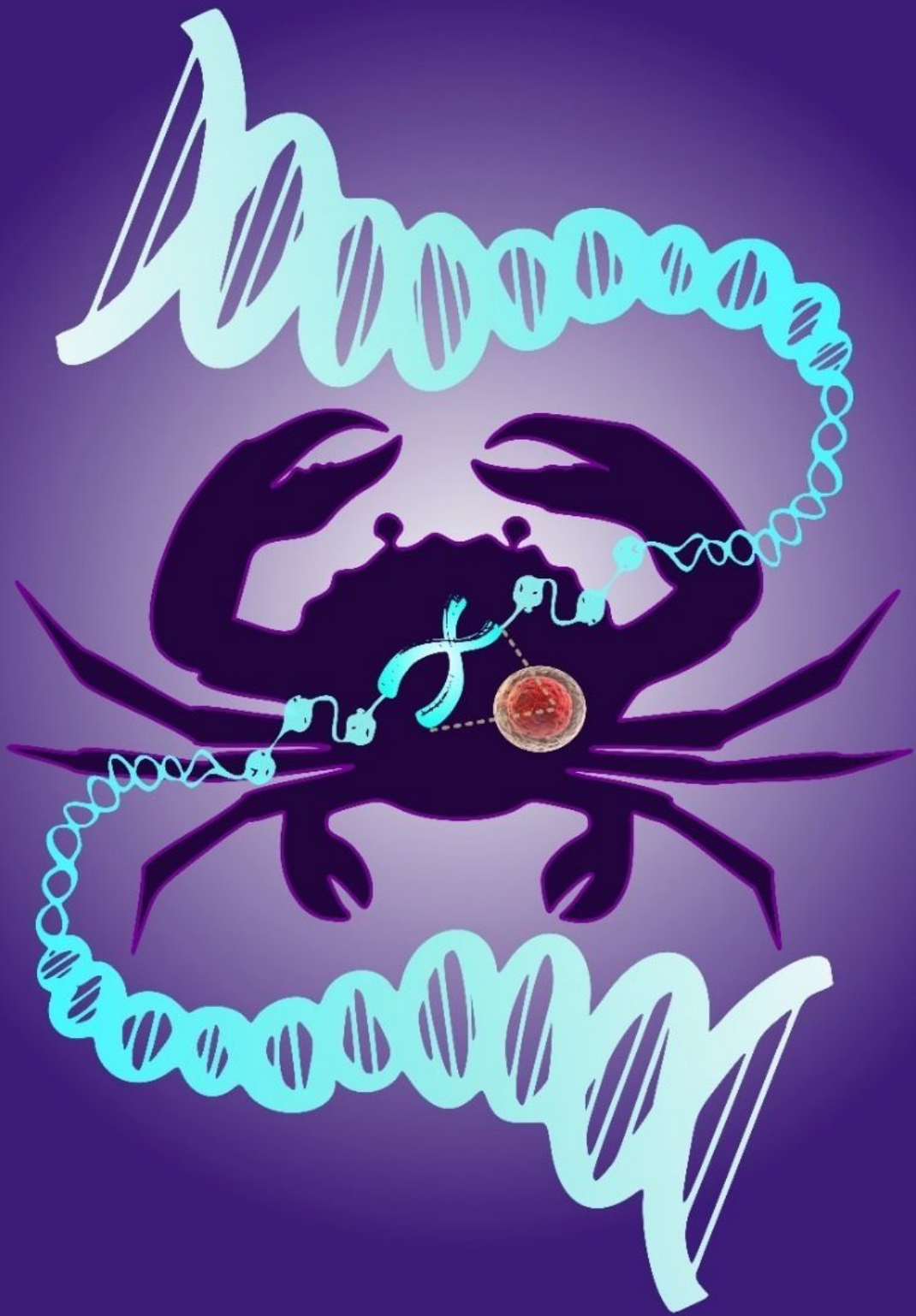
Current Oncological Abstract Service

COAS (Monthly)

March 2025, Volume 2 Issue 3



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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.

Current Oncological Abstract Service (COAS)

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Current Oncologocial Abstruct Services (COAS)

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Contents

Anesthesiology

25COASMA1

Title: National practice patterns for the use of regional anesthesia for pediatric cardiac surgery: An analysis of the Society of Thoracic Surgeons congenital heart surgery database,

Lisa M. Einhorn, Benjamin Y. Andrew, Kevin D. Hill, Levi N. Bonnell, Robert H. Habib, Marshall L. Jacobs,

Journal of Clinical Anesthesia,Volume 102,2025,111774,
https://doi.org/10.1016/j.jclinane.2025.111774.

Abstract: Background Complications associated with suboptimal pain management after pediatric cardiac surgery have increased interest in regional anesthesia (RA). We sought to evaluate national trends and explore the association of RA with postoperative outcomes following pediatric cardiac surgery. Methods Patients <18 years in the Society of Thoracic Surgeons Congenital Cardiac Anesthesia Society Database from 01/2016–05/2023 were analyzed. Non-OR operations and records with missing data on RA were excluded. Data on patients, centers, operations, year, and RA type and medication were collected, and trends over the 8-year study period were analyzed. The association of RA with outcomes was analyzed with multivariable modeling in a subpopulation of children without preoperative risk factors who underwent index atrial and ventricular septal defect (ASD/VSD) repairs and Fontan procedures. Results The cohort included 95,514 operations from 62 U.S. centers. RA was used in 8.4 % (N = 7997) and increased annually from 6.1 % in 2016 to 12.5 % in 2023. Prevalence was highest in cases performed in children 1–11 years, characterized as low risk, and conducted low volume centers. There were statistically significant increases ($p < 0.001$) in RA use across all age groups and surgical risk categories during the study period. While the number of neuraxial techniques remained constant year-to-year, the number of non-neuraxial techniques (i.e., fascial plane blocks) increased sixfold during the study period. In the sub-analysis cohort (N = 7931), patients with RA for septal defect repairs and Fontan procedures were more likely to be extubated in the OR compared to non-RA patients ($p < 0.001$). ASD and VSD patients with RA were also more likely to have a short length of stay compared to those without RA ($p < 0.001$). Conclusions RA use is increasing in pediatric cardiac surgery in the U.S. and may be associated with surgery-specific outcome improvements.

Keywords: Pediatric cardiac surgery; Regional anesthesia; Fascial plane blocks; Analgesia; Perioperative outcomes

25COASMA2

Title: Anesthesia-induced electroencephalogram oscillations and perioperative outcomes in older adults undergoing cardiac surgery,

Isaac G. Freedman, Gonzalo Boncompte, Jason Z. Qu, Zain Q. Khawaja, Isabella Turco, Ariel Mueller,

Journal of Clinical Anesthesia,Volume 102,2025,111770,
https://doi.org/10.1016/j.jclinane.2025.111770.

Abstract: Background Electroencephalogram oscillations during general anesthesia may change as a function of cognitive and physical health. This study aimed to characterize associations between anesthesia-induced oscillations and postoperative outcomes in cardiac surgery patients over 60 years. Methods This was a prespecified secondary data analysis from the Minimizing Intensive Care Unit Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study. Participants were admitted from home for elective cardiac surgery with cardiopulmonary bypass. The primary outcome was postoperative delirium obtained using the Confusion Assessment Method. Secondary outcomes were non-home discharge and 30-day readmission. The exposure of interest was alpha power measured during the maintenance phase of isoflurane-general anesthesia. Confounding cognitive and physical health variables were collected. Results Of 394 participants in the MINDDS study, 302 had analyzable electroencephalograms. The incidence of postoperative delirium was 11.1 %. Odds of postoperative delirium decreased by 14 % for every decibel increase in alpha power (OR 0.86, 95 % CI: 0.78 to 0.95; P = 0.004). This finding was not significant in adjusted analysis (ORadj 0.92, 95 % CI: 0.81 to 1.03; P = 0.154). Non-home discharge setting findings were not associated with alpha power. The odds of 30-day readmission decreased by 20 % for every decibel increase in alpha power (ORadj 0.80, 95 % CI: 0.71 to 0.91; P < 0.001). Findings were conserved in exploratory and sensitivity analyses. Conclusions In this study anesthesia-induced oscillations were associated with postoperative outcomes; however, these were not independently associated with delirium or discharge disposition after considering preoperative cognitive and physical health. These oscillations were robustly associated with 30-day readmission however, which may help anesthesiologists identify high-risk patients, offering benefits beyond the operating room.

Keywords: Intraoperative electroencephalogram; Postoperative delirium; Perioperative outcomes; Intraoperative alpha power; Elective cardiac surgery

25COASMA3

Title: Assessing the accuracy of ChatGPT in interpreting blood gas analysis results ChatGPT-4 in blood gas analysis,

Engin İhsan Turan, Abdurrahman Engin Baydemir, Anıl Berkay Balıtatlı, Ayça Sultan Şahin, Journal of Clinical Anesthesia,Volume 102,2025,111787,
https://doi.org/10.1016/j.jclinane.2025.111787.

Abstract: Background Arterial blood gas (ABG) analysis is a critical component of patient management in intensive care units (ICUs), operating rooms, and general wards, providing essential information on acid-base balance, oxygenation, and metabolic status. Interpretation requires a high level of expertise, potentially leading to variability in accuracy. This study explores the feasibility and accuracy of ChatGPT-4, an AI-based model, in interpreting ABG results compared to experienced anesthesiologists. Methods This prospective observational study, approved by the institutional ethics board, included 400 ABG samples from ICU patients, anonymized and assessed by ChatGPT-4. The model analyzed parameters including acid-base status, oxygenation, hemoglobin levels, and metabolic markers, and provided both diagnostic and treatment recommendations. Two anesthesiologists, trained in ABG interpretation, independently evaluated the model's predictions to determine accuracy in

potential diagnoses and treatment. Results ChatGPT-4 achieved high accuracy across most ABG parameters, with 100 % accuracy for pH, oxygenation, sodium, and chloride. Hemoglobin accuracy was 92.5 %, while bilirubin interpretation showed limitations at 72.5 %. In several cases, the model recommended unnecessary bicarbonate treatment, suggesting an area for improvement in clinical judgment for acid-base balance management. The model's overall performance was statistically significant across most parameters ($p < 0.05$). Discussion ChatGPT-4 demonstrated potential as a supplementary tool for ABG interpretation in high-demand clinical settings, supporting rapid, reliable decision-making. However, the model's limitations in interpreting complex metabolic markers highlight the need for clinician oversight. Future refinements should focus on enhancing AI training for nuanced metabolic interpretation, particularly for markers like bilirubin, to ensure safe and effective application across diverse clinical contexts.

Keywords: Arterial blood gas analysis; Acid-base imbalance; Oxygenation; Artificial intelligence; Clinical decision support

25COASMA4

Title: Comparison of continuous non-invasive blood pressure measurement using Vitalstream™ to invasive Intraarterial pressure in pediatric surgery,

Karen R. Boretsky, Viviane G. Nasr, Douglas Atkinson, Martin Baruch,

Journal of Clinical Anesthesia,Volume 102,2025,111763,
https://doi.org/10.1016/j.jclinane.2025.111763.

Abstract: Background Accurate blood pressure monitoring is essential in many clinical scenarios for adults and children and, when continuous measurement is critical, necessitates the insertion of an arterial line. A novel continuous non-invasive arterial pressure monitoring device using a pulse contour algorithm (Pulse Decomposition Analysis), Vitalstream™, is approved by the United States Food and Drug Administration for use in adults. In this study the performance and accuracy of the device compared to intraarterial blood pressure monitoring were assessed in children ages 2–17 undergoing major surgeries. We report the results using comparison to aspects of the recently published ISO 81060–3:2022 standard for continuous automated blood pressure measurement. Methods 31 children ages 2–17 years scheduled for major surgery requiring invasive arterial blood pressure monitoring were consented to participate. Systolic, diastolic, and mean arterial blood pressure readings were obtained from both systems during at least thirty minutes of simultaneous monitoring during hemodynamically stable periods of the surgical procedure and statistically compared. Results The correlations of systolic and, diastolic, and mean arterial pressures were, respectively, 0.77, 0.68 and 0.7. The Bland-Altman comparisons yielded bias of −3.79 (9.74) mmHg, 1.72 (8.45) mmHg and 2.41 (8.75) mmHg respectively, for systolic, diastolic, and mean arterial pressures, ($p < 0.001$ for all comparisons). Concordances for systole, diastole and MAP were, respectively, 0.82, 0.85 and 0.83. Conclusions Most values fell within +/−20mmhg of the corresponding arterial line values. While this meets the basic requirement for such devices published by professional societies, clinicians will need to be aware of the potential variances and make clinical decisions accordingly. The Vitalstream™ may offer low risk, accurate continuous pressure monitoring in children ages 2–17.

Keywords: Pediatric; Blood pressure; Noninvasive continuous blood pressure monitoring

25COASMA5

Title: Association of the Revised Cardiac Risk Index with 1-year postoperative mortality: A single-center retrospective study,

Jing Hao, Yue Qian, Min Hou, Yan Yang, Luyang Zhou, Zhuanyun Zhang, Wei Zhu, Yu-e Sun, Xiaoping Gu, Zhengliang Ma,

Journal of Clinical Anesthesia,Volume 102,2025,111765,
https://doi.org/10.1016/j.jclinane.2025.111765.

Abstract: Objective To explore risk factors for 1-year postoperative mortality and to identify its association with the Revised Cardiac Risk Index (RCRI). Methods This was a retrospective cohort study involving 54,933 patients aged 18 years and above who were surgically treated under general or regional anesthesia in a tertiary hospital in Singapore. Independent risk factors for 1-year postoperative mortality were identified by univariate Cox regression analysis. The association between the RCRI and 1-year postoperative mortality was assessed by the Kaplan-Meier estimator and multivariate Cox regression analysis and was further validated in subgroup analyses stratified by the sex, age, and type of anesthesia. Results A total of 54,933 eligible patients were enrolled in this study that included 23,922 patients classified as RCRI Class I, 25,979 as Class II, 3700 as Class III, and 1332 as Class IV. Cox regression analysis demonstrated that male sex, age, higher American Society of Anesthesiologists (ASA) physical status classification level, regional anesthesia, emergency surgery, degree of anemia, and increased RCRI were significantly associated with the increased risk of 1-year postoperative mortality ($HR > 1$, all $P < 0.001$). The significant association between RCRI and 1-year postoperative mortality still existed after adjusting for confounding factors. An RCRI Class IV was associated with a mortality risk greater than two-fold larger than that observed at an RCRI Class I (adjusted HR 2.14, 95 % CI 1.78 to 2.56, $p < 0.001$). Subgroup analyses revealed that the 1-year postoperative mortality was significantly higher in patients with RCRI Class IV than that of Classes I-III regardless of the sex, age, and type of anesthesia. Conclusion RCRI is significantly correlated with 1-year postoperative mortality regardless of sex, age, and type of anesthesia. Further studies to validate these findings are warranted.

Keywords: Revised Cardiac Risk Index; 1-year postoperative mortality; Retrospective study

25COASMA6

Title: Ten-year analysis of non-research industry payments to anesthesiologists in the United States between 2014 and 2023,

Anju Murayama,

Journal of Clinical Anesthesia,Volume 102,2025,111742,
https://doi.org/10.1016/j.jclinane.2025.111742.

Abstract: Study objective This study aimed to examine extent, fraction, and trends of general payments to anesthesiologists and non-physician anesthesia providers (NPAPs) in the United States. Design This is a cross-sectional analysis of general payments by pharmaceutical and medical device industry to all anesthesiologists (2014–2023) and NPAPs (2021−2023) for

non-research purposes using the Open Payments Database, a federal transparency database under the Physician Payments Sunshine Act between 2014 and 2023. Setting The United States. Participants All active practicing anesthesiologists and NPAPs, including certified registered nurse anesthetists and anesthesiologist assistants, in the United States. Measurements Fraction of providers receiving non-research payments; total payment amounts; median payment amounts per provider; relative annual average percentage change from 2014 to 2023. Main results A total of $297.8 million general payments were made by industry to 75.4 % of all active anesthesiologists from 2014 to 2023, while $7.2 million was made to 46.8 % of NPAPs from 2021 to 2023. Median annual payments ranged from $59–$120 for anesthesiologists and $37–$38 for NPAPs. The proportion of anesthesiologists receiving payments declined at a relative annual average percentage change (RAAPC) of −2.9 % from 2014 to 2019, followed by a substantial decrease in 2020. Subsequently, the number of payment recipients increased at an RAAPC of 15.4 % (2020−2023) for anesthesiologists and 9.0 % (2021–2023) for NPAPs. Payment distribution was highly concentrated, with the top 1 % of anesthesiologists and NPAPs receiving 78.2 % and 52.5 % of total payments in 2023, respectively. Among anesthesiology subspecialties, pain medicine physicians consistently received the highest median payments ($332–$767) throughout the study period. Conclusions This study demonstrated large financial relationships between industry and anesthesia providers, with a disproportionate concentration of payments among a minority of providers.

Keywords: Open payments database; Physician payments sunshine act; United States; Ethics; Conflict of interest, pain medicine

25COASMA7

Title: Functional MRI-based machine learning strategy for prediction of postoperative delirium in cardiac surgery patients: A secondary analysis of a prospective observational study,

Mei-Yan Zhou, Yi-Bing Shi, Sheng-Jie Bai, Yao Lu, Yan Zhang, Wei Zhang, Wei Wang, Yang-Zi Zhu, Jun-Li Cao, Li-Wei Wang,

Journal of Clinical Anesthesia, Volume 102,2025,111771,
https://doi.org/10.1016/j.jclinane.2025.111771.

Abstract: Study objective Delirium is a common complication after cardiac surgery and is associated with poor prognosis. An effective delirium prediction model could identify high-risk patients who might benefit from targeted prevention strategies. We introduce machine learning models that employ resting-state functional MRI datasets obtained before surgery to predict postoperative delirium. Design A secondary analysis of a prospective observational study. Setting The study was conducted at one tertiary hospital in China. Patients The study involved 103 patients who underwent preoperative functional MRI scan and cardiac valve replacement. Measurements Delirium was assessed twice daily for the first seven postoperative days using the Confusion Assessment Method. We used three whole-brain functional connectivity (FC) measures (parcel-wise connectivity matrix, mean FC and degree of FC) and trained three machine models, namely, random forest, logistic regression, and linear support vector machine, to distinguish delirium patients from patients without delirium.

The top performing model was selected for further training with functional MRI datasets and clinical variables. Main results This study included 103 participants. A total of 29 participants (28.2 %) met postoperative delirium criteria. Based solely on functional MRI datasets, the random forest model trained using the degree of FC achieved the highest accuracy (0.864), precision (0.887), specificity (0.894), F1 score (0.859) and area under the curve (0.924), and this model was further optimized for accuracy (0.879), sensitivity (0.909), F1 score (0.882) and area under the curve (0.928) by fusing clinical variables. The most discriminative nodes for predicting postoperative delirium were located in the default, cingulo-opercular, and frontoparietal networks. Conclusions This study found that the random forest model using preoperative functional MRI data and clinical variables was accurate in identifying patients at high risk of developing delirium after cardiac surgery.
Keywords: Postoperative delirium; Functional magnetic resonance imaging; Machine learning; Prediction model; Cardiac surgery

25COASMA8

Title: Regional lung ventilation during supraglottic and subglottic jet ventilation: A randomized cross-over trial,

Marita Windpassinger, Michal Prusak, Jana Gemeiner, Maximilian Edlinger-Stanger, Imme Roesner,

Journal of Clinical Anesthesia,Volume 102,2025,111773,
https://doi.org/10.1016/j.jclinane.2025.111773.

Abstract: Objective Test the hypothesis that the center of ventilation, a measure of ventro-dorsal atelectasis, is posterior during supraglottic ventilation indicating better dependent-lung ventilation. Secondarily, we tested the hypothesis that supraglottic ventilation improves oxygenation and carbon dioxide elimination. Background Supraglottic and subglottic jet ventilation are both used during laryngotracheal surgery. Supraglottic jet ventilation may better prevent atelectasis and provide superior ventilation. Design Randomized, cross-over trial. Setting Operating rooms. Patients Patients having elective micro-laryngotracheal surgery. Interventions Patients were sequentially ventilated for 5 min with one randomly selected type of jet ventilation before being switched to the alternative method. Measurements Regional ventilation distribution was estimated using electrical impedance tomography, with arterial oxygenation and carbon dioxide partial pressures being simultaneously evaluated. Results Thirty patients completed the study. There were no statistically significant or clinically meaningful differences in the center of ventilation with supraglottic and subglottic ventilation. However, ventilation with the supraglottic approach was about 4 % higher in the ventromedial lung region and about 4 % lower in the dorsal lung. Surprisingly, arterial blood oxygenation was considerably worse with supraglottic (173 [156, 199] mmHg) than subglottic ventilation (293 [244, 340] mmHg). Arterial carbon dioxide partial pressure was near 40 mmHg with each approach, although slightly lower with supraglottic jet ventilation. Conclusion The center of ventilation distribution, a measure of atelectasis, was similar with supraglottic and subglottic jet ventilation. Subglottic jet ventilation improved the dorsal-dependent lung region and provided superior arterial

oxygenation. Both techniques effectively eliminated carbon dioxide, with the supraglottic approach demonstrating slightly superior efficacy.

Keywords: Anesthesia; Jet ventilation; Electrical impedance tomography; Supraglottic jet ventilation; Subglottic jet ventilation; Laryngotracheal surgery; Regional lung ventilation distribution; Center of ventilation; Tidal impedance variation

25COASMA9

Title: Implications of packed red bloods cells production and transfer on post transfusion hemoglobin increase,

Heidi Ehrentraut, Gregor Massoth, Achilles Delis, Ben Thewes, Jochen Hoch, Mario Majchrzak

Journal of Clinical Anesthesia,Volume 102,2025,111743,
https://doi.org/10.1016/j.jclinane.2025.111743.

Abstract: Background Blood loss resulting in severe anemia is the most common indication for postoperative allogenic red blood cell (RBC) transfusions. In high-income countries, the majority of transfusions is received by elderly patients. Preservatives extend the storage of RBCs, though concerns exist about potential harm from transfusing older RBCs. This study tested the hypothesis that RBC storage duration effects hemoglobin increase in patients older than 70 years who underwent non-cardiac surgery. Method Observations on surgical cohorts from two study sites of the LIBERAL-Trial were collected. Transfusion events and hemoglobin between 2018 and 2022 assessments in addition to manufacturing and product specific quality review information were evaluated. Results A total of 1626 transfusion events in 505 patients were analyzed. A linear mixed effects model was used to estimate the effect size of different predictors on hemoglobin increment upon red blood cell transfusion. No statistically significant effect of the RBC unit storage duration was found. Confounding variables resulting in higher hemoglobin increase included lower hemoglobin values prior to transfusion, the length of Hb measurement intervals before and after transfusion, as well as the method of RBC cell separation in line with different manufacturer hemoglobin values. Conclusions The aspired increase in hemoglobin can be achieved with red blood cell concentrates of any storage duration. In general, elderly patients exhibit a sufficient hemoglobin rise following transfusion. However, if this is associated with improved outcomes cannot be answered.

Keywords: Red blood cell; Transfusion; Storage; Non-cardiac surgery; Elderly; Hemoglobin

25COASMA10

Title: Difficult airway management in 25 hospitals across China: A multicenter cross-sectional study,

Zhi-hang Tang, Qi Chen, Wei Huang, Jia-nan Wang, Xiao-hua Zou, Yang Xiao, Xiao-tong Shi,

Journal of Clinical Anesthesia, Volume 102,2025,111766,
https://doi.org/10.1016/j.jclinane.2025.111766.

Abstract: Study objective Difficult airway management is a significant challenge in clinical anesthesia, critical care, and emergency medicine. Inadequate management can lead to severe

complications including organ damage and death. This study assessed the variability in difficult airway management across China and focused on how patient and operator factors influenced outcomes in operating rooms. Design A multicenter observational cross-sectional study. Setting This study was conducted from November 2022 to November 2023 and included 25 secondary and tertiary hospitals across various regions in China. Patients In the total of 181,399 general anesthesia patients, 384 (0.21 %) were identified as having difficult airways. Interventions Data were gathered from a specialized questionnaire comprising four sections with 27 questions and analyzed using logistic regression in SPSS to identify key factors that influenced effective management of difficult airways. Measurements This study focused on preoperative assessment, anesthesia selection, intubation attempts, and contingency planning for difficult airway management practices among anesthesiologists. Main results In anticipated difficult airways, rapid sequence induction was used in 51.7 % of the cases, maintaining spontaneous breathing under general anesthesia in 11.1 %, and awake intubation in 36 %. For unanticipated difficult airways, 95.9 % of the anesthesiologists opted for rapid sequence induction. Limited mouth opening was the most common cause of difficult airways and obesity and ankylosing spondylitis were identified as significant factors. The logistic regression analysis identified the type of difficult airway, anesthesiologist experience, and assessment methods as key factors influencing the first attempt intubation success. Conclusions The accuracy of difficult airway assessment and first attempt intubation success is influenced by both patient-related factors and the anesthesiologist's expertise. Regional and institutional variability in decision-making and tool selection underscores the critical need for standardized guidelines and comprehensive training to enhance airway management outcomes across diverse clinical settings in China.

Keywords: Airway management; Awake intubation; General anesthesia; Patient safety; Surveys

25COASMA11

Title: Progression of chronic kidney disease after non-cardiac surgery: A retrospective cohort study,

Julian Rössler, Sascha Ott, Yufei Li, Alparslan Turan, Mehmet Yazar, Lukas M. Müller-Wirtz,

Journal of Clinical Anesthesia,Volume 102,2025,111745,
https://doi.org/10.1016/j.jclinane.2025.111745.

Abstract: Background Chronic-kidney-disease (CKD) is prevalent among adults undergoing noncardiac surgery, with surgery-related factors potentially worsening CKD or triggering acute kidney injury (AKI). We hypothesized that CKD patients experience more kidney function decline within one to two years post-surgery than those without CKD, particularly if they develop AKI. Methods We conducted a single-center retrospective cohort study, including noncardiac surgery patients with documented creatinine preoperative and between 1 and 2 years after surgery. The primary outcome was long-term course of kidney function, defined as the change in estimated glomerular filtration rate (eGFR) in mL/min/1.73m2. Results Of 58,175 included cases, 17 % had preoperative CKD. Mean eGFR changed from 90.1 ± 16.7 to 92.0 ± 18.8 in non-CKD patients and from 45.6 ± 11.9 to 55.6 ± 20.1 in

patients with CKD, with an estimated difference in means of 8.9 (95 % CI: 8.5, 9.3; P < 0.0001). There was a significant interaction between CKD-dependent eGFR change from baseline to follow-up and postoperative AKI (P = 0.001). For cases with preoperative CKD, eGFR increase from baseline to follow-up was 11.7 ± 18.0 with no AKI, 7.7 ± 17.9 with AKI stage 1, 2.4 ± 15.0 with AKI stage 2, and 7.3 ± 25.8 with AKI stage 3. For non-CKD patients, eGFR increased from baseline by 2.3 ± 13.7 with no AKI but decreased by 5.5 ± 19.0 with AKI stage 1, 7.7 ± 21.8 with AKI stage 2, and 9.3 ± 21.3 with AKI stage 3. Conclusions Contrary to expectations, patients with preoperative CKD experienced a significant improvement in eGFR postoperatively. Patients without CKD exhibited minimal change. Postoperative AKI negated the eGFR improvement in CKD patients and exacerbated the decline in non-CKD patients.

Keywords: Chronic kidney disease; Acute kidney injury; Non-cardiac surgery; Disease-progression

25COASMA12

Title: Impact of intraoperative anesthesia handover on major adverse cardiovascular events after thoracic surgery: A propensity-score matched retrospective cohort study,

Xiao-Ling Zhang, Yan Zhou, Mo Li, Jia-Hui Ma, Lin Liu, Dong-Xin Wang,

Journal of Clinical Anesthesia,Volume 102,2025,111778,
https://doi.org/10.1016/j.jclinane.2025.111778.

Abstract: Handover of anesthesia care is often required in busy clinical settings. Herein, we investigated whether intraoperative anesthesia handover was associated with an increased risk of major adverse cardiovascular events (MACEs) after thoracic surgery. A retrospective cohort study. A tertiary hospital. PatientsAdult patients who underwent elective thoracic surgery. Exposures A complete handover of intraoperative anesthesia care was defined when the outgoing anesthesiologist transferred patient care to the incoming anesthesiologist and no longer returned. Measurements Our primary endpoint was a composite of MACEs, including acute myocardial infarction, new-onset congestive heart failure, non-fatal cardiac arrest, and cardiac death, that occurred within 7 days after surgery. The impact of complete anesthesia handover on postoperative MACEs was analyzed using propensity score matching. Main results Of 6962 patients (mean age 59.7 years; 57.4 % female) included in the analysis, 2319 (33.3 %) surgeries were conducted with anesthesia handover whereas 4643 (66.7 %) were conducted without. After propensity score matching, 2165 (50.0 %) surgeries were conducted with anesthesia handover whereas the other half were conducted without. Patients with anesthesia handover developed more MACEs when compared with those without (10.4 % [225/2165] vs. 8.4 % [181/2165]; relative risk 1.24, 95 % CI 1.03 to 1.50, P = 0.022). Specifically, myocardial infarction was more common in patients with anesthesia handover than in those without (9.2 % [199/2165] vs. 7.4 % [160/2165]; relative risk 1.24, 95 % CI 1.02 to 1.52, P = 0.032). Conclusions For adult patients undergoing thoracic surgery, a complete handover of intraoperative anesthesia care was associated with an increased risk of MACEs after surgery.

Keywords: Adult patients; Elective thoracic surgery; Handover of anesthesia care; Major adverse cardiovascular events

25COASMA13

Title: Perioperative goal-directed therapy with artificial intelligence to reduce the incidence of intraoperative hypotension and renal failure in patients undergoing lung surgery: A pilot study,

Marit Habicher, Sara Marie Denn, Emmanuel Schneck, Amir Ali Akbari, Götz Schmidt, Melanie Markmann,

Journal of Clinical Anesthesia, Volume 102,2025,111777,
https://doi.org/10.1016/j.jclinane.2025.111777.

Abstract: Study objective The aim of this study was to investigate whether goal-directed treatment using artificial intelligence, compared to standard care, can reduce the frequency, duration, and severity of intraoperative hypotension in patients undergoing single lung ventilation, with a potential reduction of postoperative acute kidney injury (AKI). Design single center, single-blinded randomized controlled trial. Setting University hospital operating room. Patients 150 patients undergoing lung surgery with single lung ventilation were included. Interventions Patients were randomly assigned to two groups: the Intervention group, where a goal-directed therapy based on the Hypotension Prediction Index (HPI) was implemented; the Control group, without a specific hemodynamic protocol. Measurements The primary outcome measures include the frequency, duration of intraoperative hypotension, furthermore the Area under MAP 65 and the time-weighted average (TWA) of MAP of 65. Other outcome parameters are the incidence of AKI and myocardial injury after non-cardiac surgery (MINS). Main results The number of hypotensive episodes was lower in the intervention group compared to the control group (0 [0–1] vs. 1 [0–2]; p = 0.01), the duration of hypotension was shorter in the intervention group (0 min [0–3.17] vs. 2.33 min [0–7.42]; p = 0.01). The area under the MAP of 65 (0 mmHg * min [0−12] vs. 10.67 mmHg * min [0–44.16]; p < 0.01) and the TWA of MAP of 65 (0 mmHg [0–0.08] vs. 0.07 mmHg [0–0.25]; p < 0.01) were lower in the intervention group. The incidence of postoperative AKI showed no differences between the groups (6.7 % vs.4.2 %; p = 0.72). There was a trend to lower incidence of MINS in the intervention group (17.1 % vs. 31.8 %; p = 0.07). A tendency towards reduced postoperative infection was seen in the intervention group (16.0 % vs. 26.8 %; p = 0.16). Conclusions The implementation of a treatment algorithm based on HPI allowed us to decrease the duration and severity of hypotension in patients undergoing lung surgery. It did not result in a significant reduction in the incidence of AKI, however we observed a tendency towards lower incidence of MINS in the intervention group, along with a slight reduction in postoperative infections.

Keywords: Artificial intelligence; Intraoperative hypotension; Hypotension prediction index; Acute kidney injury; Thoracic surgery

25COASMA14

Title: Preoperative LDL-C and major cardiovascular and cerebrovascular events after non-cardiac surgery,

David Rehe, Varun Subashchandran, Yan Zhang, Germaine Cuff, Mitchell Lee, Jeffrey S. Berger, Nathaniel R. Smilowitz,

Journal of Clinical Anesthesia, Volume 102,2025,111783,
https://doi.org/10.1016/j.jclinane.2025.111783.

Abstract: Study objective To determine whether preoperative LDL-C concentration affects the risk of perioperative major adverse cardiovascular or cerebrovascular events (MACCE) after noncardiac surgery. Design Single center retrospective cohort study. Setting Hospital (including medical and surgical floor, intensive care unit) and patient disposition location (including the patient's home or any other receiving facility). Patients 43,348 non-cardiac surgeries at NYU Langone Health between January 2016 and September 2020. Interventions Patients were grouped based on preoperative LDL-C. Measurements Complete serum lipid panel obtained within one year prior to the date of noncardiac surgery and rate of perioperative MACCE, defined as a composite of in-hospital non-fatal myocardial infarction, in-hospital acute ischemic stroke, myocardial injury after noncardiac surgery, and death from any cause within 30 days of surgery. Main results Perioperative MACCE occurred in 1093 patients (2.5 %) overall. After multivariable adjustment, odds of MACCE were significantly lower in patients with higher (≥100 mg/dL) versus lower (<100 mg/dL) LDL-C (adjusted odds ratio [aOR] 0.783, 95 % CI, 0.660–0.926]). Conclusions In a large cohort of patients undergoing non-cardiac surgery at a major academic health system in New York City, lower LDL-C concentrations were not associated with a lower incidence of perioperative MACCE. Further investigation into modifiable perioperative cardiovascular risk factors is needed to improve perioperative outcomes.

Keywords: Perioperative period; Low density lipoprotein cholesterol; Anesthesia; Surgical procedures, operative; Hydroxymethylglutaryl-CoA reductase inhibitors; Cardiovascular disease

25COASMA15

Title: Perioperative glucagon-like peptide-1 receptor agonist use and retained gastric contents: A retrospective analysis of patients undergoing elective upper endoscopy,

Jacqueline A. Quinn, Kevin M. Welch, Erina Fujino, Carlos A. Jimenez Rosado, Xinming An, Jay W. Schoenherr, Lindsey N. Gouker,

Journal of Clinical Anesthesia, Volume 102,2025,111776,
https://doi.org/10.1016/j.jclinane.2025.111776.

Abstract: Introduction Glucagon-like peptide-1 receptor (GLP-1R) agonists have been increasingly prescribed for weight loss and glycemic control. The potential side effect of slowed gastric emptying may increase risk of regurgitation and aspiration. Our primary aim was to investigate the incidence of retained gastric contents (RGCs) among appropriately fasted patients taking a GLP-1R agonist compared to those not taking a GLP-1R agonist presenting for upper gastrointestinal endoscopy (UE). Methods A retrospective chart review of patients undergoing UE was conducted. For the GLP-1R group, included were patients aged 18 years or older who had documentation of taking a GLP-1R agonist within 30 days prior to the procedure, adhered to standard fasting guidelines, and had clear documentation in the electronic medical record of gastric findings during endoscopy. This group was compared to a group of agematched controls. The primary outcome was the incidence of RGCs. Secondary outcome included a propensity-weighted analysis of the odds ratio of taking a

GLP-1R and having RGCs. Results Included were 940 patients who presented for UE between July 2022 and December 2023 (470 GLP-1R and 470 controls). RGCs were found in 59/470 (12.6 %) of GLP-1R patients compared to 26/470 (5.5 %) of controls (P < 0.001). Propensity-weighted analysis found a significant association between the use of GLP-1R and retained gastric contents [OR = 1.92, 95 % CI (1.04, 3.53)]. Conclusions A higher incidence of RGCs was found in appropriately fasted patients on a GLP-1R agonist who presented for UE. After controlling for the differences between the two study groups, RGC's were correlated to GLP-1R agonist use. Anesthesiologists should remain vigilant regarding a potential increased risk of RGCs in appropriately fasted patients taking a GLP-1R agonist who present for surgery.

25COASMA16

Title: Association of rapid response system with clinical outcomes after surgery under general anesthesia,

In-Ae Song, Tak Kyu Oh,

Journal of Clinical Anesthesia,Volume 102,2025,111749,
https://doi.org/10.1016/j.jclinane.2025.111749.

Abstract: Background In this population-based cohort study involving a nationwide database from South Korea, we aimed to determine whether rapid response system (RRS) implementation is associated with mortality and morbidity after surgery under general anesthesia. Methods Patients who underwent surgery under general anesthesia at the hospital between January 1, 2021, and December 31, 2021. Patients admitted to hospitals with an RRS were categorized into the RRS group, whereas those without an RRS were categorized into the non-RRS group. The endpoints were 30-day mortality, 90-day mortality, and CPR performance in the event of cardiac arrest. Results A total of 1,416,844 patients who underwent surgery under general anesthesia were included. The RRS and non-RRS groups included 512,911 and 903,933 patients, respectively. After propensity score (PS) matching, 447,998 patients were included in both groups (223,999 patients per group). In the PS-matched cohort, compared with the non-RRS group, the RRS group had 7 % (odds ratio [OR]: 0.93, 95 % confidence interval [CI]: 0.89, 0.97; P = 0.001), 6 % (OR: 0.94, 95 % CI: 0.91, 0.97; P < 0.001), and 9 % (OR: 0.91, 95 % CI: 0.83, 0.98; P = 0.020) lower incidences of 30-day mortality, 90-day mortality, and CPR, respectively. Conclusions The RRS group had lower 30-day and 90-day mortality rates than the non-RRS group after surgery under general anesthesia. Moreover, RRS was associated with a lower rate of CPR episodes resulting from cardiac arrest in patients undergoing general anesthesia after surgery.

Keywords: Surgery; Mortality; Cohort studies; Population; Rapid response system

25COASMA17

Title: Opioid use in treated and untreated obstructive sleep apnoea: remifentanil pharmacokinetics and pharmacodynamics in adult volunteers,

Anil R. Maharaj, Michael C. Montana, Christoph P. Hornik, Evan D. Kharasch,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 681-692,
https://doi.org/10.1016/j.bja.2024.10.042.

Abstract: Patients with obstructive sleep apnoea (OSA) are considered more sensitive to opioids and at increased risk of opioid-induced respiratory depression. Nonetheless, whether OSA treatment (continuous positive airway pressure, CPAP; or bilevel positive airway pressure, BIPAP) modifies this risk remains unknown. Greater opioid sensitivity can arise from altered pharmacokinetics or pharmacodynamics. This preplanned analysis of a previous cohort study of remifentanil clinical effects in OSA tested the null hypothesis that the pharmacokinetics, pharmacodynamics, or both of remifentanil, a representative μ-opioid agonist, are not altered in adults with treated or untreated OSA. Methods A single-centre, prospective, open-label, cohort study administered a stepped-dose, target-controlled remifentanil infusion (target effect-site concentrations 0.5, 1, 2, 3, 4 ng ml−1) to awake adult volunteers (median age 52 yr, range 23–70) without OSA (n=20), with untreated OSA (n=33), or with treated OSA (n=21). Type III (in-home) polysomnography verified OSA. Remifentanil plasma concentrations, end-expired CO2, thermal heat tolerance, and pupil diameter (miosis) were assessed. Population pharmacokinetic (clearance, volume of distribution) and pharmacodynamic (miosis, thermal heat tolerance, end-expired CO2) models were developed. Results Remifentanil clearance (median) was 147, 143, and 155 L h−1 (P=0.472), and volume of distribution was 19.6, 15.5, and 17.7 L (P=0.473) for subjects without OSA, untreated OSA, or treated OSA, respectively. Total body weight was an influential covariate on both remifentanil clearance and central volume of distribution. There were no statistically or clinically significant differences between the three groups in miosis EC50 or Emax, or the slopes of thermal heat tolerance or end-expired CO2 vs remifentanil concentration. At a plasma remifentanil concentration of 4 ng ml−1, in participants without OSA, with untreated OSA, or with treated OSA, respectively, model-estimated pupil area (12%, 13%, and 17% of baseline, P=0.086), thermal heat tolerance (50°C, 51°C, and 51°C, P=0.218), and end-expired CO2 (6.3 kPa, 6.4 kPa, and 6.7 kPa, P=0.257) were not statistically different between groups. Conclusions OSA (untreated or treated) did not influence remifentanil pharmacokinetics or pharmacodynamics (miosis, analgesia, respiratory depression). Results support the null hypothesis that neither pharmacokinetics nor pharmacodynamics of remifentanil, a representative μ-opioid, are altered in adults with treated or untreated OSA. These findings provide a mechanistic explanation for the lack of influence of OSA or OSA treatment on the clinical miotic, sedative, analgesic, or respiratory depressant response to remifentanil in awake adults. The conventional notion that OSA alters sensitivity to the effects of opioids in awake adults is not supported by our findings, such that opioid dosing might not need adjustment for pharmacokinetic or pharmacodynamic considerations.

Keywords: analgesia; miosis; obstructive sleep apnoea; opioids; pharmacodynamics; remifentanil; respiratory depression

25COASMA18

Title: Effect of intraperitoneal ropivacaine during and after cytoreductive surgery on time-interval to adjuvant chemotherapy in advanced ovarian cancer: a randomised, double-blind phase III trial,

Emma Hasselgren, Nina Groes-Kofoed, Henrik Falconer, Håkan Björne, Diana Zach, Daniel Hunde,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 662-670,
https://doi.org/10.1016/j.bja.2024.10.015.

Abstract: In a previous phase II trial, intraperitoneal local anaesthetics shortened the time interval between surgery and adjuvant chemotherapy, an endpoint associated with improved survival in advanced ovarian cancer. Our objective was to test this in a phase III trial. Methods A double-blind, phase III parallel superiority trial was conducted at two university hospitals in Sweden, within a public and centralised healthcare system. Women >18 yr with advanced ovarian cancer scheduled for cytoreductive surgery, an ASA physical status of 1–3 with no speech/language issues, were eligible. Participants were randomly assigned using a central computerised system to receive either ropivacaine 0.2% or saline 0.9% (placebo) intraperitoneally during and after surgery. The primary endpoint was time to return to intended oncologic therapy (RIOT), analysed using t-test and linear regression adjusted for centre. Results Of the 225 women randomised between August 2020 and December 2023 (ropivacaine n=113; placebo n=112), 175 were included in the modified intention-to-treat analysis (ropivacaine n=86; placebo n=89). Median age: ropivacaine group 64 yr (56–73 yr), placebo group: 66 yr (57–74 yr). The mean RIOT in the ropivacaine group was 26.5 days vs 25.8 days in the placebo group, with a mean difference of 0.7 days (−2.2 to 3.4 days; P=0.65). Per-protocol analysis of 166 women yielded similar results, mean difference of 0.5 days (−2.4 to 3.4 days; P=0.74) days. There were no differences in short-term recovery or postoperative morbidity. Conclusion Intraperitoneal local anaesthetic did not shorten the time to RIOT among women undergoing surgery for advanced ovarian cancer in this trial.

Keywords: cytoreductive surgery; intraperitoneal; local anaesthetic; ovarian cancer; ropivacaine; return to intended oncologic therapy; time interval to chemotherapy

25COASMA19

Title: The relationship of bispectral index values to conscious state: an analysis of two volunteer cohort studies,

Jordan J. Wehrman, Peter J. Schuller, Cameron P. Casey, Annalotta Scheinin, Roosa E. Kallionpää,

British Journal of Anaesthesia,Volume 134, Issue 3,2025,Pages 727-735
https://doi.org/10.1016/j.bja.2024.09.032.

Abstract: The ability of current depth-of-anaesthesia monitors to differentiate subtle changes in the conscious state has not been well characterised. We examine the variability in bispectral index (BIS) scores associated with disconnected conscious and unconscious states as confirmed by a novel serial awakening paradigm. Seventy adult participants, given propofol or dexmedetomidine, had a cumulative 1381 electroencephalographic (EEG) recordings across two centres. Participants were awakened periodically, and their recent conscious experience interrogated by structured questioning. BIS were reconstructed from EEG using openibis, and the distribution of BIS scores were compared using linear mixed effects modelling. The predictive capacity of BIS across states of consciousness was also examined. Reconstructed BIS scores correlated significantly with blood concentrations of propofol and dexmedetomidine (all P<0.001). However, while the average BIS was different between baseline wakefulness (mean BIS=95.1 [standard deviation=3.5]); connected

consciousness with drug present (84.0 [10.9]); disconnected consciousness (70.0 [16.9]); and unconsciousness (68.1 [16.1]), the interquartile range of these states (3.6, 15.1, 23.3 and 26.8, respectively) indicated high degrees of overlap and individual variability. Connected consciousness could be differentiated from either disconnected consciousness or unconsciousness with 86% accuracy (i.e. 14% error rate), and disconnected consciousness differentiated from unconsciousness with 74% accuracy. These results agree with previous studies that BIS scores fail to reliably differentiate between states of consciousness, exacerbated by segregating connected, disconnected, and unconscious states. To develop a method that reliably identifies the conscious state of an individual (not an average), work is needed to establish the causal mechanisms of disconnection and unconsciousness.

Keywords: BIS; bispectral index; consciousness assessment; dexmedetomidine; openibis; propofol; serial awakening

25COASMA20

Title: Genome-wide association study on chronic postsurgical pain in the UK Biobank,

Song Li, Masja K. Toneman, Luda Diatchenko, Marc Parisien, Kris C.P. Vissers, Richard P.G. ten Broek,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 783-792,
https://doi.org/10.1016/j.bja.2024.12.008.

Abstract: Chronic postsurgical pain (CPSP) persists beyond the expected healing period after surgery, imposing a substantial burden on overall patient well-being. Unfortunately, CPSP often remains underdiagnosed and undertreated. To better understand the mechanism of CPSP development, we aimed to identify genetic variants associated with CPSP. A genome-wide association study was conducted in a cohort of 95,931 individuals from the UK Biobank who had undergone different surgical procedures. Three analyses were performed: (1) case–control analysis (2923 cases with CPSP and 93,008 controls), (2) ordinal analysis in three groups based on time of analgesics use (n=95,931), and (3) a meta-analysis combining our dataset with a recent publication (n=97,281). In the case–control analysis, one genetic locus within GLRA3 displayed a genome-wide significant ($P<2.5\times10-8$) association with CPSP, and nine loci displayed suggestively significant associations ($P<1\times10-6$). The ordinal analysis aligned with the case–control analysis, with an additional locus (rs140330443) reaching genome-wide significance. In the meta-analysis with the recently published dataset, the single nucleotide polymorphism (SNP) rs17298280 in the GLRA3 gene remained significant ($P=2.19\times10-9$). This study contributes new insights into the genetic factors associated with CPSP. The top hit GLRA3 is known for involvement in prostaglandin E2-induced pain processing pathways. Our study provides a foundation for future investigations into the function of these risk variants and the mechanisms underlying CPSP by offering summary statistics. However, further validation in other cohorts is required to confirm these findings.

Keywords: chronic postsurgical pain; genetics; genome-wide association study; GLRA3; glycine receptor; risk prediction; UK Biobank

25COASMA21

Title: Procedural sedation competencies: a review and multidisciplinary international consensus statement on knowledge, skills, training, and credentialing,

Piet L. Leroy, Baruch S. Krauss, Luciane R. Costa, Egidio Barbi, Michael G. Irwin, Douglas W. Carlson,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 817-829,
https://doi.org/10.1016/j.bja.2024.07.036.

Abstract: Procedural sedation is practised by a heterogeneous group of practitioners working in a wide array of settings. However, there are currently no accepted standards for the competencies a sedation practitioner should have, the content of sedation training programmes, and guidelines for credentialing. The multidisciplinary International Committee for the Advancement of Procedural Sedation sought to develop a consensus statement on the following: which competencies should medical or dental practitioners have for procedural sedation and how are they obtained, assessed, maintained, and privileged. Using the framework of Competency-Based Medical Education, the practice of procedural sedation was defined as a complex professional task requiring demonstrable integration of different competencies. For each question, the results of a literature review were synthetised into preliminary statements. Following an iterative Delphi review method, final consensus was reached. Using multispeciality consensus, we defined procedural sedation competence by identifying a set of core competencies in the domains of knowledge, skills, and attitudes across physical safety, effectiveness, psychological safety, and deliberate practice. In addition, we present a standardised framework for competency-based training and credentialing of procedural sedation practitioners.

Keywords: competencies; credentialing; entrustable professional activity; medical education; privileging; procedural sedation; quality and patient safety

25COASMA22

Title: The number of central nervous system-driven symptoms predicts subsequent chronic primary pain: evidence from UK Biobank,

Eoin Kelleher, Chelsea M. Kaplan, Dorna Kheirabadi, Andrew Schrepf, Irene Tracey, Daniel J. Clauw, Anushka Irani,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 772-782,
https://doi.org/10.1016/j.bja.2024.12.009.

Abstract: Chronic primary pain describes conditions where pain is the principal problem rather than a consequence of another disease. Primary pain is thought to be primarily owing to nociplastic pain (i.e. pain as a result of altered nociception despite the absence of tissue damage). Primary pain is often accompanied by other bothersome central nervous system (CNS)-driven symptoms, including disturbed sleep, mood, and cognition; however, it is unclear whether these symptoms precede onset of primary pain. In a prospective cohort study of the UK Biobank, we examined adults with no self-reported recent or chronic pain at baseline. Using linked primary care record data, we investigated the association between the number of CNS-driven symptoms and subsequent incidence of primary pain conditions. Multivariable regression analyses adjusted for sociodemographic and lifestyle factors. Of 502

369 participants, 70 630 (14.0%) met the inclusion criteria, with a mean (range) age of 56.7 (40-70) yr, 51% being female. After 7.4 (range 0.5–11.02) yr, 12.2% developed a primary pain condition. We observed a positive relationship between the number of CNS-driven symptoms at baseline and risk of future primary pain (HR 1.43, 95% CI 1.34–1.52, P<0.001). Participants with more CNS-driven symptoms at baseline were also more likely to have chronic and more severe nociplastic pain, but not non-nociplastic pain at follow-up. In adults with no current self-reported pain, those with a greater number of CNS-driven symptoms at baseline were more likely to develop a primary pain condition. This suggests a potential opportunity for early intervention in mitigating the burden of primary pain.

Keywords: chronic pain; epidemiology; musculoskeletal pain; nociplastic pain; primary pain

25COASMA23

Title: Effect of telemedicine support for intraoperative anaesthesia care on postoperative outcomes: the TECTONICS randomised clinical trial,

Christopher R. King, Bradley A. Fritz, Stephen H. Gregory, Thaddeus P. Budelier, Arbi Ben Abdallah,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 671-680,
https://doi.org/10.1016/j.bja.2024.11.017.

Abstract: Telemedicine may help improve care quality and patient outcomes. Telemedicine for intraoperative decision support has not been rigorously studied. This was a single-centre randomised clinical trial of unselected adult surgical patients. Patients were randomised to receive usual care or decision support from a telemedicine service, which provided real-time recommendations to intraoperative anaesthesia clinicians based on case reviews and physiological alerts. ORs were randomised 1:1. The co-primary outcomes were 30-day all-cause mortality, respiratory failure, acute kidney injury, and delirium in the intensive care unit, analysed by intention to treat. Between July 1, 2019, and January 31, 2023, a total of 35,302 patients were randomised to receive telemedicine support, with 36,625 receiving usual care. Telemedicine clinicians provided review in 11,812/35,302 cases, with alerts delivered to 2044/35,302 patients. Telemedicine support had no effect on any of the co-primary outcomes. Within 30 days, 630/35,302 (1.8%) patients randomised to telemedicine died within 30 days, compared with 649/36,625 (1.8%) receiving usual care (relative risk [RR]1.01, 95% confidence interval [CI] 0.87–1.16, P=0.98). Telemedicine support did not alter postoperative respiratory failure [telemedicine 1071/33,996 (3.2%) vs usual care 1130/35,236 (3.2%), RR 0.98, 95% CI 0.88–1.09, P=0.98], acute kidney injury [telemedicine 2316/33 251 (7.0%) vs usual care 2432/34,441 (7.1%); RR 0.99, 95% CI 0.92–1.06, P=0.98], or delirium [telemedicine 1264/3873 (32.6%) vs usual care 1298/4044 (32.1%), RR 1.02, 95% CI 0.94–1.10, P=0.98]. In this large randomised clinical trial, intraoperative telemedicine decision support using real-time alerts and case reviews had no impact on adverse postoperative outcomes.

Keywords: acute kidney injury; decision support; delirium; machine learning; postoperative mortality; randomised trial; respiratory failure; telemedicine

25COASMA24

Title: Sprouting sympathetic fibres release CXCL16 and norepinephrine to synergistically mediate sensory neuronal hyperexcitability in a rodent model of neuropathic pain,

Chen Wang, Anjie Di, Yan Wu, Meng Liu, Ming Wei, Zhengkai Liang, Feng Liu, Haiting Fan,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 804-816,
https://doi.org/10.1016/j.bja.2024.10.019.

Abstract: Chronic neuropathic pain generally has a poor response to treatment with conventional drugs. Sympathectomy can alleviate neuropathic pain in some patients, suggesting that abnormal sympathetic-somatosensory signaling interactions might underlie some forms of neuropathic pain. The molecular mechanisms underlying sympathetic-somatosensory interactions in neuropathic pain remain obscure. Lumbar sympathectomy was performed in spared nerve injury (SNI) mice or rats, and the up-down method was used to measure the mechanical paw withdrawal threshold. Dorsal root ganglia (DRG) injection and perfusion were used to deliver virus or drugs. Methylated RNA immunoprecipitation sequencing, RNA-sequencing, and immunoelectron microscopy were used to identify neurotransmitters. We found that sprouting tyrosine hydroxylase-positive sympathetic fibres in DRG mediated the maintenance of mechanical allodynia after SNI (day 28, $P<0.001$). We further found that SNI significantly increased the N6-methyladenosine level of CXCL16 messenger RNA (day 28, $P<0.001$), which was attributable to the reduced N6-methyladenosine demethylase fat mass and obesity-associated protein ($P=0.002$) and increased interaction with YTHDF1 ($P=0.013$) in the sympathetic ganglion. Enhanced expression of CXCL16 in the sympathetic ganglia can lead to increases release into the DRG and act synergistically with norepinephrine from sympathetic terminals to enhance DRG neuronal excitability. Norepinephrine and CXCL16 co-released from sympathetic nerve terminals in the DRG synergistically contribute to maintenance of neuropathic pain in a rodent model.

Keywords: chronic neuropathic pain; CXC motif chemokine ligand 16; N6-methyladenosine; norepinephrine; sympathetic ganglion

25COASMA25

Title: Kappa opioid receptor internalisation-induced p38 nuclear translocation suppresses glioma progression,

Yong Li, Wenying Wang, Han She, Zhibo Cui, Zhengchao Liu, Hai Yang, Jun Zhang, Xiaoqiong Zhou,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 759-771,
https://doi.org/10.1016/j.bja.2024.09.031.

Abstract: Recent studies have implicated a role for perioperative medications in determining patient outcomes after surgery for malignant tumours, including relapse and metastasis. A combined approach spanned molecular, cellular, and organismal levels, including bioinformatics, immunohistochemical staining of clinical and animal samples, RNA sequencing of glioblastoma multiforme (GBM) cells with Ingenuity Pathway Analysis, lentiviral-mediated gene expression modulation, in vitro cell experiments, and in vivo

orthotopic tumour transplantation. We observed a significant correlation between increased kappa opioid receptor (KOP receptor) expression and better prognosis in patients with glioma. Exogenous KOP receptor overexpression in GBM cells in vitro induced cell cycle arrest, suppressed cell growth, and promoted apoptosis. Conversely, reducing KOP receptor expression in GBM cells reduced the proportion of cells in S and G2/M phases, accelerating cell growth. KOP receptor overexpression inhibited glioma cell growth and prolonged survival in mice in vivo, while KOP receptor knockdown had the opposite effect. Mechanistically, internalised KOP receptors were found to bind cytoplasmic p38, facilitating its nuclear translocation and phosphorylation, which influences downstream gene expression. The selective KOP receptor agonist TRK-820 triggered KOP receptor internalisation, activated the p38 pathway, and diminished glioma cell viability in vitro. This combined molecular, cellular, and in vivo approach supports use of KOP receptor agonists as potential adjuvant therapeutics for glioma.

Keywords: glioblastoma multiforme; KOP agonist; KOP receptor; p38 MAP kinase; receptor internalisation

25COASMA26

Title: Qnox index for quantification of intraoperative nociception and analgesia: a prospective single-centre validation study,

Hao Kong, Dan-Dan Ma, Jia-Hui Ma, Yu-Xiu Zhang, Hong Zhang, Dong-Xin Wang,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 736-745,
https://doi.org/10.1016/j.bja.2024.10.051.

Abstract: The Qnox index is a novel monitor to quantify intraoperative nociception based on an electroencephalographic algorithm. We evaluated the ability of the Qnox index to discriminate noxious from non-noxious stimuli, respond to stimuli, and discriminate different levels of analgesia in patients under propofol anaesthesia with neuromuscular block. Qnox was compared with heart rate and mean arterial pressure with five designated stimuli: tetanic stimulations without (tetanic 1) and with sufentanil (tetanic 2), skin incision, tracheal intubation, and a non-noxious period. The response around the skin incision was also evaluated at two target remifentanil concentrations. In 83 adult patients scheduled for elective surgery, Qnox performed worse than heart rate and mean arterial pressure in discriminating tetanic 2, tetanic 1, skin incision, and tracheal intubation noxious stimuli from the non-noxious period, with an area under curve of 0.52 (95% confidence interval 0.43–0.61), 0.54 (0.45–0.62), 0.67 (0.58–0.75), and 0.65 (0.57–0.73), respectively. The post-stimulus values of Qnox increased significantly after tracheal intubation and skin incision, but not after tetanic 1 or tetanic 2. Qnox values after skin incision were similar between the low- and high-remifentanil-concentration groups. Qnox had a poor ability to discriminate noxious stimuli from non-noxious stimuli. Although Qnox responded to tracheal intubation and skin incision, it did not respond to tetanic stimulations and failed to discriminate different levels of analgesia. The Qnox index was not superior to heart rate or mean arterial pressure in assessing nociception during general anaesthesia.

Keywords: analgesia; heart rate; intraoperative nociception; mean arterial pressure; noxious stimuli; Qnox index

25COASMA27

Title: Effect of a driving pressure-limiting strategy for patients with acute respiratory distress syndrome secondary to community-acquired pneumonia: the STAMINA randomised clinical trial,

Israel Silva Maia, Alexandre Biasi Cavalcanti, Lucas Tramujas, Viviane Cordeiro Veiga, Júlia Souza Oliveira,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 693-702,
https://doi.org/10.1016/j.bja.2024.10.012.

Abstract: This study aimed to assess whether a driving pressure-limiting strategy based on positive end-expiratory pressure (PEEP) titration according to best respiratory system compliance and tidal volume adjustment increases the number of ventilator-free days within 28 days in patients with moderate to severe acute respiratory distress syndrome (ARDS). This is a multi-centre, randomised trial, enrolling adults with moderate to severe ARDS secondary to community-acquired pneumonia. Patients were randomised to a driving pressure-limiting strategy or low PEEP strategy based on a PEEP:FiO2 table. All patients received volume assist-control mode until day 3 or when considered ready for spontaneous modes of ventilation. The primary outcome was ventilator-free days within 28 days. Secondary outcomes were in-hospital and intensive care unit mortality at 90 days. The trial was stopped because of recruitment fatigue after 214 patients were randomised. In total, 198 patients (n=96 intervention group, n=102 control group) were available for analysis (median age 63 yr, [interquartile range 47–73 yr]; 36% were women). The mean difference in driving pressure up to day 3 between the intervention and control groups was –0.7 cm H2O (95% confidence interval –1.4 to –0.1 cm H2O). Mean ventilator-free days were 6 (sd 9) in the driving pressure-limiting strategy group and 7 (9) in the control group (proportional odds ratio 0.72, 95% confidence interval 0.39–1.32; P=0.28). There were no significant differences regarding secondary outcomes. In patients with moderate to severe ARDS secondary to community-acquired pneumonia, a driving pressure-limiting strategy did not increase the number of ventilator-free days compared with a standard low PEEP strategy within 28 days.

Keywords: acute respiratory distress syndrome; driving pressure; positive end-expiratory pressure; tidal volume; ventilator-induced lung injury

25COASMA28

Title: Correlation between Altmetric Attention Scores and citation scores across the high impact-factor journals each in Medicine, Surgery, and Anaesthesia,

Amanda Koh, Christopher A. Lewis-Lloyd, Tiffany Wong, Dileep N. Lobo,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 703-712,
https://doi.org/10.1016/j.bja.2024.09.034.

Abstract: Citation scores (CS) are traditionally used to measure the impact of scientific publications. Altmetric Attention Scores (AAS), in contrast, consider the digital dissemination of articles across social media platforms to track their audience reach. In this

cross-sectional study, we aimed to determine the correlation between AAS and CS in 12 high-impact-factor journals in the category of 'Clinical Medicine'. The 12 journals with the highest 2023 journal impact factor (published in June 2024), four each in General and Internal Medicine, General Surgery, and Anaesthesia, were included. Articles published in final version between January 1 and December 31, 2021 were selected, and up-to-date AAS and CS for each article were obtained on July 2, 2024 from Dimensions (https://app.dimensions.ai/discover/publication). Spearman's rank order correlations (ϱ) were used to assess the strength of the association between AAS and CS. A total of 5193 outputs (2747 in Medicine, 1345 in Surgery, and 1101 in Anaesthesia) were analysed, with median (interquartile range) AAS and CS of 37 (10–157) and 16 (6–52), respectively. Medicine journals had the highest AAS and CS (124 [47–384] and 28 [8–113]), followed by Anaesthesia (12 [5–27] and 12 [5–24]) and Surgery (9 [2–24] and 11 [4–27]), respectively. There was a moderate positive correlation between AAS and CS overall (ϱ=0.589), with a moderate correlation for Medicine (ϱ=0.681) and Anaesthesia (ϱ=0.427) and a weak correlation for Surgery (ϱ=0.354) (all P<0.0001). Altmetric Attention Scores correlated with citation scores, suggesting that audience engagement via social media can influence the future impact of publications and their citation scores.

Keywords: altmetrics; Altmetric Attention Score; bibliometrics; citation count; journal impact factor

25COASMA29

Title: Spread of local anaesthetic after erector spinae plane block: a randomised, three-dimensional reconstruction, imaging study,

Tao Shan, Xiaodan Zhang, Zhenyu Zhao, Xiao Zhou, Hongguang Bao, Chuan Su, Qilian Tan, Liu Han, Jun Yin,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 830-838,
https://doi.org/10.1016/j.bja.2024.10.046.

Abstract: Spread of local anaesthetic solution in the paravertebral space after erector spinae plane block (ESPB) is variable. We evaluated whether paravertebral spread of local anaesthetic is affected by patient position after ESPB. We randomised 84 patients to receive ESPB at T7 with a mixture of 0.375% ropivacaine and radiocontrast dye (30 ml). Participants were positioned supine, prone, or lateral for 30 min after ESPB before computed tomography scanning. The primary outcome was paravertebral space local anaesthetic spread, with secondary assessments of craniocaudal spread and distribution to neural foramina, and intercostal and epidural spaces. Loss of sensation to cold was recorded. Local anaesthetic–contrast mix reached the paravertebral space, intercostal space, and neural foramina in 96.5%, 94.2%, and 77.9% of individuals, respectively. Epidural space spread occurred in 20 cases. Prone positioning consistently allowed paravertebral and intercostal spread in all patients, with more thoracic level spread compared with supine positioning (5.0 [1.9] vs 3.1 [1.7], difference [95% confidence interval, CI]: 1.9 [0.8–3.0] levels, P<0.001 for paravertebral space spread; 2.8 [1.9] vs 1.4 [1.4], difference [95% CI] levels: 1.4 [0.4–2.5], P=0.004 for neural foramina spread; 4.3 [1.3] vs 3.2 [1.5], difference [95% CI] levels: 1.0 [0.1–1.9], P=0.019 for intercostal space spread). Local anaesthetic–contrast extended to the intercostal

space further in the prone than in the lateral position group (4.3 [1.3] vs 2.6 [1.5] thoracic levels, difference [95% CI]: 1.7 [0.8–2.6], P<0.001). Sensory block in ventral dermatomes was variable in all participants. Prone positioning after ESPB significantly enhanced local anaesthetic–contrast spread to the paravertebral space, intercostal space, and neural foramina, suggesting that gravity plays a substantial role in spread.

Keywords: computed tomography; erector spinae plane block; local anaesthetic spread; patient position; regional anaesthesia; three-dimensional imaging

25COASMA30

Title: Associations between endogenous sex hormones and multisite chronic musculoskeletal pain,

Zemene Demelash Kifle, Jing Tian, Dawn Aitken, Phillip E. Melton, Flavia Cicuttini, Graeme Jones, Feng Pan,

British Journal of Anaesthesia, Volume 134, Issue 3,2025,Pages 793-803,
https://doi.org/10.1016/j.bja.2024.11.021.

Abstract: Sex-differences in pain perception have been documented; however, the role of sex hormones in chronic musculoskeletal pain (CMP) remains unclear. Therefore, this study investigated whether sex hormones and sex hormone-binding globulin (SHBG) are associated with CMP. We utilised data from the UK Biobank (n=357 424; females: 51.6%; white: 95.2%). Serum concentrations of oestradiol (E2), testosterone (T), and SHBG were measured at baseline. Chronic pain (≥3 months) in the neck/shoulder, back, hip, knee, or 'all over the body' was assessed at baseline and three follow-ups. Mixed-effects multinomial/logistic regression models were used. In multivariable analyses, greater concentrations of T and T/SHBG were associated with a lower number of CMP sites in both males (T: relative risk ratio=0.81 per standard deviation, 95% confidence interval [0.77–0.86] and T/SHBG: 0.85 [0.80–0.92]) and females (T: 0.85 [0.81–0.89] and T/SHBG: 0.93 [0.89–0.97] [all P-values for trend ≤0.001]). Greater T concentrations and T/SHBG were also associated with lower odds of CMP across all sites, while higher concentrations of SHBG were associated with lower odds of neck/shoulder CMP in both sexes. There was no association between concentrations of E2, SHBG, or E2/SHBG and number of CMP or site-specific CMP in either sex. In both sexes, greater T concentrations and T/SHBG were associated with lower number of CMP sites and site-specific CMP, while greater concentrations of SHBG were linked to lower odds of neck/shoulder CMP. These findings suggest a potential involvement of sex steroids in the pathogenesis of CMP and underscore the need for further investigation into their potential in chronic pain management strategies.

Keywords: multisite chronic pain; oestradiol; sex hormones; sex hormone-binding globulin; testosterone

25COASMA31

Title: Structural basis for the inhibition of cystathionine-β-synthase by isoflurane and its role in anaesthesia-induced social dysfunction in mice,

Mengfan He, Hanxi Wan, Peilin Cong, Xinyang Li, Chun Cheng, Xinwei Huang, Qian Zhang, Huanghui Wu, Li Tian, Ke Xu, Lize Xiong,

British Journal of Anaesthesia,Volume 134, Issue 3,2025,Pages 746-758,
https://doi.org/10.1016/j.bja.2024.09.023.

Abstract: Anaesthesia has been shown to impair social functioning, but the underlying mechanisms remain largely unknown. The volatile anaesthetic isoflurane potentially disrupts the methionine cycle and trans-sulphuration pathway, contributing to social deficits. Cystathionine-β-synthase (CBS), a key enzyme in this pathway, might be targeted by isoflurane. We investigated the CBS–isoflurane interaction and its role in neuronal function and social behaviour. Mice aged 3–15 months were anaesthetised with 2 vol% isoflurane for 2 h, and social behaviours were tested 24 h after exposure. Alterations in neuronal activity were assessed using electrophysiological analysis in vivo. Pharmacological activators (S-adenosylmethionine [SAM]) or inhibitors (amino-oxyacetic acid [AOAA]), and adeno-associated virus (AAV) were used to modulate CBS activity. The binding site of isoflurane on CBS was determined using X-ray crystallography. A novel transgenic model with a point mutation knock-in was constructed to eliminate the CBS–isoflurane interaction. Isoflurane inhibited CBS activity (by 0.35-fold [0.07] vs 1.00-fold [0.05]; P<0.001), leading to neuronal hypoactivity in the anterior cingulate cortex (ACC) and social impairments in adult and elderly mice. SAM, AOAA, and AAV interventions demonstrated a causal link. Structural and functional analysis identified the lysine 273 (K273) in CBS to be involved in isoflurane inhibition. CBS K273A knock-in mice exhibited increased CBS activity compared with wild-type littermates after isoflurane exposure (2.2-fold [0.22] vs 1.0-fold [0.28]; P<0.001), with successful alleviation of ACC neuronal hypoactivity and social dysfunction. These findings reveal a crucial role for CBS inhibition by isoflurane in anaesthesia-induced social impairment.

