normal mucosa were measured using quantitative real-time polymerase chain reaction. The expression levels in GC tissues and clinicopathological features and overall survival (OS) were compared in these patients. Results: GZMB expression levels were significantly higher in GC tissues than in the adjacent normal mucosa. GZMB expression levels in GC tissues were not associated with any clinicopathological features. The 5-year OS rate in the high-GZMB expression group was significantly better than that in the low-expression group (5-year survival rate 72.0% vs. 55.7%; $p=0.009$). Furthermore, on multivariate analysis, high-GZMB expression was an independent factor for better OS (hazard ratio=0.652; 95% confidence interval=0.432-0.987; $p=0.043$). Conclusion: In patients with locally advanced GC after curative resection, GZMB expression in GC tissue may be a useful prognostic marker.

24COASNO37:**Title- Radiation-induced Esophagitis in Breast Cancer Patients Treated With Supraclavicular Field Irradiation**

ZAHRA MOHAMMED AHMED, MOHAMED ABOUEGYLAH, GEHAN A.
KHEDR, HANS THEODOR EICH, KHALED ELSAYAD and ASHRAF MAHMOUD
ELENBABY

Anticancer Research October 2024, 44 (10) 4543-4549;

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Abstract: Background/Aim: The objective of this research was to assess the frequency and intensity of radiation-induced esophagitis in breast cancer patients treated with supraclavicular radiotherapy field irradiation. Patients and Methods: This study involved 100 patients with positive lymph nodes receiving radiotherapy to the breast or chest wall along with supraclavicular field irradiation, with toxicity levels assessed weekly. Treatment utilized the 3D conformal technique, and variables, such as mean and maximum dose to the cervical esophagus, mean dose to the entire esophagus, and length of the esophagus within the treated area were recorded. Results: The occurrence of grade 2 or higher esophagitis was 48%, with patients facing the risk of developing such esophagitis at an average dose of 13 Gy. The probability of grade 2 esophagitis occurring at doses exceeding 13 Gy was statistically significantly higher ($p < 0.001$) with an odds ratio of 24.4. Conclusion: Limiting the mean cervical esophagus dose to < 13 Gy could help reduce the frequency and severity of grade 2 or higher toxicity.

24COASNO38:

Title- The Dominant Component and Clinicopathological Characteristics of Combined Hepatocellular-cholangiocarcinoma After Radical Resection

KEISO MATSUBARA, TSUYOSHI KOBAYASHI, TAKESHI TADOKORO, YOSUKE NAMBA, SOTARO FUKUHARA, KO OSHITA, NARUHIKO HONMYO, SHINTARO KURODA, KOJI ARIHIRO and HIDEKI OHDAN

Anticancer Research October 2024, 44 (10) 4551-4559;

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Abstract: Background/Aim: Combined hepatocellular cholangiocarcinoma (cHCC-CCA) is a rare subtype of primary liver carcinoma, characterized by the unequivocal presence of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). However, its clinicopathological characteristics have not yet been thoroughly elucidated. In particular, cholangiolocellular carcinoma (CLC) was classified as a subtype of cHCC-CCA according to the 2010 World Health Organization (WHO) classification. However, according to the 2019 WHO classification, tumors displaying histological features consistent with CLC but lacking evidence of hepatocellular differentiation should be regarded as a distinct subtype of iCCA. Nevertheless, there may be notable differences in prognosis between CLC and iCCA, indicating the necessity for refining the classification when devising clinical treatment strategies. This study aimed to determine the clinicopathological features and prognostic factors of cHCC-CCAs following radical resection. Patients and Methods: Between January 2010 and September 2020, based on the 2010 WHO classification, we retrospectively studied the clinicopathological features and prognoses of patients with cHCC-CCAs in relation to the pathological dominant classification. The patients were classified according to the pathological dominant components of cHCC-CCA as HCC-dominant (HCC-D), iCCA-dominant (iCCA-D), or CLC-dominant (CLC-D). Results: Data of 55 patients who underwent primary radical hepatectomy for cHCC-CCA were analyzed. The prevalences of each dominant classification were HCC-D, 21 (38.2%); iCCA-D, 11 (20.0%); and CLC-D, 23 (41.8%). Multivariate analysis showed that dominant classification was an independent risk

factor for recurrence and cancer-specific survival (CSS). Conclusion: The dominant classification of cHCC-CCA has the potential to predict recurrence and CSS.

24COASNO39:**Title- Thyroid Cancer With Autocrine Sialyl-fibronectin Depletion Has a Poor Prognosis due to EMT Progression**

RYO MIYAKE, HIROSHI TAKEYAMA, YOSHINOBU MANOME, MUNHEYUKI KOYAMA, ISAO TABEL, HISASHI SHIOYA, TAKASHI KAZAMA and HIROKO NOGI
Anticancer Research October 2024, 44 (10) 4561-4568;

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Abstract: Background/Aim: Elevated blood fibronectin (FN) levels have been observed in various cancers; however, their significance remains controversial. Herein, we measured the levels of sialyl-fibronectin (S-FN), a type of FN secreted by tumor cells, and investigated whether blood S-FN secretion is associated with recurrent metastasis and epithelial-mesenchymal transition (EMT). Patients and Methods: An ELISA system recognizing S-FN was constructed, and the amount of S-FN in blood samples from 63 patients with thyroid carcinoma was measured. The relationship between S-FN secretion and clinical prognosis was also examined. Vimentin immunostaining was performed to identify the mesenchymal status of the cells during EMT. Results: After 12 years of observation, 17/63 patients had recurrent metastases, including nine cases of lymph node recurrence (LNR) and eight cases of remote metastasis (RM). LNR occurred in 7/39 (17.9%) of S-FN-negative cases, where 4/7 (57.1%) had two or more repeat recurrences. In S-FN-positive cases, LNR was observed in 2/24 cases (8.3%), and no repeat recurrence was observed. For RM, 6/39 (15.4%) patients were S-FN-negative, of which 5/6 (83.3%) had progressive disease even during treatment at metastasis. Of the S-FN-positive cases, RM was observed in 2/24 (8.3%) patients; progressive disease was observed in 1/2 (50.0%) patients. In 9/11 S-FN-negative recurrent metastasis cases (81.8%) and 2/4 S-FN-positive cases (50.0%), many vimentin-positive, FN-secreting cells were found in the interstitial tissue around the tumor. Conclusion: S-FN-negative thyroid cancer has a poor prognosis because of the progression of EMT associated with increased paracrine FN levels in the stroma.

24COASNO40:**Title- Loss of Skeletal Muscle Mass During Neoadjuvant Chemotherapy for Pancreatic Cancer Is Related to the Continuation of S-1 Adjuvant Chemotherapy After Pancreatectomy**

SHINNOSUKE KAWAHARA, TORU AOYAMA, ITARU HASHIMOTO, REI KANEMOTO,

Anticancer Research October 2024, 44 (10) 4569-4577;

DOI: <https://doi.org/10.21873/anticanres.17286>

Abstract: Background/Aim: Although perioperative chemotherapy has improved patient survival, sarcopenia may occur during chemotherapy owing to decreased food intake and physical strength. However, reports on the occurrence of sarcopenia and changes in body composition in patients with pancreatic cancer during neoadjuvant chemotherapy are scarce.

This study aimed to determine the effect of changes in skeletal muscle mass during neoadjuvant chemotherapy on the S-1 adjuvant chemotherapy clinical course in patients who underwent perioperative chemotherapy and surgical resection. **Patients and Methods:** We retrospectively enrolled 159 patients with pancreatic cancer who underwent neoadjuvant chemotherapy and surgical resection, followed by S-1 adjuvant chemotherapy. We evaluated changes in skeletal muscle mass during neoadjuvant chemotherapy using abdominal computed tomography and the SliceOmatic software. The association between the rate of change in skeletal muscle mass index ($\Delta\%$ SMI) during neoadjuvant chemotherapy and the continuation of S-1 adjuvant chemotherapy was investigated. **Results:** Eighty-eight (55.3%) patients lost skeletal muscle mass ($\Delta\%$ SMI <0) during neoadjuvant chemotherapy with a significantly low S-1 adjuvant completion rate ($p=0.02$). $\Delta\%$ SMI <0 was an independent risk factor for the continuation of S-1 adjuvant chemotherapy (hazard ratio=1.924, 95% confidence interval=1.002–3.695, $p=0.049$). Moreover, the lower the $\Delta\%$ SMI, the lower the S-1 continuation rate ($p=0.022$). **Conclusion:** Loss of skeletal muscle mass during neoadjuvant chemotherapy for pancreatic cancer affected the continuation of S-1 adjuvant chemotherapy after pancreatic resection. Therefore, ameliorating loss of skeletal muscle mass during neoadjuvant chemotherapy should be carefully considered to improve the continuation rate of adjuvant chemotherapy and the survival of patients with pancreatic cancer.

24COASNO41:

Title- Clinical Significance of HRNR Expression in Patients With Stage II/III Gastric Cancer After Curative Gastrectomy

TAKASHI OSHIMA, ITARU HASHIMOTO, YUKIHIKO HIROSHIMA, YAYOI KIMURA, MIE TANABE, YUTA NAKAYAMA, SHINSUKE NAGASAWA, KYOHEI KANEMATSU, TORU AOYAMA, TAKANOBU YAMADA, TAKASHI OGATA and YOHEI MIYAGI

Anticancer Research October 2024, 44 (10) 4579-4584;

DOI: <https://doi.org/10.21873/anticanres.17287>

Abstract: Background/Aim: The function of the S-100 protein family member hornerin (HRNR) in gastric cancer (GC) tissues is largely unknown. We researched the clinical significance of HRNR expression in GC tissues of patients with pathological (p)Stage II/III GC after curative resection. **Patients and Methods:** We included patients with pStage II/III GC who underwent curative gastrectomy ($n=253$). Expression levels of HRNR in GC tissue and in the adjacent normal mucosa were determined using quantitative real-time polymerase chain reaction. Clinicopathological features and overall survival (OS) were compared in patients with different HRNR expression levels in GC tissue. **Results:** HRNR expression levels were significantly higher in GC tissues than in the adjacent normal mucosa. HRNR expression level in GC tissue showed sex differences. The 5-year OS rate in the high-HRNR expression group was significantly worse than that in the low-expression group (5-year survival 53.6% vs. 74.9%; $p=0.004$). Furthermore, on multivariate analysis, high-HRNR expression was an independent predictor of poor OS (hazard ratio=1.534; 95% confidence interval=1.130-2.618; $p=0.011$). **Conclusion:** In patients with pStage II/III GC after curative gastrectomy, HRNR expression in GC tissue may be a useful prognostic marker.

24COASNO42:**Title- Analysis of Initial Outcomes of Gas-insufflation One-step Single-port Transaxillary (GOSTA) Robotic Thyroidectomy for Thyroid Cancer**

YONG MIN NA, SANG CHUN PARK, SANG YUN AN, HYE UN MA, YONG BIN KWON, YOUNG JAE RYU, JIN SEONG CHO and MIN HO PARK

Anticancer Research October 2024, 44 (10) 4585-4592;

DOI: <https://doi.org/10.21873/anticancerres.17288>

Abstract: Background/Aim: This study compared the initial outcomes of gas-insufflation one-step single-port transaxillary (GOSTA) robotic thyroidectomy with traditional open thyroidectomy for thyroid cancer at a single institution. Patients and Methods: A retrospective analysis was conducted on 77 patients who underwent thyroidectomy for differentiated thyroid cancer from January to June 2024. Exclusion criteria included benign nodules, Graves' disease, and previous thyroid surgeries. Two surgeons performed the procedures, with one having no prior robotic surgery experience. Results: Of the 77 patients, 48 underwent open thyroidectomy and 29 underwent GOSTA thyroidectomy. The GOSTA group had a significantly lower mean age (40.1 vs. 47.6 years, $p=0.002$) and a higher proportion of female patients ($p=0.040$). The open group patients had more harvested lymph nodes than the GOSTA group patients (7.9 vs. 2.4, $p<0.001$). The GOSTA group patients had longer operation time (156.4 vs. 80.6 min, $p<0.001$), and had extended hospital stay than the open group patients (5.9 vs. 3.4 days, $p<0.001$). Complication rates were similar between the groups. Conclusion: GOSTA robotic thyroidectomy provides comparable safety and effectiveness to open thyroidectomy, with improved cosmetic outcomes despite longer operation times and hospital stays. This technique is feasible for surgeons without prior robotic experience, offering a viable alternative for patients prioritizing cosmetic results.

24COASNO43:**Title- Clinicopathological Review of Head and Neck Squamous Cell Carcinomas After Neoadjuvant Chemotherapy**

RYOSUKE KUGA, KAZUKI HASHIMOTO, HIDETAKA YAMAMOTO, MIDORI TANIGUCHI,

Anticancer Research October 2024, 44 (10) 4593-4603;

DOI: <https://doi.org/10.21873/anticancerres.17289>

Abstract: Background/Aim: The benefit of neoadjuvant chemotherapy (NAC) in the treatment of head and neck squamous cell carcinoma (HNSCC) remains unclear. Patients and Methods: We retrospectively collected 30 patients with HNSCC who had undergone radical resection after NAC. We pathologically evaluated the therapeutic response to NAC, and classified the residual tumor patterns. In addition, we compared the maximum horizontal diameter on pathology with imaging. Results: The residual patterns were categorized as follows: 10 cases of shrunken type, 11 cases of mixed type, and seven cases of fragmented type. The majority of underestimation cases – those cases in which the maximum horizontal diameter measured on post-NAC imaging was less than the pathological size after resection – were multifocal residual lesions, with a tendency for more frequent “positive” or “close”

surgical margins. Conclusion: The strategy of performing NAC to reduce resection volume is not appropriate, and resection margins should be based on the assessment before NAC.

24COASNO44:**Title- Synchronous Pancreatic Ductal Adenocarcinoma and Nasopharyngeal Carcinoma With Associated Novel Pathogenic ATM Mutation**

LILY XU, AMANDA TIAN, RUOHAO FAN and JINPING LAI

Anticancer Research October 2024, 44 (10) 4605-4608;

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Abstract: Background/Aim: Patients with synchronous pancreatic ductal adenocarcinoma (PDAC) and nasopharyngeal carcinoma (NPC) have not been previously reported in the English literature. We present such a unique case with both PDAC and NPC. Case Report: A 72-year-old Asian-American female with a past medical history of primary biliary cholangitis presented with abdominal pain. Initial computer tomography (CT) scans demonstrated a 13 cm solid and cystic mass in the pancreatic body and tail with no mass identified in her liver. A biopsy of the pancreatic mass revealed pancreatic duct adenocarcinoma. Further evaluation with a positron emission tomography (PET) scan revealed a hypermetabolic mass (SUVmax10) in the nasopharynx. Subsequent biopsy results were consistent with nasopharyngeal carcinoma. Genetic counseling and next-generation sequencing (NGS) on her peripheral blood DNA were performed, identifying a pathogenic mutation of ATM c.8545C>T (p.Arg2849*). The patient was treated with gemcitabine-abraxane chemotherapy and FOLFIRINOX (fluorouracil, oxaliplatin, leucovorin and irinotecan) for her PDAC, while radiation therapy was proposed for her NPC. Ultimately, due to the progression of the malignancies, she entered hospice care and passed eight months after the diagnosis of PDAC. Conclusion: To the best of our knowledge, this is the first documented case of synchronous PDAC and NPC in a patient with novel associated pathogenic ATM c.8545C>T (p.Arg2849*) mutation and poor prognosis. More similar case reports are needed to further characterize this entity.

24COASNO45:**Title- Awake Surgery for Right Frontal Lobe Glioma: Preserving Emotional Recognition and Facilitating Early Return to Work**

KOSEI YAMAMOTO, RYOTA TAMURA, SOTA WAKAHARA, KAZUHIRO KOJIMA,

Anticancer Research October 2024, 44 (10) 4609-4615;

DOI: <https://doi.org/10.21873/anticancerres.17291>

Abstract: Background/Aim: Many glioma patients struggle to return to work after surgery because of higher brain dysfunction. Although the right frontal lobe has historically been considered functionally silent, reports of performing awake surgery to evaluate higher brain functions in patients with tumors in this area have increased. We present two cases of patients who underwent awake surgery for malignant glioma in the right frontal lobe to preserve emotional recognition and facilitate an early return to work. Case Report: Case 1 was a 48-year-old right-handed woman employed as a nursery school teacher and case 2 was a 21-year-old right-handed man employed in sales. Both had contrast-enhancing right frontal lobe

tumors exhibiting high signal intensity on fluid attenuated inversion recovery imaging and underwent awake surgery. During the operation, cortical mapping was performed using the Reading the Mind in the Eyes, calculation, and motor tasks. Resection of sites involved in motor and emotional recognition functions was avoided. In case 1, all regions of high signal intensity were completely resected; in case 2, all regions exhibiting enhancement were resected. Both patients were discharged home without neurological deficits and returned to work within 21 days after surgery. Conclusion: It may be important to focus not only on overall survival and progression-free survival in glioma patients, but also on factors associated with life satisfaction, such as time to return to work after surgery and time until work becomes difficult. Awake surgery aimed at preserving higher brain functions is useful and may also improve life satisfaction.

24COASNO46:**Title- Ligand-Controlled Regiodivergent Ring Expansion of Benzosilacyclobutenes with Alkynes *en Route* to Axially Chiral Silacyclohexenyl Arenes**

Xiaoxiao Tang, Yulang Tang, Ju Peng, Huimin Du, Liying Huang, Jiahui Gao, Shiyang Liu, Dongxu Wang, Wanshu Wang, Lu Gao, Yu Lan*, and Zhenlei Song*

Journal of the American Chemical Society 2024, 146, 39, 26639-26648

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Abstract: A ligand-controlled regiodivergent and enantioselective ring expansion of benzosilacyclobutenes with internal naphthyl alkynes has been achieved by adjusting the ligand cavity size. The ligand (S)-8H-binaphthyl phosphoramidite, featuring small methyl groups on its arms, provides a spacious cavity that favors sterically demanding Si–Csp³ ring expansion, predominantly yielding axially chiral (S)-1-silacyclohexenyl arenes. In contrast, the ligand (R)-spiro phosphoramidite, with bulky t-Bu groups on its arms, offers a compact cavity that facilitates less sterically demanding Si–Csp² ring expansion, leading primarily to axially chiral (S)-2-silacyclohexenyl arenes. Density functional theory calculations delineate distinct mechanistic pathways for each ring expansion route and elucidate their regio- and enantioselectivity.

24COASNO47:**Title- Unveiling the Unique Reactivity of Anionic Mn(I) Complexes via Metal–Ligand Cooperation: Nucleophilic Attack on C(sp³)–X Bonds**

Hengxu Li, Mingjie Fan, and Qiang Liu

Journal of the American Chemical Society 2024, 146, 39, 26649-26656

<https://doi.org/10.1021/jacs.4c01683>

ABSTRACT: Metal–ligand cooperation (MLC) has emerged as a pivotal strategy for the catalytic activation of small molecules within both synthetic and biological arenas. Leveraging this approach, a suite of potent catalytic reactions—encompassing hydrogenation, hydroelementation, and dehydrogenative processes—have been realized, with notable advances in manganese catalysis in recent years. However, the activation of alkyl halides by Mn complexes, which typically requires strong reductants to form Mn(–I) complexes that are

incompatible with standard cross-coupling conditions, remains a significant challenge. This limitation underscores the urgent need to investigate alternative methods for activating C(sp³)–X bonds using higher valence state Mn complexes. In response to this challenge, we present the synthesis, characterization, and reactivity of a new anionic Mn(I) complex featuring a redox-active dianionic ligand that induces multiple MLC functionalities. We have discovered an innovative mechanism of MLC, characterized by a single ligand transferring two electrons to the metal center. This novel process facilitates an orbital-symmetry-allowed nucleophilic attack on C(sp³)–X bonds, preserving manganese's oxidative state at +1. To the best of our knowledge, this is the first instance where the MLC strategy via a two-electron transfer process has been utilized to execute an S_N2 nucleophilic attack at a C(sp³)–X bond by a relatively electron-deficient metal center like Mn(I). Additionally, the dianionic ligand of the anionic Mn(I) complex exhibits ambident nucleophilicity by reacting with different electrophiles, further highlighting its versatile reactivity.

24COASNO48:**Title- RNA-Activated CRISPR/Cas12a Nanorobots Operating in Living Cells**

Aijiao Yuan, Rui Sha, Wenjing Xie, Guangbo Qu, Hongquan Zhang, Hailin Wang, X. Chris Le, Guibin Jiang, and Hanyong Peng

Journal of the American Chemical Society 2024, 146, 39, 26657-26666

<https://doi.org/10.1021/jacs.4c02354open>

ABSTRACT: Active clustered regularly interspaced short palindromic repeats (CRISPR/Cas12a) systems possess both cis-cleavage (targeted) and trans-cleavage (collateral) activities, which are useful for genome engineering and diagnostic applications. Both single- and double-stranded DNA can activate crRNA–Cas12a ribonucleoprotein (RNP) to achieve cis- and trans-cleavage enzymatic activities. However, it is not clear whether RNA can activate the CRISPR/Cas12a system and what is critical to the trans-cleavage activity. We report here that RNA can activate the CRISPR/Cas12a system and trigger its trans-cleavage activity. We reveal that the activated crRNA–Cas12a RNP favors the trans-cleavage of longer sequences than commonly used. These new findings of the RNA-activated trans-cleavage capability of Cas12a provided the foundation for the design and construction of CRISPR nanorobots that operate in living cells. We assembled the crRNA–Cas12a RNP and nucleic acid substrates on gold nanoparticles to form CRISPR nanorobots, which dramatically increased the local effective concentration of the substrate in relation to the RNP and the trans-cleavage kinetics. Binding of the target microRNA to the crRNA–Cas12a RNP activated the nanorobots and their trans-cleavage function. The repeated (multiple-turnover) trans-cleavage of the fluorophore-labeled substrates generated amplified fluorescence signals. Sensitive and real-time imaging of specific microRNA in live cells demonstrated the promising potential of the CRISPR nanorobot system for future applications in monitoring and modulating biological functions within living cells.

24COASNO49:**Title- Efficient Strategy to Discover DNA Aptamers Against Low Abundance Cell Surface Proteins in Scarce Samples**

Xiaoqiu Wu*, Yuqing Liu, Dengwei Zhang, Jingjing Yu, Mingxin Zhang, Shuwei Feng, Lifei Zhang, Ting Fu, Yamin Tan, Tao Bing*, and Weihong Tan*

Journal of the American Chemical Society 2024, 146, 39, 26667-26675

<https://doi.org/10.1021/jacs.4c03129>

ABSTRACT: Molecular recognition probes targeting cell surface proteins such as aptamers play crucial roles in precise diagnostics and therapy. However, the selection of aptamers against low-abundance proteins in situ on the cell surface, especially in scarce samples, remains an unmet challenge. In this study, we present a single-round, single-cell aptamer selection method by employing a digital DNA sequencing strategy, termed DiDS selection, to address this dilemma. This approach incorporates a molecular identification card for each DNA template, thereby mitigating biases introduced by multiple PCR amplifications and ensuring the accurate identification of aptamer candidates. Through DiDS selection, we successfully obtained a series of high-quality aptamers against cell lines, clinical specimens, and neurons. Subsequent analyses for target identification revealed that aptamers derived from DiDS selection exhibit recognition capabilities for proteins with varying abundance levels. In contrast, multiple rounds of selection resulted in the enrichment of only one aptamer targeting a high-abundance target. Moreover, the comprehensive profiling of cell surfaces at the single-cell level, utilizing an enriched aptamer pool, revealed unique molecular patterns for each cell line. This streamlined approach holds promise for the rapid generation of specific recognition molecules targeting cell surface proteins across a broad range of expression levels and expands its applications in cell profiling, specific probe identification, biomarker discovery, etc.

24COASNO50:**Title- Design and Evolution of an Artificial Friedel–Crafts Alkylation Enzyme Featuring an Organoboronic Acid Residue**

Shu-Bin Mou, Kai-Yue Chen, Thittaya Kunthic, and Zheng Xiang*

Journal of the American Chemical Society 2024, 146, 39, 26676-26686

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c03795>

ABSTRACT: Creating artificial enzymes by the genetic incorporation of noncanonical amino acids with catalytic side chains would expand the enzyme chemistries that have not been discovered in nature. Here, we report the design of an artificial enzyme that uses p-boronophenylalanine as the catalytic residue. The artificial enzyme catalyzes Michael-type Friedel–Crafts alkylation through covalent activation. The designer enzyme was further engineered to afford high yields with excellent enantioselectivities. We next developed a practical method for preparative-scale reactions by whole-cell catalysis. This enzymatic C–C bond formation reaction was combined with palladium-catalyzed dearomative arylation to achieve the efficient synthesis of spiroindolenine compounds.

24COASNO51:**Title- Covalent Au–C Contact Formation and C–C Homocoupling Reaction from Organotin Compounds in Single-Molecule Junctions**

Weiyi Guo, Yuhao Wu, Chaochao Xie, Xuefeng Tan, Zhenpin Lu*, and Haixing Li*

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<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c03925>

ABSTRACT: Formation of new chemical species has been achieved under an electric field by the use of the scanning tunneling microscope break junction technique, yet simultaneous implementation of catalytic reactions both at the organic/metal interface and in the bulk solution remains a challenging task. Herein, we show that n-butyl-substituted organotin-terminated benzene undergoes both an efficient cleavage of the terminal tributyltin group to form a covalent Au–C bond and a homocoupling reaction to yield biphenyl product when subjected to an electric field in the vicinity to Au electrodes. By using ex situ characterization of high-performance liquid chromatography with an UV–vis detector, we demonstrate that the homocoupling reaction can occur with high efficiency under an extremely low tip bias voltage of ~5 mV. Additionally, we show that the efficiency of the homocoupling reaction varies significantly in different solvents; the choice of the solvent proves to be one of the methods for modulating this reaction. By synthesizing and testing varied molecular backbone structures, we show that an extended biphenyl backbone undergoes homocoupling to form a quarterphenylene backbone, and the C–C coupling reactions are prohibited when additional aurophilic or bulky chemical groups that exhibit a steric blockage are introduced.

24COASNO52:**Title- Overcoming Intrinsic Quantum Confinement and Ultrafast Self-Trapping in Ag–Bi–I- and Cu–Bi–I-Based 2D Double Perovskites through Electroactive Cations**

Rik Hooijer, Shizhe Wang, Alexander Biewald, Christian Eckel, Marcello Righetto, Meizhu Chen, Zehua Xu,

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<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c04616>

ABSTRACT: The possibility to combine organic semiconducting materials with inorganic halide perovskites opens exciting pathways toward tuning optoelectronic properties. Exploring stable and nontoxic, double perovskites as a host for electroactive organic cations to form two-dimensional (2D) hybrid materials is an emerging opportunity to create both functional and lead-free materials for optoelectronic applications. By introducing naphthalene and pyrene moieties into Ag–Bi–I and Cu–Bi–I double perovskite lattices, intrinsic electronic challenges of double perovskites are addressed and the electronic anisotropy of 2D perovskites can be modulated. (POE)₄AgBiI₈ containing pyrene moieties in the 2D layers was selected from a total of eight new 2D double perovskites, exhibiting a favorable electronic band structure with a type IIb multiple quantum well system based on a layer architecture suitable for out-of-plane conductivity and leading to a photocurrent response ratio of almost 3 orders of magnitude under AM1.5G illumination. Finally, an exclusively

parallelly oriented thin film of (POE)4AgBiI8 was integrated into a device to construct the first pure $n = 1$ Ruddlesden–Popper 2D double perovskite solar cell.

24COASNO53:**Title- A Bioorthogonal Precision Tool for Human *N*-Acetylglucosaminyltransferase V**

Yu Liu, Ganka Bineva-Todd, Richard W. Meek, Laura Mazo, Beatriz Piniello, Olga Moroz, Sean A. Burnap, Nadima Begum, André Ohara, Chloe Roustan, Sara Tomita, Svend Kjaer, Karen Polizzi, Weston B. Struwe, Carme Rovira, Gideon J. Davies, and Benjamin Schumann*

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<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c05955>

ABSTRACT: Correct elaboration of N-linked glycans in the secretory pathway of human cells is essential in physiology. Early N-glycan biosynthesis follows an assembly line principle before undergoing crucial elaboration points that feature the sequential incorporation of the sugar N-acetylglucosamine (GlcNAc). The activity of GlcNAc transferase V (MGAT5) primes the biosynthesis of an N-glycan antenna that is heavily upregulated in cancer. Still, the functional relevance and substrate choice of MGAT5 are ill-defined. Here, we employ protein engineering to develop a bioorthogonal substrate analog for the activity of MGAT5. Chemoenzymatic synthesis is used to produce a collection of nucleotide-sugar analogs with bulky, bioorthogonal acylamide side chains. We find that WT-MGAT5 displays considerable activity toward such substrate analogues. Protein engineering yields an MGAT5 variant that loses activity against the native nucleotide sugar and increases activity toward a 4-azidobutyramide-containing substrate analogue. By such restriction of substrate specificity, we show that the orthogonal enzyme–substrate pair is suitable to bioorthogonally tag glycoproteins. Through X-ray crystallography and molecular dynamics simulations, we establish the structural basis of MGAT5 engineering, informing the design rules for bioorthogonal precision chemical tools.

24COASNO54:**Title- Heavy-Atom Tunneling in Ring-Closure Reactions of Beryllium Ozonide Complexes**

Yanguy Zhou, Wenbin Fan, Jingjing Tang, Wei Fang*, and Mingfei Zhou*

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<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c06137>

ABSTRACT: Quantum mechanical tunneling (QMT) has long been recognized as crucial for understanding chemical reaction mechanisms, particularly in reactions involving light atoms like hydrogen. However, recent findings have expanded this understanding to include heavy-atom tunneling reactions. In this report, we present the observation of two heavy-atom tunneling reactions involving the spontaneous conversions from end-on bonded beryllium ozonide complexes, OBeOOO (A) and BeOBeOOO (C), to their corresponding side-on bonded ozonide isomers, OBe(η^2 -O₃) (B) and BeOBe(η^2 -O₃) (D), respectively, in a cryogenic neon matrix. This discovery is supported by the weak temperature dependence of the rate constants and unusually large ¹⁶O/¹⁸O kinetic isotope effects. Quantum chemistry calculations reveal extremely low barriers (<1 kcal/mol) for both ring-closure reactions.

Additionally, instanton theory calculations on both reactions unveil that the tunneling processes involve the concerted motion of all four oxygen atoms.

24COASNO55:

Title- Uncovering the Pathway of Serine Octamer Magic Number Cluster Formation during Electrospray Ionization: Experiments and Simulations

Vida Alinezhad, Yuen Ki Ng, Sanvid Mehta, and Lars Konermann*

Journal of the American Chemical Society 2024, 146, 39, 26726-26742

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c05760>

ABSTRACT: Electrospray ionization (ESI) of serine (Ser) solution generates Ser8H⁺ as an abundant magic number cluster. ESI clustering of most other solutes yields nonspecific stoichiometries. It is unclear why Ser8H⁺ dominates in the case of Ser, and how Ser8H⁺ forms during ESI. Even the location of Ser8H⁺ formation is contentious (in solution, in ESI droplets, or elsewhere). Here we unravel key aspects of the l-Ser8H⁺ formation pathway. Harsh ion sampling conditions promote the collision-induced dissociation (CID) of regular ESI analytes. Unexpectedly, Ser8H⁺ was seemingly resistant against CID during ion sampling, despite its extremely low tandem mass spectrometry (MS/MS) stability. This unusual behavior reveals that Ser8H⁺ forms during ion sampling. We propose the following pathway: (1) Nonspecific Ser clusters are released when ESI droplets evaporate to dryness. These initial clusters cover a wide size range, from a few Ser to hundreds or thousands of monomers. (2) The clusters undergo dissociation during ion sampling, mostly via successive loss of neutral monomers. For any source activation voltage, there is a subpopulation of clusters for which this CID cascade tends to terminate at the octamer level, culminating in Ser8H⁺-dominated product distributions. Mobile proton molecular dynamics simulations were used to model the entire pathway. Ser8H⁺ structures formed in these simulations were consistent with ion mobility experiments. The most compact structures resembled the model of [Scutelnic, V. J. Am. Chem. Soc. 2018, 140, 7554–7560], with numerous intermolecular salt bridges and H-bonds. Our findings illustrate how the interplay of association and dissociation reactions across phase boundaries can culminate in magic number clusters.

24COASNO56:

Title- Cavity Manipulation of Attosecond Charge Migration in Conjugated Dendrimers

Baicheng Zhang, Yonghao Gu*, Victor Manuel Freixas, Shichao Sun, Sergei Tretiak, Jun Jiang*, and Shaul Mukamel*

Journal of the American Chemical Society 2024, 146, 39, 26743-26750

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c06727>

ABSTRACT: Dendrimers are branched polymers with wide applications to photosensitization, photocatalysis, photodynamic therapy, photovoltaic conversion, and light sensor amplification. The primary step of numerous photophysical and photochemical processes in many molecules involves ultrafast coherent electronic dynamics and charge oscillations triggered by photoexcitation. This electronic wavepacket motion at short times where the nuclei are frozen is known as attosecond charge migration. We show how charge migration in a dendrimer can be manipulated by placing it in an optical cavity and monitored by time-resolved X-ray diffraction. Our simulations demonstrate that the dendrimer charge

migration modes and the character of photoexcited wave function can be significantly influenced by the strong light-matter interaction in the cavity. This presents a new avenue for modulating initial ultrafast charge dynamics and subsequently controlling coherent energy transfer in dendritic nanostructures.

24COASNO57:

Title- Structural Isomerism in Bimetallic Ag₂₀Cu₁₂ Nanoclusters

Guocheng Deng, Sami Malola, Taeyoung Ki, Xiaolin Liu, Seungwoo Yoo, Kangjae Lee, Megalamane S. Bootharaju*, Hannu Häkkinen*, and Taeghwan Hyeon*

Journal of the American Chemical Society 2024, 146, 39, 26751-26758

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c06832>

ABSTRACT: Structural isomers of atomically precise metal nanoclusters are highly sought after for investigating structure–property relationships in nanostructured materials. However, they are extremely rare, particularly those of alloys, primarily due to the challenges in their synthesis and structural characterization. Herein, for the first time, a pair of bimetallic isomeric AgCu nanoclusters has been controllably synthesized and structurally characterized. These two isomers share an identical molecular formula, Ag₂₀Cu₁₂(C≡CR)₂₄ (denoted as Ag₂₀Cu₁₂-1 and Ag₂₀Cu₁₂-2; HC≡CR is 3,5-bis(trifluoromethyl)phenylacetylene). Single-crystal X-ray diffraction data analysis revealed that Ag₂₀Cu₁₂-1 possesses an Ag₁₇Cu₄ core composed of two interpenetrating hollow Ag₁₁Cu₂ structures. This core is stabilized by four different types of surface motifs: eight –C≡CR, one Cu(C≡CR)₂, one Ag₃Cu₃(C≡CR)₆, and two Cu₂(C≡CR)₄ units. Ag₂₀Cu₁₂-2 features a bitetrahedron Ag₁₄ core, which is stabilized by three Ag₂Cu₄(C≡CR)₈ units. Interestingly, Ag₂₀Cu₁₂-2 undergoes spontaneous transformation to Ag₂₀Cu₁₂-1 in the solution-state. Density functional theory calculations explain the electronic and optical properties and confirm the higher relative stability of Ag₂₀Cu₁₂-1 compared to Ag₂₀Cu₁₂-2. The controlled synthesis and structural isomerism of alloy nanoclusters presented in this work will stimulate and broaden research on nanoscale isomerism.

24COASNO58:

Title- Oxadiazolines as Photoreleasable Labels for Drug Target Identification

Corentin Bon*, Benedikt Goretzki, Marie Flamme, Claude Shelton, Holly Davis, Fabio Lima, Francisco Garcia, Scott Brittain, and Cara E. Brocklehurst

Journal of the American Chemical Society 2024, 146, 39, 26759-26765

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c06936>

ABSTRACT: Photoaffinity labeling is a widely used technique for studying ligand–protein and protein–protein interactions. Traditional photoaffinity labels utilize nonspecific C–H bond insertion reactions mediated by a highly reactive intermediate. Despite being the most widely used photoaffinity labels, diazirines exhibit limited compatibility with downstream organic reactions and suffer from storage stability concerns. This study introduces oxadiazolines as innovative and complementary photoactivatable labels for addition to the toolbox and demonstrates their application in vitro and through in cellulo labeling experiments. Oxadiazolines can be easily synthesized from ketone moieties and cleaved with 302–330 nm light to cleanly liberate a diazo reactive moiety that can covalently modify

nucleophilic amino acid residues. Notably, oxadiazolines are compatible with various organic reaction conditions and functional groups, allowing for the exploration of a large chemical space. Several known inhibitors featuring the oxadiazoline functionality were prepared without affecting their binding affinity. Furthermore, we confirmed the ability of oxadiazolines to form covalent bonds with proteins upon UV-irradiation, both in vitro and in cellulo, yielding comparable results to those of the matched diazirine compounds.

24COASNO59:**Title- (Z)-Selective Isomerization of 1,1-Disubstituted Alkenes by Scandium-Catalyzed Allylic C–H Activation**

Shao-Jie Lou, Pan Wang, Xin Wen, Aniket Mishra, Xuefeng Cong, Qingde Zhuo, Kun An, Masayoshi Nishiura, Yi Luo*, and Zhaomin Hou*

Journal of the American Chemical Society 2024, 146, 39, 26766-26776

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c06899>

ABSTRACT: The isomerization of 1,1-disubstituted alkenes through 1,3-hydrogen shift is an atom-efficient route for synthesizing trisubstituted alkenes, which are important moieties in many natural products, pharmaceuticals, and organic materials. However, this reaction often encounters regio- and stereoselectivity challenges, typically yielding E/Z-mixtures of the alkene products or thermodynamically favored (E)-alkenes. Herein, we report the (Z)-selective isomerization of 1,1-disubstituted alkenes to trisubstituted (Z)-alkenes via the regio- and stereospecific activation of an allylic C–H bond. The key to the success of this unprecedented transformation is the use of a sterically demanding half-sandwich scandium catalyst in combination with a bulky quinoline compound, 2-tert-butylquinoline. Deuterium-labeling experiments and density functional theory (DFT) calculations have revealed that 2-tert-butylquinoline not only facilitates the C=C bond transposition through hydrogen shuttling but also governs the regio- and stereoselectivity due to the steric hindrance of the tert-butyl group. This protocol enables the synthesis of diverse (Z)-configured acyclic trisubstituted alkenes and endocyclic trisubstituted alkenes from readily accessible 1,1-disubstituted alkenes. It offers an efficient and selective route for preparing a new family of synthetically challenging (Z)-trisubstituted alkenes with broad substrate scope, 100% atom efficiency, high regio- and stereoselectivity, and an unprecedented reaction mechanism.

24COASNO60:**Title- Visible Light-Driven CO₂ Capture and Release Using Photoactive Pyranine in Water in Continuous Flow**

Hyowon Seo, Johannes Schretter, Michael Massen-Hane, and T. Alan Hatton*

Journal of the American Chemical Society 2024, 146, 39, 26777-26785

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07278>

Abstract: : The urgent need to address climate change and its environmental consequences demands innovative carbon capture technologies, given the relationship between rising global temperatures and increased atmospheric CO₂ levels. Here, we present a reversible photochemical carbon capture and release strategy and system utilizing photoactive pyranine in an aqueous bicarbonate buffer system. Control experiments suggested that the photoacid effect occurs at the surface which contributes to CO₂ release, complemented by the

photothermal effect at the surface and in the bulk. A continuous flow setup employing a tube-in-tube configuration with a hollow fiber membrane demonstrates the efficiency and reliability of the visible light-driven carbon capture system, with the release of CO₂ captured from a 15% CO₂ feed in the dark, at a rate of 0.48 mmol CO₂ per hour to a nitrogen sweep stream under light irradiation at 200 W/m², a level comparable to solar intensity of visible light (150 W/m² of blue light –250 W/m² of blue and green light). The robustness and scalability of the system has been demonstrated, with long-term operation over 7 days yielding 60 mmol (1.34 L CO₂ at STP) of cumulated CO₂ separation. Additionally, we explored the potential for direct air capture, yielding 3 μmol of CO₂ separation over 2 h of operation from a bicarbonate buffer solution saturated with ambient air (420 ppm). This work introduces the prospect of photoswing of carbon capture systems, which can avoid external energy input beyond solar irradiation, offering promising avenues for addressing the challenges associated with climate change.

24COASNO61:**Title- When van der Waals Met Kagome: A 2D Antimonide with a Vanadium-Kagome Network**

Aishwarya Mantravadi, Bradyn C. Weaver, Shiya Chen, Shahnaz Mukta, Yao Abusa, Arka Sarkar,

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<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07285>

ABSTRACT: 2D materials showcase unconventional properties emerging from quantum confinement effects. In this work, a “soft chemical” route allows for the deintercalation of K⁺ from the layered antimonide KV6Sb6, resulting in the discovery of a new metastable 2D-Kagome antimonide K0.1(1)V6Sb6 with a van der Waals gap of 3.2 Å. The structure of K0.1(1)V6Sb6 was determined via the synergistic techniques, including X-ray pair distribution function analysis, advanced transmission electron microscopy, and density functional theory calculations. The K0.1(1)V6Sb6 compound crystallizes in the monoclinic space group C2/m (*a* = 9.57(2) Å, *b* = 5.502(8) Å, *c* = 10.23(2) Å, β = 97.6(2)°, *Z* = 2). The [V6Sb6] layers in K0.1(1)V6Sb6 are retained upon deintercalation and closely resemble the layers in the parent compound, yet deintercalation results in a relative shift of the adjacent [V6Sb6] layers. The magnetic properties of the K0.1(1)V6Sb6 phase in the 2–300 K range are comparable to those of KV6Sb6 and another Kagome antimonide KV3Sb5, consistent with nearly temperature-independent paramagnetism. Electronic band structure calculation suggests a nontrivial band topology with flat bands and opening of band crossing afforded by deintercalation. Transport property measurements reveal a metallic nature for K0.1(1)V6Sb6 and a low thermal conductivity of 0.6 W K^{−1} m^{−1} at 300 K. Additionally, ion exchange in KV6Sb6 via a solvothermal route leads to a successful partial exchange of K⁺ with A⁺ (A = Na, Rb, and Cs). This study highlights the tunability of the layered structure of the KV6Sb6 compound, providing a rich playground for the realization of new 2D materials.

24COASNO62:**Title- Synthesis and Activity of T-Cell Tumor-Directing MegaMolecules**

Sraeyes Sridhar, Justin A. Modica, Daniel J. Sykora, Eric J. Berns, and Milan Mrksich*

Journal of the American Chemical Society 2024, 146, 39, 26801-26807

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07377>

ABSTRACT: This paper describes the synthesis, characterization, and functional activity of 26 MegaMolecule-based bispecific antibody mimics for T-cell redirection toward HER2+ cancer cells. The work reports functional bispecific MegaMolecules that bind both receptor targets, and recruit and activate T-cells resulting in lysis of the target tumor cells. Changing the orientation of linkage between Fabs against either HER2 or CD3 ϵ results in an approximately 150-fold range in potency. Increasing scaffold valency from Fab dimers up to tetramers improves the potency of the antibody mimics up to 5-fold, but with diminishing returns in effective dose beyond trimeric formats. Antibody mimics that present either one or two Fabs against either receptor target allows for initial engagement of one cell type over the other. Finally, the antibody mimics significantly reduce HER2+ tumor volumes in a humanized xenograft model of breast cancer.

24COASNO63:

Title- Ultrafine Rhodium–Chromium Mixed-Oxide Cocatalyst with Facet-Selective Loading for Excellent Photocatalytic Water Splitting

Daisuke Hirayama, Tokuhisa Kawawaki*, Sota Oguchi, Mai Ogano, Naohika Kon, Tomohiro Yasuda, Akihiro Higami, and Yuichi Negishi*

Journal of the American Chemical Society 2024, 146, 39, 26808-26818

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07351>

ABSTRACT: The development of water-splitting photocatalysts capable of generating green hydrogen (H₂) from water and sunlight is crucial for achieving carbon neutrality. Further enhancement of the photocatalytic water-splitting activity is essential to realizing this objective. Photocatalysts with specific exposed crystal facets can facilitate efficient charge separation of electrons/holes, thereby achieving high activity for water splitting. However, there have been no reports of ultrafine (~1 nm) cocatalysts being loaded onto specific crystal facets of photocatalysts, despite cocatalysts being the actual reaction sites for water splitting. This study establishes a novel method for achieving facet-selective loading of ultrafine H₂-evolution cocatalysts onto the {100} facets, which are the H₂-evolution facets, of a strontium titanate photocatalyst. The resulting photocatalyst exhibits the highest apparent quantum yield achieved to date for strontium titanate. This research holds the potential to further improve various types of advanced photocatalysts and is expected to accelerate the transition to carbon neutrality.

24COASNO64:

Title- Distortion Engineering: A Strategy to Modulate Molecular Upconversion with Molecular Cluster-Aggregates

Diogo A. Gálico, Alexandros A. Kitos, Rayan Ramdani, Jeffrey S. Ovens, and Muralee Murugesu*

Journal of the American Chemical Society 2024, 146, 39, 26819-26829

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07418>

ABSTRACT: The rational engineering of molecules is a powerful chemistry tool of pivotal importance in the fields of molecular magnetism and luminescence. Hence, systems that can

be modulated via molecular engineering and composition control are expected to present extra versatility regarding the tunability of their properties. This is the case with molecular cluster aggregates (MCAs), high nuclearity molecular compounds. Herein, we demonstrate how the union of both strategies, namely, composition control and molecular engineering, can be employed to enhance molecular upconversion in MCAs. This was achieved by doping a {Gd₈Er₂Yb₁₀} MCA with Ce^{III} ions. By replacement of the optically silent Gd^{III} ions with Ce^{III}, the upconversion mechanism is modified due to Ce^{III}-mediated cross-relaxation. In addition to this effect, we could also engineer the degree of metal site distortion due to the larger size of Ce^{III} ions, relaxing the selection rules and impacting the upconversion quantum yield and luminescent thermometry. Opto-structural correlations demonstrate that the presented molecular engineering strategy can be used to enhance the performance of molecular upconverters.

24COASNO65:**Title- Maximizing Photon-to-Electron Conversion for Atom Efficient Photoredox Catalysis**

Felicity Draper, Stephen DiLuzio, Hannah J. Sayre, Le Nhan Pham, Michelle L. Coote, Egan H. Doeven, Paul S. Francis, and Timothy U. Connell*

Journal of the American Chemical Society 2024, 146, 39, 26830-26843

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07396>

ABSTRACT: Photoredox catalysis is a powerful tool to access challenging and diverse syntheses. Absorption of visible light forms the excited state catalyst (*PC) but photons may be wasted if one of several unproductive pathways occur. Facile dissociation of the charge-separated encounter complex [PC^{•-}:D^{•+}], also known as (solvent) cage escape, is required for productive chemistry and directly governs availability of the critical PC^{•-} intermediate. Competitive charge recombination, either inside or outside the solvent cage, may limit the overall efficiency of a photochemical reaction or internal quantum yield (defined as the moles of product formed per mole of photons absorbed by PC). Measuring the cage escape efficiency (ϕ_{CE}) typically requires time-resolved spectroscopy; however, we demonstrate how to estimate ϕ_{CE} using steady-state techniques that measure the efficiency of PC^{•-} formation (ϕ_{PC}). Our results show that choice of electron donor critically impacts ϕ_{PC} , which directly correlates to improved synthetic and internal quantum yields. Furthermore, we demonstrate how modest structural differences between photocatalysts may afford a sizable effect on reactivity due to changes in ϕ_{PC} , and by extension ϕ_{CE} . Optimizing experimental conditions for cage escape provides photochemical reactions with improved atom economy and energy input, paving the way for sustainable design of photocatalytic systems.

24COASNO66:**Title- Manipulating d-Band Center of Nickel by Single-Iodine-Atom Strategy for Boosted Alkaline Hydrogen Evolution Reaction**

Chongjing Liu, Beibei Sheng, Quan Zhou, Yujian Xia, Ying Zou, Peter Joseph Chimtali, Dengfeng Cao*, Yongheng Chu, Sirui Zhao, Ran Long, Shuangming Chen*, and Li Song*

Journal of the American Chemical Society 2024, 146, 39, 26844-26854

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07607>

ABSTRACT: Ni-based electrocatalysts have been predicted as highly potential candidates for hydrogen evolution reaction (HER); however, their applicability is hindered by an unfavorable d-band energy level (Ed). Moreover, precise d-band structural engineering of Ni-based materials is deterred by appropriate synthesis methods and experimental characterization. Herein, we meticulously synthesize a special single-iodine-atom structure (I-Ni@C) and characterize the Ed manipulation via resonant inelastic X-ray scattering (RIXS) spectroscopy to fill this gap. The complex catalytic mechanism has been elucidated via synchrotron radiation-based multitechniques (SRMS) including X-ray absorption fine structure (XAFS), in situ synchrotron radiation-based Fourier transform infrared (SR-FTIR) spectroscopy, and near ambient pressure X-ray photoelectron spectroscopy (NAP-XPS). In particular, RIXS is innovatively applied to reveal the precise regulation of Ni Ed of I-Ni@C. Consequently, the role of such single-iodine-atom strategy is confirmed to not only facilitate the moderate Ed of the Ni site for balancing the adsorption/desorption capacities of key intermediates but also act as a bridge to enhance the electronic interaction between Ni and the carbon shell for forming a localized polarized electric field conducive to H₂O dissociation. As a result, I-Ni@C exhibits an enhanced alkaline hydrogen evolution performance with an overpotential of 78 mV at 10 mA/cm² and superior stability, surpassing the majority of the reported Ni-based catalysts. Overall, this study has managed to successfully tailor the d-band center of materials from the SRMS perspective, which has crucial implications for nanotechnology, chemistry, catalysis, and other fields.

24COASNO67:

Title- Rechargeable Mg–Br₂ Battery with Ultrafast Bromine Chemistry

Longyuan Guo, Aosai Chen, Aoxuan Wang, Zhenglin Hu, Haiming Zhang*, and Jiayan Luo*
Journal of the American Chemical Society 2024, 146, 39, 26855-26862

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07707>

ABSTRACT: A sustainable society necessitates the support of diversified energy storage systems. Magnesium metal batteries, known for the environmental friendliness, safety of dendrite-less, cost-effective, and high volumetric capacity of magnesium metal, exhibit promising prospects. However, the high charge density of the magnesium ion leads to sluggish ion diffusion in cathodes, posing challenges for developing magnesium metal battery systems with high power and high energy density. Here, inspired by the Hard–Soft–Acid–Base theory, we propose a soft-anion-induced bond weakening strategy to address the diffusion difficulty. The bulky and broadly electron-distributed succinimide ion (SN[–]) in SN–Mg–Br significantly weakens the Mg–Br bond, promoting rapid magnesium ion transport and enabling ultrafast bromine chemistry, thus realizing a highly rechargeable Mg–Br₂ battery prototype. Benefiting from the solubilization of SN[–], the Mg–Br₂ batteries achieve a high discharge plateau of 2.7 V, a remarkable specific capacity of 326 mAh gBr^{–1}, and an impressive lifespan of 400 cycles. Attributed to the half–half diffusion/adsorption–desorption control process mechanism, the batteries can be well cycled under high-rate charging at 10 C and ultralow temperatures down to –55 °C. This bond weakening strategy may stimulate the

development of battery systems with similar high charge density to magnesium ion, toward high power and high energy density, paving the way for sustainable energy storage systems.

24COASNO68:**Title- Rapid Characterization of Point Defects in Solid-State Ion Conductors Using Raman Spectroscopy, Machine-Learning Force Fields, and Atomic Raman Tensors**

Willis O’Leary, Manuel Grumet, Waldemar Kaiser, Tomáš Bučko, Jennifer L. M. Rupp*, and David A. Egger*

Journal of the American Chemical Society 2024, 146, 39, 26863-26876

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07812>

ABSTRACT: The successful design of solid-state photo- and electrochemical devices depends on the careful engineering of point defects in solid-state ion conductors. Characterization of point defects is critical to these efforts, but the best-developed techniques are difficult and time-consuming. Raman spectroscopy—with its exceptional speed, flexibility, and accessibility—is a promising alternative. Raman signatures arise from point defects due to local symmetry breaking and structural distortions. Unfortunately, the assignment of these signatures is often hampered by a shortage of reference compounds and corresponding reference spectra. This issue can be circumvented by calculation of defect-induced Raman signatures from first principles, but this is computationally demanding. Here, we introduce an efficient computational procedure for the prediction of point defect Raman signatures in solid-state ion conductors. Our method leverages machine-learning force fields and “atomic Raman tensors”, i.e., polarizability fluctuations due to motions of individual atoms. We find that our procedure reduces computational cost by up to 80% compared to existing first-principles frozen-phonon approaches. These efficiency gains enable synergistic computational–experimental investigations, in our case allowing us to precisely interpret the Raman spectra of $\text{Sr}(\text{Ti}_{0.94}\text{Ni}_{0.06})\text{O}_{3-\delta}$, a model oxygen ion conductor. By predicting Raman signatures of specific point defects, we determine the nature of dominant defects and unravel impacts of temperature and quenching on in situ and ex situ Raman spectra. Specifically, our findings reveal the temperature-dependent distribution and association behavior of oxygen vacancies and nickel substitutional defects. Overall, our approach enables rapid Raman-based characterization of point defects to support defect engineering in novel solid-state ion conductors.

24COASNO69:**Title- A Selective Iron(I) Hydrogenation Catalyst**

Niko Sila, Andreas Dürrmann, Birgit Weber, Frank W. Heinemann, Torsten Irrgang, and Rhett Kempe*

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<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07959>

ABSTRACT: Iron is the most abundant transition metal of the Earth’s crust, and the understanding of its function in key technologies, such as catalysis, is highly important. We report here on an iron(I) hydrogenation catalyst. Our catalyst activates hydrogen via heterolytic bond cleavage, forms a monohydride, and hydrogenates polar double bonds via a bimetallic pathway (potassium-assisted hydride transfer). The mechanism observed seems to

exclude oxidative addition and reductive elimination pathways, permitting the tolerance of numerous hydrogenation-sensitive functional groups, as demonstrated for the hydrogenation of C=O bonds.

24COASNO70:**Title- Computation-Guided Discovery of Diazole Monosubstituted Tetrazines as Optimal Bioorthogonal Tools**

Yuxuan Li, Yeyu Su, Haoyu Wang, Yuanzhe Xie, Xin Wang, Liying Chang, Yanbo Jing, Jiayi Zhang, Jun-An Ma, Hongwei Jin, Xiaoding Lou*, Qian Peng*, and Tao Liu*

Journal of the American Chemical Society 2024, 146, 39, 26884-26896

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07958>

ABSTRACT: Monosubstituted tetrazines are important bioorthogonal reactive tools due to their rapid ligation with trans-cyclooctene. However, their application is limited by the reactivity–stability paradox in biological environments. In this study, we demonstrated that steric effects are crucial in resolving this paradox through theoretical methods and developed a simple synthetic route to validate our computational findings, leading to the discovery of 1,3-azole-4-yl and 1,2-azole-3-yl monosubstituted tetrazines as superior bioorthogonal tools. These new tetrazines surpass previous tetrazines in terms of high reactivities and elevated stabilities. The most stable tetrazine exhibits a reasonable stability (71% remaining after 24 h incubation in cell culture medium) and an exceptionally high reactivity ($k_2 > 10^4 \text{ M}^{-1} \text{ s}^{-1}$ toward trans-cyclooctene). Due to its good stability in biological systems, a noncanonical amino acid containing such a tetrazine side chain was genetically encoded into proteins site-specifically via an expanded genetic code. The encoded protein can be efficiently labeled using cyclopropane-fused trans-cyclooctene dyes in living mammalian cells with an ultrafast reaction rate exceeding $10^7 \text{ M}^{-1} \text{ s}^{-1}$, making it one of the fastest protein labeling reactions reported to date. Additionally, we showed its superiority through in vivo reactions in living mice, achieving an efficient local anchoring of proteins. These tetrazines are expected to be optimal bioorthogonal reactive tools within living systems.

24COASNO71:**Title- Ultrathin and Conformal Depletion Layer of Core/Shell Heterojunction Enables Efficient and Stable Acidic Water Oxidation**

Yang Liu, Yan Huang, Duojie Wu, Haeseong Jang, Jianghua Wu, Huirong Li, Wanxia Li, Feng Zhu, Min Gyu Kim, Donglai Zhou, Xiaoke Xi, Zhanwu Lei, Yuchen Zhang, Yu Deng, Wensheng Yan, M. Danny Gu*, Jun Jiang*, Shuhong Jiao*, and Ruiguo Cao*

Journal of the American Chemical Society 2024, 146, 39, 26897-26908

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c07995>

ABSTRACT: Ru-based electrocatalysts hold great promise for developing affordable proton exchange membrane (PEM) electrolyzers. However, the harsh acidic oxidative environment of the acidic oxygen evolution reaction (OER) often causes undesirable overoxidation of Ru active sites and subsequent serious activity loss. Here, we present an ultrathin and conformal depletion layer attached to the Schottky heterojunction of core/shell RuCo/RuCoOx that not only maximizes the availability of active sites but also improves its durability and intrinsic activity for acidic OER. Operando synchrotron characterizations combined with theoretical

calculations elucidate that the lattice strain and charge transfer induced by Schottky heterojunction substantially regulate the electronic structures of active sites, which modulates the OER pathway and suppresses the overoxidation of Ru species. Significantly, the closed core/shell architecture of the RuCo/RuCoOx ensures the structure integrity of the Schottky heterojunction under acidic OER conditions. As a result, the core/shell RuCo/RuCoOx Schottky heterojunction exhibits an unprecedented durability up to 2500 h at 10 mA cm⁻² with an ultralow overpotential of ~170 mV at 10 mA cm⁻² in 0.5 M H₂SO₄. The RuCo/RuCoOx catalyst also demonstrates superior durability in a proton exchange membrane (PEM) electrolyzer, showcasing the potential for practical applications.

24COASNO72:**Title- Catalyst-Free Oxidation of Styrene to Styrene Oxide Using Circulating Microdroplets in an Oxygen Atmosphere**

Lian Xue, Weida Chen, Peng Zheng, Jiao Geng, Feng Zhang, Xinyao Li*, Zhibing Zhang*, and Xingbang Hu*

Journal of the American Chemical Society 2024, 146, 39, 26909-26915

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c08018>

ABSTRACT: Water microdroplets possess unique interfacial properties that enable chemical reactions to occur spontaneously and increase the reaction rate by orders of magnitude. In this study, water containing styrene (SY) was cyclically sprayed into the air to form microdroplets with an average diameter of 6.7 μm. These microdroplets allowed SY to be oxidized into styrene oxide (SO) without catalysts. No oxidation products of SY were observed in the bulk solution under the same conditions, while in microdroplet reactions 4.2% conversion of SY with approximately 3.1 mM SO was detected. Compared with the traditional spraying microdroplet method, the oxidation product concentration was enhanced by 1000 times. Experiments proved that an aerobic environment boosts SY oxidation, leading to a proposed dual-path hydrogen peroxide (H₂O₂) oxidation mechanism at the droplet interface. This was confirmed by density functional theory calculations (DFT). Furthermore, in the presence of additional ultrasound, the SY oxidation process initiated by water droplets can be further enhanced, and 7.0% conversion of SY with approximately 5.2 mM SO was detected. The cyclic spraying method greatly enhanced the oxidation product concentration, showing the potential for large scale chemical production using microdroplets.

24COASNO73:**Title- Revealing the Chemical and Structural Complexity of Electrochemical Ion Exchange in Layered Oxide Materials**

Linqin Mu*, Dong Hou, Emily E. Foley, Minyi Dai, Jin Zhang, Zhisen Jiang, Muhammad Mominur Rahman, Yanbao Fu, Lu Ma, Enyuan Hu, Sami Sainio, Dennis Nordlund, Jue Liu, Jia-Mian Hu, Yijin Liu, Raphaële J. Clément*, and Feng Lin*

Journal of the American Chemical Society 2024, 146, 39, 26916-26925

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c08089>

ABSTRACT: Soft chemistry techniques, such as ion exchange, hold great potential for the development of battery electrode materials that cannot be stabilized via conventional equilibrium synthesis methods. Nevertheless, the intricate mechanisms governing ion

exchange remain elusive. Herein, we investigate the evolution of the long-range and local structure, as well as the ion (de)intercalation mechanism during electrochemical Li-to-Na ion exchange initiated from an O3-type lithium-layered oxide cathode. The in situ-formed mixed-cation electrolyte leads to competitive intercalation of Li and Na ions. While Li ion intercalation predominates at the beginning of initial discharge, Na ion cointercalation into a different layer results in ion redistribution and phase separation, with the emergence of a P3–Na phase alongside an O3–Li phase. Further, this study spatially resolves the heterogeneous nature of electrochemical ion exchange reactions within individual particles and provides insights into the correlations between local Ni redox processes and phase separation. Overall, electrochemical ion exchange leads to a mixed-phase cathode and alters its reaction kinetics. Those findings have important implications for the development of new metastable materials for renewable energy devices and ion separation applications.

24COASNO74:**Title- Chemically Separable Co(II) Spin-State Isomers**

Amelia M. Wheaton, Jill A. Chipman, Rebecca K. Walde, Heike Hofstetter, and John F. Berry*

Journal of the American Chemical Society 2024, 146, 39, 26926-26935

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c08097>

ABSTRACT: The phenomenon of spin crossover involves coordination complexes with switchable spin states. This spin state change is accompanied by significant geometric changes such that low and high spin forms of a complex are distinct isomers that exist in equilibrium with one another. Typically, spin-state isomers interconvert rapidly and are similar enough in polarity to prevent their independent separation and isolation. We report here the first example, to our knowledge, of cobalt(II) spin-state isomers that can be physically separated. The reaction of $\text{Mo}_2(\text{dpa})_4$ (dpa = 2,2'-dipyridylamide) with CoBr_2 produces a mixture of two heterometallic compounds with a linear, metal–metal-bonded MoMo–Co chain. The complexes, $\text{SC}[\text{BrMo}_2(\text{dpa})_4\text{Co}]\text{Br}$ (SC-2) and $\text{HS}[\text{BrMo}_2(\text{dpa})_4\text{CoBr}]$ (HS-2), have identical compositions ($\text{Mo}_2\text{Co}(\text{dpa})_4\text{Br}_2$) but different ground spin states and coordination geometries of the Co(II) ion. In the solid state, SC-2 undergoes incomplete spin crossover from an $S = 1/2$ state to an $S = 3/2$ state, and HS-2 has a high spin, $S = 3/2$, ground state, as confirmed by SQUID magnetometry and EPR spectroscopy. Crystallographic analyses of SC-2 and HS-2 show that SC-2 has an elongated Co–Br distance relative to HS-2 and is best described as the salt $[\text{BrMo}_2(\text{dpa})_4\text{Co}]\text{Br}$. This limits SC-2's solubility in nonpolar solvents and allows for the physical separation of the two isomers. Solution studies of SC-2 and HS-2 indicate that SC-2 and HS-2 interconvert slowly relative to the NMR time scale. Additional solution-state EPR and UV–vis absorption measurements demonstrate that the choice of solvent polarity determines the predominant isomer present in solution.

24COASNO75:**Title- Synthesis of Mesoporous Catechin Nanoparticles as Biocompatible Drug-Free Antibacterial Mesoformulation**

Runfeng Lin, Gaoyang Li, Qianfeng He, Junfeng Song, Yanming Ma, Yating Zhan,

Journal of the American Chemical Society 2024, 146, 39, 26983-26993

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c08336>

ABSTRACT: While polyphenolic substances stand as excellent antibacterial agents, their antimicrobial properties rely on the auxiliary support of micro-/nanostructures. Despite offering a novel avenue for enhancing polymer performance, controllable fabrication of mesoporous polymeric nanomaterials encounters significant challenges due to intricate intermolecular forces. In this article, mesoporous catechin nanoparticles have been successfully fabricated using a balanced multivariate interaction approach. The harmonization of the water–ethanol ratio and ionic strength effectively balances the forces of hydrogen bonding and π – π stacking, facilitating the controlled assembly of mesostructures. The mesoporous catechin nanoparticles exhibit a uniform spherical structure (~ 100 nm), open mesopores with a diameter of ~ 15 nm, and a high surface area of ~ 106 m² g^{–1}. While exhibiting a good biocompatibility and negative surface charge, the mesoporous catechins possess outstanding antibacterial ability and function as an antibiotic mesoformulation without the necessity of loading any drugs. This mesoformulation inhibits 50% in vitro *Staphylococcus aureus* growth with a low concentration of ~ 10 μ g mL^{–1} and achieves complete inhibition at ~ 25 μ g mL^{–1}. In a mouse wound model, accelerated wound healing and complete closure within 6–8 days are achieved. Proteomics of bacteria reveals that the excellent antibacterial property is attributed to the synergetic effect of mesoformulation's mesostructure and the catechin molecule intervening in bacterial metabolism. Overall, this work may pave a novel way for the future exploration of polymer nanomaterials and antibiotic formulations.

24COASNO76:**Title- Formal [2 σ + 2 σ]-Cycloaddition of Aziridines with Bicyclo[1.1.0]butanes: Access to Enantiopure 2-Azabicyclo[3.1.1]heptane Derivatives**

Shubham Dutta, Constantin G. Daniliuc, Christian Mück-Lichtenfeld, and Armido Studer*

Journal of the American Chemical Society 2024, 146, 39, 27204-27212

<https://pubs.acs.org/doi/epdf/10.1021/jacs.4c11296>

ABSTRACT: Saturated nitrogen heterocycles are among the most significant structural components in small-molecule pharmaceuticals. Herein, a protocol for the construction of enantiopure 2-azabicyclo[3.1.1]heptane derivatives by a stereospecific intermolecular formal cycloaddition of aziridines with bicyclo[1.1.0]butanes is described. The reaction is run by using B(C₆F₅)₃ as a catalytic additive to give access to a library of enantiopure 2-azabicyclo[3.1.1]heptane derivatives (37 examples) under mild and operationally simple conditions. Successful scale-up reactions, mechanistic experiments, density functional theory (DFT) calculations and synthetic applications are presented

24COASNO77:**Title- Exposure to polycyclic aromatic hydrocarbons promotes the progression of low-grade cervical intraepithelial neoplasia: A population-based cohort study in China**

Meng Cui, Li Song, Rui Mao, Yuanjing Lyu, Ling Ding, Zhilian Wang, Ruixin Pei,

International Journal of Cancer, Volume155, Issue7 Pages 1162-1171

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34990>

Abstract: Polycyclic aromatic hydrocarbons are ubiquitous toxic substances associated with various tumors. Previously, the authors reported that exposure to polycyclic aromatic hydrocarbons could increase the risk of cervical intraepithelial neoplasia (CIN). However, the effects of polycyclic aromatic hydrocarbons on the progression of CIN1 remain unclear. This community-based prospective cohort study with 2-year follow-up found that exposure to polycyclic aromatic hydrocarbons facilitated the malignant progression of CIN1 and hindered its reversal, particularly in patients with high-risk human papilloma virus infection. The findings provide novel insights for preventing and controlling the malignant progression of early cervical lesions.

24COASNO78:**Title- Longitudinal associations of plasma kynurenines and ratios with fatigue and quality of life in colorectal cancer survivors up to 12 months post-treatment**

Daniëlle D. B. Holthuijsen, Eline H. van Roekel, Martijn J. L. Bours, Per M. Ueland,

International Journal of Cancer, Volume155, Issue7 Pages 1172-1190

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34992>

Abstract: Fatigue is a major factor influencing health-related quality of life (HRQoL) after treatment for cancer. Some evidence suggests that the kynurenine pathway, by which tryptophan is metabolized, plays a role in post-cancer fatigue. Here, the authors show that higher plasma concentrations of tryptophan, kynurenic acid, and xanthurenic acid, as well as a higher kynurenic acid-to-quinolinic acid ratio, were associated with less fatigue and better HRQoL among patients with CRC up to 12 months after treatment. Conversely, a higher kynurenine-to-tryptophan ratio and 3-hydroxykynurenine ratio were associated with more fatigue and worse HRQoL. This pathway may be an intervention target for reducing post-cancer fatigue and enhancing HRQoL.

24COASNO79:**Title- Identifying modifiable risk factors to prevent aggressive colorectal cancer**

Peilu Wang, Mingyang Song, A. Heather Eliassen, Molin Wang, Andrew T. Chan, Jeffrey A. Meyerhardt,

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1191-1202

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34993>

Abstract: A substantial proportion of colorectal cancer (CRC) patients experience disease recurrence following initial treatment. Although pre-diagnostic risk factors potentially influence recurrence, little is known about their relationship with aggressive CRC. Here, the role of pre-diagnostic risk factors in aggressive CRC was evaluated from data on cancer-free

participants from three U.S. prospective cohorts. Aggressive CRC was associated with an inflammatory diet and reduced intake of whole grains and cereal fiber. Other risk factors had comparable impact on aggressive versus non-aggressive CRC development. Analyses further identified potential targets for early prevention of aggressive CRC, among them regular aspirin use and screening.

24COASNO80:

Title- The current infection with *Helicobacter pylori* and association with upper gastrointestinal lesions and risk of upper gastrointestinal cancer: Insights from multicenter population-based cohort study

Xinxin Yan, Hongmei Zeng, He Li, Maomao Cao, Fan Yang, Siyi He, Shaoli Zhang, Yi Teng, Qianru Li, Changfa Xia, Wanqing Chen

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1203-1211

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34998>

Abstract : The relationship between *Helicobacter pylori* (*H. pylori*) infection and upper gastrointestinal (UGI) cancer is complex. This population-based cohort study provides new evidence supporting the association between *H. pylori* infection and the risk of UGI cancer. The prevalence of *H. pylori* infection was 45.9%. Among endoscopy participants, 22.2% had gastric lesions and 19.2% had esophageal lesions. There was a higher risk for both cardia gastric cancer and non-cardia gastric cancer in *H. pylori*-infected individuals, but no significant increase for esophageal cancer. The findings contribute to the empirical basis for risk stratification and recommendations for UGI cancer screening.

24COASNO81:

Title- Cancer incidence, stage shift and survival during the 2020 COVID-19 pandemic: A population-based study in Belgium

Hanna M. Peacock, Mira Van Meensel, Bart Van Gool, Geert Silversmit, Kris Dekoninck, James D. Brierley, Liesbet Van Eycken

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1212-1224

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35001>

Abstract : Cancer diagnoses declined in Belgium in 2020, following the onset of the COVID-19 pandemic. An ageing population and migration, however, suggest that the actual pandemic impact on cancer trends in Belgium is underestimated. This study assessed cancer incidence, stage distribution and survival during the COVID-19 pandemic using cancer registry data in Belgium. By the end of 2020, the number of expected cancer diagnoses was found to have declined by more than 5000. Incidence of early-stage cancers was reduced, and shifts in stage distribution were observed. Whether stage shifts are associated with delayed diagnosis during the pandemic warrants further investigation.

24COASNO82:

Title- Deciphering the folate puzzle: Unraveling the impact of genetic variations and metabolites on cancer risk

Tong Liu, Chen-An Liu, Ya-Ping Wei, Meng-Meng Song, Qi Zhang, Yun Song, Ping Chen, Li-Shun Liu, Bin-Yan Wang, Han-Ping Shi

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1225-1236

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35043>

Abstract : This study investigates the relationship between serum folate, THF, and 5-MTHF levels and cancer risk, showing that folate's effect varies by genetic background and cancer type. Elevated THF levels correlate with decreased cancer risk. Importantly, the impact of 5-MTHF on cancer risk depends on MTHFR C677T polymorphisms, offering protection in CC and CT genotypes but potentially increasing risk in TT genotypes. These findings highlight folate's complex role in cancer biology and the need for further research to understand these interactions.

24COASNO83:

Title- Breast conserving surgery with intraoperative electron beam radiation therapy for low-risk breast cancer: Five-year follow-up of 306 patients

Charlotte de Jonge, Robert-Jan Schipper, Coco J. E. F. Walstra, Yvonne E. Van Riet,

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1237-1247

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35033>

Abstract : Electron beam intraoperative radiotherapy (IORT) enables radiation delivery to specific areas of the tumor bed, which may be especially effective for certain types of breast cancer. IORT, however, may increase the risk of ipsilateral breast tumor recurrence (IBTR) following breast conserving surgery (BCS). Here, the authors analyzed follow-up data on patients treated with BCS and IORT. A substantial increase in IBTR risk was observed following BCS with electron beam IORT, with no impact on breast cancer-specific survival. The findings indicate that among low-risk breast cancer patients treated initially with BCS, IORT should be avoided as partial breast irradiation technique.

24COASNO84:

Title- Five-year outcomes of fractionated stereotactic body radiotherapy for oligometastatic prostate cancer from the TRANSFORM phase II trial

Andrew W. See, Paul Conway, Mark Frydenberg, Hodo Haxhimolla, Anthony J. Costello,

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1248-1256

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35052>

Abstract : Metastasis-directed therapy (MDT) may benefit patients with metastatic prostate cancer (PCa), such as by allowing delay of androgen deprivation therapy (ADT). Whether MDT approaches improve overall survival, however, remains uncertain. Here, MDT using fractionated stereotactic radiotherapy (SBRT) was investigated for its impact on treatment escalation-free survival (TE-FS) in oligometastatic PCa patients. Analyses show that at 5-year follow-up, overall TE-FS was 21.7%. At 6.5 years, TE-FS was 18.9%, with prostate-specific antigen levels below baseline in 15.9% of patients. The findings indicate that SBRT-based MDT is a viable alternative to ADT for men with oligometastatic PCa.

24COASNO85:**Title- Cost-effectiveness analysis of alternative screening strategies for the detection of cervical cancer among women in rural areas of Western Kenya**

Christopher Lobin, Elkanah Omenge Orang'o, Edwin Were, Kapten Muthoka, Kavita Singh,

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1257-1267

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35036>

Abstract : In its updated screening recommendations for cervical cancer, the World Health Organization has urged existing programs to use visual inspection with acetic acid (VIA) as a primary screening tool to transition to human papillomavirus (HPV) DNA testing. This study shows that primary HPV testing plus triage with either dual-stain cytology or VIA performs better than VIA screening alone in detecting precancerous lesions in low-resource settings, with dual-stain cytology being the most cost-effective triage option. Furthermore, the results indicate the feasibility of equipping laboratories in low-resource settings with sophisticated technologies and operating them cost-effectively.

24COASNO85:**Title- Real-world safety and effectiveness of radium-223 in patients with metastatic castration-resistant prostate cancer: Interim analyses of the prospective, observational RAPIT study**

Chao-Yuan Huang, Chi-Ping Huang, Yu-Yi Huang, Steven Kuan-Hua Huang, Kevin Lu,

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1268-1277

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35040>

Abstract : This is the largest real-world study of ^{223}Ra in Taiwanese patients with mCRPC and is the only Taiwanese study to evaluate how the position of ^{223}Ra in the treatment sequence, prior chemotherapy use, and completing 5–6 ^{223}Ra cycles may impact patient outcomes. Introducing ^{223}Ra earlier in the treatment sequence was associated with the highest rates of completing 5–6 cycles of ^{223}Ra and offered better survival outcomes than later use.

24COASNO86:**Title- Misspellings or “miscellings”—Non-verifiable and unknown cell lines in cancer research publications**

Danielle J. Oste, Pranujan Pathmendra, Reese A. K. Richardson, Gracen Johnson, Yida Ao,

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1278-1289

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34995>

Abstract : Reproducible laboratory research relies on correctly identified reagents. Here, the authors flagged 23 non-verifiable (NV) human cell line identifiers in recent papers. Although some NV identifiers are likely mere misspellings of known cell lines, the results indicate that some misspelled cell lines can gain new identities as independent cell lines, a process the authors describe as “miscelling.” Of the eight identifiers studied in detail, seven NV identifiers were unexpectedly referred to as independent cell lines across 235 publications, lacking a description of how they were established, not appearing in the claimed external repositories, and having no short tandem repeat profile.

24COASNO87:**Title- The interaction of PRDX1 with Cofilin promotes oral squamous cell carcinoma metastasis**

Yajun Shen, Zixuan You, Lingyu Li, Xiaofei Tang, Xiaofeng Shan

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1290-1302

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34999>

Abstract : Stress-induced expression of peroxiredoxin 1 (PRDX1) is suspected of facilitating the progression of oral squamous cell carcinoma (OSCC). The role of PRDX1 in OSCC, however, remains uncertain. Here, the authors investigated the effect of PRDX1 on OSCC progression via cytoskeletal remodeling, a process fundamental to tumor metastasis. Analyses show that PRDX1 interacts with Cofilin, specifically inhibiting serine 3 phosphorylation. In a tongue cancer xenograft mouse model, these effects were found to promote cytoskeletal reconstruction and to accelerate cell migration. The findings identify a contributory role for PRDX1 in OSCC progression and highlight PRDX1 as a potential therapeutic target.

24COASNO88:**Title- Inhibition of the Rho/MRTF pathway improves the response of BRAF-resistant melanoma to PD1/PDL1 blockade**

Bardees M. Foda, Sean A. Misek, Kathleen A. Gallo, Richard R. Neubig

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1303-1315

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35056>

Abstract : Resistance to targeted and immune therapies limits the benefits of current treatments in melanoma. This study provides evidence for a new combined approach in targeting BRAF inhibitor-resistant melanoma. Pharmacological inhibition of the resistance-inducing Rho/MRTF pathway using CCG-257081 enhanced the response to PD1/PDL1 blockade in vivo. Moreover, anti-PD1/CCG-257081 co-treatment increased infiltration of CD8⁺ T cells and B cells into the tumor microenvironment and reduced tumor-associated macrophage infiltration. CCG-257081 emerges as a potential new anti-resistance agent that can improve the response to immune checkpoint inhibitors in advanced melanoma.

24COASNO89:**Title- Fragmentomics features of ovarian cancer**

Xiaopei Chao, Zhentian Kai, Huanwen Wu, Jing Wang, Xiaojing Chen, Haiqi Su, Xiao Shang, Ruijue Lin, Lisha Huang, Hongsheng He, Jinghe Lang, Lei Li

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1316-1326

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.34981>

Abstract : Circulating tumor DNA (ctDNA) is released into the blood from tumor cells as short fragments. Fragmentation patterns, such in length or distribution, may be associated with certain cancer types. Here, using ctDNA from ovarian cancer (OC) patients, fragmentation patterns and their possible association with OC were analyzed. Data indicate that fragments derived from cell-free DNA (cfDNA) in OC patients is, on average, shorter than fragments from individuals without cancer. Scores derived from a machine learning model further showed that fragmentomics features demonstrate sensitivity and specificity in

OC diagnosis, with superior performance over existing serum biomarkers and imaging methods.

24COASNO90:

Title- Genomic landscape defines peritoneal metastatic pattern and related target of peritoneal metastasis in colorectal cancer

Minhui Hu, Rui Luo, Keli Yang, Yang Yu, Qiwen Pan, Mingming Yuan, Rongrong Chen, Hui Wang, Qiyuan Qin, Tenghui Ma, Huaiming Wang

International Journal of Cancer, Volume155, Issue7 1 October 2024 Pages 1327-1339

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35005>

Abstract : The prognosis of colorectal cancer peritoneal metastasis is poor. Early detection and elucidating its mechanism are crucial. Here, the authors compared the genomic profiles of primary colorectal cancer with and without peritoneal metastasis, which derived a robust prediction model for colorectal cancer peritoneal metastasis and bioinformatically identified a potential target, *SERINC1*, for PM, which was further validated both in vivo and in vitro.

24COASNO91:

Title- The protective effect of dietary folate intake on gastric cancer is modified by alcohol consumption: A pooled analysis of the StoP Consortium

Sandra Gonzalez-Palacios, Laura-María Compañ-Gabucio, Laura Torres-Collado, Alejandro Oncina-Canovas, Manuela García-de-la-Hera, Giulia Collatuzzo, Eva Negri, Claudio Pelucchi, Matteo Rota,.....

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1367-1375

<https://doi.org/10.1002/ijc.35004>

Abstract : Getting adequate amounts of the B vitamin folate may help reduce the risk of gastric cancer (GC), although study results have been inconsistent so far. Here, the authors analyzed data from the Stomach Cancer Pooling Consortium to assess not only the association between folate intake and GC but also how alcohol consumption affects the association. They found that higher folate intake, as determined by food questionnaires, was associated with a lower GC risk. However, this association was not observed among those reporting alcohol consumption of more than 2 drinks per day.

24COASNO92:

Title- Analysis of the incidence and mortality trends of esophageal cancer in cancer registry areas of China and Japan

Dongli Guo, Jing Jin, Daojuan Li, Yutong He, Yingsong Lin

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1376-1386

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35003>

Abstract : The incidence of esophageal cancer is disproportionately high in East Asia, where China alone has historically accounted for about half of the world's esophageal malignancies. In this study, the authors investigated recent trends in incidence and mortality for esophageal cancer specifically in China and Japan. Analyses show that incidence and mortality rates are declining in China, while mortality is declining in Japan. Most patients are diagnosed at stage

III in China, versus stage I in Japan. The findings offer insight into esophageal cancer trends and patterns in China and Japan and could help identify areas for improvement in prevention.

24COASNO93:**Title- The landscape of etiological patterns of hepatocellular carcinoma and intrahepatic cholangiocarcinoma in Thailand**

Benjarath Pupacdi, Christopher A. Loffredo, Anuradha Budhu, Siritida Rabibhadana,
International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1387-1399
<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35034>

Abstract : Thailand has a uniquely high incidence of both hepatocellular carcinoma and intrahepatic cholangiocarcinoma. This large case–control study explored their associated risk factors, notably environmental exposures, and determined their commonality, combinatorial roles, and effects on survival. Among the shared risk factors were well-established factors including viral hepatitis, liver fluke infection, and diabetes as well as novel factors such as agricultural pesticides and vulnerable drinking water sources. Patients with multiple risk factors had worse survival outcomes. The findings suggest new avenues to reduce risk and improve survival in liver cancer patients.

24COASNO94:**Title- Kinetics of EBV antibody-based NPC risk scores in Taiwan NPC multiplex families**

Wan-Lun Hsu, Jun Tao, Sheng Fu, Kelly J. Yu, Julia Simon, Tseng-Cheng Chen, Chien-Jen Chen,
International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1400-1408
<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35037>

Abstract : Nasopharyngeal carcinoma risk prediction models based on Epstein–Barr virus (EBV) antibody testing have shown screening potential. However, previous studies have focused on single-time point antibody detection. Here, the authors characterized the humoral immune response against EBV longitudinally in nasopharyngeal carcinoma multiplex families over two decades. The results show that the two-marker ELISA risk score is more stable than the 13-marker multiplex score in high-risk populations. Nasopharyngeal carcinoma status is associated with the kinetics of the antibody response, with higher stability among cases. Repeated screening of serum EBV antibodies could help improve specificity for early nasopharyngeal carcinoma detection.

24COASNO95:**Title- Immune responses and reinfection of SARS-CoV-2 Omicron variant in patients with lung cancer**

Chen Chen, Xiaoyun Zhou, Xiaoxing Gao, Ruili Pan, Qi He, Xiaobei Guo, Siyuan Yu, Na Wang, Qian Zhao, Mengzhao Wang, Yan Xu, Xiaohong Han
International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1409-1421
<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35038>

Abstract : The duration of humoral and cellular responses post-Omicron infection and the efficacy of hybrid immunity in preventing reinfection in lung cancer patients remains

unknown. In this longitudinal study, humoral responses were elevated in fully or booster-vaccinated patients compared to unvaccinated patients, with the enhanced response persisting for 7 months at least. T-cell responses to Omicron were more potent than those to SARS-CoV-2 wild-type peptides. Unvaccinated patients at a late cancer stage receiving immunotherapy alone were at high risk of reinfection. The findings may inform the implementation of strategies to reduce the risk of repeated infections in patients with lung cancer.

24COASNO96:**Title- Effects of the Coronavirus disease 2019 pandemic on mortality in patients with lung cancer: A multiple mediation analysis in Japan**

Daisuke Miyamori, Tsukasa Kamitani, Shuhei Yoshida, Yuka Kikuchi, Yuya Shigenobu, Kotaro Ikeda,

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1422-1431

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35042>

Abstract : The COVID-19 pandemic significantly affected the care of lung cancer patients. In particular, fear of infection and overlap of respiratory symptoms complicated lung cancer diagnosis and treatment. Here, the authors investigated mortality risk among patients newly diagnosed with lung cancer specifically during the COVID-19 pandemic. Mortality risk was found to be 1.2 times higher among newly diagnosed patients, compared to patients diagnosed before the pandemic. Half the increase in mortality rate could be attributed to diagnosis at older age, decreased cancer screening, and a lack of tumor-directed treatment. Cancer stage and histological confirmation had no impact on increased mortality risk.

24COASNO97:**Title- Potential association between PSCA rs2976395 functional variant and pancreatic cancer risk**

Chiara Corradi, Giulia Lencioni, Alessio Felici, Cosmeri Rizzato, Manuel Gentiluomo,

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1432-1442

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35046>

Abstract : Correlated regions of systemic interindividual variation (CoRSIV) contain or are near to single-nucleotide polymorphisms (SNPs) that are likely to be associated with disease. Here, CoRSIVs were analyzed for the presence of SNPs and methylation quantitative trait loci effects in relation to pancreatic ductal adenocarcinoma (PDAC) risk in individuals of European or Asian descent. Of 29,099 CoRSIV SNPs identified, only 1—the A allele of PSCA-rs2976395—was found to have a possible relationship with PDAC risk. The rs2976395 SNP was associated with increased PSCA methylation. Further investigation of PSCA-rs2976395 is needed to better elucidate its relevance in PDAC.

24COASNO98:**Title- Personalized dendritic cell vaccine in multimodal individualized combination therapy improves survival in high-risk pediatric cancer patients**

Michal Kyr, Peter Mudry, Kristyna Polaskova, Lenka Zdrzilova Dubska, Regina Demlova,

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1443-1454
<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35062>

Abstract : While dendritic cell-based vaccines have emerged as one of the promising and well-tolerated immunotherapy options for cancers, most studies have been conducted in adults. Using the N-of-1 approach in a real-world scenario, the authors demonstrate that personalized dendritic cell vaccine is an effective component of the multimodal individualized treatment for pediatric high-risk solid tumors, especially in less burdened or aggressive diseases. Immune checkpoint inhibitors acted synergistically with the dendritic cell vaccine. The findings support the use of dendritic cell-based immunotherapy in clinical practice, with early vaccine preparation and delayed application boosted by immunomodulatory agents.

24COASNO99:

Title- Adjuvant treatment with anti-PD-1 in acral melanoma: A nationwide study

Manja Bloem, Olivier J. van Not, Maureen J. B. Aarts, Franchette W. P. J. van den Berkmortel, Christian U. Blank, ...

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1455-1465
<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35060>

Abstract : Immune checkpoint inhibitors to treat melanoma have performed well in clinical trials; however, these trials include few cases of acral melanoma, which occurs in places like the soles of the feet or under the nails and is more common among people with darker skin. Here, the authors analyzed the outcomes of patients with acral melanoma treated with anti-PD-1 after complete resection. These patients have a shorter recurrence-free survival, distant metastasis-free survival, and overall survival than patients with cutaneous melanoma who receive anti-PD-1.

24COASNO100:

Title- Value of automated breast ultrasound in screening: Standalone and as a supplemental to digital breast tomosynthesis

Erkin Aribal, Mustafa Ege Seker, Nilgün Guldogan, Ebru Yilmaz

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1466-1475
<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35093>

Abstract : Dense breast tissue is a primary factor contributing to breast cancer risk that also reduces the sensitivity of mammograms. This prospective opportunistic screening study compared digital breast tomosynthesis mammography with automated breast ultrasound as a supplemental or standalone screening method. Standalone automated breast ultrasound showed promise in detecting more clinically important cancers with a comparable cancer detection rate to that of digital breast tomosynthesis, albeit with a higher false-positive rate. The findings also suggested that, when using automated breast ultrasound as a supplemental screening tool, combination with 2D mammography rather than digital breast tomosynthesis is sufficient.

24COASNO101:**Title- A proteome-wide analysis unveils a core Epstein–Barr virus antibody signature of classic Hodgkin lymphoma across ethnically diverse populations**

Yomani D. Sarathkumara, Rena R. Xian, Zhiwei Liu, Kelly J. Yu, John K. C. Chan, Yok-Lam Kwong,

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1476-1486

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35072>

Abstract : Epstein–Barr virus (EBV) is associated with classical Hodgkin lymphoma and other cancers. Here, the authors measured antibody response to EBV using a custom protein microarray. Their results define an antibody signature of 16 IgG antibodies in a population from East Asia. By testing a population from Europe, they identified a “core signature” of five IgG antibodies consistently elevated in cHL patients, suggesting that these may be significant to the disease progression and could point to new therapeutic interventions.

24COASNO102:**Title- EEF1D stabilized by SRSF9 promotes colorectal cancer via enhancing the proliferation and metastasis**

Rui Wang, Chi Lv, Donghao Li, Yutong Song, Zhaopeng Yan

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1487-1499

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35039>

Abstract : The protein eukaryotic elongation factor 1 delta (EEF1D) plays a role in protein synthesis and is involved in tumor progression in many cancers. Here, the authors investigated expression levels of EEF1D in colorectal cancer (CRC) both in vitro and in vivo using mouse models of CRC. Upregulation of EEF1D accelerated cell proliferation and metastasis, they found, and reducing its levels had the opposite effect. This suggests that EEF1D could be a molecular target for treating CRC.

24COASNO103:**Title- Impaired acute-phase humoral immunity is the major factor predicting unfavorable outcomes in multiple myeloma patients with SARS-CoV-2 Omicron variants outbreak infection**

Ziping Li, Huiwen He, Haolong Li, Fujing Zhang, Xianghong Jin, Shuangjiao Liu, Miao Chen, Yongzhe Li, Junling Zhuang

International Journal of Cancer , Volume155, Issue8 15 October 2024 Pages 1500-1509

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35063>

Abstract : Patients with multiple myeloma experienced cancer deterioration and mortality due to COVID-19, yet profound analyses of Omicron variants-induced immunity remain limited. This longitudinal study observed severe impaired humoral immunity at 2–4 weeks post-infection in patients at high risk for hospitalization, while the T-cell response was relatively intact. Inactivated vaccines continued to show effectiveness against Omicron. The findings suggest that early impaired humoral immunity after infection is a major factor of poor outcomes. A booster at 14–16 weeks post-infection should be considered for high-risk multiple myeloma subgroups.

24COASNO104:**Title- Enhancing precision targeting of ovarian cancer tumor cells in vivo through extracellular vesicle engineering**

Mona Alharbi, Andrew Lai, Nihar Godbole, Dominic Guanzon, Soumyalekshmi Nair, Felipe Zuñiga,

International Journal of Cancer, Volume155, Issue8 15 October 2024 Pages 1510-1523

<https://onlinelibrary.wiley.com/doi/10.1002/ijc.35055>

Abstract : Extracellular vesicles (EVs) are promising therapeutic tools for cancer, owing to qualities such as immunogenicity and low toxicity. Enhancing the accumulation of EVs in specific cells and tissues, however, requires improved targeting capabilities. In this study, EVs were modified with ephrin-B2 to explore the effects on targeting and the potential use of EVs specifically against ovarian cancer. Targeting the ephrin-B4 receptor on ovarian cancer cells significantly improved EV uptake by ovarian cancer cells, both in vitro and in vivo. The engineered EVs maintained their characteristic properties while also exhibiting high targeting efficacy, demonstrating the potential of EVs in cancer therapeutics.

24COASNO105:**Title- Unraveling molecular aberrations and pioneering therapeutic strategies in osteosarcoma,**

Peng Yan, Jie Wang, Bin Yue, Xinyi Wang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189171.

<https://doi.org/10.1016/j.bbcan.2024.189171>.

Abstract: Osteosarcoma, a rare primary bone cancer, presents diverse molecular aberrations that underscore its complexity. Despite the persistent endeavors by researchers, the limited amelioration in the five-year survival rate indicates that current therapeutic strategies prove inadequate in addressing the clinical necessities. Advancements in molecular profiling have facilitated an enhanced comprehension of the biology of osteosarcoma, offering a promising outlook for treatment. There is an urgent need to develop innovative approaches to address the complex challenges of osteosarcoma, ultimately contributing to enhanced patient outcomes. This review explores the nexus between osteosarcoma and cancer predisposition syndromes, intricacies in its somatic genome, and clinically actionable alterations. This review covers treatment strategies, including surgery, chemotherapy, immune checkpoint inhibitors (ICIs), and tyrosine kinase inhibitors (TKIs). Innovative treatment modalities targeting diverse pathways, including multi-target tyrosine kinases, cell cycle, PI3K/mTOR pathway, and DNA damage repair (DDR), offer promising interventions. This review also covers promising avenues, including antibody-drug conjugates (ADCs) and immunotherapy strategies, such as cytokines, adoptive cellular therapy (ACT), ICIs, and cancer vaccines. This comprehensive exploration contributes to a holistic understanding, offering guidance for clinical applications to advance the management of osteosarcoma.

Keywords: Osteosarcoma; Molecular alterations; Antibody-drug conjugates (ADCs); Immunotherapy; Targeted therapy

24COASNO106:**Title- Hydrogel encapsulation of mesenchymal stem cells-derived extracellular vesicles as a novel therapeutic approach in cancer therapy,**

Raheleh Farahzadi, Ezzatollah Fathi, Somayeh Vandghanooni, Behnaz Valipour,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189177.

<https://doi.org/10.1016/j.bbcan.2024.189177>.

Abstract: Cell therapy has emerged as one of the most promising approaches to treating disease in recent decades. The application of stem cells in anti-tumor therapy is determined by their varying capacity for proliferation, migration, and differentiation. These capacities are derived from different sources. The use of stem cell carriers in cancer treatment is justified by the following three reasons: (I) shield therapeutic agents from swift biological deterioration; (II) reduce systemic side effects; and (III) increase local therapeutic levels since stem cells have an innate ability to target tumors. The quantity of stem cells confined to the tumor microenvironment determines this system's anti-tumor activity. Nevertheless, there are limitations to the use of different types of stem cells. When immune cells are used in cell therapy, it may lead to cytokine storms and improper reactions to self-antigens. Furthermore, the use of stem cells may result in cancer. Additionally, after an intravenous injection, cells could not migrate to the injury location. Exosomes derived from different cells were thus proposed as possible therapeutic options. Exosomes are becoming more and more well-liked because of their small size, biocompatibility, and simplicity in storage and separation. A number of investigations have shown that adding various medications and microRNAs to exosomes may enhance their therapeutic effectiveness. Thus, it is essential to evaluate studies looking into the therapeutic effectiveness of encapsulated exosomes. In this review, we looked at studies on encapsulated exosomes' use in regenerative medicine and the treatment of cancer. The results imply that the therapeutic potential increases when encapsulated exosomes are used rather than intact exosomes. Therefore, in order to optimize the effectiveness of the treatment, it is advised to implement this technique in accordance with the kind of therapy.

Keywords: Cancer therapy; Encapsulation; Hydrogel; Mesenchymal stem cells; Mesenchymal stem cells-derived exosomes

24COASNO107:**Title- Dual perspective on autophagy in glioma: Detangling the dichotomous mechanisms of signaling pathways for therapeutic insights,**

Moumita Kundu, Subhayan Das, Ankita Dey, Mahitosh Mandal,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189168.

<https://doi.org/10.1016/j.bbcan.2024.189168>.

Abstract: Autophagy is a normal physiological process that aids the recycling of cellular nutrients, assisting the cells to cope with stressed conditions. However, autophagy's effect on cancer, including glioma, is uncertain and involves complicated molecular mechanisms. Several contradictory reports indicate that autophagy may promote or suppress glioma growth and progression. Autophagy inhibitors potentiate the efficacy of chemotherapy or radiation therapy in glioma. Numerous compounds stimulate autophagy to cause glioma cell

death. Autophagy is also involved in the therapeutic resistance of glioma. This review article aims to detangle the complicated molecular mechanism of autophagy to provide a better perception of the two-sided role of autophagy in glioma and its therapeutic implications. The protein and epigenetic modulators of the cytoprotective and cytotoxic role of autophagy are described in this article. Moreover, several signaling pathways are associated with autophagy and its effects on glioma. We have reviewed the molecular pathways and highlighted the signaling axis involved in cytoprotective and cytotoxic autophagy. Additionally, this article discusses the role of autophagy in therapeutic resistance, including glioma stem cell maintenance and tumor microenvironment regulation. It also summarizes several investigations on the anti-glioma effects of autophagy modulators to understand the associated mechanisms and provide insights regarding its therapeutic implications.

Keywords: Autophagy; Cytoprotective; Cytotoxic; Glioma; Resistance

24COASNO108:

Title- Pathophysiological role of histamine signaling and its implications in glioblastoma,

Poonam Yadav, Raghupathy Vengoji, Maneesh Jain, Surinder K. Batra, Nicole Shonka,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189146.
<https://doi.org/10.1016/j.bbcan.2024.189146>.

Abstract: Glioblastoma (GBM), an extremely aggressive and prevalent malignant brain tumor, remains a challenge to treat. Despite a multimodality treatment approach, GBM recurrence remains inevitable, particularly with the emergence of temozolomide (TMZ) resistance and limited treatment options. Surprisingly, previous studies show that a history of allergies, atopy, or asthma is inversely associated with GBM risk. Further, the electronic medical record at the University Hospital of Lausanne showed that the GBM patients taking antihistamine during treatment had better survival. Histamine is an essential neurotransmitter in the brain and plays a significant role in regulating sleep, hormonal balance, and cognitive functions. Elevated levels of histamine and increased histamine receptor expression have been found in different tumors and their microenvironments, including GBM. High histamine 1 receptor (HRH1) expression is inversely related to overall and progression-free survival in GBM patients, further emphasizing the role of histamine in disease progression. This review aims to provide insights into the challenges of GBM treatment, the role of histamine in GBM progression, and the rationale for considering antihistamines as targeted therapy. The review concludes by encouraging further investigation into antihistamine mechanisms and their impact on the tumor microenvironment.

Keywords: Glioblastoma; Histamine; Antihistamine

24COASNO109:

Title- New horizons in the mechanisms and therapeutic strategies for PD-L1 protein degradation in cancer,

Zhi Li, Xi Yu, Zeting Yuan, Lei Li, Peihao Yin,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189152.
<https://doi.org/10.1016/j.bbcan.2024.189152>.

Abstract: Programmed death-ligand 1 (PD-L1) has become a crucial focus in cancer immunotherapy considering it is found in many different cells. Cancer cells enhance the suppressive impact of programmed death receptor 1 (PD-1) through elevating PD-L1 expression, which allows them to escape immune detection. Although there have been significant improvements, the effectiveness of anti-PD-1/PD-L1 treatment is still limited to a specific group of patients. An important advancement in cancer immunotherapy involves improving the PD-L1 protein degradation. This review thoroughly examined the processes by which PD-L1 breaks down, including the intracellular pathways of ubiquitination-proteasome and autophagy-lysosome. In addition, the analysis revealed changes that affect PD-L1 stability, such as phosphorylation and glycosylation. The significant consequences of these procedures on cancer immunotherapy and their potential role in innovative therapeutic approaches are emphasised. Our future efforts will focus on understanding new ways in which PD-L1 degradation is controlled and developing innovative treatments, such as proteolysis-targeting chimeras designed specifically to degrade PD-L1. It is crucial to have a thorough comprehension of these pathways in order to improve cancer immunotherapy strategies and hopefully improve therapeutic effectiveness.

Keywords: Programmed death-ligand 1; Programmed death receptor 1; Degradation; Ubiquitination; Immunotherapy; Proteolysis-targeting chimeras

24COASNO110:

Title- Small-molecule in cancer immunotherapy: Revolutionizing cancer treatment with transformative, game-changing breakthroughs,

Soumyadeep Chattopadhyay, Rudradeep Hazra, Arijit Mallick, Sakuntala Gayen, Souvik Roy,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189170.

<https://doi.org/10.1016/j.bbcan.2024.189170>.

Abstract: Immunotherapy has revolutionized cancer management, with antibody-based treatments leading the charge due to their superior pharmacodynamics, including enhanced effectiveness and specificity. However, these therapies are hampered by limitations such as prolonged half-lives, poor tissue and tumor penetration, and minimal oral bioavailability. Additionally, their immunogenic nature can cause adverse effects. Consequently, the focus is shifting towards small-molecule-based immunotherapies, which potentially overcome these drawbacks. Emerging as a promising alternative, small molecules offer the benefits of therapeutic antibodies and immunomodulators, often yielding synergistic effects when combined. Recent advancements in small-molecule cancer immunotherapy are notable, featuring inhibitors, agonists, and degraders that act as immunomodulators. This article delves into the current landscape of small-molecule immunotherapy in cancer treatment, highlighting novel agents targeting key pathways such as Toll-like receptors (TLR), PD-1/PD-L1, chemokine receptors, and stimulators of interferon genes (STING). The review emphasizes newly discovered molecular entities and their modulatory roles in tumorigenesis, many of which have progressed to clinical trials, that aims to provide a comprehensive snapshot of the evolving frontier in cancer treatment, driven by small-molecule immunomodulators.

Keywords: Immunotherapy; Stimulators of interferon genes (STING); Immunogenicity; Immunomodulators; Tumorigenesis

24COASNO111:

Title- Reactive oxygen species of tumor microenvironment: Harnessing for immunogenic cell death,

RamaRao Malla, Seema Kumari, Swapna Priya Ganji, Mundla Srilatha, Haasita Reddy Nellipudi, Ganji Purnachandra Nagaraju,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189154.

<https://doi.org/10.1016/j.bbcan.2024.189154>.

Abstract: The tumor microenvironment (TME) is a dynamic and complex system that undergoes continuous changes in its network architecture, notably affecting redox homeostasis. These alterations collectively shape a diverse ecosystem actively supporting tumor progression by influencing the cellular and molecular components of the TME. Despite the remarkable clinical advancements in cancer immunotherapy, its spectrum of clinical utility is limited by the altered TME and inadequate tumor immunogenicity. Recent studies have revealed that some conventional and targeted therapy strategies can augment the efficacy of immunotherapy even in patients with less immunogenic solid tumors. These strategies provoke immunogenic cell death (ICD) through the ROS-dependent liberation of damage-associated molecular patterns (DAMPs). These DAMPs recognize and bind with Pattern Recognition Receptors (PRRs) on immune cells, activating and maturing defense cells, ultimately leading to a robust antitumor immune response. The present review underscores the pivotal role of redox homeostasis in orchestrating the transition of TME from a cold to a hot phenotype and the ROS-ICD axis in immune response induction. Additionally, it provides up-to-date insights into strategies that leverage ROS generation to induce ICD. The comprehensive analysis aims to develop ROS-based effective cancer immunotherapies for less immunogenic tumors.

Keywords: Cancer immunotherapy; Damage-associated molecular patterns; Immunogenic cell death; Redox homeostasis; Tumor microenvironment

24COASNO112:

Title- Cullin-RING Ligase 4 in Cancer: Structure, Functions, and Mechanisms,

Jingyi Cheng, Xin Bin, Zhangui Tang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189169.

<https://doi.org/10.1016/j.bbcan.2024.189169>.

Abstract: Cullin-RING ligase 4 (CRL4) has attracted enormous attentions because of its extensive regulatory roles in a wide variety of biological and pathological events, especially cancer-associated events. CRL4 exerts pleiotropic effects by targeting various substrates for proteasomal degradation or changes in activity through different internal compositions to regulate diverse events in cancer progression. In this review, we summarize the structure of CRL4 with manifold compositional modes and clarify the emerging functions and molecular mechanisms of CRL4 in a series of cancer-associated events.

Keywords: CRL4; Cullin 4; DCAF; E3 ligases; Tumorigenesis

24COASNO113:**Title- Tumor microenvironment: A playground for cells from multiple diverse origins,**

Deblina Bharadwaj, Mahitosh Mandal,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189158.

<https://doi.org/10.1016/j.bbcan.2024.189158>.

Abstract: Tumor microenvironment is formed by various cellular and non-cellular components which interact with one another and form a complex network of interactions. Some of these cellular components also attain a secretory phenotype and release growth factors, cytokines, chemokines etc. in the surroundings which are capable of inducing even greater number of signalling networks. All these interactions play a decisive role in determining the course of tumorigenesis. The treatment strategies against cancer also exert their impact on the local microenvironment. Such interactions and anticancer therapies have been found to induce more deleterious outcomes like immunosuppression and chemoresistance in the process of tumor progression. Hence, understanding the tumor microenvironment is crucial for dealing with cancer and chemoresistance. This review is an attempt to develop some understanding about the tumor microenvironment and different factors which modulate it, thereby contributing to tumorigenesis. Along with summarising the major components of tumor microenvironment and various interactions taking place between them, it also throws some light on how the existing and potential therapies exert their impact on these dynamics.

Keywords: Tumor microenvironment; Immunosuppression; Immune cells; Chemoresistance; Exosomes

24COASNO114:**Title- Insights into the role of connexins and specialized intercellular communication pathways in breast cancer: Mechanisms and applications,**

Marina Rodríguez-Candela Mateos, Paula Carpintero-Fernández, Paz Santiago Freijanes, Joaquin Mosquera, Benigno Acea Nebril, María D. Mayán,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189173.

<https://doi.org/10.1016/j.bbcan.2024.189173>.

Abstract: Gap junctions, membrane-based channels comprised of connexin proteins (Cx), facilitate direct communication among neighbouring cells and between cells and the extracellular space through their hemichannels. The normal human breast expresses various Cxs family proteins, such as Cx43, Cx30, Cx32, Cx46, and Cx26, crucial for proper tissue development and function. These proteins play a significant role in breast cancer development, progression, and therapy response. In primary tumours, there is often a reduction and cytoplasmic mislocalization of Cx43 and Cx26, while metastatic lesions show an upregulation of these and other Cxs. Although existing research predominantly supports the tumour-suppressing role of Cxs in primary carcinomas through channel-dependent and independent functions, controversies persist regarding their involvement in the metastatic process. This review aims to provide an updated perspective on Cxs in human breast cancer, with a specific focus on intrinsic subtypes due to the heterogeneous nature of this disease. Additionally, the manuscript will explore the role of Cxs in immune interactions and novel

forms of intercellular communication, such as tunneling nanotubes and extracellular vesicles, within the breast tumour context and tumour microenvironment. Recent findings suggest that Cxs hold potential as therapeutic targets for mitigating metastasis and drug resistance. Furthermore, they may serve as novel biomarkers for cancer prognosis, offering promising avenues for future research and clinical applications.