Keywords: crystallography; cystathionine-β-synthase; isoflurane; neuronal hypoactivity; social behaviour

25COASMA32

Title: Bereaved Family Quality of Life Varies With Comorbid Psychological Distress and ICU-Care Quality,

Fur-Hsing Wen, Holly G. Prigerson, Li-Pang Chuang, Wen-Chi Chou, Tsung-Hui Hu, Chung-Chi Huang, Siew Tzuh Tang,

Journal of Pain and Symptom Management, Volume 69, Issue 3, 2025, Pages 251-260.e3,
https://doi.org/10.1016/j.jpainsymman.2024.11.023.

Abstract: Health-related quality of life (HRQOL) is highly endorsed, but HRQOL studies scarcely investigate the following: ICU family members; modifiable end-of-life (EOL) ICU-care factors; conjoint associations with prolonged grief disorder (PGD), post-traumatic stress disorder (PTSD), and depression; and long-term bereavement outcomes. Exploratorily investigate associations of PGD-PTSD-depressive-symptom states (resilient, subthreshold-depression dominant, PGD dominant, and PGD-PTSD-depression comorbid) and quality of EOL ICU care with families' HRQOL 6–24 months post loss. This cohort study examined symptoms of PGD (11 items of the PG-13), PTSD (Impact of Event Scale-Revised), and depression (Hospital Anxiety and Depression Scale), and HRQOL (Medical Outcomes Study 36-Item Short-Form Health Survey) among 303 ICU family members. Quality of EOL ICU

care was measured by objective process-based care-quality indicators abstracted from medical records and classified by subjective family-assessed quality of patient dying and death (QODD). Associations were simultaneously examined by multivariate hierarchical linear modeling with resilient state and high QODD class as reference. Physical and mental HRQOL were worse in the 3 more distressed symptom states, especially mental HRQOL which showed an incremental dose-response effect: subthreshold depression-dominant (β [95% CI]=-2.419 [-3.374, -1.464]), PGD-dominant (-8.366 [-10.116, -6.616]), and PGD-PTSD-depression comorbid (-14.736 [-17.772, -11.700]) states. Mental HRQOL was significantly worse in the 3 poorer QODD classes: moderate (-1.085 [-2.138, -0.032]), poor to uncertain (-4.362 [-5.616, -3.108]), and worst (-3.239 [-4.433, -2.045]). HRQOL was not associated with objective care-quality indicators. Bereaved family members' HRQOL was significantly associated with PGD-PTSD-depressive-symptom states and QODD classes—both modifiable through high-quality EOL ICU care.

Keywords: Prolonged grief disorder, post-traumatic stress disorder, depression; quality of life, bereavement; family members, critical care

25COASMA33

Title: Clinician Perspectives Highlight the Need for Early Dyadic Coping Skills for People Living With Amyotrophic Lateral Sclerosis,

Christina L. Rush, Chris Lyons, Jenna Gittle, Morgan Seward, Jennifer Scalia, Doreen Ho, Suma Babu,

Journal of Pain and Symptom Management,Volume 69, Issue 3,2025,Pages 236-242.e4,
https://doi.org/10.1016/j.jpainsymman.2024.12.010.

Abstract: A diagnosis of ALS can be challenging, and many people find ways to adapt. At the same time, emotional distress can arise early after an ALS diagnosis even when high quality multidisciplinary care is provided. When emotional distress occurs, it can become chronic over time, and can affect both the person living with ALS and their care-partner (together called a dyad). We set out to understand ALS multidisciplinary clinicians' perception of the challenges experienced by people with ALS and care-partners who experience emotional distress after diagnosis and potential benefits of a coping skills program to help these patients and their care-partners, Resilient Together-ALS (RT-ALS). We conducted semi-structured focus groups and individual interviews with 17 clinicians at the Sean M. Healey & AMG Center for ALS at MGH (N = 2 focus groups and five interviews) to elicit feedback on four domains: 1) Psychosocial Needs of ALS Dyads seen in the clinic; 2) Clinic Flow and Referral System to RT-ALS; 3) Clinic Partnership Approach in Support of RT-ALS; 4) RT-ALS Program Content and Manual Format. We conducted rapid data analyses for a time-efficient hybrid inductive-deductive thematic approach. Clinicians noted that dyadic distress (distress experienced by both patient and their care-partner individually and as a unit), though not universal, is often present early after diagnosis. The response to the proposed program content (dyadic and individual coping skills) and structure (6 weekly virtual sessions delivered within about 2 months after diagnosis) was positive. Multidisciplinary clinicians emphasized the importance of a skills-based program for dyads experiencing elevated early emotional distress for which referral can be easily integrated

within clinic flow so as not to not increase provider and dyad burden. RT-ALS program content and structure is acceptable to clinicians. It is imperative to next seek further input from dyads about whether this type of program would be of interest and if yes, to pilot and refine the program for feasibility testing and then efficacy.

Keywords: Amyotrophic lateral sclerosis; coping; psychosocial; intervention; qualitative

25COASMA34

Title: Navigating Uncertainty during Family Meetings in the Pediatric Cardiac Intensive Care Unit: A Qualitative Investigation of Team Communication and Family Engagement,

Colette Gramszlo, Arzu Cetin, Jennifer K. Walter,

Journal of Pain and Symptom Management, Volume 69, Issue 3,2025,Pages 261-268,
https://doi.org/10.1016/j.jpainsymman.2024.11.014.

Abstract: Uncertainty is a known barrier to effective communication during family meetings in the pediatric cardiac intensive care unit (CICU), however, limited data has characterized patterns of communication during these meetings, limiting our ability to make best practice recommendations to clinicians. To characterize how uncertainty is communicated by cardiac critical care teams during family meetings, to characterize family responses to uncertainty, and to explore how expressions of uncertainty impact specific responses. We conducted a retrospective study of 58 family meetings recorded in a pediatric CICU. Participants were families of patients admitted to the CICU and members of the interprofessional CICU team. We coded uncertainty statements expressed by clinicians and family responses to uncertainty statements. Codes were extracted and analyzed for thematic content. We identified three themes around which clinicians expressed uncertainty: prognosis, treatment trajectories, and discharge planning. Expressions were most frequently unburied (62.3%) and implicit (66.5%). Five themes were identified within family responses to uncertainty: Brief acknowledgment (36.7%); clarification (30.0%); summary (12.3%); child information (12.3%); and emotions, preferences, and reflections (8.6%). Brief acknowledgements often followed lengthy, complex medical information provided by clinicians. Families often responded to implicitly communicated uncertainty by summarizing, clarifying, and providing additional details about their experiences, observations, and preferences. Our results encourage clinicians to communicate uncertainty in an unburied and explicit manner, which may reduce the burden on families to engage in effective communication strategies, such as clarifying and summarizing opaquely stated information.

Keywords: Family meetings; uncertainty; communication; cardiac intensive care unit; pediatrics

25COASMA35

Title: Designing and Delivering a Poetry Workshop for Clinician Well-Being During the COVID-19 Pandemic: A Case Study,

Halia Melnyk, Jin Jun, Jennifer L. Eramo, Ann Scheck McAlearney, Laura J. Rush, Ramona G. Olvera,

Journal of Pain and Symptom Management, Volume 69, Issue 3,2025,Pages e191-e199,

https://doi.org/10.1016/j.jpainsymman.2024.11.019.

Abstract: Facilitated poetry writing workshops are used in healthcare settings as a therapeutic approach to address stressful factors that negatively influence clinician well-being. However, owing to the novelty of this intervention and a tendency to combine poetry with other types of narrative-based techniques, proponents of poetic medicine are calling for harmonization across programs in the US. This would facilitate the study of poetry in medicine and the multiple facets of well-being it is said to promote. To address these points, we partnered with a well-established poetry center to develop and study a facilitated poetry writing workshop program for palliative care and emergency medicine clinicians during the COVID-19 pandemic. Our qualitative aim was to describe how the workshop provided a creative outlet for the sharing and processing of clinician experiences. We conducted a multiple-case study of six workshop sessions using transcripts, model poems, writing prompts, and participant-created poems to describe the program's structure and processes. Our workshop contained the core components of reading, writing, and reflection; however, our program was unique in its inclusion of a website and a prewriting component. The facilitator's instruction on and fostering the use of poetic technique coupled with website interaction were key promoters of participant engagement with their peers in the processing of complex experiences and related emotions. Healthcare systems seeking to incorporate poetry into their wellness programming may build upon our findings to create flexible workshops suited to their clinician audience and program intent.

Keywords: Facilitated Poetry Writing Workshop; Clinician Well-being; Creative Pursuits; Case Study Methodology; Health Services Research

25COASMA36

Title: Impact of a Criteria-Based Inpatient Palliative Oncology Consultation Model on End-of-Life Outcomes,

Kathryn E. Norman, Mary K. Buss, Kathleen A. Lee, Abigail Escobar, Jonathan Thomas, Julia Berg,

Journal of Pain and Symptom Management, Volume 69, Issue 3,2025,Pages 229-235.e1,
https://doi.org/10.1016/j.jpainsymman.2024.11.011.

Abstract: Early, integrated palliative care (PC) improves outcomes in advanced cancer; however, inpatient PC referrals still exceed outpatient referrals nationwide. Recognizing need for enhanced integration, our cancer center implemented a criteria-based PC consultation model in inpatient oncology. To compare decedent outcomes pre- and postimplementation of a new criteria-based PC consultation model in inpatient oncology. We implemented an embedded, interdisciplinary “Palliative Oncology” consult team on the oncology floor. Admitted patients were screened for advanced/metastatic solid cancer or moderate/severe symptoms. The oncology team received prompting regarding eligible patients; PC referral remained at their discretion. We compared outcomes between patients who died pre-(10/1/2019-6/30/2020) and postimplementation (7/1/2020–6/30/2022) by t-test (continuous variables) and chi-square test (categorical variables). Of 820 decedents, 186 died preintervention and 634 died postintervention. Postintervention, more decedents saw

inpatient PC (59%–72%, P < 0.001) and outpatient PC (23%–34%, P < 0.01), and had earlier first PC visit before death (76–159 days, P < 0.001). Postintervention, fewer decedents had hospitalizations (71%–57%, P < 0.001) and intensive care encounters (25%–17%, P < 0.01) within last 30 days of life. Hospice length-of-stay increased (22–36 days, P < 0.01). There were trends toward fewer emergency room visits within last 30 days of life (51%–42%, P = 0.02), less systemic cancer therapy within last 14 days of life (9%–5%, P = 0.03), and more deaths at home (41%–50%, P = 0.03). Embedded, criteria-based PC consultation in inpatient oncology was associated with earlier PC involvement, longer hospice LOS, and reduced EOL care intensity.

Keywords: palliative care; supportive oncology; care delivery

25COASMA37

Title: Large Language Models to Identify Advance Care Planning in Patients With Advanced Cancer,

Nicole D. Agaronnik, Joshua Davis, Christopher R. Manz, James A. Tulsky, Charlotta Lindvall,

Journal of Pain and Symptom Management, Volume 69, Issue 3,2025,Pages 243-250.e1,
https://doi.org/10.1016/j.jpainsymman.2024.11.016.

Abstract: Efficiently tracking Advance Care Planning (ACP) documentation in electronic heath records (EHRs) is essential for quality improvement and research efforts. The use of large language models (LLMs) offers a novel approach to this task.To evaluate the ability of LLMs to identify ACP in EHRs for patients with advanced cancer and compare performance to gold-standard manual chart review and natural language processing (NLP). EHRs from patients with advanced cancer followed at seven Dana Farber Cancer Center (DFCI) clinics in June 2024. We utilized GPT-4o-2024-05-13 within DFCI's HIPAA-secure digital infrastructure. We designed LLM prompts to identify ACP domains: goals of care, limitation of life-sustaining treatment, hospice, and palliative care. We developed a novel hallucination index to measure production of factually-incorrect evidence by the LLM. Performance was compared to gold-standard manual chart review and NLP.60 unique patients associated with 528 notes were used to construct the gold-standard data set. LLM prompts had sensitivity ranging from 0.85 to 1.0, specificity ranging from 0.80 to 0.91, and accuracy ranging from 0.81 to 0.91 across domains. The LLM had better sensitivity than NLP for identifying complex topics such as goals of care. Average hallucination index for notes identified by LLM was less than 0.5, indicating a low probability of hallucination. Despite lower precision compared to NLP, false positive documentation identified by LLMs was clinically-relevant and useful for guiding management.LLMs can capture ACP domains from EHRs, with sensitivity exceeding NLP methods for complex domains such as goals of care. Future studies should explore approaches for scaling this methodology.

Keywords: Large language models; Advance care planning; Goals of care; Artificial intelligence

25COASMA38

Title: Optimizing tracheostomy anesthesia: A comparative study of nerve blocks,

Tarek I. Ismail, Rabab S.S. Mahrous, Ahmed A. Bedewy,

Trends in Anaesthesia and Critical Care, Volume 61,2025,101541
https://doi.org/10.1016/j.tacc.2025.101541.

Abstract: Tracheostomy is increasingly performed as a planned procedure for a wide range of indications. While superficial cervical plexus block (SCPB) is widely used as regional anesthesia for tracheostomy, its limitation in suppressing laryngeal reflexes may lead to discomfort and complications. Combining bilateral SCPB with bilateral superior laryngeal nerve block (SLNB) could potentially improve patient outcomes by reducing airway reflexes. This study aimed to compare the effectiveness of bilateral SCPB alone versus bilateral SCPB combined with bilateral SLNB in sedated patients undergoing surgical tracheostomy. A double-blind, randomized controlled trial was conducted at Alexandria University Hospital. A total of 120 adult patients, both intubated and non-intubated, requiring elective tracheostomy was randomly allocated into two groups: Group 1 received an ultrasound-guided bilateral SCPB alone, while Group 2 received a combination of ultrasound-guided bilateral SCPB and bilateral SLNB. The primary outcome was the incidence of intraoperative coughing and laryngospasm. Secondary outcomes included postoperative pain, cumulative analgesic requirements, time to first analgesic request, postoperative complications and patients' satisfaction. Group 2 (SCPB + SLNB) demonstrated a significantly lower occurrence of coughing and laryngospasm compared to Group 1 ($p < 0.05$). No significant difference was observed in postoperative pain intensity between the two groups. Additionally, postoperative complications and patients' satisfaction were comparable between both groups, with no significant differences noted. The addition of bilateral SLNB to SCPB significantly suppresses airway-related reflexes during tracheostomy.

Keywords: Tracheostomy; Superficial cervical plexus block; Superior laryngeal nerve block; Airway reflexes; Regional anesthesia

Cancer Research

25COASMA1

Title: Noncancerous Exosomes Establish a Growth Promoting Paracrine Effect on Triple Negative Breast Cancer Cells

Letitia A. Yearby, Manasa Kotina, Afia Ohemeng, Bipika Banjara, Mounika Pamukuntla, Paige Roberts,

Anticancer Research February 2025, 45 (2) 419-431;
DOI: https://doi.org/10.21873/anticanres.17431

Abstract: Background/Aim: Previous studies have demonstrated that breast cancer cells secrete exosomes into the tumor microenvironment, promoting tumor progression. However, the paracrine influence of noncancerous breast epithelial cells on the growth of triple-negative breast cancer (TNBC) cells has largely been overlooked. We hypothesize that exosomes from noncancerous breast epithelial cells are secreted into the tumor microenvironment, stimulating TNBC growth. Materials and Methods: Exosome-containing media were prepared using exosomes isolated from triple-negative patient-derived xenografts (PDX) or noncancerous MCF-10A breast epithelial cells and used to treat MCF-7 or TNBC cells. Exosome-containing media from MCF-10A cells were characterized using ELISA. Subsequently, MDA-MB-231 and MDA-MB-468 cells treated with the MCF-10A exosome-containing media, and their impact on proliferation, migration, protein expression and gene expression were analyzed using Alamar blue assays, wound healing assays, western blotting, immunofluorescence, and gene expression arrays, respectively. Results: Exosomes extracted from the PDX and MCF-10A cells stimulated the growth of all examined cell lines. The MCF-10A exosome-containing media expressed CD9 and CD63; however, the MDA-MB-231 and MDA-MB-468 cells treated with these media exhibited differential expression of these proteins. Exposure of MDA-MB-231 and MDA-MB-468 cells to the MCF-10A exosome-containing media stimulated their growth and migration. Exposure of MDA-MB-231 cells to MCF-10A exosome-containing media caused down-regulation of genes involved in cell-cell adhesion, DNA damage response, epithelial-mesenchymal transition drivers, tumor suppression, and up-regulation of the MYC oncogene. Conclusion: Secreted factors from noncancerous cells, identified as exosomes, induce cancer cell proliferation and prime the tumor microenvironment by enhancing disease progression-associated pathways.

Keywords: Exosomestriple negative breast cancer, tumor microenvironment

25COASMA2

Title: Acyclic Retinoid Inhibits the EGFR/AKT Signaling Pathway and Cancels Cisplatin-resistant Cell Characteristics

Makito Motoyama, Ryota Shigefuku, Noriyoshi Tanaka, Mitsuaki Nishizawa, Keigo Oshio, Yoshitomo Suhara And Ichiro Yajima

Anticancer Research February 2025, 45 (2) 433-443;
DOI: https://doi.org/10.21873/anticanres.17432

Abstract: Background/Aim: Lung cancer is among the most prevalent and lethal malignancies worldwide, with non-small cell lung cancer (NSCLC) accounting for the majority of cases. Overactivation of the EGFR/AKT signaling pathway contributes

significantly to NSCLC progression and metastasis. Cisplatin, a widely used chemotherapeutic agent, faces limitations due to severe side effects and the emergence of resistant cancer cells. Acyclic retinoid (ACR), a synthetic derivative of vitamin A, has shown antitumor effects in hepatocellular carcinoma, but its efficacy against NSCLC and cisplatin-resistant cells remains unclear. This study aimed to investigate whether ACR could inhibit EGFR/AKT signaling and enhance therapeutic efficacy against NSCLC and cisplatin-resistant cells. Materials and Methods: Human NSCLC A549 cells, cisplatin-resistant A549 (A549CR) cells, and normal lung epithelial BEAS-2B cells were treated with ACR, alone or in combination with cisplatin. Cell viability, apoptosis, and changes in expression/phosphorylation of EGFR, AKT, and cell cycle regulators were assessed using cell viability assay, immunostaining, and immunoblotting. Results: ACR selectively reduced viability of A549 cells with less toxicity to BEAS-2B cells and induced apoptosis via cleaved Caspase-3 activation. ACR inhibited EGFR/AKT signaling and up-regulated p27KIP1 in A549 cells. The combination of ACR and cisplatin synergistically reduced cell viability and suppressed AKT phosphorylation. Notably, ACR also inhibited EGFR/AKT signaling in A549CR cells, restoring sensitivity to cisplatin and reversing EMT-like characteristics. Conclusion: ACR effectively inhibits EGFR/AKT signaling and enhances cisplatin sensitivity in NSCLC and cisplatin-resistant cells, suggesting its potential as a promising therapeutic strategy for lung cancer.

Keywords: Acyclic retinoid, ACR lung cancer, NSCLCAKT, tumorigenesis, cisplatin-resistant cell

25COASMA3

Title: Correlation of HLA-A and HLA-B/C Expression With ESR1 Expression in Patients With Metastatic Breast Cancer as a Potential Prognosticator of Favorable Distant Disease-free Survival

Lukas Goerdt, Aleksandra Stefanovic, Ralph Wirtz, Uros Karic, Thomas M. Deutsch, Maximilian Kohler,

Anticancer Research February 2025, 45 (2) 445-450;
DOI: https://doi.org/10.21873/anticanres.17433

Abstract: Background/Aim: The loss of breast cancer cell differentiation during metastatic progression leads to a down-regulation of class 1 human leukocyte antigen (HLA) expression, which in turn hinders cytotoxic T lymphocytes from effectively preventing tumor cell proliferation. Consequently, one would expect that decreased HLA expression would correlate with decreased 5-year survival. However, estrogen receptor alpha (ESR1) is known to be positively associated with overall survival. The study aimed to determine the expression levels of HLA-A, HLA-B/C, and ESR1 and to assess their influence on distant disease-free survival (DDFS). Materials and Methods: This retrospective subgroup analysis of the initial prospective, single-center, double-blind cohort study included a total of 34 patients who underwent a new treatment line for metastatic breast cancer (MBC). The MBC cells were examined using RT-qPCR. Results: The acquired data and the subsequent survival and ROC analyses indicated a positive association of reduced expression of HLA-A and HLA-B/C with DDFS. A statistically significant association of ESR1 with DDFS could not be shown. Conclusion: A potential positive association between reduced expression of HLA-A and

HLA-B/C and DDFS is observed. This contrasts with the generally observed association between HLA expression loss and poor prognosis, as reported in previous protein-based studies. In metastatic settings, reduced expression of particular HLA subsets, measured at the mRNA level, might have a protective effect against disease progression.
Keywords: Breast cancer, HLA-A, HLA-B/C, ESR1, prognosticator, survival

25COASMA4

Title: Recombinant Methioninase (rMETase) Synergistically Sensitizes Ivermectin-resistant MCF-7 Breast Cancer Cells 9.9 Fold to Low-dose Ivermectin

Sei Morinaga, Qinghong Han, Kohei Mizuta, Byung Mo Kang, Chihiro Hozumi, Michael Bouvet, Norio Yamamoto,

Anticancer Research February 2025, 45 (2) 451-455;
DOI: https://doi.org/10.21873/anticanres.17434

Abstract: Background/Aim: Ivermectin is a widely-used anti-parasitic agent and has shown early promise as an anticancer agent. Recombinant methioninase (rMETase) is a methionine-depleting enzyme targeting the methionine addiction of cancer and has broad efficacy against all tested cancer types. However, the combination efficacy of ivermectin and rMETase on breast cancer cells remains unexplored. The present study aimed to determine the synergistic efficacy of ivermectin and rMETase on MCF-7 human breast cancer cells in vitro. Materials and Methods: The IC10 of ivermectin and IC50 of rMETase were determined on MCF-7 cells using the WST-8 reagent to measure cell viability in vitro. MCF-7 cells were treated with four groups: untreated control; ivermectin alone (4.89 μM, IC10); rMETase alone (2.75 U/ml, IC50); and a combination of ivermectin (4.89 μM) and rMETase (2.75 U/ml). Cell viability was assessed 72 hours after treatment with the WST-8 reagent. Results: Treatment with ivermectin (4.89 μM) did not significantly reduce the viability of MCF-7 cells. rMETase (2.75 U/ml) alone significantly reduced MCF-7 cell viability compared to the control group. The combination of ivermectin and rMETase resulted in a significantly greater reduction in cell viability than either agent alone, including a 9.9-fold greater efficacy than ivermectin alone, demonstrating synergistic efficacy ($p<0.05$). Conclusion: The combination of ivermectin and rMETase had synergistic efficacy against MCF-7 breast cancer cells in vitro. The present findings suggest that the combination of ivermectin and rMETase is a promising strategy for breast cancer requiring further preclinical and clinical evaluation.
Keywords: Ivermectin, recombinant methioninase, synergy, in vitro, breast cancer cell, smethionine addiction, Hoffman effect

25COASMA5

Title: Synthesis of Polymethoxylated 3-Styrylflavones and their Antiproliferative Activity in HL60 Cells

Arisa Tsutsumi, Satoru Kawaii And Yuko Yoshizawa

Anticancer Research February 2025, 45 (2) 457-464;
DOI: https://doi.org/10.21873/anticanres.17435

Abstract: Background/Aim: Flavonoids are a large group of naturally occurring compounds with a wide range of biological properties and thus they represent a privileged scaffold in medicinal chemistry. We designed and synthesized a series of polymethoxylated 3-

styrylflavones as a novel class of styryl-bearing flavone compounds. Materials and Methods: 3-Styrylflavones were systematically synthesized using Wittig reaction between various benzaldehyde derivatives and polymethoxylated 3-(bromomethyl)flavones, and evaluated their antiproliferative activity against HL60. Results: Among the compounds synthesized, 2′,3′,4′-trimethoxy-3-(E)-styrylflavone (IC50=68 μM) and 2′,3′,3‴,4′,4‴,5‴-hexamethoxy-3-(E)-styrylflavone (IC50=92 μM) demonstrated potent anti-proliferative activity. Conclusion: Introduction of 3-styryl substituent in 3-methylflavone increased the antiproliferative activity. Structure-activity relationship studies and theoretical calculations indicated the importance of 2′,3′,4′-trimethoxy-phenyl substituent in enhancing the activity.

Keywords: 3-styrylflavone, styryl-flavone hybrid molecule, Wittig reaction, antiproliferative activity, HL60 cells

25COASMA6

Title: Association of *Matrix Metalloproteinase-1* Promoter Genotypes With Endometriosis Risk

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DOI: https://doi.org/10.21873/anticanres.17436

Abstract: Background/Aim: Over-expression of matrix metalloproteinase-1 (MMP-1) has been suggested as a biomarker for endometriosis. However, the genetic influence of MMP-1 in the pathogenesis of endometriosis remains unclear, with its role yet to be fully elucidated. This study aimed to investigate the association between MMP-1 rs1799750 promoter polymorphisms and the risk of developing endometriosis. Patients and Methods: This hospital-based case-control study included 203 women diagnosed with endometriosis and 636 age-matched controls. Genotyping of the MMP-1 rs1799750 polymorphism was conducted using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. Results: Among the patients with endometriosis, the distribution of genotypes 2G/2G, 2G/1G, and 1G/1G at MMP-1 rs1799750 was 52.7%, 41.4%, and 5.9%, respectively. This distribution significantly differed from that of the control group, which exhibited frequencies of 41.3%, 48.3%, and 10.4%, respectively (p for trend=0.0092). In the dominant model, carriers of the 2G/1G and 1G/1G genotypes had a reduced prevalence in the endometriosis group compared to 2G/2G carriers [odds ratio (OR)=0.63, 95% confidence interval (95%CI)=0.46-0.87, p=0.0058]. Additionally, the 1G allele frequency in the endometriosis group was 26.6%, significantly lower than the 34.5% observed in controls (OR=0.69, 95%CI=0.54-0.88, p=0.0037). Conclusion: The 1G allele of MMP-1 rs1799750 is associated with reduced susceptibility to endometriosis in the Taiwanese population. These results highlight the potential of MMP-1 rs1799750 polymorphism as a protective genetic marker, warranting further investigations to explore its genotype-phenotype correlation and underlying biological mechanisms.

Keywords: Endometriosis, metalloproteinase-1, polymorphism, Taiwan

25COASMA7

Title: MiR-5586-5p Suppresses Hypoxia-induced Angiogenesis Through Multiple Targeting of HIF-1α, HBEGF and ADAM17 in Breast Cancer

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Abstract: Background/Aim: Hypoxia-inducible factor-1 alpha (HIF-1α) plays a key role in the cellular response to hypoxia, which plays a crucial role in the induction of abnormal angiogenesis and metastasis. Understanding the mechanism for the regulation of angiogenesis by HIF-1α-regulating miRNA will contribute to developing the strategy to prevent metastasis. Materials and Methods: We conducted a functional screening for HIF-1α-inhibiting miRNAs by evaluating the effects of miRNA mimics on HIF-1α expression and identified miR-5586-5p as an angiogenesis inhibitor through a mechanistic study. Angiogenic activity was assessed by tube formation assays using HUVEC cells exposed to conditioned media from miRNA-transfected breast cancer cells. In vivo activity of miR-5586-5p was examined through intratumoral injection of miRNA in orthotopic xenograft mice established by injecting MDA-MB-231 cells into the mammary fat pads of BALB/c nu/nu mice. Results: The expression of the critical proangiogenic factors vascular endothelial growth factor A (VEGFA) and angiopoietin-like protein 4 (ANGPTL4) was inhibited by miR-5586-5p. Migration and tube formation of human umbilical vein endothelial cells were reduced in the conditioned medium prepared from miR-5586-5p-transfected cells. miR-5586-5p also suppressed the expression of heparin-binding EGF-like growth factor (HBEGF) and a disintegrin and metalloprotease 17 (ADAM17), which play a role in hypoxic signaling to induce the expression of VEGFA and ANGPTL4. HIF-1α, HBEGF, and ADAM17 were verified as the direct targets of miR-5586-5p responsible for the angiogenesis-suppressing function of miR-5586-5p. Expression levels of miR-5586-5p were lower in tumor tissues than in neighboring normal tissues of breast cancer patients. The expression of miR-5586-5p was inversely correlated to those of HIF-1α, HBEGF, ADAM17, VEGFA, and ANGPTL4. Angiogenesis and subsequent tumor growth were suppressed by intratumoral injection of miR-5586-5p in orthotopic MDA-MB-231 xenografts in mice. Conclusion: A potent tumor-suppressive function of miR-5586-5p applicable for the development of a novel cancer treatment strategy is herein described.

Keywords: miR-5586-5p, angiogenesis, HIF-1α, HBEGF, ADAM17, VEGFA, ANGPTL4

25COASMA8

Title: Adjusting Treatment Strategies Using Circulating Tumor Cells: Preliminary Results on Metastatic Colorectal Cancer

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Abstract: Background/Aim: To assess the effectiveness of circulating tumor cells (CTCs) in proposing second-line treatments for metastatic colorectal cancer (mCRC). Patients and Methods: We analyzed CTCs from 21 patients (first group) with mCRC, for whom first-line

treatment regimens were ineffective. CTCs were isolated and used for chemo-sensitivity/viability assays on several chemotherapeutic drugs. Based on these assays, a second-line treatment was recommended for each patient. Using overall survival (OS) as primary endpoint, statistical analysis was performed, comparing the survival of a group of 21 mCRC patients (first group) with the survival of 12 mCRC patients treated only with best supportive care (BSC) (second group), as well as with the survival estimated by meta-analysis of the BSC summary statistics (medians) published in various papers and clinical trials. Furthermore, the statistical significance of the difference between the two groups was examined by applying statistical tests that can deal efficiently with small datasets, non-proportional hazard patterns, and crossing curves, such as K-sample omnibus, MaxCombo, multiple-direction, and weighted log-rank tests. Results: The median OS (mOS) for the first group (9 months) was found longer than the mOS of the BSC group (about 5 months). This result was further verified since the weighted mOS, estimated by meta-analysis, was found at 5.15 months. This difference was found statistically significant for central and late hazards. Conclusion: The preliminary results indicate that treatment based on CTCs' response in vitro prolongs mOS of mCRC patients compared with BSC patients, whereas a beneficial effect is gained for the prediction of treatment response in mCRC.

Keywords: Metastatic colorectal cancer, circulating tumor cells, non-proportional hazards, crossing hazards, max-combo test, multiple-directions-test, weighted log-rank tests, meta-analysis, K-sample omnibus non-proportional hazards test

25COASMA9

Title: Anti-tumor Effects of Erlotinib *via* Thymidylate Synthase Down-regulation in Pancreatic Cancer Cells

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Anticancer Research February 2025, 45 (2) 503-510;
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Abstract: Background/Aim: In pancreatic cancer, gemcitabine and EGFR tyrosine kinase inhibitors (EGFR-TKIs) are common chemotherapy options. Reports have shown that EGFR-TKIs suppress the expression of thymidine synthase (TS), an important enzyme for DNA biosynthesis, and increase sensitivity to gemcitabine in lung cancer. However, no such reports have been made in pancreatic cancer. Materials and Methods: Human pancreatic cancer cell lines MiaPaCa2, Panc1, and BxPc3 were used. TS mRNA and protein expression levels in the cells were analyzed after erlotinib treatment. In addition, the anti-tumor effect of TS knockdown was verified using TS siRNA, along with its synergistic effect when combined with gemcitabine. Results: TS expression was high in MiaPaCa2 and Panc1 cells and low in BxPc3 cells. After erlotinib treatment, TS mRNA and protein levels decreased markedly in MiaPaCa2 cells dose-dependently, but not in Panc1 cells. TS siRNA caused specific down-regulation of TS in MiaPaCa2 and Panc1 cells. TS down-regulation resulted in an anti-tumor effect in these cells (MiaPaCa2 42%; Panc1 38%; $p<0.05$), showing a synergistic effect when combined with gemcitabine. Conclusion: Erlotinib could have a synergistic anti-tumor effect when combined with gemcitabine via down-regulation of TS expression.

Keywords: Pancreatic cancer cell, epidermal growth factor receptor-tyrosine kinase inhibitor, thymidylate synthase, erlotinib, gemcitabine

25COASMA10

Title: Pterostilbene Suppressed Cell Viability, Induced Apoptosis and Autophagy of Cisplatin-resistant Gastric Cancer Cells

Chien-Jung Huang, Po-Chuen Shieh, Jai-Sing Yang, Yi-Chia Li, Yu-Jen Chiu, Da-Tian Bau And Chih-Hsin Hung

Anticancer Research February 2025, 45 (2) 511-523;
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Abstract: Background/Aim: Gastric cancer (GC) is one of the most common cancers worldwide. Cisplatin is a key therapeutic agent for treating GC. Currently, the resistance of GC cells to cisplatin remains a major concern. Pterostilbene (PTS) is a natural phytochemical found in blueberry and grape. The anti-cisplatin-resistant GC effects and pharmacological mechanisms of PTS are unknown. Materials and Methods: We investigated the anticancer activity of PTS in cisplatin-resistant GC cells and explored its pharmacological mechanisms of action via cell viability assay, cell confluence assay, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining, acridine orange (AO) staining, monodansylcadaverine (MDC) staining, caspase-9/-3 activity assay, and RNA sequencing (RNA-Seq) analysis. Results: Our results showed that PTS inhibited cell viability and cell confluence of cisplatin-resistant GC cells using the CCK-8 assay and the IncuCyte S3 ZOOM System. The TUNEL assay showed that PTS promoted apoptosis in cisplatin-resistant GC cells. PTS induced apoptosis by increasing caspase-9 and caspase-3 activity. PTS promoted cell autophagy by increasing vacuole formation and acidic vesicular organelles using MDC and AO staining. We also observed an increase in the expression of LC3B in PTS-treated cisplatin-resistant GC cells. RNA-Seq analysis demonstrated that PTS induced apoptosis and autophagy in cisplatin-resistant GC cells by decreasing the expression of ATM/ATR, HIF-1, PI3K, RB1CC, TBK1, and mitochondria-related genes. Conclusion: Our results suggested that PTS is a promising phytochemical for GC therapy, particularly against cisplatin resistance.

Keywords: RNA sequencing, gastric cancer, cisplatin-resistant, apoptosis, autophagy

25COASMA11

Title: Immunosuppressive State May Lead to Brain Metastases in Lung Squamous Cell Carcinoma: Gene Expression and Immunohistochemical Analysis

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Anticancer Research February 2025, 45 (2) 525-534;
DOI: https://doi.org/10.21873/anticanres.17441

Abstract: Background/Aim: Brain metastases (BMs) are rare in lung squamous cell carcinoma (LUSC). Therefore, research on biomarkers or mechanisms that can be used to predict them is limited. To verify whether mRNA profiles can accurately predict BMs, we used a machine learning approach on 20 TNM-matched LUSC tissue samples. Materials and Methods: We conducted pathway and immunohistochemical analyses to investigate the underlying mechanisms of BM. Results: A total of 15 mRNAs linked to BM were identified.

The 15-mRNA signature was highly accurate in predicting BM, with an area under the curve and accuracy of 0.940 and 0.9, respectively. The pathway analysis revealed that immune-related pathways (leukocyte transendothelial migration, Fc gamma R-mediated phagocytosis, and natural killer cell-mediated cytotoxicity) were suppressed, suggesting that an immunosuppressive state may be involved in the development of BM. In the validation set confirmed by immunohistochemical staining, the BM group exhibited significantly lower levels of CD4+ T cells or CD8+ T cells than the group without BM. BM in patients with LUSC was associated with an immunosuppressive state. Conclusion: Immunotherapy may be effective in preventing BM in patients with LUSC.

Keywords: Lung squamous cell carcinoma, brain metastases, gene expression analysis, CD4CD8, immunosuppressive state

25COASMA12

Title: A New PD-L1 Nanobody Enhances Cell Death in Lung Cancer *In Vitro* and *In Vivo*

Xiao-Tong Tan, Shi-Wei Huang, Yu-Chuan Lin, Fang-Yu Lin, Der-Yang Cho And Shao-Chih Chiu

Anticancer Research February 2025, 45 (2) 535-547;
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Abstract: Background/Aim: The development of immune checkpoint blockade (ICB) agents targeting programmed death protein 1(PD-1), PD-1 ligand (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and CD40 has gained increasing interest in clinical cancer treatment. Among these targets, blocking of PD-1 binding to its ligand PD-L1 managed to induce immune responses and inhibit tumor growth. In this work, we aimed to screen a specific PD-L1 nanobody against human PD-L1, derived through phage display assay, and further study its biological characteristics and antitumor ability. Materials and Methods: Specific PD-L1 nanobody was screened through phage display and its biological characteristics were explored by surface plasmon resonance (SPR) analysis. In addition, its cytotoxicity and antitumor ability was confirmed in vitro and in vivo. Results: After all, an anti-PD-L1 nanobody with high specificity and affinity was generated. This PD-L1 nanobody was highly specific for human PD-L1 and had strong penetration ability due to its size. PD-L1 nanobody enhanced immune cell-killing ability by inhibiting the immune checkpoint and further activating innate response. Furthermore, this new PD-L1 nanobody also had high binding affinity, as shown by its use in western blotting, flow cytometry staining and immunofluorescence staining methods. Conclusion: The new PD-L1 nanobody substantially improved upon the FDA-approved PD-L1 monoclonal antibody by surpassing the disadvantage of having large molecular weight (MW) and low tissue penetration. The cytotoxicity and antitumor ability of PD-L1 nanobody, in vitro and in vivo, also support its potential as a therapeutic agent for lung cancer immunotherapy.

Keywords: PD-L1 nanobody, immunotherapy, NKG2A, immune checkpoint blockage

25COASMA13

Title: PRPF4 Knockdown Suppresses Glioblastoma Progression *via* the p38 MAPK and ERK Signaling Pathways

Wansoo Kim, Song Park, Se-Hyeon Han, Hee-Yeon Kim, Seoung-Woo Lee, Daehwan

Kim, Soyoung Jang,
Anticancer Research February 2025, 45 (2) 549-564;
DOI: https://doi.org/10.21873/anticanres.17443
Abstract: Background/Aim: Pre-mRNA processing factor 4 (PRPF4), a core protein of U4/U6 small nuclear ribonucleoproteins (snRNPs), is crucial for maintaining their structure by interacting with PRPF3 and Cyclophilin H. Beyond its role in splicing, PRPF4 has been implicated in cell survival, apoptosis, and oncogenesis. Although PRPF4 mutations have been associated with retinitis pigmentosa, its role in glioblastoma (GBM) remains unclear. This study aimed to investigate the function of PRPF4 in GBM progression and its potential as a therapeutic target. Materials and Methods: Gene expression profiling was conducted to compare PRPF4 levels between GBM tumors and normal tissues. PRPF4 expression was also evaluated in various cancer and GBM cell lines. Stable PRPF4 knockdown cell lines were established using A172 and T98G GBM cell lines. Cellular proliferation, apoptosis, migration, and invasion were assessed through gene expression and functional assays. Additionally, molecular pathways affected by PRPF4 knockdown were examined, focusing on the p38 MAPK signaling pathway. Finally, metabolic processes in PRPF4 knockdown cells were estimated through proteomic analysis. Results: PRPF4 expression was elevated in GBM. Knockdown of PRPF4 reduced cell proliferation, induced apoptosis, and suppressed migration and invasion in GBM cells. PRPF4 knockdown also suppressed MKK3/6-p38-ATF2 and RAS-MEK-ERK1/2 signaling pathways. Proteome analysis revealed disruptions in metabolic pathways, including glutathione and carbon metabolisms, which are associated with GBM progression. Conclusion: PRPF4 knockdown inhibits GBM progression by reducing p38 MAPK and ERK signaling cascade with metabolic alterations. Targeting PRPF4 may offer novel therapeutic strategies for GBM treatment.
Keywords: Glioblastoma, PRPF4, proliferation, apoptosis, EMT, p38 MAPK signaling, ERK signaling

25COASMA14

Title: Camptothecin Triggers Apoptosis in Human and Mouse Drug-resistant Glioblastoma Cells *via* ROS-mediated Activation of the p53-p21-CD1/CDK2-E2F1-Bcl-xL Signaling Axis

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Anticancer Research February 2025, 45 (2) 565-577;
DOI: https://doi.org/10.21873/anticanres.17444
Abstract: Background/Aim: Glioblastoma multiforme (GBM) is the most aggressive brain tumor. Temozolomide (TMZ) is the first-line treatment for GBM. However, most patients with GBM develop drug resistance. Our previous study showed the effects of camptothecin (CPT) and CRLX101, a nanoparticle of CPT, in suppressing GBM growth by targeting drug-sensitive glioblastoma cells. This study evaluated the effects of CPT on drug-resistant glioblastoma cells and explored the underlying molecular mechanisms. Materials and Methods: Expression of type I topoisomerase (Topo-1) gene in GBM was analyzed using the UALCAN database. Human U87MG-R and mouse GL261-R TMZ-resistant glioblastoma cells were developed. After CPT treatment, apoptotic events were successively determined.

The role of the p53-p21-cyclin D1 (CD1)/cyclin-dependent kinase 6 (CDK6)-E2F1-Bcl-xL signaling axis was subsequently investigated. Results: The expression of Topo-1 gene was up-regulated in human GBM compared to normal human brains. Treatment of human U87MG-R cells with CPT decreased cell viability. Sequentially, exposure to CPT led to activation of caspase-3, fragmentation of chromosomal DNA, and cell apoptosis. Furthermore, intracellular reactive oxygen species (iROS) were augmented following CPT treatment. Suppression of iROS production concurrently alleviated CPT-triggered apoptotic insults. CPT enhanced the levels of p53, phosphorylated p53, and p21. In contrast, levels of CDK6, CD1, E2F1, and Bcl-xL were decreased by CPT. Attenuating p53 transactivation activity using pifithrin-α also mitigated the CPT-induced apoptosis. The effects of CPT on killing drug-resistant glioblastoma cells were further confirmed in mouse GL261-R cells. Conclusion: CPT could effectively induce apoptosis in drug-resistant glioblastoma cells via iROS-mediated activation of the p53-p21-CD1/CDK6-E2F1-Bcl-xL axis.

Keywords: Glioblastomas, camptothecin, apoptosis, iROS, p53-p21-CD1/CDK6-E2F1-Bcl-xL signaling axis

25COASMA15

Title: Characterization of Patient-derived Xenograft Models of Liver Fluke-associated Cholangiocarcinoma: From Establishment to Molecular Profiling

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Anticancer Research February 2025, 45 (2) 579-592;
DOI: https://doi.org/10.21873/anticanres.17445

Abstract: Background/Aim: Cholangiocarcinoma (CCA) is an aggressive cancer with limited effective chemotherapy and targeted therapy options. Existing cell lines and animal models only partially mimic the characteristics of the tumor, highlighting the need for more effective models to study the biology of cancer and drug responses. This study aimed to establish and characterize patient-derived xenograft (PDX) models of CCA. Materials and Methods: Tumor samples from 40 CCA patients were subcutaneously implanted into non-obese diabetic/ShiJic-severe combined immunodeficiency Jcl mice to establish patient-derived xenograft (PDX) models. Successfully engrafted tumors were passaged across three generations. Histological features were analyzed using H&E staining and immunohistochemistry for cytokeratin-19, cytokeratin-7, heppar-1 and arginase-1. Whole exome sequencing (WES) was performed to assess genetic stability and identify somatic mutations. Results: A total of eight PDX models were successfully created, representing 20% of the total cases. Histological comparisons showed strong concordance between patient tumors and their corresponding xenografts in the eight PDX models across generations. WES analysis confirmed the genetic stability of the PDX models, with significant somatic mutations identified in key genes such as TTN, MUC12, ARID1A, TP53, and RNF43. Conclusion: The CCA PDX model could reflect both the histological and genetic characteristics of the original tumors, providing a valuable tool for studying tumor biology and serving as a preclinical model to develop personalized treatment options for CCA.

Keywords: Cholangiocarcinoma, patient-derived xenograft model, personalized medicine

25COASMA16

Title: Computational Exploration of a Diverse Flavonoid Library for Targeted Allosteric Inhibition of AKT1 in Cancer Therapy

Mohd Rehan, Ishfaq A. Sheikh, Mohd Suhail, Shams Tabrez And Shazi Shakil

Anticancer Research February 2025, 45 (2) 593-604;
DOI: https://doi.org/10.21873/anticanres.17446

Abstract: Background/Aim: AKT serine/threonine kinase 1 (AKT1) is an established therapeutic target in cancer therapy due to its role in promoting cell survival and proliferation. This study aimed to identify potential allosteric inhibitors of AKT1 from a large flavonoid library using computational methods. Materials and Methods: A computational screening of a comprehensive flavonoid library to identify novel allosteric inhibitors targeting the AKT1 allosteric site was performed. Molecular docking identified compounds with favorable binding interactions and the top 10 were selected for binding pose analysis. Molecular dynamics simulations for 200 ns were further employed to assess the stability of the highest-ranked compound. Results: The study proposed 10 flavonoids as potential allosteric AKT1 inhibitors. The docking analysis highlighted critical interactions between the 10 flavonoids and AKT1, with residues such as Trp-80, Ile-84, Tyr-272, Arg-273 and Asp-292 playing significant roles in binding stability. Trp-80 emerged as a pivotal residue, consistently forming the highest number of non-bonding contacts across most compounds, corresponding with prior studies that identified it as essential for allosteric inhibition. The highest-ranked flavonoid, CID 108790283, demonstrated the strongest binding affinity, with a binding energy of −10.64 kcal/mol, 56 non-bonding contacts, and a hydrogen bond. Molecular dynamics simulations further confirmed the stability of this flavonoid within the allosteric site, exhibiting minimal conformational fluctuation throughout the 200-ns simulation. Conclusion: This computational investigation identified 10 flavonoids with strong interaction profiles and stable binding within the allosteric site of AKT1, suggesting their potential as novel AKT1 inhibitors. These findings provide a basis for further experimental studies to validate their efficacy in cancer treatment.

Keywords: AKT1, cancer, virtual screening, flavonoids, molecular docking, MD simulation

25COASMA17

Title: Paired Comparison of Whole Genome Sequencing and Comprehensive Targeted Sequencing of Pancreatic Cancer Tissue

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Anticancer Research February 2025, 45 (2) 605-612;
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Abstract: Background/Aim: As an increasing number of drugs are approved for targeted cancer therapy, comprehensive genomic profiling of cancer patients is frequently conducted to identify potentially relevant genetic variants. Different sequencing technologies are used for this purpose; targeted gene panels cover a selected set of biomarker genes and hotspot regions, while whole genome sequencing (WGS) delivers genome-wide data. This comparison study aimed at evaluating whether one method performs superiorly to the other regarding the detection of targetable variants. Patients and Methods: To evaluate the

performance of the two sequencing technologies, we compared the results of targeted sequencing using the Ion Torrent Oncomine Comprehensive Assay Plus (OCA-Plus) panel to Illumina WGS reports in 11 patients diagnosed with pancreatic cancer (PC). All pathogenic and likely pathogenic variants, including those relevant for targeted therapy, reported by WGS and OCA-Plus, were included in the final comparison. Results: Both techniques identified common driver mutations implicated in PC with high concordance (81%) across all variants. For variants relevant to targeted therapy, a 100% concordance between the technologies was observed. Conclusion: A comparable number of variants were reported by WGS and OCA-Plus, and all genetic variants relevant for targeted therapy were identified by both technologies. Thus, WGS does not provide substantial additional information in this patient group.

Keywords: Targeted sequencing, whole genome sequencing, pancreatic cancer, targeted treatment

25COASMA18

Title: Unusual Presentation of Advanced Urothelial Cancer in a Young Patient

Daniela Guevara, Nara Shin, Alexandra Boiko, Ivan Valiev, Ahmed G. Elsaeed, Juan Miguel Mosquera,

Anticancer Research February 2025, 45 (2) 613-618;
DOI: https://doi.org/10.21873/anticanres.17448

Abstract: Background/Aim: Urothelial carcinoma, common in older adults, is rare in younger populations and even less common in the prostatic urethra. Advanced disease is typically managed with platinum-based chemotherapy, immune checkpoint inhibitors, and targeted therapies. However, rare presentations in young patients with aggressive disease highlight the need for innovative and personalized treatment strategies. Case Report: This case report presents a rare instance of metastatic urothelial carcinoma originating in the prostatic urethra of a 37-year-old male. Initial symptoms led to diagnosis through imaging, biopsy, and genetic profiling, revealing mutations in TP53 and RB1. The patient underwent multiple treatments, including dose-dense chemotherapy, pembrolizumab immunotherapy, and targeted antibody-drug conjugates (Enfortumab Vedotin and Sacituzumab Govitecan). Despite aggressive therapies, disease management remained challenging, leading to experimental treatments, including a personalized vaccine. Conclusion: This case underscores the importance of precision medicine and the need for innovative treatment options for rare and aggressive cancers.

Keywords: Urothelial carcinoma, prostatic urethra, immunotherapy, precision medicine

25COASMA19

Title: Mesonephric Adenocarcinoma in a Young Male Patient

Daniela Guevara, Nara Shin, Alexandra Boiko, Ivan Valiev, Ahmed G. Elsaeed, Juan Miguel Mosquera,

Anticancer Research February 2025, 45 (2) 619-623;
DOI: https://doi.org/10.21873/anticanres.17449

Abstract: Background/Aim: Mesonephric adenocarcinoma in males is an exceptionally rare malignancy arising from mesonephric remnants. Accurate diagnosis requires thorough

histopathological and molecular analysis. Case Report: A 33-year-old male presented with right lower quadrant pain, and imaging revealed a pelvic mass compressing adjacent structures. Biopsy confirmed mesonephric adenocarcinoma. Genetic profiling revealed mutations in tuberous sclerosis complex 2 (TSC2) and phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha (PIK3CA), offering potential for targeted therapy. Conclusion: This case highlights the diagnostic and therapeutic challenges of mesonephric adenocarcinoma in males. Molecular profiling provided insights into tumor biology and potential targeted treatments. Multidisciplinary collaboration and surveillance remain essential for managing rare malignancies effectively.
Keywords: Mesonephric adenocarcinoma, targeted therapy, whole genome sequencing

25COASMA20

Title:Cyclin E Expression and p16 Loss Are Strong Prognostic Biomarkers in Primary Invasive Cutaneous Melanoma

Ioannis G. Gkionis, Maria Tzardi, Athanasios Alegakis, Galateia Datseri, Eleni Moustou, Georgios Saridakis,

Anticancer Research February 2025, 45 (2) 625-637;
DOI: https://doi.org/10.21873/anticanres.17450

Abstract: Background/Aim: The traditional melanoma staging system is not ideal for predicting patients' individual risk of disease recurrence and death. Subsequently, suboptimal adjuvant treatment may be offered. Hence, identification of biomarkers to optimize risk stratification is warranted. Cyclins and cyclin-dependent kinase inhibitors, key players in the cell cycle regulation, are candidate prognostic biomarkers. Herein, their expression and prognostic value in melanoma are studied. Patients and Methods: The expression of Cyclin D1, Cyclin E, p16, p21, and p27 were assessed using immunohistochemistry in samples from 59 patients with melanoma and correlated with clinicopathological parameters, as well as relapse-free survival (RFS) and overall survival (OS). Results: Cyclin E expression in the nucleus, observed in 19% of patients, was correlated with Breslow thickness (p=0.017), whereas p16 loss in the cytoplasm and nucleus, detected in 68% and 61% of patients respectively, was correlated with Breslow thickness (p=0.001) and ulceration (p=0.035). The high expression of Cyclin E in the nucleus (p<0.001) and the loss of p16 in the cytoplasm (p=0.012) and nucleus (p=0.002) were associated with shorter OS. Cyclin E in the nucleus was a prognostic factor for RFS and OS at least as strong as Breslow thickness. Conclusion: Expression of Cyclin E and loss of p16 appeared to be significant prognostic biomarkers, with Cyclin E being prognostically at least as strong as Breslow thickness regarding RFS and OS. Both biomarkers may potentially be used to improve stratification of individual patient's risk of recurrent disease and survival, and subsequently optimize adjuvant treatment.
Keywords: Melanoma, prognostic biomarkers, cyclins, cyclin-dependent kinase inhibitors, Cyclin D1Cyclin Ep16p21p27

25COASMA21

Title: Efficacy of Second-line Nivolumab Versus Tyrosine Kinase Inhibitors for Renal Cell Carcinoma With Bone Metastases

Gaku Yamamichi, Taigo Kato, Akihiro Yoshimura, Masaru Tani, Yuki Horibe, Yutong

Liu, Nesrine Sassi,
Anticancer Research February 2025, 45 (2) 639-650;
DOI: https://doi.org/10.21873/anticanres.17451
Abstract: Background/Aim: Combination therapy with immune checkpoint inhibitors has become the standard first-line treatment for metastatic renal cell carcinoma (mRCC), leading to changes in second-line treatment options, such as nivolumab or tyrosine kinase inhibitors (TKIs). However, very few studies have compared the efficacy of these drugs in patients with mRCC, particularly those with bone metastases (BM), which are associated with a poor prognosis. This study compared the efficacy of nivolumab and TKIs as second-line treatments for mRCC patients with BM and examined the microenvironments of primary tumors and BM lesions. Patients and Methods: This multi-institutional retrospective study included 87 mRCC patients with BM who received either nivolumab or TKIs as second-line treatments. We analyzed tumor-infiltrating immune cells expressing CD8 and CD20, along with PD-L1, HIF2α, c-MET, VEGFR2, and AXL, in primary tumors and BM sites using immunohistochemistry. Results: This analysis indicated that poor-risk classification, as per the International Metastatic RCC Database Consortium criteria ($p<0.01$), and elevated serum alkaline phosphatase levels ($p=0.031$) were significantly associated with poor prognosis. No significant difference in overall survival was observed between patients receiving nivolumab and those receiving TKIs. However, the objective response rate of patients with BM lesions was significantly higher when receiving TKIs than when receiving nivolumab ($p=0.014$). Immunohistochemistry revealed significantly higher VEGFR2 expression in BM lesions than primary tumors. Conclusion: TKIs could be a promising second-line treatment option for mRCC patients with bone-limited metastases.
Keywords: Renal cell carcinoma, bone metastasis, second-line treatment, nivolumabtyrosine kinase inhibitor, overall survival

25COASMA22

Title: Clinical Impact of Cellular Senescence and RNA Dysregulation in HCC Is Associated With MASLD and HCV-SVR

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Anticancer Research February 2025, 45 (2) 651-659;
DOI: https://doi.org/10.21873/anticanres.17452
Abstract: Background/Aim: The incidence of hepatocellular carcinoma (HCC) associated with metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatitis C virus sustained virologic response (HCV-SVR) are increasing. However, the mechanisms driving HCC development in these patients remain unclear. This study aimed to evaluate the role of cellular senescence and RNA editing in HCC by examining cyclin-dependent kinase inhibitor 2A (p16) and adenosine deaminase acting on RNA (ADAR1) expression. Patients and Methods: HCC specimens from patients with MASLD or HCV-SVR were analyzed by immunohistochemistry to assess p16 and ADAR1 expression. Statistical analyses were conducted using the Chi-squared test, Fisher's exact test, and Mann–Whitney U-test. Survival analyses were performed using the Kaplan–Meier method, the log-rank test, and Cox regression analysis. Results: Among 122 patients, 59 (48.4%) had MASLD and 63 (51.6%)

had HCV-SVR. p16 expression was observed in 69 cases (57.0%) in the noncancerous areas and 53 cases (44.5%) in the cancerous areas. ADAR1 expression was positive in 28 cases (23.5%) in the cancerous areas and significantly associated with p16 expression in the cancerous areas (p=0.039). Patients with p16 expression in the noncancerous areas were older (p=0.045) and had elevated serum ALT levels (p=0.024). p16 expression in the cancerous areas were correlated with a shorter recurrence-free survival (HR=1.65, 95%CI=1.00-2.73, p=0.046). Conclusion: Cellular senescence and RNA editing may play a key role in MASLD- and HCV-SVR-related HCC. p16 expression in the cancerous areas may serve as a prognostic biomarker for surgical outcomes.

Keywords: Hepatocellular carcinoma, cellular senescence, RNA dysregulation, metabolic dysfunction-associated steatotic liver disease, hepatitis C virus-sustained virologic response

25COASMA23

Title: Use of Indocyanine Green Fluorescence Angiography to Assess Bowel Anastomosis in Ovarian Cancer Surgery

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DOI: https://doi.org/10.21873/anticanres.17453

Abstract: Background/Aim: The aim of this study was to investigate the efficacy of indocyanine green (ICG) fluorescence angiography in preventing anastomotic leaks and reducing the need for ostomies during cytoreductive surgery in ovarian cancer. 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 bowel resection during primary or secondary cytoreductive surgery at our institution between July 2021 to April 2023. Rates of ostomy performance and anastomotic leak were assessed in the ICG angiography group and the non-ICG angiography group. Frequency distributions between categorical variables were compared using Fisher's exact or Chi-squared test. Wilcoxon rank-sum test and t-test were used to compare continuous variables. Results: During the study period, we reviewed the data of 59 consecutive patients with ovarian cancer with bowel resection; in 30 (50.85%) patients, bowel anastomosis was assessed using ICG angiography and in 29 (49.15%) patients, bowel anastomosis was not assessed using ICG angiography. Anastomotic leak rate was found to be 6.9% (n=2) in the non-ICG angiography group, and 3.33% in the ICG angiography group (n=1) (p=0.612). More diverting ostomies were performed in the non-ICG angiography group (n=6, 20.69%) compared to the ICG angiography group in which no ostomies were performed (p=0.011). Conclusion: ICG angiography is not associated with a decrease in anastomotic leak rates, but it may avoid ostomy formation.

Keywords: Ovarian neoplasm, ostomy, anastomotic leak, angiography

25COASMA24

Title: Free Interleukin 18 (IL-18F) Blood Levels Following Midline Laparotomy: A Prospective Randomized Study of Patients With Benign Disease and Patients With Cancer

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Anticancer Research February 2025, 45 (2) 667-675;
DOI: https://doi.org/10.21873/anticanres.17454
Abstract: Background/Aim: The purpose of this work was to assess blood level correlations of free IL-18 (IL-18F) and various cytokines (CYTs), caspase-1 (Casp1), high sensitive C-reactive protein (hs-CRP), and 4-hydroxynonenal (4-HNE) in 56 patients subjected to midline laparotomy (MLa) and to investigate their link to pain scales. Patients and Methods: Blood levels of IL-18F and seven CYTs (IL-18, IL-18BP, IL-1ra, IL-6, IL-8, IL-10, IL-1β), Casp1, hs-CRP, and 4-HNE were measured and the pain surveys were reported using numerical rating scale (NRS) and the Brief Pain Inventory (BPI) scales conducted preoperatively (PRE) and postoperatively (POP). Results: The IL-18F levels decreased at POP and the decrease between POP1 (immediately after MLa) and POP2 (24 hours after MLa) blood levels (26.5 versus 20.0) was significant ($p<0.001$). Moreover, the IL-18F levels at POP2 were slightly higher in patients with cancer than in patients with benign disease (21.2 versus 17.8). Interestingly, the IL-18F levels correlated to IL-18 ($r=0.523$, $p<0.001$), IL-18BP ($r=-0.475$, $p<0.001$), and 4-HNE ($r=0.414$, $p<0.001$) levels. Furthermore, the IL-18F levels correlated with BPI score values ($r=-0.459$, $p=0.05$). Conclusion: This is the first report to demonstrate a link between increased IL-18F levels and pain scales in MLa. IL-18F levels decreased significantly after operation and correlated with IL-18, IL-18BP, and 4-HNE blood levels, and inversely correlated with BPI pain scores. These results support the applicability of acute phase response biomarkers in understanding pain in patients subjected to MLa.
Keywords: Free IL-18, benign disease, cancer, midline laparotomy

25COASMA25

Title: Prognostic Significance of the Detection of Human Papilloma Virus L1 Protein in Smears of Cervical Intraepithelial Neoplasia Grade 3 in Pregnant Women

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Anticancer Research February 2025, 45 (2) 677-683;
DOI: https://doi.org/10.21873/anticanres.17455
Abstract: Background/Aim: Cervical intraepithelial neoplasia (CIN) III/high-grade squamous lesions (HSIL) remains a significant challenge during pregnancy. Current data on the course of disease are contradictory, with cases of progression to cervical cancer (CC) during pregnancy being observed. Evidence suggests that the expression of L1 capsid protein is associated with a favorable prognosis in non-pregnant women. The aim of this study was to evaluate L1 expression in pregnant women with CIN III/HSIL. Patients and Methods: Between 2008 and 2021, the conventional PAP-smears from pregnant women were retrospectively analyzed for the expression of L1. Only women with histologically confirmed CIN III/HSIL during pregnancy were included. Results: A total of 161 women were included in this study; among them, 32 women (19.9%) had regressive disease postpartum. The majority of women (n=123, 76.4%) had persistent disease. In six cases, invasive CC was histologically proven postpartum (3.7%). In 113 women (70.2%) the PAP-Smears were L1− and 29.2% (n=48) of women were L1+. The rates of regression for L1+ were higher than for

L1−, 25% vs. 17.7%, respectively. Rates for persistence were similar, at 75% and 78%, respectively. All cases of progression to CC were L1 negative during pregnancy. Conclusion: In pregnant women, the rates of regression were higher in L1+ CIN III/HSIL cases. All women who progressed to CC were L1−. Therefore, detecting L1 expression could serve as a valuable test to rule out progression to CC in pregnant women. This approach may provide reassurance to women, allowing them to continue their pregnancies with reduced fear and anxiety about CIN III/HSIL during pregnancy.

Keywords: Colposcopy, CIN III/HSIL, pregnancy, L1 capsid protein, cervical cancer

25COASMA26

Title: Enhanced Potential of Durvalumab in the Initial Treatment of Advanced Biliary Tract Cancer

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Anticancer Research February 2025, 45 (2) 685-690;
DOI: https://doi.org/10.21873/anticanres.17456

Abstract: Background/Aim: The prognosis of biliary tract cancer is extremely poor, with a 5-year survival rate of 20%. Surgery is the only treatment that can be expected to cure biliary tract cancer, but because many cases are unresectable or recurrent, chemotherapy has become the standard treatment. The effects of first-line administration of durvalumab have not been explored. This study examined whether durvalumab has an additive effect in the first line. Patients and Methods: Twenty-three patients who were diagnosed with recurrent or non-resected biliary tract cancer requiring anticancer chemotherapy were recruited. Three of these cases were excluded because they had only received one course of durvalumab. We retrospectively collected clinical and laboratory data. Progression-free survival (PFS) and overall survival (OS) were compared between patients who received durvalumab as first-line therapy (first group, FG) and those who received it as second-line or later therapy (second group, SG). PFS and OS were also compared in durvalumab-treated patients aged 75 years and older (older group) and in younger patients. Immune-related adverse events (irAEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE v5) based on the clinical notation available in the patient charts. Results: Kaplan–Meier curves showed that SG was significantly associated with worse PFS (p=0.018), and the FG group also showed significantly prolonged OS (p=0.030). In addition, PFS from the start of durvalumab treatment was significantly longer in the older group compared to the younger group. However, no significant difference in OS was observed between the two groups. Conclusion: Durvalumab appears to contribute to prolonged PFS and OS when administered as an initial treatment. It may also contribute to improved outcomes in older patients with biliary tract cancer.

Keywords: Durvalumab, advanced biliary tract cancer, old age

25COASMA27

Title: Peak-postoperative Serum Transaminases Correlate With Post-hepatectomy Liver Failure and Inflow Occlusion After Laparoscopic Liver Resection

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Kiuchi, Kenji Nanishi,
Anticancer Research February 2025, 45 (2) 691-700;
DOI: https://doi.org/10.21873/anticanres.17457
Abstract: Background/Aim: Peak-postoperative serum transaminases (PST) may indicate hepatocellular damage caused by liver resection and ischemia-reperfusion injuries induced by inflow occlusion. However, the potential of PST to predict postoperative outcomes and its correlation with the duration of inflow occlusion remains controversial. Moreover, there have been no reports regarding PST after laparoscopic liver resection (LLR). This study aimed to evaluate the efficacy of PST after LLR and the correlation between PST and the duration of inflow occlusion. Patients and Methods: A total of 313 consecutive patients who underwent LLR between 2012 and 2023 were included in this study. Results: The area under the receiver-operating characteristic curve values of PST-AST and PST-ALT for predicting post-hepatectomy liver failure (PHLF) was 0.801 and 0.790, respectively. We defined PST-AST or PST-ALT ≥1,000 U/l as an exceptionally high PST. Multivariate analysis revealed that an exceptionally high PST was an independent risk factor for PHLF [p<0.001; odds ratio (OR)=25.50 (95% CI=5.35-121.00)]. PST-AST and PST-ALT correlated with the duration of inflow occlusion (Spearman's ϱ=0.5306 and 0.5632, p<0.001). Conclusion: Exceptionally high PST (≥1,000 U/l) is an independent risk factor for PHLF. The duration of inflow occlusion correlates with PST following LLR.
Keywords: Transaminases, laparoscopic liver resection, duration of inflow occlusion, post hepatectomy liver failure, postoperative hospital stay

25COASMA28

Title: Bladder Volume <200 ml During a Course of Moderate Hypofractionated Irradiation in Patients With Localized Prostate Cancer

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Anticancer Research February 2025, 45 (2) 701-708;
DOI: https://doi.org/10.21873/anticanres.17458
Abstract: Background/Aim: Hypo-fractionated radiotherapy (HF-RT) is gaining popularity in prostate cancer treatment. HF-RT can lead to cystitis, particularly in cases with small bladder volumes. This study evaluated the bladder volume during a course of moderate HF-RT. This knowledge is required for the protocol of a prospective trial. Patients and Methods: Seventy-six patients receiving HF-RT (20×3.0 Gy) for prostate cancer were retrospectively evaluated. The number of HF-RT sessions with a bladder volume <200 ml and corresponding risk factors were investigated. Results: Mean and median numbers of sessions with a bladder volume <200 ml were 13.4 (±6.7) and 16.0 (interquartile range=8.0-19.0), respectively. Higher numbers of radiotherapy sessions with a bladder volume <200 ml were associated with a pre-radiotherapy volume <200 ml (p<0.001). Mean numbers of sessions with a bladder volume <200 ml were 16.0 (±5.5) in patients with a pre-radiotherapy bladder volume <200 ml and 7.9 (±5.9) in patients with a bladder volume ≥200 ml, respectively. Conclusion: Bladder volume was <200 ml during many HF-RT sessions. Patients with a pre-radiotherapy bladder volume <200 ml may benefit from an app reminding them to drink water before their HF-RT sessions.

Keywords: Localized prostate cancer, hypo-fractionated radiotherapy, urinary bladder volume, filling status

25COASMA29

Title: The Impact of Tonsillectomy on Oropharyngeal Cancer Development

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Anticancer Research February 2025, 45 (2) 709-718;
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Abstract: Background/Aim: Decreasing numbers of tonsillectomies (TE) and an increasing frequency of oropharyngeal squamous cell carcinoma (OPSCC) is a well-known finding in western societies. A retrospective cohort study was performed to investigate the association between a history of TE and the development of OPSCC. Patients and Methods: This study included all OPSCC patients who were treated between 2004 and 2023 at the Department of Otorhinolaryngology in University Medical Centre Ruppin Brandenburg in Germany. Digital patient charts were used to collect patient information. Results: Of the 320 patients with OPSCC, 19 (5.9%) had a history of TE. In 63.2% of cases, the procedure was performed in childhood, and 36.8% in adulthood. Our results indicate significant differences in terms of tumor location between the patients with and without a history of TE (p=0.010). In patients without TE, OPSCC was localized in the tonsillar region (45%), in the base of the tongue (29%), and other regions (26%). In patients with a history of TE the frequency was 16%, 63%, and 21%, respectively. Age at initial diagnosis, initial tumor size, p16/HPV status, residual tumor, venous and lymphatic extracapsular extension, recurrence, and alcohol abuse significantly influenced overall survival without any difference between the two groups. Conclusion: A history of TE is associated with a decreased risk of tumor localization in the tonsillar region, especially when TE was performed in adulthood. Additionally, in patients with OPSCC and a history of TE, the tumor is more frequently localized at the base of the tongue. A history of TE does not affect demographics, the outcomes of tumor parameters or the prognosis of our patients.