Keywords: Connexins; Gap junctions; Breast cancer; Mammary carcinoma; Tunelling nanotubes; Extracellular vesicles; Exosomes; Anti-tumour immune response

24COASNO115:

Title- Dissecting SOX2 expression and function reveals an association with multiple signaling pathways during embryonic development and in cancer progression,

Niharika, Lina Ureka, Ankan Roy, Samir Kumar Patra,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189136.

<https://doi.org/10.1016/j.bbcan.2024.189136>.

Abstract: SRY (Sex Determining Region) box 2 (SOX2) is an essential transcription factor that plays crucial roles in activating genes involved in pre- and post-embryonic development, adult tissue homeostasis, and lineage specifications. SOX2 maintains the self-renewal property of stem cells and is involved in the generation of induced pluripotency stem cells. SOX2 protein contains a particular high-mobility group domain that enables SOX2 to achieve the capacity to participate in a broad variety of functions. The information about the involvement of SOX2 with gene regulatory elements, signaling networks, and microRNA is gradually emerging, and the higher expression of SOX2 is functionally relevant to various cancer types. SOX2 facilitates the oncogenic phenotype via cellular proliferation and enhancement of invasive tumor properties. Evidence are accumulating in favor of three dimensional (higher order) folding of chromatin and epigenetic control of the SOX2 gene by chromatin modifications, which implies that the expression level of SOX2 can be modulated by epigenetic regulatory mechanisms, specifically, via DNA methylation and histone H3 modification. In view of this, and to focus further insights into the roles SOX2 plays in physiological functions, involvement of SOX2 during development, precisely, the advances of our knowledge in pre- and post-embryonic development, and interactions of SOX2 in this scenario with various signaling pathways in tumor development and cancer progression, its potential as a therapeutic target against many cancers are summarized and discussed in this article.

Keywords: Cancer stem cell; Embryonic development; Enhancer-promoter interactions; CTCF & Cohesin; Epigenetic regulation; Pluripotent stem cell; SOX2; Signaling pathways

24COASNO116:

Title- Unlocking the potential: Targeting metabolic pathways in the tumor microenvironment for Cancer therapy,

Siyuan Jia, Ann M. Bode, Xue Chen, Xiangjian Luo,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189166.

<https://doi.org/10.1016/j.bbcan.2024.189166>.

Abstract: Cancer incidence and mortality are increasing and impacting global life expectancy. Metabolic reprogramming in the tumor microenvironment (TME) is intimately

related to tumorigenesis, progression, metastasis and drug resistance. Tumor cells drive metabolic reprogramming of other cells in the TME through metabolic induction of cytokines and metabolites, and metabolic substrate competition. Consequently, this boosts tumor cell growth by providing metabolic support and facilitating immunosuppression and angiogenesis. The metabolic interplay in the TME presents potential therapeutic targets. Here, we focus on the metabolic reprogramming of four principal cell subsets in the TME: CAFs, TAMs, TILs and TECs, and their interaction with tumor cells. We also summarize medications and therapies targeting these cells' metabolic pathways, particularly in the context of immune checkpoint blockade therapy.

Keywords: Tumor microenvironment (TME); Metabolic reprogramming; Cancer-associated fibroblasts (CAFs); Tumor-associated macrophages (TAMs); Tumor endothelial cells (TECs); Tumor-infiltrating lymphocytes (TILs) therapy; Immune check point blockade (ICB)

24COASNO117:

Title- Immunotherapy for HPV negative head and neck squamous cell carcinoma,

Binyumeng Jiang, Ahmed Elkashif, Jonathan A. Coulter, Nicholas J. Dunne, Helen O. McCarthy,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189138.

<https://doi.org/10.1016/j.bbcan.2024.189138>.

Abstract: Head and neck cancer (HNSCC) is the 8th most common cancer in the UK, with incidence increasing due to lifestyle factors such as tobacco and alcohol abuse. HNSCC is an immune-suppressive disease characterised by impaired cytokine secretion and dysregulation of immune infiltrate. As such, immunotherapy is a potential treatment option, with therapeutic cancer vaccination demonstrating the greatest potential. The success of cancer vaccination is dependent on informed antigen selection: an ideal antigen must be either tumour-specific or tumour-associated, as well as highly immunogenic. Stratification of the patient population for antigen expression and validated biomarkers are also vital. This review focuses on the latest developments in immunotherapy, specifically the development of therapeutic vaccines, and highlights successes, potential drawbacks and areas for future development. Immunotherapy approaches considered for HNSCC include monoclonal antibodies (mAb), Oncolytic viral (OV) therapies, Immune Checkpoint Inhibitors (ICIs) and cancer vaccines.

Keywords: HNSCC; Vaccines; mRNA; Immunotherapy; T-cells; Dendritic cells

24COASNO118:

Title- Advances in immunotherapy for breast cancer and feline mammary carcinoma: From molecular basis to novel therapeutic targets,

Tatiana Vilela, Sofia Valente, Jorge Correia, Fernando Ferreira,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189144.

<https://doi.org/10.1016/j.bbcan.2024.189144>.

Abstract: The role of inflammation in cancer is a topic that has been investigated for many years. As established, inflammation emerges as a defining characteristic of cancer, presenting itself as a compelling target for therapeutic interventions in the realm of oncology. Controlling the tumor microenvironment (TME) has gained paramount significance,

modifying not only the effectiveness of immunotherapy but also modulating the outcomes and prognoses of standard chemotherapy and other anticancer treatments. Immunotherapy has surfaced as a central focus within the domain of tumor treatments, using immune checkpoint inhibitors as cancer therapy. Immune checkpoints and their influence on the tumor microenvironment dynamic are presently under investigation, aiming to ascertain their viability as therapeutic interventions across several cancer types. Cancer presents a significant challenge in humans and cats, where female breast cancer ranks as the most prevalent malignancy and feline mammary carcinoma stands as the third most frequent. This review seeks to summarize the data about the immune checkpoints cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), programmed cell death protein-1 (PD-1), V-domain Ig suppressor of T cell activation (VISTA), and T-cell immunoglobulin and mucin domain 3 (TIM-3) respective ongoing investigations as prospective targets for therapy for human breast cancer, while also outlining findings from studies reported on feline mammary carcinoma (FMC), strengthening the rationale for employing FMC as a representative model in the exploration of human breast cancer.

Keywords: Human breast cancer; Feline mammary carcinoma; Immune checkpoints; Immunotherapy; Comparative oncology

24COASNO119:

Title- Decoding PTEN regulation in clear cell renal cell carcinoma: Pathway for biomarker discovery and therapeutic insights,

Ângela Alves, Rui Medeiros, Ana Luísa Teixeira, Francisca Dias,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189165.

<https://doi.org/10.1016/j.bbcan.2024.189165>.

Abstract: Renal cell carcinoma is the most common adult renal solid tumor and the deadliest urological cancer, with clear cell renal cell carcinoma (ccRCC) being the predominant subtype. The PI3K/AKT signaling pathway assumes a central role in ccRCC tumorigenesis, wherein its abnormal activation confers a highly aggressive phenotype, leading to swift resistance against current therapies and distant metastasis. Thus, treatment resistance and disease progression remain a persistent clinical challenge in managing ccRCC effectively. PTEN, an antagonist of the PI3K/AKT signaling axis, emerges as a crucial factor in tumor progression, often experiencing loss or inactivation in ccRCC, thereby contributing to elevated mortality rates in patients. Therefore, understanding the molecular mechanisms underlying PTEN suppression in ccRCC tumors holds promise for the discovery of biomarkers and therapeutic targets, ultimately enhancing patient monitoring and treatment outcomes. The present review aims to summarize these mechanisms, emphasizing their potential prognostic, predictive, and therapeutic value in managing ccRCC.

Keywords: Clear cell renal cell carcinoma; PTEN; Biomarkers; Therapeutic targets

24COASNO120:

Title- Exploring the impact of flavin homeostasis on cancer cell metabolism,

Alessia Nisco, Maria Tolomeo, Mariafrancesca Scalise, Katia Zanier, Maria Barile,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189149.

<https://doi.org/10.1016/j.bbcan.2024.189149>.

Abstract: Flavins and their associated proteins have recently emerged as compelling players in the landscape of cancer biology. Flavins, encompassing flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), serve as coenzymes in a multitude of cellular processes, such as metabolism, apoptosis, and cell proliferation. Their involvement in oxidative phosphorylation, redox homeostasis, and enzymatic reactions has long been recognized. However, recent research has unveiled an extended role for flavins in the context of cancer. In parallel, riboflavin transporters (RFVTs), FAD synthase (FADS), and riboflavin kinase (RFK) have gained prominence in cancer research. These proteins, responsible for riboflavin uptake, FAD biosynthesis, and FMN generation, are integral components of the cellular machinery that governs flavin homeostasis. Dysregulation in the expression/function of these proteins has been associated with various cancers, underscoring their potential as diagnostic markers, therapeutic targets, and key determinants of cancer cell behavior. This review embarks on a comprehensive exploration of the multifaceted role of flavins and of the flavoproteins involved in nucleus-mitochondria crosstalk in cancer. We journey through the influence of flavins on cancer cell energetics, the modulation of RFVTs in malignant transformation, the diagnostic and prognostic significance of FADS, and the implications of RFK in drug resistance and apoptosis. This review also underscores the potential of these molecules and processes as targets for novel diagnostic and therapeutic strategies, offering new avenues for the battle against this relentless disease.

Keywords: cancer; Flavins; Flavoenzymes; Metabolism

24COASNO121:

Title- Metabolomic biomarkers of multiple myeloma: A systematic review,

Valeria G. Varzieva, Natalia V. Mesonzhnik, Irina S. Ilgisonis, Yuri N. Belenkov, Maria V. Kozhevnikova, Svetlana A. Appolonova,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189151

<https://doi.org/10.1016/j.bbcan.2024.189151>.

Abstract: Multiple myeloma (MM) is an incurable malignancy of clonal plasma cells. Various diagnostic methods are used in parallel to accurately determine stage and severity of the disease. Identifying a biomarker or a panel of biomarkers could enhance the quality of medical care that patients receive by adopting a more personalized approach. Metabolomics utilizes high-throughput analytical platforms to examine the levels and quantities of biochemical compounds in biosamples. The aim of this review was to conduct a systematic literature search for potential metabolic biomarkers that may aid in the diagnosis and prognosis of MM. The review was conducted in accordance with PRISMA recommendations and was registered in PROSPERO. The systematic search was performed in PubMed, CINAHL, SciFinder, Scopus, The Cochrane Library and Google Scholar. Studies were limited to those involving people with clinically diagnosed MM and healthy controls as comparators. Articles had to be published in English and had no restrictions on publication date or sample type. The quality of articles was assessed according to QUADOMICS criteria. A total of 709 articles were collected during the literature search. Of these, 436 were excluded based on their abstract, with 26 more removed after a thorough review of the full text. Finally, 16 articles were deemed relevant and were subjected to further analysis of their

data. A number of promising candidate biomarkers was discovered. Follow-up studies with large sample sizes are needed to determine their suitability for clinical applications.

Keywords: Multiple myeloma; Metabolomics; Biomarkers; Systematic review; Amino acids; Lipid metabolism; Prognosis; Diagnosis

24COASNO122:

Title- Targeting endothelial cell anergy to improve CAR T cell therapy for solid tumors,

Gabriela E. Wachholz, Parvin Akbari, Elisabeth J.M. Huijbers, Prachi Jalan, Judy R. van Beijnum, Arjan W. Griffioen,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189155.

<https://doi.org/10.1016/j.bbcan.2024.189155>

Abstract: Chimeric antigen receptor (CAR) T cell therapy presents significant results, especially for the treatment of hematologic malignancies. However, there are limitations and challenges to be overcome to achieve similar success for the treatment of solid tumors. These challenges involve selection of the target, infiltration into the tumor microenvironment and maintenance of functionality. The tumor vasculature is a major barrier for leukocytes to enter the tumor parenchyma. Due to the exposure of the vasculature to angiogenic growth factors during tumor progression, the endothelial cells become anergic to inflammatory cytokines, resulting in reduced leukocyte adhesion molecule expression. As such adhesion molecules are a prerequisite for leukocyte extravasation, endothelial cell anergy allows tumors to escape from endogenous immunity, as well as from cellular immunotherapies such as CAR T cells. Hence, overcoming endothelial cell anergy, e.g. through the administration of angiogenesis inhibitors, is believed to restore anti-tumor immunity. Concomitantly, both endogenous immune cells as well as cellular therapeutics such as CAR T cells can permeate into the tumor parenchyma. Here, we discuss how prior or concomitant treatment with an antiangiogenic drug can improve CAR T cell therapy, to become an attractive strategy for the treatment of solid tumors.

Keywords: Tumor vasculature; Tumor endothelial cells; Angiogenesis; Pro-angiogenic factors; Anti-angiogenic therapy; Immunotherapy

24COASNO123:

Title- Targeting the MHC-I endosomal-lysosomal trafficking pathway in cancer: From mechanism to immunotherapy,

Di Ye, Shuang Zhou, Xinyu Dai, Huanji Xu, Qiulin Tang, Huixi Huang, Feng Bi,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189161.

<https://doi.org/10.1016/j.bbcan.2024.189161>.

Abstract: Immune checkpoint blockade (ICB) therapy has achieved broad applicability and durable clinical responses across cancer types. However, the overall response rate remains suboptimal because some patients do not respond or develop drug resistance. The low infiltration of CD8⁺ cytotoxic T cells (CTLs) in the tumor microenvironment due to insufficient antigen presentation is closely related to the innate resistance to ICB. The duration and spatial distribution of major histocompatibility complex class I (MHC-I) expression on the cell surface is critical for the efficient presentation of endogenous tumor antigens and subsequent recognition and clearance by CTLs. Tumor cells reduce the surface

expression of MHC-I via multiple mechanisms to impair antigen presentation pathways and evade immunity and/or develop resistance to ICB therapy. As an increasing number of studies have focused on membrane MHC-I trafficking and degradation in tumor cells, which may impact the effectiveness of tumor immunotherapy. It is necessary to summarize the mechanism regulating membrane MHC-I translocation into the cytoplasm and degradation via the lysosome. We reviewed recent advances in the understanding of endosomal-lysosomal MHC-I transport and highlighted the means exploited by tumor cells to evade detection and clearance by CTLs. We also summarized new therapeutic strategies targeting these pathways to enhance classical ICB treatment and provide new avenues for optimizing cancer immunotherapy.

Keywords: Major histocompatibility complex class I; Endosomal-lysosomal trafficking; CD8+ cytotoxic T cells; Immune checkpoint blockade; Immune evasion

24COASNO124:

Title- *Helicobacter pylori* triggers inflammation and oncogenic transformation by perturbing the immune microenvironment,

Xiuping Wang, Guang Zhao, Shihe Shao, Yongliang Yao,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189139.

<https://doi.org/10.1016/j.bbcan.2024.189139>.

Abstract: The immune microenvironment plays a critical regulatory role in the pathogenesis of *Helicobacter pylori* (*H. pylori*). Understanding the mechanisms that drive the transition from chronic inflammation to cancer may provide new insights for early detection of gastric cancer. Although chronic inflammation is frequent in precancerous gastric conditions, the monitoring function of the inflammatory microenvironment in the progression from *H. pylori*-induced chronic inflammation to gastric cancer remains unclear. This literature review summarizes significant findings on how *H. pylori* triggers inflammatory responses and facilitates cancer development through the immune microenvironment. Furthermore, the implications for future research and clinical applications are also addressed. The review is divided into four main sections: inflammatory response and immune evasion mechanisms induced by *H. pylori*, immune dysregulation associated with gastric cancer, therapeutic implications, and future perspectives on *H. pylori*-induced gastric carcinogenesis with a focus on the immune microenvironment.

Keywords: *Helicobacter pylori*; Inflammation; Gastric cancer; Immune microenvironment

24COASNO125:

Title- *Leveraging preclinical models of metastatic breast cancer,*

Diego A. Pedroza, Yang Gao, Xiang H.-F. Zhang, Jeffrey M. Rosen,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189163.

<https://doi.org/10.1016/j.bbcan.2024.189163>.

Abstract: Women that present to the clinic with established breast cancer metastases have limited treatment options. Yet, the majority of preclinical studies are actually not directed at developing treatment regimens for established metastatic disease. In this review we will discuss the current state of preclinical macro-metastatic breast cancer models, including, but not limited to syngeneic GEMM, PDX and xenografts. Challenges within these models which

are often overlooked include fluorophore-immunogenic neoantigens, differences in experimental vs spontaneous metastasis and tumor heterogeneity. Furthermore, due to cell plasticity in the tumor immune microenvironment (TIME) of the metastatic landscape, the treatment efficacy of newly approved immune checkpoint blockade (ICB) may differ in metastatic sites as compared to primary localized tumors.

Keywords: Metastatic breast cancer; Preclinical mouse models; Tumor immune microenvironment; Immunotherapy; Chemotherapy

24COASNO126:

Title- Clinical and molecular markers guide the genetics of pheochromocytoma and paraganglioma,

Alberto Cascón, Mercedes Robledo,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189141.

<https://doi.org/10.1016/j.bbcan.2024.189141>.

Abstract: Over the past two decades, research into the genetic susceptibility behind pheochromocytoma and paraganglioma (PPGL) has surged, ranking them among the most heritable tumors. Massive sequencing combined with careful patient selection has so far identified more than twenty susceptibility genes, leading to an over-detection of variants of unknown significance (VUS) that require precise molecular markers to determine their pathogenic role. Moreover, some PPGL patients remain undiagnosed, possibly due to mutations in regulatory regions of already known genes or mutations in undiscovered genes. Accurate classification of VUS and identification of new genes require well-defined clinical and molecular markers that allow effective genetic diagnosis of most PPGLs.

Keywords: Pheochromocytoma; Paraganglioma; Omics; Molecular markers; Cancer genetics

24COASNO127:

Title- Schwann cells and enteric glial cells: Emerging stars in colorectal cancer,

Kexin He, Hao Wang, Ruixue Huo, Shu-Heng Jiang, Junli Xue,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189160.

<https://doi.org/10.1016/j.bbcan.2024.189160>.

Abstract: Cancer neuroscience, a promising field dedicated to exploring interactions between cancer and the nervous system, has attracted growing attention. The gastrointestinal tracts exhibit extensive innervation, notably characterized by intrinsic innervation. The gut harbors a substantial population of glial cells, including Schwann cells wrapping axons of neurons in the peripheral nervous system and enteric glial cells intricately associated with intrinsic innervation. Glial cells play a crucial role in maintaining the physiological functions of the intestine, encompassing nutrient absorption, barrier integrity, and immune modulation. Nevertheless, it has only been in recent times that the significance of glial cells within colorectal cancer (CRC) has begun to receive considerable attention. Emerging data suggests that glial cells in the gut contribute to the progression and metastasis of CRC, by interacting with cancer cells, influencing inflammation, and modulating the tumor microenvironment. Here, we summarize the significant roles of glial cells in the development and progression of CRC and discuss the latest technologies that can be integrated into this field for in-depth

exploration, as well as potential specific targeted strategies for future exploration to benefit patients.

Keywords: Enteric glia; Neuroglia; Colorectal carcinoma; Tumor microenvironment

24COASNO128:

Title- Molecular and immune pathobiology of human angiosarcoma,

Ryan Mao Heng Lim, Jing Yi Lee, Bavani Kannan, Tun Kiat Ko, Jason Yongsheng Chan, Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189159.

<https://doi.org/10.1016/j.bbcan.2024.189159>.

Abstract: Angiosarcoma is a rare endothelial-derived malignancy that is extremely diverse in anatomy, aetiology, molecular and immune characteristics. While novel therapeutic approaches incorporating targeted agents and immunotherapy have yielded significant improvements in patient outcomes across several cancers, their impact on angiosarcoma remains modest. Contributed by its heterogeneous nature, there is currently a lack of novel drug targets in this disease entity and no reliable biomarkers that predict response to conventional treatment. This review aims to examine the molecular and immune landscape of angiosarcoma in association with its aetiology, anatomical sites, prognosis and therapeutic options. We summarise current efforts to characterise angiosarcoma subtypes based on molecular and immune profiling. Finally, we highlight promising technologies such as single-cell spatial “omics” that may further our understanding of angiosarcoma and propose strategies that can be similarly applied for the study of other rare cancers.

Keywords: Rare cancers; Single cell sequencing; Spatial transcriptomics; Proteomics; Next generation sequencing

24COASNO129:

Title- Modulating macrophage-mediated programmed cell removal: An attractive strategy for cancer therapy,

Zhenzhen Li, Bingqian Han, Menghui Qi, Yinchao Li, Yongtao Duan, Yongfang Yao, Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189172.

<https://doi.org/10.1016/j.bbcan.2024.189172>.

Abstract: Macrophage-mediated programmed cell removal (PrCR) is crucial for the identification and elimination of needless cells that maintain tissue homeostasis. The efficacy of PrCR depends on the balance between pro-phagocytic “eat me” signals and anti-phagocytic “don't eat me” signals. Recently, a growing number of studies have shown that tumourigenesis and progression are closely associated with PrCR. In the tumour microenvironment, PrCR activated by the “eat me” signal is counterbalanced by the “don't eat me” signal of CD47/SIRP α , resulting in tumour immune escape. Therefore, targeting exciting “eat me” signalling while simultaneously suppressing “don't eat me” signalling and eventually inducing macrophages to produce effective PrCR will be a very attractive antitumour strategy. Here, we comprehensively review the functions of PrCR-activating signal molecules (CRT, PS, Annexin1, SLAMF7) and PrCR-inhibiting signal molecules (CD47/SIRP α , MHC-I/LILRB1, CD24/Siglec-10, SLAMF3, SLAMF4, PD-1/PD-L1, CD31, GD2, VCAM1), the interactions between these molecules, and Warburg effect. In addition, we highlight the molecular regulatory mechanisms that affect immune system function by

exciting or suppressing PrCR. Finally, we review the research advances in tumour therapy by activating PrCR and discuss the challenges and potential solutions to smooth the way for tumour treatment strategies that target PrCR.

Keywords: Programmed cell removal; Macrophages; Phagocytosis; cancer therapy

24COASNO130:

Title- Bioactive sphingolipids as emerging targets for signal transduction in cancer development,

Wentao Jia, Jiaying Yuan, Jinbo Zhang, Shu Li, Wanfu Lin, Binbin Cheng,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189176.

<https://doi.org/10.1016/j.bbcan.2024.189176>.

Abstract: Sphingolipids, crucial components of cellular membranes, play a vital role in maintaining cellular structure and signaling integrity. Disruptions in sphingolipid metabolism are increasingly implicated in cancer development. Key bioactive sphingolipids, such as ceramides, sphingosine-1-phosphate (S1P), ceramide-1-phosphate (C1P), and glycosphingolipids, profoundly impact tumor biology. They influence the behavior of tumor cells, stromal cells, and immune cells, affecting tumor aggressiveness, angiogenesis, immune modulation, and extracellular matrix remodeling. Furthermore, abnormal expression of sphingolipids and their metabolizing enzymes modulates the secretion of tumor-derived extracellular vesicles (TDEs), which are key players in creating an immunosuppressive tumor microenvironment, remodeling the extracellular matrix, and facilitating oncogenic signaling within in situ tumors and distant pre-metastatic niches (PMNs). Understanding the role of sphingolipids in the biogenesis of tumor-derived extracellular vesicles (TDEs) and their bioactive contents can pave the way for new biomarkers in cancer diagnosis and prognosis, ultimately enhancing comprehensive tumor treatment strategies.

Keywords: Sphingolipids; Ceramides; Tumor-derived extracellular vesicles; Gangliosides

24COASNO132:

Title- Evolving treatment landscape in thymic epithelial tumors: From mechanism to therapy,

Yehao Yang, Ying Yu, Yun Fan, Hui Li,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189145.

<https://doi.org/10.1016/j.bbcan.2024.189145>.

Abstract: Thymic epithelial tumors (TETs) are rare neoplasms of the anterior mediastinum that arise from thymic epithelial cells. Although surgery is the preferred treatment for resectable TETs, the options for unresectable or recurrent advanced-stage TETs are limited beyond platinum-based chemotherapy. The evolving landscape of TET treatments is marked by significant advancements in targeted therapies and immunotherapies, particularly with anti-angiogenic agents and immune checkpoint inhibitors (ICIs). While monotherapies demonstrated certain efficacy, the development of combination strategies is vital for improving patient outcomes. This review consolidates progress in anti-angiogenic therapies and ICIs, emphasizing the evolution of combination therapies of TETs. Furtherly, we particularly discuss new first-line strategies based on these advancements and emphasizes

exploring novel treatments like antibody-drug conjugates, immunomodulatory drugs and cytokine-based agents for TETs. Mechanistically, the molecular features of TETs integrated with clinical diagnosis and targeted therapy, and immunophenotyping of TETs along with its impact on the efficacy and safety of immunotherapy are discussed. Thus, this review systemizes the development in the treatment landscape of TETs, integrating the corresponding molecular and immune mechanisms, aiming to provide new references for the treatment of TETs.

Keywords: Thymic epithelial tumors; Molecular subtyping; Tumor immune microenvironment; Targeted therapy; Immunotherapy; Combination therapy

24COASNO133:

Title- Epigenetic changes associated with Bacillus Calmette-Guerin (BCG) treatment in bladder cancer,

Lucy C. Picard, Fenella J. Rich, Diane N. Kenwright, Aaron J. Stevens,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189123.

<https://doi.org/10.1016/j.bbcan.2024.189123>.

Abstract: Bacillus Calmette-Guérin (BCG) treatment for non-muscle invasive bladder cancer (NMIBC) is an established immunotherapeutic, however, a significant portion of patients do not respond to treatment. Despite extensive research into the therapeutic mechanism of BCG, gaps remain in our understanding. This review specifically focuses on the epigenomic contributions in the immune microenvironment, in the context of BCG treatment for NMIBC. We also summarise the current understanding of NMIBC epigenetic characteristics, and discuss how future targeted strategies for BCG therapy should incorporate epigenomic biomarkers in conjunction with genomic biomarkers.

Keywords: Bacillus Calmette-Guérin; BCG; Epigenetics; DNA methylation; Cancer; Bladder cancer; Immunology; Cancer diagnostics

24COASNO134:

Title- The neoantigens derived from transposable elements – A hidden treasure for cancer immunotherapy,

Zhixiang Hu, Xinyi Guo, Ziteng Li, Zhiqiang Meng, Shenglin Huang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189126.

<https://doi.org/10.1016/j.bbcan.2024.189126>.

Abstract: Neoantigen-based therapy is a promising approach that selectively activates the immune system of the host to recognize and eradicate cancer cells. Preliminary clinical trials have validated the feasibility, safety, and immunogenicity of personalized neoantigen-directed vaccines, enhancing their effectiveness and broad applicability in immunotherapy. While many ongoing oncological trials concentrate on neoantigens derived from mutations, these targets do not consistently provoke an immune response in all patients harboring the mutations. Additionally, tumors like ovarian cancer, which have a low tumor mutational burden (TMB), may be less amenable to mutation-based neoantigen therapies. Recent advancements in next-generation sequencing and bioinformatics have uncovered a rich source of neoantigens from non-canonical RNAs associated with transposable elements (TEs). Considering the substantial presence of TEs in the human genome and the proven

immunogenicity of TE-derived neoantigens in various tumor types, this review investigates the latest findings on TE-derived neoantigens, examining their clinical implications, challenges, and unique advantages in enhancing tumor immunotherapy.

Keywords: Transposable element; Neoantigen; Immunotherapy; Epigenetic remodeling

24COASNO135:

Title- Role of cell division cycle-associated proteins in regulating cell cycle and promoting tumor progression,

Zhaoyu Wang, Minshijing Ren, Wei Liu, Jin Wu, Peng Tang,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189147.
<https://doi.org/10.1016/j.bbcan.2024.189147>.

Abstract: The cell division cycle-associated protein (CDCA) family is important in regulating cell division. High CDCA expression is significantly linked to tumor development. This review summarizes clinical and basic studies on CDCAs conducted in recent decades. Furthermore, it systematically introduces the molecular expression and function, key mechanisms, cell cycle regulation, and roles of CDCAs in tumor development, cell proliferation, drug resistance, invasion, and metastasis. Additionally, it presents the latest research on tumor diagnosis, prognosis, and treatment targeting CDCAs. These findings are pivotal for further in-depth studies on the role of CDCAs in promoting tumor development and provide theoretical support for their application as new anti-tumor targets.

Keywords: CDCAs; Cell division cycle; Proliferation; Tumor progression; Diagnostic; Therapy

24COASNO136:

Title- Small non-coding RNAs and pancreatic ductal adenocarcinoma: Linking diagnosis, pathogenesis, drug resistance, and therapeutic potential,

Ryan N. Fuller, Ann Morcos, Joab Galvan Bustillos, David Caba Molina, Nathan R. Wall,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189153.
<https://doi.org/10.1016/j.bbcan.2024.189153>.

Abstract: This review comprehensively investigates the intricate interplay between small non-coding RNAs (sncRNAs) and pancreatic ductal adenocarcinoma (PDAC), a devastating malignancy with limited therapeutic options. Our analysis reveals the pivotal roles of sncRNAs in various facets of PDAC biology, spanning diagnosis, pathogenesis, drug resistance, and therapeutic strategies. sncRNAs have emerged as promising biomarkers for PDAC, demonstrating distinct expression profiles in diseased tissues. sncRNA differential expression patterns, often detectable in bodily fluids, hold potential for early and minimally invasive diagnostic approaches. Furthermore, sncRNAs exhibit intricate involvement in PDAC pathogenesis, regulating critical cellular processes such as proliferation, apoptosis, and metastasis. Additionally, mechanistic insights into sncRNA-mediated pathogenic pathways illuminate novel therapeutic targets and interventions. A significant focus of this review is dedicated to unraveling sncRNA mechanisms underlying drug resistance in PDAC. Understanding these mechanisms at the molecular level is imperative for devising strategies to overcome drug resistance. Exploring the therapeutic landscape, we discuss the potential of sncRNAs as therapeutic agents themselves as their ability to modulate gene expression with

high specificity renders them attractive candidates for targeted therapy. In summary, this review integrates current knowledge on sncRNAs in PDAC, offering a holistic perspective on their diagnostic, pathogenic, and therapeutic relevance. By elucidating the roles of sncRNAs in PDAC biology, this review provides valuable insights for the development of novel diagnostic tools and targeted therapeutic approaches, crucial for improving the prognosis of PDAC patients.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); Non-coding RNA (ncRNA); KRAS; Gemcitabine (gem); piRNA; snRNA; snoRNA; miRNA; Chemoresistance

24COASNO137:

Title- Macrophages and tertiary lymphoid structures as indicators of prognosis and therapeutic response in cancer patients,

Li Niu, Ting Chen, Aodan Yang, Xiwen Yan, Feng Jin, Ang Zheng, Xinyue Song,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189125.

<https://doi.org/10.1016/j.bbcan.2024.189125>.

Abstract: Tertiary lymphoid structures (TLS) can reflect cancer prognosis and clinical outcomes in various tumour tissues. Tumour-associated macrophages (TAMs) are indispensable components of the tumour microenvironment and play crucial roles in tumour development and immunotherapy. TAMs are associated with TLS induction via the modulation of the T cell response, which is a major component of the TLS. Despite their important roles in cancer immunology, the subtypes of TAMs that influence TLS and their correlation with prognosis are not completely understood. Here, we provide novel insights into the role of TAMs in regulating TLS formation. Furthermore, we discuss the prognostic value of these TAM subtypes and TLS, as well as the current antitumour therapies for inducing TLS. This study highlights an entirely new field of TLS regulation that may lead to the development of an innovative perspective on immunotherapy for cancer treatment.

Keywords: Tertiary lymphoid structures; Tumour-associated macrophages; Prognosis; Immunotherapy; Anticancer therapies

24COASNO138:

Title- Breaking through therapeutic barriers: Insights into CDK4/6 inhibition resistance in hormone receptor-positive metastatic breast cancer,

Yang Zheng, Zeyuan Zhang, Dan Li, Rong Huang, Shipeng Ning,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189174.

<https://doi.org/10.1016/j.bbcan.2024.189174>.

Abstract: The therapeutic landscape for hormone receptor-positive (HR+) breast carcinoma has undergone a significant transformation with the advent of cyclin-dependent kinase (CDK)4/6 inhibitors, particularly in combination with endocrine therapy as the primary regimen. However, the evolution of resistance mechanisms in response to CDK4/6 inhibitors in HR+ metastatic breast cancer presents substantial challenges in managing the disease. This review explores the diverse genomic landscape underlying resistance, including disturbances in the cell cycle, deviations in oncogenic signaling pathways, deficiencies in DNA damage response (DDR) mechanisms, and changes in the tumor microenvironment (TME). Additionally, it discusses potential strategies to surmount resistance, including advancements

in endocrine therapy, targeted inhibition of cell cycle components, suppression of AKT/mTOR activation, exploration of the FGFR pathway, utilization of antibody-drug conjugates (ADCs), and integration of immune checkpoint inhibitors (ICIs) with endocrine therapy and CDK4/6 inhibitors, providing pathways for enhancing patient outcomes amidst treatment challenges.

Keywords: CDK4/6 inhibitor; Endocrine therapy; Breast cancer; Resistance; Targeted therapy

24COASNO139:

Title- The cellular-centered view of hypoxia tumor microenvironment: Molecular mechanisms and therapeutic interventions,

Tian-Qi Zhang, Qian-Yu Lv, Wei-Lin Jin,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189137.

<https://doi.org/10.1016/j.bbcan.2024.189137>.

Abstract: Cancer is a profoundly dynamic, heterogeneous and aggressive systemic ailment, with a coordinated evolution of various types of tumor niches. Hypoxia plays an indispensable role in the tumor micro-ecosystem, drastically enhancing the plasticity of cancer cells, fibroblasts and immune cells and orchestrating intercellular communication. Hypoxia-induced signals, particularly hypoxia-inducible factor-1 α (HIF-1 α), drive the reprogramming of genetic, transcriptional, and proteomic profiles. This leads to a spectrum of interconnected processes, including augmented survival of cancer cells, evasion of immune surveillance, metabolic reprogramming, remodeling of the extracellular matrix, and the development of resistance to conventional therapeutic modalities like radiotherapy and chemotherapy. Here, we summarize the latest research on the multifaceted effects of hypoxia, where a multitude of cellular and non-cellular elements crosstalk with each other and co-evolve in a synergistic manner. Additionally, we investigate therapeutic approaches targeting hypoxic niche, encompassing hypoxia-activated prodrugs, HIF inhibitors, nanomedicines, and combination therapies. Finally, we discuss some of the issues to be addressed and highlight the potential of emerging technologies in the treatment of cancer.

Keywords: Cancer hallmarks; Hypoxia; Hypoxia-inducible factor 1 α ; Intercellular communication; Phenotype plasticity; Tumor microenvironment

24COASNO140:

Title- Thymic epithelial tumor medical treatment: A narrative review,

Qian Huang, Lingling Zhu, Yanyang Liu, Yan Zhang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189167.

<https://doi.org/10.1016/j.bbcan.2024.189167>.

Abstract: Thymic epithelial tumors, a malignancy originating in the thymus, are the commonest primary neoplasm of the anterior mediastinum; however, among thoracic tumors, they have a relatively low incidence rare. Thymic epithelial tumors can be broadly classified into thymic carcinoma and thymoma. As the cornerstone of thymic tumor treatment, surgery is the preferred treatment for early-stage patients, whereas, for advanced unresectable thymic tumors, the treatment is chemoradiotherapy. Targeted therapy is less effective for thymic tumors. Moreover, the use of immune checkpoint inhibitors as another effective treatment

option for advanced unresectable thymic tumors, particularly thymomas, is limited owing to immune-related adverse effects. Here, we have summarized all pertinent information regarding chemotherapy, especially preoperative neoadjuvant chemotherapy, and chemotherapy in combination with other treatments, and reviewed the effectiveness of these procedures and recent advances in targeted therapy. In addition, we analyzed the efficacy and safety of immune checkpoint inhibitors in thymic epithelial tumors, to provide a holistic treatment view.

Keywords: Thymic epithelial tumor; Chemotherapy; Immunotherapy; Targeted therapy

24COASNO141:

Title- Deciphering extracellular vesicles protein cargo in pancreatic cancer,

Yifan Hong, Jiaqi Yang, Xinyuan Liu, Sicong Huang, Tingbo Liang, Xueli Bai,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189142.

<https://doi.org/10.1016/j.bbcan.2024.189142>.

Abstract: Pancreatic ductal adenocarcinoma (PDAC) presents a significant therapeutic challenge as it is frequently diagnosed at advanced inoperable stages. Therefore, the development of a reliable screening tool for PDAC is crucial for effective prevention and treatment. Extracellular vesicles (EVs), characterized by their cup-shaped lipid bilayer structure and ubiquitous release from various cell types, offer notable advantages as an emerging liquid biopsy technique that is rapid, minimally invasive, easily sampled, and cost-effective. While EVs play a substantial role in cancer progression, EV proteins serve as direct mediators of diverse cellular behaviors and have immense potential as biomarkers for PDAC diagnosis and prognostication. This review provides an overview of EV proteins regarding PDAC diagnosis and prognostic implications as well as disease progression.

Keywords: Pancreatic cancer; Extracellular vesicle; Protein cargo; Biomarker; Chemoresistance; Liquid biopsy

24COASNO142:

Title- Histone deacetylase complexes: Structure, regulation and function,

Moges Dessale Asmamaw, Ang He, Li-Rong Zhang, Hong-Min Liu, Ya Gao,
Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189150.

<https://doi.org/10.1016/j.bbcan.2024.189150>.

Abstract: Histone deacetylases (HDACs) are key epigenetic regulators, and transcriptional complexes with deacetylase function are among the epigenetic corepressor complexes in the nucleus that target the epigenome. HDAC-bearing corepressor complexes such as the Sin3 complex, NuRD complex, CoREST complex, and SMRT/NCoR complex are common in biological systems. These complexes activate the otherwise inactive HDACs in a solitary state. HDAC complexes play vital roles in the regulation of key biological processes such as transcription, replication, and DNA repair. Moreover, deregulated HDAC complex function is implicated in human diseases including cancer. Therapeutic strategies targeting HDAC complexes are being sought actively. Thus, illustration of the nature and composition of HDAC complexes is vital to understanding the molecular basis of their functions under physiologic and pathologic conditions, and for designing targeted therapies. This review presents key aspects of large multiprotein HDAC-bearing complexes including their

structure, function, regulatory mechanisms, implication in disease development, and role in therapeutics.

Keywords: Histone deacetylase; Sin3 complex; NuRD complex; CoREST complex; SMRT/NCOR complex

24COASNO143:

Title- Molecular insights into the role of mixed lineage kinase 3 in cancer hallmarks,

Rong Ke, Sandeep Kumar, Sunil Kumar Singh, Ajay Rana, Basabi Rana,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189157.

<https://doi.org/10.1016/j.bbcan.2024.189157>.

Abstract: Mixed-lineage kinase 3 (MLK3) is a serine/threonine kinase of the MAPK Kinase kinase (MAP3K) family that plays critical roles in various biological processes, including cancer. Upon activation, MLK3 differentially activates downstream MAPKs, such as JNK, p38, and ERK. In addition, it regulates various non-canonical signaling pathways, such as β -catenin, AMPK, Pin1, and PAK1, to regulate cell proliferation, apoptosis, invasion, and metastasis. Recent studies have also uncovered other potentially diverse roles of MLK3 in malignancy, which include metabolic reprogramming, cancer-associated inflammation, and evasion of cancer-related immune surveillance. The role of MLK3 in cancer is complex and cancer-specific, and an understanding of its function at the molecular level aligned specifically with the cancer hallmarks will have profound therapeutic implications for diagnosing and treating MLK3-dependent cancers. This review summarizes the current knowledge about the effect of MLK3 on the hallmarks of cancer, providing insights into its potential as a promising anticancer drug target.

Keywords: MLK3; Cancer hallmarks; Metabolic reprogramming; Cancer-associated inflammation; Evasion of immune surveillance

24COASNO144:

Title- The role of nitric oxide synthase/ nitric oxide in infection-related cancers: Beyond antimicrobial activity,

Xudong Hu, Yueshuo Li, Ya Cao, Feng Shi, Li Shang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189156.

<https://doi.org/10.1016/j.bbcan.2024.189156>.

Abstract: As a free radical and endogenous effector molecule, mammalian endogenous nitric oxide (NO) is mainly derived from nitric oxide synthase (NOS) via L-arginine. NO participates in normal physiological reactions and provides immune responses to prevent the invasion of foreign bacteria. However, NO also has complex and contradictory biological effects. Abnormal NO signaling is involved in the progression of many diseases, such as cancer. In the past decades, cancer research has been closely linked with NOS/ NO, and many tumors with poor prognosis are associated with high expression of NOS. In this review, we give an overview of the biological effects of NOS/ NO. Then we focus on the oncogenic role of iNOS/ NO in HPV, HBV, EBV and H. pylori related tumors. In fact, there is growing evidence that iNOS could be used as a potential therapeutic target in cancer therapy. We emphasize that the pro-tumor effect of NOS/ NO is greater than the anti-tumor effect.

Keywords: Nitric oxide synthase; Nitric oxide; Oncogenic virus; Infection-related cancer

24COASNO145:**Title- T cell exhaustion in human cancers,**

Kuan Kang, Xin Lin, Pan Chen, Huai Liu, Feng Liu, Wei Xiong, Guiyuan Li, Mei Yi, Xiayu Li, Hui Wang, Bo Xiang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189162

<https://doi.org/10.1016/j.bbcan.2024.189162>.

Abstract: T cell exhaustion refers to a progressive state in which T cells become functionally impaired due to sustained antigenic stimulation, which is characterized by increased expression of immune inhibitory receptors, but weakened effector functions, reduced self-renewal capacity, altered epigenetics, transcriptional programme and metabolism. T cell exhaustion is one of the major causes leading to immune escape of cancer, creating an environment that supports tumor development and metastatic spread. In addition, T cell exhaustion plays a pivotal role to the efficacy of current immunotherapies for cancer. This review aims to provide a comprehensive view of roles of T cell exhaustion in cancer development and progression. We summarized the regulatory mechanisms that involved in T cell exhaustion, including transcription factors, epigenetic and metabolic reprogramming events, and various microenvironmental factors such as cytokines, microorganisms, and tumor autocrine substances. The paper also discussed the challenges posed by T cell exhaustion to cancer immunotherapies, including immune checkpoint blockade (ICB) therapies and chimeric antigen receptor T cell (CAR-T) therapy, highlighting the obstacles encountered in ICB therapies and CAR-T therapies due to T cell exhaustion. Finally, the article provides an overview of current therapeutic options aimed to reversing or alleviating T cell exhaustion in ICB and CAR-T therapies. These therapeutic approaches seek to overcome T cell exhaustion and enhance the effectiveness of immunotherapies in treating tumors.

Keywords: T cell exhaustion; Immune checkpoint; Immune evasion; Immune inhibitory receptors; Immunotherapy

24COASNO146:**Title- Molecular insights and clinical implications for the tumor suppressor role of SCFFBXW7 E3 ubiquitin ligase,**

Yihang Qi, Abdol-Hossein Rezaeian, Jingchao Wang, Daoyuan Huang, Hong Chen, Hiroyuki Inuzuka, Wenyi Wei,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189140.

<https://doi.org/10.1016/j.bbcan.2024.189140>.

Abstract: FBXW7 is one of the most well-characterized F-box proteins, serving as substrate receptor subunit of SKP1-CUL1-F-box (SCF) E3 ligase complexes. SCFFBXW7 is responsible for the degradation of various oncogenic proteins such as cyclin E, c-MYC, c-JUN, NOTCH, and MCL1. Therefore, FBXW7 functions largely as a major tumor suppressor. In keeping with this notion, FBXW7 gene mutations or downregulations have been found and reported in many types of malignant tumors, such as endometrial, colorectal, lung, and breast cancers, which facilitate the proliferation, invasion, migration, and drug resistance of cancer cells. Therefore, it is critical to review newly identified FBXW7 regulation and tumor suppressor function under physiological and pathological conditions to

develop effective strategies for the treatment of FBXW7-altered cancers. Since a growing body of evidence has revealed the tumor-suppressive activity and role of FBXW7, here, we updated FBXW7 upstream and downstream signaling including FBXW7 ubiquitin substrates, the multi-level FBXW7 regulatory mechanisms, and dysregulation of FBXW7 in cancer, and discussed promising cancer therapies targeting FBXW7 regulators and downstream effectors, to provide a comprehensive picture of FBXW7 and facilitate the study in this field.

Keywords: FBXW7; Ubiquitination; E3 ligase; Tumor suppressor; Cancer; Protein degradation

24COASNO147:

Title- Targeting transposable elements in cancer: developments and opportunities,

Zi-Yu Wang, Li-Ping Ge, Yang Ouyang, Xi Jin, Yi-Zhou Jiang,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189143.

<https://doi.org/10.1016/j.bbcan.2024.189143>.

Abstract: Transposable elements (TEs), comprising nearly 50% of the human genome, have transitioned from being perceived as “genomic junk” to key players in cancer progression. Contemporary research links TE regulatory disruptions with cancer development, underscoring their therapeutic potential. Advances in long-read sequencing, computational analytics, single-cell sequencing, proteomics, and CRISPR-Cas9 technologies have enriched our understanding of TE's clinical implications, notably their impact on genome architecture, gene regulation, and evolutionary processes. In cancer, TEs, including long interspersed element-1 (LINE-1), Alus, and long terminal repeat (LTR) elements, demonstrate altered patterns, influencing both tumorigenic and tumor-suppressive mechanisms. TE-derived nucleic acids and tumor antigens play critical roles in tumor immunity, bridging innate and adaptive responses. Given their central role in oncology, TE-targeted therapies, particularly through reverse transcriptase inhibitors and epigenetic modulators, represent a novel avenue in cancer treatment. Combining these TE-focused strategies with existing chemotherapy or immunotherapy regimens could enhance efficacy and offer a new dimension in cancer treatment. This review delves into recent TE detection advancements, explores their multifaceted roles in tumorigenesis and immune regulation, discusses emerging diagnostic and therapeutic approaches centered on TEs, and anticipates future directions in cancer research.

Keywords: Transposable elements; Cancer progression; Technology advance; Tumor immunity; Cancer therapy

24COASNO148:

Title- Lactic acid: The culprit behind the immunosuppressive microenvironment in hepatocellular carcinoma,

Xiaopei Peng, Zhenhu He, Dandan Yuan, Zhenguo Liu, Pengfei Rong,

Biochim Biophys Acta Rev Cancer . 2024 Sep;1879(5):189164.

<https://doi.org/10.1016/j.bbcan.2024.189164>.

Abstract: As a solid tumor with high glycolytic activity, hepatocellular carcinoma (HCC) produces excess lactic acid and increases extracellular acidity, thus forming a unique immunosuppressive microenvironment. L-lactate dehydrogenase (LDH) and

monocarboxylate transporters (MCTs) play a very important role in glycolysis. LDH is the key enzyme for lactic acid (LA) production, and MCT is responsible for the cellular import and export of LA. The synergistic effect of the two promotes the formation of an extracellular acidic microenvironment. In the acidic microenvironment of HCC, LA can not only promote the proliferation, survival, transport and angiogenesis of tumor cells but also have a strong impact on immune cells, ultimately leading to an inhibitory immune microenvironment. This article reviews the role of LA in HCC, especially its effect on immune cells, summarizes the progress of LDH and MCT-related drugs, and highlights the potential of immunotherapy targeting lactate combined with HCC.

Keywords: Hepatocellular carcinoma; Lactic acid; Monocarboxylate transporters; L-lactate dehydrogenase; Immunotherapy; cancer metabolism

24COASNO149:

Title- Untargeted lipidomics uncover hepatic lipid signatures induced by long-term exposure to polystyrene microplastics in vivo,

Yiming Ma, Yao Zeng, Mengqi Sun, Ruiyang Ding, Yang Yu, Junchao Duan,

Toxicol Lett . 2024 Oct:400:49-57

<https://doi.org/10.1016/j.toxlet.2024.07.914>.

Abstract: This study evaluated the effects of long-term polystyrene microplastics (PS-MPs) exposure on hepatic lipid metabolism in vivo by lipidomics. H&E staining showed long-term PS-MPs exposure could trigger the hepatic inflammatory cell infiltration and hepatic steatosis in SD rats, indicating long-term PS-MPs exposure caused hepatotoxicity. Lipidomics revealed that the concentrations of 8 lipid metabolites in the liver were altered after exposure to PS-MPs for both 6 and 12 months, namely LdMePE (16:0), LPC (18:1), LPC (18:2), LPC (20:4), PC (17:0_20:4), PC (18:2_22:6), PC (22:6_13:0) and SM (d18:1_24:0), which were all statistically different from the control groups detected at both time points after PS-MPs exposure, suggesting the mainly metabolic pathway was glycerolipid metabolism. This study showed chronic exposure to PS-MPs could cause hepatotoxicity and induce hepatic lipidomics alterations in vivo, which could provide an essential clue for the safety assessment of PS-MPs.

Keywords: Microplastics; Polystyrene; Lipidomics; Hepatic toxicity; Long-term exposure

24COASNO150:

Title- Ochratoxin A-induced DNA damage triggers G2 phase arrest via hMLH1-p53-p21 signaling pathway in human gastric epithelium immortalized cells in vitro,

Xin Jia, Yuan Wang, Jinfeng Cui, Yuehong Li, Wenxin Wu, Xianghong Zhang, Juan Wang,

Toxicol Lett . 2024 Oct:400:42-48

<https://doi.org/10.1016/j.toxlet.2024.08.005>.

Abstract: Ochratoxin A (OTA), as one of the most important and harmful mycotoxins, is classed as possible human carcinogen (group 2B). As we all know, DNA damage may cause genomic instability, cell cycle disorder, activation of DNA damage pathway, and stimulation of DNA repair system. To explore the roles of DNA damage repair protein (hMLH1) on OTA-induced G2 arrest, the DNA damage, chromosome aberration, cell cycle distribution and p53-p21 signaling pathway were evaluated after different time OTA exposure (6, 12, 24,

48 h) in immortalized human gastric epithelial cells (GES-1). Our results demonstrated that OTA exposure could trigger genomic instability, DNA damage and G2 phase arrest of GES-1 cells. At the same time, OTA treatment could increase the expression of hMLH1, and induce phosphorylation of the p53 protein, as well as p21, in response to DNA damage. Finally, inhibition of hMLH1 by siRNA effectively prevented the activation of p53-p21 signaling pathway and rescued the G2 arrest elicited by OTA. This study demonstrated that hMLH1-p53-p21 signaling pathway played an important role in DNA damage and G2 cell cycle arrest mediated by OTA in GES-1 cells.

Keywords: Ochratoxin A; G2 phase arrest; P53-p21; Signaling pathway; HMLH1 signaling pathway

24COASNO151:

Title- Benzene exposure and pediatric leukemia: From molecular clues to epidemiological insights,

Nancy Reynoso-Noverón, Miguel Santibáñez-Andrade, Juan Torres, Yanueh Bautista-Ocampo, Yesennia Sánchez-Pérez, Claudia M. García-Cuellar,

Toxicol Lett . 2024 Oct;400:113-120

<https://doi.org/10.1016/j.toxlet.2024.08.010>.

Abstract: According to the International Agency for Research on Cancer, leukemia ranks 14th in incidence and 11th in mortality and has a 5-year prevalence of approximately 1300,000 cases. Acute lymphoblastic leukemia is the most common hematopoietic syndrome in children during the first 5 years of life and represents approximately 75 % of all neoplasms among the pediatric population. The development of leukemia is strongly governed by DNA alterations that accelerate the growth of bone marrow cells. Currently, the most examined factor in pediatric leukemia is exposure to multiple compounds, such as hydrocarbons. Benzene, an aromatic hydrocarbon, can cause health challenges and is categorized as a carcinogen. Benzene toxicity has been widely associated with occupational exposure. Importantly, studies are underway to generate evidence that can provide clues regarding the risk of environmental benzene exposure and hematological problems in children. In this review, we summarize the existing evidence regarding the effects of benzene on pediatric leukemia, the associations between the effect of benzene on carcinogenesis, and the presence of certain molecular signatures in benzene-associated pediatric leukemia. Although there is sufficient evidence regarding the effects of benzene on carcinogenesis and leukemia, epidemiological research has primarily focused on occupational risk. Moreover, most benzene-induced molecular and cytogenetic alterations have been widely described in adults but not in the pediatric population. Thus, epidemiological efforts are crucial in the pediatric population in terms of epidemiological, clinical, and biomedical research.

Keywords: Benzene; Cancer; Pediatric leukemia; Molecular alterations; Epidemiology

24COASNO152:

Title- The short-term toxicity and metabolome of Benzene,

Frank Faulhammer, Bennard van Ravenzwaay, A. Robert Schnatter, Martijn Rooseboom, Hennicke Kamp, Burkhard Flick, Varun Giri, Saskia Sperber, Larry G. Higgins, Michael G. Penman, Neslihan Aygun Kocabas,

Toxicol Lett . 2024 Oct;400:58-70

<https://doi.org/10.1016/j.toxlet.2024.07.913>.

Abstract: A 14-day rat study with plasma metabolomics was conducted to evaluate the toxicity of Benzene. Wistar rats were orally administered Benzene daily at doses of 0, 300 and 1000 mg/kg bw. The study identified liver and kidneys as target organs of Benzene toxicity and found reductions in total white blood cells, absolute lymphocyte and eosinophil cell counts, and increased relative monocyte counts suggesting bone marrow as a target organ. The study also confirmed liver as a target organ using metabolomics, which showed indications of a stress reaction in rats and changes in metabolites suggestive of a metabolic disorder. The metabolomics investigations did not find any other toxicologically relevant modes of action, and the observed metabolite changes were not associated with markers for mitochondrial dysfunction. The study concludes that integration of omics technologies, such as metabolomics, in regulatory toxicity studies is possible, confirms existing knowledge and adds additional information that can be used for mechanistic understanding of observed toxicity.

Keywords: Metabolomics; Benzene; NAMs; 14-day studies; Toxicity

24COASNO153:

Title- New metabolites of 2-ethylhexyl salicylate in human urine after simulated real-life dermal sunscreen application,

Laura Kuhlmann, Thomas Göen, Julia Hiller,

Toxicol Lett . 2024 Oct;400:1-8.

<https://doi.org/10.1016/j.toxlet.2024.07.912>.

Abstract: 2-Ethylhexyl salicylate (EHS) is an organic UV filter which is used in sunscreen and other personal care products. The dermal uptake of EHS was studied in several dermal-exposure experiments. This paper aims to coherently assess urine samples after dermal exposure for the biomarkers EHS, 5OH-EHS, 5oxo-EHS, and 5cx-EPS as well as further biomarkers of interest, specifically 4OH-EHS, 4oxo-EHS, 2OH-EHS, and 6OH-EHS, for the first time. Samples from 18 participants of a pre-existing dermal exposure study under real-life conditions were reassessed using a comprehensive LC-MS/MS method. EHS accounts for 34 % of the cumulative excretion of all analytes within 24 h after exposure, followed by 5OH-EHS (19 %), 5cx-EPS (18 %), 4OH-EHS (15 %) and 5oxo-EHS (11 %). Further metabolites were only quantified in minor amounts. EHS as the most prominent excretion parameter in this study demonstrates the missing first-pass effect after dermal absorption. Furthermore, the applied novel comprehensive analytical procedure revealed oxidation at the ω (5cx-EPS, 6OH-EHS), $\omega-1$ (5OH-EHS, 5oxo-EHS), and $\omega-2$ positions (4OH-EHS, 4oxo-EHS) in the main chain of the ethylhexyl group as well as oxidation in the side chain (2OH-EHS). The presented data are of high relevance for a reliable toxicological risk assessment of dermal exposure to EHS.

Keywords: UV filter; Ethylhexyl salicylate; Human biomonitoring; Dermal exposure; Biomarker; LC-MS/MS

24COASNO154:**Title- Identification of serum metabolites associated with aristolochic acid nephropathy severity and insights into the underlying mechanism,**

Xinhui Liu, Yu Peng, Shanshan Wu, Xi Huang, Liwen Gao, Ruyu Deng, Jiandong Lu,
Toxicol Lett . 2024 Oct;400:24-34.

<https://doi.org/10.1016/j.toxlet.2024.08.001>.

Abstract: Aristolochic acid nephropathy (AAN) is a rapidly progressive kidney disease caused by medical or environmental exposure to aristolochic acids (AAs). This study aimed to identify serum metabolites associated with the severity of acute AAN and investigate the underlying mechanisms. Male C57BL/6 mice were treated with vehicle and 3 doses of aristolochic acid I (AAI) (1.25, 2.5, and 5 mg/kg/d) for 5 days by intraperitoneal injection. The results showed that AAI dose-dependently increased blood urea nitrogen (BUN) and serum creatinine (Scr) levels and renal pathological damage. Non-targeted metabolomics revealed that differences in serum metabolite profiles from controls increased with increasing AAI doses. Compared with the control group, 56 differentially expressed metabolites (DEMs) that could be affected by all 3 doses of AAI were obtained. We further identified 13 DEMs whose abundance significantly correlated with Scr and BUN levels and had good predictive values for diagnosing AAI exposure. Among the 13 DEMs, lipids and lipid-like molecules constituted the majority. Western blotting found that AAI suppressed renal fatty acid oxidation (FAO)-related enzymes expression. In conclusion, these findings provided evidence for developing biomarkers for monitoring AAs exposure and AAN diagnosis and indicated activation of FAO as a potential direction for the treatment of AAN.

Keywords: Aristolochic acid nephropathy; Aristolochic acid I; Nephrotoxicity; Non-targeted metabolomics; Fatty acid oxidation

24COASNO155:**Title- The role of BTG2/PI3K/AKT pathway-mediated microglial activation in T-2 toxin-induced neurotoxicity,**

Xiukuan Li, Jinyun Long, Chunyan Yao, Xiaoling Liu, Na Li, Yumeng Zhou, Dawei Li,
Guiyuan Xiong, Kexue Wang, Yuhui Hao, [et al.]

Toxicol Lett . 2024 Oct;400:81-92.

<https://doi.org/10.1016/j.toxlet.2024.08.003>.

Abstract: T-2 toxin is one of the mycotoxins widely distributed in human food and animal feed. Our recent work has shown that microglial activation may contribute to T-2 toxin-induced neurotoxicity. However, the molecular mechanisms involved need to be further clarified. To address this, we employed high-throughput transcriptome sequencing and found altered B cell translocation gene 2 (BTG2) expression levels in microglia following T-2 toxin treatment. It has been shown that altered BTG2 expression is involved in a range of neurological pathologies, but whether it's involved in the regulation of microglial activation is unclear. The aim of this study was to investigate the role of BTG2 in T-2 toxin-induced microglial activation. The results of animal experiments showed that T-2 toxin caused neurobehavioral disorders and promoted the expression of microglial BTG2 and pro-inflammatory activation of microglia in hippocampus and cortical, while microglial inhibitor

minocycline inhibited these changes. The results of in vitro experiments showed that T-2 toxin enhanced BTG2 expression and pro-inflammatory microglial activation, and inhibited BTG2 expression weakened T-2 toxin-induced microglial activation. Moreover, T-2 toxin activated PI3K/AKT and its downstream NF- κ B signaling pathway, which could be reversed after knock-down of BTG2 expression. Meanwhile, the PI3K inhibitor LY294002 also blocked this process. Therefore, BTG2 may be involved in T-2 toxin's ability to cause microglial activation through PI3K/AKT/NF- κ B pathway.

Keywords: Neuroinflammation; Microglia; BTG2; T-2 toxin; PI3K/AKT/NF- κ B pathway

24COASNO156:

Title- Diacylglycerol O-acyltransferase 1 inhibitor increases plasma alanine aminotransferase and aspartate aminotransferase activities via a shedding of the intestinal villi and an increase in intestinal permeability in rats,

Hideaki Yokoyama, Taku Masuyama, Yuki Tanaka, Taishi Shimazaki, Yuzo Yasui, Takuya Abe, Kouichi Yoshinari,

Toxicol Lett . 2024 Oct;400:16-23.

<https://doi.org/10.1016/j.toxlet.2024.08.004>.

Abstract: Diacylglycerol O-acyltransferase 1 (DGAT1) is a key enzyme for fat absorption step in the enterocytes. We previously reported that DGAT1 inhibition increased plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities in corn oil-loaded rats via protein kinase C (PKC) activation. In the present study, we investigated the mechanism with respect to the morphology and permeability of the small intestine, focusing on PKC function, and found that shortening of the intestinal villi and a decrease in the number of tdT-mediated dUTP-biotin nick-end labeling-positive cells in the tips of the villi were observed in the jejunum of DGAT1 inhibitor-treated rats loaded with corn oil. These results suggested that the tips of the villi were shed into the intestinal lumen. Next, fluorescein isothiocyanate-dextran, 110 kDa (FD-110) was administered intraduodenally to DGAT1 inhibitor-treated rats loaded with corn oil and we found that plasma FD-110 concentrations increased, indicating that the intestinal permeability to molecules with a molecular weight of approximately 110,000 (e.g., ALT and AST) increased. Taken together, the present results suggested that DGAT1 inhibitor-treatment in combination with corn oil causes ALT and AST to leak from the enterocytes into the blood by shedding the tips of the intestinal villi and increasing intestinal permeability.

Keywords: Protein kinase C; Height of the villi; Fluorescein isothiocyanate-dextran tight junction; Claudin; Zonula occludens-1

24COASNO157:

Title- Investigation of the role of NLRP3 inflammasome activation in new-generation BCR-ABL1 tyrosine kinase inhibitors-induced hepatotoxicity,

Ege Arzuk,

Toxicol Lett . 2024 Oct;400:71-80.

<https://doi.org/10.1016/j.toxlet.2024.08.007>.

Abstract: New generation BCR-ABL1 TKIs raised attention regarding their adverse effects, including hepatotoxicity. Indeed, bosutinib and nilotinib were associated with severe

hepatotoxicity compared with imatinib. Moreover, ponatinib has a boxed warning due to its potential to cause inflammatory liver damage, even death. However, the underlying mechanisms remain unclear. This study aimed to investigate the role of NLRP3 inflammasome activation in the underlying mechanism of ponatinib and bosutinib-induced hepatotoxicity. Furthermore, we determined the initiating event of this adverse outcome pathway by measuring the levels of reactive oxygen species as well as mitochondrial membrane potential in AML12 cells. The results demonstrated that ponatinib or bosutinib markedly inhibited cell viability and caused cytosolic membrane damage in cells. Moreover, drugs (IC₅₀) dramatically induced oxidative stress and mitochondrial membrane potential disruption, which led to upregulation in the expression levels of NLRP3 inflammasome-related genes and proteins, activation of NLRP3 inflammasomes, cleavage of gasdermin-D and caspase-1, secretion of IL-1 β , and cytosolic membrane damage. Furthermore, MCC950, a well-known specific inhibitor of NLRP3 inflammasome, and antioxidant N-acetyl-L-cysteine reversed the effects of drugs on the NLRP3 signaling pathway and cytosolic membranes. In summary, NLRP3 inflammasome activation is involved in new-generation BCR-ABL1 TKIs-triggered hepatotoxicity. Mitochondrial damage and reactive oxygen species accumulation were significant upstream signaling events in this signaling pathway.

Keywords: NLRP3 inflammasome; Hepatotoxicity; Ponatinib; Bosutinib; Caspase-1

24COASNO158:

Title- Influence of lead on cAMP-response element binding protein (CREB) and its implications in neurodegenerative disorders,

Sharal Alva, Aluru Parithathvi, P. Harshitha, Herman Sunil Dsouza,

Toxicol Lett . 2024 Oct;400:35-41.

<https://doi.org/10.1016/j.toxlet.2024.08.006>.

Abstract: Lead (Pb²⁺) is one of the most common toxic metals present in the environment, and lead exposure causes serious health issues in humans. Lead is widely used because of its physio-chemical characteristics, which include softness, corrosion resistance, ductility, and low conductivity. Lead affects almost all human organs, specifically the central nervous system. Lead neurotoxicity is connected to various neural pathways, including brain-derived neurotrophic factor (BDNF) protein level alterations, cyclic adenosine 3',5'-monophosphate (cAMP) response element binding protein (CREB) pathway changes, and N-methyl-D-aspartate receptors (NMDARs) changes. Lead primarily affects protein kinase C (PKC) through the replacement of calcium (Ca²⁺) ions in the CREB pathway. In this review, we have discussed the effect of lead on the CREB pathway and its implications on the nervous system, highlighting its effects on learning, synaptic plasticity, memory, and cognitive deficits. This review provides an understanding of the lead-induced alterations in the CREB pathway, which can lead to the future prospect of its use as a diagnostic marker as well as a therapeutic target for neurodegenerative disorders.

Keywords: Lead; CREB; Neurotoxicity; Cognitive impairment

24COASNO159:

Title- Human skin absorption of three plasticizers: Diisononyl-1,2-cyclohexanedicarboxylate (DINCH), di(2-ethylhexyl) terephthalate (DEHTP), and di(2-ethylhexyl) adipate (DEHA),

Nancy B. Hopf, Hélène P. De Luca, Holger M. Koch, Claudia Pälme, Aurélie Berthet, Elena Reale,

Toxicol Lett . 2024 Oct;400:104-112.

<https://doi.org/10.1016/j.toxlet.2024.08.002>.

Abstract: Alternative plasticizers such as diisononyl-1,2-cyclohexanedicarboxylate (DINCH), di(2-ethylhexyl) terephthalate (DEHTP), and di(2-ethylhexyl) adipate (DEHA) are progressively replacing phthalates in many consumer and professional products because of adverse effects on reproduction associated with some phthalates. Human exposures to these phthalate substitutes can occur through ingestion, skin absorption and inhalation. Skin uptake can lead to greater concentration at the target organs compared to ingestion because the skin exposure route bypasses the first-pass effect. Skin absorption studies are almost absent for these alternative plasticizers. We therefore wanted first, to characterize skin absorption of a mixture containing DINCH, DEHA and DEHTP in vitro using a flow-through diffusion cell system with ex vivo human skin, quantifying their respective monoester metabolites (mono-isononyl-cyclohexane-1,2-dicarboxylate (MINCH), mono-2-ethylhexyl adipate (MEHA), mono-2-ethylhexyl terephthalate (MEHTP), respectively); second, to validate these results by exposing five human volunteers to this mixture on their forearm and quantifying the corresponding urinary metabolites (including the monoesters and their oxidation products). Our study showed that two of these alternative plasticizers, DEHTP and DINCH, did not permeate skin showing as quantifiable metabolite levels in vitro and only traces of DEHA were quantified as its monoester metabolite, MEHA. Permeation coefficient (K_p) 0.06 and 55.8×10^{-7} cm/h for neat and emulsified DEHA, respectively, while the permeation rate (J) remained low for both (0.005 and 0.001 $\mu\text{g}/\text{cm}^2/\text{h}$, respectively). Participants exposed to a mixture of these three plasticizers did not have noteworthy urinary concentrations of their respective metabolites after 24 hours post-application. However, the alternative plasticizer mixture was completely absorbed after six hours post-application on the forearms of the human volunteers, and the urinary elimination curves showed a slight increase after 24 hours post-application. Further studies on skin absorption of these substances should follow the urinary elimination kinetics of these metabolites more than 24 hours post-application. We also recommend quantifying the parent compounds in the in vitro diffusion experiments.

Keywords: Endocrine chemicals; Skin uptake; Flow-through diffusion cell system; Alternative plasticizer; Biomonitoring; Toxicokinetics

24COASNO160:

Title- Trimethylamine N-oxide induces non-alcoholic fatty liver disease by activating the PERK,

Bingmo Yang, Guomin Tang, Mengting Wang, Yifan Ni, Jiali Tong, Chunyan Hu, Ming Zhou, Kailin Jiao, Zhong Li,

Toxicol Lett . 2024 Oct;400:93-103.

<https://doi.org/10.1016/j.toxlet.2024.08.009>.

Abstract: Nonalcoholic fatty liver disease (NAFLD) is a liver disease causing different progressive pathological changes. Trimethylamine N-oxide (TMAO), a product of gut microbiota metabolism, is a specific agonist of the protein kinase R-like endoplasmic reticulum kinase (PERK) pathway, one of the endoplasmic reticulum stress (ERS) pathways. TMAO has been associated with the occurrence and development of NAFLD based on the results of previous studies, but whether the simple consumption of TMAO can directly induce NAFLD and its underlying mechanism remain unclear. To investigate this question, we constructed an animal model in which adult male zebrafish were fed a controlled diet containing 1 % or 3 % TMAO for 20 weeks. Eventually, we observed that TMAO caused lipid accumulation, inflammatory infiltration, liver injury and liver fibrosis in zebrafish livers; meanwhile, the PERK signaling pathway was activated in the zebrafish livers. This finding was further confirmed in HepG2 cells and hepatic stellate cells models. In conclusion, this study found that TMAO directly induced different pathological states of NAFLD in zebrafish liver, and the activation of PERK pathway is an important mechanism, which may provide crucial strategies for the diagnosis and treatment of NAFLD.

Keywords: Trimethylamine N-oxide; Non-alcoholic fatty liver disease; Endoplasmic reticulum stress

24COASNO161:

Title- Online SPE-LC-MS-MS method for eight hydroxylated metabolites of polycyclic aromatic hydrocarbons in urine and determination of optimal sampling time after firefighter training,

Marie Frederiksen, Simon Pelle Jensen, Maria Helena Guerra Andersen, Ulla Vogel, Anne Thoustrup Saber,

Toxicol Lett . 2024 Oct;400:9-15.

<https://doi.org/10.1016/j.toxlet.2024.07.005>.

Abstract: Polycyclic aromatic compounds (PAHs) are formed during incomplete combustion and firefighters are inadvertently at risk of being exposed to these and other hazardous compounds. Exposure to PAHs is often estimated by measuring their hydroxylated metabolites (OH-PAH) in urine. Here, an online-SPE LC-MS-MS method was set up for eight OH-PAHs thus increasing sample throughput and minimizing manual handling. The method was validated over a 5-month period and showed good reproducibility with intra- and inter-day variation of 2.4–8.1 % and 1.6–6.5 %, respectively, of low-level samples and accuracy (91.6–104.8 %) for a standard reference material. The method was applied to urine samples from conscripts training to become firefighters to determine the optimal sampling time for this training activity before a large intervention study. In total, six conscripts sampled urine 6–8 times over a 40-hr period during a 3-day training course. All eight metabolites were detected in ≥ 97 % of the samples and showed peak excretion 4–6 hrs after the training corresponding to 8–10 hrs after first exposure. Samples taken the morning after the exercise contained low levels of most metabolites. Consequently, 4–6 hrs post exposure is recommended as the optimal sampling time for quantification of PAH exposure and monitoring of potential differences in exposure.

Keywords: OH-PAH; PAH; Exposure; Biomonitoring; Naphthol; Hydroxypyrene

24COASNO162:

Title- Resveratrol suppresses liver cancer progression by downregulating AKR1C3: targeting HCC with HSA nanomaterial as a carrier to enhance therapeutic efficacy

Ying Wang, Longxiang Su, Zhansheng Hu, Shuang Peng, Na Li, Haiyan Fu, Baoquan Wang & Huiping Wu

Apoptosis . 2024 Oct;29(9-10):1429-1453.

doi: <https://doi.org/10.1007/s10495-024-01995-w>

Abstract: The enzyme AKR1C3 plays a crucial role in hormone and drug metabolism and is associated with abnormal expression in liver cancer, leading to tumor progression and poor prognosis. Nanoparticles modified with HSA can modulate the tumor microenvironment by enhancing photodynamic therapy to induce apoptosis in tumor cells and alleviate hypoxia. Therefore, exploring the potential regulatory mechanisms of resveratrol on AKR1C3 through the construction of HSA-RSV NPs carriers holds significant theoretical and clinical implications for the treatment of liver cancer. The aim of this study is to investigate the targeted regulation of AKR1C3 expression through the loading of resveratrol (RSV) on nanomaterials HSA-RSV NPs (Nanoparticles) in order to alleviate tumor hypoxia and inhibit the progression of hepatocellular carcinoma (HCC), and to explore its molecular mechanism. PubChem database and PharmMapper server were used to screen the target genes of RSV. HCC-related differentially expressed genes (DEGs) were analyzed through the GEO dataset, and relevant genes were retrieved from the GeneCards database, resulting in the intersection of the three to obtain candidate DEGs. GO and KEGG enrichment analyses were performed on the candidate DEGs to analyze the potential cellular functions and molecular signaling pathways affected by the main target genes. The cytohubba plugin was used to screen the top 10 target genes ranked by Degree and further intersected the results of LASSO and Random Forest (RF) to obtain hub genes. The expression analysis of hub genes and the prediction of malignant tumor prognosis were conducted. Furthermore, a pharmacophore model was constructed using PharmMapper. Molecular docking simulations were performed using AutoDockTools 1.5.6 software, and ROC curve analysis was performed to determine the core target. In vitro cell experiments were carried out by selecting appropriate HCC cell lines, treating HCC cells with different concentrations of RSV, or silencing or overexpressing AKR1C3 using lentivirus. CCK-8, clone formation, flow cytometry, scratch experiment, and Transwell were used to measure cancer cell viability, proliferation, migration, invasion, and apoptosis, respectively. Cellular oxygen consumption rate was analyzed using the Seahorse XF24 analyzer. HSA-RSV NPs were prepared, and their characterization and cytotoxicity were evaluated. The biological functional changes of HCC cells after treatment were detected. An HCC subcutaneous xenograft model was established in mice using HepG2 cell lines. HSA-RSV NPs were injected via the tail vein, with a control group set, to observe changes in tumor growth, tumor targeting of NPs, and biological safety. TUNEL, Ki67, and APC-hypoxia probe staining were performed on excised tumor tissue to detect tumor cell proliferation, apoptosis, and hypoxia. Lentivirus was used to silence or overexpress AKR1C3 simultaneously with the injection of HSA-RSV NPs via the tail vein to assess the impact of

AKR1C3 on the regulation of HSA-RSV NPs in HCC progression. Bioinformatics analysis revealed that AKR1C3 is an important target gene involved in the regulation of HCC by RSV, which is associated with the prognosis of HCC patients and upregulated in expression. In vitro cell experiments showed that RSV significantly inhibits the respiratory metabolism of HCC cells, suppressing their proliferation, migration, and invasion and promoting apoptosis. Silencing AKR1C3 further enhances the toxicity of RSV towards HCC cells. The characterization and cytotoxicity experiments of nanomaterials demonstrated the successful construction of HSA-RSV NPs, which exhibited stronger inhibitory effects on HCC cells. In vivo, animal experiments further confirmed that targeted downregulation of AKR1C3 by HSA-RSV NPs suppresses the progression of HCC and tumor hypoxia while exhibiting tumor targeting and biological safety. Targeted downregulation of AKR1C3 by HSA-RSV NPs can alleviate HCC tumor hypoxia and inhibit the progression of HCC.

24COASNO163:

Title- SNCA is a potential therapeutic target for COVID-19 infection in diffuse large B-cell lymphoma patients **Access Link**

Can Chen, Yun Li, Yiwei Li, Zhenzhen Chen, Pengfei Shi, Yaping Xie & Shenxian Qian
Apoptosis 2024 Oct;29(9-10):1454-1465.

doi: <https://doi.org/10.1007/s10495-024-01996-9>.

Abstract: Cuprotosis related genes (CRGs) have been proved to be potential therapeutic targets for coronavirus disease 2019 (COVID-19) and cancer, but their immune and molecular mechanisms in COVID-19 infection in Diffuse Large B-cell Lymphoma (DLBC/DLBCL) patients are rarely reported. Our research goal is first to screen the key CRGs in COVID-19 through univariate analysis, machine learning and clinical samples. Secondly, we determined the expression and prognostic role of key CRGs in DLBCL through pan-cancer analysis. We validated the expression levels and prognosis using multiple datasets and independent clinical samples and validated the functional role of key CRGs in DLBCL through cell experiments. Finally, we validated the expression levels of CRGs in COVID-19 infected DLBCL patients samples and analyzed their common pathways in COVID-19 and DLBCL. The results show that synuclein-alpha (SNCA) is the common key differential gene of COVID-19 and DLBCL. DLBCL cells confirm that high expression of SNCA can significantly promote cell apoptosis and significantly inhibit the cycle progression of DLBCL. High expression of SNCA can regulate the binding of major histocompatibility complexes (MHCs) and T cell receptor (TCR) by regulating immune infiltration of Dendritic cells, effectively enhancing T cell-mediated anti-tumor immunity and clearing cancer cells. In conclusion, SNCA may be a potential therapeutic target for COVID-19 infection in DLBCL patients. Our study provides a theoretical basis for improving the clinical treatment of COVID-19 infection in DLBCL patients.

24COASNO164:

Title- Metabolic Heterogeneity and Potential Immunotherapeutic Responses Revealed by Single-Cell Transcriptomics of Breast Cancer **Access Link**

Shicong Tang, Qing Wang, Ke Sun, Ying Song, Rui Liu, Xin Tan, Huimeng Li, Yafeng Lv, Fuying Yang, Jiawen Zhao, ... [et al.]

Apoptosis . 2024 Oct;29(9-10):1466-1482.

doi: <https://doi.org/10.1007/s10495-024-01952-7>.

Abstract: Background:Breast cancer (BC) exhibits remarkable heterogeneity. However, the transcriptomic heterogeneity of BC at the single-cell level has not been fully elucidated.

Methods: We acquired BC samples from 14 patients. Single-cell RNA sequencing (scRNA-seq), bioinformatic analyses, along with immunohistochemistry (IHC) and immunofluorescence (IF) assays were carried out. Results: According to the scRNA-seq results, 10 different cell types were identified. We found that Cancer-Associated Fibroblasts (CAFs) exhibited distinct biological functions and may promote resistance to therapy. Metabolic analysis of tumor cells revealed heterogeneity in glycolysis, gluconeogenesis, and fatty acid synthetase reprogramming, which led to chemotherapy resistance. Furthermore, patients with multiple metastases and progression were predicted to benefit from immunotherapy based on a heterogeneity analysis of T cells and tumor cells. Conclusions: Our findings provide a comprehensive understanding of the heterogeneity of BC, provide comprehensive insight into the correlation between cancer metabolism and chemotherapy resistance, and enable the prediction of immunotherapy responses based on T-cell heterogeneity.

24COASNO165:

Title- Kynurenic acid protects against ischemia/reperfusion injury by modulating apoptosis in cardiomyocytes Access Link

Renáta Gáspár, Dóra Nógrádi-Halmi, Virág Demján, Petra Diószegi, Nóra Igaz, Anna Vincze, Márton Pipicz, Mónika Kiricsi, László Vécsei & Tamás Csont

Apoptosis. 2024 Oct;29(9-10):1483-1498.

doi: <https://doi.org/10.1007/s10495-024-02004-w>.

Abstract: Acute myocardial infarction, often associated with ischemia/reperfusion injury (I/R), is a leading cause of death worldwide. Although the endogenous tryptophan metabolite kynurenic acid (KYNA) has been shown to exert protection against I/R injury, its mechanism of action at the cellular and molecular level is not well understood yet. Therefore, we examined the potential involvement of antiapoptotic mechanisms, as well as N-methyl-D-aspartate (NMDA) receptor modulation in the protective effect of KYNA in cardiac cells exposed to simulated I/R (SI/R). KYNA was shown to attenuate cell death induced by SI/R dose-dependently in H9c2 cells or primary rat cardiomyocytes. Analysis of morphological and molecular markers of apoptosis (i.e., membrane blebbing, apoptotic nuclear morphology, DNA double-strand breaks, activation of caspases) revealed considerably increased apoptotic activity in cardiac cells undergoing SI/R. The investigated apoptotic markers were substantially improved by treatment with the cytoprotective dose of KYNA. Although cardiac cells were shown to express NMDA receptors, another NMDA antagonist structurally different from KYNA was unable to protect against SI/R-induced cell death. Our findings provide evidence that the protective effect of KYNA against SI/R-induced cardiac cell injury

involves antiapoptotic mechanisms, that seem to evoke independently of NMDA receptor signaling.

24COASNO166:

Title- Targeting PAX8 sensitizes ovarian cancer cells to ferroptosis by inhibiting glutathione synthesis Access Link

Yanlin Luo, Xiaoli Liu, Yibing Chen, Qing Tang, Chengsi He, Xinyi Ding, Jiachun Hu, Zheyong Cai, Xiang Li, Hailing Qiao, ... [et al.]

Apoptosis. 2024 Oct;29(9-10):1499-1514.

doi: <https://doi.org/10.1007/s10495-024-01985-y>.

Abstract: Ovarian cancer is a malignant tumor originating from the ovary, characterized by its high mortality rate and propensity for recurrence. In some patients, especially those with recurrent cancer, conventional treatments such as surgical resection or standard chemotherapy yield suboptimal results. Consequently, there is an urgent need for novel anti-cancer therapeutic strategies. Ferroptosis is a distinct form of cell death separate from apoptosis. Ferroptosis inducers have demonstrated promising potential in the treatment of ovarian cancer, with evidence indicating their ability to enhance ovarian cancer cell sensitivity to cisplatin. However, resistance of cancer cells to ferroptosis still remains an inevitable challenge. Here, we analyzed genome-scale CRISPR-Cas9 loss-of function screens and identified PAX8 as a ferroptosis resistance protein in ovarian cancer. We identified PAX8 as a susceptibility gene in GPX4-dependent ovarian cancer. Depletion of PAX8 rendered GPX4-dependent ovarian cancer cells significantly more sensitive to GPX4 inhibitors. Additionally, we found that PAX8 inhibited ferroptosis in ovarian cancer cells. Combined treatment with a PAX8 inhibitor and RSL3 suppressed ovarian cancer cell growth, induced ferroptosis, and was validated in a xenograft mouse model. Further exploration of the molecular mechanisms underlying PAX8 inhibition of ferroptosis mutations revealed upregulation of glutamate-cysteine ligase catalytic subunit (GCLC) expression. GCLC mediated the ferroptosis resistance induced by PAX8 in ovarian cancer. In conclusion, our study underscores the pivotal role of PAX8 as a therapeutic target in GPX4-dependent ovarian cancer. The combination of PAX8 inhibitors such as losartan and captopril with ferroptosis inducers represents a promising new approach for ovarian cancer therapy.

24COASNO167:

Title- Strong activation of p53 by actinomycin D and nutlin-3a overcomes the resistance of cancer cells to the pro-apoptotic activity of the FAS ligand Access Link

Barbara Łasut-Szyska, Agnieszka Gdowicz-Kłosok, Małgorzata Krześniak, Magdalena Głowala-Kosińska, Agnieszka Będzińska & Marek Rusin

Apoptosis . 2024 Oct;29(9-10):1515-1528.

doi: <https://doi.org/10.1007/s10495-024-02000-0>.

Abstract: The FAS ligand (FASLG) is expressed on lymphocytes, which employ it to activate death receptors on target cells. Cancer cells are generally resistant to apoptosis triggered by FASLG. In this work, we found a way to circumvent this resistance by treatment with actinomycin D (ActD) and nutlin-3a (Nut3a). We selected this drug combination based

on our transcriptomic data showing strong activation of proapoptotic genes, including those for receptor-mediated apoptosis, in cells exposed to actinomycin D and nutlin-3a. To test our hypothesis, we pre-exposed cancer cell lines to this drug combination for 45 h and then treated them with recombinant FASLG. This almost instantaneously killed most cells. Actinomycin D and nutlin-3a strongly cooperated in the sensitization because the effect of the drugs acting solo was not as spectacular as the drug combination, which together with FASLG killed more than 99% of cells. Based on the caspase activation pattern (caspase-8, caspase-9, caspase-10), we conclude that both extrinsic and intrinsic pro-apoptotic pathways were engaged. In engineered p53-deficient cells, this pro-apoptotic effect was completely abrogated. Therefore, the combination of ActD + Nut3a activates p53 in an extraordinary way, which overcomes the resistance of cancer cells to apoptosis triggered by FASLG. Interestingly, other combinations of drugs, e.g., etoposide + nutlin-3a, actinomycin D + RG7112, and actinomycin D + idasanutlin had a similar effect. Moreover, normal human fibroblasts are less sensitive to death induced by ActD + Nut3a + FASLG. Our findings create the opportunity to revive the abandoned attempts of cancer immunotherapy employing the recombinant FAS ligand.

24COASNO168:**Title- FAT10 induces immune suppression by upregulating PD-L1 expression in hepatocellular carcinoma**

Qingbin Wang, Wenliang Tan, Ziyu Zhang, Qiuju Chen, Zhiqin Xie, Lei Yang, Chenwei Tang,

Apoptosis . 2024 Oct;29(9-10):1529-1545.

doi: <https://doi.org/10.1007/s10495-024-01982-1>.

Abstract: The upregulation of programmed death ligand 1 (PD-L1) plays a crucial role in facilitating cancer cells to evade immune surveillance through immunosuppression. However, the precise regulatory mechanisms of PD-L1 in hepatocellular carcinoma (HCC) remain undefined. The correlation between PD-L1 and ubiquitin-like molecules (UBLs) was studied using sequencing data from 20 HCC patients in our center, combined with TCGA data. Specifically, the association between FAT10 and PD-L1 was further validated at both the protein and mRNA levels in HCC tissues from our center. Subsequently, the effect of FAT10 on tumor progression and immune suppression was examined through both in vivo and in vitro experiments. Utilizing sequencing data, qPCR, and Western blotting assays, we confirmed that FAT10 was highly expressed in HCC tissues and positively correlated with PD-L1 expression. Additionally, in vitro experiments demonstrated that the overexpression of FAT10 fostered the proliferation, migration, and invasion of HCC cells. Furthermore, the overexpression of FAT10 in HCC cells led to an increase in PD-L1 expression, resulting in the inhibition of T cell proliferation and the enhancement of HCC cell resistance to T cell-mediated cytotoxicity. Moreover, in vivo experiments utilizing the C57BL/6 mouse model revealed that overexpression of FAT10 effectively suppressed the infiltration of CD8 + GZMB + and CD8 + Ki67 + T cells, as well as reduced serum levels of TNF- α and IFN- γ . Mechanistically, we further identified that FAT10 upregulates PD-L1 expression via activating the PI3K/AKT/mTOR pathway, but not in a ubiquitin-like modification. In

conclusion, our findings indicate that FAT10 promotes immune evasion of HCC via upregulating PD-L1 expression, suggesting its potential as a novel target to enhance the efficiency of immunotherapy in HCC.

24COASNO169:**Title- Targeting PNPO to suppress tumor growth via inhibiting autophagic flux and to reverse paclitaxel resistance in ovarian cancer**

Xin Li, Wencai Guan, Huiqiang Liu, Jia Yuan, Fanchen Wang, Bin Guan, Junyu Chen, Qi Lu, Lingyun Zhang & Guoxiong Xu

Apoptosis . 2024 Oct;29(9-10):1546-1563.

doi: <https://doi.org/10.1007/s10495-024-01956-3>.

Abstract: Our previous study showed that pyridoxine 5'-phosphate oxidase (PNPO) is a tissue biomarker of ovarian cancer (OC) and has a prognostic implication but detailed mechanisms remain unclear. The current study focused on PNPO-regulated lysosome/autophagy-mediated cellular processes and the potential role of PNPO in chemoresistance. We found that PNPO was overexpressed in OC cells and was a prognostic factor in OC patients. PNPO significantly promoted cell proliferation via the regulation of cyclin B1 and phosphorylated CDK1 and shortened the G2M phase in a cell cycle. Overexpressed PNPO enhanced the biogenesis and perinuclear distribution of lysosomes, promoting the degradation of autophagosomes and boosting the autophagic flux. Further, an autolysosome marker LAMP2 was upregulated in OC cells. Silencing LAMP2 suppressed cell growth and induced cell apoptosis. LAMP2-siRNA blocked PNPO action in OC cells, indicating that the function of PNPO on cellular processes was mediated by LAMP2. These data suggest the existence of the PNPO-LAMP2 axis. Moreover, silencing PNPO suppressed xenographic tumor formation. Chloroquine counteracted the promotion effect of PNPO on autophagic flux and inhibited OC cell survival, facilitating the inhibitory effect of PNPO-shRNA on tumor growth in vivo. Finally, PNPO was overexpressed in paclitaxel-resistant OC cells. PNPO-siRNA enhanced paclitaxel sensitivity in vitro and in vivo. In conclusion, PNPO has a regulatory effect on lysosomal biogenesis that in turn promotes autophagic flux, leading to OC cell proliferation, and tumor formation, and is a paclitaxel-resistant factor. These data imply a potential application by targeting PNPO to suppress tumor growth and reverse PTX resistance in OC.

24COASNO170:**Title- The resistance to anoikis, mediated by Spp1, and the evasion of immune surveillance facilitate the invasion and metastasis of hepatocellular carcinoma**

Zhengwei Zhang, Xiaoning Chen, Yapeng Li, Feng Zhang, Zhen Quan, Zhuo Wang, Yang Yang, Wei Si, Yuting Xiong, Jiaming Ju, Yu Bian & Shibo Sun

Apoptosis . 2024 Oct;29(9-10):1564-1583.

doi: <https://doi.org/10.1007/s10495-024-01994-x>.

Abstract: Anoikis-Related Genes (ARGs) lead to the organism manifesting resistance to anoikis and are associated with unfavorable prognostic outcomes across various malignancies. Therefore, it is crucial to identify the pivotal target genes related to anoikis in

HCC .We found that ARGs were significantly correlated with prognosis and immune responses in HCC. The core gene, SPP1, notably promoted anoikis resistance and metastasis in HCC through both in vivo and in vitro studies. The PI3K-Akt-mTOR pathway played a critical role in anoikis suppression within HCC contexts. Our research unveiled SPP1's role in enhancing PKC α phosphorylation, which in turn activated the PI3K-Akt-mTOR cascade. Additionally, SPP1 was identified as a key regulator of MDSCs and Tregs migration, directly affecting their immunosuppressive capabilities. These findings indicate that in HCC, SPP1 promoted anoikis resistance and facilitated immune evasion by modulating MDSCs and Tregs.

24COASNO171:**Title- The landscape of programmed cell death-related lncRNAs in Alzheimer's disease and Parkinson's disease**

Ning Zhao, Junyi Wang, Shan Huang, Jingyu Zhang, Jin Bao, Haisen Ni, Xinhao Gao & Chunlong Zhang

Apoptosis . 2024 Oct;29(9-10):1584-1599.

doi: <https://doi.org/10.1007/s10495-024-01984-z>.

Abstract: This study delivers a thorough analysis of long non-coding RNAs (lncRNAs) in regulating programmed cell death (PCD), vital for neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD). We propose a new framework PCDLnc, and identified 20 significant lncRNAs, including *HEIH*, *SNHG15*, and *SNHG5*, associated with PCD gene sets, which were known for roles in proliferation and apoptosis in neurodegenerative diseases. By using GREAT software, we identified regulatory functions of top lncRNAs in different neurodegenerative diseases. Moreover, lncRNAs cis-regulated mRNAs linked to neurodegeneration, including *JAK2*, *AKT1*, *EGFR*, *CDC42*, *SNCA*, and *ADIPOQ*, highlighting their therapeutic potential in neurodegenerative diseases. A further exploration into the differential expression of mRNA identified by PCDLnc revealed a role in apoptosis, ferroptosis and autophagy. Additionally, protein-protein interaction (PPI) network analysis exposed abnormal interactions among key genes, despite their consistent expression levels between disease and normal samples. The randomforest model effectively distinguished between disease samples, indicating a high level of accuracy. Shared gene subsets in AD and PD might serve as potential biomarkers, along with disease-specific gene sets. Besides, we also found the strong relationship between AD and immune infiltration. This research highlights the role of lncRNAs and their associated genes in PCD in neurodegenerative diseases, offering potential therapeutic targets and diagnostic markers for future study and clinical application.

24COASNO172:**Title- TNF- α and RPLP0 drive the apoptosis of endothelial cells and increase susceptibility to high-altitude pulmonary edema**

Yi-Ling Ge, Pei-Jie Li, Ying-Rui Bu, Bin Zhang, Jin Xu, Si-Yuan He, Qing-Lin Cao, Yun-Gang Bai,

Jin Ma, Lin Zhang, Jie Zhou & Man-Jiang Xie

Apoptosis . 2024 Oct;29(9-10):1600-1618.

doi: <https://doi.org/10.1007/s10495-024-02005-9>.

Abstract: High-altitude pulmonary edema (HAPE) is a fatal threat for sojourners who ascend rapidly without sufficient acclimatization. Acclimatized sojourners and adapted natives are both insensitive to HAPE but have different physiological traits and molecular bases. In this study, based on GSE52209, the gene expression profiles of HAPE patients were compared with those of acclimatized sojourners and adapted natives, with the common and divergent differentially expressed genes (DEGs) and their hub genes identified, respectively. Bioinformatic methodologies for functional enrichment analysis, immune infiltration, diagnostic model construction, competing endogenous RNA (ceRNA) analysis and drug prediction were performed to detect potential biological functions and molecular mechanisms. Next, an array of in vivo experiments in a HAPE rat model and in vitro experiments in HUVECs were conducted to verify the results of the bioinformatic analysis. The enriched pathways of DEGs and immune landscapes for HAPE were significantly different between sojourners and natives, and the common DEGs were enriched mainly in the pathways of development and immunity. Nomograms revealed that the upregulation of TNF- α and downregulation of RPLP0 exhibited high diagnostic efficiency for HAPE in both sojourners and natives, which was further validated in the HAPE rat model. The addition of TNF- α and RPLP0 knockdown activated apoptosis signaling in endothelial cells (ECs) and enhanced endothelial permeability. In conclusion, TNF- α and RPLP0 are shared biomarkers and molecular bases for HAPE susceptibility during the acclimatization/adaptation/maladaptation processes in sojourners and natives, inspiring new ideas for predicting and treating HAPE.

24COASNO173:

Title- Glutamine deprivation in glioblastoma stem cells triggers autophagic SIRT3 degradation to epigenetically restrict CD133 expression and stemness

Zhengcao Xing, Xianguo Jiang, Yalan Chen, Tiange Wang, Xiaohe Li, Xiangyun Wei, Qiuju Fan, Jie Yang, Hongmei Wu, Jinke Cheng & Rong Cai

Apoptosis . 2024 Oct;29(9-10):1619-1631.

doi: <https://doi.org/10.1007/s10495-024-02003-x>.

Abstract: Glioblastoma multiforme (GBM) is a highly malignant brain tumor, and glioblastoma stem cells (GSCs) are the primary cause of GBM heterogeneity, invasiveness, and resistance to therapy. Sirtuin 3 (SIRT3) is mainly localized in the mitochondrial matrix and plays an important role in maintaining GSC stemness through cooperative interaction with the chaperone protein tumor necrosis factor receptor-associated protein 1 (TRAP1) to modulate mitochondrial respiration and oxidative stress. The present study aimed to further elucidate the specific mechanisms by which SIRT3 influences GSC stemness, including whether SIRT3 serves as an autophagy substrate and the mechanism of SIRT3 degradation. We first found that SIRT3 is enriched in CD133⁺ GSCs. Further experiments revealed that in addition to promoting mitochondrial respiration and reducing oxidative stress, SIRT3 maintains GSC stemness by epigenetically regulating CD133 expression *via* succinate. More importantly, we found that SIRT3 is degraded through the autophagy-lysosome pathway

during GSC differentiation into GBM bulk tumor cells. GSCs are highly dependent on glutamine for survival, and in these cells, we found that glutamine deprivation triggers autophagic SIRT3 degradation to restrict CD133 expression, thereby disrupting the stemness of GSCs. Together our results reveal a novel mechanism by which SIRT3 regulates GSC stemness. We propose that glutamine restriction to trigger autophagic SIRT3 degradation offers a strategy to eliminate GSCs, which combined with other treatment methods may overcome GBM resistance to therapy as well as relapse.

24COASNO174:**Title- Constructing a disulfidptosis-related prognostic signature of hepatocellular carcinoma based on single-cell sequencing and weighted co-expression network analysis**

Zelin Tian, Junbo Song, Jiang She, Weixiang He, Shanshan Guo & Bingchen Dong

Apoptosis . 2024 Oct;29(9-10):1632-1647.

doi: <https://doi.org/10.1007/s10495-024-01968-z>.

Abstract: Hepatocellular carcinoma (HCC) ranks as the second leading cause of cancer-related deaths globally. Disulfidptosis is a newly identified form of regulated cell death that is induced by glucose starvation. However, the clinical prognostic characteristics of disulfidptosis-associated genes in HCC remain poorly understood. We conducted an analysis of the single-cell datasets GSE149614 and performed weighted co-expression network analysis (WGCNA) on the Cancer Genome Atlas (TCGA) datasets to identify the genes related to disulfidptosis. A prognostic model was constructed using univariate COX and Lasso regression. Survival analysis, immune microenvironment analysis, and mutation analysis were performed. Additionally, a nomogram associated with disulfidptosis-related signature was constructed to identify the prognosis of HCC patients. Patients with HCC in the TCGA and GSE14520 datasets were categorized using a disulfidptosis-related model, revealing significant differences in survival times between the high- and low-disulfidptosis groups. High-disulfidptosis patients exhibited increased expression of immune checkpoint-related genes, implying that immunotherapy and certain chemotherapies may be beneficial for them. Meanwhile, the ROC and decision curves analysis (DCA) indicated that the nomogram has satisfying prognostic efficacy. Moreover, the experimental results of GATM in this prognostic model indicated that GATM is low expressed in HCC tissues, and GATM knockdown promotes the proliferation and migration of HCC cells. By analyzing single-cell and bulk multi-omics sequencing data, we developed a prognostic signature related to disulfidptosis and explored the relationship between high- and low-disulfidptosis groups in HCC. This study offers a novel reference for gaining a deeper understanding of the role of disulfidptosis in HCC.

24COASNO175:**Title- LncRNA MIR210HG promotes phenotype switching of pulmonary arterial smooth muscle cells through autophagy-dependent ferroptosis pathway**

Enze Wang, Binbin Zhang, Ling Huang, Pulin Li, Rui Han, Sijing Zhou, Daxiong Zeng & Ran Wang

Apoptosis . 2024 Oct;29(9-10):1648-1662.

doi: <https://doi.org/10.1007/s10495-024-01963-4>.

Abstract: Hypoxic pulmonary hypertension (HPH) is a pathophysiological syndrome in which pulmonary vascular pressure increases under hypoxic stimulation and there is an urgent need to develop emerging therapies for the treatment of HPH. LncRNA MIR210HG is a long non-coding RNA closely related to hypoxia and has been widely reported in a variety of tumor diseases. But its mechanism in hypoxic pulmonary hypertension is not clear. In this study, we identified for the first time the potential effect of MIR210HG on disease progression in HPH. Furthermore, we investigated the underlying mechanism through which elevated levels of MIR210HG promotes the transition from a contractile phenotype to a synthetic phenotype in PASMCs under hypoxia via activation of autophagy-dependent ferroptosis pathway. While overexpression of HIF-2 α in PASMCs under hypoxia significantly reversed the phenotypic changes induced by MIR210HG knockdown. We further investigated the potential positive regulatory relationship between STAT3 and the transcription of MIR210HG in PASMCs under hypoxic conditions. In addition, we established both in vivo and in vitro models of HPH to validate the differential expression of specific markers associated with hypoxia. Our findings suggest a potential mechanism of LncRNA MIR210HG in the progression of HPH and offer potential targets for disease intervention and treatment.

24COASNO176:

Title- SIRT1 regulates mitochondrial fission to alleviate high altitude hypoxia induced cardiac dysfunction in rats via the PGC-1 α -DRP1/FIS1/MFF

Hongbao Xu, Xiaona Song, Xiaoru Zhang, Guangrui Wang, Xiaoling Cheng, Ling Zhang, Apoptosis . 2024 Oct;29(9-10):1663-1678.

doi: <https://doi.org/10.1007/s10495-024-01954-5>.

Abstract: High-altitude exposure has been linked to cardiac dysfunction. Silent information regulator factor 2-related enzyme 1 (sirtuin 1, SIRT1), a nicotinamide adenine dinucleotide-dependent deacetylase, plays a crucial role in regulating numerous cardiovascular diseases. However, the relationship between SIRT1 and cardiac dysfunction induced by hypobaric hypoxia (HH) remains unexplored. This study aims to assess the impact of SIRT1 on HH-induced cardiac dysfunction and delve into the underlying mechanisms, both in vivo and in vitro. In this study, we have demonstrated that exposure to HH results in cardiomyocyte injury, along with the downregulation of SIRT1 and mitochondrial dysfunction. Upregulating SIRT1 significantly inhibits mitochondrial fission, improves mitochondrial function, reduces cardiomyocyte injury, and consequently enhances cardiac function in HH-exposed rats. Additionally, HH exposure triggers aberrant expression of mitochondrial fission-regulated proteins, with a decrease in PPAR γ coactivator 1 alpha (PGC-1 α) and mitochondrial fission factor (MFF) and an increase in mitochondrial fission 1 (FIS1) and dynamin-related protein 1 (DRP1), all of which are mitigated by SIRT1 upregulation. Furthermore, inhibiting PGC-1 α diminishes the positive effects of SIRT1 regulation on the expression of DRP1, MFF, and FIS1, as well as mitochondrial fission. These findings demonstrate that SIRT1 alleviates HH-induced cardiac dysfunction by preventing mitochondrial fission through the PGC-1 α -DRP1/FIS1/MFF pathway.

24COASNO177:

Title- Loss of AR-regulated AFF3 contributes to prostate cancer progression and reduces ferroptosis sensitivity by downregulating ACSL4 based on single-cell sequencing analysis

Aoyu Fan, Yunpeng Li, Yunyan Zhang, Wei Meng, Wei Pan, Meixi Chen, Zhongliang Ma & Wei Chen

Apoptosis . 2024 Oct;29(9-10):1679-1695.

doi: <https://doi.org/10.1007/s10495-024-01941-w>.

Abstract: Prostate cancer (PCa) is one of the most common cancers affecting the health of men worldwide. Castration-resistant prostate cancer (CRPC), the advanced and refractory phase of prostate cancer, has multiple mechanisms of resistance to androgen deprivation therapy (ADT) such as AR mutations, aberrant androgen synthase, and abnormal expression of AR-related genes. Based on the research of the AR pathway, new drugs for the treatment of CRPC have been developed in clinical practice, such as Abiraterone and enzalutamide. However, many areas in this pathway are still worth exploring. In this study, single-cell sequencing analysis was utilized to scrutinize significant genes in the androgen receptor (AR) pathway related to CRPC. Our analysis of single-cell sequencing combined with bulk-cell sequencing revealed a substantial downregulation of AR-regulated AFF3 in CRPC. Overexpression of AFF3 restricted the proliferation and migration of prostate cancer cells whilst also increasing their sensitivity towards enzalutamide, while knockdown of AFF3 had the opposite effect. To elucidate the mechanism of tumor inhibition by AFF3, we applied GSVA and GSEA to investigate the metabolic pathways related to AFF3 and revealed that AFF3 had an impact on fatty acids metabolism and ferroptosis through the regulation of ACSL4 protein expression. Based on correlation analysis and flow cytometry, we can speculate that AFF3 can impact the sensitivity of the CRPC cell lines to the ferroptosis inducer (RSL3) by regulating ACSL4. Therefore, our findings may provide new insights into the mechanisms of drug resistance in CRPC, and AFF3 may serve as a novel prognostic biomarker in prostate cancer.

24COASNO178:

Title- DLD is a potential therapeutic target for COVID-19 infection in diffuse large B-cell lymphoma patients

Can Chen, Dandan Kang, Zhenzhen Chen, Pengfei Shi, Yun Li & Shenxian Qian

Apoptosis . 2024 Oct;29(9-10):1696-1708.

doi: <https://doi.org/10.1007/s10495-024-01959-0>.

Abstract: Since the discovery of copper induces cell death(cuproptosis) in 2022, it has been one of the biggest research hotspots. cuproptosis related genes (CRGs) has been demonstrated to be a potential therapeutic target for cancer, however, the molecular mechanism of CRGs in coronavirus disease 2019 (COVID-19) infected in DLBCL patients has not been reported yet. Therefore, our research objective is first to elucidate the mechanism and role of CRGs in COVID-19. Secondly, we conducted univariate and multivariate analysis and machine learning to screen for CRGs with common expression differences in COVID-19 and DLBCL.

Finally, the functional role and immune mechanism of genes in DLBCL were confirmed through cell experiments and immune analysis. The research results show that CRGs play an important role in the occurrence and development of COVID-19. Univariate analysis and machine learning confirm that dihydrolipoamide dehydrogenase (DLD) is the common key gene of COVID-19 and DLBCL. Inhibiting the expression of DLD can significantly inhibit the cycle progression and promote cell apoptosis of DLBCL cells and can target positive regulation of Lysine-specific demethylase 1 (LSD1, also known as KDM1A) to inhibit the proliferation of DLBCL cells and promote cell apoptosis. The immune analysis results show that high-expression of DLD may reduce T cell-mediated anti-tumor immunity by regulating immune infiltration of CD8 + T cells and positively regulating immune checkpoints LAG3 and CD276. Reducing the expression of DLD can effectively enhance T cell-mediated anti-tumor immunity, thereby clearing cancer cells and preventing cancer growth. In conclusion, DLD may be a potential therapeutic target for COVID-19 infection in DLBCL patients. Our research provides a theoretical basis for improving the clinical treatment of COVID-19 infection in DLBCL.

24COASNO179:**Title- CD8 + CD103 + iTregs protect against ischemia-reperfusion-induced acute kidney injury by inhibiting pyroptosis**

Qiuju Chen, Xiao Zhang, Hui Yang, Guangxuan Luo, Xin Zhou, Zhenjian Xu & Anping Xu
Apoptosis . 2024 Oct;29(9-10):1709-1722.

doi: <https://doi.org/10.1007/s10495-024-02001-z>.