Keywords: Oropharyngeal cancer, squamous cell carcinoma, tonsillectomy, HPV-status, prognosis, prevention

25COASMA30

Title: Clinicopathological and Molecular Insights into Primary Retroperitoneal Squamous Cell Carcinoma: HPV Association and Discovery of Recurrent PIK3CA E545K Mutation

Han Gyeol Kim, Sung Kyoung Moon, Hyun-Soo Kim And Kiyong Na

Anticancer Research February 2025, 45 (2) 719-731;
DOI: https://doi.org/10.21873/anticanres.17460

Abstract: Background/Aim: Primary retroperitoneal squamous cell carcinoma (PRSCC) is extremely rare, and its diagnosis and management are challenging. Previous reports have highlighted the potential role of human papillomavirus (HPV) in the pathogenesis of PRSCC. This study aimed to determine the clinicopathological and molecular characteristics of PRSCC. Patients and Methods: We searched PubMed for previously published PRSCC cases. Immunostaining, human papillomavirus (HPV) testing, and targeted DNA and RNA

sequencing were performed. Results: A total of 25 cases of PRSCC were analyzed. The mean age was 54.3 years, with the majority being women. They presented with pain in the lower abdomen, pelvis, and lower extremities; deep vein thrombosis; urinary symptoms; hydronephrosis; and ureteral obstruction. Treatment modalities included chemotherapy, radiation therapy, and concurrent chemoradiotherapy, with varying outcomes. HPV DNA was detected in most cases, with tumors exhibiting diffuse p16 positivity. Additionally, two patients carried a hotspot E545K mutation in phosphatidylinositol-4,5-bis-phosphate 3-kinase catalytic subunit alpha (PIK3CA). Conclusion: This study provides insights into the clinico-pathological features of PRSCC and identified a novel recurrent PIK3CA mutation in HPV-associated PRSCCs. Our findings suggest the potential utility of next-generation sequencing for identifying therapeutic targets. Further studies are warranted to clarify whether PIK3CA E545K mutation has diagnostic and therapeutic potential in patients with PRSCC.
Keywords: Retroperitoneum, squamous cell carcinoma, human papillomavirus, next-generation sequencing, PIK3CA

25COASMA31

Title: Efficacy and Safety of Amrubicin Monotherapy After Chemoradiotherapy in Patients With Relapsed Limited Disease Small-cell Lung Cancer

Akira Matsukida, Hisao Imai, Ayako Shiono, Yasuhiro Ryuno, Kosuke Hashimoto, Yu Miura, Satoshi Endo,

Anticancer Research February 2025, 45 (2) 733-741;
DOI: https://doi.org/10.21873/anticanres.17461

Abstract: Background/Aim: Amrubicin is recognized as a second-line treatment for refractory small-cell lung cancer (SCLC) and is administered immediately after chemotherapy; however, it has not been evaluated in patients with recurrent SCLC following chemoradiotherapy (CRT). This study aimed to examine the activity and safety of amrubicin monotherapy in patients with relapsed SCLC previously treated with CRT. Patients and Methods: This retrospective study evaluated patients with relapsed SCLC who had been previously treated with CRT, followed by amrubicin monotherapy between April 2007 and June 2021. The clinical efficacy and toxicity were assessed. Results: Overall, 30 patients (20 men and 10 women) were enrolled. The response rate was 50.0% [95% confidence interval (CI)=33.1-66.8%]. The median progression-free survival and overall survival from the first amrubicin treatment was 4.1 months (95%CI=2.3-6.0 months) and 13.5 months (95%CI=7.5-16.0 months), respectively. Grade ≥3 hematological adverse events occurred as follows: decreased white blood cells in 63.3% of patients, decreased neutrophil count in 70.0%, and febrile neutropenia in 10.0%. Grade 3 pneumonitis was observed in one patient. No treatment-related deaths occurred. Conclusion: Amrubicin is both feasible and effective in patients with relapsed SCLC who were previously treated with CRT. The efficacy and toxicity of amrubicin in this study were consistent with those of previous reports, indicating that amrubicin retained its effectiveness post-CRT. Consequently, amrubicin following CRT may be the optimal chemotherapeutic choice for patients with relapsed limited-disease SCLC.
Keywords: Amrubicin, chemoradiotherapy, limited disease, relapsed small-cell lung cancer

25COASMA32

Title: Negative Impact of Low Serum Cholinesterase on Short- and Long-term Outcomes in Elderly Patients Undergoing Scheduled Surgery for Colorectal Cancer

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Anticancer Research February 2025, 45 (2) 743-750;
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Abstract : Background/Aim: Cholinesterase (ChE) is important for estimating nutritional status and can be easily measured. This study aimed to investigate the effect of ChE on the short- and long-term prognoses of elderly patients with colorectal cancer. Patients and Methods: This study included 120 elderly patients who underwent scheduled surgery for colorectal cancer. ChE is a biomarker that can be easily measured using blood tests. The optimal cut-off level of ChE was determined using receiver operating characteristic analysis. We investigated the relationship of ChE with disease-free and overall survival using univariate and multivariate analyses. Results: Seventy-two (60%) patients had low ChE levels (<255 U/l). In the multivariate analysis, low ChE (p=0.04) was an independent and significant predictor of postoperative complications. Low ChE (p=0.049), low prognostic nutritional index (p=0.04), and lymph node metastasis (p<0.01) were independent and significant prognostic predictors of poor disease-free survival. American Society of Anesthesiologists Physical Status 3 (p<0.01), low ChE (p<0.01), and lymph node metastasis (p<0.01) were independent and significant predictors of poor overall survival. Conclusion: ChE level is a significant predictor of short- and long-term outcomes in elderly patients undergoing scheduled surgery for colorectal cancer.

Keywords: Cholinesterase, colorectal cancer, elderly patients

25COASMA33

Title: Prognostic Stratification Using Early Prostate-specific Antigen Kinetics in Men With Metastatic Hormone-sensitive Prostate Cancer

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Anticancer Research February 2025, 45 (2) 751-759;
DOI: https://doi.org/10.21873/anticanres.17463

Abstract: Background/Aim: The prognostic significance of prostate-specific antigen (PSA) kinetics in metastatic castration-sensitive prostate cancer (mCSPC) patients treated with upfront therapy remains unclear. This study investigated the correlation between early PSA response and clinical outcomes in patients with mCSPC who received upfront therapy. Patients and Methods: We analyzed 106 patients with mCSPC who received upfront therapies [abiraterone acetate (ABI), enzalutamide (ENZ), apalutamide (APA), and docetaxel (DOC)] at Kurume University Hospital and its affiliated hospitals. Results: Thirty-nine, 15, 38, and 14 patients were treated with ABI, DOC, ENZ, and APA, respectively. Among the total number of patients, 67 met the criteria for high-volume disease. Additionally, 83 patients were categorized as high risk. Patients with a PSA decline rate of ≥90% at 4 and 12 weeks post-upfront therapies had a significantly longer time to develop CRPC than those with a PSA decline of <90%. PSA cutoff values >26 ng/ml at 4 weeks post-upfront therapies and a

PSA decline rate of ≥90% at 12 weeks post-upfront therapies were independent predictors of poor prognosis. Furthermore, patients were stratified into three groups based on PSA levels at 4 weeks and PSA decline rate at 12 weeks. Conclusion: A larger PSA decline within three months of initiating upfront therapy is significantly associated with a longer time to CRPC in patients with mCSPC treated with upfront therapy. A combination of early PSA kinetics can be used to stratify the risk of CRPC progression in patients with mCSPC treated with upfront therapies.

Keywords: Early PSA kinetics, time to CRPC, mCRPC, upfront therapies

25COASMA34

Title: Negative Impact of High FOXP3 Status in Lymph Nodes of Esophageal Squamous Cell Carcinoma Patients

Yukiko Nonaka, Taisuke Baba, Shizuki Sugita, Kazushi Miyata, Masaki Sunagawa, Junpei Yamaguchi,

Anticancer Research February 2025, 45 (2) 781-787;
DOI: https://doi.org/10.21873/anticanres.17466

Abstract: Background/Aim: Available data on the immune profiles of regional lymph nodes in individuals with esophageal squamous cell carcinoma (ESCC) are limited. This study investigated the immune profiles of proximal regional lymph nodes (PLNs) and evaluated the association between PLNs and the outcomes of patients with ESCC. Patients and Methods: This study included 39 patients with ESCC who underwent subtotal esophagectomy with three-field lymph node dissection. The immune profiles of tumor-infiltrating lymphocytes and PLNs were evaluated through immunohistochemistry. Furthermore, the impact of this immune profile on long-term outcomes was analyzed. Results: Cox proportional-hazards analysis for overall survival revealed that ypT ≥3 [hazard ratio (HR)=8.91; 95% confidence interval (CI)=1.59-49.8] and high FOXP3 status in PLNs (HR=4.29; 95%CI=1.06-17.4) are significant independent prognostic factors. Meanwhile, analysis of disease-free survival (DFS) revealed that ypT ≥3 (HR=5.52; 95%CI=1.15-26.6) and ypN ≥1 (HR=7.74; 95%CI=1.58-37.9) are independent prognostic factors. Furthermore, high FOXP3 status in PLNs was associated with low DFS rate, although the association was not statistically significant (HR=1.70; 95%CI=0.58-5.02). Conclusion: High FOXP3 status in PLNs is associated with poor prognosis in patients with ESCC.

Keywords: Esophageal cancerforkhead box protein 3programmed cell death 1-ligand 1lymph node

25COASMA35

Title: Clinical Utility of Sentinel Lymph Node Biopsy Using the Medical Imaging Projection System in Breast Cancer Patients, Including Those Following Neoadjuvant Chemotherapy

Aoi Oshiro, Masayuki Nagahashi, Yusa Togashi, Haruka Kanaoka, Akira Hattori, Junko Tsuchida,

Anticancer Research February 2025, 45 (2) 789-796;
DOI: https://doi.org/10.21873/anticanres.17467

Abstract: Background/Aim: The Medical Imaging Projection System (MIPS) is a real-time

projection mapping system with a highly sensitive fluorescence sensing system. The aim of this study was to investigate the clinical utility of sentinel lymph node (SLN) biopsy using MIPS and radioisotopes (RI) in patients with breast cancer including those who had undergone neoadjuvant chemotherapy (NAC). Patients and Methods: This retrospective observational study included patients with breast cancer who underwent SLN biopsy using both MIPS and RI at Hyogo Medical University Hospital from August 2023 to August 2024. Results: In all, 151 patients with breast cancer (157 axillary lesions, considering bilateral cancer as two lesions) were included in this study. MIPS identified significantly more SLNs than RI (median, 2 vs. 1, p<0.001). MIPS alone identified SLNs in 96.2% of lesions, and when combined with RI, identified SLNs in 99.4% of lesions, including in patients who had undergone NAC. Eleven of 157 lesions (7.0%) had positive SLNs, and the combination method identified positive nodes in 10 of these 11 lesions (90.9%). Importantly, all five lesions with metastases after NAC were observed in patients with cN1/ycN0 disease and the luminal subtype. Conclusion: MIPS combined with RI achieves a high identification rate of SLNs in patients with breast cancer, including those who had undergone NAC. Patients with cN1 disease prior to NAC should undergo axillary surgery tailored to their characteristics.
Keywords: Breast cancer, Medical Imaging Projection System, neoadjuvant chemotherapy, sentinel lymph node biopsy, tailored axillary surgery

25COASMA36

Title: Safety and Survival Benefit of Adjuvant Chemotherapy for Elderly Patients With Stage II/III Colon Cancer

In Jun Yang, Dong Ha Kim, Kyung-Ha Lee And Ji Yeon Kim
Anticancer Research February 2025, 45 (2) 797-809;
DOI: https://doi.org/10.21873/anticanres.17468
Abstract: Background/Aim: To evaluate the safety and survival benefits of adjuvant chemotherapy (AC) in elderly patients who underwent radical resection for stage II/III colon cancer. Patients and Methods: This retrospective study included patients aged >70 years treated at a tertiary hospital between January 2012 and December 2017. We evaluated the clinical and pathological characteristics and adverse events of chemotherapy. The 5-year overall survival (OS) and disease-free survival (DFS) of the surgery-only (SO) and AC groups were compared by stage using the Kaplan–Meier method and Cox-regression analysis. Results: Of the 163 patients included in the study, 75 were diagnosed with stage II cancer, with 43 patients in the SO group and 32 in the AC group. A total of 88 patients were diagnosed with stage III cancer, including 20 in the SO group and 68 in the AC group. Patients with stage II disease in the SO group were older, with less frequent venous invasion than the AC group. Comorbidities, tumor location, and surgical methods did not differ. In stage III, age, comorbidities, tumor location, surgical methods, and pathological outcomes did not differ. The 5-year OS and DFS did not differ significantly in those with stage II disease but were significantly better in the AC than the SO group in stage III cases (48.2% vs. 71.6%, p=0.012; and 42.6% vs. 60.0%, p=0.029). Conclusion: AC may provide a survival advantage in elderly patients with stage III colon cancer.
Keywords: Adjuvant chemotherapy, colon cancer, frail elderly

25COASMA37

Title: Up-regulated DDX39 in Adrenocortical Carcinoma Is Associated With Patient Survival

Yoshiatsu Tanaka, Shin-Nosuke Yamashita, Shajedul Islam, Takao Kitagawa, Kazuhiro Tokuda, Durga Paudel,

Anticancer Research February 2025, 45 (2) 811-815;
DOI: https://doi.org/10.21873/anticanres.17469

Abstract : Background/Aim: Adrenocortical carcinoma is a very rare tumor characterized by poor prognosis and high mortality. The origin of this tumor is primarily the adrenal cortex. The 5-year overall survival rate of patients with adrenocortical carcinoma has not improved despite therapeutic advances. Early detection of this malignancy remains difficult, and no standard curative therapy currently exists. Therefore, it is important to understand the biology of adrenocortical carcinoma, and to identify prognostic biomarkers and molecular targets for its therapy. DDX39 is an Asp-Glu-Ala-Asp (DEAD)-box RNA helicase, which is required for transcription, splicing and transport of mRNA. There are some reports about overexpression of DDX39 in tumor tissues and cells (lung squamous cell cancer, gastrointestinal stromal tumor, urinary bladder cancer, malignant pleural mesothelioma). However, the clinicopathological involvement of DDX39 in adrenocortical carcinoma has not yet been documented. Materials and Methods: The GEPIA, GEPIA2, and UALCAN platforms were used to analyze DDX39 mRNA expression and survival in patients with adrenocortical carcinoma. Results: DDX39 was found to be significantly up-regulated in adrenocortical carcinoma tissues, and this up-regulation inversely correlated with prolonged patient survival. Conclusion: DDX39 may be a potential prognostic biomarker in patients with adrenocortical carcinoma.

Keywords: DDX39, adrenocortical carcinoma, Kaplan–Meier survival plot

25COASMA38

Title: Impact of Perioperative Rehabilitation on Postoperative Length of Hospital Stay for Patients With Gastric Cancer

Keisuke Komori, Fumiyo Abiko, Taku Ichikawa, Kanako Ando, Rika Shigeeda, Tomohiro Yamaguchi,

Anticancer Research February 2025, 45 (2) 817-822;
DOI: https://doi.org/10.21873/anticanres.17470

Abstract: Background/Aim: Perioperative rehabilitation is effective in preventing postoperative complications and is associated with a shorter length of hospital stay after gastrectomy. However, its impact on short-term outcomes in patients without post-gastrectomy complications has not yet been clarified. This study aimed to evaluate the usefulness of perioperative rehabilitation beyond preventing postoperative complications. Patients and Methods: Of the 142 patients who underwent surgery for gastric cancer at our hospital between November 2017 and December 2022 and were treated according to the Enhanced Recovery After Surgery (ERAS) protocol during the perioperative period, 106 patients who were discharged without postoperative complications (with Clavien-Dindo classification < Grade 1) and did not undergo readmission within 30 days after surgery were included in the study. Perioperative rehabilitation was provided from August 2020. Patients

were divided into the following two groups: Group A (with cancer rehabilitation; n=55) and Group B (without cancer rehabilitation; n=51), and their clinicopathological characteristics and short-term results were compared. Risk factor analysis was performed based on the number of days of postoperative hospitalization. Results: The number of days of postoperative hospitalization in Group A (average 8.6 days) was significantly shorter than that in group B (average 9.9 days) (p=0.032). Multivariate analysis of postoperative hospital stay revealed that older age (p=0.003), female sex (p=0.043), heavy bleeding (p=0.026), and no rehabilitation (p=0.004) were independent risk factors. Conclusion: Even in patients without postoperative complications, perioperative rehabilitation for gastric cancer could be effective in shortening the postoperative hospital stay.
Keywords: Gastric cancer, rehabilitation, hospital stay

25COASMA39

Title: DNA Ligase 4 Inhibition Sensitizes Prostate Cancer to Immune Checkpoint Blockade In Vivo

Jianchun Wu, Angelica M. Lagunas And David L. Crowe
Anticancer Research March 2025, 45 (3) 883-896;
DOI: https://doi.org/10.21873/anticanres.17476
Abstract: Background/Aim: Prostate cancer is a common malignant tumor in men. DNA ligase IV (LIG4) expression correlated with poor prognosis in prostate cancer patients. LIG4 joins DNA double strand breaks and is essential for repair of these genetic lesions. Prostate cancers have not demonstrated clinically significant responses to anti-PD-1 immunotherapy. Prostate cancers express low PD-L1 levels and exhibit limited cytotoxic T lymphocyte infiltrates. To determine the effects of LIG4 inhibition on prostate tumorigenesis, we created a new genetically engineered in vivo model.Materials and Methods: Lig4+/+;TAg and Lig4+/−;TAg prostate glands and tumors were processed for histopathology. Separate groups of prostate tumor-bearing mice were treated with anti-PD1 antibody or preimmune IgG. LIG4 and PD-L1 expression was determined by quantitative reverse transcription polymerase chain reaction. Expression of DNA damage repair proteins, cell senescence, and cell death markers was determined by immunohistochemistry and immunofluorescence microscopy. The prostate cancer stem cell fraction was analyzed by Sca1/CD49f flow cytometry and tumorsphere culture. PD-L1 protein expression was determined by western blot.Results: LIG4 inhibition induced DNA double strand breaks and cellular senescence in prostate glands and cancers and significantly reduced prostate intraepithelial neoplasia and tumorigenesis. LIG4 inhibition reduced the prostate cancer stem cell fraction and proliferation in stem cell cultures. Prostate cancers resistant to LIG4 inhibition evaded anti-tumor immune response due to increased PD-L1 expression. PD-1 antibody treatment of these cancers induced CD8+ T lymphocyte infiltration and reduced tumor volume.Conclusion: Inhibition of LIG4 sensitized prostate cancers to immune checkpoint inhibition.
Keywords: DNA damagesenescenceprogrammed death receptor 1apoptosiscancer stem cells

25COASMA40

Title: LncRNA XIST Promotes Proliferation, Migration and Invasion of Esophageal Squamous Cell Carcinoma Cells via Regulation of miR-186-5p/ZEB1

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Anticancer Research March 2025, 45 (3) 897-908;
DOI: https://doi.org/10.21873/anticanres.17477
Abstract : Background/Aim: Accumulating evidence has indicated that long non-coding RNAs (lncRNAs) are crucial molecules for tumor progression in various human cancers. However, the function of lncRNA X-inactive specific transcript (XIST) in esophageal squamous cell carcinoma (ESCC) remains to be determined. The current study aimed to explore the function and molecular mechanism of lncRNA XIST in ESCC progression.Materials and Methods: The expression level of lncRNA XIST in ESCC cell lines was measured by qRT-PCR. The effects of lncRNA XIST on cell proliferation, migration, and invasion on ESCC were detected by CCK-8, transwell, and scratch assays. The expression levels of proteins were determined by western blot and luciferase reporter assays were used to identify specific target relationships.Results: LncRNA XIST was overexpressed in ESCC cell lines when compared to normal cell lines. The inhibitor of lncRNA XIST markedly inhibited ESCC cell proliferation, migration, and invasion. Furthermore, miR-186-5p was down-regulated in ESCC cells. LncRNA XIST could sponge miR-186-5p and knockdown of lncRNA XIST could increase the expression of miR-186-5p. We also confirmed Zinc finger E-box binding homeobox 1 (ZEB1) as the target for miR-186-5p, while overexpression of ZEB1 reversed the effects of miR-186-5p inhibition on the malignant behavior of EC9706 and KYSE30 cells.Conclusion: Our data revealed that lncRNA XIST promotes ESCC metastasis by regulating the miR-186-5p/ZEB1 axis. This study may provide a theoretical basis for the molecular mechanisms involved in esophageal cancer.
Keywords: Esophageal squamous cell carcinoma, long non-coding RNAX-inactive specific transcriptmicro, RNA-186-5p

25COASMA41

Title: Peripheral CD4+ T Cells Predict T Cell Immunity in Lung Tissues of Non-small Cell Lung Cancer Patients

Mari Tone, Tomomi Isono, Yoko Yamamoto, Yoshito Takeda, Yasushi Shintani, Atsushi Kumanogoh, Hisashi Wada And Kota Iwahori
Anticancer Research March 2025, 45 (3) 909-920;
DOI: https://doi.org/10.21873/anticanres.17478
Abstract : Background/Aim: Previous investigations showed that non-small cell lung cancer (NSCLC) patients with a high percentage of a peripheral CD4+ T cell subset were more likely to have severe immune-related adverse events (irAEs) due to anti-PD-1 therapy. The present study investigated the relationship between a peripheral CD4+ T cell subset and T cell immunity in the non-tumor lung tissues of patients with NSCLC to clarify the rationale of predictive biomarkers for anti-PD-1-related pneumonitis.Patients and Methods: We analyzed the T cell profiles and functions in peripheral blood and non-tumor lung tissues surgically resected from patients with NSCLC.Results: In patients with NSCLC with a high percentage of the peripheral CD4+ T cell subset (CD45RA+CD25+CD4+ T cells), non-tumor lung tissues had a high percentage of PD-1+CD4+ T cells and a low percentage of PD-1+ effector regulatory T (Treg) cells. The percentage of PD-1+ effector Treg cells negatively

correlated with IFNγ and TNFα production by CD4+ T cells in the lung tissues of patients with NSCLC.Conclusion: Patients with NSCLC with a high percentage of the peripheral CD4+ T cell subset are at an increased risk of anti-PD-1-related pneumonitis, which activates PD-1+CD4+ T cells in the absence of the suppressive activity of effector Treg cells in lung tissues.

Keywords: Non-small cell lung cancerperipheral CD4+ T cellsPD-1regulatory T cells

25COASMA42

Title: Cryptic Rearrangement of the KMT2A Gene in a B-cell Acute Lymphoblastic Leukemia

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Anticancer Research March 2025, 45 (3) 921-928;
DOI: https://doi.org/10.21873/anticanres.17479

Abstract: Background/Aim: A 30-year-old female diagnosed with B cell acute lymphoblastic leukemia (B-ALL) had a normal karyotype at diagnosis.Case Report: The case was investigated further by fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), and reverse-transcription polymerase chain reaction (RT-PCR) followed by Cycle sequencing. The diagnostic karyotype was normal (46,XX), but FISH studies on tumor cells using a KMT2A break-apart probes showed that the proximal part of KMT2A was inserted into an apparently normal chromosome 4 with concomitant loss of the distal part of the probe. aCGH identified losses within 11q23.3 and 4q21.3q22.1 with the breakpoints mapping inside the KMT2A and AFF1 loci. The presence of the putative KMT2A::AFF1 fusion gene was confirmed by FISH analysis and RT-PCR/Cycle sequencing; an in-frame fusion was detected between KMT2A (exon 9) and AFF1 (exon 6). The patient underwent allogenic stem cell transplantation and reached complete remission.Conclusion: This case highlights the need to supplement banding cytogenetics with appropriate molecular (cyto)genetic techniques whenever the karyotype does not reveal characteristic aberrations. Although KMT2A rearrangements in both lymphoblastic and myeloid acute leukemias usually arise through karyotypically visible chromosomal recombinations, this is not always the case.

Keywords: B-lymphoblastic leukemiacytogeneticsKMT2Afluorescence in situ hybridizationarray comparative genomic hybridizationfusion gene

25COASMA43

Title: Super Methotrexate-resistant Osteosarcoma Cells Retain Their Sensitivity to Recombinant Methioninase: Targeting Methionine Addiction to Overcome Extreme Cancer-Chemotherapy Resistance

Yusuke Aoki, Qinghong Han, Yutaro Kubota, Noriyuki Masaki, Yasunori Tome, Michael Bouvet, Kotaro Nishida And Robert M. Hoffman

Anticancer Research March 2025, 45 (3) 929-934;
DOI: https://doi.org/10.21873/anticanres.17480

Abstract: Background/Aim: Drug-resistance in osteosarcoma results in a very poor clinical prognosis and has been a recalcitrant problem over many decades. We have previously

reported the development of super methotrexate (MTX)-resistant osteosarcoma cells (143B-MTXSR), selected from parental 143B osteosarcoma cells (143B-P) 143B-MTXSR cells were previously selected by culturing the cells with increasing concentrations of MTX, resulting in osteosarcoma cells which are 5,500 times more MTX-resistant than the parental cells, due to extreme over-expression of dihydrofolate reductase (DHFR). In the present study, the potential therapeutic efficacy of methionine restriction, using recombinant methioninase (rMETase), was explored to overcome super MTX-resistant osteosarcoma cells.Materials and Methods: Previously-selected 143B-MTXSR cells were used for the present study. Sensitivity to methionine restriction by rMETase was determined using the WST-8 assay and compared between 143B-MTXSR and parental 143B-P cells.Results: 143B-MTXSR cells (rMETase IC50: 0.38 U/ml) were very sensitive to methionine restriction by rMETase, very similar to 143B-P (rMETase IC50: 0.36 U/ml).Conclusion: rMETase overcame a 5,500-fold MTX-resistance of osteosarcoma cells. The present results suggest methionine restriction by rMETase can be a potential clinical strategy to overcome recalcitrant drug-resistance in osteosarcoma.

Keywords: Osteosarcoma, methotrexate, resistance, methionine addiction, Hoffman Effect, methionine restriction, recombinant methioninase, rMETase

25COASMA44

Title: Highly Synergistic Eradication of 143B Osteosarcoma Cells In Vitro by the Combination of Recombinant Methioninase, Chloroquine, and Rapamycin Targeting Methionine Addiction, Autophagy, and mTOR, Respectively

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Anticancer Research March 2025, 45 (3) 935-941;
DOI: https://doi.org/10.21873/anticanres.17481

Abstract: Background/Aim: Drug-resistant osteosarcoma is a highly aggressive malignancy with limited therapeutic options. Recombinant methioninase (rMETase) targets the methionine addiction of cancer and acts synergistically with many cancer-chemotherapy agents. The present study investigated the synergistic efficacy of the combination of rMETase, chloroquine (CQ) which targets autophagy, and rapamycin (RAPA) which targets mTOR, on human 143B osteosarcoma cells in vitro.Materials and Methods: 143B human osteosarcoma cells. 143B cells were treated under eight conditions at the IC30 of each agent: untreated control; rMETase alone (0.31 U/ml); CQ alone (61.9 μM); RAPA alone (30.9 μM); rMETase (0.31 U/ml) + CQ (61.9 μM); rMETase (0.31 U/ml) + RAPA (30.9 μM); CQ (61.9 μM) + RAPA (30.9 μM); and rMETase (0.31 U/ml) + CQ (61.9 μM) + RAPA (30.9 μM). Cell viability was measured with the WST-8 reagent.Results: Each of the single-agents, rMETase, CQ, and RAPA demonstrated moderate cytotoxicity when administered alone to 143B cells. The dual combination of CQ plus RAPA had the highest efficacy compared to single agents and compared to rMETase plus CQ and rMETase plus RAPA, which had moderate efficacy. In contrast, the triple combination of rMETase, CQ, plus RAPA exhibited strong synergistic efficacy, eradicating 143B cells.Conclusion: The triple combination of rMETase, CQ, and RAPA demonstrated strong synergy and effectively eradicated 143B osteosarcoma cells. Therefore, the triple treatment with rMETase, CQ, and RAPA has

potential as a novel, effective therapeutic approach for osteosarcoma.
Keywords: Recombinant methioninase, chloroquine, rapamycin, synergy, osteosarcoma, methionine addiction, Hoffman effect

25COASMA45

Title: Elevated Plasma Interleukin-18 Levels in Head and Neck Squamous Cell Carcinoma: Correlation With IL-18 Binding Protein But Not Ferritin

Jonas Fleckner, Christian Idel, Anke Leichtle, Armin Steffen, Kirstin Plötze-Martin, Dirk Rades, Marie-Nicole Theodoraki,

Anticancer Research March 2025, 45 (3) 943-954;
DOI: https://doi.org/10.21873/anticanres.17482

Abstract: Background/Aim: Head and neck squamous cell carcinoma (HNSCC) is an aggressive epithelial malignancy of the upper aerodigestive tract, associated with poor survival. As part of the HNSCC microenvironment, the interleukin-18 (IL-18)/IL-18 binding protein (IL-18BP) signaling is becoming increasingly interesting as a potential biomarker and therapeutic target. However, the systemic expression levels of IL-18BP in the context of the immunological environment in HNSCC patients remain unexplored.Materials and Methods: ELISA measurements of plasma IL-18-BP were carried out with regard to associated inflammatory markers such as C-reactive protein, acute phase protein ferritin, and IL-18 in 34 patients with HNSCC before and during the course of radio(chemo)therapeutic treatment and in correlation to the clinicopathological parameters.Results: Plasma IL-18BP concentrations were significantly elevated in HNSCC patients compared to healthy controls and correlated strongly with IL-18 levels before and after treatment. However, plasma ferritin levels, which were also elevated, showed no correlation with IL-18 or IL-18BP. Notably, changes in IL-18BP and IL-18 levels following therapy exhibited a well-maintained balance, indicating a functional feedback mechanism.Conclusion: The results demonstrate a robust IL-18/IL-18BP feedback regulation in HNSCC, which likely aids tumor cells in evading anti-tumor immune responses. This balance, unaffected by radiotherapy or chemoradiotherapy, underscores the potential of IL-18BP as a therapeutic target and a prognostic biomarker in HNSCC.
Keywords: HNSCCIL-18-binding proteininterleukin-18ferritinliquid biomarker

25COASMA46

Title: The Appropriate Conditions for the Cell Sparing (FLASH) Effect Exist in Ultra-high Dose Rate Carbon Ion Irradiation

Kazumasa Minami, Masashi Yagi, Kazuki Fujita, Kana Nagata, Ryo Hidani, Noriaki Hamatani, Toshiro Tsubouchi,

Anticancer Research March 2025, 45 (3) 955-963;
DOI: https://doi.org/10.21873/anticanres.17483

Abstract: Background/Aim: Ultra-high dose rate irradiation (uHDR) (>40 Gy/s), commonly referred to as FLASH, has garnered attention in radiation therapy research due to its potential to mitigate damage to normal tissues while maintaining tumoricidal effects. Research on FLASH therapy using electron beams, X-rays, and proton beams has preceded studies using carbon ion beams. However, the clinical potential of FLASH carbon ion irradiation is increasingly being recognized, similar to other radiation modalities. This study aimed to

evaluate the cell-sparing effect of carbon ion beams under normoxic conditions – a phenomenon that has not been previously reported.Materials and Methods: Human salivary gland cell line (HSGc-c5), human dermal fibroblast (HDF) and human lung bronchial epithelial cell line (Nuli-1) were employed. In this study, we compared two types of linear energy transfer (19 and 50 keV/μm) and two oxygen concentrations (4% and 21%) to thoroughly investigate the cell-sparing effect, with cell death as the endpoint.Results: A significant cell-sparing effect was observed with carbon ion beam uHDR irradiation under normoxic conditions. Linear energy transfer (LET) influenced the manifestation of the sparing effect, with higher LET (50 keV/μm) demonstrating a stronger protective effect compared to lower LET (19 keV/μm). DNA damage, as indicated by γH2AX foci, was significantly reduced under uHDR compared to conventional dose rates.Conclusion: Carbon ion uHDR irradiation induces a cell-sparing effect under normoxic conditions, which is influenced by LET and oxygen concentration. These findings provide essential insights into the mechanisms underlying the FLASH effect and pave the way for advancing the clinical application of uHDR carbon ion therapy.

Keywords: Carbon ion beamultra-high dose-rate (uHDR)FLASH

25COASMA47

Title: Expression of the Niemann-Pick C1-like 1 Protein in Gastric Cancer

Takeharu Imai, Manabu Futamura, Ryutaro Mori, Itaru Yasufuku, Toshiyuki Tanahashi, Chiemi Saigo,

Anticancer Research March 2025, 45 (3) 965-975;
DOI: https://doi.org/10.21873/anticanres.17484

Abstract: Background/Aim: 5-Fluorouracil (5-FU) plays a major role in the treatment of gastric cancer (GC), and overcoming resistance to this drug remains a critical challenge. This study aimed to identify genes associated with resistance to 5-FU in GC.Materials and Methods: Gene expression levels were analyzed in 5-FU-resistant MKN-45/F2R cells compared to the parental MKN-45 strain before and after 5-FU treatment (24 and 72 h). Among the consistently over-expressed genes, those with high expression were further investigated for their roles in resistance and expression patterns in GC tissues.Results: NPC1L1, a protein hypothesized to influence 5-FU resistance, did not exhibit resistance-related effects in tested cells. Its expression was subsequently studied in gastric cells. NPC1L1 was detected in the stomach, jejunum, duodenum, and liver, with increased mRNA levels in several GC samples. Immunostaining of samples from 95 GC patients revealed that 39 (41.0%) exhibited ≥10% higher NPC1L1 expression. Patients with NPC1L1-positive tumors had poorer prognoses than those with negative tumors.Conclusion: NPC1L1 is expressed in both normal gastric tissues and GC tissues, with elevated levels at invasive sites associated with poor prognosis.

Keywords: NPC1L1protein expressiongastric cancer

25COASMA48

Title: Effects of YAP Inhibitors and Activators on the Growth of Leukemia Cells

Honoka Sezutsu, Mai Itoh And Shuji Tohda

Anticancer Research March 2025, 45 (3) 977-987;

DOI: https://doi.org/10.21873/anticanres.17485
Abstract: Background/Aim: The Hippo signaling pathway is involved in cell proliferation through the regulation of its downstream molecule YAP. The dysregulation of Hippo signaling is associated with cancer cell proliferation. This study aimed to investigate the effects of YAP inhibitors and activators on the proliferation of human leukemia cell lines in vitro to examine whether YAP functions as a tumor suppressor or promoter.Materials and Methods: In total, six leukemia cell lines (THP-1, HL-60, and U-937, derived from acute myeloid leukemia; K-562 from chronic myeloid leukemia; and KOPT-K1 and Jurkat from T-lymphoblastic leukemia) were treated with the YAP inhibitors CA3, Peptide17, and Verteporfin or YAP activators SBP-3264 and XMU-MP-1. Colorimetric assay was conducted to assess cell growth. Immunoblotting was used to evaluate the expression of signaling proteins.Results: Treatment with YAP activators suppressed cell growth in all cell lines, with apoptotic induction involving an increase in cleaved caspase-3. Moreover, the treatment down-regulated NOTCH1, cleaved NOTCH1, and MYC expression. Treatment with the YAP inhibitor CA3 suppressed the growth of HL-60 and KOPT-K1 cells without inducing apoptosis, accompanied by decreased MYC expression. As the other two YAP inhibitors did not suppress growth, off-target effects might contribute to inhibition by CA3.Conclusion: YAP activators suppressed the growth of leukemia cells through induction of apoptosis. This suggested that YAP might function as a tumor suppressor in leukemia. SBP-3264 and XMU-MP-1 could be novel candidate molecular-targeted drugs for leukemia; however, further investigations are required.
Keywords: YAPHippo signaling pathwayleukemia

25COASMA49

Title: Knockdown of RFC2 Prevents the Proliferation, Migration and Invasion of Cervical Cancer Cells

Jae Woong Koh And Seon-Joo Park
Anticancer Research March 2025, 45 (3) 989-1000;
DOI: https://doi.org/10.21873/anticanres.17486
Abstract: Background/Aim: Replication factor C subunit 2 (RFC2) is a component of the replication factor C (RFC) complex, which plays a critical role in DNA replication and repair. Recent studies have reported the involvement of RFC2 in several cancers. In this study, we investigated the functional role of RFC2 in cervical cancer progression.Materials and Methods: RFC2 expression in cervical cancer cells was analyzed using quantitative real-time PCR (qRT-PCR) and western blotting. HeLa, ME-180, and SiHa cells were transfected with siRNAs targeting RFC2. Cell viability and proliferation were assessed using the MTT and colony formation assays, and cell cycle distribution was analyzed by flow cytometry. Migration and invasion abilities were evaluated through Transwell assays with or without Matrigel.Results: RFC2 knockdown significantly reduced cell proliferation in cervical cancer cells. Flow cytometry analysis revealed cell cycle arrest at the S phase. Additionally, RFC2 knockdown markedly inhibited the migration and invasion of cervical cancer cells. These results demonstrate the critical involvement of RFC2 in regulating proliferation and metastatic potential in cervical cancer cells.Conclusion: RFC2 plays a pivotal role in promoting cervical cancer progression by enhancing cell growth, regulating the cell cycle,

and promoting metastatic behavior. Further studies on the molecular mechanisms of RFC2 in cancer-associated pathways may provide a novel therapeutic target for developing cervical cancer treatment strategies.

Keywords: RFC2cervical cancer, proliferation, migration, invasion

25COASMA50

Title: Evaluation of the Therapeutic Potential of DPP4 Inhibitor in Upper Tract Urothelial Carcinoma Cells

Hao-Lun Luo, Yen-Ting Wu, Yi-Yang Liu, Hui-Ying Liu And Yin-Lun Chang

Anticancer Research March 2025, 45 (3) 1001-1013;
DOI: https://doi.org/10.21873/anticanres.17487

Abstract: Background/Aim: Dipeptidyl peptidase-4 (DPP4) inhibitors like sitagliptin are recognized for their therapeutic role in diabetes. Elevated levels of DPP4 are strongly linked to the clinical aggressiveness of upper tract urothelial carcinoma (UTUC). However, sitagliptin's impact on UTUC is poorly understood and requires further research.Patients and Methods: This research utilized real-time PCR and immunohistochemistry to measure DPP4 mRNA and protein expression in UTUC. Sitagliptin's effects on cell proliferation and apoptosis were assessed using the alamarBlue assay and annexin V staining in UTUC cell lines. Migration ability was evaluated through wound-healing and transwell migration assays. The combined effect of sitagliptin and cisplatin on UTUC cell viability was also examined using both UTUC cell lines and patient-derived organoids.Results: Elevated DPP4 expression correlates with advanced tumor stages and reduced cancer-specific survival in UTUC. Sitagliptin treatment significantly reduced cell proliferation and enhanced apoptosis. Moreover, sitagliptin inhibited UTUC cell migration. Western blot results showed that sitagliptin treatment led to increased levels of apoptotic markers and reduced phosphorylation of AKT. It also influenced the phenotypical markers associated with epithelial-mesenchymal transition. Adding sitagliptin to cisplatin therapy did not show diminished antitumor efficacy compared with the effects of cisplatin alone.Conclusion: Sitagliptin inhibits the proliferation and migration of UTUC cells, promotes apoptosis, and influences the phenotypical transition from mesenchymal to epithelial states, likely via modulation of the AKT pathway. Sitagliptin may not cause chemotherapy resistance when combined with cisplatin treatment. These findings highlight its potential as an adjuvant therapy in UTUC.

Keywords: DPP4sitagliptinpatient-derived organoidupper tract urothelial carcinoma

25COASMA51

Title: NRASQ61K/R/L Mutant Allele Frequency in Melanoma and its Correlation With Clinicopathological Characteristics

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Anticancer Research March 2025, 45 (3) 1015-1024;
DOI: https://doi.org/10.21873/anticanres.17488

Abstract: Background/Aim: Approximately 80% of NRAS mutations in melanoma occur at codon 61, locking the NRAS protein into a GTP-bound state.We aimed to evaluate the mutant allele frequency (MAF) of NRASQ61R/K/L as a possible prognostic biomarker,

expanding the classical histopathological prognostic criteria.Materials and Methods: Twenty-six NRASQ61R/K/L mutated melanomas were analysed using next generation sequencing, to assess the possible correlation between MAF and clinicopathological characteristics.Results: A statistically significant difference (p-value <0.05) was found between the ratio of patients with MAF ≤30% (12/26, 46%) and MAF >30% (14/26, 54%). MAF ≤30% was more common in primary melanomas (10/12, 83.3%) and was also observed in patients with MAF >30%. Cases with MAF ≤30% had a higher percentage of Breslow's depth ≤1 mm (5/12, 41.7%) and a low Clark level (III) (6/12, 50%). Patients with MAF >30% and a high Clark level (V) showed a higher percentage (5/14, 57.2%). Nodular/epithelioid cell types were more frequently observed in MAF ≤30% (9/12, 75%) and MAF >30% (8/14, 57.2%) groups. A slightly higher number of MAF ≤30% cases were found with tumor cell percentages ranging from 11-40% (5/14, 41.7%), while MAF >30% cases were more common in patients with ≥71% tumor cells (9/14, 64.3%) and this difference was statistically significant.Conclusion: The MAF of NRAS was highly heterogeneous but was found to correlate with the percentage of tumor cells. To corroborate these data, the evaluation of NRAS MAF in a larger cohort of melanomas is necessary and fundamental.

Keywords: NRAS mutationsmutant allele frequencymelanomanext generation frequency

25COASMA52

Title: Angiogenin-induced Osteoclastogenesis Mediates Bone Destruction in Oral Squamous Carcinoma

Kasumi Aoki, Nana Yoshitani, Naito Kurio, Norie Yoshioka, Jumpei Teramachi, Mika Ikegame, Hirohiko Okamura And Soichiro Ibaragi

Anticancer Research March 2025, 45 (3) 1025-1033;
DOI: https://doi.org/10.21873/anticanres.17489

Abstract: Background/Aim: Bone destruction caused by oral cancer severely impacts patient quality of life. This study aimed to clarify the role of angiogenin (ANG) in osteoclastogenesis and oral cancer-induced bone destruction.Materials and Methods: Recombinant ANG was used to assess its effects on osteoclast formation and bone resorption activity in bone marrow cultures. ANG-knockdown oral squamous carcinoma HSC-2 cells (ANG-RNAi) were transplanted into intramedullary cavities of femurs. Bone destruction was radiologically analyzed, while angiogenesis and osteoclast induction in the surrounding area of the transplanted lesion were histologically examined.Results: Recombinant ANG promoted osteoclast formation and bone resorption activity. Transplantation of ANG-RNAi cells significantly reduced tumor growth and bone destruction properties compared to transplantation of control cells. Histological analysis revealed lower angiogenesis and fewer osteoclast induction in the ANG-RNAi cells-transplanted group.Conclusion: ANG mediates oral cancer-induced bone destruction by promoting osteoclast formation and resorption. These findings suggest that ANG could be a potential therapeutic target for suppressing tumor growth, angiogenesis, and bone destruction in oral cancer therapy.

Keywords:Angiogeninosteoclastogenesisoral squamous cell carcinoma, osteoclasts

25COASMA53

Title: A Phase II Trial of Trastuzumab Combined With Irinotecan in Patients With Advanced HER2-positive Chemotherapy-refractory Gastric Cancer (OGSG1203 HERBIS-5): Final Results

Junji Kawada, Daisuke Sakai, Yutaka Kimura, Motohiro Hirao, Kazuhiro Nishikawa, Naotoshi Sugimoto, Yoshio Oka,

Anticancer Research March 2025, 45 (3) 1077-1085;
DOI: https://doi.org/10.21873/anticanres.17495

Abstract: Background/Aim: Irinotecan is a key drug for patients with advanced gastric cancer. We assessed the efficacy and safety of combination chemotherapy with trastuzumab and irinotecan in patients with advanced human epidermal growth factor receptor type 2 (HER2)-positive chemotherapy-refractory gastric cancer.Patients and Methods: Eligibility criteria included unresectable or recurrent HER2-positive gastric cancer patients who were refractory to at least one regimen of chemotherapy. Irinotecan was administered at a dose of 150 mg/m2 every 2 weeks, and trastuzumab at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. The primary endpoint was the disease control rate (DCR). The secondary endpoints were adverse events (AEs), overall response rate (ORR), time-to-treatment failure (TTF), progression-free survival (PFS), and overall survival (OS).Results: Thirty patients were enrolled, of whom 18 previously received a single chemotherapy regimen whereas 12 received two or more regimens. As one patient withdrew before the study treatment, 29 patients were assessable for efficacy and safety. The DCR was 65.5%, and the ORR was 20.7%. The median PFS and OS were 3.7 and 7.5 months, respectively. The major grade 3/4 AEs were neutropenia (24%), anemia (24%), leukopenia (21%), anorexia (11%), fatigue (14%), hypoalbuminemia (24%), and hypokalemia (14%). One treatment-related death occurred.Conclusion: These findings indicate that irinotecan plus trastuzumab is feasible with modest potential efficacy against chemotherapy-refractory advanced HER2-positive gastric cancer.

Keywords: HER2-positivegastric cancer, chemotherapy, trastuzumab, irinotecan

25COASMA54

Title: Male Breast Cancer: A Single Institutional Clinicopathological Profiling

Shubha De Sarkar, Soirindhri Banerjee, Ayden Ismail, Avenie Mavadia, Sunyoung Choi, Aruni Ghose And Stergios Boussios

Anticancer Research March 2025, 45 (3) 1097-1104;
DOI: https://doi.org/10.21873/anticanres.17497

Abstract: Background/Aim: Male breast cancer (MBC) is an infrequent occurrence accounting for <1% of overall breast cancers. With limited data, MBC remains a therapeutic challenge, warranting the need for meticulous recording of all cases encountered.Patients and Methods: A retrospective observational study in an Indian tertiary public hospital where 29 MBC cases registered between August 2020 and July 2023 were recorded and their epidemiological data, clinical profile, treatment history and survival data were analyzed.Results: MBC was 3% of all breast cancer cases reported in three years, and the most common age group affected was between 41 and 60 years. Most cases presented at Stage IIIB, with the majority showing axillary nodal involvement. Invasive ductal carcinoma

was the most frequent histology with luminal B and triple-negative variants having the highest incidence. Most patients underwent upfront surgery followed by adjuvant chemotherapy. At the end of one year, 50% of patients were found to survive with no disease progression.Conclusion: Our results corroborate with previously recorded experience with MBC in terms of age distribution, stage of presentation, histology and treatment offered. However, our results demonstrated a higher proportion of triple-negative breast cancer (TNBC) cases, as compared to previous literature. The increment of TNBC cases among males, therefore, reassures the need for breast cancer (BRCA) gene testing among all males afflicted with breast cancer.

Keywords: Male breast cancer, low middle-income country, triple-negative breast cancerBRCA1/2 genetic testing, prognosis

25COASMA55

Title: Efficacy of Molecular-targeted Agents in Vertebral Metastasis Management in Non-small Cell Lung Cancer

Midori Yui, Satoaki Nakamura, Yuhei Koike, Kazuki Hirota, Ken Yoshida, Asami Yoshida, Kenichi Ueda,

Anticancer Research March 2025, 45 (3) 1105-1115;
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Abstract: Background/Aim: The effect of modern molecular-targeted agents (MTAs), on vertebral metastases in non-small cell lung cancer (NSCLC) remains inadequately characterized. We investigated the local control effects of MTAs on vertebral metastases in patients with NSCLC.Patients and Methods: We retrospectively analyzed 307 vertebral metastases in 85 patients with NSCLC, treated between 2019 and 2021. Patients were categorized based on prior systemic therapy exposure (19 with vs. 66 without) and the type of first-line therapy administered (32 MTA vs. 34 non-MTAs). Multivariate analyses were performed for the vertebral progression-free period (vPFP) and overall survival (OS) using a Cox proportional hazards model with propensity scores as covariates. p-Value correction for multiple pairwise comparisons was performed using the Bonferroni method.Results: In treatment-naïve patients, MTAs presented superior outcomes compared with non-MTAs [1-year vPFP: 93.6% vs. 85.1%, p=0.02; 1-year overall survival (OS): 90.3% vs. 60.9%, p=0.004]. Patients without prior systemic therapy had significantly better outcomes than previously treated patients (1-year vPFP: 89.5% vs. 49.1%, p<0.001; 1-year OS: 75.2% vs. 34.2%, p=0.011). The multivariate analysis identified prior systemic therapy as a significant predictor of poor outcomes [vPFP: hazard ratio (HR)=6.78, p<0.001; OS: HR=2.13, p=0.030].Conclusion: Modern systemic therapies, particularly MTAs, present significant efficacy in controlling vertebral metastases in patients with NSCLC without prior systemic therapy. Deferring local treatments may be feasible in patients without prior systemic therapy, whereas those who develop vertebral metastases after treatment may require additional treatment.

Keywords: Non-small cell lung cancer, vertebral metastasis, molecular-targeted therapy, systemic therapy

25COASMA56

Title: Stereotactic Body Radiotherapy Using CyberKnife for Metastatic Liver Tumors: A Single-center Retrospective Study

Yasuhiro Ryuno, Takanori Abe, Keita Tsukahara, Jun Watanabe, Misaki Iino, Satoshi Saito, Tomomi Aoshika,

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Abstract: Background/Aim: Liver metastases are a major cause of cancer-related mortality and present significant therapeutic challenges. Chemotherapy is preferred for multiple metastases, while surgery or stereotactic body radiotherapy (SBRT) is used for solitary or few metastases, particularly in oligometastatic cases. This study aimed to evaluate the safety and efficacy of CyberKnife SBRT (CK-SBRT) for liver oligometastases.Patients and Methods: This retrospective study analyzed patients with one to three liver metastases treated with CK-SBRT. The prescribed dose was typically 60 Gy in four fractions to 95% of the target volume, with reductions allowed if organ-at-risk (OAR) constraints could not be met. The local control (LC) and overall survival (OS) rates were estimated using the Kaplan–Meier method, and liver dose-volume parameters were assessed.Results: A total of 39 liver lesions in 27 patients were treated. At a median follow-up of 17 months, the 1-year LC and OS rates were 90% and 80%, respectively. In patients receiving 60 Gy in four fractions, these rates were 95% and 86%. No severe liver toxicity or radiation-induced liver disease occurred. Most patients met liver dose constraints, with low liver V15 and mean liver dose values.Conclusion: CK-SBRT provides effective tumor control with minimal toxicity for liver oligometastases. Careful dose planning and adherence to OAR constraints are essential to minimize toxicity risks.

Keywords: Liver metastasis, stereotactic body radiotherapy, oligo, metastasis, Cyber, Knife

25COASMA57

Title: Genomic Profiling of Small Cell Neuroendocrine Prostate Cancer and its Implications for Targeted Therapies

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Anticancer Research March 2025, 45 (3) 1137-1147;
DOI: https://doi.org/10.21873/anticanres.17501

Abstract: Background/Aim: This study aimed to investigate the genomic features of small cell neuroendocrine prostate cancer (SCPC) in Japanese patients, assess their relationships with platinum-based chemotherapy efficacy, and evaluate the potential treatment eligibility for therapies using cancer genomic profiling.Patients and Methods: This retrospective study included 21 patients diagnosed with SCPC between 2018 and 2022. An expert pathologist reviewed the biopsy specimens according to the World Health Organization prostate cancer classification. Biopsy samples from primary or metastatic lesions were analyzed using FoundationOne® CDx to identify genomic mutations, focusing on DNA damage repair (DDR) mutations and other clinically relevant alterations. Platinum-based chemotherapy efficacy was assessed using progression-free survival (PFS) and overall survival (OS) outcomes.Results: DDR mutations were detected in eight (38.1%) patients, and BRCA

mutations were present in three (14.3%) cases. TP53 and RB1 mutations were identified in 15 (71.4%) and 12 (57.1%) cases, respectively. Three (14.8%) patients were identified with microsatellite instability-high or tumor mutational burden-high, making them eligible for immune checkpoint inhibitor treatment. PFS/OS rates suggested that the presence of these mutations did not significantly impact platinum-based chemotherapy efficacy. Six (28.6%) patients were eligible for treatments approved for prostate cancer in Japan as of 2024.Conclusion: This study is the first to reveal the SCPC genomic landscape in Japanese patients. Although genomic mutations, including DDR mutations, were not predictive of platinum-based chemotherapy efficacy, active genomic testing may improve access to targeted therapies for this challenging malignancy, especially where treatment options are limited.

Keywords: Neuroendocrine prostate cancer, comprehensive genomic profiling, DNA damage repair gene, targeted therapy

25COASMA58

Title: Radiotherapy for Bone Metastases in Patients With Excellent Performance Status: Patterns of Care and Prognostic Factors for Survival

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Anticancer Research March 2025, 45 (3) 1149-1158;
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Abstract: Background/Aim: The aim was to analyze patterns of care, e.g., fractionation of radiotherapy and treatment completion, and prognostic factors for survival in patients irradiated for bone metastases who had excellent Eastern Cooperative Oncology Group (ECOG) performance status (PS), defined as ECOG PS 0.Patients and Methods: A retrospective analysis was performed (2010-2024, n=1,244 radiotherapy courses) that included patients with bone metastases treated with conventional palliative or stereotactic single- or multi-fraction regimens (SBRT).Results: Patients with ECOG PS 0 (n=129, 10%) had 0% 30-day mortality, 99% 3-months survival, and 83% 12-months survival. Only three of 129 (2%) did not complete radiotherapy. Most patients had prostate or breast cancer with bone-only metastases. In restricted analysis without inclusion of blood test results, five significant predictors of unfavorable survival emerged: steroid medication, no continuation of systemic therapy, progressive disease outside of the irradiated target volume(s), adrenal gland metastasis, and prescription of fewer radiotherapy fractions. With blood tests included, the final multivariate model suggested that survival varied with lactate dehydrogenase (strata: normal/elevated), adrenal gland metastases (yes/no), progressive disease outside of the irradiated target volume(s) (yes/no), and fraction number (>10/≤10).Conclusion: Many patients with ECOG PS 0 experience long-term survival, influenced by disease behavior and choice of fractionation, among others. The impact of fractionation was due to imbalances in baseline characteristics, e.g., proportion of patients with de novo hormone-sensitive prostate cancer with low-volume disease receiving fractionated radiotherapy to both prostate and bone metastases. No clear impact of equivalent radiation dose in 2-Gy fractions on survival emerged.

Keywords: Palliative radiation therapy, stereotactic radiotherapy, quality of care, treatment completion, fractionation, metastatic cancer

25COASMA59

Title: Clinical Outcomes of Patients Receiving Stereotactic Body Radiotherapy Dose De-escalation for Hepatocellular Carcinoma at the Hepatic Hilum

Takeshi Fujisawa, Hidehiro Hojo, Masaki Nakamura, Kenji Makita, Hidenari Hirata, Hidekazu Oyoshi,

Anticancer Research March 2025, 45 (3) 1159-1169;
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Abstract: Background/Aim: Stereotactic body radiation therapy (SBRT) for centrally located hepatocellular carcinomas (HCCs) can cause severe central biliary toxicity. However, dose de-escalation SBRT has the potential to reduce biliary toxicity with excellent tumor control. Therefore, we aimed to retrospectively evaluate the efficacy and toxicity of de-escalated SBRT in patients with hepatic hilum HCC.Patients and Methods: Patients diagnosed with peripherally located HCC received SBRT (40 Gy in five fractions), and those with centrally located HCC received de-escalated SBRT (35 Gy in five fractions) between January 2016 and August 2023 in National Cancer Center Hospital East.Results: Of the total 42 consecutive patients evaluated, 16 (38%) were diagnosed with centrally located HCC. The median observation time was 25 months (interquartile range=10-43). The 2-year cumulative incidences of local recurrence were 17.3% and 8.1% in patients with centrally and peripherally located HCC, respectively. No statistically significant differences were observed in the cumulative incidence of local recurrence, OS, or PFS between patients with centrally and peripherally located HCC. Univariate analysis of OS showed that a smaller clinical target volume of <20 ml was significantly associated with a better OS compared to a larger volume (p=0.017). No patient experienced grade 3 or higher treatment-related adverse events.Conclusion: Dose de-escalation SBRT for centrally located HCC showed good local control with no grade 3 or more RT related toxicities, suggesting it may be a safe alternative.

Keywords: Local recurrence, hepatocellular carcinoma, stereotactic body radiation therapy

25COASMA60

Title: Proprotein Convertase Subtilisin/Kexin Type 9 Induction in Hypercholesterinemic Patients With Primary and Metastatic Liver Tumors

Thomas S. Weiss And Christa Buechler

Anticancer Research March 2025, 45 (3) 1171-1180;
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Abstract: Background/Aim: Serum proprotein convertase subtilisin/kexin type 9 (PCSK9) levels are positively associated with serum cholesterol levels, which contribute to the growth of cancers. PCSK9 levels are low in patients with liver cirrhosis, with a high incidence of hepatocellular carcinoma (HCC). PCSK9 expression is increased in colorectal cancer (CRC), but serum levels in these patients have not been analyzed. Therefore, serum PCSK9 may serve as a diagnostic marker to differentiate between liver metastases from CRC and HCC.Patients and Methods: Serum PCSK9 was measured by ELISA in 36 patients with CRC metastases, 32 patients with HCC and 59 healthy controls.Results: The serum PCSK9 levels of these three cohorts were similar. Serum PCSK9 levels were not associated with the tumor node metastasis (TNM) stage. Liver steatosis, inflammation and fibrosis scores did not correlate with serum PCSK9 levels. Cancer patients with hypercholesterolemia had elevated

PCSK9 levels. These patients had higher TNM stages and Union for International Cancer Control scores in both cohorts. PCSK9 levels were also elevated in patients with viral hepatitis. When patients with hepatitis and hypercholesterolemia were excluded, serum PCSK9 levels were low in cancer patients compared to controls. Serum PCSK9 levels did not correlate with the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in HCC and CRC patients. In the latter cohort, PCSK9 and alpha-fetoprotein were positively correlated.Conclusion: Serum PCSK9 is increased in patients with CRC metastases or HCC with hypercholesterolemia. This suggests that patients with high cholesterol levels may benefit most from PCSK9 blockage.
Keywords: Hepatocellular carcinoma, colorectal cancer, hypercholesterolemia

25COASMA61

Title: Real-world Outcomes in Recurrent/Metastatic Squamous Cell Carcinoma of Head and Neck With Nivolumab: Galician Study

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Anticancer Research March 2025, 45 (3) 1181-1191;
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Abstract: Background/Aim: Real-world evidence regarding the use of nivolumab in metastatic squamous cell carcinoma of head and neck (R/M SCCHN) is limited. This study aimed to describe the clinical characteristics, outcomes, and safety of nivolumab in R/M SCCHN patients treated in routine clinical practice.Patients and Methods: This retrospective, observational study evaluated the efficacy/safety of nivolumab in 116 patients with R/M SCCHN treated at nine centers within the Galician Group of Head and Neck Cancer health network between 2017 and 2019.Results: Basal characteristics of patients included a median age of 60 years, ECOG performance status −2 (14%) and −3 (1%) and a first diagnosis of stage IV a/b/c (74%). Nivolumab was used as first line, second line, and third line therapy in 17%, 66%, and 17% of patients, respectively. After a median follow-up of 14 months (range=1-69 months), the median progression-free survival was 2.30 months (95%CI=1.45-3.14) and the median overall survival was 8.1 months (95%CI=5.93-10.23). Outcomes were better when nivolumab was administered earlier in treatment course. Grade 3/4 adverse events were observed in 21.27% of patients.Conclusion: These findings support the efficacy and safety of nivolumab in the real-world treatment of R/M SCCHN.
Keywords: Nivolumab, recurrent or metastatic disease, squamous cell carcinoma of the head and neck, real-life data, adverse events

25COASMA62

Title: Impact of Postoperative Therapy on Survival Outcomes in Non-small Cell Lung Cancer Patients With Microscopic Residual Disease

Hiroki Watanabe, Shota Nakamura, Yoshito Imamura, Shoji Okado, Yuji Nomata, Yuta Kawasumi,

Anticancer Research March 2025, 45 (3) 1193-1204;
DOI: https://doi.org/10.21873/anticanres.17506

Abstract: Background/Aim: The aim of the study was to describe the specific characteristics

of patients with microscopic residual disease (R1) after surgical resection for non-small cell lung cancer and to evaluate the effect of postoperative therapy in R1 patients.Patients and Methods: We retrospectively reviewed the clinical data of 3,296 patients. Enrolled R1 patients were divided into two groups: those who received postoperative therapy (PT) and those who did not receive postoperative therapy (NPT).Results: A total of 52 R1 patients were enrolled. Of those, 27 (51.9%) underwent extended resections in addition to the standard surgery, 37 patients were assigned to the PT group and 15 to the NPT group. The PT group exhibited significantly longer overall survival (OS) than the NPT group ($p<0.01$, 5-year OS rate: 62.7% vs. 17.9%). There was no difference in progression-free survival (PFS) between the two groups ($p=0.34$, 5-year PFS rate: 38.7% vs. 22.2%). Age (<70 years old) and postoperative therapy positively impacted OS ($p=0.03$, and $p=0.01$, respectively).Conclusion: R1 resection after surgical resection for non-small cell lung cancer was more likely to occur in the patients receiving extended surgical resection. The PT group demonstrated a significantly better prognosis than the NPT group.

Keywords: R1 resection, microscopic residual disease, non-small cell lung cancer, postoperative therapy

25COASMA63

Title: Clinical Significance of Residual Lymph Node Metastasis in Predicting Recurrence After Preoperative Chemotherapy and Surgery for Gastric Cancer

Keisuke Komori, Takanobu Yamada, Shuji Ando, Shinsuke Nagasawa, Kyohei Kanematsu, Junya Morita,

Anticancer Research March 2025, 45 (3) 1205-1214;
DOI: https://doi.org/10.21873/anticanres.17507

Abstract: Background/Aim: Neoadjuvant chemotherapy is gaining recognition for its potential to improve survival outcomes, with combined neoadjuvant and adjuvant therapies under investigation. However, the prognostic significance of post-chemotherapy pathological staging (ypStage) on recurrence-free survival (RFS) remains unclear. This study aimed to evaluate the utility of ypStage, ypT, ypN classification, and histological response rate in predicting recurrence after gastrectomy.Patients and Methods: This retrospective study included 125 patients who underwent radical gastrectomy after preoperative chemotherapy at the Kanagawa Cancer Center between January 2007 and November 2019. RFS was analyzed based on ypStage, ypT, ypN classification, and histological response rate, with prognostic factors also assessed.Results: The 5-year RFS rates were 81.6% for ypStage I, 49.0% for ypStage II, and 42.9% for ypStage III. Significant differences were observed between ypStage I and ypStage II ($p=0.025$) but not between ypStage II and ypStage III ($p =0.633$). In ypStage II/III cases, the 5-year RFS rate was significantly higher for ypN0/1/2 (55.4%) compared to ypN3 (21.5%) ($p=0.003$). ypN was selected as an independent predictor for relapse in multivariate analysis.Conclusion: ypStage effectively predicts recurrence in ypStage I cases after preoperative chemotherapy and surgery for gastric cancer. However, prognosis in patients with ypStage II/III is better stratified using the ypN classification, particularly ypN3.

Keywords: Gastric cancer, ypTNM, histological response rates

25COASMA64

Title: Perioperative and Oncologic Outcomes of Robot-assisted Versus Laparoscopic Radical Cystectomy in Patients With Bladder Cancer

Noriya Yamaguchi, Shuichi Morizane, Hiroshi Yamane, Ryutaro Shimizu, Ryoma Nishikawa,

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Abstract: Background/Aim: Few studies have verified the relationship between treatment outcomes of robot-assisted radical cystectomy (RARC) and laparoscopic radical cystectomy (LRC). This study aimed to compare the perioperative and oncologic outcomes between RARC and LRC.Patients and Methods: Medical records of 75 patients (45 RARC and 30 LRC) who underwent radical cystectomy and standard or higher lymph node dissection between April 2013 and December 2019 at the Tottori University and other satellite hospitals were reviewed.Results: The operative time was shorter in the LRC group. Mean estimated blood loss was lower in the RARC group. No differences were noted in the complication rates. The mean number of lymph nodes removed was 23.1 in the RARC group and 13.9 in the LRC group ($p<0.001$). Cox proportional hazards regression analysis showed that the tumor variant of the transurethrally resected bladder tumor (TUR-BT) tissue ($p=0.032$) and lymph node metastasis ($p= 0.041$) were significantly associated with a higher risk of cancer-specific survival (CSS). No difference in the CSS ($p= 0.337$) and recurrence-free survival ($p=0.448$) was found in all patients having either RARC or LRC. However, the CSS of RARC was higher than that of LRC ($p=0.032$) in patients with locally advanced stages of bladder cancer such as pathological T stage ≥3 or pathological lymph node positivity.Conclusion: In patients with locally advanced bladder cancer pathological T stage ≥3 or pathological lymph node positivity, LRC appears to be associated with shorter CSS than RARC.

Keywords: Robot-assisted, laparoscopic, radical cystectomy, locally advanced

25COASMA65

Title: Prognostic Relationship Between the Cachexia Index and Osteopenia in Patients With Pancreatic Cancer

Teruhisa Sakamoto, Mikiya Kishino, Yuki Murakami, Kozo Miyatani, Yuji Shishido, Kyoichi Kihara,

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Abstract: Background/Aim: The cachexia index (CXI) is a novel biomarker for cancer cachexia. Osteopenia is defined as low bone mineral density (BMD), which is closely associated with cancer cachexia. Osteopenia has received recent attention because of its association with survival outcomes in cancer. The aim of this study was to investigate the relationship between the CXI and BMD in combination as a prognosticator in patients with pancreatic cancer.Patients and Methods: This study included 121 patients who had undergone pancreatectomy for pancreatic cancer. Data were retrospectively analyzed to evaluate the prognostic relationship between the CXI and BMD.Results: Five-year overall survival in the high CXI group was significantly better than that in the low CXI group ($p= 0.004$).

Additionally, patients with osteopenia (i.e., low BMD) had significantly worse 5-year overall survival rates than patients without osteopenia (p=0.026). Multivariate analysis revealed that the CXI was an independent prognostic factor for patients with pancreatic cancer (p=0.020). Regarding the combination of the CXI and osteopenia, patients with both low CXI and osteopenia had a worse prognosis compared with patients with other combinations of the CXI and osteopenia (p=0.007). The area under the curve of the combination of the CXI and BMD to predict 5-year overall survival was greater than those of the CXI or BMD alone.Conclusion: There is a close prognostic relationship between the CXI and osteopenia in patients with pancreatic cancer, and patients with both a low CXI and osteopenia have low survival rates.

Keywords: CXI, osteopenia, pancreatic cancer

25COASMA66

Title: Oncologic Relevance and Anal Preservation Potential of Transanal Total Mesorectal Excision for Rectal Cancer Invading Adjacent Organs

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Anticancer Research March 2025, 45 (3) 1233-1239;
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Abstract: Background/Aim: Locally advanced rectal cancer (LARC) with adjacent organ invasion presents significant surgical challenges, particularly in achieving negative circumferential resection margins (CRM). Transanal total mesorectal excision (TaTME) offers improved visualization and dissection in the deep pelvis, potentially enhancing oncologic and functional outcomes. This study evaluates the feasibility, oncologic safety and the possibility of anal preservation of TaTME in cT4b rectal cancer requiring combined organ resection.Patients and Methods: This retrospective study analyzed 19 patients with cT4b rectal adenocarcinoma undergoing combined organ resection between January 2015 and December 2023. Surgical approaches included TaTME (n=4) and conventional transabdominal techniques (n=15). Patients requiring total cystectomy or combined uterine and posterior vaginal wall resection were included. Surgical parameters, postoperative complications, and oncologic outcomes were compared. Statistical analyses were conducted using Fisher's exact test and Student's t-test, with significance set at $p<0.05$.Results: TaTME demonstrated superior anorectal preservation rates (100% vs. 33%; p=0.1772) and comparable surgical outcomes, including operative time (585 min vs. 550 min) and blood loss (397 ml vs. 380 ml). Negative distal margins were achieved in all cases, although tumor-positive resection surfaces were observed in 13% of conventional cases (p=0.0787). Local recurrence was absent, with minimal distant metastases reported.Conclusion: TaTME is a safe and effective approach for cT4b rectal cancer, enabling enhanced pelvic dissection and anorectal preservation. While technical challenges remain, TaTME complements conventional methods, particularly for low rectal tumors, offering potential for improved functional outcomes and quality of life in select patients.