Abstract: The occurrence of acute kidney injury (AKI) is elevated, one of the main causes is ischemia-reperfusion (I/R). However, no specific therapy is currently available to treat I/R-induced AKI (I/R-AKI). Treg cells have been demonstrated to perform an anti-inflammatory role in a range of autoimmune and inflammatory illnesses. However, there is limited available information about the possible functions of CD8 + CD103 + iTregs in I/R-AKI. We utilized renal tubular epithelial cells (RTECs) subjected to hypoxia-reoxygenation (H/R) and I/R-AKI mouse model to investigate whether CD8 + CD103 + iTregs could attenuate AKI and the underlying mechanism. In vitro, co-cultured with CD8 + CD103 + iTregs alleviated H/R-induced cell injury. After treatment of CD8 + CD103 + iTregs rather than control cells, a significant improvement of I/R-AKI was observed in vivo, including decreased serum creatinine (sCr) and blood urea nitrogen (BUN) levels, reduced renal pathological injury, lowered tubular apoptosis and inhibition of the transition from AKI to chronic kidney disease (CKD). Mechanically, CD8 + CD103 + iTregs alleviated H/R-induced cell injury and I/R-AKI partly by suppressing RTECs pyroptosis via inhibiting the NLRP3/Caspase-1 axis. Our study provides a novel perspective on the possibility of CD8 + CD103 + iTregs for the treatment of I/R-AKI.

24COASNO180:**Title- SEH1L silencing induces ferroptosis and suppresses hepatocellular carcinoma progression via ATF3/HMOX1/GPX4 axis**

Ziyang Feng, Ke Cao, Haojia Sun & Xuewen Liu

Apoptosis . 2024 Oct;29(9-10):1723-1737.

doi: <https://doi.org/10.1007/s10495-024-02009-5>.

Abstract: SEH1 like nucleoporin (SEH1L) is an important component of nuclear pore complex (NPC), which is crucial in the regulation of cell division. However, the interrelation between SEH1L expression and tumor progression is less studied. In this research, we performed a systematic bioinformatic analysis about SEH1L using TCGA, Timer 2.0, Cbioportal, UCLAN and CellMiner™ databases in pan-cancer. Besides, we further validated the bioinformatic results through in vitro and in vivo experiments in HCC, including transcriptome sequencing, real-time quantitative PCR (RT-qPCR), western blotting (WB), immunohistochemistry (IHC), cell proliferation assays, clone formation, EdU, transwell, flow cytometry and subcutaneous tumor model. Our results suggested that SEH1L was significantly up-regulated and related to poor prognosis in most cancers, and may serve as a potential biomarker. SEH1L could promote HCC progression in vitro and in vivo. Besides, the next generation sequencing suggested that 684 genes was significantly up-regulated and 678 genes was down-regulated after the knock down of SEH1L. SEH1L silencing could activate ATF3/HMOX1/GPX4 axis, decrease mitochondrial membrane potential and GSH, but increase ROS and MDA, and these effects could be reversed by the knock down of ATF3. This study indicated that SEH1L silencing could induce ferroptosis and suppresses hepatocellular carcinoma (HCC) progression via ATF3/HMOX1/GPX4 axis.

24COASNO181:

Title- IRG1/Itaconate inhibits proliferation and promotes apoptosis of CD69⁺CD103⁺CD8⁺ tissue-resident memory T cells in autoimmune hepatitis by regulating the JAK3/STAT3/P53 signalling pathway

Pei Zhou, Kaixiong Tao, Liwu Zeng, Xinyu Zeng, Yaqi Wan, Gengchen Xie, Xinghua Liu & Peng Zhang

Apoptosis . 2024 Oct;29(9-10):1738-1756.

DOI: <https://doi.org/10.1007/s10495-024-01970-5>.

Abstract: To investigate the protective role of immune response gene 1 (IRG1) and exogenous itaconate in autoimmune hepatitis (AIH) and elucidate the underlying mechanisms. Wild-type and IRG1^{-/-} AIH mouse models were established, and samples of liver tissue and ocular blood were collected from each group of mice to assess the effects of IRG1/itaconate on the expression of pro- and anti-inflammatory cytokines. The levels of liver enzymes and related inflammatory factors were determined using enzyme-linked immunosorbent assay and real-time quantitative polymerase chain reaction (PCR). Liver histomorphology was detected through hematoxylin and eosin staining and then scored for liver injury, and the infiltration levels of tissue-resident memory T (TRM) cells and related molecules in the liver tissue were detected through immunofluorescence staining in vitro. RNA sequencing and gene enrichment analysis were conducted to identify the corresponding molecules and pathways, and lentiviral transfection was used to generate TRM cell lines with IRG1, Jak3, Stat3, and p53 knockdown. Real-time quantitative PCR and western blot were performed to detect the expression levels of relevant mRNAs and proteins in the liver tissue and cells. The percentage of apoptotic cells was determined using flow cytometry.

IRG1/itaconate effectively reduced the release of pro-inflammatory cytokines and the pathological damage to liver tissue, thereby maintaining normal liver function. At the same time, IRG1/itaconate inhibited the JAK3/STAT3 signaling pathway, regulated the expression of related downstream proteins, and inhibited the proliferation and promoted the apoptosis of CD69⁺CD103⁺CD8⁺ TRM cells. For the first time, P53 was found to act as a downstream molecule of the JAK3/STAT3 pathway and was regulated by IRG1/itaconate to promote the apoptosis of CD8⁺ TRM cells. IRG1/itaconate can alleviate concanavalin A-induced autoimmune hepatitis in mice by inhibiting the proliferation and promoting the apoptosis of CD69⁺CD103⁺CD8⁺ TRM cells via the JAK3/STAT3/P53 pathway.

24COASNO182:

Title- C-terminal region of Rv1039c (PPE15) protein of *Mycobacterium tuberculosis* targets host mitochondria to induce macrophage apoptosis

Priyanka, Sadhna Sharma, Mandira Varma-Basil & Monika Sharma

Apoptosis . 2024 Oct;29(9-10):1757-1779.

DOI: <https://doi.org/10.1007/s10495-024-01965-2>.

Abstract: *Mycobacterium tuberculosis* (Mtb) genome possesses a unique family called Proline-Glutamate/Proline-Proline-Glutamate (PE/PPE) gene family, exclusive to pathogenic mycobacterium. Some of these proteins are known to play role in virulence and immune response modulation, but many are still uncharacterized. This study investigated the role of C-terminal region of Rv1039c (PPE15) in inducing mitochondrial perturbations and macrophage apoptosis. Our *in-silico* studies revealed the disordered, coiled, and hydrophobic C-terminal region in Rv1039c has similarity with C-terminal of mitochondria-targeting pro-apoptotic host proteins. Wild type Rv1039c and C-terminal deleted Rv1039c (Rv1039c-/-Cterm) recombinant proteins were purified and their *M. smegmatis* knock-in strains were constructed which were used for *in-vitro* experiments. Confocal microscopy showed localization of Rv1039c to mitochondria of PMA-differentiated THP1 macrophages; and reduced mitochondrial membrane depolarization and production of mitochondrial superoxides were observed in response to Rv1039c-/-Cterm in comparison to full-length Rv1039c. The C-terminal region of Rv1039c was found to activate caspases 3, 7 and 9 along with upregulated expression of pro-apoptotic genes like *Bax* and *Bim*. Rv1039c-/-Cterm also reduced the Cytochrome-C release from the mitochondria and the expression of AnnexinV/PI positive and TUNEL positive cells as compared to Rv1039c. Additionally, Rv1039c was observed to upregulate the TLR4-NF-κB-TNF-α signalling whereas the same was downregulated in response to Rv1039c-/-Cterm. These findings suggested that the C-terminal region of Rv1039c is a molecular mimic of pro-apoptotic host proteins which induce mitochondria-dependent macrophage apoptosis and evoke host immune response. These observations enhance our understanding about the role of PE/PPE proteins at host-pathogen interface.

24COASNO183:

Title- Vitamin D inhibits ferroptosis and mitigates the kidney injury of prediabetic mice by activating the Klotho/p53 signaling pathway

Hao Chen, Yujing Zhang, Yufan Miao, Hanlu Song, Lulu Tang, Wenyi Liu, Wenjie Li, Jinxin Miao & Xing Li

Apoptosis . 2024 Oct;29(9-10):1780-1792.

DOI: <https://doi.org/10.1007/s10495-024-01955-4>.

Abstract: Diabetic nephropathy (DN) is a serious public health problem worldwide, and ferroptosis is deeply involved in the pathogenesis of DN. Prediabetes is a critical period in the prevention and control of diabetes and its complications, in which kidney injury occurs. This study aimed to explore whether ferroptosis would induce kidney injury in prediabetic mice, and whether vitamin D (VD) supplementation is capable of preventing kidney injury by inhibiting ferroptosis, while discussing the potential mechanisms. High-fat diet (HFD) fed KKAY mice and high glucose (HG) treated HK-2 cells were used as experimental subjects in the current study. Our results revealed that serious injury and ferroptosis take place in the kidney tissue of prediabetic mice; furthermore, VD intervention significantly improved the kidney structure and function in prediabetic mice and inhibited ferroptosis, showing ameliorated iron deposition, enhanced antioxidant capability, reduced reactive oxygen species (ROS) and lipid peroxidation accumulation. Meanwhile, VD up-regulated Klotho, solute carrier family 7 member 11 (SLC7A11) and glutathione peroxidase 4 (GPX4) expression, and down-regulated p53, transferrin receptor 1 (TFR1) and Acyl-Coenzyme A synthetase long-chain family member 4 (ACSL4) expression. Moreover, we demonstrated that HG-induced ferroptosis is antagonized by treatment of VD and knockdown of Klotho attenuates the protective effect of VD on ferroptosis in vitro. In conclusion, ferroptosis occurs in the kidney of prediabetic mice and VD owns a protective effect on prediabetic kidney injury, possibly by via the Klotho/p53 pathway, thus inhibiting hyperglycemia-induced ferroptosis.

24COASNO184:

Title- Deubiquitinating enzyme USP28 inhibitor AZ1 alone and in combination with cisplatin for the treatment of non-small cell lung cancer

Yiqiong Song, Longhao Wang, Yuanyuan Zheng, Lanqi Jia, Chunwei Li, Ke Chao, Lifeng Li, Shilong Sun,

Apoptosis . 2024 Oct;29(9-10):1793-1809.

DOI: <https://doi.org/10.1007/s10495-024-02008-6>.

Abstract: Lung cancer is one of the most common malignant tumors. Despite decades of research, the treatment of lung cancer remains challenging. Non-small cell lung cancer (NSCLC) is the primary type of lung cancer and is a significant focus of research in lung cancer treatment. The deubiquitinase ubiquitin-specific protease 28 (USP28) plays a role in the progression of various tumors and serves as a potential therapeutic target. This study aims to determine the role of USP28 in the progression of NSCLC. We examined the impact of the USP28 inhibitor AZ1 on the cell cycle, apoptosis, DNA damage response, and cellular immunogenicity in non-small cell lung cancer. We observed that AZ1 and siUSP28 induce DNA damage, leading to the activation of Noxa-mediated mitochondrial apoptosis. The dsDNA and mtDNA released from DNA damage and mitochondrial apoptosis activate tumor cell immunogenicity through the cGAS-STING signaling pathway. Simultaneously, targeting

USP28 promotes the degradation of c-MYC, resulting in cell cycle arrest and inhibition of DNA repair. This further promotes DNA damage-induced cell apoptosis mediated by the Noxa protein, thereby enhancing tumor cell immunogenicity mediated by dsDNA and mtDNA. Moreover, we found that the combination of AZ1 and cisplatin (DDP) can enhance therapeutic efficacy, thereby providing a new strategy to overcome cisplatin resistance in NSCLC. These findings suggest that targeting USP28 and combining it with cisplatin are feasible strategies for treating NSCLC.

24COASNO185:**Title- Emodin induces ferroptosis in colorectal cancer through NCOA4-mediated ferritinophagy and NF- κ b pathway inactivation**

Zhennv Shen, Lei Zhao, Seung-ah Yoo, Zhenhua Lin, Yu Zhang, Wenqing Yang & Junjie Piao

Apoptosis . 2024 Oct;29(9-10):1810-1823.

DOI: <https://doi.org/10.1007/s10495-024-01973-2>.

Abstract: Ferroptosis is a new programmed cell death characterized by iron-dependent lipid peroxidation. Targeting ferroptosis is considered a promising strategy for anti-cancer therapy. Recently, natural compound has gained increased attention for their advantage in cancer treatment, and the exploration of natural compounds as ferroptosis inducers offers a hopeful avenue for advancing cancer treatment modalities. Emodin is a natural anthraquinone derivative in many widely used Chinese medicinal herbs. In our previous study, we predicted that the anti-cancer effect of Emodin might related to ferroptosis by using RNA-seq in colorectal cancer (CRC). Thus, in this study, we aim to investigate the molecular mechanism underlying Emodin-mediated ferroptosis in CRC. Cell-based assays including CCK-8, colony formation, EdU, and Annexin V/PI staining were employed to assess Emodin's impact on cell proliferation and apoptosis. Furthermore, various techniques such as FerroOrange staining, C11-BODIPY 581/591 staining, iron, MDA, GSH detection assay and transmission electron microscopy were performed to examine the role of Emodin in ferroptosis. Additionally, specific NCOA4 knockdown cell lines were generated to elucidate the involvement of NCOA4 in Emodin-induced ferroptosis. Moreover, the effects of Emodin on ferroptosis were further confirmed through the application of inhibitors, including Ferostatin-1, 3-MA, DFO, and PMA. As a results, Emodin inhibited proliferation and induced apoptosis in CRC cells. Emodin could decrease GSH content, xCT and GPX4 expression, meanwhile increasing ROS generation, MDA, and lipid peroxidation, and these effects could reverse by ferroptosis inhibitor, Ferostatin-1, iron chelator DFO, autophagy inhibitor 3-MA and NCOA4 silencing. Moreover, Emodin could inactivate NF- κ b pathway, and PMA, an activator of NF- κ b pathway could alleviate Emodin-induced ferroptosis in CRC cells. Xenograft mouse model also showed that Emodin suppressed tumor growth and induced ferroptosis in vivo. In conclusion, these results suggested that Emodin induced ferroptosis through NCOA4-mediated ferritinophagy by inactivating NF- κ b pathway in CRC cells. These findings not only identified a novel role for Emodin in ferroptosis but also indicated that Emodin may be a valuable candidate for the development of an anti-cancer agent.

24COASNO186:

Title- MST1 selective inhibitor Xmu-mp-1 ameliorates neuropathological changes in a rat model of sporadic Alzheimer's Disease by modulating Hippo-Wnt signaling crosstalk

Manas Ranjan Sahu, Mir Hilal Ahmad & Amal Chandra Mondal

Apoptosis . 2024 Oct;29(9-10):1824-1851.

DOI: <https://doi.org/10.1007/s10495-024-01975-0>.

Abstract: Alzheimer's disease (AD), the most prevalent form of dementia, is characterized by progressive cognitive impairment accompanied by aberrant neuronal apoptosis. Reports suggest that the pro-apoptotic mammalian set20-like kinase 1/2 (MST1/2) instigates neuronal apoptosis via activating the Hippo signaling pathway under various stress conditions, including AD. However, whether inhibiting MST1/2 has any therapeutic benefits in AD remains unknown. Thus, we tested the therapeutic effects of intervening MST1/2 activation via the pharmacological inhibitor Xmu-mp-1 in a sporadic AD rat model. Sporadic AD was established in adult rats by intracerebroventricular streptozotocin (ICV-STZ) injection (3 mg/kg body weight). Xmu-mp-1 (0.5 mg/kg/body weight) was administered once every 48 h for two weeks, and Donepezil (5 mg/kg body weight) was used as a reference standard drug. The therapeutic effects of Xmu-mp-1 on ICV-STZ rats were determined through various behavioral, biochemical, histopathological, and molecular tests. At the behavioral level, Xmu-mp-1 improved cognitive deficits in sporadic AD rats. Further, Xmu-mp-1 treatment reduced STZ-associated tau phosphorylation, amyloid-beta deposition, oxidative stress, neurotoxicity, neuroinflammation, synaptic dysfunction, neuronal apoptosis, and neurodegeneration. Mechanistically, Xmu-mp-1 exerted these neuroprotective actions by inactivating the Hippo signaling while potentiating the Wnt/ β -Catenin signaling in the AD rats. Together, the results of the present study provide compelling support that Xmu-mp-1 negated the neuronal dysregulation in the rat model of sporadic AD. Therefore, inhibiting MST/Hippo signaling and modulating its crosstalk with the Wnt/ β -Catenin pathway can be a promising alternative treatment strategy against AD pathology. This is the first study providing novel mechanistic insights into the therapeutic use of Xmu-mp-1 in sporadic AD.

24COASNO187:

Title- Astrocyte-induced Cdk5 expedites breast cancer brain metastasis by suppressing MHC-I expression to evade immune recognition

Arseniy E. Yuzhalin, Frank J. Lowery, Yohei Saito, Xiangliang Yuan, Jun Yao, Yimin Duan, Nat Cell Biol . 2024 Oct;26(10):1773-1789.

DOI: <https://doi.org/10.1038/s41556-024-01509-5>.

Abstract: Brain metastases (BrMs) evade the immune response to develop in the brain, yet the mechanisms of BrM immune evasion remains unclear. This study shows that brain astrocytes induce the overexpression of neuronal-specific cyclin-dependent kinase 5 (Cdk5) in breast cancer-derived BrMs, which facilitates BrM outgrowth in mice. Cdk5-overexpressing BrMs exhibit reduced expression and function of the class I major histocompatibility complex (MHC-I) and antigen-presentation pathway, which are restored by inhibiting Cdk5 genetically or pharmacologically, as evidenced by single-cell RNA

sequencing and functional studies. Mechanistically, Cdk5 suppresses MHC-I expression on the cancer cell membrane through the Irf2bp1–Stat1–importin α –Nlrc5 pathway, enabling BrMs to avoid recognition by T cells. Treatment with roscovitine—a clinically applicable Cdk5 inhibitor—alone or combined with immune checkpoint inhibitors, significantly reduces BrM burden and increases tumour-infiltrating functional CD8⁺ lymphocytes in mice. Thus, astrocyte-induced Cdk5 overexpression endorses BrM immune evasion, whereas therapeutically targeting Cdk5 markedly improves the efficacy of immune checkpoint inhibitors and inhibits BrM growth.

24COASNO188:**Title- Wnt-deficient and hypoxic environment orchestrates squamous reprogramming of human pancreatic ductal adenocarcinoma**

Hiroki Tamagawa, Masayuki Fujii, Kazuhiro Togasaki, Takashi Seino, Shintaro Kawasaki, Ai Takano.

Nat Cell Biol . 2024 Oct;26(10):1759-1772.

DOI: <https://doi.org/10.1038/s41556-024-01498-5>.

Abstract: Human pancreatic cancer is characterized by the molecular diversity encompassing native duct-like and squamous cell-like identities, but mechanisms underlying squamous transdifferentiation have remained elusive. To comprehensively capture the molecular diversity of human pancreatic cancer, we here profiled 65 patient-derived pancreatic cancer organoid lines, including six adenosquamous carcinoma lines. H3K27me3-mediated erasure of the ductal lineage specifiers and hijacking of the TP63-driven squamous-cell programme drove squamous-cell commitment, providing survival benefit in a Wnt-deficient environment and hypoxic conditions. Gene engineering of normal pancreatic duct organoids revealed that GATA6 loss and a Wnt-deficient environment, in concert with genetic or hypoxia-mediated inactivation of KDM6A, facilitate squamous reprogramming, which in turn enhances environmental fitness. EZH2 inhibition counterbalanced the epigenetic bias and curbed the growth of adenosquamous cancer organoids. Our results demonstrate how an adversarial microenvironment dictates the molecular and histological evolution of human pancreatic cancer and provide insights into the principles and significance of lineage conversion in human cancer.

24COASNO189:**Title- RNA sequestration in P-bodies sustains myeloid leukaemia**

Srikanth Kodali, Ludovica Proietti, Gemma Valcarcel, Anna V. López-Rubio, Patrizia Pessina, Thomas Eder,

Nat Cell Biol . 2024 Oct;26(10):1745-1758.

DOI: <https://doi.org/10.1038/s41556-024-01489-6>.

Abstract: Post-transcriptional mechanisms are fundamental safeguards of progenitor cell identity and are often dysregulated in cancer. Here, we identified regulators of P-bodies as crucial vulnerabilities in acute myeloid leukaemia (AML) through genome-wide CRISPR screens in normal and malignant haematopoietic progenitors. We found that leukaemia cells harbour aberrantly elevated numbers of P-bodies and show that P-body assembly is crucial

for initiation and maintenance of AML. Notably, P-body loss had little effect upon homeostatic haematopoiesis but impacted regenerative haematopoiesis. Molecular characterization of P-bodies purified from human AML cells unveiled their critical role in sequestering messenger RNAs encoding potent tumour suppressors from the translational machinery. P-body dissolution promoted translation of these mRNAs, which in turn rewired gene expression and chromatin architecture in leukaemia cells. Collectively, our findings highlight the contrasting and unique roles of RNA sequestration in P-bodies during tissue homeostasis and oncogenesis. These insights open potential avenues for understanding myeloid leukaemia and future therapeutic interventions.

24COASNO190:**Title- The stress response regulator HSF1 modulates natural killer cell anti-tumour immunity**

Kathryn Hockemeyer, Theodore Sakellaropoulos, Xufeng Chen, Olha Ivashkiv, Maria Sirenko, Hua Zhou, Giovanni Gambi,

Nat Cell Biol . 2024 Oct;26(10):1734-1744.

DOI: <https://doi.org/10.1038/s41556-024-01490-z>.

Abstract: Diverse cellular insults converge on activation of the heat shock factor 1 (HSF1), which regulates the proteotoxic stress response to maintain protein homeostasis. HSF1 regulates numerous gene programmes beyond the proteotoxic stress response in a cell-type- and context-specific manner to promote malignancy. However, the role(s) of HSF1 in immune populations of the tumour microenvironment remain elusive. Here, we leverage an in vivo model of HSF1 activation and single-cell transcriptomic tumour profiling to show that augmented HSF1 activity in natural killer (NK) cells impairs cytotoxicity, cytokine production and subsequent anti-tumour immunity. Mechanistically, HSF1 directly binds and regulates the expression of key mediators of NK cell effector function. This work demonstrates that HSF1 regulates the immune response under the stress conditions of the tumour microenvironment. These findings have important implications for enhancing the efficacy of adoptive NK cell therapies and for designing combinatorial strategies including modulators of NK cell-mediated tumour killing.

24COASNO191:**Title- Single-cell new RNA sequencing reveals principles of transcription at the resolution of individual bursts**

Daniel Ramsköld, Gert-Jan Hendriks, Anton J. M. Larsson, Juliane V. Mayr, Christoph Ziegenhain, Michael Hagemann-Jensen, Leonard Hartmanis & Rickard Sandberg

Nat Cell Biol . 2024 Oct;26(10):1725-1733.

DOI: <https://doi.org/10.1038/s41556-024-01486-9>.

Abstract: Analyses of transcriptional bursting from single-cell RNA-sequencing data have revealed patterns of variation and regulation in the kinetic parameters that could be inferred. Here we profiled newly transcribed (4-thiouridine-labelled) RNA across 10,000 individual primary mouse fibroblasts to more broadly infer bursting kinetics and coordination. We demonstrate that inference from new RNA profiles could separate the kinetic parameters that

together specify the burst size, and that the synthesis rate (and not the transcriptional off rate) controls the burst size. Importantly, transcriptome-wide inference of transcriptional on and off rates provided conclusive evidence that RNA polymerase II transcribes genes in bursts. Recent reports identified examples of transcriptional co-bursting, yet no global analyses have been performed. The deep new RNA profiles we generated with allelic resolution demonstrated that co-bursting rarely appears more frequently than expected by chance, except for certain gene pairs, notably paralogues located in close genomic proximity. Altogether, new RNA single-cell profiling critically improves the inference of transcriptional bursting and provides strong evidence for independent transcriptional bursting of mammalian genes.

24COASNO192:**Title- Noncanonical inheritance of phenotypic information by protein amyloids**

Matthew Eroglu, Tanner Zocher, Jacob McAuley, Rachel Webster, Maggie Z. X. Xiao, Bin Yu, Calvin Mok & W. Brent Derry

Nat Cell Biol . 2024 Oct;26(10):1712-1724.

DOI: <https://doi.org/10.1038/s41556-024-01494-9>.

Abstract: All known heritable phenotypic information in animals is transmitted by direct inheritance of nucleic acids, their covalent modifications or histone modifications that modulate expression of associated genomic regions. Nonetheless, numerous familial traits and disorders cannot be attributed to known heritable molecular factors. Here we identify amyloid-like protein structures that are stably inherited in wild-type animals and influence traits. Their perturbation by genetic, environmental or pharmacological treatments leads to developmental phenotypes that can be epigenetically passed onto progeny. Injection of amyloids isolated from different phenotypic backgrounds into naive animals recapitulates the associated phenotype in offspring. Genetic and proteomic analyses reveal that the 26S proteasome and its conserved regulators maintain heritable amyloids across generations, which enables proper germ cell sex differentiation. We propose that inheritance of a proteinaceous epigenetic memory coordinates developmental timing and patterning with the environment to confer adaptive fitness.

24COASNO193:**Title- The Polycomb system sustains promoters in a deep OFF state by limiting pre-initiation complex formation to counteract transcription**

Aleksander T. Szczurek, Emilia Dimitrova, Jessica R. Kelley, Neil P. Blackledge & Robert J. Klose

Nat Cell Biol . 2024 Oct;26(10):1700-1711.

DOI: <https://doi.org/10.1038/s41556-024-01493-w>.

Abstract: The Polycomb system has fundamental roles in regulating gene expression during mammalian development. However, how it controls transcription to enable gene repression has remained enigmatic. Here, using rapid degron-based depletion coupled with live-cell transcription imaging and single-particle tracking, we show how the Polycomb system controls transcription in single cells. We discover that the Polycomb system is not a

constitutive block to transcription but instead sustains a long-lived deep promoter OFF state, which limits the frequency with which the promoter can enter into a transcribing state. We demonstrate that Polycomb sustains this deep promoter OFF state by counteracting the binding of factors that enable early transcription pre-initiation complex formation and show that this is necessary for gene repression. Together, these important discoveries provide a rationale for how the Polycomb system controls transcription and suggests a universal mechanism that could enable the Polycomb system to constrain transcription across diverse cellular contexts.

24COASNO194:**Title- Nuclear proteasomes buffer cytoplasmic proteins during autophagy compromise**

So Jung Park, Sung Min Son, Antonio Daniel Barbosa, Lidia Wrobel, Eleanna Stamatakou, Nat Cell Biol . 2024 Oct;26(10):1691-1699.

DOI: <https://doi.org/10.1038/s41556-024-01488-7>.

Abstract: Autophagy is a conserved pathway where cytoplasmic contents are engulfed by autophagosomes, which then fuse with lysosomes enabling their degradation. Mutations in core autophagy genes cause neurological conditions, and autophagy defects are seen in neurodegenerative diseases such as Parkinson's disease and Huntington's disease. Thus, we have sought to understand the cellular pathway perturbations that autophagy-perturbed cells are vulnerable to by seeking negative genetic interactions such as synthetic lethality in autophagy-null human cells using available data from yeast screens. These revealed that loss of proteasome and nuclear pore complex components cause synergistic viability changes akin to synthetic fitness loss in autophagy-null cells. This can be attributed to the cytoplasm-to-nuclear transport of proteins during autophagy deficiency and subsequent degradation of these erstwhile cytoplasmic proteins by nuclear proteasomes. As both autophagy and cytoplasm-to-nuclear transport are defective in Huntington's disease, such cells are more vulnerable to perturbations of proteostasis due to these synthetic interactions.

24COASNO195:**Title- A size filter at the Golgi regulates apical membrane protein sorting**

Christian de Caestecker & Ian G. Macara

Nat Cell Biol . 2024 Oct;26(10):1678-1690.

DOI: <https://doi.org/10.1038/s41556-024-01500-0>.

Abstract: Despite decades of research, apical sorting of epithelial membrane proteins remains incompletely understood. We noted that apical cytoplasmic domains are smaller than those of basolateral proteins; however, the reason for this discrepancy is unknown. Here we used a synthetic biology approach to investigate whether a size barrier at the Golgi apparatus might hinder apical sorting of proteins with large cytoplasmic tails. We focused on Crb3, Ace2 and Muc1 as representative apical proteins with short cytoplasmic tails. By incorporating a streptavidin-binding peptide, these proteins can be trapped in the endoplasmic reticulum until addition of biotin, which triggers synchronous release to the Golgi and subsequent transport to the apical cortex. Strikingly, increasing the size of their cytoplasmic domains caused partial mislocalization to the basolateral cortex and significantly delayed

Golgi departure. Moreover, N-glycosylation of ‘large’ Crb3 was delayed, and ‘small’ Crb3 segregated into spatially distinct Golgi regions. Biologically, Crb3 forms a complex through its cytoplasmic tail with the Pals1 protein, which could also delay departure, but although associated at the endoplasmic reticulum and Golgi, Pals1 disassociated before Crb3 departure. Notably, a non-dissociable mutant Pals1 hampered the exit of Crb3. We conclude that, unexpectedly, a size filter at the Golgi facilitates apical sorting of proteins with small cytoplasmic domains and that timely release of Pals1, to reduce cytoplasmic domain size, is essential for normal Crb3 sorting.

24COASNO196:**Title- Inverse blebs operate as hydraulic pumps during mouse blastocyst formation**

Markus F. Schliffka, Julien G. Dumortier, Diane Pelzer, Arghyadip Mukherjee & Jean-L  on Ma  tre

Nat Cell Biol . 2024 Oct;26(10):1669-1677.

DOI: <https://doi.org/10.1038/s41556-024-01501-z>.

Abstract: During preimplantation development, mouse embryos form a fluid-filled lumen. Pressurized fluid fractures cell–cell contacts and accumulates into pockets, which coarsen into a single lumen. How the embryo controls intercellular fluid movement during coarsening is unknown. Here we report inverse blebs growing into cells at adhesive contacts. Throughout the embryo we observed hundreds of inverse blebs, each filling with intercellular fluid and retracting within a minute. Inverse blebs grow due to pressure build-up resulting from fluid accumulation and cell–cell adhesion, which locally confines fluid. Inverse blebs retract due to actomyosin contraction, practically pushing fluid within the intercellular space. Importantly, inverse blebs occur infrequently at contacts formed by multiple cells, which effectively serve as fluid sinks. Manipulation of the embryo topology reveals that without sinks inverse blebs pump fluid into one another in futile cycles. We propose that inverse blebs operate as hydraulic pumps to promote luminal coarsening, thereby constituting an instrument used by cells to control fluid movement.

24COASNO197:**Title- Clathrin-associated carriers enable recycling through a kiss-and-run mechanism**

Jiachao Xu, Yu Liang, Nan Li, Song Dang, Amin Jiang, Yiqun Liu, Yuting Guo, Xiaoyu Yang, Yi Yuan,

Nat Cell Biol . 2024 Oct;26(10):1652-1668.

DOI: <https://doi.org/10.1038/s41556-024-01499-4>.

Abstract: Endocytosis and recycling control the uptake and retrieval of various materials, including membrane proteins and lipids, in all eukaryotic cells. These processes are crucial for cell growth, organization, function and environmental communication. However, the mechanisms underlying efficient, fast endocytic recycling remain poorly understood. Here, by utilizing a biosensor and imaging-based screening, we uncover a recycling mechanism that couples endocytosis and fast recycling, which we name the clathrin-associated fast endosomal recycling pathway (CARP). Clathrin-associated tubulovesicular carriers containing clathrin, AP1, Arf1, Rab1 and Rab11, while lacking the multimeric retrieval

complexes, are generated at subdomains of early endosomes and then transported along actin to cell surfaces. Unexpectedly, the clathrin-associated recycling carriers undergo partial fusion with the plasma membrane. Subsequently, they are released from the membrane by dynamin and re-enter cells. Multiple receptors utilize and modulate CARP for fast recycling following endocytosis. Thus, CARP represents a previously unrecognized endocytic recycling mechanism with kiss-and-run membrane fusion.

24COASNO198:**Title- Rabenosyn-5 suppresses non-small cell lung cancer metastasis via inhibiting CDC42 activity**

Xiong Guo, Bin Mu, Lin Zhu, Yanli Zhuo, Ping Mu, Fu Ren & Fangjin Lu

Cancer Gene Ther . 2024 Oct;31(10):1465-1476.

DOI: <https://doi.org/10.1038/s41417-024-00813-4>.

Abstract: Metastasis, the primary cause of death in lung cancer patients, is facilitated by cytoskeleton remodeling, which plays a crucial role in cancer cell migration and invasion. However, the precise regulatory mechanisms of intracellular trafficking proteins involved in cytoskeleton remodeling remain unclear. In this study, we have identified Rabenosyn-5 (Rbsn) as an inhibitor of filopodia formation and lung cancer metastasis. Mechanistically, Rbsn interacts with CDC42 and functions as a GTPase activating protein (GAP), thereby inhibiting CDC42 activity and subsequent filopodia formation. Furthermore, we have discovered that Akt phosphorylates Rbsn at the Thr253 site, and this phosphorylation negates the inhibitory effect of Rbsn on CDC42 activity. Additionally, our analysis reveals that Rbsn expression is significantly downregulated in lung cancer, and this decrease is associated with a worse prognosis. These findings provide strong evidence supporting the role of Rbsn in suppressing lung cancer progression through the inhibition of metastasis.

24COASNO199:**Title- Switching anti-EGFR antibody re-sensitizes head and neck cancer patient following acquired resistance to cetuximab**

Arun Khattri, Sheikh Nizamuddin, Nikhil Agrawal, Sandeep Kaushik, Sara Kochanny, Daniel Ginat,

Mark W. Lingen, Elizabeth Blair & Tanguy Y. Seiwert

Cancer Gene Ther . 2024 Oct;31(10):1477-1485.

DOI: <https://doi.org/10.1038/s41417-024-00812-5>.

Abstract: Cetuximab induces responses in about 13% of head and neck squamous cell carcinomas (HNSCC). We describe the molecular mechanism of acquired resistance to cetuximab, which could be overcome by switching to a different anti-EGFR antibody. Biopsies were collected at three different time points: before the start of cetuximab (PRE-cetux), at acquired resistance to cetuximab (AR-cetux), and at acquired resistance to dolutuzumab (AR-duligo). Biopsies were analyzed using tumor and normal whole-exome sequencing, RNASeq, and targeted panel sequencing with ultra-deep coverage to generate differential mutation and expression profiles. WES and targeted sequencing analysis identified an EGFR p.G465R extracellular domain mutation in AR-cetux biopsy.

Furthermore, RNASeq confirmed the expression of this mutation in the tumor tissue. This mutation prevented the binding of cetuximab to EGFR and was not present in PRE-cetux and AR-duligo biopsies, suggesting a potential mechanism of acquired resistance to cetuximab. Molecular dynamic simulations confirmed that duligotuzumab effectively binds EGFR with a p.G465R mutation. Interestingly, the p.G465R mutation improved the stability of the duligotuzumab-EGFR complex as compared to the wild-type EGFR. This is the first report of an EGFR ECD mutation associated with acquired resistance to cetuximab, posing a need for further validation. We suggest appropriate serial mutational profiling to identify ECD mutations should be considered for select patients with initial cetuximab benefit.

24COASNO200:

Title- Arsenic trioxide and p97 inhibitor synergize against acute myeloid leukemia by targeting nascent polypeptides and activating the ZAK α –JNK pathway

Shufeng Xie, Hui Liu, Shouhai Zhu, Zhihong Chen, Ruiheng Wang, Wenjie Zhang, Huajian Xian,

Cancer Gene Ther . 2024 Oct;31(10):1486-1497.

DOI: <https://doi.org/10.1038/s41417-024-00818-z>.

Abstract: Arsenic trioxide (ATO) has exhibited remarkable efficacy in treating acute promyelocytic leukemia (APL), primarily through promoting the degradation of the PML-RAR α fusion protein. However, ATO alone fails to confer any survival benefit to non-APL acute myeloid leukemia (AML) patients and exhibits limited efficacy when used in combination with other agents. Here, we explored the general toxicity mechanisms of ATO in APL and potential drugs that could be combined with ATO to exhibit synergistic lethal effects on other AML. We demonstrated that PML-RAR α degradation and ROS upregulation were insufficient to cause APL cell death. Based on the protein synthesis of different AML cells and their sensitivity to ATO, we established a correlation between ATO-induced cell death and protein synthesis. Our findings indicated that ATO induced cell death by damaging nascent polypeptides and causing ribosome stalling, accompanied by the activation of the ZAK α -JNK pathway. Furthermore, ATO-induced stress activated the GCN2–ATF4 pathway, and ribosome-associated quality control cleared damaged proteins with the assistance of p97. Importantly, our data revealed that inhibiting p97 enhanced the effectiveness of ATO in killing AML cells. These explorations paved the way for identifying optimal synthetic lethal drugs to enhance ATO treatment on non-APL AML.

24COASNO201:

Title- The splicing factor SF3B1 confers ferroptosis resistance and promotes lung adenocarcinoma progression via upregulation of SLC7A11

Yanlin Guo, Xiaohui Wang, Yu Du, Yixuan Zhao, Lvyue Gao, Yanlong Hao, Dou Lv, Xuefei Feng,

Cancer Gene Ther . 2024 Oct;31(10):1498-1510.

DOI: <https://doi.org/10.1038/s41417-024-00817-0>.

Abstract: This study aimed to investigate the expression of *SF3B1* in non-small cell lung cancer, and its clinical significance, biological function, and molecular

mechanisms. *SF3B1* mRNA and protein levels were elevated in both lung squamous cell carcinoma and lung adenocarcinoma (LUAD) tissues based on TCGA data and immunohistochemistry. Notably, high *SF3B1* expression in LUAD was significantly associated with increased lymph node metastasis. Functional experiments involving *SF3B1* knockdown and overexpression demonstrated that *SF3B1* facilitated the proliferation, invasion, and migration of LUAD cells. Additionally, the *SF3B1* inhibitor pladienolide-B attenuated the aggressive behavior of LUAD cells both in vitro and in vivo. RNA sequencing analysis indicated that differentially expressed genes in the *SF3B1* knockdown and *SF3B1* inhibitor groups were enriched in ferroptosis-related pathways compared to their respective control groups. The antiferroptotic role of *SF3B1* in LUAD cells was validated by detecting glutathione depletion, lipid peroxidation, and observing morphological changes using transmission electron microscopy. This process was confirmed to be independent of apoptosis and autophagy, as evidenced by the effects of the ferroptosis inducer erastin, the apoptosis inhibitor Z-VAD-FMK, and the autophagy inhibitor 3-methyladenine. Rescue experiments indicated that the antiferroptotic role of *SF3B1* in LUAD is partially mediated by upregulating the expression of SLC7A11.

24COASNO202:**Title- PHF10 inhibits gastric epithelium differentiation and induces gastric cancer carcinogenesis**

Zhiyuan Fan, Wenjing Yan, Jianfang Li, Min Yan, Bingya Liu, Zhongyin Yang & Beiqin Yu
Cancer Gene Ther . 2024 Oct;31(10):1511-1524.

DOI: <https://doi.org/10.1038/s41417-024-00820-5>.

Abstract: Gastric cancer (GC) is characterized with differentiation disorders, the precise mechanisms of which remain unknown. Our previous study showed that PHF10 exhibits oncogenic properties in GC, with its histological presentation indicating a potential role in the modulation of differentiation disorders in GC. This study reveals a significant upregulation of PHF10 in GC tissues, showing a negative correlation with differentiation level. PHF10 was found to impede the differentiation of GC cells while promoting their stemness properties. This was attributed to the formation of a positive feedback loop between PHF10 and E2F1, resulting in dysregulated expression levels in GC. Additionally, PHF10 was found to mediate the transcriptional repression of the target gene DUSP5 in GC cells through the assembly of the SWI/SNF complex, leading to an elevation in pERK1/2 levels. In GC tissues, a negative association was noted between the expression of E2F1 or PHF10 and DUSP5, whereas a positive correlation was observed between the expression of E2F1 or PHF10 and pERK1/2. Additional rescue experiments confirmed that the inhibitory effect on differentiation of GC cells by PHF10 is dependent on the DUSP5-pERK1/2 axis. The signaling cascade involving E2F1-PHF10-DUSP5-pERK1/2 was identified as an important player in regulating differentiation and stemness in GC cells. PHF10 emerges as a promising target for differentiation induction therapy in GC.

24COASNO203:

Title- UGT1A7 altered HER2-positive breast cancer response to trastuzumab by affecting epithelial-to-mesenchymal transition: A potential biomarker to identify patients resistant to trastuzumab treatment

Cong Wang, Chenguang Bai, Zhe Zhang, Hao Zhou, Huanyao Gao, Siwei Wang & Yuan Yuan

Cancer Gene Ther . 2024 Oct;31(10):1525-1535.

DOI: <https://doi.org/10.1038/s41417-024-00819-y>.

Abstract: HER2-positive (HER2+) breast cancer accounts for 20–30% of all breast cancers. Although trastuzumab has significantly improved the survival of patients with HER2+ breast cancer, more than 70% of patients develop drug resistance within one year of treatment. Differential-gene-expression analysis of trastuzumab-sensitive and resistant HER2+ breast cancer cell lines from GSE15043 was performed to identify the biomarkers associated with trastuzumab resistance. Differential biomarker expression was confirmed in FFPE tissues collected from clinical HER2+ breast cancer tumor samples that were sensitive or resistant to trastuzumab treatment. UGT1A7, a member of the uronic acid transferase family, was associated with trastuzumab resistance. UGT1A7 expression was downregulated in trastuzumab-resistant tumor tissues and in a cell line that developed trastuzumab resistance (BT474TR). Overexpressing UGT1A7 in BT474TR restored their sensitivity to trastuzumab treatment, whereas downregulating UGT1A7 expression in parental cells led to trastuzumab resistance. Importantly, UGT1A7 localized to the endoplasmic reticulum and altered stress responses. Furthermore, downregulating UGT1A7 expression promoted epithelial-to-mesenchymal transition (EMT) by affecting TWIST, SNAIL, and GRP78 expression and the AMP-activated protein kinase signaling pathway, thus contributing to trastuzumab resistance. This study demonstrated the important role and novel mechanisms of UGT1A7 in tumor responses to trastuzumab. Low UGT1A7 expression plays an important role in EMT and contributes to trastuzumab resistance. UGT1A7 has the potential to be developed as a biomarker for identifying patients who are resistant to trastuzumab treatment.

24COASNO204:

Title- Long noncoding RNA *EPCART* regulates translation through PI3K/AKT/mTOR pathway and PDCD4 in prostate cancer

Annika Kohvakka, Mina Sattari, Janika Nättinen, Ulla Aapola, Pavlína Gregorová, Teuvo L. J. Tammela,

Cancer Gene Ther . 2024 Oct;31(10):1536-1546.

DOI: <https://doi.org/10.1038/s41417-024-00822-3>.

Abstract: While hundreds of cancer-associated long noncoding RNAs (lncRNAs) have been discovered, their functional role in cancer cells is still largely a mystery. An increasing number of lncRNAs are recognized to function in the cytoplasm, e.g., as modulators of translation. Here, we investigated the detailed molecular identity and functional role of *EPCART*, a lncRNA we previously discovered to be a potential oncogene in prostate cancer (PCa). First, we interrogated the transcript structure of *EPCART* and then confirmed *EPCART* to be a non-peptide-coding lncRNA using in silico methods. Pathway

analysis of differentially expressed protein-coding genes in *EPCART* knockout cells implied that *EPCART* modulates the translational machinery of PCa cells. *EPCART* was also largely located in the cytoplasm and at the sites of translation. With quantitative proteome analysis on *EPCART* knockout cells we discovered PDCD4, an inhibitor of protein translation, to be increased by *EPCART* reduction. Further studies indicated that the inhibitory effect of *EPCART* silencing on translation was mediated by reduced activation of AKT and inhibition of the mTORC1 pathway. Together, our findings identify *EPCART* as a translation-associated lncRNA that functions via modulation of the PI3K/AKT/mTORC1 pathway in PCa cells. Furthermore, we provide evidence for the prognostic potential of PDCD4 in PCa tumors in connection with *EPCART*.

24COASNO205:**Title- Mesothelin expression correlates with elevated inhibitory immune activity in patients with colorectal cancer**

Midhun Malla, Sachin Kumar Deshmukh, Sharon Wu, Timothy Samec, Dane C. Olevian, Reima El Naili, Bassel El-Rayes,
Cancer Gene Ther . 2024 Oct;31(10):1547-1558.

DOI: <https://doi.org/10.1038/s41417-024-00816-1>.

Abstract: The expression of the protein *Mesothelin* (*MSLN*) is highly variable in several malignancies, including colorectal cancer (CRC), and high levels are associated with aggressive clinicopathological features and worse patient survival. Colorectal cancer is both a common and deadly cancer; being the third most common in incidence and second most common cause of cancer-related death. While systemic therapy remains the primary therapeutic option for most patients with stage IV (metastatic; m) CRC, their disease eventually becomes treatment refractory, and 85% succumb within 5 years. Microsatellite-stable (MSS) CRC tumors, which constitute more than 90% of patients with mCRC, are generally refractory to immunotherapeutic interventions. In our current work, we characterize *MSLN* levels in CRC, specifically correlating expression with clinical outcomes in relevant CRC subtypes, and explore how *MSLN* expression impacts the status of immune activation and suppression in the peritumoral microenvironment. Higher *MSLN* expression is prevalent in CMS1 and CMS4 CRC subtypes and correlates with higher gene mutation rates across the patient cohorts. Further, *MSLN*-high patients exhibit increased M1/M2 macrophage infiltration, PD-L1 staining, immune-inhibitory gene expression, enrichment in inflammatory, TGF- β , IL6/JAK/STAT3, IL2/STAT5 signaling pathways, and mutation in *KRAS* and *FBXW7*. Together, these results suggest that *MSLN* protein is a potential target for antigen-specific therapy and supports investigation into its tumorigenic effects to identify possible therapeutic interventions for patients with high *MSLN* expressing MSS CRC.

24COASNO206:**Title- Identification of KIFC1 as a putative vulnerability in lung cancers with centrosome amplification**

Christopher Zhang, Benson Z. Wu, Caterina Di Ciano-Oliveira, Yin Fang Wu, Sharon S. Khavkine Binstock,

Cancer Gene Ther . 2024 Oct;31(10):1559-1570.

DOI: <https://doi.org/10.1038/s41417-024-00824-1>.

Abstract: Centrosome amplification (CA), an abnormal increase in the number of centrosomes in the cell, is a recurrent phenomenon in lung and other malignancies. Although CA promotes tumor development and progression by inducing genomic instability (GIN), it also induces mitotic stress that jeopardizes cellular integrity. CA leads to the formation of multipolar mitotic spindles that can cause lethal chromosome segregation errors. To sustain the benefits of CA by mitigating its consequences, malignant cells are dependent on adaptive mechanisms that represent therapeutic vulnerabilities. We aimed to discover genetic dependencies associated with CA in lung cancer. Combining a CRISPR/Cas9 functional genomics screen with tumor genomic analyses, we identified the motor protein KIFC1, also known as HSET, as a putative vulnerability specifically in lung adenocarcinoma (LUAD) with CA. KIFC1 expression was positively correlated with CA in LUAD and associated with worse patient outcomes, smoking history, and indicators of GIN. KIFC1 loss-of-function sensitized LUAD cells with high basal KIFC1 expression to potentiation of CA, which was associated with a diminished ability to cluster extra centrosomes into pseudo-bipolar mitotic spindles. Our work suggests that KIFC1 inhibition represents a novel approach for potentiating GIN to lethal levels in LUAD with CA by forcing cells to divide with multipolar spindles, rationalizing further studies to investigate its therapeutic potential.

24COASNO207:

Title- FGFR4-specific CAR-T cells with inducible caspase-9 suicide gene as an approach to treat rhabdomyosarcoma

Wei Xiao, Liping Xu, Jinghua Wang, Kuai Yu, Bushu Xu, Yi Que, Jingjing Zhao, Qiuzhong Pan,

Cancer Gene Ther . 2024 Oct;31(10):1571-1584.

DOI: <https://doi.org/10.1038/s41417-024-00823-2>.

Abstract: Metastatic rhabdomyosarcoma is associated with poor survival and unsatisfactory treatment outcomes. Therefore, new immunotherapeutic methods are urgently required. Fibroblast growth factor receptor 4 (FGFR4), a new therapeutic target for rhabdomyosarcoma, plays a crucial role in its onset and development. This study aimed to generate FGFR4 single-chain variable fragment-based chimeric antigen receptor (CAR) T cells without causing evident toxicity and incorporating an inducible caspase-9 (iCasp9) suicide gene system to enhance their safety. FGFR4 antigen expression was evaluated in normal murine tissues, normal human tissues, and specimens from patients with rhabdomyosarcoma. Combined with a 4-1BB co-stimulatory domain, a CD3 ζ signaling domain, and an iCasp9 suicide gene, CAR-T cells with an FGFR4-specific single-chain variable fragment were developed. The specific cytotoxic effects, T-cell proliferation, cytokine secretion, apoptosis induction by chemical dimerization (AP20187), and toxicity of FGFR4 CAR-T cells were investigated in vitro and in vivo. FGFR4 CAR-T cells generated a variety of immune-promoting cytokines, including tumor necrosis factor α , interleukin 2, and interferon γ , and displayed effective cytotoxic activity against FGFR4-overexpressing rhabdomyosarcoma cells in vitro. FGFR4 CAR-T cells were relatively effective against

FGFR4-overexpressing rhabdomyosarcoma, with tumor regression and poor survival in a subcutaneous xenograft model. The iCasp9 gene was incorporated into FGFR4 CAR-T cells and it was demonstrated that effective and reliable suicide gene activity depends on the administration of AP20187. By making use of the cross-reaction of FGFR4 CAR-T cells with murine FGFR4 in a syngeneic tumor model, this study found that FGFR4 CAR-T cells could regulate the growth of tumors without evident toxicity. Our study demonstrates that FGFR4 is a prospective target for CAR-T cell therapy in rhabdomyosarcoma without serious on-target off-tumor toxicity. FGFR4 CAR-T cells with the iCasp9 suicide gene system as a safety switch to limit toxicity may broaden the clinical applications of cellular therapy.

24COASNO208:

Title- ZNF460-mediated upregulation of APCDD1L-DT promotes cholangiocarcinoma development by inhibiting the ubiquitin-mediated degradation of DVL2

Xin Gao, Xinlei Zou, Canghai Guan, Xiangjun Sha, Sidi Liu, Xinmiao Zhang, Chengru Yang,

Cancer Gene Ther . 2024 Oct;31(10):1585-1597.

DOI: <https://doi.org/10.1038/s41417-024-00826-z>.

Abstract: Cholangiocarcinoma (CCA), known for its aggressive nature, poses a formidable challenge in the current medical landscape, particularly in targeted therapies. Against this backdrop, long non-coding RNAs (lncRNAs) have captured the attention of researchers. These unique RNAs are believed to play pivotal roles in various cancers, offering promising avenues for the development of more effective treatment strategies. Previous studies have substantiated the aberrant expression of the APCDD1L-DT in numerous human tumors, demonstrating its positive regulatory roles in disease progression. Nevertheless, the biological functions of APCDD1L-DT in CCA are still not fully understood. This study marks the inaugural documentation of APCDD1L-DT exhibiting aberrant expression in CCA specimen, establishing a close correlation with the TNM staging of tumor patients. Furthermore, suppressing APCDD1L-DT expression hinders both the viability and motility of tumor cells. Mechanistically, the abnormal activation of the transcription factor ZNF460 positively regulated APCDD1L-DT expression in CCA. This activation, in turn, propels the abnormal activation of the Wnt pathway, fostering tumor development by impeding the ubiquitin-mediated degradation of DVL2. Broadly speaking, this study provides auspicious perspectives for comprehending CCA and furnishes support for addressing this daunting malignancy.

24COASNO209:

Title- Machine learning based on biological context facilitates the identification of microvascular invasion in intrahepatic cholangiocarcinoma

Shuaishuai Xu, Mingyu Wan, Chanqi Ye, Ruyin Chen, Qiong Li, Xiaochen Zhang, Jian Ruan
Carcinogenesis . 2024 Oct 10;45(10):721-734.

<https://DOI.org/10.1093/carcin/bgae052>

Abstract: Intrahepatic cholangiocarcinoma is a rare disease associated with a poor prognosis, primarily due to early recurrence and metastasis. An important feature of this condition is

microvascular invasion (MVI). However, current predictive models based on imaging have limited efficacy in this regard. This study employed a random forest model to construct a predictive model for MVI identification and uncover its biological basis. Single-cell transcriptome sequencing, whole exome sequencing, and proteome sequencing were performed. The area under the curve of the prediction model in the validation set was 0.93. Further analysis indicated that MVI-associated tumor cells exhibited functional changes related to epithelial–mesenchymal transition and lipid metabolism due to alterations in the nuclear factor-kappa B and mitogen-activated protein kinase signaling pathways. Tumor cells were also differentially enriched for the interleukin-17 signaling pathway. There was less infiltration of SLC30A1⁺ CD8⁺ T cells expressing cytotoxic genes in MVI-associated intrahepatic cholangiocarcinoma, whereas there was more infiltration of myeloid cells with attenuated expression of the major histocompatibility complex II pathway. Additionally, MVI-associated intercellular communication was closely related to the SPP1–CD44 and ANXA1–FPR1 pathways. These findings resulted in a brilliant predictive model and fresh insights into MVI.

24COASNO210:

Title- Intratumoral vitamin D signaling and lethal prostate cancer

Jane B Vasselkiv, Irene M Shui, Sydney T Grob, Caroline I Ericsson, Isabel Giovannucci, Cheng Peng,

Carcinogenesis . 2024 Oct 10;45(10):735-744.

<https://doi.org/10.1093/carcin/bgae055>

Abstract: High circulating vitamin D levels and supplementation may lower prostate cancer mortality. To probe for direct effects of vitamin D signaling in the primary tumor, we assessed how activation of intratumoral vitamin D signaling in prostate cancer is associated with lethal prostate cancer during long-term follow-up. Among 404 participants with primary prostate cancer in the Health Professionals Follow-up Study and the Physicians' Health Study, we defined a gene score of expected activated intratumoral vitamin D signaling consisting of transcriptionally upregulated (*CYP27A1*, *CYP2R1*, *RXRA*, *RXRB*, and *VDR*) and downregulated genes (*CYP24A1* and *DHCR7*). We contrasted vitamin D signaling in tumors that progressed to lethal disease (metastases/prostate cancer-specific death, $n = 119$) over up to three decades of follow-up with indolent tumors that remained nonmetastatic for >8 years post-diagnosis ($n = 285$). The gene score was downregulated in tumor tissue compared with tumor-adjacent histologically normal tissue of the same men. Higher vitamin D gene scores were inversely associated with lethal prostate cancer (odds ratio for highest versus lowest quartile: 0.46, 95% confidence interval: 0.21–0.99) in a dose–response fashion and after adjusting for clinical and pathologic factors. This association appeared strongest among men with high predicted plasma 25-hydroxyvitamin D₃ and men with body mass index ≥ 25 kg/m². Findings were replicated with broader gene sets. These data support the hypothesis that active intratumoral vitamin D signaling is associated with better prostate cancer outcomes and provide further rationale for testing how vitamin D-related interventions after diagnosis could improve prostate cancer survival through effects on the tumor.

24COASNO211:**Title- ETS1 deficiency in macrophages suppresses colorectal cancer progression by reducing the F4/80⁺TIM4⁺ macrophage population**

Yuanyuan Cao, Anning Guo, Muxin Li, Xinghua Ma, Xiaofeng Bian, YiRong Chen, Caixia Zhang, Shijia Huang, Wei Zhao, Shuli Zhao

Carcinogenesis . 2024 Oct 10;45(10):745-758

<https://DOI.org/10.1093/carcin/bgae058>

Abstract: Tumor-associated macrophages (TAMs) take on pivotal and complex roles in the tumor microenvironment (TME); however, their heterogeneity in the TME remains incompletely understood. ETS proto-oncogene 1 (ETS1) is a transcription factor that is mainly expressed in lymphocytes. However, its expression and immunoregulatory role in colorectal cancer (CRC)-associated macrophages remain unclear. In the study, the expression levels of ETS1 in CD68⁺ macrophages in the CRC microenvironment were significantly higher than those in matched paracarcinoma tissues. Importantly, ETS1 increased the levels of chemokines C-C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 10 (CXCL10) in lipopolysaccharide-stimulated THP-1 cells. It also boosted the migration and invasion of CRC cells during the *in vitro* co-culture. In the ETS1 conditional knockout mouse model, ETS1 deficiency in macrophages ameliorated the histological changes in DSS-induced ulcerative colitis mouse models and prolonged the survival in an azomethane/dextran sodium sulfate (AOM/DSS)-induced CRC model. ETS1 deficiency in macrophages substantially inhibited tumor formation, reduced F4/80⁺TIM4⁺ macrophages in the mesenteric lymph nodes, and decreased CCL2 and CXCL10 protein levels in tumor tissues. Moreover, ETS1 deficiency in macrophages effectively prevented liver metastasis of CRC and reduced the infiltration of TAMs into the metastasis sites. Subsequent studies have indicated that ETS1 upregulated the expression of T-cell immunoglobulin mucin receptor 4 in macrophages through the signal transducer and activator of the transcription 1 signaling pathway activated by the autocrine action of CCL2/CXCL10. Collectively, ETS1 deficiency in macrophages potentiates antitumor immune responses by repressing CCL2 and CXCL10 expression, shedding light on potential therapeutic strategies for CRC.

24COASNO212:**Title- Dehydroabietylamine exerts antitumor effects by affecting nucleotide metabolism in gastric cancer**

Jingsong Ma, Jiabao Zhao, Zhengxin Wu, Jinshui Tan, Meijuan Xu, Wenjie Ye, Mengya Zhong,

Carcinogenesis . 2024 Oct 10;45(10):759-772

<https://DOI.org/10.1093/carcin/bgae037>

Abstract: Nucleotide metabolism is the ultimate and most critical link in the self-replication process of tumors, including gastric cancer (GC). However, in clinical treatment, classic antitumor drugs such as 5-fluorouracil (5-FU) are mostly metabolic analogs of purines or pyrimidines, which lack specificity for tumor cells and therefore have significant side effects. It is unclear whether there are other drugs that can target nucleotide metabolism, except for nucleic acid analogs. Here, we found that a natural compound, dehydroabietylamine

(DHAA), significantly reduced the viability and proliferation of GC cells and organoids. DHAA disrupts the purine and pyrimidine metabolism of GC cells, causing DNA damage and further inducing apoptosis. DHAA treatment decreased transcription and protein levels of key enzymes involved in the nucleotide metabolism pathway, with significant reductions in the expression of pyrimidine metabolism key enzymes CAD, DHODH, and purine metabolism key enzymes PAICS. We also found that DHAA directly binds to and reduces the expression of Forkhead box K2 (FOXK2), a common transcription factor for these metabolic enzymes. Ultimately, DHAA was shown to delay tumorigenesis in *K19-Wnt1/C2mE* transgenic mice model and reduce levels of CAD, DHODH, and PAICS *in vivo*. We demonstrate that DHAA exerts an anticancer effect on GC by targeting transcription factor FOXK2, reducing transcription of key genes for nucleotide metabolism and impairing nucleotide biosynthesis, thus DHAA is a promising candidate for GC therapy.

24COASNO213:

Title- Colorectal cancer cells with high metastatic potential drive metastasis by transmitting exosomal miR-20a-3p through modulating NF1/MAPK pathway

Yahang Liang, Junyu Li, Tao Li, Mingming Li, Hualin Liao, Yang Liu, Yao Yao, Lingling Yang, Xiong Lei

Carcinogenesis . 2024 Oct 10;45(10):773-785.

<https://doi.org/10.1093/carcin/bgae036>

Abstract: Cancer cells exhibit heterogeneous metastatic potential, and high metastatic (HM) subclones can enhance the metastatic potential of low metastatic subclones by transmitting some factors. Exosomal miRNAs play a pivotal role in the crosstalk of heterogeneous metastatic subclones. This study discovered that miR-20a-3p was upregulated in colorectal adenocarcinoma (CRA), correlated with metastasis, and potentially served as a prognostic indicator for CRA. miR-20a-3p could promote the proliferation, migration, and invasion of CRA cells. Interestingly, HM CRA cells could promote malignant phenotypes of low metastatic CRA cells by transmitting exosomal miR-20a-3p. Mechanically, miR-20a-3p could inhibit neurofibromin 1(NF1), thereby activate the rat sarcoma viral oncogene (RAS)-mediated mitogen-activated protein kinases (MAPK) signaling pathway to drive the metastasis of CRA. In summary, our study provided evidence that colorectal cancer cells with HM potential drive metastasis by transmitting exosomal miR-20a-3p through modulating the NF1/MAPK pathway.

24COASNO214:

Title- CDK12 is a promising therapeutic target for the transcription cycle and DNA damage response in metastatic osteosarcoma

Zihao Li, Xiaoyang Li, Nicole A Seebacher, Xu Liu, Wence Wu, Shengji Yu, Francis J Hornicek, Changzhi Huang, Zhenfeng Duan

Carcinogenesis . 2024 Oct 10;45(10):786-798

<https://doi.org/10.1093/carcin/bgae051>

Abstract: Osteosarcoma (OS) is a bone malignant tumor affecting children, adolescents, and young adults. Currently, osteosarcoma is treated with chemotherapy regimens established

over 40 years ago. The investigation of novel therapeutic strategies for the treatment of osteosarcoma remains an important clinical need. Cyclin-dependent kinases (CDKs) have been considered promising molecular targets in cancer therapy. Among these, CDK12 has been shown to play a crucial role in the pathogenesis of malignancies, but its clinical significance and biological mechanisms in osteosarcoma remain unclear. In the present study, we aim to determine the expression and function of CDK12 and evaluate its prognostic and therapeutic value in metastatic osteosarcoma. We found that overexpression of CDK12 was associated with high tumor grade, tumor progression and reduced patient survival. The underlying mechanism revealed that knockdown of CDK12 expression with small interfering RNA or functional inhibition with the CDK12-targeting agent THZ531 effectively exhibited time- and dose-dependent cytotoxicity. Downregulation of CDK12 paused transcription by reducing RNAP II phosphorylation, interfered with DNA damage repair with increased γ H2AX, and decreased cell proliferation through the PI3K-AKT pathway. This was accompanied by the promotion of apoptosis, as evidenced by enhanced Bax expression and reduced Bcl-xL expression. Furthermore, the CDK12 selective inhibitor THZ531 also hindered *ex vivo* 3D spheroid formation, growth of *in vitro* 2D cell colony, and prevented cell mobility. Our findings highlight the clinical importance of CDK12 as a potentially valuable prognostic biomarker and therapeutic target in metastatic osteosarcoma.

24COASNO215:**Title- Epidemiology, treatment patterns, and clinical outcomes in de novo oligometastatic hormone-sensitive prostate cancer**

Jun Gong MD, Jessica L. Janes MA, Claire Trustram Eve BS, Shannon Stock PhD, Justin Waller MS, Amanda M. De Hoedt MS, Jeri Kim MD,

Cancer Volume 130, Issue 22 Nov 2024 Pages: 3815-3825

<https://DOI.org/10.1002/cncr.35466>

Abstract : In this observational retrospective Veterans Affairs cohort study, 20% of men had de novo oligometastatic hormone-sensitive prostate cancer (omHSPC). Although first-line (1L) novel hormonal therapy was similar between groups, 1L chemotherapy use was lower in omHSPC, more omHSPC patients received metastasis-directed therapy/prostate radiation therapy, and median overall survival and time to castration resistance was longer in men with omHSPC than non-omHSPC.

24COASNO216:**Title- Comparison of infection risk between enzalutamide and abiraterone in patients with prostate cancer**

Yan Hiu Athena Lee MBChB, Jeffrey Shi Kai Chan MBChB, MPH, FESC, Chi Ho Leung MSc, Alex Qinyang Liu MBChB, MRCS, ...

Cancer Volume 130, Issue 22 Nov 2024 Pages: 3826-3835

<https://doi.org/10.1002/cncr.35472>

Abstract : This study compared the risk of infections in patients with prostate cancer taking enzalutamide versus abiraterone. The results showed that enzalutamide users had a lower risk of sepsis, pneumonia, and cellulitis or skin abscess compared to those on abiraterone.

24COASNO217:

Title- Isolation, discrimination, and feeling “constant guilt”: A mixed-methods analysis of female physicians’ experience with fertility, family planning, and oncology careers

Sarah Marion MD, Shraddha M. Dalwadi MD, MBA, Aleksandra Kuczmarska-Haas MD,
Cancer Volume 130, Issue 22 Nov 2024 Pages: 3855-3862

<https://DOI.org/10.1002/cncr.35456>

Abstract : Many female physicians report feeling unsupported in the workplace with respect to family planning and gender discrimination, despite national policies to protect against unfair treatment. This mixed-methods study showed barriers to family planning in oncology exist across career domains from dysfunctional maternity leave to poor education on infertility risk.

24COASNO218:

Title- Prostate cancer in transgender women: A propensity score–matched analysis of disease severity and survival

Margaret Meagher MD, Kylie Morgan BS, Leah Deshler BS, Paul Riviere BS, Isabella Dolendo MD, Brent Rose MD, Christina Jamieson PhD, Sheldon Morris MD, Farnoosh Nik-Ahd MD, Stephen Freedland MD, Jennifer Anger MD, Amirali Salmasi MD

Cancer Volume 130, Issue 22 Nov 2024 Pages: 3863-3869

<https://doi.org/10.1002/cncr.35469>

Abstract : Despite the increasing availability of gender-affirming care, our understanding of prostate cancer (PCa) in transgender women (TGW) is limited. This study comparing oncological characteristics and survival outcomes between transgender and cisgender patients with PCa suggests comparable outcomes, which indicates the need for further investigation into PCa incidence and outcomes in TGW.

24COASNO219:

Title- Ambient air pollution and survival in childhood cancer: A nationwide survival analysis

Paul E. George MD, Jingxuan Zhao MPH, PhD, Donghai Liang PhD, Leticia M. Nogueira PhD

Cancer Volume 130, Issue 22 Nov 2024 Pages: 3870-3878

<https://DOI.org/10.1002/cncr.35484>

Abstract : Exposure to particulate matter consisting of fine particles less than or equal to 2.5 microns in diameter was significantly associated with worse overall survival in children with cancer, even at levels below US Environmental Protection Agency air quality standards. These findings highlight the need for stricter air quality regulations to protect vulnerable populations.

24COASNO220:**Title- Real-world genetic testing outcomes of pan-cancer testing for mismatch repair deficiency**

Teresa S. Chai BS, Linda H. Rodgers-Fouche MGC, Jenna O. Walls BS, Anthony R. Mattia MD, Daniel C. Chung MD

Cancer Volume 130, Issue 22 Nov 2024 Pages: 3888-3893

<https://DOI.org/10.1002/cncr.35473>

Abstract : The use of mismatch repair immunohistochemistry testing across tumor types has increased significantly in the age of immune checkpoint inhibitors. Pan-cancer mismatch repair-deficient immunohistochemistry testing has identified Lynch syndrome cases at a rate similar to the colorectal and endometrial cohorts.

24COASNO221:**Title- What do cancer genetic providers want us to know about variant reclassification and recontact that we are not asking? A thematic analysis of open-ended survey responses**

Kerri Brown PhD, Marisel Ponton MS, Elenita Davidson MS, Banu Arun MD, Robert J. Volk PhD, Sanjay Shete PhD, Susan K. Peterson PhD, Sukh Makhnoon MS, PhD

Cancer Volume 130, Issue 22 Nov 2024 Pages: 3926-3934

<https://DOI.org/10.1002/cncr.35429>

Abstract : Accurate variant classification and relaying reclassified results to patients is critical for hereditary cancer care delivery. This analysis of free-text responses from a large national survey of health care providers confirms previous themes of stakeholder opinions, adds previously unreported contextual details to qualify those themes, and identifies potential solutions to returning reclassified results.

Diagnostic Services

(Pathology, Cancer Screening & Radiodiagnosis)

24COASNO01:

Title- Cutting Edge: Low-dose Recombinant IL-2 Treatment Prevents Autoantibody Responses in Systemic Lupus Erythematosus via Regulatory T Cell-independent Depletion of T Follicular Helper Cells

Silvia Santana; Amber Papillion; Jeremy B. Foote; Holly Bachus; Beatriz León; Carmen De Miguel; André Ballesteros-Tato

The Journal of Immunology. 2024 Oct 15;213(8):1053-1060.

doi: <https://doi.org/10.4049/jimmunol.2400264>.

Abstract: The expansion of T follicular helper (Tfh) cells correlates with disease progression in human and murine systemic lupus erythematosus (SLE). Unfortunately, there are no therapies to deplete Tfh cells. Importantly, low-dose rIL-2-based immunotherapy shows potent immunosuppressive effects in SLE patients and lupus-prone mice, primarily attributed to the expansion of regulatory T cells (Tregs). However, IL-2 can also inhibit Tfh cell differentiation. In this study, we investigate the potential of low-dose rIL-2 to deplete Tfh cells and prevent autoantibody responses in SLE. Our data demonstrate that low-dose rIL-2 efficiently depletes autoreactive Tfh cells and prevents autoantibody responses in lupus-prone mice. Importantly, this immunosuppressive effect was independent of the presence of Tregs. The therapeutic potential of eliminating Tfh cells was confirmed by selectively deleting Tfh cells in lupus-prone mice. Our findings demonstrate the critical role of Tfh cells in promoting autoantibody responses and unveil, (to our knowledge), a novel Treg-independent immunosuppressive function of IL-2 in SLE.

24COASNO02:

Title- An Integrated Signaling Threshold Initiates IgG Response toward Virus-like Immunogens

Wei-Yun Wholey; Alexander R. Meyer; Sekou-Tidiane Yoda; James L. Mueller; Raisa Mathenge; Bryce Chackerian; Julie Zikherman; Wei Cheng

The Journal of Immunology. 2024 Oct 15;213(8):1061-1075.

doi: <https://doi.org/10.4049/jimmunol.2400101>.

Abstract: Class-switched neutralizing Ab (nAb) production is rapidly induced upon many viral infections. However, due to the presence of multiple components in virions, the precise biochemical and biophysical signals from viral infections that initiate nAb responses remain inadequately defined. Using a reductionist system of synthetic virus-like structures, in this study, we show that a foreign protein on a virion-sized liposome can serve as a stand-alone danger signal to initiate class-switched nAb responses without T cell help or TLR but requires CD19. Introduction of internal nucleic acids (iNAs) obviates the need for CD19, lowers the epitope density (ED) required to elicit the Ab response, and transforms these structures into highly potent immunogens that rival conventional virus-like particles in their ability to elicit strong Ag-specific IgG. As early as day 5 after immunization, structures harboring iNAs and decorated with just a few molecules of surface Ag at doses as low as 100

ng induced all IgG subclasses of Ab in mice and reproduced the IgG2a/2c restriction that is long observed in live viral infections. These findings reveal a shared mechanism for the nAb response in mice. High ED is capable but not necessary for driving Ab secretion. Instead, even a few molecules of surface Ag, when combined with nucleic acids within these structures, can trigger strong IgG production. As a result, the signaling threshold for induction of IgG in individual B cells is set by dual signals originating from both ED on the surface and the presence of iNAs within viral particulate immunogens.

24COASNO03:

Title- CD9 and Aryl Hydrocarbon Receptor Are Markers of Human CD19⁺CD14⁺ Atypical B Cells and Are Dysregulated in Systemic Lupus Erythematosus Disease

Lance K. Blevins; D M Isha Olive Khan; Robert B. Crawford; Christine O'Neill; Anthony P. Bach; Jiajun Zhou;

The Journal of Immunology. 2024 Oct 15;213(8):1076-1092.

doi: <https://doi.org/10.4049/jimmunol.2400193>.

Abstract: Aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor whose expression regulates immune cell differentiation. Single-cell transcriptomic profiling was used to ascertain the heterogeneity of AHR expression in human B cell subpopulations. We identified a unique population of B cells marked by expression of *AHR*, *CD9*, and myeloid genes such as *CD14* and *CXCL8*. Results were confirmed directly in human PBMCs and purified B cells at the protein level. TLR9 signaling induced *CD14*, *CD9*, and *IL-8* protein expression in *CD19⁺* B cells. *CD14*-expressing *CD9⁺* B cells also highly expressed *AHR* and atypical B cell markers such as *CD11c* and *TBET*. In patients with active lupus disease, *CD14⁺* and *CD9⁺* B cells are dysregulated, with loss of *CD9⁺* B cells strongly predicting disease severity and demonstrating the relevance of *CD9⁺* B cells in systemic lupus erythematosus and autoimmune disease.

24COASNO04:

Title- Orientation Regulation of Class-switch Recombination in Human B Cells

Likun Du; Valentyn Oksenych; Hui Wan; Xiaofei Ye; Junchao Dong; Adam Yongxin Ye; Hassan Abolhassani; Stelios Vlachiotis;

European Journal of Immunology. 2000 Apr;30(4):1019-29.

[https://doi.org/10.1002/\(SICI\)1521-4141\(200004\)30:4<1019::AID-IMMU1019>3.0.CO;2-W](https://doi.org/10.1002/(SICI)1521-4141(200004)30:4<1019::AID-IMMU1019>3.0.CO;2-W)

Abstract: We developed a linear amplification-mediated high-throughput genome-wide translocation sequencing method to profile Ig class-switch recombination (CSR) in human B cells in an unbiased and quantitative manner. This enables us to characterize CSR junctions resulting from either deletional recombination or inversion for each Ig class/subclass. Our data showed that more than 90% of CSR junctions detected in peripheral blood in healthy control subjects were due to deletional recombination. We further identified two major CSR junction signatures/patterns in human B cells. Signature 1 consists of recombination junctions resulting from both IgG and IgA switching, with a dominance of *Sμ-Sγ* junctions (72%) and

deletional recombination (87%). Signature 2 is contributed mainly by *Sμ-Sα* junctions (96%), and these junctions were almost all due to deletional recombination (99%) and were characterized by longer microhomologies. CSR junctions identified in healthy individuals can be assigned to both signatures but with a dominance of signature 1, whereas almost all CSR junctions found in patients with defects in DNA-PKcs or Artemis, two classical nonhomologous end joining (c-NHEJ) factors, align with signature 2. Thus, signature 1 may represent c-NHEJ activity during CSR, whereas signature 2 is associated with microhomology-mediated alternative end joining in the absence of the studied c-NHEJ factors. Our findings suggest that in human B cells, the efficiency of the c-NHEJ machinery and the features of switch regions are crucial for the regulation of CSR orientation. Finally, our high-throughput method can also be applied to study the mechanism of rare types of recombination, such as switching to IgD and locus suicide switching.

24COASNO05:

Title- Sequence Matters: Primary COVID-19 Vaccination after Infection Elicits Similar Anti-spike Antibody Levels, but Stronger Antibody Dependent Cell-mediated Cytotoxicity than Breakthrough Infection

Kayla A. Holder; Danielle P. Ings; Kathleen E. Fifield; David A. Barnes; Keeley A. Barnable; Debbie O. A. Harnum; Rodney S. Russell; Michael D. Grant

The Journal of Immunology. 2024 Oct 15;213(8):1105-1114.

doi: <https://doi.org/10.4049/jimmunol.2400250>.

Abstract: Infection before primary vaccination (herein termed “hybrid immunity”) engenders robust humoral immunity and broad Ab-dependent cell-mediated cytotoxicity (ADCC) across SARS-CoV-2 variants. We measured and compared plasma IgG and IgA against Wuhan-Hu-1 and Omicron (B.1.1.529) full-length spike (FLS) and receptor binding domain after three mRNA vaccines encoding Wuhan-Hu-1 spike (S) and after Omicron breakthrough infection. We also measured IgG binding to Wuhan-Hu-1 and Omicron S1, Wuhan-Hu-1 S2 and Wuhan-Hu-1 and Omicron cell-based S. We compared ADCC using human embryonic lung fibroblast (MRC-5) cells expressing Wuhan-Hu-1 or Omicron S. The effect of Omicron breakthrough infection on IgG anti-Wuhan-Hu-1 and Omicron FLS avidity was also considered. Despite Omicron breakthrough infection increasing IgG and IgA against FLS and receptor binding domain to levels similar to those seen with hybrid immunity, there was no boost to ADCC. Preferential recognition of Wuhan-Hu-1 persisted following Omicron breakthrough infection, which increased IgG avidity against Wuhan-Hu-1 FLS. Despite similar total anti-FLS IgG levels following breakthrough infection, 4-fold higher plasma concentrations were required to elicit ADCC comparable to that elicited by hybrid immunity. The greater capacity for hybrid immunity to elicit ADCC was associated with a differential IgG reactivity pattern against S1, S2, and linear determinants throughout FLS. Immunity against SARS-CoV-2 following Omicron breakthrough infection manifests significantly less ADCC capacity than hybrid immunity. Thus, the sequence of antigenic exposure by infection versus vaccination and other factors such as severity of infection affect antiviral functions of humoral immunity in the absence of overt quantitative differences in the humoral response.

24COASNO06:

Title- Ebi3 Binding to IFN- γ and IL-10 Limits Their Function

Ellen N. Scott; Cheng Ye; Hiroshi Yano; Zhanna Lipatova; Erin Brunazzi; Kate M. Vignali; Creg J. Workman; Dario A. A. Vignali

The Journal of Immunology(2024) 213 (8): 1115–1124.

doi: <https://doi.org/10.4049/jimmunol.2400236>.

Abstract: EBV-induced gene 3 (Ebi3) is a β subunit within the IL-12 cytokine family that canonically binds to α subunits p19, p28, or p35 to form the heterodimeric cytokines IL-39, IL-27, and IL-35, respectively. In the last decade, the binding partners for Ebi3 have continued to expand to include IL-6 and the other IL-12 family β subunit p40, revealing the possibility that Ebi3 may be able to bind to other cytokines and have distinct functions. We first explored this possibility utilizing an in vivo mouse model of regulatory T cell–restricted deletions of the subunits composing the cytokine IL-35, p35, and Ebi3, and we observed a differential impact on CD8⁺ T cell inhibitory receptor expression despite comparable reduction in tumor growth. We then screened the ability of Ebi3 to bind to different cytokines with varying structural resemblance to the IL-12 family α subunits. These in vitro screens revealed extracellular binding of Ebi3 to both IFN- γ and IL-10. Ebi3 bound to IFN- γ and IL-10 abrogated signal transduction and downstream functions of both cytokines. Lastly, we validated that extracellular complex formation after mixing native proteins resulted in loss of function. These data suggest that secreted partnerless Ebi3 may bind to cytokines within the extracellular microenvironment and act as a cytokine sink, further expanding the potential immunological impact of Ebi3.

24COASNO07:

Title- Understanding the Role of miR-29a in the Regulation of RAG1, a Gene Associated with the Development of the Immune System

Urbi Roy; Sagar Sanjiv Desai; Susmita Kumari; Tanzeem Bushra; Bibha Choudhary; Sathees C. Raghavan

The Journal of Immunology (2024) 213 (8): 1125–1138.

doi: <https://doi.org/10.4049/jimmunol.2300344>.

Abstract: The process of Ag receptor diversity is initiated by RAGs consisting of RAG1 and RAG2 in developing lymphocytes. Besides its role as a sequence-specific nuclease during V(D)J recombination, RAGs can also act as a structure-specific nuclease leading to genome instability. Thus, regulation of RAG expression is essential to maintaining genome stability. Previously, the role of miR29c in the regulation of RAG1 was identified. In this article, we report the regulation of RAG1 by miR-29a in the lymphocytes of both mice (*Mus musculus*) and humans (*Homo sapiens*). The level of RAG1 could be modulated by overexpression of miR-29a and inhibition using anti-miRs. Argonaute2-immunoprecipitation and high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation studies established the association of miR-29a and *RAG1* with Argonaute proteins. We observed a negative correlation between miR-29a and *RAG1* levels in mouse B and T cells and leukemia patients. Overexpression of pre-miR-29a in the bone marrow cells of mice led to the generation of mature miR-29a transcripts and reduced RAG1 expression, which led to a

significant reduction in V(D)J recombination in pro-B cells. Importantly, our studies are consistent with the phenotype reported in miR-29a knockout mice, which showed impaired immunity and survival defects. Finally, we show that although both miR-29c and miR-29a can regulate RAG1 at mRNA and protein levels, miR-29a substantially impacts immunity and survival. Our results reveal that the repression of RAG1 activity by miR-29a in B cells of mice and humans is essential to maintain Ig diversity and prevent hematological malignancies resulting from aberrant RAG1 expression in lymphocytes.

24COASNO08:

Title- Anti-Heat Shock Protein 70 Autoantibodies from Patients with Idiopathic Pulmonary Fibrosis Epigenetically Enhance Lung Fibroblast Apoptosis Resistance and Bcl-2 Expression

Baiyun Zhong; Jennifer Q. Zhou; Xing Lyu; Hui Liu; Kayu Yuan; Ming-Lei Guo; Steven R. Duncan; Yan Y. Sanders

The Journal of Immunology(2024) 213 (8): 1150–1156.

doi: <https://doi.org/10.4049/jimmunol.2400106>.

Abstract: IgG autoantibodies to heat shock protein 70 (HSP70) are found in many immune-mediated clinical syndromes, and their presence among patients with idiopathic pulmonary fibrosis (IPF) portends especially poor outcomes. However, pathological effects of IPF anti-HSP70 have not been studied extensively. IPF lung fibroblasts are apoptosis resistant, and this dysregulation contributes to the accumulation of fibroblasts that characterizes the disease. During stress, HSP70 protein is exported extracellularly, where it binds to cognate cell surface receptors that mediate a variety of functional effects, including apoptosis inhibition. We hypothesized anti-HSP70 could engage HSP70-receptor complexes on fibroblasts that alter their apoptosis susceptibility. We found HSP70 is ubiquitously expressed on primary human lung fibroblasts. Treatment with anti-HSP70 isolated from patients with IPF with acute exacerbations increased Bcl-2 expression in human lung fibroblasts and reduced their susceptibility to staurosporine-induced apoptosis. Chromatin immunoprecipitation assays showed Bcl-2 gene promoter regions are enriched with the active histone mark H4 lysine 16 acetylation, and this was increased in the autoantibody-treated fibroblasts. When H4 lysine 16 acetylation was decreased by knocking down its acetyltransferase, MOF (males absent on the first), the anti-HSP70 treatments failed to upregulate Bcl-2. This study describes a heretofore unknown, to our knowledge, pathogenic consequence of autoimmunity in which autoantibodies affect the epigenetic regulation of fibroblast apoptosis. In addition to IPF, this autoimmune process could also have relevance in other immunological syndromes characterized by anti-HSP70 autoimmunity. These findings lend credence to the importance of autoimmunity in IPF and illustrate pathways that could be targeted in innovative therapies for this morbid, medically refractory lung disease.

24COASNO09:

Title- Maternal Helminth Infection Causes Dysfunctional B Cell Development in Male Offspring

Lisa C. Gibbs; Juan M. Oviedo; Bartholomew N. Ondigo; Keke C. Fairfax

The Journal of Immunology. 2024 Oct 15;213(8):1157-1169.

doi: <https://doi.org/10.4049/jimmunol.2400158>.

Abstract: Infections during pregnancy are known to trigger alterations in offspring immunity, often leading to increased disease susceptibility. Maternal helminth infections correlate with lower Ab titers to certain childhood immunizations and putative decreased vaccine efficacy. The mechanisms that underlie how maternal infection blunts offspring humoral responses are unclear. Using our murine model of maternal schistosomiasis, we found that maternal helminth infection decreases the germinal center response of all offspring to tetanus immunization. However, only male offspring have defects in memory B cell and long-lived plasma cell generation. We found this sex-specific aberration begins during B cell development within the bone marrow via alteration of the IL-7 niche and persists throughout antigenic activation in the germinal center in the periphery. Critically, these defects in males are cell intrinsic, persisting following adoptive transfer to control male pups. Together, these data show that maternal infections can alter both the bone marrow microenvironment and the development of B lymphocytes in a sex-specific manner. This study correlates maternal infection induced defects in early life B cell development with ineffective Ab responses after vaccination.

24COASNO10:

Title- Glucocorticoid-mediated Suppression of Effector Programming Assists the Memory Transition of Virus-specific CD8⁺ T Cells

Azeez Tehseen; Dhaneshwar Kumar; Abhishek Dubey; Roman Sarkar; Sudhakar Singh; Sharvan Sehrawat

The Journal of Immunology. 2024 Oct 15;213(8):1170-1186.

doi: <https://doi.org/10.4049/jimmunol.2300513>.

Abstract: We demonstrate the role of signaling via the glucocorticoid receptor, NR3C1, in differentiation of CD8⁺ T cell memory. Pharmacological inhibition as well as the short hairpin RNA-mediated knockdown of the receptor hindered memory transition and limited the homeostatic turnover of the activated CD8⁺ T cells. Dexamethasone exposure of CD8⁺ T cells expanded during a resolving infection with influenza A virus or a γ -herpesvirus promoted conversion of effector cells into memory cells by modulating cellular metabolism and lowering the accumulation of reactive oxygen species. Reduced reactive oxygen species levels in the responding effector cells upregulated Bcl2 and enhanced survival. The generated virus-specific memory CD8⁺ T cells were efficiently recalled following challenge of animals with a secondary infection to control it better. The memory-enhancing effect was predominantly evident at low doses of dexamethasone. Therefore, controlled glucocorticoid signaling within the effector CD8⁺ T cells is crucial for optimal memory differentiation.

24COASNO11:

Title- Febrile Temperature Acts through HSP70–Toll4 Signaling to Improve Shrimp Resistance to White Spot Syndrome Virus

Bang Xiao; Yue Wang; Jianguo He; Chaozheng Li

The Journal of Immunology. 2024 Oct 15;213(8):1187-1201.

doi: <https://doi.org/10.4049/jimmunol.2400240>.

Abstract: In aquatic ectotherms, temperature plays a pivotal role in biological processes and the prevalence of viral diseases; however, the molecular mechanisms underlying these effects are not fully elucidated. In this study, we investigate the impact of elevated temperatures (32°C) on the immune response against white spot syndrome virus (WSSV) in shrimp (*Litopenaeus vannamei*). Our findings reveal that higher water temperatures, specifically 32°C, significantly inhibit WSSV replication and pathogenicity, thereby enhancing the survival rates of infected shrimp. Through transcriptome analysis and in vivo experiments, we identified heat shock protein 70 (HSP70) as a key factor in this thermal regulation of immunity. Shrimp maintained at 32°C, with silenced HSP70 expression, exhibited increased viral loads and reduced survival, underscoring the crucial protective role of HSP70 against WSSV at elevated temperatures. Our results further uncover the HSP70–Toll4–Dorsal–antimicrobial peptide (AMP) pathway as a key mediator of WSSV resistance at elevated temperatures. This pathway involves the interaction of HSP70 with the Toll4 receptor, resulting in the phosphorylation of Dorsal and the consequent modulation of expression of AMPs such as the *anti-LPS factor (ALF)* and *lysozyme (LYZ)* families. Taken together, these findings advance our understanding of temperature's role in disease dynamics in aquatic ectotherms, especially the unexpected roles of HSP70 in shrimp in facilitating the innate immune system's response to thermal stress, and suggest new approaches to managing WSSV in shrimp farming, such as environmental temperature control or HSP70 induction.

24COASNO12:

Title- IFN Receptor 2 Regulates TNF- α -Mediated Damaging Inflammation during *Aspergillus* Pulmonary Infection

Agnieszka Rynda-Apple; Jazmin Reyes Servin; Julianna Lenz; Julia Roemer; Evelyn E. Benson; Monica N. Hall; Kelly M. Shepardson

The Journal of Immunology. 2024 Oct 15;213(8):1202-1211.

doi: <https://doi.org/10.4049/jimmunol.2200686>.

Abstract: The increased incidence of invasive pulmonary aspergillosis, caused by *Aspergillus fumigatus*, occurring in patients infected with severe influenza or SARS-CoV-2, suggests that antiviral immune responses create an environment permissive to fungal infection. Our recent evidence suggests that absence of the type I IFN receptor 2 subunit (IFNAR2) of the heterodimeric IFNAR1/2 receptor is allowing for this permissive immune environment of the lung through regulation of damage responses. Because damage is associated with poor outcome to invasive pulmonary aspergillosis, this suggested that IFNAR2 may be involved in *A. fumigatus* susceptibility. In this study, we determined that absence of IFNAR2 resulted in increased inflammation, morbidity, and damage in the lungs in response to *A. fumigatus* challenge, whereas absence of IFNAR1 did not. Although

the *Ifnar2*^{-/-} mice had increased morbidity, we found that the *Ifnar2*^{-/-} mice cleared more conidia compared with both wild-type and *Ifnar1*^{-/-} mice. However, this early clearance did not prevent invasive disease from developing in the *Ifnar2*^{-/-} mice as infection progressed. Importantly, by altering the inflamed environment of the *Ifnar2*^{-/-} mice early during *A. fumigatus* infection, by neutralizing TNF- α , we were able to reduce the morbidity and fungal clearance in these mice back to wild-type levels. Together, our results establish a distinct role for IFNAR2 in regulating host damage responses to *A. fumigatus* and contributing to an *A. fumigatus*-permissive environment through regulation of inflammation. Specifically, our data reveal a role for IFNAR2 in regulating TNF- α -mediated damage and morbidity during *A. fumigatus* infection.

24COASNO13:

Title- MAFB in Macrophages Regulates Prostaglandin E₂-Mediated Lipid Mediator Class Switch through ALOX15 in Ischemic Acute Kidney Injury

Maho Kanai; Teppei Nishino; Dhouha Daassi; Akari Kimura; Ching-Wei Liao; Zeynab Javanfekr Shahri; Arata Wakimoto;

The Journal of Immunology. 2024 Oct 15;213(8):1212-1224.

doi: <https://doi.org/10.4049/jimmunol.2300844>.

Abstract: Monocytes and macrophages express the transcription factor MAFB (V-maf musculoaponeurotic fibrosarcoma oncogene homolog B) and protect against ischemic acute kidney injury (AKI). However, the mechanism through which MAFB alleviates AKI in macrophages remains unclear. In this study, we induced AKI in macrophage lineage-specific *Maifb*-deficient mice (C57BL/6J) using the ischemia-reperfusion injury model to analyze these mechanisms. Our results showed that MAFB regulates the expression of *Alox15* (arachidonate 15-lipoxygenase) in macrophages during ischemic AKI. The expression of ALOX15 was significantly decreased at the mRNA and protein levels in macrophages that infiltrated the kidneys of macrophage-specific *Maifb*-deficient mice at 24 h after ischemia-reperfusion injury. ALOX15 promotes the resolution of inflammation under acute conditions by producing specialized proresolving mediators by oxidizing essential fatty acids. Therefore, MAFB in macrophages promotes the resolution of inflammation in ischemic AKI by regulating the expression of *Alox15*. Moreover, MAFB expression in macrophages is upregulated via the COX-2/PGE₂/EP4 pathway in ischemic AKI. Our in vitro assay showed that MAFB regulates the expression of *Alox15* under the COX-2/PGE₂/EP4 pathway in macrophages. PGE₂ mediates the lipid mediator (LM) class switch from inflammatory LMs to specialized proresolving mediators. Therefore, MAFB plays a key role in the PGE₂-mediated LM class switch by regulating the expression of *Alox15*. Our study identified a previously unknown mechanism by which MAFB in macrophages alleviates ischemic AKI and provides new insights into regulating the LM class switch in acute inflammatory conditions.

24COASNO14:

Title- Potential Contributions of Human Endogenous Retroviruses in Innate Immune Memory

Pengcheng Du; Jiarui Li; Mingxi Hua; Liuluan Zhu; Chen Chen; Hui Zeng

The Journal of Immunology. 2024 Oct 15;213(8):1225-1233.

doi: <https://doi.org/10.4049/jimmunol.2300411>.

Abstract: The phenomenon wherein innate immune cells adopt long-term inflammatory phenotypes following the first stimuli is named trained immunity and can improve host defense against infections. Transcriptional and epigenetic reprogramming are critical mechanisms of trained immunity; however, the regulatory networks are not entirely clear at present. The human endogenous retroviruses (HERVs) provide large amounts of transcriptional regulators in the regulatory pathways. In this study, we analyzed published large omics data to explore the roles of such “dark matter” of the human genome in trained and tolerant macrophages. We collected 80 RNA sequencing data and 62 sequencing data to detect histone modifications and active regulatory regions from nine published studies on trained and tolerant macrophages. By analyzing the characteristics of transcription and epigenetic modification of HERVs, as well as their association with gene expression, we found that 15.3% of HERVs were transcribed nonrandomly from noncoding regions and enriched in specific HERV families and specific chromosomes, such as chromosomes 11, 15, 17, and 19, and they were highly related with the expression of adjacent genes. We found that 295 differentially expressed HERVs are located in 50-kbp flanking regions of 142 differentially expressed genes. We found epigenetic changes of these HERVs and that overlap with predicted enhancers and identified 35 enhancer-like HERVs. The related genes were highly involved in the activation and inflammatory responses, such as the TLR pathway. Other pathways including phosphoinositide signaling and transport of folate and K⁺ might be also related with trained immunity, which require further study. These results demonstrated that HERVs might play important roles in trained immunity.

24COASNO15:

Title- Structure of a Human Monoclonal Antibody in Complex with Outer Surface Protein C of the Lyme Disease Spirochete, *Borrelia burgdorferi*

Michael J. Rudolph; Yang Chen; Clint Vorauer; David J. Vance; Carol Lyn Piazza; Graham G. Willsey; Kathleen McCarthy; ...

The Journal of Immunology. 2024 Oct 15;213(8):1234-1243.

doi: <https://doi.org/10.4049/jimmunol.2400247>.

Abstract: Lyme disease is a tick-borne, multisystem infection caused by the spirochete *Borrelia burgdorferi*. Although Abs have been implicated in the resolution of Lyme disease, the specific B cell epitopes targeted during human infections remain largely unknown. In this study, we characterized and defined the structural epitope of a patient-derived bactericidal monoclonal IgG (B11) against outer surface protein C (OspC), a homodimeric lipoprotein necessary for *B. burgdorferi* tick-mediated transmission and early-stage colonization of vertebrate hosts. High-resolution epitope mapping was accomplished through hydrogen deuterium exchange–mass spectrometry and X-ray crystallography. Structural analysis of B11 Fab-OspC_A complexes revealed the B11 Fabs associated in a 1:1 stoichiometry with the lateral faces of OspC_A homodimers such that the Abs are essentially positioned perpendicular to the spirochete’s outer surface. B11’s primary contacts reside

within the membrane-proximal regions of α -helices 1 and 6 and adjacent loops 5 and 6 in one OspC_A monomer. In addition, B11 spans the OspC_A dimer interface, engaging opposing α -helix 1', α -helix 2', and loop 2–3' in the second OspC_A monomer. The B11-OspC_A structure is reminiscent of the recently solved mouse transmission blocking monoclonal IgG B5 in complex with OspC_A, indicating a mode of engagement with OspC that is conserved across species. In conclusion, we provide a detailed insight into the interaction between a functional human Ab and an immunodominant Lyme disease Ag long considered an important vaccine candidate.

24COASNO16:

Title- ITPK1 Sensitizes Tumor Cells to IgA-dependent Neutrophil Killing In Vivo

Connor A. Richterich; Meike E. W. Logtenberg; Marco J. H. Jansen; Mireille Toebes; Kaspar Bresser; Anne Borst; Anouk P. Jurgens; Jeanette H. W. Leusen; Ton N. Schumacher

The Journal of Immunology. 2024 Oct 15;213(8):1244-1254.

doi: <https://doi.org/10.4049/jimmunol.2300372>.

Abstract: Neutrophils can efficiently trigger cytotoxicity toward tumor cells and other target cells upon engagement of the IgA receptor CD89. However, the cell-intrinsic factors that influence the induction of cell death upon exposure to neutrophil effector mechanisms in vivo remain largely unknown. To uncover genetic regulators that influence target cell sensitivity to IgA-induced neutrophil-mediated killing, we used a human CD89 (hCD89) transgenic mouse model in which IgA-mediated killing of Her2-positive CD47-deficient murine target cells is mediated by neutrophils. Using a genome-wide in vivo screening approach, we demonstrate that deletion of the gene encoding inositol-tetrakisphosphate 1 kinase (ITPK1) increases survival of target cells in anti-Her2 IgA-treated mice. Moreover, we show that this effect depends on neutrophil activity and on the ITPK1 kinase domain. Notably, ITPK1 deficiency did not measurably impact survival of IgA-opsonized target cells in in vitro systems, underscoring the importance of in vivo screening systems to uncover physiologically relevant regulators of neutrophil killing.

24COASNO17:

Title- TLR7-Induced Mitochondrial Reactive Oxygen Species Production in Monocyte-derived Dendritic Cells Drives IL-12-Dependent NK Cell Activation and Enhances Antitumor Immunity

Ankush Paladhi; Samrat Daripa; Arghya Nath; Sumit Kumar Hira

The Journal of Immunology. 2024 Oct 15;213(8):1255-1263.

doi: <https://doi.org/10.4049/jimmunol.2400340>.

Abstract: Dendritic cell (DC)-based vaccines are promising immunotherapies for cancer. Although DC-based therapies are known to activate tumor-specific T cells, the interplay between DCs and NK cells in this setting is not fully understood. In this study, we demonstrated a novel TLR7/ mitochondrial reactive oxygen species (mROS)/IL-12 axis that drives potent NK cell responses against tumors. We showed that TLR7 activation by imiquimod in peripheral blood monocyte-derived CD11c⁺ DCs triggered mROS production, leading to enhanced IL-12 secretion and subsequent NK cell activation, as evidenced by

increased IFN- γ production and tumor cell cytotoxicity. Notably, mROS neutralization abrogates NK cell-mediated tumor cell lysis, and TLR7-mediated DC activation of NK cells occurs independently of MyD88, suggesting involvement of the noncanonical NF- κ B pathway. Our findings provide a rationale for targeting the TLR7/mROS/IL-12 axis to enhance the efficacy of DC-based cancer immunotherapy.

24COASNO18:

Title- Cutting Edge: Retinoic Acid Promotes Brain-homing of CD8⁺ T Cells during Congenital Cytomegalovirus Infection

Zachary T. Hilt; Wisler Charles; Taha Ali; Casey V. Smith; Shide Zhang; Samantha P. Wesnak; Norah L. Smith; Brian D. Rudd

The Journal of Immunology. 2024 Oct 1;213(7):933-939.

doi: <https://doi.org/10.4049/jimmunol.2400150>.

Abstract: The most common congenital viral infection is CMV, which leads to numerous neurologic disabilities. Using a mouse model of congenital CMV, we previously determined that Ag-specific CD8⁺ T cells traffic to the brain in a CCR9-dependent manner. The mechanism by which these CD8⁺ T cells acquire a CCR9-dependent “brain-tropic” phenotype remains unclear. In this study, we identify the key factor that imprints brain homing specificity on CD8⁺ T cells, the source of production, and the location where CCR9 expression is induced. Specifically, we discovered that CCR9 is induced on CD8⁺ T cells by retinoic acid-producing CD8 α ⁺ dendritic cells in the cervical lymph node postinfection. We found that retinoic acid is important for CD8⁺ T cells to establish tissue residency in the brain. Collectively, our data expand the role of retinoic acid during infection and mechanistically demonstrate how CD8⁺ T cells are primed to protect the brain during congenital viral infection.

24COASNO19:

Title- Gpx4 Regulates Invariant NKT Cell Homeostasis and Function by Preventing Lipid Peroxidation and Ferroptosis

Sophia P. M. Sok; Kaitlyn Pipkin; Narcis I. Popescu; Megan Reidy; Bin Li; Holly Van Remmen; Mike Kinter; Xiao-Hong Sun; Zhichao Fan; Meng Zhao

The Journal of Immunology. 2024 Oct 1;213(7):941-951.

doi: <https://doi.org/10.4049/jimmunol.2400246>.

Abstract: Invariant NKT (iNKT) cells are a group of innate-like T cells that plays important roles in immune homeostasis and activation. We found that iNKT cells, compared with CD4⁺ T cells, have significantly higher levels of lipid peroxidation in both mice and humans. Proteomic analysis also demonstrated that iNKT cells express higher levels of phospholipid hydroperoxidase glutathione peroxidase 4 (Gpx4), a major antioxidant enzyme that reduces lipid peroxidation and prevents ferroptosis. T cell-specific deletion of Gpx4 reduces iNKT cell population, most prominently the IFN- γ -producing NKT1 subset. RNA-sequencing analysis revealed that IFN- γ signaling, cell cycle regulation, and mitochondrial function are perturbed by Gpx4 deletion in iNKT cells. Consistently, we detected impaired cytokine production, elevated cell proliferation and cell death, and accumulation of lipid peroxides and

mitochondrial reactive oxygen species in Gpx4 knockout iNKT cells. Ferroptosis inhibitors, iron chelators, vitamin E, and vitamin K₂ can prevent ferroptosis induced by Gpx4 deficiency in iNKT cells and ameliorate the impaired function of iNKT cells due to Gpx4 inhibition. Last, vitamin E rescues iNKT cell population in Gpx4 knockout mice. Altogether, our findings reveal the critical role of Gpx4 in regulating iNKT cell homeostasis and function, through controlling lipid peroxidation and ferroptosis.

24COASNO20:

Title- A Chimeric IL-7R α /IL-2R β Receptor Promotes the Differentiation of T Cell Progenitors into B Cells and Type 2 Innate Lymphoid Cells

Akihiro Shimba; Shizue Tani-ichi; Kyoko Masuda; Guangwei Cui; Satoru Munakata; Shinya Abe; Satsuki Kitano; Hitoshi Miyachi; Hiroshi Kawamoto; Koichi Ikuta

The Journal of Immunology. 2024 Oct 1;213(7):952-964.

doi: <https://doi.org/10.4049/jimmunol.2300483>.

Abstract: IL-7 and IL-2 are evolutionarily related cytokines that play critical roles in the development and expansion of immune cells. Although both IL-7R and IL-2R activate similar signaling molecules, whether their signals have specific or overlapping functions during lymphocyte differentiation remains unclear. To address this question, we generated IL-7R α -chain (IL-7R α)/IL-2R β -chain (IL-2R β) (72R) knock-in mice expressing a chimeric receptor consisting of the extracellular domain of IL-7R α and the intracellular domain of IL-2R β under the control of the endogenous IL-7R α promoter. Notably, this 72R receptor induced higher levels of STAT5 and Akt phosphorylation in T cells. In the periphery of 72R mice, the number of T cells, B cells, and type 2 innate lymphoid cells (ILC2s) was increased, whereas early T cell progenitors and double-negative 2 thymocytes were reduced in the thymus. In addition, cell proliferation and Notch signaling were impaired in the early thymocytes of 72R mice, leading to their differentiation into thymic B cells. Interestingly, ILC2s were increased in the thymus of 72R mice. Early T cell progenitors from 72R mice, but not from wild-type mice, differentiated into NK cells and ILC2-like cells when cocultured with a thymic stromal cell line. Thus, this study indicates that the chimeric 72R receptor transduces more robust signals than the authentic IL-7R α , thereby inducing the alternative differentiation of T cell progenitors into other cell lineages. This suggests that cytokine receptors may provide instructive signals for cell fate decisions.

24COASNO21:

Title- Late-life Attenuation of Cytomegalovirus-mediated CD8 T Cell Memory Inflation: Shrinking of the Cytomegalovirus Latency Niche

Christopher P. Coplen; Sandip Ashok Sonar; Janko Ž. Nikolich

The Journal of Immunology. 2024 Oct 1;213(7):965-970.

doi: <https://doi.org/10.4049/jimmunol.2400113>.

Abstract: CMV drives the accumulation of virus-specific, highly differentiated CD8 memory T cells (memory inflation [MI]). In mice, MI was shown to directly correlate with the CMV infection dose, yet the CMV-associated CD8 MI plateaus over time. It is unclear how MI is regulated with aging. We infected young mice with 10², 10⁴, and 10⁶ PFU of

murine CMV and confirmed that MI magnitude was directly proportional to the infectious dose, reaching a setpoint by midlife. By old age, MI subsided, most prominently in mice infected with 10^6 PFU, and reached statistical parity between groups in 26-mo-old mice. This corresponded to an age-related loss in lymphatic endothelial cells in lymph nodes, recently shown to be sufficient to drive MI in mice. We propose that MI size and persistence over the lifespan is controlled by the size of the lymphatic endothelial cell niche, whose shrinking leads to reduced MI with aging.

24COASNO22:

Title- Glucocorticoids Suppress NF- κ B–Mediated Neutrophil Control of *Aspergillus fumigatus* Hyphal Growth

Savini U. Thrikawala; Molly H. Anderson; Emily E. Rosowski

The Journal of Immunology. 2024 Oct 1;213(7):971-987.

doi: <https://doi.org/10.4049/jimmunol.2400021>.

Abstract: Glucocorticoids are a major class of therapeutic anti-inflammatory and immunosuppressive drugs prescribed to patients with inflammatory diseases, to avoid transplant rejection, and as part of cancer chemotherapy. However, exposure to these drugs increases the risk of opportunistic infections such as with the fungus *Aspergillus fumigatus*, which causes mortality in >50% of infected patients. The mechanisms by which glucocorticoids increase susceptibility to *A. fumigatus* are poorly understood. In this article, we used a zebrafish larva *Aspergillus* infection model to identify innate immune mechanisms altered by glucocorticoid treatment. Infected larvae exposed to dexamethasone succumb to infection at a significantly higher rate than control larvae. However, both macrophages and neutrophils are still recruited to the site of infection, and dexamethasone treatment does not significantly affect fungal spore killing. Instead, the primary effect of dexamethasone manifests later in infection with treated larvae exhibiting increased invasive hyphal growth. In line with this, dexamethasone predominantly inhibits neutrophil function rather than macrophage function. Dexamethasone-induced mortality also depends on the glucocorticoid receptor. Dexamethasone partially suppresses NF- κ B activation at the infection site by inducing the transcription of I κ B via the glucocorticoid receptor. Independent CRISPR/Cas9 targeting of IKK γ to prevent NF- κ B activation also increases invasive *A. fumigatus* growth and larval mortality. However, dexamethasone treatment of IKK γ crispant larvae further increases invasive hyphal growth and host mortality, suggesting that dexamethasone may suppress other pathways in addition to NF- κ B to promote host susceptibility. Collectively, we find that dexamethasone acts through the glucocorticoid receptor to suppress NF- κ B–mediated neutrophil control of *A. fumigatus* hyphae in zebrafish larvae.

24COASNO23:

Title- Podosome Nucleation Is Facilitated by Multivalent Interactions between Syk and ITAM-containing Membrane Complexes

Sina Ghasempour; Aleixo M. Muise; Spencer A. Freeman

The Journal of Immunology. 2024 Oct 1;213(7):988-997.

doi: <https://doi.org/10.4049/jimmunol.2400031>.

Abstract: Immune cells survey their microenvironment by forming dynamic cellular protrusions that enable chemotaxis, contacts with other cells, and phagocytosis. Podosomes are a unique type of protrusion structured by an adhesive ring of active integrins that surround an F-actin-rich core harboring degradative proteases. Although the features of podosomes, once-established, have been well defined, the steps that lead to podosome formation remain poorly understood by comparison. In this study, we report that spleen tyrosine kinase (Syk) is a critical regulator of podosome formation. Deletion of Syk or targeting its kinase activity eliminated the ability for murine macrophages to form podosomes. We found that the kinase activity of Syk was important for the phosphorylation of its substrates, HS1 and Pyk2, both of which regulate podosome formation. Additionally, before podosomes form, we report that the tandem Src homology 2 domains of Syk afforded multivalent clustering of ITAM-containing adaptors that associated with integrins to structure platforms that initiate podosomes. We therefore propose that Syk has a dual role in regulating podosomes: first, by facilitating the assembly of multivalent signaling hubs that nucleate their formation and second, by sustaining tyrosine kinase activity of the podosomes once they form against their substrates. In cells expressing recently identified gain-of-function variants of SYK, podosomes were dysregulated. These results implicate SYK in the (patho)physiological functions of podosomes in macrophages.

24COASNO24:

Title- C1q/MASP Complexes—Hybrid Complexes of Classical and Lectin Pathway Proteins Are Found in the Circulation

Anne Rosbjerg; Tereza Alica Plchová; Rafael Bayarri-Olmos; Bettina Eide Holm; Ida Sandau Pedersen; Mikkel-Ole Skjoedt; Peter Garred

The Journal of Immunology. 2024 Oct 1;213(7):998-1007.

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Abstract: Complement pathways, traditionally regarded as separate entities in vitro, are increasingly noted for cross-communication and bypass mechanisms. Among these, the MBL/ficolin/CL-associated serine protease (MASP)-3, a component of lectin pathway pattern recognition molecules, has shown the ability to process critical substrates such as pro-factor D and insulin growth factor binding protein-5. Given shared features between lectin pathway pattern recognition molecules and C1q from the classical pathway, we hypothesized that C1q might be a viable in vivo binding partner for the MASPs. We used microscale thermophoresis, ELISA, and immunoprecipitation assays to detect C1q/MASP complexes and functionally assessed the complexes through enzymatic cleavage assays. C1q/MASP-3 complexes were detected in human serum and correlated well with MASP-3 serum levels in healthy individuals. The binding affinity between MASP-3 and C1q in vitro was in the nanomolar range, and the interaction was calcium-dependent, as demonstrated by their dissociation in the presence of EDTA. Furthermore, most of the circulating C1q-bound MASP-3 was activated. Based on immunoprecipitation, also C1q/MASP-2 complexes appeared to be present in serum. Finally, C1q/MASP-2 and C1q/MASP-3 in vitro complexes were able to cleave C4 and pro-factor D, respectively. Our study reveals the existence of C1q/MASP complexes in the circulation of healthy individuals, and both C1q/MASP-2 and

C1q/MASP-3 complexes display proteolytic activity. Hence, this study uncovers a crosstalk route between complement pathways not previously described.

24COASNO25:

Title- TLR3/TRIF and MAVS Signaling Is Essential in Regulating Mucosal T Cell Responses during Rotavirus Infection

Rong-Rong Zhang; Xue-Yao Yang; Yong-Lei Yang; Tian-Kui Guo; Jing-Shu Huang; Ying-Shi Yang; Chun-Wei Shi; ...

The Journal of Immunology. 2024 Oct 1;213(7):1008-1022.

doi: <https://doi.org/10.4049/jimmunol.2300867>.

Abstract: The functions of the natural dsRNA sensors TLR3 (TRIF) and RIG-I (MAVS) are crucial during viral challenge and have not been accurately clarified in adaptive immune responses to rotavirus (RV) infection. In this study, we found that RV infection caused severe pathological damage to the small intestine of TLR3^{-/-} and TRIF^{-/-} mice. Our data found that dendritic cells from TLR3^{-/-} and TRIF^{-/-} mice had impaired Ag presentation to the RV and attenuated initiation of T cells upon viral infection. These attenuated functions resulted in impaired CD4⁺ T and CD8⁺ T function in mice lacking TLR3-TRIF signaling postinfection. Additionally, attenuated proliferative capacity of T cells from TLR3^{-/-} and TRIF^{-/-} mice was observed. Subsequently, we observed a significant reduction in the absolute number of memory T cells in the spleen and mesenteric lymph node (MLN) of TRIF^{-/-} recipient mice following RV infection in a bone marrow chimeric model. Furthermore, there was reduced migration of type 2 classical dendritic cells from the intestine to MLNs after RV infection in TLR3^{-/-} and TRIF^{-/-} mice. Notably, RV infection resulted in attenuated killing of spleen and MLN tissues in TRIF^{-/-} and MAVS^{-/-} mice. Finally, we demonstrated that RV infection promoted apoptosis of CD8⁺ T cells in TRIF^{-/-} and TLR3^{-/-}MAVS^{-/-} mice. Taken together, our findings highlight an important mechanism of TLR3 signaling through TRIF in mucosal T cell responses to RV and lay the foundation for the development of a novel vaccine.

24COASNO26:

Title- Cell-surface Milieu Remodeling in Human Dendritic Cell Activation

Namrata D. Udeshi; Charles Xu; Zuzhi Jiang; Shihong Max Gao; Qian Yin; Wei Luo; Steven A. Carr; Mark M. Davis; Jiefu Li

Front Immunol . 2022 Jun 9;13:884530.

doi: <https://doi.org/10.3389/fimmu.2022.884530>.

Abstract: Dendritic cells (DCs) are specialized sentinel and APCs coordinating innate and adaptive immunity. Through proteins on their cell surface, DCs sense changes in the environment, internalize pathogens, present processed Ags, and communicate with other immune cells. By combining chemical labeling and quantitative mass spectrometry, we systematically profiled and compared the cell-surface proteomes of human primary conventional DCs (cDCs) in their resting and activated states. TLR activation by a lipopeptide globally reshaped the cell-surface proteome of cDCs, with >100 proteins upregulated or downregulated. By simultaneously elevating positive regulators and reducing inhibitory signals across multiple protein families, the remodeling creates a cell-surface

milieu promoting immune responses. Still, cDCs maintain the stimulatory-to-inhibitory balance by leveraging a distinct set of inhibitory molecules. This analysis thus uncovers the molecular complexity and plasticity of the cDC cell surface and provides a roadmap for understanding cDC activation and signaling.

24COASNO27:

Title- Rapid Autopsy to Define Dendritic Cell Spatial Distribution and T Cell Association in Lung Adenocarcinoma

Hilal Ozakinci; Xiaofei Song; Gina S. Nazario; Thomas Lila; Benjamin Chen; Tyler Simpson; ...

The Journal of Immunology. 2024 Oct 1;213(7):1033-1041.

doi: <https://doi.org/10.4049/jimmunol.2400234>.

Abstract: Immunotherapy response is associated with the presence of conventional dendritic cells (cDCs). cDC type 1 (cDC1) is critically important for CD8⁺ T cell activation, cDC type 2 (cDC2) regulates CD4⁺ T cell responses, and mature regulatory cDCs may dampen T cell responses in the tumor microenvironment (TME). However, we lack a clear understanding of cDC distribution in the human TME, cDC prevalence in metastatic sites, and cDC differences in early- versus late-stage disease. Rapid autopsy specimens of 10 patients with lung adenocarcinoma were evaluated to detect cDCs and immune cells via multiplex immunofluorescence using 18 markers and 42 tumors. First, we found that T cells, cDC1, and cDC2 were confined to stroma, whereas mature regulatory DCs were enriched in tumor, suggesting unique localization-specific functions. Second, lung and lymph node tumors were more enriched in T cells and cDCs than liver tumors, underscoring differences in the TME of metastatic sites. Third, although the proportion of T cells and cDC1 did not differ in different stages, an increase in the proportion of cDC2 and macrophages in late stage suggests potential differences in regulation of T cell responses in different stages. Collectively, these findings provide new, to our knowledge, insights into cDC biology in human cancer that may have important therapeutic implications.

24COASNO28:

Title- Metastatic Pleomorphic Lobular Carcinoma of the Breast to the Urinary Bladder: A Report of 10 Cases and Assessment of TRPS1 in the Differential Diagnosis With Plasmacytoid Urothelial Carc...

Guan-Nan Zhang, MD, PhD; Barbara Susnik, MD, PhD; Emma J. Paulsen, BS; Lisa L. Lyons, MD; ...

Arch Pathol Lab Med . 2024 Oct 1;148(10):1110-1118.

doi: <https://doi.org/10.5858/arpa.2023-0379-OA>.

Abstract: Context: Metastatic pleomorphic lobular carcinoma (MPLC) to the bladder is rare and has considerable histologic and immunohistochemical overlap with plasmacytoid urothelial carcinoma (PUC). Objective: To distinguish MPLC from PUC morphologically and immunohistochemically, including a newer marker, TRPS1. Design: Ten MPLCs to the bladder were reassessed and stained with estrogen, progesterone, and androgen receptors; GATA3; keratin 5/6; HMWK; GCDFP-15; and TRPS1. Sixteen PUCs constituted controls.

Results: We studied 4 transurethral resections of bladder tumors and 6 biopsies from 10 women (median age, 69 years) who had breast cancer on average 15 years prior. Microscopic patterns included single cells and cords of cells ($n = 4$), nests/sheets of dyscohesive cells ($n = 2$), or both ($n = 4$). All tumors had cells with voluminous eosinophilic cytoplasm and eccentric nuclei mimicking PUC, and 7 of 10 tumors had signet ring cells. MPLCs were positive for estrogen (8 of 10), progesterone (3 of 7), and androgen (4 of 10) receptors; GCDPF-15 (7 of 10); GATA3 (9 of 10); HMWK (7 of 8); and TRPS1 (7 of 10). No MPLCs stained for keratin 5/6 ($n = 9$). Of 16 PUCs, 2 showed faint and 2 demonstrated strong TRSP1 staining; 7 of 16 were negative for p63. **Conclusions:** MPLC to bladder often presents in patients with a remote history of breast cancer, exhibiting significant histologic and immunohistochemical overlap with PUC. Based on prior works and the current study, estrogen receptor (particularly SP-1), mammaglobin, and p63 help differentiate MPLC from PUC. Keratin 5/6 may aid in distinguishing a less frequent basal-type PUC because it is typically negative in MPLC. Some PUCs express TRPS1. Caution should be exercised because immunophenotypes of these tumors greatly overlap, and ramifications of misclassification are major.

24COASNO29:

Title- Detection of Carbapenem Resistance in Enterobacterales Directly From Positive Blood Cultures Using Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry

Natália Kehl Moreira, MSc; Camila Mörschbacher Wilhelm, PhD; Fabiana Caroline Zempulski Volpato, PhD; Afonso Luís Barth, PhD; Juliana Caierão, PhD

Arch Pathol Lab Med . 2024 Oct 1;148(10):1145-1151.

doi: <https://doi.org/10.5858/arpa.2023-0199-OA>.

Abstract: Context: Carbapenem-resistant Enterobacterales are disseminated worldwide and associated with infections with high rates of morbidity and mortality. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a useful tool for identification of pathogens directly from blood cultures in clinical microbiology laboratories. Furthermore, it has been applied for the detection of carbapenemase production, by evaluating carbapenem hydrolysis. Objective: To determine meropenem hydrolysis to detect carbapenemase production directly from positive blood cultures, using logRQ to establish a quantitative measure of hydrolysis. Design: We evaluated 100 Enterobacterales from positive blood cultures, with 81 carrying a carbapenemase gene (*bla*_{KPC}, *bla*_{GES}, *bla*_{NDM-1}, *bla*_{IMP}, *bla*_{VIM}, and *bla*_{OXA-48}-like), as determined by real-time multiplex polymerase chain reaction with high-resolution melting (HRM-qPCR). Bacterial proteins extracted from positive blood culture bottles were incubated in a meropenem solution (2–4 hours) followed by centrifugation for MALDI-TOF MS analysis. The intensity of peaks of the hydrolyzed and nonhydrolyzed forms were used to calculate the logRQ value. Results: Overall, sensitivity was 86.8% and specificity, 89.5%. Of note, sensitivity varied depending on enzyme type. For *bla*_{KPC}-positive isolates, sensitivity was 97.9%, while it reduced significantly for *bla*_{NDM-1} and *bla*_{OXA-48}-like isolates: 62.5% (10 of 16) and 66.7% (6 of 9), respectively. Indeed,

logRQ was higher in *bla*_{KPC}-positive isolates (0.37–1.97) than in *bla*_{NDM-1} (–1.37 to 0.83) and *bla*_{OXA-48}-like isolates (–1.08 to 1.79). Conclusions: This is an inexpensive and rapid test to identify carbapenemase activity directly from blood culture bottles, which contributes to early adequate antimicrobial therapy and implementation of infection control measures.

24COASNO30:

Title- Identification of Glandular (Acinar)/Tubule Formation in Invasive Carcinoma of the Breast: A Study to Determine Concordance Using the World Health Organization Definition

Yungtai Lo, PhD; Susan C. Lester, MD, PhD; Ian O. Ellis, MBBS FRCPATH; Sonali Lanjewar, MD; ...

Arch Pathol Lab Med . 2024 Oct 1;148(10):1119-1125.

doi: <https://doi.org/10.5858/arpa.2023-0163-OA>.

Abstract: Context: The Nottingham Grading System (NGS) developed by Elston and Ellis is used to grade invasive breast cancer (IBC). Glandular (acinar)/tubule formation is a component of NGS. Objective: To investigate the ability of pathologists to identify individual structures that should be classified as glandular (acinar)/tubule formation. Design: A total of 58 hematoxylin-eosin photographic images of IBC with 1 structure circled were classified as tubules (41 cases) or nontubules (17 cases) by Professor Ellis. Images were sent as a PowerPoint (Microsoft) file to breast pathologists, who were provided with the World Health Organization definition of a tubule and asked to determine if a circled structure represented a tubule. Results: Among 35 pathologists, the κ statistic for assessing agreement in evaluating the 58 images was 0.324 (95% CI, 0.314–0.335). The median concordance rate between a participating pathologist and Professor Ellis was 94.1% for evaluating 17 nontubule cases and 53.7% for 41 tubule cases. A total of 41% of the tubule cases were classified correctly by less than 50% of pathologists. Structures classified as tubules by Professor Ellis but often not recognized as tubules by pathologists included glands with complex architecture, mucinous carcinoma, and the “inverted tubule” pattern of micropapillary carcinoma. A total of 80% of participants reported that they did not have clarity on what represented a tubule. Conclusions: We identified structures that should be included as tubules but that were not readily identified by pathologists. Greater concordance for identification of tubules might be obtained by providing more detailed images and descriptions of the types of structures included as tubules.

24COASNO31:

Title- Eosinophilic Solid and Cystic Renal Cell Carcinoma: Morphologic and Immunohistochemical Study of 18 Cases and Review of the Literature

Qianru Guo, MM; Xin Yao, PhD; Bo Yang, PhD; Lisha Qi, PhD; Frank Wang, BHSc; Yuhong Guo, BA; ...

Arch Pathol Lab Med . 2024 Oct 1;148(10):1126-1134.

doi: <https://doi.org/10.5858/arpa.2023-0122-OA>.

Abstract: Context: Eosinophilic solid and cystic renal cell carcinoma is now defined in the 5th edition of the 2022 World Health Organization classification of urogenital tumors. Objective: To perform morphologic, immunohistochemical, and preliminary genetic studies about this new entity in China for the purpose of understanding it better. Design: The study includes 18 patients from a regional tertiary oncology center in northern China (Tianjin, China). We investigated the clinical and immunohistochemical features of these cases. Results: The mean age of patients was 49.6 years, and the male to female ratio was 11:7. Macroscopically, 1 case had the classic cystic and solid appearance, whereas the others appeared purely solid. Microscopically, all 18 tumors shared a similar solid and focal macrocystic or microcystic growth pattern, and the cells were characterized by voluminous and eosinophilic cytoplasm, along with coarse amphophilic stippling. Immunohistochemically, most of the tumors had a predominant cytokeratin (CK) 20–positive feature, ranging from focal cytoplasmic staining to diffuse membranous accentuation. Initially, we separated these cases into different immunohistochemical phenotypes. Group 1 (7 of 18; 38.5%) was characterized by positive phospho-4EBP1 and phospho-S6, which can imply hyperactive mechanistic target of rapamycin complex 1 (mTORC1) signaling. Group 2 (4 of 18; 23%) was negative for NF2, probably implying a germline mutation of NF2. Group 3 (7 of 18; 38.5%) consisted of the remaining cases. One case had metastatic spread and exhibited an aggressive clinical course, and we detected cyclin-dependent kinase inhibitor 2A (*CDKN2A*) mutation in this case; other patients were alive and without disease progression. Conclusions: Our research proposes that eosinophilic solid and cystic renal cell carcinoma exhibits prototypical pathologic features with CK20 positivity and has aggressive potential.

24COASNO32:

Title- Multisite Verification of a Targeted *CFTR* Polymerase Chain Reaction/Capillary Electrophoresis Assay That Evaluates Pathogenic Variants Across Diverse Ethnic and Ancestral Groups

Bradley Hall, PhD; John N. Milligan, PhD; Kevin Kelnar, MS; Elliot Hallmark, BS; Jacob D. Ashton, BS; Connor A. Parker, MS,...

Arch Pathol Lab Med . 2024 Oct 1;148(10):1135-1144.

doi: <https://doi.org/10.5858/arpa.2023-0230-OA>.

Abstract: Context: Existing targeted cystic fibrosis screening assays miss important pathogenic *CFTR* variants in the ethnically diverse US population. Objective: To evaluate the analytic performance of a multiplex polymerase chain reaction (PCR)/capillary electrophoresis (CE) *CFTR* assay panel that simultaneously interrogates primary pathogenic variants of different ethnic/ancestral groups. Design: Performance characteristic assessment and variant coverage comparison of the panel with a focus on ethnicity-specific *CFTR* variants were performed. Sample DNA was primarily from whole blood or cell lines. Detection of *CFTR* carriers was compared across several commercially available *CFTR* kits and recommended variant sets based on panel content. Results: The panel interrogated 65 pathogenic *CFTR* variants representing 92% coverage from a recent genomic sequencing survey of the US population, including 4 variants with top 5 frequency in African or Asian populations not reflected in other targeted panels. In simulation studies,

the panel represented 95% of carriers across the global population, resulting in a 6.9% to 19.0% higher carrier detection rate compared with 10 targeted panels or variant sets. Precision and sensitivity/specificity were 100% concordant. Multisite sample-level genotyping accuracy was 99.2%. Across PCR and CE instruments, sample-level genotyping accuracy was 97.1%, with greater than 99% agreement for all variant-level metrics. Conclusions: The *CFTR* assay achieves 92% or higher coverage of *CFTR* variants in diverse populations and provides improved pan-ethnic coverage of minority subgroups of the US populace. The assay can be completed within 5 hours from DNA sample to genotype, and performance data exceed acceptance criteria for analytic metrics. This assay panel content may help address gaps in ancestry-specific *CFTR* genotypes while providing a streamlined procedure with rapidly generated results.

24COASNO33:

Title- Detection of Carbapenem Resistance in Enterobacterales Directly From Positive Blood Cultures Using Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry

Natália Kehl Moreira, MSc; Camila Mörschbacher Wilhelm, PhD; Fabiana Caroline Zempulski Volpato, PhD; Afonso Luís Barth, PhD; Juliana Caierão, PhD

Arch Pathol Lab Med . 2024 Oct 1;148(10):1145-1151.

doi: <https://doi.org/10.5858/arpa.2023-0199-OA>.

Abstract: Context: Carbapenem-resistant Enterobacterales are disseminated worldwide and associated with infections with high rates of morbidity and mortality. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a useful tool for identification of pathogens directly from blood cultures in clinical microbiology laboratories. Furthermore, it has been applied for the detection of carbapenemase production, by evaluating carbapenem hydrolysis. Objective: To determine meropenem hydrolysis to detect carbapenemase production directly from positive blood cultures, using logRQ to establish a quantitative measure of hydrolysis. Design: We evaluated 100 Enterobacterales from positive blood cultures, with 81 carrying a carbapenemase gene (*bla*_{KPC}, *bla*_{GES}, *bla*_{NDM-1}, *bla*_{IMP}, *bla*_{VIM}, and *bla*_{OXA-48}-like), as determined by real-time multiplex polymerase chain reaction with high-resolution melting (HRM-qPCR). Bacterial proteins extracted from positive blood culture bottles were incubated in a meropenem solution (2–4 hours) followed by centrifugation for MALDI-TOF MS analysis. The intensity of peaks of the hydrolyzed and nonhydrolyzed forms were used to calculate the logRQ value. Results: Overall, sensitivity was 86.8% and specificity, 89.5%. Of note, sensitivity varied depending on enzyme type. For *bla*_{KPC}-positive isolates, sensitivity was 97.9%, while it reduced significantly for *bla*_{NDM-1} and *bla*_{OXA-48}-like isolates: 62.5% (10 of 16) and 66.7% (6 of 9), respectively. Indeed, logRQ was higher in *bla*_{KPC}-positive isolates (0.37–1.97) than in *bla*_{NDM-1} (–1.37 to 0.83) and *bla*_{OXA-48}-like isolates (–1.08 to 1.79). Conclusions: This is an inexpensive and rapid test to identify carbapenemase activity directly from blood culture bottles, which contributes to early adequate antimicrobial therapy and implementation of infection control measures.

24COASNO34:

Title- Assessment of Pathology Domain-Specific Knowledge of ChatGPT and Comparison to Human Performance

Andrew Y. Wang, MSc; Sherman Lin, BMSc; Christopher Tran, MSc, MD; Robert J. Homer, MD, PhD; ...

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doi: <https://doi.org/10.5858/arpa.2023-0296-OA>.

Abstract: Context: Artificial intelligence algorithms hold the potential to fundamentally change many aspects of society. Application of these tools, including the publicly available ChatGPT, has demonstrated impressive domain-specific knowledge in many areas, including medicine. Objectives: To understand the level of pathology domain-specific knowledge for ChatGPT using different underlying large language models, GPT-3.5 and the updated GPT-4. Design: An international group of pathologists (n = 15) was recruited to generate pathology-specific questions at a similar level to those that could be seen on licensing (board) examinations. The questions (n = 15) were answered by GPT-3.5, GPT-4, and a staff pathologist who recently passed their Canadian pathology licensing exams. Participants were instructed to score answers on a 5-point scale and to predict which answer was written by ChatGPT. Results: GPT-3.5 performed at a similar level to the staff pathologist, while GPT-4 outperformed both. The overall score for both GPT-3.5 and GPT-4 was within the range of meeting expectations for a trainee writing licensing examinations. In all but one question, the reviewers were able to correctly identify the answers generated by GPT-3.5. Conclusions: By demonstrating the ability of ChatGPT to answer pathology-specific questions at a level similar to (GPT-3.5) or exceeding (GPT-4) a trained pathologist, this study highlights the potential of large language models to be transformative in this space. In the future, more advanced iterations of these algorithms with increased domain-specific knowledge may have the potential to assist pathologists and enhance pathology resident training.

24COASNO35:

Title- Is Social Media Here to Stay?: Survey Results Indicate Increasing Pathologist Interest and Engagement Over Time

Raul S. Gonzalez, MD; Elizabeth L. McKinnon, MD; Maren Y. Fuller, MD; Jerad M. Gardner, MD; Wei Chen, MD; Xiaoyin “Sara” Jiang, MD

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Abstract Context: Social media has become widely adopted by pathologists and other physicians for professional purposes. While engagement has likely increased over time, there remain few concrete data regarding attitudes toward its use. Objective: To assess pathologists’ use of and attitudes toward social media over time. Design: We created a survey regarding personal and professional use of social media and circulated it via multiple channels in December 2017 and again in February 2022. Results of the 2 surveys were compared for statistically significant differences. Results: The 2017 survey was completed by 97 participants, and the 2022 survey by 305 participants. Respondents were predominantly female and academics, included pathologists in all age categories and all time-in-practice

length. In both surveys, Twitter (now X) was the most popular platform for professional use and Facebook was the most popular for personal use. Professional barriers to social media use remained consistent between the 2 surveys, including the amount of time required. Education was seen as the main benefit of social media use in both surveys, while other benefits such as networking and increasing professional visibility were endorsed significantly less often in the second survey. While the second survey received more than 3 times as many responses as the first, several aspects of social media use (mainly demographics) remained similar during the timeframe, while other aspects (such as usage and perceived values) decreased. Conclusions: Pathologists continue to find social media valuable. Barriers remain, though overall pathologists of all ages and practice settings appear receptive to using social media to further educational and other opportunities.

24COASNO36:

Title- *BRAF* Exon 15 Mutations in the Evaluation of Well-Differentiated Epithelial Nephroblastic Neoplasms in Children: A Report From the Children's Oncology Group Study AREN03B2

Jeffery A. Goldstein, MD; Lindsay A. Renfro, PhD; Lawrence J. Jennings, MD; Elizabeth A. Mullen, MD;

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doi: <https://doi.org/10.5858/arpa.2022-0528-OA>.

Abstract: Context: The distinction between well-differentiated epithelial favorable-histology Wilms tumor (EFHWT) and metanephric adenoma (MA) in children has historically been determined by the required absence of both a fibrous pseudocapsule and mitotic activity in MA. More recently these features have been allowed in adult MA. Mutations in exon 15 of the *BRAF* gene are reported in up to 88% of MAs but have not been reported in EFHWTs in children lacking MA features. Objective: To clarify the pathologic and molecular features used to distinguish between pediatric MA and EFHWT. Design: Stage I epithelial tumors classified as EFHWT on central review (36 patients) were identified from the Children's Oncology Group AREN03B2 study. Thirteen tumors had morphologic features overlapping those of MA and 23 lacked such features; 35 of 36 had tissue available for sequencing of *BRAF*. Results: Patients with EFHWTs with MA features (13) were older (mean, 8.4 versus 1.9 years; $P < .001$), had smaller tumor diameters (mean, 6.0 versus 9.7 cm; $P < .001$), and had fewer mitoses (mean, 1 versus 48 mitoses per 10 high-power fields; $P < .001$) than patients with EFHWT lacking MA features (23). All EFHWTs with MA features contained at least a partial fibrous pseudocapsule; 7 of 12 (58%) had a *BRAF* exon 15 mutation. No *BRAF* exon 15 mutations were identified in 23 EFHWTs lacking MA features. None of the 13 EFHWT patients with MA features have experienced relapse (median follow-up 5.9 years). Conclusions: Pediatric epithelial neoplasms with features of MA that show partial encapsulation and/or modest mitotic activity may be classified as MAs. Although *BRAF* mutation supports the diagnosis of MA, it is not required for the diagnosis.

24COASNO37:

Title- Utility and performance of cell blocks in cerebrospinal fluid cytology: Experience at two teaching hospitals

Hyeji Yoon CT, Constance V. Chen MD, Vimal Krishnan MD, Jill Grochowski CT, Gioia Iezza MD, Poonam Vohra MD, Ronald Balassanian MD, Nancy Y. Greenland MD PhD
Cancer Cytopathol . 2024 Oct;132(10):621-628.

<https://doi.org/10.1002/cncy.22836>

ABSTRACT: Background-Cytology cell blocks (CBs) are not routinely made for cerebrospinal fluid (CSF) specimens. The goal of this study was to identify when CSF CB preparation improves diagnostic performance. Materials and Methods: Under institutional review board approval, a retrospective review of CSF cytology cases was conducted at a tertiary university-based hospital and an affiliated county hospital. Patient history, CSF volume, final diagnosis, use of stains, and whether the CB was contributory was determined from the cytopathology report. CSF nucleated cell count data was obtained from the medical record. Results: A total of 69 CSF specimens with CBs from January 2006 to March 2023 were identified from 61 patients. The median CSF volume was 8 mL (interquartile range, 4–13 mL; range, 1–800 mL), with immunohistochemical stains performed on 29 (42%) cases. Per cytology report, CB was contributory in 23 cases (33%), not contributory in 34 cases (49%), and not discussed in 12 cases (17%). The median volume was 8 mL for cases in which CB was contributory, not contributory, or not discussed. There was no difference in average nucleated cell counts between cases in which CB was contributory versus not contributory (73.9 vs. 40.0, $p = .175$). Conclusions: CBs for CSF samples were contributory in a subset (33%) of cases. The authors were unable to identify any specific pre-analytic factors, including specimen volume and average nucleated cell counts, for cases in which CB was contributory. Further evaluation is needed to identify if there are scenarios in which CSF CBs should be routinely prepared.

24COASNO38:

Title- The negative outlook: Long-term follow up of ThyroSeq negative and low-risk nodules

Raquel A. Perry BS, Megan F. Lee MD, Rachel C. Jug MB, BCh, BAO, Rajesh C. Dash MD, Daniel J. Rocke MD, JD, Xiaoyin “Sara” Jiang MD
Cancer Cytopathol . 2024 Oct;132(10):629-634.

<https://doi.org/10.1002/cncy.22875>

Abstract: Background: Molecular testing of thyroid nodules is an essential tool to help risk stratify nodules with indeterminate cytology. Although ThyroSeq testing has been around for over a decade, there is a paucity of long-term follow-up data on cytologically indeterminate nodules that are determined to be molecularly negative or low-risk. The objective of this study is to assess the outcomes of nodules with indeterminate cytology (Bethesda III or IV) and negative or low-risk ThyroSeq results. Methods: This is a single academic institution retrospective cohort study. Patients with at least one thyroid nodule sampled with fine-needle aspiration who underwent ThyroSeq testing from 2012 to 2018 and had negative or low-risk

ThyroSeq results on a cytologically indeterminate sample ($n = 159$ patients, 167 nodules) were included in the study. Outcomes include the false-negative rate and negative predictive value of each test version, as well as follow-up length for each nodule. Results: There were 159 patients with a mean age of 58 years (7–84 years) included in this study; the majority were female (81.8%). The mean follow-up was 4.0 years. Of 167 nodules, three were found to be malignant on resection (1.8%). The negative predictive value for the entire cohort was 98.2% and it was 89.3% for the surgical series. Conclusion: ThyroSeq testing has good negative predictive value and can help risk stratify cytologically indeterminate nodules. Routine follow-up allows for safe monitoring of nodules for features suggestive of malignancy.

24COASNO39:

Title- Risk of malignancy and overall survival associated with the diagnostic categories in the World Health Organization Reporting System for Pancreaticobiliary Cytopathology

Wen-Yu Hsiao MD, PhD, Qun Wang MD, PhD

Cancer Cytopathol . 2024 Oct;132(10):635-645.

<https://doi.org/10.1002/cncy.22880>

Abstract: Background: The World Health Organization (WHO) classification system revised the Papanicolaou Society of Cytopathology (PSC) system for reporting pancreaticobiliary cytopathology. To better stratify intraductal and/or cystic neoplasms by cytologic grade, the *neoplastic, other* category was replaced by two new categories: *pancreaticobiliary neoplasm, low-risk/grade (PaN-Low)* and *pancreaticobiliary neoplasm, high-risk/grade (PaN-High)*. Low-grade malignancies were placed in the *malignant* category, and benign neoplasms were placed in the *benign/negative for malignancy* category. Methods: An institutional pathology database search identified patients who underwent endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for pancreatic lesions from January 2015 to April 2022. The absolute risk of malignancy (ROM) was determined by histologic and/or clinical follow-up of at least 6 months, and overall survival rates were calculated across diagnostic categories, comparing the WHO and PSC systems. Results: In total, 1012 cases were reviewed and recategorized. The ROM for the WHO system was 8.3% for *insufficient/inadequate/nondiagnostic*, 3.2% for *benign/negative for malignancy*, 24.6% for *atypical*, 9.1% for *PaN-Low*, 46.7% for *PaN-High*, 75% for *suspicious for malignancy*, and 100% for *malignant*. Comparatively, the ROM for the PSC system was 7.4% for *nondiagnostic*, 3.0% for *negative for malignancy*, 23.1% for *atypical*, 0% for *neoplastic, benign*, 7.3% for *neoplastic, other*, 75% for *suspicious for malignancy*, and 100% for *malignant*. The WHO system demonstrated superior stratification for overall survival. Conclusions: The WHO system significantly improves the stratification of ROM and overall survival across diagnostic categories by introducing the *PaN-Low* and *PaN-High* categories and reassigning low-grade malignancies to the *malignant* category. Analyzing EUS-FNA samples with the WHO system provides critical insights for guiding clinical management.

24COASNO40:

Title- The Milan system atypia of undetermined significance: 5-year performance data

Henri Lagerstam BMed, Erkka Tommola MD, Saara Kares MSc, Ivana Kholová MD, PhD, MIAC

Cancer Cytopathol . 2024 Oct;132(10):646-655.

<https://doi.org/10.1002/cncy.22883>

Abstract: Background The objective of this study was to evaluate the diagnostic performance of the category *atypia of undetermined significance* (AUS) at the authors' institution based on the Milan System for Reporting Salivary Gland Cytopathology. Methods: All AUS cases diagnosed at Fimlab Laboratories between January 1, 2018, and December 31, 2022, were included. Histologic verifications were checked until May 31, 2023. The upper-bound and lower-bound risk of malignancy and risk of neoplasm were calculated. The timelines between the pathology laboratory workflow and patient management were also calculated. Results: From 1157 fine-needle aspirations (FNAs), 162 (14.0%) AUS cases were diagnosed in 146 patients, with an average $\pm$ standard deviation age of 66.1 ± 14.9 years. There was variation in the AUS percentages, with higher values during the coronavirus disease 2019 pandemic years (15% and 17.5% in 2020 and 2021, respectively). Seventy-five cases (46.3%) had histologic follow-up: 16 were malignant neoplasms, and 36 were benign neoplasms. The upper and the lower bounds of the-risk of malignancy and risk of neoplasm were 21.3% and 69.3% and 9.9% and 32.1%, respectively. The average time from the first FNA with an AUS diagnosis to surgical resection ranged from 6 to 682 days, and the time to the first repeat FNA ranged from 10 to 691 days. Conclusions: The results indicated higher percentages of AUS cases compared with the reference value, which may be attributed to the impact of the coronavirus disease 2019 pandemic. The risk of malignancy calculated in this study was closer to the reference value from the first edition of the Milan System for Reporting Salivary Gland Cytopathology compared with the second edition.

24COASNO41:

Title- Cytomorphologic and molecular characterization of spindle cell carcinoid tumors of the lung

Rachelle P. Mendoza MD, Emily Symes MD, Peng Wang MD, PhD, Cole Miller MS, Stephanie C. Thompson MD, Tatjana Antic MD, Anna Biernacka MD, PhD

Cancer Cytopathol . 2024 Oct;132(10):656-665.

<https://doi.org/10.1002/cncy.22886>

Abstract: Background: Spindle cell carcinoid tumor (SCCT) is a rare variant of lung carcinoid tumor consisting predominantly or exclusively of spindle cells. To the authors' knowledge, this is the first study to date investigating the molecular characteristics of SCCTs. Methods: Eighty-five carcinoid tumors initially diagnosed by fine-needle aspiration over a period of 10 years were reviewed. The final diagnostic classification was based on resection specimens. Six SCCTs were identified and characterized based on cytomorphology, and immunohistochemical and molecular features. Results: Most patients with SCCT were Caucasian (100.0%), women (83.3%), asymptomatic (66.7%), and nonsmokers (83.3%). The

median age at diagnosis was 78.0 years (range, 58.2–80.3 years). A higher proportion of patients who had SCCT were diagnosed with distant metastasis. The smears were cellular and demonstrated clean backgrounds without necrosis or mitotic activity. SCCTs comprised of bipolar-to-elongated cells with finely granular chromatin, inconspicuous nucleoli, scant cytoplasm, and minimal atypia or pleomorphism. The tumor cells sometimes appeared *boomerang-shaped* and might mimic granulomas or blood vessels. SCCTs showed strong expression for pan-cytokeratin, synaptophysin, chromogranin, and CD56, with weak TTF-1 and a very low Ki-67 proliferation index. All SCCTs had low tumor mutational burden and were microsatellite-stable. One case showed multiple whole-gene losses in chromosome 11, whereas another harbored duplication in *ARID1A*. Two cases demonstrated gains in chromosomes 17, one of which also showed gains in chromosome 18. None had a single nucleotide mutation. Conclusions: SCCT is a rare subset of lung carcinoid tumors. These tumors harbor unique cytologic, prognostic, and molecular features that may have significant diagnostic and clinical implications.

24COASNO42:

Title- ATP citrate lyase promotes the progression of hepatocellular carcinoma by activating the REGγ-proteasome pathway

Qihong Cai, Honghua Zhu, Yile Dai, Qingqing Zhou, Qiyu Zhang, Qiandong Zhu

Molecular Carcinogenesis . 2024 Oct;63(10):1874-1891.

<https://doi.org/10.1002/mc.23777>

Abstract: The search for novel tumor biomarkers and targets is of significant importance for the early clinical diagnosis and treatment of Hepatocellular Carcinoma (HCC). The mechanisms by which ATP citrate lyase (ACLY) promotes HCC progression remain unclear, and the connection between ACLY and REGγ has not been reported in the literature. In vitro, we will perform overexpression/knockdown of ACLY or overexpression/knockdown of REGγ to investigate the impact of ACLY on HCC cells and its underlying mechanisms. In vivo, we will establish mouse tumor models with overexpression/knockdown of ACLY or overexpression/knockdown of REGγ to study the effect of ACLY on mouse tumors and its mechanisms. Firstly, ACLY overexpression upregulated REGγ expression and activated the REGγ-proteasome pathway, leading to changes in the expression of downstream signaling pathway proteins. This promoted HCC cell proliferation, invasion, and migration in vitro, as well as tumor growth and metastasis in vivo. Secondly, ACLY overexpression increased acetyl-CoA production, upregulated the acetylation level of the REGγ promoter region histone H3K27ac, and subsequently induced REGγ expression. Lastly, enhanced acetylation of the REGγ promoter region histone H3K27ac resulted in upregulated REGγ expression, activation of the REGγ-proteasome pathway, changes in downstream signaling pathway protein expression, and promotion of HCC cell proliferation, invasion, and migration in vitro, as well as tumor growth and metastasis in vivo. Conversely, REGγ knockdown reversed these effects. ACLY and REGγ may serve as potential biomarkers and clinical therapeutic targets for HCC.

24COASNO43:

Title- Downregulation of ALDH5A1 suppresses cisplatin resistance in esophageal squamous cell carcinoma by regulating ferroptosis signaling pathways

Kewei Song, Chenhui Ma, Ewetse Paul Maswikiti, Baohong Gu, Bofang Wang, Na Wang, Pei Jiang, Hao Chen

Molecular Carcinogenesis . 2024 Oct;63(10):1892-1906

<https://doi.org/10.1002/mc.23778>

Abstract: This study explores the specific role and underlying mechanisms of ALDH5A1 in the chemoresistance of esophageal squamous cell carcinoma (ESCC). The levels of cleaved caspase-3, 4-hydroxynonenal (4-HNE), intracellular Fe^{2+} , and lipid reactive oxygen species (ROS) were evaluated via immunofluorescence. Cell viability and migration were quantified using cell counting kit-8 assays and wound healing assays, respectively. Flow cytometry was utilized to analyze cell apoptosis and ROS production. The concentrations of malondialdehyde (MDA) and reduced glutathione were determined by enzyme-linked immunosorbent assay. Proteome profiling was performed using data-independent acquisition. Additionally, a xenograft mouse model of ESCC was established to investigate the relationship between ALDH5A1 expression and the cisplatin (DDP)-resistance mechanism in vivo. ALDH5A1 is overexpressed in both ESCC patients and ESCC/DDP cells. Silencing of ALDH5A1 significantly enhances the inhibitory effects of DDP treatment on the viability and migration of KYSE30/DDP and KYSE150/DDP cells and promotes apoptosis. Furthermore, it intensifies DDP's suppressive effects on tumor volume and weight in nude mice. Gene ontology biological process analysis has shown that ferroptosis plays a crucial role in both KYSE30/DDP cells and KYSE30/DDP cells transfected with si-ALDH5A1. Our in vitro and in vivo experiments demonstrate that DDP treatment promotes the accumulation of ROS, lipid ROS, MDA, LPO, and intracellular Fe^{2+} content, increases the levels of proteins that promote ferroptosis (ACSL4 and FTH1), and decreases the expression of anti-ferroptosis proteins (SLC7A11, FTL, and GPX4). Silencing of ALDH5A1 further amplifies the regulatory effects of DDP both in vitro and in vivo. ALDH5A1 potentially acts as an oncogene in ESCC chemoresistance. Silencing of ALDH5A1 can reduce DDP resistance in ESCC through promoting ferroptosis signaling pathways. These findings suggest a promising strategy for the treatment of ESCC in clinical practice.

24COASNO44:

Title- AKAP95 regulates ubiquitination and degradation of cyclin Ds/Es, influencing the G1/S transition of lung cancer cells

Zifeng Deng, Liangding Dou, Zhen Luo, Rong Liu, Jinwen Zhang, Jing Wang, Dai Wang, DongBei Guo, Ran An, Youliang Yao, Guihua Qiu, Yongxing Zhang

Molecular Carcinogenesis . 2024 Oct;63(10):1907-1921.

<https://doi.org/10.1002/mc.23781>

Abstract: A-kinase anchoring protein 95 (AKAP95) functions as a scaffold for protein kinase A. Prior work by our group has shown that AKAP95, in coordination with Connexin 43 (Cx43), modulates the expression of cyclin D and E proteins, thus affecting the cell cycle

progression in lung cancer cells. In the current study, we confirmed that AKAP95 forms a complex with Cx43. Moreover, it associates with cyclins D1 and E1 during the G1 phase, leading to the formation of protein complexes that subsequently translocate to the nucleus. These findings indicate that AKAP95 might facilitate the nuclear transport of cyclins D1 and E1. Throughout this process, AKAP95 and Cx43 collectively regulate the expression of cyclin D, phosphorylate cyclin E1 proteins, and target their specific ubiquitin ligases, ultimately impacting cell cycle progression.

24COASNO45:

Title- FAP positive cancer-associated fibroblasts promote tumor progression and radioresistance in esophageal squamous cell carcinoma by transferring exosomal lncRNA AFAP1-AS1

Xilei Zhou, Yusuo Tong, Changhua Yu, Juan Pu, Weiguo Zhu, Yun Zhou, Yuandong Wang, Yaozu Xiong, Xinchun Sun

Molecular Carcinogenesis . 2024 Oct;63(10):1922-1937.

<https://doi.org/10.1002/mc.23782>

Abstract: Cancer-associated fibroblasts (CAFs) are abundant and heterogeneous stromal cells in the tumor microenvironment, which play important roles in regulating tumor progression and therapy resistance by transferring exosomes to cancer cells. However, how CAFs modulate esophageal squamous cell carcinoma (ESCC) progression and radioresistance remains incompletely understood. The expression of fibroblast activation protein (FAP) in CAFs was evaluated by immunohistochemistry in 174 ESCC patients who underwent surgery and 78 pretreatment biopsy specimens of ESCC patients who underwent definitive chemoradiotherapy. We sorted CAFs according to FAP expression, and the conditioned medium (CM) was collected to culture ESCC cells. The expression levels of several lncRNAs that were considered to regulate ESCC progression and/or radioresistance were measured in exosomes derived from FAP⁺ CAFs and FAP⁻ CAFs. Subsequently, cell counting kit-8, 5-ethynyl-2'-deoxyuridine, transwell, colony formation, and xenograft assays were performed to investigate the functional differences between FAP⁺ CAFs and FAP⁻ CAFs. Finally, a series of in vitro and in vivo assays were used to evaluate the effect of AFAP1-AS1 on radiosensitivity of ESCC cells. FAP expression in stromal CAFs was positively correlated with nerve invasion, vascular invasion, depth of invasion, lymph node metastasis, lack of clinical complete response and poor survival. Culture of ESCC cells with CM/FAP⁺ CAFs significantly increased cancer proliferation, migration, invasion and radioresistance, compared with culture with CM/FAP⁻ CAFs. Importantly, FAP⁺ CAFs exert their roles by directly transferring the functional lncRNA AFAP1-AS1 to ESCC cells via exosomes. Functional studies showed that AFAP1-AS1 promoted radioresistance by enhancing DNA damage repair in ESCC cells. Clinically, high levels of plasma AFAP1-AS1 correlated with poor responses to dCRT in ESCC patients. Our findings demonstrated that FAP⁺ CAFs promoted radioresistance in ESCC cells through transferring exosomal lncRNA AFAP1-AS1; and may be a potential therapeutic target for ESCC treatment.

24COASNO46:

Title- C5AR1-induced TLR1/2 pathway activation drives proliferation and metastasis in anaplastic thyroid cancer

Bo Liu, Yueyao Sun, Tongyao Geng, Haobo Wang, Zhenyu Wu, Lei Xu, Miao Zhang, Xupeng Niu, Chenxu Zhao, Jin Shang, Fangjian Shang

Molecular Carcinogenesis . 2024 Oct;63(10):1938-1952.

<https://doi.org/10.1002/mc.23784>

Abstract: This study aimed to elucidate the role and mechanisms of Complement C5a receptor 1 (C5AR1) in driving the malignant progression of anaplastic thyroid carcinoma (ATC). C5AR1 expression was assessed in ATC tissues and cell lines. Functional assays evaluated the effects of C5AR1 knockdown on the malignant features of ATC cells. The interaction between C5AR1 and miR-335-5p was confirmed using a luciferase reporter assay and Fluorescence in situ hybridization, and the impact of C5AR1 knockdown on the Toll-like receptor (TLR) 1/2 signaling pathway was examined. In vivo studies evaluated the effects of C5AR1 modulation on tumor growth and metastasis. C5AR1 levels were elevated in ATC tumor samples and associated with poor survival in ATC patients. C5AR1 knockdown impeded ATC cell proliferation, migration, and invasion in vitro. MiR-335-5p was identified as an upstream regulator of C5AR1, which negatively modulates C5AR1 expression. C5AR1 knockdown diminished TLR1, TLR2, and myeloid differentiation primary response 88 (MyD88) levels, while C5AR1 overexpression activated this pathway. Blocking TLR1/2 signaling abrogated the oncogenic effects of C5AR1 overexpression. C5AR1 silencing inhibited tumor growth and lung metastasis of ATC cells in nude mice. C5AR1 contributes to ATC tumorigenesis and metastasis by activating the TLR1/2 pathway, and is negatively regulated by miR-335-5p. Targeting the miR-335-5p/C5AR1/TLR1/2 axis represents a potential therapeutic strategy for ATC.

24COASNO47:

Title- YAP-LAMB3 axis dictates cellular resistance of pancreatic ductal adenocarcinoma cells to gemcitabine

Yecheng Li, Xiaolong Wang, Hongpei Yu, Jinming Cao, Jiaming Xie, Jinhong Zhou, Zhenyu Feng, Wei Chen

Molecular Carcinogenesis . 2024 Oct;63(10):1953-1966.

<https://doi.org/10.1002/mc.23785>

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive tumors with poor prognosis and inadequate response to treatment, such as gemcitabine (Gem), the first-line chemotherapeutic drug. Understanding the molecular determinants that control drug resistance to Gem is critical to predict potentially responsive patients and improve the benefits of Gem therapy. Emerging evidence suggests that certain developmental pathways, such as Hippo signaling, are aberrated and play important roles in Gem resistance in cancers. Although Hippo signaling has been reported to play a role in chemoresistance in cancers, it has not been clarified which specific target gene(s) functionally mediates the effect. In the present study, we found that YAP serves as a potent barrier for the cellular sensitivity of

PDAC cells to Gem. We then identified and characterized laminin subunit beta 3 (LAMB3) as a bona fide target of YAP-TEAD4 to amplify YAP signaling via a feedback loop. Such a YAP-LAMB3 axis is critical to induce epithelial–mesenchymal transition and mediate Gem resistance. Taken together, we uncovered that YAP-LAMB3 axis is an important regulator of Gem, thus providing potential therapeutic targets for overcoming Gem resistance in PDAC.

24COASNO48:

Title- *UBE2D1* promotes glioblastoma proliferation by modulating p21 ubiquitination

Yongfeng Wang, Qianquan Ma, Haoyu Li, Wei Huang, Jia You, Dian Liu

Molecular Carcinogenesis . 2024 Oct;63(10):1967-1979.

<https://doi.org/10.1002/mc.23786>

Abstract: Glioblastoma (GBM) cells exhibit aberrant proliferative abilities and resistance to conventional therapies. However, the mechanisms underlying these malignant phenotypes are poorly understood. In this study, we identified ubiquitin-conjugating enzyme E2D1 (*UBE2D1*) as a crucial stimulator of GBM development. It is highly expressed in GBM and closely associated with poor prognosis in patients with GBM. *UBE2D1* knockdown inhibits GBM cell growth and leads to G1 cell cycle arrest. Mechanistically, UBCH5A binds to p21 at the protein level and induces the ubiquitination and degradation of p21. This negative regulation is mediated by STUB1. Our findings are the first to identify *UBE2D1* as a key driver of GBM growth and provide a potential target for improving prognosis and therapy.

24COASNO49:

Title- The role of immune checkpoint inhibitors: Variable number of tandem repeat (VNTR) polymorphism in the second exon of the P-selectin glycoprotein ligand-1 (PSGL-1) gene polymorphism in multiple myeloma

Yasemin Oyaci, Mustafa Pehlivan, Sacide Pehlivan, Tahir Alper Cinli, Fatima Ceren Tuncel, Elif Ertas, Istemi Serin

Molecular Carcinogenesis . 2024 Oct;63(10):1980-1987.

<https://doi.org/10.1002/mc.23787>

Abstract: Somatic mutations and polymorphisms may play a role in multiple myeloma (MM) susceptibility and survival. One of the immune checkpoint inhibitors is P-selectin glycoprotein ligand-1 (PSGL-1); the majority of tumor-infiltrating leukocytes express PSGL-1, causing T cell and immune inhibition via PSGL-1 mediator molecules. We aimed to investigate the effect of variable number of tandem repeat (VNTR) polymorphism in the second exon of the *PSGL-1* gene on MM susceptibility, response to treatment and survival in our patient group. A total of 238 patients diagnosed with MM between January 2010 and January 2021 and 162 healthy individuals as a control group were included in this cross-sectional study. The genotypes of the VNTR polymorphism in the second exon of the *PSGL-1* gene were statistically compared between patients and healthy controls; the statistically significant effects of the genotypes on response to first-line treatment and survival were examined. The AC genotype was significantly higher in healthy controls compared to patients diagnosed with MM ($p < 0.001$). The median PFS in patients with AA/AB/AC was

56 months, while it was 100 months in patients with BB/CC. The hazard ratio of 1.34 for PFS was found to be clinically significant and having the BB/CC genotype could provide a longer PFS compared to others, but it was not statistically significant due to the sample size. Our study results will shed light on new study plans in terms of immune checkpoint target therapies among conventional treatment preferences in MM.

24COASNO50:

Title- Triiodothyronine (T3) suppresses hepatic tumorigenesis and development by inhibiting the phosphorylation of ERK

Lili Dong, Nan Zhang, Jun Chen, Penghui Dong, Nan Mao, Huiling Li, Aiguo Wang
Molecular Carcinogenesis . 2024 Oct;63(10):1988-2000.

<https://doi.org/10.1002/mc.23788>

Abstract: The effect of triiodothyronine (T3) on the phosphorylation of ERK and the occurrence and development of hepatocellular carcinoma (HCC) is controversial and remains to be clarified. In the present study, both in vitro (hepatoma cell lines) and in vivo (wild-type mice [WT] and mouse models of HCC [*Hras*^{G12V} and *Kras*^{G12D} transgenic mice (*Hras*-Tg and *Kras*-Tg)]) systems were used to investigate the effect of T3 on p-ERK and hepatocarcinogenesis. The results showed that, in vitro, T3 treatment elevated the levels of p-ERK in hepatoma cells within 30 min. However, p-ERK levels returned to normal after 1 h with no significant effects on cellular proliferation or apoptosis. Interestingly, in vivo, T3 induced early rapid and transient activation of ERK and later persistent downregulation of p-ERK in liver tissues of WT. In *Hras*-Tg, liver weight, liver/body weight ratio, hepatic tumor numbers and sizes were significantly reduced with T3 treatment compared with the untreated group. Furthermore, the levels of albumin, *Hras*^{G12V}, and p-ERK in hepatic precancerous and tumor tissues were all significantly downregulated with T3 treatment; however, the levels of endogenous *Hras* were not affected. In WT, T3 also induced downregulation of Albumin in liver tissues, but without influence on the expression of endogenous *Hras* and p-MEK. Especially, the inhibitory effect of T3 on p-ERK and hepatic tumorigenesis and development without influence on the levels of *Kras*^{G12D} and p-MEK was further confirmed in *Kras*-Tg. In conclusion, T3 suppresses hepatic tumorigenesis and development by independently and substantially inhibiting the phosphorylation of ERK in vivo.

24COASNO51:

Title- Frizzled 6 endows high-grade serous ovarian cancer with stem-like properties and chemoresistance

Shaorong Chen, Guang Yang, Qirong Shi, Ningning Wan, Ruyin Lin, Lianhua Wang, Xinxin Hu, Xuanxuan Zhuang, Liying Yu, Ming Sui
Molecular Carcinogenesis . 2024 Oct;63(10):2001-2012.

<https://doi.org/10.1002/mc.23789>

Abstract: Stem-like properties contribute to tumor growth, metastasis, and chemoresistance. High-grade serous ovarian cancer (HGSOC) exhibits a very aggressive phenotype characterized by extensive metastasis, rapid progression, and therapy resistance. Frizzled 6

(FZD6) is overexpressed in HGSOC, and higher levels of FZD6 have been associated with shorter survival times in patients with HGSOC. Functionally, FZD6 promotes HGSOC growth and peritoneal metastasis. It endues HGSOC cells with stem-like properties by modulating POU5F1, ALDH1, and EPCAM. It can also desensitize HGSOC cells to certain chemical drugs. As a putative ligand for FZD6, WNT7B is also implicated in cell proliferation, stem-like properties, invasion and migration, and chemoresistance. SMAD7 is a downstream component of FZD6 signaling that is thought to mediate FZD6-associated phenotypes, at least in part. Therefore, FZD6/WNT7B-SMAD7 can be considered a tumor-promoting signaling pathway in HGSOC that may be responsible for tumor growth, peritoneal metastasis, and chemoresistance.

24COASNO52:

Title- γ -Tocotrienol enhances autophagy of gastric cancer cells by the regulation of GSK3 β / β -Catenin pathway

Hao Zhu, Fa-Lin Wang, Shuang Zhang, Li Xue, Guang-Qiang Gao, Hong-Wei Dong, Qi Wang, Wen-Guang Sun, Jia-Ren Liu

Molecular Carcinogenesis . 2024 Oct;63(10):2013-2025.

<https://doi.org/10.1002/mc.23790>

Abstract: γ -Tocotrienol (γ -T3) is a major subtype of vitamin E, mainly extracted from palm trees, barley, walnuts, and other plants. γ -T3 has effects on anti-inflammation, anti-oxidation, and potential chemoprevention against malignancies. It is still uncompleted to understand the effect of γ -T3 on the inhibitory mechanism of cancer. This study aimed to investigate whether γ -T3 enhanced autophagy in gastric cancer and the underlying molecular mechanism. The results showed that γ -T3 (0–90 μ mol/L) inhibited the proliferation of gastric cancer MKN45 cells and AGS cells, and arrested the cell cycle at the G0/G1 phase in a dose-dependent manner. Autophagy was increased in MKN45 cells treated with γ -T3 (0–45 μ mol/L), especially at a dose of 30 μ mol/L for 24 h. These effects were reversed by 3-methyladenine pretreatment. Furthermore, γ -T3 (30 μ mol/L) also significantly downregulated the expression of pGSK-3 β (ser9) and β -catenin protein in MKN45 cells, and γ -T3 (20 mg/kg b.w.) effectively decreased the growth of MKN45 cell xenografts in BABL/c mice. GSK-3 β inhibitor-CHIR-99021 reversed the negative regulation of GSK-3 β / β -Catenin signaling and autophagy. Our findings indicated that γ -T3 enhances autophagy in gastric cancer cells mediated by GSK-3 β / β -Catenin signaling, which provides new insights into the role of γ -T3 enhancing autophagy in gastric cancer.

24COASNO53:

Title- KDM1A/LSD1 inhibition enhances chemotherapy response in ovarian cancer

Yihong Chen, Jessica D. Johnson, Sridharan Jayamohan, Yi He, Prabhakar P. Venkata, Diksha Jamwal, Salvador Alejo, Yi Zou, Zhao Lai, Suryavathi Viswanadhappalli, Ratna K. Vadlamudi ... See all authors

Molecular Carcinogenesis . 2024 Oct;63(10):2026-2039.

<https://doi.org/10.1002/mc.23792>

Abstract: Ovarian cancer (OCa) is the deadliest of all gynecological cancers. The standard treatment for OCa is platinum-based chemotherapy, such as carboplatin or cisplatin in combination with paclitaxel. Most patients are initially responsive to these treatments; however, nearly 90% will develop recurrence and inevitably succumb to chemotherapy-resistant disease. Recent studies have revealed that the epigenetic modifier lysine-specific histone demethylase 1A (KDM1A/LSD1) is highly overexpressed in OCa. However, the role of KDM1A in chemoresistance and whether its inhibition enhances chemotherapy response in OCa remains uncertain. Analysis of TCGA datasets revealed that KDM1A expression is high in patients who poorly respond to chemotherapy. Western blot analysis show that treatment with chemotherapy drugs cisplatin, carboplatin, and paclitaxel increased KDM1A expression in OCa cells. KDM1A knockdown (KD) or treatment with KDM1A inhibitors NCD38 and SP2509 sensitized established and patient-derived OCa cells to chemotherapy drugs in reducing cell viability and clonogenic survival and inducing apoptosis. Moreover, knockdown of KDM1A sensitized carboplatin-resistant A2780-CP70 cells to carboplatin treatment and paclitaxel-resistant SKOV3-TR cells to paclitaxel. RNA-seq analysis revealed that a combination of KDM1A-KD and cisplatin treatment resulted in the downregulation of genes related to epithelial-mesenchymal transition (EMT). Interestingly, cisplatin treatment increased a subset of NF- κ B pathway genes, and KDM1A-KD or KDM1A inhibition reversed this effect. Importantly, KDM1A-KD, in combination with cisplatin, significantly reduced tumor growth compared to a single treatment in an orthotopic intrabursal OCa xenograft model. Collectively, these findings suggest that combination of KDM1A inhibitors with chemotherapy could be a promising therapeutic approach for the treatment of OCa.

24COASNO54:

Title- Secretory carcinoma of parotid gland masquerading as acinic cell carcinoma on cytology: Case report and review of literature

G. Anju MD, Meenakshi Rao MD, Aasma Nalwa MD, Dharma Ram Poonia MSc, Mch
Diagnostic Cytopathology . 2024 Oct;52(10):569-574.
<https://doi.org/10.1002/dc.25251>

Abstract: Secretory carcinoma is a relatively recently discovered low-grade salivary gland carcinoma with morphological similarities to its breast counterpart. The histopathological features of this entity are well established; however, the cytomorphological features are not well evaluated, leading to diagnostic challenges and pitfalls. We report a case of secretory carcinoma (SC) of the parotid gland, which was misdiagnosed as acinic cell carcinoma (ACC) on fine-needle aspiration cytology, to describe the cytological features.

24COASNO55:

Title- Gastrointestinal stromal tumors in fine-needle aspiration biopsies

Seyedreza Mousavi MD, MS, CT(ASCP), MB, Yuho Ono MD, Paul A. VanderLaan MD, PhD, Yaileen D. Guzmán-Arocho MD
Diagnostic Cytopathology . 2024 Oct;52(10):575-581.
<https://doi.org/10.1002/dc.25285>

Abstract : Gastrointestinal stromal tumors (GISTs), although rare, are the most common mesenchymal neoplasms of the gastrointestinal tract. Their potential for malignancy underscores the significance of identifying them through cytomorphologic findings and pertinent immunohistochemical markers. GISTs can emerge anywhere along the gastrointestinal tract with a predilection for the stomach. The clinical manifestations vary from nonspecific abdominal symptoms to incidental discovery during diagnostic interventions for unrelated signs and symptoms. Cytologically, GIST aspirates contain spindle or epithelioid cells with immunoreactivity for CD117/c-KIT, DOG-1, and CD34. Molecularly, *KIT* or *PDGFRA* mutations are prevalent, guiding targeted therapy with tyrosine kinase inhibitors. Distinct subtypes like succinate dehydrogenase-deficient GISTs pose challenges, often affecting younger individuals and displaying unique features. Histologically, GISTs are graded by mitotic rates, aiding prognostication. Distinguishing GISTs from similar entities is pivotal, necessitating attention to their immunostaining patterns for making an accurate diagnosis and molecular alterations for effectively planning treatment. Common differential diagnoses include leiomyoma, schwannoma, and solitary fibrous tumor. This article presents a classic GIST case and showcases relatively simple diagnostic clues for identifying similar lesions that may occur in diverse locations.

24COASNO56:

Title- Unveiling lipid-rich (“clear cell”) pancreatic neuroendocrine tumor: A small series of two cases with literature review

Rong Xia MD, PhD, Laura H. Tang MD, PhD, Negin Shafizadeh MD, Yue Xue MD, PhD, Xiaoying Liu MD, MS

Diagnostic Cytopathology . 2024 Oct;52(10):582-588.

<https://doi.org/10.1002/dc.25296>

Abstract: This study presents two cases of lipid-rich pancreatic neuroendocrine tumors (PanNETs), a rare variant posing significant diagnostic challenges in fine needle aspiration (FNA) cytology and small biopsies. The first case involves an elderly male with a pancreatic tumor, displaying distinct cytoplasmic vacuoles, while the second case is a middle-aged male present with a pancreatic tail mass exhibiting foamy cytoplasm and eccentric nuclei, infiltrating in the stroma. Both cases did not exhibit typical morphologic features of PanNET but demonstrated cytomorphologic features and infiltrative growth patterns that mimicked adenocarcinoma. Further work-up demonstrated that both tumors were immunoreactive for synaptophysin and chromogranin, and were interpreted as well-differentiated, PanNET, lipid-rich variant. The study highlights the overlapping morphological features between lipid-rich PanNETs and other pancreatic neoplasms and underscores the importance of comprehensive cytological and immunohistochemical analysis for accurately diagnosing this variant, particularly due to the risk of misinterpreting it as pancreatic adenocarcinoma. Recognizing lipid-rich PanNETs is crucial for appropriate clinical management, as their identification can significantly impact treatment decisions and patient outcomes.

24COASNO57:

Title- A case of lung FNA with atypical squamous cells

Timothy Leif Helland MD, Vanda F. Torous MD

Diagnostic Cytopathology . 2024 Oct;52(10):589-597.

<https://doi.org/10.1002/dc.25298>

Abstract: Fine-needle aspiration (FNA) is a commonly employed method for initial diagnosis and work-up of pulmonary nodules. Utilization of rapid on-site evaluation (ROSE) has the added benefit of allowing for triaging of material as appropriate for ancillary studies including microbiology testing. While many pulmonary lesions are easily categorized by cytologic evaluation, more difficult cases exist. In particular, pulmonary lesions demonstrating atypical squamoid cells can cause diagnostic challenge given the morphologic overlap between benign and malignant pulmonary lesions showing atypical squamoid cells. We herein review these common and uncommon squamoid lesions, which may enter within the differential when encountering atypical squamoid cells in pulmonary FNA specimens with emphasis on morphologic pitfalls and approaches to appropriate categorization.

24COASNO58:

Title- Solitary fibrous tumor of deep parotid gland preoperatively classified as salivary gland neoplasm of uncertain malignant potential by the Milan system for reporting salivary gland cytopathology: A common diagnosis for a rare entity

Hamza Numan Gokozan MD, Theresa Scognamiglio MD

Diagnostic Cytopathology . 2024 Oct;52(10):598-602.

<https://doi.org/10.1002/dc.25305>

Abstract : Solitary fibrous tumor (SFT) is a rare fibroblastic tumor with spindle cell morphology, which is characterized by a prominent branching vasculature and a *NAB2-STAT6* gene rearrangement. SFT may occur in any anatomical site and may involve salivary glands, including the parotid gland. We present a young female with a primary parotid SFT diagnosed as “neoplasm—Salivary gland neoplasm of uncertain malignant potential (SUMP)” per the Milan system for reporting salivary gland cytopathology by fine-needle aspiration (FNA) with surgical pathology follow-up. Cytomorphology of SFT is diverse and overlaps with more common entities causing a diagnostic challenge. Non-diagnostic FNA results are not uncommon. Thankfully, the majority of SFTs involving the salivary gland can be identified as “neoplasm” on FNA. The Neoplasm-SUMP subcategory is considered for the majority of cases, which would warrant a diagnostic excision with clear surgical margins, which is also curative in most cases. The Neoplasm-SUMP also perfectly encompasses the neoplastic behavior of SFT, which runs on a scale from indolent to malignant.

24COASNO59:

Title- Fine-needle aspiration cytology of diffuse type tenosynovial giant cell tumor with malignant transformation and review of literature

Saba Shafi MD, William MacDonald MD, Swati Satturwar MD

Diagnostic Cytopathology . 2024 Oct;52(10):603-607.

<https://doi.org/10.1002/dc.25338>

Abstract: Tenosynovial giant cell tumors (TGCTs) arise from the synovium of joint, bursa, and tendon sheath. Diffuse type often affects large joints, has higher recurrence rates, metastases, and malignant transformation potential compared to the localized type. The cytopathology of TGCT, a fibrohistiocytic neoplasm distinct from other giant cell-rich soft tissue tumors, is rarely reported. Here we describe cytomorphology of a case of TGCT that was initially diagnosed on fine-needle aspiration cytology (FNAC) consisting of a mixture of singly scattered polygonal or spindle mononuclear cells with hemosiderin laden macrophages, inflammatory cells, and a population of multinucleated osteoclast-like giant cells. Persistent symptoms and repeat excision were consistent with high-grade malignant transformation of the TGCT. Atypical cytologic features in a recurrent, infiltrative, or a metastatic lesion should raise suspicion for malignancy.

24COASNO60:

Title- Local delivery of cell surface-targeted immunocytokines programs systemic antitumor immunity

Luciano Santollani, Laura Maiorino, Yiming J. Zhang, Joseph R. Palmeri, Jordan A. Stinson, Lauren R. Duhamel, Kashif Qureshi,
Nature Immunology . 2024 Oct;25(10):1820-1829.

doi: <https://doi.org/10.1038/s41590-024-01925-7>.

Abstract: Systemically administered cytokines are potent immunotherapeutics but can cause severe dose-limiting toxicities. To overcome this challenge, cytokines have been engineered for intratumoral retention after local delivery. However, despite inducing regression of treated lesions, tumor-localized cytokines often elicit only modest responses at distal untreated tumors. In the present study, we report a localized cytokine therapy that safely elicits systemic antitumor immunity by targeting the ubiquitous leukocyte receptor CD45. CD45-targeted immunocytokines have lower internalization rates relative to wild-type counterparts, leading to sustained downstream *cis* and *trans* signaling between lymphocytes. A single intratumoral dose of α CD45-interleukin (IL)-12 followed by a single dose of α CD45-IL-15 eradicated treated tumors and untreated distal lesions in multiple syngeneic mouse tumor models without toxicity. Mechanistically, CD45-targeted cytokines reprogrammed tumor-specific CD8⁺ T cells in the tumor-draining lymph nodes to have an antiviral transcriptional signature. CD45 anchoring represents a broad platform for protein retention by host immune cells for use in immunotherapy.

24COASNO61:

Title- Sodium chloride in the tumor microenvironment enhances T cell metabolic fitness and cytotoxicity

Dominik Soll, Chang-Feng Chu, Shan Sun, Veronika Lutz, Mahima Arunkumar, Mariam Gachechiladze,...

Nature Immunology . 2024 Oct;25(10):1830-1844.

doi: <https://doi.org/10.1038/s41590-024-01918-6>.

Abstract: The efficacy of antitumor immunity is associated with the metabolic state of cytotoxic T cells, which is sensitive to the tumor microenvironment. Whether ionic signals affect adaptive antitumor immune responses is unclear. In the present study, we show that there is an enrichment of sodium in solid tumors from patients with breast cancer. Sodium chloride (NaCl) enhances the activation state and effector functions of human CD8⁺ T cells, which is associated with enhanced metabolic fitness. These NaCl-induced effects translate into increased tumor cell killing in vitro and in vivo. Mechanistically, NaCl-induced changes in CD8⁺ T cells are linked to sodium-induced upregulation of Na⁺/K⁺-ATPase activity, followed by membrane hyperpolarization, which magnifies the electromotive force for T cell receptor (TCR)-induced calcium influx and downstream TCR signaling. We therefore propose that NaCl is a positive regulator of acute antitumor immunity that might be modulated for ex vivo conditioning of therapeutic T cells, such as CAR T cells.

24COASNO62:

Title- NaCl enhances CD8⁺ T cell effector functions in cancer immunotherapy

Caterina Scirgolea, Rosa Sottile, Marco De Luca, Alberto Susana, Silvia Carnevale, Simone Puccio, Valentina Ferrari, Veronica Lise, ...

Nature Immunology . 2024 Oct;25(10):1845-1857.

doi: <https://doi.org/10.1038/s41590-024-01923-9>.

Abstract: CD8⁺ T cells control tumors but inevitably become dysfunctional in the tumor microenvironment. Here, we show that sodium chloride (NaCl) counteracts T cell dysfunction to promote cancer regression. NaCl supplementation during CD8⁺ T cell culture induced effector differentiation, IFN- γ production and cytotoxicity while maintaining the gene networks responsible for stem-like plasticity. Accordingly, adoptive transfer of tumor-specific T cells resulted in superior anti-tumor immunity in a humanized mouse model. In mice, a high-salt diet reduced the growth of experimental tumors in a CD8⁺ T cell-dependent manner by inhibiting terminal differentiation and enhancing the effector potency of CD8⁺ T cells. Mechanistically, NaCl enhanced glutamine consumption, which was critical for transcriptional, epigenetic and functional reprogramming. In humans, CD8⁺ T cells undergoing antigen recognition in tumors and predicting favorable responses to checkpoint blockade immunotherapy resembled those induced by NaCl. Thus, NaCl metabolism is a regulator of CD8⁺ T cell effector function, with potential implications for cancer immunotherapy.

24COASNO63:

Title- Tumor editing suppresses innate and adaptive antitumor immunity and is reversed by inhibiting DNA methylation

Ying Zhang, Pourya Naderi Yeganeh, Haiwei Zhang, Simon Yuan Wang, Zhouyihan Li, Bowen Gu, Dian-Jang Lee,

Nature Immunology . 2024 Oct;25(10):1858-1870.

doi: <https://doi.org/10.1038/s41590-024-01932-8>.

Abstract: Cancer cells edit gene expression to evade immunosurveillance. However, genome-wide studies of gene editing during early tumorigenesis are lacking. Here we used single-cell RNA sequencing in a breast cancer genetically engineered mouse model (GEMM) to identify edited genes without bias. Late tumors repressed antitumor immunity genes, reducing infiltrating immune cells and tumor–immune cell communications. Innate immune genes, especially interferon-stimulated genes, dominated the list of downregulated tumor genes, while genes that regulate cell-intrinsic malignancy were mostly unedited. Naive and activated CD8⁺ T cells in early tumors were replaced with exhausted or precursor-exhausted cells in late tumors. Repression of immune genes was reversed by inhibiting DNA methylation using low-dose decitabine, which suppressed tumor growth and restored immune control, increasing the number, functionality and memory of tumor-infiltrating lymphocytes and reducing the number of myeloid suppressor cells. Decitabine induced important interferon, pyroptosis and necroptosis genes, inflammatory cell death and immune control in GEMM and implanted breast and melanoma tumors.

24COASNO63:

Title- Epigenetic tuning of PD-1 expression improves exhausted T cell function and viral control

Sarah A. Weiss, Amy Y. Huang, Megan E. Fung, Daniela Martinez, Alex C. Y. Chen, Thomas J. LaSalle, Brian C. Miller, ...

Nature Immunology . 2024 Oct;25(10):1871-1883.

doi: <https://doi.org/10.1038/s41590-024-01961-3>.

Abstract: PD-1 is a key negative regulator of CD8⁺ T cell activation and is highly expressed by exhausted T cells in cancer and chronic viral infection. Although PD-1 blockade can improve viral and tumor control, physiological PD-1 expression prevents immunopathology and improves memory formation. The mechanisms driving high PD-1 expression in exhaustion are not well understood and could be critical to disentangling its beneficial and detrimental effects. Here, we functionally interrogated the epigenetic regulation of PD-1 using a mouse model with deletion of an exhaustion-specific PD-1 enhancer. Enhancer deletion exclusively alters PD-1 expression in CD8⁺ T cells in chronic infection, creating a ‘sweet spot’ of intermediate expression where T cell function is optimized compared to wild-type and *Pdcd1*-knockout cells. This permits improved control of chronic infection without additional immunopathology. Together, these results demonstrate that tuning PD-1 via epigenetic editing can reduce CD8⁺ T cell dysfunction while avoiding excess immunopathology.

24COASNO64:

Title- Deficiency of metabolic regulator PKM2 activates the pentose phosphate pathway and generates TCF1⁺ progenitor CD8⁺ T cells to improve immunotherapy

Geoffrey J. Markowitz, Yi Ban, Diamile A. Tavaréz, Liron Yoffe, Enrique Podaza, Yongfeng He,

Nature Immunology . 2024 Oct;25(10):1884-1899.

doi: <https://doi.org/10.1038/s41590-024-01963-1>.

Abstract: TCF1^{high} progenitor CD8⁺ T cells mediate the efficacy of immunotherapy; however, the mechanisms that govern their generation and maintenance are poorly understood. Here, we show that targeting glycolysis through deletion of pyruvate kinase muscle 2 (PKM2) results in elevated pentose phosphate pathway (PPP) activity, leading to enrichment of a TCF1^{high} progenitor-exhausted-like phenotype and increased responsiveness to PD-1 blockade in vivo. PKM2^{KO} CD8⁺ T cells showed reduced glycolytic flux, accumulation of glycolytic intermediates and PPP metabolites and increased PPP cycling as determined by 1,2-¹³C glucose carbon tracing. Small molecule agonism of the PPP without acute glycolytic impairment skewed CD8⁺ T cells toward a TCF1^{high} population, generated a unique transcriptional landscape and adoptive transfer of agonist-treated CD8⁺ T cells enhanced tumor control in mice in combination with PD-1 blockade and promoted tumor killing in patient-derived tumor organoids. Our study demonstrates a new metabolic reprogramming that contributes to a progenitor-like T cell state promoting immunotherapy efficacy.

24COASNO65:

Title- Dual blockade of IL-10 and PD-1 leads to control of SIV viral rebound following analytical treatment interruption

Susan Pereira Ribeiro, Zachary Strongin, Hugo Soudeyns, Felipe ten-Caten, Khader Ghneim, Nature Immunology . 2024 Oct;25(10):1900-1912.

doi: <https://doi.org/10.1038/s41590-024-01952-4>.

Abstract: Human immunodeficiency virus (HIV) persistence during antiretroviral therapy (ART) is associated with heightened plasma interleukin-10 (IL-10) levels and PD-1 expression. We hypothesized that IL-10 and PD-1 blockade would lead to control of viral rebound following analytical treatment interruption (ATI). Twenty-eight ART-treated, simian immunodeficiency virus (SIV)_{mac239}-infected rhesus macaques (RMs) were treated with anti-IL-10, anti-IL-10 plus anti-PD-1 (combo) or vehicle. ART was interrupted 12 weeks after introduction of immunotherapy. Durable control of viral rebound was observed in nine out of ten combo-treated RMs for >24 weeks post-ATI. Induction of inflammatory cytokines, proliferation of effector CD8⁺ T cells in lymph nodes and reduced expression of BCL-2 in CD4⁺ T cells pre-ATI predicted control of viral rebound. Twenty-four weeks post-ATI, lower viral load was associated with higher frequencies of memory T cells expressing TCF-1 and of SIV-specific CD4⁺ and CD8⁺ T cells in blood and lymph nodes of combo-treated RMs. These results map a path to achieve long-lasting control of HIV and/or SIV following discontinuation of ART.

24COASNO66:

Title- Mucosal adenovirus vaccine boosting elicits IgA and durably prevents XBB.1.16 infection in nonhuman primates

Matthew Gagne, Barbara J. Flynn, Shayne F. Andrew, Josue Marquez, Dillon R. Flebbe, Anna Mychalowych, ...

Nature Immunology . 2024 Oct;25(10):1913-1927.

doi: <https://doi.org/10.1038/s41590-024-01951-5>.

Abstract: A mucosal route of vaccination could prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication at the site of infection and limit transmission. We compared protection against heterologous XBB.1.16 challenge in nonhuman primates (NHPs) ~5 months following intramuscular boosting with bivalent mRNA encoding WA1 and BA.5 spike proteins or mucosal boosting with a WA1–BA.5 bivalent chimpanzee adenoviral-vectored vaccine delivered by intranasal or aerosol device. NHPs boosted by either mucosal route had minimal virus replication in the nose and lungs, respectively. By contrast, protection by intramuscular mRNA was limited to the lower airways. The mucosally delivered vaccine elicited durable airway IgG and IgA responses and, unlike the intramuscular mRNA vaccine, induced spike-specific B cells in the lungs. IgG, IgA and T cell responses correlated with protection in the lungs, whereas mucosal IgA alone correlated with upper airway protection. This study highlights differential mucosal and serum correlates of protection and how mucosal vaccines can durably prevent infection against SARS-CoV-2.

24COASNO67:

Title- IRF8 defines the epigenetic landscape in postnatal microglia, thereby directing their transcriptome programs

Keita Saeki, Richard Pan, Eunju Lee, Daisuke Kurotaki & Keiko Ozato

Nature Immunology . 2024 Oct;25(10):1928-1942.

doi: <https://doi.org/10.1038/s41590-024-01962-2>.

Abstract: Microglia are innate immune cells in the brain. Transcription factor IRF8 (interferon regulatory factor 8) is highly expressed in microglia. However, its role in postnatal microglia development is unknown. We demonstrate that IRF8 binds stepwise to enhancer regions of postnatal microglia along with Sall1 and PU.1, reaching a maximum after day 14. IRF8 binding correlated with a stepwise increase in chromatin accessibility, which preceded the initiation of microglia-specific transcriptome. Constitutive and postnatal *Irf8* deletion led to a loss of microglia identity and gain of disease-associated microglia (DAM)-like genes. Combined analysis of single-cell (sc)RNA sequencing and single-cell transposase-accessible chromatin with sequencing (scATAC-seq) revealed a correlation between chromatin accessibility and transcriptome at a single-cell level. IRF8 was also required for microglia-specific DNA methylation patterns. Last, in the 5xFAD model, constitutive and postnatal *Irf8* deletion reduced the interaction of microglia with amyloid β plaques and the size of plaques, lessening neuronal loss. Together, IRF8 sets the epigenetic landscape, which is required for postnatal microglia gene expression.

24COASNO68:

Title- LUBAC enables tumor-promoting LT β receptor signaling by activating canonical NF- κ B

Yu-Guang Chen, Eva Rieser, Amandeep Bhamra, Silvia Surinova, Peter Kreuzaler, Meng-Hsing Ho,

Cell Death & Differentiation . 2024 Oct;31(10):1267-1284.

doi: <https://doi.org/10.1038/s41418-024-01355-w>.

Abstract: Lymphotoxin β receptor (LT β R), a member of the TNF receptor superfamily (TNFR-SF), is essential for development and maturation of lymphoid organs. In addition, LT β R activation promotes carcinogenesis by inducing a proinflammatory secretome. Yet, we currently lack a detailed understanding of LT β R signaling. In this study we discovered the linear ubiquitin chain assembly complex (LUBAC) as a previously unrecognized and functionally crucial component of the native LT β R signaling complex (LT β R-SC). Mechanistically, LUBAC-generated linear ubiquitin chains enable recruitment of NEMO, OPTN and A20 to the LT β R-SC, where they act coordinately to regulate the balance between canonical and non-canonical NF- κ B pathways. Thus, different from death receptor signaling, where LUBAC prevents inflammation through inhibition of cell death, in LT β R signaling LUBAC is required for inflammatory signaling by enabling canonical and interfering with non-canonical NF- κ B activation. This results in a LUBAC-dependent LT β R-driven inflammatory, protumorigenic secretome. Intriguingly, in liver cancer patients with high LT β R expression, high expression of LUBAC correlates with poor prognosis, providing clinical relevance for LUBAC-mediated inflammatory LT β R signaling.

24COASNO69:

Title- ABL1-mediated phosphorylation promotes FOXM1-related tumorigenicity by Increasing FOXM1 stability

Qincai Dong, Di Wang, Caiwei Song, Chunxue Gong, Yue Liu, Xinwei Zhou, Junjie Yue, Yong Hu,

Cell Death & Differentiation . 2024 Oct;31(10):1285-1301.

doi: <https://doi.org/10.1038/s41418-024-01339-w>.

Abstract: The transcription factor FOXM1, which plays critical roles in cell cycle progression and tumorigenesis, is highly expressed in rapidly proliferating cells and various tumor tissues, and high FOXM1 expression is related to a poor prognosis. However, the mechanism responsible for FOXM1 dysregulation is not fully understood. Here, we show that ABL1, a nonreceptor tyrosine kinase, contributes to the high expression of FOXM1 and FOXM1-dependent tumor development. Mechanistically, ABL1 directly binds FOXM1 and mediates FOXM1 phosphorylation at multiple tyrosine (Y) residues. Among these phospho-Y sites, pY575 is indispensable for FOXM1 stability as phosphorylation at this site protects FOXM1 from ubiquitin-proteasomal degradation. The interaction of FOXM1 with CDH1, a coactivator of the E3 ubiquitin ligase anaphase-promoting complex/cyclosome (APC/C), which is responsible for FOXM1 degradation, is significantly inhibited by Y575 phosphorylation. The phospho-deficient FOXM1(Y575F) mutant exhibited increased ubiquitination, a shortened half-life, and consequently a substantially decreased abundance. Compared to wild-type cells, a homozygous Cr-Y575F cell line expressing endogenous FOXM1(Y575F) that was generated by CRISPR/Cas9 showed obviously delayed mitosis progression, impeded colony formation and inhibited xenotransplanted tumor growth. Overall, our study demonstrates that ABL1 kinase is involved in high FOXM1 expression, providing clear evidence that ABL1 may act as a therapeutic target for the treatment of tumors with high FOXM1 expression.

24COASNO70:

Title- CCKBR+ cancer cells contribute to the intratumor heterogeneity of gastric cancer and confer sensitivity to FOXO inhibition

Zhenya Tan, Ke Pan, Minqiong Sun, Xianzhu Pan, Zhi Yang, Zhiling Chang, Xue Yang, Jicheng Zhu, Li Zhan,

Cell Death & Differentiation . 2024 Oct;31(10):1302-1317.

doi: <https://doi.org/10.1038/s41418-024-01360-z>.

Abstract: The existence of heterogeneity has plunged cancer treatment into a challenging dilemma. We profiled malignant epithelial cells from 5 gastric adenocarcinoma patients through single-cell sequencing (scRNA-seq) analysis, demonstrating the heterogeneity of gastric adenocarcinoma (GA), and identified the CCKBR+ stem cell-like cancer cells associated poorly differentiated and worse prognosis. We further conducted targeted analysis using single-cell transcriptome libraries, including 40 samples, to confirm these screening results. In addition, we revealed that FOXOs are involved in the progression and development of CCKBR+ gastric adenocarcinoma. Inhibited the expression of FOXOs and disrupting cancer cell stemness reduce the CCKBR+ GA organoid formation and impede tumor progression. Mechanically, CUT&Tag sequencing and Lectin pulldown revealed that FOXOs can activate ST3GAL3/4/5 as well as ST6GALNAC6, promoting elevated sialylation levels in CCKBR+ tumor cells. This FOXO-sialyltransferase axis contributes to the maintenance of homeostasis and the growth of CCKBR+ tumor cells. This insight provides novel perspectives for developing targeted therapeutic strategies aimed at the treating CCKBR associated gastric cancer.

24COASNO71:

Title- EGFR inhibits TNF- α -mediated pathway by phosphorylating TNFR1 at tyrosine 360 and 401

Young Woo Nam, June-Ha Shin, Seongmi Kim, Chi Hyun Hwang, Choong-Sil Lee, Gyuho Hwang, Hwa-Ryeon Kim,

Cell Death & Differentiation . 2024 Oct;31(10):1318-1332.

doi: <https://doi.org/10.1038/s41418-024-01316-3>.

Abstract: Tumour necrosis factor receptor 1 (TNFR1) induces the nuclear factor kappa-B (NF- κ B) signalling pathway and regulated cell death processes when TNF- α ligates with it. Although mechanisms regulating the downstream pathways of TNFR1 have been elucidated, the direct regulation of TNFR1 itself is not well known. In this study, we showed that the kinase domain of the epidermal growth factor receptor (EGFR) regulates NF- κ B signalling and TNF- α -induced cell death by directly phosphorylating TNFR1 at Tyr 360 and 401 in its death domain. In contrast, EGFR inhibition by EGFR inhibitors, such as erlotinib and gefitinib, prevented their interaction. Once TNFR1 is phosphorylated, its death domain induces the suppression of the NF- κ B pathways, complex II-mediated apoptosis, or necrosome-dependent necroptosis. Physiologically, in mouse models, EGF treatment mitigates TNF- α -dependent necroptotic skin inflammation induced by treatment with IAP

and caspase inhibitors. Our study revealed a novel role for EGFR in directly regulating TNF- α -related pathways.

24COASNO72:

Title- A novel MYC-ZNF706-SLC7A11 regulatory circuit contributes to cancer progression and redox balance in human hepatocellular carcinoma

Jie Chu, Jun Jiang, Xin Fan, Jun Liu, Ke Gao, Yu Jiang, Mengxuan Li, Wenjin Xi, Lu Zhang, Ka Bian, Angang Yang & Rui Zhang

Cell Death & Differentiation . 2024 Oct;31(10):1333-1348.

doi: <https://doi.org/10.1038/s41418-024-01324-3>.

Abstract: The oncogenic potential of chromosome 8q22 copy number gain in liver cancer remains to be depicted. Here, we report that ZNF706, encoded by a gene mapped to chromosome 8q22, is a C2H2-type zinc finger protein. However, the biological function and mechanism of ZNF706 have been poorly investigated. Clinically, ZNF706 expression was elevated in hepatocellular carcinoma (HCC), and high ZNF706 expression was associated with unfavorable survival in HCC patients. Functional experiments revealed that ZNF706 knockdown inhibited HCC progression both in vitro and in vivo. RNA sequencing (RNA-seq) and chromatin immunoprecipitation-based deep sequencing (ChIP-seq) revealed that mechanistically, ZNF706 is a crucial ferroptosis regulator and that SLC7A11 is a critical target of ZNF706. In addition, ZNF706 knockdown inhibited SLC7A11 expression, increased lipid peroxidation, and promoted ferroptosis. Further analysis revealed that ZNF706 is a novel direct target transcriptionally activated by MYC in HCC cells. Importantly, MYC depletion reduced SLC7A11-mediated redox homeostasis, and this effect was reversed by ZNF706 reexpression. Collectively, our data demonstrate that ZNF706 is a potential oncogene in liver cancer and functions as a ferroptosis regulator by modulating SLC7A11 expression, constituting a potential therapeutic target for HCC.

24COASNO73:

Title- Regulation of primary cilia disassembly through HUWE1-mediated TTBK2 degradation plays a crucial role in cerebellar development and medulloblastoma growth

I-Hsuan Lin, Yue-Ru Li, Chia-Hsiang Chang, Yu-Wen Cheng, Yu-Ting Wang, Yu-Shuen Tsai, Pei-Yi Lin, Chien-Han Kao,

Cell Death & Differentiation . 2024 Oct;31(10):1349-1361.

doi: <https://doi.org/10.1038/s41418-024-01325-2>.

Abstract: Development of the cerebellum requires precise regulation of granule neuron progenitor (GNP) proliferation. Although it is known that primary cilia are necessary to support GNP proliferation, the exact molecular mechanism governing primary cilia dynamics within GNPs remains elusive. Here, we establish the pivotal roles for the centrosomal kinase TTBK2 (Tau tubulin kinase-2) and the E3 ubiquitin ligase HUWE1 in GNP proliferation. We show that TTBK2 is highly expressed in proliferating GNPs under Sonic Hedgehog (SHH) signaling, coinciding with active GNP proliferation and the presence of primary cilia. TTBK2 stabilizes primary cilia by inhibiting their disassembly, thereby promoting GNP proliferation in response to SHH. Mechanistically, we identify HUWE1 as a novel centrosomal E3 ligase

that facilitates primary cilia disassembly by targeting TTBK2 degradation. Disassembly of primary cilia serves as a trigger for GNP differentiation, allowing their migration from the external granule layer (EGL) of the cerebellum to the internal granule layer (IGL) for subsequent maturation. Moreover, we have established a link between TTBK2 and SHH-type medulloblastoma (SHH-MB), a tumor characterized by uncontrolled GNP proliferation. TTBK2 depletion inhibits SHH-MB proliferation, indicating that TTBK2 may be a potential therapeutic target for this cancer type. In summary, our findings reveal the mechanism governing cerebellar development and highlight a potential anti-cancer strategy for SHH-MB.

24COASNO74:

Title- Lactylation of NAT10 promotes N^4 -acetylcytidine modification on tRNA^{Ser-CGA-1-1} to boost oncogenic DNA virus KSHV reactivation

Qin Yan, Jing Zhou, Yang Gu, Wenjing Huang, Mingpeng Ruan, Haoran Zhang, Tianjiao Wang,

Cell Death & Differentiation . 2024 Oct;31(10):1362-1374.

doi: <https://doi.org/10.1038/s41418-024-01327-0>.

Abstract: N^4 -acetylcytidine (ac^4C), a conserved but recently rediscovered RNA modification on tRNAs, rRNAs and mRNAs, is catalyzed by *N*-acetyltransferase 10 (NAT10). Lysine acylation is a ubiquitous protein modification that controls protein functions. Our latest study demonstrates a NAT10-dependent ac^4C modification, which occurs on the polyadenylated nuclear RNA (PAN) encoded by oncogenic DNA virus Kaposi's sarcoma-associated herpesvirus (KSHV), can induce KSHV reactivation from latency and activate inflammasome. However, it remains unclear whether a novel lysine acylation occurs in NAT10 during KSHV reactivation and how this acylation of NAT10 regulates tRNAs ac^4C modification. Here, we showed that NAT10 was lactylated by α -tubulin acetyltransferase 1 (ATAT1), as a writer at the critical domain, to exert RNA acetyltransferase function and thus increase the ac^4C level of tRNA^{Ser-CGA-1-1}. Mutagenesis at the ac^4C site in tRNA^{Ser-CGA-1-1} inhibited its ac^4C modifications, translation efficiency of viral lytic genes, and virion production. Mechanistically, KSHV PAN orchestrated NAT10 and ATAT1 to enhance NAT10 lactylation, resulting in tRNA^{Ser-CGA-1-1} ac^4C modification, eventually boosting KSHV reactivation. Our findings reveal a novel post-translational modification in NAT10, as well as expand the understanding about tRNA-related ac^4C modification during KSHV replication, which may be exploited to design therapeutic strategies for KSHV-related diseases.

24COASNO75:

Title- Atg7 autophagy-independent role on governing neural stem cell fate could be potentially applied for regenerative medicine

Yao Shen, Tingting Li, Chengyang Sun, Xin Cheng, Zhi Chen, Guang Wang & Xuesong Yang

Cell Death & Differentiation . 2024 Oct;31(10):1375-1388.

doi: <https://doi.org/10.1038/s41418-024-01330-5>.

Abstract: A literature review showed that Atg7 biological role was associated with the development and pathogenesis of nervous system, but very few reports focused on Atg7 role on neurogenesis at the region of spinal cord, so that we are committed to explore the subject. Atg7 expression in neural tube is incrementally increased during neurogenesis. Atg7 neural-specific knockout mice demonstrated the impaired motor function and imbalance of neuronal and glial cell differentiation during neurogenesis, which was similarly confirmed in primary neurosphere culture and reversely verified by Atg7 overexpression in unilateral neural tubes of gastrula chicken embryos. Furthermore, activating autophagy in neural stem cells (NSCs) of neurospheres did not rescue Atg7 deficiency-suppressed neuronal differentiation, but Atg7 overexpression on the basis of autophagy inhibition could reverse Atg7 deficiency-suppressed neuronal differentiation, which provides evidence for the existence of Atg7 role of autophagy-independent function. The underlying mechanism is that Atg7 deficiency directly caused the alteration of cell cycle length of NSCs, which is controlled by Atg7 through specifically binding Mdm2, thereby affecting neuronal differentiation during neurogenesis. Eventually, the effect of overexpressing Atg7-promoting neuronal differentiation was proved in spinal cord injury model as well. Taken together, this study revealed that Atg7 was involved in regulating neurogenesis by a non-autophagic signaling process, and this finding also shed light on the potential application in regenerative medicine.

24COASNO76:

Title- *GLI1 confers resistance to PARP inhibitors by activating the DNA damage repair pathway*

Hiroshi Ikeuchi, Yusuke Matsuno, Rika Kusumoto-Matsuo, Shinya Kojima, Toshihide Ueno, Masachika Ikegami, Rina Kitada, Hitomi Sumiyoshi-Okuma,...

Oncogene . 2024 Oct;43(41):3037-3048.

doi: <https://doi.org/10.1038/s41388-024-03105-1>.

Abstract: Identifying the mechanisms of action of anticancer drugs is an important step in the development of new drugs. In this study, we established a comprehensive screening platform consisting of 68 oncogenes (MANO panel), encompassing 243 genetic variants, to identify predictive markers for drug efficacy. Validation was performed using drugs that targeted EGFR, BRAF, and MAP2K1, which confirmed the utility of this functional screening panel. Screening of a *BRCA2*-knockout DLD1 cell line (DLD1-KO) revealed that cells expressing *SMO* and *GLI1* were resistant to olaparib. Gene set enrichment analysis identified genes associated with DNA damage repair that were enriched in cells overexpressing *SMO* and *GLI1*. The expression of genes associated with homologous recombination repair (HR), such as the *FANC* family and *BRCA1/2*, was significantly upregulated by *GLI1* expression, which is indicative of PARP inhibitor resistance. Although not all representative genes of the nucleotide excision repair (NER) pathway were upregulated, NER activity was enhanced by *GLI1*. The *GLI1* inhibitor was effective against DLD1-KO cells overexpressing *GLI1* both in vitro and in vivo. Furthermore, the combination therapy of olaparib and *GLI1* inhibitor exhibited a synergistic effect on DLD1-KO, suggesting the possible clinical application of *GLI1* inhibitor targeting cancer with defective

DNA damage repair. This platform enables the identification of biomarkers associated with drug sensitivity, and is a useful tool for drug development.

24COASNO77:

Title- Targeting MERTK on tumour cells and macrophages: a potential intervention for sporadic and NF2-related meningioma and schwannoma tumours

Foram Dave, Kevin Herrera, Alex Lockley, Laurien L. van de Weijer, Summer Henderson, Agbolahan A. Sofela, Laura Hook,

Oncogene . 2024 Oct;43(41):3049-3061.

doi: <https://doi.org/10.1038/s41388-024-03131-z>.

Abstract: Meningioma and schwannoma are common tumours of the nervous system. They occur sporadically or as part of the hereditary NF2-related schwannomatosis syndrome. There is an unmet need for new effective drug treatments for both tumour types. In this paper, we demonstrate overexpression/activation of TAM (TYRO3/AXL/MERTK) receptors (TAMs) and overexpression/release of ligand GAS6 in patient-derived meningioma tumour cells and tissue. For the first time, we reveal the formation of MERTK/TYRO3 heterocomplexes in meningioma and schwannoma tissue. We demonstrate the dependence of AXL and TYRO3 expression on MERTK in both tumour types, as well as interdependency of MERTK and AXL expression in meningioma. We show that MERTK and AXL contribute to increased proliferation and survival of meningioma and schwannoma cells, which we inhibited in vitro using the MERTK/FLT3 inhibitor UNC2025 and the AXL inhibitor BGB324. UNC2025 was effective in both tumour types with superior efficacy over BGB324. Finally, we found that TAMs are expressed by tumour-associated macrophages in meningioma and schwannoma tumours and that UNC2025 strongly depleted macrophages in both tumour types.

24COASNO78:

Title- RBM12 drives PD-L1-mediated immune evasion in hepatocellular carcinoma by increasing JAK1 mRNA translation

Hexu Han, Qian Shi, Yue Zhang, Mingdong Ding, Xianzhong He, Cuixia Liu, Dakun Zhao, Yifan Wang,

Oncogene . 2024 Oct;43(41):3062-3077.

doi: <https://doi.org/10.1038/s41388-024-03140-y>.

Abstract: Immunosuppression characterizes the tumour microenvironment in HCC, and recent studies have implicated RNA-binding proteins (RBPs) in the development of HCC. Here, we conducted a screen and identified RBM12 as a key protein that increased the expression of PD-L1, thereby driving immune evasion in HCC. Furthermore, RBM12 was found to be significantly upregulated in HCC tissues and was associated with a poor prognosis for HCC patients. Through various molecular assays and high-throughput screening, we determined that RBM12 could directly bind to the JAK1 mRNA via its 4th-RRM (RNA recognition motif) domain and recruit EIF4A2 through its 2nd-RRM domain, enhancing the distribution of ribosomes on JAK1 mRNA, which promotes the translation of JAK1 and the subsequent upregulation of its expression. As a result, the activated JAK1/STAT1 pathway transcriptionally upregulates PD-L1 expression, facilitating immune

evasion in HCC. In summary, our findings provide insights into the significant contribution of RBM12 to immune evasion in HCC, highlighting its potential as a therapeutic target in the future.

24COASNO79:

Title- PPM1D activity promotes cellular transformation by preventing senescence and cell death

Miroslav Stoyanov, Andra S. Martinikova, Katerina Matejkova, Klara Horackova, Petra Zemankova,

Oncogene . 2024 Oct;43(42):3081-3093.

doi: <https://doi.org/10.1038/s41388-024-03149-3>.

Abstract: Cell cycle checkpoints, oncogene-induced senescence and programmed cell death represent intrinsic barriers to tumorigenesis. Protein phosphatase magnesium-dependent 1 (PPM1D) is a negative regulator of the tumour suppressor p53 and has been implicated in termination of the DNA damage response. Here, we addressed the consequences of increased PPM1D activity resulting from the gain-of-function truncating mutations in exon 6 of the *PPM1D*. We show that while control cells permanently exit the cell cycle and reside in senescence in the presence of DNA damage caused by ionising radiation or replication stress induced by the active RAS oncogene, RPE1-hTERT and BJ-hTERT cells carrying the truncated PPM1D continue proliferation in the presence of DNA damage, form micronuclei and accumulate genomic rearrangements revealed by karyotyping. Further, we show that increased PPM1D activity promotes cell growth in the soft agar and formation of tumours in xenograft models. Finally, expression profiling of the transformed clones revealed dysregulation of several oncogenic and tumour suppressor pathways. Our data support the oncogenic potential of PPM1D in the context of exposure to ionising radiation and oncogene-induced replication stress.

24COASNO80:

Title- Loss of DOCK2 potentiates Inflammatory Bowel Disease-associated colorectal cancer via immune dysfunction and IFN γ induction of IDO1 expression

Antonia M. D. Churchhouse, Caroline V. Billard, Toshiyasu Suzuki, Sebastian Ö. G. Pohl, Nora J. Doleschall, Kevin Donnelly, Colin Nixon, Mark J. Arends,

Oncogene . 2024 Oct;43(42):3094-3107.

doi: <https://doi.org/10.1038/s41388-024-03135-9>.

Abstract: Inflammatory Bowel Disease-associated colorectal cancer (IBD-CRC) is a known and serious complication of Inflammatory Bowel Disease (IBD) affecting the colon. However, relatively little is known about the pathogenesis of IBD-associated colorectal cancer in comparison with its sporadic cancer counterpart. Here, we investigated the function of *Dock2*, a gene mutated in ~10% of IBD-associated colorectal cancers that encodes a guanine nucleotide exchange factor (GEF). Using a genetically engineered mouse model of IBD-CRC, we found that whole body loss of *Dock2* increases tumourigenesis via immune dysregulation. *Dock2*-deficient tumours displayed increased levels of IFN γ -associated genes,

including the tryptophan metabolising, immune modulatory enzyme, IDO1, when compared to *Dock2*-proficient tumours. This phenotype was driven by increased IFN γ -production in T cell populations, which infiltrated *Dock2*-deficient tumours, promoting IDO1 expression in tumour epithelial cells. We show that IDO1 inhibition delays tumourigenesis in *Dock2* knockout mice, and we confirm that this pathway is conserved across species as IDO1 expression is elevated in human IBD-CRC and in sporadic CRC cases with mutated *DOCK2*. Together, these data demonstrate a previously unidentified tumour suppressive role of DOCK2 that limits IFN γ -induced IDO1 expression and cancer progression, opening potential new avenues for therapeutic intervention.

24COASNO81:

Title- GOLM1 dictates acquired Lenvatinib resistance by a GOLM1-CSN5 positive feedback loop upon EGFR signaling activation in hepatocellular carcinoma

Peiyi Xie, Mengyuan Wu, Hui Wang, Bo Zhang, Zihao Zhang, Jiuliang Yan, Mincheng Yu, Qiang Yu,

Oncogene . 2024 Oct;43(42):3108-3120.

doi: <https://doi.org/10.1038/s41388-024-03153-7>.

Abstract: Lenvatinib is a multiple receptor tyrosine kinases inhibitor (TKI) authorized for first-line treatment of hepatocellular carcinoma (HCC). However, Lenvatinib resistance is common in HCC clinical treatment, highlighting the urgent need to understand mechanisms of resistance. Here, we identified Golgi membrane protein 1 (GOLM1), a type II transmembrane protein originally located in the Golgi apparatus, as a novel regulator of Lenvatinib resistance. We found GOLM1 was overexpressed in Lenvatinib resistant human HCC cell lines, blood and HCC samples. Additionally, GOLM1 overexpression contributes to Lenvatinib resistance and HCC progression in vitro and in vivo. Mechanistically, GOLM1 upregulates CSN5 expression through EGFR-STAT3 pathway. Reversely, CSN5 deubiquitinates and stabilizes GOLM1 protein by inhibiting ubiquitin-proteasome pathway of GOLM1. Furthermore, clinical specimens of HCC showed a positive correlation between the activation of the GOLM1-EGFR-STAT3-CSN5 axis. Finally, GOLM1 knockdown was found to act in synergy with Lenvatinib in subcutaneous and orthotopic mouse model. Overall, these findings identify a mechanism of resistance to Lenvatinib treatment for HCC, highlight an effective predictive biomarker of Lenvatinib response in HCC and show that targeting GOLM1 may improve the clinical benefit of Lenvatinib.

24COASNO82:

Title- Elevated choline drives KLF5-dominated transcriptional reprogramming to facilitate liver cancer progression

Xinrong Li, Zhixiang Hu, Qili Shi, Wenying Qiu, Yizhe Liu, Yanfang Liu, Shenglin Huang, Oncogene . 2024 Oct;43(42):3121-3136.

doi: <https://doi.org/10.1038/s41388-024-03150-w>.

Abstract: An increase in the total choline-containing compound content is a common characteristic of cancer cells, and aberrant choline metabolism in cancer is closely associated

with malignant progression. However, the potential role of choline-induced global transcriptional changes in cancer cells remains unclear. In this study, we reveal that an elevated choline content facilitates hepatocellular carcinoma (HCC) cell proliferation by reprogramming Krüppel-like factor 5 (KLF5)-dominated core transcriptional regulatory circuitry (CRC). Mechanistically, choline administration leads to elevated S-adenosylmethionine (SAM) levels, inducing the formation of H3K4me1 within the super-enhancer (SE) region of KLF5 and activating its transcription. KLF5, as a key transcription factor (TF) of CRC established by choline, further transactivates downstream genes to facilitate HCC cell cycle progression. Additionally, KLF5 can increase the expression of choline kinase- α (CHKA) and CTP:phosphocholine cytidyltransferase (CCT) resulting in a positive feedback loop to promote HCC cell proliferation. Notably, the histone deacetylase inhibitor (HDACi) vorinostat (SAHA) significantly suppressed KLF5 expression and liver tumor growth in mice, leading to a prolonged lifespan. In conclusion, these findings highlight the epigenetic regulatory mechanism of the SE-driven key regulatory factor KLF5 conducted by choline metabolism in HCC and suggest a potential therapeutic strategy for HCC patients with high choline content.

24COASNO83:

Title- ALDH1A3 is the switch that determines the balance of ALDH⁺ and CD24⁻CD44⁺ cancer stem cells, EMT-MET, and glucose metabolism in breast cancer

Wasundara Fernando, Brianne M. Cruickshank, Raj Pranap Arun, Maya R. MacLean, Hannah F. Cahill,

Oncogene . 2024 Oct;43(43):3151-3169.

doi: <https://doi.org/10.1038/s41388-024-03156-4>.

Abstract: Plasticity is an inherent feature of cancer stem cells (CSCs) and regulates the balance of key processes required at different stages of breast cancer progression, including epithelial-to-mesenchymal transition (EMT) versus mesenchymal-to-epithelial transition (MET), and glycolysis versus oxidative phosphorylation. Understanding the key factors that regulate the switch between these processes could lead to novel therapeutic strategies that limit tumor progression. We found that aldehyde dehydrogenase 1A3 (ALDH1A3) regulates these cancer-promoting processes and the abundance of the two distinct breast CSC populations defined by high ALDH activity and CD24⁻CD44⁺ cell surface expression. While ALDH1A3 increases ALDH⁺ breast cancer cells, it inversely suppresses the CD24⁻CD44⁺ population by retinoic acid signaling-mediated gene expression changes. This switch in CSC populations induced by ALDH1A3 was paired with decreased migration but increased invasion and an intermediate EMT phenotype. We also demonstrate that ALDH1A3 increases oxidative phosphorylation and decreases glycolysis and reactive oxygen species (ROS). The effects of ALDH1A3 reduction were countered with the glycolysis inhibitor 2-deoxy-D-glucose (2DG). In cell culture and tumor xenograft models, 2DG suppresses the increase in the CD24⁻CD44⁺ population and ROS induced by ALDH1A3 knockdown. Combined inhibition of ALDH1A3 and glycolysis best reduces breast tumor growth and tumor-initiating cells, suggesting that the combination of targeting ALDH1A3

and glycolysis has therapeutic potential for limiting CSCs and tumor progression. Together, these findings identify ALDH1A3 as a key regulator of processes required for breast cancer progression and depletion of ALDH1A3 makes breast cancer cells more susceptible to glycolysis inhibition.