Keywords: Ta, TMEcT4b rectal cancer, invading adjacent organs

25COASMA67

Title: Urethral Visualization Using Near-infrared Light Observation During Transanal/Perineal Total Mesorectal Excision

Keisuke Goto, Shunjin Ryu, Yuta Imaizumi, Sotaro Iwauchi, Takehiro Kobayashi, Ryusuke Ito And Yukio Nakabayashi

Anticancer Research March 2025, 45 (3) 1241-1249;
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Abstract: Background/Aim: Transanal total mesorectal excision is a useful technique while performing lower rectal cancer and deep pelvic surgery. However, it is a relatively difficult procedure, and unique complications such as urethral injury have been reported. Although there have been a few reports on urethral visualization, we investigated whether it is possible to visualize the urethra using a fluorescent urethral catheter.Patients and Methods: We retrospectively examined the background and short-term surgical outcomes in 17 patients who, between April 2022 and December 2023, underwent transanal total mesorectal excision and transperineal total mesorectal excision with fluorescent ureteral catheters in place due to high risk of urethral injury.Results: The urethra was recognized in one out of 11 patients (9.1%) in laparoscopic abdominoperineal resection and all three patients (100%) in laparoscopic total pelvic extenteration. No urethral injury was observed.Conclusion: Visualization of the urethra by inserting a fluorescent ureteral catheter may prevent urethral injury in patients undergoing transanal/transperineal total mesorectal excision who are at high risk of urethral injury.

Keywords: Transanal/transperineal total mesorectal excision, urethral injury, fluorescent urethral navigation, urethral visualization

25COASMA68

Title: The CONUT Score Can Predict the Prognosis of Gastric Cancer Patients After Curative Treatment

Ryuki Esashi, Toru Aoyama, Sosuke Yamamoto, Yukio Maezawa, Itaru Hashimoto, Keisuke Kazama,

Anticancer Research March 2025, 45 (3) 1251-1260;
DOI: https://doi.org/10.21873/anticanres.17512

Abstract: Background/Aim: Malnutrition is a reported prognostic factor in patients with cancer. The controlling nutritional status (CONUT) score, an index calculated from routine laboratory tests, is correlated with the prognosis of various cancers. This study examined the relationship between the CONUT score and prognosis of patients with gastric cancer (GC) after radical gastrectomy.Patients and Methods: Patients with GC who underwent curative gastrectomy were retrospectively reviewed. Patient characteristics, laboratory data, pathological findings, perioperative clinical course, and survival outcomes were recorded. The CONUT score was calculated using serum albumin (mg/dl), total cholesterol (mg/dl), and lymphocyte count (cells/mm3). Based on previous studies, patients were categorized into normal (CONUT score <2) and malnutrition (CONUT score ≥2) groups. Prognostic factors were compared between the groups.Results: In total, 155 patients were included (median age, 69 years; male, n=110; female, n=45). Five-year overall survival (OS) was significantly lower in the malnutrition group (malnutrition group, 42.2%; normal group, 82.7% p<0.001).

A multivariate analysis identified the CONUT score as an independent prognostic factor for OS [HR=2.506; 95% confidence interval (CI)=1.288-4.873, p=0.007]. Similar results were obtained for recurrence-free survival (RFS). Additionally, postoperative complications were more frequent (malnutrition group, 44.2%; normal group, 25.9%; p=0.027) and the chemotherapy introduction rate for pStage III or III was lower (malnutrition group, 55.6%; normal group, 78.8%, p=0.054) in the malnutrition group.Conclusion: The CONUT score may be an independent prognostic factor for OS and RFS in patients with GC after curative gastrectomy. CONUT scores of ≥2 were associated with higher postoperative complications and lower chemotherapy rates, which may contribute to a poor prognosis.
Keywords: CONUTgastric cancersurvival

25COASMA69

Title: Tailoring Neoadjuvant Therapy for Rectal Cancer: A Single-center Study of Local Recurrence Patterns

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Anticancer Research March 2025, 45 (3) 1261-1271;
DOI: https://doi.org/10.21873/anticanres.17513

Abstract: Background/Aim: Postoperative local recurrence remains an important issue in rectal cancer, and the optimal treatment strategy, surgical approach, and prognosis after treatment are yet to be addressed.Patients and Methods: We reviewed 21 patients who underwent surgical resection at our department for postoperative pelvic local recurrence of rectal cancer between January 2013 and December 2022, and performed a retrospective analysis of outcomes in terms of preoperative treatment and surgical approach.Results: Of the 21 patients, four (19%) were treated with upfront surgery (Upfront surgery group), 13 (62%) with chemotherapy (Chemotherapy group), and four (19%) with neoadjuvant chemoradiotherapy (NACRT; NACRT group). The surgical approach was open laparotomy (Open group) in 10 (47.6%) patients and minimally invasive surgery (MIS, MIS group) in 11 (52.4%). Seventeen (81.0%) had a negative resection margin (RM). Overall median postoperative survival was 71 months and median relapse-free survival was 6.2 months. The most common form of recurrence was pelvic local re-recurrence in seven patients (33.3%). By preoperative treatment type, the RM securement rate was higher in the Chemotherapy and NACRT groups than in the Upfront surgery group, and the postoperative recurrence rate was lowest in the NACRT group. By surgical approach, intraoperative blood loss and incidence of Clavien–Dindo Grade 3 or higher postoperative adverse events were both significantly lower in the MIS group than in the Open group.Conclusion: Surgical intervention for postoperative recurrence of rectal cancer results in good survival, but short relapse-free survival. NACRT can deter local re-recurrence after resection, and MIS may contribute to reducing complications.
Keywords: Rectal cancer, local recurrencene, oadjuvant chemoradiotherapy, minimally invasive surgery

25COASMA70

Title: 18F-Fluorocholine PET/CT as an Imaging Biomarker in Patients With Hepatocellular Carcinoma Receiving Atezolizumab Plus Bevacizumab

Wonseok Whi, Hyunjong Lee, Jung Yong Hong, Wonseok Kang, Young Seok Cho, Seung Hwan Moon,

Anticancer Research March 2025, 45 (3) 1273-1280;
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Abstract: Background/Aim: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and treatment outcomes for advanced disease remain suboptimal. Immunotherapy, particularly atezolizumab plus bevacizumab, has shown promise in improving survival. This study aimed to evaluate the prognostic value of 18F-fluorocholine positron emission tomography/computed tomography (FCH PET/CT) in patients with unresectable HCC undergoing this combination therapy.Patients and Methods: This prospective study included 29 patients with unresectable HCC treated with atezolizumab plus bevacizumab. All participants underwent FCH PET/CT prior to treatment. The tumor-to-liver ratio (TLR) of FCH uptake was calculated and analyzed as a potential prognostic biomarker. Progression-free survival (PFS) was assessed using Kaplan–Meier analysis, and Cox proportional hazards models evaluated associations between TLR and clinical outcomes.Results: Patients with higher TLR values of FCH uptake (cutoff: 1.36) demonstrated significantly shorter PFS compared to those with lower TLR values (hazard ratio=4.29, p=0.032). Other clinical variables, including age, sex, tumor size, and viral hepatitis status, were not significantly associated with PFS.Conclusion: TLR of FCH uptake is a valuable non-invasive biomarker for predicting PFS in unresectable HCC patients treated with immunotherapy.

Keywords: PET, hepatocellular carcinoma, fluorocholine, prognosis, immunotherapy

25COASMA71

Title: Safety and Outcomes of Intraoperative Ventriculoperitoneal Shunt Clamping During Robotic-assisted Radical Prostatectomy: Retrospective Cohort Analysis

Jhe-Yuan Hsu, Hsien-Che Ou, Yen-Chuan Ou, Yi-Sheng Lin, Li-Hua Huang, Wei-Chun Weng, Chao-Yu Hsu And Min-Che Tung

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Abstract: Background/Aim: This study aimed to assess the safety and outcomes of intraoperative ventriculoperitoneal (VP) shunt clamping during robotic-assisted radical prostatectomy (RaRP) in patients with VP shunts.Patients and Methods: A retrospective analysis of nine patients with VP shunts who underwent RaRP between February 2016 and October 2024 was conducted. Data on preoperative prostate-specific antigen (PSA) levels, surgical margins, complications, and follow-up durations were collected. Patients were stratified into subgroups based on PSA levels (≤10 vs. >10 ng/ml), operative time (<200 vs. ≥200 min), and estimated blood loss (<150 vs. ≥150 ml). Outcomes were analyzed using descriptive statistics, focusing on PSA trends, biochemical recurrence, and VP shunt functionality.Results: All procedures were completed without intraoperative or VP shunt-related complications. The median operative time was 180 min (range=180-330 min), and the

median estimated blood loss was 170 ml (range=50-700 ml). Most patients showed significant PSA suppression, with a median PSA of <0.008 ng/ml at one year. Patients with initial PSA levels >10 ng/ml had greater variability in PSA trends, including persistent elevation or biochemical recurrence, whereas those with PSA levels ≤10 ng/ml had stable outcomes. No differences in oncological outcomes were noted based on operative time or blood loss. Median follow-up was 54 months (range=2-105 months).Conclusion: VP shunt clamping during RaRP is safe and effective, with favorable surgical and oncological outcomes and preserved shunt functionality. Larger studies are needed to confirm these findings and establish standardized protocols.

Keywords: Ventriculoperitoneal shunt, robotic-assisted radical prostatectomy, prostate cancer, prostate-specific antigen, follow-up, perioperative management

25COASMA72

Title: Short-term Safety of Robot-assisted Rectal Surgery in Patients Aged ≥75 Years: A Single-center Retrospective Study

Fuminori Teraishi, Yusuke Yoshida, Ryohei Shoji, Nobuhiko Kanaya, Yuki Matsumi, Kunitoshi Shigeyasu,

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Abstract: Background/Aim: The aging population challenges surgical management of rectal cancer. This study evaluated the short-term safety of robot-assisted rectal surgery (RARS) in patients aged 75 years and older, examining perioperative complications and surgical outcomes in this vulnerable population.Patients and Methods: A single-center retrospective cohort study was conducted at Okayama University Hospital from September 2020 to December 2024, including 109 patients undergoing RARS. Patients were divided into older (≥75 years, n=19) and non-older (<75 years, n=90) groups. Surgical procedures utilized the da Vinci Xi system, with comprehensive assessment of perioperative characteristics and complications using the Clavien-Dindo classification.Results: The older group demonstrated significantly higher American Society of Anesthesiologists classification (89.5% ≥2 vs. 58.9% in non-older group, p=0.036). Postoperative complications were more frequent in the older group (8 vs. 18 cases, p=0.04), though severe complications were similar to those in the non-older group. Median postoperative hospital stay was longer in the older group (12 vs. 9 days, p=0.01), but this difference disappeared when excluding stoma cases. Critically, no postoperative mortality was observed within 30 days in either group.Conclusion: Robot-assisted rectal surgery appears safe for patients aged 75 years and older. While the older group experienced more complications, these were predominantly manageable. The findings suggest that careful patient selection and experienced surgical teams can successfully employ robotic techniques in older patients while maintaining oncological standards.

Keywords: Robot assisted surgery, older patients, rectal cancer, short-term outcome

25COASMA73

Title: Evaluation of the causal effects of perfluorooctanesulfonate on COVID-19 and its associated mechanisms: Integrated Mendelian randomization and network toxicology analyses

Wenting Tao , Liang Chen
Toxicology Letters, Volume 405, March 2025, Pages 1-8
DOI: https://doi.org/10.1016/j.toxlet.2025.01.008
Abstract: Observational reports have suggested that exposure to perfluorooctanesulfonate (PFOS) can influence COVID-19 infection-related parameters. This study thus sought to use integrated Mendelian randomization (MR) and network toxicology approaches to clarify the potential causal link between PFOS exposure and COVID-19 severity and the molecular mechanisms underlying this relationship. Inverse-variance-weighted analyses highlighted a causal link between plasma PFOS concentrations and a greater risk of sCOVID-19 (OR 1.293, 95 % CI 1.077–1.552, p = 0.006), but not of SARS-CoV-2 infection (p = 0.257) or COVID-19 hospitalization (p = 0.516). No causal link between PFOS concentration and sCOVID-19 was found by reverse MR. In total, 65 targets were tentatively linked to the relationship between PFOS exposure and sCOVID-19. GO and KEGG analyses highlighted involvement in pathways associated with kinase activity, inflammatory responses, and epithelial and endothelial cell migration. In molecular docking analyses, PFOS was confirmed to readily bind to all five analyzed core targets (IL10, ALB, NOTCH1, PPARG, and NFE2L2). These results suggest that PFOS exposure is causally linked to sCOVID-19 risk, while also offering promising insights into the mechanisms that may underlie this association and candidate targets for treatments aimed at limiting the negative effects of PFOS on COVID-19 severity.
Keywords : Perfluorooctanesulfonate, Severe COVID-19, Mendelian randomization, Network toxicology

25COASMA74

Title: Emerging nicotine analog 6-methyl nicotine increases reactive oxygen species in aerosols and cytotoxicity in human bronchial epithelial cells

Felix Effah, Yehao Sun, Alan Friedman, Irfan Rahman
Toxicology Letters, Volume 405, March 2025, Pages 9-15
DOI: https://doi.org/10.1016/j.toxlet.2025.01.007
Abstract: Nicotine-contained e-cigarettes (E-cigs) generate reactive oxygen species (ROS), volatile organic compounds, and heavy metals. Inhalation toxicology studies suggest that exposure to these toxicants may adversely impact human health. These findings led to the U.S. Food and Drug Administration's (FDA) regulation of nicotine-containing E-cigs under the Tobacco Regulation Act (TRA) of 2020. Manufacturers aiming to sell nicotine products in the U.S. must submit a Premarket Tobacco Product Application (PMTA) and obtain FDA approval before marketing their products. However, due to the lengthy PMTA process, some companies have exploited a loophole in the TRA (2020) by introducing nicotine analogs, such as 6-methyl nicotine (6-MN) into E-cig products. 6-MN is marketed as a 'safer' alternative to nicotine, offering comparable satisfaction despite not being derived from tobacco or nicotine. Nonetheless, its safety profiles are unknown. Therefore, this study tested the toxicity of 6-MN compared to traditional nicotine in vitro. We observed that thermal degradation of 6-MN in e-liquids significantly generated more ROS in the aerosols than nicotine. We investigated the dose-response cytotoxicity of 6-MN vs nicotine when exposed to HBEC3-KT human bronchial epithelial cells. 6-MN-contained e-liquids significantly

increased cytotoxicity and intracellular ROS induction in a dose-specific manner compared to nicotine. Further, we observed that 6-MN (pure compound) transiently increased metabolic activity significantly at all doses tested compared to nicotine. Given the potential risks associated with 6-MN, it cannot be deemed 'safer' than nicotine. Therefore, further primary toxicological research is urgently needed to provide regulatory agencies with more robust data to implement regulations.

Keywords: 6-Methyl nicotine, E-cigarettes, Toxicity, Nicotine analogs, Regulatory science

25COASMA75

Title: The herbicide 2,4-dichlorophenoxyacetic acid induces pancreatic β-cell death via oxidative stress-activated AMPKα signal downstream-regulated apoptotic pathway

Ken-An Lin , Chin-Chuan Su, Kuan-I Lee, Shing-Hwa Liu , Kai-Min Fang , Chih-Hsin Tang, Wei-Cheng Lia ,

Toxicology Letters, Volume 405, March 2025, Pages 16-29
DOI: https://doi.org/10.1016/j.toxlet.2025.01.009

Abstract: 2,4-Dichlorophenoxyacetic acid (2,4-D) is one of commonly and widely used organic herbicides in agriculture. It has been reported that 2,4-D can induce adverse effects in mammalian cells. Epidemiological and animal studies have indicated that exposure to 2,4-D is associated with poorer glycemic control and impaired pancreatic β-cell function. However, limited information is available on 2,4-D-induced toxicological effects in β-cells, with the underlying toxicological mechanisms remains unclear. Herein, our results showed that 2,4-D exposure (30–500 μg/mL) significantly reduced cell viability, induced mitochondria dysfunction (including the mitochondrial membrane potential (MMP) loss, the increase in cytosolic cytochrome c release, and the change in Bcl-2 and Bax protein expression), and triggered apoptotic events (including the increased population of apoptotic cells, caspase-3 activity, and caspase-3/-7 and PAPR activation) in RIN-m5F β-cells, accompanied with insulin secretion inhibition. Exposure of cells to 2,4-D could also evoke JNK, ERK1/2, p38, and AMP-activated protein kinase (AMPK)α activation as well as reactive oxygen species (ROS) generation. Pretreatment of cells with compound C (an AMPK inhibitor) and the antioxidantN-acetylcysteine (NAC), but not that SP600125/PD98059/SB203580 (the inhibitors of JNK/ERK/p38, respectively), obviously attenuated the 2,4-D-triggered AMPKα phosphorylation, MMP loss, apoptotic events, and insulin secretion dysfunction,as similar effects with the transfection with AMPKα1-specific siRNA. Of note, buffering the ROS production with NAC obviously prevented the 2,4-D-induced ROS generation as well as AMPKα activation, but the either compound C and AMPKα1-specific siRNA transfection could not effectively reduce 2,4-D-induced ROS generation. Collectively, these findings indicate that the induction of oxidative stress-activated AMPKα signaling is a crucial mechanism underlying 2,4-D-triggered mitochondria-dependent apoptosis, ultimately leading to β-cell death.

Keywords: 2,4-dichlorophenoxyacetic acid, Pancreatic β-cells, Apoptosis, Mitochondria, AMPKαROS

25COASMA76

Title: Mitigation of gentamycin induced acute kidney injury due to benzothiazole derivatives N1 and N5: Antioxidant and renoprotective mechanisms in-vivo zebrafish

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Toxicology Letters, Volume 405, March 2025, Pages 30-40
DOI: https://doi.org/10.1016/j.toxlet.2025.02.001

Abstract: Acute kidney injury (AKI) is marked by a rapid decline in renal function, often caused by oxidative stress and nephrotoxic agents. Complications limit current therapeutic strategies, and no specific drugs are available to prevent renal injury or accelerate recovery. In the present research, we investigated the therapeutic efficacy of synthesized 2-aminobenzothiazole derivatives, N1 and N5, in mitigating Gentamicin (Gen) -induced renal damage in vivo zebrafish. The preliminary work of radical scavenging and hemolysis inhibition assay revealed that, both compounds exhibited strong antioxidant and anti-inflammatory activities. Furthermore, acute toxicity assays in zebrafish embryo/larvae revealed no adverse effects at concentrations up to 200 μM were tested, highlighting the safety of these compounds. In the zebrafish AKI model, Gen exposure led to oxidative stress, inflammation, and impaired glomerular filtration with tissue damage. Treatment with N1 and N5 significantly reduced ROS levels, apoptosis, and lipid peroxidation and restored antioxidant enzyme activities. Furthermore, N5 treatment improved renal filtration and reduced proteinuria levels, indicating its ability to mitigate nephrotoxic effects. Gene expression analysis showed that N1 and N5 downregulated pro-inflammatory markers (cox-2, tnfα, mpo) and angiogenic mediators (vegf, vegfr2), demonstrating anti-inflammatory and anti-angiogenic properties. Histological analyses revealed that N1 and N5 attenuated glomerular and tubular damage, reduced necrosis, and promoted tissue repair. These findings highlight the potential of 2-aminothiazole derivatives as effective therapeutic agents for AKI, offering antioxidant, anti-inflammatory, and cytoprotective benefits and warranting further investigation into their long-term efficacy in chronic kidney disease models.

Keywords: Gentamycin, Acute kidney injury, Benzothiazole derivatives, Anti-inflammation, Renoprotection

25COASMA77

Title: Low doses of bisphenol F and S affect human ovarian granulosa cells by reducing the number of active mitochondria and ATP synthesis

Paulina Głód , Weronika Marynowicz , Joanna Homa , Joanna Smoleniec , Dawid Maduzia , Anna Ptak

Toxicology Letters, Volume 405, March 2025, Pages 41-50
DOI: https://doi.org/10.1016/j.toxlet.2025.02.002

Abstract: Bisphenols (BPs) are a group of environmental pollutants mainly represented by bisphenol S (BPS) and F (BPF). In ovaries, BPs can accumulate in follicular fluid (FF), changing the follicular microenvironment and simultaneously affecting ovarian granulosa cells (GCs) function. In the present study, we determined the effects of BPS and BPF on oxidative stress and mitochondrial function in human ovarian GCs. Single, short-term treatment with BPs at doses reflecting their concentrations in FF (10 nM) did not affect

reactive oxygen species (ROS) levels but induced mitochondrial membrane depolarization. BPF-induced mitophagy decreased the number of active mitochondria and consequently reduced the ATP production rate. The observed changes did not translate into lowered viability of GCs, but long-term treatment with BPF influenced the intrinsic apoptosis pathway by increasing caspase 9 activity without affecting apoptosis. GCs are crucial for ovarian function as they produce primary steroid hormones and regulate oocyte maturation and follicle growth. Mitochondrial dysfunction caused by BPs, manifesting as reduced ATP production in GCs, can directly cause ovarian disorders such as infertility. Therefore, this study highlights the significance of investigating the effects of BPs on reproductive health.

Keywords: Bisphenol S and F, Human ovarian granulosa cells, Mitochondrial function, Apoptosis, MitophagyIGF-1

25COASMA78

Title: Neurotoxic implications of gliotoxin and ochratoxin A in SH-SY5Y cells: ROS-induced apoptosis and genotoxicity

Raquel Penalva-Olcina, Cristina Juan, Mónica Fernández-Franzón, Ana Juan-García

Toxicology Letters, Volume 405, March 2025, Pages 51-58

DOI: **https://doi.org/10.1016/j.toxlet.2025.02.004**

Abstract: Gliotoxin (GTX) and ochratoxin A (OTA) are naturally produced toxins by fungi and are known for their potential health risks. With the aim of shed some light on the mechanisms by which GTX, OTA, and their combination exert toxicity at neuronal level, the following in vitro studies were conducted in SH-SY5Y cells: a) intracellular ROS monitorization by the H2-DCFDA assay b) study of the expression of pro-apoptotic genes Bcl2, Casp-3, and Bax by RT-qPCR c) study of the apoptotic-necrotic progression of SH-SY5Y cells by flow cytometry; d) study of the genotoxic potential through the in vitro micronucleus (MN) assay also by flow cytometry following OECD TG 487 guidelines. ROS production was increased when cells were exposed to mycotoxins at all scenarios tested highlighting the effects of GTX. Regarding gene expression, increases of Bax and Casp-3 genes at 1.3- and 3- folds respectively were observed when cells were exposed to GTX at 0.75 μM, with a more prominent increase after exposure to the binary combination [GTX + OTA] at [0.2 + 0.1] μM, increasing 3 and 5-folds more, respectively when compared to the control. MN formation increased a 30 % compared to control when exposed to GTX at 0.4 μM, 43 % for OTA at 0.8 μM, with the highest increase observed when cells were exposed to the combination [GTX + OTA] at [0.2 + 1.5] μM, obtaining a 65 % more MN formation. Based on the results obtained, we can conclude that for the proposed scenarios of exposure to GTX, OTA, and their combination, genotoxic effects together with oxidative effects at neuronal level in SH-SY5Y cell line, were found to play a key role in their mechanisms of toxic action.

Keywords: Gliotoxin, Ochratoxin A, Mixtures, Genotoxicity, Apoptosis, Neurotoxicity

25COASMA79

Title: Toxicological mode-of-action and developmental toxicity of different carbon chain length PFAS

Kamlesh Sodani, Bas Ter Braak , Sabine Hartvelt , Mark Boelens , Amer Jamalpoor, Sandeep

Mukhi
Toxicology Letters, Volume 405, March 2025, Pages 59-66
DOI: https://doi.org/10.1016/j.toxlet.2025.02.003
Abstract: Per-and polyfluoro alkyl substances (PFAS), also known as “forever chemicals”, are deemed as highly toxic with similar toxicological mode-of-action (MoA) and potency. However, varying carbon chain length and functional head-group of PFAS can affect their physicochemical properties, resulting in different toxicological properties. To assess PFAS toxicological MoA and to distinguish between high toxic PFAS and the low-toxic analogs, we tested a set of eight PFAS with varying carbon chain length (C2-C10) in the ToxProfiler assay. ToxProfiler is a human in vitro assay containing seven fluorescent reporters to visualize and quantify activation of the major cellular stress pathways: oxidative stress, cell cycle stress, endoplasmic reticulum (ER) stress, autophagy, ion stress, protein stress and inflammation. In addition, we evaluated teratogenicity potential of long-chain PFAS perfluorooctanoic acid (PFOA; C8), and the ultrashort-chain PFAS trifluoroacetic acid (TFA; C2) in ReproTracker, a human induced pluripotent stem cell (hiPSCs)-based assay in which differentiation into cardiomyocytes, hepatocytes, and neural rosettes is followed to identify developmental toxicity hazards of new drugs and chemicals. In this study, we identified long-chain PFAS (C8-C10), such as PFOA (C8) to be more cytotoxic than ultrashort-chain PFAS and to predominantly induce ER and oxidative stress at 130 μM. PFAS with a carbon chain length of C4-C7 primarily induced autophagy (300 μM) in ToxProfiler. Ultrashort-chain PFAS trifluoroacetic acid (TFA; C2) and perfluoropropionic acid (PFPrA; C3) did not activate any of the ToxProfiler stress response reporters and were not cytotoxic at their maximum tested concentrations (10 mM). In concordance, exposure of differentiating cells to PFOA in ReproTracker led to a concentration-dependent decrease in the hepatocyte-specific and neuroectodermal biomarker genes and disrupted their morphology at 30 and 60 μM, respectively. TFA had no significant effect on biomarker expression, nor on the morphology/functionality of the three differentiated cells. Altogether, we demonstrated that the carbon chain length of PFAS can determine their in vitro toxicity and ultrashort-chain PFAS (TFA) were found to be less toxic when compared to long-chain PFAS.
Keywords: TFA, PFAS, Ultrashort-chain PFAS, New Approach Method (NAM), Developmental toxicity

25COASMA80

Title: The effects of citalopram and sertraline on adipogenesis and lipogenesis in 3T3-L1 cells

Deniz Bozdag, Bita Entezari , Hande Gurer-Orhan
Toxicology Letters, Volume 405, March 2025, Pages 67-75
DOI: https://doi.org/10.1016/j.toxlet.2025.02.007
Abstract: Selective serotonin reuptake inhibitors (SSRIs), widely used antidepressants, have been associated with metabolic adverse effects, including weight gain and disrupted lipid metabolism. This study investigates the potential adipogenic and lipogenic effects of two commonly prescribed SSRIs, citalopram (CIT) and sertraline (SER), using the murine 3T3-L1 preadipocyte cell line. Key markers, such as adiponectin secretion, G3PDH activity, and the expression of critical transcription factors (PPARγ, CEBPα, SREBP1) and lipogenic

enzymes (FASN, LPL), were evaluated. Furthermore, assessment of intracellular lipid accumulation via Oil Red O staining was used as a measure for enhanced adipogenesis. The results show that CIT significantly increased adiponectin secretion and G3PDH activity, with comparable potency to the positive control, rosiglitazone. Both SSRIs upregulated the transcription of key adipogenic genes but displayed discrepancies in protein expression. Despite these molecular changes, neither CIT nor SER promoted lipid accumulation, indicating disruption of adipogenic and lipogenic processes without direct stimulation of fat storage. These findings underscore the complexity of SSRI-induced metabolic effects and the need for further studies to evaluate their long-term impact.

Keywords: Sertraline, Citalopram, Adipogenesis, Lipogenesis, Metabolic dysregulation, 3T3-L1, In vitro

25COASMA81

Title: Mitochondrial protein import stress

Nikolaus Pfanner, Fabian den Brave & Thomas Becker

Nature Cell Biology volume 27, pages188–201 (2025)
DOI: https://doi.org/10.1038/s41556-024-01590-w

Abstract: Mitochondria have to import a large number of precursor proteins from the cytosol. Chaperones keep these proteins in a largely unfolded state and guide them to the mitochondrial import sites. Premature folding, mitochondrial stress and import defects can cause clogging of import sites and accumulation of non-imported precursors, representing a critical burden for cellular proteostasis. Here we discuss how cells respond to mitochondrial protein import stress by regenerating clogged import sites and inducing stress responses. The mitochondrial protein import machinery has a dual role by serving as sensor for detecting mitochondrial dysfunction and inducing stress-response pathways. The production of chaperones that fold or sequester precursor proteins in deposits is induced and the proteasomal activity is increased to remove the excess precursor proteins. Together, these pathways reveal how mitochondria are tightly integrated into a cellular proteostasis and stress response network to maintain cell viability.

25COASMA82

Title: H3K36 methylation regulates cell plasticity and regeneration in the intestinal epithelium

Alison R. S. Pashos, Anne R. Meyer, Cameron Bussey-Sutton, Erin S. O'Connor, Mariel Coradin, Marilyne Coulombe,

Nature Cell Biology volume 27, pages202–217 (2025)
DOI: https://doi.org/10.1038/s41556-024-01580-y

Abstract: Plasticity is needed during development and homeostasis to generate diverse cell types from stem and progenitor cells. Following differentiation, plasticity must be restricted in specialized cells to maintain tissue integrity and function. For this reason, specialized cell identity is stable under homeostatic conditions; however, cells in some tissues regain plasticity during injury-induced regeneration. While precise gene expression controls these processes, the regulatory mechanisms that restrict or promote cell plasticity are poorly understood. Here we use the mouse small intestine as a model system to study cell plasticity.

We find that H3K36 methylation reinforces expression of cell-type-associated genes to maintain specialized cell identity in intestinal epithelial cells. Depleting H3K36 methylation disrupts lineage commitment and activates regenerative gene expression. Correspondingly, we observe rapid and reversible remodelling of H3K36 methylation following injury-induced regeneration. These data suggest a fundamental role for H3K36 methylation in reinforcing specialized lineages and regulating cell plasticity and regeneration.

25COASMA83

Title: Metabolic rewiring in skin epidermis drives tolerance to oncogenic mutations

Anupama Hemalatha, Zongyu Li, David G. Gonzalez, Catherine Matte-Martone, Karen Tai, Elizabeth Lathrop, Daniel Gil,

Nature Cell Biology volume 27, pages218–231 (2025)
DOI: https://doi.org/10.1038/s41556-024-01574-w

Abstract: Skin epithelial stem cells correct aberrancies induced by oncogenic mutations. Oncogenes invoke different strategies of epithelial tolerance; while wild-type cells outcompete β-catenin-gain-of-function (βcatGOF) cells, HrasG12V cells outcompete wild-type cells. Here we ask how metabolic states change as wild-type stem cells interface with mutant cells and drive different cell-competition outcomes. By tracking the endogenous redox ratio (NAD(P)H/FAD) with single-cell resolution in the same mouse over time, we discover that βcatGOF and HrasG12V mutations, when interfaced with wild-type epidermal stem cells, lead to a rapid drop in redox ratios, indicating more oxidized cellular redox. However, the resultant redox differential persists through time in βcatGOF, whereas it is flattened rapidly in the HrasG12Vmodel. Using 13C liquid chromatography–tandem mass spectrometry, we find that the βcatGOF and HrasG12V mutant epidermis increase the fractional contribution of glucose through the oxidative tricarboxylic acid cycle. Treatment with metformin, a modifier of cytosolic redox, inhibits downstream mutant phenotypes and reverses cell-competition outcomes of both mutant models.

25COASMA84

Title: The nuclear matrix stabilizes primed-specific genes in human pluripotent stem cells

Gang Ma, Xiuling Fu, Lulu Zhou, Isaac A. Babarinde, Liyang Shi, Wenting Yang, Jiao Chen, Zhen Xiao, Yu Qiao, Lisha Ma,

Nature Cell Biology volume 27, pages232–245 (2025)
DOI: https://doi.org/10.1038/s41556-024-01595-5

Abstract: The nuclear matrix, a proteinaceous gel composed of proteins and RNA, is an important nuclear structure that supports chromatin architecture, but its role in human pluripotent stem cells (hPSCs) has not been described. Here we show that by disrupting heterogeneous nuclear ribonucleoprotein U (HNRNPU) or the nuclear matrix protein, Matrin-3, primed hPSCs adopted features of the naive pluripotent state, including morphology and upregulation of naive-specific marker genes. We demonstrate that HNRNPU depletion leads to increased chromatin accessibility, reduced DNA contacts and increased nuclear size. Mechanistically, HNRNPU acts as a transcriptional co-factor that anchors promoters of primed-specific genes to the nuclear matrix with POLII to promote their expression and their

RNA stability. Overall, HNRNPU promotes cell-type stability and when reduced promotes conversion to earlier embryonic states.

25COASMA85

Title: SNORD113–114 cluster maintains haematopoietic stem cell self-renewal via orchestrating the translation machinery

Hui Wang, Zhaoru Zhang, Chenxi Han, Penglei Jiang, Jiayue Xu, Yingli Han, Deyu Huang, Jian Li, Jie Zhou,

Nature Cell Biology volume 27, pages246–261 (2025)
DOI: https://doi.org/10.1038/s41556-024-01593-7

Abstract: Haematopoietic stem cells (HSCs) self-renew and differentiate to replenish the pool of blood cells, which require a low but finely tuned protein synthesis rate. Nonetheless, the translatome landscape in HSCs and how the translation machinery orchestrates HSC self-renewal remain largely elusive. Here we perform ultra-low-input Ribo-seq in HSCs, progenitor and lineage cells, and reveal HSC-specific translated genes involved in rRNA processing. We systematically profile small nucleolar RNAs (snoRNAs) and uncover an indispensable role of the SNORD113–114 cluster in regulating HSC self-renewal. Maternal knockout (Mat-KO) of this cluster substantially impairs HSC self-renewal, whereas loss of the paternal allele shows no obvious phenotype. Mechanistically, Mat-KO results in dysregulation of translation machinery (rRNA 2′-O-Me modifications, pre-rRNA processing, 60S ribosome assembly and translation) and induces nucleolar stress in HSCs, which exempts p53 from Mdm2-mediated proteasomal degradation and leads to apoptosis. Collectively, our study provides a promising facet to our understanding of snoRNA-mediated regulation in HSC homeostasis.

25COASMA86

Title: MDM2 functions as a timer reporting the length of mitosis

Luke J. Fulcher, Tomoaki Sobajima, Caleb Batley, Ian Gibbs-Seymour & Francis A. Barr

Nature Cell Biology volume 27, pages262–272 (2025)
DOI: https://doi.org/10.1038/s41556-024-01592-8

Abstract: Delays in mitosis trigger p53-dependent arrest in G1 of the next cell cycle, thus preventing repeated cycles of chromosome instability and aneuploidy. Here we show that MDM2, the p53 ubiquitin ligase, is a key component of the timer mechanism triggering G1 arrest in response to prolonged mitosis. This timer function arises due to the attenuation of protein synthesis in mitosis. Because MDM2 has a short half-life and ongoing protein synthesis is therefore necessary to maintain its steady-state concentration, the amount of MDM2 gradually falls during mitosis but normally remains above a critical threshold for p53 regulation at the onset of G1. When mitosis is extended by prolonged spindle assembly checkpoint activation, the amount of MDM2 drops below this threshold, stabilizing p53. Subsequent p53-dependent p21 accumulation then channels G1 cells into a sustained cell-cycle arrest, whereas abrogation of the response in p53-deficient cells allows them to bypass this crucial defence mechanism.

25COASMA87

Title: Cytoplasmic flow is a cell size sensor that scales anaphase

Olga Afonso, Ludovic Dumoulin, Karsten Kruse & Marcos Gonzalez-Gaitan

Nature Cell Biology volume 27, pages273–282 (2025)
DOI: https://doi.org/10.1038/s41556-024-01605-6

Abstract: During early embryogenesis, fast mitotic cycles without interphase lead to a decrease in cell size, while scaling mechanisms must keep cellular structures proportional to cell size. For instance, as cells become smaller, if the position of nuclear envelope reformation (NER) did not adapt, NER would have to occur beyond the cell boundary. Here we found that NER position in anaphase scales with cell size via changes in chromosome motility, mediated by cytoplasmic flows that themselves scale with cell size. Flows are a consequence of friction between viscous cytoplasm and bulky cargo transported by dynein on astral microtubules. As an emerging property, confinement in cells of different sizes yields scaling of cytoplasmic flows. Thus, flows behave like a cell geometry sensor: astral microtubules approach the boundary causing flow velocity changes, which then affect the velocity of chromosome separation, thus scaling NER.

25COASMA88

Title: Phase separation of initiation hubs on cargo is a trigger switch for selective autophagy

Mariya Licheva, Jeremy Pflaum, Riccardo Babic, Hector Mancilla, Jana Elsässer, Emily Boyle, David M. Hollenstein,

Nature Cell Biology volume 27, pages283–297 (2025)
DOI: https://doi.org/10.1038/s41556-024-01572-y

Abstract: Autophagy is a key cellular quality control mechanism. Nutrient stress triggers bulk autophagy, which nonselectively degrades cytoplasmic material upon formation and liquid–liquid phase separation of the autophagy-related gene 1 (Atg1) complex. In contrast, selective autophagy eliminates protein aggregates, damaged organelles and other cargoes that are targeted by an autophagy receptor. Phase separation of cargo has been observed, but its regulation and impact on selective autophagy are poorly understood. Here, we find that key autophagy biogenesis factors phase separate into initiation hubs at cargo surfaces in yeast, subsequently maturing into sites that drive phagophore nucleation. This phase separation is dependent on multivalent, low-affinity interactions between autophagy receptors and cargo, creating a dynamic cargo surface. Notably, high-affinity interactions between autophagy receptors and cargo complexes block initiation hub formation and autophagy progression. Using these principles, we converted the mammalian reovirus nonstructural protein μNS, which accumulates as particles in the yeast cytoplasm that are not degraded, into a neo-cargo that is degraded by selective autophagy. We show that initiation hubs also form on the surface of different cargoes in human cells and are key to establish the connection to the endoplasmic reticulum, where the phagophore assembly site is formed to initiate phagophore biogenesis. Overall, our findings suggest that regulated phase separation underscores the initiation of both bulk and selective autophagy in evolutionarily diverse organisms.

25COASMA89

Title: Triacylglycerol mobilization underpins mitochondrial stress recovery

Zakery N. Baker, Yunyun Zhu, Rachel M. Guerra, Andrew J. Smith, Aline Arra, Lia R. Serrano,

Nature Cell Biology volume 27, pages298–308 (2025)
DOI: https://doi.org/10.1038/s41556-024-01586-6

Abstract: Mitochondria are central to myriad biochemical processes, and thus even their moderate impairment could have drastic cellular consequences if not rectified. Here, to explore cellular strategies for surmounting mitochondrial stress, we conducted a series of chemical and genetic perturbations to Saccharomyces cerevisiae and analysed the cellular responses using deep multiomic mass spectrometry profiling. We discovered that mobilization of lipid droplet triacylglycerol stores was necessary for strains to mount a successful recovery response. In particular, acyl chains from these stores were liberated by triacylglycerol lipases and used to fuel biosynthesis of the quintessential mitochondrial membrane lipid cardiolipin to support new mitochondrial biogenesis. We demonstrate that a comparable recovery pathway exists in mammalian cells, which fail to recover from doxycycline treatment when lacking the ATGL lipase. Collectively, our work reveals a key component of mitochondrial stress recovery and offers a rich resource for further exploration of the broad cellular responses to mitochondrial dysfunction.

25COASMA90

Title: Mitochondrial YME1L1 governs unoccupied protein translocase channels

Meng-Chieh Hsu, Hiroki Kinefuchi, Linlin Lei, Reika Kikuchi, Koji Yamano & Richard J. Youle

Nature Cell Biology volume 27, pages309–321 (2025)
DOI: https://doi.org/10.1038/s41556-024-01571-z

Abstract: Mitochondrial protein import through the outer and inner membranes is key to mitochondrial biogenesis. Recent studies have explored how cells respond when import is impaired by a variety of different insults. Here, we developed a mammalian import blocking system using dihydrofolate reductase fused to the N terminus of the inner membrane protein MIC60. While stabilization of the dihydrofolate reductase domain by methotrexate inhibited endogenous mitochondrial protein import, it neither activated the transcription factor ATF4, nor was affected by ATAD1 expression or by VCP/p97 inhibition. On the other hand, notably, plugging the channel of translocase of the outer membrane) induced YME1L1, an ATP-dependent protease, to eliminate translocase of the inner membrane (TIM23) channel components TIMM17A and TIMM23. The data suggest that unoccupied TIM23 complexes expose a C-terminal degron on TIMM17A to YME1L1 for degradation. Import plugging caused a cell growth defect and loss of YME1L1 exacerbated the growth inhibition, showing the protective effect of YME1L1 activity. YME1L1 seems to play a crucial role in mitochondrial quality control to counteract precursor stalling in the translocase of the outer membrane complex and unoccupied TIM23 channels.

25COASMA91

Title: Nuclear speckles regulate functional programs in cancer

Katherine A. Alexander, Ruofan Yu, Nicolas Skuli, Nathan J. Coffey, Son Nguyen, Christine L. Faunce,

Nature Cell Biology volume 27, pages322–335 (2025)
DOI: https://doi.org/10.1038/s41556-024-01570-0

Abstract: Nuclear speckles are dynamic nuclear bodies characterized by high concentrations of factors involved in RNA production. Although the contents of speckles suggest multifaceted roles in gene regulation, their biological functions are unclear. Here we investigate speckle variation in human cancer, finding two main signatures. One speckle signature was similar to healthy adjacent tissues, whereas the other was dissimilar, and considered an aberrant cancer speckle state. Aberrant speckles show altered positioning within the nucleus, higher levels of the TREX RNA export complex and correlate with poorer patient outcomes in clear cell renal cell carcinoma (ccRCC), a cancer typified by hyperactivation of the HIF-2α transcription factor. We demonstrate that HIF-2α promotes physical association of certain target genes with speckles depending on HIF-2α protein speckle-targeting motifs, defined in this study. We identify homologous speckle-targeting motifs within many transcription factors, suggesting that DNA-speckle targeting may be a general gene regulatory mechanism. Integrating functional, genomic and imaging studies, we show that HIF-2α gene regulatory programs are impacted by speckle state and by abrogation of HIF-2α-driven speckle targeting. These findings suggest that, in ccRCC, a key biological function of nuclear speckles is to modulate expression of select HIF-2α-regulated target genes that, in turn, influence patient outcomes. Beyond ccRCC, tumour speckle states broadly correlate with altered functional pathways and expression of speckle-associated gene neighbourhoods, exposing a general link between nuclear speckles and gene expression dysregulation in human cancer.

25COASMA92

Title: An avoidance segment resolves a lethal nuclear–mitochondrial targeting conflict during ribosome assembly

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Nature Cell Biology volume 27, pages336–346 (2025)
DOI: https://doi.org/10.1038/s41556-024-01588-4

Abstract: The correct sorting of nascent ribosomal proteins from the cytoplasm to the nucleus or to mitochondria for ribosome production poses a logistical challenge for cellular targeting pathways. Here we report the discovery of a conserved mitochondrial avoidance segment (MAS) within the cytosolic ribosomal protein uS5 that resolves an evolutionary lethal conflict between the nuclear and mitochondrial targeting machinery. MAS removal mistargets uS5 to the mitochondrial matrix and disrupts the assembly of the cytosolic ribosome. The resulting lethality can be rescued by impairing mitochondrial import. We show that MAS triages nuclear targeting by disabling a cryptic mitochondrial targeting activity within uS5 and thereby prevents fatal capture by mitochondria. Our findings identify MAS as an essential acquisition by the primordial eukaryote that reinforced organelle targeting

fidelity while developing an endosymbiotic relationship with its mitochondrial progenitor.

25COASMA93

Title: Mapping the developmental trajectory of human astrocytes reveals divergence in glioblastoma

Caitlin Sojka, Hsiao-Lin V. Wang, Tarun N. Bhatia, Yangping Li, Pankaj Chopra, Anson Sing, Anna Voss,

Nature Cell Biology volume 27, pages347–359 (2025)
DOI: https://doi.org/10.1038/s41556-024-01583-9

Abstract: Glioblastoma (GBM) is defined by heterogeneous and resilient cell populations that closely reflect neurodevelopmental cell types. Although it is clear that GBM echoes early and immature cell states, identifying the specific developmental programmes disrupted in these tumours has been hindered by a lack of high-resolution trajectories of glial and neuronal lineages. Here we delineate the course of human astrocyte maturation to uncover discrete developmental stages and attributes mirrored by GBM. We generated a transcriptomic and epigenomic map of human astrocyte maturation using cortical organoids maintained in culture for nearly 2 years. Through this approach, we chronicled a multiphase developmental process. Our time course of human astrocyte maturation includes a molecularly distinct intermediate period that serves as a lineage commitment checkpoint upstream of mature quiescence. This intermediate stage acts as a site of developmental deviation separating IDH-wild-type neoplastic astrocyte-lineage cells from quiescent astrocyte populations. Interestingly, IDH1-mutant tumour astrocyte-lineage cells are the exception to this developmental perturbation, where immature properties are suppressed as a result of d-2-hydroxyglutarate oncometabolite exposure. We propose that this defiance is a consequence of IDH1-mutant-associated epigenetic dysregulation, and we identified biased DNA hydroxymethylation (5hmC) in maturation genes as a possible mechanism. Together, this study illustrates a distinct cellular state aberration in GBM astrocyte-lineage cells and presents developmental targets for experimental and therapeutic exploration.

25COASMA94

Title: Emerging roles of exosomes in diagnosis, prognosis, and therapeutic potential in ovarian cancer: a comprehensive review

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Cancer Gene Therapy volume 32, pages149–164 (2025)
DOI: https://doi.org/10.1038/s41417-025-00871-2

Abstract: Ovarian cancer is a leading cause of cancer-related deaths in women, and the development of chemoresistance remains a major challenge during and after its treatment. Exosomes, small extracellular vesicles involved in intercellular communication, have emerged as potential biomarkers and therapeutic targets in ovarian cancer. This review summarizes the current literature on differences in exosomal protein/gene expression between chemosensitive and chemoresistant ovarian cancer, and the effects of exosomal modifications on chemotherapeutic response. Clinical studies have identified alterations in several exosomal components from ovarian cancer tissues and serum samples arising as a

consequence of chemosensitivity, which indicates their potential usefulness as potential biomarkers for predicting the development of chemoresistance. Interventional investigations from in vitro and in vivo studies demonstrated that modulation of specific exosomal components can influence ovarian cancer cell phenotypes and individual responses to chemotherapy. Exosomal delivery of chemotherapeutic agents, such as cisplatin, has presented as a potential targeted drug delivery strategy for overcoming chemoresistance in preclinical models. In summary, this review highlights the potential for exosomal proteins and genes to be useful biomarkers for predicting chemotherapy response and being therapeutic targets for overcoming chemoresistance in ovarian cancer. However, future research is still needed to validate these findings and explore the clinical utility of exosomal biomarkers and therapeutics in ovarian cancer management. In addition, understanding the molecular mechanisms underlying exosome-mediated chemoresistance may provide valuable insights for the development of personalized therapeutic strategies, improving outcomes for patients with ovarian cancer.

25COASMA95

Title: Exploring metabolic reprogramming in esophageal cancer: the role of key enzymes in glucose, amino acid, and nucleotide pathways and targeted therapies

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Cancer Gene Therapy volume 32, pages165–183 (2025)
DOI: https://doi.org/10.1038/s41417-024-00858-5

Abstract: Esophageal cancer (EC) is one of the most common malignancies worldwide with the character of poor prognosis and high mortality. Despite significant advancements have been achieved in elucidating the molecular mechanisms of EC, for example, in the discovery of new biomarkers and metabolic pathways, effective treatment options for patients with advanced EC are still limited. Metabolic heterogeneity in EC is a critical factor contributing to poor clinical outcomes. This heterogeneity arises from the complex interplay between the tumor microenvironment and genetic factors of tumor cells, which drives significant metabolic alterations in EC, a process known as metabolic reprogramming. Understanding the mechanisms of metabolic reprogramming is essential for developing new antitumor therapies and improving treatment outcomes. Targeting the distinct metabolic alterations in EC could enable more precise and effective therapies. In this review, we explore the complex metabolic changes in glucose, amino acid, and nucleotide metabolism during the progression of EC, and how these changes drive unique nutritional demands in cancer cells. We also evaluate potential therapies targeting key metabolic enzymes and their clinical applicability. Our work will contribute to enhancing knowledge of metabolic reprogramming in EC and provide new insights and approaches for the clinical treatment of EC.

25COASMA96

Title: LRP11-AS1 mediates enterotoxigenic Bacteroides fragilis-related carcinogenesis in colorectal Cancer via the miR-149-3p/CDK4 pathway

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Cancer Gene Therapy volume 32, pages184–197 (2025)
DOI: https://doi.org/10.1038/s41417-024-00862-9

Abstract: Long noncoding RNAs (lncRNAs) are critical in tumorigenesis and show potential for tumor diagnosis and therapy. Enterotoxigenic Bacteroides fragilis (ETBF), known for producing enterotoxins, is implicated in human gut tumorigenesis, yet the underlying mechanisms are not fully elucidated. This study aims to clarify the molecular mechanisms by which lncRNAs contribute to ETBF-induced tumorigenesis, with a focus on LRP11-AS1's role in modulating ETBF's colorectal carcinogenesis. We found a marked increase in LRP11-AS1 expression in colorectal cancer (CRC) tissues compared to adjacent non-tumorous tissues. In vitro, CRC cells exposed to ETBF showed elevated LRP11-AS1 levels. Mechanistically, LRP11-AS1 was shown to enhance CDK4 expression by competitively binding to miR-149-3p. These results indicate that LRP11-AS1 may facilitate ETBF-related carcinogenesis in CRC and could serve as a therapeutic target and diagnostic biomarker for ETBF-associated CRC.

25COASMA97

Title: FBXO22 promotes HCC angiogenesis and metastasis via RPS5/AKT/HIF-1α/VEGF-A signaling axis

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Cancer Gene Therapy volume 32, pages198–213 (2025)
DOI: https://doi.org/10.1038/s41417-024-00861-w

Abstract: The gene F-box only protein 22 (FBXO22) has been discovered to promote the development of liver cancer tumors. Nevertheless, there remains considerable ambiguity regarding the involvement of FBXO22 in the processes of angiogenesis and metastasis in hepatocellular carcinoma (HCC). Our study has confirmed a significant upregulation of FBXO22 expression in both HCC samples and cellular models. The increased level of FBXO22 correlates strongly with the number of tumors, presence of vascular invasion, and poor prognosis. Experimental investigations have shown that FBXO22 significantly enhances angiogenesis and metastasis of HCC both in vitro and in vivo. Mechanistically, FBXO22 interacts with and ubiquitinates 40S ribosomal protein S5 (RPS5) on Lys85, thereby promoting its K48-linked ubiquitin-mediated degradation in the cytoplasm. Following a decrease in the expression of RPS5, activation of downstream PI3K/AKT signaling pathway occurs, leading to elevated levels of HIF-1α and vascular endothelial growth factor A (VEGF-A). Our study has shown that FBXO22 facilitates HCC angiogenesis and metastasis via the RPS5/AKT/HIF-1α/VEGF-A signaling axis. Notably, inhibition of FBXO22 enhances the efficacy of Lenvatinib both in vitro and in vivo. Therefore, FBXO22 may present itself as a potential target for therapeutic intervention in the treatment of HCC.

25COASMA98

Title: Has_circ_ASH1L acts as a sponge for miR-1254 to promote the malignant progression of cervical cancer by targeting CD36

Jun Zhang, Yan Zhang, Xing Li, Yindi Bao & Jing Yang

Cancer Gene Therapy volume 32, pages214–226 (2025)
DOI: https://doi.org/10.1038/s41417-024-00866-5

Abstract: Cervical cancer (CC) is a prevalent gynecological malignancy. Increasing

evidence suggests that circular RNAs (circRNAs) play a pivotal role in the pathogenesis of CC. However, the regulatory function of circ_ASH1L in CC remains elusive. In this study, we aim to elucidate the precise role and underlying mechanism of circ_ASH1L in the malignant progression of CC. The human CC dataset GSE102686 was extracted from the Gene Expression Omnibus (GEO) database for the analysis of differentially expressed circRNAs. Target gene prediction softwares were utilized to predict the binding of miRNAs to circ_ASH1L sponge. The expression level of circ_ASH1L in CC tissues and cells was detected by quantitative real-time polymerase chain reaction (qRT-PCR). The characteristics of circ_ASH1L were determined by RNase R digestion, actinomycin D, and nucleo-plasmic separation assays. The effects of circ_ASH1L, miR-1254, and CD36 gain-and-loss on the malignant progression of CC were investigated using Cell Counting Kit-8 (CCK-8), colony formation, flow cytometry, wound scratch, transwell, and Western blot assay. The effect of circ_ASH1L on tumorigenicity of CC cells in vivo was evaluated in nude mice through tumor xenograft assay. The targeted regulatory relationship between circ_ASH1L/miR-1254 as well as miR-1254/CD36 was validated by dual-luciferase reporter assay. We screened the differentially expressed circ_ASH1L from the GEO dataset GSE102686 and confirmed its circular structure. Furthermore, we observed a significant upregulation of circ_ASH1L in both CC tissues and cells. Overexpression of circ_ASH1L promotes proliferation, invasion, and migration of CC cells while inhibiting cell apoptosis. However, silencing circ_ASH1L showed opposite results and inhibited tumorigenicity of CC cells in nude mice. Furthermore, we have identified circ_ASH1L as a miR-1254 sponge in CC cells. Notably, our in vitro experiments demonstrated that exogenously modulating the expression of miR-1254 effectively counteracted the impact of circ_ASH1L on the malignant phenotypic characteristics of CC cells. Similarly, modulation of CD36 expression efficiently counteracted the effect of miR-1254 on the malignant biological behavior of CC cells. In conclusion, circ_ASH1L promoted the malignant progression of CC via upregulating CD36 expression through sponging miR-1254.

25COASMA99

Title: CRISPR knock-in of a chimeric antigen receptor into GAPDH 3'UTR locus generates potent B7H3-specific NK-92MI cells

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Cancer Gene Therapy volume 32, pages227–239 (2025)
DOI: https://doi.org/10.1038/s41417-025-00872-1

Abstract: CAR-NK therapy is becoming a promising approach to treat solid tumors. However, the random insertion of the CAR gene and inflexible CAR expression caused by common preparation methods significantly impact its efficacy and safety. Here we successfully established a novel type of CAR-NK cells by integrating CAR sequences into the GAPDH 3'UTR locus of NK-92MI cells (CRISPR-CAR-NK), achieving site-specific integration of the CAR gene and allowing endogenous regulatory components to govern CAR expression. CRISPR-CAR-NK cells had comparable growth capacity but displayed superior anti-tumor activity compared with their lentiviral counterparts. They activated and degranulated more effectively when co-cultured with tumor cells, due to increased expression

of activating receptors and decreased expression of inhibitory molecules. They also enhanced the production of Granzyme B and IFN-γ, and more effectively triggered the IFN-γ pathway. Moreover, CRISPR-CAR-NK cells demonstrated distinct properties from conventional CAR-NK concerning metabolic features and signal dependence. Notably, CRISPR-CAR-NK cells exhibited lower metabolic levels without compromising antitumor activity, and their function was less reliant on the PI3K-AKT pathway, implying that the CRISPR-CAR-NK cells have significant potential for enhanced synergy with AKT inhibitors and adaptation to nutrient stress within the tumor microenvironment. These findings provide a novel potential strategy for cancer immunotherapy and an experimental foundation and paradigm for optimizing CAR-NK cells utilizing CRISPR technology, highlighting the potential of CRISPR to advance immunotherapies.

25COASMA100

Title: ITGA3 promotes pancreatic cancer progression through HIF1α- and c-Myc-driven glycolysis in a collagen I-dependent autocrine manner

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Cancer Gene Therapy volume 32, pages240–253 (2025)

DOI: https://doi.org/10.1038/s41417-024-00864-7

Abstract: Pancreatic cancer is characterized by severe metabolic stress due to its prominent desmoplasia and poor vascularization. Integrin subunit alpha 3 (ITGA3) is a cell surface adhesion protein involved in tumor progression. However, the role of ITGA3 in pancreatic cancer progression, especially in metabolic reprogramming, remains largely unknown. In this study, we found that ITGA3 expression is elevated in pancreatic cancer tissues and predicts poor prognosis for patients with pancreatic cancer. Functional assays revealed that ITGA3 promotes the growth and liver metastasis of pancreatic cancer via boosting glycolysis. Mechanistically, Collagen I (Col1) derived from cancer cells acts as a ligand for ITGA3 to activate the FAK/PI3K/AKT/mTOR signaling pathway in an autocrine manner, thereby increasing the expression of HIF1α and c-Myc, two critical regulators of glycolysis. Blockade of Col1 by siRNA or of ITGA3 by a blocking antibody leads to specific inactivation of the FAK/PI3K/AKT/mTOR pathway and impairs malignant tumor behaviors induced by ITGA3. Thus, our data indicate that ITGA3 enhances glycolysis to promote pancreatic cancer growth and metastasis via increasing HIF1α and c-Myc expression in a Col1-dependent autocrine manner, making ITGA3 as a candidate diagnostic biomarker and a potential therapeutic target for pancreatic cancer.

25COASMA101

Title: PIK3CA mutation fortifies molecular determinants for immune signaling in vascular cancers

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Cancer Gene Therapy volume 32, pages254–267 (2025)

DOI: https://doi.org/10.1038/s41417-024-00867-4

Abstract: Angiosarcomas are a group of vascular cancers that form malignant blood vessels.

These malignancies are seemingly inflamed primarily due to their pathognomonic nature, which consists of irregular endothelium and tortuous blood channels. PIK3CA mutations are oncogenic and disrupt the PI3K pathway. In this study, we aimed to define the molecular and functional consequences of oncogenic PIK3CA mutations in angiosarcoma. We first generated two isogenic hemangiosarcoma cell lines harboring the H1047R hotspot mutations in PIK3CA gene using CRISPR/Cas9. We found PIK3CA-mutant cells established distinct molecular signatures in global gene expression and chromatin accessibility, which were associated with enrichment of immune cytokine signaling, including IL-6, IL-8, and MCP-1. These molecular processes were disrupted by the PI3K-α specific inhibitor, alpelisib. We also observed that the molecular distinctions in PIK3CA-mutant cells were linked to metabolic reprogramming in glycolytic activity and mitochondrial respiration. Our multi-omics analysis revealed that activating PIK3CA mutations regulate molecular machinery that contributes to phenotypic alterations and resistance to alpelisib. Furthermore, we identified potential therapeutic vulnerabilities of PIK3CA mutations in response to PI3K-α inhibition mediated by MAPK signaling. In summary, we demonstrate that PIK3CA mutations perpetuate PI3K activation and reinforce immune enrichment to promote drug resistance in vascular cancers.

25COASMA102

Title: Adjuvant chemotherapy in localized, resectable extremity and truncal soft tissue sarcoma and survival outcomes – A systematic review and meta-analysis of randomized controlled trials

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Cancer, Volume131, Issue5, 1 March 2025
DOI: https://doi.org/10.1002/cncr.35792

Abstract: Introduction: The role of adjuvant chemotherapy in localized, resectable soft tissue sarcomas (STSs) remains controversial. Despite positive findings reported in previous meta-analyses, the majority of randomized controlled trials (RCTs) fail to show a meaningful benefit. We conducted an updated meta-analysis to reassess the role of adjuvant chemotherapy in treating localized, resectable STSs.Methods: A comprehensive literature review was conducted to identify RCTs that compared local therapy (surgery with or without radiotherapy) to local therapy with adjuvant chemotherapy. Articles were independently reviewed, and risk of bias was assessed by two authors. The outcomes assessed were overall survival (OS) and disease-free survival (DFS). The meta-analysis was performed using a random effects model (to account for possible heterogeneity across studies) for survival endpoints with the inverse-variance method, in which each study is weighted with the inverse of the variance of its effect estimate.Results: A total of 19 RCTs comprising 2128 patients were included. Our study found that adjuvant chemotherapy improved OS (hazard ratio [HR], 0.80; p = .002) and DFS (HR, 0.78; p = .002). Doxorubicin-based monotherapy significantly improved OS (HR, 0.80; p = .01) and DFS (HR, 0.74; p = .0003), whereas doxorubicin-ifosfamide combined therapy did not significantly improve OS (HR, 0.78; p = .078) or DFS (HR, 0.94; p = .770). Doxorubicin-based ifosfamide combined therapy had moderate heterogeneity across studies.Conclusion: This study partially supports the benefit of adjuvant chemotherapy in the treatment of localized, resectable STSs. Nevertheless, because of the

heterogeneity of STSs, the benefit and the risks of treatment with adjuvant chemotherapy need to be evaluated on an individual benefit–risk basis.

25COASMA103

Title: Treatment-free remission in nontransplanted patients with Philadelphia chromosome-positive acute lymphoblastic leukemia

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Cancer, Volume131, Issue5, 1 March 2025
DOI: https://doi.org/10.1002/cncr.35773

Abstract: Background: The BCR::ABL1 tyrosine kinase inhibitors (TKIs) have significantly improved the outcomes of patients with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL). However, the optimal duration of TKI therapy in patients who achieve a complete molecular response (CMR; undetectable BCR::ABL1 transcripts) and who do not undergo allogeneic stem cell transplantation (allo-SCT) remains undefined.Methods The authors conducted a retrospective analysis of patients with Ph-positive ALL in first complete remission who achieved a CMR and discontinued TKI therapy, most commonly due to treatment-related side effects.Results In total, 14 patients were identified. The regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine was the primary backbone chemotherapy and was received by 12 patients (86%) combined with either imatinib (14%), dasatinib (43%), or ponatinib (29%) during induction. Two patients received blinatumomab and ponatinib. The median duration of TKI therapy was 60 months. The median CMR duration before TKI discontinuation was 46.1 months (range, 2.7–121.3 months). After a median follow-up of 42.5 months from TKI discontinuation, three patients (21%) experienced relapse (two molecular, one morphologic), whereas 11 patients (79%) maintained treatment-free remission. The median time to relapse was 6.4 months (range, 4–16 months), and two of three relapsed patients regained CMR after resuming TKI therapy. Importantly, none of the six patients with a CMR duration >48 months before TKI discontinuation relapsed.Conclusions The current findings suggest that TKI discontinuation may be safe for highly selected patients with Ph-positive ALL in first complete remission who maintain CMR for at least 48 months. Larger studies are needed to confirm these findings.

25COASMA104

Title: Anti-Müllerian hormone for assessing ovarian toxicity of cancer treatment in young women: It's complicated

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Cancer, Volume131, Issue5, 1 March 2025
DOI: https://doi.org/10.1002/cncr.35774

Abstract: The rising incidence of cancer among young women highlights the importance of understanding treatment-related gonadotoxicity, which can lead to infertility and long-term health complications from premature estrogen decline. Although anti-Müllerian hormone is considered the most reliable indicator of ovarian reserve, its interpretation among oncology

patients is complex because it is dependent on the treatment modality, necessitating further research to fully understand the impact of specific treatments on anti-Müllerian hormone and to identify alternative markers to reliably assess the ovarian toxicity of newer cancer therapies.

25COASMA105

Title: Impact of race/ethnicity on MammaPrint genomic assay risk and prognosis in early breast cancer: A National Cancer Data Base analysis

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Cancer, Volume131, Issue5, 1 March 2025
DOI: https://doi.org/10.1002/cncr.35771

Abstract: Background: Black race is associated with poorer prognosis in hormone receptor (HR)–positive, HER2-negative early breast cancer (EBC). The impact of race/ethnicity on the risk distribution and prognostic information provided by the 70-gene MammaPrint assay was evaluated.Methods Women with HR-positive EBC with tumors up to 5 cm in size and zero to three involved lymph nodes, who were diagnosed between 2009 and 2018, and who had an available MammaPrint result were identified in the National Cancer Data Base (NCDB). t-tests and $\chi 2$ tests were used to compare patient characteristics, whereas log-rank tests assessed differences in overall survival (OS) between racial/ethnic subgroups.Results Of the 6137 women included, 82.8% (n = 5084) were non-Hispanic White, 8.9% (n = 545) were non-Hispanic Black (NHB), 4.8% (n = 292) were Hispanic, and the remainder were other/unknown (n = 216). Of these women, 58.4% (n = 3587) were MammaPrint low risk and 41.6% (n = 2550) were MammaPrint high risk. NHB and Hispanic women were more likely to have a high-risk MammaPrint result ($p < .001$) than other racial/ethnic subgroups. Five-year OS was worse for the MammaPrint high-risk versus low-risk group (92.6% vs. 96.6%; $p < .0001$). There were no significant differences in OS on the basis of race/ethnicity in the MammaPrint low-risk ($p = .34$) or high-risk ($p = .79$) subgroups. However, Black race did not affect mortality in the overall population (hazard ratio, 1.15; 95% confidence interval, 0.84–1.58).Conclusions NHB and Hispanic women were more likely to have high-risk MammaPrint results in this NCDB cohort. Although there were no differences in survival by race/ethnicity in the MammaPrint low- and high-risk groups, these findings are limited by the lack of association between race/ethnicity and mortality in the overall population when adjusting for other clinicopathologic prognostic covariates.

25COASMA106

Title: Clinician's primer for soft tissue sarcomas: Nuances of histologic subtypes

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Cancer, Volume131, Issue5, 1 March 2025
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Abstract: Soft tissue sarcomas are a rare group of mesenchymal malignancies, with greater than 100 histologic subtypes. Advancements in understanding these subtypes has enabled histology-tailored management. This primer describes the workup and management of

generalized soft tissue sarcomas of the extremity, trunk, and retroperitoneum while also highlighting the unique attributes of many subtypes. The subtypes chosen for review include those that are most common as well as those demonstrating unique behaviors or targets for management. The focus is on initial management of localized disease; however, for situations in which novel systemic agents have been discovered, the treatment of metastatic disease is discussed. This report is a reference to be used in addition to other comprehensive reviews, such as guidelines from the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the American Society for Radiation Oncology. It is not a substitute for referral to an expert sarcoma center for critical pathology review and management by an experienced team. Importantly, patients who are treated at expert sarcoma centers have better outcomes than those who are not.

25COASMA107

Title: Disparities in the cancer continuum experienced by transgender and gender-diverse patients: A rapid review

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Cancer, Volume131, Issue5, 1 March 2025
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Abstract: Transgender and gender-diverse (TGD) populations experience health disparities across all areas of health care due to issues of bias, discrimination, and structural barriers to care. Existing literature on cancer screening in TGD populations demonstrates significant gaps in care; for example, transgender men receive Pap smears at lower rates than cisgender women. Because of known disparities in cancer screening, and gaps in our understanding in terms of diagnosis, treatment, and survivorship, the authors conducted a rapid review of the literature to examine cancer care continuum (screening, treatment, and survivorship) disparities among TGD persons. The results reported disparities across the cancer care continuum. Although there is currently limited research on cancer diagnosis, treatment, and survivorship, the available evidence indicates TGD patients are diagnosed with cancer at later stages than cisgender patients. TGD patients were also less likely than cisgender patients to receive treatment for some types of cancer. The results of this rapid review demonstrate the need for more research across the cancer care continuum for TGD patients with significant gaps in knowledge for cancer treatment and survivorship.