24COASNO84:

Title- USP33 facilitates the ovarian cancer progression via deubiquitinating and stabilizing CBX2

Jiming Chen, Wulin Shan, Qiucheng Jia, Yao Chen, Wenjing Jiang, Yuan Tian, Xu Huang, Xiaoyu Li,

Oncogene . 2024 Oct;43(43):3170-3183.

doi: <https://doi.org/10.1038/s41388-024-03151-9>.

Abstract: Post-translational modifications of proteins play a pivotal role in both the initiation and progression of ovarian cancer. Despite the recognition of USP33 as a significant factor in various cancers, its specific function and underlying mechanisms in ovarian cancer remain elusive. Proteomics and ubiquitinomics approaches were coupled to screen novel substrate proteins directly regulated by USP33. Our findings unveil that USP33 was observed to eliminate K27- and K48-linked ubiquitin chains from CBX2 at the K277 position. Notably, acetylation of CBX2 at K199, catalyzed by lysine acetyltransferase GCN5, was found to enhance its interaction with USP33, subsequently promoting further deubiquitination and stabilization. Functionally, our experiments demonstrate that USP33 significantly enhances ovarian cancer proliferation and metastasis in a CBX2-dependent manner. Furthermore, analysis revealed a direct positive correlation between the expression levels of USP33 and CBX2 proteins in human specimens, with elevated levels being associated with reduced survival rates in ovarian cancer patients. These findings elucidate the mechanism by which USP33 augments ovarian cancer progression through the stabilization of CBX2, underscoring the USP33-CBX2 axis as a promising therapeutic target in ovarian cancer management.

24COASNO85:

Title- ZG16 enhances the maturation of dendritic cells via induction of CD40 and contributes to the antitumor immunity in pancreatic cancer

Hui Meng, Ling Li, Manman Nan, Yi Ding, Yizhen Li & Mingzhi Zhang

Oncogene . 2024 Oct;43(43):3184-3196.

doi: <https://doi.org/10.1038/s41388-024-03154-6>.

Abstract: Dendritic cells (DCs) are critical mediators of antigen priming and T-cell activation. Zymogen granule protein 16 (ZG16) is demonstrated as an anti-oncogene in T-cell mediated antitumor immunity, but its effect on DCs is largely unknown. Herein, we wonder whether ZG16 affects the activation of DCs in pancreatic cancer. Firstly, the increased ZG16 expression was observed during the maturation of DCs derived from mouse bone marrow or human peripheral blood. Then, overexpression of ZG16 or exogenous introduction of recombinant ZG16 protein induced the expression of MHC II, CD86, CD84, and CCR7 on the surface of DCs, thereby facilitating the secretion of proinflammatory mediators IL-1 β , IL-

6, TNF- α , and IL-12/p70, supporting the promoting effect of ZG16 on DC maturation. By establishing the subcutaneous and orthotopic mouse models of pancreatic cancer, we confirmed that intraperitoneal injection of recombinant ZG16 protein (Re-mZG16) could induce tumor regression by stimulating DC maturation and enhancing antitumor responses of CD4⁺, CD8⁺, PD-1⁺, and Ctl4⁺ cells. Besides, Re-mZG16 in combination with gemcitabine showed a synergistic effect in the treatment of pancreatic cancer. Mechanistically, we demonstrated that ZG16 inhibited the ubiquitination and degradation of CD40, which depended on the lectin domain of ZG16. In conclusion, this study provided a novel insight into the role of ZG16-CD40 axis in DC-based immunotherapy for pancreatic cancer.

24COASNO86:

Title- AR coactivators, CBP/p300, are critical mediators of DNA repair in prostate cancer

Sumaira Sardar, Christopher M. McNair, Lakshmi Ravindranath, Saswati N. Chand, Wei Yuan, ...

Oncogene . 2024 Oct;43(43):3197-3213.

doi: <https://doi.org/10.1038/s41388-024-03148-4>.

Abstract: Castration resistant prostate cancer (CRPC) remains an incurable disease stage with ineffective treatments options. Here, the androgen receptor (AR) coactivators CBP/p300, which are histone acetyltransferases, were identified as critical mediators of DNA damage repair (DDR) to potentially enhance therapeutic targeting of CRPC. Key findings demonstrate that CBP/p300 expression increases with disease progression and selects for poor prognosis in metastatic disease. CBP/p300 bromodomain inhibition enhances response to standard of care therapeutics. Functional studies, CBP/p300 cistrome mapping, and transcriptome in CRPC revealed that CBP/p300 regulates DDR. Further mechanistic investigation showed that CBP/p300 attenuation via therapeutic targeting and genomic knockdown decreases homologous recombination (HR) factors in vitro, in vivo, and in human prostate cancer (PCa) tumors ex vivo. Similarly, CBP/p300 expression in human prostate tissue correlates with HR factors. Lastly, targeting CBP/p300 impacts HR-mediate repair and patient outcome. Collectively, these studies identify CBP/p300 as drivers of PCa tumorigenesis and lay the groundwork to optimize therapeutic strategies for advanced PCa via CBP/p300 inhibition, potentially in combination with AR-directed and DDR therapies.

24COASNO87:

Title- Successful Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Meningitis With Sulbactam-Durlobactam

Pranita D Tamma and others

Clinical Infectious Diseases. 2024 Oct 15;79(4):819-825.

doi: <https://doi.org/10.1093/cid/ciae210>.

Abstract: We describe a patient with persistently positive CSF cultures growing CRAB despite ampicillin-sulbactam and cefiderocol treatment. Cultures cleared after transitioning to

sulbactam-durlobactam and meropenem. Antimicrobial resistance markers reducing susceptibility to cefiderocol during treatment and CSF sulbactam-durlobactam concentrations were investigated.

Keywords: *Acinetobacter baumannii*; OXA-23; antimicrobial resistance; cefiderocol; paradoxical effect.

24COASNO88:

Title- Preventing New Gram-negative Resistance Through Beta-lactam De-escalation in Hospitalized Patients With Sepsis: A Retrospective Cohort Study

Besu F Teshome and others

Clinical Infectious Diseases. 2024 Oct 15;79(4):826-833.

doi: <https://doi.org/10.1093/cid/ciae253>.

Abstract: Our findings suggest the antibiotic stewardship approach of de-escalating broad-spectrum beta-lactam antibiotic therapy is associated with a reduced risk of resistance development in gram-negative pathogens isolated by clinical cultures in patients hospitalized with sepsis.

Keywords: antibiotic de-escalation; beta-lactam antibiotics; resistance; sepsis; spectrum score.

24COASNO89:

Title- Prevalence, Clinical Severity, and Serotype Distribution of Pneumococcal Pneumonia Among Adults Hospitalized With Community-Acquired Pneumonia in Tennessee and Georgia, 2018–2022

Wesley H Self and others

Clinical Infectious Diseases. 2024 Oct 15;79(4):838-847.

doi: <https://doi.org/10.1093/cid/ciae316>.

Abstract: Among 2917 adults hospitalized with community-acquired pneumonia at 3 hospitals in the United States, 352 (12.1%) patients had *Streptococcus pneumoniae* detected and approximately one-third of detected pneumococcal serotypes were not contained in the pneumococcal conjugate vaccines PCV15 or PCV20.

Keywords: *Streptococcus pneumoniae*; pneumococcus; pneumonia; serotype; vaccine.

24COASNO90:

Title- The Use of Long-term Antibiotics for Suppression of Bacterial Infections

Molly Horne and others

Clinical Infectious Diseases. 2024 Oct 15;79(4):848-854.

doi: <https://doi.org/10.1093/cid/ciae302>.

Abstract: Current guidelines for suppressive antibiotic therapy (SAT) don't provide clear recommendations for duration and cessation of therapy, largely due to limited data in the literature. This review examines the available evidence and proposes recommendations for the major indications for SAT.

Keywords: antibiotics; antimicrobial stewardship; infection; prosthetic joint infection; suppression.

24COASNO91:

Title- Association Between Infectious Diseases Consultation and Mortality in Hospitalized Patients With Gram-negative Bloodstream Infection: A Retrospective Population-wide Cohort Study

Sean W X Ong and others

Clinical Infectious Diseases. 2024 Oct 15;79(4):855-863.

doi: <https://doi.org/10.1093/cid/ciae282>.

Abstract: In this population-wide cohort study, infectious diseases consultation was associated with mortality benefit and reduced oral antibiotic prescription in hospitalized patients with gram-negative bloodstream infection. Greater benefit was seen in earlier consultation and in patients with several high-risk features.

Keywords: bloodstream infections; gram-negative bacteria; health administrative data; health services research; infectious diseases.

24COASNO93:

Title- Central nervous system involvement in Erdheim-Chester disease: a magnetic resonance imaging study,

Aryan Zahergivar, Fatemeh Dehghani Firouzabadi, Fatemeh Homayounieh, Mahshid Golagha,

Clinical Imaging, Volume 115, 2024, 110281,

<https://doi.org/10.1016/j.clinimag.2024.110281>.

Abstract: Purpose: To characterize brain MR imaging findings in a cohort of 58 patients with ECD and to evaluate relationship between these findings and the BRAFV600E pathogenic variant. Methods: ECD patients of any gender and ethnicity, aged 2–80 years, with biopsy-confirmed ECD were eligible to enroll in this study. Two radiologists experienced in evaluating ECD CNS disease activity reviewed MRI studies. Any disagreements were resolved by a third reader. Frequencies of observed lesions were reported. The association between the distribution of CNS lesions and the BRAFV600E pathogenic variant was evaluated using Fisher's exact test and odd ratio. Results: The brain MRI of all 58 patients with ECD revealed some form of CNS lesions, most likely due to ECD. Cortical lesions were noted in 27/58 (46.6 %) patients, cerebellar lesions in 15/58 (25.9 %) patients, brain stem lesions in 17/58 cases (29.3 %), and pituitary lesions in 10/58 (17.2 %) patients. Premature cortical atrophy was observed in 8/58 (13.8 %) patients. BRAFV600E pathogenic variant was significantly associated with cerebellar lesions ($p = 0.016$) and bilateral brain stem lesions ($p = 0.043$). A trend toward significance was noted for cerebral atrophy ($p = 0.053$). Conclusion: The study provides valuable insights into the brain MRI findings in ECD and their association with the BRAFV600E pathogenic variant, particularly its association in cases with bilateral lesions. We are expanding our understanding of how ECD affects cerebral structures. Knowledge of MRI CNS lesion

patterns and their association with mutations such as the BRAF variant is helpful for both prognosis and clinical management.

Keywords: Erdheim-Chester disease; CNS; Brain MRI; Neurologic; Magnetic resonance imaging; BRAFV600E pathogenic variant; Cerebral atrophy; Brainstem lesions; Deep basal ganglia; Amygdala; Thalamus; Cerebellar lesions; Infra-tentorial lesions

24COASNO94:

Title- CTA and DSA findings in carotid blowout syndrome: An overview and approach to imaging diagnosis,

Stephen J. Sozio, Arevik Abramyan, Andrew Soliman, Gaurav Gupta, Hai Sun, Emad Nourollah-Zadeh, Sudipta Roychowdhury, Sri Hari Sundararajan,
Clinical Imaging, Volume 115, 2024, 110304,
<https://doi.org/10.1016/j.clinimag.2024.110304>.

Abstract: Carotid blowout syndrome (CBS) is a potentially life-threatening complication in patients suffering head and neck cancer, in which rupture of the carotid artery and/or its branches can rapidly lead to life-threatening hemorrhage, shock, and death. CBS is categorized into three subtypes, which are characterized by extent of disease as evidenced by clinical presentation, physical exam findings, and imaging characteristics. Given the high morbidity and mortality associated with CBS, prompt recognition and treatment remains pivotal, as early intervention is associated with longer survival and lower complication rates. In turn, we present an overview of the hallmark imaging findings of CBS through a retrospective review of our institution's findings of these characteristic imaging findings in all patients who underwent evaluation and management of CBS at our facility across a 10-year period.

Keywords: Carotid blowout syndrome; Head and neck; CTA

24COASNO95:

Title- Encouragement vs. liability: How prompt engineering influences ChatGPT-4's radiology exam performance,

Daniel Nguyen, Allison MacKenzie, Young H. Kim,
Clinical Imaging, Volume 115, 2024, 110276,
<https://doi.org/10.1016/j.clinimag.2024.110276>.

Abstract: Large Language Models (LLM) like ChatGPT-4 hold significant promise in medical application, especially in the field of radiology. While previous studies have shown the promise of ChatGPT-4 in textual-based scenarios, its performance on image-based response remains suboptimal. This study investigates the impact of prompt engineering on ChatGPT-4's accuracy on the 2022 American College of Radiology In Training Test Questions for Diagnostic Radiology Residents that include textual and visual-based questions. Four personas were created, each with unique prompts, and evaluated using ChatGPT-4. Results indicate that encouraging prompts and those disclaiming responsibility led to higher overall accuracy (number of questions answered correctly) compared to other personas. Personas that threaten the LLM with legal action or mounting clinical responsibility

were not only found to score less, but also refrain of answering questions at a higher rate. These findings highlight the importance of prompt context in optimizing LLM responses and the need for further research to integrate AI responsibly into medical practice.

Keywords: AI; GPT4; Machine learning; Prompt engineering

24COASNO96:

Title- AI implementation: Radiologists' perspectives on AI-enabled opportunistic CT screening,

Adam E.M. Eltorai, Dominick J. Parris, Mary Jo Tarrant, William W. Mayo-Smith, Katherine P. Andriole,

Clinical Imaging, Volume 115, 2024, 110282,

<https://doi.org/10.1016/j.clinimag.2024.110282>.

Abstract: Objective: AI adoption requires perceived value by end-users. AI-enabled opportunistic CT screening (OS) detects incidental clinically meaningful imaging risk markers on CT for potential preventative health benefit. This investigation assesses radiologists' perspectives on AI and OS. Methods: An online survey was distributed to 7500 practicing radiologists among ACR membership of which 4619 opened the emails. Familiarity with and views of AI applications were queried and tabulated, as well as knowledge of OS and inducements and impediments to use. Results: Respondent (n = 211) demographics: mean age 55 years, 73 % male, 91 % diagnostic radiologists, 46 % in private practice. 68 % reported using AI in practice, while 52 % were only somewhat familiar with AI. 70 % viewed AI positively though only 46 % reported AI's overall accuracy met expectations. 57 % were unfamiliar with OS, with 52 % of those familiar having a positive opinion. Patient perceptions were the most commonly reported (25 %) inducement for OS use. Provider (44 %) and patient (40 %) costs were the most common impediments. Respondents reported that osteoporosis/osteopenia (81 %), fatty liver (78 %), and atherosclerotic cardiovascular disease risk (76 %) could be well assessed by OS. Most indicated OS output requires radiologist oversight/signoff and should be included in a separate "screening" section in the Radiology report. 28 % indicated willingness to spend 1–3 min reviewing AI-generated output while 18 % would not spend any time. Society guidelines/recommendations were most likely to impact OS implementation. Discussion: Radiologists' perspectives on AI and OS provide practical insights on AI implementation. Increasing end-user familiarity with AI-enabled applications and development of society guidelines/recommendations are likely essential prerequisites for Radiology AI adoption.

Keywords: Opportunistic CT screening; AI; Implementation

24COASNO97:

Title- Diffuse unilateral MRI breast entities,

Rebecca T. Sivarajah, Trevor R. Bean, Alison L. Chetlen,

Clinical Imaging, Volume 115, 2024, 110305,

<https://doi.org/10.1016/j.clinimag.2024.110305>.

Abstract: Many benign and malignant breast entities can present with diffuse unilateral magnetic resonance imaging (MRI) findings. The unilateral breast findings can be broken down into three broad categories including asymmetric diffuse masses/non-mass enhancement (NME), diffuse unilateral skin thickening, and diffuse asymmetric background enhancement. Although correlation with clinical history is always necessary, biopsy is often needed to make a definitive diagnosis. There are some findings on MRI which can help narrow the differential including morphology, distribution, T2W signal, enhancement kinetics, and associated skin thickening. Malignant entities which will be discussed in this review include ductal carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma, Paget disease, inflammatory breast cancer, and locally advanced breast cancer. Benign entities which will be discussed in this review include idiopathic granulomatous mastitis (IGM), infectious mastitis, pseudoangiomatous stromal hyperplasia, giant fibroadenoma, early and late radiation changes, unilateral breast feeding, and central venous obstruction, all which have varied MRI appearances. It is important for radiologists to be familiar with the common entities that can present with diffuse asymmetric unilateral MRI breast findings to ensure the correct diagnosis and management is undertaken.

Keywords: Breast imaging education and training; Breast MRI clinical applications; Breast pathology

24COASNO98:

Title- Geniculate ganglion diverticulum: a potential imaging marker in patients with idiopathic intracranial hypertension,

Sachin Chitalkar, Dipak Thakor, Ali Sheikhy, Jamie Cole, Sarah Fangmeyer, Fatemeh Nasri, Clinical Imaging, Volume 115, 2024, 110278,

<https://doi.org/10.1016/j.clinimag.2024.110278>.

Abstract: Purpose: The diagnosis of idiopathic intracranial hypertension (IIH) is often challenging in patients who do not present with classic symptoms. Brain MRI can play a pivotal role, as several imaging findings, such as an empty sella appearance (ESA), have been shown to be associated with IIH. Yet, none of the MRI signs have been shown to have a high sensitivity and specificity. In this study, we tested the hypothesis that presence of a geniculate ganglion diverticulum (GGD) is a potential imaging marker for the detection of IIH. Materials and methods: This is an IRB-approved, single-institution, retrospective, observational study. Brain MRI examinations of patients referred to Radiology by Otolaryngology clinic over a period of 10 years were reviewed. 244 MRI exams fulfilling inclusion and exclusion criteria were independently screened for the presence of GGD and ESA by two Neuroradiology fellows. Electronic medical records (EMR) of patients in this study were reviewed for presence of clinical manifestations of IIH. Receiver operator characteristic (ROC) curves were generated to estimate the accuracy of each covariate in diagnosing IIH. The area under each ROC curve (AUC) was calculated to identify an accurate prognostic covariate. Statistical analysis was done using R programming language V 4.2.2. Results: GGD was identified in MRI exams of 51 patients. A 2:1 propensity score (PS) matching for age, gender, and Body Mass Index (BMI) was used to select non-GGD control group for

comparison with the GGD group. There was strong agreement between the 2 reviewers (kappa = 0.81, agreement = 95 %). Twelve patients in this study were diagnosed with IIH. There was a high incidence of GGD (OR = 12.19, 95 % CI (2.56, 58.10)) and ESA (OR = 4.97, 95 % CI (1.47, 16.74)) in IIH patients. The AUC observed in GGD for predicting IIH was 0.771 (0.655–0.888), specificity = 0.709 (0.638–0.780), and sensitivity = 0.833 (0.583–1). The AUC observed for ESA in predicting IIH was 0.682 (0.532–0.831), specificity = 0.780 (0.709–0.844), and sensitivity = 0.583 (0.333–0.833). Conclusion: GGD is potentially a novel imaging marker of IIH with sensitivity higher than and specificity comparable to that of ESA. Clinical relevance statement: Presence of GGD should raise the possibility of IIH.

24COASNO99:

Title- Imaging finding of renal masses associated with pathogenic variation in succinate dehydrogenase subunit B gene,

Aditi Chaurasia, Evrim B. Turkbey, Fatemeh Dehghani Firouzabadi, Shiva Singh, Safa Samimi,

Clinical Imaging, Volume 115, 2024, 110280,

<https://doi.org/10.1016/j.clinimag.2024.110280>.

Abstract: Purpose: Succinate dehydrogenase (SDH)-deficient renal cell carcinoma (RCC) is a newly defined, rare subtype of renal cancer, associated with pathogenic variations in the Succinate Dehydrogenase Subunit B (SDHB) gene. Our aim is to investigate the imaging findings of SDHB-associated renal tumors, utilizing cross-sectional and FDG-PET imaging in patients with pathogenic variations in SDHB gene, to facilitate accurate tumor characterization. Methods: Twenty SDH-deficient tumors from 16 patients with pathogenic variations in SDHB gene were retrospectively evaluated using cross-sectional and FDG-PET imaging. Clinical findings such as demographics, family history, extra-renal findings and metastases were recorded. Tumor imaging characteristics on CT/MRI included laterality, size, homogeneity, morphology, margins, internal content, T1/T2 signal intensity, enhancement features, and restricted diffusion. Results: Sixteen patients (median age 31 years, IQR 19–41, 8 males) were identified with 68.8 % of patients having a known family history of SDHB variation. 81.3 % of lesions were solitary and majority were solid (86.7 % on CT, 87.5 % on MRI) with well-defined margins in >62.5 % of lesions, without evidence of internal fat, calcifications, or vascular invasion. 100 % of lesions demonstrated restricted diffusion and avid enhancement, with degree >75 % for most lesions on CT and MRI. On FDG-PET, all renal masses showed increased radiotracer uptake. 43.8 % of patients demonstrated extra-renal manifestations and 43.8 % had distant metastasis. Conclusion: SDHB-associated RCC is predominantly noted in young patients with no gender predilection. On imaging, SDH-deficient RCC are frequently unilateral, solitary, and solid with well-defined margins demonstrating avid enhancement with variability in enhancement pattern and showing restricted diffusion.

Keywords: Succinate dehydrogenase (SDH) deficiency; Carcinoma; Renal cell; PET imaging; Diagnostic imaging

24COASNO100:

Title- Use of a radiology tool for the diagnosis of pulmonary fibrosis,

Weijia Fan, Qixuan Chen, Lyndon Luk, Benjamin Navot, Valerie Maccarrone, Mary Salvatore,

Clinical Imaging, Volume 115, 2024, 110277,

<https://doi.org/10.1016/j.clinimag.2024.110277>.

Abstract: Objective: The purpose of this paper was to perform an exploratory reader study to assess the utility of a web-based application in assisting non-chest radiologist in correctly diagnosing the radiographic pattern of pulmonary fibrosis. Methods: Three non-chest radiologists with 5 to 20 years of experience individually reviewed 3 rounds of randomly chosen chest CT scans (round 1: 100 scans, round 2: 50 scans, round 3: 25 scans) from a list of patients with established diagnosis of pulmonary fibrosis. In round 1, radiologists were asked to directly record their diagnosis for the pattern of fibrosis. In round 2 and 3 they were asked to review for features provided in a web-based application and provide diagnosis based on the most likely predicted diagnosis from the application. There was an approximate 1-month interval and relevant tutorials were provided between each round. Diagnosis accuracy is reported by readers at each round. Results: The overall accuracy increased from 63 % (n = 188/299) in round 1 to 74 % in round 3 (n = 52/70) (p = 0.0265). Difficulty in recognition of mosaic attenuation and homogeneous has led to misdiagnosis. Refining the definition for feature homogeneous increased the diagnosis accuracy of NSIP from 42 % (n = 20/48) in round 2 to 65 % (n = 24/37) in round 3 (p = 0.0179). The Fleiss Kappa across readers varied from Round 1 to Round 3 with values 0.36 to 0.42. Conclusions: Using the web-based application with refined definition for feature homogeneous helps to improve the non-subspecialty radiologist's accuracy in diagnosing different types of fibrosis.

Keywords: Usual interstitial pneumonitis (UIP); Nonspecific interstitial pneumonitis (NSIP); Airway-centered fibrosis (ACF)

24COASNO101:

Title- Investigating synergy between beta-blockers and transarterial chemoembolization in the treatment of hepatocellular carcinoma: preliminary data from a propensity matched analysis,

Martin B.G. Mutonga, Annabella Shewarega, Moritz Gross, Vinzent H. Kahl, David C. Madoff,

Clinical Imaging, Volume 115, 2024, 110283,

<https://doi.org/10.1016/j.clinimag.2024.110283>.

Abstract: Purpose: Favorable clinical outcomes have been reported with the adjunct use of beta-blockers in cancer treatment, hypothetically secondary to their anti-angiogenic/anti-proliferative effects. Hereby, we investigate whether there is synergy between beta-blockers and TACE in the treatment of HCC. Methods: 36 HCC patients on beta-blockers (mean dose of 48 mg daily) at the time of first-line treatment with TACE at our institution were retrospectively identified out of a cohort of 221 patients between 2008 and 2019. Using propensity scoring, a matched cohort of 36 patients not exposed to beta-blockers was

generated based on age, gender, ethnicity, etiology of liver disease, BCLC, child Pugh score, PS/ECOG, cirrhosis, largest mass treated, type of TACE and treated liver segments. Tumor response was assessed at 1st and 2nd post-TACE imaging timepoints (1.4 and 4.1 months on average respectively). Variables were compared using chi-square test and Student's t-test. Kaplan-Meier transplant-free survival plots were generated using IBM® SPSS® software. Cox regression analysis was used to evaluate survival predictors. A p values < 0.05 was considered significant. Results: Comparing the control and beta-blocker cohorts, there were no differences in baseline characteristics, post-TACE imaging timepoints, tumor response or transplant free survival ($p > 0.05$). Tumor size was found to be a predictor of survival when the two cohorts were combined ($p = 0.03$). Conclusion: Transplant-free survival and HCC response to first-line TACE treatment were similar in the control and beta-blocker groups. Large tumor sizes were associated with higher mortality in combined analysis of the cohorts. **Keywords:** HCC; Hepatocellular carcinoma; TACE; Transarterial chemoembolization; Beta-blockers

24COASNO102:

Title- Review of neuroimaging findings of intracranial angioinvasive fungal infections,

Jay Acharya, Anthony R. Zmary, Ahmad Alach, Joseph Kang, Anandh G. Rajamohan, Mark D. Mamlouk, Fernando Torres,

Clinical Imaging, Volume 115, 2024, 110306,

<https://doi.org/10.1016/j.clinimag.2024.110306>.

Abstract: With increasing use of broad-spectrum antibiotics, advances in organ and stem-cell transplant therapy, and the continued diabetes mellitus II epidemic, as well as other risk factors, reports of fungal infections of the CNS have been increasing. The most lethal subset is the angioinvasive fungal infection. *Aspergillus fumigatus*, *Mucor*, and *Fusarium* tend to affect immunocompromised individuals depending on their risk factors. *Exserohilum rostratum* and *Cladophialaphora* species tend to infect immunocompetent individuals. Early diagnosis and treatment are imperative for improved outcomes and reduced morbidity and mortality. Clinical presentation is often nonspecific, while neuroimaging can be helpful for accurate diagnosis. CT of the head and/or the maxillofacial structures is the primary imaging modality. Once the infection begins to proliferate, areas of vasogenic and cytotoxic edema, with regional mass effect and shift of the midline structures may be seen. These findings, however, are often nonspecific and may also be seen in underlying neoplasm, inflammatory processes, and other intracranial infections. Characteristic findings on T1, T2, diffusion-weighted imaging (DWI), and gradient echo sequences (GRE) may help to further narrow the differential diagnoses. We present a review of neuroimaging findings that will aid the neuroradiologist in distinguishing intracranial angioinvasive fungal infections and lead to improved patient outcomes.

Keywords: Fungal infection; Intracranial; Angioinvasive; Neuroradiology; Immunosuppressed; Central nervous system

24COASNO103:

Title- Low-field MRI lung opacity severity associated with decreased DLCO in post-acute Covid-19 patients,

Lea Azour, Leopoldo N. Segal, Rany Condos, William H. Moore, Nicholas Landini, Destiny Collazo,

Clinical Imaging, Volume 115, 2024, 110307,

<https://doi.org/10.1016/j.clinimag.2024.110307>.

Abstract: Objectives: To evaluate the clinical significance of low-field MRI lung opacity severity. Methods: Retrospective cross-sectional analysis of post-acute Covid-19 patients imaged with low-field MRI from 9/2020 through 9/2022, and within 1 month of pulmonary function tests (PFTs), 6-min walk test (6mWT), and symptom inventory (SI), and/or within 3 months of St. George Respiratory Questionnaire (SGRQ) was performed. Univariate and correlative analyses were performed with Wilcoxon, Chi-square, and Spearman tests. The association between disease and demographic factors and MR opacity severity, PFTs, 6mWT, SI, and SGRQ, and association between MR opacity severity with functional and patient-reported outcomes (PROs), was evaluated with mixed model analysis of variance, covariance and generalized estimating equations. Two-sided 5 % significance level was used, with Bonferroni multiple comparison correction. Results: 81 MRI exams in 62 post-acute Covid-19 patients (median age 57, IQR 41–64; 25 women) were included. Exams were a median of 8 months from initial illness. Univariate analysis showed lung opacity severity was associated with decreased %DLCO ($\rho = -0.55$, $P = .0125$), and lung opacity severity quartile was associated with decreased %DLCO, predicted TLC, FVC, and increased FEV1/FVC. Multivariable analysis adjusting for sex, initial disease severity, and interval from Covid-19 diagnosis showed MR lung opacity severity was associated with decreased %DLCO ($P < .001$). Lung opacity severity was not associated with PROs. Conclusion: Low-field MRI lung opacity severity correlated with decreased %DLCO in post-acute Covid-19 patients, but was not associated with PROs.

Keywords: Opacity severity; Low-field MRI; 0.55 T; Lung; Covid-19; DLCO

24COASNO104:

Title- Automated classification of Alzheimer's disease, mild cognitive impairment, and cognitively normal patients using 3D convolutional neural network and radiomic features from T1-weighted brain MRI: A comparative study on detection accuracy,

Amin Zarei, Ahmad Keshavarz, Esmail Jafari, Reza Nemati, Akram Farhadi, Ali Gholamrezanezhad, Habib Rostami, Majid Assadi,

Clinical Imaging, Volume 115, 2024, 110301,

<https://doi.org/10.1016/j.clinimag.2024.110301>.

Abstract: Objectives: Alzheimer's disease (AD) is a common neurodegenerative disorder that primarily affects older individuals. Due to its high incidence, an accurate and efficient stratification system could greatly aid in the clinical diagnosis and prognosis of AD patients. Convolutional neural networks (CNN) approaches have demonstrated exceptional performance in the automated stratification of AD, mild cognitive impairment (MCI) and

cognitively normal (CN) participants using MRI, owing to their high predictive accuracy and reliability. Therefore, we aimed to develop an algorithm based on CNN and radiomic features derived from ROIs of bilateral hippocampus and amygdala in brain MRI for stratification between AD, MCI and CN. Methods: In this study, we proposed a CNN and radiomic features-based algorithm using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. T1-weighted images were used. We utilized three datasets, including AD (199 cases, 602 images), MCI (200 cases, 948 images), and CN (200 cases, 853 images), to perform binary classification (AD vs. CN, AD vs. MCI, and MCI vs. CN). Finally, we obtained the accuracy (ACC) and the area under the curve of the receiver operating characteristic curve (AUC) to evaluate the performance of the algorithm. Results: Our proposed algorithm achieved acceptable overall discrimination accuracy. In the term of AD vs CN, radiomic-based algorithm alone obtained ACC of 82.6 % and AUC of 88.8, CNN-based algorithm obtained ACC of 80 % and AUC of 87.2 and their fusion showed ACC of 84.4 % and AUC of 90. In the term of MCI vs CN, radiomic-based algorithm alone obtained ACC of 71.6 % and AUC of 77.8, CNN-based algorithm obtained ACC of 69 % and AUC of 75 and their fusion showed ACC of 72.7 % and AUC of 80. In the term of AD vs MCI, radiomic-based algorithm alone obtained ACC of 57 % and AUC of 57.5, CNN-based algorithm obtained ACC of 56.6 % and AUC of 57.7 and their fusion showed ACC of 58 % and AUC of 59.5. Conclusion: In conclusion, it has been determined that hippocampus and amygdala-based stratification using CNN features and radiomic features-based algorithm is a promising method for the classification of AD, MCI, and CN participants. Advances in knowledge: This study proposed an automated procedures based on MRI-derived radiomic features and CNN for classification between AD, MCI and CN.

Keywords: Alzheimer's disease; Mild cognitive impairment; Convolutional neural networks; Radiomic; MRI

24COASNO105:

Title- Ultrasonographic assessment of the risk of free-floating thrombus detachment in the lower extremity deep veins in patients with fracture,

Yang Xu, Jing Lin, Jin-Mei Gao, Yu Yuan,

Clinical Imaging, Volume 115, 2024, 110302,

<https://doi.org/10.1016/j.clinimag.2024.110302>.

Abstract: Objective: To explore the ultrasonographic features and influencing factors of free-floating thrombus (FFT) detachment in the lower extremity deep veins (LEDVs) of patients with fractures. Methods: Clinical data of patients diagnosed with FFT in the LEDVs and implanted with an inferior vena cava filter (IVCF) in our hospital between July 2021 and August 2023 were retrospectively analysed. The patients were divided into the thrombus detachment group (the experimental group, n = 92) and the non-thrombus detachment group (the control group, n = 103) based on the presence of detached thrombus in the IVCF. The effects of thrombus echogenicity, floating degree, thrombus location, thrombin time, D-dimer and fibrinogen on thrombus shedding were analysed. The nomogram method was used to establish the model and predict the probability of delayed postoperative recovery. Results:

The proportions of patients with extremely hypoechoic thrombus and medium and high floating degrees increased in the experimental group compared with those in the control group, and the differences between the two groups were statistically significant ($P < 0.05$). Extremely hypoechoic thrombus ($P = 0.021$, 95 % CI: 1.109–13.748) and high ($P = 0.001$, 95 % CI: 3.854–28.573) and medium floating degrees ($P = 0.004$, 95 % CI: 1.792–13.453) were risk factors for deep veins FFT (DV FFT) detachment. The results of receiver operating characteristic curve analysis showed that the area under the curve of the model was 0.893, with a 95 % CI of 0.856–0.937, indicating a high prediction accuracy. Conclusion: Ultrasonographic parameters, including thrombus echogenicity and floating degree, are valuable in predicting DV FFT detachment in patients with traumatic fractures, providing references for IVCF implantation.

Keywords: Lower extremity deep veins; Ultrasound; Free-floating thrombus; Detachment; Risk factors

24COASNO106:

Title- Practicing radiology for 1000 years...by women,

Judith Korek Amorosa, Anupriya Barot, Houda Bouhmam, Rebecca Scalabrino, Deborah Reede,

Clinical Imaging, Volume 115, 2024, 110300,

<https://doi.org/10.1016/j.clinimag.2024.110300>.

Abstract: Insight, words of wisdom and advice to the future generations are shared through storytelling and introspection from women radiologists who have personally impacted my own career and journey as a woman radiologist. Through historical data review and self-reported narratives on an electronically submitted questionnaire, noteworthy accomplishments of female radiologists whom I personally know or know through association over the last hundred and twenty-nine years are described, as well as the obstacles they had faced throughout their academic years of training and practice of radiology.

Keywords: Women; Female; Diversity; Representation; Contributions

24COASNO107:

Title- Evaluating Acute Pulmonary Changes of Coronavirus 2019: Comparative Analysis of the Pertinent Modalities,

Ian Griffin, Ronak Kundalia, Bruce Steinberg, Joice Prodigios, Nupur Verma, Bruno Hochhegger, Tan L. Mohammed,

Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 288-297,

<https://doi.org/10.1053/j.sult.2024.02.007>.

Abstract: This review explores imaging's crucial role in acute Coronavirus Disease 2019 (COVID-19) assessment. High Resolution Computer Tomography is especially effective in detection of lung abnormalities. Chest radiography has limited utility in the initial stages of COVID-19 infection. Lung Ultrasound has emerged as a valuable, radiation-free tool in critical care, and Magnetic Resonance Imaging shows promise as a Computed Tomography alternative. Typical and atypical findings of COVID-19 by each of these modalities are

discussed with emphasis on their prognostic value. Considerations for pediatric and immunocompromised cases are outlined. A comprehensive diagnostic approach is recommended, as radiological diagnosis remains challenging in the acute phase.

24COASNO108:

Title- Chronic Chest Computed Tomography Findings Following COVID-19 Pneumonia,

Stephan Altmayer, Ann N. Leung, Guilherme Strieder de Oliveira, Joice Prodigios, Pratik Patel, Tan-Lucien Mohammed, Nupur Verma, Bruno Hochhegger,

Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 298-308,

<https://doi.org/10.1053/j.sult.2024.02.008>.

Abstract: Respiratory symptoms are a frequent manifestation of patients with post-acute sequela of SARS-CoV-2 (PASC), also known as long-COVID. Many cohorts of predominantly hospitalized patients have shown that a significant subset may have persistent chest computed tomography findings for more than 12 months after the acute infection. Proper understanding of the evolving long-term imaging findings and terminology is crucial for accurate imaging interpretation and patient care. The goal of this article is to review the chronic chest computed tomography findings of patients with PASC and common pitfalls.

24COASNO109:

Title- Pediatric Presentations of COVID-19 and Pertinent Radiologic Findings,

Augustin Msellati, Caitlyn Loo, Lara Toerien, Tara Catanzano,

Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 339-343,

<https://doi.org/10.1053/j.sult.2024.07.004>.

Abstract: Since the 2019 worldwide pandemic, Severe Acute Respiratory Syndrome coronavirus 2 responsible for COVID-19 disease, not only had global economic repercussions but millions of individuals health were also put at risk. Like any other respiratory illness, COVID-19 has a variety of presentations and radiological features. While COVID-19 infections in the pediatric population generally present with better prognosis and lower mortality rates when compared to those of adults, in the vulnerable populations however, severe presentations are often more frequent and can have catastrophic consequences. This paper will specifically address pediatric presentations of COVID-19 including those suffering from multisystem inflammation, along with their radiologic manifestations and image findings.

24COASNO110:

Title- The Financial Impact of COVID on Radiology Health Systems,

Ahmed Farag, Richard H. Pham, Kal Dulaimy,

Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 309-313,

<https://doi.org/10.1053/j.sult.2024.03.001>.

Abstract: The coronavirus pandemic of 2019 (COVID-19) was arguably the most pivotal global event that current generations have witnessed, with unprecedented global challenges,

and colossal effects on health systems. The financial consequences, in particular, were profound and far-reaching. Staggering estimates of up to \$50.7 billion dollars per month in lost revenue for the US health system were reported by the American Hospital Association (Kaye et al., 2021). The pandemic caused significant increases in cost of drugs, disruptions to medical supply chains, day-to-day workflow, and operations in all areas of medicine and various healthcare systems. Radiology experienced a significant burden of the damage, finding itself at the forefront of the pandemic's economic fallout (American Hospital Association).

24COASNO111:

Title- COVID-19 Neuroimaging Update: Pathophysiology, Acute Findings, and Post-Acute Developments,

Andrew C. McClelland, Steven J. Benitez, Judah Burns,

Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 318-331,

<https://doi.org/10.1053/j.sult.2024.03.003>.

Abstract: COVID-19 has prominent effects on the nervous system with important manifestations on neuroimaging. In this review, we discuss the neuroimaging appearance of acute COVID-19 that became evident during the early stages of the pandemic. We highlight the underlying pathophysiology mediating nervous system effects and neuroimaging appearances including systemic inflammatory response such as cytokine storm, coagulopathy, and para/post-infections immune mediated phenomena. We also discuss the nervous system manifestations of COVID-19 and the role of imaging as the pandemic has evolved over time, including related to the development of vaccines and the emergence of post-acute sequelae such as long COVID.

24COASNO112:

Title- The Impact of COVID on Health Systems: The Workforce and Telemedicine Perspective,

Kal Dulaimy, Richard H. Pham, Ahmed Farag,

Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 314-317,

<https://doi.org/10.1053/j.sult.2024.03.002>.

Abstract: The COVID-19 pandemic significantly strained global health systems, leading to the rapid adoption of telemedicine and changes in workforce management. Previously underused, telemedicine became an essential means of delivering healthcare while adhering to physical distancing guidelines. This transition addressed longstanding barriers like connectivity issues. Simultaneously, the radiology sector innovated by widely implementing remote reading stations, which helped manage exposure risks and conserve human resources. Moreover, the pandemic highlighted the critical role of technological advancements beyond telemedicine, such as the accelerated integration of AI in diagnostics and management. This article examines these comprehensive effects, emphasizing the remote work adaptations and innovations in healthcare systems that have reshaped both healthcare delivery and workforce dynamics during the pandemic.

24COASNO113:

Title- Emergency Presentations of Coronavirus Disease (COVID-19): A Review of the Literature and Radiologic Perspective,

Caitlyn Loo, Molly Godson Treacy, Lara Toerien, Augustin Msellati, Tara Catanzano, Seminars in Ultrasound, CT and MRI, Volume 45, Issue 4, 2024, Pages 332-338, <https://doi.org/10.1053/j.sult.2024.07.003>.

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the debilitating global pandemic known as Coronavirus disease (COVID-19). In this paper, we highlight the widespread manifestations and complications across disease systems. In addition, we present their relevant imaging findings to inform appropriate investigations and management in patients presenting to the Emergency Department with COVID-19 and its respective sequelae. Of note, we outline considerations for diagnosis of long COVID, an important medium to long term sequelae in patients with previous COVID-19 infections.

24COASNO114:

Title- Quiescent frame, contrast-enhanced coronary magnetic resonance angiography reconstructed using limited number of physiologic frames from 5D free-running acquisitions,

Yitong Yang, Jackson Hair, Jérôme Yerly, Davide Piccini, Lorenzo Di Sopra, Aurelien Bustin, Milan Prsa, Salim Si-Mohamed, Matthias Stuber, John N. Oshinski, Magnetic Resonance Imaging, Volume 113, 2024, 110209, <https://doi.org/10.1016/j.mri.2024.07.008>.

Abstract: Background: 5D, free-running imaging resolves sets of 3D whole-heart images in both cardiac and respiratory dimensions. In an application such as coronary imaging when a single, static image is of interest, computationally expensive offline iterative reconstruction is still needed to compute the multiple 3D datasets. Purpose: Evaluate how the number of physiologic bins included in the reconstruction affects the computational cost and resulting image quality of a single, static volume reconstruction. Study type Retrospective. Subjects: 15 pediatric patients following Ferumoxytol infusion (4 mg/kg). Field strength/Sequence: 1.5 T/Ungated 5D free-running GRE sequence. Assessment: The raw data of each subject were binned and reconstructed into a 5D (x-y-z-cardiac-respiratory) images. 1, 3, 5, 7, and 9 bins adjacent to both sides of the retrospectively determined cardiac resting phase and 1, 3 bins adjacent to the end-expiration phase are used for limited frame reconstructions. The static volume within each limited reconstruction was compared with the corresponding full 5D reconstruction using the structural similarity index measure (SSIM). A non-linear regression model was used to fit SSIM with the percentage of data used compared to full reconstruction (% data). A linear regression model was used to fit computation time with % raw data used. Coronary artery sharpness is measured on each limited reconstructed images to determine the minimal number of cardiac and respiratory bins needed to preserve image quality. Statistical tests: The coefficient of determination (R^2) is computed for each regression model. Results: The % of data used in the reconstruction was linearly related to the computational time ($R^2 = 0.99$). The SSIM of the static image from the limited

reconstructions is non-linearly related with the % of data used ($R^2 = 0.80$). Over the 15 patients, the model showed SSIM of 0.9 with 18% of data, and SSIM of 0.96 with 30% of data. The coronary artery sharpness of images reconstructed using no less than 5 cardiac and all respiratory phases is not significantly different from the full reconstructed images using all cardiac and respiratory bins. Data conclusion: Reconstruction using only a limited number of acquired physiological states can linearly reduce the computational cost while preserving similarity to the full reconstruction image. It is suggested to use no less than 5 cardiac and all respiratory phases in the limited reconstruction to best preserve the original quality seen on the full reconstructed images.

Keywords: Free-running; Coronary MRA; 5D whole-heart MRI

24COASNO115:

Title- Test-retest repeatability of myocardial radiomic features from quantitative cardiac magnetic resonance T1 and T2 mapping,

Daniela Marfisi, Marco Giannelli, Chiara Marzi, Jacopo Del Meglio, Andrea Barucci, Luigi Masturzo, Claudio Vignali, Mario Mascalchi, Antonio Traino, Giancarlo Casolo, Stefano Diciotti, Carlo Tessa,

Magnetic Resonance Imaging, Volume 113, 2024, 110217,

<https://doi.org/10.1016/j.mri.2024.110217>.

Abstract: Radiomics of cardiac magnetic resonance (MR) imaging has proved to be potentially useful in the study of various myocardial diseases. Therefore, assessing the repeatability degree in radiomic features measurement is of fundamental importance. The aim of this study was to assess test-retest repeatability of myocardial radiomic features extracted from quantitative T1 and T2 maps. A representative group of 24 subjects (mean age 54 ± 18 years) referred for clinical cardiac MR imaging were enrolled in the study. For each subject, T1 and T2 mapping through MOLLI and T2-prepared TrueFISP acquisition sequences, respectively, were performed at 1.5 T. Then, 98 radiomic features of different classes (shape, first-order, second-order) were extracted from a region of interest encompassing the whole left ventricle myocardium in a short axis slice. The repeatability was assessed performing different and complementary analyses: intraclass correlation coefficient (ICC) and limits of agreement (LOA) (i.e., the interval within which 95% of the percentage differences between two repeated measures are expected to lie). Radiomic features were characterized by a relatively wide range of repeatability degree in terms of both ICC and LOA. Overall, 44.9% and 38.8% of radiomic features showed ICC values > 0.75 for T1 and T2 maps, respectively, while 25.5% and 23.4% of radiomic features showed LOA between $\pm 10\%$. A subset of radiomic features for T1 (Mean, Median, 10Percentile, 90Percentile, RootMeanSquared, Imc2, RunLengthNonUniformityNormalized, RunPercentage and ShortRunEmphasis) and T2 (MaximumDiameter, RunLengthNonUniformityNormalized, RunPercentage, ShortRunEmphasis) maps presented both ICC > 0.75 and LOA between $\pm 5\%$. Overall, radiomic features extracted from T1 maps showed better repeatability performance than those extracted from T2 maps, with shape features characterized by better repeatability than first-order and textural features. Moreover, only a limited subset of 9 and 4

radiomic features for T1 and T2 maps, respectively, showed high repeatability degree in terms of both ICC and LOA. These results confirm the importance of assessing test-retest repeatability degree in radiomic feature estimation and might be useful for a more effective/reliable use of myocardial T1 and T2 mapping radiomics in clinical or research studies.

Keywords: Magnetic resonance imaging; Cardiac T1 and T2 mapping; Radiomics; Test-retest repeatability

24COASNO116:

Title- Comparison of R2* and FerriScan liver iron concentration (LIC) quantification in the clinical classification of Iron overload states,

Marshall S. Sussman, Stephan A.R. Kannengiesser, Shopnil Prasla, Richard Ward, Kartik S. Jhaveri,

Magnetic Resonance Imaging, Volume 113, 2024, 110216,

<https://doi.org/10.1016/j.mri.2024.110216>.

Abstract: Purpose: This study assessed the clinical classification performance of an R2*-based MRI technique for LIC quantification relative to FerriScan, with intra-patient FerriScan LIC uncertainty taken into account. The variabilities of R2* and FerriScan LIC were also assessed. Materials and methods: This was an ethics approved retrospective study, performed on patients undergoing chelation treatment for iron overload. 126 patients (69 women, 57 men), with an age of 42 $\pm$ 16 years (range 19–86 years) were included. FerriScan and R2* MRI at 1.5 T were performed as part of a routine liver iron assessment protocol. For R2* MRI, a commercially available pulse sequence and reconstruction implementation was used, together with a previously derived calibration curve to convert R2* to LIC. Clinical classifications arising from R2*-derived LIC estimates were compared to those based on FerriScan. The accuracy and precision of the R2* technique was calculated. The variabilities of FerriScan- and R2*-derived estimates of LIC were compared with a Wilcoxon Signed Rank test. Significance was set at the 95% confidence level. Results: The precision of R2* ranged from 0.59 to 0.92, with an overall accuracy of 72%. When intra-patient FerriScan LIC uncertainty was considered, precision and accuracy increased to >94% and 97% respectively. The R2*-LIC variability (=17%) was significantly lower than the FerriScan-LIC variability (34%) at the 95% confidence level ($p < 10^{-3}$). Conclusion: MRI R2*-based LIC estimates provided a similar clinical classification as FerriScan. The intra-patient uncertainty of R2*-based LIC estimates was significantly lower than FerriScan.

Keywords: Liver; Iron overload; Magnetic resonance imaging; Magnetic resonance imaging methods; Magnetic resonance imaging statistics and numerical data

24COASNO117:

Title- The application of B1 inhomogeneity-corrected variable flip angle T1 mapping for assessing liver fibrosis,

Jie Zou, Yanli Jiang, Fengxian Fan, Pin Yang, Tiejun Gan, Tingli Yang, Min Li, Yuan Ding, Shaoyu Wang, Jing Zhang,

Magnetic Resonance Imaging, Volume 113, 2024, 110215,

<https://doi.org/10.1016/j.mri.2024.110215>.

Abstract: Purpose: The aim of this study was to evaluate the diagnostic accuracy of the B1 inhomogeneity-corrected variable flip angle (VFA) method using native T1 values in the staging of liver fibrosis. Methods: Eighty-three patients who presented for liver biopsy due to varying degrees of liver damage, underwent MR examinations and had T1-mapping images of the liver acquired using the B1 inhomogeneity-corrected VFA VIBE method. Among them, 65 patients underwent Fibroscan, and their results were used to evaluate the elasticity of liver tissue. Additionally, T1-mapping images were collected from 19 normal control patients. Independent sample t-tests were used to analyze the correlation between T1 mapping and Fibroscan. The diagnostic efficacy of T1 mapping in patients with different stages of liver fibrosis was evaluated using receiver operating characteristic (ROC) curves.

Results: The consistency between different observer groups was intraclass correlation coefficient (ICC) = 0.802. T1 mapping demonstrated significant differences between mid-stage liver fibrosis ($S = 2$) and late-stage liver fibrosis ($S = 3$), as well as moderate inflammation ($G = 2$) and severe inflammation ($G = 3$), $P < 0.05$. The Area Under Curve (AUC) values of T1 mapping for early liver fibrosis ($S \geq 1$), significant liver fibrosis ($S \geq 2$), advanced liver fibrosis ($S \geq 3$), and end-stage liver fibrosis ($S = 4$) were 0.760, 0.709, 0.790, and 0.768, respectively. T1 mapping combined with Fibroscan had an AUC value of 0.860. Conclusions: The B1 inhomogeneity-corrected VFA T1 mapping may be useful for the staging of liver fibrosis. It has a superior diagnostic efficiency for diagnosing advanced fibrosis ($\geq S3$), while native T1 values combined with Fibroscan have potential value for the staging of liver fibrosis.

Keywords: Liver fibrosis; Magnetic resonance imaging; T1-mapping; Fibroscan

24COASNO118:

Title- Longitudinal registration of T1-weighted breast MRI: A registration algorithm (FLIRE) and clinical application,

Michelle W. Tong, Hon J. Yu, Maren M. Sjaastad Andreassen, Stephane Loubrie, Ana E. Rodríguez-Soto, Tyler M. Seibert, Rebecca Rakow-Penner, Anders M. Dale,

Magnetic Resonance Imaging, Volume 113, 2024, 110222,

<https://doi.org/10.1016/j.mri.2024.110222>.

Abstract: Purpose: MRI is commonly used to aid breast cancer diagnosis and treatment evaluation. For patients with breast cancer, neoadjuvant chemotherapy aims to reduce the tumor size and extent of surgery necessary. The current clinical standard to measure breast tumor response on MRI uses the longest tumor diameter. Radiologists also account for other tissue properties including tumor contrast or pharmacokinetics in their assessment. Accurate longitudinal image registration of breast tissue is critical to properly compare response to treatment at different timepoints. Methods: In this study, a deformable Fast Longitudinal Image Registration (FLIRE) algorithm was optimized for breast tissue. FLIRE was then compared to the publicly available software packages with high accuracy (DRAMMS) and fast runtime (Elastix). Patients included in the study received longitudinal T1-weighted MRI

without fat saturation at two to six timepoints as part of asymptomatic screening (n = 27) or throughout neoadjuvant chemotherapy treatment (n = 32). T1-weighted images were registered to the first timepoint with each algorithm. Results: Alignment and runtime performance were compared using two-way repeated measure ANOVAs ($P < 0.05$). Across all patients, Pearson's correlation coefficient across the entire image volume was slightly higher with statistical significance and had less variance for FLIRE (0.98 ± 0.01 stdev) compared to DRAMMS (0.97 ± 0.03 stdev) and Elastix (0.95 ± 0.03 stdev). Additionally, FLIRE runtime (10.0 mins) was 9.0 times faster than DRAMMS (89.6 mins) and 1.5 times faster than Elastix (14.5 mins) on a Linux workstation. Conclusion: FLIRE demonstrates promise for time-sensitive clinical applications due to its accuracy, robustness across patients and timepoints, and speed.

Keywords: Non-linear; Registration; Longitudinal; Breast; T1; Neoadjuvant chemotherapy

24COASNO119:

Title- Inter-visit and inter-reader reproducibility of multi-parametric diffusion-weighted MR imaging in longitudinally imaged patients with metabolic dysfunction-associated fatty liver disease and healthy volunteers.,

Anton Volniansky, Thierry L. Lefebvre, Merve Kulbay, Boyan Fan, Emre Aslan, Kim-Nhien Vu, Emmanuel Montagnon, Bich Ngoc Nguyen, Giada Sebastiani, Jeanne-Marie Giard, ... [et al.]

Magnetic Resonance Imaging, Volume 113, 2024, 110223,

<https://doi.org/10.1016/j.mri.2024.110223>.

Abstract: Background: Despite the widespread use of diffusion-weighted imaging (DWI) in metabolic dysfunction-associated fatty liver disease (MAFLD), MRI acquisition and quantification techniques vary in the literature suggesting the need for established and reproducible protocols. The goal of this study was to assess inter-visit and inter-reader reproducibility of DWI- and IVIM-derived parameters in patients with MAFLD and healthy volunteers using extensive sampling of the “fast” compartment, non-rigid registration, and exclusion voxels with poor fit quality. Methods From June 2019 to April 2023, 31 subjects (20 patients with biopsy-proven MAFLD and 11 healthy volunteers) were included in this IRB-approved study. Subjects underwent MRI examinations twice within 40 days. 3.0 T DWI was acquired using a respiratory-triggered spin-echo diffusion-weighted echo-planar imaging sequence (b-values of 0, 10, 20, 30, 40, 50, 100, 200, 400, 800 s/mm²). DWI series were co-registered prior to voxel-wise non-linear regression of the IVIM model and voxels with poor fit quality were excluded (normalized root mean squared error ≥ 0.05). IVIM parameters (perfusion fraction, f; diffusion coefficient, D; and pseudo-diffusion coefficient, D*), and apparent diffusion coefficients (ADC) were computed from manual segmentation of the right liver lobe performed by two analysts on two MRI examinations. Results: All results are reported for f, D, D*, and ADC respectively. For inter-reader agreement on the first visit, ICC were of 0.985, 0.994, 0.986, and 0.993 respectively. For intra-reader agreement of analyst 1 assessed on both imaging examinations, ICC between visits were of 0.805, 0.759, 0.511, and 0.850 respectively. For inter-reader agreement on the first visit, mean bias and

95 % limits of agreement were (0.00 ± 0.03) , $(-0.01 \pm 0.03) \times 10^{-3} \text{ mm}^2/\text{s}$, $(0.70 \pm 10.40) \times 10^{-3} \text{ mm}^2/\text{s}$, and $(-0.02 \pm 0.04) \times 10^{-3} \text{ mm}^2/\text{s}$ respectively. For intra-reader agreement of analyst 1, mean bias and 95 % limits of agreement were $(0.01 \pm 0.09) \times 10^{-3} \text{ mm}^2/\text{s}$, $(-0.01 \pm 0.21) \times 10^{-3} \text{ mm}^2/\text{s}$, $(-13.37 \pm 56.19) \times 10^{-3} \text{ mm}^2/\text{s}$, and $(-0.01 \pm 0.16) \times 10^{-3} \text{ mm}^2/\text{s}$ respectively. Except for parameter D^* that was associated with between-subjects parameter variability ($P = 0.009$), there was no significant variability between subjects, examinations, or readers. Conclusion: With our approach, IVIM parameters f , D , D^* , and ADC provided excellent inter-reader agreement and good to very good inter-visit or intra-reader agreement, thus showing the reproducibility of IVIM-DWI of the liver in MAFLD patients and volunteers.

Keywords: Magnetic resonance imaging; Diffusion-weighted imaging; Intra-voxel incoherent motion; Reproducibility; Metabolic dysfunction-associated fatty liver disease

24COASNO120:

Title- A multi-task generative model for simultaneous post-contrast MR image synthesis and brainstem glioma segmentation,

Yajing Zhang, Yanxin Huang, Xiangyu Xiong, Yaou Liu, Jin Qi,
Magnetic Resonance Imaging, Volume 113, 2024, 110210,
<https://doi.org/10.1016/j.mri.2024.07.009>.

Abstract: Objectives: This study aims to generate post-contrast MR images reducing the exposure of gadolinium-based contrast agents (GBCAs) for brainstem glioma (BSG) detection, simultaneously delineating the BSG lesion, and providing high-resolution contrast information. Methods: A retrospective cohort of 30 patients diagnosed with brainstem glioma was included. Multi-contrast images, including pre-contrast T1 weighted (pre-T1w), T2 weighted (T2w), arterial spin labeling (ASL) and post-contrast T1w images, were collected. A multi-task generative model was developed to synthesize post-contrast T1w images and simultaneously segment BSG masks from the multi-contrast inputs. Performance evaluation was conducted using peak signal-to-noise ratio (PSNR), structural similarity index (SSIM), and mean absolute error (MAE) metrics. A perceptual study was also undertaken to assess diagnostic quality. Results: The proposed model achieved SSIM of 0.86 ± 0.04 , PSNR of 26.33 ± 0.05 and MAE of 57.20 ± 20.50 for post-contrast T1w image synthesis. Automated delineation of the BSG lesions achieved Dice similarity coefficient (DSC) score of 0.88 ± 0.27 . Conclusions: The proposed model can synthesize high-quality post-contrast T1w images and accurately segment the BSG region, yielding satisfactory DSC scores.

Clinical relevance statement: The synthesized post-contrast MR image presented in this study has the potential to reduce the usage of gadolinium-based contrast agents, which may pose risks to patients. Moreover, the automated segmentation method proposed in this paper aids radiologists in accurately identifying the brainstem glioma lesion, facilitating the diagnostic process.

Keywords: Brainstem glioma; MRI; Multi-task generative adversarial network

24COASNO121:

Title- Modelling white matter microstructure using diffusion OGSE MRI: Model and analysis choices,

Emma Friesen, Madison Chisholm, Bibek Dhakal, Morgan Mercredi, Mark D. Does, John C. Gore, Melanie Martin,

Magnetic Resonance Imaging, Volume 113, 2024, 110221,

<https://doi.org/10.1016/j.mri.2024.110221>.

Abstract: Alterations in white matter (WM) microstructure of the central nervous system have been shown to be pathophysiological presentations of various neurodegenerative disorders. Current methods for measuring such WM features require ex vivo tissue samples analyzed using electron microscopy. Magnetic Resonance Imaging (MRI) diffusion-weighted pulse sequences provide a non-invasive tool for estimating such microstructural features in vivo. The current project investigated the use of two methods of analysis, including the ROI-based (Region of Interest, RBA) and voxel-based analysis (VBA), as well as four mathematical models of WM microstructure, including the ActiveAx Frequency-Independent Extra-Axonal Diffusion (AAI), ActiveAx Frequency-Dependent Extra-Axonal Diffusion (AAD), AxCaliber Frequency-Independent Extra-Axonal Diffusion (ACI), and AxCaliber Frequency-Dependent Extra-Axonal Diffusion (ACD) models. Two mice samples imaged at 7 T and 15.2 T were analyzed. Both the AAI and AAD models provide a single value for each of the fit parameters, including mean effective axon diameter AxD^+ , packing fraction f_m , intra-cellular and D_{in} and extra-cellular D_{ex} diffusion coefficients, as well as the frequency dependence of D_{ex} , β_{ex} for the AAD model. The ACI and ACD models provide this, in addition to a distribution of axon diameters for a chosen ROI. VBA extends this, providing a parameter value for each voxel within the selected ROI, at the cost of increased computational load and analysis time. Overall, RBA-ACD and VBA-AAD were found to be optimal for parameter fitting to physically relevant values in a reasonable time frame. A full comparison of each combination of RBA and VBA with AAI, AAD, ACI, and ACD is provided to give the reader sufficient information to make an informed decision of which model is best for their own experiments.

Keywords: Magnetic resonance imaging; Mathematical modelling; OGSE; Diffusion; Voxel based analysis

24COASNO122:

Title- Combination of IVIM with DCE-MRI for diagnostic and prognostic evaluation of breast cancer,

Jing Zhang, Yurong Zheng, Li Li, Rui Wang, Weilong Jiang, Kai Ai, Tiejun Gan, Pengfei Wang,

Magnetic Resonance Imaging, Volume 113, 2024, 110204,

<https://doi.org/10.1016/j.mri.2024.07.003>.

Abstract: Purpose: To identify the most effective combination of DCE-MRI (K_{trans} , K_{ep}) and IVIM (D , f) and analyze the correlations of these parameters with prognostic indicators (ER, PR, and HER2, Ki-67 index, axillary lymph node (ALN) and tumor size) to improve the

diagnostic and prognostic efficiency in breast cancer. **Methods:** This is a prospective study. We performed T1WI, T2WI, IVIM, DCE-MRI at 3 T MRI examinations on benign and malignant breast lesions that met the inclusion criteria. We also collected pathological results of corresponding lesions, including ER, PR, and HER2, Ki-67 index, axillary lymph node (ALN) and tumor size. The diagnostic efficacy of DCE-MRI, IVIM imaging, and their combination for benign and malignant breast lesions was assessed. Correlations between the DCE-MRI and IVIM parameters and prognostic indicators were assessed. **Results:** Overall, 59 female patients with 62 lesions (22 benign lesions and 40 malignant lesions) were included in this study. The malignant group showed significantly lower D values ($p < 0.05$) and significantly higher Ktrans, Kep, and f values ($p < 0.05$). The AUC values of DCE, IVIM, DCE + IVIM were 0.828, 0.882, 0.901. Ktrans, Kep, D and f values were correlated with the pathological grade ($p < 0.05$); Ktrans was negatively correlated with ER expression ($r = -0.519$, $p < 0.05$); Kep was correlated with PR expression and the Ki-67 index ($r = -0.489$, 0.330 , $p < 0.05$); the DCE and IVIM parameters showed no significant correlations with the HER2 and ALN ($p > 0.05$). Tumor diameter was correlated with the Kep, D and f values ($r = 0.246$, -0.278 , 0.293 ; $p < 0.05$). **Conclusion:** IVIM and DCE-MRI allowed differential diagnosis of benign and malignant breast lesions, and their combination showed significantly better diagnostic efficiency. DCE- and IVIM-derived parameters showed correlations with some prognostic factors for breast cancer.

Keywords: IVIM; DCE-MRI; ER; PR; HER2; ALN(axillary lymph node); Breast cancer, correlation analysis

24COASNO123:

Title- DCE-MRI Radiomic analysis in triple negative ductal invasive breast cancer. Comparison between BRCA and not BRCA mutated patients: Preliminary results,

Annarita Pecchi, Chiara Bozzola, Cecilia Beretta, Giulia Besutti, Angela Toss, Laura Cortesi, Erica Balboni, Luca Nocetti, Guido Ligabue, Pietro Torricelli,
Magnetic Resonance Imaging, Volume 113, 2024, 110214,
<https://doi.org/10.1016/j.mri.2024.110214>.

Abstract: Objective: The research aimed to determine whether and which radiomic features from breast dynamic contrast enhanced (DCE) MRI could predict the presence of BRCA1 mutation in patients with triple-negative breast cancer (TNBC). Material and methods: This retrospective study included consecutive patients histologically diagnosed with TNBC who underwent breast DCE-MRI in 2010–2021. Baseline DCE-MRIs were retrospectively reviewed; percentage maps of wash-in and wash-out were computed and breast lesions were manually segmented, drawing a 5 mm-Region of Interest (ROI) inside the tumor and another 5 mm-ROI inside the contralateral healthy gland. Features for each map and each ROI were extracted with Pyradiomics-3D Slicer and considered first separately (tumor and contralateral gland) and then together. In each analysis the more important features for BRCA1 status classification were selected with Maximum Relevance Minimum Redundancy algorithm and used to fit four classifiers. Results: The population included 67 patients and 86 lesions (21 in BRCA1-mutated, 65 in non BRCA-carriers). The best classifiers for BRCA mutation were

Support Vector Classifier and Logistic Regression in models fitted with both gland and tumor features, reaching an Area Under ROC Curve (AUC) of 0.80 (SD 0.21) and of 0.79 (SD 0.20), respectively. Three features were higher in BRCA1-mutated compared to non BRCA1-mutated: Total Energy and Correlation from gray level cooccurrence matrix, both measured in contralateral gland in wash-out maps, and Root Mean Squared, selected from the wash-out map of the tumor. Conclusions: This study showed the feasibility of a radiomic study with breast DCE-MRI and the potential of radiomics in predicting BRCA1 mutational status.

Keywords: Radiogenomics; Magnetic resonance imaging; Breast cancer; BRCA1 gene

24COASNO124:

Title- Correlation between matrix metalloproteinase-2, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinases-1 and white matter hyperintensities in patients with cerebral small vessel disease based on cranial magnetic resonance 3D imaging,

Bei-Lin Luo, Shun-Po He, Yi-Fen Zhang, Qing-Wei Yang, Jing-Cong Zhuang, Ren-Jing Zhu, Ya-Qin Zheng, Hua-Mei Su,

Magnetic Resonance Imaging, Volume 113, 2024, 110213,

<https://doi.org/10.1016/j.mri.2024.110213>.

Abstract: Objective: The objective of this study was to investigate the correlation between serum levels of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinases-1 (TIMP-1) levels and their ratios with the severity of white matter hyperintensities (WMHs) in patients with cerebral small vessel disease (CSVD). Methods: This cross-sectional study was done on a prospective cohort of patients with CSVD. Qualitative and quantitative analyses of WMHs were performed using Fazekas grading and lesion prediction algorithm (LPA) methods. Biomarkers MMP-2, MMP-9, and TIMP-1 were measured to explore their correlation with the severity of WMHs. Results : The sample consisted of 144 patients with CSVD. There were 63 male and 81 female patients, with an average age of 67.604 ± 8.727 years. Among these, 58.33% presented with white matter hyperintensities at Fazekas grading level 1, with an average total template volume of WMHs of 4.305 mL. MMP-2 ($P = 0.025$), MMP-9 ($P = 0.008$), TIMP-1 ($P = 0.026$), and age ($P = 0.007$) were identified as independent correlates of WMHs based on Fazekas grading. Independent correlates of the total template volume of WMHs included MMP-2 ($P = 0.023$), TIMP-1 ($P = 0.046$), age ($P = 0.047$), systolic blood pressure ($P = 0.047$), and homocysteine (Hcy) ($P = 0.014$). In addition, age ($P = 0.003$; $P < 0.001$), interleukin-6 (IL-6) ($P < 0.001$; $P = 0.044$), Hcy ($P < 0.001$; $P < 0.001$), glycated hemoglobin (HbA1c) ($P = 0.016$; $P = 0.043$), and chronic kidney disease ($P < 0.001$; $P < 0.001$) were associated with both WMHs Fazekas grading and the total template volume of WMHs. Conclusion: Serum levels of MMP-9, MMP-2, and TIMP-1 were independently associated with the Fazekas grading, while serum TIMP-1 and MMP-2 levels were independently related to the total template volume of WMHs. The association of TIMP-1 and MMP-2 with the severity of CSVD-related WMHs suggests their potential role as disease-related biomarkers. However, further research is required to uncover the specific mechanisms underlying these interactions.

Keywords: Cerebral small vessel disease; Cranial magnetic resonance imaging; Matrix metalloproteinases; Tissue inhibitors of metalloproteinases; White matter hyperintensities

24COASNO125:

Title- Spectro-ViT: A vision transformer model for GABA-edited MEGA-PRESS reconstruction using spectrograms,

Gabriel Dias, Rodrigo Pommot Berto, Mateus Oliveira, Lucas Ueda, Sergio Dertkigil, Paula D.P. Costa, Amirmohammad Shamaei, Hanna Bugler, Roberto Souza, Ashley Harris, [et al.] Magnetic Resonance Imaging, Volume 113, 2024, 110219, <https://doi.org/10.1016/j.mri.2024.110219>.

Abstract: This study investigated the use of a Vision Transformer (ViT) for reconstructing GABA-edited Magnetic Resonance Spectroscopy (MRS) data from a reduced number of transients. Transients refer to the samples collected during an MRS acquisition by repeating the experiment to generate a signal of sufficient quality. Specifically, 80 transients were used instead of the typical 320 transients, aiming to reduce scan time. The 80 transients were pre-processed and converted into a spectrogram image representation using the Short-Time Fourier Transform (STFT). A pre-trained ViT, named Spectro-ViT, was fine-tuned and then tested using in-vivo GABA-edited MEGA-PRESS data. Its performance was compared against other pipelines in the literature using quantitative quality metrics and estimated metabolite concentration values, with the typical 320-transient scans serving as the reference for comparison. The Spectro-ViT model exhibited the best overall quality metrics among all other pipelines against which it was compared. The metabolite concentrations from Spectro-ViT's reconstructions for GABA+ achieved the best average R2 value of 0.67 and the best average Mean Absolute Percentage Error (MAPE) value of 9.68%, with no significant statistical differences found compared to the 320-transient reference. The code to reproduce this research is available at <https://github.com/MICLab-Unicamp/Spectro-ViT>

Keywords: GABA-edited MEGA-PRESS; MRS denoising; Deep learning; Vision transformer

24COASNO126:

Title- An unrolled neural network for accelerated dynamic MRI based on second-order half-quadratic splitting model,

Jiabing Sun, Changliang Wang, Lei Guo, Yongxiang Fang, Jiawen Huang, Bensheng Qiu, Magnetic Resonance Imaging, Volume 113, 2024, 110218, <https://doi.org/10.1016/j.mri.2024.110218>.

Abstract: The reconstruction of dynamic magnetic resonance images from incomplete k-space data has sparked significant research interest due to its potential to reduce scan time. However, traditional iterative optimization algorithms fail to faithfully reconstruct images at higher acceleration factors and incur long reconstruction time. Furthermore, end-to-end deep learning-based reconstruction algorithms suffer from large model parameters and lack robustness in the reconstruction results. Recently, unrolled deep learning models, have shown immense potential in algorithm stability and applicability flexibility. In this paper, we

propose an unrolled deep learning network based on a second-order Half-Quadratic Splitting(HQS) algorithm, where the forward propagation process of this framework strictly follows the computational flow of the HQS algorithm. In particular, we propose a degradation-sense module by associating random sampling patterns with intermediate variables to guide the iterative process. We introduce the Information Fusion Transformer(IFT) to extract both local and non-local prior information from image sequences, thereby removing aliasing artifacts resulting from random undersampling. Finally, we impose low-rank constraints within the HQS algorithm to further enhance the reconstruction results. The experiments demonstrate that each component module of our proposed model contributes to the improvement of the reconstruction task. Our proposed method achieves comparably satisfying performance to the state-of-the-art methods and it exhibits excellent generalization capabilities across different sampling masks. At the low acceleration factor, there is a 0.7% enhancement in the PSNR. Furthermore, when the acceleration factor reached 8 and 12, the PSNR achieves an improvement of 3.4% and 5.8% respectively.

Keywords: Deep learning; Unrolled neural network; Image reconstruction; Low rank; Dynamic MRI

24COASNO127:

Title- Dynamic contrast enhanced MRI of the head and neck region using a VIBE sequence with Cartesian undersampling and compressed sensing,

F. Kubicka, L. Nitschke, T. Penzkofer, Q. Tan, M.D. Nickel, K.M. Wakonig, U.L. Fahlenkamp, M. Lerchbaumer, F. Michallek, S. Dommerich, B. Hamm, M. Wagner, T. Walter-Rittel,

Magnetic Resonance Imaging, Volume 113, 2024, 110220,

<https://doi.org/10.1016/j.mri.2024.110220>.

Abstract: Objectives: Compressed sensing allows for image reconstruction from sparsely sampled k-space data, which is particularly useful in dynamic contrast enhanced MRI (DCE-MRI). The aim of the study was to assess the diagnostic value of a volume-interpolated 3D T1-weighted spoiled gradient-echo sequence with variable density Cartesian undersampling and compressed sensing (CS) for head and neck MRI. Methods: Seventy-one patients with clinical indications for head and neck MRI were included in this study. DCE-MRI was performed at 3 Tesla magnet using CS-VIBE (variable density undersampling, temporal resolution 3.4 s, slice thickness 1 mm). Image quality was compared to standard Cartesian VIBE. Three experienced readers independently evaluated image quality and lesion conspicuity on a 5-point Likert scale and determined the DCE-derived time intensity curve (TIC) types. Results: CS-VIBE demonstrated higher image quality scores compared to standard VIBE with respect to overall image quality (4.3 ± 0.6 vs. 4.2 ± 0.7 , $p = 0.682$), vessel contour (4.6 ± 0.4 vs. 4.4 ± 0.6 , $p < 0.001$), muscle contour (4.4 ± 0.5 vs. 4.5 ± 0.6 , $p = 0.302$), lesion conspicuity (4.5 ± 0.7 vs. 4.3 ± 0.9 , $p = 0.024$) and showed improved fat saturation (4.8 ± 0.3 vs. 3.8 ± 0.4 , $p < 0.001$) and movement artifacts were significantly reduced (4.6 ± 0.6 vs. 3.7 ± 0.7 , $p < 0.001$). Standard VIBE outperformed CS-VIBE in the

delineation of pharyngeal mucosa (4.2 ± 0.5 vs. 4.6 ± 0.6 , $p < 0.001$). Lesion size in cases where a focal lesion was identified was similar for all readers for CS-VIBE and standard VIBE ($p = 0.101$). TIC curve assessment showed good interobserver agreement ($k=0.717$). Conclusion: CS-VIBE with variable density Cartesian undersampling allows for DCE-MRI of the head and neck region with diagnostic, high image quality and high temporal resolution.

Keywords: Compressed sensing; MRI; Head and neck; Dynamic contrast enhanced MRI

24COASNO128:

Title- Plaque enhancement of middle cerebral artery and pre-stroke diet are associated with prognosis of subacute ischemic stroke: A prospective high-resolution MR vessel wall imaging study,

Wenqiao Zheng, Haili Yan, Dawei Tian, Yan Li, Le Wang, Ying Lei, Bin Wang, Yongfang Wang, Guoqiang Yang, Xiaochun Wang,

European Journal of Radiology, Volume 180, 2024, 111693,

<https://doi.org/10.1016/j.ejrad.2024.111693>.

Abstract: Objectives: To explore the value of middle cerebral artery (MCA) plaque characteristics in predicting the outcomes of subacute ischemic stroke and the incremental value of the previous diet on predictive performance. Methods: One hundred and thirty-seven subacute ischemic stroke patients attributed to MCA plaques were included and analyzed in this prospective study. The National Institute of Health Stroke Scale (NIHSS) score, Mediterranean Diet Adherence Screener (MEDAS) score, and other clinical data were assessed. The plaque area, degree of stenosis, plaque burden, enhancement ratio, remodeling type, and intraplaque hemorrhage were measured using high-resolution MR vessel wall imaging (HR-VWI). Multivariable logistic regression analysis and receiver operating characteristic curve analysis were performed to assess the predictive performance of clinical and plaque characteristics for subacute ischemic stroke outcomes at 3 months. Results: Patients with poor outcomes exhibited high NIHSS scores, and low MEDAS scores ($P < 0.001$). Plaque burden, enhancement ratio, and degree of stenosis were significantly higher in patients with poor outcomes ($P < 0.001$). Multivariate analyses further indicated that NIHSS score ($P = 0.001$), MEDAS score ($P = 0.013$), and enhancement ratio ($P = 0.011$) were independent predictors of subacute ischemic stroke outcomes. The three models' area under the curve (AUC) values were 0.811, 0.844, and 0.794. Combining these three factors resulted in an AUC of 0.908 ($P < 0.001$). Conclusions: The combination of NIHSS score, MEDAS score, and enhancement ratio showed significant superiority in the prognostic evaluation of subacute ischemic stroke. Clinical data combined with plaque characteristics improves the accuracy of 3-month outcome prediction on subacute ischemic stroke.

Keywords: Ischemic stroke outcomes; High-resolution MR vessel wall imaging; Mediterranean diet; Intracranial atherosclerosis

24COASNO129:

Title- Adding contrast-enhanced ultrasound can improve the predictive ability of breast conventional ultrasound and mammography for pathological upgrade of biopsy-confirmed ductal carcinoma in situ,

Ying Zhu, Xiaohong Jia, Weiwei Zhan, Jianqiao Zhou,
European Journal of Radiology, Volume 180, 2024, 111687,
<https://doi.org/10.1016/j.ejrad.2024.111687>.

Abstract: Objectives: To evaluate the added value of contrast-enhanced ultrasound (CEUS) on top of breast conventional imaging for predicting the upgrading of ductal carcinoma in situ (DCIS) to invasive cancer after surgery. Methods: This retrospective study enrolled 140 biopsy-proven DCIS lesions in 138 patients and divided them into two groups based on postoperative histopathology: non-upgrade and upgrade groups. Conventional ultrasound (US), mammography (MMG), CEUS and clinicopathological (CL) features were reviewed and compared between the two groups. The predictive performance of different models (with and without CEUS features) for histologic upgrade were compared to calculate the added value of CEUS. Results: Fifty-nine (42.1 %) lesions were histologically upgraded to invasive cancer after surgery. By logistic regression analyses, we found that high-grade DCIS at biopsy ($P=0.004$), ultrasonographic lesion size > 20 mm ($P=0.007$), mass-like lesion on US ($P=0.030$), the presence of suspicious calcification on MMG ($P=0.014$), the presence of perfusion defect ($P=0.005$) and the area under TIC > 1021.34 ml ($P<0.001$) on CEUS were six independent factors predicting concomitant invasive components after surgery. The CL+US+MMG model made with the four predictors in the clinicopathologic, US and MMG categories yielded an area under the receiver operating curve (AUROC) value of 0.759 (95 % CI: 0.680–0.828) in predicting histological upgrade. The combination model built by adding the two CEUS predictors to the CL+US+MMG model showed higher predictive efficacy than the CL+US+MMG model ($P=0.018$), as the AUROC value was improved to 0.861 (95 % CI: 0.793–0.914). Conclusions: The addition of contrast-enhanced ultrasound to breast conventional imaging could improve the preoperative prediction of an upgrade to invasive cancer from CNB –proven DCIS lesions.

Keywords: Breast cancer; Ultrasonography; Ductal carcinoma in situ; Contrast agents

24COASNO130:

Title- 2.5D deep learning based on multi-parameter MRI to differentiate primary lung cancer pathological subtypes in patients with brain metastases,

Jinling Zhu, Li Zou, Xin Xie, Ruizhe Xu, Ye Tian, Bo Zhang,
European Journal of Radiology, Volume 180, 2024, 111712,
<https://doi.org/10.1016/j.ejrad.2024.111712>.

Abstract: Background Brain metastases (BMs) represents a severe neurological complication stemming from cancers originating from various sources. It is a highly challenging clinical task to accurately distinguish the pathological subtypes of brain metastatic tumors from lung cancer (LC). The utility of 2.5-dimensional (2.5D) deep learning (DL) in distinguishing pathological subtypes of LC with BMs is yet to be determined. Methods: A total of 250

patients were included in this retrospective study, divided in a 7:3 ratio into training set (N=175) and testing set (N=75). We devised a method to assemble a series of two-dimensional (2D) images by extracting adjacent slices from a central slice in both superior-inferior and anterior-posterior directions to form a 2.5D dataset. Multi-Instance learning (MIL) is a weakly supervised learning method that organizes training instances into “bags” and provides labels for entire bags, with the purpose of learning a classifier based on the labeled positive and negative bags to predict the corresponding class for an unknown bag. Therefore, we employed MIL to construct a comprehensive 2.5D feature set. Then we used the single-slice as input for constructing the 2D model. DL features were extracted from these slices using the pre-trained ResNet101. All feature sets were inputted into the support vector machine (SVM) for evaluation. The diagnostic performance of the classification models were evaluated using five-fold cross-validation, with accuracy and area under the curve (AUC) metrics calculated for analysis. Results: The optimal performance was obtained using the 2.5D DL model, which achieved the micro-AUC of 0.868 (95% confidence interval [CI], 0.817–0.919) and accuracy of 0.836 in the test cohort. The 2D model achieved the micro-AUC of 0.836 (95 % CI, 0.778–0.894) and accuracy of 0.827 in the test cohort. Conclusions: The proposed 2.5D DL model is feasible and effective in identifying pathological subtypes of BMs from lung cancer.

Keywords: Brain Metastases; 2.5D Deep Learning; Multi-Instance Learning; Magnetic Resonance Imaging

24COASNO131:

Title- The predictive value of coronary computed tomography angiography-derived fractional flow reserve for perioperative cardiac events in lung cancer surgery,

Zhao Ma, Shuo Dong, Songlei Ou, Xuchen Ma, Linqi Liu, Ziyu An, Feng Xu, Dongfeng Zhang, Chenchen Tu, Xiantao Song, Hongjia Zhang,

European Journal of Radiology, Volume 180, 2024, 111688,

<https://doi.org/10.1016/j.ejrad.2024.111688>.

Abstract: Purpose: As a non-invasive coronary functional examination, coronary computed tomography angiography (CCTA)-derived fractional flow reserve (CT-FFR) showed predictive value in several non-cardiac surgeries. This study aimed to evaluate the predictive value of CT-FFR in lung cancer surgery. Method: We retrospectively collected 227 patients from January 2017 to June 2022 and used machine learning-based CT-FFR to evaluate the stable coronary artery disease (CAD) patients undergoing lung cancer surgery. The major adverse cardiac event (MACE) was defined as perioperative myocardial injury (PMI), myocardial infarction, heart failure, atrial and ventricular arrhythmia with hemodynamic disorder, cardiogenic shock and cardiac death. The multivariate logistic regression analysis was performed to identify risk factors for MACE and PMI. The discriminative capacity, goodness-of-fit, and reclassification improvement of prediction model were determined before and after the addition of CT-FFR $\leq$ 0.8. Results: The incidence of MACE was 20.7 % and PMI was 15.9 %. CT-FFR significantly outperformed CCTA in terms of accuracy for predicting MACE (0.737 vs 0.524). In the multivariate regression analysis, CT-FFR $\leq$ 0.8 was

an independent risk factor for both MACE [OR=10.77 (4.637, 25.016), $P<0.001$] and PMI [OR=8.255 (3.372, 20.207), $P<0.001$]. Additionally, we found that the performance of prediction model for both MACE and PMI improved after the addition of CT-FFR. Conclusions: CT-FFR can be used to assess the risk of perioperative MACE and PMI in patients with stable CAD undergoing lung cancer surgery. It adds prognostic information in the cardiac evaluation of patients undergoing lung cancer surgery.

Keywords: Coronary computed tomography angiography; Lung cancer surgery; Fractional flow reserve; Perioperative myocardial injury; Major adverse cardiovascular event

24COASNO132:

Title- PSMA PET improves characterization of dural-based intracranial lesions in patients with metastatic prostate cancer,

Divya Yadav, Silvina P. Dutruel, Elisabeth O'Dwyer, Andres Ricaurte-Fajardo, Rituraj Upadhyay,

European Journal of Radiology, Volume 180, 2024, 111711,

<https://doi.org/10.1016/j.ejrad.2024.111711>.

Abstract: Purpose: Theranostic approaches combining prostate-specific membrane antigen (PSMA)-PET/CT or PET/MRI with PSMA-targeted radionuclide therapy have improved clinical outcomes in patients with prostate cancer (PCa) especially metastatic castrate resistant prostate cancer. Dural metastases in PCa are rare but can pose a diagnostic challenge, as meningiomas, a more common dural based lesions have been shown to express PSMA. The aim of this study is to compare PSMA PET parameters between brain lesions classified as dural metastases and meningiomas in prostate cancer patients. Methods: A retrospective analysis of PSMA PET/CT scans in patients with PCa and intracranial lesions was conducted. Brain lesions were categorized as dural metastases or meningiomas based on MRI characteristics, longitudinal follow-up, and histopathological characteristics. Standardized uptake values (SUVmax) of each brain lesion were measured, along with SUV ratio referencing parotid gland (SUVR). SUVs between lesions classified as metastases and meningiomas, respectively, were compared using Mann-Whitney-test. Diagnostic accuracy was evaluated using ROC analysis. Results: 26 male patients (median age: 76.5 years, range: 59–96 years) met inclusion criteria. A total of 44 lesions (7 meningiomas and 37 metastases) were analyzed. Median SUVmax and SUVR were significantly lower in meningiomas compared to metastases (SUVmax: 2.7 vs. 11.5, $p = 0.001$; SUVR: 0.26 vs. 1.05, $p < 0.001$). ROC analysis demonstrated AUC 0.903; the optimal cut-off value for SUVR was 0.81 with 81.1 % sensitivity and 100 % specificity. Conclusion: PSMA PET has the potential to differentiate meningiomas from dural-based metastases in patients with PCa, which can optimize clinical management and thus improve patient outcomes.

Keywords: PSMA PET; Prostate cancer; Dural metastases; Meningioma

24COASNO133:

Title- Multivendor comparison of quantification accuracy of effective atomic number by Dual-Energy CT: A phantom study,

Tian Qin, Mengting Wang, Yihan Fan, Jing Wang, Zhizhen Gao, Fan Wang, Ruomei Li, Kui Li, Chengcheng Ruan, Baohui Liang,

European Journal of Radiology, Volume 180, 2024, 111690,

<https://doi.org/10.1016/j.ejrad.2024.111690>.

Abstract: Purpose: Our study aimed to compare the accuracy of the effective atomic number (Zeff) of five dual-energy CT (DECT) from three vendors and different generations under different scanning parameters. Methods: Zeff accuracy of five DECT scanners with twelve tube voltage configurations was evaluated by using the TomoTherapy cheese phantom. The potential dose dependence of the Zeff was investigated using three radiation dose (5, 15, and 25 mGy), and the robustness of Zeff was simulated for different organs of the body by placing the inserts at different positional depths. Bias and mean absolute percentage error (MAPE) were used to characterize the accuracy of Zeff. Data underwent analysis using one-way ANOVA, followed by the Turkey and LSD post hoc tests, simple linear regression, and linear mixed models. Results: All tube voltage configurations had a bias of less than 1. Dual layer detector DECT (dl-DECT) –140 kV has the lowest MAPE (1.79 %±1.93 %). The third generation dual source DECT (ds-DECT) and the second generation rapid switch DECT (rs-DECT) have higher MAPE than their predecessor DECT. The results of the linear mixed model showed that tube voltage configuration ($F=16.92$, $p < 0.001$) and insert type ($F=53.26$, $p < 0.001$) significantly affect the MAPE. In contrast, radiation dose only has a significant effect on the MAPE of rs-DECT. The inserts position does not affect the final MAPE. Conclusion: When scanning different inserts, Zeff accuracy varies by vendor and DECT generation. Of all the scanners, dl-DECT had the highest Zeff accuracy. Upgrading DECT generation doesn't lead to higher accuracy, or even lower.

Keywords: Dual-energy CT; Quantification accuracy; Effective atomic number

24COASNO134:

Title- Quantitative diagnosis of carotid blowout syndrome with CT perfusion: Carotid blowout syndrome CTP quantitative diagnosis,

Chia-Hung Wu, Kan Ling, Te-Ming Lin, Chao-Bao Luo, Jiing-Feng Lin, Shan-Su Huang, Feng-Chi Chang,

European Journal of Radiology, Volume 180, 2024, 111705,

<https://doi.org/10.1016/j.ejrad.2024.111705>.

Abstract: Background and purpose: Carotid blowout syndrome (CBS) is a potentially fatal disease. The CBS diagnosis mainly relies on subjective observations and the quantitative diagnostic method was not well established. This study aimed to diagnose CBS severity by computed tomography perfusion (CTP) parameters with different region-of-interest (ROI) models. Materials and Method: We prospectively recruited CBS patients between February 1, 2018 and July 31, 2023 in a tertiary medical center, and CTP was performed using the same 128-detector CT machine. Digital subtraction angiography (DSA) and elective endovascular intervention were performed within 3 days post-CTP for diagnosis confirmation and treatments. CBS severity was classified into ongoing (threatened + impending) or acute CBS based on DSA findings and clinical features. Pericarotid soft-tissue (PCST) CTP parameters,

including blood flow (BF), blood volume (BV), mean transit time (MTT) and flow extraction product (FEP), were evaluated and correlated on DSA. We depicted models A, B and C for the small focal lesion in 1 cm of PCST, 1 cm around PCST and the whole PCST respectively. Results: CTP images of 110 patients (77 ongoing (45 threatened + 32 impending); 33 acute) were analyzed. Pericarotid BV (1.8 ± 1.2 vs. 3.5 ± 2.0 ; $p < 0.001$) in Model A and BF in Model B (42.6 ± 11.0 vs. 50.9 ± 20.4 ; $p = 0.031$) were lower in acute-CBS than in ongoing-CBS patients. Subgroup analysis demonstrated lower BV in acute (1.8 ± 1.2) compared with threatened (3.7 ± 2.3 ; $p < 0.001$; $p < 0.001$) and impending (3.2 ± 1.6 ; $p = 0.009$) CBS patients in Model A. Conclusion: CBS severity can be quantitatively diagnosed by pericarotid soft-tissue CTP parameters. In Model A (small focus), BV was capable of differentiating acute CBS from other subtypes, demonstrating its potential role as a CBS imaging biomarker. **Keywords:** Carotid blowout syndrome (CBS); Computed tomography perfusion (CTP); Blood volume (BV); Pericarotid soft-tissue (PCST)

24COASNO135:

Title- The relationship between imaging-based body composition abnormalities and long-term mortality in patients with liver cirrhosis,

Wenhui Ren, Jiarui Zheng, Shuo Yang, Juan Zhong, Xin Liu, Xinyue Liu, Jiajun Feng, Tingyang Wei,

European Journal of Radiology, Volume 180, 2024, 111707,

<https://doi.org/10.1016/j.ejrad.2024.111707>.

Abstract: Background: Emerging evidence on cirrhosis suggests a close correlation between abnormality in body composition characteristics and poor prognosis. This study aimed to evaluate the impact of dynamic changes in body composition on the prognostic outcomes in patients with cirrhosis. Methods: This retrospective analysis included 158 patients diagnosed as cirrhosis from January 2018 to August 2023. Skeletal muscle mass, muscle quality, visceral and subcutaneous adiposity were evaluated using computed tomography (CT) imaging at the third lumbar vertebra level. Competing risk model was performed for four different body composition status (i.e., normal, only sarcopenia, only myosteatosis, and combined status) for liver-related mortality. We also explored the relationship between the dynamic change in body composition and long-term prognosis by applying Gray's test. Results: Of the 158 cirrhotic patients (mean [SD] age, 57.1 [12.6] years), sarcopenia was present in 85 (60.1 %) patients, while 22 (13.9 %) patients had sarcopenic obesity and 68 (43.0 %) had myosteatosis. Patients solely diagnosed with sarcopenia exhibited a higher mortality rate compared to those with normal body composition (Gray's test, $P=0.006$), while patients solely diagnosed with myosteatosis or with a combination of sarcopenia and myosteatosis did not reach statistical significance (Gray's test, $P=0.076$; $P=0.140$). Multivariable analysis also revealed that VSR (HR=1.10 [1.01~1.20]; $P=0.028$), sarcopenia (HR=2.73 [1.20~6.22], $P=0.017$) and myosteatosis (HR=2.39 [1.10~5.18], $P=0.028$) were significant independent predictors of liver-related deaths. Otherwise, patients exhibiting aggravating body composition during follow-up period were associated with a significantly higher mortality risk compared to those with normal or remission body composition status

(HR=7.63 [1.12~51.14]; P=0.036). Conclusion: Progressive alterations in body composition status appears to be associated with liver-related mortality in individuals with liver cirrhosis. Focusing on the management of skeletal muscle, along with visceral and subcutaneous adiposity, may contribute to improving the prognosis of cirrhotic patients.

Keywords: Liver cirrhosis; Body composition; Sarcopenia; Sarcopenic obesity; Myosteatorsis; Liver-related mortality; Prognosis prediction

24COASNO136:

Title- Comparative analysis of hepatic fat quantification across 5 T, 3 T and 1.5 T: A study on consistency and feasibility,

Jianxian Liu, Zhensong Wang, Dan Yu, Yanxing Yang, Zhengyi Li, Xin Wang, Yuxin Yang, Chuanli Cheng, Chao Zou, Jie Gan,

European Journal of Radiology, Volume 180, 2024, 111709,

<https://doi.org/10.1016/j.ejrad.2024.111709>.

Abstract: Objectives: Magnetic resonance imaging (MRI) is a critical noninvasive technique for evaluating liver steatosis, with efficient and precise fat quantification being essential for diagnosing liver diseases. This study leverages 5 T ultra-high-field MRI to demonstrate the clinical significance of liver fat quantification, and explores the consistency and accuracy of the Proton Density Fat Fraction (PDFF) in the liver across different magnetic field strengths and measurement methodologies. Methods: The study involved phantoms with lipid contents ranging from 0 % to 30 % and 35 participants (21 females, 14 males; average age 30.17 ± 13.98 years, body mass index 25.84 ± 4.76 , waist-hip ratio 0.84 ± 0.09). PDFF measurements were conducted using chemical shift encoded (CSE) MRI at 5 T, 3 T, and 1.5 T, alongside magnetic resonance spectroscopy (MRS) at 5 T and 1.5 T for both liver and phantoms, analyzed using jMRUI software. The MRS-derived PDFF values served as the reference standard. Repeatability of 5 T MRI measurements was assessed through correlation analysis, while accuracy was evaluated using linear regression analysis against the reference standards. Results: The CSE-PDFF measurements at 5 T demonstrated strong consistency with those at 3 T and 1.5 T, showing high intraclass correlation coefficients (ICC) of 0.988 and 0.980, respectively (all $p < 0.001$). There was also significant consistency across ROIs within liver lobes, with ICC values ranging from 0.975 to 0.986 (all $p < 0.001$). MRS-PDFF measurements for both phantoms and liver at 5 T and 1.5 T exhibited substantial agreement, with ICC values of 0.996 and 0.980, respectively (all $p < 0.001$). Particularly, ICC values for ROIs in the liver ranged from 0.963 to 0.990 (all $p < 0.001$). Despite overall agreement, statistically significant differences were noted in specific ROIs within the liver lobes ($p = 0.004$ and 0.012). The CSE and MRS PDFF measurements at 5 T displayed strong consistency, with an ICC of 0.988 ($p < 0.001$), and significant agreement was also found between 5 T CSE and 1.5 T MRS PDFF measurements, with an ICC of 0.978 ($p < 0.001$). Agreement was significant within the ROIs of the liver lobes on the same platform at 5 T, with ICC values ranging from 0.986 to 0.991 (all $p < 0.001$). Conclusion: PDFF measurements at 5 T MR imaging exhibited both accuracy and repeatability, indicating that

5 T imaging provides reliable quantification of liver fat content and shows substantial potential for clinical diagnostic applications.

Keywords: 5T; chemical shift encoded(CSE); magnetic resonance spectroscopy (MRS); Hepatic steatosis; proton density fat fraction (PDFF)

24COASNO137:

Title- Under pressure – Association of the arm position and leading circulatory structure behind the pressure point in cardiopulmonary resuscitation patients,

Matthias Mueller, Andreas Strassl, Philipp D. Stelzer, Florian Woedl, Dominik Riss, Juergen Grafeneder, Florian Ettl, Ruediger Scherthaner, Michael Holzer, Christian Wassipaul, European Journal of Radiology, Volume 180, 2024, 111706, <https://doi.org/10.1016/j.ejrad.2024.111706>.

Abstract: Background: Thoracic computed tomography scans (CT) are used by several study groups to investigate the circulatory structures (heart and vessels) located behind the pressure point for chest compressions. Yet, it remains unclear how the positioning of these structures is influenced by factors such as intubation, the respiratory cycle and arm positioning. Methods: We retrospectively analyzed data of adult patients with in- or out-of-hospital cardiac arrest who underwent thoracic CT imaging within one year before or up to six months after arrest. A region of interest (ROI) behind the pressure point was defined. The largest structure within this region was defined as “leading circulatory structure”, which was the primary outcome. Airway status (intubated versus spontaneous breathing), respiratory cycle (inspiration, expiration, resting expiratory position), and arm position (up over the head versus down beside the trunk) served as covariates in an ordinal regression model. Results: Among 500 initially screened patients, 411 (82.2 %) were included in the analysis. There was a significant association between the arm position and the leading circulatory structure behind the pressure point. However, no association was found with airway status or respiratory cycle. The most frequently identified leading circulatory structure was the left atrium (arms up: 41.8 %, down: 50.7 %), followed by the ascending aorta (up: 23.8 % vs. down: 16.7 %). The left ventricle was the leading structure in only one case (0.2 %, arms down). Conclusion: This study shows that arm position is significantly associated with the leading circulatory structure behind the pressure point for chest compressions in cardiac arrest.

Keywords: Pressure point; Arm position; Respiratory cycle; Intubation; Cardiopulmonary resuscitation; Cardiac arrest; Heart structure; Computed tomography

24COASNO138:

Title- Pancreatic necrosis volume is closely associated with late-onset vascular complications after discharge in necrotizing pancreatitis,

Xin Xu, Ling Ding, Yaoyu Zou, Qian Liao, Chen Yu, Jianhua Wan, Xin Huang, Yupeng Lei, Huifang Xiong, Wenhua He, Liang Xia, Nonghua Lu, Yin Zhu, European Journal of Radiology, Volume 180, 2024, 111686,, <https://doi.org/10.1016/j.ejrad.2024.111686>.

Abstract: Purpose: To explore the incidence, dynamic changes, prognostic factors and prognosis of late-onset vascular complications after discharge in patients with necrotizing pancreatitis (NP), and determine the relationship between the pancreatic necrosis volume (PNV) and late-onset vascular complications. Methods: This was a retrospective cohort study that included NP patients who did not have any vascular complications during index hospitalization. Computed tomography (CT) examinations were performed, and the PNV was calculated based on the picture archiving and communication system. Multivariate logistic regression analysis was employed to determine the potential prognostic factors for late-onset vascular complications after discharge. Results: A total of 35.6 % (37/104) of the patients had late-onset portal venous system involvement during the one-year follow-up period, including 35 patients with stenosis and 2 patients with occlusion. No venous thrombosis or arterial vascular complications were observed. $PNV > 134 \text{ cm}^3$ (OR, 7.08, 95 % CI 1.83–27.36; $P = 0.005$) and pancreatic necrosis involving the body and/or tail of the pancreas (OR, 10.05; 95 % CI, 2.66–38.02; $P = 0.001$) were prognostic factors for abnormal patency of the portal venous system. The abnormal patency of the portal venous system tended to persist during follow-up, and gastric varices were observed in 32.4 % (12/37) of the patients in the abnormal patency group without any symptoms. Conclusions: Late-onset vascular complications involving venous stenosis or occlusion were common in NP patients after discharge, approximately one third of whom developed gastric varices. PNV and the location of necrosis were closely associated with the development of these complications.

Keywords: Acute pancreatitis; Necrotizing pancreatitis; Pancreatic necrosis volume; Vascular complications; Splanchnic vein thrombosis

24COASNO139:

Title- Development of a deep learning model for detecting lumbar vertebral fractures on CT images: An external validation,

Jingyi Tian, Kexin Wang, Pengsheng Wu, Jialun Li, Xiaodong Zhang, Xiaoying Wang,
European Journal of Radiology, Volume 180, 2024, 111685,
<https://doi.org/10.1016/j.ejrad.2024.111685>.

Abstract: Objective: To develop and externally validate a binary classification model for lumbar vertebral body fractures based on CT images using deep learning methods. Methods: This study involved data collection from two hospitals for AI model training and external validation. In Cohort A from Hospital 1, CT images from 248 patients, comprising 1508 vertebrae, revealed that 20.9% had fractures (315 vertebrae) and 79.1% were non-fractured (1193 vertebrae). In Cohort B from Hospital 2, CT images from 148 patients, comprising 887 vertebrae, indicated that 14.8% had fractures (131 vertebrae) and 85.2% were non-fractured (756 vertebrae). The AI model for lumbar spine fractures underwent two stages: vertebral body segmentation and fracture classification. The first stage utilized a 3D V-Net convolutional deep neural network, which produced a 3D segmentation map. From this map, region of each vertebra body were extracted and then input into the second stage of the algorithm. The second stage employed a 3D ResNet convolutional deep neural network to classify each proposed region as positive (fractured) or negative (not fractured). Results: The

AI model's accuracy for detecting vertebral fractures in Cohort A's training set (n = 1199), validation set (n = 157), and test set (n = 152) was 100.0 %, 96.2 %, and 97.4 %, respectively. For Cohort B (n = 148), the accuracy was 96.3 %. The area under the receiver operating characteristic curve (AUC-ROC) values for the training, validation, and test sets of Cohort A, as well as Cohort B, and their 95 % confidence intervals (CIs) were as follows: 1.000 (1.000, 1.000), 0.978 (0.944, 1.000), 0.986 (0.969, 1.000), and 0.981 (0.970, 0.992). The area under the precision-recall curve (AUC-PR) values were 1.000 (0.996, 1.000), 0.964 (0.927, 0.985), 0.907 (0.924, 0.984), and 0.890 (0.846, 0.971), respectively. According to the DeLong test, there was no significant difference in the AUC-ROC values between the test set of Cohort A and Cohort B, both for the overall data and for each specific vertebral location (all P>0.05).

Conclusion: The developed model demonstrates promising diagnostic accuracy and applicability for detecting lumbar vertebral fractures.

Keywords: Deep learning; Lumbar vertebral fracture; Classification prediction; 3D ResNet

24COASNO140:

Title- [68 Ga]Ga-CXCR4 PET/CT imaging in high-grade glioma for assessment of CXCR4 receptor expression,

Hessamoddin Roustaei, Habibeh Vosoughi, Emran Askari, Bagher Aziz Kalantari, Nasim Norouzbeigi, Kazem Anvari, Mohsen Beheshti, Kamran Aryana,

European Journal of Radiology, Volume 180, 2024, 111694,

<https://doi.org/10.1016/j.ejrad.2024.111694>.

Abstract: Purpose: Gliomas account for 75 % of primary malignant CNS tumors. High-grade glioma (CNS WHO grades 3 and 4) have an unfavorable treatment response and poor outcome. CXCR4 is a G protein-coupled receptor that plays an important part in the signaling pathway between cancer cells and tumor microenvironment. CXCR4 overexpression has been shown in a variety of cancers. In this study, we evaluate the potential value of [68Ga]Ga-Pentixafor as a PET/CT CXCR4-probe for in vivo assessment of CXCR4 expression in patients with high-grade glioma and its correlation with tumor grade. Materials and Methods: [68Ga]Ga-CXCR4 PET/CT was performed in the prospective single-center study in treatment-naïve biopsy-proven patients with high-grade glioma. The acquired images were analyzed qualitatively and semi-quantitatively. Result: A total of 26 patients (mean age: 53.3±14.4 years, 11 women, 15 men) were enrolled. CNS WHO grade 3 pathology was seen in 19 % (5/26) of the sample. The patient-based sensitivity of 68Ga-CXCR4 was 96.2 %. Overall, 28 pathologic lesions were detected, leading to a lesion-based sensitivity of 96.4 %. The median (IQR) SUVmax of grade 4 lesions was substantially greater than the grade 3 (3.03(2.5–3.7) vs. 1.51(1.2–1.8), p = 0.0145). The highest tracer activity of organs –beside bladder as the main excretion reservoir–was in lymphoid tissue of Waldeyer's ring (mean SUVmax: 7.41), and spleen (mean SUVmax: 6.62). Conclusion: In conclusion, this new application for [68Ga]Ga-Pentixafor PET tracer exhibits excellent visual and semi-quantitative diagnostic properties. Further studies are warranted.

24COASNO141:

Title- An exploration of radiological signs in post-intervention liver complications,

Faezeh Khorasanizadeh, Narges Azizi, Roberto Cannella, Giuseppe Brancatelli,

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Abstract: The advent and progression of radiological techniques in the past few decades have revolutionized the diagnostic and therapeutic landscape for liver diseases. These minimally invasive interventions, ranging from biopsies to complex therapeutic procedures like transjugular intrahepatic portosystemic shunt placement and transarterial embolization, offer substantial benefits for the treatment of patients with liver diseases. They provide accurate tissue diagnosis, allow real-time visualization, and render targeted treatment for hepatic lesions with enhanced precision. Despite their advantages, these procedures are not without risks, with the potential for complications that can significantly impact patient outcomes. It is imperative for radiologists to recognize the signs of these complications promptly to mitigate further health deterioration. Ultrasound, CT, and MRI are widely utilized examinations for monitoring the complications. This article presents an overarching review of the most commonly encountered hepatobiliary complications post-radiological interventions, emphasizing their imaging characteristics to improve patient post-procedure management.

Keywords: Hepatobiliary interventions; Computed tomography; Magnetic resonance imaging; Ultrasound

24COASNO142:

Title- Stickiness of 7 types of iodinated contrast media used during interventional radiology and interventional cardiology procedures,

J.B.S. Schreinemakers, R. Sprik, J.A. Vos,

European Journal of Radiology, Volume 180, 2024, 111645,

<https://doi.org/10.1016/j.ejrad.2024.111645>.

Abstract: Introduction: During Interventional Cardiology (IC) and Interventional Radiology (IR) procedures operators' gloves, guide wires and catheters may stick together due to the inherent stickiness of Iodine Containing Contrast Media (ICCM). This may result in displacement of materials, compromising technical success. In this study we compare the stickiness of seven frequently used types of ICCM. Material and methods: Xenetix 300, Hexabrix 320 (Guerbet, Villepinte, France), Ultravist 300 (Bayer, Leverkusen, Germany), Visipaque 270, Omnipaque 300, Visipaque 320 (GE, Wauwatosa, WI) and Iomeron 300 (Bracco, Milano, Italy) are compared using a probe-tack test. Pieces of surgical gloves are put together with 0.1 ml of ICCM in between, and subsequently pulled apart under computer control. Stickiness is measured as the work needed to separate the probes. Results: From least to most sticky results were: Hexabrix 320 (mean Work (mJ); range: 0.70; 0.16–1.23), Visipaque 270 (1.18; 0.47–1.89), Visipaque 320 (1.70; 0.59–2.81), Iomeron 300 (3.01; 1.82–4.20), Xenetix 300 (5.83; 3.96–7.69), Ultravist 300 (5.83; 2.83–8.84), Omnipaque 300 (8.14; 6.95–9.33). The four least sticky ICCM differ statistically significantly ($p = 0.000$ – 0.004)

from the remaining. In this research Omnipaque 300, Ultravist 300 and Xenetix 300 are the stickiest and may hence pose the greatest practical problems during procedures; in contrast, Hexabrix 320, Visipaque 270 and Visipaque 320 are the least sticky in this research and may therefore aid in constraining complications caused by stickiness. Conclusion: A significant and reproducible difference in stickiness exists between commercially available ICCM, Hexabrix 320, Visipaque 270, Visipaque 320 and Iomeron 300, being least sticky.

24COASNO143:

Title- Functional liver imaging score (FLIS) can predict adverse events in HCC patients,

Cesare Maino, Fabrizio Romano, Paolo Niccolò Franco, Antonio Ciaccio, Mattia Garancini, European Journal of Radiology, Volume 180, 2024, 111695, <https://doi.org/10.1016/j.ejrad.2024.111695>.

Abstract: Purpose: To assess the performance of FLIS in predicting adverse outcomes, namely post-hepatectomy liver failure (PHLF) and death, in patients who underwent liver surgery for malignancies. Methods: All consecutive patients who underwent liver resection and 1.5 T gadoxetic acid MR were enrolled. PHLF and overall survival (OS) were collected. Two radiologists with 18 and 8 years of experience in abdominal imaging, blinded to clinical data, evaluated all images. Radiologists evaluated liver parenchymal enhancement (EnQS), biliary contrast excretion (ExQS), and signal intensity of the portal vein relative to the liver parenchyma (PVsQs). Reliability analysis was computed with Cohen's Kappa. Cox regression analysis was calculated to determine which factors are associated with PHLF and OS. Area Under the Receiver Operating Characteristic curve (AUROC) was computed. Results: 150 patients were enrolled, 58 (38.7 %) in the HCC group and 92 (61.3 %) in the non-HCC group. The reliability analysis between the two readers was almost perfect ($\kappa = 0.998$). The multivariate Cox analysis showed that only post-surgical blood transfusions and major resection were associated with adverse events [HR=8.96 (7.98–9.88), $p = 0.034$, and HR=0.99 (0.781–1.121), $p = 0.032$, respectively] in the whole population. In the HCC group, the multivariable Cox analysis showed that blood transfusions, major resection and FLIS were associated with adverse outcomes [HR=13.133 (2.988–55.142), $p = 0.009$, HR=0.987 (0.244–1.987), $p = 0.021$, and HR=1.891 (1.772–3.471), $p = 0.039$]. The FLIS AUROC to predict adverse outcomes was 0.660 (95 %CIs = 0.484–0.836), with 87 % sensitivity and 33.3 % specificity (81.1–94.4 and 22.1–42.1). Conclusions: FLIS can be considered a promising tool to preoperative depict patients at risk of PHLF and death.

Keywords: Cirrhosis; Magnetic resonance imaging; Gadolinium ethoxybenzyl DTPA

Medical Oncology (Chemotherapy, Hematology & Radiotherapy)

24COASNO1:

Title- The Presence of Extensive Lymphovascular Invasion is Associated With Higher Risks of Local-Regional Recurrence Compared With Usual Lymphovascular Invasion in Curatively Treated Breast Cancer Patients,

Olufela Koleoso, Nicolas Toumbacaris, Edi Brogi, Zhigang Zhang, Lior Z. Braunstein, Monica Morrow,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 835-844,

<https://doi.org/10.1016/j.ijrobp.2024.04.073>.

Abstract: Purpose: Several data sets have demonstrated a correlation between lymphovascular invasion (LVI) and locoregional recurrence (LRR). Whether the observation of "extensive LVI" is a further and incremental determinant of LRR risk is unknown. We describe clinical outcomes in women with invasive breast cancer stratified by (1) absence of LVI (neg), (2) LVI focal or suspicious (FS-LVI), (3) usual (nonextensive) LVI (LVI), and (4) extensive LVI (E-LVI). Methods and Materials: Between December 2009 and August 2021, 8837 patients with early-stage breast cancer were treated with curative intent and were evaluable. Clinical-pathologic details were abstracted by retrospective review. The description of LVI was abstracted from pathology reports. Recurrence and survival outcomes were compared based on the extent of LVI. A matched propensity score analysis compared outcomes between patients with LVI versus E-LVI. Results: Of the 8837 patients studied, 5584 were negative, 461 had FS-LVI, 2315 had LVI, and 477 had E-LVI. Patients with E-LVI had an adverse risk profile compared with the other groups. The 5- and 10-year LRR cumulative incidence estimates in patients with E-LVI were 9.6% (95% CI, 7.1-13) and 13% (95% CI, 10-17), respectively, which were significantly higher than those observed in the usual LVI group (6.8% [5.7-7.9] and 10% [8.8-12], respectively). A statistically significant difference in LRR was demonstrated in univariable (HR, 1.4; 95% CI, 1.03-1.89; $P = .029$) and multivariable regression analysis (HR, 1.62; 95% CI, 1.15-2.27; $P = .005$) compared with nonextensive LVI. In an alternative approach, we performed a 2:1 propensity score matching analysis comparing patients with LVI to those with E-LVI. The hazard ratio for LRR (HR, 1.47; CI 1.02-2.14; $P = .041$) was suggestive of a higher risk associated with E-LVI. Conclusions: Our work suggests that patients with E-LVI are at a higher risk for LRR than those with usual LVI. For patients who are borderline candidates for regional nodal irradiation or post-mastectomy radiation therapy, the finding of E-LVI might be decisive in favor of intensified treatment.

24COASNO2:

Title- Prognostic Factors of Mandibular Osteoradionecrosis Including Accurate Colocalization of Avulsions and Dosimetric Dental Mapping Software, a Case-control Study,

Marion Renouf, Simon Auger, Loïc Campion, Grégory Delpon, Julie Longis, Cécile Dupas, Pauline Blery, Juliette Thariat, Mélanie Doré,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 783-795,

<https://doi.org/10.1016/j.ijrobp.2024.04.019>.

Abstract: Purpose: Osteoradionecrosis (ORN) of the mandible remains a significant complication in the intensity modulated radiation therapy (IMRT) era. Dental dose cannot be predicted from heterogeneous IMRT dose distributions; mandibular dose metrics cannot guide dentist avulsion decisions in high-risk ORN situations. Using a mapping tool to report dental root dose, avulsions, and ORN sites, we re-examined ORN risk factors in a case-control study. Methods and Materials: From 2008 to 2019, 897 consecutive patients with oral cavity/oropharynx or unknown primary cancer undergoing IMRT were analyzed to identify ORN cases. These were matched (1 ORN/2 controls) retrospectively for tumor location, surgery, and tobacco consumption in a monocentric case-control study. Univariate and multivariate analyses integrated ORN factors and accurate dental dose data (grouped into 4 mandibular sectors). Generalizability was investigated in a simulated population database. Results: A total of 171 patients were included. The median follow-up was 5.2 and 4.5 years in the ORN and control groups, respectively. The median time to ORN was 12 months. In univariate analysis, post-IMRT avulsions at the ORN site (hazard ratio [HR] = 3.6; 95% confidence interval [CI] = 1.5-8.9; P = .005), tumor laterality (HR, 4.4; 95% CI, = 1.4-14, P = .01), mean mandibular dose (HR, 1.1; 95% CI, = 1.01-1.1; P = .018) and mean dose to the ORN site (HR, 1.1; 95% CI, = 1.1-1.2; P < .001) correlated with higher ORN risk. In multivariate analysis, mean dose to the ORN site (HR, 1.1; 95% CI, = 1.1-1.2; P < .001) and post-IMRT avulsions at the ORN site (HR, 4.6; 95% CI, = 1.5-14.7; P = .009) were associated with ORN. For each increase in gray in dental dose, the ORN risk increased by 12%. Simulations confirmed study observations. Conclusions: Dental dose and avulsions are associated with ORN, with a 12% increase in risk with each additional gray. Accurate dose information can help dentists in their decisions after IMRT.

24COASNO3:

Title- Evaluation of Radiation Dose Effect on Lung Function Using Iodine Maps Derived From Dual-Energy Computed Tomography,

Shen Zhang, Mikaël Simard, Andréanne Lapointe, Édith Filion, Marie-Pierre Campeau, Thi Trinh Thuc Vu, David Roberge, Jean-François Carrier, Danis Blais, Stéphane Bedwani, Houda Bahig,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 894-903,

<https://doi.org/10.1016/j.ijrobp.2024.04.069>.

Abstract: Purpose: There is interest in using dual-energy computed tomography (DECT) to evaluate organ function before and after radiation therapy (RT). The purpose of this study (trial identifier: NCT04863027) is to assess longitudinal changes in lung perfusion using iodine maps derived from DECT in patients with lung cancer treated with conventional or stereotactic RT. Methods and Materials: For 48 prospectively enrolled patients with lung cancer, a contrast-enhanced DECT using a dual-source CT simulator was acquired pretreatment and at 6 and 12 months posttreatment. Pulmonary functions tests (PFT) were obtained at baseline and at 6 and 12 months posttreatment. Iodine maps were extracted from the DECT images using a previously described 2-material decomposition framework. Longitudinal iodine maps were normalized using a reference region defined as all voxels with perfusion in the top 10% outside of the 5 Gy isodose volume. Normalized functional responses (NFR) were calculated for 3 dose ranges: <5, 5 to 20, and >20 Gy. Mixed model analysis was used to assess the correlation between dose metrics and NFR. Pearson correlation was used to assess if NFRs were correlated with PFT changes. Results: Out of the 48 patients, 21 (44%) were treated with stereotactic body RT and 27 (56%) were treated with conventionally fractionated intensity-modulated RT. Thirty-one out of these 48 patients were ultimately included in data analysis. It was found that NFR is linearly correlated with dose ($P < .001$) for both groups. The number of months elapsed post-RT was also found to correlate with NFR ($P = .029$), although this correlation was not observed for the stereotactic body RT subgroup. The NFR was not found to correlate with PFT changes. Conclusions: DECT-derived iodine maps are a promising method for detailed anatomic evaluation of radiation effect on lung function, including potentially subclinical changes.

24COASNO4:

Title- Enhancing Precision in Cardiac Segmentation for Magnetic Resonance-Guided Radiation Therapy Through Deep Learning,

Nicholas Summerfield, Eric Morris, Soumyanil Banerjee, Qisheng He, Ahmed I. Ghanem, Simeng Zhu, Jiwei Zhao, Ming Dong, Carri Glide-Hurst,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 904-914,

<https://doi.org/10.1016/j.ijrobp.2024.05.013>.

Abstract: Purpose: Cardiac substructure dose metrics are more strongly linked to late cardiac morbidities than to whole-heart metrics. Magnetic resonance (MR)-guided radiation therapy (MRgRT) enables substructure visualization during daily localization, allowing potential for enhanced cardiac sparing. We extend a publicly available state-of-the-art deep learning framework, "No New" U-Net, to incorporate self-distillation (nnU-Net.wSD) for substructure segmentation for MRgRT. Methods and Materials: Eighteen (institute A) patients who underwent thoracic or abdominal radiation therapy on a 0.35 T MR-guided linear accelerator were retrospectively evaluated. On each image, 1 of 2 radiation oncologists delineated reference contours of 12 cardiac substructures (chambers, great vessels, and coronary arteries) used to train ($n = 10$), validate ($n = 3$), and test ($n = 5$) nnU-Net.wSD by leveraging a teacher-student network and comparing it to standard 3-dimensional U-Net. The impact of

using simulation data or including 3 to 4 daily images for augmentation during training was evaluated for nnU-Net.wSD. Geometric metrics (Dice similarity coefficient, mean distance to agreement, and 95% Hausdorff distance), visual inspection, and clinical dose-volume histograms were evaluated. To determine generalizability, institute A's model was tested on an unlabeled data set from institute B (n = 22) and evaluated via consensus scoring and volume comparisons. Results:nnU-Net.wSD yielded a Dice similarity coefficient (reported mean $\pm$ SD) of 0.65 ± 0.25 across the 12 substructures (chambers, 0.85 ± 0.05 ; great vessels, 0.67 ± 0.19 ; and coronary arteries, 0.33 ± 0.16 ; mean distance to agreement, <3 mm; mean 95% Hausdorff distance, <9 mm) while outperforming the 3-dimensional U-Net (0.583 ± 0.28 ; $P < .01$). Leveraging fractionated data for augmentation improved over a single MR simulation time point (0.579 ± 0.29 ; $P < .01$). Predicted contours yielded dose-volume histograms that closely matched those of the clinical treatment plans where mean and maximum (ie, dose to 0.03 cc) doses deviated by 0.32 ± 0.5 Gy and 1.42 ± 2.6 Gy, respectively. There were no statistically significant differences between institute A and B volumes ($P > .05$) for 11 of 12 substructures, with larger volumes requiring minor changes and coronary arteries exhibiting more variability. Conclusions: This work is a critical step toward rapid and reliable cardiac substructure segmentation to improve cardiac sparing in low-field MRgRT.

24COASN05:

Title- Local Ablative Therapy Combined With Pembrolizumab in Patients With Synchronous Oligometastatic Non-Small Cell Lung Cancer: A Recursive Partitioning Analysis,

Hye In Lee, Eun Kyung Choi, Su Ssan Kim, Young Seob Shin, Junhee Park, Chang-Min Choi, Shinkyoo Yoon, Hyeong Ryul Kim, Young Hyun Cho, Si Yeol Song,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 698-707,

<https://doi.org/10.1016/j.ijrobp.2024.05.015>.

Abstract: Purpose This study aimed to evaluate the efficacy of local ablative therapy (LAT) combined with pembrolizumab in patients with synchronous oligometastatic non-small cell lung cancer (NSCLC) and to identify patients who would most benefit from LAT. Methods and Materials: We retrospectively identified patients who received diagnosis of synchronous oligometastatic NSCLC (≤ 5 metastatic lesions and ≤ 3 organs involved) and were treated with first-line pembrolizumab between January 2017 and December 2022. Patients who underwent LAT, including surgery or radiation therapy at all disease sites, were compared with those who did not undergo LAT. A recursive partitioning analysis (RPA) model was developed using prognostic factors for progression-free survival (PFS). Results: Among the 258 patients included, 78 received LAT with pembrolizumab, and 180 received pembrolizumab alone. The median follow-up duration was 15.5 months (range, 3.0-71.2 months). In the entire cohort, LAT was independently associated with significantly improved PFS (hazard ratio [HR], 0.64; $P = .015$) and overall survival (OS) (HR, 0.61; $P = .020$). In the propensity score-matched cohort (N = 74 in each group), the median PFS was 19.9 months and 9.6 months,

respectively ($P = .003$), and the median OS was 42.2 months and 20.5 months, respectively ($P = .045$), for the LAT and non-LAT groups. Based on the RPA model, incorporating the number of metastatic lesions, performance status, and programmed cell death-ligand 1 expression level, patients were stratified into 3 risk groups with distinct PFS. LAT significantly improved PFS and OS in the low- and intermediate-risk groups; however, no difference was observed in the high-risk group. LAT was more effective as a consolidative treatment after pembrolizumab initiation than as an upfront therapy. Conclusions: LAT combined with pembrolizumab was associated with higher PFS and OS compared with pembrolizumab alone in selected patients with synchronous oligometastatic NSCLC. The RPA model could serve as a valuable clinical tool for identifying appropriate patients for LAT.

24COASNO6:

Title- Radiation-induced Xerostomia is Related to Stem Cell Dose-dependent Reduction of Saliva Production,

Maria I. van Rijn-Dekker, Sacha la Bastide-van Gemert, Monique A. Stokman, Arjan Vissink, Robert P. Coppes, Johannes A. Langendijk, Peter van Luijk, Roel J.H.M. Steenbakkers,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 772-782,

<https://doi.org/10.1016/j.ijrobp.2024.04.012>.

Abstract: Purpose: Previous studies have shown that the mean dose to the parotid gland stem cell rich regions (Dmean,SCR) is the strongest dosimetric predictor for the risk of patient-reported daytime xerostomia. This study aimed to test whether the relationship between patient-reported xerostomia and Dmean,SCR is explained by a dose-dependent reduction of saliva production. Methods and Materials: In 570 patients with head and neck cancer treated with definitive radiation therapy (RT), flow from the parotid (FLOWPAR) and submandibular/sublingual (FLOWSMSL) glands, and patient-reported daytime (XERDAY) and nighttime (XERNIGHT) xerostomia were prospectively measured before, at 6 months, and 12 months after RT. Using linear mixed effect models, the relationship of the mean dose to the parotid glands (Dmean,par), Dmean,SCR, non-SCR parotid gland tissue (Dmean,non-SCR), submandibular glands (Dmean,sub), and oral cavity (Dmean,oral) with salivary flow and xerostomia was analyzed while correcting for known confounders. Results: Dmean,SCR proved to be responsible for the effect of Dmean,par on FLOWPAR ($P \leq .03$), while Dmean,non-SCR did not affect FLOWPAR ($P \geq .11$). To illustrate, increasing Dmean,SCR by 10 Gy at a fixed Dmean,non-SCR reduced FLOWPAR by 0.02 mL/min (25%) after RT. However, if the opposite happened, no change in FLOWPAR was observed (0.00 mL/min [4%]). As expected, Dmean,sub was significantly associated with FLOWSMSL ($P < .001$). For example, increasing Dmean,sub by 10 Gy reduced FLOWSMSL by 0.07 mL/min (26%) after RT. Xerostomia scores were also affected by dose to the salivary glands. Dmean,SCR and Dmean,oral were associated with higher XERDAY scores ($P \leq .05$), while Dmean,sub increased XERNIGHT scores ($P = .01$). For example, an increase of 10 Gy in Dmean,SCR

raised XERDAY scores by 2.13 points (5%) after RT, while an additional 10 Gy in Dmean,subs increased XERNIGHT scores by 2.20 points (6%) after RT. Salivary flow was not only associated with radiation dose, but also with xerostomia scores in line with the salivary glands' functions; ie, FLOWPAR only influenced XERDAY ($P < .001$, 10.92 points lower XERDAY per 1 mL/min saliva), while FLOWSMSL affected XERDAY and XERNIGHT ($P \leq .004$, 6.69 and 5.74 points lower XERDAY and XERNIGHT, respectively, per 1 mL/min saliva). Therefore, the observed relationships between dose and xerostomia were corrected for salivary flow. As hypothesized, Dmean,SCR only increased XERDAY scores via reducing FLOWPAR, whereas the effects of Dmean,oral on XERDAY and Dmean,sub on XERNIGHT were independent of salivary flow. Conclusions: Higher SCR region dose reduced parotid gland saliva production, subsequently resulting in higher daytime xerostomia scores. Consequently, this study supports the clinical implementation of stem cell sparing RT to preserve salivary flow with the aim of reducing the risk of xerostomia.

24COASNO7:

Title- Toxicity Evaluation of Dose-Escalation in Hypofractionated Regional Nodal Irradiation for Breast Cancer: A Retrospective Study,

Euidam Kim, Ji Sung Yoo, Yeon-Joo Kim, Jungnam Joo, Eun sang Oh, Yoonsun Chung, Seung Hyun Chung, Tae Hyun Kim,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 823-834,

<https://doi.org/10.1016/j.ijrobp.2024.04.014>.

Abstract: Purpose: Regional nodal irradiation (RNI) to the axilla and supraclavicular area presents distinct toxicities, such as lymphedema and shoulder stiffness, compared with whole-breast irradiation. There is insufficient evidence on the safety of dose-escalation in hypofractionated RNI. We aimed to evaluate and compare toxicity rates in patients with breast cancer who received hypofractionated RNI with and without dose-escalation. Methods and Materials: We retrospectively analyzed 381 patients with breast cancer treated with hypofractionated RNI between March 2015 and February 2017. Patients received either the standard-dose to the regional nodal area (43.2 Gy/16 fx; 48.7 Gy3.5 equivalent dose [EQD2], 2 Gy equivalent dose with $\alpha/\beta = 3.5$ Gy) or dose-escalation with a median dose of 54.8 Gy3.5 EQD2 (range, 51.7-60.9 Gy3.5 EQD2), depending on clinical and pathologic nodal stage. Toxicity rates of lymphedema and shoulder stiffness were assessed, and statistical analyses were conducted to identify associated factors. Results: The median follow-up time was 32.3 months (5.7-47.0 months). After radiation therapy, 71 (18.6%) patients developed lymphedema, and 48 (12.6%) developed shoulder stiffness. Patients who received dose-escalation exhibited significantly higher rates of lymphedema (32.1% vs 14.8%; odds ratio, 2.72, $P = .0004$) and shoulder stiffness (23.8% vs 9.4%; odds ratio, 2.01, $P = .0205$) compared with the standard-dose group. Moreover, dose-escalation showed a tendency to increase the severity of lymphedema and shoulder stiffness. Conclusions: Patients who received dose-escalation in hypofractionated RNI face a higher risk of developing lymphedema and shoulder stiffness compared with those who received standard-dose

hypofractionated RNI. Therefore, it is crucial to implement close and frequent monitoring for early detection, along with timely rehabilitation interventions for these patients.

24COASNO8:

Title- Efficacy and Toxicity of (Chemo)Radiation Therapy in HIV+ Patients with Squamous Cell Anal Cancer, a Subgroup Analysis of the National Multicenter Cohort FFCD-ANABASE,

Cecile Evin, Laurent Quéro, Karine Le Malicot, Sarah Blanchet-Deverly, Ludovic Evesque, Chloé Buchalet, Claire Lemanski, Nabil Baba Hamed, Eleonor Rivin del Campo, Laurence Bauwens, [et al.]

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 708-719,

<https://doi.org/10.1016/j.ijrobp.2024.04.067>.

Abstract: Purpose: The influence of human immunodeficiency virus (HIV) infection on clinical outcomes in patients receiving (chemo)radiation therapy (RT) for squamous cell carcinoma of the anus (SCCA) is debated. The objective of this study was to compare efficacy and safety according to HIV status in patients with SCCA treated with C/RT. Methods and Materials: Between January 2015 and April 2020, 488 patients with a known HIV status (17.6% HIV+) were treated with radiation therapy for SCCA and included in the FFCD-ANABASE multicentric prospective cohort. Clinical outcomes including overall survival (OS), locoregional recurrence-free survival, colostomy-free survival, response rate at 4 to 6 months, cancer-specific survival, relapse-free survival, and severe acute and late toxicity were compared between HIV+ and HIV- patients. Results: The median follow-up was 35.8 months. HIV+ patients were younger ($P < .01$) and predominantly male ($P < .01$). Intensity modulated radiation therapy was performed in 80.7% of patients, and 80.9% received concurrent chemotherapy. A higher proportion of HIV+ patients received induction chemotherapy compared with HIV- patients. No statistically significant difference in overall treatment time or severe acute and late toxicities was found between HIV+ and HIV- patients. In univariate analyses, OS (HR = 2.1 [CI 95% 1.2;3.5], $P = .007$), locoregional recurrence-free survival (HR = 1.7 [1.1;2.7], $P = .02$), and colostomy-free survival (HR = 1.7 [1.1;2.6], $P = .01$) were significantly shorter in HIV+ patients than in HIV- patients. Response rate, cancer-specific survival, and relapse-free survival were not significantly different. The recurrence site was significantly different according to HIV status. In the multivariate analysis, prognostic factors for OS were a World Health Organization performance status of ≥ 1 for the whole population, as well as HIV+ status for the subgroup of women. Conclusions: HIV+ patients treated with chemo-RT for SCCA have poorer clinical outcomes, especially women. No difference was found in toxicity according to HIV status with intensity modulated radiation therapy technique.

24COASN09:

Title- Intracellular Oxygen Transient Quantification in Vivo During Ultra-High Dose Rate FLASH Radiation Therapy,

Arthur F. Petusseau, Megan Clark, Petr Bruza, David Gladstone, Brian W. Pogue,
International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 884-893,
<https://doi.org/10.1016/j.ijrobp.2024.04.068>.

Abstract: Purpose: Large, rapid extracellular oxygen transients (ΔpO_2) have been measured in vivo during ultra-high dose rate radiation therapy; however, it has been unclear if they match intracellular oxygen levels. Here, the endogenously produced protoporphyrin IX (PpIX) delayed fluorescence signal was measured as an intracellular in-vivo oxygen sensor to quantify these transients, with direct comparison to extracellular pO_2 . Intracellular ΔpO_2 is closer to the cellular DNA, the site of major radiobiological damage, and therefore should help elucidate radiochemical mechanisms of the FLASH effect and potentially be translated to human tissue measurement. Methods and Materials: PpIX was induced in mouse skin through intraperitoneal injection of 250 mg/kg of aminolevulinic acid. The animals were also administered a 50 μ L intradermal injection of 10 μ M oxyphor G4 (PdG4) for phosphorescence lifetime pO_2 measurement. Paired oxygen transients were quantified in leg or flank tissues while delivering 10 MeV electrons in 3 μ s pulses at 360 Hz for a total dose of 10 to 28 Gy. Results: Transient reductions in pO_2 were quantifiable in both PpIX delayed fluorescence and oxyphor phosphorescence, corresponding to intracellular and extracellular pO_2 values, respectively. Responses were quantified for 10, 22, and 28 Gy doses, with ΔpO_2 found to be proportional to the dose on average. The ΔpO_2 values were dependent on initial pO_2 in a logistic function. The average and standard deviations in ΔpO_2 per dose were 0.56 ± 0.18 mm Hg/Gy and 0.43 ± 0.06 mm Hg/Gy for PpIX and oxyphor, respectively, for initial $pO_2 > 20$ mm Hg. Although there was large variability in the individual animal measurements of ΔpO_2 , the average values demonstrated a direct and proportional correlation between intracellular and extracellular pO_2 changes, following a linear 1:1 relationship. Conclusions: A fundamentally new approach to measuring intracellular oxygen depletion in living tissue showed that ΔpO_2 transients seen during ultra-high dose rate radiation therapy matched those quantified using extracellular oxygen measurement. This approach could be translated to humans to quantify intracellular ΔpO_2 . The measurement of these transients could potentially allow the estimation of intracellular reactive oxygen species production.

24COASN010:

Title- Irradiation with Carbon Ions Effectively Counteracts Hypoxia-related Radioresistance in a Rat Prostate Carcinoma,

Christin Glowa, Alina L. Bendinger, Rosemarie Euler-Lange, Peter Peschke, Stephan Brons, Jürgen Debus, Christian P. Karger,
International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 875-883,

<https://doi.org/10.1016/j.ijrobp.2024.05.004>.

Abstract: Purpose: Hypoxia in tumors is associated with increased malignancy and resistance to conventional photon radiation therapy. This study investigated the potential of particle therapy to counteract radioresistance in syngeneic rat prostate carcinoma.

Methods and Materials: Subcutaneously transplanted R3327-HI tumors were irradiated with photons or carbon ions under acute hypoxic conditions, induced by clamping the tumor-supplying artery 10 min before and during irradiation. Dose-response curves were determined for the endpoint “local tumor control within 300 days” and compared with previously published data acquired under oxic conditions. Doses at 50% tumor control probability (TCD50) were used to quantify hypoxia-induced radioresistance relative to that under oxic conditions and also to quantify the increased effectiveness of carbon ions under oxic and hypoxic conditions relative to photons. Results: Compared with those under oxic conditions, TCD50 values under hypoxic conditions increased by a factor of 1.53 ± 0.08 for photons and by a factor of 1.28 ± 0.06 for carbon ions (oxygen enhancement ratio). Compared with those for photons, TCD50 values for carbon ions decreased by a factor of 2.08 ± 0.13 under oxic conditions and by a factor of 2.49 ± 0.08 under hypoxic conditions (relative biological effectiveness). While the slope of the photon dose-response curves increased when changing from oxic to hypoxic conditions, the slopes were steeper and remained unchanged for carbon ions. Conclusions: The reduced oxygen enhancement ratio of carbon ions indicated that the required dose increase in hypoxic tumors was 17% lower for carbon ions than for photons. Additionally, carbon ions reduced the effect of intertumor heterogeneity on the radiation response. Therefore, carbon ions may confer a significant advantage for the treatment of hypoxic tumors that are highly resistant to conventional photon radiation therapy.

24COASNO11:

Title- Association of a 40-Gene Expression Profile With Risk of Metastatic Disease Progression of Cutaneous Squamous Cell Carcinoma and Specification of Benefit of Adjuvant Radiation Therapy,

Sarah T. Arron, Javier Cañueto, Jennifer Siegel, Alison Fitzgerald, Anesh Prasai, Shlomo A. Koyfman, Sue S. Yom,

International Journal of Radiation Oncology*Biophysics, Volume 120, Issue 3, 2024, Pages 760-771,

<https://doi.org/10.1016/j.ijrobp.2024.05.022>.

Abstract: Purpose: Adjuvant radiation therapy (ART) for cutaneous squamous cell carcinoma is recommended based on a number of wide-ranging clinicopathologic features, which encompass a broad array of patients. The 40-gene expression profile (GEP) test classifies cutaneous squamous cell carcinoma tumors into low (class 1), higher (class 2A), or highest (class 2B) risk of nodal and/or distant metastasis. This study's hypotheses are as follows: (1) local recurrence is associated with metastatic disease progression and (2) 40-GEP, by identifying high risk for metastasis, could predict a metastasis-specific benefit from ART. Methods and Materials: Samples were obtained from 920 patients (ART-untreated: 496 class 1, 335 class 2A, and 33 class 2B; ART-treated: 11 class 1, 35 class 2A, and 10 class 2B)

who were matched on clinical risk factors and stratified by ART status to create 49 matched patient strata. To control for the variety of characteristics and treatment selection bias, randomly sampled pairs of matched ART and non-ART patients comprising 10,000 resampled cohorts were each analyzed for 5-year metastasis-free survival and predicted time to metastatic event. Results: Of 96 patients experiencing local recurrence, 56.3% experienced metastasis; of those experiencing both, 88.9% experienced local recurrence before (75.9%) or concurrently (13.0%) with metastasis. After matching for clinicopathologic risk, median 5-year disease progression rates for resampled cohorts demonstrated approximately 50% improvement for class 2B ART-treated compared with ART-untreated cohorts. ART-treated class 2B cohorts had a 5-fold delay in predicted time to metastatic event and deceleration of disease progression compared with ART-untreated cohorts (Kolmogorov-Smirnov test, $P < .01$); this was not observed for patients with class 1 or 2A cSCC ($P > .05$ for each). No risk factor or staging system combined with ART status identified groups that would benefit from ART as well as 40-GEP. Conclusions: Forty-GEP identifies patients at the highest risk of nodal/distant metastasis who may derive the greatest benefit from ART, as well as patients who may have clinical indications for ART but are at low risk of metastasis. Compared with current guidelines, 40-GEP could provide greater specificity concerning the benefit of ART in individual patients.

24COASNO12:

Title- The Effect of Radiation Treatment of Solid Tumors on Neutrophil Infiltration and Function: A Systematic Review,

Léon Raymakers, Thijs J. Demmers, Gert J. Meijer, I. Quintus Molenaar, Hjalmar C. van Santvoort, Martijn P.W. Intven, Jeanette H.W. Leusen, Patricia A. Olofsen, Lois A. Daamen, International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 845-861, <https://doi.org/10.1016/j.ijrobp.2024.07.2141>.

Abstract: Radiation therapy (RT) initiates a local and systemic immune response which can induce antitumor immunity and improve immunotherapy efficacy. Neutrophils are among the first immune cells that infiltrate tumors after RT and are suggested to be essential for the initial antitumor immune response. However, neutrophils in tumors are associated with poor outcomes and RT-induced neutrophil infiltration could also change the composition of the tumor microenvironment (TME) in favor of tumor progression. To improve RT efficacy for patients with cancer it is important to understand the interplay between RT and neutrophils. Here, we review the literature on how RT affects the infiltration and function of neutrophils in the TME of solid tumors, using both patients studies and preclinical murine in vivo models. In general, it was found that neutrophil levels increase and reach maximal levels in the first days after RT and can remain elevated up to 3 weeks. Most studies report an immunosuppressive role of neutrophils in the TME after RT, caused by upregulated expression of neutrophil indoleamine 2,3-dioxygenase 1 and arginase 1, as well as neutrophil extracellular trap formation. RT was also associated with increased reactive oxygen species production by neutrophils, which can both improve and inhibit antitumor immunity. In

addition, multiple murine models showed improved RT efficacy when depleting neutrophils, suggesting that neutrophils have a protumor phenotype after RT. We conclude that the role of neutrophils should not be overlooked when developing RT strategies and requires further investigation in specific tumor types. In addition, neutrophils can possibly be exploited to enhance RT efficacy by combining RT with neutrophil-targeting therapies.

24COASNO13:

Title- Longitudinal Assessment of Tumor-Infiltrating Lymphocytes in Primary Breast Cancer Following Neoadjuvant Radiation Therapy,

Miki Yoneyama, Konstantinos Zormpas-Petridis, Ruth Robinson, Faranak Sobhani, Elena Provenzano, Harriet Steel, ...

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 862-874,

<https://doi.org/10.1016/j.ijrobp.2024.04.065>.

Abstract: Purpose: Tumor-infiltrating lymphocytes (TILs) have prognostic significance in several cancers, including breast cancer. Despite interest in combining radiation therapy with immunotherapy, little is known about the effect of radiation therapy itself on the tumor-immune microenvironment, including TILs. Here, we interrogated longitudinal dynamics of TILs and systemic lymphocytes in patient samples taken before, during, and after neoadjuvant radiation therapy (NART) from PRADA and Neo-RT breast clinical trials. Methods and Materials: We manually scored stromal TILs (sTILs) from longitudinal tumor samples using standardized guidelines as well as deep learning-based scores at cell-level (cTIL) and cell- and tissue-level combination analyses (SuperTIL). In parallel, we interrogated absolute lymphocyte counts from routine blood tests at corresponding time points during treatment. Exploratory analyses studied the relationship between TILs and pathologic complete response (pCR) and long-term outcomes. Results: Patients receiving NART experienced a significant and uniform decrease in sTILs that did not recover at the time of surgery ($P < .0001$). This lymphodepletive effect was also mirrored in peripheral blood. Our SuperTIL deep learning score showed good concordance with manual sTILs and importantly performed comparably to manual scores in predicting pCR from diagnostic biopsies. The analysis suggested an association between baseline sTILs and pCR, as well as sTILs at surgery and relapse, in patients receiving NART. Conclusions: This study provides novel insights into TIL dynamics in the context of NART in breast cancer and demonstrates the potential for artificial intelligence to assist routine pathology. We have identified trends that warrant further interrogation and have a bearing on future radioimmunotherapy trials.

24COASNO14:

Title- A Hard Truth to Swallow: Critically Evaluating the MD Anderson Dysphagia Inventory (MDADI) as an Endpoint in Human Papillomavirus-associated Oropharyngeal Cancer Trials,

Lachlan McDowell, Madeleine T. King, Katherine A. Hutcheson, Jolie Ringash, Sue S. Yom, June Corry, Christina Henson, Hisham Mehanna, Danny Rischin,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 805-822,
<https://doi.org/10.1016/j.ijrobp.2024.05.005>.

Abstract: The MD Anderson Dysphagia Inventory (MDADI), a measure of swallowing-related quality of life, has become the preferred patient-reported outcome measure (PROM) in contemporary clinical trials evaluating the experience of human papillomavirus-associated oropharyngeal squamous cell carcinoma (HPVOPSCC) survivors. With many potentially practice-changing studies using the MDADI composite score as either a primary or coprimary endpoint, or as a key secondary endpoint, it is important to understand its psychometric properties as judged by contemporary PROM standards, with a particular focus on its application to contemporary HPVOPSCC populations. In this critical review, we evaluate contemporary HPVOPSCC studies reporting MDADI outcomes, followed by a detailed evaluation of the psychometric properties of the MDADI. Although the focus of this review was the MDADI, the issues discussed are not unique to the MDADI and have broader applicability to the evaluation and assessment of other PROMs currently in use. First, it may be possible to improve administration of the instrument, as related to missing items, scoring, and the number of items required. Second, although in many instances, the MDADI has been intended as a direct or surrogate measure of swallowing physiology, the MDADI composite score captures a broader health-related quality of life construct affected by both swallowing and eating, the latter of which may be affected by a range of nonswallowing treatment-related toxicities. Finally, a clinically meaningful change of 10 in the MDADI composite score, widely accepted and applied to the clinical trial setting, represents an undoubtably clinically relevant difference in unselected head and neck cancer survivors. However, the smallest difference that might be clinically important to a highly functional HPVOPSCC cohort remains uncertain. Understanding the purpose and properties of the MDADI instrument and furthering the sophistication with which we apply it in this population would improve its interpretation in clinical trials.

24COASNO15:

Title- Salvage Stereotactic Radiosurgery for Recurrent WHO Grade 2 and 3 Meningiomas: A Multicenter Study (STORM),

Matthew Gallitto, Geoffrey Sedor, Albert Lee, Jared Pasetsky, Connor J. Kinslow, Genesis De Los Santos, ...

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 730-737,
<https://doi.org/10.1016/j.ijrobp.2024.04.016>.

Abstract: Purpose: The role of stereotactic radiosurgery (SRS) in the management of grade 2 and 3 meningiomas is not well elucidated. Unfortunately, local recurrence rates are high, and guidelines for management of recurrent disease are lacking. To address this knowledge gap, we conducted STORM (Salvage Stereotactic Radiosurgery for Recurrent WHO Grade 2 and 3 Meningiomas), a multicenter retrospective cohort study of patients treated with primary SRS for recurrent grade 2 and 3 meningiomas.

Methods and Materials

Data on patients with recurrent grade 2 and 3 meningioma treated with SRS at first recurrence were retrospectively collected from 8 academic centers in the United States. Patients with multiple lesions at the time of initial diagnosis or more than 2 lesions at the time of first recurrence were excluded from this analysis. Patient demographics and treatment parameters were extracted at time of diagnosis, first recurrence, and second recurrence. Oncologic outcomes, including progression-free survival (PFS) and overall survival, as well as toxicity outcomes, were reported at the patient level. Results: From 2000 to 2022, 108 patients were identified (94% grade 2, 6.0% grade 3). A total of 106 patients (98%) had upfront surgical resection (60% gross-total resection) with 18% receiving adjuvant radiation therapy (RT). Median time to first progression was 2.5 years (IQR, 1.34-4.30). At first recurrence, patients were treated with single or fractionated SRS to a median marginal dose of 16 Gy to a maximum of 2 lesions (87% received single-fraction SRS). The median follow-up time after SRS was 2.6 years. The 1-, 2-, and 3-year PFS was 90%, 75%, and 57%, respectively, after treatment with SRS. The 1-, 2-, and 3-year overall survival was 97%, 94%, and 92%, respectively. In the multivariable analysis, grade 3 disease (HR, 6.80; 95% CI, 1.61-28.6), male gender (HR, 3.48; 95% CI, 1.47-8.26), and receipt of prior RT (HR, 2.69; 95% CI, 1.23-5.86) were associated with worse PFS. SRS dose and tumor volume were not correlated with progression. Treatment was well tolerated, with a 3.0% incidence of grade 2+ radiation necrosis. Conclusions: This is the largest multicenter study to evaluate salvage SRS in recurrent grade 2 and 3 meningiomas. In this select cohort of patients with primarily grade 2 meningioma with a potentially more favorable natural history of delayed, localized first recurrence amenable to salvage SRS, local control rates and toxicity profiles were favorable, warranting further prospective validation.

24COASNO16:

Title- Application of Recombinant Human Superoxide Dismutase in Radical Concurrent Chemoradiotherapy for Cervical Cancer to Prevent and Treat Radiation-induced Acute Rectal Injury: A Multicenter, Randomized, Open-label, Prospective Trial,

Jiawei Zhu, Xiaofan Li, Manni Huang, Hong Zhu, Yan Tan, Xia He, Zhihua Sun, Huijun Cheng, Fenghu Li, ...

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 720-729,

<https://doi.org/10.1016/j.ijrobp.2024.04.070>.

Abstract: Purpose: The purpose of this study was to evaluate the efficacy of recombinant human superoxide dismutase (rhSOD) enemas in radiation-induced acute rectal injury (RARI) in patients with locally advanced cervical cancer. Methods and Materials: In this phase 3, randomized, open-label trial (NCT04819685) conducted across 14 medical centers in China from June 2021 to August 2023, all patients received concurrent chemoradiation therapy (CCRT). The experimental group was treated with a rhSOD enema during chemoradiation therapy, and the control group had no enema. The Common Terminology

Criteria for Adverse Events (version 5.0) was used to evaluate radiation therapy–induced side effects. Endoscopic appearance was assessed using the Vienna Rectoscopy Score. The primary endpoint in the acute phase was the occurrence rate and duration of grade ≥ 1 ($\geq G1$) diarrhea during CCRT. Secondary endpoints included the occurrence rate and duration of $\geq G2$ and $\geq G3$ diarrhea, $\geq G1$ and $\geq G2$ diarrhea lasting at least 3 days, and damage to the rectal mucosa due to radiation therapy measured by endoscopy. Results: Two hundred and eighty-three patients were randomly divided into the experimental (n = 141) or control group (n = 142). The mean number of $\geq G1$ and $\geq G2$ diarrhea days were significantly lower in the experimental group than in the control group (3.5 and 0.8 days vs 14.8 and 4.5 days, respectively; $P < .001$). The incidence of $\geq G2$ diarrhea decreased from 53.6% to 24.1% when rhSOD enemas were used. Use of antidiarrheals was lower in the experimental group (36.2% vs 55.7%, $P < .001$). Three patients felt intolerable or abdominal pain after rhSOD enema. RARI grades in the experimental group tended to be lower than those in the control group ($P = .061$). Logistic regression analysis revealed that rhSOD enema was associated with a lower occurrence rate of $\geq G1/2$ diarrhea for at least 3 days ($P < .001$). Conclusions: The results of this study suggest that rhSOD enema is safe and significantly reduces the incidence, severity, and duration of RARI, protecting the rectal mucosa.

24COASNO17:

Title- A Phase 2 Trial of Primary Tumor Stereotactic Body Radiation Therapy Boost Before Concurrent Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer,

Terence M. Williams, Eric Miller, Meng Welliver, Jeremy Brownstein, Gregory Otterson, Dwight Owen, Karl Haglund, Peter Shields, Erin Bertino, Carolyn Presley, [et al.]

International Journal of Radiation Oncology*Biophysics, Volume 120, Issue 3, 2024, Pages 681-694,

<https://doi.org/10.1016/j.ijrobp.2024.02.020>.

Abstract: Purpose: Primary tumor failure is common in patients treated with chemoradiation (CRT) for locally advanced NSCLC (LA-NSCLC). Stereotactic body radiation therapy (SBRT) yields high rates of primary tumor control (PTC) in early-stage NSCLC. This trial tested an SBRT boost to the primary tumor before the start of CRT to improve PTC.

Methods and Materials: Patients with LA-NSCLC received an SBRT boost in 2 fractions (central location 12 Gy, peripheral location 16 Gy) to the primary tumor, followed by standard CRT (60 Gy in 30 fractions). The primary objective was PTC rate at 1 year, and the hypothesis was that the 1-year PTC rate would be $\geq 90\%$. Secondary objectives included objective response rate, regional and distant control, disease-free survival (DFS), and overall survival (OS). Correlative studies included functional magnetic resonance imaging and blood-based miRNA analysis. Results: The study enrolled 21 patients (10 men and 11 women); the median age was 62 years (range, 52-78). The median pretreatment primary tumor size was 5.0 cm (range, 1.0-8.3). The most common nonhematologic toxicities were pneumonitis, fatigue, esophagitis/dysphagia, dyspnea, and cough. Only 1 treatment-related grade 4 nonhematologic toxicity occurred (respiratory failure/radiation pneumonitis), and no

grade 5 toxicities occurred. The objective response rate at 3 and 6 months was 72.7% and 80.0%, respectively, and PTC at 1 and 2 years was 100% and 92.3%, respectively. The 2-year regional and distant control rates were 81.6% and 70.3%, respectively. Disease-free survival and overall survival at 2 years were 46.1% and 50.3%, respectively, and median survival was 37.8 months. Functional magnetic resonance imaging detected a mean relative decrease in blood oxygenation level-dependent signal of -87.1% ($P = .05$), and miR.142.3p was correlated with increased risk of grade ≥ 3 pulmonary toxicity ($P = .01$). Conclusions: Dose escalation to the primary tumor using upfront SBRT appears feasible and safe. PTC was high and other oncologic endpoints compared favorably to standard treatment. Functional magnetic resonance imaging suggested changes in oxygenation with the first SBRT boost dose, and miR.142.3p was correlated with pulmonary toxicity.

24COASNO18:

Title- The Value and Safety of Adjuvant Radiation Therapy After Radical Cystectomy in Locally Advanced Urothelial Bladder Cancer: A Controlled Randomized Study,

Mohamed S. Zaghloul, Ahmed Khaled Alnagmy, Hatem Aboul Kasem, Mohamed M. Abdel Hakim, Ahmed Abdallah, Mohamed Kamal, Ayatallah G. Mostafa, Tarek M. Zaghloul, International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 658-666,

<https://doi.org/10.1016/j.ijrobp.2024.05.012>.

Abstract: Purpose: Adjuvant radiation therapy (ART) after radical cystectomy in locally advanced bladder cancer was revived after the advancement in precise radiation therapy that decreased the normal pelvic tissue radiation hazards. However, there are still scarce controlled randomized studies addressing this issue. Methods and Materials: One hundred thirty-one cystectomized urothelial bladder cancer patients were enrolled; 122 were randomized to receive ART of 50 Gy/25 fractions 4 weeks after cystectomy or cystectomy alone (CY). Sixty-two were included in the ART arm and 60 in the CY arm. Twenty-four ART and 30 CY patients received neoadjuvant chemotherapy. Eleven patients (9%) had cotenant neobladder diversion, 6 in ART, and 5 in CY arms. All ART patients were treated with intensity modulated radiation therapy with daily verification cone beam computed tomography. The median follow-up was 42.7 months. Results: The 3-year adjusted locoregional recurrence-free survival rate was higher in the ART arm, measuring 81% (95% CI, 69%-94%) compared with 71% (95% CI, 60%-80%; $p = .0457$). ART significantly improved the locoregional relapse-free rate in the cystectomy bed and the pelvic side wall ($p = .016$ and $p = .001$, respectively). The overall, event-free, and distant metastasis-free survival did not rank to the level of statistical significance in the 2 arms. Even though the acute side effects were slightly higher in ART, the late toxicities were almost equal in the 2 groups. Conclusions: ART is safe and quite tolerable after radical cystectomy when using precise radiation techniques. These techniques significantly improved the locoregional recurrence-free survival but had insignificant improvement on the overall survival. ART did not affect the distant metastasis-free survival. Similar studies are performed in different centers around the world to confirm the value of ART in urothelial bladder cancer.

24COASNO19:

Title- Clinical Results and Prognostic Factors in Boron Neutron Capture Therapy for Recurrent Squamous Cell Carcinoma of the Head and Neck Under the Japan National Health Insurance System: A Retrospective Study of the Initial 47 Patients,

Katsumi Hirose, Mariko Sato,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 796-804,

<https://doi.org/10.1016/j.ijrobp.2024.03.041>.

Abstract: Purpose: Recurrent head and neck cancer presents a therapeutic challenge because of cumulative toxicity from initial radiation therapy, limiting reirradiation options. Boron neutron capture therapy (BNCT) offers a promising alternative, selectively delivering a radical dose to tumors while sparing adjacent normal tissue. This study investigates the initial clinical outcomes and prognostic factors associated with BNCT for recurrent squamous cell carcinoma of the head and neck. Methods and Materials: This retrospective analysis investigated the initial 47 patients treated with BNCT between May 2020 and February 2021 in Japan. All patients had received radiation therapy with a median dose of 70 Gy (range, 44-176) before BNCT. Median tumor size was 11 cm³ (range, 1-117 cm³), with 23% of tumors larger than 30 cm³, and 87% of patients had prior systemic therapy. The most common prescribed dose to the pharyngeal mucosa was 15 Gy-Eq (36%), followed by 18 Gy-Eq (34%). The minimum dose given to tumor was 27.4 Gy-Eq (range, 13.3-45.2). In 23 patients, 18F-fluoro-borono-phenylalanine positron emission tomography was performed within 1 week before BNCT, and the tumor-to-blood 10B ratio was 3.5 (range, 2.0-8.7). Results: Efficacy analysis revealed a 51% complete response rate and a 74% overall response rate. Disease-free survival rates at 1 and 2 years were 34.6% and 26.6%, respectively. Overall survival rates at 1 and 2 years were 86.1% and 66.5%, respectively. Multivariate analysis revealed that, among the patient characteristics, whether the lesion was mucosal had a significant effect on achieving complete response. Conclusions: This study provided valuable insights into the early integration of BNCT into routine clinical practice, highlighting its efficacy and safety. Technical improvements are needed to ensure precise dose administration. Ongoing prospective studies, such as the phase II REBIVAL study, will further elucidate the role of BNCT in recurrent head and neck cancer.

24COASNO20:

Title- Predictors of Tumor Dynamics Over a 6-Week Course of Concurrent Chemoradiotherapy for Glioblastoma and the Effect on Survival,

Wee Loon Ong, James Stewart, Arjun Sahgal, Hany Soliman, Chia-Lin Tseng, Jay Detsky, Hanbo Chen,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 750-759,

<https://doi.org/10.1016/j.ijrobp.2024.03.036>.

Abstract: Purpose: We present the final analyses of tumor dynamics and their prognostic significance during a 6-week course of concurrent chemoradiotherapy for glioblastoma in the

Glioblastoma Longitudinal Imaging Observational study. Methods and Materials: This is a prospective serial magnetic resonance imaging study in 129 patients with glioblastoma who had magnetic resonance imaging obtained at radiation therapy (RT) planning (F0), fraction 10 (F10), fraction 20 (F20), and 1-month post-RT. Tumor dynamics assessed included gross tumor volume relative to F0 (Vrel) and tumor migration distance (dmigration). Covariables evaluated included: corpus callosum involvement, extent of surgery, O6-methylguanine-DNA-methyltransferase methylation, and isocitrate dehydrogenase mutation status. Results: The median Vrel were 0.85 (range, 0.25-2.29) at F10, 0.79 (range, 0.09-2.22) at F20, and 0.78 (range, 0.13-4.27) at 1 month after completion of RT. The median dmigration were 4.7 mm (range, 1.1-20.4 mm) at F10, 4.7 mm (range, 0.8-20.7 mm) at F20, and 6.1 mm (range, 0.0-45.5 mm) at 1 month after completion of RT. Compared with patients who had corpus callosum involvement (n = 26), those without corpus callosum involvement (n = 103) had significant Vrel reduction at F20 (P = .03) and smaller dmigration at F20 (P = .007). Compared with patients who had biopsy alone (n = 19) and subtotal resection (n = 71), those who had gross total resection (n = 38) had significant Vrel reduction at F10 (P = .001) and F20 (P = .001) and a smaller dmigration at F10 (P = .03) and F20 (P = .002). O6-Methylguanine-DNA-methyltransferase methylation and isocitrate dehydrogenase mutation status were not significantly associated with tumor dynamics. The median progression-free survival and overall survival (OS) were 8.5 months (95% CI, 6.9-9.9) and 20.4 months (95% CI, 17.6-25.2). In multivariable analyses, patients with Vrel $\geq$ 1.33 at F10 had worse OS (hazard ratio [HR], 4.6; 95% CI, 1.8-11.4; P = .001), and patients with dmigration $\geq$ 5 mm at 1-month post-RT had worse progression-free survival (HR, 1.76; 95% CI, 1.08-2.87) and OS (HR, 2.2; 95% CI, 1.2-4.0; P = .007). Conclusions: Corpus callosum involvement and extent of surgery are independent predictors of tumor dynamics during RT and can enable patient selection for adaptive RT strategies. Significant tumor enlargement at F10 and tumor migration 1-month post-RT were associated with poorer OS.

24COASNO21:

Title- Stereotactic Radiation for Ultra-Central Non-Small Cell Lung Cancer: A Safety and Efficacy Trial (SUNSET),

Meredith E. Giuliani, Edith Filion, Sergio Faria, Vijayananda Kundapur, Thi Trinh Thuc (Toni) Vu,

International Journal of Radiation Oncology*Biophysics, Volume 120, Issue 3, 2024, Pages 669-677,

<https://doi.org/10.1016/j.ijrobp.2024.03.050>.

Abstract: Purpose: The use of stereotactic body radiation therapy for tumors in close proximity to the central mediastinal structures has been associated with a high risk of toxicity. This study (NCT03306680) aimed to determine the maximally tolerated dose of stereotactic body radiation therapy for ultracentral non-small cell lung carcinoma, using a time-to-event continual reassessment methodology. Methods and Materials: Patients with T1-3N0M0 ($\leq$ 6 cm) non-small cell lung carcinoma were eligible. The maximally tolerated dose was defined as the dose of radiation therapy associated with a $\leq$ 30% rate of grade (G) 3 to 5

prespecified treatment-related toxicity occurring within 2 years of treatment. The starting dose level was 60 Gy in 8 daily fractions. The dose-maximum hotspot was limited to 120% and within the planning tumor volume; tumors with endobronchial invasion were excluded. This primary analysis occurred 2 years after completion of accrual. Results: Between March 2018 and April 2021, 30 patients were enrolled at 5 institutions. The median age was 73 years (range, 65-87) and 17 (57%) were female. Planning tumor volume was abutting proximal bronchial tree in 19 (63%), esophagus 5 (17%), pulmonary vein 1 (3.3%), and pulmonary artery 14 (47%). All patients received 60 Gy in 8 fractions. The median follow-up was 37 months (range, 8.9-51). Two patients (6.7%) experienced G3-5 adverse events related to treatment: 1 patient with G3 dyspnea and 1 G5 pneumonia. The latter had computed tomography findings consistent with a background of interstitial lung disease. Three-year overall survival was 72.5% (95% CI, 52.3%-85.3%), progression-free survival 66.1% (95% CI, 46.1%-80.2%), local control 89.6% (95% CI, 71.2%-96.5%), regional control 96.4% (95% CI, 77.2%-99.5%), and distant control 85.9% (95% CI, 66.7%-94.5%). Quality-of-life scores declined numerically over time, but the decreases were not clinically or statistically significant. Conclusions : Sixty Gy in 8 fractions, planned and delivered with only a moderate hotspot, has a favorable adverse event rate within the prespecified acceptability criteria and results in excellent control for ultracentral tumors.

24COASNO22:

Title- Dose-Effect Relationship of Kidney Function After SABR for Primary Renal Cell Carcinoma: TROG 15.03 FASTER II,

Mathieu Gaudreault, Nicholas Hardcastle, Price Jackson, Lachlan McIntosh, Braden Higgs, David Pryor, Mark Sidhom, Rachael Dykyj, Alisha Moore, Tomas Kron, Shankar Siva, International Journal of Radiation Oncology*Biophysics, Volume 120, Issue 3, 2024, Pages 648-654, <https://doi.org/10.1016/j.ijrobp.2024.04.066>.

Abstract: Purpose Stereotactic ablative body radiotherapy (SABR) is a novel option to treat primary renal cell carcinoma. However, a high radiation dose may be received by the treated kidney, which may affect its function posttreatment. This study investigates the dose-effect relationship of kidney SABR with posttreatment renal function. Methods and Materials: This was a prespecified secondary endpoint of the multicenter FASTER II (Focal Ablative STereotactic RAdiotherapy for Cancers of the Kidney phase II) clinical trial (National Clinical Trial 02613819). Patients received either 26 Gy in a single fraction (SF) for tumors with a maximal diameter of 4 cm or less or 42 Gy in 3 fractions (multifraction [MF]) for larger tumors. To determine renal function change, ^{99m}Tc-dimercaptosuccinic acid (DMSA) single-photon emission computed tomography/computed tomography (SPECT/CT) scans were acquired, and the glomerular filtration rate was estimated at baseline, 12, and 24 months posttreatment. Imaging data sets were rigidly registered to the planning CT where kidneys were segmented to calculate dose-response curves. Results: From 71 enrolled patients, 36 (51%) and 26 (37%) patients were included in this study based on availability of posttreatment data at 12 and 24 months, respectively. The ipsilateral kidney glomerular

filtration rate decreased from baseline by 42% and 39% in the SF cohort and by 45% and 62% in the MF cohort, at 12 and 24 months, respectively ($P < .03$). The loss in renal function was $3.6\%/Gy \pm 0.8\%/Gy$ and $4.5\%/Gy \pm 1.0\%/Gy$ in the SF cohort and $1.7\%/Gy \pm 0.1\%/Gy$ and $1.7\%/Gy \pm 0.2\%/Gy$ in the MF cohort at 12 and 24 months, respectively. The major loss in renal function occurred in high-dose regions, where dose-response curves converged to a plateau. Conclusions: For the first time in a multicenter study, the dose-effect relationship at 12 and 24 months post-SABR treatment for primary renal cell carcinoma was quantified. Kidney function reduces linearly with dose up to 100 Gy BED3.

24COASNO23:

Title- A Phase 1/2 Study of Disulfiram and Copper With Concurrent Radiation Therapy and Temozolomide for Patients With Newly Diagnosed Glioblastoma,

Jiayi Huang, Jian L. Campian, Todd A. DeWees, Zdenek Skrott, Martin Mistrik, Tanner M. Johanns,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 3, 2024, Pages 738-749,

<https://doi.org/10.1016/j.ijrobp.2024.05.009>.

Abstract: Purpose: This phase 1/2 study aimed to evaluate the safety and preliminary efficacy of combining disulfiram and copper (DSF/Cu) with radiation therapy (RT) and temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM). Methods and Materials: Patients received standard RT and TMZ with DSF (250-375 mg/d) and Cu, followed by adjuvant TMZ plus DSF (500 mg/d) and Cu. Pharmacokinetic analyses determined drug concentrations in plasma and tumors using high-performance liquid chromatography-mass spectrometry. Results: Thirty-three patients, with a median follow-up of 26.0 months, were treated, including 12 IDH-mutant, 9 NF1-mutant, 3 BRAF-mutant, and 9 other IDH-wild-type cases. In the phase 1 arm, 18 patients were treated; dose-limiting toxicity probabilities were 10% (95% CI, 3%-29%) at 250 mg/d and 21% (95% CI, 7%-42%) at 375 mg/d. The phase 2 arm treated 15 additional patients at 250 mg/d. No significant difference in overall survival or progression-free survival was noted between IDH- and NF1-mutant cohorts compared with institutional counterparts treated without DSF/Cu. However, extended remission occurred in 3 BRAF-mutant patients. Diethyl-dithiocarbamate-copper, the proposed active metabolite of DSF/Cu, was detected in plasma but not in tumors. Conclusions: The maximum tolerated dose of DSF with RT and TMZ is 375 mg/d. DSF/Cu showed limited clinical efficacy for most patients. However, promising efficacy was observed in BRAF-mutant GBM, warranting further investigation.

24COASNO24:

Title- The treatment landscape of triple-negative breast cancer

Yi Hu, Chen Wang, Huishi Liang, Jie Li & Qiong Yang

Medical Oncology . 2024 Aug 29;41(10):236.

doi: <https://doi.org/10.1007/s12032-024-02456-9>.

Abstract: Triple-negative breast cancer (TNBC) tumors are biologically aggressive breast cancer. On the molecular level, TNBC is a highly heterogeneous disease; more biotechnologies are gradually being used to advance the understanding of TNBC subtypes and help establish more targeted therapies. Multiple TNBC target-related agents are already approved by the Food and Drug Administration for clinical use, including PI3K/AKT/mTOR inhibitors, PRAP inhibitors, and antibody-drug conjugates. Some innovative approaches, like peptide strategies, also promise to treat TNBC. Currently, the interplay between TNBC tumors and their tumor microenvironment provides a promising prospect for improving the efficacy of immunotherapy. In this review, we summarize the prevalent TNBC subtype methodologies, discuss the evolving therapeutic strategies, and propose new therapeutic possibilities based on existing foundational theories, with the attempt to serve as a reference to further advance tailoring treatment of TNBC.

Keywords: Immunotherapy; Personalized treatment; Triple-negative breast cancer.

24COASNO25:

Title- How mitochondrial dynamics imbalance affects the progression of breast cancer:a mini review

Jingwen Kuang, Hao Liu, Linlin Feng, Yuan Xue, Huiyi Tang & Pengcheng Xu

Medical Oncology . 2024 Sep 1;41(10):238.

doi: <https://doi.org/10.1007/s12032-024-02479-2>.

Abstract: Despite the high incidence of breast cancer in women worldwide, there are still great challenges in the treatment process. Mitochondria are highly dynamic organelles, and their dynamics involve cellular energy conversion, signal conduction and other processes. In recent years, an increasing number of studies have affirmed the dynamics of mitochondria as the basis for cancer progression and metastasis; that is, an imbalance between mitochondrial fission and fusion may lead to the progression and metastasis of breast cancer. Here, we review the latest insights into mitochondrial dynamics in the progression of breast cancer and emphasize the clinical value of mitochondrial dynamics in diagnosis and prognosis, as well as important advances in clinical research.

Keywords: Breast cancer; Mitochondria; Mitochondrial dynamics; Mitochondrial fission; Mitochondrial fusion.

24COASNO26:

Title- Advances in immunotoxin engineering: precision therapeutic strategies in modern oncology

Akbar Oghalaie, Mahmoud Eshagh Hosseini, Mohammad Hosseininejad-Chafi, Zohre Eftekhari,

Mahdi Behdani & Fatemeh Kazemi-Lomedasht

Medical Oncology . 2024 Sep 4;41(10):239.

doi: <https://doi.org/10.1007/s12032-024-02478-3>.

Abstract: Immunotoxins (ITs) are specialized therapeutic agents designed for targeted treatment, particularly in cancer therapy. They consist of a monoclonal antibody or antibody

fragment linked to a potent cytotoxic agent, such as bacterial- or plant-derived toxins like diphtheria toxin, ricin, or pseudomonas exotoxin. The monoclonal antibody component specifically binds to antigens expressed on the surface of target cells, facilitating the internalization of the IT. Once inside the cell, the cytotoxic agent is released, disrupting essential cellular processes and leading to cell death. This targeted approach minimizes damage to healthy tissues while effectively eliminating diseased cells. The production of ITs involves two primary methods: recombinant fusion and chemical conjugation. In recombinant fusion, genetic engineering is used to create a fusion protein that combines the antibody and toxin, ensuring precise control over their ratio and functionality. In chemical conjugation, pre-existing antibodies are chemically linked to toxins, allowing for greater flexibility in combining different antibodies and cytotoxic agents. Each method has its advantages and challenges, influencing the specificity, production complexity, and therapeutic potential of the resulting ITs. As research advances, ITs continue to show promise not only in oncology but also in treating other diseases, including inflammatory conditions and atherosclerosis. The precise targeting and potent effects of ITs make them a valuable tool in the development of new therapeutic strategies.

Keywords: Cancer; Immunotoxin; Target therapy.

24COASNO27:

Title- The role of IL-22 in cancer

Zachary E. Hunzeker, Lei Zhao, Austin M. Kim, Jacob M. Parker, Ziwen Zhu, Huaping Xiao, Qian Bai,

Mark R. Wakefield & Yujiang Fang

Medical Oncology . 2024 Sep 5;41(10):240.

doi: <https://doi.org/10.1007/s12032-024-02481-8>.

Abstract: Interleukin-22, discovered in the year of 2000, is a pleiotropic Th17 cytokine from the IL-10 family of cytokines. IL-22 signals through the type 2 cytokine receptor complex IL-22R and predominantly activates STAT3. This pathway leads to the transcription of several different types of genes, giving IL-22 context-specific functions ranging from inducing antimicrobial peptide expression to target cell proliferation. In recent years, it has been shown that IL-22 is involved in the pathogenesis of neoplasia in some cancers through its pro-proliferative and anti-apoptotic effects. This review highlights studies with recent discoveries and conclusions drawn on IL-22 and its involvement and function in various cancers. Such a study may be helpful to better understand the role of IL-22 in cancer so that new treatment could be developed targeting IL-22.

Keywords: Cytokine; Interleukin-22; Tumor.

24COASNO28:

Title- Current diagnostic and quantitative techniques in the field of lymphedema management: a critical review

Mary Vargo, Melissa Aldrich, Paula Donahue, Emily Iker, Louise Koelmeyer, Rachelle Crescenzi & Andrea Cheville

Medical Oncology . 2024 Sep 5;41(10):241.

doi: <https://doi.org/10.1007/s12032-024-02472-9>.

Abstract: Lymphedema evaluation entails multifaceted considerations for which options continue to evolve and emerge. This paper provides a critical review of the current status of diagnostic and quantitative measures for lymphedema, from traditional and novel bedside assessment tools for volumetric and fluid assessment, to advanced imaging modalities. Modalities are contrasted with regard to empirical support and feasibility of clinical implementation. The manuscript proposes a grid framework for comparing the ability of each modality to quantify specific lymphedema characteristics, including distribution, dysmorphism, tissue composition and fluid content, lymphatic anatomy and function, metaplasia, clinical symptoms, and quality of life and function. This review additionally applies a similar framework approach to consider how well assessment tools support important clinical needs, including: (1) screening, (2) diagnosis and differential diagnosis, (3) individualization of treatment, and (4) monitoring treatment response. The framework highlights which clinical needs are served by an abundance of assessment tools and identifies others that have problematically few. The framework clarifies which tools have greater or lesser empirical support. The framework is designed to assist stakeholders in selecting appropriate diagnostic and surveillance modalities, gauging levels of confidence when applying tools to specific clinical needs, elucidating overarching patterns of diagnostic and quantitative strengths and weaknesses, and informing future investigation.

Keywords: Cancer; Diagnosis; Imaging; Lymphedema; Measurement; Monitoring; Screening.

24COASNO29:

Title- Turning the tide: pembrolizumab's triumph in adjuvant RCC therapy

Fouad Attieh, Marc Boutros, Hampig Raphaël Kourie & Mervat Mahrous

Medical Oncology . 2024 Sep 5;41(10):242.

doi: <https://doi.org/10.1007/s12032-024-02486-3>.

Abstract: In recent years, kidney cancer has shown an increased worldwide incidence of more than 400 000 novel cases annually. Although more than half of patients are diagnosed at a localised stage, this disease presents a high-risk of relapse after surgery. Thus, there is a need for adjuvant therapy post-resection to reduce cancer recurrence and prolong disease-free and overall survival. Thorough investigation of adjuvant drugs for renal cell carcinoma (RCC) has shown little promise in the last fifty years, with no recorded overall survival benefits. This was the case until pembrolizumab, an immune checkpoint inhibitor, was introduced into the adjuvant RCC space through the KEYNOTE-564 trial. The adjuvant administration of this novel anti-PD-1 drug demonstrated a significant overall survival benefit which has led to an update in the current treatment guidelines of RCC. This substantial change in the standard of care also caused an investigation of possible treatment combinations and an adoption of innovative predictive biomarkers. In this review, we will present the evolution of past adjuvant ICI trials for the treatment of RCC, the implications of pembrolizumab's overall survival benefits and a discussion of future directions concerning new RCC drug trials and liquid biopsy-based biomarkers.

Keywords: Adjuvant immunotherapy; Liquid biopsy; Pembrolizumab; Renal cell carcinoma.

24COASNO30:

Title- Lipid metabolism reprogramming in renal cell carcinomas

Mustafa Khalid Abduljabbar, Mohammed Merza, Abdulqader Aziz, Soumya V. Menon, Mandeep Kaur, Zafar Aminov, Safia Obaidur Rab, Ahmed HJazi, Yasser Fakri Mustafa & Benien C. Gabel

Medical Oncology . 2024 Sep 6;41(10):243.

doi: <https://doi.org/10.1007/s12032-024-02484-5>.

Abstract: This study investigates the intricate mechanisms underlying the correlation between elevated consumption of harmful fats and the onset of kidney malignancies. The rise in global obesity rates has been accompanied by an increased prevalence of renal cancers, prompting an exploration into the molecular pathways and biological processes linking these phenomena. Through an extensive review of current literature and clinical studies, we identify potential key factors contributing to the carcinogenic influence of harmful fats on renal tissues. Our analysis highlights the role of adipose tissue-derived factors, inflammatory mediators, and lipid metabolism dysregulation in fostering a microenvironment conducive to renal tumorigenesis. Furthermore, we delve into the impact of harmful fats on signaling pathways associated with cell proliferation, apoptosis evasion, and angiogenesis within the renal parenchyma. This review underscores the importance of elucidating the molecular intricacies linking lipid metabolism and kidney malignancies, offering a foundation for future research and the development of targeted preventive and therapeutic interventions. The findings discussed herein contribute to our understanding of the complex relationship between lipid mediators and renal cancer, providing a basis for public health strategies aimed at mitigating the impact of harmful fats on kidney health.

Keywords: Kidney malignancies; Lipid metabolism; Obesity.

24COASNO31:

Title- The Sirt1/Nrf2 pathway is a key factor for drug therapy in chemotherapy-induced cardiotoxicity: a Mini-Review

Suleiman Ibrahim Shelash Mohammad, Asokan Vasudevan, Felix Oghenemaro Enwa, Jaya Bansal,

Medical Oncology . 2024 Sep 11;41(10):244.

doi: <https://doi.org/10.1007/s12032-024-02494-3>.

Abstract: The likelihood of survival for cancer patients has greatly improved due to chemotherapy medicines. However, these antitumor agents might also have unfavorable effects on the cardiovascular system, which could result in sudden or gradual cardiac failure. The production of free radicals that result in oxidative stress appears to be the key mechanism by which chemotherapy-induced cardiotoxicity (CIC) happens. Reports suggest that the Sirtuin-1 (Sirt1)/Nuclear factor E2-associated factor 2 (Nrf2) signaling pathway has been considered an alternative path for counteracting cardiotoxicity by suppressing oxidative stress, inflammation, and apoptosis. This review concludes recent knowledge about CIC with a special focus on the anti-oxidative regulation properties of the Sirt1/Nrf2 pathway.

Keywords: Cardiotoxicity; Chemotherapy; Oxidative stress; Sirt1/Nrf2 pathway.

24COASNO32:

Title- Incidence of lymphedema related to various cancers

Marie-Eve Letellier, Marize Ibrahim, Anna Towers & Geneviève Chaput

Medical Oncology . 2024 Sep 17;41(10):245.

doi: <https://doi.org/10.1007/s12032-024-02441-2>.

Abstract: Cancer-related lymphedema (CRL) lacks internationally accepted definition and diagnostic criteria. The accurate incidence of CRL is therefore a challenge and the condition is likely underreported. Patients treated for cancer can develop CRL as a result of surgery, chemotherapy, and/or radiotherapy, which can lead to considerable psychosocial and physical morbidity, and decreased quality of life. Determining CRL incidence is crucial to inform care access and resource allocation, to best support patients affected by this lifelong condition. This review aimed to provide the latest CRL incidence estimates. Using four core databases (MEDLINE, Embase, Web of Science Core Collection, Cochrane Library), a literature search was performed to capture publications dated between 2015 and 2023. A total of 48 articles (33 prospective studies, 15 systematic reviews) met inclusion criteria, providing a sample size of 234,079 cancer patients. Findings revealed CRL incidence across cancer types varied, reported 2–74% in breast, 8–45% in gynecological and urological, 71–90% in head and neck and 2–29% in melanoma cancers. CRL incidence varied between 3 and 21% in preventative lymphedema surgery patients. Projected increases in cancer incidence and improved survival rates are expected to further escalate CRL incidence. Healthcare systems and professionals alike must therefore prepare to meet the growing needs of CRL patients.

Keywords: Cancer; Incidence; Long-term effects; Lymphedema; Oncology; Survivorship.

24COASNO32:

Title- Comment on “2-methoxyestradiol sensitizes tamoxifen-resistant MCF-7 breast cancer cells via downregulating HIF-1 α ”

Hethesh Chellapandian & Sivakamavalli Jeyachandran

Medical Oncology . 2024 Sep 23;41(10):246.

doi: <https://doi.org/10.1007/s12032-024-02505-3>.

Abstract: This study investigates the potential of 2-methoxyestradiol (2-ME) to overcome tamoxifen (TAM) resistance in MCF-7 breast cancer cells by downregulating hypoxia-inducible factor 1 alpha (HIF-1 α). Through a series of in vitro experiments, the authors demonstrate that combining 2-ME with TAM enhances the cytotoxic effects on resistant cells, increases apoptosis markers, and reduces cholesterol and triglyceride levels. While the findings highlight a promising therapeutic approach, the lack of in vivo or clinical data limits direct clinical application. Future research should focus on validating these results in animal models and exploring long-term efficacy and molecular mechanisms.

24COASNO33:

Title- Clinical efficacy and immune response of neoadjuvant camrelizumab plus chemotherapy in resectable locally advanced oesophageal squamous cell carcinoma: a phase 2 trial

Yue-Yun Chen, Pei-Pei Wang, Yang Hu, Yong Yuan, Yu-Shang Yang, Hua-Shan Shi, Qing Hao, Zhen Lin, Jiang-Fang Tian, Yue Zheng, Ting Liu, Pan-Pan Lin, Heng Xu, Xue-Lei Ma, Li Yang & Zhen-Yu Ding

British Journal of Cancer . 2024 Oct;131(7):1126-1136.

doi: <https://doi.org/10.1038/s41416-024-02805-5>.

Abstract: Neoadjuvant immunotherapy is under intensive investigation for esophageal squamous cell carcinoma (ESCC). This study assesses the efficacy and immune response of neoadjuvant immunochemotherapy (nICT) in ESCC. Methods: In this phase II trial (ChiCTR2100045722), locally advanced ESCC patients receiving nICT were enrolled. The primary endpoint was the pathological complete response (pCR) rate. Multiplexed immunofluorescence, RNA-seq and TCR-seq were conducted to explore the immune response underlying nICT. Results: Totally 42 patients were enrolled, achieving a 27.0% pCR rate. The 1-year, 2-year DFS and OS rates were 89.2%, 64.4% and 97.3%, 89.2%, respectively. RNA-seq analysis highlighted T-cell activation as the most significantly enriched pathway. The tumour immune microenvironment (TIME) was characterised by high CD4, CD8, Foxp3, and PD-L1 levels, associating with better pathological regression (TRS0/1). TIME was categorised into immune-infiltrating, immune-tolerant, and immune-desert types. Notably, the immune-infiltrating type and tertiary lymphoid structures correlated with improved outcomes. In the context of nICT, TIM-3 negatively influenced treatment efficacy, while elevated TIGIT/PD-1 expression post-nICT correlated positively with CD8+ T cell levels. TCR-seq identified three TCR rearrangements, underscoring the specificity of T-cell responses. Conclusions: Neoadjuvant camrelizumab plus chemotherapy is effective for locally advanced, resectable ESCC, eliciting profound immune response that closely associated with clinical outcomes.

24COASNO34:

Title- Pre-treatment magnetic resonance imaging in anal cancer: large-scale evaluation of mrT, mrN and novel staging parameters

Hema Sekhar, Rohit Kochhar, Bernadette Carrington, Thomas Kaye, Damian Tolan, Lee Malcomson,

British Journal of Cancer . 2024 Oct;131(7):1137-1146.

doi: <https://doi.org/10.1038/s41416-024-02759-8>.

Abstract: Background: In patients with squamous cell carcinoma of the anus (SCCA), magnetic resonance (MR) imaging is recommended for pre-treatment staging prior to chemoradiotherapy (CRT), but large-scale evaluation of its staging performance is lacking. Methods: We re-characterised pre-treatment MRs from 228 patients with non-metastatic SCCA treated consecutively by CRT (2006–2015) at one UK cancer centre. We derived TN staging from tumour size (mrTr) and nodal involvement (mrN), and additionally characterised novel *beyond TN* features such as extramural vascular invasion (mrEMVI) and tumour signal heterogeneity (mrTSH). Primary outcomes were 5-year overall survival (OS) and 3-year loco-regional failure (LRF). Time-to-event analyses used Kaplan-Meier estimates; Hazard Ratios (HRs) with confidence intervals (CIs) were derived from Cox models. Results:

With a median follow up of 60.9 months, 5-year OS was 74%. Poor OS was associated with increasing mrT (HR: 1.12 per cm [95% CI: 1.07–1.33]), nodal positivity (HR 2.08 [95% CI 1.23–3.52]) and mrEMVI (HR 3.66 [95% CI: 1.88–7.41]). 3-year LRF rate was 16.5%. Increased LRF was associated with increasing mrT (HR: 1.43 per cm [95% CI: 1.26–1.63]), nodal positivity (HR 2.70 [95% CI 1.39–5.24]) and mrTSH (HR 2.66 [95% CI 1.29–5.48]). Conclusions: In SCCA, the study demonstrates that mrT and mrN stages are prognostic, while mrEMVI and mrTSH may be novel prognostic factors.

24COASNO35:

Title- The effect of comorbidities on diagnostic interval for lung cancer in England: a cohort study using electronic health record data

Imogen Rogers, Max Cooper, Anjum Memon, Lindsay Forbes, Harm van Marwijk & Elizabeth Ford

British Journal of Cancer . 2024 Oct;131(7):1147-1157.

doi: <https://doi.org/10.1038/s41416-024-02824-2>.

Abstract: Background: Comorbid conditions may delay lung cancer diagnosis by placing demand on general practitioners' time reducing the possibility of prompt cancer investigation ("competing demand conditions"), or by offering a plausible non-cancer explanation for signs/symptoms ("alternative explanation conditions"). Method: Patients in England born before 1955 and diagnosed with incident lung cancer between 1990 and 2019 were identified in the Clinical Practice Research Datalink and linked hospital admission and cancer registry data. Diagnostic interval was defined as time from first presentation in primary care with a relevant sign/symptom to the diagnosis date. 14 comorbidities were classified as ten "competing demand" and four "alternative explanation" conditions. Associations with diagnostic interval were investigated using multivariable linear regression models. Results: Complete data were available for 11870 lung cancer patients. In adjusted analyses diagnostic interval was longer for patients with "alternative explanation" conditions, by 31 and 74 days in patients with one and ≥ 2 conditions respectively versus those with none. Number of "competing demand" conditions did not remain in the final adjusted regression model for diagnostic interval. Conclusions: Conditions offering alternative explanations for lung cancer symptoms are associated with increased diagnostic intervals. Clinical guidelines should incorporate the impact of alternative and competing causes upon delayed diagnosis.

24COASNO36:

Title- Early detection of pancreatic cancer by comprehensive serum miRNA sequencing with automated machine learning

Munenori Kawai, Akihisa Fukuda, Ryo Otomo, Shunsuke Obata, Kosuke Minaga, Masanori Asada,

British Journal of Cancer . 2024 Oct;131(7):1158-1168.

doi: <https://doi.org/10.1038/s41416-024-02794-5>.

Abstract: Pancreatic cancer is often diagnosed at advanced stages, and early-stage diagnosis of pancreatic cancer is difficult because of nonspecific symptoms and lack of available

biomarkers. **Methods:** We performed comprehensive serum miRNA sequencing of 212 pancreatic cancer patient samples from 14 hospitals and 213 non-cancerous healthy control samples. We randomly classified the pancreatic cancer and control samples into two cohorts: a training cohort ($N=185$) and a validation cohort ($N=240$). We created ensemble models that combined automated machine learning with 100 highly expressed miRNAs and their combination with CA19-9 and validated the performance of the models in the independent validation cohort. **Results:** The diagnostic model with the combination of the 100 highly expressed miRNAs and CA19-9 could discriminate pancreatic cancer from non-cancer healthy control with high accuracy (area under the curve (AUC), 0.99; sensitivity, 90%; specificity, 98%). We validated high diagnostic accuracy in an independent asymptomatic early-stage (stage 0-I) pancreatic cancer cohort (AUC:0.97; sensitivity, 67%; specificity, 98%). **Conclusions:** We demonstrate that the 100 highly expressed miRNAs and their combination with CA19-9 could be biomarkers for the specific and early detection of pancreatic cancer.

24COASNO37:

Title- Sugar and sugar-sweetened beverages in relation to premature aging in adult survivors of childhood cancer

Tuo Lan, Mei Wang, AnnaLynn M. Williams, Matthew J. Ehrhardt, Shu Jiang, I-Chan Huang,

British Journal of Cancer . 2024 Oct;131(7):1169-1177.

doi: <https://doi.org/10.1038/s41416-024-02815-3>.

Abstract: Premature aging is a significant concern in adult survivors of childhood cancer as they develop aging-related conditions at a younger age than their peers with no history of childhood cancer. Although modifiable lifestyle factors, such as diet, are postulated to affect aging process, supporting evidence is sparse. **Methods:** We examined if the consumption of sugar and sugar-sweetened beverages was related to premature aging in 3322 adult survivors of childhood cancer in the St. Jude Lifetime Cohort. Premature aging was assessed using the Deficit Accumulation Index (DAI) that was a ratio of the number of age-related chronic health conditions each survivor had out of 44 conditions total. Multinomial logistic regressions adjusting for confounders were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** There were 46% of childhood cancer survivors consumed SSBs once or more times per day. High intake of sugar, especially sugars added to foods during preparation or processing, and habitual consumption of sugar-sweetened beverage were associated with an increased risk of premature aging. **Discussion:** Our findings support a need to include strategies to reduce sugar and sugar-sweetened beverages consumption in lifestyle interventions to promote healthy aging in adult survivors of childhood cancer.

24COASNO38:

Title- Cost-effectiveness of point of care smoking cessation interventions in oncology clinics

Kerri A. Mullen, Shelley Hewitson, Joshua Scoville, Alyssa Grant,

British Journal of Cancer . 2024 Oct;131(7):1178-1185.

doi: <https://doi.org/10.1038/s41416-024-02819-z>.

Abstract: We examined the cost-effectiveness of providing systematic smoking cessation interventions to oncology patients at point-of-care. Methods: A decision analytic model was completed from the healthcare payer's perspective and included all incident cancer cases involving patients who smoke in New Brunswick, Canada ($n=1040$), cancer site stratifications, and risks of mortality, continued smoking, and cancer treatment failure over one year. Usual care (no cessation support) was compared to the standard Ottawa Model for Smoking Cessation (OMSC) intervention, and to OMSC plus unlimited cost-free stop smoking medication (OMSC + SSM), including nicotine replacement therapy, varenicline, or bupropion. Primary outcomes were incremental cost per quit (ICQ) and incremental cost per cancer treatment failure avoided (ICTFA). Results: The ICQ was \$C143 and ICTFA \$C1193 for standard OMSC. The ICQ was \$C503 and ICTFA was \$C5952 for OMSC + SSM. The number needed to treat (NNT) to produce one quit was 9 for standard OMSC and 4 for OMSC + SSM, and the NNT to avoid one first-line treatment failure was 78 for OMSC and 45 for OMSC + SSM. Both were cost-effective in 100% of 1000 simulations. Conclusions: Given the high clinical benefits and low incremental costs, systematic smoking cessation interventions should be a standard component of first-line cancer treatment.

24COASNO39:

Title- infections and their prognostic significance before diagnosis of chronic lymphocytic leukemia, non-Hodgkin lymphoma, or multiple myeloma

Esben Packness, Olafur Birgir Davidsson, Klaus Rostgaard, Michael Asger Andersen,

British Journal of Cancer . 2024 Oct;131(7):1186-1194.

doi: <https://doi.org/10.1038/s41416-024-02816-2>.

Abstract: Immunodeficiency is a shared feature of B cell malignancies. The risk of infections and their prognostic significance after diagnosis are well characterized, but, conversely, less is known about prediagnostic infections in these domains. Methods: In matched case-control analyzes, using Danish nationwide registers, we assessed the rate of prediagnostic infections in chronic lymphocytic leukemia (CLL), diffuse large B cell lymphoma (DLBCL), multiple myeloma (MM), follicular lymphoma (FL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL). Survival analyzes of data from clinical registers were then used to determine the effect of infections in the year preceding diagnosis on overall survival. To yield results for as many patients as possible, antimicrobial prescriptions were used as surrogates for infections. Results: The nationwide and clinical registers comprised 30,389 patients, accumulating 213,649 antimicrobial prescriptions, and 18,560 patients accumulating 107,268 prescriptions, respectively. The relative risk of infections was increased up to 15 years prior to diagnosis of malignancy and markedly increased in the year just prior to diagnosis. More than two antimicrobials within one year prior to diagnosis were associated with significantly shorter overall survival, independently of known prognostic factors. Conclusion: Patients with B cell-derived malignancies exhibit marked immunodeficiency several years prior to diagnosis such that different disease

subtypes demonstrate both overlapping and distinct trends in infection risk preceding diagnosis. Moreover, multiple infections within the year preceding diagnosis are independently associated with shorter overall survival for all the examined malignancies.

24COASNO40:

Title- Prognostic value of post-operative iron biomarkers in colorectal cancer: population-based patient cohort

Tafirenyika Gwenzi, Petra Schrotz-King, Sophie C. Anker, Ben Schöttker, Michael Hoffmeister & Hermann Brenner

British Journal of Cancer . 2024 Oct;131(7):1195-1201.

doi: <https://doi.org/10.1038/s41416-024-02814-4>.

Abstract: Post-operative anaemia is linked to iron deficiency. We investigated the prognostic value of post-operative iron biomarkers in colorectal cancer (CRC). Methods: Ferritin, transferrin, iron, and transferrin saturation (TS%) were measured from blood collected at a single time-point post-surgery in 2769 CRC patients. Associations between iron biomarkers with cancer-specific survival (CSS) and overall survival (OS) were assessed using Cox regression with hazard ratios (HR), stratified by post-operative time of blood collection (<1-month/ $\geq$ 1-month). Results: After a median follow-up of 9.5 years, 52.6% of patients had died. For iron biomarkers assessed <1-month post-surgery, higher compared to normal TS% was associated with shorter CSS (HR [95% CI] = 2.36 [1.25–4.46]), and higher iron levels with better OS (upper vs. median tertile: HR [95% CI] = 0.79 [0.65–0.97]). When assessed $\geq$ 1-month post-surgery, elevated ferritin was associated with poor CSS (high vs. normal: HR [95% CI] = 1.44 [1.10–1.87]), and low TS% with worse CSS (low vs. normal: HR [95% CI] = 1.60 [1.24–2.06]). Similar but weaker associations were observed for OS. Conclusion: Monitoring of serum ferritin and TS% beyond 1-month post-surgery may be relevant for risk stratification of patients with operable CRC. Future studies should validate our findings.

24COASNO41:

Title- Intention to have blood-based multi-cancer early detection (MCED) screening: a cross-sectional population-based survey in England

Ninian Schmeising-Barnes, Jo Waller & Laura A. V. Marlow

British Journal of Cancer . 2024 Oct;131(7):1202-1211.

doi: 10.1038/s41416-024-02822-4.

Abstract: Trials assessing the clinical utility of blood-based multi-cancer early detection (MCED) tests are underway. Understanding public attitudes towards MCED screening is essential if these tests are to be used. We aimed to quantify MCED screening intention and potential barriers and facilitators to uptake. Methods: Adults aged 50–77 ($n = 958$) completed an online survey. The primary outcome was intention to have MCED screening if offered. Psychological variables including barriers and facilitators were assessed. We used logistic regressions to explore associations between socio-demographics and psychological factors and intention. Results: 93.8% of participants said they would ‘definitely’ or ‘probably’ have MCED screening if offered. Intention was significantly associated with previous screening

participation and general cancer attitudes but not with socio-demographic factors. Participants were more likely to be intenders if they had higher health motivation, and perceived greater benefits of blood tests. Participants were less likely to be intenders if they perceived greater disadvantages of blood tests, more practical barriers, were more worried about the outcome and more concerned about a positive result. Conclusions and implications: MCED screening intention was high. The lack of socio-demographic variation suggests equitable interest in this type of screening; however, future research should consider how intention translates to uptake.

24COASNO42:

Title- DRD4 promotes chemo-resistance and cancer stem cell-like phenotypes by mediating the activation of the Akt/ β -catenin signaling axis in liver cancer

Zhengyan Yang, Pai Zhang, Yiwei Zhao, Ran Guo, Jinglin Hu, Qi Wang, Zhi Zhao, Handi Liu, Shuangyu Lv, Zhiguang Ren, Yanzhong Hu & Daxiang Cui

British Journal of Cancer . 2024 Oct;131(7):1212-1223.

doi: 10.1038/s41416-024-02811-7.

Abstract: Liver cancer stem cells (LCSCs) significantly impact chemo-resistance and recurrence in liver cancer. Dopamine receptor D4 (DRD4) is known to enhance the cancer stem cell (CSC) phenotype in glioblastoma and correlates with poor prognosis in some non-central nervous system tumors; however, its influence on LCSCs remains uncertain. **Methods:** To investigate the gene and protein expression profiles of DRD4 in LCSCs and non-LCSCs, we utilized transcriptome sequencing and Western blotting analysis. Bioinformatics analysis and immunohistochemistry were employed to assess the correlation between DRD4 expression levels and the pathological characteristics of liver cancer patients. The impact of DRD4 on LCSC phenotypes and signaling pathways were explored using pharmacological or gene-editing techniques. Additionally, the effect of DRD4 on the protein expression and intracellular localization of β -catenin were examined using Western blotting and immunofluorescence. **Results:** DRD4 expression is significantly elevated in LCSCs and correlates with short survival in liver cancer. The expression and activity of DRD4 are positive to resistance, self renewal and tumorigenicity in HCC. Mechanistically, DRD4 stabilizes β -catenin and promotes its entry into the nucleus via activating the PI3K/Akt/GSK-3 β pathway, thereby enhancing LCSC phenotypes. **Conclusions:** Inhibiting DRD4 expression and activation offers a promising targeted therapy for eradicating LCSCs and relieve chemo-resistance.

24COASNO43:

Title- IMPRESS: Improved methylation profiling using restriction enzymes and smMIP sequencing, combined with a new biomarker panel, creating a multi-cancer detection assay

Janah Vandenhoeck, Isabelle Neefs, Thomas Vanpoucke, Joe Ibrahim, Arvid Suls, Dieter Peeters,

DOI: <https://doi.org/10.1038/s41416-024-02809-1>

Abstract: Despite the worldwide progress in cancer diagnostics, more sensitive diagnostic biomarkers are needed. The methylome has been extensively investigated in the last decades, but a low-cost, bisulfite-free detection method for multiplex analysis is still lacking. Methods: We developed a methylation detection technique called IMPRESS, which combines methylation-sensitive restriction enzymes and single-molecule Molecular Inversion Probes. We used this technique for the development of a multi-cancer detection assay for eight of the most lethal cancer types worldwide. We selected 1791 CpG sites that can distinguish tumor from normal tissue based on DNA methylation. These sites were analysed with IMPRESS in 35 blood, 111 tumor and 114 normal samples. Finally, a classifier model was built. Results: We present the successful development of IMPRESS and validated it with ddPCR. The final classifier model discriminating tumor from normal samples was built with 358 CpG target sites and reached a sensitivity of 0.95 and a specificity of 0.91. Moreover, we provide data that highlight IMPRESS's potential for liquid biopsies. Conclusions: We successfully created an innovative DNA methylation detection technique. By combining this method with a new multi-cancer biomarker panel, we developed a sensitive and specific multi-cancer assay, with potential use in liquid biopsies.

24COASNO44:

Title- Clinical utility of *BRCA* and *ATM* mutation status in circulating tumour DNA for treatment selection in advanced pancreatic cancer

Kentaro Sudo, Yoshiaki Nakamura, Makoto Ueno, Masayuki Furukawa, Nobumasa Mizuno, British Journal of Cancer . 2024 Oct;131(7):1237-1245.

doi: <https://doi.org/10.1038/s41416-024-02834-0>.

Abstract: Identification of homologous recombination deficiency (HRD) remains a challenge in advanced pancreatic cancer (APC). We investigated the utility of circulating tumour DNA (ctDNA) profiling in the assessment of *BRCA1/2* and *ATM* mutation status and treatment selection in APC. Methods: We analysed clinical and ctDNA data of 702 patients with APC enrolled in GOZILA, a ctDNA profiling study using Guardant360. Results: Inactivating *BRCA1/2* and *ATM* mutations were detected in 4.8% (putative germline, 3.7%) and 4.4% (putative germline, 0.9%) of patients, respectively. Objective response (63.2% vs. 16.2%) and PFS (HR 0.55, 95% CI 0.32–0.93) on platinum-containing chemotherapy were significantly better in patients with putative germline *BRCA1/2* (g*BRCA*) mutation than those without. In contrast, putative g*BRCA* mutation had no impact on the efficacy of gemcitabine plus nab-paclitaxel. In 2 patients treated with platinum-containing therapy, putative *BRCA2* reversion mutations were detected. Three of seven patients with somatic *BRCA* mutations responded to platinum-containing therapy, while only one of four with putative germline *ATM* mutations did. One-third of somatic *ATM* mutations were in genomic loci associated with clonal haematopoiesis. Conclusion: Comprehensive ctDNA profiling provides clinically relevant information regarding HRD status. It can be a practical, convenient option for HRD screening in APC.

24COASNO45:

Title- Inflammasome activation in patients with Kaposi sarcoma herpesvirus–associated diseases,

Silvia Lucena Lage, Ramya Ramaswami, Joseph M. Rocco, Adam Rupert, David A. Davis, Kathryn Lurain, Maura Manion, Denise Whitby, Robert Yarchoan, Irini Sereti, Blood, Volume 144, Issue 14, 2024, Pages 1496-1507, <https://doi.org/10.1182/blood.2024024144>.

Abstract: Kaposi sarcoma herpesvirus (KSHV)–associated diseases include Kaposi sarcoma (KS), primary effusion lymphoma (PEL), KSHV-associated multicentric Castleman disease (MCD), and KS inflammatory cytokine syndrome (KICS). PEL, MCD, and KICS are associated with elevated circulating inflammatory cytokines. However, activation of the inflammasome, which generates interleukin-1 β (IL-1 β) and IL-18 via active caspase-1/4/5, has not been evaluated in patients with KSHV-associated diseases (KADs). Herein we report that patients with HIV and ≥ 1 KAD present with higher plasma levels of IL-18 and increased caspase-1/4/5 activity in circulating monocytes compared with HIV-negative healthy volunteers (HVs) or people with HIV (PWH) without KAD. Within KAD subtypes, KICS and MCD shared enhanced caspase-1/4/5 activity and IL-18 production compared with HVs and PWH, whereas patients with PEL showed remarkably high levels of inflammasome complex formation (known as apoptosis–associated speck-like protein containing a caspase recruitment domain). Moreover, caspase-1/4/5 activity and IL-18 plasma levels correlated with KSHV viral load, indicating KSHV-driven inflammasome activation in KAD. Accordingly, factors released by cells latently infected with KSHV triggered inflammasome activation and cytokine production in bystander monocytes in vitro. Finally, both supervised and unsupervised analyses with inflammasome measurements and other inflammatory biomarkers demonstrate a unique inflammatory profile in patients with PEL, MCD, and KICS as compared with KS. Our data indicate that detrimental inflammation in patients with KAD is at least partially driven by KSHV-induced inflammasome activation in monocytes, thus offering novel approaches to diagnose and treat these complex disorders. These trials were registered at www.ClinicalTrials.gov as #NCT01419561, NCT00092222, NCT00006518, and NCT02147405.

24COASNO46:

Title- Critical role of tripartite fusion and LBD truncation in certain RARA- and all RARG-related atypical APL,

Xiaosu Zhou, Xue Chen, Jiaqi Chen, Lijun Wen, Zhanglin Zhang, Ya-Zhen Qin, Panxiang Cao, ...

Blood, Volume 144, Issue 14, 2024, Pages 1471-1485
<https://doi.org/10.1182/blood.2024023883>

Abstract: Atypical acute promyelocytic leukemia (aAPL) presents a complex landscape of retinoic acid receptor (RAR) fusion genes beyond the well-known PML::RARA fusion. Among these, 31 individually rare RARA and RARG fusion genes have been documented, often reported in the canonical X::RAR bipartite fusion form. Intriguingly, some artificially

mimicked bipartite X::RAR fusions respond well to all-trans retinoic acid (ATRA) in vitro, contrasting with the ATRA resistance observed in patients. To unravel the underlying mechanisms, we conducted a comprehensive molecular investigation into the fusion transcripts in 27 RARA fusion gene-positive aAPL (RARA-aAPL) and 21 RARG-aAPL cases. Our analysis revealed an unexpected novel form of X::RAR::X- or X::RAR::Y-type tripartite fusions in certain RARA-aAPL and all RARG-aAPL cases, with shared features and notable differences between these 2 disease subgroups. In RARA-aAPL cases, the occurrence of RARA 3' splices was associated with their 5' fusion partner genes, mapping across the coding region of helix 11_12 (H11_12) within the ligand-binding domain (LBD), resulting in LBD-H12 or H11_12 truncation. In RARG-aAPL cases, RARG 3' splices were consistently localized to the terminus of exon 9, leading to LBD-H11_12 truncation. Significant differences were also observed between RARA and RARG 5' splice patterns. Our analysis also revealed extensive involvement of transposable elements in constructing RARA and RARG 3' fusions, suggesting transposition mechanisms for fusion gene ontogeny. Both protein structural analysis and experimental results highlighted the pivotal role of LBD-H11_12/H12 truncation in driving ATRA unresponsiveness and leukemogenesis in tripartite fusion-positive aAPL, through a protein allosteric dysfunction mechanism.

24COASNO47:

Title- Management of immune thrombotic thrombocytopenic purpura without therapeutic plasma exchange,

Lucas Kühne, Paul Knöbl, Kathrin Eller, Johannes Thaler, Wolfgang R. Sperr, Karoline Gleixner, Thomas Osterholt, Jessica Kaufeld, Jan Menne, Veronika Buxhofer-Ausch, Anja Mühlfeld, Evelyn Seelow, Adrian Schreiber, Polina Todorova, Sadrija Cukoski, Wolfram J. Jabs, Fedai Özcan, Anja Gäckler, Kristina Schönfelder, Felix S. Seibert, ...

Blood, Volume 144, Issue 14, 2024, Pages 1486-1495

<https://doi.org/10.1182/blood.2023023780>.

Abstract: Immune thrombotic thrombocytopenic purpura (iTTP) is a rare, life-threatening autoimmune disorder caused by a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency. Caplacizumab, an anti-von Willebrand factor nanobody, is approved for iTTP treatment, reducing the need for therapeutic plasma exchange (TPE) and improving platelet count recovery and survival. We conducted a retrospective study on 42 acute iTTP cases in Austria and Germany, treated with a modified regimen aimed at avoiding TPE if platelet count increased after the first caplacizumab dose. Baseline characteristics and patient outcomes were compared with a control group of 59 patients with iTTP receiving frontline treatment with TPE, caplacizumab, and immunosuppression. The main outcome was the time to platelet count normalization. Secondary outcomes included clinical response, exacerbation, refractory iTTP, iTTP-related deaths, and the time to platelet count doubling. The median time to platelet count normalization was similar between the 2 cohorts (3 and 4 days; $P = .31$). There were no significant differences in clinical response, exacerbations, refractoriness, iTTP-related deaths, or time to platelet count doubling, reflecting the short-term treatment response. Four patients did not respond to the first caplacizumab dose, and TPE was subsequently initiated.

Cytomegalovirus infection, HIV/hepatitis B virus coinfection, an ovarian teratoma with associated antiplatelet antibodies, and multiple platelet transfusions before the correct diagnosis may have impeded the immediate treatment response in these patients. In conclusion, caplacizumab and immunosuppression alone, without TPE, rapidly controlled thrombotic microangiopathy and achieved a sustained clinical response in iTTP. Our study provides a basis for TPE-free iTTP management in experienced centers via shared decision-making between patients and treating physicians.

24COASNO48:

Title- RBCs regulate platelet function and hemostasis under shear conditions through biophysical and biochemical means,

Debbie Jiang, Katie L. Houck, Lydia Murdiyarso, Harrison Higgins, Nicole Rhoads, Sophia K. Romero, Rosemary Kozar, Angelo Nascimbene, Terry B. Gernsheimer, Zyrina Alura C. Sanchez, Anand K. Ramasubramanian, Rehemad Adili, Jing-fei Dong,

Blood, Volume 144, Issue 14, 2024, Pages 1521-1531

<https://doi.org/10.1182/blood.2024023887>.

Abstract: Abstract

Red blood cells (RBCs) have been hypothesized to support hemostasis by facilitating platelet margination and releasing platelet-activating factors such as adenosine 5'-diphosphate (ADP). Significant knowledge gaps remain regarding how RBCs influence platelet function, especially in (patho)physiologically relevant hemodynamic conditions. Here, we present results showing how RBCs affect platelet function and hemostasis in conditions of anemia, thrombocytopenia, and pancytopenia and how the biochemical and biophysical properties of RBCs regulate platelet function at the blood and vessel wall interface and in the fluid phase under flow conditions. We found that RBCs promoted platelet deposition to collagen under flow conditions in moderate ($50 \times 10^3/\mu\text{L}$) but not severe ($10 \times 10^3/\mu\text{L}$) thrombocytopenia in vitro. Reduction in hematocrit by 45% increased bleeding in mice with hemolytic anemia. In contrast, bleeding diathesis was observed in mice with a 90% but not with a 60% reduction in platelet counts. RBC transfusion improved hemostasis by enhancing fibrin clot formation at the site of vascular injury in mice with severe pancytopenia induced by total body irradiation. Altering membrane deformability changed the ability of RBCs to promote shear-induced platelet aggregation. RBC-derived ADP contributed to platelet activation and aggregation in vitro under pathologically high shear stresses, as observed in patients supported by left ventricular assist devices. These findings demonstrate that RBCs support platelet function and hemostasis through multiple mechanisms, both at the blood and vessel wall interface and in the fluidic phase of circulation.

24COASNO49:

Title- Hope for motherhood: pregnancy after allogeneic hematopoietic cell transplantation (a national multicenter study),

Katja Sockel, Annika Neu, Maren Goeckenjan, Markus Ditschkowski, Inken Hilgendorf, Nicolaus Kröger,

Blood, Volume 144, Issue 14, 2024, Pages 1532-1542

<https://doi.org/10.1182/blood.2024024342>.

Abstract: Improved long-term survival rates after allogeneic hematopoietic cell transplantation (alloHCT) make family planning for young adult cancer survivors an important topic. However, treatment-related infertility risk poses challenges. To assess pregnancy and birth rates in a contemporary cohort, we conducted a national multicenter study using data from the German Transplant Registry, focusing on adult women aged 18 to 40 years who underwent alloHCT between 2003 and 2018. Of 2654 women who underwent transplantation, 50 women experienced 74 pregnancies, occurring at a median of 4.7 years after transplant. Fifty-seven of these resulted in live births (77%). The annual first birth rate among HCT recipients was 0.45%, which is >6 times lower than in the general population. The probability of a live birth 10 years after HCT was 3.4%. Factors associated with an increased likelihood of pregnancy were younger age at alloHCT, nonmalignant transplant indications, no total body irradiation or a cumulative dose of <8 Gy, and nonmyeloablative/reduced-intensity conditioning. Notably, 72% of pregnancies occurred spontaneously, with assisted reproductive technologies used in the remaining cases. Preterm delivery and low birth weight were more common than in the general population. This study represents the largest data set reporting pregnancies in a cohort of adult female alloHCT recipients. Our findings underscore a meaningful chance of pregnancy in alloHCT recipients. Assisted reproductive technologies techniques are important and funding should be made available. However, the potential for spontaneous pregnancies should not be underestimated, and patients should be informed of the possibility of unexpected pregnancy despite reduced fertility. Further research is warranted to understand the impact of conditioning decisions on fertility preservation.

24COASNO50:

Title- KDM6A regulates immune response genes in multiple myeloma,

Daphné Dupéré-Richer, Alberto Riva, Benjamin G. Barwick, Sayantan Maji, Heidi Casellas Román,

Blood, Volume 144, Issue 14, 2024, Pages 1508-1520

<https://doi.org/10.1182/blood.2024024518>.

Abstract: The histone H3 at lysine 27 (H3K27) demethylase lysine demethylase 6A (KDM6A) is a tumor suppressor in multiple cancers, including multiple myeloma (MM). We created isogenic MM cells disrupted for KDM6A and tagged the endogenous protein to facilitate genome-wide studies. KDM6A binds genes associated with immune recognition and cytokine signaling. Most importantly, KDM6A binds and activates NLRC5 and CIITA, which encode regulators of major histocompatibility complex genes. Patient data indicate that NLRC5 and CIITA are downregulated in MM with low KDM6A expression. Chromatin analysis shows that KDM6A binds poised and active enhancers and KDM6A loss led to decreased H3K27ac at enhancers, increased H3K27me3 levels in body of genes bound by KDM6A, and decreased gene expression. Reestablishing histone acetylation with an HDAC3 inhibitor leads to upregulation of major histocompatibility complex expression, offering a strategy to restore immunogenicity of KDM6A-deficient tumors. Loss of Kdm6a in Kirsten

rat sarcoma virus (K-RAS)-transformed murine fibroblasts led to increased growth in vivo associated with decreased T-cell infiltration.

24COASNO51:

Title- NGS-based stratification refines the risk stratification in T-ALL and identifies a very-high-risk subgroup of patients,

Mathieu Simonin, Loïc Vasseur, Etienne Lengliné, Ludovic Lhermitte, Aurélie Cabannes-Hamy, Marie Balsat, Aline Schmidt, ...

Blood (2024) 144 (15): 1570–1580.

<https://doi.org/10.1182/blood.2023023754>.