25COASMA108

Title: The association of physical activity with survival in colon cancer versus a matched general population: Data from Cancer and Leukemia Group B 89803 and 80702 (Alliance)

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Cancer, Volume131, Issue5, 1 March 2025
DOI: https://doi.org/10.1002/cncr.35727

Abstract: Background: Colon cancer patients have inferior overall survival than a matched general population (MGP). It is unknown if physical activity is associated with a reduction in

this survival disparity.Methods Data were analyzed from two National Cancer Institute–sponsored postoperative treatment trials in stage III colon cancer, Cancer and Leukemia Group B (CALGB) 89803 and 80702, with 2876 patients who self-reported physical activity. Physical activity was converted to metabolic equivalents (MET-hours/week). The MGP was derived from the National Center for Health Statistics and matched on age, sex, and year.Results In CALGB 89803, among patients who were alive at 3 years, those with <3.0 and ≥18.0 MET-hours/week had subsequent 3-year overall survival rates that were −17.1% (95% confidence interval [CI], −22.4 to −11.8) and −3.5% (95% CI, −7.7 to 0.3) lower than MGP, respectively. In CALGB 80702, among patients who were alive at 3 years, those with <3.0 and ≥18.0 MET-hours/week had subsequent 3-year overall survival rates that were −10.8% (95% CI, −15.4 to −6.9) and −4.4% (95% CI, −7.6 to −1.6) lower than MGP, respectively. In pooled analyses, among patients who were alive and did not have tumor recurrence by year 3 (n = 1908), those with <3.0 and ≥18.0 MET-hours/week had subsequent 3-year overall survival rates that were −3.1% (95% CI, −6.2 to −0.3) lower and 2.9% (95% CI, 1.5–4.2) higher than MGP, respectively. Conclusions Physical activity is associated with an attenuation of the survival disparity between patients with stage III colon cancer participating in clinical trials and MGP. Colon cancer survivors who are physically active may achieve survival that approximates the MGP.

25COASMA109

Title: Glioma mutational signatures associated with haloalkane exposure are enriched in firefighters

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Abstract: Background: Glioma is the most common malignant primary brain tumor and is associated with significant morbidity and mortality. Modifiable risk factors remain unidentified. New advances in exposure assessment, genomic analyses, and statistical techniques permit more accurate evaluation of glioma risk associated with exogenous occupational or environmental exposures.Methods: By using whole-exome sequencing data from matched germline and glioma tumor samples, the authors compared tumor mutational signatures for 17 persons with glioma and a documented occupational history of firefighting with those of 18 persons with glioma without an occupational history of firefighting. All 35 individuals were participants in the University of California, San Francisco Adult Glioma Study.Results: There was a positive correlation among firefighters between the median number of sample variants attributable to single-base substitution signature 42, a single-base substitution mutational signature associated with haloalkane exposure (from the Catalogue of Somatic Mutational Signatures in Cancer) and firefighting years (p = .04; R2 = 0.29). Among nonfirefighters, the individuals with the highest number of median variants attributable to single-base substitution signature 42 also had occupations that possibly exposed them to haloalkanes, such as painting and being a mechanic. Conclusions: In summary, the authors identified gliomas that had mutational signatures associated with haloalkane exposure that were enriched in firefighters and other occupations.

25COASMA110

Title: Utilization, health care expenditures, and patient costs of definitive treatment modalities for localized prostate cancer in the United States

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Abstract: Background: Radical prostatectomy (RP) and radiotherapy (RT) are standard-of-care treatments for localized prostate cancer. The authors studied the utilization and total health care and patient-incurred costs of RP and RT in the United States using the Merative MarketScan Medicare (Medicare Supplemental and Coordination of Benefits [MDCR]) and Commercial (Commercial Claims and Encounters [CCAE]) databases.Methods: Men were identified who had nonmetastatic prostate cancer treated with RP, external-beam RT (EBRT), brachytherapy (BT), EBRT combined with BT (EBRT + BT), stereotactic body RT (SBRT), or proton-beam therapy (PBT) between 2009 and 2022. Year-to-year treatment utilization was compared using the Kendall Tau-b test. Mean total health care and patient out-of-pocket costs within 12 months of treatment were compared using the Kruskal–Wallis test.Results: In the MDCR database, 44,937 patients were identified who received treatment with RP (n = 12,879), EBRT (n = 26,193), BT (n = 926), EBRT + BT (n = 4706), PBT (n = 57), or SBRT (n = 176). Between 2009 and 2021, EBRT use increased from 52.5% to 62.2% (p for trend < .001), SBRT increased from 0.4% to 0.5% (p < .001), BT decreased from 3.1% to 1.0% (p < .001), and EBRT + BT decreased from 14.8% to 6.8% (p < 0.001); whereas use remained similar for RP (from 29.1% to 29.4%; p = .82) and PBT (from 0.1% to 0.1%; p = .93). In the CCAE database, 75,626 patients were identified who received treatment with RP (n = 50,278), EBRT (n = 16,985), BT (n = 1243), EBRT + BT (n = 6811), PBT (n = 92), or SBRT (n = 217). EBRT use increased from 20.0% to 24.9% (p < .001), SBRT increased from 0.1% to 0.8% (p < .001), BT decreased from 2.5% to 0.7% (p < .001), and EBRT + BT decreased from 10.6% to 7.4% (p < .001); whereas use remained similar for RP (from 66.8% to 66.1%; p for trend = .82), and PBT (from 0.1% to 0.1%; p for trend = .76). In the MDCR and CCAE databases, PBT had the highest total cost, whereas BT had the lowest.Conclusions: Between 2009 and 2021, there was increasing use of EBRT and SBRT, whereas use of RP remained stable. Although BT was the least costly, its utilization as monotherapy and combined with EBRT declined.

25COASMA111

Title: Health literacy and all-cause mortality among cancer patients

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Abstract: Background: The association between health literacy and all-cause mortality among cancer patients remains unclear.Methods: This is a retrospective cohort study of 9603 patients diagnosed with prostate, lung, breast, renal, colorectal, brain, head and neck, bladder, pancreatic, liver, sarcoma, and gastric cancers who were screened for health literacy between

2008 and 2018, using the Brief Health Literacy Screen (BHLS). Higher scores (range, 3–15) indicate higher health literacy. The association between all-cause mortality and health literacy was estimated using multivariable Cox proportional hazards models. Results: A total of 8608 (89%) patients were non-Hispanic White. The median follow-up was 3.1 years. Patients with a BHLS score of 15 had a median survival improvement of 9.4 months (95% confidence interval [CI], 6.0–13.2 months) compared to those with a score of 9. Lower BHLS scores (9 vs. 15) were associated with higher mortality in stages II (adjusted hazard ratio [aHR], 2.6 [95% CI, 1.5–5.1]) and III (aHR 2.9 [95% CI, 1.4-6.0]) prostate cancer; stages I (aHR 1.7 [95% CI, 1.1–2.5]) and IV (aHR, 1.6 [95% CI, 1.2–2.1]) lung cancer; stage I colorectal cancer (aHR, 2.2 [95% CI, 1.3–4.7]); stage I renal cancer (aHR, 1.8 [95% CI, 1.1–3.4]); stages I (aHR, 2.6 [95% CI, 1.3–7.1]) and IV (aHR, 1.7 [95% CI, 1.2–2.7]) head and neck cancer; stage II bladder cancer (aHR, 1.6 [95% CI, 1.0–2.8]); stage I liver cancer (aHR, 4.1 [95% CI, 1.9–9.3]); and all stages of breast cancer.Conclusions: Lower health literacy was associated with higher all-cause mortality among patients with 12 different types of cancer, varying by cancer type and stage.

25COASMA112

Title: The effect of online cognitive behavioral therapy for insomnia in adolescents and young adults after childhood cancer: Results from a randomized controlled trial

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Cancer, Volume131, Issue6, 15 March 2025
DOI: https://doi.org/10.1002/cncr.35796

Abstract: Background: Insomnia is common during and after childhood cancer and associated with negative health outcomes and impaired quality of life. Many adolescents and young adults do not receive treatment. Internet-delivered cognitive behavioral therapy for insomnia (iCBT-i) can fill this gap. This study assesses the effectiveness of the iCBT-i intervention “iSleep youth”.Methods: Patients (12–30 years old) with an Insomnia Severity Index ≥8, ≥6 months after treatment, and <10 years after diagnosis were 1:1 randomized to iSleep youth or the wait list-control group. iSleep youth consists of five online sessions with a coach. Outcomes were sleep efficiency (actigraph-based), insomnia, fatigue, and health-related quality of life (HRQOL). Differences over time between iSleep youth and controls, 3 months (T3) and 6 months (T6) from baseline, were assessed with linear mixed models, controlling for age, sex, and time since end of treatment. iSleep youth also had a follow-up measurement after 12 months (T12). Results: Fifty-four (response rate, 49%) patients participated: 68.9% females, mean age, 18.5 years (SD = 3.5), and mean time since end of treatment 3.8 years (SD = 2.3). No significant effects between the two groups were found for sleep efficiency. However, iSleep youth had a beneficial effect on insomnia severity at T3 (β = –0.79) and T6 (β = –0.55), on fatigue at T3 (β = –1.08) and T6 (β = –0.52) and on HRQOL at T3 (β = 0.46) and T6 (β = 0.62). The scores did not change from T6 to T12 in iSleep youth. Conclusions: iSleep youth is effective in treating insomnia and concurrent fatigue in adolescents and young adults after childhood cancer and should be implemented.

25COASMA113

Title: Serine Hydrolase-Catalyzed Polyol Lipids are Necessary for Rodlet Layer Formation on the Cell Wall of Entomopathogenic Fungi

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J. Am. Chem. Soc. 2025, 147, 6, 4701–4706
DOI: https://doi.org/10.1021/jacs.4c15577

Abstract: Some key secondary metabolism genes are important for driving the infection process of entomopathogenic fungi; however, their chemical substance basis has not been well investigated. Here, mixtures of polyol lipids are discovered, which are synthesized through iterative chain transfer–esterification–hydrolysis cycles catalyzed by serine hydrolase during the release of online highly reducing polyketide intermediates. Importantly, an in vivo gene knockout experiment revealed that the synthesis of polyol lipids is necessary for rodlet layer formation on the cell wall of Beauveria bassiana. Our work uncovers an unexpected way for the synthesis of polyol lipids and illuminates a new perspective on their part in significant physiological processes in entomopathogenic fungi.

Keyword: Cells, Cluster chemistry, Lipids, Peptides and proteins, Polyols

25COASMA114

Title: Facilitated Channeling of Fixed Carbon and Energy into Chemicals in Artificial Phototrophic Communities

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J. Am. Chem. Soc. 2025, 147, 6, 4707–4713
DOI: https://doi.org/10.1021/jacs.4c15940

Abstract: Light-driven CO2 biovalorization offers a promising route for coupling carbon mitigation with petrochemical replacement. Synthetic phototrophic communities that mimic lichens can reduce the metabolic burden with improved CO2 utilization. However, inefficient channeling of carbon and energy between species seriously hinders the collaborative CO2-to-molecule route. Herein, we report a universal carbon sequestration (UCS) module based on photosynthetic microbes that provides a high-speed tunnel for channeling carbon and energy to heterotrophs. Compared to that of the traditional CO2-to-sucrose module, the UCS module sequestered 30% more carbon into glycerol, a generally available carbon source with high energy density. We demonstrated that the UCS module can be highly compatible with various industrial chassis and genetically recalcitrant microbes, enabling the rapid development of synthetic phototrophic communities without additional genetic manipulation. Notably, the accelerated electron transport and nutrient recycling systems may facilitate carbon and energy communications between cooperative partners. These UCS module-based communities efficiently channeled CO2 into a wide range of chemicals, with a negative carbon footprint of −25.04 to −440.74 kgCO2e/kg of products. This strategy widens the boundaries of artificial photosynthetic communities and may boost carbon-negative biomanufacturing.

Keyword: Alcohols, Bacteria, Carbohydrates, Fungi, Luminescence.

25COASMA115

Title: In-Cell Mass Spectrometry and Ultraviolet Photodissociation Navigates the Intracellular Protein Heterogeneity

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J. Am. Chem. Soc. 2025, 147, 6, 4714–4719
DOI: https://doi.org/10.1021/jacs.4c16376

Abstract: Directly probing the heterogeneous conformations of intracellular proteins within their native cellular environment remains a significant challenge in mass spectrometry (MS). Here, we establish an in-cell MS and ultraviolet photodissociation (UVPD) strategy that directly ejects proteins from living cells into a mass spectrometer, followed by 193 nm UVPD for structural analysis. Applying this approach to calmodulin (CaM), we reveal that it adopts more extended conformations within living cells compared with purified samples in vitro, highlighting the unique influence of intracellular environments on protein folding. Furthermore, UVPD analysis of calcium ion (Ca2+)-binding variants of CaM unveils not only the conformational heterogeneity induced by multiple Ca2+ modulations but also reveals distinct preferences of Ca2+ binding sites across different conformations. This strategy provides a powerful tool for interrogating the structure–function relationships of intracellular protein variants with sophisticated metal ion binding, paving the way for a deeper understanding of protein conformations within their native cellular context.

Keyword: Conformation, Ions, Peptides and proteins, Physical and chemical properties, Protein structure

25COASMA116

Title: Photolytic and Thermal Reactions of [C6H4(PPh2)2(μ-N2)] and Its Lewis Acid Adducts: N–N Bond Cleavage and Liberation of N2

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J. Am. Chem. Soc. 2025, 147, 6, 4720–4725
DOI: https://doi.org/10.1021/jacs.4c16123

Abstract: The known species (Ph3P)2N2 was previously described as two phosphine donors associated with a doubly Lewis acidic N2-unit based on its thermal liberation of N2. Herein, we prepare the related species [C6H4(PPh2)2(μ-N2)] 4, where the cisoid chelation of the N2 fragment facilitates both N2 liberation and N–N bond cleavage reactions. In addition, these reactions can be achieved selectively via thermolysis of a Lewis acid adduct of 4 or by direct photolysis, respectively. These findings provide insights on avenues to P(V) reduction, photochemical N–C bond formation, and the design of donor–acceptor combinations for N2 capture and functionalization.

25COASMA117

Title: Molecular Uranium Dioxide-Mediated CO2 Photoreduction

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J. Am. Chem. Soc. 2025, 147, 6, 4726–4730

DOI: https://doi.org/10.1021/jacs.4c17188
Abstract: The reduction of CO2 mediated by transition metals has garnered significant interest, yet little is known about the reduction of CO2 using f-element compounds. Herein, the reduction of CO2 to CO by tetravalent uranium (UIV) compound UO2 is investigated via matrix isolation infrared spectroscopy and quantum chemical study. Our results reveal that a stable carbonate intermediate OUIVCO3 (A) can be prepared at low temperatures (4–12 K). Through photolytic reactions of A under visible-light irradiations (495 nm < λ < 580 nm), the charge-separated pentavalent UV isomer [UVO2]+[(η2-O2C)]− (B) is produced through electron transfer from the quasi-atomic U-7s orbital to the CO2 moiety. Sequentially, one C═O bond in CO2 breaks by successive UV–visible irradiation (250 nm < λ < 580 nm), and the photolysis generates the products CO and hexavalent UVI compound UVIO3 following two intermediates UVIO3(CO) (C) and UVIO3(OC) (D) with a physiosorbed carbonyl group. Moreover, the evolution of oxidation states from electron-rich UIV to UVI on multiple potential energy surfaces of different electronic states involving configurations U(f1s1 → f2 → f1 → f0) is further demonstrated. Our findings unveil a mechanism for the photoreduction of CO2 by a UO2 molecule. This strategy can be used to design molecular and solid-state catalysts for depleted uranium for CO2 reduction reactions.

25COASMA118

Title: Asymmetric Total Synthesis of Janthinoid A

Fu Tang, Zhong-Chao Zhang, Zhi-Lin Song, Yuan-He LiZi-Hao Zhou, Jia-Jun ChenZhen Yang

J. Am. Chem. Soc. 2025, 147, 6, 4731–4735
DOI: https://doi.org/10.1021/jacs.4c17480
Abstract: The asymmetric total synthesis of janthinoid A has been accomplished for the first time in 14 steps without using a protecting group. The trans-decalin subunit and the rigid oxabicyclo[3.2.1]octane motif were constructed via an epoxide-initiated cationic π-cyclization reaction and a Fe(ClO4)3-mediated oxidative cascade cyclization reaction, respectively.

25COASMA119

Title: Single-Molecule Oxidoreductase Activity Analysis for Activity-Based Diagnosis Based on Proteoform Alterations

Mayano, Minoda, Junpei Hatakeyama, Norimichi Nagano, Tadahaya Mizuno, Takumi Iwasaka, Sho Shiga,

J. Am. Chem. Soc. 2025, 147, 6, 4743–4751
DOI: https://doi.org/10.1021/jacs.4c07624
Abstract: We developed a single-molecule enzyme activity assay platform for NAD(P)+-dependent oxidoreductases, leveraging a new NAD(P)H-responsive fluorogenic probe optimized for microdevice-based fluorometric detection. This platform enabled the detection of enzyme activities in blood and cerebrospinal fluid (CSF), including lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and hexokinases. We demonstrate its potential for activity-based diagnosis by detecting altered populations of enzyme activity species in blood and CSF from liver damage in brain tumor patients.

25COASMA120

Title: Energizing Robust Sulfur/Lithium Electrochemistry via Nanoscale-Asymmetric-Size Synergism

Youzhang Huang, Jiantao Li, Yinggan Zhang

J. Am. Chem. Soc. 2025, 147, 6, 4752–4765
DOI: https://doi.org/10.1021/jacs.4c10238

Abstract: Sluggish redox kinetics and dendrite growth perplex the fulfillment of efficient electrochemistry in lithium–sulfur (Li–S) batteries. The complicated sulfur phase transformation and sulfur/lithium diversity kinetics necessitate an all-inclusive approach in catalyst design. Herein, a compatible mediator with nanoscale-asymmetric-size configuration by integrating Co single atoms and defective CoTe2–x (CoSA-CoTe2–x@NHCF) is elaborately developed for regulating sulfur/lithium electrochemistry synchronously. Substantial electrochemistry and theoretical analyses reveal that CoTe2–x exhibits higher catalytic activity in long-chain polysulfide transformation and Li2S decomposition, while monodispersed Co sites are more effective in boosting sulfur reduction kinetics to regulate Li2S deposition. Such cascade catalysis endows CoSA-CoTe2–x@NHCF with the all-around service of “trapping-conversion-recuperation” for sulfur species during the whole redox reaction. Furthermore, it is demonstrated by in situ transmission electron microscopy that initially formed electronic-conductive Co and ionic-conductive Li2Te provide sufficient lithiophilic sites to regulate homogeneous Li plating and stripping with markedly suppressed dendrite growth. Consequently, by coupling the CoSA-CoTe2–x@NHCF interlayer and Li@CoSA-CoTe2–x@NHCF anode, the constructed Li–S full batteries deliver superior cycling stability and rate performance, and the flexible pouch cell exhibits stable cycling performance at 0.3 C. The gained insights into the synergistic effect of asymmetric-size structures pave the way for the integrated catalyst design in advanced Li–S systems.

25COASMA121

Title: Disentangling Driving Force Effects, Polar Effects, e–/H+ Imbalance, and Other Influences on H-Atom Transfer Reactions

Benjamin D. Groff, Mauricio Cattaneo

J. Am. Chem. Soc. 2025, 147, 6, 4766–4777
DOI: **https://doi.org/10.1021/jacs.4c10596**

Abstract: Hydrogen atom transfer (HAT) reactions and their kinetic barriers ΔGHAT‡ are important in organic and inorganic chemistry. This study examines factors that influence ΔGHAT‡, reporting the kinetics and thermodynamics of HAT from various ruthenium bis(acetylacetonate) pyridine-imidazole complexes to nitroxyl radicals. Across these 36 reactions, the ΔGPT° and ΔGHAT° can be independently varied, with different sets of Ru complexes primarily tuning either their pKas or their E°s. The ΔΔGHAT‡ are analyzed using multiple linear free energy relationships (LFERs), the first largely experimental study of its kind. The barriers vary most strongly with the overall driving force, ΔΔGHAT‡ = 0.28 × ΔΔGHAT°, but are also affected by HAT intrinsic barriers (λ), sterics, and the thermochemical e–/H+ imbalance of the reactions, |ΔGPT° – ΔGET°|. The latter is a small but significant effect, revealed only by comparing LFERs. The imbalance analysis is closely related to traditional explanations of polar effects, but it is quantitative: ΔGHAT‡ shifts by

∼4% with changes in |ΔGPT° – ΔGET°|. This is the same dependence as was observed for purely organic HAT from toluenes─a remarkable result because traditional explanations of organic polar effects, e.g., using X–H bond polarities, do not apply to the Ru complexes in which the e– and H+ are spatially separated. This work demonstrates the strong similarities between different kinds of HAT reactions when viewed through the lens of H+/e– (PCET) free energies. This lens also shows that ΔGHAT‡ are ∼10-fold more sensitive to changes in ΔGHAT° and λ than to the e–/H+ free-energy imbalance.

25COASMA122

Title: Surface Copassivation Strategy for Developing Water-Soluble InP Colloidal Quantum Dots with High Luminescence and Suppressed Blinking

Zhe Liu, Xiaoqi Hou, Huangpeng You, Zheng Wang, Kaijie Zhu

J. Am. Chem. Soc. 2025, 147, 6, 4778–4789

DOI: **https://doi.org/10.1021/jacs.4c10731**

Abstract: Colloidal quantum dots (QDs) are promising emitters for biological applications because of their excellent fluorescence, convenient surface modification, and photostability. However, the toxic cadmium composition in the state-of-the-art QDs and their inferior properties in the aqueous phase greatly restrict further use. The performance of water-soluble indium phosphide (InP) QDs lags far behind those of Cd-containing counterparts due to the lack of effective surface protection. Here, we present an efficient copassivation strategy via dual hydrophilic ligands to achieve water-soluble InP-based QDs with ideal optical properties. A record photoluminescence quantum yield of near-unity and monoexponential decay dynamics for water-soluble InP-based QDs are achieved. For the first time, we realize a single water-soluble InP-based QD with significantly suppressed blinking. Furthermore, the novel QDs exhibit superior cellular imaging capabilities and high resistance to photobleaching compared with commonly used organic dyes. The results presented here will inspire the development of environmentally friendly water-soluble QDs as a promising class of fluorescence labels for biological applications.

25COASMA123

Title: Four-Electron-Transferred Pyrene-4,5,9,10-tetraone Derivatives Enabled High-Energy-Density Aqueous Organic Flow Batteries

Guangxu Ge, Chenkai Mu, Yonggang Wang, Changkun Zhang, Xianfeng Li

J. Am. Chem. Soc. 2025, 147, 6, 4790–4799

DOI: **https://doi.org/10.1021/jacs.4c12506**

Abstract: Multielectron-transferred molecules hold great potential to enhance the energy density and reduce the cost for aqueous organic flow batteries (AOFBs). However, the extended conjugated units required for increasing redox-active sites and stabilizing the multielectron reaction always decrease the molecular polarity, limiting the solubility in the electrolyte. Herein, we presented an asymmetrical pyrene-4,5,9,10-tetraone-1-sulfonate (PTO–PTS) monomer which not only could reversibly store four electrons but also exhibited a high theoretical electron concentration of 4.0 M and the strongly heat-resistant intermediate semiquinone free radical. As a result, PTO–PTS-based AOFBs demonstrated a high energy density of 59.6 Wh Lcatholyte–1 (89 Ah L–1) with an ultrastable capacity retention of nearly

100% for above 5200 cycles (60 days). Moreover, the heat-stable PTO–PTS structure further enabled both symmetric and full cells to achieve remarkable cycling durability for over a thousand cycles at 60 °C. The outstanding cell performance and high thermal stability suggest its promising application in large-scale energy storage.

25COASMA124

Title: Entropy-Tailored Fast-Charging Sodium Layered Cathodes

Haoji Wang, Yu Mei, Jinqiang Gao, Lianshan Ni, Ningyun Hong, Lu Ma

J. Am. Chem. Soc. 2025, 147, 6, 4810–4820
DOI: **https://doi.org/10.1021/jacs.4c12733**

Abstract: O3-type layered transition metal (TM) oxides are widely used as cathode materials for Na-ion batteries due to their high energy density potential, enabled by the state of charge (SoC)-dependent transition from octahedral (O-type) to prismatic (P-type) structures during Na-ion (de)sodiation. However, the O–P transition is often criticized for compromising the Na-ion mobility and limiting the cycle life. Herein, we reveal the intrinsic correlation between O–P transitions, oxygen behaviors, and Na-ion kinetics. We demonstrate that a compositionally versatile, entropy-tailored approach can promote preferred transitions (characterized by large lattice parameter deviations in the O-type region and rapid O–P biphasic reactions), enhancing Na-ion migration, as revealed by in situ high-energy synchrotron X-ray diffraction (HEXRD). Additionally, irreversible oxygen loss at high SoC is effectively mitigated, while TM migration and surface reconstruction are greatly suppressed, further accelerating Na-ion transport and stabilizing the structure, as confirmed by X-ray absorption spectroscopy (XAS) and theoretical analyses. The result is an exceptionally high rate capability of 88.7 mAh g–1 at 20 C (2.4 A g–1) with a superior normalized retention of 72.6%, accompanied by a prolonged lifetime with 74.3% retention after 1000 cycles. This work advances the understanding of the chemistry–property relationships in O3-type layered cathodes and broadens the prospects for fabricating high-power-density electrodes.

25COASMA125

Title: Disulfide-Directed Multicyclic Peptides with N-Terminally Extendable α-Helices for Recognition and Activation of G Protein-Coupled Receptors

Shihui FanJie LiJie Zhuang

J. Am. Chem. Soc. 2025, 147, 6, 4821–4832
DOI: https://doi.org/10.1021/jacs.4c12808

Abstract: Many peptide hormones adopt long α-helical structures upon interacting with their cognate receptors but often exhibit flexible conformations when unbound. Strategies that can stabilize long α-helices without disrupting their binding to receptors are still lacking, which hinders progress in their biological applications and drug development. Here, we present an approach that combines rational design with library screening to create and identify a unique disulfide-directed multicyclic peptide (DDMP) scaffold, which could effectively stabilize N-terminally extendable α-helices while displaying exceptional efficiency in disulfide pairing and oxidative folding. This DDMP scaffold was then utilized for stabilizing the α-helical structure of glucagon-like peptide-1 (GLP-1), resulting in a potent GLP-1 receptor (GLP-1R)

agonist with a significantly improved α-helicity and proteolytic stability. By incorporating external α-helices into the DDMP scaffold, we can effectively preserve the native N-terminal α-helical structures while allowing for extensive evolution of the C-terminal disulfide-rich domain for enhancing target binding, as demonstrated by the generation of the DDMP-stabilized GLP-1 (g1:Ox). The cryo-electron microscopy structure of the g1:Ox–GLP-1R in complex with heterotrimeric Gs reveals the molecular basis for the potent binding between g1:Ox and GLP-1R. Specifically, the DDMP moiety establishes additional interactions with the extracellular domain of GLP-1R, which are absent in the case of GLP-1. Thus, this work offers a novel and effective approach for engineering therapeutic peptides and other peptide α-helices, ensuring that both the N- and C-terminal regions remain essential for target recognition and activation.

25COASMA126

Title: Atomic-Level Tin Regulation for High-Performance Zinc–Air Batteries

Yunrui Li, Jiaqi XuFan Lan

J. Am. Chem. Soc. 2025, 147, 6, 4833–4843

DOI: https://doi.org/10.1021/jacs.4c12601

Abstract: The trade-off between the performances of the oxygen reduction reaction (ORR) and oxygen evolution reaction (OER) presents a challenge in designing high-performance aqueous rechargeable zinc–air batteries (a-r-ZABs) due to sluggish kinetics and differing reaction requirements. Accurate control of the atomic and electronic structures is crucial for the rational design of efficient bifunctional oxygen electrocatalysts. Herein, we designed a Sn–Co/RuO2 trimetallic oxide utilizing dual-active sites and tin (Sn) regulation strategy by dispersing Co (for ORR) and auxiliary Sn into the near-surface and surface of RuO2 (for OER) to enhance both ORR and OER performances. Both theoretical calculations and advanced dynamic monitoring experiments revealed that the auxiliary Sn effectively regulated the atomic/electronic environment of Ru and Co dual-active sites, which optimized the *OOH/*OH adsorption behavior and promoted the release of the final products, thus breaking the reaction limits. Therefore, the as-designed Sn–Co/RuO2 catalysts exhibited superb bifunctional performance with an oxygen potential difference (ΔE) of 0.628 V and negligible activity degradation after 200,000 (ORR) or 20,000 (OER) CV cycles. The a-r-ZABs based on the Sn–Co/RuO2 catalyst exhibited a higher performance at a wide temperature range of −30 to 65 °C. They demonstrated an ultralong lifespan of 138 days (20,000 cycles) at 5 mA cm–2, 39.7 times higher than that of Pt/C + IrO2 coupled catalysts at a low temperature of −20 °C. Additionally, they maintained an initial power density of 85.8% after long-term tests, significantly outperforming previously reported catalysts. More importantly, the a-r-ZABs also showed excellent stability of 766.45 h (about 4598 cycles) at a high current density of 10 mA cm–2.

25COASMA127

Title: Reticular Synthesis of Covalent Organic Frameworks with kgd-v Topology and Trirhombic Pores

Yuan-Zhe ChengHui-Yuan Kong

J. Am. Chem. Soc. 2025, 147, 6, 4844–4852

DOI: https://doi.org/10.1021/jacs.4c12973
Abstract: Two-dimensional (2D) covalent organic frameworks (COFs) with designable pore structures can be synthesized under the guidance of topology diagrams. Among the five existing edge-transitive topological nets, kgd topology is considered a fine candidate for constructing COFs with ultramicropores. However, all of the reported COFs with kgd topology need the use of C6-symmetric monomers, which are limited in compound type and difficult to synthesize. Here, we first develop a new approach to construct 2D COFs (clv-COFs) with a similar geometrical shape of kgd topology, named kgd-v topology, through the combination of C2v- and C3-symmetric monomers. The size of micropores in these clv-COFs is consistent with the rhombic pores in kgd topology and can be easily tuned by varying the length of C2v- and C3-symmetric monomers. These clv-COFs exhibit excellent atmospheric water harvesting (AWH) ability due to regular small micropores. An efficient water harvester based on clv-COF-1 can produce 1.73 L kg–1 day–1 at 45% relative humidity under solar illumination. Our approach enriches the reticular chemistry and can facilitate the research of COF-based AWH systems.

25COASMA128

Title: Intermolecular Misfolding Captured in Parallelly Organized Titin

Jiacheng Zuo, Hongbin Li

J. Am. Chem. Soc. 2025, 147, 6, 4853–4861
DOI: **https://doi.org/10.1021/jacs.4c13008**

Abstract: The giant muscle protein titin is largely responsible for the passive elasticity of the muscles. The I-band part of titin is elastic, and its constitutive immunoglobulin (Ig) domains undergo force-induced unfolding and refolding when the muscle is stretched toward or beyond the end of the physiological range of sarcomere length. Correct folding of the titin Ig domains is essential to the structure and functions of titin. Although our knowledge of titin elasticity at the molecular level has been largely obtained from single molecule experiments, titin does not exist as an isolated molecule. Instead, six titins are parallelly organized in the muscle sarcomeres. It remains unknown what impact such a parallel organization brings on the folding of titin Ig domains and titin elasticity. Using the two-molecule force spectroscopy technique, here, we report the direct observation of the intermolecular misfolding of titin Ig domains that are arranged in parallel. Our results reveal that when parallelly arranged, two I94 domains can misfold into an intermolecular domain-swapped state that is thermally and mechanically stable. Such intermolecular misfolding may play important structural and functional roles in titin organization and elasticity.

25COASMA129

Title: A Second Near-Infrared Window-Responsive Metal–Organic-Framework-Based Photosensitizer for Tumor Immunotherapy via Synergistic Ferroptosis and STING Activation

Huan ZhaoShujuan JinYang LiuQian Wang

J. Am. Chem. Soc. 2025, 147, 6, 4871–4885
DOI: https://doi.org/10.1021/jacs.4c13241

Abstract: Photodynamic therapy (PDT) holds promise as a cancer treatment modality due to

its potential for enhanced therapy precision and safety. To enhance deep tissue penetration and minimize tissue adsorption and phototoxicity, developing photosensitizers activated by second near-infrared window (NIR-II) light shows significant potential. However, the efficacy of PDT is often impeded by tumor microenvironment hypoxia, primarily caused by irregular tumor vasculature. Fortunately, the stimulator of interferon genes (STING) pathway, known for immune activation, has been linked to vasculature normalization. In this study, we developed a nanoplatform (Fe-THBQ/SR) by loading a STING agonist (SR-717) into an iron-tetrahydroxy-1,4-benzoquinone (Fe-THBQ) metal–organic framework. Fe-THBQ was proven to be an effective NIR-II photosensitizer, generating numerous reactive oxygen species (ROS) under 1064 nm laser irradiation. These ROS downregulated heat shock protein expression, consequently promoting mild-photothermal therapy (mild-PTT), and facilitated ferroptosis by depleting glutathione (GSH)/glutathione peroxidase 4. Moreover, Fe-THBQ/SR released SR-717 upon GSH stimulation, synergizing with the ROS-mediated double-stranded DNA leakage to enhance STING activation. This process contributed to tumor vasculature normalization and hypoxia alleviation, thereby enhancing the PDT efficacy. Overall, we presented a versatile single-laser-triggered nanoplatform (Fe-THBQ/SR) for NIR-II PDT and NIR-II mild-PTT and simultaneously coupled it with the effective activation of STING to form a reinforcing cycle. These synergistic enhancements increased the immunogenicity of tumor cells, remodeled the immunosuppressive tumor microenvironment, increased T lymphocyte infiltration, and improved therapeutic outcomes.

25COASMA130

Title: Suspended" Single Rhenium Atoms on Nickel Oxide for Efficient Electrochemical Oxidation of Glucose

Xunzhu Jiang, Xianhong Wu, Mingyue Lv, Xiaoli Pan

J. Am. Chem. Soc. 2025, 147, 6, 4886–4895
DOI: **https://doi.org/10.1021/jacs.4c13368**

Abstract: Well-defined single-atom catalysts (SACs) serve as ideal model systems for directly comparing experimental results with theoretical calculations, offering profound insights into heterogeneous catalytic processes. However, precisely designing and controllably synthesizing SACs remain challenging due to the unpredictable structure evolution of active sites and generation of embedded active sites, which may bring about steric hindrance during chemical reactions. Herein, we present the precious nonpyrolysis synthesis of Re SACs with a well-defined phenanthroline coordination supported by NiO (Re1-phen/NiO). Multiple experimental characterizations together with theoretical calculations unravel the idea that the isolated Re atoms are suspended on the NiO surface, connected by phenanthroline ligands standing perpendicular to the surface. This unique structure provides the Re1-phen/NiO SAC with a strong capability to activate glucose molecules, enabling fully exposed Re=O double bonds in an open-ended reaction environment to simultaneously react with hydroxyl and aldehyde groups at both ends of the glucose molecule, rapidly forming glucaric acid.

25COASMA131

Title: Structural Modulation and Enhanced Magnetic Ordering in Incommensurate

K1–xCrSe2 Crystals

Felix Eder, Catherine Witteveen, Enrico Giannini, Fabian O. von Roh

J. Am. Chem. Soc. 2025, 147, 6, 4896–4903
DOI: **https://doi.org/10.1021/jacs.4c13545**

Abstract: Layered delafossite-type compounds and related transition metal dichalcogenides, characterized by their triangular net structures, serve as prototypical systems for exploring the intricate interplay between crystal structure and magnetic behavior. Herein, we report on the discovery of the compound K1–xCrSe2 (x ≈ 0.13), an incommensurately modulated phase. Single crystals of this compound were grown for the first time using a K/Se self-flux. We find a monoclinic crystal structure with incommensurate modulation that can be rationalized by a 3 + 1-dimensional model. This modulation compensates for the under-stoichiometry of K cations, creating pronounced undulations in the CrSe2 layers. Our anisotropic magnetization measurements reveal that K1–xCrSe2 undergoes a transition to a long-range magnetically ordered state below TN = 133 K, a temperature 1.6 to 3.3 times higher than in earlier reported KCrSe2 compounds. Our findings open new avenues for tuning the magnetic properties of these layered materials through structural modulation.

25COASMA132

Title: Breaking Barcode Limits: Metal Nanoparticle Lego Brick Self-Assembly for High-Throughput Screening

Zili Huang, Xiaobo Xie, Yi WuRui Liu, Yi Lv

J. Am. Chem. Soc. 2025, 147, 6, 4904–4914
DOI: **https://doi.org/10.1021/jacs.4c13706**

Abstract: As precision medicine increasingly reveals the biological diversity among individuals, the demand for higher-throughput screening techniques, particularly suspension array technologies capable of more multiplexing from smaller samples in a single run, is intensifying. However, advancements in the multiplexing capability of current suspension platforms have lagged with limited alleviation, necessitating breakthroughs for innovative solutions that enable larger-scale measurements. Here, we introduce such a breakthrough with a novel mass-cytometric barcode engineering by metal nanoparticle-based “Lego Brick”-like self-assembly for high-throughput barcode design and capacity amplification. The suspension array capacity can be expanded to over 20,500 unique barcodes by flexibly assembling just 10 types of barcoding units (metal nanoparticles) onto the surface of the barcoding center (magnetic spheres) through a universal biotin–streptavidin binding template, significantly enhancing both throughput and versatility. Further multiplexed immunoassay, termed MassMAP, demonstrates high-throughput profiling of cancer biomarkers, highlighting the revolutionary potential of Lego Brick self-assembly in massive cytometric screening for higher-throughput applications.

25COASMA133

Title: Spatial Scale Matters: Hydrolysis of Aryl Methyl Ethers over Zeolites

Xian Wu, Mathias Bal, Qiang Zhang, Shao-Tao Bai, Ivan Scodeller

J. Am. Chem. Soc. 2025, 147, 6, 4915–4929
DOI: **https://doi.org/10.1021/jacs.4c13729**

Abstract: The local environment of the active site, such as the confinement of hydronium ions within zeolite pores, significantly influences catalytic turnover, similar to enzyme functionality. This study explores these effects in the hydrolysis of guaiacols─lignin-derived compounds─over zeolites in water. In addition to the interesting catechol products, this reaction is advantageous for study due to its bimolecular hydrolysis pathway, which involves a single energy barrier and no intermediates, simplifying kinetic studies and result interpretation. As in alcohol dehydration, hydronium ions show enhanced activity in ether hydrolysis due to undercoordination and increased electrophilicity when confined within zeolite pores, compared to bulk water. In addition, a volcano-shaped relationship between hydronium ion activity and Brønsted acid density was observed. However, unlike alcohol dehydration, this activity distribution cannot be attributed to variations in ionic strength within the pores, as the rate-determining step in the hydrolysis of guaiacols involves the attack of a neutral water molecule, unaffected by ionic strength. Instead, a detailed transition state analysis revealed a significant thermodynamic energy compensation effect, driven by the spatial organization of the transition state. This organization is influenced by the available reaction space, the interaction between the reacting species and the zeolite environment, leading to the volcano-shaped dependence. This phenomenon also explains the unusual reactivity order of the 4-R-guaiacol derivatives (R = H, Me, Et, Pr) with zeolite catalysis, extending beyond the traditional steric and electronic effects to provide a deeper understanding of reactant reactivity. The work concludes that the critical spatial parameters for fast ether hydrolysis─resulting in the highest hydronium activity─are determined by a combination of zeolite properties (topology and acid density) and reactant size.

25COASMA134

Title: Enhancing Chemoselectivity of On-Surface Reactions on Reconstructed Au(110): The Case of a Pentalene-Bridged Polyacene Analogue

Feifei Xiang, Amogh Kinikar, Markus Mühlinghaus

J. Am. Chem. Soc. 2025, 147, 6, 4930–4936

DOI: **https://doi.org/10.1021/jacs.4c13944**

Abstract: Polyacene analogues, consisting of short acene segments separated by nonbenzenoid rings, offer intriguing electronic properties and magnetic interactions. Pentalene-bridged polyacenes (PPs), in particular, hold promise for enhancing the electrical conductivity and potential open-shell ground states. However, PPs have remained elusive in solution chemistry due to poor solubility and limited synthetic protocols. Here, we report the on-surface synthesis of PPs through the annulation between ortho-xylene groups. Scanning tunneling microscopy and atomic force microscopy reveal that the reconstructed Au(110) surface significantly enhances the chemoselectivity of the annulation process. Scanning tunneling spectroscopy combined with density functional theory suggests that PP exhibits a narrow direct band gap, similar to long acenes. This work demonstrates the potential for band structure engineering in polyacene analogues by incorporating nonbenzenoid rings, paving the way to advancements in organic electronics and spintronics.

25COASMA135

Title: Theoretical Insights into the Selectivity of Single-Atom Fe–N–C Catalysts for

Electrochemical NOx Reduction

Yao Tan, Junwei Fu, Tao Luo,Kang Liu, Min Liu

J. Am. Chem. Soc. 2025, 147, 6, 4937–4944
DOI: **https://doi.org/10.1021/jacs.4c14021**

Abstract: Single-atom Fe–N–C catalysts have attracted significant attention in the NOx reduction reaction (NOxRR). However, the origin of their selectivity in the NOxRR remains unclear, impeding further advancements in application. Herein, we investigate the potential-driven competitive mechanism for NH3 and NH2OH production in the NOxRR over single-atom pyridinic-FeN4 and pyrrolic-FeN4 sites using constant-potential density functional theory calculations. The origin of selectivity in the NOxRR is linked to the switching of Fe 3d orbitals as they interact with intermediates. The selectivity between NH3 and NH2OH is determined by the applied potentials. The pyridinic-FeN4 predominantly generates NH3 at higher reduction potentials (−0.6 to −1.2 V, vs SHE), while NH2OH is favored at lower reduction potentials (0.6 to −0.6 V). The pyrrolic-FeN4 shows a similar potential-dependent product distribution, with a crossover potential of −1.0 V. The selectivity-determining intermediates (SDIs) in the NOxRR are *NH2OH and *NH2 + *OH. The potential-dependent selectivity is governed by the switching of Fe 3d orbitals interacting with SDIs, from dumbbell-shaped Fe 3dz2 to four-leaf clover-like Fe 3dxz, 3dyz, and 3dx2-y2, which plays a crucial role in controlling product distribution based on applied potentials. These findings offer new insights into the product selectivity of single-atom catalysts for the NOxRR.

25COASMA136

Title: Pressure-Induced Engineering of Surface Oxygen Vacancies on Metal Oxides for Heterogeneous Photocatalysis

Xiaoyi Wang, Sikang Xue, Meirong Huang, Wei Lin, Yidong Hou, Zhiyang Yu, Masakazu Anpo, Jimmy C. Yu, Jinshui Zhang, Xinchen Wang

J. Am. Chem. Soc. 2025, 147, 6, 4945–4951
DOI: **https://doi.org/10.1021/jacs.4c14073**

Abstract: Oxygen vacancies (OVs) spatially confined on the surface of metal oxide semiconductors are advantageous for photocatalysis, in particular, for O2-involved redox reactions. However, the thermal annealing process used to generate surface OVs often results in undesired bulk OVs within the metal oxides. Herein, a high pressure-assisted thermal annealing strategy has been developed for selectively confining desirable amounts of OVs on the surface of metal oxides, such as tungsten oxide (WO3). Applying a pressure of 1.2 gigapascal (GPa) on WO3 induces significant lattice compression, which would strengthen the W–O bonds and increase the diffusion activation energy for the migration of the O migration. This pressure-induced compression effectively inhibits the formation of bulk OVs, resulting in a high density of surface-confined OVs on WO3. These well-defined surface OVs significantly enhance the photocatalytic activation of O2, facilitating H2O2 production and aerobic oxidative coupling of amines. This strategy holds promise for the defect engineering of other metal oxides, enabling abundant surface OVs for a range of emerged applications.

25COASMA137

Title: Fractional Spinon Quasiparticles in Open-Shell Triangulene Spin-1/2 Chains

Zhangyu Yuan, Xin-Yu Zhang, Yashi Jiang, Xiangjian Qian, Ying Wang, Yufeng Liu

J. Am. Chem. Soc. 2025, 147, 6, 5004–5013

DOI: **https://doi.org/10.1021/jacs.4c14712**

Abstract: The emergence of spinon quasiparticles, which carry spin but lack charge, is a hallmark of collective quantum phenomena in low-dimensional quantum spin systems. While the existence of spinons has been demonstrated through scattering spectroscopy in ensemble samples, real-space imaging of these quasiparticles within individual spin chains has remained elusive. In this study, we construct individual Heisenberg antiferromagnetic spin-1/2 chains using open-shell [2]triangulene molecules as building blocks. Each [2]triangulene unit, owing to its sublattice imbalance, hosts a net spin-1/2 in accordance with Lieb's theorem, and these spins are antiferromagnetically coupled within covalent chains with a coupling strength of J = 45 meV. Through scanning tunneling microscopy and spectroscopy, we probe the spin states, excitation gaps, and their spatial excitation weights within covalent spin chains of varying lengths with atomic precision. Our investigation reveals that the excitation gap decreases as the chain length increases, extrapolating to zero for long chains, consistent with Haldane's gapless prediction. Moreover, inelastic tunneling spectroscopy reveals an m-shaped energy dispersion characteristic of confined spinon quasiparticles in a one-dimensional quantum box. These findings establish a promising strategy for exploring the unique properties of excitation quasiparticles and their broad implications for quantum information.

25COASMA138

Title: Conformationally Adaptable Extractant Flexes Strong Lanthanide Reverse-Size Selectivity

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J. Am. Chem. Soc. 2025, 147, 6, 5080–5088

DOI: **https://doi.org/10.1021/jacs.4c15074**

Abstract: Chemical selectivity is traditionally understood in the context of rigid molecular scaffolds with precisely defined local coordination and chemical environments that ultimately facilitate a given transformation of interest. By contrast, nature leverages dynamic structures and strong coupling to enable specific interactions with target species in otherwise complex media. Taking inspiration from nature, we demonstrate unconventional selectivity in the solvent extraction of light over heavy lanthanides using a conformationally flexible ligand called octadecyl acyclopa (ODA). This novel ligand forms pseudocyclic molecular complexes with lanthanide ions at organic/aqueous interfaces, revealed by vibrational sum frequency generation spectroscopy. These complexes are extracted into the organic phase, where femtosecond structural dynamics are probed by two-dimensional infrared spectroscopy and ab initio molecular dynamics simulations to mechanistically frame the macroscopic selectivity trends. We find larger-than-expected structural fluctuations and bond lengths for heavy Ln–ODA complexes that arise from an inability of ODA to contort around the smaller ions to satisfy all would-be bonding interactions, despite forming some individually strong

bonds. This finding contrasts with the binding of ODA with lighter lanthanides where, despite individually weaker bonds, collective interactions manifest that minimize structural fluctuations and give rise to enhanced thermodynamic stability. These results point to a new paradigm where conformational dynamics and cumulative bonding interactions can be used to facilitate unconventional chemical transformations.

25COASMA139

Title: Stability Frontiers in the AM6X6 Kagome Metals: The LnNb6Sn6 (Ln:Ce–Lu,Y) Family and Density-Wave Transition in LuNb6Sn6

Brenden R. Ortiz, William R. Meie, Ganesh Pokharel, Juan Chamorro, Fazhi Yang, Shirin Mozaffari, Alex Thaler,

J. Am. Chem. Soc. 2025, 147, 6, 5279–5292

DOI: https://doi.org/10.1021/jacs.4c16347

Abstract: The kagome motif is a versatile platform for condensed matter physics, hosting rich interactions between magnetic, electronic, and structural degrees of freedom. In recent years, the discovery of a charge density wave (CDW) in the AV3Sb5 superconductors and structurally-derived bond density waves (BDW) in FeGe and ScV6Sn6 have stoked the search for new kagome platforms broadly exhibiting density wave (DW) transitions. In this work, we evaluate the known AM6X6 chemistries and construct a stability diagram that summarizes the structural relationships among the >125 member family. Subsequently, we introduce our discovery of the broader LnNb6Sn6 (Ln:Ce–Nd,Sm,Gd–Tm,Lu,Y) family of kagome metals and an analogous DW transition in LuNb6Sn6. Our X-ray scattering measurements clearly indicate a (1/3, 1/3, 1/3) ordering wave vector (3—√×3—√×3 superlattice) and diffuse scattering on half-integer L-planes. Our analysis of the structural data supports the “rattling mode” DW model proposed for ScV6Sn6 and paints a detailed picture of the steric interactions between the rare-earth filler element and the host Nb–Sn kagome scaffolding. We also provide a broad survey of the magnetic properties within the HfFe6Ge6-type LnNb6Sn6 members, revealing a number of complex antiferromagnetic and metamagnetic transitions throughout the family. This work integrates our new LnNb6Sn6 series of compounds into the broader AM6X6 family, providing new material platforms and forging a new route forward at the frontier of kagome metal research.

25COASMA140

Title: Recycling Sulfur-Poisoned Pd Catalysts via Thermal Atomization for Semi-Hydrogenation of Acetylene

Qiheng Li, Shoujie Liu, Jin-Cheng Liu, Zhi Li, Yadong

J. Am. Chem. Soc. 2025, 147, 7, 5615–5623

DOI: **https://doi.org/10.1021/jacs.4c11305**

Abstract: Palladium catalysts are highly efficient for a variety of chemical industrial processes but are prone to being affected by poisons during practical application. Sulfur is one of the major poisons in Pd-based catalysts. The recycling of deeply poisoned Pd species like Pd sulfides is challenging due to the strong Pd–S bond. Herein, we proposed a top-down strategy to degrade Pd sulfides and create Pd single-atom sites simultaneously by one-step thermal atomization. Pd4S model nanoparticles were successfully converted to Pd single-

atom sites supported on nitrogen and sulfur-codoped carbon (Pd1/N, S–C) after loading them on ZIF-8 and thermal treatment. PdZn intermediates were formed during the atomization process. Density functional theory revealed that the formation of PdZn helped the generation of vacancies adjacent to metal nanoparticles, which prompted the atomization process. This strategy can be facilely applied to the atomization of sulfur-poisoned commercial Pd/C, which shows the potential for recycling commercial catalysts. The optimal Pd1/N, S–C catalyst showed good activity and much enhanced selectivity than Pd4S for the semi-hydrogenation of acetylene.

25COASMA141

Title: Pyrochlore NaYbO2: A Potential Quantum Spin Liquid Candidate

Chuanyan Fan, Tieyan Chang, Longlong Fan, Simon J. Teat, Feiyu Li, Xiaoran Feng

J. Am. Chem. Soc. 2025, 147, 7, 5693–5702

DOI: **https://doi.org/10.1021/jacs.4c13166**

Abstract: The search for quantum spin liquids (QSL) and chemical doping in such materials to explore superconductivity have continuously attracted intense interest. Here, we report the discovery of a potential QSL candidate, pyrochlore-lattice β-NaYbO2. Colorless and transparent NaYbO2 single crystals, layered α-NaYbO2 (∼250 μm on edge) and octahedral β-NaYbO2 (∼50 μm on edge), were grown for the first time. Synchrotron X-ray single-crystal diffraction unambiguously determined that the newfound β-NaYbO2 belongs to the three-dimensional pyrochlore structure characterized by the $R\bar{3}m$ space group, corroborated by synchrotron X-ray and neutron powder diffraction and pair distribution function. Magnetic measurements revealed no long-range magnetic order or spin glass behavior down to 0.4 K with a low boundary spin frustration factor of 17.5, suggesting a potential QSL ground state. Under high magnetic fields, the potential QSL state was broken and spins order. Our findings reveal that NaYbO2 is a fertile playground for studying novel quantum states.

25COASMA142

Title: Copper Chelate Targeting Externalized Phosphatidylserine Inhibits PD-L1 Expression and Enhances Cancer Immunotherapy

Fan Gao, Wei You, Lei Zhang, Ai-Zong Shen, Guang Chen, Ze Zhang, Xuan Nie, Lei Xia, Wei-Qiang Huang,

J. Am. Chem. Soc. 2025, 147, 7, 5796–5807

DOI: **https://doi.org/10.1021/jacs.4c14394**

Abstract: Inhibitors of the PD-1/PD-L1 immune checkpoint have revolutionized cancer treatment. However, the clinical response remains limited, with only 20% of patients benefiting from treatment and approximately 60% of PD-L1-positive patients exhibiting resistance. One key factor contributing to resistance is the externalization of phosphatidylserine (PS) on the surface of cancer cells, which suppresses immune responses and promotes PD-L1 expression, further hindering the efficacy of PD-L1 blockade therapies. Here, we introduce a copper chelate composed of a terpyridine–Cu complex with a farnesol tail designed to selectively target and cap the externalized PS on cancer cells. This approach not only promotes dendritic cell maturation and effector T-cell proliferation and tumor infiltration but also significantly inhibits PD-L1 expression, thereby amplifying T-cell-

mediated immune responses. Our results demonstrate that this strategy induces robust immunological memory and leads to the eradication of tumors in over 70% of mice with colorectal and melanoma cancers. These findings highlight a promising, antibody-independent strategy for cancer immunotherapy where targeting externalized PS could overcome current limitations of checkpoint blockade therapies.

25COASMA143

Title: Photosensitized Gold-Catalyzed Cross-Couplings of Aryl Bromides

Jiawen Wu, Fusheng Guo, Chenju Yi, Rongjie Yang, Xiaoguang Lei, Zhonghua Xia

J. Am. Chem. Soc. 2025, 147, 7, 5839–5850

DOI: **https://doi.org/10.1021/jacs.4c14501**

Abstract: Recently, ligand-promoted Au(I)/Au(III)-catalyzed cross-coupling reactions with aryl iodides have garnered considerable attention. Here, we report the first visible-light-driven gold-catalyzed cross-couplings of challenging aryl bromides. In the presence of a (P, N)-gold(I) catalyst and an acridinium photocatalyst under blue LED irradiation, C–O coupling of aryl bromides with carboxylic acids was achieved, and soon it was found that this photoinduced gold-catalyzed cross-coupling of aryl bromides was appliable for other C–C, C–N, and C–S bond formation. Experimental and computational studies suggest that this visible-light-driven gold-catalyzed cross-couplings of aryl bromides involves two discrete photoinduced energy transfer (EnT) events: first, energy transfer (EnT) from a photosensitizer produces an excited-state gold(I) complex that allows the bottleneck oxidative addition of aryl bromides to form an aryl Au(III) complex and second, the reductive elimination of aryl-Au(III) complex to regenerate Au(I). Collectively, the new synergistic catalytic method developed here highlights the tremendous potential of photochemical gold catalysis via excited-state organogold complexes, as well as its potential to facilitate drug discovery due to the biocompatibility and mildness of the reaction conditions.

25COASMA144

Title: Synthesis, Characterization, and Catalytic Activity of Ni(0) (DQ)dtbbpy, an Air-Stable, Bifunctional Red-Light-Sensitive Precatalyst

Jingsheng Li, Pengpeng Wang, Baoyu Bai, Yulin Xiao, Ya-Fei Wan, Yonggang Yan, Fei Li, Geyang Song,

J. Am. Chem. Soc. 2025, 147, 7, 5851–5859

DOI: **https://doi.org/10.1021/jacs.4c14533**

Abstract: Despite a well-established and growing body of work on nickel(0) precatalysts, the potential of nickel(0) complexes as bifunctional precatalysts remains underexplored. In this study, we synthesized, characterized, and evaluated the catalytic activity of (Ni(0)(DQ)dtbbpy), a bifunctional, red-light-sensitive, and air-stable nickel(0) complex. Owing to its unique photophysical properties, it effectively catalyzed the etherification and amination of aryl bromides under 620–630 nm light irradiation, functioning as both a photocatalyst and an active metal catalyst. Mechanistic studies and density functional theory (DFT) calculations further confirmed the exceptional absorption properties of Ni(0)(DQ)dtbbpy in the red-light region, as well as the electron transfer process triggered by red-light irradiation.

25COASMA145

Title: Total Synthesis of DMOA-Derived Meroterpenoids: Achieving Selectivity in the Synthesis of (+)-Berkeleyacetal D and (+)-Peniciacetal I

Jianpeng Zhang, Xiaotong Luo, Jingfu Zhang, Chao Li

J. Am. Chem. Soc. 2025, 147, 7, 5933–5942
DOI: **https://doi.org/10.1021/jacs.4c15205**

Abstract: The synthesis of complex natural products requires efficient control over chemoselectivity, stereoselectivity, and regioselectivity. Berkeleyacetals, a subfamily of 3,5-dimethylorsellinic acid (DMOA)-derived meroterpenoids, pose substantial synthetic challenges due to their densely functionalized and highly oxidized architectures, which have constrained synthetic efforts. Here, we present the first total synthesis of this class of DMOA-derived meroterpenoids, specifically (+)-berkeleyacetal D and (+)-peniciacetal I. Our approach features a chemoselective deprotonation followed by an intramolecular single-electron transfer (SET) from an enolate to an alkyl bromide, enabling the construction of the 2,3-dihydrofuran ring in berkeleyacetal D. Additional selective transformations include an endo-selective intramolecular Diels–Alder reaction, chemoselective methylations and semihydrogenation of [3]dendralene, and a solvent-controlled diastereoselective epoxidation. Beyond providing a synthetic route to these densely congested natural products, our study offers mechanistic insights into achieving selectivity in the assembly of architecturally demanding molecules.

25COASMA146

Title: opological Design of Highly Conductive Weakly Solvating Electrolytes for Ultrastable Sodium Metal Batteries Operating at −60 °C and Below

Zhiling Wang, Tao Zheng, Shuzhan Wang, Xia-Guang Zhang, Yu Gu, Shuai , Tang, Yongzhu Fu

J. Am. Chem. Soc. 2025, 147, 7, 5962–5970
DOI: **https://doi.org/10.1021/jacs.4c16076**

Abstract: Weakly solvating electrolytes (WSE) can favor reversible Na batteries at −40 °C for some extreme applications because of the low desolvation energy. However, it is challenging to enable reversible Na batteries at lower temperatures. Herein, we uncover that the low ionic conductivity of WSE reduces reaction kinetics at −60 °C. Accordingly, a highly conductive weakly solvating electrolyte (HCWSE) is designed by introducing additives of strongly solvating solvents and the dilution of NaPF6. The additive can dominate the solvation sheath, increase the dissociation of NaPF6 and the fluidity of the electrolyte, and thus greatly improve the ionic conductivity. Furthermore, the binding energy between Na+ and solvents is proposed as a descriptor to determine the solvating power of solvents, based on which a series of ultralow-temperature HCWSEs have been topologically designed by facilely introducing strong-solvation ether additives into the weak-solvation solvents. As a demonstration, the HCWSE showcases the long cycling of Na||Na cell at −60 °C with an overpotential of 42 mV under 1 mA cm–2 for 1200 h. The Na||NNFM (Na0.75Ni0.25Fe0.25Mn0.5O2) cell exhibits a reversible capacity of 79.2 mAh g–1 after 160 cycles. The cells also achieve impressive performances at −70 °C.

25COASMA147

Title: Small Ligand-Involved Pickering Droplet Interface Controls Reaction Selectivity of Metal Catalysts

Jie Yang, Yue Sun, Hu Shi, Houbing Zou, Yabin Zhang, Xinxin Tian, Hengquan Yang

J. Am. Chem. Soc. 2025, 147, 7, 5984–5995
DOI: **https://doi.org/10.1021/jacs.4c16128**

Abstract: Developing efficient methods to improve catalytic selectivity, particularly without sacrificing catalytic activity, is of paramount significance for chemical synthesis. In this work, we report a small ligand-involved Pickering droplet interface as a brand-new strategy to effectively regulate reaction selectivity of metal catalysts. It was found that small ligands such as polar arenes could engineer the surface structure of Pt catalysts that were assembled at Pickering droplet interfaces. Due to the strong hydrogen-bonding interactions with water, the polar arenes preferentially adsorbed with the water adlayer that covered Pt surfaces, forming water-mediated metal–organic interfaces on the Pickering emulsion droplets. Such an interface system displayed a significantly enhanced p-vinylaniline selectivity from 8.7 to 94.2% with an unreduced conversion in p-nitrostyrene hydrogenation. The selectivity was found to follow a negatively linear correlation with the bond length of the interfacial hydrogen bonds. Theoretical calculations revealed that the small arene ligands could closely array at the interface, which modulated the adsorption patterns of reactant/product molecules to prevent the C═C group from approaching Pt surfaces without suppressing their accessibility toward reactant molecules. Such a remarkable interfacial steric effect contributed to the efficient control of the hydrogenation selectivity. Our work provides an innovative strategy to modulate the surface structure of metal catalysts, opening a new venue to tune catalytic selectivity.

25COASMA148

Title: Three-Dimensional Covalent Organic Frameworks with lil Topology

Xinyu Wu, Hanwen Wang, Ning Huang

J. Am. Chem. Soc. 2025, 147, 7, 6016–6022
DOI: **https://doi.org/10.1021/jacs.4c16422**

Abstract: The diversity of covalent organic frameworks (COFs) is continuously expanding, providing various materials with tailor-made structures and properties. However, the development of crystalline three-dimensional (3D) COFs with new topologies is an essential but arduous challenge. In this study, we first developed one kind of 3D COFs with the lil topological structure, which were assembled by D4h- and C2h-symmetric building blocks. The 3D COFs were determined in a space group of Imma, in which each D4h-symmetric unit is connected with four C2h-symmetric units, forming a noninterpenetrated network. The densely packed copper phthalocyanine and stable polyimide linkage render these COFs as a polymeric material with high dielectric constant and low dielectric loss at high frequencies (>1 kHz). Significantly, the dielectric constant was determined as high as 63, which constitutes a new record value among phthalocyanine-based and polyimide polymers. Therefore, this study not only provides important guidance for the design of 3D lil-net COFs but also supplies promising materials for application in high-energy-density and pulsed capacitors.

25COASMA149

Title: Harnessing the FBXW7 Somatic Mutant R465C for Targeted Protein Degradation

Ananya A. Basu, Chenlu Zhang, Milad Rouhimoghadam, Anil Vasudevan, Justin M. Reitsma, Xiaoyu Zhang

J. Am. Chem. Soc. 2025, 147, 7, 6108–6115
DOI: **https://doi.org/10.1021/jacs.4c17331**

Abstract: Targeted protein degradation (TPD) is a pharmacological strategy that eliminates specific proteins from cells by harnessing cellular proteolytic degradation machinery. In proteasome-dependent TPD, expanding the repertoire of E3 ligases compatible with this approach could enhance the applicability of this strategy across various biological contexts. In this study, we discovered that a somatic mutant of FBXW7, R465C, can be exploited by heterobifunctional compounds for targeted protein degradation. This work demonstrates the potential of utilizing mutant E3 ligases that occur exclusively in diseased cells for TPD applications.

25COASMA150

Title: Regio- and Stereoselective Hydroalkynylation of Internal Alkynes with Terminal Alkynes by Half-Sandwich Rare-Earth Catalysts

Na Hao, Tenggang Jiao, Zhou Sun, Aniket Mishra, Qingde Zhuo, Masayoshi Nishiura, Zhaomin Hou, Xuefeng Cong

J. Am. Chem. Soc. 2025, 147, 7, 6149–6161
DOI: **https://doi.org/10.1021/jacs.4c17210**

Abstract: The regio- and stereoselective hydroalkynylation of internal alkynes with terminal alkynes is of great interest and importance as a straightforward route for synthesizing multisubstituted 1,3-enynes. However, this transformation often suffers from regio- and stereoselectivity issues when working with unsymmetrical internal alkynes. Herein, we report for the first time the regio- and syn-stereoselective hydroalkynylation of a variety of heteroatom-functionalized unsymmetrical internal alkynes including homopropargyl ethers, thioethers, and tertiary amines with terminal alkynes by half-sandwich rare-earth catalysts. This protocol provides an atom-efficient and straightforward route for the synthesis of a new family of heteroatom (O, S, or N)-functionalized 1,3-enynes, featuring 100% atom-efficiency, broad substrate scope, and high regio- and syn-stereoselectivity (>19:1 r.r. and >19:1 syn/anti). The mechanistic details have been elucidated by deuterium-labeling experiments, control experiments, and isolation and transformations of key reaction intermediates, revealing that the reaction proceeded through the C(sp)–H deprotonation of a terminal alkyne by a half-sandwich scandium alkyl species to form a catalytically active dimeric half-sandwich scandium tetraalkynyl species followed by heteroatom-assisted insertion of internal alkyne into the Sc–alkynyl bond and the subsequent protonolysis of the resulting Sc–alkenyl bond with another terminal alkyne molecule. The coordination of the heteroatom (O, S, or N) of internal alkynes to the catalyst metal center plays a critically important role in achieving a high level of reactivity and regio- and stereoselectivity. Remarkably, the catalytically active dimeric half-sandwich scandium tetraalkynyl species can be recovered and reused, constituting the first example of a recyclable catalyst system for the

hydroalkynylation of internal alkynes.

25COASMA151

Title: High-Energy, High-Power Sodium-Ion Batteries from a Layered Organic Cathode

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J. Am. Chem. Soc. 2025, 147, 7, 6181–6192
DOI: **https://doi.org/10.1021/jacs.4c17713**

Abstract: Sodium-ion batteries (SIBs) attract significant attention due to their potential as an alternative energy storage solution, yet challenges persist due to the limited energy density of existing cathode materials. In principle, redox-active organic materials can tackle this challenge because of their high theoretical energy densities. However, electrode-level energy densities of organic electrodes are compromised due to their poor electron/ion transport and severe dissolution. Here, we report the use of a low-bandgap, conductive, and highly insoluble layered metal-free cathode material for SIBs. It exhibits a high theoretical capacity of 355 mAh g–1 per formula unit, enabled by a four-electron redox process, and achieves an electrode-level energy density of 606 Wh kg–1electrode (90 wt % active material) along with excellent cycling stability. It allows for facile two-dimensional Na+ diffusion, which enables a high intrinsic rate capability. Growth of the active cathode material in the presence of as little as 2 wt % carboxyl-functionalized carbon nanotubes improves charge transport and charge transfer kinetics and further enhances the power performance. Altogether, these allow the construction of SIB cells built from an affordable, sustainable organic small molecule, which provide a cathode energy density of 472 Wh kg–1electrode when charging/discharging in 90 s and a top specific power of 31.6 kW kg–1electrode.

25COASMA152

Title: Single-Electron Catalysis of Reversible Cycloadditions under Nanoconfinement

Xin Zhu, Hongliang Chen, Jinying Wang, Agostino Migliore, Xingxing Li, Yanwei LiBoyu Wang

J. Am. Chem. Soc. 2025, 147, 7, 6203–6213
DOI: **https://doi.org/10.1021/jacs.4c18064**

Abstract: Electron transfer (ET) is crucial in many chemical reactions, but its mechanism and role are hardly understood in nanobiotechnology due to the complexity of reaction species and pathways involved. By modulating and monitoring electron behavior at the single-molecule level, we can better understand the fundamental mechanisms and ways to control them for technological use. Here, we unravel a mechanism of single-electron catalysis under positively charged nanoconfinement. We demonstrate that both (2 + 2) and (4 + 4) cycloadditions can be catalyzed reversibly by a single electron. Key reaction pathways are discovered by monitoring sequential electrical signals in the cycloadditions through advanced single-molecule detection platforms. Experimental and theoretical results consistently demonstrate that combining single ET processes with nanoconfinement involving cucurbit[8]uril can lower the reaction energy barrier and promote reversible cycloaddition. Moreover, we show that the bias voltage can fine-tune ET processes and chemical equilibria

in bond formation and cleavage. Our results provide a novel approach to elucidate, modulate, and design electron-involved reactions and functionalized device.

25COASMA153

Title: Ligand-Governed Regio- and Enantioselective [2 + 2 + 2] Cycloaddition of 1,7-Enynes: Assembly of the Benzo[c]chromen-1-ol Backbone and Access to Enantioenriched Cannabinol Bioisostere

King Hung Nigel Tang, Taichi Kishi, Natsuhiko Sugimura, Yuto Horio, Takanori Shibata

J. Am. Chem. Soc. 2025, 147, 7, 6214–6226
DOI: **https://doi.org/10.1021/jacs.4c18319**

Abstract: We herein report a regioselective synthesis of the benzo[c]chromenol core via cationic rhodium-catalyzed [2 + 2 + 2] cycloaddition of 1,7-enynes with tetrolic acid derivatives. With the selection of an appropriate ligand, both regioisomers could be obtained in excellent regiomeric ratio and enantiomeric excess. The regioselectivity was governed by different factors, which was suggested by computational studies. Furthermore, the asymmetric synthesis of an axially chiral cannabinol bioisostere candidate was achieved by the transformation from central chirality to axial chirality. Demonstration of the synthesis of a natural compound was also depicted.