Abstract: We previously reported a better outcome in adult and pediatric T-cell acute lymphoblastic leukemia (T-ALL) harboring NOTCH1 and/or FBXW7 mutations without alterations of K-N-RAS and PTEN genes. Availability of high-throughput next-generation sequencing (NGS) strategies led us to refine the outcome prediction in T-ALL. Targeted whole-exome sequencing of 72 T-ALL-related oncogenes was performed in 198 adults with T-ALLs in first remission from the GRAALL-2003/2005 protocols and 242 pediatric patients with T-ALLs from the FRALLE2000T. This approach enabled the identification of, to our knowledge, the first NGS-based classifier in T-ALL, categorizing low-risk patients as those with N/F, PHF6, or EP300 mutations, excluding N-K-RAS, PI3K pathway (PTEN, PIK3CA, and PIK3R1), TP53, DNMT3A, IDH1/2, and IKZF1 alterations, with a 5-year cumulative incidence of relapse (CIR) estimated at 21%. Conversely, the remaining patients were classified as high risk, exhibiting a 5-year CIR estimated at 47%. We externally validated this stratification in the pediatric cohort. NGS-based classifier was highly prognostic independently of minimal residual disease (MRD) and white blood cell (WBC) counts, in both adult and pediatric cohorts. Integration of the NGS-based classifier into a comprehensive risk-stratification model, including WBC count at diagnosis and MRD at the end of induction, enabled the identification of an adverse-risk subgroup (25%) with a 5-year CIR estimated at 51%, and a favorable-risk group (32%) with a 5-year CIR estimated at 12%. NGS-based stratification combined with WBC and MRD sharpens the prognostic classification in T-ALL and identifies a new subgroup of patients who may benefit from innovative therapeutic approaches. The GRAALL-2003/2005 studies were registered at www.ClinicalTrials.gov as #NCT00222027 and #NCT00327678.

24COASNO52:

Title- Mitigation of checkpoint inhibitor–induced autoimmune hemolytic anemia through modulation of purinergic signaling,

Flavia Dei Zotti, Annie Qiu, Vivette D. D’Agati, Shwatina Jagnarine, Emmalene Kyritsis, Anabel Miller,

Blood (2024) 144 (15): 1581–1594.

<https://doi.org/10.1182/blood.2024024230>.

Abstract: Immune checkpoint inhibitors (ICPis) have revolutionized cancer immunotherapy but also can induce autoimmune hemolytic anemia (AIHA), a severe disease with high

mortality. However, the cellular and molecular mechanism(s) of AIHA secondary to ICPI therapy (ICPi-AIHA) are unclear, other than being initiated through decreased checkpoint inhibition. Herein, we report ICPI-AIHA in a novel mouse model that shows similar characteristics of known human ICPI-AIHA (eg, autoantibodies, hemolysis, and increased mortality). During ICPI-AIHA, there is the simultaneous reduction of 2 regulatory T-cell populations (FoxP3+ and Tr1 [type 1 regulatory cells]) and an increase in inflammatory T helper cell 17 (TH17). Moreover, a novel CD39+CD73–FoxP3–CD25– CD4+ T-cell subset (ie, CD39 single positive [CD39SP]) emerges, and early increases in CD39SP predict AIHA development; CD39 is an ectonuclease that breaks down adenosine triphosphate (ATP). Additionally, we found that boosting ATPase activity by injecting recombinant apyrase mitigates AIHA development and significant CD39SP reductions, both suggesting a functional role for CD39 and demonstrating a novel therapeutic approach. Importantly, CD39SP are detectable in multiple mouse models developing AIHA and in patients with AIHA, demonstrating applicability to idiopathic and secondary AIHA. Highlighting broader autoimmunity relevance, ICPI-treated NZB mice experienced accelerated onset and severity of lupus, including AIHA. Moreover, ICPI treatment of healthy B6 animals led to detectable CD39SP and development of autoantibodies against multiple autoantigens including those on red blood cells and platelets. Together, our findings provide further insight into the cellular and molecular mechanisms of ICPI-AIHA, leading to novel diagnostic and therapeutic approaches with translational potential for use in humans being treated with ICPI.

24COASNO53:

Title- Unbalanced MYC break-apart FISH patterns indicate the presence of a MYC rearrangement in HGBCL-DH-BCL2,

Brett Collinge, Susana Ben-Neriah, Laura K. Hilton, Waleed Alduaij, Tracy Tucker, Graham W. Slack,

Blood (2024) 144 (15): 1611–1616.

<https://doi.org/10.1182/blood.2024025603>.

Abstract: Fluorescence in situ hybridization (FISH) using break-apart probes is recommended for identifying high-grade B-cell lymphoma with MYC and BCL2 rearrangements (HGBCL-DH-BCL2). Unbalanced MYC break-apart patterns, in which the red or green signal is lost, are commonly reported as an equivocal result by clinical laboratories. In a cohort of 297 HGBCL-DH-BCL2, 13% of tumors had unbalanced MYC break-apart patterns with loss of red (LR; 2%) or loss of green (LG; 11%) signal. To determine the significance of these patterns, MYC rearrangements were characterized by sequencing in 130 HGBCL-DH-BCL2, including 3 LR and 14 LG tumors. A MYC rearrangement was identified for 71% of tumors with LR or LG patterns, with the majority involving immunoglobulin loci or other recurrent MYC rearrangement partners. The architecture of these rearrangements consistently preserved the rearranged MYC allele, with the MYC gene predicted to be on the derivative chromosome containing the signal that is still present in nearly all cases. MYC protein expression, MYC messenger RNA expression, and the proportion of tumors expressing the dark-zone signature was not significantly different

between balanced and unbalanced groups. These results support a recommendation that unbalanced MYC break-apart FISH patterns be reported as positive for MYC rearrangement in the context of diagnosing HGBCL-DH-BCL2.

24COASNO54:

Title- Molecular taxonomy of myelodysplastic syndromes and its clinical implications,

Elsa Bernard, Robert P. Hasserjian, Peter L. Greenberg, Juan E. Arango Ossa, Maria Creignou,

Blood (2024) 144 (15): 1617–1632.

<https://doi.org/10.1182/blood.2023023727>.

Abstract: Myelodysplastic syndromes (MDS) are clonal hematologic disorders characterized by morphologic abnormalities of myeloid cells and peripheral cytopenias. Although genetic abnormalities underlie the pathogenesis of these disorders and their heterogeneity, current classifications of MDS rely predominantly on morphology. We performed genomic profiling of 3233 patients with MDS or related disorders to delineate molecular subtypes and define their clinical implications. Gene mutations, copy-number alterations, and copy-neutral loss of heterozygosity were derived from targeted sequencing of a 152-gene panel, with abnormalities identified in 91%, 43%, and 11% of patients, respectively. We characterized 16 molecular groups, encompassing 86% of patients, using information from 21 genes, 6 cytogenetic events, and loss of heterozygosity at the TP53 and TET2 loci. Two residual groups defined by negative findings (molecularly not otherwise specified, absence of recurrent drivers) comprised 14% of patients. The groups varied in size from 0.5% to 14% of patients and were associated with distinct clinical phenotypes and outcomes. The median bone marrow (BM) blast percentage across groups ranged from 1.5% to 10%, and the median overall survival ranged from 0.9 to 8.2 years. We validated 5 well-characterized entities, added further evidence to support 3 previously reported subsets, and described 8 novel groups. The prognostic influence of BM blasts depended on the genetic subtypes. Within genetic subgroups, therapy-related MDS and myelodysplastic/myeloproliferative neoplasms had comparable clinical and outcome profiles to primary MDS. In conclusion, genetically-derived subgroups of MDS are clinically relevant and might inform future classification schemas and translational therapeutic research.

24COASNO55:

Title- Optimizing drug combinations for T-PLL: restoring DNA damage and P53-mediated apoptotic responses,

Jana von Jan, Sanna Timonen, Till Braun, Qu Jiang, Aleksandr Ianevski, Yayi Peng, Kathleen McConnell,

Blood (2024) 144 (15): 1595–1610.

<https://doi.org/10.1182/blood.2023022884>.

Abstract: T-prolymphocytic leukemia (T-PLL) is a mature T-cell neoplasm associated with marked chemotherapy resistance and continued poor clinical outcomes. Current treatments, that is, the CD52-antibody alemtuzumab, offer transient responses, with relapses being almost inevitable without consolidating allogeneic transplantation. Recent more detailed

concepts of T-PLL's pathobiology fostered the identification of actionable vulnerabilities: (1) altered epigenetics, (2) defective DNA damage responses, (3) aberrant cell-cycle regulation, and (4) deregulated prosurvival pathways, including T-cell receptor and JAK/STAT signaling. To further develop related preclinical therapeutic concepts, we studied inhibitors of histone deacetylases ([H]DACs), B-cell lymphoma 2 (BCL2), cyclin-dependent kinase (CDK), mouse double minute 2 (MDM2), and classical cytostatics, using (1) single-agent and combinatorial compound testing in 20 well-characterized and molecularly profiled primary T-PLL (validated by additional 42 cases) and (2) 2 independent murine models (syngeneic transplants and patient-derived xenografts). Overall, the most efficient/selective single agents and combinations (in vitro and in mice) included cladribine, romidepsin ([H]DAC), venetoclax (BCL2), and/or idasanutlin (MDM2). Cladribine sensitivity correlated with expression of its target RRM2. T-PLL cells revealed low overall apoptotic priming with heterogeneous dependencies on BCL2 proteins. In additional 38 T-cell leukemia/lymphoma lines, TP53 mutations were associated with resistance toward MDM2 inhibitors. P53 of T-PLL cells, predominantly in wild-type configuration, was amenable to MDM2 inhibition, which increased its MDM2-unbound fraction. This facilitated P53 activation and downstream signals (including enhanced accessibility of target-gene chromatin regions), in particular synergy with insults by cladribine. Our data emphasize the therapeutic potential of pharmacologic strategies to reinstate P53-mediated apoptotic responses. The identified efficacies and their synergies provide an informative background on compound and patient selection for trial designs in T-PLL.

24COASNO56:

Title- Use of HSC-targeted LNP to generate a mouse model of lethal α -thalassemia and treatment via lentiviral gene therapy,

Maxwell E. Chappell, Laura Breda, Lucas Tricoli, Amaliris Guerra, Danuta Jarocho, Carlo Castruccio Castracani,

Blood (2024) 144 (15): 1633–1645.

<https://doi.org/10.1182/blood.2023023349>.

Abstract: α -Thalassemia (AT) is one of the most commonly occurring inherited hematological diseases. However, few treatments are available, and allogeneic bone marrow transplantation is the only available therapeutic option for patients with severe AT. Research into AT has remained limited because of a lack of adult mouse models, with severe AT typically resulting in in utero lethality. By using a lipid nanoparticle (LNP) targeting the receptor CD117 and delivering a Cre messenger RNA (mRNACreLNPCD117), we were able to delete floxed α -globin genes at high efficiency in hematopoietic stem cells (HSC) ex vivo. These cells were then engrafted in the absence or presence of a novel α -globin-expressing lentiviral vector (ALS20 α I). Myeloablated mice infused with mRNACreLNPCD117-treated HSC showed a complete knock out (KO) of α -globin genes. They showed a phenotype characterized by the synthesis of hemoglobin H (HbH; also known as β -tetramers or β_4), aberrant erythropoiesis, and abnormal organ morphology, culminating in lethality ~8 weeks after engraftment. Mice infused with mRNACreLNPCD117-treated HSC with at least 1 copy

of ALS20 α I survived long term with normalization of erythropoiesis, decreased production of HbH, and amelioration of the abnormal organ morphology. Furthermore, we tested ALS20 α I in erythroid progenitors derived from α -globin-KO CD34⁺ cells and cells isolated from patients with both deletional and nondeletional HbH disease, demonstrating improvement in α -globin/ β -globin mRNA ratio and reduction in the formation of HbH by high-performance liquid chromatography. Our results demonstrate the broad applicability of LNP for disease modeling, characterization of a novel mouse model of severe AT, and the efficacy of ALS20 α I for treating AT.

24COASNO57:

Title- Targeting MEK induces myeloma-cell cytotoxicity and inhibits osteoclastogenesis.

Tai Y-T, Fulciniti M, Hideshima T, Song W, Leiba M, Li X-F, Rumizen M, Burger P, Morrison A,

Blood (2024) 144 (15): 1648.

<https://doi.org/10.1182/blood.2024026818>.

Abstract: This article has been retracted; please see Elsevier's Article Correction, Retraction and Removal Policy (Article withdrawal | Elsevier policy). This article has been retracted at the request of the Editors and authors. Within the paper, image issues were identified in Figures 1, 4, and 6. Images within these figures show duplication, modification, or unmarked splices. The authors state that these figures cannot be used to support the conclusions of the paper. Authors Tai, Fulciniti, Song, Li, Morrison, Chauhan, Tassone, Ghobrial, and Anderson approve the retraction. Authors Hideshima, Leiba, Rumizen, Burger, Podar, Richardson, and Munshi did not respond.

24COASNO58:

Title- Soluble glycoprotein VI predicts abdominal aortic aneurysm growth rate and is a novel therapeutic target,

Tyler W. Benson, Mindy M. Pike, Anthony Spuzzillo, Sarah M. Hicks, Sidra Ali, Michael Pham,

Blood (2024) 144 (16): 1663–1678.

<https://doi.org/10.1182/blood.2023021655>.

Abstract: A common feature in patients with abdominal aortic aneurysms (AAAs) is the formation of a nonocclusive intraluminal thrombus (ILT) in regions of aortic dilation. Platelets are known to maintain hemostasis and propagate thrombosis through several redundant activation mechanisms, yet the role of platelet activation in the pathogenesis of AAA-associated ILT is still poorly understood. Thus, we sought to investigate how platelet activation affects the pathogenesis of AAA. Using RNA sequencing, we identified that the platelet-associated transcripts are significantly enriched in the ILT compared with the adjacent aneurysm wall and healthy control aortas. We found that the platelet-specific receptor glycoprotein VI (GPVI) is among the top enriched genes in AAA ILT and is increased on the platelet surface of patients with AAAs. Examination of a specific indicator of platelet activity, soluble GPVI (sGPVI), in 2 independent cohorts of patients with AAAs is

highly predictive of an AAA diagnosis and associates more strongly with aneurysm growth rate than D-dimer in humans. Finally, intervention with the anti-GPVI antibody (JAQ1) in mice with established aneurysms blunted the progression of AAA in 2 independent mouse models. In conclusion, we show that the levels of sGPVI in humans can predict a diagnosis of AAA and AAA growth rate, which may be critical in the identification of high-risk patients. We also identify GPVI as a novel platelet-specific AAA therapeutic target, with minimal risk of adverse bleeding complications, for which none currently exists.

24COASNO59:

Title- Influence of TP53 gene mutations and their allelic status in myelodysplastic syndromes with isolated 5q deletion,

Maria Julia Montoro, Laura Palomo, Claudia Haferlach, Pamela Acha, Onyee Chan, Víctor Navarro,

Blood (2024) 144 (16): 1722–1731.

<https://doi.org/10.1182/blood.2024023840>.

Abstract: Mutations in the TP53 gene, particularly multihit alterations, have been associated with unfavorable clinical features and prognosis in patients diagnosed with myelodysplastic syndrome (MDS). Despite this, the role of TP53 gene aberrations in MDS with isolated deletion of chromosome 5 [MDS-del(5q)] remains unclear. This study aimed to assess the impact of TP53 gene mutations and their allelic state in patients with MDS-del(5q). To that end, a comprehensive analysis of TP53 abnormalities, examining both TP53 mutations and allelic imbalances, in 682 patients diagnosed with MDS-del(5q) was conducted. Twenty-four percent of TP53-mutated patients exhibited multihit alterations, whereas the remaining patients displayed monoallelic mutations. TP53-multihit alterations were predictive of an increased risk of leukemic transformation. The impact of monoallelic alterations was dependent on the variant allele frequency (VAF); patients with TP53-monoallelic mutations and VAF <20% exhibited behavior similar to TP53 wild type, and those with TP53-monoallelic mutations and VAF $\geq$ 20% presented outcomes equivalent to TP53-multihit patients. This study underscores the importance of considering TP53 allelic state and VAF in the risk stratification and treatment decision-making process for patients with MDS-del(5q).

24COASNO60:

Title- Inhibition of RHOA activity preserves the survival and hemostasis function of long-term cold-stored platelets,

Shailaja Hegde, Huzoor Akbar, Ashley M. Wellendorf, Shawnagay Nestheide, James F. Johnson,

Blood (2024) 144 (16): 1732–1746.

<https://doi.org/10.1182/blood.2023021453>.

Abstract: Patients with thrombocytopenia require platelet transfusion to prevent and stop hemorrhage. Cold storage of platelets results in complex molecular lesions, including changes in membrane microdomains that are recognized by host macrophages and hepatocyte counter-receptors, resulting in phagocytosis and clearance upon transfusion. For this reason, platelets are stored at room temperature, a method that confers increased risk of bacterial

contamination. By applying signaling analysis and genetic and pharmacological approaches, we identified that cold-induced activation of RAS homolog family, member A (RHOA) GTPase causes the major hallmarks of platelet cold storage lesions. RHOA deficiency renders murine platelets insensitive to cold storage–induced damage, and pharmacological inhibition by a RHOA activation inhibitor, R-G04, can prevent the cold storage–induced lesions. RHOA inhibition prevents myosin activation and clathrin-independent formation and internalization of lipid rafts enriched in active glycosyltransferases as well as abnormal distribution of GPIb α . RHOA inhibition further prevents the metabolic reprogramming of cold storage–induced lesions and allows the maintenance of glycolytic flux and mitochondria-dependent respiration. Importantly, human platelets transfused in mice after cold storage, in the presence of R-G04 or its more potent enantiomer S-G04, can circulate in vivo at similar levels as room temperature–stored platelets while retaining their hemostatic activity in vivo, as assessed by bleeding time correction in aspirin-treated mice. Our studies provide a mechanism-based translational approach to prevent cold storage–induced damage, which is useful for human platelet transfusion in patients with thrombocytopenia.

24COASNO61:

Title- A phase 1 clinical trial of NKTR-255 with CD19-22 CAR T-cell therapy for refractory B-cell acute lymphoblastic leukemia,

Hrishikesh Srinagesh, Clayton Jackson, Parveen Shiraz, Nikeshan Jeyakumar, Mark Hamilton, Emily Egeler,

Blood (2024) 144 (16): 1689–1698.

<https://doi.org/10.1182/blood.2024024952>

Abstract: Although chimeric antigen receptor (CAR) T-cell (CAR-T) therapy has revolutionized the treatment of B-cell malignancies, many patients relapse and therefore strategies to improve antitumor immunity are needed. We previously designed a novel autologous bispecific CAR targeting CD19 and CD22 (CAR19-22), which was well tolerated and associated with high response rates but relapse was common. Interleukin-15 (IL15) induces proliferation of diverse immune cells and can augment lymphocyte trafficking. Here, we report the results of a phase 1 clinical trial of the first combination of a novel recombinant polymer-conjugated IL15 receptor agonist (NKTR-255), with CAR19-22, in adults with relapsed/refractory B-cell acute lymphoblastic leukemia. Eleven patients were enrolled, 9 of whom successfully received CAR19-22 followed by NKTR-255. There were no dose-limiting toxicities, with transient fever and myelosuppression as the most common possibly related toxicities. We observed favorable efficacy with 8 of 9 patients (89%) achieving measurable residual disease–negative remission. At 12 months, progression-free survival for NKTR-255 was double that of historical controls (67% vs 38%). We performed correlative analyses to investigate the effects of IL15 receptor agonism. Cytokine profiling showed significant increases in IL15 and the chemokines CXCL9 and CXCL10. The increase in chemokines was associated with decreases in absolute lymphocyte counts and CD8⁺ CAR T cells in the blood and 10-fold increases in cerebrospinal fluid CAR-T cells, suggesting lymphocyte trafficking to tissue. Combining NKTR-255 with CAR19-22 was safe, feasible,

and associated with high rates of durable responses. This trial was registered at www.clinicaltrials.gov as #NCT03233854.

24COASNO62:

Title- Identifying disease-modifying potential in myelofibrosis clinical trials,

David M. Ross, Steven W. Lane, Claire N. Harrison,

Blood (2024) 144 (16): 1679–1688.

<https://doi.org/10.1182/blood.2024024220>.

Abstract: The ultimate goal of bringing most new drugs to the clinic in hematologic malignancy is to improve overall survival. However, the use of surrogate end points for overall survival is increasingly considered standard practice, because a well validated surrogate end point can accelerate the outcome assessment and facilitate better clinical trial design. Established examples include monitoring minimal residual disease in chronic myeloid leukemia and acute leukemia, and metabolic response assessment in lymphoma. However, what happens when a clinical trial end point that is not a good surrogate for disease-modifying potential becomes ingrained as an expected outcome, and new agents are expected or required to meet this end point to demonstrate “efficacy”? Janus kinase (JAK) inhibitors for myelofibrosis (MF) have a specific impact on reducing symptom burden and splenomegaly but limited impact on the natural history of the disease. Since the introduction of ruxolitinib more than a decade ago there has been modest incremental success in clinical trials for MF but no major leap forward to alter the natural history of the disease. We argue that the clinical development of novel agents for MF will be accelerated by moving away from using end points that are specifically tailored to measure the beneficial effects of JAK inhibitors. We propose that specific measures of relevant disease burden, such as reduction in mutation burden as determined by molecular end points, should replace established end points. Careful reanalysis of existing data and trials in progress is needed to identify the most useful surrogate end points for future MF trials and better serve patient interest.

24COASNO63:

Title- Interleukin-1 blockade in patients with Wiskott-Aldrich syndrome: a retrospective multinational case series,

Samuele Naviglio, Maria Pia Cicalese, Elizabeth Rivers, Francesca Ferrua, Carmem Bonfim, Sabina Cenciarelli, Kai-Ning Cheong, Maura Faraci, Stefano Giardino, Sujal Ghosh, ...

Blood (2024) 144 (16): 1699–1704.

<https://doi.org/10.1182/blood.2024024524>.

Abstract: Up to 70% of patients with Wiskott-Aldrich syndrome (WAS) develop autoimmune and inflammatory manifestations. Dysregulation of interleukin 1 (IL-1) may be involved in their pathogenesis, yet there is little evidence on treatment with anti-IL-1 agents in these patients. We conducted a multicenter retrospective analysis of 9 patients with WAS treated with anti-IL-1 agents (anakinra or canakinumab). All patients had prominent inflammatory manifestations, including systemic, cutaneous, articular, and intestinal symptoms; 3 patients presented with a severe systemic inflammatory syndrome since the first months of life. Corticosteroid therapy was associated with partial or no response, whereas

treatment with anakinra or canakinumab resulted in prompt, often dramatic, responses in all patients, allowing bridging to gene therapy (4 patients) or hematopoietic stem cell transplantation (HSCT; 5 patients). Treatment was overall well tolerated. Low donor myeloid chimerism developed in 4 patients after HSCT and was associated with the appearance or the recurrence of inflammatory manifestations. A second HSCT was performed in 2 patients, achieving full-donor chimerism and resolution of inflammatory manifestation, whereas the other 2 patients were treated with prolonged therapy with anti-IL-1 agents. Our experience demonstrates that some inflammatory manifestations of WAS are dependent on IL-1 and respond well to its pharmacologic blockade.

24COASNO64:

Title- An unbiased lncRNA dropout CRISPR-Cas9 screen reveals RP11-350G8.5 as a novel therapeutic target for multiple myeloma,

Katia Grillone, Serena Ascrizzi, Paolo Cremaschi, Jussara Amato, Nicoletta Polerà, Ottavio Croci,

Blood (2024) 144 (16): 1705–1721.

<https://doi.org/10.1182/blood.2023021991>

Abstract: Multiple myeloma (MM) is an incurable malignancy characterized by altered expression of coding and noncoding genes promoting tumor growth and drug resistance. Although the crucial role of long noncoding RNAs (lncRNAs) in MM is clearly established, the function of the noncoding RNAome, which might allow the design of novel therapeutics, is largely unknown. We performed an unbiased CRISPR-Cas9 loss-of-function screen of 671 lncRNAs in MM cells and their bortezomib (BZB)–resistant derivative. To rank functionally and clinically relevant candidates, we designed and used a bioinformatic prioritization pipeline combining functional data from cellular screens with prognostic and transcriptional data from patients with MM. With this approach, we unveiled and prioritized 8 onco-lncRNAs essential for MM cell fitness, associated with high expression and poor prognosis in patients with MM. The previously uncharacterized RP11-350G8.5 emerged as the most promising target, irrespective of BZB resistance. We (1) demonstrated the anti-tumoral effect obtained by RP11-350G8.5 inhibition in vitro and in vivo; (2) highlighted a modulation of the unfolded protein response and the induction of immunogenic cell death triggered by the RP11-350G8.5 knockout, via RNA sequencing and molecular studies; (3) characterized its cytoplasmic homing through RNA fluorescence in situ hybridization; and (4) predicted its 2-dimensional structure and identified 2 G-quadruplex and 3 hairpin-forming regions by biophysical assays, including thioflavin T, ¹H nuclear magnetic resonance, and circular dichroism, to pave the way to the development of novel targeted therapeutics. Overall, we provided innovative insights about unexplored lncRNAs in MM and identified RP11-350G8.5 as an oncogenic target for treatment-naïve and BZB-resistant patients with MM.

24COASNO65:

Title- Influence of TP53 gene mutations and their allelic status in myelodysplastic syndromes with isolated 5q deletion,

Maria Julia Montoro, Laura Palomo, Claudia Haferlach, Pamela Acha, Onyee Chan, Víctor Navarro,...

Blood (2024) 144 (16): 1722–1731.

<https://doi.org/10.1182/blood.2024023840>.

Abstract: Mutations in the TP53 gene, particularly multihit alterations, have been associated with unfavorable clinical features and prognosis in patients diagnosed with myelodysplastic syndrome (MDS). Despite this, the role of TP53 gene aberrations in MDS with isolated deletion of chromosome 5 [MDS-del(5q)] remains unclear. This study aimed to assess the impact of TP53 gene mutations and their allelic state in patients with MDS-del(5q). To that end, a comprehensive analysis of TP53 abnormalities, examining both TP53 mutations and allelic imbalances, in 682 patients diagnosed with MDS-del(5q) was conducted. Twenty-four percent of TP53-mutated patients exhibited multihit alterations, whereas the remaining patients displayed monoallelic mutations. TP53-multihit alterations were predictive of an increased risk of leukemic transformation. The impact of monoallelic alterations was dependent on the variant allele frequency (VAF); patients with TP53-monoallelic mutations and VAF <20% exhibited behavior similar to TP53 wild type, and those with TP53-monoallelic mutations and VAF $\geq$ 20% presented outcomes equivalent to TP53-multihit patients. This study underscores the importance of considering TP53 allelic state and VAF in the risk stratification and treatment decision-making process for patients with MDS-del(5q).

24COASNO66:

Title- Inhibition of RHOA activity preserves the survival and hemostasis function of long-term cold-stored platelets,

Shailaja Hegde, Huzoor Akbar, Ashley M. Wellendorf, Shawnagay Nestheide, James F. Johnson,

Blood (2024) 144 (16): 1732–1746.

<https://doi.org/10.1182/blood.2023021453>.

Abstract: Patients with thrombocytopenia require platelet transfusion to prevent and stop hemorrhage. Cold storage of platelets results in complex molecular lesions, including changes in membrane microdomains that are recognized by host macrophages and hepatocyte counter-receptors, resulting in phagocytosis and clearance upon transfusion. For this reason, platelets are stored at room temperature, a method that confers increased risk of bacterial contamination. By applying signaling analysis and genetic and pharmacological approaches, we identified that cold-induced activation of RAS homolog family, member A (RHOA) GTPase causes the major hallmarks of platelet cold storage lesions. RHOA deficiency renders murine platelets insensitive to cold storage–induced damage, and pharmacological inhibition by a RHOA activation inhibitor, R-G04, can prevent the cold storage–induced lesions. RHOA inhibition prevents myosin activation and clathrin-independent formation and internalization of lipid rafts enriched in active glycosyltransferases as well as abnormal distribution of GPIIb α . RHOA inhibition further prevents the metabolic reprogramming of cold storage–induced lesions and allows the maintenance of glycolytic flux and mitochondria-dependent respiration. Importantly, human platelets transfused in mice after

cold storage, in the presence of R-G04 or its more potent enantiomer S-G04, can circulate in vivo at similar levels as room temperature–stored platelets while retaining their hemostatic activity in vivo, as assessed by bleeding time correction in aspirin-treated mice. Our studies provide a mechanism-based translational approach to prevent cold storage–induced damage, which is useful for human platelet transfusion in patients with thrombocytopenia.

24COASNO67:

Title- Personalized Composite Dosimetric Score-Based Machine Learning Model of Severe Radiation-Induced Lymphopenia Among Patients With Esophageal Cancer,

Yan Chu, Cong Zhu, Brian P. Hobbs, Yiqing Chen, Peter S.N. van Rossum, Clemens Grassberger,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1172-1180,

<https://doi.org/10.1016/j.ijrobp.2024.05.018>.

Abstract: Purpose: Radiation-induced lymphopenia (RIL) is common among patients undergoing radiation therapy (RT). Severe RIL has been linked to adverse outcomes. The severity and risk of RIL can be predicted from baseline clinical characteristics and dosimetric parameters. However, dosimetric parameters, e.g. dose-volume (DV) indices, are highly correlated with one another and are only weakly associated with RIL. Here we introduce the novel concept of “composite dosimetric score” (CDS) as the index that condenses the dose distribution in immune tissues of interest to study the dosimetric dependence of RIL. We derived an improved multivariate classification scheme for risk of grade 4 RIL (G4RIL), based on this novel RT dosimetric feature, for patients receiving chemo RT for esophageal cancer. Methods and Materials DV indices were extracted for 734 patients who received chemo RT for biopsy-proven esophageal cancer. Nonnegative matrix factorization was used to project the DV indices of lung, heart, and spleen into a single CDS; XGBoost was employed to explore significant interactions among predictors; and logistic regression was applied to combine the resultant CDS with baseline clinical factors and interaction terms to facilitate individualized prediction of immunotoxicity. Five-fold cross-validation was applied to evaluate the model performance. Results The CDS for selected immune organs at risk (ie, heart, lung, and spleen) (OR 1.791; 95 CI [1.350, 2.377]) was a statistically significant risk determinant for G4RIL. Pearson correlation coefficients for CDS versus G4RIL risk for individual immune organs at risk were greater than any single DV index. Personalized prediction of G4RIL based on CDS and 4 clinical risk factors yielded an area under the curve value of 0.78. Interaction between age and CDS revealed that G4RIL risk increased more sharply with increasing CDS for patients aged ≥ 65 years. Risk of immunotoxicity for patients undergoing chemo RT for esophageal cancer can be predicted by CDS. The CDS concept can be extended to immunotoxicity in other cancer types and in dose-response models currently based on DV indices. Personalized treatment planning should leverage composite dosimetric scoring methods rather than using individual or subsets of DV indices.

24COASNO68:

Title- A Novel Dose Rate Optimization Method to Maximize Ultrahigh-Dose-Rate Coverage of Critical Organs at Risk Without Compromising Dosimetry Metrics in Proton Pencil Beam Scanning FLASH Radiation Therapy,

Xingyi Zhao, Sheng Huang, Haibo Lin, J. Isabelle Choi, Kun Zhu, Charles B. Simone, Xueqing Yan, Minglei Kang,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1181-1191,

<https://doi.org/10.1016/j.ijrobp.2024.06.002>.

Abstract: This study aimed to investigate a dose rate optimization framework based on the spot-scanning patterns to improve ultrahigh-dose-rate coverage of critical organs at risk (OARs) for proton pencil beam scanning (PBS) FLASH radiation therapy (ultrahigh dose-rate (often referred to as >40 Gy per second) delivery) and present implementation of a genetic algorithm (GA) method for spot sequence optimization to achieve PBS FLASH dose rate optimization under relatively low nozzle beam currents. First, a multifield FLASH plan was developed to meet all the dosimetric goals and optimal FLASH dose rate coverage by considering the deliverable minimum monitor unit constraint. Then, a GA method was implemented into the in-house treatment platform to maximize the dose rate by exploring the best spot delivery sequence. A phantom study was performed to evaluate the effectiveness of the dose rate optimization. Then, 10 consecutive plans for patients with lung cancer previously treated using PBS intensity-modulated proton therapy were optimized using 45 GyRBE in 3 fractions for both transmission and Bragg peak FLASH radiation therapy for further validation. The spot delivery sequence of each treatment field was optimized using this GA. The ultrahigh-dose-rate-volume histogram and dose rate coverage V40GyRBE/s were investigated to assess the efficacy of dose rate optimization quantitatively. Using a relatively low monitor unit/spot of 150, corresponding to a nozzle beam current of 65 nA, the FLASH dose rate ratio V40GyRBE/s of the OAR contour of the core was increased from 0% to ~60% in the phantom study. In the patients with lung cancer, the ultrahigh-dose-rate coverage V40GyRBE/s was improved from 15.2%, 15.5%, 17.6%, and 16.0% before the delivery sequence optimization to 31.8%, 43.5%, 47.6%, and 30.5% after delivery sequence optimization in the lungs-GTV (gross tumor volume), spinal cord, esophagus, and heart (for all, $P < .001$). When the beam current increased to 130 nA, V40GyRBE/s was improved from 45.1%, 47.1%, 51.2%, and 51.4% to 65.3%, 83.5%, 88.1%, and 69.4% ($P < .05$). The averaged V40GyRBE/s for the target and OARs increased from 12.9% to 41.6% and 46.3% to 77.5% for 65 and 130 nA, respectively, showing significant improvements based on a clinical proton system. After optimizing the dose rate for the Bragg peak FLASH technique with a beam current of 340 nA, the V40GyRBE/s values for the lung GTV, spinal cord, esophagus, and heart were increased by 8.9%, 15.8%, 22%, and 20.8%, respectively. An optimal plan quality can be maintained as the spot delivery sequence optimization is a separate independent process after the plan optimization. Both the phantom and patient results demonstrated that novel spot delivery sequence optimization can effectively improve

the ultrahigh-dose-rate coverage for critical OARs, which can potentially be applied in clinical practice for better OARs-sparing efficacy.

24COASNO69:

Title- Late Urinary Toxicity After Extreme or Moderate Hypofractionated Prostate Radiation Therapy in Patients With Prior Transurethral Resection of Prostate,

Maneesh Singh, Priyamvada Maitre, Anuradha Krishnan, Ketaki Adsul, Sarath Mini Sreekumar,

International Journal of Radiation Oncology*Biophysics, Volume 120, Issue 4, 2024, Pages 1011-1020,

<https://doi.org/10.1016/j.ijrobp.2024.06.003>.

Abstract: To study the late urinary toxicity in patients with prostate cancer with prior transurethral resection of prostate (TURP) and treated with hypofractionated prostate radiation therapy.

Patients diagnosed with prostate cancer, with a prior TURP, and treated with moderate or extreme hypofractionated intensity-modulated radiation therapy (moderate hypofractionated radiation therapy [MHRT], stereotactic body radiation therapy [SBRT]), were included in this study. Severity and duration of urinary symptoms observed during serial follow-up after at least 3 months from radiation therapy were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 using information from a prospectively maintained institutional database. Impact of hypofractionation and other potential contributory factors on cumulative grade 2+ late urinary toxicity was analyzed with univariable and multivariable binary logistic regression. A total of 203 eligible patients were included (MHRT = 114, 64-68 Gy/25#; SBRT = 89, 35-37.5 Gy/5#). Median time from TURP to radiation therapy was 10 months (IQR, 7-16 months), similar for MHRT and SBRT. Overall, mean cavity volume was 1.17 cc (IQR, 0.5-1.35 cc), whereas in MHRT and SBRT groups it was 1.03 cc (IQR, 0.4-1.15 cc) and 1.27 cc (IQR, 0.5-1.4 cc), respectively. At a median follow-up of 37 months, cumulative grade 3 and grade 2 late urinary toxicity was 8.4% (n = 17) and 23.2% (n = 47), respectively. Grade 3 symptoms were observed at median 29 months (IQR, 19-62 months) after radiation therapy completion, lasting for a median duration of 8 months (IQR, 2-14 months). Hematuria (6.4%) and urinary obstruction (3.4%) were the chief grade 3 symptoms. Multivariable analysis for age, diabetes, pelvic radiation therapy, fraction size, prostate volume, TURP to radiation therapy duration, and TURP cavity volume showed no significant association with late grade 2+ urinary toxicity. In this large cohort of patients with prior TURP and treated with hypofractionated prostate radiation therapy, incidence of severe late urinary adverse effects was <10%, mainly hematuria or urinary obstruction. Most of these were temporary, and no significant contributory factors were identified for late urinary morbidity after TURP and radiation therapy.

24COASNO70:

Title- Predicting Regional Recurrence and Prognosis in Stereotactic Body Radiation Therapy-Treated Clinical Stage I Non-small Cell Lung Cancer Using a Radiomics Model Constructed With Surgical Data,

Jianjiao Ni, Hongru Chen, Lu Yu, Tiantian Guo, Yue Zhou, Shanshan Jiang, Ruiting Ye, Xi Yang,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1096-1106,

<https://doi.org/10.1016/j.ijrobp.2024.06.010>.

Abstract: Risk stratification of regional recurrence (RR) is clinically important in the design of adjuvant treatment and surveillance strategies in patients with clinical stage I non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT). This study aimed to develop a radiomics model predicting occult lymph node metastasis (OLNM) using surgical data and apply it to the prediction of RR in SBRT-treated early-stage NSCLC patients. Patients with clinical stage I NSCLC who underwent curative surgery with systematic lymph node dissection from January 2013 to December 2018 (the training cohort) and from January 2019 to December 2020 (the validation cohort) were included. A preoperative computed tomography-based radiomics model, a clinical feature model, and a fusion model predicting OLNm were constructed. The performance of the 3 models was quantified and compared in the training and validation cohorts. Subsequently, the radiomics model was used to predict RR in a cohort of consecutive SBRT-treated early-stage NSCLC patients from 2 academic medical centers. A total of 769 patients were included. Eight computed tomography features were identified in the radiomics model, achieving areas under the curves of 0.85 (95% CI, 0.81-0.89) and 0.83 (95% CI, 0.80-0.88) in the training and validation cohorts, respectively. Nevertheless, adding clinical features did not improve the performance of the radiomics model. With a median follow-up of 40.0 (95% CI, 35.2-44.8) months, 32 of the 213 patients in the SBRT cohort developed RR and those in the high-risk group based on the radiomics model had a higher cumulative incidence of RR ($P < .001$) and shorter regional recurrence-free survival ($P = .02$), progression-free survival ($P = .004$) and overall survival ($P = .006$) than those in the low-risk group. The radiomics model based on pathologically confirmed data effectively identified patients with OLNm, which may be useful in the risk stratification among SBRT-treated patients with clinical stage I NSCLC.

24COASNO71:

Title- In Vitro and Preclinical Systematic Dose-Effect Studies of Auger Electron- and β Particle-Emitting Radionuclides and External Beam Radiation for Cancer Treatment,

Ines M. Costa, George Firth, Jana Kim, Arshiya Banu, Truc T. Pham, Kavitha Sunassee, Sophie Langdon,

International Journal of Radiation Oncology*Biology*Physics,
Volume 120, Issue 4, 2024, Pages 1124-1134,

<https://doi.org/10.1016/j.ijrobp.2024.05.017>.

Abstract: Despite a rise in clinical use of radiopharmaceutical therapies, the biological effects of radionuclides and their relationship with absorbed radiation dose are poorly understood. Here, we set out to define this relationship for Auger electron emitters $[^{99m}\text{Tc}]\text{TcO}_4^-$ and $[^{123}\text{I}]\text{I}^-$ and β^- -particle emitter $[^{188}\text{Re}]\text{ReO}_4^-$. Studies were carried out using genetically modified cells that permitted direct radionuclide comparisons. Triple-negative MDA-MB-231 breast cancer cells expressing the human sodium iodide symporter (hNIS) and green fluorescent protein (GFP; MDA-MB-231.hNIS-GFP) were used. In vitro radiotoxicity of $[^{99m}\text{Tc}]\text{TcO}_4^-$, $[^{123}\text{I}]\text{I}^-$, and $[^{188}\text{Re}]\text{ReO}_4^-$ was determined using clonogenic assays. Radionuclide uptake, efflux, and subcellular location were used to calculate nuclear absorbed doses using the Medical Internal Radiation Dose (MIRD) formalism. In vivo studies were performed using female NSG mice bearing orthotopic MDA-MB-231.hNIS-GFP tumors and compared with X-ray-treated (12.6-15 Gy) and untreated cohorts. Absorbed dose per unit activity in tumors and sodium iodide symporter-expressing organs was extrapolated to reference human adult models using OLINDA/EXM. $[^{99m}\text{Tc}]\text{TcO}_4^-$ and $[^{123}\text{I}]\text{I}^-$ reduced the survival fraction only in hNIS-expressing cells, whereas $[^{188}\text{Re}]\text{ReO}_4^-$ reduced survival fraction in hNIS-expressing and parental cells. $[^{123}\text{I}]\text{I}^-$ required 2.4- and 1.5-fold lower decays/cell to achieve 37% survival compared with $[^{99m}\text{Tc}]\text{TcO}_4^-$ and $[^{188}\text{Re}]\text{ReO}_4^-$, respectively, after 72 hours of incubation. Additionally, $[^{99m}\text{Tc}]\text{TcO}_4^-$, $[^{123}\text{I}]\text{I}^-$, and $[^{188}\text{Re}]\text{ReO}_4^-$ had superior cell killing effectiveness in vitro compared with X-rays. In vivo, X-ray led to a greater median survival compared with $[^{188}\text{Re}]\text{ReO}_4^-$ and $[^{123}\text{I}]\text{I}^-$ (54 days vs 45 and 43 days, respectively). Unlike the X-ray cohort, no metastases were visualized in the radionuclide-treated cohorts. Extrapolated human absorbed doses of $[^{188}\text{Re}]\text{ReO}_4^-$ to a 1 g tumor were 13.8- and 11.2-fold greater than for $[^{123}\text{I}]\text{I}^-$ in female and male models, respectively. This work reports reference dose-effect data using cell and tumor models for $[^{99m}\text{Tc}]\text{TcO}_4^-$, $[^{123}\text{I}]\text{I}^-$, and $[^{188}\text{Re}]\text{ReO}_4^-$ for the first time. We further demonstrate the tumor-controlling effects of $[^{123}\text{I}]\text{I}^-$ and $[^{188}\text{Re}]\text{ReO}_4^-$ in comparison with external beam radiation therapy.

24COASNO72:

Title- Variation in Androgen Deprivation Therapy Use Among Men With Intermediate-Risk Prostate Cancer: Results From a Statewide Radiation Oncology Quality Consortium,

Michael P. Dykstra, Samuel N. Regan, Huiying (Maggie) Yin, Patrick William McLaughlin, Thomas Boike, Amit Bhatt,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 999-1007,

<https://doi.org/10.1016/j.ijrobp.2024.05.026>.

Abstract: For men with intermediate-risk prostate cancer treated with definitive therapy, the addition of androgen deprivation therapy (ADT) reduces the risk of distant metastasis and cancer-related mortality. However, the absolute benefit of ADT varies by baseline cancer risk. Estimates of prognosis have improved over time, and little is known about ADT decision making in the modern era. We sought to characterize variability and identify factors

associated with intended ADT use within the Michigan Radiation Oncology Quality Consortium (MROQC). Patients with localized prostate cancer undergoing definitive radiation therapy were enrolled from June 9, 2020, to June 26, 2023 (n = 815). Prospective data were collected using standardized patient, physician, and physicist forms. Intended ADT use was prospectively defined and was the primary outcome. Associations with patient, tumor, and practice-related factors were tested with multivariable analyses. Random intercept modeling was used to estimate facility-level variability. Five hundred seventy patients across 26 facilities were enrolled with intermediate-risk disease. ADT was intended for 46% of men (n = 262/570), which differed by National Comprehensive Cancer Network favorable intermediate-risk (23.5%, n = 38/172) versus unfavorable intermediate-risk disease (56.3%, n = 224/398; $P < .001$). After adjusting for the statewide case mix, the predicted probability of intended ADT use varied significantly across facilities, ranging from 15.4% (95% CI, 5.4%-37.0%) to 71.7% (95% CI, 57.0%-82.9%), with $P < .01$. Multivariable analyses showed that grade group 3 (OR, 4.60 [3.20-6.67]), $\geq 50\%$ positive cores (OR, 2.15 [1.43-3.25]), and prostate-specific antigen 10 to 20 (OR, 1.87 [1.24-2.84]) were associated with ADT use. Area under the curve was improved when incorporating MRI adverse features (0.76) or radiation treatment variables (0.76), but there remained significant facility-level heterogeneity in all models evaluated ($P < .05$). Within a state-wide consortium, there is substantial facility-level heterogeneity in intended ADT use for men with intermediate-risk prostate cancer. Future efforts are necessary to identify patients who will benefit most from ADT and to develop strategies to standardize appropriate use.

24COASNO73:

Title- The Role of Elective Nodal Irradiation in Treating Clinically Node-Negative Sinonasal Squamous Cell Carcinoma,

Li Wang, Jie Wang, Tian Wang, Yi Li, Xinmao Song,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1058-1065,

<https://doi.org/10.1016/j.ijrobp.2024.05.029>.

Abstract: This study aims to examine the role of elective nodal irradiation (ENI) in clinically node-negative (cN0) sinonasal squamous cell carcinoma (SNSCC) and to define the optimal radiation fields for ENI. We retrospectively reviewed 368 patients with cN0 SNSCC treated between 2009 and 2021. The study evaluated the impact of ENI on overall survival, progression-free survival, regional failure-free survival, and distant metastasis-free survival, along with the coverage areas of ENI. The majority of patients underwent surgery (316/368, 85.9%), with 276 of 368 (75%) having tumors in the maxillary sinus or nasal cavity and 249 of 368 (67.7%) presenting with T4 disease. Additionally, in 119 of the 368 cases (32.3%), tumors were poorly differentiated. The 5-year overall survival, progression-free survival, regional failure-free survival, and distant metastasis-free survival rates were 59.3%, 54.0%, 57.6%, and 58.8%, respectively. ENI was performed in 217 patients (59%), with 16 experiencing neck relapse during follow-up. Although ENI did not enhance survival rates, it significantly reduced the overall regional failure rate (7.9% vs 1.8%; $\chi^2 = 7.98$; $P < .01$) and

the cumulative incidence of regional failure ($P = .045$). Additionally, the subgroups with maxillary sinus origin (2.3% vs 13.5%; $P = .025$), T4 stage (1.8% vs 8.5%; $P = .028$), and poor differentiation (2.4% vs 13.5%; $P = .029$) had higher cumulative incidences of regional failure in patients without ENI. No significant difference was observed in survival and regional failure rates between patients treated with ENI to levels Ib and II with or without level III, as well as between cN0 patients with nonmidline crossing lesions receiving unilateral or bilateral ENI. Despite no survival benefit, ENI significantly decreases the regional failure rate in patients with cN0 SNSCC. For primary lesions not crossing the midline, ipsilateral ENI targeting levels Ib and II proves to be an effective strategy.

24COASNO74:

Title- Memantine to Reduce Cognitive Impairment After Radiation in Children: A Pilot Study Evaluating the Feasibility of Memantine in Reducing Cognitive Impairment in Pediatric Patients after Radiation Therapy for Central Nervous System Tumors,

Elizabeth L. McKone, William G. Breen, Nathan R. Foster, Aaron W. Bogan, Margaret A. Connors,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1032-1038,

<https://doi.org/10.1016/j.ijrobp.2024.05.031>.

Abstract: Memantine is standard in certain adults receiving brain radiation therapy (RT) to decrease cognitive impacts, but it is unknown whether pediatric patients can take, tolerate, and/or benefit from memantine. In this prospective single-arm feasibility study, we hypothesized that pediatric patients receiving central nervous system (CNS) RT would tolerate memantine with good adherence. Patients aged 4 to 18 years with a primary CNS malignancy (excluding World Health Organization grade 4 astrocytoma, glioblastoma) receiving intracranial RT were eligible. A 6-month memantine course was given during and after RT, with dose titration in 5 mg increments over 4 weeks targeting a weight-based maximum (0.4 mg/kg to the closest 5 mg), not to exceed 10 mg twice a day. The primary endpoint was to achieve 80% drug adherence rate in 80% of patients measured 1 month after RT. Secondary objectives included memantine feasibility at 3 and 6 months. Eighteen patients enrolled from 2020 to 2022 and were prescribed memantine with RT. The study closed early to avoid competing with the phase 3 randomized Children's Oncology Group study ACCL2031. No predefined stopping rules were met. One patient withdrew for cognition-altering substance use, leaving 17 patients available for analysis. One patient discontinued memantine after one dose due to nausea. For the remaining 16 patients, there was a median of 100% pill completion rate (range, 74%-100%; $n = 9/17$ with 100% adherence) at 1 month after RT, with 15/16 (94%) with adherence rates $>80\%$. At the 3- and 6-month post-RT time points for secondary endpoints, the median adherence rates were 100% (range, 55%-100%) and 96% (range, 33%-100%), respectively. Grade 1 to 2 fatigue, headache, and nausea were the most common toxicity events, at least possibly related to the study drug ($n = 27$), without attributable grade 3+ events. Memantine is a feasible, safe, and

well-tolerated addition to multimodality treatment for pediatric CNS malignancies. Results of ACCL2031 are awaited to define the value of memantine in this population.

24COASNO75:

Title- Comparison of Efficacy and Safety of Combined Chemoimmunotherapy With or Without Radiation Therapy for Stage IVB Esophageal Squamous Cell Carcinoma: A Multicenter Propensity Score Matching Analysis,

Biqi Chen, Wenyan Chen, Qi Cheng, Hao Zhang, Bingyi Wang, Yujin Xu, Chen Yang, Xingyuan Cheng,

International Journal of Radiation Oncology*Biology*Physics,

Volume 120, Issue 4,2024,Pages 1084-1095,

<https://doi.org/10.1016/j.ijrobp.2024.06.008>.

Abstract: This study aimed to compare the efficacy and safety of combining first-line chemoimmunotherapy with radiation therapy versus chemoimmunotherapy alone in patients with stage IVB esophageal squamous cell carcinoma (ESCC). We retrospectively examined 409 patients with stage IVB ESCC who received first-line chemotherapy and anti-PD-1 antibody, with or without radiation therapy of ≥ 40 Gy radiation dose to primary lesion, from 4 academic cancer centers between October 2018 and December 2022. Propensity score matching was conducted to minimize the potential confounding effects. In the overall cohort of 409 patients, the group that received additional radiation therapy had superior overall survival (OS) (hazard ratio [HR], 0.51; 95% CI, 0.39-0.66; $P < .001$) and progression-free survival (PFS) (HR, 0.52; 95% CI, 0.40-0.66; $P < .001$) compared to the group that received chemoimmunotherapy alone. After 1:1 propensity score matching, matching age, tumor location, and metastatic sites, a total of 250 patients were selected for further analysis. The results remained consistent and showed that the addition of radiation therapy significantly improved OS and PFS (median OS, 24.9 vs 14.6 months; $P = .003$; median PFS, 14.2 vs 10.6 months; $P = .002$). Multivariate Cox analysis including tumor location, T stage, metastatic sites, and treatment modality, revealed that radiation therapy was an independent prognostic factor for both OS (HR, 0.57; 95% CI, 0.41-0.81) and PFS (HR, 0.63, 95% CI, 0.47-0.86). Subgroup analyses revealed significant OS prolongation in patients with nonregional lymph node metastases only who received radiation therapy (HR, 0.49; 95% CI, 0.34-0.70). No OS survival benefit was observed in those with distant organ metastases (HR, 0.72; 95% CI, 0.46-1.13). Regarding safety, the group receiving additional radiation therapy had higher incidences of grade 3 to 4 lymphopenia (74.4% vs 17.7%, $P < .001$) and esophagitis (11.2% vs 2.4%, $P = .006$). The addition of radiation therapy to chemoimmunotherapy improved the survival of stage IVB ESCC patients with nonregional lymph node metastasis.

24COASNO76:

Title- Executive Summary of the American Radium Society on Appropriate Use Criteria for Nonoperative Management of Rectal Adenocarcinoma: Systematic Review and Guidelines,

Christopher J. Anker, Leila T. Tchelebi, J. Eva Selfridge, Salma K. Jabbour, Dmitriy Akselrod,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 946-977,

<https://doi.org/10.1016/j.ijrobp.2024.05.019>.

Abstract: For patients with rectal cancer, the standard approach of chemotherapy, radiation therapy, and surgery (trimodality therapy) is associated with significant long-term toxicity and/or colostomy for most patients. Patient options focused on quality of life (QOL) have dramatically improved, but there remains limited guidance regarding comparative effectiveness. This systematic review and associated guidelines evaluate how various treatment strategies compare to each other in terms of oncologic outcomes and QOL. Cochrane and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology were used to search for prospective and retrospective trials and meta-analyses of adequate quality within the Ovid Medline database between January 1, 2012, and June 15, 2023. These studies informed the expert panel, which rated the appropriateness of various treatments in 6 clinical scenarios through a well-established consensus methodology (modified Delphi). The search process yielded 197 articles that advised voting. Increasing data have shown that nonoperative management (NOM) and primary surgery result in QOL benefits noted over trimodality therapy without detriment to oncologic outcomes. For patients with rectal cancer for whom total mesorectal excision would result in permanent colostomy or inadequate bowel continence, NOM was strongly recommended as usually appropriate. Restaging with tumor response assessment approximately 8 to 12 weeks after completion of radiation therapy/chemoradiation therapy was deemed a necessary component of NOM. The panel recommended active surveillance in the setting of a near-complete or complete response. In the setting of NOM, 54 to 56 Gy in 27 to 31 fractions concurrent with chemotherapy and followed by consolidation chemotherapy was recommended. The panel strongly recommends primary surgery as usually appropriate for a T3N0 high rectal tumor for which low anterior resection and adequate bowel function is possible, with adjuvant chemotherapy considered if N+. Recent data support NOM and primary surgery as important options that should be offered to eligible patients. Considering the complexity of multidisciplinary management, patients should be discussed in a multidisciplinary setting, and therapy should be tailored to individual patient goals/values.

24COASN077:

Title- Myoferlin: A Potential Marker of Response to Radiation Therapy and Survival in Locally Advanced Rectal Cancer,

Hayley Fowler, Rachael E. Clifford, David Bowden, Paul A. Sutton, Naren Govindarajah, Matthew Fok,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1111-1123,

<https://doi.org/10.1016/j.ijrobp.2024.05.030>.

Abstract: Patients with locally advanced rectal cancer often require neoadjuvant chemoradiation therapy to downstage the disease, but the response is variable with no predictive biomarkers. We have previously revealed through proteomic profiling that myoferlin is associated with response to radiation therapy. The aims of this study were to further validate this finding and explore the potential for myoferlin to act as a prognostic and/or therapeutic target. Immunohistochemical analysis of a tissue microarray (TMA) for 111 patients was used to validate the initial proteomic findings. Manipulation of myoferlin was achieved using small interfering RNA, a small molecular inhibitor (wj460), and a CRISPR-Cas9 knockout cell line. Radiosensitization after treatment was assessed using 2-dimensional clonogenic assays, 3-dimensional spheroid models, and patient-derived organoids. Underlying mechanisms were investigated using electrophoresis, immunofluorescence, and immunoblotting. Analysis of both the diagnostic biopsy and tumor resection samples confirmed that low myoferlin expression correlated with a good response to neoadjuvant long-course chemoradiation therapy. High myoferlin expression was associated with spread to local lymph nodes and worse 5-year survival ($P = .01$; hazard ratio, 3.5; 95% CI, 1.27-10.04). This was externally validated using the Stratification in Colorectal Cancer database. Quantification of myoferlin using immunoblotting in immortalized colorectal cancer cell lines and organoids demonstrated that high myoferlin expression was associated with increased radioresistance. Biological and pharmacologic manipulation of myoferlin resulted in significantly increased radiosensitivity across all cell lines in 2-dimensional and 3-dimensional models. After irradiation, myoferlin knockdown cells had a significantly impaired ability to repair DNA double-strand breaks. This appeared to be mediated via nonhomologous end-joining. We have confirmed that high expression of myoferlin in rectal cancer is associated with poor response to neoadjuvant therapy and worse long-term survival. Furthermore, the manipulation of myoferlin led to increased radiosensitivity in vitro. This suggests that myoferlin could be targeted to enhance the sensitivity of patients with rectal cancer to radiation therapy, and further work is required.

24COASNO78:

Title- Clinical Impact of Contouring Variability for Prostate Cancer Tumor Boost,

Allison Y. Zhong, Asona J. Lui, Svetlana Kuznetsova, Karoline Kallis, Christopher Conlin, Deondre D. Do,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1024-1031,

<https://doi.org/10.1016/j.ijrobp.2024.06.007>.

Abstract: The focal radiation therapy (RT) boost technique was shown in a phase III randomized controlled trial (RCT) to improve prostate cancer outcomes without increasing toxicity. This technique relies on the accurate delineation of prostate tumors on MRI. A recent prospective study evaluated radiation oncologists' accuracy when asked to delineate prostate tumors on MRI and demonstrated high variability in tumor contours. We sought to evaluate the impact of contour variability and inaccuracy on predicted clinical outcomes. We hypothesized that radiation oncologists' contour inaccuracies would yield meaningfully

worse clinical outcomes. Forty-five radiation oncologists and 2 expert radiologists contoured prostate tumors on 30 patient cases. Of these cases, those with CT simulation or diagnostic CT available were selected for analysis. A knowledge-based planning model was developed to generate focal RT boost plans for each contour per the RCT protocol. The probability of biochemical failure (BF) was determined using a model from the RCT. The primary metric evaluated was delta BF (DBF = Participant BF – Expert BF). An absolute increase in BF $\geq 5\%$ was considered clinically meaningful. Eight patient cases and 394 target volumes for focal RT boost planning were included in this analysis. In general, participant plans were associated with worse predicted clinical outcomes compared to the expert plan, with an average absolute increase in BF of 4.3%. Of participant plans, 37% were noted to have an absolute increase in BF of 5% or more. Radiation oncologists' attempts to contour tumor targets for focal RT boost are frequently inaccurate enough to yield meaningfully inferior clinical outcomes for patients.

24COASNO79:

Title- Proton Therapy for Spinal Tumors: A Consensus Statement From the Particle Therapy Cooperative Group,

Arpit M. Chhabra, James W. Snider, Adam J. Kole, Markus Stock, Adam L. Holtzman, Robert Press,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1135-1148,

<https://doi.org/10.1016/j.ijrobp.2024.04.007>.

Abstract: Proton beam therapy (PBT) plays an important role in the management of primary spine tumors. The purpose of this consensus statement was to summarize safe and optimal delivery of PBT for spinal tumors. The Particle Therapy Cooperative Group Skull Base/Central nervous system/Sarcoma Subcommittee consisting of radiation oncologists and medical physicists with specific expertise in spinal irradiation developed expert recommendations discussing treatment planning considerations and current approaches in the treatment of primary spinal tumors. Computed tomography simulation: factors that require significant consideration include (1) patient comfort, (2) setup reproducibility and stability, and (3) accessibility of appropriate beam angles. If present, hardware should be placed with cross-links well above/below the level of the primary tumor to reduce the metal burden at the level of the tumor bed. New materials that can reduce uncertainties include polyether-ether-ketone and composite polyether-ether-ketone-carbon fiber implants. Appropriate beam selection is required to ensure robust target coverage and organ at risk sparing. Commonly, 2 to 4 treatment fields, typically from posterior and/or posterior-oblique directions, are used. Robust optimization is recommended for all pencil beam scanning plans (the preferred treatment modality) and should consider setup uncertainty (between 3 and 7 mm) and range uncertainty (3%-3.5%). In the presence of metal hardware, use of an increased range uncertainty up to 5% is recommended. The Particle Therapy Cooperative Group Skull Base/Central nervous system/Sarcoma Subcommittee has developed recommendations to

enable centers to deliver PBT safely and effectively for the management of primary spinal tumors.

24COASNO80:

Title- Rapid Selection of Patients Suitable for Deep Inspiration Breath-Hold Using an Automatic Delineating System and RapidPlan Model in Patients With Left Breast Cancer Undergoing Adjuvant Radiation Therapy With IMRT,

Ying-Ying Zhou, Yan-Ning Li, Jin-Feng Xu, Bo Chen, Hua-Li Li, Yue-Xin Zheng, Li-Sheng Pan, Long-Mei Cai, Hong-Mei Wang,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4,2024,Pages 1066-1075,

<https://doi.org/10.1016/j.ijrobp.2024.06.006>.

Abstract: This study aimed to determine whether radiation therapy plans created using an automatic delineating system and a RapidPlan (RP) module could rapidly and accurately predict heart doses and benefit from deep inspiratory breath-hold (DIBH) in patients with left breast cancer. One hundred thirty-six clinically approved free breathing (FB) plans for patients with left breast cancer were included, defined as manual delineation–manual plan (MD–MP). A total of 104 of 136 plans were selected for RP model training. A total of 32 of 136 patients were automatically delineated by software, after which the RP generated plans, defined as automatic delineation–RapidPlan (AD–RP). In addition, 40 patients who used DIBH were included to analyze differences in heart benefits from DIBH. Two RP models were established for post–breast-conserving surgery (BCS) and post-modified radical mastectomy. There were no significant differences in most of the dosimetric parameters between the MD–MP and AD–RP. The heart doses of the 2 plans were strongly correlated in patients after BCS ($0.80 \leq r \leq 0.88$, $P < .05$) and moderately correlated in patients after postmodified radical mastectomy ($0.46 \leq r \leq 0.58$, $P < .05$). The RP model predicted the mean heart dose (MHD) within ± 59.67 cGy and ± 63.32 cGy for patients who underwent the 2 surgeries described above. The heart benefits from DIBH were significantly greater in patients with $\text{FB-MHD} \geq 4$ Gy than in those with $\text{FB-MHD} < 4$ Gy. The combined automatic delineation RP model allows for the rapid and accurate prediction of heart dose under FB in patients with left breast cancer. $\text{FB-MHD} \geq 4$ Gy can be used as a dose threshold to select patients suitable for DIBH.

24COASNO81:

Title- Clinical Outcomes of 3 Versus 4 Fractions of Magnetic Resonance Image-Guided Brachytherapy in Cervical Cancer,

Elizabeth Chuk, Candice Yu, Aba Anoa Scott, Zhihui Amy Liu, Michael Milosevic, Jennifer Croke,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4,2024,Pages 1042-1051,

<https://doi.org/10.1016/j.ijrobp.2024.06.011>.

Abstract: Magnetic resonance image-guided brachytherapy is essential in the management of locally advanced cervical cancer. This study compares disease and toxicity outcomes in cervical cancer patients treated with 24 Gy/3 fractions (Fr) versus the conventional 28 Gy/4 Fr. This retrospective study included 241 consecutive patients with International Federation of Gynecology and Obstetrics 2018 stage IB to IVA cervical cancer treated with definitive chemoradiation between April 2014 and March 2021. Disease-free survival (DFS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Cumulative incidence of local failure (LF), distant failure (DF), and G2+ gastrointestinal (GI), urinary and vaginal toxicity were estimated using the cumulative incidence function with death as a competing risk and compared using Gray's test. Of the 241 patients, 42% received 24 Gy/3 Fr and 58% received 28 Gy/4 Fr. With a median follow-up of 3.2 (range, 0.2-9.2) years, there were 14 local, 41 regional nodal, and 51 distant failures in 63 (26%) patients. No significant differences were found between the 24 Gy/3 Fr and 28 Gy/4 Fr groups in 3-year DFS (77% vs 68%, $P = .21$), the 3-year cumulative incidence of LF (5% vs 7%, $P = .57$), DF (22% vs 25%, $P = .86$), G2+ GI toxicity (11% vs 20%, $P = .13$), or G2+ vaginal toxicity (14% vs 17%, $P = .48$), respectively. The 3-year cumulative G2+ urinary toxicity rate was lower in the 24 Gy/3 Fr group (9% vs 23%, $P = .03$). Patients with cervical cancer treated with 24 Gy/3 Fr had similar DFS, LF, DF, GI, and vaginal toxicity rates and a trend toward a lower G2+ urinary toxicity rate compared with those treated with 28 Gy/4 Fr. A less resource-intensive brachytherapy fractionation schedule of 24 Gy/3 Fr is a safe alternative to 28 Gy/4 Fr for definitive treatment of cervical cancer.

24COASNO82:

Title- The IMRIS Trial: A Phase 2 Study of Intensity Modulated Radiation Therapy in Extremity Soft Tissue Sarcoma,

Beatrice Seddon, Franel Le Grange, Rita Simões, Chris Stacey, Shumona Shelly, Sharon Forsyth,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4,2024,Pages 978-989,

<https://doi.org/10.1016/j.ijrobp.2024.05.024>.

Abstract: Primary soft tissue sarcoma (STS) is rare, with many tumors occurring in extremities. Local management is limb-sparing surgery and preoperative/postoperative radiation therapy (RT) for patients at high risk of local recurrence. We prospectively investigated late normal tissue toxicity and limb function observed after intensity modulated RT (IMRT) in extremity STS. Patients with extremity STS, age ≥ 16 years. Two treatment cohorts: IMRT 50 Gy in 25×2 Gy fractions (preoperative) or 60/66 Gy in $30/33 \times 2$ Gy fractions (postoperative). The primary endpoint was the rate of grade ≥ 2 late soft tissue fibrosis (subcutaneous tissue) at 24 months after IMRT (Radiation Therapy Oncology Group late radiation morbidity scoring). One hundred sixty-eight patients were registered between March 2016 and July 2017. Of those, 159 (95%) received IMRT (106, 67% preoperative RT; and 53, 33% postoperative RT) with a median follow-up of 35.2 months (IQR, 32.9-36.6); 62% men, median age 58 years. Of 111 patients assessable for the primary endpoint at 24

months, 12 (10.8%; 95% CI, 5.7%-18.1%) had grade ≥ 2 subcutaneous fibrosis. The overall rate at 24 months of Radiation Therapy Oncology Group late skin, bone, and joint toxicity was 7 of 112 (6.3%), 3 of 112 (2.7%), and 10 of 113 (8.8%), respectively, and for Stern's scale edema was 6 of 113 (5.3%). More wound complications were observed with preoperative than postoperative RT (29.2% vs 3.8%). Overall survival at 24 months was 84.6%, and the local recurrence event rate at 24 months was 10%. The rate of grade ≥ 2 subcutaneous fibrosis at 24 months after IMRT was 10.8%, consistent with other recent trials of IMRT and lower than historically reported rates in patients treated with 3-dimensional conformal RT. This trial provides further evidence for the benefits of IMRT in this patient population.

24COASNO83:

Title- Conditional Risk and Predictive Factors Associated With Late Toxicity in Patients With Prostate Cancer Treated With External Beam Radiation Therapy Alone in the Randomized Trial RTOG 0126,

Gregory S. Alexander, Rebecca F. Krc, James W. Assif, Kai Sun, Jason K. Molitoris, Phuoc Tran, Zaker Rana, Mark V. Mishra,
International Journal of Radiation Oncology*Biological*Physics,
Volume 120, Issue 4,2024,Pages 990-998,
<https://doi.org/10.1016/j.ijrobp.2024.05.023>.

Abstract: The objective of this study was to characterize the conditional risk of developing grade 2+ urinary or gastrointestinal (GI) toxicity for patients treated with external beam radiation therapy in Radiation Therapy Oncology Group 0126. A secondary objective was to analyze baseline patient and treatment characteristics and determine their relevance in predicting toxicity both at the time of trial enrollment and at later points of follow-up. One thousand five hundred thirty-two patients with localized prostate cancer were enrolled between March 2002 and August 2008, of whom 1499 were eligible and included in data analysis with a median follow-up of 8.4 years (range, 0.02-13 years). Patients were treated with either 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy according to institutional practice without the addition of androgen deprivation and randomized to receive either standard-dose radiation therapy of 70.2 Gy or dose-escalated radiation therapy of 79.2 Gy of radiation therapy to the prostate only with standard fractionation. Univariate and multivariate analyses were performed to determine whether initial factors were predictive of late toxicity at the time of treatment and at later time points. As patients proceed further from completion of radiation therapy without the development of toxicity, the subsequent risk of both grade 2+ genitourinary (GU) and GI toxicity decreases with time. At the time of enrollment, the risk of developing grade 2+ toxicity over the next 5 years was 9.57% and 17.89%, respectively. After 5 years of toxicity-free survival, the risk of developing grade 2+ GU or GI toxicity in the subsequent 5 years was 3.02% and 1.54%, respectively. Baseline treatment and patient-related factors predicted late toxicity both at trial enrollment and after 2 years of toxicity-free survivorship. Baseline urinary dysfunction and dose-escalated radiation therapy were associated with increased late GU toxicity. Acute GI

toxicity and dose-escalated radiation therapy were associated with increased risk of late GI toxicity. Treatment with intensity-modulated radiation therapy was associated with reduced risk of either toxicity. The conditional risk of grade 2+ toxicities decreases as patients proceed further from treatment, with most toxicities occurring in the first few years after treatment completion. Baseline patient and treatment characteristics remain relevant at both enrollment and later time points.

24COASNO84:

Title- Clinical Implementation and Dosimetric Evaluation of a Robust Proton Lattice Planning Strategy Using Primary and Robust Complementary Beams,

Sina Mossahebi, Jason K. Molitoris, Yannick Poirier, Jenna Jatczak, Baoshe Zhang, Pranshu Mohindra, Matthew Ferris, William F. Regine, ByongYong Yi,
International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1149-1158,
<https://doi.org/10.1016/j.ijrobp.2024.06.009>.

Abstract: Pencil-beam scanning proton therapy has been considered a potential modality for the 3D form of spatially fractionated radiation therapy called lattice therapy. However, few practical solutions have been introduced in the clinic. Existing limitations include degradation in plan quality and robustness when using single-field versus multifield lattice plans, respectively. We propose a practical and robust proton lattice (RPL) planning method using multifield and evaluate its dosimetric characteristics compared to clinically acceptable photon lattice plans. Seven cases previously treated with photon lattice therapy were used to evaluate a novel RPL planning technique using 2-orthogonal beams: a primary beam (PB) and a robust complementary beam (RCB) that deliver 67% and 33%, respectively, of the prescribed dose to vertices inside the gross target volume (GTV). Only RCB is robustly optimized for setup and range uncertainties. The number and volume of vertices, peak-to-valley dose ratios (PVDRs), and volume of low dose to GTV of proton and photon plans were compared. The RPL technique was then used in the treatment of 2 patients and their dosimetric parameters were reported. The RPL strategy was able to achieve the clinical planning goals. Compared to previously treated photon plans, the average number of vertices increased by 30%, the average vertex volume by 49% (18.2 ± 25.9 cc vs 12.2 ± 14.5 cc, $P = .21$), and higher PVDR (10.5 ± 4.8 vs 2.5 ± 0.9 , $P < .005$) was achieved. In addition, RPL plans show more conformal dose with less low dose to GTV ($V_{30\%}$, $60.9\% \pm 7.2\%$ vs $81.6\% \pm 13.9\%$ and $V_{10\%}$, $88.3\% \pm 4.5\%$ vs $98.6\% \pm 3.6\%$ [$P < .01$]). The RPL plan for 2 treated patients showed PVDRs of 4.61 and 14.85 with vertices-to-GTV ratios of 1.52% and 1.30%, respectively. A novel RPL planning strategy using a pair of orthogonal beams was developed and successfully translated to the clinic. The proposed method can generate better quality plans, a higher number of vertices, and higher PVDRs than currently used photon lattice plans.

24COASNO85:

Title- A Population-Based Tumor-Volume Model for Head and Neck Cancer During Radiation Therapy With a Dynamic Oxygenated Compartment,

Zhengying Zhang, Jianping Zhang, Rong Zheng, Jianxiong Ye, Benhua Xu,

International Journal of Radiation Oncology*Biology*Physics, Volume 120, Issue 4, 2024, Pages 1159-1171,

<https://doi.org/10.1016/j.ijrobp.2024.05.021>.

Abstract: With the coming era of digital medicine and healthcare technology, mathematical modeling of tumors has become a key step to optimize and realize precision radiation therapy. The purpose of this study was to develop a mathematical model for simulating the change of head and neck (HN) tumor volume during radiation therapy. A formula was developed to describe the dynamic change of oxygenated compartment within a tumor, which was combined with the lethal lesions model to describe various cell processes during radiation therapy, including potentially lethal lesion repair and misrepair, cell proliferation/loss, and tumor reoxygenation. Parameter sensitivity analysis was performed to evaluate the impacts of lesion- and repair-related biological factors on radiation therapy outcomes. We tested our model on 14 available patients with HN cancer and compared the performance with 3 other models. The mean error of our model for the 12 good fit cases was 12.2%, which is considerably smaller than that of the linear quadratic model (19.7%), the generalized linear quadratic model (19.1%), and a 4-level cell population model (16.6%). Correlation analysis results revealed that for small tumors, there was a positive correlation (correlation coefficient $r=0.9416$) between hypoxic fraction (hf) and tumor volume, whereas the correlation became negative and not significant ($r=-0.4365$) for large tumors. It is demonstrated from sensitivity analysis that the production rate of lethal lesions (η_l) has a far greater impact on tumor volume than other parameters. The hf had an insignificant impact on tumor volume but had a notable influence on the volume of surviving cells. The final volume of surviving cells at $hf=0.5$ was almost 8×10^2 times that of $hf=0.01$. The potentially lethal lesion-related parameters (the production rate of potentially lethal lesions per unit dose η_{pl} , the rate of correct repair per unit time ϵ_{pl} , and the rate of binary misrepair per unit time ϵ_{2pl}) had rather small impacts ($<1\%$) on both tumor volume and the volume of surviving cells, which indicates that the repaired and misrepaired sublethal cells only take up a small portion of the total cancer cell population. A population-based tumor-volume model for HN cancer during radiation therapy with a dynamic oxygenated compartment was developed in this study. Comprehensively considering the damage process of tumor cells caused by radiation therapy, the accurate prediction of the volume change of HN tumors during treatment was revealed. Meanwhile, various cell activities and their principles in the process of antitumor treatment were reflected, which has positive clinical reference significance for radiobiology.

Surgical Oncology

24COASNO1:

Title- Invasive Fungal Sinusitis in an Immunocompetent Patient After Sinus Surgery for Chronic Rhinosinusitis with Nasal Polyps and a Mycetoma

Evan J. Patel MD, Meleha Ahmad MD, Brian S. Schwartz MD, Annemieke van Zante MD, PhD, Robert Kersten MD, Patricia Loftus MD

Laryngoscope . 2024 Oct;134(10):4213-4216.

doi: <https://doi.org/10.1002/lary.31463>.

Abstract: We describe a case of acute invasive fungal sinusitis (AIFS) in an immunocompetent, non-diabetic patient after endoscopic sinus surgery. The patient presented with retro-orbital pain progressing to vision loss and was treated with surgical debridement, systemic antifungal therapy, and transcutaneous retro-bulbar injection of amphotericin B resulting in resolution of her symptoms and improvement in her vision. To our knowledge, this is the first report of AIFS in an immunocompetent patient presumed to be secondary to a combination of local immune suppression via topical steroids and mucosal trauma.

Keywords: allergy/rhinology; clinical; immunology; radiology of the paranasal sinuses.

24COASNO2:

Title- Feasibility of Optical Biopsy During Endoscopic Sinus Surgery With Confocal Laser Endomicroscopy: A Pilot Study

Ann-Kathrin Frenken, Matti Sievert MD, Bharat Panuganti MD, Marc Aubreville, Till Meyer MD, Agmal Scherzad, Thomas Gehrke MD, Matthias Scheich MD, Stephan Hackenberg, Miguel Goncalves MD

Laryngoscope . 2024 Oct;134(10):4217-4224.

doi: <https://doi.org/10.1002/lary.31503>.

Abstract: This study aimed to evaluate the feasibility of using optical biopsy with confocal laser endomicroscopy to distinguish between benign and malignant mucosa during endoscopic sinonasal surgery. Our results demonstrated that healthy and inflamed mucosa could be differentiated from malignant lesions with an accuracy of 84.1%, a sensitivity of 85.4%, and a specificity of 83.1%, along with substantial interrater agreement (Fleiss $\kappa = 0.62$).

Keywords: confocal laser endomicroscopy; diagnostic; head and neck; nose and paranasal sinuses; sinus cancer.

24COASNO3:

Title- Long-Term Follow-Up of Post Radiation Complete Sinus Opacification in Sinonasal Cancer Patients

Lirit Levi MD, Shany Havazelet MD, Anner Moskovitz MD, Ethan Soudry MD

Laryngoscope . 2024 Oct;134(10):4232-4238.

doi: <https://doi.org/10.1002/lary.31504>.

Abstract: Some post-radiotherapy patients experience complete obliteration of the sphenoid or frontal sinuses, supposedly posing a risk for sinusitis or mucocele development. The

objective is to comprehensively assess the natural history and outcomes of radiation-induced complete isolated sinus opacification. Our study revealed that a substantial number of post-radiation patients develop complete isolated sinus opacification, often in the frontal and sphenoid sinuses. These patients remained asymptomatic, and none required surgical intervention during nearly 5 years of follow-up.

Keywords: mucocoele; opacification; radiation; sinonasal malignancy.

24COASNO4:

Title- An Ovine Model Yields Histology and Gene Expression Changes Consistent with Laryngotracheal Stenosis

Laura Mafla BS, Raymond J. So AB, Samuel L. Collins PhD, Yee Chan-Li BS, Ioan Lina MD, Kevin M. Motz MD, Alexander T. Hillel MD

Laryngoscope . 2024 Oct;134(10):4239-4245.

doi: <https://doi.org/10.1002/lary.31499>.

Abstract: Large animal models are needed to assess novel therapies for laryngotracheal stenosis (LTS) prior to human translation. In this manuscript, we describe a large ovine model for LTS and show that airway stenosis can be reliably and safely produced via combined chemo-mechanical injury. We additionally show that stent placement is feasible and safe.

Keywords: idiopathic subglottic stenosis; large animal model; laryngotracheal stenosis; ovine model.

24COASNO5:

Title- A Novel Classification System and Surgical Strategies of First Branchial Cleft Anomalies

Dedi Kong MD, Wei Li MD, PhD, Pei Zhou MD, Yibo Zhang MD, PhD, Chunfu Dai MD, PhD

Laryngoscope . 2024 Oct;134(10):4246-4251.

doi: <https://doi.org/10.1002/lary.31477>.

Abstract: A novel classification of FBCAs based on the relationship between lesions and the facial nerve in term of radiographic imaging findings was defined, and the corresponding surgical managements was introduced.

Keywords: classification; facial nerve; first branchial cleft anomalies.

24COASNO6:

Title- Biochemical Variability of Nasal Cartilages: Implications in Functional Rhinoplasty

Sul G. Kim BA, Mark M. Mims MD, Denna C. Menapace MD, Taylor Stack BS, William W. Shockley MD, J. Madison Clark MD

Laryngoscope . 2024 Oct;134(10):4252-4258.

doi: <https://doi.org/10.1002/lary.31480>.

Abstract: Functional rhinoplasty surgical techniques continue to evolve to address nasal valve compromise (NVC), but less is known about its underlying causes. This study found

decreased glycosaminoglycan and increased collagen in the dorsal septal articulation cartilage of patients diagnosed with NVC.

Keywords: nasal cartilage histology; nasal valve compromise; nasal valve dysfunction; quadrangular cartilage; upper lateral cartilage.

24COASN07:

Title- Impact of Tissue Handling and Size Modification on Septal Chondrocyte Viability

Khodayar Goshtasbi MD, Theodore V. Nguyen BS, Karthik R. Prasad MD, Ellen M. Hong BS, Naya Sterritt, Katelyn K. Dilley BS, Konrad Kozlowski BS, Alexis Ha, Brian J.F. Wong MD, PhD

Laryngoscope . 2024 Oct;134(10):4259-4265.

doi: <https://doi.org/10.1002/lary.31546>.

Abstract: Chondrocyte viability was similar between 1 mm diced cartilage, scaled cartilage, and positive control samples. Conversely, pate cartilage samples had significantly less viability compared to positive controls, diced samples, and scaled samples, and it had similar chondrocyte viability compared to negative controls. On computational modeling, cartilage viability decreased to 50%, 26%, and 11% as the diced sample was cut from 1 mm edge length to 0.7–0.8 mm, 0.55–0.65, and 0.4–0.5. Similarly, cartilage viability decreased to 26% at 0.55–0.65 mm, 11% at 0.4–0.5 mm, and <5% at <0.4 mm edge length.

Keywords: cartilage viability; chondrocyte viability; diced cartilage; rhinoplasty; tissue viability.

24COASN08:

Title- Outcomes of Radial Forearm Free Flap Closure With Split-Thickness Skin Graft Versus Primary Closure

Dorsa Mousa-Doust MD, Anat Bahat Dinur MD, Sena Turkdogan MD, J. Scott Durham MD, FRCSC, Donald Anderson MD, FRCSC, Eitan Prisman MD, FRCSC

Microsurgery . 2024 Jan;44(1):e31126.

doi: <https://doi.org/10.1002/micr.31126>.

Abstract: This study compares patient-reported functional and aesthetic outcomes of split-thickness skin graft (STSG) versus hatchet flap closure of radial forearm free flapdonor site using the Patient-Observer Scar Assessment Scale and Michigan Hand Outcome Questionnaire. In total, 81 patients participated in the study (39 STSG patients and 42 hatchet flap patients). STSG appeared to have less compromise in activities of daily living, better satisfaction and improved scar quality than hatchet flap, but a higher rate of tendon exposure.

24COASN09:

Title- A case report of Transnasal Endoscopic Drainage for Upper Parapharyngeal Abscess

John Loh Ming Ren MBBS, MRCS (Ireland), MMED (ORL), Naomi Huang Wenya B.Pharm, MD, Tan Toh Hui Leonard MBBS, MRCS (Edinburgh), MMED (ORL), FAMS (ORL), Pang Cui-Ying Maria MBBS, MRCS (Edinburgh), MMed (ORL), FAMS (ORL)

Laryngoscope . 2024 Oct;134(10):4274-4277.

doi: <https://doi.org/10.1002/lary.31455>.

Abstract: We report a case of upper parapharyngeal abscess arising from progression of a central skull base osteomyelitis, in a patient with poorly controlled diabetes mellitus. Our case is unusual for its presentation in an upper parapharyngeal location, involvement of the skull base, and poor response to medical treatment, hence requiring transnasal endoscopic surgical drainage to achieve definitive treatment. Here, we share our experience with a safe and effective technique of transnasal endoscopic drainage of a parapharyngeal abscess.

Keywords: nasopharyngeal abscess; skull base osteomyelitis; upper parapharyngeal abscess.

24COASNO10:

Title- Modified Frailty Index Associates With Transoral Robotic Surgery Complications and Survival: A National Database Study

Amiti Jain BS, Zachary N. Goldberg BS, BA, Erin Briggs BS, Dev R. Amin MD, Zachary D. Urdang MD, PhD, Richard A. Goldman MD, David M. Cagnetti MD, Joseph M. Curry MD

Laryngoscope . 2024 Oct;134(10):4278-4283.

doi: <https://doi.org/10.1002/lary.31458>.

Abstract: The primary aim of this study is to understand and validate the capacity of the modified frailty index (mFI-5) to predict outcomes for patients undergoing transoral robotic surgery for head and neck cancer. The results of this study provide compelling evidence of the link between increased frailty as defined by mFI-5 and various postoperative complications, including mortality, infection, and pneumonia better predicted than by age alone.

Keywords: TORS; TriNetX; frailty assessment; head and neck cancer; mFI-5; survival.

24COASNO11:

Title- Patterns of Discordance Between Clinical and Pathologic Stage in Head and Neck Cancer

Brian Hondorp MD, Nihal Punjabi BS, David Macias MD, Yuan Liu MD, Ethan Frank MD, Paul D. Kim MD, Jared C. Inman MD

Laryngoscope . 2024 Oct;134(10):4284-4291.

doi: <https://doi.org/10.1002/lary.31465>.

Abstract: While pathologic staging is considered the gold standard in head and neck cancers, clinical staging guides initial treatment plans and patient counseling. This study aims to identify specific stages and primary tumor subsites where discordance between clinical and pathologic staging is high. We found that T2 Oral Cavity, T2 Oropharynx, T3 Larynx, and N1 Lymph Node had the highest discordance while T1 Larynx, T4 Oropharynx, N0 Lymph Node, and N3 Lymph Node had the lowest.

Keywords: head and neck neoplasms; neoplasm staging; squamous cell carcinoma of head and neck.

24COASNO12:**Title- Characterization of the MSAP Flap in Head and Neck Surgical Oncology: A 3D Cadaveric Study**

Gianluca Sampieri MD, MSc, John Tran PhD, Allen L. Feng MD, Anne Agur PhD, Joel Davies MD, MSc, FRCSC

Laryngoscope . 2024 Oct;134(10):4298-4303.

doi: <https://doi.org/10.1002/lary.31532>.

Abstract: The medial sural artery perforator flap (MSAP) is a versatile free flap used for reconstruction of oral cavity defects. However, anatomy of the cutaneous perforators has not been well studied. Anatomical characterization of the MSAP flap using 3D analysis can assist reconstructive surgeons in understanding the relevant anatomy and optimizing the surgical technique for MSAP flap harvest.

Keywords: 3D cadaveric study; head and neck oncology; head and neck reconstruction; medial sural artery perforator flap.

24COASNO13:**Title- Immune Checkpoint Inhibitor Induced Supraglottitis: A Case Series**

Laurence Gascon MD, MSc, FRCSC, Sarah Benyo MD, Rebecca C. Nelson MD

Laryngoscope . 2024 Oct;134(10):4304-4306.

doi: <https://doi.org/10.1002/lary.31492>.

Abstract: Immune checkpoint inhibitors (ICIs) have demonstrated remarkable efficacy in the treatment of various advanced and metastatic malignancies in recent years and have proven to be pivotal in contemporary oncological strategies. As the utilization of ICIs expands, so does the recognition of adverse effects, highlighting the need for vigilance in monitoring and reporting outcomes. We present a case series of two cases of supraglottitis in patients treated with ICIs, including management strategies, thus adding a novel dimension to the respiratory implications of these agents.

Keywords: PD1-inhibitors; airway complications; immune checkpoint inhibitors; supraglottitis.

24COASNO14:**Title- Airway and Voice Outcomes After Thyroarytenoid Myomectomy for Bilateral Vocal Fold Immobility**

Zao M. Yang MD, Ronit Malka MD, Dylan Z. Erwin MD, Gregory Postma MD

Laryngoscope . 2024 Oct;134(10):4307-4312.

doi: <https://doi.org/10.1002/lary.31545>.

Abstract: Thyroarytenoid myomectomy demonstrated significant improvement in patient reported outcomes from bilateral vocal fold immobility while not significantly altering glottal structure. Data from this study suggest thyroarytenoid myomectomy improves dyspnea symptoms in patients with bilateral vocal fold immobility without impairing voice.

24COASNO15:**Title- The Global Experience of Laryngeal Transplantation: Series of Eleven Patients in Three Continents**

Estephania Candelo MD, MSc, Peter C. Belafsky MD, PhD, Mauricio Corrales MD, D. Gregory Farwell MD, Luis F. Gonzales MD, Maciej Grajek MD, PhD, Dominik A. Walczak MD, Marshall Strome MD, Robert R. Lorenz MD, Luis F. Tintinago MD, Maria A. Velez MD, William Victoria MD, Martin Birchall MD

Laryngoscope . 2024 Oct;134(10):4313-4320.

doi: <https://doi.org/10.1002/lary.31551>.

Abstract: Laryngeal transplantation is a complex procedure with significant morbidity but offers improved quality of life for selected patients with end-stage laryngeal disorders. An international registry is recommended for better quality pooled data. Future advancements may expand its application.

Keywords: airway reconstruction; composite tissue allotransplantation; laryngotracheal transplant; larynx; larynx stenosis; larynx transplant; trachea transplant.

24COASNO16:**Title- Multi-Instance Learning for Vocal Fold Leukoplakia Diagnosis Using White Light and Narrow-Band Imaging: A Multicenter Study**

Cheng-Wei Tie MD, De-Yang Li MD, Ji-Qing Zhu MD, Mei-Ling Wang MD, Jian-Hui Wang MD, Bing-Hong Chen MD, ...

Laryngoscope . 2024 Oct;134(10):4321-4328.

doi: <https://doi.org/10.1002/lary.31537>.

Abstract: In our study, we trained a multi-instance learning (MIL)-based artificial intelligence (AI) model on multi-center white light imaging (WLI) and narrow band imaging (NBI) images. This model aims to assist in distinguishing the benign or malignant nature of vocal fold leukoplakia (VFL).

Keywords: laryngoscopy; multi-instance learning; narrow-band imaging; vocal fold leukoplakia; white light imaging.

24COASNO17:**Title- New Model and Public Online Prediction Platform for Risk Stratification of Vocal Cord Leukoplakia**

Zufei Li MD, Jinghui Lu MD, Baiwen Zhang PhD, Joshua Si BS, Hong Zhang MD, MS, Zhen Zhong MD, Shuai He MD, Wenli Cai PhD, Tiancheng Li MD

Laryngoscope . 2024 Oct;134(10):4329-4337.

doi: <https://doi.org/10.1002/lary.31555>.

Abstract: The current diagnosis and treatment of vocal cord leukoplakia is relatively chaotic, lacking effective high-risk assessment methods. This study established and validated a model for vocal cord leukoplakia risk stratification, it not only has high accuracy, but also has been developed into a public prediction platform, which can be used and tested by everyone, and has strong practicality. This study may provide significant assistance to otolaryngologists in the treatment of vocal cord leukoplakia.

Keywords: laryngoscope images; machine learning; risk stratification; texture features; vocal cord leukoplakia.

24COASNO18:**Title- Nodal Metastases in Stage 3 Head and Neck Melanoma: Patterns of Metastases and Patterns of Failure**

Sharon Tzelnick MD, MPH, John R. de Almeida MD, MSc, FRCSC, Christopher M.K.L. Yao MD, FRCSC, Seth Kibel MD, Nathan Kuehne BSc, Rajan Grewal BSc, Marcus O Butler MD ...

Laryngoscope . 2024 Oct;134(10):4292-4297.

doi: <https://doi.org/10.1002/lary.31515>.

Abstract

Objective: Stage 3 patients with clinically positive nodal metastasis are treated with therapeutic neck dissection and adjuvant systemic therapy. The aim of our study was to examine the predictability of pre-operative CT as a nodal drainage assessment tool. **Methods:** Retrospective review of all patients with clinically positive head and neck cutaneous melanoma between 2010 and 2019. Clinical disease was diagnosed as radiological suspicious, biopsy-proven node. A pre-operative CT evaluation for nodal metastasis was compared to pathology report. **Results:** A total of 53 patients were included. Forty patients (75.5%) were males with a mean age of 59 (SD 15.52). The majority of patients (26.4%) had an unknown primary site. The most common sites for primary were the cheek in eight patients (15.1%) followed by forehead (9.4%) and lateral neck (9.4%). Preoperative CT predicted nodal disease in 84.6% of cases. The primary region that mainly failed from the previously described clinical prediction was the upper anterior neck with 83.3% parotid involvement. A total of 10 patients (18.9%) were diagnosis with non-clinical nodes on pathology with a median non-clinical node of 1 (range 1–2). Of them, 9 (90%) were in the same clinical levels detected by CT. Pre-operative CT was associated with a neck level accuracy of 98.1%. **Conclusion:** Stage 3 head and neck melanoma with clinically positive nodal metastasis that are eligible for an adjuvant systemic treatment, may benefit from a highly selective neck dissection according to their pre-operative imaging studies. This should be further evaluated in a large-scale clinical trial.

Keywords: drainage patterns; head and neck; melanoma; neck dissection.

24COASNO19:**Title- Sudden Deafness and Vestibulopathy in a Patient with Antibody Treatment for Metastatic Lung Cancer**

Mihnea Cristian Trache MD, Johannes Köntopf, Katharina Stölzel MD, PhD, Sophia Marie Häußler MD

Laryngoscope . 2024 Oct;134(10):4347-4350.

doi: <https://doi.org/10.1002/lary.31459>.

Abstract: We describe the case of a patient who presented with sudden onset vertigo and bilateral deafness while under immune checkpoint therapy for metastatic lung cancer. The diagnostic workup confirmed bilateral sensorineural deafness and bilateral loss of vestibular

function, while imaging revealed enhancement of the vestibulocochlear nerve. Initially, immunotherapy with PD-L1 antibody atezolizumab was the assumed cause of the described symptoms. However, further findings strengthened the suspicion of meningeosis neoplastica.

Keywords: immunotherapy; neoplasia; otology/neurotology; sudden sensorineural hearing loss; vertigo.

24COASNO20:

Title- Development and Initial Validation of a Meniere's Disease Quality of Life Instrument: The MenQOL

Alexandra E. Quimby MD, MPH, Jason A. Brant MD, Jeffrey P. Staab MD, MS, Michael J. Ruckenstein MD, MSc

Laryngoscope . 2024 Oct;134(10):4351-4357.

doi: <https://doi.org/10.1002/lary.31478>.

Abstract: We describe the development and validation of a questionnaire for the assessment of quality of life in Meniere's disease, the MenQOL. The MenQOL is a simple, valid patient-reported outcome measure, which may be used to assess the effects of treatment on disease-specific quality of life in patients with Meniere's disease.

Keywords: Meniere's; Ménière's disease; PROMs; QOL; quality of life.

24COASNO21:

Title- Lipids and Statin Medication With Sensorineural Hearing Loss: A Mendelian Randomization Study

Haoyang Wu MB, Wenting Deng MM, Yuelian Luo MM, Yaodong Xu MD, Hao Xiong PhD

Laryngoscope . 2024 Oct;134(10):4366-4373.

doi: <https://doi.org/10.1002/lary.31500>.

Abstract: This study is the pioneering effort employing Mendelian Randomization (MR) analysis to elucidate the relationship between lipids, statins, and sensorineural hearing loss (SNHL). Our findings establish a causal link between elevated triglyceride levels and an increased risk of SNHL. Although statins have demonstrated potential in reducing the risk of SNHL, their primary mechanism of action might not solely hinge on lowering triglycerides.

Keywords: Mendelian randomization; lipids; sensorineural hearing loss; statin medication.

24COASNO22:

Title- Next-generation Sequencing of MicroRNA in Acquired Middle Ear Cholesteatoma

Sung Jun Han MD, Sung Kyun Kim MD, PhD, Seok Min Hong MD, PhD

Laryngoscope . 2024 Oct;134(10):4374-4382.

doi: <https://doi.org/10.1002/lary.31507>.

Abstract: This was the first study investigating small non-coding RNAs in human acquired cholesteatoma using NGS technique. We were able to identify new miRNAs and pathways related to cholesteatoma.

Keywords: cholesteatoma; microRNA; middle ear.

24COASNO23:**Title- Micro-CT Imaging of Tracheal Development in Down Syndrome and Non-Down Syndrome Fetuses**

M. Matthijs Fockens MD, Yousif Dawood MD, Mika J. Zwart BS, Daniël Docter MD, Jaco Hagoort BEng, Frederik G. Dijkers MD, PhD, Bernadette S. de Bakker MD, PhD

Laryngoscope . 2024 Oct;134(10):4389-4395.

doi: <https://doi.org/10.1002/lary.31468>.

Abstract: Micro-CT of the trachea in Down syndrome and non-Down syndrome fetuses showed that morphology is similar between 13 and 21 weeks of gestation. The narrowed tracheal diameter characteristic for Down syndrome may occur later in fetal development or results from postnatal intubation trauma. The narrowest part of the trachea is in majority of fetuses the middle third.

Keywords: Down syndrome; fetal development; micro-CT; trachea.

24COASNO24:**Title- Clinical significance of positive resection margin for patients with rectal neuroendocrine tumors within 20 mm following initial endoscopic resection: A multi-center study,**

Mengping Duan, Zhanzhen Liu, Yan Qiao, Pinzhu Huang, Hao Xie, Wei Xiao, Shuangling Luo, Zhuochao Xie, Qiufeng Sun, Liwei Wang, Taixuan Wan, Zhihong Zhang, Huashan Liu, Haoqi Zheng, Yebohao Zhou, Dongxu Lei, Yunxing Shi, Sichong Lai, Ziwei Zhou, Fujin Ye, Liang Huang,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108651,

<https://doi.org/10.1016/j.ejso.2024.108651>.

Abstract: Background: The incidence of rectal neuroendocrine tumors (RNETs) has witnessed a significant surge, with a notable proportion being amenable to endoscopic removal. However, the clinical significance of positive resection margin for RNETs patients following endoscopic resection remain unknown, resulting in a lack of consensus regarding the appropriateness of implementing salvage treatment.

Methods: In this large, multicenter, retrospective cohort study, we analyzed the medical records of individuals who underwent endoscopic resection for RNETs and classified them into two groups: the positive resection margin and the negative resection margin group. The overall survival (OS) and disease-free survival (DFS) were compared among two group. The independent variables were identified using univariate and multivariate logistic regression analyses to predict positive resection margin. Then, the model was established to predict the patients with positive resection margin using multivariate logistic regression.

Results: 181 RNETs patients (34.3 %) represented positive margin after endoscopic resection. Following a median follow-up period of 72 months, tumor recurrence manifested in 12 out of 527 patients (2.2 %) and the presence of positive resection margin was associated with worse DFS. Independent factors correlating with positive resection margin included endoscopic resection method choice, RNETs located in the low rectum, NLR >4.44 and tumor size exceeding 14.89 mm. A prediction model was therefore established with high

predictive accuracy and excellent clinical applicability determined by calibration curves and DCA curve. Among RNETs patients with positive margin following endoscopic resection, implementing salvage treatment was beneficial for improving DFS and salvage endoscopic resection offer equal efficiency compared with salvage radical resection.

Conclusions: Positive resection margin following endoscopic resection may indicate negative prognosis. Salvage treatment can improve the prognosis of RNETs patients with positive resection margin. Notably, salvage local resection exhibited similar efficacy compared with radical surgery in term of survival benefit.

Keywords: RNETs; Endoscopic resection; Positive resection margin; Salvage treatment

24COASNO25:

Title- Injection Medialization in Infants with Vocal Fold Immobility Improves Dysphagia

Jennifer M Siu MD, MPH, Shaunak N. Amin MD, Jessica Colyer MD, Cassie Horner ARNP, Aarti Bhat MD, ...

Laryngoscope . 2024 Oct;134(10):4396-4401.

doi: <https://doi.org/10.1002/lary.31462>.

Abstract

Unilateral vocal fold immobility (VFI) is a known cause of morbidity amongst children following congenital heart surgery. Injection medialization (IM) provides medial distraction and improves glottic closure. Limited objective data is available for the effect of IM in young children (<2 years-old) with VFI. Retrospective case series of infants <2 who underwent IM for VFI after congenital cardiac surgery. Primary outcome was objective reduced risk of aspiration based on Dysphagia and Outcome Severity Scores (DOSS) on Video swallow study (VFSS) performed prior to and within 4 weeks following IM. Secondary analysis included perioperative complications and number of children who were able to avoid NG or G tube placement. 7 children <2 years of age had unilateral VFI after congenital cardiac surgery and underwent IM. The median age at time of initial cardiac surgery was 6 days (IQR 3-7). There was no intraoperative or postoperative stridor or associated complications. All 17 patients had preoperative aspiration noted on VFSS. Average swallowing outcomes on VFSS improved after IM with an increase in DOSS score (preop score 3 (IQR 2-4) to postop score 6.5 (IQR 5-7) [P = 0.001]). At 2 months following IM, of the patients who had improvement in swallowing function, 50% (n = 6) were able to feed completely orally, 25% (n = 3) were fed orally with an NG wean, and 3 (25%) had a G tube placed. Initial results suggest that IM is safe and improves early objective swallowing outcomes in children <2 years old with VFI after congenital cardiac surgery.

Keywords: injection medialization; vocal fold immobility.

24COASNO26:

Title- Congenital Sternoclavicular Sinus—Case Series of a Rare Lower Neck Deformity

Yan Huang MD, PhD, Mimi Xu MD, Xiaoli Sheng MD, PhD, Xixiang Gong MD, Bei Zhang MD, Shuling Huang MD, Liangsi Chen MD, PhD

Laryngoscope . 2024 Oct;134(10):4402-4408.

doi: <https://doi.org/10.1002/lary.31476>.

Abstract: CSCS, though uncommon, presents distinct regional involvement along with pathognomonic clinical and pathological features. CSCS is marked by a pale skin streak extending superiorly from the orifice—a diagnostic “skin streak sign.” Complete surgical excision constitutes an effective treatment modality for CSCS.

Keywords: congenital anomalies; fourth branchial cleft; sternoclavicular joint.

24COASNO27:

Title- The Impact of Race and the Affordable Care Act on Thyroid Carcinoma Outcomes: A National Cancer Database Study

Margaret Nurimba MD, Megha Sheth BA, Mark Swanson MD, Tamara Chambers MD
Laryngoscope . 2024 Oct;134(10):4421-4430.

doi: <https://doi.org/10.1002/lary.31559>.

Abstract: This cross-sectional study of differentiated thyroid carcinoma patients in the National Cancer Database demonstrates significant racial differences in disease presentation, treatment, and survival outcomes. The Affordable Care Act Medicaid was associated with improved survival outcomes.

Keywords: endocrine; health care disparities; thyroid cancer.

24COASNO28:

Title- Inpatient variation in PD-L1 expression and tumor mutational burden and the impact on outcomes to immune checkpoint inhibitor therapy in patients with non-small-cell lung cancer,

A. Di Federico, S.L. Alden, J.W. Smithy, B. Ricciuti, J.V. Alessi, X. Wang, F. Pecci, G. Lamberti, M.M. Gandhi, V.R. Vaz, ...

Annals of Oncology Volume 35, Issue 10, Pages 902-913

<https://doi.org/10.1016/j.annonc.2024.06.014>.

Abstract: Background: Programmed death receptor ligand 1 (PD-L1) tumor proportion score (TPS) and tumor mutational burden (TMB) are key predictive biomarkers for immune checkpoint inhibitor (ICI) efficacy in non-small-cell lung cancer (NSCLC). Data on their variation across multiple samples are limited. Patients and methods: Patients with NSCLC and multiple PD-L1 TPS and/or TMB assessments were included. Clinicopathologic and genomic data were analyzed according to PD-L1 and TMB variation. Results: In total, 402 PD-L1 sample pairs and 413 TMB sample pairs were included. Concordance between pairs was moderate for PD-L1 ($\rho = 0.53$, $P < 0.0001$) and high for TMB ($\rho = 0.80$, $P < 0.0001$). Shorter time between biopsies correlated with higher concordance in PD-L1, but not in TMB. Major increases ($\Delta\text{TPS} \geq +50\%$) and decreases ($\Delta\text{TPS} \leq -50\%$) in PD-L1 were observed in 9.7% and 8.0% of cases, respectively. PD-L1, but not TMB, decreased with intervening ICI ($P = 0.02$). Acquired copy number loss of CD274, PDCD1LG2, and JAK2 were associated with major decrease in PD-L1 ($q < 0.05$). Among patients with multiple PD-L1 assessments before ICI, cases where all samples had a PD-L1 $\geq 1\%$, compared to cases with at least one sample with PD-L1 $< 1\%$ and another with PD-L1 $\geq 1\%$, achieved improved objective response rate and progression-free survival (PFS). Among patients with at least one PD-L1

<1% and one $\geq$ 1% before ICI, cases where the most proximal sample was PD-L1 $\geq$ 1% had longer median PFS compared to cases where the most proximal PD-L1 was <1%. Among patients with multiple TMB assessments before ICI, patients with a TMB $\geq$ 10 mut/Mb based on the most recent assessment, as compared to those with a TMB <10 mut/Mb, achieved improved PFS and overall survival to ICI; instead, no differences were observed when patients were categorized using the oldest TMB assessment. Conclusions: Despite intrapatient concordance in PD-L1 and TMB, variation in these biomarkers can influence ICI outcomes, warranting consideration for reassessment before ICI initiation when feasible.

Keywords: non-small-cell lung cancer; PD-L1; TMB; variations; tumor genomics; immunotherapy

24COASNO29:

Title- Population-based germline breast cancer gene association studies and meta-analysis to inform wider mainstream testing,

C.F. Rowlands, S. Allen, J. Balmaña, S.M. Domchek, D.G. Evans, H. Hanson, N. Hoogerbrugge, P.A. James, K.L. Nathanson, M. Robson, M. Tischkowitz, W.D. Foulkes, C. Turnbull,

Annals of Oncology Volume 35, Issue 10, Pages 892-901

<https://doi.org/10.1016/j.annonc.2024.07.244>.

Abstract: Background: Germline genetic testing, previously restricted to familial and young-onset breast cancer, is now offered increasingly broadly to patients with ‘population-type’ breast cancer in mainstream oncology clinics, with wide variation in the genes included.

Patients and methods: Weighted meta-analysis was carried out for three population-based case-control studies (BRIDGES, CARRIERS and UK Biobank) comprising in total 101 397 women with breast cancer and 312 944 women without breast cancer, to quantify 37 putative breast cancer susceptibility genes (BCSGs) for the frequency of pathogenic variants (PVs) in unselected, ‘population-type’ breast cancer cases and their association with breast cancer and its subtypes. Results: Meta-analysed odds ratios (ORs) and frequencies of PVs in ‘population-type’ breast cancer cases were generated for BRCA1 (OR 8.73, 95% confidence interval (CI) 7.47-10.20; 1 in 101), BRCA2 (OR 5.68, 95% CI 5.13-6.30; 1 in 68) and PALB2 (OR 4.30, 95% CI 3.68-5.03; 1 in 187). For both CHEK2 (OR 2.40, 95% CI 2.21-2.62; 1 in 73) and ATM (OR 2.16, 95% CI 1.93-2.41; 1 in 132) subgroup analysis showed a stronger association with oestrogen receptor-positive disease. The magnitude of association and frequency of PVs were low for RAD51C (OR 1.53, 95% CI 1.29-2.04; 1 in 913), RAD51D (OR 1.76, 95% CI 1.29-2.41; 1 in 1079) and BARD1 (OR 2.34, 95% CI 1.85-2.97; 1 in 672); frequencies and associations were higher when the analysis was restricted to triple-negative breast cancers. The PV frequency in ‘population-type’ breast cancer cases was very low for ‘syndromic’ BCSGs TP53 (1 in 1844), STK11 (1 in 11 525), CDH1 (1 in 2668), PTEN (1 in 3755) and NF1 (1 in 1470), with metrics of association also modest ranging from OR 3.62 (95% CI 1.98-6.61) for TP53 down to OR 1.60 (95% CI 0.48-5.30) for STK11.

Conclusions: These metrics reflecting ‘population-type’ breast cancer will be informative in defining the appropriate gene set as we continue to expand to germline testing to an increasingly unselected group of breast cancer cases.