25COASMA154

Title: Light-Induced Increase in Bond Strength─from Chalcogen Bond to Three-Electron σ Bond upon Excitation

Zoe Nonie Scheller, Saber Mehrparvar, Gebhard Haberhauer

J. Am. Chem. Soc. 2025, 147, 7, 6249–6258
DOI: **https://doi.org/10.1021/jacs.4c18435**

Abstract: Chalcogen bonds are σ hole interactions between a chalcogen center and a Lewis base center and have been applied in recent years as an alternative to hydrogen bonds in supramolecular chemistry and catalysis. While the electronic interactions of chalcogen bonds in the ground state have been intensively analyzed, there is barely any knowledge about the electron structure in the excited state. This is despite the fact that in some cases photoswitches containing chalcogen bonds exhibit exceptional switching behavior. Here, we investigate the effect of light absorption on chalcogen bonds containing divalent chalcogen centers. Quantum chemical calculations reveal that in the excited S1 state the noncovalent chalcogen bond converts to a covalent three-electron σ bond. The bond between the chalcogen center and the Lewis base center is thus significantly reinforced by light excitation. This change in bond type explains the previously experimentally observed nonswitchability of some tellurium-containing azo compounds. Furthermore, we were able to demonstrate that the switchability of certain selenium-containing compounds is temperature-dependent, whereby the ratio of the less stable cis compound is higher for higher temperatures. These results highlight the potential for designing responsive materials and dynamic molecular systems based on light-induced chalcogen bond modulation.

25COASMA155

Title: Enantioselective Decarboxylative Hydrogen-Atom Transfer Reaction

Yugui Xu, Chaoren Shen, Kaiwu Don
J. Am. Chem. Soc. 2025, 147, 7, 6259–6267
DOI: **https://doi.org/10.1021/jacs.4c18464**
Abstract: Direct enantioselective decarboxylative transformations of carboxylic acids have become powerful tools for constructing structurally and functionally diverse molecules. Herein, an unprecedented organocatalyzed protocol for enantioconvergent decarboxylative reduction was established by leveraging dual catalysis of photoredox-mediated radical generation and a thiol-catalyzed asymmetric hydrogen-atom transfer process. With this hydrodecarboxylation, a variety of chiral 3-substituted indolines were attained from the acids in moderate to excellent yields with high enantioselectivities.

25COASMA156

Title: Non-noble Metal Single-Molecule Photocatalysts for the Overall Photosynthesis of Hydrogen Peroxide

Fan FuYongxin LiuMingliang LiuZhengguang LiWanying ZhongYaqin LiKaixiu LiJun WangYongchao
J. Am. Chem. Soc. 2025, 147, 8, 6390–6403
DOI: **https://doi.org/10.1021/jacs.4c09445**
Abstract: Despite the great progress in molecule photocatalytic solar energy conversion, it is particularly challenging to realize a photocatalytic overall reaction in a non-noble metal complex, which represents a new paradigm for photosynthesis. In this study, a class of novel non-noble metal complexes with head-to-tail geometry were designed and readily synthesized via the coordination of triphenylamine-modified 2,2′: 6′,2″-terpyridine ligands with Zn2+. As expected, these complexes exhibited the desired through-space charge-transfer transition, generating both long-lived excited states (on the order of microseconds) and separate redox centers under visible-light irradiation. These complexes have particularly low exciton binding energies, which make them excellent heterogeneous single molecular photocatalysts for the overall photosynthetic production of H2O2. Remarkably, a high H2O2 evolution rate (8862 μmol g–1 h–1) was achieved in pure H2O under an air atmosphere via precise molecular tailoring, revealing the unparalleled advantages of molecular photocatalysts in improving the catalytic rate of H2O2 production. This is the first time that single-molecule photocatalysts have been used to efficiently complete the photosynthesis of H2O2. This study presents a new paradigm for photocatalytic energy conversion and provides unique insights into the design of molecular photocatalysts.

25COASMA157

Title: Helix-Guarded Molecular Clips for Cell-Free DNA Scavenging and Treatment of Systemic Lupus Erythematosus

Yang Zhou, Huan Ye, Yi Yu, Chenglong Ge, Mengyuan Yin, Zhongmin Liu, Jingrui ShenRenxiang ZhouYouyong Li, Kam W. Leong*Lichen Yin
J. Am. Chem. Soc. 2025, 147, 8, 6612–6622
DOI: https://doi.org/10.1021/jacs.4c15646
Abstract: Immune disorders induced by cell-free DNA (cfDNA) account for the incidence and deterioration of systemic lupus erythematosus (SLE). Scavenging of cfDNA using

cationic polymers represents a promising modality for SLE management. However, they bind cfDNA mainly via electrostatic interaction, which would result in an undesired discharge of the captured cfDNA upon competitive replacement by the negatively charged serum/intracellular components. Inspired by the natural recognition mechanism of biomacromolecules via spatial matching, we herein developed a library of dendrimer-templated, spherical, α-helical, and guanidine-rich polypeptides as molecular clips for cfDNA scavenging. Upon optimization of the polypeptide length and density on the dendrimer surface, the top-performing G3-8 was identified, which could tightly confine cfDNA within the cavity between the adjacent, rod-like α-helices. As thus, the helical G3-8 but not the random-coiled analogue D,L-G3-8 enabled robust cfDNA scavenging under serum-rich conditions to inhibit TLR9 activation and inflammation. In SLE mice, i.v. injected G3-8 efficiently prevented organ failure and inhibited inflammation by scavenging cfDNA. This study provides an enlightened strategy to stably bind and scavenge cfDNA and may shift the current paradigm of SLE management.

25COASMA158

Title: Harnessing Oxidized Amines as Robust Sorbents for Carbon Capture

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J. Am. Chem. Soc. 2025, 147, 8, 6786–6794

DOI: https://doi.org/10.1021/jacs.4c16764

Abstract: Carbon capture and sequestration (CCS) is imperative to mitigating global climate change, but current implementation falls far short of that needed to reach net-zero global emissions by 2050. Aqueous amine solutions, conceived over a century ago, are the current leading technology for CO2 separations. However, amines suffer from chemical instability under scrubbing conditions, corrosiveness, and toxicity, hindering their long-term implementation at multiton scales. Herein, we demonstrate for the first time that tertiary amine N-oxides, an oxidative degradation product of amines, can remove CO2 from dilute streams, including flue gas from a natural gas-fired power plant. Our extensive spectroscopic and computational studies support that the nontoxic, noncorrosive, and inexpensive 4-methylmorpholine N-oxide (MMNO) captures CO2 under humid conditions via the formation of a hydrogen-bond-stabilized bicarbonate (HCO3–) species, despite being significantly less basic than an amine. Accelerated aging studies show that MMNO exhibits superior oxidative and thermal stability compared to structurally similar amines, highlighting the potential of eco-friendly N-oxides in industrial carbon capture applications.

25COASMA159

Title: Half-Sandwich Ru(II) Complexes Featuring Metal-Centered Chirality: Configurational Stabilization by Ligand Design, Preparation via Kinetic Resolution, and Application in Asymmetric Catalysis

Hui Liang, Gabriel N. Morais, Gang Chen, Wei Tang, Jing Zhao, Chuanyong Wang, K. N. Houk, Shuming Chen, Jiajia Ma

J. Am. Chem. Soc. 2025, 147, 8, 6825–6834

DOI: https://doi.org/10.1021/jacs.4c16928

Abstract: While it is well established that half-sandwich Ru(II) complexes possess metal-

centered chirality, effective strategies to leverage their metal-centered chirality toward asymmetric synthesis have been challenging due to the configurational lability of the metal stereocenters. The metal-centered chirality is typically mediated by enantiopure ligands, which occupy a relatively narrow chemical space compared to their achiral counterparts. We demonstrate that achiral ligands can be used to access chiral-at-ruthenium half-sandwich complexes with exceptionally high configurational stability. Key to success is the introduction of a rigid bidentate ligand with a minimized dihedral angle between the pyridyl and phenolic moieties, which proved effective for preventing racemization. Computational studies revealed the energetic factors contributing to the exceptional configurational stability enabled by the rigid and planar structure of the successful ligand design. These optically active chiral-at-ruthenium complexes incorporating aldehyde moieties were obtained by NHC-catalyzed kinetic resolution with excellent selectivities (s-factor up to >200, ee up to 99%). We further demonstrate that they are highly effective chiral aldehyde catalysts for the asymmetric 1,6-conjugate addition of glycine ester and para-quinone methide.

25COASMA160

Title: Cyclic (Alkenyl)(Amino)Carbene (SMeCAenAC): Introducing a Member to the Cyclic (Alkyl)(Amino)Carbenes Family Featuring a Narrow Energy Gap

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J. Am. Chem. Soc. 2025, 147, 8, 6905–6913
DOI: https://doi.org/10.1021/jacs.4c17319

Abstract: Herein, we report the carbene-like activity of a nonisolable, highly ambiphilic cyclic (alkenyl)(amino)carbene (SMeCAenAC, 3), which is stabilized as [(SMeCAenAC)(H)N(SiMe3)2] (4). This protected form (4) is stable in air and moisture. Compound 4 can be used as a carbene source through deamination upon heating to 130–140 °C. Moreover, density functional theory (DFT) calculations indicate that SMeCAenAC has the smallest singlet–triplet gap (37.05 kcal/mol) and a narrow highest occupied molecule orbital (HOMO)–lowest unoccupied molecular orbital (LUMO) gap (3.92 eV) among the cyclic (alkyl)(amino)carbenes (CAACs). The precursor of carbene (3) can be synthesized on a multigram scale with a good yield. Moreover, the SMeCAenAC-coordinated copper complex showed excellent efficiency in the catalytic addition of phenols to electron-deficient olefins. This study also highlights that [SMeCAenAC-H]OTf can be used for metal-free catalysis, a property uniquely characteristic of an ambiphilic carbene, even though the formation of free SMeCAenAC (3) was not achieved.

25COASMA161

Title: Development of a Thioetherification of Heteroarene Electrophiles with Broad Scope via a Proton Transfer Dual Ionization Mechanism

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J. Am. Chem. Soc. 2025,
DOI: https://doi.org/10.1021/jacs.4c18304

Abstract: Sulfur-derived functional groups represent prevalent motifs in highly sought-after small molecules, such as active pharmaceutical ingredients (APIs). Thioethers are one such

example, being commonly encountered in APIs, prodrugs, and as valuable synthetic "linchpins" to access an array of sulfur-derived functional groups. While nucleophilic aromatic substitution (SNAr) has traditionally been used to synthesize aryl thioethers, modern approaches leverage transition metals to catalyze thermal or photochemical cross-coupling. While studying photochemical thioetherification reactions, we uncovered a remarkably mild condition that does not require light, transition metals, or exogenous bases. An array of thiols and halogenated heterocycles were coupled to produce >70 diverse products. Reaction progress kinetic analysis (RPKA) and computational studies support a unique mechanism termed proton transfer dual ionization (PTDI) SNAr. Finally, a predictive statistical model was constructed aided by high-throughput experimentation (HTE) to understand when the PTDI processes are successful, resulting in the completion of ten target-oriented syntheses. This transformation complements modern approaches to thioether synthesis and motivates additional research evaluating PTDI as a general activation mode between reaction partners.

25COASMA162

Title: Enhancing Selective Hydrofluorocarbon Greenhouse Gas Capture via Halogenation of Metal–Organic Frameworks

Ronald T. Jerozal, Jaehwan Kim, Carolyn Ma, Tristan A. Pitt, Jung-Hoon Lee, Phillip J. Milner

J. Am. Chem. Soc. 2025, 147, 8, 7127–7136

DOI: https://doi.org/10.1021/jacs.5c00393

Abstract: Hydrofluorocarbons (HFCs) are anthropogenically produced greenhouse gases with longer atmospheric lifetimes and higher global warming potentials than those of carbon dioxide. General strategies to abate their emissions from industrial point sources, such as via adsorptive capture, remain scarce. Herein, we uncover the key structure–property relationships that lead to strong binding of HFCs such as fluoroform (CHF3) and difluoromethane (CH2F2) in metal–organic frameworks (MOFs) under the low pressures relevant to flue gas scrubbing. Extensive gas sorption and computational studies support that the Zr-based microporous framework MOF-801-Br or HHU-2-Br (HHU = Heinrich-Heine-University Düsseldorf) strongly binds HFCs due to its synergistic combination of Zr-OH sites on the nodes and bromine sites on the linkers. As such, MOF-801-Br demonstrates a record-setting performance for separating CHF3 from N2 under dilute conditions. Our work highlights that the combination of multiple hydrogen-bonding sites in microporous MOFs represents a generalizable strategy for HFC capture, enabling their selective removal from industrial waste streams.

25COASMA163

Title: CD24 flags anastasis in melanoma cells

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Apoptosis, Volume 30, pages 1–15, (2025)

DOI: https://doi.org/10.1007/s10495-024-01990-1

Abstract: Anastasis is a phenomenon observed in cancer cells, where cells that have initiated apoptosis are able to recover and survive. This molecular event is increasingly recognized as

a potential contributor to cancer metastasis, facilitating the survival and migration of tumor cells. Nevertheless, the identification of a specific surface marker for detecting cancer cells in anastasis remained elusive. Here we report our observation that the cell surface expression of CD24 is preferentially enriched in a non-adherent FSClowSSChigh melanoma subpopulation, which is generally considered a non-viable population in cultivated melanoma cell lines. More than 90% of non-adherent FSClowSSChighCD24+ve metastatic melanoma cells exhibited bonafide features of apoptosis on the cell surface and in the nucleus, marking apoptotic or seemingly apoptotic subpopulations of the in vitro cultivated metastatic melanoma cell lines. Unexpectedly, however, the CD24+ve subpopulation, despite being apoptotic, showed evidence of metabolic activity and exhibited proliferative capacities, including anchorage-independent growth, when inoculated in soft agarose growth medium. These findings indicate that apoptotic FSClowSSChighCD24+ve melanoma subpopulations are capable of reversing the progression of apoptosis. We report CD24 as the first novel cell surface marker for anastasis in melanoma cells.

25COASMA164

Title: PRELP inhibits colorectal cancer progression by suppressing epithelial-mesenchymal transition and angiogenesis via the inactivation of the FGF1/PI3K/AKT pathway

Apoptosis, Volume 30, pages 16–34, (2025)
DOI: https://doi.org/10.1007/s10495-024-02015-7

Abstract: Proline/arginine-rich end and leucine-rich protein (PRELP) is identified as a small proteoglycan in the extracellular matrix that has been tightly associated with cell adhesion. At present, the role of PRELP in colorectal cancer (CRC) remains largely unknown. PRELP expression in human CRC tissue samples was analyzed by qRT-PCR and immunochemistry. CCK-8, colony formation, transwell, and tube formation assays were utilized to determine the influences of PRELP on the malignant phenotypes of CRC cells. Mouse xenograft and tumor metastasis models were constructed to further validate the function of PRELP. Furthermore, we investigated the efficacy of PRELP combined with bevacizumab treatment in a mouse xenograft model of CRC. Additionally, RNA-seq was performed to analyze the potential signaling pathways regulated by PRELP. Immunofluorescence staining and coimmunoprecipitation were conducted to confirm the interaction between PRELP and fibroblast growth factor 1 (FGF1). In this study, we found that PRELP exerted a tumor-suppressive effect on CRC. The expression level of PRELP was significantly reduced in CRC tissues and cell lines. Both in vivo and in vitro experiments confirmed that PRELP inhibited CRC cell proliferation, promoted apoptosis, and suppressed migration and invasion via a reduction in the epithelial-mesenchymal transition and attenuated angiogenesis, thereby dampening tumor progression. In addition, PRELP markedly potentiated the efficacy of bevacizumab in a mouse xenograft model. Mechanistically, PRELP bound to FGF1 and reduced the stability of the FGF1 protein, accompanied by an increase in its degradation, which subsequently inactivated the PI3K/AKT/mTOR pathway, thereby leading to reduction in tumor angiogenesis and metastasis. Our study for the first time unveiled the tumor-suppressive role of PRELP in CRC and provided a potential effective strategy for the treatment of CRC.

25COASMA165

Title: β-glucan nanoparticles alleviate acute asthma by suppressing ferroptosis and DNA damage in mice

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Apoptosis, Volume 30, pages 35–54, (2025)
DOI: https://doi.org/10.1007/s10495-024-02013-9

Abstract: Asthma is a severe respiratory disease marked by airway inflammation, remodeling, and oxidative stress. β-Glucan (BG), a polysaccharide constituent of fungal cellular structures, exhibits potent immunomodulatory activities. The investigational focus was on the anti-asthmatic and anti-ferroptotic properties of beta-glucan nanoparticles (BG-NPs) in a murine model of allergic asthma induced by ovalbumin (OVA). BG was extracted from Chaga mushrooms (Inonotus obliquus), and its BG-NPs were characterized utilizing techniques including FT-IR, UV visible spectroscopy, zeta potential analysis, DLS, XRD, and TEM. The Balb/C mice were allocated into five groups: control, untreated asthmatic, dexamethasone (Dexa)-treated (1 mg/kg), BG-treated (100 mg/kg), BG-NPs-treated (45 mg/kg), and BG-treated (100 mg/kg). Treatment with BG-NPs markedly diminished the entry of inflammatory cells into the respiratory passage, serum IgE concentrations, DNA damage, and markers of oxidative stress through the reduction of malonaldehyde (MDA) levels and enhancing the levels of reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT). Furthermore, BG-NPs reduced iron deposition and promoted the transcriptional activity of the GPx4 gene in pulmonary cells, attenuating ferroptosis. The results demonstrated that BG-NPs reduced asthma by inhibiting oxidative stress, inflammation, DNA damage, and ferroptosis. Our results suggest that BG-NPs could be used as potential treatments for allergic asthma.

25COASMA166

Title: Anti-PD-L1 blockade facilitates antitumor effects of radiofrequency ablation by improving tumor immune microenvironment in hepatocellular carcinoma

Jiahua Liang, Mingjian Ma, Wei Feng, Qiongcong Xu, Dong Chen, Jiaming Lai & Jiancong Chen

Apoptosis, Volume 30, pages 55–68, (2025)
DOI: https://doi.org/10.1007/s10495-024-02019-3

Abstract: Hepatocellular carcinoma (HCC) is a complex disease with advanced presentation that significantly affects survival rates. Therefore, novel therapeutic strategies are needed. In this study, we investigate the tumor microenvironment (TME) in HCC by analyzing 13 HCC samples at single cell level. We identified key cell populations, including CD8 + T cells, Tregs, M1/M2 macrophages, and CD4 + memory T cells, and explored their roles and interactions. Our research revealed an early enrichment of CD8 + T cells, which could potentially lead to their exhaustion and facilitate tumor progression. We also investigated the impact of percutaneous radiofrequency ablation (RFA) on the immune microenvironment. Using a dual tumor mouse model, we demonstrated that RFA induces necrosis, enhancing antigen presentation and altering immune responses. Our results indicate that RFA increases PD-L1 expression in residual liver tissue, suggesting potential immune escape mechanisms.

Furthermore, the combination of RFA and anti-PD-L1 therapy in the mouse model resulted in significant improvements in immune modulation. This included increased CD8 + T cell efficacy and decreased Treg infiltration. This combination shows promise as an approach to counteract HCC progression by altering the immune landscape. This study highlights the critical interaction within the TME of HCC and suggests the possibility of improving patient outcomes by targeting immune evasion mechanisms through combined therapeutic strategies.

25COASMA167

Title: Phosphatidylserine-mediated uptake of extracellular vesicles by hepatocytes ameliorates liver ischemia-reperfusion injury

Rongrong Li, Chen Wang, Xiaoniao Chen, Enze Fu, Kaiyue Zhang, Hongyan Tao, Zhibo Han, Zhong-Chao Han & Zongjin Li

Apoptosis, Volume 30, pages 69–82, (2025)
DOI: https://doi.org/10.1007/s10495-024-02030-8

Abstract: Compelling evidence suggests that mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) promote regeneration in animal models of liver injury by delivering signaling molecules. However, their target cells and uptake mechanism remain elusive. In this study, MSC-EVs were intravenously administered in a mouse model of liver ischemia-reperfusion injury (IRI). Our results revealed that MSC-EVs exhibit enhanced liver targeting in IRI mice, and injured hepatocytes display a greater capacity for MSC-EV uptake. We found that phosphatidylserine (PS) displayed on the exterior of injured hepatocytes promotes MSC-EV internalization, possibly by binding to MFGE8, a protein expressed on the MSC-EV membrane. Furthermore, the therapeutic effect of MSC-EVs on liver IRI is highly dependent on this PS-mediated uptake pathway. Our findings provide evidence that MSC-EVs preferentially target injured hepatocytes, relying on a PS-dependent uptake route to exert hepatoprotective effects, which are critical for the future design of EV-based therapeutic strategies for liver IRI.

25COASMA168

Title: SHCBP1 promotes cisplatin resistance of ovarian cancer through AKT/mTOR/Autophagy pathway

Gonghua Qi, Hanlin Ma, Kai Teng, Panpan Gai, Yanmin Gong, Jingying Chen, Xia Luo & Beihua Kong

Apoptosis, Volume 30, pages 83–98, (2025)
DOI: https://doi.org/10.1007/s10495-024-02027-3

Abstract: Ovarian cancer caused the highest cancer-related mortality among female reproductive system malignancies. Platinum-based chemotherapy is still the footstone of the chemotherapy for ovarian cancer. However, the molecular mechanisms underlying cisplatin insensitivity and resistance remain unclear. SHC SH2 domain-binding protein 1 (SHCBP1) plays critical roles in the progression and drug resistance of different types of cancer. However, the biological function of SHCBP1 in ovarian cancer progression and cisplatin resistance remains obscure. In this study, we found that SHCBP1 was upregulated in ovarian cancer and the upregulated SHCBP1 has growth-promoting effect on ovarian cancer cells. Furthermore, SHCBP1 silencing sensitize ovarian cancer cells to cisplatin (hereafter referred

to as CDDP). Mechanism analysis revealed that SHCBP1 activated the Akt/mTOR pathway and further inhibited autophagy in ovarian cancer cells. Meanwhile, autophagy inhibitors combined with SHCBP1 knockdown enhances CDDP sensitivity. In addition, knockdown of SHCBP1 restricted the proliferation of tumors and increased the cisplatin sensitivity in vivo. These findings suggested that upregulated SHCBP1 promoted the proliferation and CDDP resistance of ovarian cancer. The combination of SHCBP1 inhibition and cisplatin treatment might lead to substantial progress in ovarian cancer targeted therapy.

25COASMA169

Title: Combination of magnetic hyperthermia and gene therapy for breast cancer

Kubra Solak, Seyda Yildiz Arslan, Melek Acar, Fatma Turhan, Yagmur Unver & Ahmet Mavi

Apoptosis, Volume 30, pages 99–116, (2025)
DOI: https://doi.org/10.1007/s10495-024-02026-4

Abstract: This study presented a novel breast cancer therapy model that uses magnetic field-controlled heating to trigger gene expression in cancer cells. We created silica- and amine-modified superparamagnetic nanoparticles (MSNP-NH2) to carry genes and release heat under an alternating current (AC) magnetic field. The heat-inducible expression plasmid (pHSP-Azu) was designed to encode anti-cancer azurin and was delivered by magnetofection. MCF-7 cells demonstrated over 93% cell viability and 12% transfection efficiency when exposed to 75 µg/ml of MSNP-NH2, 3 µg of DNA, and PEI at a 0.75 PEI/DNA ratio (w: w), unlike non-tumorigenic cells (MCF-10 A). Magnetic hyperthermia (MHT) increased azurin expression by heat induction, leading to cell death in dual ways. The combination of MHT and heat-regulated azurin expression induced cell death, specifically in cancer cells, while having negligible effects on MCF-10 A cells. The proposed strategy clearly shows that simultaneous use of MHT and MHT-induced azurin gene expression may selectively target and kill cancer cells, offering a promising direction for cancer therapy.

25COASMA170

Title: The contributory role of GSK3β in hypertension exacerbating atherosclerosis by regulating the OMA1/PGC1α pathway

Hongjia Bao, Changyuan Wang, Yue Jin, Qiang Meng, Jingjing Wu, Qi Liu & Huijun Sun

Apoptosis, Volume 30, pages 117–130, (2025)
DOI: https://doi.org/10.1007/s10495-024-02029-1

Abstract: Atherosclerosis is closely related to endothelial dysfunction and hypertension. GSK3β is a critical regulator in atherosclerosis. This study was carried out to investigate the effects of GSK3β on hypertension exacerbating atherosclerosis in vitro and in vivo. L-NAME + HFD-ApoE−/− mice were used for this study for 12 weeks, and their endothelial dysfunction and inflammation were analyzed. Oil red O and H&E staining revealed that treatment with LiCl, an inhibitor of GSK3β, reduced atherosclerotic lesions and lipid accumulation. The levels of lipid homeostasis and oxidation stress were attenuated following LiCl administration. LiCl-treated ApoE-/- mice showed lowered blood pressure. LiCl also suppressed the expressions of Drp1, Bax, ICAM1, VCAM1 and TNF-α compared to HFD + L-NAME induced mice and oxLDL + L-NAME-treated Human aorta endothelial cell

line(HAECs). LiCl treatment increased the expressions of MFN2 and Bcl2. Mitotracker-red, MitoSOX and JC-1 staining indicated that LiCl treatment reduced mitochondrial division and ROS production, increased mitochondrial ΔΨm compared to oxLDL + L-NAME-treated HAECs. The expression of OMA1 was decreased by LiCl treatment, while PGC1α expression was increased. In HAECs, we found that OMA1 knockdown increased mitochondrial function and the expression of PGC1α. We also demonstrated LiCl increased OMA1 ubiquitination compared with the Control group, thus decreased OMA1 expression. Furthermore, siOMA1 antagonized the increased protein expressions of ICAM1, VCAM1, TNF-α, Bax and Drp1, decreased the protein expressions of Bcl2 and MFN2 by siPGC1α. Taken together, we demonstrated that GSK3β could play a contributory role in hypertension exacerbating atherosclerosis by regulating the OMA1/PGC1α pathway and inhibiting mitochondrial function.

25COASMA171

Title: Dysregulation of R-loop homeostasis shapes the immunosuppressive microenvironment and induces malignant progression in melanoma

Yan Ouyang, Yan Gu, Shuqin Li, Xianpeng Wei, Yang Liu, Zejun Wang, Fuzhou Tang & Shichao Zhang

Apoptosis, Volume 30, pages 131–148, (2025)
DOI: https://doi.org/10.1007/s10495-024-02039-z

Abstract: Dysregulated R-loop homeostasis leads to DNA replication stress and genomic instability, a major driver of cancer. However, the role of R-loops in melanoma development remains unclear. We established an R-loop scoring model based on a single-cell RNA sequencing dataset and evaluated the association between the R-loop score with the melanoma immune microenvironment and treatment response. We explored the role of CENPA-mediated changes in R-loop distribution during melanoma progression by DNA/RNA immunoprecipitation and sequencing and a series of functional experiments. We found that malignant cells with high R-loop scores may be involved in melanoma progression by modulating immune evasion, metabolic reprogramming, and cancer-related pathways. A cell communication analysis revealed that high-score R-loops play an important role in altering cell–cell interactions and limiting the CD8 + cytotoxic T cell response and T cell accumulation. CENPA silencing induced changes in R-loop distribution, upregulated Hippo signaling activity, and inhibited tumor cell proliferation and migration. Moreover, the R-loop score can predict the prognosis and immunotherapy effect of melanoma patients. Our work reveals the potential molecular mechanism by which abnormal R-loops promote melanoma progression, which may help develop anticancer therapies based on R-loops or R-loop regulators.

25COASMA172

Title: MRG15 promotes cell apoptosis through inhibition of mitophagy in hyperlipidemic acute pancreatitis

Boyuan Gu, Wenhao Yu, Zhiwei Huang, Junjie Bai, Shenglu Liu, Bingyu Ren, Pengru Wang, Lei Sun, Jian Wen,

Apoptosis, Volume 30, pages 149–166, (2025)

DOI: https://doi.org/10.1007/s10495-024-02034-4

Abstract: Hyperlipidemia is a common cause of acute pancreatitis (AP), often leading to more severe clinical symptoms. The mortality factor 4-like protein 1 (MORF4L1, also called MRG15) plays a crucial role in regulating lipid metabolism. Therefore, this study aimed to explore the mechanism of MRG15 in hyperlipidemic acute pancreatitis (HAP). Mendelian randomization, transcriptome analysis, and single-cell analysis were employed to explore the association between MRG15 and AP by utilizing publicly available databases. In vivo, hypertriglyceridemia mouse models were created by intraperitoneal injection of P407 or using APOE-deficient mice. Subsequently, the HAP model was induced by cerulean. In vitro, a cell model of HAP was established by initially exposing cells to palmitic acid to simulate a high-fat environment, followed by cerulein treatment. Subsequently, MRG15-related indicators were measured. Through Mendelian randomization, it was discovered that there is a positive correlation between genetic expression of MRG15 and the risk of AP. Transcriptome and single-cell analysis revealed that elevated MRG15 expression in AP contributes to lipid metabolism disorders and the activation of apoptosis pathways in pancreatic acinar cells. MRG15 is found to be significantly upregulated in cases of HAP. Knocking down MRG15 led to an increase in mitophagy and a decrease in apoptosis in pancreatic cells, and this effect was reversed when the mitochondrial Tu translation elongation factor (TUFM) was simultaneously knocked down. MRG15 inhibits mitophagy by degrading TUFM, ultimately promoting cell apoptosis and worsening the progression of HAP.

25COASMA173

Title: FBXO2 as a switch guides a special fate of tumor clones evolving into a highly malignant transcriptional subtype in oral squamous cell carcinoma

Jingyi Cheng, Ousheng Liu, Xin Bin & Zhangui Tang

Apoptosis, Volume 30, pages 167–184, (2025)
DOI: https://doi.org/10.1007/s10495-024-02033-5

Abstract: Tumors comprise a heterogeneous collection of tumor cells with distinct genetic and phenotypic characteristics that differentially promote malignant progression. Therefore, it is essential to depict the heterogeneous landscape of clones for understanding the cancer biology and overcoming the resistance of cancer therapy. To determine the dynamic clonal feature of OSCC, we constructed the evolutionary trajectory of tumor cells based on single-cell RNA sequencing data. A special transcriptional states of clones with distinct highly malignant features was identified, and FBXO2 was determined as the key switch gene causing the transition of tumor cells into this special state. FBXO2 exhibited a significantly high expression in OSCC than normal samples, especially in those with high clinical stages. The knockdown or overexpression of FBXO2 in OSCC cells correspondingly inhibited or promoted the abilities of proliferation, G1-S phase transition, migration, invasion, EMT, and resisting apoptosis. Moreover, FBXO2 was indicated to be involved in an intricate network to regulate multiple processes, modifying the interactions between tumor cells and other cells and thus defining different functional subtypes of tumor cells to affect tumor progression. These results provide new insights into clonal fate and pave the way for more effective therapy of OSCC.

25COASMA174

Title: Lenvatinib inhibits cholangiocarcinoma progression by targeting the FGF19/PI3K/AKT signaling pathway

Yingcheng Wei, Lei Yang, Chenwei Tang, Hongkai Zhuang, Xinming Chen, Xiaowu Ma, Xuesong Deng,

Apoptosis, Volume 30, pages 185–196, (2025)
DOI: https://doi.org/10.1007/s10495-024-02028-2

Abstract: Cholangiocarcinoma (CCA) is known for its high aggressiveness and dismal prognosis, whose effectiveness of systemic therapy remains limited. As a multi-target drug, lenvatinib has exhibited promising effects in many solid tumors. However, the therapeutic role of lenvatinib in CCA is rarely investigated. Here, the in vitro assays including EdU, colony formation, transwell, wound healing, and apoptosis analyses demonstrated that lenvatinib significantly inhibited the proliferation, migration, and invasion, while simultaneously inducing apoptosis of CCA cells. Mechanistically, lenvatinib downregulated the expression of FGF19 and inactivated the PI3K/AKT signaling pathway. Depletion of FGF19 enhanced the anti-tumor effects of lenvatinib, which was attributed to the inhibition of p-PI3K and p-AKT expression in CCA cells. In contrast, overexpression of FGF19 activated the PI3K/AKT signaling pathway, thereby impairing the inhibitory effects of lenvatinib against CCA. In addition, the AKT inhibitor, MK-2206, reinforced the lenvatinib-induced CCA inhibition. Notably, the in vivo experiment confirmed that the subcutaneous tumorigenicity of CCA cells in nude mice was weakened by lenvatinib. Lenvatinib markedly downregulated the expression of FGF19, p-AKT, Ki-67, vimentin, and VEGF in the xenograft tumor tissues. Collectively, these findings demonstrated that lenvatinib inhibits CCA progression by targeting the FGF19/PI3K/AKT signaling pathway. The present study provides novel experimental evidence for the potential clinical application of lenvatinib in CCA, which also highlights the promising role of targeting FGF19 in combined therapeutic approaches for CCA.

25COASMA175

Title: Golgi-derived extracellular vesicle production induced by SARS-CoV-2 envelope protein

Qiguang Li, Qian Liu, Shuangqu Li, Xiaoli Zuo, Hu Zhou, Zhaobing Gao & Bingqing Xia

Apoptosis, Volume 30, pages 197–209, (2025)
DOI: https://doi.org/10.1007/s10495-024-02035-3

Abstract: Extracellular vesicles facilitate cell-to-cell communication, and some enveloped viruses utilize these vesicles as carriers to mediate viral transmission. SARS-CoV-2 envelope protein (2-E) forms a cation channel and overexpression of 2-E led to the generation of a distinct type of large extracellular vesicles (2-E-EVs). Although 2-E-EVs have been demonstrated to facilitate viral transmission in a receptor-independent way, the characteristics and biogenesis mechanism remain enigmatic. Via lipidomics and proteomic analysis, we found 2-E-EVs are distinct from endosome-derived exosomes. 2-E-EVs are notably enriched in Golgi apparatus components, aligning with the observed fragmentation in Golgi morphology. Through live cell imaging, we established a connection between 2-E-EVs formation, Golgi fragmentation, and channel activity, emphasizing the role of 2-E-EVs as ion

channel-induced extracellular vesicles. Our work highlights 2-E-EVs as distinctive Golgi-derived vesicles, contributing to a deeper understanding of 2-E channel-mediated virus-host dynamics, with implications for therapeutic strategies and drug delivery.

25COASMA176

Title: The gut microbial metabolite phenylacetylglutamine increases susceptibility to atrial fibrillation after myocardial infarction through ferroptosis and NLRP3 inflammasome

Guangji Wang, Qin He, Wei Shuai, Hongjie Yang, Bin Kong, Shimin Lu & Yang Gong

Apoptosis, Volume 30, pages 210–225, (2025)
DOI: **https://doi.org/10.1007/s10495-024-02046-0**

Abstract: Myocardial infarction (MI) is an important risk factor for the development of atrial fibrillation (AF), and the gut microbial metabolite phenylacetylglutamine (PAGln) is strongly associated with the prognosis of MI patients. However, whether PAGln is involved in the regulation of AF after MI is currently unknown. Therefore, the present study aimed to explore the effect of PAGln on the susceptibility to AF after MI. MI model was constructed by surgically ligating the left anterior descending branch of the coronary artery. PAGln was administered by intraperitoneal injection for 7 consecutive days starting after surgery and then investigated by histopathologic, molecular biological, and electrophysiologic studies. Myocardial ischemia resulted in intestinal barrier dysfunction and significantly increased circulating levels of PAGln. Compared with the myocardial ischemia group, administration of PAGln significantly exacerbated atrial fibrosis and atrial electrical remodeling in mice after myocardial ischemia, as evidenced by shortening of the ERP (at varying pacing cycle lengths of 40, 60, 80, and 100), ion channel remodeling (Nav1.5, Cav1.2, and Kv1.5), and decreased expression of CX40, which led to an increase in the susceptibility to AF (54.5% vs. 90.9%, $P < 0.05$). In addition, administration of PAGln further exacerbated MI-induced intestinal barrier dysfunction compared with the MI group. Mechanistically, PAGln may affect atrial remodeling and AF susceptibility after MI by modulating ferroptosis and NLRP3 inflammasome. The present study preliminarily reveals that the gut microbial metabolite PAGln exacerbates post-MI AF remodeling and AF susceptibility, possibly through ferroptosis and activation of NLRP3 inflammasome.

25COASMA177

Title : The N6-methyladenosine writer METTL3 promotes breast cancer progression through YTHDF2-dependent posttranscriptional silencing of GSDMD

You Shuai, Zhonghua Ma, Jie Ju, Chunxiao Li, Xiaorong Bai, Jian Yue, Xue Wang, Peng Yuan & Haili Qian

Apoptosis, Volume 30, pages 226–238, (2025)
DOI: **https://doi.org/10.1007/s10495-024-02037-1**

Abstract: Cell pyroptosis is a form of programmed cell death, with Gasdermin-D (GSDMD) acting as its key executor. While activating pyroptosis represents a promising therapeutic strategy for cancer, the regulatory mechanisms governing GSDMD expression during cell death remain poorly understood. In this study, we identified METTL3 as a negative regulator of GSDMD-mediated pyroptosis, with high expression in breast cancer (BC) cells. YTHDF2

was found to recognize the m6A modification of GSDMD, thereby decreasing its stability. Finally, in vivo experiments further demonstrated the inhibitory effect of the METTL3 inhibitor STM2457 on tumors. Overall, these findings suggest that inhibition of METTL3 can enhance GSDMD-mediated pyroptosis and reveal a novel regulatory mechanism governing GSDMD expression, presenting a novel strategy for cancer treatment.

25COASMA178

Title: Probiotic DNA regulates intestinal Th2 polarization by inducing epithelial cells to produce PD-L1

Shuo Song, Hanqing Zhang, Le Liu, Minyao Li, Xiangyu Wang, Haotao Zeng, Miao Zhao, Pixin Ran,

Apoptosis, Volume 30, pages 239–249, (2025)
DOI: https://doi.org/10.1007/s10495-024-02043-3

Abstract: Th2 polarization is a characteristic feature of many immune diseases; its pathogenesis is still being elucidated. Probiotics have immune regulatory effects. This study is aimed at testing the impact of Lactobacillus rhamnosus (LR) DNA on regulating Th2 polarization and elucidating its underlying mechanism. In this study, ovalbumin plus alum protocol was used to establish the Th2 polarization status in the mouse intestine. Mice received LR-DNA gavage daily for five days. The expression of programmed cell death ligand-1 (PD-L1) in intestinal epithelial cells was assessed using RT-qPCR, enzyme-linked immunosorbent assay, and immunohistochemistry. The results showed that the expression of PD-L1 was detected in mouse intestinal epithelial cells, which was up regulated by LR-DNA gavage daily for 5 days. The expression of PD-L1 was also detected in T84 cells, which could be increased by exposing them to LR-DNA in culture. RNA sequencing results showed that the gene activities of Kdm5a, foxo1 and Pdl1 could be upregulated by LR-DNA in mouse intestinal epithelial cells. The epithelial cell-derived PD-L1 induced the activated Th2 cell apoptosis by interacting with programmed cell death protein-1 (PD-1). Administration of LR-DNA, but not live probiotics, alleviated experimental Th2 polarization in a food allergy mouse model. In conclusion, LR-DNA induces intestinal epithelial cells to produce PD-L1, which induces the activated Th2 cell apoptosis. Administration of LR-DNA mitigated experimental Th2 polarization in the intestine.

25COASMA179

Title: Machine learning-based analysis of programmed cell death types and key genes in intervertebral disc degeneration

Yigang Lv, Jiawei Du, Haoning Xiong, Lei Feng, Di Zhang, Hengxing Zhou & Shiqing Feng

Apoptosis, Volume 30, pages 250–266, (2025)
DOI: https://doi.org/10.1007/s10495-024-02047-z

Abstract: Intervertebral disc degeneration (IVDD) is intricately associated with various forms of programmed cell death (PCD). Identifying key PCD types and associated genes is essential for understanding the molecular mechanisms underlying IVDD and discovering potential therapeutic targets. This study aimed to elucidate core PCD types, related genes, and potential drug interactions in IVDD using comprehensive bioinformatic and experimental approaches. Using datasets GSE167199, GSE176205, GSE34095, GSE56081, and

GSE70362, relevant gene expression and clinical data were analyzed. Differential expression gene (DEG) analysis identified upregulated genes linked to 15 PCD types. Gene Set Variation Analysis (GSVA) was employed to pinpoint key PCD types contributing to disc degeneration. Core genes were identified through machine learning techniques, while immune infiltration and single-cell analysis helped identify apoptosis-related cell types. Molecular docking, along with in vivo and in vitro experiments using a murine IVDD model, validated potential drug interactions. The results identified apoptosis, autophagy, ferroptosis, and necroptosis as key PCD types in IVDD. A gene module associated with apoptosis showed a strong correlation with the severity of disc degeneration, revealing 34 central genes in the gene network. Drug screening identified Glibenclamide as effectively interacting with PDCD6 and UBE2K. Subsequent in vitro and in vivo experiments demonstrated that Glibenclamide reduced apoptosis and delayed disc degeneration progression. This study provides a comprehensive bioinformatics analysis of PCD in IVDD, identifying four primary PCD types contributing to the disease's progression. The findings offer novel insights into the molecular pathology of disc degeneration and suggest promising therapeutic strategies for future treatment development.

25COASMA180

Title: Single-cell RNA sequencing analysis reveals the dynamic changes in the tumor microenvironment during NMIBC recurrence

Ziang Chen, Tianxiang Zhang, Weijian Li, Jia Hu, Yuxi Ou, Fangdie Ye, Jinhao Zhang, Haowen Jiang & Shenghua Liu

Published: 04 December 2024
Apoptosis, Volume 30, pages 282–296, (2025)
DOI: https://doi.org/10.1007/s10495-024-02044-2

Abstract: Background: Due to the clinical characteristic of frequent recurrence in urothelial bladder cancer (UBC), patients face significant health impacts and economic burdens. Therefore, understanding the molecular mechanisms involved in UBC recurrence is crucial for reducing its recurrence rate. The aim of our study is to help urologists and clinical researchers gain a deeper understanding of the changes in the tumor microenvironment (TME) during UBC recurrence. Methods: We collected 10 samples from primary and recurrent non-muscle-invasive bladder cancer (NMIBC) and performed single-cell RNA sequencing. By distinguishing and annotating cell subpopulations, we identified tissue preferences of some novel cell subgroups. Next, pseudotime trajectory analysis, cell-cell communication analysis, and function enrichment analysis were applied to evaluate the dynamic changes in the TME and biological functions. Finally, we validated the distribution of some of these cell subgroups using multiplex immunofluorescence experiments.Results: We identified a tumor-associated fibroblast (CAF) subtype with high COL18A1 expression that is highly expressed in recurrent NMIBC, suggesting that the stromal component of the tumor may play a crucial role in the recurrence process. Additionally, pseudotime trajectory analysis revealed a macrophage subtype with high IL-6 expression at the terminal stage of macrophage differentiation, exhibiting significant immunosuppressive features. This indicated the presence of immune exhaustion during NMIBC recurrence. Lastly, we found an upregulation of estrogen in recurrent urothelial cancer cells, which may partially explain the

gender disparity observed in UBC.Conclusion: This study identified several cell subpopulations influencing NMIBC recurrence, which were heavily infiltrated in the TME of recurrent NMIBC. Additionally, the enrichment of estrogen in urothelial cancer cells from various sources suggested a role of sex hormones in NMIBC recurrence.

25COASMA181

Title: HIG-2 promotes glioma stemness and radioresistance mediated by IGFBP2-rich microparticles in hypoxia

Ying Yang, Ting Sun, Xuefei Xue, Huiling Tan, Yanyan Li & Wei Yang

Apoptosis, Volume 30, pages 297–319, (2025)
DOI: https://doi.org/10.1007/s10495-024-02045-1

Abstract: Hypoxia can weaken the efficacy of radiotherapy and decrease tumor immunogenicity leading to immune escape. Thus, a thorough understanding of the key signaling pathways regulated by hypoxia is vitally important to enhance the radiosensitivity and improve immunosuppressive microenvironment of glioma. In this study, we verified the crucial role of hypoxia-inducible gene 2 (HIG-2) in lipid droplet (LD) accumulation and demonstrated that HIG-2 binding to frizzled class receptor 10 (FZD10) activated Wnt/β-catenin signaling pathway and increased its downstream insulin-like growth factor binding protein 2 (IGFBP2) level in microparticles (MPs) derived from glioma stem cells (GSCs), leading to decreased radiosensitivity and immunogenicity of MPs-receiving cells via the cross-talk between GSCs and non-stem glioma cells (GCs). These findings suggest that HIG-2 may be a promising target in glioma radiotherapy and/or immunotherapy.

25COASMA182

Title: GAS5 long non-coding RNA interacts with microRNA-205 to relieve fibroblast-like synoviocyte inflammation and ferroptosis in osteoarthritis

Yanglin Gu, Guangchang Wang & Peng Chen

Apoptosis, Volume 30, pages 320–333, (2025)
DOI: https://doi.org/10.1007/s10495-024-02051-3

Abstract: This study aimed to explore the role of the growth arrest-specific five gene (GAS5) long non-coding RNA (lncRNA) in fibroblast-like synoviocytes (FLSs) during the development of osteoarthritis (OA). A total of 25 OA synovial tissues and nine healthy control tissues were collected, and their GAS5 expression was compared. To confirm GAS5 expression in vitro, interleukin (IL)-1β was used to mimic a cellular OA model based on isolated FLSs. Quantitative polymerase chain reaction revealed higher expression levels of GAS5 in OA samples than in non-OA samples. In vitro, the stimulation of FLSs by IL-1β induced high GAS5 expression. The IL-1β-exposed cells exhibited impaired growth, viability, and antioxidant capacity, as well as increased cell death, production of cellular and lipid ROS, and inflammatory cytokine levels. The expression levels of ferroptosis-related proteins in FLSs were also altered in IL-1β-exposed cells. GAS5 was observed to directly target and inhibit micro-RNA 205, partially reversing the effect of GAS5 silencing on cell proliferation, cell death, oxidative stress, inflammation, and FLS ferroptosis. FLS ferroptosis is recognized to be involved in OA development, and the downregulation of the GAS5 lncRNA exhibits protective effects by suppressing ferroptosis and sponging miR-205 in FLSs

in OA, thereby providing a novel strategy for the treatment of OA. The GAS5–miR–205 axis can regulate inflammation and oxidative stress in the FLSs of patients with OA.

25COASMA183

Title: Mitochondrial CLPB is a pro-survival factor at the onset of granulocytic differentiation of mouse myeloblastic cells

Tomasz Wenta, Guanpeng Wang, Tessa Van Buren, Michal Zolkiewski & Anna Zolkiewska

Apoptosis, Volume 30, pages 334–348, (2025)
DOI: https://doi.org/10.1007/s10495-024-02053-1

Abstract: Loss-of-function mutations in the CLPB gene lead to congenital neutropenia due to impaired neutrophil differentiation. CLPB, a member of the AAA+ family of proteins, resides in the intermembrane space of mitochondria. The mechanism by which a loss of CLPB elicits defects in the differentiation program of neutrophil precursor cells is not understood. Here, we used 32D clone 3 (32Dcl3) cells, an interleukin-3 (IL-3)-dependent mouse myeloblastic cell line model, to investigate the effects of CLPB knockout on myeloblast-to-neutrophil differentiation in vitro. We found that CLPB-deficient 32Dcl3 cells showed a decreased mitochondrial membrane potential and increased levels of insoluble HAX1 aggregates in mitochondria, as compared to control cells. Despite those abnormalities, CLPB loss did not affect cell proliferation rates in the presence of IL-3 but it increased apoptosis after IL-3 withdrawal and simultaneous induction of cell differentiation with granulocytic colony stimulating factor (G-CSF). CLPB-deficient cells that survived the stress associated with IL-3 withdrawal/G-CSF treatment expressed the same levels of differentiation markers as control cells. Moreover, we found that increased apoptosis of CLPB-deficient cells is linked to production of reactive oxygen species (ROS). N-acetylcysteine, exogenous free fatty acids, or exogenous citrate protected CLPB-deficient 32Dcl3 cells from apoptosis at the onset of differentiation. The protective effect of citrate was abolished by inhibition of ATP-citrate lyase (ACLY), an enzyme that converts cytosolic citrate into acetyl-CoA, a substrate for protein acetylation. We propose that citrate supplementation may help mitigate the effects of CLPB loss by facilitating ACLY-dependent ROS detoxification in granulocytic precursor cells.

25COASMA184

Title: EFNA4-enhanced deubiquitination of SLC7A11 inhibits ferroptosis in hepatocellular carcinoma

Xingyi Zhong, Zhiqin Zhu, Yangfeng Du, Lingzhi Long, Ziping Xie, Yangfeng Zhang, Huijun Yao,

Apoptosis, Volume 30, pages 349–363, (2025)
DOI: https://doi.org/10.1007/s10495-024-02042-4

Abstract: EFNA4, a member of the Ephrin-A ligand family, may influence hepatocellular carcinoma cells through two distinct mechanisms: one reliant on specific Eph receptor binding and the other independent of receptor involvement. However, EFNA4's influence on HCC via non-Eph receptor pathways remains unclear. In this study, we aimed to investigate the role of EFNA4 in a receptor-independent environment. Firstly, we constructed an environment lacking Eph receptors via CRISPR/Cas9 and found that EFNA4 could still

partially promote HCC proliferation and metastasis in vivo and in vitro. Further analyses of apoptosis, ROS, and GPX4 expression revealed that overexpression of EFNA4 would inhibit ferroptosis in HCC. Mechanistically, EFNA4 was positively correlated with SLC7A11 and directly interacted with SLC7A11 in HCC via bioinformatics analysis. We demonstrated that the structural domain (a.a. 161–201) of EFNA4 specifically binds to the domain (a.a. 222–501) of SLC7A11, which led to the deubiquitination of SLC7A11. Subsequently, we found that EFNA4 would recruit the deubiquitinase USP9X, resulting in inhibition of SLC7A11 degradation, which ultimately inhibits ferroptosis and enhances the proliferation and metastasis of HCC. In conclusion, we demonstrated that EFNA4 promotes the proliferation and metastasis of HCC independent of Eph receptors by inhibiting ferroptosis and advancing the deubiquitination of SLC7A11 by recruiting the deubiquitinase USP9X. This indicates that EFNA4 could act as a potential prognostic marker and a prospective therapeutic target in patients with HCC.

25COASMA185

Title: Integrated explainable machine learning and multi-omics analysis for survival prediction in cancer with immunotherapy response

Alphonse Houssou Hounye, Li Xiong & Muzhou Hou

Apoptosis, Volume 30, pages 364–388, (2025)
DOI: https://doi.org/10.1007/s10495-024-02050-4

Abstract: To demonstrate the efficacy of machine learning models in predicting mortality in melanoma cancer, we developed an interpretability model for better understanding the survival prediction of cancer. To this end, the optimal features were identified, ten different machine learning models were utilized to predict mortality across various datasets. Then we have utilized the important features identified by those machines learning methods to construct a new model named NKECLR to forecast mortality of patient with cancer. To explicitly clarify the model's decision-making process and uncover novel findings, an interpretable technique incorporating machine learning and SHapley Additive exPlanations (SHAP), as well as LIME, has been employed, and four genes EPGN, PHF11, RBM34, and ZFP36 were identified from those machine learning(ML). The experimental analysis conducted on training and validation datasets demonstrated that the proposed model has a good performance com- pared to existing methods with AUC value 81.8%, and 79.3%, respectively. Moreover, when combined our NKECLR with PD-L1, PD-1, and CTLA-4 the AUC value was 83%0. Finally, these findings have been applied to comprehend the response of drugs and immunotherapy. Our research introduced an innovative predictive NKECLR model utilizing natural killer(NK) cell marker genes for cohorts with melanoma cancer. The NKECLR model can effectively predict the survival of melanoma cancer cohorts and treatment results, revealing distinct immune cell infiltration in the high-risk group.

25COASMA186

Title: The STING signaling pathways and bacterial infection

Jiayi You, Ailing Xu, Ye Wang, Guangmin Tu, Rui Huang & Shuyan Wu

Apoptosis, Volume 30, pages 389–400, (2025)
DOI: https://doi.org/10.1007/s10495-024-02031-7

Abstract: As antibiotic-resistant bacteria continue to emerge frequently, bacterial infections have become a significant and pressing challenge to global public health. Innate immunity triggers the activation of host responses by sensing “non-self” components through various pattern recognition receptors (PRRs), serving as the first line of antibacterial defense. Stimulator of interferon genes (STING) is a PRR that binds with cyclic dinucleotides (CDN) to exert effects against bacteria, viruses, and cancer by inducing the production of type I interferon and inflammatory cytokines, and facilitating regulated cell death. Currently, drugs targeting the STING signaling pathway are predominantly applied in the fields of modulating host immune defense against cancer and viral infections, with relatively limited application in treating bacterial infections. Given the significant immunomodulatory functions of STING in the interaction between bacteria and hosts, this review summarizes the research progress on STING signaling pathways and their roles in bacterial infection, as well as the novel functions of STING modulators, aiming to offer insights for the development of antibacterial drugs.

25COASMA187

Title: Advancements in programmed cell death research in antitumor therapy: a comprehensive overview

Shuxin Wei, Chuangye Han, Shutian Mo, Hailian Huang & Xiaoling Luo

Apoptosis, Volume 30, pages 401–421, (2025)
DOI: https://doi.org/10.1007/s10495-024-02038-0

Abstract: Cell death is a normal physiological process within cells that involves multiple pathways, such as normal DNA damage, cell cycle arrest, and programmed cell death (PCD). Cell death has been a hot spot of research in tumor-related fields, especially programmed cell death, which is a key form of cell death and is classified into different types according to the mechanism of occurrence, such as apoptosis, autophagy, necroptosis, pyroptosis, ferroptosis, and disulfidptosis. Given the important role of PCD in maintaining tissue homeostasis and inhibiting tumorigenesis and development, more and more basic and clinical studies are devoted to revealing its potential application in anti-tumor strategies. The purpose of this review is to systematically review the regulatory mechanisms of PCD and to summarize the latest research progress of anti-tumor treatment strategies based on PCD.

25COASMA188

Title: Isolation, identification, and challenges of extracellular vesicles: emerging players in clinical applications

Xiaoxiao Ma, Lanwei Peng, Xiaohui Zhu, Tianqi Chu, Changcheng Yang, Bohao Zhou, Xiangwei Sun, Tianya Gao,

Apoptosis, Volume 30, pages 422–445, (2025)
DOI: https://doi.org/10.1007/s10495-024-02036-2

Abstract: Extracellular vesicles (EVs) serve as critical mediators of intercellular communication, encompassing exosomes, microvesicles, and apoptotic vesicles that play significant roles in diverse physiological and pathological contexts. Numerous studies have demonstrated that EVs derived from mesenchymal stem cells (MSC-EVs) play a pivotal role in facilitating tissue and organ repair, alleviating inflammation and apoptosis, enhancing the

proliferation of endogenous stem cells within tissues and organs, and modulating immune function—these functions have been extensively utilized in clinical applications. The precise classification, isolation, and identification of MSC-EVs are essential for their clinical applications. This article provides a comprehensive overview of the biological properties of EVs, emphasizing both their advantages and limitations in isolation and identification methodologies. Additionally, we summarize the protein markers associated with MSC-EVs, emphasizing their significance in the treatment of various diseases. Finally, this article addresses the current challenges and dilemmas in developing clinical applications for MSC-EVs, aiming to offer valuable insights for future research.

25COASMA189

Title: Microglia programmed cell death in neurodegenerative diseases and CNS injury

Ling Cai, Qiuyue Fan, Rui Pang, Chen Chen, Yueman Zhang, Haiyi Xie, Jingyi Huang, Yu Wang,

Apoptosis, Volume 30, pages 446–465, (2025)
DOI: https://doi.org/10.1007/s10495-024-02041-5

Abstract: Programmed cell death (PCD) has emerged as a critical regulatory mechanism in the initiation and progression of various pathological conditions. PCD in microglia, including necroptosis, pyroptosis, apoptosis, ferroptosis, and autophagy, occurs in a variety of central nervous system (CNS) diseases. Dysregulation of microglia can lead to excessive tissue damage or neuronal death in CNS injury. Various injury stimuli trigger aberrant activation of the PCD pathway of microglia, which then further leads to inflammatory cascades that exacerbates CNS pathology in a vicious cycle. Therefore, targeting PCD in microglia is considered an important avenue for the treatment of various neurodegenerative diseases and CNS injury. In this review, we summarize the major and recent findings focusing on the mechanisms of PCD in microglia modulating functions in neurodegenerative diseases and CNS injury and provide a systematic overview of the current inhibitors targeting various PCD pathways, which may provide important therapeutic targets that merit further investigation.

25COASMA190

Title: Necroptosis in obesity: a complex cell death event

Zunhai Liu, Simeng Wang, Wentao Wang, Rui Lv & Chao Sun

Apoptosis, Volume 30, pages 466–487, (2025)
DOI: https://doi.org/10.1007/s10495-024-02055-z

Abstract: Obesity is an exceedingly prevalent and frequent health issue in today's society. Fat deposition is accompanied by low-grade inflammation in fat tissue and throughout the body, leading to metabolic disorders that ultimately promote the onset of obesity-related diseases. The development of obesity is accompanied by cell death events such as apoptosis as well as pyroptosis, however, the role of necroptosis in obesity has been widely reported in recent years. Necroptosis, a mode of cell death distinct from apoptosis and necrosis, is associated with developing many inflammatory conditions and their associated diseases. It also exhibits modulation of apoptosis and pyroptosis. It is morphologically similar to necroptosis, characterized by the inhibition of caspase-8, the formation of membrane pores,

and the subsequent rupture of the plasma membrane. This paper focuses on the key pathways and molecules of necroptosis, exploring its connections with apoptosis and pyroptosis, and its implications in obesity. This paper posits that the modulation of necroptosis-related targets may represent a novel potential therapeutic avenue for the prevention and treatment of obesity-induced systemic inflammatory responses, and provides a synopsis of potential molecular targets that may prove beneficial in obesity-associated inflammatory diseases.

25COASMA191

Title: Involvement of copper in cell death and cancer

Jiahao Xie, Yue Su, Wenzhong Shang, Yanfang Wu, Junjia He, Ting Li, Yeyu Shen, Youni Zhang,

Apoptosis, Volume 30, pages 488–505, (2025)
DOI: https://doi.org/10.1007/s10495-024-02059-9

Abstract: Copper (cu) is an essential micronutrient required for numerous metabolic processes. It plays a crucial role in cellular respiration by participating in the electron transport chain and facilitating numerous biological reactions. Various diseases, including cancer, demonstrate localized elevation of copper levels and/or alterations in the overall distribution of copper. Modulating local or systemic copper levels as a novel therapeutic approach for treating and ameliorating diseases has emerged as a prominent trend in disease management, particularly in the realm of cancer therapy, which is currently under investigation. The objective of this review is to offer a thorough examination of copper metabolism in both physiological and pathological contexts. Specifically, it delves into how copper ions can effectively target and stimulate tumor cell death via the process known as cuproptosis in cancer patients. Furthermore, this review explores the utilization of three categories of anticancer medications (copper ion carriers, copper complexes, and copper chelating agents) pertaining to copper metabolism within the realm of cancer therapy, elucidating on the distinct mechanisms through which they exert their effects.

Diagnostic Services
(Pathology, Cancer Screening & Radio-diagnosis)

25COASMA1:
Title: IRF8 Demonstrates Positivity in a Significant Subset of Histiocytic and Dendritic Cell Neoplasms
Patwardhan, Pranav P. MBBS, MD[*]; Bailey, Nathanael G. MD[*]; Monaghan, Sara A. MD[*]; Singhi, Aatur D. MD, PhD[*];
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Abstract: Histiocytic and dendritic cell neoplasms, especially histiocytic sarcoma, can show morphologic and phenotypic overlap with immature monocytic neoplasms. IRF8 immunohistochemical staining has been demonstrated to be useful in identifying monoblasts, but it has not been extensively studied in histiocytic and dendritic cell neoplasms. IRF8 immunohistochemistry was performed on cases of histiocytic sarcoma (HS, n=6), Langerhans cell histiocytosis (LCH, n=25), Rosai Dorfman disease (RDD, n=17), follicular dendritic cell sarcoma (FDCS, n=3), and Erdheim Chester disease (ECD, n=5), along with a control group that included a subset of myeloid neoplasms with monocytic differentiation. Of 89 total cases, IRF8 was positive in 3/6 cases of HS, 3/5 cases of ECD, 12/17 cases of RDD, 7/25 cases of LCH, and 0/3 cases of FDCS. Control cases were stained similarly to previous reports, with IRF8 expression roughly correlating to monoblast count and normal staining in other control groups. We demonstrate that IRF8 is expressed in a significant subset of tested neoplasms of histiocytic and dendritic cell lineage. While we confirmed that IRF8 is useful to identify monoblasts, these results highlight that IRF8 cannot be reliably used to distinguish histiocytic sarcomas from myeloid neoplasms of monocytic lineages, and caution is advised interpreting IRF8 staining in that setting.

25COASMA2:
Title: TFE3-rearranged Head and Neck Neoplasms
Twenty-two Cases Spanning the Morphologic Continuum Between Alveolar Soft Part Sarcoma and PEComa and Highlighting Genotypic Diversity
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The American Journal of Surgical Pathology 49(2):p 104-112, February 2025.
DOI: https://doi.org/10.1097/PAS.0000000000002334
Abstract: TFE3 rearrangements characterize histogenetically, topographically, and biologically diverse neoplasms. Besides being a universal defining feature in alveolar soft part sarcoma (ASPS) and clear cell stromal tumor of the lung, TFE3 fusions have been reported in subsets of renal cell carcinoma, perivascular epithelioid cell tumor (PEComa), epithelioid hemangioendothelioma and ossifying fibromyxoid tumors. TFE3-related neoplasms are rare in the head and neck and may pose diagnostic challenges. We herein describe 22 TFE3 fusion neoplasms affecting 11 males and 11 females aged 4 to 79 years (median, 25) and involving different head and neck sites: sinonasal cavities (n = 8), tongue (n = 4), oral cavity/oropharynx (n = 3), salivary glands (n = 2), orbit (n = 2), and soft tissue or

unspecified sites (n = 3). Based on morphology and myomelanocytic immunophenotype, 10 tumors qualified as ASPS, 7 as PEComas (3 melanotic; all sinonasal), and 5 showed intermediate (indeterminate) histology overlapping with ASPS and PEComa. Immunohistochemistry for TFE3 was homogeneously strongly positive in all cases. Targeted RNA sequencing/FISH testing confirmed TFE3 fusions in 14 of 16 successfully tested cases (88%). ASPSCR1 was the most frequent fusion partner in ASPS (4 of 5 cases); one ASPS had a rare VCP::TFE3 fusion. The 6 successfully tested PEComas had known fusion partners as reported in renal cell carcinoma and PEComas (NONO, PRCC, SFPQ, and PSPC1). The indeterminate tumors harbored ASPSCR1::TFE3 (n = 2) and U2AF2::TFE3 (n = 1) fusions, respectively. This large series devoted to TFE3-positive head and neck tumors illustrates the recently proposed morphologic overlap in the spectrum of TFE3-associated mesenchymal neoplasms. While all PEComas were sinonasal, ASPS was never sinonasal and occurred in diverse head and neck sites with a predilection for the tongue. The indeterminate (PEComa-like) category is molecularly more akin to ASPS but shows different age, sex, and anatomic distribution compared with classic ASPS. We report VCP as a novel fusion partner in ASPS and PSPC1 as a novel TFE3 fusion partner in PEComa (detected in one PEComa). Future studies should shed light on the most appropriate terminological subtyping of these highly overlapping tumors.

25COASMA3:

Title: A Proposal for Revised and Simplified Renal Pelvic Urothelial Carcinoma Staging Criteria: A Clinicopathologic Study of 141 Tumors

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Abstract: Staging of renal pelvic urothelial carcinoma can be challenging due to anatomic variation at the renal pelvis compared with ureter and bladder and calls into question the prognostic accuracy of the current TNM staging. In this study, we determined staging and cancer-specific survival (CSS) in 141 patients undergoing nephroureterectomy for renal pelvic urothelial carcinoma (pTa=50, pT1=29, pT2=10, pT3=36, and pT4=16). Under current staging criteria, we found no significant difference in CSS between adjacent staging categories step-wise across pTa, pT1, pT2, and pT3 tumors. When pT3 tumors were subcategorized into renal medulla, peripelvic adipose, or renal cortex invasion with or without peripelvic adipose invasion, we found that cortical invasion was associated with significantly worse CSS compared with medulla or peripelvic adipose invasion only. We next revised staging criteria such that pT1 correlated with invasion of lamina or muscularis propria (n=37), T2 with invasion of medulla or peripelvic adipose only (n=26), and pT3 with cortical invasion (n=12). Under the new criteria, better separation of survival curves was achieved; however, pT1 and pT2 remained statistically insignificant. When further redefining pT3 as invasive of cortex only (n=12) and combining medulla with lamina and muscularis propria invasion as a lower stage (pT1, n=63), there was further improvement in the prognostic stratification. Therefore, our data show that consideration of revised and simplified T staging criteria at the renal pelvis is warranted, wherein invasion of any anatomic structure up to the

cortex shows a similar prognosis (combined pT1 category) and invasion of cortex showing significantly worse prognosis (pT3).

25COASMA4:

Title: Stratified Mucin-producing Lesions of the Anus

Insights into an Emerging Histologic Type of HPV-driven Anal Neoplasia

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The American Journal of Surgical Pathology 49(2):p 121-129, February 2025. |
DOI: https://doi.org/ 10.1097/PAS.0000000000002312

Abstract: Primary anal cancers are rare and typically driven by high-risk human papillomavirus (HPV) infection. Though squamous cell carcinoma is most common, a spectrum of HPV-related nonsquamous anogenital neoplasms with similarities to cervical stratified mucin-producing carcinoma has been reported. In this study, we mined our institutional archives to characterize the clinicopathologic features of this emerging entity. Six cases were identified from the files at 2 institutions, including 4 cases of invasive stratified mucin-producing carcinoma and 2 stratified mucin-producing intraepithelial lesions (SMILE). Four patients were women, and the mean age was 70 years. Patients presented with rectal/anal mass or polyp, rectal bleeding or pain, weight loss, or at the time of screening colonoscopy. Tumors displayed histologic features as described in the gynecologic tract. Cases of invasive stratified mucinous carcinoma showed infiltrative tumor nests with variable intracytoplasmic mucin, peripheral palisading, prominent apoptosis, and neutrophilic infiltrate. One invasive stratified mucinous carcinoma associated with high grade glandular dysplasia, whereas 1 SMILE was next to conventional low-grade squamous intraepithelial lesion. All lesions stained with p16 showed block-like p16 expression. HPV in situ hybridization was performed in 5 cases, 4 of which were positive; one was interpreted as equivocal. Follow-up information, available in 4 patients, revealed 1 local recurrence followed by death due to unrelated causes in a patient with invasive stratified mucin-producing carcinoma. We report the first series of HPV-associated primary anal stratified mucin-producing neoplasms analogous to those seen in the gynecologic tract, further broadening the spectrum of HPV-related anal neoplasia.

25COASMA5:

Title: DEK::AFF2 Fusion Sinonasal and Skull Base Nonkeratinizing Squamous Cell Carcinoma

A Clinical Outcome Study Compared With Conventional Sinonasal Squamous Cell Carcinoma

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The American Journal of Surgical Pathology ,49(2):p 130-137, February 2025.
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Abstract: DEK::AFF2 fusion nonkeratinizing squamous cell carcinoma (NKSCC) is an emerging entity in the sinonasal tract, temporal bone, and skull base. However, the clinical behavior of these tumors has not been well studied. Here, we report the largest cohort

of DEK::AFF2 carcinomas to determine if morphology, mitotic rate, and/or Ki-67 IHC are associated with patient outcomes, including a comparison with high-risk human papillomavirus (HPV)-associated and independent patients. We solicited cases of molecularly or AFF2 immunohistochemistry (IHC) proven DEK::AFF2 SCC from surgical pathologists to collect patient demographic, clinical, and outcome data. Using representative H&E slides, we characterized the morphology and counted mitoses. Ki-67 immunohistochemistry was performed. We also compared the DEK::AFF2 survival rates to those in a cohort of AFF2 IHC-negative HPV-associated and HPV-independent SCC. DEK::AFF2 carcinomas most commonly arose in the nasal cavity (13/30, 43%), and the average number of recurrences was 1.8 (range: 0 to 10). At the last follow-up, most patients were disease free (19/30, 63%) or were alive with disease (9/30, 30%). There was an average mitotic rate of 2 per 2 mm^2 (range: 0 to 9) and Ki-67 proliferation rate of 26% (range: 3% to 60%). Local recurrence was common, but morphology, mitotic activity, and Ki-67 index were not associated with recurrence or survival. On Kaplan-Meier survival analysis, DEK::AFF2 patients had lower disease-free survival but otherwise had similar outcomes to conventional SCC patients. Our multi-institutional study shows that local recurrence is common in DEK::AFF2 fusion nonkeratinizing SCC patients, but patients have survival rates similar to conventional SCC. Despite showing a range of different features and proliferation rates, traditional grading by morphology, mitotic rate, and/or Ki-67 activity does not seem to be predictive of outcome.

25COASMA6:

Title: Multiple Pulmonary Sclerosing Pneumocytomas (PSPs)
A Comprehensive Analysis of Clinicopathological Characteristics and Whole-exome Sequencing (WES) Results

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The American Journal of Surgical Pathology 49(2):p 138-149, February 2025.
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Abstract: Pulmonary sclerosing pneumocytoma (PSP) is a rare neoplasm with indolent clinical behavior and usually presents as a solitary nodule, while only a few cases involving multiple nodules. Recent studies have revealed frequent AKT1 mutations in PSP; however, the molecular genetics of multiple PSPs remain unclear. To better understand the genetic background, eleven patients (4.2%, 11/260) with multiple PSP nodules were identified, and whole-exome sequencing (WES) was performed on 6 patients. Among 5 patients with 2 or 3 PSP nodules, AKT1 alterations were the most common (50%, 7/14), and the predominant alteration was p.E17K (21.4%, 3/14). Novel ARID1A mutations were the second most common driver (14.3%, 2/14), and we first identified these mutations cooccurred with AKT1 p.E17K mutation. Moreover, we observed limited concordance in the mutation spectra and few comutated genes among different lesions from these 5 patients, indicating that PSP with 2 or 3 nodules were independent arising tumors. No AKT1 mutations were identified in 3 PSP samples from a patient with multiple diffuse nodules. However, there were 17 shared genetic alterations among the 3 lesions, but none were typical driver mutations. The findings on multiple diffuse PSP nodules may also have independent origins, but the potential that some of these nodules are metastatic nodules cannot be excluded. In

conclusion, this retrospective study is the largest series of multiple PSP cases and provides new insights into the genomic underpinning of PSP. This work has a potential to broaden our understanding of the pathogenesis and development of these lesions and warrants analysis in larger cohorts.

25COASMA7:

Title: Sarcoid Vasculitis in the Skin

A Clinicopathologic Study of 8 Cases With Various Skin Lesions but the Common Unique Cannonball-like Vessel Destruction by Sarcoid Granulomas

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The American Journal of Surgical Pathology 49(2):p 150-158, February 2025.
DOI: https://doi.org/ 10.1097/PAS.0000000000002333

Abstract: While the skin is a common target organ for sarcoidosis, cutaneous granulomatous vasculitis is rare among patients with sarcoidosis. Due to the lack of detailed studies on cutaneous sarcoid vasculitis, both dermatologists and pathologists remain unfamiliar with this rare but important vasculitic disorder. We clinicopathologically evaluated eight cases with biopsy-proven cutaneous vasculitis and cutaneous sarcoidosis and analyzed morphologic changes in the process of vasculitis for both small vessels and muscular vessels in detail. The various skin lesions ranged from papulonodular erythema, annular erythema, maculopapular erythema, livedo reticularis-like eruptions, erythema nodosum-like lesions, subcutaneous nodules to ulcerative lesions. The extremities were the most frequently affected sites. Bilateral hilar lymphadenopathy with pulmonary sarcoidosis was the most common extracutaneous comorbidity. Skin-limited sarcoidosis was identified in 3 cases. All cases demonstrated a common histopathologic feature with sarcoid granulomas impinging on the target vessels with resultant vessel destruction. Perivascular infiltration of sarcoid granulomas resulted in compression and destruction of small vessels. In muscular arteries and veins, sarcoid granulomas closely attached to the muscular vessel wall, infiltrated the muscular layers and either occupied or penetrated the vessel walls, eventually invading the vascular lumen and replacing the entire muscular layers. The intimal infiltration of sarcoid granulomas resulted in a marked luminal narrowing. The scarcity of reports on cutaneous sarcoid vasculitis may be due to the overlooking or misinterpretation of vascular destruction caused by sarcoid granuloma infiltration as a feature of sarcoid granuloma masses.

25COASMA8:

Title: High Prevalence of MYD88 and CD79B Mutations in Primary Sinonasal Diffuse Large B-Cell Lymphoma

Identification of an MCD-like Subtype

Peng, Fangli MD[*]; Igawa, Takuro MD, PhD[*]; Urata, Tomohiro MD[†]; Kobayashi, Hiroki MD, PhD[‡];

The American Journal of Surgical Pathology 49(2):p 159-168, February 2025.
DOI: https://doi.org/ 10.1097/PAS.0000000000002329

Abstract: Primary sinonasal diffuse large B-cell lymphoma (PSDLBCL) is a rare aggressive lymphoma. Recently, genetic classification using Next Generation Sequencing (NGS)

demonstrated that PSDLBCL largely consists of the MCD genotype, which has a poor prognosis mainly driven by MYD88 L265P and CD79B gene abnormalities. This study investigated the prevalence and clinicopathological significance of MYD88 L265P and CD79B Y196 mutations using droplet digital PCR in 55 patients with PSDLBCL, as well as the translocation of BCL2/BCL6/c-Myc with FISH. We found mutations in MYD88 L265P (29/55, 52.7%) and CD79B Y196 (20/55, 36.4%). The MCD-like subtype, defined by the mutation of MYD88 and/or CD79B, was found in 32 out of 55 cases (58.2%). This subtype largely consists of non-GCB type (31/32, 96.9%; P<0.01) and double-expressor cases (20/32, 62.5%; P=0.01) compared with the MYD88/CD79B co-wild type, with BCL6 translocation in a small subset (2/32, 6.3%) and no translocations of BCL2 (0/32) or c-Myc (0/32). The MCD-like subtype tended to relapse in specific sites such as the central nervous system, testis, and/or skin compared with the co-wild type (P=0.03), showing poorer outcomes in overall survival (P=0.02) and progression-free survival (P=0.01). In conclusion, our study highlights a high prevalence of MYD88 and CD79B mutations in PSDLBCL, identifying an aggressive MCD-like subtype with a distinct relapse pattern. This molecular subclassification can be helpful for both prognostic prediction and therapeutic strategy in patients with PSDLBCL.

25COASMA9:

Title: High Prevalence of MYD88 and CD79B Mutations in Primary Sinonasal Diffuse Large B-Cell Lymphoma

Identification of an MCD-like Subtype

Peng, Fangli MD[*]; Igawa, Takuro MD, PhD[*]; Urata, Tomohiro MD[†]; Kobayashi, Hiroki MD, PhD[‡];

The American Journal of Surgical Pathology 49(2):p 159-168, February 2025.
DOI: https://doi.org/ 10.1097/PAS.0000000000002329

Abstract: Primary sinonasal diffuse large B-cell lymphoma (PSDLBCL) is a rare aggressive lymphoma. Recently, genetic classification using Next Generation Sequencing (NGS) demonstrated that PSDLBCL largely consists of the MCD genotype, which has a poor prognosis mainly driven by MYD88 L265P and CD79B gene abnormalities. This study investigated the prevalence and clinicopathological significance of MYD88 L265P and CD79B Y196 mutations using droplet digital PCR in 55 patients with PSDLBCL, as well as the translocation of BCL2/BCL6/c-Myc with FISH. We found mutations in MYD88 L265P (29/55, 52.7%) and CD79B Y196 (20/55, 36.4%). The MCD-like subtype, defined by the mutation of MYD88 and/or CD79B, was found in 32 out of 55 cases (58.2%). This subtype largely consists of non-GCB type (31/32, 96.9%; P<0.01) and double-expressor cases (20/32, 62.5%; P=0.01) compared with the MYD88/CD79B co-wild type, with BCL6 translocation in a small subset (2/32, 6.3%) and no translocations of BCL2 (0/32) or c-Myc (0/32). The MCD-like subtype tended to relapse in specific sites such as the central nervous system, testis, and/or skin compared with the co-wild type (P=0.03), showing poorer outcomes in overall survival (P=0.02) and progression-free survival (P=0.01). In conclusion, our study highlights a high prevalence of MYD88 and CD79B mutations in PSDLBCL, identifying an aggressive MCD-like subtype with a distinct relapse pattern. This molecular subclassification can be helpful for both prognostic prediction and therapeutic strategy in

patients with PSDLBCL.

25COASMA10:

Title: Impact of Implementing a Grossing Tumor-margin Distance Threshold for Frozen Section in Oncologic Lung Surgery

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The American Journal of Surgical Pathology 49(2):p 169-175, February 2025.
DOI: https://doi.org/ 10.1097/PAS.0000000000002337

Abstract: Intraoperative frozen section (FS) examination of oncologic surgical specimens is frequently performed to ensure complete surgical resection. Data on the gross evaluation of surgical margins are limited. We recently published a study suggesting the use of a macroscopic 2.0 cm tumor-margin cutoff during intraoperative evaluation to decrease the number of unnecessary FS. This study aimed to validate the safety and the clinical impacts of implementing a 2.0 cm tumor-margin threshold for FS diagnosis in evaluating surgical margins during oncologic lung surgery. This retrospective analysis included patients who underwent lung resection for primary or metastatic neoplasms between 2018 and 2022 at the Institut Universitaire de Cardiologie et de Pneumologie de Québec, following the implementation of this practice. Clinicopathological data were retrieved from the medical files. Univariate and multivariate analyses were used to identify the variables associated with positive margins. This study included 1575 tumors in 1299 patients. FS evaluations were performed in 24.4% of patients. No positive margins were observed when the tumor-margin distance was >2.0 cm. The incidence rate of positive margins was 2.95%, with parenchymal margins being the most affected. Multivariate analysis identified the tumor-margin distance as a significant predictor of positive margin status. This practice led to a 79.9% reduction in FS evaluations without compromising the margin assessment accuracy or patient safety. A 2.0 cm tumor-margin distance threshold for intraoperative FS evaluation in oncologic lung surgery is safe and effective in reducing unnecessary FS evaluations while maintaining accurate margin assessments.

25COASMA11:

Title: Interpretation of p16 and p53 in the Classification of Squamous Cell Carcinoma of the Vulva—An Interobserver Agreement Study

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The American Journal of Surgical Pathology 49(2):p 176-187, February 2025.
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Abstract: Squamous cell carcinoma of the vulva (vSCC) is currently categorized either as human papillomavirus (HPV) associated or independent. Immunohistochemical stains, $p16^{INK4a}$ (p16) and p53 are helpful biomarkers to support the designation of vSCC into 1 of the 3 tumor pathways: (1) HPV-associated, (2) HPV-independent, TP53 mutant, or (3) HPV-independent, TP53 wild type. Recently, a framework of p53 expression patterns in vSCC was proposed. In this international and multi-institutional study, we evaluated the interrater agreement for p53 and p16 and tumor pathway classification in a cohort of 50 invasive vSCC

across a variety of practice settings (private practice, academic medicine) and levels of expertise (trainees, gynecologic pathologists, dermatopathologists, private practice pathologists). Our study shows that the overall interrater agreement for the interpretation of p16 in vSCC is strong to near perfect, while the agreement for p53 and tumor pathway assignment is overall moderate. Interrater agreement for p53 and tumor pathway is higher (strong) in the academic practice setting. Pathologists without gynecologic subspecialty expertise benefited the most from a brief educational module, which fostered a better understanding and improved comfort level with the p16/p53 stain interpretation and tumor pathway designation in the diagnosis of vSCC. Some interpretative challenges remain, particularly in regard to select p53 patterns and high-risk HPV-in situ hybridization utilization, warranting additional research.

25COASMA12:

Title: Clinicopathologic Features of Breast Tumors in Germline TP53 Variant–Associated Li-Fraumeni Syndrome

Narasimhamurthy, Mohan MBBS[*]; Le, Anh BS[†]; Boruah, Nabamita PhD[†]; Moses, Renyta BS[†];

The American Journal of Surgical Pathology 49(3):p 195-205, March 2025.
DOI: https://doi.org/ 10.1097/PAS.0000000000002338

Abstract: We present one of the largest cohorts of TP53-pathogenic germline variants (PGVs) associated with patients with Li-Fraumeni syndrome (n = 82) with breast tumors (19 to 76 y; median age: 35). Most had missense variants (77%), followed by large gene rearrangements (LGRs; 12%), truncating (6%), and splice-site (5%) variants. Twenty-one unique germline missense variants were found, with hotspots at codons 175, 181, 245, 248, 273, 334, and 337. Of 100 total breast tumors, 63% were invasive (mostly ductal), 30% pure ductal carcinoma in situ, 4% fibroepithelial lesions, and 3% with unknown histology. Unlike BRCA-associated tumors, approximately half of the breast cancers exhibited HER2-positivity, of which ~50% showed estrogen receptor coexpression. Pathology slides were available for review for 61 tumors (44 patients), and no significant correlation between the type of TP53 PGVs and histologic features was noted. High p53 immunohistochemistry expression (>50%) was seen in 67% of tumors tested (mostly missense variant). Null pattern (<1% cells) was seen in 2 (LGR and splicing variants carriers). Surprisingly, 2 tumors from patients with an LGR and 1 tumor from a patient with a truncating variant showed p53 overexpression (>50%). The subset of patients with the Brazilian p.R337H variant presented at a higher age than those with non-p.R337H variant (46 vs 35 y) though statistically insignificant (P = 0.071) due to an imbalance in the sample size, and were uniquely negative for HER2-overexpressing tumors. To conclude, breast cancer in carriers of TP53 PGVs has some unique clinicopathological features that suggest differential mechanisms of tumor formation. p53 immunohistochemistry cannot be used as a surrogate marker to identify germline TP53-mutated breast cancers.

25COASMA13:

Title:Claudin-18 and Mutation Surrogate Immunohistochemistry in Gastric-type Endocervical Lesions and their Differential Diagnoses

Lin, Lawrence Hsu MD, PhD[*,†]; Kaur, Harsimar MBBS[*]; Kolin, David L. MD, PhD[*]; Nucci, Marisa R. MD[*]; Parra-Herran, Carlos MD[*]

The American Journal of Surgical Pathology 49(3):p 206-216, March 2025.
DOI: https://doi.org/10.1097/PAS.0000000000002342

Abstract: Gastric-type endocervical adenocarcinomas (GAS) are aggressive HPV-independent neoplasms with molecular alterations in TP53, STK11, CDKN2A, and SMAD4. Claudin-18 (CLDN18) has emerged as a useful marker to distinguish GAS from HPV-associated neoplasia. Its role in separating GAS from benign proliferations and exuberant endocervical glands is unknown. We studied the utility of immunohistochemistry for CLDN18, progesterone receptor (PR), and mutation surrogate stains (P53, STK11/LKB1, MTAP, SMAD4/DPC4) in 46 GAS, 12 benign gastric-type endocervical lesions, 54 benign Mullerian endocervical populations, and 11 HPV-associated endocervical adenocarcinomas. PD-L1 and HER2 immunostains were evaluated in GAS. Gastric-type lesions were more often positive for CLDN18 (100% benign, 78% GAS, most often well to moderately differentiated) compared to benign Mullerian endocervical specimens (all negative) and HPV-associated neoplasia (18%, always focal). Conversely, PR was negative in all gastric-type lesions and positive in 92% of benign Mullerian endocervical populations. GAS revealed aberrant/mutant expression of P53 in 35%, STK11/LKB1 in 25%, MTAP in 23%, and SMAD4/DPC4 in 9% of cases. Abnormal staining in at least one of these 4 mutation surrogate markers was present in 63% of GAS. HER2 score of 3+ was seen in 25% of GAS, and PD-L1 was positive in 37% based on a combined positive score. CLDN18 is a sensitive and highly specific marker of gastric-type benign and malignant endocervical lesions. Once a gastric-type phenotype is confirmed, mutation surrogate immunostains can be used to support a diagnosis of GAS. PD-L1 and HER2 expression is seen in a subset of GAS offering therapeutic options for this aggressive tumor.

25COASMA14:

Title:Renal Juxtaglomerular Cell Tumors Exhibit Distinct Genomic and Epigenomic Features and Lack Recurrent Gene Fusions

Comprehensive Molecular Analysis of a Multi-institutional Series

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The American Journal of Surgical Pathology 49(3):p 217-226, March 2025.
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Abstract: Juxtaglomerular cell tumor (JxGCT) is a rare type of renal neoplasm demonstrating morphologic overlap with some mesenchymal tumors such as glomus tumor (GT) and solitary fibrous tumor (SFT). Its oncogenic drivers remain elusive, and only a few cases have been analyzed with modern molecular techniques. In prior studies, loss of chromosomes 9 and 11 appeared to be recurrent. Recently, whole-genome analysis identified alterations involving genes of MAPK-RAS pathway in a subset, but no major pathogenic alterations have been discovered in prior whole transcriptome analyses. Considering the limited understanding of the molecular features of JxGCTs, we sought to assess a collaborative series with a multiomic approach to further define the molecular characteristics of this entity. Fifteen tumors morphologically compatible with JxGCTs were evaluated using

immunohistochemistry for renin, single-nucleotide polymorphism array (SNP), low-pass whole-genome sequencing, and RNA sequencing (fusion assay). In addition, methylation analysis comparing JxGCT, GT, and SFT was performed. All cases tested with renin (n=11) showed positive staining. Multiple chromosomal abnormalities were identified in all cases analyzed (n=8), with gains of chromosomes 1p, 10, 17, and 19 and losses of chromosomes 9, 11, and 21 being recurrent. A pathogenic HRAS mutation was identified in one case as part of the SNP array analysis. Thirteen tumors were analyzed by RNA sequencing, with 2 revealing in-frame gene fusions: TFG::GPR128 (interpreted as stochastic) and NAB2::STAT6. The latter, originally diagnosed as JxGCT, was reclassified as SFT and excluded from the series. No fusions were detected in the remaining 11 cases; of note, no case harbored NOTCH fusions previously described in GT. Genomic methylation analysis showed that JxGCT, GT, and SFT form separate clusters, confirming that JxGCT represents a distinct entity (ie, different from GT). The results of our study show that JxGCTs are a distinct tumor type with a recurrent pattern of chromosomal imbalances that may play a role in oncogenesis, with MAPK-RAS pathway activation being likely a driver in a relatively small subset.

25COASMA15:

Title: Molecular Profiling of Sinonasal Adenoid Cystic Carcinoma Canonical and Noncanonical Gene Fusions and Mutation

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The American Journal of Surgical Pathology 49(3):p 227-242, March 2025.
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Abstract: Adenoid cystic carcinomas (AdCC) of salivary gland origin have long been categorized as fusion-defined carcinomas owing to the almost universal presence of the gene fusion MYB::NFIB, or less commonly MYBL1::NFIB. Sinonasal AdCC is an aggressive salivary gland malignancy with no effective systemic therapy. Therefore, it is urgent to search for potentially targetable genetic alterations associated with AdCC. We have searched the authors' registries and selected all AdCCs arising in the sinonasal tract. The tumors were examined histologically, immunohistochemically, by next generation sequencing (NGS) and/or fluorescence in situ hybridization (FISH) looking for MYB/MYBL1 and/or NFIB gene fusions or any novel gene fusions and/or mutations. In addition, all tumors were tested for HPV by genotyping using (q)PCR. Our cohort comprised 88 cases of sinonasal AdCC, predominantly characterized by canonical MYB::NFIB (49 cases) and MYBL1::NFIB (9 cases) fusions. In addition, noncanonical fusions EWSR1::MYB; ACTB::MYB; ESRRG::DNM3, and ACTN4::MYB were identified by NGS, each of them in 1 case. Among nine fusion-negative AdCCs, FISH detected rearrangements in MYB (7 cases), NFIB (1 case), and EWSR1 (1 case). Six AdCCs lacked fusions or gene rearrangements, while 11 cases were unanalyzable. Mutational analysis was performed by NGS in 31/88 (35%) AdCCs. Mutations in genes with established roles in oncogenesis were identified in 21/31 tumors (68%), including BCOR (4/21; 19%), NOTCH1 (3/21; 14%), EP300 (3/21; 14%), SMARCA4 (2/21; 9%), RUNX1 (2/21; 9%), KDM6A (2/21; 9%), SPEN (2/21; 9%), and RIT1, MGA, RB1, PHF6, PTEN,

CREBBP, DDX41, CHD2, ROS1, TAF1, CCD1, NF1, PALB2, AVCR1B, ARID1A, PPM1D, LZTR1, GEN1, PDGFRA, each in 1 case (1/21; 5%). Additional 24 cases exhibited a spectrum of gene mutations of uncertain pathogenetic significance. No morphologic differences were observed between AdCCs with MYBL1::NFIB and MYB::NFIB fusions. Interestingly, mutations in the NOTCH genes were seen in connection with both canonical and noncanonical fusions, and often associated with high-grade histology or metatypical phenotype, as well as with poorer clinical outcome. Noncanonical fusions were predominantly observed in metatypical AdCCs. These findings emphasize the value of comprehensive molecular profiling in correlating morphologic characteristics, genetic landscape, and clinical behavior in AdCC.

25COASMA16:

Title:Immature PIT1-lineage Pituitary Neuroendocrine Tumors/Adenomas, a Morphologically Unique Pituitary Neuroendocrine Tumors/Adenomas Commonly With Cytologic Atypia Features and a Predilection for Aggressive Clinical Potential

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Abstract: Immature PIT1-lineage pituitary neuroendocrine tumors (PitNETs)/adenomas (Immature PIT1-lineage tumors) are a rare and underrecognized subtype of PitNETs that exhibits distinct cytologic atypia features and aggressive clinical potential. This study characterizes the clinical, radiological, histologic, and immunohistochemical features of 15 immature PIT1-lineage tumors identified from 1084 PitNETs patients over 5 years. Our cohort of 6 males and 9 females had a median age of 37.00 years (range: 23 to 68 y). All patients presented with pituitary macrotumors with an average size of 27.13×22.60×22.13 mm (length×width×height). The invasive growth pattern was identifiable, with 40.00% of tumors presenting with advanced stage (Knosp type 3 and 4) disease, followed by 20.00% Knosp type 2, 26.67% type 1, and 13.33% type 0. Clinical follow-up in 11 patients (median duration: 10.91 mo) revealed local recurrence in 1 case (9.09%). Microscopically, immature PIT1-lineage tumors comprised epithelioid (n=14) or spindle-shaped (n=1) chromophobic or weak basophilic cells with marked cytologic atypia, macronucleoli, and nuclear pseudoinclusions. By immunohistochemistry, most cases showed a consistent stain for PIT1 but limited expression of PIT1 family hormones in conjunction with diffuse or focal expression of CK8/18 (Cam 5.2), whereas none of the mimics showed a similar stain pattern in such a distinct way. We corroborate that immature PIT1-lineage tumors are rare, aggressive, and morphologically unique PitNETs/adenomas with cytologic atypia features. Immunohistochemistry may facilitate diagnosis in the distinction from histologic mimics.

25COASMA17:

Title:The Spectrum of B-cell and Plasma Cell Proliferations in Nodal T Follicular Helper Cell Lymphomas

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The American Journal of Surgical Pathology 49(3):p 251-264, March 2025.
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Abstract: B-cell and plasma cell proliferations are frequently observed in nodal T follicular helper (nTfh) cell lymphomas and can present a diagnostic challenge. These proliferations can be monotypic or monoclonal and morphologically resemble lymphoma or plasmacytoma, but their clinical behavior is poorly defined. In this study, we reviewed 414 cases of nTfh lymphoma seen over the past decade at our institution. We identified 78 (19%) cases that exhibited B-cell or plasma cell proliferation detected by morphology, flow cytometry, immunohistochemistry, and/or molecular techniques. The B-cell/plasma cell proliferations occurred before (22%), concurrently with (50%), or after (28%) the diagnosis of nTfh lymphoma. We divided them into 3 categories: (1) focal or scattered B-immunoblastic proliferations recognized morphologically without a monotypic/monoclonal B-cell population (17%), (2) monotypic/monoclonal B-cell/plasma cells identified solely by flow cytometry or molecular clonality studies without morphologic confirmation (11%), and (3) unequivocal B-cell/plasma cell expansions recognized by morphologic assessment (72%). We further subdivided group 3 into proliferations associated with and possibly dependent on neoplastic Tfh cells versus those proliferations occurring in the absence of neoplastic Tfh cells and likely bona fide lymphomas. Follow-up biopsy specimens showed persistence of B-cell/plasma cell proliferations in various patient subcategories, with transformation to higher-grade B-cell proliferation or persistence without Tfh cells in some cases. In conclusion, our data support the notion that most B-cell and plasma cell proliferations associated with neoplastic Tfh clones have little impact on the clinical course of patients with nTfh lymphoma and likely do not constitute an independent B-cell lymphoma, especially those of small B cells of plasma cells. However, B-cell expansions exhibiting aggressive morphologic features may represent an independent B-cell lymphoma.

25COASMA18:

Title: Clinicopathologic Features of a Rare and Underrecognized Variant of Early-stage Primary Biliary Cholangitis With Ductopenia

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The American Journal of Surgical Pathology 49(3):p 265-272, March 2025.
DOI: https://doi.org/ 10.1097/PAS.0000000000002343
Abstract: Primary biliary cholangitis (PBC) with early cholestasis and extensive bile duct loss but no significant fibrosis or cirrhosis is rare and underrecognized. We aimed to clarify the clinicopathology features and prognosis of these variants of patients with early-stage PBC with ductopenia. From January 2009 to January 2023, we retrospectively collected the laboratory and pathologic data of patients with early-stage PBC and recorded their liver-related events with a median follow-up of 4.5 years. Finally, a total of 141 patients with PBC in the early stage were included and divided into 2 groups: one with ductopenia (n = 36) and the other without ductopenia (n = 105). The median age of the participants was 50 years, with 90.8% being female. The ductopenia group exhibited significantly elevated alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl

transpeptidase, total bilirubin, total bile acid, and total cholesterol (CHOL). Conversely, they showed a reduced biochemical response to ursodeoxycholic acid according to the Paris II, Barcelona, and Rotterdam criteria. A relatively poorer prognosis was observed in patients with early-stage PBC with ductopenia but with no statistical difference (11.8% vs 4.9%, P = 0.352). Baseline total CHOL levels were identified as an independent factor for the presence of ductopenia in early-stage PBC (odds ratio = 1.771, 95% CI: 1.264-2.479, P = 0.001). In conclusion, ductopenia was a significant risk factor for worse biochemical profiles and poor treatment response in patients with early-stage PBC. High levels of total CHOL at baseline are associated with the presence of ductopenia in early-stage PBC.

25COASMA19:

Title: Follicular Helper T-cell Lymphoma With Hodgkin/Reed-Sternberg–Like Cells Versus Classic Hodgkin Lymphoma

A Comparative Study

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Abstract: Lymphomas of T-follicular helper origin (T-follicular helper–cell lymphoma [TFHL]) are often accompanied by an expansion of B-immunoblasts, occasionally with Hodgkin/Reed-Sternberg-like (HRS-like) cells, making the differential diagnosis with classic Hodgkin lymphoma (CHL) difficult. We compared the morphologic, immunophenotypic, and molecular features of 15 TFHL and 12 CHL samples and discussed 4 challenging cases of uncertain diagnosis. Compared with CHL, TFHL disclosed more frequent sparing of subcortical sinuses, high-endothelium venule proliferation, dendritic cell meshwork expansion, T-cell atypia, and aberrant T-cell immunophenotype. HRS-like and HRS cells were CD30+, often CD15+ and EBV infected. There was a variable loss of B-cell markers in both diseases, with an expression of CD20, CD79a, CD19, or OCT-2 more frequently preserved in HRS-like cells of TFHL. The T-cell infiltrate was predominantly CD4+/CD8-, with expression of at least 2 TFH-markers in all TFHL and 75% of CHL. The most useful TFH marker was CD10 (positive in 86% TFHL and no CHL). Twelve/15 TFHL contained CD30+ neoplastic TFH cells, whereas CD30 expression was mostly restricted to HRS cells in CHL. We detected monoclonal TR rearrangements in 75% of TFHL and no CHL; and monoclonal IG rearrangements in 23% of TFHL and 42% of CHL. All TFHL had TET2 mutations; 13/14 presented RHOA mutations, 3 accompanied by DNMT3A and 1 DNMT3A+IDH2 mutations. Three CHL had TET2 mutations, likely attributable to clonal hematopoiesis. Our study further underlines that HRS(-like) cells are not pathognomonic of CHL. Since no single pathologic criterion distinguishes TFHL and CHL, an integrative approach ideally comprising molecular investigations is fundamental.

25COASMA20:

Title: Intraductal Polypoid Neoplasm in the Intrahepatic Large Bile Ducts of Small Duct-type Intrahepatic Cholangiocarcinoma May Result From Cancerization of Ducts

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Abstract: To survey and characterize intraductal polypoid neoplasms in the intrahepatic large bile ducts of small duct-type intrahepatic cholangiocarcinoma (small duct-iCCA), a total of 121 cases of small duct-iCCA presenting mass-forming growth were surveyed for intraductal polypoid neoplasms that were compared with mass-forming tumors in individual cases and with intraductal papillary neoplasm of bile duct (IPNB) (20 cases). Polypoid neoplasms were found in intrahepatic bile ducts in 8 (6.6%) of 121 cases of small duct-iCCA. They showed cast-like growth involving several adjoining bile ducts adjacent to or in the peripheries of mass-forming tumors as well as well-differentiated papillary or tubular/cribriform patterns and no stromal invasion. Intraductal polypoid neoplasms were histologically and immunohistochemically similar to mass-forming tumors in individual cases, and both components were of biliary subtype. There was an abrupt transition between these polypoid neoplasms and normal lining epithelia in the affected bile ducts, suggesting that intraductal polypoid neoplasms reflect the cancerization of ducts. IPNB presented with biliary (5 cases), intestinal (8 cases), gastric (5 cases), and oncocytic subtypes (2 cases), and about half of IPNBs were noninvasive, thus differing from intraductal polypoid neoplasms of small duct-iCCA. In conclusion, small duct-iCCA occasionally presents as intraductal polypoid neoplasms in adjoining bile ducts, reflecting the cancerization of ducts. These intraductal polypoid neoplasms should be considered in the differential diagnosis of heterogeneous intraductal tumors of bile ducts.

25COASMA21:

Title: Ipsilateral Breast Carcinoma Recurrence

True Recurrence or New Primary? A Clinicopathologic and Molecular Study

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Abstract: Determining whether an ipsilateral breast carcinoma recurrence is a true recurrence or a new primary remains challenging based solely on clinicopathologic features. Algorithms based on these features have estimated that up to 68% of recurrences might be new primaries. However, few studies have analyzed the clonal relationship between primary and secondary carcinomas to establish the true nature of recurrences. This study analyzed 70 breast carcinomas from 33 patients using immunohistochemistry, FISH, and massive parallel sequencing. We compared 35 primary carcinomas with the associated recurrences, identifying 24 (68.6%) as true recurrences, 7 (20%) as new primaries, and 4 (11%) as undetermined. Twenty-eight primary carcinomas were invasive carcinomas (22 of no special type, 5 invasive lobular, and 1 invasive micropapillary carcinoma), and 7 were in situ (6 ductal and 1 lobular). Time to recurrence was longer for new primaries (median 12.8 y) than for true recurrences (median 6.8 y). Among the new primary cases, 6 of 7 (85%) patients had undergone mastectomy as their initial treatment. Clinicopathologic classifications of invasive carcinomas overestimated the number of new primaries (41.6% to 68.6%), partially due to

phenotype conversion in 14% of true recurrences. Although 41.7% of recurrences showed private mutations or amplifications relevant to tumor progression, such as PIK3CA, PIK3R1, MAP3K1, AKT1, GATA3, CCND1, MDM4, or T P 5 3; a common mutational progression pattern was not identified. Further studies, including larger series, are necessary to evaluate the prognostic significance of the molecular classification of recurrences.

25COASMA22:

Title: A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial

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Abstract: NATALEE assessed efficacy and tolerability of 3 years of adjuvant ribociclib plus a nonsteroidal aromatase inhibitor (NSAI) compared with an NSAI alone in a broad population of patients with hormone receptor (HR)-positive/human epidermal growth factor 2 (HER2)-negative early breast cancer, including a select group without nodal involvement. This is the final preplanned analysis of invasive disease-free survival (iDFS). Patients and methods Premenopausal/postmenopausal women and men were randomized 1 : 1 to ribociclib (n = 2549; 400 mg/day, 3 weeks on/1 week off for 36 months) plus NSAI (letrozole 2.5 mg/day or anastrozole 1 mg/day for 60 months) or NSAI alone (n = 2552). Men and premenopausal women also received goserelin (3.6 mg once every 28 days). Patients had anatomical stage IIA (N0 with additional risk factors or N1), IIB, or III disease. The primary endpoint was iDFS. Secondary efficacy endpoints were recurrence-free survival (RFS), distant DFS, and overall survival. This final iDFS analysis was planned after ∼500 events.

At data cut-off (21 July 2023), ribociclib was stopped for 1996 patients (78.3%); 1091 (42.8%) completed 3 years of ribociclib, and ribociclib treatment was ongoing for 528 (20.7%). Median follow-up for iDFS was 33.3 months. Overall, 226 and 283 iDFS events occurred with ribociclib plus NSAI versus NSAI alone, respectively. Ribociclib plus NSAI demonstrated significant iDFS benefit over NSAI alone [hazard ratio 0.749, 95% confidence interval (CI) 0.628-0.892; P = 0.0012]. The 3-year iDFS rates were 90.7% (95% CI 89.3% to 91.8%) versus 87.6% (95% CI 86.1% to 88.9%). A consistent benefit was observed across prespecified subgroups, including stage (II/III) and nodal status (positive/negative). Distant DFS and RFS favored ribociclib plus NSAI. Overall survival data were immature. No new safety signals were observed.With longer follow-up and most patients off ribociclib, NATALEE continues to demonstrate iDFS benefit with ribociclib plus NSAI over NSAI alone in the overall population and across key subgroups. Observed adverse events remained stable.

Keywords: cyclin-dependent kinase 4 and 6 inhibitors, hormone receptor-positive, human epidermal growth factor receptor 2-negative, breast cancer
ribociclib

25COASMA23:

Title: TNBC-DX genomic test in early-stage triple-negative breast cancer treated with

neoadjuvant taxane-based therapy☆

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Abstract: Background Identification of biomarkers to optimize treatment strategies for early-stage triple-negative breast cancer (TNBC) is crucial. This study presents the development and validation of TNBC-DX, a novel test aimed at predicting both short- and long-term outcomes in early-stage TNBC. The objective of this study was to evaluate the association between TNBC-DX and efficacy outcomes [pathologic complete response (pCR), distant disease-free survival (DDFS) or event-free survival (EFS), and overall survival (OS)] in the validation cohorts. Information from 1259 patients with early-stage TNBC (SCAN-B, CALGB-40603, and BrighTNess) was used to establish the TNBC-DX scores. Independent validation of TNBC-DX was carried out in three studies: (i) WSG-ADAPT-TN; (ii) MMJ-CAR-2014-01; and (iii) NeoPACT, including 527 patients with stage I-III TNBC undergoing neoadjuvant chemotherapy. In WSG-ADAPT-TN, patients were randomized to receive nab-paclitaxel plus gemcitabine or carboplatin. In MMJ-CAR-2014-01, patients received carboplatin plus docetaxel. In NeoPACT, patients received carboplatin plus docetaxel and pembrolizumab. TNBC-DX test was created incorporating the 10-gene Core Immune Gene module, the 4-gene tumor cell proliferation signature, tumor size, and nodal staging. In the two independent validation cohorts without pembrolizumab, the TNBC-DX pCR score was significantly associated with pCR after adjustment for clinicopathological variables and treatment regimen [odds ratio per 10-unit increment 1.34, 95% confidence interval (CI) 1.20-1.52, P < 0.001]. pCR rates for the TNBC-DX pCR-high, pCR-medium, and pCR-low categories were 56.3%, 53.6%, and 22.5% respectively (odds ratio for pCR-high versus pCR-low 3.48, 95% CI 1.72-7.15, P < 0.001). In addition, the TNBC-DX risk score was significantly associated with DDFS [hazard ratio (HR) high-risk versus low-risk 0.24, 95% CI 0.15-0.41, P < 0.001] and OS (HR 0.19, 95% CI 0.11-0.35, P < 0.001). In the validation cohort with pembrolizumab, the TNBC-DX scores were significantly associated with pCR, EFS, and OS. TNBC-DX predicts pCR to neoadjuvant taxane–carboplatin in stage I-III TNBC and helps to forecast the patient's long-term survival in the absence of neoadjuvant anthracycline–cyclophosphamide, and independent of pembrolizumab use.

Keywords: early-stage breast cancer, triple negative, biomarkers, TNBC-DX, genomic test

25COASMA24:

Title: Pathologic complete response (pCR) rates for patients with HR+/HER2− high-risk, early-stage breast cancer (EBC) by clinical and molecular features in the phase II I-SPY2 clinical trial

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Doi-https://doi.org/10.1016/j.annonc.2024.10.018

Abstract: Hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative early-stage breast cancer (EBC) is a heterogenous disease. Identification of better clinical and molecular biomarkers is essential to guide optimal therapy for each patient.

Patients and methods-We analyzed rates of pathologic complete response (pCR) and distant recurrence-free survival (DRFS) for patients with HR+/HER2-negative EBC in eight neoadjuvant arms in the I-SPY2 trial by clinical/molecular features: age, stage, histology, percentage estrogen receptor (ER) positivity, ER/progesterone receptor status, MammaPrint (MP)-High1 (0 to −0.57) versus MP-High2 (<−0.57), BluePrint (BP)-Luminal-type versus BP-Basal-type, and ImPrint immune signature. We quantified the clinical/molecular heterogeneity, assessed overlap among these biomarkers, and evaluated associations with pCR and DRFS. Three hundred and seventy-nine patients with HR+/HER2-negative EBC were included in this analysis, with an observed pCR rate of 17% across treatment arms. pCR rates were higher in patients with stage II versus III disease (21% versus 9%, P = 0.0013), ductal versus lobular histology (19% versus 11%, P = 0.049), lower %ER positivity (≤66% versus >66%) (35% versus 9%, P = 3.4E-09), MP-High2 versus MP-High1 disease (31% versus 11%, P = 1.1E-05), BP-Basal-type versus BP-Luminal-type disease (34% versus 10%, P = 1.62E-07), and ImPrint-positive versus -negative disease (38% versus 10%, P = 1.64E-09). Patients with lower %ER were more likely to have MP-High2 and BP-Basal-type disease. At a median follow-up of 4.8 years, patients who achieved pCR had excellent outcomes irrespective of clinical/molecular features. Among patients who did not achieve pCR, DRFS events were more frequent in patients with MP-High2 and BP-Basal-type disease than those with MP-High1 and BP-Luminal-type disease. Conclusions Among patients with high molecular-risk HR+/HER2-negative EBC, the MP-High2, BP-Basal-type, and ImPrint-positive signatures identified a partially overlapping subset of patients who were more likely to achieve pCR in response to neoadjuvant chemotherapy ± targeted agents or immunotherapy compared to patients with MP-High1, BP-Luminal-type, and ImPrint-negative disease. I-SPY2.2 is incorporating the use of these biomarkers to molecularly define specific patient populations and optimize treatment selection.

Keywords: neoadjuvant therapy, molecular subtype, luminal, basal, MammaPrint, intrinsic subtype

25COASMA25:

Title: Efficacy of subsequent therapies in patients with advanced ovarian cancer who relapse after first-line olaparib maintenance: results of the PAOLA-1/ENGOT-ov25 trial

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Abstract: The use of first-line poly(ADP-ribose) polymerase (PARP) inhibitor maintenance therapy is increasing in advanced ovarian cancer. Understanding the efficacy of first subsequent therapy (FST) in patients experiencing disease progression in the first-line setting is important to optimize postprogression treatments. We evaluated the efficacy of FST in patients from PAOLA-1/ENGOT-ov25 (NCT02477644) who received first-line olaparib maintenance. Patients and methods-This post hoc analysis evaluated the efficacy of subsequent chemotherapy following disease progression by assessing time from FST to second subsequent therapy (SST) according to whether progression occurred during versus

after first-line olaparib maintenance and FST type. A multivariate Cox model was used in the olaparib plus bevacizumab arm to identify prognostic factors influencing the efficacy of subsequent chemotherapy. Of 806 randomized patients, 544 (67.5%) progressed and received subsequent chemotherapy. The median time from FST to SST was shorter in patients in the olaparib plus bevacizumab arm who progressed during first-line olaparib maintenance (6.1 months) than in those who progressed after first-line olaparib maintenance (11.4 months). Multivariate analysis indicated that progression after (versus during) first-line olaparib maintenance influenced time from FST to SST (hazard ratio 0.65, 95% confidence interval 0.50-0.84; P = 0.0011) independently of platinum-free interval or clinical risk. Among patients who progressed and received platinum-based chemotherapy with a PARP inhibitor as FST, the efficacy of subsequent therapies was also dependent on whether progression occurred during versus after first-line olaparib maintenance. These results suggest that the timing of disease progression relative to first-line olaparib maintenance may impact the efficacy of subsequent platinum-based chemotherapy. Although results should be interpreted with caution, across all subgroups, including patients who received platinum-based chemotherapy with PARP inhibitor rechallenge as FST, the median time from FST to SST was longer if progression occurred after versus during first-line olaparib maintenance.

Keywords: olaparib, ovarian cancer, first subsequent therapy, rechallenge, PARP inhibitor PAOLA-1/ENGOT-ov25

25COASMA26:

Adjuvant immunotherapy in patients with resected gastric and oesophagogastric junction cancer following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1): European Organisation of Research and Treatment of Cancer (EORTC) 1707 VESTIGE study

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Abstract: Patients with gastro-oesophageal adenocarcinoma with tumour-positive lymph nodes (ypN+) or positive surgical margins (R1) following neoadjuvant chemotherapy and resection are at high risk of recurrence. Adjuvant nivolumab is effective in oesophageal/oesophagogastric junction cancer and residual pathological disease following chemoradiation and surgery. Immune checkpoint inhibition has shown efficacy in advanced gastro-oesophageal cancer. We hypothesised that nivolumab/ipilimumab would be more effective than adjuvant chemotherapy in high-risk (ypN+ and/or R1) patients with gastro-oesophageal adenocarcinoma following neoadjuvant chemotherapy and resection. VESTIGE was an academic international, multicentre, open-label, randomised phase II trial evaluating the efficacy of adjuvant nivolumab/ipilimumab versus chemotherapy in gastro-oesophageal adenocarcinoma at high risk of recurrence. Patients were randomised 1 : 1 to receive standard adjuvant chemotherapy (same regimen as neoadjuvant) or nivolumab 3 mg/kg intravenously (i.v.) every 2 weeks plus ipilimumab 1 mg/kg i.v. every 6 weeks for 1 year. Key inclusion criteria included ypN+ and/or R1 status after neoadjuvant chemotherapy plus surgery. The primary endpoint was disease-free survival in the intent-to-treat population. Secondary endpoints included overall survival, locoregional and distant failure rates, and safety

according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Results-The independent Data Monitoring Committee reviewed data from 189 of the planned 240 patients in June 2022 and recommended stopping recruitment due to futility. At the time of final analysis, median follow-up was 25.3 months for 195 patients (98 nivolumab/ipilimumab and 97 chemotherapy). Median disease-free survival for the nivolumab/ipilimumab group was 11.4 months [95% confidence interval (CI) 8.4-16.8 months] versus 20.8 months (95% CI 15.0-29.9 months) for the chemotherapy group, hazard ratio 1.55 (95% CI 1.07-2.25, one-sided P = 0.99). The 12-month disease-free survival rates were 47.1% and 64.0%, respectively. There were no toxicity concerns or excess early discontinuations. Nivolumab/ipilimumab did not improve disease-free survival compared with chemotherapy in patients with ypN+ and/or R1 gastro-oesophageal adenocarcinoma following neoadjuvant chemotherapy and surgery.

Keywords: gastric cancer, oesophagogastric junction cancer, perioperative, immunotherapy chemotherapy

25COASMA27:

Title: A phase III randomised trial on the addition of a contact X-ray brachytherapy boost to standard neoadjuvant chemo-radiotherapy for organ preservation in early rectal adenocarcinoma: 5 year results of the OPERA trial

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Abstract: The OPERA trial has shown that a contact X-ray brachytherapy 50 kV (CXB) boost with neoadjuvant chemoradiotherapy (NCRT) can increase organ preservation (OP) rate for early rectal adenocarcinoma (ADK) of low-mid rectum. We report the results after 5 years of follow-up. Patients and methods OPERA was a multicentre, phase III trial that included operable patients (pts), with cT2-cT3b low-mid rectal ADK, tumours <5 cm, cN0 or cN1 <8 mm. All pts received external beam radiotherapy (EBRT): 45 Gy in 25 fractions with concurrent capecitabine. Pts were randomly assigned (1:1) to receive a boost of EBRT in group A (9 Gy/5 fractions) or a boost with CXB (90 Gy/3 fractions) in group B. The primary end point was OP rate. Out of 148 patients randomised, 141 were eligible. Between week 14-24, a clinical complete (or near) response was observed in 44 pts in group A (64%) versus 66 in group B (92%); P < 0.001. The 3-year OP rate was 59% in group A versus 81% in group B (P = 0.003). After update the median follow-up was 61.1 months [56.8-64.5]. The 5-year local regrowth was 39% in group A and 17% in group B (P = 0.1). The difference in OP was still highly significant between both groups: A 56% versus B 79% (P = 0.004). The difference was more significant if tumours <3 cm, with an OP rate of 93% in group B compared to 54% in group A. Of the 28 local regrowths, 3 occurred after 3 years of follow-up. Rectal bleeding (grade 1-2), which was the most prevalent toxicity during follow-up, disappeared most of the time after three years. Bowel function was not worsened by the CXB boost. The OPERA trial was the first trial to demonstrate that CXB dose escalation was increasing the OP rate with good bowel function at 3 years. At 5 years, these results are sustained, especially in small early-stage tumours. The occurrence of some local regrowth

after 3 years necessitates close surveillance of these pts during the 5-year period.

Keywords: organ preservation, rectal cancer, neoadjuvant treatment, contact X-ray brachytherapy, TME surgery, randomised trial

25COASMA28:

Title: PD-L1 expression in recurrent or metastatic head and neck squamous cell carcinoma in China (EXCEED study): a multicentre retrospective study

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Journal of Clinical Pathology, Volume 78, Issue 2
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Abstract: Aims Programmed death-ligand 1 (PD-L1) is known to be highly expressed in various malignancies, including head and neck squamous cell carcinoma (HNSCC). We aimed to determine the prevalence of PD-L1 expression in recurrent or metastatic HNSCC (R/M HNSCC) among Chinese patients. Methods This multicentre, retrospective analysis of data from six centres in China included patients with R/M HNSCC treated from 9 August 2021 to 28 February 2022. PD-L1 expression in tumour tissue was assessed and represented using a combined positive score (CPS). The χ^2 and Cochran-Mantel-Haenszel χ^2 tests were used to compare the prevalence of different PD-L1 expression statuses according to related co-variables. Results For all 402 examined patients with R/M HNSCC, 168 cases (41.8%) had PD-L1 expression with a CPS ≥20, and 337 cases (83.8%) had PD-L1 expression with a CPS ≥1. Between the PD-L1 CPS ≥20 group and PD-L1 CPS <20 group, statistically significant differences were observed for variables of sex ($p<0.001$), smoking habit ($p=0.0138$ for non-smokers vs current smokers) and primary tumour site ($p<0.001$ for hypopharynx vs oral cavity and $p=0.0304$ for larynx vs oral cavity, respectively). Conclusion PD-L1 with CPS ≥20 was expressed in about 41.8% of cases with R/M HNSCC among Chinese patients, and PD-L1 expression was significantly associated with sex, smoking history and primary tumour site. Our findings regarding the variables related to PD-L1 expression level provide insight for clinical practice and a solid basis for future research on immunotherapy in HNSCC.

25COASMA29:

Title: Schaumann bodies deposited along myenteric plexus of the muscularis propria is a unique histopathological feature of Crohn's disease

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Journal of Clinical Pathology, Volume 78, Issue 2
https://doi.org/10.1136/jcp-2023-209271

Abstract: Aims Schaumann bodies were first identified in sarcoidosis by Dr Schaumann in 1941. They were also detected in 10% of Crohn's disease (CD) cases in a study involving patients with surgically resected CD. However, the characteristics and significance of Schaumann bodies in CD have yet to be fully elucidated. This study aimed to determine the pathological features and diagnostic significance of Schaumann bodies in various bowel diseases. Methods Overall, 278 bowel specimens were collected from patients with CD, intestinal tuberculosis, ulcerative colitis, intestinal schistosomiasis, diverticulosis and idiopathic mesenteric vasculopathy. The frequency, pathology and clinical features of

patients with Schaumann bodies were studied. Results **S**chaumann bodies were present exclusively in CD (27.0%, 38 of 141) and were not detected in other intestinal diseases within the series. In CD, Schaumann bodies were deposited along the myenteric plexus of the muscularis propria (84.2%, 32 of 38). These bodies were small (diameter: 60.3±32.7 μm) and exhibited a low density in the intestinal wall (1.1±0.4 per low-power field). The majority were located within the cytoplasm of multinucleated giant cells (84.2%, 32 of 38) and were not found within or adjacent to granulomas. Notably, the number of female patients with CD and Schaumann bodies was higher than that of males. Conclusion Schaumann bodies are common in resected CD specimens, and their characteristic deposition pattern may serve as a diagnostic indication for CD.

25COASMA30:

Title: Morphological subtypes of colorectal low-grade intraepithelial neoplasia: diagnostic reproducibility, frequency and clinical impact

Corinna Lang-Schwarz1, Maike Büttner-Herold2, Stephan Burian1,

Journal of Clinical Pathology, Volume 78, Issue 2
https://doi.org/10.1136/jcp-2023-209206

Abstract: Aims Special histomorphological subtypes of colorectal low-grade intraepithelial neoplasia (LGIN) with variable prognostic impact were recently described in patients with inflammatory bowel disease (IBD) referred to as non-conventional dysplasia. However, they can also be found in patients without IBD. We aimed to analyse the reproducibility, frequency and prognostic impact of non-conventional colorectal LGIN in patients with and without IBD. Methods Six pathologists evaluated 500 specimens of five different LGIN-cohorts from patients with and without IBD. Non-conventional LGIN included hypermucinous, goblet cell-deficient, Paneth cell-rich and crypt cell dysplasia. A goblet cell-rich type and non-conventional LGIN, not otherwise specified were added. Results were compared with the original expert-consented diagnosis from archived pathology records. Results Four or more pathologists agreed in 86.0% of all cases. Non-conventional LGIN was seen in 44.4%, more frequently in patients with IBD (52%; non-IBD: 39.3%, p=0.005). In patients with IBD non-conventional LGIN associated with more frequent and earlier LGIN relapse (p=0.006, p=0.025), high-grade intraepithelial neoplasia (p=0.003), larger lesion size (p=0.001), non-polypoid lesions (p=0.019) and additional risk factors (p=0.034). Results were highly comparable with expert-consented diagnoses. In patients without IBD, non-conventional LGIN may indicate a higher risk for concurrent or subsequent colorectal carcinoma (CRC, p=0.056 and p=0.061, respectively). Frequencies and association with high-grade intraepithelial neoplasia or CRC varied between the different LGIN subtypes. Conclusions Non-conventional histomorphology in colorectal LGIN is frequent and highly reproducible. Our results indicate an increased risk for CRC in patients with non-conventional LGIN, probably independent of IBD. We recommend reporting non-conventional LGIN in routine pathology reports.

25COASMA31:

Title: Postoperative Hirschsprung's associated enterocolitis (HAEC): transition zone as putative histopathological predictive factor

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Journal of Clinical Pathology, Volume 78, Issue 2
Doi-https://doi.org/10.1136/jcp-2023-209129
Abstract: Hirschsprung's-associated enterocolitis (HAEC) is the most severe complication of Hirschsprung disease (HD), and its pathogenesis is still unknown. Length of transition zone (TZ) interposed between aganglionic and normal bowel has been poorly explored as predictor for postoperative HAEC (post-HAEC). This study aimed to identify potential predictive factors for post-HAEC, with a particular focus on histopathological findings.
Data from Hirschsprung patients treated in a single Italian centre between 2010 and 2022 with a follow-up >6 months were collected. Thorough histopathological examination of the resected bowel was conducted, focusing on length of TZ and aganglionic bowel.The degree of inflammatory changes in ganglionic resected bowel was further obtained. Ultra-long HD, total colonic aganglionosis and ultra-short HD were excluded. Bivariate and multivariate regression analysis were performed. Thirty-one patients were included; 5 experienced preoperative HAEC (pre-HAEC) and later post-HAEC (16.1%), further 10 patients developed post-HAEC (total post-HAEC 48.38%). Pre-HAEC-history and a TZ<2.25 cm correlated with an early development of post-HAEC. Multivariate analysis identified a TZ<2.25 cm as an independent post-HAEC predictive factor (p=0.0096). Inflammation within the ganglionic zone and a TZ<2.25 cm correlated with higher risk of post-HAEC (p=0.0074, 0.001, respectively). Severe post-HAEC more frequently occurred in patients with pre-HAEC (p=0.011), histological inflammation (p=0.0009) and short TZ (p=0.0015).
Conclusions This study suggests that TZ<2.25 cm predicts the risk of post-HAEC. Preoperative clinical and histopathology inflammation may predispose to worst post-HAEC. Readily available histopathological findings might help identifying patients at higher risk for HAEC and implementing prevention strategies.

25COASMA32:

Title: Staging of operative link on gastritis assessment and operative link on gastric intestinal metaplasia systems for risk assessment of early gastric cancer: a case–control study

Yu Huang, Jinnan Chen, Yixian Guo
Journal of Clinical Pathology, Volume 78, Issue 2
https://doi.org/10.1136/jcp-2023-209209
Abstract: Operative link on gastritis assessment (OLGA) and operative link on gastric intestinal metaplasia assessment (OLGIM) systems are histological staging systems of gastritis for gastric cancer (GC) risk estimation. Intermediate OLGA/OLGIM stages are of concern in a region with high incidence of GC. This study aimed to validate OLGA and OLGIM staging systems for early GC (EGC) in Chinese population. This single-centre, case–control study included 196 patients with EGC and 196 age-matched and sex-matched health screening control subjects. OLGA and OLGIM systems, and other clinical parameters were evaluated using logistic regression analysis. OLGA and OLGIM stages II/III/IV were more prevalent in patients with EGC than in the control subjects. Multivariable analysis revealed family history of GC, previous Helicobacter pylori (H. pylori) infection, OLGA stages II and III-IV, OLGIM stages II and III-IV as independent risk factors for EGC (ORs, 4.04, 1.87,

2.52, 6.79, 4.11 and 10.78, respectively). Area under the receiver operating characteristic curve on EGC risk estimation was improved for OLGIM compared with OLGA (0.78 vs 0.71, p<0.001). Autoantibody seropositivity of gastric mucosa was not associated with EGC risk stratified by H. pylori status. Surveillance of intermediate-risk patients (OLGA/OLGIM II) should be emphasised in our region. The OLGIM may be preferred over the OLGA for EGC risk estimation.

25COASMA33:

Title: Predictors of an informative or actionable cytological diagnosis on repeat breast aspiration after an insufficient aspirate: a multicentre retrospective review

Joshua Li1, Billy S W Lai2, Joanna K M Ng3

Journal of Clinical Pathology, Volume 78, Issue 2
https://doi.org/10.1136/jcp-2023-209250

Abstract: An insufficient/inadequate diagnosis on fine-needle aspiration cytology (FNAC) of the breast is not an uncommon diagnostic dilemma. This study aims to review the rate and clinical features predicting an informative or actionable diagnosis on repeating breast aspiration after an insufficient aspirate. Unsatisfactory/insufficient/inadequate or equivalent breast aspirates were retrieved from the involved institutions, and those with a repeat aspiration performed within 365 days were included. Clinical and radiological information were retrieved. Available cytological slides were reviewed. Totally 539 paired aspirates were retrieved, with 61.2% (n=330/539) and 10.9% (n=59/539) cytological diagnosis being informative (not insufficient) and actionable (not insufficient nor benign) on repeat aspiration. Younger age (p=0.005) was associated with an informative diagnosis and prior radiotherapy (p=0.097) and insufficient aspirates performed under free-hand (p=0.097) trended with an actionable diagnosis. Radiological findings of calcification (p=0.026) and hyperechogenicity (p=0.045), a small lesion size on initial (p=0.037) and repeat (p=0.059) radiological assessment and interval size increment (p=0.019) correlated with informative/actionable diagnoses. Cytomorphological parameters, except for a trend with crushing artefact (p=0.063), do not correlate with the cytologic diagnosis of the repeat aspirate. Conclusions **R**epeating breast FNAC on patients after an insufficient diagnosis yields an informative (‘sufficient’) result in over 60% of cases. Small lesions with calcification, hyperechogenicity and/or interval size increment are more likely to yield diagnostic results on repeat aspiration and indicate select patients suitable for repeat FNAC over more invasive procedures. The lack of associations with cytomorphological parameters cautions against overinterpretation of insufficient breast aspirates.

25COASMA34:

Title: Application of cloud server-based machine learning for assisting pathological structure recognition in IgA nephropathy

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Journal of Clinical Pathology, Volume 78, Issue 2
https://doi.org/10.1136/jcp-2023-209215

Abstract: Background Machine learning (ML) models can help assisting diagnosis by rapidly localising and classifying regions of interest (ROIs) within whole slide images

(WSIs). Effective ML models for clinical decision support require a substantial dataset of 'real' data, and in reality, it should be robust, user-friendly and universally applicable. Methods WSIs of primary IgAN were collected and annotated. The H-AI-L algorithm which could facilitate direct WSI viewing and potential ROI detection for clinicians was built on the cloud server of matpool, a shared internet-based service platform. Model performance was evaluated using F1-score, precision, recall and Matthew's correlation coefficient (MCC). Results **T**he F1-score of glomerular localisation in WSIs was 0.85 and 0.89 for the initial and pretrained models, respectively, with corresponding recall values of 0.79 and 0.83, and precision scores of 0.92 and 0.97. Dichotomous differentiation between global sclerotic (GS) and other glomeruli revealed F1-scores of 0.70 and 0.91, and MCC values of 0.55 and 0.87, for the initial and pretrained models, respectively. The overall F1-score of multiclassification was 0.81 for the pretrained models. The total glomerular recall rate was 0.96, with F1-scores of 0.68, 0.56 and 0.26 for GS, segmental glomerulosclerosis and crescent (C), respectively. Interstitial fibrosis/tubular atrophy lesion similarity between the true label and model predictions was 0.75**.** Conclusions Our results underscore the efficacy of the ML integration algorithm in segmenting ROIs in IgAN WSIs, and the internet-based model deployment is in favour of widespread adoption and utilisation across multiple centres and increased volumes of WSIs.

25COASMA35:

Title: Cytomorphology and clinicopathologic correlation of TFE3-rearranged renal cell carcinoma

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Cancer Cytopathology, vol-133, Issue-2

https://doi.org/10.1002/cncy.22933

Abstract: Background TFE3-rearranged renal cell carcinoma (TFE3-rRCC) harbors gene fusions involving TFE3 with one of many different partner genes. Because of their diverse morphologies, the differential diagnosis is broad and challenging. Publications focusing on the cytomorphology of TFE3-rRCC are sparse. Methods Fifteen cytology cases of TFE3-rRCC from 12 patients were retrieved, comprising seven primary kidney cases and eight metastatic cases. Results Cytology smears showed tumor cells with moderate granular or vacuolated cytoplasm, arranged in diverse patterns, such as three-dimensional clusters, nested/sheeted formations, isolated cells, papillary, and tubular/acinar structures. The tumor cells exhibited enlarged eccentric, round or oval nuclei, possibly situated peripherally, with small to prominent nucleoli and irregular nuclear membranes. Macrophages, hyalinized globules, or necrosis were occasionally seen. Core and cell block histology often showed papillae with surface-oriented nuclei. Tumor cells were also arranged in nested, sheeted, and tubular patterns. Tumor cells were immunoreactive to TFE3 (100%), AMACR (100%), PAX8 (88%), and CD10 (83%) and showed focal staining for CA9 (64%), CK7 (20%), and CD117 (25%). TFE3 rearrangement was confirmed in 13 of 15 cases through fluorescence in situ hybridization or RNA fusion next-generation sequencing testing. Metastasis was observed in nine of 12 patients (80%), with retroperitoneal lymph nodes being the most common site, followed by distant lymph nodes, lung, brain, adrenal gland, and bone. Six patients (50%) underwent nephrectomy alone, two patients (17%) received chemotherapy

alone, and four patients (33%) received combined nephrectomy and chemotherapy. Conclusions Timely recognition of TFE3-rRCC's distinct cytomorphologic and histomorphologic features is essential for accurate diagnosis and effective treatment.

25COASMA36:

Pericardial fluid evaluation: Diagnostic yield and cytology–histology correlation

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Cancer Cytopathology, vol-133, Issue-2

https://doi.org/10.1002/cncy.70000

Abstract: Background Pericardial effusion can be due to any etiology but may cause significant morbidity and mortality; however, malignant effusions are rare, and accurate and timely diagnosis is essential for appropriate further management. Data on the actual comparison of pericardial cytology and surgical specimens are limited, and this study was conducted to evaluate an institutional cohort and compare these two samples. Methods -The institutional electronic database system was retrospectively searched between January 2019 and December 2023 for pericardial biopsies/surgical specimens (PSSs) and cytology.

Results-A total of 202 surgical specimens of the pericardium were identified from patients with a median age of 67 years and a range of 18–97 years. Of these 202 cases, 190 specimens also underwent cytological evaluation, which included 153 cases that were negative for malignancy, nine cases that were indeterminate/atypical, and 28 cases that were positive for malignancy. Agreement between cytology and PSSs was reached in 172 cases, with 153 being benign and 19 being malignant. However, a cytology–histology discrepancy was found in 18 cases. Of these 18 cases, nine showed positive cytology but all had negative concurrent PSSs except for one with focal atypia, and the remaining nine were indeterminate/atypical on cytology. Eight of these nine indeterminate cases were negative on the PSS, whereas one atypical cytology case with low cellularity showed a positive PSS. Conclusions-If atypical cases are excluded, cytology demonstrates a better diagnostic yield for detecting malignancy compared to surgical specimens (n = 28 cases vs. n = 20 cases, respectively).

25COASMA37:

Cytologic, histologic, and clinical correlation of minor mutations in pancreatic cysts

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Cancer Cytopathology, vol-133, Issue-2

https://doi.org/10.1002/cncy.22935

Abstract: Background Major mutations (e.g., KRAS, GNAS, TP53, SMAD4) in pancreatic cyst fluid (PCF) are useful for classifying and risk stratifying certain cyst types, particularly in cases with nondiagnostic cytology. However, the significance of uncommon minor mutations in PCF has yet to be reported. Methods In total, 127 PCF specimens (2014–2021) from 121 patients that underwent molecular analysis were identified, and detailed clinicopathologic data were recorded. Molecular testing was performed using a laboratory-developed next-generation sequencing panel. Results Forty-five variants other than KRAS, GNAS, RNF43, TP53, CDKN2A, and SMAD4 were detected. Variants that were detected in five or more cases included ARID1A (n = 28), VHL (n = 17), BRAF (n = 12), ATM (n = 8), APC (n = 8), MEN

1 (n = 5), serine threonine kinase 11 (STK11; n = 5), PIK3CA (n = 5), and CDH1 (n = 5). Thirty-eight of 121 patients (31%) had histologic confirmation on follow-up resection. Twenty-seven of 28 cysts (96%) with ARID1A mutations had concurrent KRAS/GNAS mutations; 17 (61%) were diagnosed as neoplastic mucinous cysts on cytology, and 10 (36%) were diagnosed as intraductal papillary mucinous neoplasm (IPMN) on histology (80% low grade). No patients developed disease recurrence or died of disease. Cysts with STK11 mutations had RAS co-mutations (KRAS, n = 5; NRAS, n = 1), and four of those five cysts (80%) were mucinous neoplasms with high-grade atypia on cytology. All three resection specimens were IPMNs with high-grade dysplasia or invasive carcinoma, and two of those patients died of disease. Conclusions In PCFs, ARID1A mutations were consistently associated with IPMNs (predominantly low grade) with no recurrences or deaths from disease. STK11 mutations appeared to be associated with high-risk mucinous cysts. The detection of minor variants may provide useful preoperative information and add value beyond single-gene genotyping of major mutations.

25COASMA38:

Title: Assessment of risk of malignancy with application of Sydney classification for reporting of lymph node cytopathology in pediatric population: An institutional experience

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Cancer Cytopathology, vol-133, Issue-2

https://doi.org/10.1002/cncy.22936

Abstract: Fine-needle aspiration cytology (FNAC) has been used as the first line approach to lymphadenopathy, which is a common presentation in pediatric age group. The Sydney system for reporting of lymph node (LN) cytology has been proposed to assess the reliability, performance, and accuracy of the aspiration procedure. This study intends to assess the role of FNAC in the pediatric population according to the Sydney system.This was a retrospective observational study from a tertiary care center in Eastern India. All the patients in the age group of 0–18 years evaluated during years 2016–2024 were reclassified according to the Sydney system. Based on the cytology and histology diagnoses, the cases were categorized into true-negative, true-positive, false-negative, and false-positive. The overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and risk of malignancy (ROM) was calculated for each category.Of 803 cases of pediatric LN-FNACs, 35 (4.35%) cases were reported as inadequate (L1), 689 (85.8%) cases as benign (L2), four (0.49%) cases as atypical cells of undetermined significance (L3), 22 cases as suspicious for malignancy (L4), and 53 (6.6%) cases as malignant (L5). The sensitivity, specificity, PPV, NPV, and accuracy was 72.34%, 98. both L4 and L5 categories.FNAC is a highly accurate and specific test for LN pathology, especially in the pediatric population. The incorporation of the Sydney system helps to achieve uniformity and reproducibility in LN cytology diagnosis. 48%, 97.14%, 83.33%, and 87.61%, respectively. The ROM was 16.67% for L2 and 100% for

25COASMA39:

Title: Cytologic diagnosis of fumarate hydratase-deficient renal cell carcinoma: A

single-institutional experience

Patrick C. Mullane MD, Xiaohua Qian MD, PhD, Hubert D. Lau MD, Alarice Cheng-Yi Lowe MD

Cancer Cytopathology, vol-133, Issue-2
Doi-**https://doi.org/10.1002/cncy.22931**

Abstract: Background-Fumarate hydratase-deficient renal cell carcinoma (FHRCC) is an aggressive carcinoma that typically presents as advanced-stage disease. Prompt recognition of FHRCC is critical for appropriate clinical care and genetic counseling for patients and family members. However, diagnosing FHRCC from cytology specimens is challenging, with limited characterization and no reports describing prospectively identified cases. MethodsCytology fine-needle aspiration (FNA) cases diagnosed as FHRCC were reviewed, including two prospectively identified cases. Results Five cases of FHRCC diagnosed by FNA cytology were identified in five unique patients. The cytologic samples included four FNAs with core biopsy and one FNA with cell block. Biopsy sites included kidney (n = 1), chest wall (n = 1), omentum (n = 1), lung (n = 1), and cervical lymph node (n = 1). All cases demonstrated cytologically malignant epithelial cells characterized by enlarged, round nuclei with variable pleomorphism, irregular nuclear membranes, prominent nucleoli, and moderate-to-abundant amounts of cytoplasm. Perinucleolar halos characterized by chromatin margination and pallor around macronucleoli were seen in all cases. Cytologic features not previously described included cytoplasmic macrovacuoles and eosinophilic globules, cytophagocytosis, and floral groups. Papillary architecture was rarely present on aspirate smears. Cell block sections showed variable architectural patterns. By immunohistochemistry, FH was definitively lost in three of five cases (60%), and 2-succinocysteine was positive in all 5 cases (100%). Conclusions-Cytologic specimens of FHRCC demonstrate salient cytomorphologic features that can support their initial diagnosis. Confirmatory immunohistochemical testing using a dual panel of fumarate hydratase and 2-succinocysteine is recommended for the diagnosis in limited biopsy samples.