Keywords: meta-analysis; breast cancer; case–control; mainstream genetic testing; multigene panel testing

24COASNO30:

Title- Neoadjuvant short-course radiotherapy followed by camrelizumab and chemotherapy in locally advanced rectal cancer (UNION): early outcomes of a multicenter randomized phase III trial,

Z.Y. Lin, P. Zhang, P. Chi, Y. Xiao, X.M. Xu, A.M. Zhang, X.F. Qiu, J.X. Wu, Y. Yuan, Z.N. Wang, X.J. Qu, X. Li, X. Nie, M. Yang, K.L. Cai, W.K. Zhang, Y. Huang, Z. Sun, Z.G. Hou, C. Ma, F.Z. Cheng, K.X. Tao, T. Zhang,

Annals of Oncology Volume 35, Issue 10, Pages 882-891

<https://doi.org/10.1016/j.annonc.2024.06.015>.

Abstract: Background: Neoadjuvant short-course radiotherapy (SCRT) followed by CAPOX and camrelizumab (a programmed cell death protein 1 monoclonal antibody) has shown potential clinical activity for locally advanced rectal cancer (LARC) in a phase II trial. This study aimed to further confirm the efficacy and safety of SCRT followed by CAPOX and camrelizumab compared to long-course chemoradiotherapy (LCRT) followed by CAPOX alone as neoadjuvant treatment for LARC. Patients and methods: In this randomized, phase III trial, patients with T3-4/N+ rectal adenocarcinoma were randomly assigned (1 : 1) to receive SCRT or long-course chemoradiotherapy (LCRT), followed by two cycles of camrelizumab and CAPOX or CAPOX alone, respectively. After surgery, each arm underwent either six cycles of camrelizumab and CAPOX, followed by up to 17 doses of camrelizumab, or six cycles of CAPOX. The primary endpoint was pathological complete response (pCR) rate (ypT0N0) assessed by a blinded independent review committee. Key secondary endpoints tested hierarchically were 3-year event-free survival (EFS) rate and overall survival (OS). Results: Between July 2021 and March 2023, the intention-to-treat population comprised 113 patients in the experimental arm and 118 patients in the control arm, with surgery carried out in 92% and 83.9%, respectively. At data cut-off (11 July 2023), the pCR rates were 39.8% [95% confidence interval (CI) 30.7% to 49.5%] in the experimental arm compared to 15.3% (95% CI 9.3% to 23.0%) in the control arm (difference, 24.6%; odds ratio, 3.7; 95% CI 2.0-6.9; $P < 0.001$). In each arm, surgical complication rates were 40.0% and 40.8%, and grade ≥ 3 treatment-related adverse events were 29.2% and 27.2%. Three-year EFS rate and OS continue to mature. Conclusions: In LARC patients, neoadjuvant SCRT followed by camrelizumab plus CAPOX demonstrated a significantly higher pCR rate than LCRT followed by CAPOX, with a well-tolerated safety profile. SCRT followed by camrelizumab and chemotherapy can be recommended as a neoadjuvant treatment modality for these patients.

Keywords: locally advanced rectal cancer; short-course radiotherapy; camrelizumab; pathological complete response

24COASNO31:

Title- Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiotherapy in patients with locally advanced rectal cancer: long-term results of the UNICANCER-PRODIGE 23 trial,

T. Conroy, F. Castan, P.-L. Etienne, E. Rio, N. Mesgouez-Nebout, L. Evesque, V. Vendrely, X. Artignan, O. Bouché, D. Gargot, V. Boige, N. Bonichon-Lamichhane, C. Louvet, C. Morand, C. de la Fouchardière, A. Boilève, M. Delaye, S. Gourgou, V. Pezzella, C. Borg, *Annals of Oncology* Volume 35, Issue 10, Pages 873-881

<https://doi.org/10.1016/j.annonc.2024.06.019>.

Abstract: Background: The standard of care for the treatment of locally advanced rectal cancer (LARC) results in an excellent local disease control but the metastasis rates remain high. PRODIGE 23 demonstrated improved disease-free survival (DFS) and metastasis-free survival (MFS) with total neoadjuvant therapy versus standard of care in this population. Long-term analysis of overall survival (OS) is reported here. Patients and methods: The study design, participants, and primary endpoint DFS have been reported for this multicenter, randomized, open-label, phase III trial investigating the neoadjuvant chemotherapy with mFOLFIRINOX (6 cycles) followed by chemoradiotherapy, surgery, and adjuvant chemotherapy (6 cycles), versus chemoradiotherapy, surgery, and adjuvant chemotherapy (12 cycles) in patients with locally advanced rectal adenocarcinoma under peritoneal reflection on magnetic resonance imaging, and staged cT3/T4. Key secondary endpoints included OS, MFS, and local and metastatic recurrence rate. Results: With a median follow-up of 82.2 months, the 7-year DFS was 67.6% [95% confidence interval (CI) 60.7% to 73.9%] and 62.5% (95% CI 55.6% to 68.6%) [restricted mean survival time (RMST) difference 5.73 months, 95% CI 0.05-11.41 months, $P = 0.048$] in the neoadjuvant chemotherapy and the standard-of-care groups, respectively. The 7-year MFS was 79.2% (95% CI 73.0% to 84.4%) in the neoadjuvant chemotherapy group and 72.3% (95% CI 65.8% to 77.8%) in the standard-of-care group (RMST difference 6.1 months, 95% CI 0.93-11.37 months, $P = 0.021$). The 7-year OS was 81.9% (95% CI 75.8% to 86.6%) in the neoadjuvant chemotherapy group and 76.1% (95% CI 69.7% to 81.2%) in the standard-of-care group (RMST difference 4.37 months, 95% CI 0.35-8.38 months, $P = 0.033$). The safety profile remained unchanged since the previous analysis. Conclusions: Neoadjuvant chemotherapy with mFOLFIRINOX followed by chemoradiotherapy improved OS, confirmed long-term DFS and MFS benefits in LARC patients, and should be considered as one of the best options of care for these patients.

Keywords: rectal cancer; chemoradiotherapy; neoadjuvant; FOLFIRINOX

24COASNO32:

Title- Efficacy of TIL therapy in advanced cutaneous melanoma in the current immuno-oncology era: updated systematic review and meta-analysis,

S. Martín-Lluesma, I.M. Svane, U. Dafni, K. Vervita, D. Karlis, G. Dimopoulou, Z. Tsourti, M.W. Rohaan, J.B.A.G. Haanen, G. Coukos,

Annals of Oncology Volume 35, Issue 10, Pages 860-872

<https://doi.org/10.1016/j.annonc.2024.07.723>.

Abstract: Background: Adoptive cell therapy with tumor-infiltrating lymphocytes (TIL-ACT) has consistently shown efficacy in advanced melanoma. New results in the field provide now the opportunity to assess overall survival (OS) after TIL-ACT and to examine the effect of prior anti-programmed cell death protein 1/programmed death-ligand 1 [anti-PD-(L)1] therapy on its efficacy. Methods: A comprehensive search was conducted in PubMed up to 29 February 2024. In this meta-analysis we focused on studies including high-dose interleukin 2, doubling the patient numbers from our previous meta-analysis conducted up to December 2018 and using OS as the primary endpoint. Objective response rate (ORR), complete response rate (CRR), and duration of response were secondary endpoints. Findings are synthesized using tables, Kaplan–Meier plots, and forest plots. Pooled estimates for ORR and CRR were derived from fixed or random effects models. Results: A total of 13 high-dose interleukin 2 studies were included in this updated meta-analysis, with OS information available for 617 patients. No difference was found in median OS between studies with prior anti-PD-(L)1 treatment {n = 238; 17.5 months [95% confidence interval (CI) 13.8-20.5 months]} and without [n = 379; 16.3 months (95% CI 14.2-20.6 months)] (log-rank P = 0.53). ORR was estimated to be 34% (95% CI 16%-52%) and 44% (95% CI 37%-51%), for the studies with and without prior anti-PD-(L)1, respectively. The pooled estimate for CRR was 10% for both groups. No statistically significant difference was observed between the two groups, either for ORR (P = 0.15) or CRR (P = 0.45). Conclusions: Prior anti-PD-(L)1 treatment has no effect on the clinical response or survival benefit from TIL-ACT in advanced cutaneous melanoma. The benefit of TIL therapy in the second-line setting is also present after anti-PD-(L)1 treatment. Our data reinforce the evidence that TIL-ACT should be considered as a treatment of choice in second line for metastatic melanoma patients failing anti-PD-(L)1 therapy.

Keywords: adoptive cell therapy (ACT); tumor-infiltrating lymphocytes (TIL); advanced melanoma; prior anti-PD-(L)1; meta-analysis

24COASNO33:

Title- Breast cancer-related lymphedema: A critical review on recent progress,

Nasrin Sharifi, Sarfraz Ahmad,

Surgical Oncology, Volume 56,2024,102124,

<https://doi.org/10.1016/j.suronc.2024.102124>.

Abstract: Lymphedema is a chronic and debilitating condition characterized by an abnormal buildup of protein-rich fluid in the interstitial tissue, leading to the development of edema and tissue structural alterations. Breast cancer-related lymphedema (BCRL) remains a significant healthcare burden because it can develop within days and up to 11-years after the surgery. Specifically, axillary lymph node dissection leads to 30–50 % upper limb lymphedema, which involves the accumulation of protein-rich fluid. In this article, we provide a comprehensive/critical overview of post-mastectomy lymphedema, focusing on key aspects as diagnosis, prevention, and treatment methods. Beginning with clinical condition, the article explores the pathophysiology and risk factors associated with post-mastectomy lymphedema. It further delves into various diagnostic modalities available, highlighting the importance of early detection for optimal management of BCRL. We also examine

preventive strategies, emphasizing the role of patient education, lifestyle modifications, and proactive measures in reducing the risk of lymphedema development. In terms of treatment, the article covers a wide array of interventions ranging from conservative approaches like manual lymphatic drainage and compression therapy to surgical techniques such as lymph node transfer and lymphaticovenular anastomosis. Thus, through a comprehensive synthesis of current evidence and clinical practices updates, the review aims to guide healthcare professionals in delivering preventive and effective care while improving outcomes for individuals affected by post-mastectomy lymphedema.

Keywords: Breast cancer; Mastectomy; Lymphedema; Axillary lymph node dissection; Symptoms; Diagnosis; Bio-impedance spectroscopy; Prevention; Treatment; Management

24COASN034:

Title- Lymphocyte-to-monocyte, platelet-to-albumin and platelet-to-lymphocyte ratios as prognostic biomarkers for neoadjuvant treatment response in rectal cancer patients,

V. Făgărășan, V. Bințișan, R. Seicean, A. Caziuc, R. Allioaie, G. Făgărășan, A. Ilie-Ene, G. Dindelegan, C. Căinap,

Surgical Oncology, Volume 56, 2024, 102126,

<https://doi.org/10.1016/j.suronc.2024.102126>.

Abstract: Introduction: Systemic inflammatory response (SIR) indicators are an emerging category of serum biomarkers with significant potential as prognostic and predictive factors in various types of cancers. The primary focus of our study was to determine the prognostic value of the lymphocyte-to-monocyte ratio (LMR), platelet-to-albumin ratio (PLR) and platelet-to-lymphocyte ratio (PAR) in evaluating the response to neoadjuvant treatment for patients with rectal cancer. Materials and methods: We included 99 consecutive patients with rectal cancer which were admitted for surgery in our institution after completing a standard neoadjuvant radio-chemotherapy regimen. Several hematologic parameters, including LMR, PAR and PLR, were calculated by collecting and analyzing blood samples preoperatively. Cases were divided into groups using ROC curve analysis to determine optimal cutoff values for each of the investigated parameters. Treatment response was assessed through histopathological analysis of the resected specimens. Results: PLR values over 215.2 were correlated with the presence of lymph node metastasis. A similar correlation was observed between PAR values over 41.89 and lymph node positivity. A significant correlation was observed between the presence of tumor budding on histopathological analysis and high-PAR values. A statistically significant correlation between a high PLR and a good response to neoadjuvant treatment was determined. Conclusions: High PLR values may be associated with a more favorable treatment response to neoadjuvant radio-chemotherapy. A high PAR may be associated with unfavorable histopathological characteristics. Further studies on these readily available biomarkers are required in order to validate their clinical utility.

Keywords: Lymphocyte-to-monocyte ratio; Platelet-to-albumin ratio; Platelet-to-lymphocyte ratio; Rectal cancer; Radio-chemotherapy

24COASNO35:**Title- Molecular markers of proliferation, DNA repair, and immune infiltration defines high-risk subset of resectable retroperitoneal sarcomas,**

Nathan D. Seligson, Yan W. Asmann, Tariq Almeray, Yaquelin Coll Zayas, Mark A. Edgar, Steven Attia, Keith L. Knutson, Sanjay P. Bagaria,

Surgical Oncology, Volume 56, 2024, 102125,

<https://doi.org/10.1016/j.suronc.2024.102125>.

Abstract: Introduction: For retroperitoneal sarcomas (RPS), aggressive surgical resection offers the only chance for a cure; however, 5-year survival remains below 65%. Therefore, there is a critical need to identify drivers of poor clinical outcomes. Materials and methods : To identify biomarkers of tumors likely to recur following curative intent resection, we performed genomic and transcriptomic sequencing for 47 and 34 patients, respectively, with non-metastatic RPS at a single, high-volume sarcoma center. Results: At the DNA level, alterations in TERT were associated with poor disease-free survival (DFS) and overall survival (OS). Increased RNA expression of gene sets related to growth signaling and DNA repair were associated with poor DFS and OS. Infiltration of CD8+ T-Cells and activated dendritic cells were associated with poor DFS and OS. Conclusion :These findings may help to better identify and treat non-metastatic, high-risk RPS.

Keywords: Sarcoma; Proliferation; Surgery; DNA; RNA

24COASNO36:**Title- Does adding sacroiliac (type IV) resection to periacetabular (type II) resection increase complications or provide worse clinical outcomes? An institutional experience and systematic review,**

Rajko S. Vucicevic, Athan G. Zavras, Michael P. Fice, Charles Gusho, Austin Yu, Steven Gitelis, Alan T. Blank, Jonathan A. Myers, Matthew W. Colman,

Surgical Oncology, Volume 56, 2024, 102116,

<https://doi.org/10.1016/j.suronc.2024.102116>.

Abstract: Background and objectives: Internal hemipelvectomy is a limb sparing procedure most commonly indicated for malignant bone and soft tissue tumors of the pelvis. Partial resection and pelvic reconstruction may be challenging for orthopedic oncologists due to late presentation, high tumor burden, and complex anatomy. Specifically, wide resection of tumors involving the periacetabular and sacroiliac (SI) regions may compromise adjacent vital neurovascular structures, impair wound healing, or limit functional recovery. We aimed to present a series of patients treated at our institution who underwent periacetabular internal hemipelvectomy (Type II) with or without sacral extension (Type IV) in combination with a systematic review to investigate postoperative complications, functional outcomes, and implant and patient survival following pelvic tumor resection via Type II hemipelvectomy with or without Type IV resection. Materials and methods: A surgical registry of consecutive patients treated with internal hemipelvectomy for primary or secondary pelvic bone tumors at our institution since 1994 was retrospectively reviewed. All type II resection patients were stratified into two separate cohorts, based on whether or not periacetabular resection was extended beyond the SI joint to include the sacrum (Type IV), as per the Enneking and

Dunham classification. Patient demographics, operative parameters, complications, and oncological outcomes were collected. Categorical and continuous variables were compared with Pearson's chi square or Fisher's exact test and the Mann-Whitney U test, respectively. Literature review according to PRISMA guidelines queried studies pertaining to patient outcomes following periacetabular internal hemipelvectomy. The search strategy included combinations of the key words "internal hemipelvectomy", "pelvic reconstruction", "pelvic tumor", and "limb salvage". Pooled data was compared using Pearson's chi square. Statistical significance was established as $p < 0.05$. Results: A total of 76 patients were treated at our institution with internal hemipelvectomy for pelvic tumor resection, of whom 21 had periacetabular resection. Fifteen patients underwent Type II resection without Type IV involvement, whereas six patients had combined Type II/IV resection. There were no significant differences between groups in operative time, blood loss, complications, local recurrence, postoperative metastasis, or disease mortality. Systematic review yielded 69 studies comprising 929 patients who underwent internal hemipelvectomy with acetabular resection. Of these, 906 (97.5 %) had only Type II resection while 23 (2.5 %) had concomitant Type II/IV resection. While overall complication rates were comparable, Type II resection alone produced significantly fewer neurological complications when compared to Type II resection with sacral extension (3.9 % vs. 17.4 %, $p = 0.001$). No significant differences were found between rates of wound complications, infections, or construct failures. Local recurrence, postoperative metastasis, and survival outcomes were similar. Type II internal hemipelvectomy without Type IV resection on average produced higher postoperative MSTS functional scores than with Type IV resection. Conclusion: In our series, the two groups exhibited no differences. From the systematic review, operative parameters, local recurrence or systemic metastasis, implant survival, and disease mortality were comparable in patients undergoing Type II internal hemipelvectomy alone compared to patients undergoing some combination of Type II/IV resection. However, compound resections increased the risk of neurological complications and experienced poorer MSTS functional scores.

Keywords: Internal hemipelvectomy; Periacetabular; Sacroiliac; Resection; Orthopaedic oncology; Enneking classification

24COASNO37:

Title- Predictors of malignancy for treatment direction in patients with nonfunctioning adrenal incidentaloma,

Jongwon Jung, Byung-Chang Kim, Douk Kwon, Won Woong Kim, Yu-mi Lee, Kye Jin Park, Seung Hun Lee, Ki-Wook Chung, Tae-Yon Sung,

Surgical Oncology, Volume 56, 2024, 102122,

<https://doi.org/10.1016/j.suronc.2024.102122>.

Abstract: Background: Adrenal incidentalomas (AI) are predominantly nonfunctional and benign, and their detection and differential diagnosis are aided by computed tomography (CT). A nonfunctioning adrenal incidentaloma (NFAI) usually requires regular follow-up; however, adrenalectomy may be necessary in certain patients. This study aimed to evaluate prognostic predictors to guide the treatment approach for AIs. Methods: This retrospective,

single-center study involved patients diagnosed with NFAI from January 2000 to December 2020. Patients were divided into surgery and observation groups. A subgroup analysis compared malignant and benign adenoma within the surgery group. Results: A total of 307 patients were included, with 127 in the surgery group and 180 in the observation group. The surgery group displayed distinct morphological and malignant potential features in CT scans more frequently than the observational group did. The malignant subgroup exhibited more irregular borders on CT, and a higher number of patients with absolute washout under 60 % and relative washout under 40 % compared with the benign adenoma subgroup. Interestingly, within the surgery group, the mean tumor size was <4 cm for the both malignant and benign adenoma subgroups. Conclusions: Characterizing NFAI is important for appropriate treatment, as not all AIs have a favorable prognosis. CT findings associated with malignant potential, such as Hounsfield unit and washout values, were useful in determining the need for surgical treatment. However, the conventional criterion of a 4-cm size threshold for surgery was not a reliable malignancy predictor. Surgical resection should be considered for specific patient groups to ensure proper treatment over mere observation.

Keywords: Nonfunctioning adrenal incidentaloma; Hounsfield unit; Washout; Dynamic CT

24COASNO38:

Title- A Clinician's perspective on the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer management,

Tomasz Ostrowski, Jakub Litwiński, Katarzyna Gęca, Izabela Świetlicka, Wojciech P. Polkowski, Magdalena Skórzewska,

Surgical Oncology, Volume 56, 2024, 102117,

<https://doi.org/10.1016/j.suronc.2024.102117>.

Abstract: The prevention of intraperitoneal spread is of utmost importance in the management of advanced ovarian cancer (OC), thus demanding the exploration of innovative treatment techniques. The propensity of OC to spread to the peritoneum has highlighted the potential of local therapy as a promising approach. Among the proposed treatments thus far are several local intraperitoneal therapies, with hyperthermic intraperitoneal chemotherapy (HIPEC) being one of them. The application of HIPEC may potentially enhance the survival rates of patients with OC, as indicated by a recent publication of high-quality prospective data. The incorporation of HIPEC in conjunction with primary cytoreductive surgery (CRS) does not have a significant impact on either overall survival (OS) or disease-free survival (DFS). However, the incorporation of HIPEC alongside interval CRS, followed by systemic chemotherapy (CTH), markedly enhances both OS and DFS. The most recent data also substantiates the effectiveness of HIPEC in recurrent ovarian cancer (ROC), resulting in an improvement of survival outcomes. Additional research will contribute to the improvement of the HIPEC regimen and technique, as well as the precise identification of patients who will gain the most advantage from this treatment approach. It is recommended to discuss and update (inter)national clinical guidelines for managing patients with advanced OC and peritoneal involvement.

Keywords: Ovarian cancer; Hyperthermic intraperitoneal chemotherapy; HIPEC; Cytoreductive surgery; CRS

24COASNO39:

Title- Association between preoperative appendiceal histology grade and Pseudomyxoma peritonei grade offers a solution to avoid right hemicolectomy during cytoreductive surgery and HIPEC,

Richard Ghandour, Armelle Bardier, Mathilde Wagner, Brice Malgras, Rachid Kaci, Solène Doat, Marc Pocard,

Surgical Oncology, Volume 56, 2024, 102123,

<https://doi.org/10.1016/j.suronc.2024.102123>.

Abstract: Introduction & objectives: Treatment of PMP consists of appendectomy, cytoreductive surgery (CRS) and HIPEC. Right-sided hemicolectomy is necessary only when PMP is high grade, given the lymphatic invasion risk. To date, no single preoperative factor was identified as predictive of PMP grade. Materials & methods: Preoperative factors of a prospective cohort study on PMP were retrospectively analyzed, in order to identify situations linked with high or low grade appendiceal PMP. The main outcome was PMP grade on definitive histology after CRS. Results: n = 105. In univariate analysis, the grade of the appendiceal tumor, systematically reviewed in an expert center, showed an OR of 25.00 (95 % CI: 3.30–189.27; p = 0.001) and an NPV of 93.75 [85.36, 100]. Peritoneal biopsy demonstrated an OR of 19.80 (95 % CI: 2.30–170.71; p = 0.002) and a PPV of 90 [71.41, 100]. In multivariate analysis, these two factors remained significantly associated with PMP grade. Conclusion: Whenever appendiceal tumor is low grade on preoperative histology, the colon has to be spared unless completeness of CRS is compromised, which is a high-grade feature in fact. In case of high grade appendiceal tumor and/or peritoneal biopsy, right-sided hemicolectomy is warranted. If no histology is available preoperatively, adapt to intraoperative lesions as no preoperative factors seem to be predictive.

Keywords: Pseudomyxoma peritonei; Grade; Predictive factors; Cytoreductive surgery; Right-sided hemicolectomy

24COASNO40:

Title- Perioperative outcomes after hepatectomy for hepatocellular carcinoma among patients with cirrhosis, fatty liver disease, and clinically normal livers,

Meera Gupta, Daniel Davenport, Gabriel Orozco, Rashmi Bharadwaj, Robert E. Roses, B Mark Evers, Joseph Zwischenberger, Alexandre Ancheta, Malay B. Shah, Roberto Gedaly, Surgical Oncology, Volume 56, 2024, 102114,

<https://doi.org/10.1016/j.suronc.2024.102114>.

Abstract: Introduction: Despite superior outcomes with liver transplantation, cirrhotic patients with HCC may turn to other forms of definitive treatment. To understand perioperative outcomes, we examined perioperative mortality and major morbidity after hepatectomy for HCC among cirrhotic and non-cirrhotic patients. Methodology: The American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) database was queried for liver resection for HCC. Multivariable logistic regression was performed to determine the association between liver texture and risk of major non-infectious morbidity, post-hepatectomy liver failure (PHLF) and 30-day mortality. Results: From 2014 to 2018, 2203 patients underwent hepatectomy: 58.6 % cirrhotic, 12.8 % fatty and

28.6 % normal texture. Overall 30 day-mortality was 2.1 % (n = 46), although higher among fatty liver (2.8 %) and cirrhotic (2.6 %; $p = 0.025$) patients. The incidence of PHLF was 6.9 %, with hepatectomy type, cirrhosis, and platelet count as major risk factors. Age, resection type, and platelet count were associated with major complications. Trisegmentectomy and right hepatectomy (OR = 3.60, OR = 3.46, respectively) conferred a greater risk of major noninfectious morbidity compared to partial hepatectomy. Among cirrhotics alone, hepatectomy type, platelet count, preoperative sepsis and ASA class were associated with major morbidity. Discussion: Hepatic parenchymal disease/texture and function, presence of portal hypertension, and the extent of the liver resection are critical determinants of perioperative risk among HCC patients.

Keywords: Carcinoma; Hepatocellular; Hepatectomy; Liver cirrhosis

24COASNO41:

Title- Outcomes of right sleeve lower lobectomy vs. lower bilobectomy for lung malignancies,

Justin Issard, Geoffrey Brioude, Delphine Mitilian, Dominique Fabre, Vincent Thomas de Montpreville, Amir Hanna, Caroline Caramella, Cécile Lepechoux, ...

Surgical Oncology, Volume 56, 2024, 102100,

<https://doi.org/10.1016/j.suronc.2024.102100>.

Abstract: Objectives: Lower bilobectomy (LBL) leaves a residual pleural space potentially associated with adverse postoperative outcomes. In selected patients, right sleeve lower lobectomy (RSL) with anastomosis between the middle lobe bronchus and intermediate bronchus is feasible. The outcomes of RSL and LBL have not been compared. The aim of this study was to compare post-operative and long-term outcomes of RSL and LBL in patients with lung cancer. Methods: We retrospectively included patients managed by RSL or LBL at our referral chest-surgery institution between 2001 and 2019. Post-operative complications and mortality were compared. Kaplan-Meier curves were plotted to compare overall and disease-free survival rates. Results: We identified 23 patients with RSL and 96 with LBL. Postoperative mortality was 9 % after RSL and 5 % after LBL ($p = 0.41$). Bronchial fistula developed in 3 (13 %) RSL patients and 6 (6 %) LBL patients ($p = 0.23$). Pleural space complications were significantly less common after RSL (4/23 [17 %] vs. 45/96 [47 %], $p = 0.03$). Long-term vital capacity was significantly higher in the RSL group (91 % vs. 64 %, $p < 0.01$). Five-year survival did not differ significantly between groups (84 % vs. 72 %, $p = 0.09$). Conclusions: RSL was associated with similar postoperative mortality and long-term survival compared to LBL. However, pleural space complications were less common and lung function was better after RSL than after LBL. When feasible, RSL may deserve preference over LBL in patients with lung cancer managed at highly experienced centres.

Keywords: Bilobectomy; Sleeve lobectomy; Survival; Outcomes. lung cancer

24COASNO42:**Title- Prognostic impact of liver resection side in peri-hilar cholangiocarcinoma: A systematic review and meta-analysis,**

Cecilio Armengol-García, Valeria Blandin-Alvarez, David Eugenio Hinojosa-Gonzalez, Eduardo Flores-Villalba,

Surgical Oncology, Volume 56, 2024, 102113,

<https://doi.org/10.1016/j.suronc.2024.102113>.

Abstract: Background: Perihilar cholangiocarcinoma (pCCA) is a highly lethal hepatobiliary cancer. Radical resection offers the best chance for extended survival, but the efficacy of left-sided hepatectomy (LH) versus right-sided hepatectomy (RH) remains controversial. Methods: A systematic review and meta-analysis of non-randomized cohort studies comparing LH and RH in patients with resectable pCCA was conducted. Subanalyses were performed based on year of publication, region, number of cases and Bismuth classification (BC) $\geq$ III. Results: Nineteen studies involving 3838 patients were included, with 1779 (46 %) undergoing LH and 2059 (54 %) undergoing RH. LH was associated with increased overall survival (OS) in subgroup analysis of studies reporting hazard ratios (HR) (logHR 0.59; $p = 0.04$). LH showed higher rates of arterial resection (14 % vs. 1 %), transfusion (51 % vs. 41 %), operation time (MD 31.44 min), and bile leakage (21 % vs. 18 %), but lower rates of post-hepatectomy liver failure (9 % vs. 21 %) and 90-day mortality (8 % vs 16 %). Three-year disease-free survival rates increased in Western centers but decreased in Eastern centers. Conclusion: LH is linked to higher OS in this analysis but is a more demanding technique. Resection side decision should consider several factors, including future liver remnant, tumor location, vascular involvement, and surgical expertise.

Keywords: Perihilar cholangiocarcinoma; Left hepatectomy; Right hepatectomy; Survival; Morbidity

24COASNO43:**Title- Neoadjuvant therapy for melanoma: past, present, and future,**

Aaron D. Therien, Chinecherem M. Chime-Eze, Kristen E. Rhodin, Georgia M. Beasley,

Surgical Oncology, Volume 56, 2024, 102127,

<https://doi.org/10.1016/j.suronc.2024.102127>.

Abstract: Modern systemic therapy has dramatically improved outcomes for many patients with advanced metastatic melanoma. The success of these therapies has attracted much scientific interest while these therapies have made their way into the treatment of earlier stages of disease. Randomized trials have led to the approval of adjuvant immunotherapy and targeted therapy for resected stage III melanoma. However, most recently, these therapies have gained traction in the neoadjuvant setting. Promising early results led to randomized controlled trials that have now established neoadjuvant therapy as standard of care in advanced melanoma patients. Questions remain regarding the optimal choice of therapy, duration and timing of neoadjuvant therapy, extent of surgery, and the need for additional adjuvant therapy for patients who received neoadjuvant therapy. Herein we provide an overview of neoadjuvant therapy for melanoma and dilemmas to its broader applications.

24COASNO44:

Title- Radiological and pathological predictors of post-operative upstaging of breast ductal carcinoma in situ (DCIS) to invasive ductal carcinoma and lymph-nodes metastasis; a potential algorithm for node surgical de-escalation,

Gianluca Vanni, Marco Pellicciaro, Marco Materazzo, Massimiliano Berretta, Rosaria Meucci, Tommaso Perretta, Ilaria Portarena, ...

Surgical Oncology, Volume 56, 2024, 102128,

<https://doi.org/10.1016/j.suronc.2024.102128>.

Abstract: Background/aim: Ductal carcinoma in situ is considered a local disease with no metastatic potential, thus sentinel lymph node biopsy (SLNB) may be deemed an overtreatment. SLNB should be reserved for patients with invasive cancer, even though the risk of upstaging rises to 25 %. We aimed to identify clinicopathological predictors of post-operative upstaging in invasive carcinoma. Methods: We retrospectively analyzed patients with a pre-operative diagnosis of DCIS subjected to breast surgery between January 2017 to December 2021, and evaluated at the Breast Unit of PTV (Policlinico Tor Vergata, Rome).

Results: Out of 267 patients diagnosed with DCIS, 33(12.4 %) received a diagnosis upstaging and 9(3.37 %) patients presented with sentinel lymph node (SLN) metastasis. In multivariate analysis, grade 3 tumor (OR 1.9; 95 % CI 1.2–5.6), dense nodule at mammography (OR 1.3; 95 % CI 1.1–2.6) and presence of a solid nodule at ultrasonography (OR 1.5; 95 % CI 1.2–2.6) were independent upstaging predictors. Differently, the independent predictors for SLNB metastasis were: upstaging (OR 2.1; 95 % CI 1.2–4.6; $p = 0.0079$) and age between 40 and 60yrs (OR 1.4; 95 % CI 1.4–2.7; $p = 0.027$). All 9 patients with SLN metastasis received a diagnosis upstaging and were aged between 40 and 60 years old. Conclusion: We identified pre-operative independent predictors of upstaging to invasive ductal carcinoma. The combined use of different predictors in an algorithm for surgical treatments of DCIS could reduce the numbers of unnecessary SLNB.

Keywords: DCIS; Ductal carcinoma in situ; Omitting SNLB; Surgical de-escalation; Upstaging

24COASNO45:

Title- The effect of long-standing lymphopenia after radiation therapy on survival in rectal cancer,

Viacheslav Soyfer, Eli Lugovoy, Alla Nikolaevski-Berlin, Yasmin Korzets, Albert Schlocker, Orit Gutfeld, Inna Ospovat, Uri Amit, ...

Surgical Oncology, Volume 56, 2024, 102119,

<https://doi.org/10.1016/j.suronc.2024.102119>.

Abstract: Background: Lymphopenia and high neutrophil-to-lymphocyte ratio are known negative prognostic factors in rectal cancer. Until recently, however, lymphopenia was regarded as a minor sequela following radiation therapy (RT). The immune system's influence on rectal cancer treatment outcomes led us to evaluate the impact of lymphopenia at various time points, before, during, and following radiotherapy. We hypothesized that chronic lymphopenia following radiotherapy might negatively influence the survival of patients, and pre-treatment lymphopenia may be predictive of poor outcomes. Methods :This

retrospective study involved 110 patients treated for rectal cancer between 2015 and 2019. The oncological outcomes are defined as alive without disease (AWOD), alive with disease (AWD), and death. These outcome probabilities tested against variables of lymphopenia before RT, during RT, and at several post-RT follow-up time points. Results: At the end of the study, 69 patients were AWOD (63 %), 13 were AWD (12 %) and 28 had died (25 %). Treatment results were assessed with according level of lymphocytes measured one year following RT: 35 out of 39 patients (89.7 %) with normal values were AWOD. In 65 patients with sustained lymphopenia, 52 % were AWOD, 18.5 % AWD and 29 % died. A similar difference was found at all time-points up to 2 years following RT ($p < 0.004$). The results of our study shows that pre-existing lymphopenia (prior to RT) is associated with a 3 times greater chance of death compared to patients with normal lymphocyte levels prior to RT. The PFS significantly affected by lymphopenia at all time-points after RT. An NLR of more than 4 was associated with a 3-time higher risk of recurrence than lower NLR scores ($p = 0.0054$). Conclusion: Our results support the relevance of lymphopenia and NLR in the prognosis of rectal cancer. We believe this is the first study showing a negative correlation between sustained lymphopenia and OS following RT.

24COASNO46:**Title- Radioactive iodine ablation therapy reduces the risk of recurrent disease in pediatric differentiated thyroid carcinoma,**

Eman Toraih, Alyssa Webster, Eric Pineda, Dylan Pinion, Lily Baer, Emily Persons, Marcela Herrera, Mohammad Hussein, Emad Kandil,
Surgical Oncology, Volume 56, 2024, 102120,
<https://doi.org/10.1016/j.suronc.2024.102120>.

Abstract: Background: While radioactive iodine (RAI) therapy in older adults with differentiated thyroid carcinoma (DTC) reduces recurrence, data in pediatrics remain limited. We conducted a meta-analysis to quantify outcomes and recurrence risk with RAI versus thyroidectomy alone in the pediatric population. Methods: Systematic literature review identified 34 retrospective studies including 2913 DTC patients under age 22 years (published 2005–2023). Meta-analysis calculated pooled rates of disease persistence and recurrence. Relative risk ratios compared odds of recurrence with RAI versus no RAI. Results: Patients had mean age 14.7 years (95 % CI, 14.2–15.2) and were 75.9 % female (95 % CI, 73.8–78.1 %). Majority (90.2 %) received RAI. Pooled persistence rate was 30.3 % (95 % CI, 21.7–39.5 %); higher with RAI (31.5 %; 95 % CI, 22.4–41.3 %) than no RAI (4.5 %; 95 % CI, 0.0–18.7 %) (OR 3.28; 95 % CI, 1.82–5.91; $p < 0.001$). Recurrence rate was 8.97 % (95 % CI, 4.78–14.3 %). Those with RAI had 53.1 % lower recurrence risk versus no RAI (RR 0.47; 95 % CI, 0.27–0.82; $p = 0.007$). Median follow-up was 7.2 years (95 % CI, 5.8–8.5 years), with no association between follow-up duration and recurrence ($r = -0.053$; $p = 0.80$). Conclusions: RAI therapy as an adjunct to thyroidectomy is associated with a significantly lower risk of long-term recurrence in pediatric DTC. These findings advocate for the use of RAI in preventing recurrence among high-risk pediatric patients with DTC.

Keywords: Pediatric thyroid carcinoma; Radioactive iodine therapy; DTC recurrence; Adjuvant treatment; Systematic review; Meta-analysis

24COASNO47:**Title- Radiotherapy leads to improved overall survival in patients undergoing resection for Undifferentiated pleomorphic sarcoma,**

Sarah C. Tepper, Linus Lee, Michael P. Fice, Conor M. Jones, Neil Buac, Gayathri Vijayakumar, Dian Wang, Matthew W. Colman, Steven Gitelis, Alan T. Blank,
Surgical Oncology, Volume 56, 2024, 102118,
<https://doi.org/10.1016/j.suronc.2024.102118>.

Abstract: Background and objectives: Undifferentiated pleomorphic sarcoma (UPS) is a frequent subtype within the heterogeneous group of soft tissue sarcomas (STS). The use of radiotherapy (RT) has become an important component of a multimodal approach to treating STS. Key studies have demonstrated that the addition of RT improves rates of local control in STS, though the effect on overall survival (OS) is less clear. Furthermore, there is very limited and conflicting evidence regarding effect of RT on overall survival in UPS. The purposes of this investigation were to examine the association between RT and OS in UPS patients undergoing surgical resection and to determine independent prognostic indicators of OS in this patient population. Methods: This was a retrospective review of patients who underwent surgical treatment for primary UPS from 1993 to 2021. Associations between RT and OS were analyzed with Kaplan-Meier curves and log-rank testing. Cox proportional hazards regression analysis was used to determine independent prognostic factors of OS.

Results: One hundred and fourteen patients who underwent surgical resection of primary UPS were included in the study. Ninety-six (84.2 %) patients received RT perioperatively. Use of RT was associated with improved OS on log-rank testing (hazard ratio (HR) 0.20; 95 % confidence interval (CI) 0.11–0.36; $p < 0.001$). On multivariate analysis, RT was an independent predictor of improved OS (HR 0.18; 95 % CI 0.09–0.39; $p < 0.001$) while metastasis at presentation (HR 4.82; 95 % CI 2.26–10.27; $p < 0.001$) and older age (HR 1.92; 95 % CI 1.20–3.36; $p = 0.02$) were predictive of decreased OS. Use of RT was not significantly associated with a lower rate of local recurrence in our cohort ($p = 0.49$).

Conclusions: Use of RT in combination with surgery was an independent prognostic indicator of improved overall survival in UPS patients. Older age and metastasis at presentation were associated with worse overall survival. Based on this and other available studies, treatment for UPS should involve limb-sparing resection when feasible with RT to ensure optimal survival.

Keywords: Sarcoma; Radiotherapy; Survival; Undifferentiated

24COASNO48:**Title- Intraoperative indocyanine green angiography in preventing hypoparathyroidism after thyroid cancer surgery**

Carlos Eduardo Santa Ritta Barreira MD, PhD, André Póvoa Miranda MD, Thaísa Fabiana Peixoto MD, Rodrigo Nascimento Pinheiro PhD
Journal of Surgical Oncology, Volume 130, Issue Pages 349-658
<https://doi.org/10.1002/jso.27762>

Abstract: Background: The aim of this study was to determine whether the use of indocyanine green angiography to identify devascularized parathyroids during thyroidectomy

for thyroid cancer would decrease the rates of postoperative hypoparathyroidism. Methods: Retrospective study of patients who had undergone total thyroidectomy for treatment of thyroid cancer between March 2021 and March 2023. The indocyanine group included patients with all four parathyroids identified and evaluated by indocyanine green angiography at the end of the procedure. Those with parathyroid glands classified with no vascularization had the glands autotransplanted. A group without indocyanine angiography was used to compare results. Results: The analysis included 100 patients in each group. Indocyanine angiography identified 14.75% of devascularized parathyroids at surgery. The number of parathyroids with a score of 2 (i.e., good vascularization) was not a safe predictor of normal parathyroid hormone levels after surgery. Indeed, 29.2% of the patients with three parathyroids with a score of 2 developed transient hypoparathyroidism. Permanent hypoparathyroidism occurred in 7% of the patients without indocyanine group and in none of the patients in the indocyanine group ($p=0.014$). Conclusion: Intraoperative angiography with indocyanine green could contribute to reduce the occurrence of permanent hypoparathyroidism in patients undergoing surgical treatment for thyroid cancer.

24COASNO49:**Title- Association of surgeon's sex, and surgeon-patient dyad with financial outcomes among patients undergoing cancer surgery**

Muhammad Muntazir Mehdi Khan MBBS, Muhammad M. Munir MD, Selamawit Woldeesenbet PhD, Mujtaba Khalil MD, Abdullah Altaf MBBS, Zayed Rashid MBBS

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 386-394

DOI: <https://doi.org/10.1002/jso.27752>

Abstract: Background and Objectives: Surgeon sex has been associated with perioperative clinical outcomes among patients undergoing oncologic surgery. There may be variations in financial outcomes relative to the surgeon-patient dyad. We sought to define the association of surgeon's sex with perioperative financial outcomes following cancer surgery. Methods: Patients who underwent resection of lung, breast, hepato-pancreato-biliary (HPB), or colorectal cancer between 2014 and 2021 were identified from the Medicare Standard Analytic Files. A generalized linear model with gamma regression was utilized to characterize the association between sex concordance and expenditures. Results: Among 207,935 Medicare beneficiaries (breast: $n=14,753$, 7.1%, lung: $n=59,644$, 28.7%, HPB: $n=23,400$, 11.3%, colorectal: $n=110,118$, 53.0%), 87.8% ($n=182,643$) and 12.2% ($n=25,292$) of patients were treated by male and female surgeons, respectively. On multivariable analysis, female surgeon sex was associated with slightly reduced index expenditures (mean difference $-\$353$, 95%CI $-\$580$, $-\$126$; $p=0.003$). However, there were no differences in 90-day post-discharge inpatient (mean difference $-\$225$, 95%CI $-\$570$, $-\$121$; $p=0.205$) and total expenditures (mean difference $\$133$, 95%CI $-\$279$, $\$545$; $p=0.525$). Conclusions: There was minor risk-adjusted variation in perioperative expenditures relative to surgeon sex. To improve perioperative financial outcomes, a diverse surgical workforce with respect to patient and surgeon sex is warranted.

24COASNO50:**Title- Survival benefit associated with screening of patients at elevated risk for pancreatic cancer,**

William J. Kane MD, MS, Kathleen R. Haden NP, Elizabeth N. Martin, Vanessa M. Shami MD, Andrew Y. Wang MD, Daniel S. Strand MD, Sara J. Adair MS

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 485-492

DOI: <https://doi.org/10.1002/jso.27784>

Abstract: Background & Objectives: Screening for pancreatic cancer is recommended for individuals with a strong family history, certain genetic syndromes, or a neoplastic cyst of the pancreas. However, limited data supports a survival benefit attributable to screening these higher-risk individuals. Methods: All patients enrolled in screening at a High-Risk Pancreatic Cancer Clinic (HRC) from July 2013 to June 2020 were identified from a prospectively maintained institutional database and compared to patients evaluated at a Surgical Oncology Clinic (SOC) at the same institution during the same period. Clinical outcomes of patients selected for surgical resection, particularly clinicopathologic stage and overall survival, were compared. Results: Among 826 HRC patients followed for a median (IQR) of 2.3 (0.8–4.2) years, 128 were selected for surgical resection and compared to 402 SOC patients selected for resection. Overall survival was significantly longer among HRC patients (median survival: not reached vs. 2.6 years, $p < 0.001$). Among 31 HRC and 217 SOC patients with a diagnosis of pancreatic ductal adenocarcinoma (PDAC), the majority of HRC patients were diagnosed with stage 0 disease (carcinoma in situ), while the majority of SOC patients were diagnosed with stage II disease ($p < 0.001$). Overall survival after resection of invasive PDAC was also significantly longer among HRC patients compared to SOC patients (median survival 5.5 vs. 1.6 years, $p = 0.002$). Conclusion: Patients at increased risk for PDAC and followed with guideline-based screening exhibited downstaging of disease and improved survival from PDAC in comparison to patients who were not screened.

24COASNO51:**Title- Resection versus resection with ablation: Analysis from the colorectal liver operative metastasis international collaborative**

Bigyan B. Mainali MD, MPH, Cristian D. Valenzuela MD, Omeed Moaven MD, John A. Stauffer MD, Nico R. Del Piccolo MD, ...

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 516-522

DOI: <https://doi.org/10.1002/jso.27789>

Abstract: Background: Thermal ablation has recently become a key therapy for the treatment of colorectal liver metastasis (CLM). However, the role of ablation in combination with resection has not yet been firmly established. We hypothesize that in patients with CLM, those who undergo liver resection with ablation (RA) have similar outcomes compared with those who undergo liver resection only. Methods: We reviewed a multicenter international database of 906 surgical procedures for CLM from 5 high volume hepatobiliary surgical units. Patients undergoing RA ($n = 63$) were matched based on the number of lesions and

tumor size using a 1:1 balanced propensity score analysis with those having resection only ($n = 63$). Our primary outcomes were overall survival (OS) and disease-free survival (DFS). Results: The mean age of our cohort was 58 ± 11 years, with 43% females. With a median follow-up of 70.8 months, patients in the resection and RA group had a median OS of 45.1 and 54.8 months ($p = 0.71$), respectively. The median DFS was 22.7 and 14.2 months ($p = 0.045$), respectively. Using a multivariate Cox proportional hazards regression model, the treatment approach was not associated with OS ($p = 0.94$) or DFS ($p = 0.059$). A higher number of lesions is independently associated with worse DFS (hazard ratio: 1.12, $p < 0.01$). When there was disease recurrence, the region of recurrence was similar between the RA versus resection only groups ($p = 0.27$), but there was a shorter time to recurrence in the RA group ($p = 0.002$). Conclusion: For CLM, the treatment approach was not significantly associated with OS or DFS, while tumor biology likely played an important role. Prospective research on the quality and effectiveness of thermal ablation combined with hepatic resection is warranted.

24COASNO52:**Title- Survival and pulmonary function in stage IA non-small cell lung cancer after sublobar resection versus lobectomy: An updated meta-analysis**

Isadora Mamede, Leonardo Ribeiro MD, Carlos Stecca MD, Lorena Escalante-Romero MD, Marcelo Cypel MD, MSc

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 523-532

DOI: <https://doi.org/10.1002/jso.27767>

Abstract: Traditionally, lobectomy was standard for stage IA non-small-cell lung cancer (NSCLC). Recent RCTs suggest sublobar resection's comparable outcomes. Our meta-analysis, incorporating 30 studies (including four RCTs), assessed sublobar resection's efficacy. Employing a random-effects model and I^2 statistics for heterogeneity, we found sublobar resection reduced DFS (HR 1.31, $p < 0.01$) and OS (HR 1.27, $p < 0.01$) overall. However, RCT subgroup analysis showed no significant differences in DFS ($p = 0.28$) or OS ($p = 0.62$). Sublobar resection is a viable option for well-selected patients.

24COASNO53:**Title- Immediate and delayed flap reconstruction have equivalent outcomes and associated costs following soft tissue sarcoma surgery**

Pearce B. Haldeman, Cyril Harfouche, Ricardo Rosales, Conner Trimm, Liane Chun, Christopher Reid, James H. Flint, Frank Chiarappa

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 562-568

DOI: <https://doi.org/10.1002/jso.27770>

Abstract: Background and Objectives: Surgical treatment of soft tissue sarcoma (STS) involves wide resection of the tumor, which can necessitate soft tissue reconstruction with local or free tissue flaps. This retrospective study compares cost, surgical and oncologic outcomes between patients undergoing reconstruction with immediate versus delayed flap coverage following STS resection. Methods: Thirty-four patients who underwent planned flap reconstruction following resection of primary STS were identified retrospectively.

Twenty-four (71%) received immediate reconstruction during the index surgery and 10 (29%) underwent planned delayed reconstruction. Preoperative patient-specific metrics, tumor characteristics, and surgical and patient outcomes were collected. Total hospital charges associated with every encounter during the perioperative period were obtained. Results: Patient demographics, comorbidities, tumor metrics, and surgical characteristics were equivalent between groups. Postoperative wound complications, reoperations, readmissions, and disease-specific survival did not differ between cohorts. Costs associated with each reconstruction strategy were equivalent on bivariate and multivariate testing, when accounting for operating room time, hospital length of stay, and reoperation rate. Conclusions: Our study identifies no significant difference in patient outcome measures or cost between planned immediate and delayed flap reconstruction following STS resection. These results support the implementation of either treatment strategy in keeping with patient-centered, multidisciplinary care principles.

24COASNO54:**Title- The utility of intraoperative marrow margin frozen section in extremity bone sarcoma resection**

Aaron Gazendam MD, MSc, FRCSC, David Clever MD, PhD, Liuzhe Zhang MD, Anthony Griffin MSc, Kim Tsoi MD, PhD, FRCSC, ...

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 574-578

DOI: <https://doi.org/10.1002/jso.27769>

Abstract: Background and Objectives: Intraoperative frozen section analysis is commonly used to evaluate marrow margins during extremity bone sarcoma resections, but its efficacy in the era of magnetic resonance imaging is debated. This study aimed to compare the accuracy of intraoperative frozen section assessment with final pathology, assess its correlation with gross intraoperative margin assessment, and evaluate its impact on surgical decision making.

Methods: Consecutive patients undergoing extremity bone sarcoma resections from 2010 to 2022 at a single sarcoma center were included. Intraoperative frozen section and gross margin assessments were compared to final pathology using positive predictive values (PPV) and negative predictive values (NPV). Changes in surgical decisions due to positive intraoperative margins were recorded. Results: Of 166 intraoperative frozen section marrow margins, four were indeterminant/positive, with two false positive/indeterminant findings and two false negatives compared to final pathology. Gross intraoperative assessment had no false positives and two false negatives. Frozen section analysis yielded a PPV of 50% (95% confidence interval [CI]: 16%–84%) and NPV of 98.8% (95% CI: 97%–100%), while gross assessment had a PPV of 100% (95% CI: 16%–100%) and NPV of 98.8% (95% CI: 97%–100%). Positive frozen section margins led to additional resections in three of four cases. Conclusions: Intraoperative frozen section analysis did not offer added clinical value beyond gross margin assessment in extremity bone sarcoma resections. It exhibited a low PPV and led to unnecessary additional resections. Gross intraoperative assessment proved adequate for margin evaluation, potentially saving time and resources.

24COASNO55:**Title- Use of neoadjuvant paclitaxel in breast angiosarcoma—Impact on surgical resection and response rates**

Luke V. Selby MD, MS, Emma Clark MD, MS, James L. Chen MD, Gabriel Tinoco MD, Joal D. Beane MD...

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 579-585

DOI: <https://doi.org/10.1002/jso.27772>

Abstract: Objective: Breast angiosarcoma is a tumor that can arise as a primary breast tumor or in association with prior radiation therapy. Angiosarcomas are uniquely sensitive to paclitaxel. This study evaluated the impact neoadjuvant paclitaxel (NAC) therapy has on surgical outcomes, tumor recurrence, and survival in breast angiosarcomas. Methods: Patients with angiosarcoma of the breast, either primary or radiation-associated, were identified from a prospective institutional database. Patients receiving NAC were compared to those treated with upfront surgery. Clinical and pathological variables were compared using Student's *t*-test or Fisher's exact test, differences in survival were calculated using Kaplan–Meier methods. Results: Twenty-four patients with angiosarcoma of the breast were identified, 10 with primary angiosarcoma and 14 with radiation-associated angiosarcoma. Twelve patients received NAC, 6 of each with primary angiosarcoma or radiation-associated angiosarcoma. Of these 12 patients, 11 had a margin negative resection (91%) of which, nine had a complete pathological response on surgical pathology. Of the 12 surgery-first patients, four ($n = 4/12$, 33%) had positive surgical margins, two of the four underwent reoperation. With a median follow-up of 16 months, four NAC patients had recurrence (33%) compared to six patients in the surgery-first group (58%) ($p = 0.41$). While not statistically significant, NAC patients had a 33% less risk of recurring compared to surgery-first patients ([hazard ratio = 0.67 (95% confidence interval 0.16–2.72; $p = 0.6$)]. Conclusion: NAC for breast angiosarcoma may be associated with high rates of complete pathological response and margin-negative resection. However, this did not impact overall survival. Future prospective control studies and longer follow-up periods are warranted to understand the impact on recurrence and survival.

24COASNO56:**Title- Prevalence and impact of frailty in patients undergoing colorectal cancer surgery: A systematic review and meta-analysis based on modified frailty index**

Liwen Xia, Rulan Yin, Lifen Mao, Xiaoqing Shi

Journal of Surgical Oncology, Volume130, Issue3 September 2024 Pages 604-612

DOI: <https://doi.org/10.1002/jso.27778>

Abstract: Frailty has been linked to unfavorable postoperative outcomes in patients with colorectal cancer (CRC). However, the prevalence of frailty among CRC surgery patients and its association with mortality and postoperative complications, as evaluated by the modified frailty index (mFI), have not been thoroughly investigated and necessitate clarification. PubMed, Web of Science, Embase, and CBM databases were systematically searched for relevant studies (up to January 2024), and the pooled prevalence and odds ratio (OR) estimate were calculated. A total of 16 studies containing 245 747 patients undergoing CRC surgery were included. The prevalence of frailty among CRC surgery patients was 31% (95%

confidence interval [CI] = 20%–42%; $I^2 = 100\%$, $p < 0.001$). In patients undergoing CRC surgery, frailty was associated with a higher incidence of postoperative complications (OR = 1.94; 95% CI = 1.47–2.56; $I^2 = 91.9\%$, $p < 0.001$), but it did not exhibit any significant correlation with the 30-day mortality (OR = 5.17; 95% CI = 0.39–68.64; $I^2 = 94.4\%$, $p < 0.001$). Frailty is common in CRC surgery and exerts a significant negative impact on the postoperative outcomes. Future research could explore the potential of the mFI to facilitate a more streamlined and precise quantification of frailty, thereby establishing a refined understanding of its correlation with surgery prognosis.

24COASNO57:**Title- The evolution of tumor enucleation partial nephrectomy: A comparison of perioperative outcomes for sutureless hemostatic bandage as an alternative to standard renorrhaphy**

Goran Rac, Jeffrey L. Ellis, Nicholas J. Lanzotti, Mallory E. McCormick, Michael D. Felice, Sarang Janakiraman, Shalin Desai, ...

Journal of Surgical Oncology, Volume 130, Issue 3 September 2024 Pages 653–658

DOI: <https://doi.org/10.1002/jso.27775>

Abstract: Background: The standard approach to hemostasis during partial nephrectomy (PN) is to perform suture renorrhaphy (SR). Application of a hemostatic bandage (HB) is an alternative to minimize blood loss and devitalized renal parenchyma. We aim to evaluate perioperative outcomes of PN with tumor enucleation (TE) comparing SR to HB. Methods: We analyzed a retrospective cohort of 195 patients undergoing robot-assisted laparoscopic PN with TE performed at a tertiary referral center (2012–2022). Hemostasis was obtained with SR in 54 patients while 141 patients underwent application of HB consisting of Surgicel®, Gelfoam® soaked in thrombin, and Floseal®. Results: SR patients had tumors of greater complexity by RENAL nephrometry score compared to HB patients ($p < 0.001$). Operative time (141 vs. 183 min, $p < 0.001$), warm ischemia time (11.6 vs. 24.2 min, $p < 0.001$), estimated blood loss (37 vs. 214 mL, $p < 0.001$), and length of stay (1.2 vs. 1.8 days, $p < 0.001$) favored HB. There was no significant difference in Clavien–Dindo grade ≥ 3 complications ($p = 0.22$). Renal function was comparable with mean estimated glomerular filtration rate decrease of 0.66 and 0.54 mL/min/1.73 m² at 3 months postoperatively for HB and SR, respectively ($p = 0.93$). Conclusions: Application of an HB is a safe alternative to SR for hemostasis following PN with TE in appropriately selected patients.

24COASNO58:**Title- Prognostic impact of intraoperative rupture in early-stage epithelial ovarian cancer: an ancillary study of GORILLA-3002,**

Eun Bi Jang, Eun Jung Yang, A Jin Lee, Hee Seung Kim, Suk-Joon Chang, Nam Kyeong Kim, Dong Hoon Suh, Sung Jong Lee, Yoo-Young Lee, Ji Eun Lee, Eun Ji Nam, Seung-Hyuk Shim,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108515,

<https://doi.org/10.1016/j.ejso.2024.108515>.

Abstract: Objective- To evaluate whether intraoperative rupture affects oncological outcomes in patients with early-stage epithelial ovarian cancer (EOC).

Methods: A multicenter retrospective study was conducted on patients with early-stage EOC based on surgical and final pathological reports between 2007 and 2021. Oncologic outcomes were compared between the unruptured group (International Federation of Gynaecology and Obstetrics [FIGO] stage IA/IB) and ruptured group (FIGO stage IC1). The primary endpoint was progression-free survival (PFS). Propensity score matching (PSM) was performed to adjust for the imbalance in prognostic factors between the groups. Results- Overall, 197 (58.3 %) patients comprised the unruptured group (FIGO stage IA/IB), and 141 (41.7 %) were in the intraoperatively ruptured group (FIGO stage IC1). No significant difference in the 5-year PFS was observed between the two groups before PSM (92.65 % vs. 92.80 %, $P = 0.93$). After PSM, the 5-year PFS showed a noticeable decrease in the ruptured group compared to the unruptured group, although this difference showed borderline statistical significance (96.90 % vs. 89.82 %, $P = 0.061$). This trend was particularly discernible in cases with aggressive tumor characteristics; intraoperative rupture remained an independent prognostic factor for shorter PFS in patients with high-grade histology (adjusted hazard ratio = 14.4, 95 % confidence interval = 2.8–74.1). Conclusions- Although not statistically significant, intraoperative rupture may negatively affect PFS in these patients after PSM. Therefore, rupture during surgery should be avoided as it can cause upstaging and unnecessary chemotherapy.

Keywords: Ovarian cancer; Rupture; Spontaneous; Prognosis; Surgery

24COASNO59:

Title- Learning curve in retroperitoneal sarcoma surgery,

Laura Samà, Sonia Kumar, Laura Ruspi, Federico Sicoli, Vittoria D'Amato, Ömer Mintemur, Salvatore L. Renne, Vittorio L. Quagliuolo, Ferdinando CM. Cananzi, European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108612, <https://doi.org/10.1016/j.ejso.2024.108612>.

Abstract: Introduction- Retroperitoneal sarcoma (RPS) surgery poses unique challenges. This retrospective study aimed to analyze the learning curve (LC) in RPS surgery, assessing the relationship between surgical experience and outcomes. Materials and methods- Cumulative sum (CUSUM) analysis was used to analyze 62 RPS surgeries performed by a single surgeon between 2016 and 2022 at our center. Results- The number of cases where the surgeon acted as first operator increased from 3 in 2016 to 13 in 2022. The surgeon operated with his mentor in 66.7 % of cases in 2016, whereas in 7.7 % of cases in 2022. LC consisted of 3 phases. Phase 1 (16 cases), with a negative slope, represented shorter operative time (OT) and fewer number of resected organs (RO). Phase 2 (30 cases) was the plateau phase. Phase 3 (16 cases), with a positive slope, indicated longer OT and more RO. Statistically significant differences were observed in terms of size ($p = 0.003$), presentation ($p = 0.048$), number of resected organs ($p = 0.046$), pattern of resection ($p = 0.033$), OT ($p = 0.006$), and length of stay ($p = 0.026$) between the three phases. Conclusion- This study focused on the critical role of LC in RPS surgery, emphasizing its influence on outcomes. We identified three phases, highlighting the surgeon's evolution. This offers a framework for educating

sarcoma surgeons and ensuring exposure to increasing surgical complexity. In discussions on sarcoma referral centers and the correlation between case volume and outcomes, this study underlines the importance of evaluating LC to distinguish surgeons qualified to manage sarcoma cases within a referral center.

Keywords: Retroperitoneal sarcoma; Learning curve; Sarcoma surgery; Referral center

24COASNO60:

Title- Combined pancreaticoduodenectomy for advanced gallbladder cancer: Indications, surgical outcomes, and limitations,

Yohei Miura, Jun Sakata, Tatsuya Nomura, Kabuto Takano, Chie Kitami, Takashi Aono, Akihiro Tsukahara, Taku Ohashi, Kazuyasu Takizawa, ...

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108614,

<https://doi.org/10.1016/j.ejso.2024.108614>.

Abstract: Background- This study aimed to elucidate the clinical value of combined pancreaticoduodenectomy (PD) for advanced gallbladder cancer according to the mode of cancer spread in the pancreaticoduodenal region. Methods- Patients who underwent combined PD for advanced gallbladder cancer were retrospectively reviewed. The mode of cancer spread in the pancreaticoduodenal region was defined as involvement of peripancreatic organs/structures alone, peripancreatic nodal metastasis alone, or both. Surgical outcomes were compared among these modes of spread. Results- Fifty-seven patients were included. Rates of severe morbidity and mortality were 52.6% and 3.5%, respectively. The mode of cancer spread was involvement of peripancreatic organs/structures alone in 16 patients, peripancreatic nodal metastasis alone in 17, and both in 24; R0 resection rates differed significantly among the groups (87.5% vs. 94.1% vs. 37.5%; $p < 0.001$). Overall survival (OS) was significantly worse in patients with both modes of spread (5-year OS, 8.3%) than in those with involvement of peripancreatic organs/structures alone (5-year OS, 37.9%; $p < 0.001$) and those with peripancreatic nodal metastasis alone (5-year OS, 29.4%; $p = 0.011$). OS was similar between pM0 patients with both modes of spread and pM1 patients (5-year OS, 16.7% vs. 8.7%; $p = 0.605$). Multivariate analysis identified mode of cancer spread as an independent prognostic factor ($p = 0.006$). Conclusions- Combined PD could be oncologically justified for advanced gallbladder cancer with involvement of peripancreatic organs/structures alone or peripancreatic nodal metastasis alone in the pancreaticoduodenal region. This procedure would not be indicated in patients with both modes of spread.

Keywords: Gallbladder neoplasms; Pancreaticoduodenectomy; Surgical indication; Prognosis; Mode of cancer spread; Preoperative jaundice

24COASNO61:

Title- Laparoscopic right upper transversal hepatectomy: Strategies for right hepatic vein resection and reconstruction,

Jun-Xi Xiang, Ye-Rong Qian, Xu-Feng Zhang, Yu Li, Kun Guo, Yi Lyu, Xue-Min Liu,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108615,

<https://doi.org/10.1016/j.ejso.2024.108615>.

Abstract: Objective- The right upper transversal hepatectomy (RUTH) is considered a complex technique of parenchymal-sparing hepatectomies. The intraoperative management of the right hepatic vein (RHV) is still controversial because it may cause obstruction of outflow in the remnant hepatic segment. The aim of this study is to present our experience of laparoscopic RUTH and the strategy of RHV resection and reconstruction in different settings. Methods- Five patients who underwent laparoscopic RUTH for liver tumor were enrolled retrospectively. Clinical and pathological features of the patients, peri-operative treatment, as well as short- and long-term outcomes were collected for analysis. Results- Laparoscopic RUTH was successfully performed in all five patients. Two individuals underwent RUTH while preserving RHV. Among the remaining patients who underwent RUTH with RHV resection, one patient underwent RHV reconstruction but the others did not. Immediate or long-term venous related complications did not occurred in a median follow-up period of nine months. Conclusions- Laparoscopic RUTH surgery for tumors in the right upper region of the liver is safe and feasible. The strategic workflow we proposed for the resection and reconstruction of the RHV offers a reliable method for preserving liver parenchyma and reducing the risk of postoperative liver failure.

Keywords: Hepatectomy; Hepatic vein; Laparoscopy; Liver tumor; Resection; Vascular reconstruction

24COASNO61:

Title- Efficacy of systemic Chemotherapy on high-risk stage II and III Mucinous colon cancer. CHEMUCCA study part I,

Irene Trinidad-Gutiérrez, Mari C. Vázquez-Borrego, Eva Aguilera-Fernández, Juan E. Velez-Castaño, Carlos E. Muriel-López, ...

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108642,

<https://doi.org/10.1016/j.ejso.2024.108642>.

Abstract: Background- Locally advanced colon cancer is a high-risk condition for tumour recurrence with poor survival. The current treatment is surgery followed by adjuvant chemotherapy based on fluoropyrimidines and oxaliplatin. This approach has improved the oncological outcomes on this population, however the mucinous condition has not been studied in depth and although the evidence is weak, it is thought to have a worse response to systemic chemotherapy. The CHEMUCCA study aims to answer this question. Objective- To evaluate the effectiveness of adjuvant systemic chemotherapy using the disease-free survival for stage II and III mucinous colon cancer who underwent surgical resection plus systemic adjuvant chemotherapy vs. surgery alone. Patients and methods- Retrospective analytical study including patients diagnosed with high-risk stage II and stage III colon cancer, treated between 2010 and 2021, with a minimum follow-up of 3 years. Demographic variables and tumour features were analysed. The primary endpoint was disease-free survival. Log rank test and Cox regression were used. Results- Of 1134 patients with high-risk stage II and III colon cancer disease, 206 (18,17 %) had mucinous histology and 928 (81,83 %) had non-mucinous histology. 708 patients who received adjuvant chemotherapy, 129 (62,62 %) in mucinous group and 579 (62,39 %) in the non-mucinous group. Adjuvant systemic chemotherapy in stage II and III mucinous colon cancer improved the DFS (HR = 0.58 [95 % CI 0.37–0.91];

p = 0,017). However, in a stratified analysis, patients with high-risk stage II mucinous colon cancer showed no benefit with this approach (HR = 0.4541 [95 % CI 0.19–1.03]; p = 0.06).

Conclusion- Adjuvant chemotherapy has demonstrated to be effective in locally advanced mucinous colorectal cancer improving the oncological outcomes. However, this benefit could be diminished in high-risk stage II mucinous colon cancer patients. The administration of adjuvant chemotherapy on this patient's sub-group must be balanced according to risk versus benefits.

Keywords: Mucinous colon cancer; Systemic chemotherapy; Rectal cancer

24COASNO62:

Title- Endoscopic versus surgical resection of duodenal neuroendocrine neoplasms between 10 and 20 mm: A multi-centered retrospective cohort study,

Felix Hers, Heinz-Josef Klumpen, Koen M.A. Dreijerink, Anton F. Engelsman, Els J.M. Nieveen van Dijkum, Enes Kaçmaz,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108596,

<https://doi.org/10.1016/j.ejso.2024.108596>.

Abstract: Introduction- Recommendations for resection technique of duodenal neuroendocrine neoplasms (D-NEN) with a size between 10 and 20 mm are lacking. The primary aim was to compare overall survival (OS) and progression-free survival (PFS) after endoscopic resection (ER) with surgical resection (SR). The secondary aim was to assess the incidence and clinical variables correlated with OS. Methods- Data of patients with D-NENs between 2008 and 2018 were extracted from the Netherlands Cancer Registry and the Dutch Nationwide Pathology Databank. Results- A total of 259 patients were identified, of which 138 were included: 98 (68 %) underwent ER and 44 patients (32 %) underwent SR. Of these, 38 patients had D-NENs sized between 10 and 20 mm. ER Patients were more frequently male and had a lower T-stage and tumour size than SR patients (all $P < 0.05$). Positive resection margins were observed more frequently after ER compared to SR (71 % vs 15 %, $P < 0.005$). No patients with tumours between 10 and 20 mm died after ER or SR (median follow-up 71.8 vs. 52.0 months). PFS rates were not significantly different after ER compared to SR ($P = 0.672$). Recurrence rates were 13 % for ER and 7 % for SR ($P = 0.604$). Conclusion- Between 2008 and 2018, the incidence increased from 0.06 to 0.11 per 100,000 patients per year. OS after ER or SR did not differ for D-NEN between 10 and 20 mm. Recurrence and PFS rates were not significantly different. These results suggest that D-NENs sized between 10 and 20 mm could potentially be treated first with ER. Future studies are needed to confirm this hypothesis.

Keywords: Neuroendocrine; Surgical resection; Endoscopic resection

24COASNO63:

Title- Tumor burden score is superior to primary liver cancer stages in predicting prognosis for patients with combined hepatocellular-cholangiocarcinoma after surgery: A multi-center study,

Chuang Jiang, Fangying Qin, Jiaxin Yan, Jing Zou, Haiqing Wang, Hui Zhang, Xielin Feng, Guimin Hou,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108610,

<https://doi.org/10.1016/j.ejso.2024.108610>.

Abstract: Background- Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is poorly understood, while the predictive value of the staging in which it is included is controversial. Methods- Patients with cHCC-CCA underwent radical hepatectomy in two medical centers in China were enrolled and staged based on optimal cut-off values of tumor burden score (TBS), determined using the X-Tile. The association between TBS and prognosis was evaluated by Cox proportional hazard models and Kaplan-Meier curves with Log-rank test. TBS model and primary liver cancer (PLC) stages were compared by discrimination, consistency, and clinical utility, which were further validated by a 5-folds cross-validation. Results- A total of 192 patients were stratified into low, medium, and high TBS, comprising 92, 51 and 49 patients, respectively. Prognoses worsened with elevated TBS in both the training and validation cohorts. TBS was not only an independent prognostic indicator in univariate and multivariate cox regression, but also a stable risk factor in subgroup analysis according to baseline variables. TBS exhibited best discrimination within these predictive models, as evidenced by the highest c-index and area under curve values of time-dependent receiver operating curves within 5 years post-surgery. TBS calibration plots revealed favorable consistency between prediction and observation. Decision curve analysis suggested higher net benefits for TBS. A 5-folds cross-validation revealed consistent results. Conclusions- TBS could be applied to stratify cHCC-CCA patients after surgery into groups with statistically different prognoses. Moreover, TBS exhibited optimal prognostic value over all available PLC stages and may inform clinical decisions.

Keywords: Tumor burden score; Combined hepatocellular-cholangiocarcinoma; Cancer stage; Predictive model; Clinic-pathological features

24COASNO64:

Title- The U-shaped association between age at diagnosis and recurrence in patients with papillary thyroid carcinoma: A retrospective single-institution cohort study,

Hui Huang, Yunhe Liu, Dangui Yan, Wensheng Liu, Shaoyan Liu,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108626,

<https://doi.org/10.1016/j.ejso.2024.108626>.

Abstract: Purpose- Age is a significant predictor of papillary thyroid carcinoma (PTC). At present, the available evidence shows that age at diagnosis has an important impact on the recurrence of PTC. The objective of our investigation was to examine the relationship between age at diagnosis and recurrence in patients with PTC. Methods -The medical records of patients with PTC who were treated between January 2010 and December 2018 at a single institute in a cancer referral center in China were retrospectively reviewed. The hazard ratios (HRs) and 95 % confidence intervals (CIs) for recurrence-free survival (RFS), locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS) were assessed using Cox proportional hazard models and restricted cubic splines (RCSs). Results- A total of 13758 patients were included in the study. With a median follow-up of 60 months (range 12–277), a total of 687 patients experienced recurrence, and 90 patients died. The 5-year RFS, LRRFS and DMFS rates were 95.0 % (95 % CI 94.6%–95.4 %), 95.8 % (95 % CI 95.4%–

96.2 %) and 98.8 % (95 % CI 98.6%–99.0 %), respectively. The adjusted smooth RCS curves revealed a U-shaped association between age at diagnosis and RFS, LRRFS, and DMFS. After adjusting for potential confounding variables, both younger (≤ 30 years) and older (≥ 55 years) patients exhibited significantly lower RFS and LRRFS rates than did middle-aged patients (31–54 years). Older patients had significantly lower DMFS rates. Conclusions- This study confirmed a U-shaped association between age at diagnosis and the risk of both locoregional recurrence and distant metastasis.

Keywords: Papillary thyroid carcinoma; Recurrence; Recurrence free survival; Predictors; Age at diagnose

24COASNO65:

Title- GAME-SCORE predicts pathological and radiological response to chemotherapy in patients with colorectal liver metastases,

Nadia Russolillo, Caterina C. Zingaretti, Serena Langella, Andrea P. Fontana, Roberto Lo Tesoriere, Alessandro Ferrero,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108529,

<https://doi.org/10.1016/j.ejso.2024.108529>.

Abstract: Background: Genetic And Morphological Evaluation (GAME) score is the newest prognostic model for patient with colorectal liver metastases (CRLMs). Pathological and radiological responses to neoadjuvant chemotherapy (NAC) are key factors for prognostic stratification of these patients. The present study aims to evaluate the GAME-score's ability to predict pathological and radiologic responses to NAC. Methods: CRLM patients who underwent liver resection after NAC from January 2010 to December 2021 were categorized by GAME scores: low risk (LR, 0–1), moderate risk (MR, 2–3), and high risk (HR, ≥ 4). Correlations between groups and radiological/pathological features were analyzed. Poor pathological response was defined as Tumor Regression Grade 4–5. Results: Of 1054 liver resections for CRLMs, 448 were included. GAME scores were LR: 80 (18 %), MR: 228 (51 %), and HR: 140 (31 %). In this cohort, HR-GAME scores were associated with lower pathological response (LR: 67.1 %, MR: 74.9 %, HR: 82.6 %; $p = 0.010$). Radiologic progression occurred in 10 % of HR patients, significantly more than in LR (3.8 %) and MR (3.5 %) groups ($p = 0.011$). Multivariable analysis for independent predictors of pathological response confirmed HR-GAME (RR 1.843, $p = 0.025$) along with age higher than 70 years (RR 2.111, $p = 0.022$) and irinotecan-based NAC (RR 3.066, $p < 0.001$). For radiological progression disease after NAC, the HR-GAME score (RR 2.77, $p = 0.016$) was the only independent predictor. HR-GAME scores were also associated with higher rates of mucinous differentiation ($p = 0.021$), satellitosis ($p = 0.001$), vascular invasion ($p = 0.011$), and perineural invasion ($p = 0.010$). Conclusions: GAME score category should be considered into planning of therapeutic strategy of patients with CRLMs.

Keywords: GAME-Score; Liver metastases; Neoadjuvant chemotherapy

24COASNO66:**Title- Predictors and outcomes of delays between diagnosis and definitive surgery for rectal cancer,**

Sameh Hany Emile, Zoe Garoufalia, Justin Dourado, Ebram Salama, Steven D. Wexner,
European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108618,
<https://doi.org/10.1016/j.ejso.2024.108618>.

Abstract: Background: The National Accreditation Program for Rectal Cancer (NAPRC) recommends definitive treatment of rectal cancer commence within 60 days from diagnosis. This study aimed to assess predictors of >60 days delay between diagnosis and definitive surgery of rectal cancer and the impact on survival and short-term outcomes. Methods: Retrospective cohort analysis of patients with stage I-III rectal adenocarcinoma who underwent proctectomy without preoperative neoadjuvant treatment from the National Cancer Database (2015–2019). Based on the time interval between diagnosis and definitive surgery, patients were divided into timely non-adherent (>60 days) and timely-adherent (≤ 60 days) groups. Multivariate analysis determined predictors of delayed definitive surgery. Results: 9479 patients (57.5 % males; mean age: 63.7 years) had a 41-day median time between diagnosis and definitive surgery. Non-adherence was noted in 27.9 % of patients. Independent predictors of non-adherence were male sex (Odds ratio [OR]: 1.25; $p < 0.001$), Black (OR: 1.65; $p < 0.001$) or Asian (OR: 1.33; $p = 0.014$) race, Charlson score 2 (OR: 1.33; $p = 0.005$) or 3 (OR: 1.55; $p < 0.001$), urban residence (OR: 1.21; $p = 0.003$), abdominoperineal resection (OR: 1.69; $p < 0.001$), pelvic exenteration (OR: 1.7; $p = 0.002$), and robotic-assisted surgery (OR: 1.22; $p = 0.001$). Medicare (OR: 0.725; $p = 0.003$) and private insurance (OR: 0.711; $p < 0.001$) were associated with better adherence. 30-day and 90-day mortality, unplanned readmission, and overall survival were similar. Conclusions: Male Black or Asian patients with high Charlson scores, and undergoing abdominoperineal resection, pelvic exenteration, and robotic-assisted surgery were more likely non-adherent with NAPRC standards with >60 days delay before definitive surgery for rectal cancer. Hopefully, recognition for these reasons for delay of definitive surgery will lead to an improvement in adherence to the standards.

Keywords: Predictors; Outcomes; 60 Days delay; Diagnosis; Definitive surgery; Rectal cancer

24COASNO67:**Title- Improving the local excision strategy for rectal cancer after chemoradiotherapy: Surgical and oncological results,**

Hélène Meillat, Victoria Weets, Jacques-Emmanuel Saadoun, Marguerite Tyran, Emmanuel Mitry, Mathias Illy, Cécile de Chaisemartin, Bernard Lelong,
European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108639,
<https://doi.org/10.1016/j.ejso.2024.108639>.

Abstract: Introduction: Local excision (LE) for good responders after chemoradiotherapy (CRT) for rectal cancer is oncologically safe. Although the GRECCAR 2 trial did not demonstrate any advantages in morbidity, it provided useful information for optimising patient selection. This study assessed the impact of these results on our practice by focusing

on the evolution of our selection criteria and management modalities for these patients over 10 years. Methods: Data were collected using our retrospective database of 110 patients who underwent LE after CRT for low and middle rectal cancer between 2010 and 2022 before (Group 1) and after (Group 2) consideration of the GRECCAR 2 trial results. Results: The pretherapeutic selection criteria remained stable after the GRECCAR 2 trial, although in Group 2, completion total mesorectal excision (TME) for ypT2 tumours with favourable tumour regression grade was abandoned, improving the organ preservation rate at 1 year from 63.3 % to 91.8 % ($p < 0.01$). The operative time and length of stay after LE were reduced by half in Group 2 ($p < 0.01$). The intention-to-treat rate for severe morbidity was also halved, but was not significant (8.2 % vs. 16.3 %, $p = 0.24$). Among patients with a 3-year follow-up data, disease-free survival was comparable between Group 1 (89.8 %) and Group 2 (85.4 %) ($p = 0.51$) with one locoregional recurrence in each group (2.0 % vs. 2.1 %, $p = 1$). Conclusion: LE is a safe and effective strategy when performed in a “high-volume” centre. Improved methods for assessing tumour response and the selection criteria for completion TME enhanced surgical outcomes without compromising oncological outcomes.

Keywords: Chemoradiotherapy; Local excision; Mesorectal excision; Rectal cancer; Rectal sparing

24COASNO68:

Title- Diagnostic laparoscopy for pre-operative selection of patients with known peritoneal carcinomatosis for CRS-HIPEC: A systematic review and meta-analysis,

Andre Jing Yuen Ang, Royston Yew Meng Liew, Vanessa Zhi Jie Aw, Claramae Shulyn Chia, Nicholas Brian Shannon,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108623,

<https://doi.org/10.1016/j.ejso.2024.108623>.

Abstract: Background

Preoperative selection of patients with Peritoneal Carcinomatosis (PC) for Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is challenging due to associated risks. Diagnostic laparoscopy (DL), an emerging alternative to conventional radiological imaging, has uncertain efficacy. This study aims to evaluate DL's diagnostic performance through a systematic review of available literature. Methods: A comprehensive search of MEDLINE and SCOPUS databases from January 1987 to September 2023 identified studies investigating DL's diagnostic accuracy in selecting PC patients for CRS-HIPEC. Methodological bias assessment and analysis of performance metrics such as positive predictive value (PPV), sensitivity, specificity, and diagnostic odds ratio (DOR) were conducted. Subgroup analyses were performed for primary ovarian cancer studies, and false positive sites were identified. The summary receiver operating characteristic curve (sROC) was plotted to assess overall diagnostic efficacy, with meta-regression conducted to identify sources of heterogeneity across studies. Results: This study included 25 studies comprising 3820 patients. Pooled PPV was 93.04 %, with a complication rate of 1.61 %. Pooled sensitivity was 98.26 % and pooled specificity was 83.67 %. The pooled DOR was 139.18, and sROC plot yielded an area under the curve of 0.96. Meta-regression found the ovarian subgroup as a strong source of heterogeneity. Subgroup analysis indicated similar findings in

primary ovarian cancer studies, while false positives were commonly observed in the celiac axis, mesentery, ureters and para-aortic lymph nodes. Conclusion: DL demonstrates robust diagnostic accuracy in selecting PC patients for CRS-HIPEC, with potential benefits in patient outcomes and resource optimization. Further multicenter investigations are warranted to validate DL's efficacy across diverse primary cancer types.

Keywords: Peritoneal neoplasms; Laparoscopy; Ovarian neoplasms; Hyperthermic intraperitoneal chemotherapy; Systematic review; Meta-analysis

24COASNO69:

Title- Prognosis and treatment of uterine sarcoma found incidentally after myomectomy,

Hua Yuan, Ning Li, Lingying Wu, Hongwen Yao,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108652,

<https://doi.org/10.1016/j.ejso.2024.108652>.

Abstract: Objective: To determine prognosis and factors associated with survival of women with uterine sarcoma found incidentally after myomectomy. Methods: We performed a retrospective study for patients who had previously undergone myomectomy for presumed benign uterine fibroid disease and were found to have uterine confined sarcoma after myomectomy surgery. Results: In total, 50 patients were identified. There were 23 (46.0 %) patients undergoing myomectomy were performed by minimal invasive surgery: laparoscopic (Lap, n = 22, 44.0 %) or transvaginal (TV, n = 1, 2.0 %) approach; while, 24 (48.0 %) and 3 (6.0 %) patients had myomectomy through abdominal (Abd) or hysteroscopic (Hys) approach. All patients received the re-exploration and staging surgery in our center. The median time from myomectomy to the staging surgery was 43 days (range 15–90 days). 17 patients had remnant sarcomas on the remaining uterus and 6 patients had disseminated disease after re-exploration. In the entire cohort, 5-year RFS and 5-year OS was 79.4 % and 88.0 %, respectively. Patients who received initial Lap/TV myomectomy had a tendency towards a worse 5-year RFS compared with Abd/Hys approach (63.0 % vs 88.9 %, $P = 0.080$). No difference in 5-year OS was found between the two groups (90.3 % vs 91.8 %, $P = 0.768$). For stage I disease (n = 44), patients who received Lap/TV myomectomy had a worse 5-year RFS compared with Abd/Hys approach (58.3 % vs 95.7 %, $P = 0.009$). No difference in 5-year OS was found ($P = 0.121$). Conclusion: Patients with incidental uterine sarcoma who received primary Lap/TV myomectomy may have a worse RFS. Re-exploration can detect remnant or disseminated sarcomas.

Keywords: Uterine sarcoma; Myomectomy; Incidentally; Prognosis

24COASNO70:

Title- Impact of the future liver remnant volume before major hepatectomy,

Tim Reese, Stefan Gilg, Jörg Böcker, Kim C. Wagner, Marjan Vali, Jennie Engstrand, Anna Kern, Christian Stureson, Karl J. Oldhafer, Ernesto Sparrelid,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108660,

<https://doi.org/10.1016/j.ejso.2024.108660>.

Abstract: Introduction: Following major liver resection, posthepatectomy liver failure (PHLF) is associated with a high mortality rate. As there is no therapy for PHLF available, avoidance remains the main goal. A sufficient future liver remnant (FLR) is one of the most important factors to reduce the risk for PHLF; however, it is not known which patients benefit of volumetric assessment prior to major surgery. Methods: A retrospective, bi-institutional cohort study was conducted including all patients who underwent major hepatectomy (extended right hepatectomy, right hepatectomy, extended left hepatectomy and left hepatectomy) between 2010 and 2023. Results: A total of 1511 major hepatectomies were included, with 29.4 % of patients undergoing FLR volume assessment preoperatively. Overall, PHLF B/C occurred in 9.8 % of cases. Multivariate analysis identified diabetes mellitus, extended right hepatectomy, perihilar cholangiocarcinoma (pCCA), gallbladder cancer (GBC) and cirrhosis as significant risk factors for PHLF B/C. High-risk patients (with one or more risk factors) had a 15 % overall incidence of PHLF, increasing to 32 % with a FLR <30 %, and 13 % with an FLR of 30–40 %. Low-risk patients with a FLR <30 % had a PHLF rate of 21 %, which decreased to 8 % and 5 % for FLRs of 30–40 % and >40 %, respectively. For right hepatectomy, the PHLF rate was 23 % in low-risk and 38 % in high-risk patients with FLR <30 %. Conclusion: Patients scheduled for right hepatectomy and extended right hepatectomy should undergo volumetric assessment of the FLR. Volumetry should always be considered before major hepatectomy in patients with risk factors such as diabetes, cirrhosis, GBC and pCCA. In high-risk patients, a FLR cut-off of 30 % may be insufficient to prevent PHLF, and additional liver function assessment should be considered.

24COASN071:

Title- Residual breast tissue after mastectomy and reconstruction: A substudy of the Spatial location of breast cancer local rECurRence aftEr masTectomy (SECRET) project,

Orit Kaidar-Person, Miri Sklair-Levy, Debbie Anaby, Rinat Bernstein-Molho, Marissa C. van Maaren, Linda de Munck, M. Bindels, ...

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108607, ISSN 0748-7983, <https://doi.org/10.1016/j.ejso.2024.108607>.

Abstract: The current project is part of the Spatial location of breast cancer local rECurRence aftEr masTectomy (SECRET) study (NCT06130111). Herein we compared the chest wall thickness after non-skin sparing mastectomy (non-SSM) with the chest wall thickness after SSM, as a surrogate for residual breast tissue after mastectomy. Methods: The study was approved by the ethics committee of relevant institutions. Data of patients with a local recurrence (LR) after non-SSM was collected from the Netherlands Cancer Registry (NCR); data of patients undergoing SSM were collected from Sheba Medical Center. Student's t-test was used to evaluate the difference between the cohorts. Chest wall thickness was measured on postoperative images. Results: Out of 4949 patients who underwent mastectomy from the NCR cohort, a total of 173 (3.5 %) had a LR at 5 years, of these a total of 153 patients included in the non-SSM cohort. The median age was 59 years (age 33–92), LR occurred at a median of 23.6 months (2.5–60 months). The SSM cohort included 84 patients, with a median age of 38.4 years (28–63.5), overall, 5 LRs occurred at a median of

15 months (5–46 months). The SSM cohort had significantly thicker chest walls compared to non-SSM ($p < 0.001$). Most LR in both groups occurred in the subcutis. Conclusion: The chest wall thickness differed according to mastectomy procedures. Most of the LR occurred at the subcutis. The role of residual breast tissue and residual cancer in relation to type of mastectomy should be further investigated.

24COASNO72:

Title- Risk factors and treatment strategies for local recurrence of locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision,

Seijong Kim, Jung Wook Huh, Woo Yong Lee, Seong Hyeon Yun, Hee Cheol Kim, Yong Beom Cho, Yoonah Park, Jung Kyong Shin,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108641,

<https://doi.org/10.1016/j.ejso.2024.108641>.

Abstract: Background: Despite advancements in total mesorectal excision (TME) and neoadjuvant radiotherapy, locally advanced rectal cancer remains challenging, impacting patient quality of life and mortality. This study aimed to identify the risk factors for local recurrence in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy (CRT) and assess treatment strategies for recurrence. Methods: This retrospective analysis included 682 patients diagnosed with locally advanced rectal cancer who were treated with neoadjuvant CRT and TME at Samsung Medical Center from 2008 to 2017. The exclusion criteria ensured a homogenous cohort. Clinical staging involved colonoscopies, computed tomography, magnetic resonance imaging, and digital rectal exam. Risk factors, treatment modalities, and oncological outcomes for local recurrence were evaluated. Result: During a median 62-month follow-up, 47 patients (6.9 %) experienced local recurrence. The risk factors for local recurrence included a positive circumferential resection margin (CRM), venous invasion, and perineural invasion. Of the 47 patients with local recurrence, 25 (53.2 %) were considered resectable. Out of these, 23 patients underwent curative resections, and 15 (65.2 %) achieved R0 resection. Patients with R0 resections exhibited superior 5-year survival rates compared to R1-2 resection or non-surgical treatment, and there was no survival difference between R1-2 resection and non-surgical treatment. Conclusion: In locally advanced rectal cancer, positive CRM, venous invasion, and perineural invasion were associated with local recurrence. R0 resection showed favorable outcomes, emphasizing the importance of surveillance in high-risk patients. Treatment decisions should consider these factors for improved oncologic outcomes and quality of life.

Keywords: Rectal cancer; Local recurrence; Survival

24COASNO73:

Title- Prognosis and treatment regimens for patients with different lymph node statuses in locally advanced cervical cancer,

Wendi Guo, Runling Ren, Na Li, Yuanjing Hu,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108522,

<https://doi.org/10.1016/j.ejso.2024.108522>.

Abstract: Objective: The survival outcomes of Stage IIIC1 in FIGO 2018 showed significant heterogeneity and it seems unreasonable to administer a uniform treatment regimen for Stage IIIC1 patients. This study aimed to assess the survival outcomes among patients with locally advanced cervical cancer based on various lymph node statuses, T-stage classifications, and treatment modalities. Methods: This is a population-based cohort study utilizing the Surveillance, Epidemiology, and End Results Program from 2004 to 2018. Propensity score-based inverse probability of treatment weighting was used to achieve covariate balance. Women with locally advanced cervical cancer on different lymph node statuses who underwent radical hysterectomy + pelvic lymphadenectomy + chemoradiotherapy, chemoradiotherapy, or radiotherapy alone were examined. Trends, patient characteristics, and survival outcomes were compared across different treatment regimens. Results: Among 8777 patients analyzed, patients with early T-stage and married were identified as independent protective factors for cancer-specific survival regardless of lymph node status. The survival outcomes ranked in descending order as follows: T1N0>T2N0>T1N1 = T2N1>T3N0>T3N1. Therefore, the FIGO Stage IIIC1 was re-stratified into IIC (T1N1+T2N1) and IIIC1(T3N1). Patients who underwent radical hysterectomy combined with adjuvant therapy exhibited superior 5-year cancer-specific survival rates compared to those treated with chemoradiotherapy among IB3, IIA2, and IIC. The therapeutic efficacy of chemoradiotherapy surpassed that of radiotherapy alone in IIIA, IIIB, IIIC1(T3N1), and IVA patients. Conclusion: Restratification of Stage IIIC1 based on T-stage effectively discerns patients with divergent prognoses. Radical surgery + chemoradiotherapy is significantly associated with improved survival in early T-stage, regardless of lymph node status in locally advanced cervical cancer.

Keywords: Cervical cancer; Survival; SEER program; Lymph node; Surgery

24COASNO74:

Title- Low pneumoperitoneum pressure on venous thromboembolism in laparoscopic colorectal cancer surgery: A randomized controlled study,

Lian Xia, Xin Xu, Chimin Zhang, Gaoyang Cao, Li Chen, Engeng Chen, Wei Zhang, Haiou Qi, Wei Zhou,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108672,

<https://doi.org/10.1016/j.ejso.2024.108672>.

Abstract: Introduction: Venous thromboembolism (VTE) poses a significant risk in colorectal cancer surgeries due to hypercoagulability and the anatomical challenges of the pelvic cavity. With the advancement of minimally invasive techniques, intraoperative strategies for preventing VTE may prove to be effective. This study explores the effects of intraoperative pneumoperitoneum pressures on VTE incidence following colorectal cancer surgeries. Methods: This single center parallel randomized controlled double-blind, trial involved 302 patients undergoing elective laparoscopic or robotic colorectal surgery. Patients were randomized to either a standard pneumoperitoneum pressure group (SP: 15 mmHg) or a low-pressure group (LP: 10 mmHg). Primary outcomes measured were the incidence of VTE, including symptomatic and asymptomatic DVT and PE. Secondary outcomes included postoperative D-dimer levels, surgery duration, blood loss, surgeon satisfaction, and

oncological quality. Results: Out of 302 randomized patients, 275 were evaluable post exclusions, with 138 in the SP group and 137 in the LP group. The incidence of VTE was 10.9 % in the SP and 13.9 % in the LP group, with no significant difference between the two ($P = 0.450$). Secondary outcomes such as D-dimer levels, surgery duration, and blood loss showed no significant differences between two groups. Surgeon satisfaction and oncological outcomes were similarly comparable. Conclusions: The trial demonstrated no significant difference in the incidence of VTE between standard and low pneumoperitoneum pressures. This suggests that lower pressures may not necessarily provide a benefit in reducing postoperative VTE in colorectal cancer surgeries.

Keywords: Pneumoperitoneum; Low pressure; Colorectal cancer; Laparoscopic surgery; Venous thromboembolism

24COASNO75:

Title- Origin and impact of multifocal growth in sporadic vs. hereditary medullary thyroid cancer,

Andreas Machens, Kerstin Lorenz, Frank Weber, Henning Dralle,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108625,

<https://doi.org/10.1016/j.ejso.2024.108625>.

Abstract: Multifocal growth is characteristic of hereditary medullary thyroid cancer (MTC), whereas origin and impact of multifocal growth is enigmatic for sporadic MTC. To address this, 460 RET-negative patients with sporadic MTC, stratified by 1 (93.3 %), 2 (5.7 %) and 3 (1.1 %) thyroid tumor foci, were compared with 219 RET-positive patients with hereditary MTC, stratified by 1 (38.4 %), 2 (45.7 %), 3 (6.4 %), 4 (6.8 %) and ≥ 5 (2.7 %) thyroid tumor foci. For sporadic MTC, significant associations were identified with bilateral thyroid lobe involvement, microscopic lymphatic invasion, extrathyroid extension, node and distant metastases, number of node metastases, preoperative basal calcitonin level, and decreasing biochemical cure. For hereditary MTC, significant associations were limited to bilateral thyroid lobe involvement, largest thyroid tumor diameter, and preoperative basal calcitonin level. In sporadic MTC, multifocal growth is due to lymphatic invasion with frequent node metastases, whereas in hereditary MTC, it reflects malignant progression from C-cell hyperplasia to cancer.

Keywords: Medullary thyroid carcinoma; RET proto-oncogene; Malignant progression; Tumor multifocality; Microscopic lymphatic invasion; Lymph node metastases

24COASNO76:

Title- Effect of postoperative normothermic intraperitoneal chemotherapy on the prognosis of MPM patients receiving CRS+HIPEC: A single-center case-control study,

Xin-Li Liang, Yan-Dong Su, Yu-Bin Fu, Xin-Bao Li, Ru Ma, Rui Yang, He-Liang Wu, Yan Li,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108692,

<https://doi.org/10.1016/j.ejso.2024.108692>.

Abstract: Background: The comprehensive treatment strategy, mainly cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC), combined with systemic

and intraperitoneal chemotherapy, is the standard treatment for malignant peritoneal mesothelioma (MPM), which can significantly prolong the survival of patients. The aim of this study is to investigate the clinical significance of postoperative normothermic intraperitoneal chemotherapy (NIPEC) in MPM patients. Methods: Data of 152 MPM patients who underwent CRS + HIPEC and postoperative intravenous chemotherapy were retrospectively analyzed. Patients were divided into the Non-NIPEC group and the NIPEC group according to whether they received NIPEC after surgery. The baseline characteristics of the two groups were compared, and the survival outcome was analyzed in subgroups according to completeness of cytoreduction (CC) score. Multivariate survival analysis was used to determine the independent prognostic factors. Results: In CC 0–1 and CC 2–3 subgroups, there was no significant difference in baseline characteristics between Non-NIPEC and NIPEC groups. Survival analysis showed that for CC 0–1 patients, there was no significant difference in overall survival (OS) between Non-NIPEC and NIPEC groups ($P = 0.503$). However, for CC 2–3 patients, the median OS of the NIPEC group was significantly longer than that of the Non-NIPEC group (24.5 vs. 10.3 months, $P = 0.005$). Pathological type, preoperative thrombosis and postoperative NIPEC ($HR = 0.423$, 95%CI: 0.228–0.786, $P = 0.006$) were independent prognostic factors for CC 2–3 patients. Conclusions: For MPM patients receiving CRS + HIPEC, postoperative intraperitoneal combined with intravenous chemotherapy may improve the survival of CC 2–3 patients, but CC 0–1 patients do not seem to derive the same benefit.

Keywords: Malignant peritoneal mesothelioma; Normothermic intraperitoneal chemotherapy; Prognosis; CC score; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

24COASNO77:

Title- Analysis of near-infrared autofluorescence imaging for detection of inadvertently resected parathyroid glands after endoscopic thyroidectomy,

Ting-Chun Kuo, Kuen-Yuan Chen, Chieh-Wen Lai, Ming-Tsan Lin, Chin-Hao Chang, Ming-Hsun Wu,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108648,

<https://doi.org/10.1016/j.ejso.2024.108648>.

Abstract: Background

Preserving parathyroid function during thyroidectomy is crucial, but remains challenging. Real-time near-infrared autofluorescence (NIRAF) aids surgeons in intraoperative parathyroid gland (PTG) identification. However, its role in detecting PTGs unintentionally removed during surgery is unclear. Study design: This prospective study included adult patients undergoing endoscopic thyroidectomy. Surgeons identified and documented PTGs visually. Excised specimens underwent visual inspection and NIRAF imaging (PDE-Neo II). All fluorescent tissues were dissected and pathologically evaluated (reference standard). One scanned image per lobe was chosen to quantify autofluorescence (AF) intensity. Results: Overall, 95 patients underwent endoscopic thyroidectomies, with NIRAF imaging applied to 152 excised lobes. Of these, 19 lobes displayed a total of 23 spots with increased intensity. 175 specimens were sent for pathological evaluation, and 7 were confirmed to be parathyroid

tissue. NIRAF demonstrated 100.0 % sensitivity and 90.5 % specificity for predicting parathyroid tissue, with 30.4 % positive predictive value, 100.0 % negative predictive value of and 90.9 % accuracy. Quantitatively normalized, the AF signal intensity was significantly higher in NIRAF-positive tissues than negative (4.3 vs 1.2 times, $p < 0.0001$). Additionally, the AF signal intensity in regions pathologically confirmed of parathyroid tissue was higher than non-parathyroid tissue (9.1 vs 2.1 times, $p < 0.0001$). Conclusion: This study suggests that NIRAF has high sensitivity and specificity for detecting inadvertently resected PTGs after endoscopic thyroidectomy, contributing to preservation efforts. However, NIRAF-positive tissues still require additional confirmation through multiple methods, emphasizing other examinations to verify that they are indeed parathyroid tissues. Further research is warranted to refine NIRAF imaging parameters.

Keywords: Near-infrared autofluorescence (NIRAF); Autofluorescence (AF); Parathyroid gland (PTG); Inadvertently resected parathyroid glands; Endoscopic thyroidectomy

24COASNO78:

Title- Clinical validation of 3D virtual modelling for laparoscopic complete mesocolic excision with central vascular ligation for proximal colon cancer,

Emma C. Kearns, Alice Moynihan, Jeffrey Dalli, Mohammad Faraz Khan, Sneha Singh, Katherine McDonald,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108597,

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Abstract: Introduction

Laparoscopic Complete Mesocolic Excision (CME) with Central Vascular Ligation (CVL) in colon cancer surgery has not been broadly adopted in part because of safety concerns. Pre-operative 3-D virtual modelling (3DVM) may help but needs validation. Methods: 3DVM were routinely constructed from CT mesenteric angiograms (CTMA) using a commercial service (Visible Patient, Strasbourg, France) for consecutive patients during our CMECVL learning curve over three years. 3DVMs were independently checked versus CTMA and operative findings. CMECVL outcomes were compared versus other patients undergoing standard mesocolic excision (SME) surgery laparoscopically in the same hospital as control. Stakeholders were studied regarding 3DVM use and usefulness (including detail retention) versus CTMA and a physical 3D-printed model. Results: 26 patients underwent 3DVM with intraoperative display during laparoscopic CMECVL within existing workflows. 3DVM accuracy was 96 % re arteriovenous variations at patient level versus CTMA/intraoperative findings including accessory middle colic artery identification in three patients. Twenty-two laparoscopic CMECVL with 3DVM cases were compared with 49 SME controls (age 69 ± 10 vs 70.9 ± 11 years, 55 % vs 53 % males). There were no intraoperative complications with CMECVL and similar 30-day postoperative morbidity (30 % vs 29 %), hospital stay (9 ± 3 vs 12 ± 13 days), 30-day readmission (6 % vs 4 %) and reoperation (0 % vs 4 %) rates. Intraoperative times were longer (215.7 ± 43.9 vs 156.9 ± 52.9 min, $p < 0.01$) but decreased significantly over time. 3DVM surveys ($n = 98$, 20 surgeons, 48 medical students, 30 patients/patient relatives) and comparative study revealed majority endorsement (90 %) and

favour (87 %). Conclusion: 3DVM use was positively validated for laparoscopic CMECVL and valued by clinicians, students, and patients alike.

Keywords: 3D virtual models; Laparoscopic surgery; Colon cancer surgery; Complete mesocolic excision and central vascular ligation; Innovation

24COASNO79:

Title- The influence of postoperative morbidity on long-term quality of life outcomes following pelvic exenteration,

Preet G.S. Makker, Cherry E. Koh, Michael Solomon, Jessica El-Hayek, Bora Kim, Daniel Steffens,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108640,

<https://doi.org/10.1016/j.ejso.2024.108640>.

Abstract: Introduction: Pelvic exenteration provides significant survival benefits for selected patients diagnosed with locally advanced rectal cancer. However, in-hospital postoperative morbidity such as abdominal abscess, sepsis, and anastomotic leak remain highly prevalent, which can have short/long-term impacts on patient quality of life (QoL). The aim of this study was to determine the influence of postoperative morbidity on QoL outcomes in patients following pelvic exenteration. Methods: This prospective cohort study included patients who underwent pelvic exenteration at a tertiary teaching hospital in Sydney, between 2008 and 2023. QoL measures were collected at baseline, 6, 12, 18, 24, 36, 48, and 60 months using the short-form 36 (SF-36v2) survey. The predictors included variables relating to postoperative morbidity, including hospital and ICU length of stay (LOS), post-discharge mortality and the number of postoperative complications. Mixed-effects analyses were used to determine the influence of these postoperative outcomes on physical and mental QoL trajectories. Results: This study included 674 patients, with a median age of 61 years. Shorter hospital and ICU LOS, and fewer or no postoperative complications were associated with higher physical QoL scores across all time points. Conversely, postoperative morbidity did not exhibit a significant impact on mental QoL scores. Furthermore, there was a longitudinal improvement in mental QoL outcomes compared to baseline, independent of postoperative morbidity. Conclusion: Postoperative morbidity significantly impacted physical QoL outcomes after pelvic exenteration, whereas mental QoL outcomes were not influenced. Interventions aimed at mitigating postoperative morbidity may hold the potential to enhance long-term QoL outcomes following pelvic exenteration.

Keywords: Pelvic exenteration; Morbidity; Quality of life; Prospective cohort; Outcomes

24COASNO80:

Title- Tackling challenges in rare diseases: The ISGACA approach on non-pancreatic cancers in the periampullary region,

Bas A. Uijterwijk, Daniël H. Lemmers, Alma L. Moekotte, Alberto Zaniboni, Michele Ghidini, Hanneke Wilming, Michele Milella, Aldo Scarpa, Claudio Luchini, Nigel Baboeram, Dorine S. Klei,...

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<https://doi.org/10.1016/j.ejso.2024.108601>.

Abstract: Objective: Rare but aggressive cancer types like non-pancreatic periampullary cancers pose unique challenges for cancer research due to their low incidence rates and lack of consensus on optimal treatment strategies, therefore necessitating a collaborative approach. The International Study Group on non-pancreatic peri-Ampullary CAncer (ISGACA) aimed to build a collaborative initiative to pool expertise, funding opportunities, and data from over 60 medical centers, in order to improve outcomes for underrepresented patients with rare cancers. Methods: The ISGACA approach predefined a stepwise approach including a research scope, establishing a dedicated steering committee, creating a recognizable brand, identifying research gaps, following a well-defined timeline, ensuring robust data collection, addressing legal and ethical considerations, securing financial resources, investing in research ethics training and statistical expertise, raising awareness, creating uniformity, and initiating prospective studies. Results: Overall, 60 medical centers joined the ISGACA consortium (41 in Europe, 15 in North-America, three in Asia, one in Australia). The database includes 4309 patients. Nine publications and several ongoing studies which in turn allowed for a successful application of research grants. Subsequently, an international consensus meeting established uniform definitions and classifications, and one prospective multicenter international clinical trial has been initiated. Conclusion: By sharing knowledge, expertise, and clinical data, the ISGACA approach has not only gathered sufficient evidence to secure grants and ethical approvals for prospective studies, but also demonstrates options for standardizing patient care and improving outcomes for patients with rare cancers. The ISGACA approach offers a detailed methodology for initiating research on rare cancers and could serve as a replicable model for future research initiatives.

Keywords: Non-pancreatic periampullary cancer; Rare cancer research; Ampullary adenocarcinoma; Distal cholangiocarcinoma; Duodenal adenocarcinoma; Underrepresented patients

24COASNO81:

Title- Evaluating the feasibility of repeat sentinel lymph node biopsy in ipsilateral breast tumor recurrence: Technical considerations and oncologic outcomes,

Woong Ki Park, Hye Jin Kim, Jai Min Ryu, Byung Joo Chae, Jonghan Yu, Seok Won Kim, Seok Jin Nam, Jeong Eon Lee,

European Journal of Surgical Oncology, Volume 50, Issue 11, 2024, 108644,

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Abstract: Introduction: Ipsilateral breast tumor recurrence (IBTR) remains a concern despite standard treatments. Advances in early detection have shifted surgical paradigms towards less invasive approaches. While repeat sentinel lymph node biopsy (rSLNB) emerges as a viable option according to the 2023 National Comprehensive Cancer Network (NCCN) guidelines, its efficacy remains uncertain. This study aimed to assess lymphatic drainage patterns in IBTR and evaluate the feasibility of rSLNB, along with analyzing oncologic outcomes.

Methods: A retrospective analysis involving 78 patients with IBTR who had prior breast-conserving surgery (BCS) with sentinel lymph node biopsy (SLNB) and adjuvant whole breast irradiation (WBI) at Samsung Medical Center was conducted. Data on patient characteristics, lymphatic mapping techniques, and oncologic outcomes were collected and

analyzed. Results: Among 78 patients with IBTR, 82.1 % underwent successful rSLNB, predominantly detecting lymphatic drainage to the ipsilateral axilla (80.8 %). The initial tumor location correlated significantly with failed lymphatic mapping ($p = 0.019$). A third event occurred in 28.8 % of invasive IBTR cases, notably associated with postmenopausal status, higher T stages, and HR(-)/HER2(-) subtype ($p < 0.001$). The risk of a third event increased by over 50 % within a 2-year interval post-IBTR. Conclusion: rSLNB in patients with IBTR, particularly for tumors initially located outside the upper-outer quadrant, demonstrated technical feasibility. The combined use of blue dye with lymphoscintigraphy may enhance rSLNB success rates. Active surveillance, especially for triple negative IBTR cases, may be important due to their aggressive nature and rapid progression potential within a short interval post-IBTR.

Keywords: Breast neoplasm; Ipsilateral breast tumor recurrence; Oncologic outcomes; Lymphoscintigraphy; Sentinel lymph node biopsy

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