25COASMA40:

Title: InterobServer AgreeMent in Pd-l1 evaLuatIoN on cytoloGical samples—SAMPLING project: A multi-institutional, international study

Gennaro Acanfora MD, Antonino Iaccarino CT, PhD, Bruna Cerbelli MD, PhD,

Cancer Cytopathology, vol-133, Issue-3
Doi-**https://doi.org/10.1002/cncy.70003**

Abstract: Introduction The aim of this project is to assess interobserver agreement for programmed death-ligand 1 (PD-L1) scoring on of non–small cell lung cancer (NSCLC) on cytological specimens in a large-scale multicenter study, by exploiting the cell block-derived tissue microarray (cbTMA) approach. Methods-A total of 65 cell blocks (CB) diagnosed as NSCLC were retrospectively collected and selected for TMA preparation. Hematoxylin–eosin and PD-L1 stained slides were digitized and uploaded on a free web sharing platform. Participants were asked to provide PD-L1 assessment by using the clinically relevant cutoff of tumor proportion score (TPS) (<1%; 1%–49%; >50%). Interobserver agreement was calculated using Fleiss's κ. Results-Of 65 CBs, 11 were deemed not suitable; therefore, an overall number of 54 cores were used for the preparation of four TMAs. A total of 1674

evaluations were provided by 31 cytopathologists from 21 different institutions in nine countries. The statistical analysis showed a moderate overall agreement (κ = 0.49). The highest agreement was achieved in the TPS >50% category (κ = 0.57); moderate agreement was observed in TPS <1% category (κ = 0.51) and the lowest κ value was obtained for TPS 1%–49% category (k = 0.32). Conclusions-The overall moderate agreement observed showed that there is still room for improvement in inter-pathologist agreement for PD-L1 evaluation on cytological samples, highlighting the need for standardization in sample preparation, focused training in PD-L1 evaluation on cytological material, and the integration of machine learning tools to improve interobserver consistency.

25COASMA41:

Title: How an epidemic of untreated malnutrition is worsening cancer: In this first of a two-part series on how nutrition can influence cancer, recent studies have underscored the imperative to identify and treat malnutrition as a serious—and preventable—risk factor.

Bryn Nelson PhD, William Faquin MD, PhD

Cancer Cytopathology, vol-133, Issue-3
https://doi.org/10.1002/cncy.70002

Abstract: Physicians have long observed that patients who have cancer and are also malnourished are more likely to die. Beyond making treatments less effective and more toxic, malnutrition can reduce a patient's functional abilities and quality of life while increasing the risk of complications. For many decades, however, the surprisingly common and largely unresolved phenomenon of malnutrition in patients with cancer was seen as an inevitability.

Jann Arends, MD, a gastroenterologist, hematologist, and medical oncologist at the University of Freiburg in Germany, says that weight loss and emaciation were once taken for granted as a standard feature of intractable cancers. "Most cancers would not respond to even aggressive anticancer treatments, and weight loss was seen as a harbinger of death and not as a condition requiring supportive care," Dr Arends says.That mindset further solidified, he says, when clinical trials testing routine artificial nutrition (delivered via feeding tubes or intravenous lines) yielded no discernable benefits for patients but higher complication rates than oral feeding. In response, the American Society for Parenteral and Enteral Nutrition recommended not using artificial nutrition to treat patients with cancer and thus furthered what Dr Arends calls "nutritional nihilism in an age of only rare oncological success."As cancer treatment successes have multiplied during the past 15 years, however, more research has helped to change recommendations, refine the benefits and limitations of nutritional care in patients, and provide better estimates of just how common malnutrition can be.

25COASMA42:

Title: Cytologic features of angiosarcoma in fluid specimens: A retrospective study of 22 cases

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Cancer Cytopathology, vol-133, Issue-3
https://doi.org/10.1002/cncy.70004

Abstract: Although histologic and fine-needle aspiration cytologic features of angiosarcoma are well established, little is known about its cytologic features in fluids. This study presents the cytomorphologic features of 22 patients who had angiosarcoma involving pleural, pericardial, ascites, and liver cyst fluids. Methods Patient data, including clinical histories, radiology, pathology, treatments, and follow-up, were collected. Results Twenty-two angiosarcoma fluid specimens (pleura, n = 17; pericardium, n = 2; ascites, n = 2; and liver cyst, n = 1) were identified. All patients had prior angiosarcoma diagnoses, and 10 (45%) had prior radiation exposure. Cellularity varied, with low cellularity predominant (73%). Cytologic architecture typically consisted of clusters of epithelioid cells (91%), single epithelioid cells (55%), and spindled cells (36%). Malignant nuclear characteristics, such as irregular nuclear membranes, chromatin clumping, and prominent nucleoli, were consistent (100%). Vasoformative features included endothelial wrapping (73%), intracytoplasmic lumina (18%), hemophagocytosis (9%), and intracytoplasmic lumina with cells (5%). Low cellularity samples usually lacked vasoformative features (27%). Prominent nucleoli, often with multiple or club-shaped forms, appeared in all cases (100%). Atypical mitotic figures (45%), associated fibromyxoid material (14%), and possible necrosis (5%) were also observed. The interval between cavity fluid involvement and primary diagnosis averaged 616 days (range, 14–2778 days). The mean time from the first positive fluid to death was 141 days (range, 3–568 days). Conclusions Angiosarcoma in fluids is rare. Cytomorphologic features, although nonspecific, include malignant nuclear features, prominent nucleoli, atypical mitoses, and occasional vasoformative features. Accurate diagnosis necessitates a careful review of the patient's history and judicious use of immunohistochemical staining.

25COASMA43:

Title: ZMIZ1::ABL1 Fusion: An Uncommon Molecular Event With Clinical Implications in Pediatric Cancer

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Arch Pathol Lab Med (2025) 149 (2): 159–164.
Doi-https://doi.org/10.5858/arpa.2024-0082-OA

Abstract: Context.—Pediatric B-cell acute lymphoblastic leukemia is genetically and phenotypically heterogeneous, with a genetic landscape including chromosomal translocations that disrupt ABL proto-oncogene 1, non–receptor tyrosine kinase (ABL1). Objective.—To characterize an uncommon chromosomal translocation in acute leukemia.
Design.—Genetic testing, including karyotype and fluorescence in situ hybridization (FISH) analysis, was used to determine the underlying genetic aberration driving the disorder and to guide disease classification and risk stratification. More-detailed testing using RNA sequencing was performed based on the results from these assays. Three-dimensional molecular modeling was used to visualize the impact of aberrant fused transcripts identified by transcriptome profiling. Results.—Karyotype analysis of the bone marrow demonstrated a complex karyotype with, most notably, a t(9;10)(q34.1;q22) translocation. ABL1 break-apart probe FISH findings supported ABL1 disruption. Bone marrow transcriptome analysis revealed mutant ZMIZ1::ABL1 (ZMIZ1, zinc finger MIZ-type containing 1) fusion transcripts as a consequence of t(9;10)(q34.1;q22). Three-dimensional modeling of the

mutant ZMIZ1::ABL1 fusion protein confirmed an altered ABL1 protein structure compared to that of the wild type, suggesting a constitutively active conformation. Conclusions.— The t(9;10) translocation resulting in ZMIZ1::ABL1 fusion transcripts is an uncommon form of BCR::ABL1-like (BCR, BCR activator of RhoGEF and GTPase) acute lymphoblastic leukemia. Although the karyotype was complex, identifying the t(9;10)(q34.1;q22) translocation, ABL1 disruption, and ZMIZ1::ABL1 transcript enabled effective ABL1-targeted treatment. Our data support the use of tyrosine kinase inhibitors to treat ZMIZ1::ABL1-derived B-cell acute lymphoblastic leukemia. B-cell acute lymphoblastic leukemia (B-ALL) is the most common childhood malignancy.1,2 B-ALL is characterized by genetic alterations that block the differentiation and maturation of lymphoid precursor cells and promote their proliferation.1,2 Identification of such alterations is important for risk stratification.1,2 Approximately 10% of children (<18 years) with B-ALL have a BCR::ABL1-like (also known as Philadelphia chromosome–like [BCR, BCR activator of RhoGEF and GTPase; ABL1, ABL proto-oncogene 1, non–receptor tyrosine kinase]) profile.3 The transcriptional profile resembles that of BCR::ABL1 leukemia, but the cells lack the typical t(9;22) rearrangement.4,5 BCR::ABL1-like B-ALL is generally associated with high-risk clinical features, poor response to induction chemotherapy, and a higher likelihood of measurable residual disease at the end of induction.

25COASMA44:

Title: Frequent Immunohistochemical Expression of Transcriptional Repressor GATA Binding 1 in Salivary Gland Neoplasms: A Sensitive but Nonspecific Marker

Sanjay Sriram, MD; Aanchal Kakkar, MD; Chetna Sarma, MSc; Ria Mahendru, MD; Rajeev Kumar, MS;

Arch Pathol Lab Med (2025) 149 (2): 165–174.

https://doi.org/10.5858/arpa.2023-0444-OA

Abstract: Context.—Salivary gland (SG) neoplasms (SGNs) display considerable immunophenotypic diversity. A significant proportion of SG carcinomas develop metastases, with increased diagnostic difficulty at metastatic sites. Transcriptional repressor GATA binding 1 (TRPS1), a novel immunohistochemical marker for breast cancer, has been found to stain certain SGNs. Objective.—To investigate TRPS1 and SRY-related HMG-box 10 (SOX10) immunoexpression in various SGNs and non-SG carcinomas, head and neck paragangliomas, and head and neck mucosal melanomas. Design.—TRPS1 immunoreactivity score (IRS) was determined as negative or low, intermediate, or high positive; SOX10 was reported as negative or positive. Results.—One hundred forty-eight SGNs, 5 breast carcinomas, 105 nonbreast–non-SG carcinomas, including 33 head and neck squamous cell carcinomas (HNSCCs), 6 head and neck paragangliomas, and 6 head and neck mucosal melanomas, were assessed for TRPS1. All 23 benign SGNs showed TRPS1 positivity, with the majority having high-positive IRS (17 of 23 cases; 74%). Among 125 SG carcinomas, 115 of 125 (92%) were TRPS1 positive, with high-positive IRS in 94 of 125 (75%), intermediate-positive IRS in 15 of 125 (12%), and low-positive IRS in 6 of 125 (5%). Among nonbreast–non-SG carcinomas, HNSCC, lung, thyroid, kidney, and ovarian carcinomas showed frequent TRPS1 staining. Nearly half of HNSCCs had high (11 of 18; 33%) or intermediate (4 of 18; 12%) positive IRS. Mean IRS in SG carcinomas was significantly

higher than that in nonbreast–non-SG carcinomas (P < .001). None of the TRPS1-positive nonbreast–non-SG carcinomas expressed SOX10. Conclusions.—TRPS1 is positive in most benign and malignant SGNs. Its expression in several nonbreast–non-SG carcinomas indicates that it lacks specificity for breast and SG carcinomas, even if considering only high-positive IRS. Addition of SOX10 can increase the discriminatory utility of TRPS1.

25COASMA45:

Title: Genetic Landscape and Its Prognostic Impact in Children With Langerhans Cell Histiocytosis

Chan-Juan Wang, MD; Lei Cui, MD; Shuang-Shuang Li, MS; Hong-Hao Ma, MD; Dong Wang, MM

Arch Pathol Lab Med (2025) 149 (2): 175–190.
Doi-https://doi.org/10.5858/arpa.2023-0236-OA

Abstract: Context.—Langerhans cell histiocytosis (LCH) is a rare myeloid neoplasm that predominantly affects young children. Objective.—To investigate genetic alterations and their correlation with clinical characteristics and prognosis in pediatric LCH. Design.—We performed targeted sequencing to detect mutations in LCH lesions from pediatric patients.Results.—A total of 30 genomic alterations in 5 genes of the MAPK pathway were identified in 187 of 223 patients (83.9%). BRAF V600E (B-Raf proto-oncogene, serine/threonine kinase) was the most common mutation (51.6%), followed by MAP2K1 (mitogen-activated protein kinase kinase 1) alterations (17.0%) and other BRAF mutations (13.0%). ARAF (A-Raf proto-oncogene, serine/threonine kinase) and KRAS (KRAS proto-oncogene, GTPase) mutations were relatively rare (2.2% and 0.9%, respectively). Additionally, FNBP1 (formin-binding protein 1)::BRAF fusion and MAP3K10 (mitogen-activated protein kinase kinase 10) mutations A17T and R823C were identified in 1 case each, with possible constitutive activation of ERK1/2 phosphorylation. BRAF V600E was more frequent in patients with risk organ involvement, while MAP2K1 mutation was more prevalent in patients with single-system LCH (P = .001). BRAF V600E was associated with craniofacial bone, skin, liver, spleen, and ear involvement (all P < .05). Patients with other BRAF mutations had a higher proportion of spinal column involvement (P = .006). Univariate analysis showed a significant difference in progression-free survival among the 4 molecular subgroups for patients treated with first-line therapy (P = .02). According to multivariate analysis, risk organ involvement was the strongest independent adverse prognostic factor (hazard ratio, 8.854; P < .001); BRAF or MAP2K1 mutation was not an independent prognostic factor. Conclusions.—Most pediatric patients with LCH carry somatic mutations involving the MAPK pathway, correlating with clinical characteristics and outcomes for first-line chemotherapy.

25COASMA46:

Title: Localized Urinary Bladder Amyloidosis as Urothelial Cancer Mimicker: A Case Series Examining Cystoscopic, Histologic, and Cytologic Findings

Aayushma Regmi, MBBS; Maitri Mehta, DO; Ahmer V. Farooq, DO; Thomas M. Turk, MD; Eva M. Wojcik, MD; Maria M. Picken, MD, PhD

Arch Pathol Lab Med (2025) 149 (2): 191–194.
https://doi.org/10.5858/arpa.2023-0559-OA

Abstract: Context.— Localized amyloidosis of the bladder is rare and often mimics bladder malignancy. It is typically associated with the extracellular deposition of monoclonal light chains, either κ or λ. The cause is unknown, but it is thought to be due to chronic inflammation/cystitis. Objective.— To highlight the importance of localized urinary bladder amyloidosis as a rare mimicker of urothelial malignancy and elucidate its clinical, histopathologic, and cytopathologic manifestations. Design.—Cases of urinary bladder amyloidosis diagnosed during 2000–2023 were retrieved retrospectively from pathology archives. Electronic medical records, including cystoscopy findings and pathology slides including Congo red stain, were reviewed. Results.— Here we present 6 patients with localized urinary bladder amyloidosis. Four of the 6 patients were women, with ages ranging from 46 to 69 years, and a mean age of 58 years. Five of 6 patients presented with hematuria, while in 1 patient, bladder amyloidosis was discovered incidentally. Cystoscopy findings invariably were concerning for malignancy, with raised erythema in 5 patients and fungating mass protruding into the bladder lumen in 1 patient. Bladder biopsies and urine cytology were negative for malignancy in all cases. Congo red–positive amyloid deposits involved lamina propria with sparing of the detrusor muscle. In 5 cases, the deposits were typed as derived from the λ light chain, whereas no information was available for 1 patient. Subsequent clinical workup ruled out systemic amyloidosis. Conclusions.—These cases of urinary bladder amyloidosis highlight the importance of considering rare amyloidosis in the differential diagnosis of hematuria and cystoscopy with a lesion mimicking malignancy.

25COASMA47:

Title: Development of a Scoring Rubric Assessing Medical Students' Explanations of Pathology Reports

Felisha M. Davis, MD; Jonathan Bowling, BS; Ashish T. Khanchandani, MS; Michael C. Larkins, BS;

Arch Pathol Lab Med (2025) 149 (2): 195–199.
Doi-https://doi.org/10.5858/arpa.2023-0462-OA

Abstract: Context.—With increasing availability of immediate patient access to pathology reports, it is imperative that all physicians be equipped to discuss pathology reports with their patients. No validated measures exist to assess how pathology report findings are communicated during patient encounters. Objective.—To pilot a scoring rubric evaluating medical students' communication of pathology reports to standardized patients. Design.—
The rubric was iteratively developed using the Pathology Competencies for Medical Education and Accreditation Council for Graduate Medical Education pathology residency milestones. After a brief training program, third- and fourth-year medical students completed 2 standardized patient encounters, presenting simulated benign and malignant pathology reports. Encounters were video recorded and scored by 2 pathologists to calculate overall and item-specific interrater reliability.Results.—All students recognized the need for pathology report teaching, which was lacking in their medical curriculum. Interrater agreement was high for malignant report scores (intraclass correlation coefficient, 0.65) but negligible for benign reports (intraclass correlation coefficient, 0). On malignant reports, most items demonstrated

good interrater agreement, except for discussing the block (cassette) summary, explaining the purpose of the pathology report, and acknowledging uncertainty. Participating students (N = 9) felt the training was valuable given their limited prior exposure to pathology reports.
Conclusions.—This pilot study demonstrates the feasibility of using a structured rubric to assess the communication of pathology reports to patients. Our findings also provide a scalable example of training on pathology report communication, which can be incorporated in the undergraduate medical curriculum to equip more physicians to facilitate patients' understanding of their pathology reports.

25COASMA48:

Title: Advancing Diagnostic Accuracy and Quality of Patient Care Through the Implementation of a Flow Cytometry Quality Assurance Program

Dylan Wang; Hong Fang, MD; Chi Young Ok, MD; Jeffrey L. Jorgensen, MD, PhD;
Arch Pathol Lab Med (2025) 149 (2): e26–e30.
Doi-https://doi.org/10.5858/arpa.2024-0020-OA
Abstract: Context.—Flow cytometry immunophenotypic analysis plays an important role in the diagnosis, classification, and disease monitoring of hematologic neoplasms. The interpretation of flow cytometry testing can be challenging. Objective.—To explore ways to improve diagnostic accuracy and in turn enhance the quality of patient care. Design.—A flow cytometry quality assurance (QA) program was developed. Cases from various complex flow cytometry panels were randomly selected and cross-reviewed. The outcomes of the QA review were categorized into 3 groups: complete agreement, minor discrepancy, and major discrepancy. Each discrepancy underwent a process of documentation, discussion, and resolution. Here we summarize our 3 years of experience with this program. Results.—In total, 6166 cases were evaluated; 6028 cases (97.7%) showed complete concordance, 120 cases (2.0%) showed minor discrepancies, and 18 cases (0.3%) showed major discrepancies. Among the top 5 panels evaluated, the panel evaluating mature T-cell abnormalities showed the highest rate of discrepancy, whereas the panel for evaluation of myelodysplastic syndromes showed the lowest discrepancy rate. When analyzing the trends of concordance and discrepancy over time, we observed a statistically significant decrease in discrepancy rate over time, from 4% at the beginning of the 6-month period to 1.5% in the final 6-month period. Conclusions.—The overall concordance rate was 97.7%. The remaining 2.3% of cases showed discrepancies that required a correction, underscoring the value and necessity of having a QA program. The overall discrepancy rates exhibited a gradual decline over time, indicative of the positive impact of the QA program on enhancing diagnostic competency and accuracy over time.

25COASMA49:

Title: Insulinoma-Associated Protein-1 Expression in Lymphoepithelial Carcinoma of the Thymus: A Potential Pitfall for Diagnosis With Neuroendocrine Carcinomas of the Thymus

David I. Suster, MD; A. Craig Mackinnon, MD, PhD; Saul Suster, MD
Arch Pathol Lab Med (2025) 149 (2): e31–e35.
https://doi.org/10.5858/arpa.2024-0045-OA

Abstract: Context.—Insulinoma-associated protein-1 (INSM1) is a recently developed immunohistochemical marker claimed to be highly specific and sensitive for the diagnosis of neuroendocrine malignancies. Recent studies, however, have demonstrated that this marker can also be expressed in non-neuroendocrine neoplasms including squamous cell carcinoma of the thymus. Objective.—To examine INSM1 expression in lymphoepithelial thymic carcinomas. Design.—Thirty-four cases of lymphoepithelial carcinoma of the thymus were examined by immunohistochemistry or in situ hybridization for INSM1, synaptophysin, chromogranin, CD5, CD117, Epstein-Barr virus–encoded small ribonucleic acid (EBER), and Ki-67. Basic clinical information was abstracted from the medical record. Results.—The patients were 14 women and 20 men, aged 20 to 85 years. The tumors arose in the anterior mediastinum without any previous history or evidence of malignancy at other sites. Immunohistochemical staining showed moderate to strong positivity of the tumor cells for INSM1 in 65% of cases (22 of 34), focal weak positivity in 20% (7 of 34), and negative staining in 5 cases. Chromogranin staining was focally and weakly positive in 1 case, and synaptophysin showed only focal weak positivity in scattered tumor cells in 12 cases. No significant correlation could be identified between the pattern and intensity of staining for INSM1 and staining for CD5, CD117, and Ki-67. Conclusions.— INSM1 positivity in lymphoepithelial carcinoma of the thymus may represent a pitfall for diagnosis, particularly in small biopsy samples. Awareness of this finding may be of importance to avoid misdiagnosis of neuroendocrine malignancy.

25COASMA50:

Title: Introduction to Generative Artificial Intelligence: Contextualizing the Future

Rajendra Singh, MD; Ji Yeon Kim, MD; Eric F. Glassy, MD; Rajesh C. Dash, MD; Victor Brodsky, MD;

Arch Pathol Lab Med (2025) 149 (2): 112–122.
Doi-https://doi.org/10.5858/arpa.2024-0221-RA

Astract: Context.—Generative artificial intelligence (GAI) is a promising new technology with the potential to transform communication and workflows in health care and pathology. Although new technologies offer advantages, they also come with risks that users, particularly early adopters, must recognize. Given the fast pace of GAI developments, pathologists may find it challenging to stay current with the terminology, technical underpinnings, and latest advancements. Building this knowledge base will enable pathologists to grasp the potential risks and impacts that GAI may have on the future practice of pathology. Objective.—To present key elements of GAI development, evaluation, and implementation in a way that is accessible to pathologists and relevant to laboratory applications.Data Sources.—Information was gathered from recent studies and reviews from PubMed and arXiv. Conclusions.—GAI offers many potential benefits for practicing pathologists. However, the use of GAI in clinical practice requires rigorous oversight and continuous refinement to fully realize its potential and mitigate inherent risks. The performance of GAI is highly dependent on the quality and diversity of the training and fine-tuning data, which can also propagate biases if not carefully managed. Ethical concerns, particularly regarding patient privacy and autonomy, must be addressed to ensure responsible use. By harnessing these emergent technologies, pathologists will be well placed to continue

forward as leaders in diagnostic medicine.

25COASMA51:

Title: Ethical and Regulatory Perspectives on Generative Artificial Intelligence in Pathology

Brian R. Jackson, MD, MS; Hooman H. Rashidi, MD, MS; Jochen K. Lennerz, MD, PhD; M. E. de Baca, MD

Arch Pathol Lab Med (2025) 149 (2): 123–129.
https://doi.org/10.5858/arpa.2024-0205-RA

Abstract: Context.—Technology companies and research groups are increasingly exploring applications of generative artificial intelligence (GenAI) in pathology and laboratory medicine. Although GenAI holds considerable promise, it also introduces novel risks for patients, communities, professionals, and the scientific process. Objective.—To summarize the current frameworks for the ethical development and management of GenAI within health care settings. Data Sources.—The analysis draws from scientific journals, organizational websites, and recent guidelines on artificial intelligence ethics and regulation. Conclusions.—The literature on the ethical management of artificial intelligence in medicine is extensive but is still in its nascent stages because of the evolving nature of the technology. Effective and ethical integration of GenAI requires robust processes and shared accountability among technology vendors, health care organizations, regulatory bodies, medical professionals, and professional societies. As the technology continues to develop, a multifaceted ecosystem of safety mechanisms and ethical oversight is crucial to maximize benefits and mitigate risks.

25COASMA52:

Title: Evaluating Use of Generative Artificial Intelligence in Clinical Pathology Practice: Opportunities and the Way Forward

Peter McCaffrey, MD, MS; Ronald Jackups, MD, PhD; Jansen Seheult, MB BCh BAO, MSc, MS, MD;

Arch Pathol Lab Med (2025) 149 (2): 130–141.
https://doi.org/10.5858/arpa.2024-0208-RA

Abstract: Context.—Generative artificial intelligence (GAI) technologies are likely to dramatically impact health care workflows in clinical pathology (CP). Applications in CP include education, data mining, decision support, result summaries, and patient trend assessments. Objective.—To review use cases of GAI in CP, with a particular focus on large language models. Specific examples are provided for the applications of GAI in the subspecialties of clinical chemistry, microbiology, hematopathology, and molecular diagnostics. Additionally, the review addresses potential pitfalls of GAI paradigms. Data Sources.—Current literature on GAI in health care was reviewed broadly. The use case scenarios for each CP subspecialty review common data sources generated in each subspecialty. The potential for utilization of CP data in the GAI context was subsequently assessed, focusing on issues such as future reporting paradigms, impact on quality metrics, and potential for translational research activities. Conclusions.—GAI is a powerful tool with the potential to revolutionize health care for patients and practitioners alike. However, GAI must be implemented with much caution considering various shortcomings of the technology

such as biases, hallucinations, practical challenges of implementing GAI in existing CP workflows, and end-user acceptance. Human-in-the-loop models of GAI implementation have the potential to revolutionize CP by delivering deeper, meaningful insights into patient outcomes both at an individual and a population level.

25COASMA53:

Harnessing the Power of Generative Artificial Intelligence in Pathology Education: Opportunities, Challenges, and Future Directions

Matthew J. Cecchini, MD, PhD; Michael J. Borowitz, MD, PhD; Eric F. Glassy, MD

Arch Pathol Lab Med (2025) 149 (2): 142–151.
https://doi.org/10.5858/arpa.2024-0187-RA

Abstract: Context.—Generative artificial intelligence (AI) technologies are rapidly transforming numerous fields, including pathology, and hold significant potential to revolutionize educational approaches. Objective.—To explore the application of generative AI, particularly large language models and multimodal tools, for enhancing pathology education. We describe their potential to create personalized learning experiences, streamline content development, expand access to educational resources, and support both learners and educators throughout the training and practice continuum. Data Sources.—We draw on insights from existing literature on AI in education and the collective expertise of the coauthors within this rapidly evolving field. Case studies highlight practical applications of large language models, demonstrating both the potential benefits and unique challenges associated with implementing these technologies in pathology education. Conclusions.—Generative AI presents a powerful tool kit for enriching pathology education, offering opportunities for greater engagement, accessibility, and personalization. Careful consideration of ethical implications, potential risks, and appropriate mitigation strategies is essential for the responsible and effective integration of these technologies. Future success lies in fostering collaborative development between AI experts and medical educators, prioritizing ongoing human oversight and transparency to ensure that generative AI augments, rather than supplants, the vital role of educators in pathology training and practice.

Medical Oncology
(Chemotherapy, Hematology & Radiotherapy)

25COASMA1:

Title: Ameliorative effect of aqueous leaf extract of Pistacia lentiscus L. against oxaliplatin-induced hepatic injury, oxidative stress, and DNA damage in vitro and in vivo

Chouikh, N., Benguedouar, L., Chaabani, H. et al.

Med Oncol 42, 54 (2025).
Doi-https://doi.org/10.1007/s12032-025-02599-3

Abstract: The current study aimed to assess the preventive effects of aqueous leaf extract of Pistacia lentiscus (ALEPL) against Oxaliplatin (OXA)-induced DNA damage, hepatic injury, and oxidative stress. The in vitro cytotoxic and genotoxic effects of OXA and ALEPL on HCT116 colon cancer cells were evaluated using the MTT (Tetrazolium salt reduction) assay and comet assay. The in vivo study involved 24 female NMRI (Naval Medical Research Institute) mice that were equally divided into four groups as follows: Control group, ALEPL-treated group (100 mg/kg), OXA-treated group (7 mg/kg), and ALEPL-treated group (100mg/kg) + OXA (7mg/kg). All animals were sacrificed 48 h after OXA treatment. Samples of liver and blood were collected for histopathological, micronucleus, and biochemical analyses. Oxidative stress parameters were also evaluated through non-enzymatic and enzymatic antioxidant activities. Our findings demonstrated that ALEPL contains high phenolic compounds. In the MTT assay, OXA exerted the most potent cytotoxic effect, but ALEPL alone showed no toxic effect in HCT116 cells. Furthermore, OXA administration caused significant DNA fragmentation both in vitro and in vivo, elevated serum biochemical parameters, and confirmed acute liver damage through histopathological observations compared to the control group. OXA exposure also led to a decrease in hepatic glutathione (GSH) and an increase in lipid peroxidation and antioxidant enzyme activities. From the results of our study, ALEPL pretreatment significantly restored the hepatic toxicity and DNA damage as well as the oxidative stress profile induced by OXA.

25COASMA2:

Title: Enhanced antitumor efficacy of nanostructured lipid carrier co-loaded with docetaxel and 5-fluorouracil for targeted gastric cancer therapy

Alyami, H., Alharthi, S., Alqahtani, A.J. et al.

Med Oncol 42, 53 (2025).
Doi- https://doi.org/10.1007/s12032-025-02603-w

Abstract- This study presents nanostructured lipid carrier (NLC) co-loaded with Docetaxel (DCT) and 5-Fluorouracil (5-FU) as a targeted therapeutic approach for gastric cancer (GC). Using nanoprecipitation, NLC-DCT/5-FU were synthesized and exhibited an average particle size of 215.3 ± 10.4 nm, a polydispersity index (PDI) of 0.29, and a zeta potential of -17.1 mV. Encapsulation efficiency reached 95.9% for DCT and 5-FU, with a loading efficiency of 11.2%. In vitro release studies demonstrated a biphasic release profile, with an initial burst and sustained release, achieving 85.6% DCT and 75.8% 5-FU release over 72 h.

Cytotoxicity assays in MKN45 cells showed a significantly lower half-maximal inhibitory concentration (IC_{50}) for NLC-DCT/5-FU (0.3 µM) compared to free DCT (3.9 µM) and free 5-FU (19.5 µM), indicating enhanced efficacy. In vivo evaluation in a GC mouse model confirmed substantial tumor volume reduction to 213 mm^3 with NLC-DCT/5-FU treatment, compared to 432 mm^3 with the free-drug combination. Systemic safety assessment showed minimal adverse effects, suggesting the nanoparticles' enhanced therapeutic index. These results demonstrate that NLC-based co-delivery systems could substantially improve the clinical outcomes of GC therapy.

25COASMA3:

Title: Fusion of tumor cells and mesenchymal stem/stroma cells: a source of tumor heterogeneity, evolution and recurrence

Liu, Z., Wang, Y., Peng, Z. et al.

Med Oncol 42, 52 (2025)

Doi- https://doi.org/10.1007/s12032-024-02595-z

Abstract: The heterogeneity and evolution of tumors remain significant obstacles in cancer treatment, contributing to both therapy resistance and relapse. Mesenchymal stem/stromal cells (MSCs) are multipotent stromal cells within the tumor microenvironment that interact with tumor cells through various mechanisms, including cell fusion. While previous research has largely focused on the effects of MSC-tumor cell fusion on tumor proliferation, migration, and tumorigenicity, emerging evidence indicates that its role in tumor maintenance, evolution, and recurrence, particularly under stress conditions, may be even more pivotal. This review examines the connection between MSC-tumor cell fusion and several critical factors like tumor heterogeneity, cancer stem cells, and therapy resistance, highlighting the crucial role of cell fusion in tumor survival, evolution, and recurrence. Additionally, we explore potential therapeutic strategies aimed at targeting this process.

25COASMA4:

Title:The impact of apoptosis-inducing MAPK and glycolytic pathways modulated by Aloe vera and royal jelly in lung and colorectal cancer.

Kul Köprülü, T., Gezer, B. & Erkal Çam, B.

Med Oncol 42, 51 (2025).

Doi-https://doi.org/10.1007/s12032-025-02606-7

Abstract: Lung and colon cancer are among the most commonly diagnosed and fatal cancer types in the world. Due to their metastatic properties, they complicate the treatment process and pose a great threat to human health. These aggressive types of cancer are resistant to chemotherapy drugs. Therefore, it is extremely important to investigate the therapeutic effects of natural compounds. In our previous study, effective doses of Royal Jelly (RJ) (100 mg/mL) and Aloe vera (AVE) (20 µg/mL) were determined and tested separately and in combination on lung and colorectal cancer cells. Glycolytic capacities were determined using the Seahorse XFe24 Analyzer, total transcriptome profiles were sequenced using NovaSeq 6000, and BAX and BCL-2 gene levels were determined using RT-qPCR. It was seen that RJ and RJ + AVE affected glycolytic capacity and more genes in lung cancer cells. In HT29,

AVE alone was seen to reduce glycolytic capacity and RJ + AVE combination was seen to reduce the expression level of genes related to cell proliferation and cycle. After RJ + AVE treatments, the apoptotic process which is triggered via MAPK pathway was found in lung cancer. Moreover, BAX levels increased and BCL-2 levels decreased both lung and colorectal cancer cells. It was observed that the combination of RJ and AVE affected the glycolysis process, cell cycle, proliferation and apoptosis on lung and colorectal cancer. In particular, the combination of RJ + AVE was found to be more effective on lung cancer.

25COASMA5:

Title: Protocatechuic aldehyde sensitizes BRAF-mutant melanoma cells to temozolomide through inducing FANCD2 degradation.

Yang, J., Zeng, X., Pei, J. et al.

Med Oncol 42, 48 (2025).

Doi- https://doi.org/10.1007/s12032-025-02601-y

Abstract: Temozolomide (TMZ)-based chemotherapy is a primary regimen for melanoma patients who have failed targeted therapy or immunotherapy. However, the low response rate of TMZ-based chemotherapy challenges the patients' prognosis. $BRAF^{V600E}$ mutation is the most frequently mutated site in melanoma. This study investigates the synergistic effect of protocatechuic aldehyde (PA) and temozolomide (TMZ) in killing $BRAF^{V600E}$ mutant melanoma cells and BRAF inhibitor-resistant melanoma cells as well as the underlying molecular mechanisms. We report that PA synergistically promoted TMZ cytotoxicity to both BRAF inhibitor-sensitive and BRAF inhibitor-resistant melanoma cells. Combination of PA and TMZ increased DNA double-strand breaks and elevated apoptosis. Mechanism study reveals that PA promoted TMZ cytotoxicity through inducing FANCD2 degradation. Our results suggest that PA is a potential compound for melanoma combinational chemotherapy, regardless of O-6-methylguanine-DNA methyltransferase (MGMT) status.

25COASMA6:

Title: Boric acid impedes glioblastoma growth in a rat model: insights from multi-approach analysis.

Turkez, H., Alper, F., Bayram, C. et al.

Med Oncol 42, 47 (2025).

Doi- https://doi.org/10.1007/s12032-025-02600-z

Abstract: Limited advancements in managing malignant brain tumors have resulted in poor prognoses for glioblastoma (GBM) patients. Standard treatment involves surgery, radiotherapy, and chemotherapy, which lack specificity and damage healthy brain tissue. Boron-containing compounds, such as boric acid (BA), exhibit diverse biological effects, including anticancer properties. This study aimed to examine whether boron supplementation, as BA, can inhibit glioblastoma growth in a xenograft animal model. Using MRI-based tumor size measurement, survival rates, hematological, clinical biochemistry analyses, and genotoxicity parameters, we assessed the impact of BA. Histopathological, immunohistochemical, and immunofluorescence examinations were also conducted. All BA doses (3.25, 6.5, and 13 mg kg^{-1} b.w.) extended survival compared to GBM controls after

14 days, with a dose-dependent anti-GBM effect observed in MRI analyses. BA treatment improved hematological (WBC and PLT counts) and biochemical parameters (LDL-C, CREA, and ALP). Histopathological examination revealed a significant reduction in tumor diameter with 6.5 and 13 mg kg^{-1} BA. Immunohistochemical and immunofluorescence staining showed modulation of intracytoplasmic Ki67, cytoplasmic CMPK2, and GFAP expressions in tumor cells post-BA treatment. Additionally, BA did not increase micronuclei formations, indicating its non-genotoxic nature. In conclusion, targeting tumor suppressor networks with boron demonstrates significant therapeutic potential for GBM treatment.

25COASMA7:

Title: PYGO2 promotes resistance to chemotherapy via reducing apoptosis and G2/M cell cycle arrest in esophageal carcinoma cells.

Ardalan Moghadam Al, F., Forghanifard, M.M. & Zarrinpour, V.

Med Oncol 42, 45 (2025).

Doi- https://doi.org/10.1007/s12032-024-02590-4

Abstract: 5-FU is a widely used chemotherapy drug for esophageal carcinomas, but therapy failure has been observed in 5-FU-resistant patients. Overcoming this resistance is a significant challenge in cancer treatment, requiring identifying and targeting important resistance mechanisms. PYGO2 expression is crucial in developing resistance to various chemotherapy drugs. In this study, we aimed to investigate the impact of PYGO2 overexpression on the sensitivity of YM-1 and KYSE-30 esophageal carcinoma cells against 5-FU. To do this, we compared cell viability, cell cycle arrest, apoptosis rate, and mRNA expressions of various apoptosis-related genes between pcDNA3-PYGO2 transfected and untransfected KYSE-30 and YM-1 esophageal carcinoma cells following treatment with 5-FU. We showed that PYGO2 expression reduces 5-FU sensitivity in YM-1 and KYSE-30 cells. PYGO2-overexpressing cells treated with 5-FU have exhibited a noteworthy reduction in both early and late apoptotic cells compared to controls. Furthermore, a significant decrease in the Bax/Bcl2 ratio and P53 gene expression was observed. 5-FU induces G2/M cell cycle arrest in YM-1 and KYSE-30 cells. However, PYGO2 overexpression impeded G2/M cell cycle arrest in 5-FU-treated cells, thereby suppressing the toxicity of 5-FU. PYGO2 may mediate its apoptotic effect by regulating cell cycle regulatory proteins, specifically cyclin D1 and p21. These results highlight PYGO2's capacity to alter how esophageal cancer cells respond to 5-FU therapy, emphasizing its importance as a potential focal point for treatment strategies.

25COASMA8:

Title: Targeting the Hippo and Rap1 signaling pathways: the anti-proliferative effects of curcumin in colorectal cancer cell lines.

Sabir, D.K.

Med Oncol 42, 41 (2025).

Doi- https://doi.org/10.1007/s12032-024-02560-w

Abstract: CRC has the third-highest cancer incidence and death. Many human cancers, including colorectal cancer, are connected to abnormal signaling pathway gene expression.

Many human malignancies include Hippo and Rap1 signaling. This research examined curcumin's therapeutic effects on colorectal cancer cell lines' Hippo and Rap1 signaling pathway genes. The role of the above signaling pathways is considered in colorectal cancer development. No research has examined curcumin's influence on key genes in these pathways; thus, this work is meant to uncover its more precise mechanism. First, the gene expression omnibus database is queried to discover GSE8671, a dataset that contains differentially expressed genes associated in CRC formation. DAVID was used to discover the corporation of these genes and signaling pathways (Hippo and Rap1), and the cancer genome atlas (TCGA) database was utilized to select genes and assess their expression and biomarker potential. MTT, apoptosis, and quantitative PCR were used to assess whether curcumin is therapeutic for colorectal cancer cell lines. An in-silico analysis identified the dysregulation of several critical genes AXIN2, MYC, TEAD4, MET, LPAR1, and ADCY9 in colorectal cancer, highlighting their involvement in the Hippo and Rap1 signaling pathways. Experimental assessments, including MTT assays, apoptosis assays, and quantitative PCR (qPCR) analysis, demonstrated that the targeted modulation of these genes effectively inhibits cancer cell proliferation. Specifically, treatment with curcumin resulted in a significant reduction in cell viability in HT-29 and HCT-116 colorectal cancer cell lines, thereby facilitating apoptotic cell death. Furthermore, curcumin administration was associated with the upregulation of LPAR1 and ADCY9 gene expression, while concurrently downregulating AXIN2, MYC, TEAD4, and MET in both cell lines. This study reveals compelling evidence of curcumin's potent anticancer properties, highlighting its transformative influence on the Hippo and Rap1 signaling pathways within colorectal cancer cells. These findings not only underscore curcumin's potential as a therapeutic agent but also pave the way for innovative strategies in the fight against colorectal cancer.

25COASMA9:

Title: Study of the effect of zinc oxide, selenium, and silver nanoparticles on the expression level of oxidative stress-associated genes in ovarian cancer

Irannejad, F., Shahbazi, S., Reiisi, S. et al.

Med Oncol 42, 39 (2025).

Doi- https://doi.org/10.1007/s12032-024-02593-1

Abstract: Reactive oxygen species (ROS) generated by oxidative stress have emerged as critical factors in the pathophysiology of malignancies. This study investigated the antioxidant and anticancer properties of zinc (Zn), selenium (Se), and silver (Ag) nanoparticles (NPs) against the A2780 human ovarian cancer cell line. Here, the bioinformatics approach was used to determine the top differentially expressed genes associated with oxidative stress. The ZnO-, Se-, and Ag-NPs were then synthesized via a green synthesis method and subsequently characterized using techniques, such as FTIR, XRD, DLS, zeta potential analysis, FESEM, and TEM. The antioxidant capacity of the NPs was evaluated using a DPPH scavenging assay and their effect on superoxide dismutase enzyme activity was determined. HDF and A2780 cells were treated with varying concentrations of ZnO-, Se-, and Ag-NPs, and cell viability and colony formation were assessed using MTT and clonogenic assays, respectively. Additionally, qPCR was performed

to analyze the expression of the candidate genes NOX4, SOD2, and NR4A4. Characterization techniques confirmed the successful synthesis of pure, crystalline, and spherical NPs. Antioxidant assays demonstrated the significant antioxidant properties of ZnO-, Se-, and Ag-NPs. In vitro studies indicated that ZnO-, Se-, and Ag-NPs effectively inhibited cell proliferation and suppressed colony formation, likely owing to the downregulation of NOX4 and upregulation of SOD2 genes. Our findings suggest that ZnO-, Se-, and Ag-NPs may serve as promising anticancer agents for ovarian cancer and NOX4 downregulation and SOD2 upregulation can be proposed as oxidative stress biomarkers; however, further experimental investigation is required to elucidate the therapeutic potential of NPs and the early detection potential of biomarkers.

25COASMA10:

Title: Investigation of potential anti-metastatic effect of metformin and caffeic acid combination therapy in breast cancer cell line in in-vitro culture model

Yavuz, H., Tülüce, Y., Karakuş, F. et al.

Med Oncol 42, 38 (2025).

Doi- https://doi.org/10.1007/s12032-024-02592-2

Abstract: The invasion and metastasis of cancer cells transform localized cancers into systemic and life-threatening diseases, posing one of the most significant challenges in cancer treatment. This study tested the hypothesis that combined treatment with Caffeic acid (CA) and metformin (MTF) could inhibit or reduce effective signaling pathways involved in the proliferation, survival, and metastasis of MCF-7 breast cancer cells. Anti-proliferation analysis determined the IC50 values for MTF (4.5 mM) and CA (163 µM) after 72 h. Cell migration analysis showed that MTF and CA significantly inhibited MCF-7 cell migration by the 72nd hour, both alone and in combination, without affecting HME1 healthy cell migration from the 48th hour. Colony formation analysis revealed that CA completely inhibited colony formation in MCF-7 cells, while MTF reduced it by 19%. ELISA results indicated that neither CA nor MTF affected the levels of VEGF-A, E-cadherin, or TINAGL-1 proteins, which are involved in MCF-7 cell migration and invasion. However, MTF significantly reduced IL-1β protein levels, and CA significantly reduced IL-4 protein levels in MCF-7 cells. RT-qPCR results largely supported the ELISA findings. Overall, CA and MTF exhibited potential to inhibit MCF-7 cell apoptosis, migration, tumor microenvironment modulation, and metastasis.

25COASMA11:

Title: Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

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N Engl J Med 2025;392:531-543, VOL. 392 NO. 6

DOI**: https://doi.org/10.1056/NEJMoa2410316**

Abstract: The alternative complement pathway plays a key role in the pathogenesis of IgA nephropathy. Iptacopan specifically binds to factor B and inhibits the alternative pathway. In this phase 3, double-blind, randomized, placebo-controlled trial, we enrolled adults with

biopsy-confirmed IgA nephropathy and proteinuria with a 24-hour urinary protein-to-creatinine ratio of 1 or higher (with protein and creatinine both measured in grams) despite optimized supportive therapy. Patients were randomly assigned, in a 1:1 ratio, to receive oral iptacopan (200 mg) or placebo twice daily for 24 months while continuing to receive supportive therapy. The primary objective of this prespecified interim analysis was to assess the efficacy of iptacopan as compared with that of placebo in reducing proteinuria at month 9; the primary end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at month 9. The proportion of patients who had a 24-hour urinary protein-to-creatinine ratio of less than 1 at month 9 without receiving rescue or alternative medication or undergoing kidney-replacement therapy (dialysis or transplantation) was a secondary end point. Safety was also assessed. The effect of iptacopan on kidney function will be assessed at the end of the 2-year double-blind treatment period. The main trial population included 222 patients in the iptacopan group and 221 in the placebo group. The interim efficacy analysis included the first 250 patients who underwent randomization in the main trial population (125 patients in each group) and who remained in the trial until month 9 or discontinued the trial by month 9. Safety was assessed in all the patients in the main trial population. At month 9, the adjusted geometric mean 24-hour urinary protein-to-creatinine ratio was 38.3% (95% confidence interval, 26.0 to 48.6; two-sided $P<0.001$) lower with iptacopan than with placebo. The reduction in proteinuria was supported by consistent results in secondary end point analyses. There were no unexpected safety findings with iptacopan. The incidence of adverse events that occurred during the treatment period was similar in the two groups; most events were mild to moderate in severity and reversible. No increased risk of infection was observed.

Among patients with IgA nephropathy, treatment with iptacopan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo.

25COASMA12:

Title: Atrasentan in Patients with IgA Nephropathy

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N Engl J Med 2025;392:544-554VOL. 392 NO. 6

DOI: **https://doi.org/10.1056/NEJMoa2409415**

Abstract: Patients with IgA nephropathy and severe proteinuria have a high lifetime risk of kidney failure. The efficacy and safety of the selective endothelin type A receptor antagonist atrasentan in reducing proteinuria in patients with IgA nephropathy are incompletely understood. We are conducting a phase 3, multinational, double-blind, randomized, controlled trial involving adults with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area. Patients were randomly assigned to receive atrasentan (0.75 mg per day) or matched placebo for 132 weeks. The primary outcome, assessed at a prespecified interim analysis of data from the first 270 patients in the main stratum, was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36; the change was estimated with the use of a repeated-measures model. (An

exploratory stratum of patients who were receiving a sodium–glucose cotransporter 2 inhibitor were included in a separate analysis.) Safety analyses were based on adverse events across the entire main stratum. A total of 340 patients were recruited into the main stratum. Among the first 270 patients in the main stratum (135 per trial group) who completed the week 36 visit, the geometric mean percentage change in the urinary protein-to-creatinine ratio relative to baseline was significantly greater with atrasentan (−38.1%) than with placebo (−3.1%), with a geometric mean between-group difference of −36.1 percentage points (95% confidence interval, −44.6 to −26.4; P<0.001). The percentage of patients with adverse events did not differ substantially between the two groups. Fluid retention was reported by 19 of 169 patients (11.2%) in the atrasentan group and in 14 of 170 (8.2%) in the placebo group but did not lead to discontinuation of the trial regimen. No apparent cases of cardiac failure or severe edema occurred. In this prespecified interim analysis, atrasentan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo in patients with IgA nephropathy.

25COASMA13:

Title: Liraglutide for Children 6 to <12 Years of Age with Obesity — A Randomized Trial

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N Engl J Med 2025;392:555-565, VOL. 392 NO. 6

DOI**: https://doi.org/10.1056/NEJMoa2407379**

Abstract: No medications are currently approved for the treatment of nonmonogenic, nonsyndromic obesity in children younger than 12 years of age. Although the use of liraglutide has been shown to induce weight loss in adults and adolescents with obesity, its safety and efficacy have not been established in children. In this phase 3a trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we randomly assigned children (6 to <12 years of age) with obesity, in a 2:1 ratio, to receive either once-daily subcutaneous liraglutide at a dose of 3.0 mg (or the maximum tolerated dose) or placebo, plus lifestyle interventions. The primary end point was the percentage change in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters). The confirmatory secondary end points were the percentage change in body weight and a reduction in BMI of at least 5%. A total of 82 participants underwent randomization; 56 were assigned to the liraglutide group and 26 to the placebo group. At week 56, the mean percentage change from baseline in BMI was −5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of −7.4 percentage points (95% confidence interval [CI], −11.6 to −3.2; P<0.001). The mean percentage change in body weight was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of −8.4 percentage points (95% CI, −13.4 to −3.3; P=0.001), and a reduction in BMI of at least 5% occurred in 46% of participants in the liraglutide group and in 9% of participants in the placebo group (adjusted odds ratio, 6.3 [95% CI, 1.4 to 28.8]; P=0.02). Adverse events occurred in 89% and 88% of participants in the liraglutide and placebo groups, respectively. Gastrointestinal adverse events were more common in the liraglutide group (80% vs. 54%); serious adverse

events were reported in 12% and 8% of participants in the liraglutide and placebo groups, respectively. Among children (6 to <12 years of age) with obesity, treatment with liraglutide for 56 weeks plus lifestyle interventions resulted in a greater reduction in BMI than placebo plus lifestyle interventions.

25COASMA14:

Title: Efficacy of Zenocutuzumab in NRG1 Fusion–Positive Cancer

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N Engl J Med 2025;392:566-576, VOL. 392 NO. 6

DOI: **https://doi.org/10.1056/NEJMoa2405008**

Abstract: Neuregulin 1 (NRG1) fusions are recurrent oncogenic drivers found in multiple solid tumors. NRG1 binds to human epidermal growth factor receptor 3 (HER3), leading to heterodimerization with HER2 and activation of downstream growth and proliferation pathways. The efficacy and safety of zenocutuzumab, a bispecific antibody against HER2 and HER3, in patients with NRG1 fusion–positive solid tumors are unclear. In this registrational, phase 2 clinical study, we assigned patients with advanced NRG1 fusion–positive cancer involving any tumor type to receive zenocutuzumab at a dose of 750 mg intravenously every 2 weeks. The primary end point was overall response (complete or partial response) according to investigator assessment. Secondary end points included duration of response, progression-free survival, and safety. A total of 204 patients with 12 tumor types were enrolled and treated. Among 158 patients who had measurable disease and were enrolled at least 24 weeks before the data-cutoff date, a response occurred in 30% (95% confidence interval [CI], 23 to 37). The median duration of response was 11.1 months (95% CI, 7.4 to 12.9); 19% of responses were ongoing at the data-cutoff date. Responses were observed in multiple tumor types — including in 27 of 93 patients (29%; 95% CI, 20 to 39) with non–small-cell lung cancer (NSCLC) and 15 of 36 patients (42%; 95% CI, 25 to 59) with pancreatic cancer — and across multiple NRG1 fusion partners. The median progression-free survival was 6.8 months (95% CI, 5.5 to 9.1). Adverse events were primarily grade 1 or 2. The most common adverse events that were considered by the investigator to be related to zenocutuzumab were diarrhea (in 18% of the patients), fatigue (in 12%), and nausea (in 11%). Infusion-related reactions (composite term) were observed in 14% of the patients. One patient discontinued zenocutuzumab owing to a treatment-related adverse event. Zenocutuzumab showed efficacy in patients with advanced NRG1 fusion–positive cancer, notably NSCLC and pancreatic cancer, with mainly low-grade adverse events.

25COASMA15:

Title: CD4+ T-Cell Lymphoma Harboring a Chimeric Antigen Receptor Integration in TP53

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N Engl J Med 2025;392:577-583, VOL. 392 NO. 6

DOI**: https://doi.org/10.1056/NEJMoa2411507**

Abstract: Malignant T-cell transformation after chimeric antigen receptor (CAR) T-cell therapy has been described, but the contribution of CAR integration to oncogenesis is not clear. Here we report a case of a T-cell lymphoma harboring a lentiviral integration in a known tumor suppressor, TP53, which developed in a patient with multiple myeloma after B-cell maturation antigen (BCMA) CAR T-cell therapy.CAR T-cell therapies have shown remarkable efficacy and are now approved for several hematologic cancers.[1] These cellular therapies are typically manufactured with the use of viral vectors for integration of the CAR into T cells.[2] Although T-cell cancer after CAR T-cell therapy is rare, several cases have been reported.[3-8] The exact causes of secondary T-cell cancers are uncertain, but one potential mechanism is insertional mutagenesis in T cells. In most T-cell cancers after CAR T-cell therapy reported to date, the vector integrations occurred in genes of unclear oncogenic potential, which makes it difficult to establish a causal association with tumorigenesis.[4,8] Here, we describe a case of T-cell lymphoma of the gastrointestinal (GI) tract occurring several weeks after treatment with ciltacabtagene autoleucel (cilta-cel), a BCMA CAR T-cell therapy for multiple myeloma. This tumor appears to be a cancer associated with integration of the CAR vector within a canonical tumor-suppressor gene (TP53, which encodes tumor protein p53).

25COASMA16:

Title: Colchicine in Acute Myocardial Infarction

Sanjit S. Jolly, M.D. , Marc-André d'Entremont, M.D., M.P.H., Shun Fu Lee, Ph.D ., Rajibul Mian, Ph.D.,

N Engl J Med 2025;392:633-642, VOL. 392 NO. 7

DOI**: https://doi.org/10.1056/NEJMoa2405922**

Abstract: Inflammation is associated with adverse cardiovascular events. Data from recent trials suggest that colchicine reduces the risk of cardiovascular events.In this multicenter trial with a 2-by-2 factorial design, we randomly assigned patients who had myocardial infarction to receive either colchicine or placebo and either spironolactone or placebo. The results of the colchicine trial are reported here. The primary efficacy outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization, evaluated in a time-to-event analysis. C-reactive protein was measured at 3 months in a subgroup of patients, and safety was also assessed. A total of 7062 patients at 104 centers in 14 countries underwent randomization; at the time of analysis, the vital status was unknown for 45 patients (0.6%), and this information was most likely missing at random. A primary-outcome event occurred in 322 of 3528 patients (9.1%) in the colchicine group and 327 of 3534 patients (9.3%) in the placebo group over a median follow-up period of 3 years (hazard ratio, 0.99; 95% confidence interval [CI], 0.85 to 1.16; P=0.93). The incidence of individual components of the primary outcome appeared to be similar in the two groups. The least-squares mean difference in C-reactive protein levels between the colchicine group and the placebo group at 3 months, adjusted according to the baseline values, was −1.28 mg per liter (95% CI, −1.81 to −0.75). Diarrhea occurred in a higher percentage of patients with colchicine than with placebo (10.2% vs. 6.6%; P<0.001), but the incidence of serious infections did not differ between groups. Among patients who had

myocardial infarction, treatment with colchicine, when started soon after myocardial infarction and continued for a median of 3 years, did not reduce the incidence of the composite primary outcome (death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization).

25COASMA17:

Title: Routine Spironolactone in Acute Myocardial Infarction

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N Engl J Med 2025;392:643-652, VOL. 392 NO. 7

DOI**: https://doi.org/10.1056/NEJMoa2405923**

Abstract: Mineralocorticoid receptor antagonists have been shown to reduce mortality in patients after myocardial infarction with congestive heart failure. Whether routine use of spironolactone is beneficial after myocardial infarction is uncertain. In this multicenter trial with a 2-by-2 factorial design, we randomly assigned patients with myocardial infarction who had undergone percutaneous coronary intervention to receive either spironolactone or placebo and either colchicine or placebo. The results of the spironolactone trial are reported here. The two primary outcomes were a composite of death from cardiovascular causes or new or worsening heart failure, evaluated as the total number of events; and a composite of the first occurrence of myocardial infarction, stroke, new or worsening heart failure, or death from cardiovascular causes. Safety was also assessed. We enrolled 7062 patients at 104 centers in 14 countries; 3537 patients were assigned to receive spironolactone and 3525 to receive placebo. At the time of our analyses, the vital status was unknown for 45 patients (0.6%). For the first primary outcome, there were 183 events (1.7 per 100 patient-years) in the spironolactone group as compared with 220 events (2.1 per 100 patient-years) in the placebo group over a median follow-up period of 3 years (hazard ratio adjusted for competing risk of death from noncardiovascular causes, 0.91; 95% confidence interval [CI], 0.69 to 1.21; P=0.51). With respect to the second primary outcome, an event occurred in 280 of 3537 patients (7.9%) in the spironolactone group and 294 of 3525 patients (8.3%) in the placebo group (hazard ratio adjusted for competing risk, 0.96; 95% CI, 0.81 to 1.13; P=0.60). Serious adverse events were reported in 255 patients (7.2%) in the spironolactone group and 241 (6.8%) in the placebo group. Among patients with myocardial infarction, spironolactone did not reduce the incidence of death from cardiovascular causes or new or worsening heart failure or the incidence of a composite of death from cardiovascular causes, myocardial infarction, stroke, or new or worsening heart failure.

25COASMA18:

Title: Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors

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N Engl J Med 2025;392:653-665, VOL. 392 NO. 7

DOI**: https://doi.org/10.1056/NEJMoa2403991**

Abstract: Treatment options for patients with advanced neuroendocrine tumors are limited.

The efficacy of cabozantinib in the treatment of previously treated, progressive extrapancreatic or pancreatic neuroendocrine tumors is unclear. We enrolled two independent cohorts of patients — those with extrapancreatic neuroendocrine tumors and those with pancreatic neuroendocrine tumors — who had received peptide receptor radionuclide therapy or targeted therapy or both. Patients were randomly assigned in a 2:1 ratio to receive cabozantinib at a dose of 60 mg daily or placebo. The primary end point was progression-free survival as assessed by blinded independent central review. Key secondary end points included objective response, overall survival, and safety. In the cohort of 203 patients with extrapancreatic neuroendocrine tumors, the median progression-free survival with cabozantinib was 8.4 months, as compared with 3.9 months with placebo (stratified hazard ratio for progression or death, 0.38; 95% confidence interval [CI], 0.25 to 0.59; P<0.001). In the cohort of 95 patients with pancreatic neuroendocrine tumors, the median progression-free survival with cabozantinib was 13.8 months, as compared with 4.4 months with placebo (stratified hazard ratio, 0.23; 95% CI, 0.12 to 0.42; P<0.001). The incidence of confirmed objective response with cabozantinib was 5% and 19% among patients with extrapancreatic and pancreatic neuroendocrine tumors, respectively, as compared with 0% with placebo. Grade 3 or higher adverse events were noted in 62 to 65% of the patients treated with cabozantinib, as compared with 23 to 27% of the patients who received placebo. Common treatment-related adverse events of grade 3 or higher included hypertension, fatigue, diarrhea, and thromboembolic events. Cabozantinib, as compared with placebo, significantly improved progression-free survival in patients with previously treated, progressive advanced extrapancreatic or pancreatic neuroendocrine tumors. Adverse events were consistent with the known safety profile of cabozantinib.

25COASMA19:

Title: Evolving Epidemiology of Mpox in Africa in 2024

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N Engl J Med 2025;392:666-676, VOL. 392 NO. 7

DOI: **https://doi.org/10.1056/NEJMoa2411368**

Abstract: For decades after the identification of mpox in humans in the Democratic Republic of Congo (DRC) in 1970, the disease was largely confined to the rural areas of Central and West Africa and thus did not garner broad attention. On August 13, 2024, mpox was declared a Public Health Emergency of Continental Security (PHECS) by the Africa Centers for Disease Control and Prevention (Africa CDC), a notice that was followed the next day by a declaration of a Public Health Emergency of International Concern (PHEIC) by the World Health Organization. In this study we analyzed all mpox cases and deaths, based on clinical or laboratory diagnosis, that were reported to the Africa CDC from January 1, 2022, to October 30, 2024, to identify temporal variations, geographic distributions, and epidemiologic trends. From January 1, 2022, to August 18, 2024, a total of 45,652 mpox cases were clinically diagnosed and laboratory-confirmed in 12 African countries. These cases resulted in 1492 deaths (case fatality rate, 3.3%). From 2022 to 2024, weekly laboratory-confirmed mpox cases increased by a factor of 2.8 (from 176 to 489 cases),

whereas all weekly reported cases (including those with a clinical diagnosis) increased by a factor of 4.3 (from 669 to 2900 cases). The DRC, which had reported approximately 88% of mpox cases in Africa in 2024, had 19,513 cases before the emergency declaration, with a case fatality rate of 3.1% — a weekly average of 591 cases as compared with 281 in 2023. In 2024, six African countries reported their first imported mpox infections, with Burundi also reporting local transmission. The high mpox disease burden in Africa, especially in the DRC — with a rising number of cases, high case fatality rate, and high degree of spread to other previously mpox-free African countries — is cause for increased international concern. Case detection, contact tracing, public health measures, and affordable vaccines are needed to implement interventions in the DRC to reduce the risk of global spread of the virus.

25COASMA20:

Title: CAR+ T-Cell Lymphoma after Cilta-cel Therapy for Relapsed or Refractory Myeloma

Simon J. Harrison, M.B., B.S., Ph.D Cyrille Touzeau, M.D., Ph.D., Nicolas Kint, M.D., Ph.D., Katherine Li, M.S.,

N Engl J Med 2025;392:677-685, VOL. 392 NO. 7

DOI**: https://doi.org/10.1056/NEJMoa2309728**

Abstract: We describe two patients in whom malignant monoclonal T-cell lymphoproliferation developed after administration of chimeric antigen receptor (CAR) T-cell therapy with ciltacabtagene autoleucel (cilta-cel) in the phase 3 CARTITUDE-4 trial. Monoclonal T cells from both patients had detectable CAR transgene expression and integration. The clinicogenomic features of these CAR transgenic T-cell lymphoproliferative neoplasms suggest that multiple potential intrinsic or extrinsic factors (or both) contributed to their pathogenesis, such as transduction of preexisting TET2-mutated T cells, followed by acquisition of further oncogenic genomic variants. Other potential contributors include germline genomic variation, viral infections, and previous treatment for myeloma. In the absence of direct evidence, the contribution of insertional mutagenesis to the development of T-cell lymphoma is currently unclear. (Funded by Johnson & Johnson and Legend Biotech USA; CARTITUDE-4 ClinicalTrials.gov number, NCT04181827.)

25COASMA21:

Title: Catheter Ablation or Antiarrhythmic Drugs for Ventricular Tachycardia

John L. Sapp, M.D. , Anthony S.L. Tang, M.D., Ratika Parkash, M.D., William G. Stevenson, M.D.,

N Engl J Med 2025;392:737-747, VOL. 392 NO. 8

DOI**: https://doi.org/10.1056/NEJMoa2409501**

Abstract: Patients with ventricular tachycardia and ischemic cardiomyopathy are at high risk for adverse outcomes. Catheter ablation is commonly used when antiarrhythmic drugs do not suppress ventricular tachycardia. Whether catheter ablation is more effective than antiarrhythmic drugs as a first-line therapy in patients with ventricular tachycardia is uncertain. In an international trial, we randomly assigned in a 1:1 ratio patients with previous

myocardial infarction and clinically significant ventricular tachycardia (defined as ventricular tachycardia storm, receipt of appropriate implantable cardioverter–defibrillator [ICD] shock or antitachycardia pacing, or sustained ventricular tachycardia terminated by emergency treatment) to receive antiarrhythmic drug therapy or to undergo catheter ablation. All the patients had an ICD. Catheter ablation was performed within 14 days after randomization; sotalol or amiodarone was administered as antiarrhythmic drug therapy according to prespecified criteria. The primary end point was a composite of death from any cause during follow-up or, more than 14 days after randomization, ventricular tachycardia storm, appropriate ICD shock, or sustained ventricular tachycardia treated by medical intervention. A total of 416 patients were followed for a median of 4.3 years. A primary end-point event occurred in 103 of 203 patients (50.7%) assigned to catheter ablation and in 129 of 213 (60.6%) assigned to drug therapy (hazard ratio, 0.75; 95% confidence interval, 0.58 to 0.97; P=0.03). Among patients in the catheter ablation group, adverse events within 30 days after the procedure included death in 2 patients (1.0%) and nonfatal adverse events in 23 patients (11.3%). Among the patients assigned to drug therapy, adverse events that were attributed to antiarrhythmic drug treatment included death from pulmonary toxic effects in 1 patient (0.5%) and nonfatal adverse events in 46 patients (21.6%). Among patients with ischemic cardiomyopathy and ventricular tachycardia, an initial strategy of catheter ablation led to a lower risk of a composite primary end-point event than antiarrhythmic drug therapy.

25COASMA22:

Title: Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia

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N Engl J Med 2025;392:748-762, VOL. 392 NO. 8

DOI**: https://doi.org/10.1056/NEJMoa2409804**

Abstract: Whether fixed-duration acalabrutinib–venetoclax (with or without obinutuzumab) would result in better progression-free survival than chemoimmunotherapy in patients with untreated chronic lymphocytic leukemia (CLL) is unknown.In this phase 3, open-label trial, we included patients 18 years of age or older who had an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (range, 0 to 5, with higher numbers indicating greater disability) and who did not have a 17p deletion or TP53 mutation. Patients were randomly assigned, in a 1:1:1 ratio, to receive acalabrutinib–venetoclax (acalabrutinib, cycles 1 to 14; venetoclax, cycles 3 to 14), acalabrutinib–venetoclax–obinutuzumab (as above, plus obinutuzumab, cycles 2 to 7), or chemoimmunotherapy with the investigator's choice of fludarabine–cyclophosphamide–rituximab or bendamustine–rituximab (cycles 1 to 6). The primary end point was progression-free survival (acalabrutinib–venetoclax vs. chemoimmunotherapy) in the intention-to-treat population, assessed by blinded independent central review. A total of 867 patients underwent randomization: 291 were assigned to receive acalabrutinib–venetoclax, 286 acalabrutinib–venetoclax–obinutuzumab, and 290 chemoimmunotherapy (of whom 143 received fludarabine–cyclophosphamide–rituximab and 147 bendamustine–rituximab). The median age of the patients was 61 years (range, 26 to 86),

64.5% were men, and 58.6% had unmutated IGHV. Estimated 36-month progression-free survival at a median follow-up of 40.8 months was 76.5% with acalabrutinib–venetoclax, 83.1% with acalabrutinib–venetoclax–obinutuzumab, and 66.5% with chemoimmunotherapy (hazard ratio for disease progression or death with acalabrutinib–venetoclax vs. chemoimmunotherapy, 0.65 [95% confidence interval {CI}, 0.49 to 0.87], P=0.004; for the comparison of acalabrutinib–venetoclax–obinutuzumab with chemoimmunotherapy, P<0.001). Estimated 36-month overall survival was 94.1% with acalabrutinib–venetoclax, 87.7% with acalabrutinib–venetoclax–obinutuzumab, and 85.9% with chemoimmunotherapy. Neutropenia, the most common adverse event of clinical interest of grade 3 or higher, was reported in 32.3%, 46.1%, and 43.2% in the three groups, respectively; death from coronavirus disease 2019 was reported in 10, 25, and 21 patients in the three groups.
Acalabrutinib–venetoclax with or without obinutuzumab significantly prolonged progression-free survival as compared with chemoimmunotherapy in fit patients with previously untreated CLL.

25COASMA23:

Title: Microvascular Inflammation of Kidney Allografts and Clinical Outcomes

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N Engl J Med 2025;392:763-776, VOL. 392 NO. 8
DOI**: https://doi.org/10.1056/NEJMoa2408835**

Abstract: The heterogeneous clinical presentation of graft microvascular inflammation poses a major challenge to successful kidney transplantation. The effect of microvascular inflammation on allograft outcomes is unclear. We conducted a cohort study that included kidney-transplant recipients from more than 30 transplantation centers in Europe and North America who had undergone allograft biopsy between 2004 and 2023. We integrated clinical and pathological data to classify biopsy specimens according to the 2022 Banff Classification of Renal Allograft Pathology, which includes two new diagnostic categories: probable antibody-mediated rejection and microvascular inflammation without evidence of an antibody-mediated response. We then assessed the association between the newly recognized microvascular inflammation phenotypes and allograft survival and disease progression. A total of 16,293 kidney-transplant biopsy specimens from 6798 patients were assessed. We identified the newly recognized microvascular inflammation phenotypes in 788 specimens, of which 641 were previously categorized as specimens with no evidence of rejection. As compared with patients without rejection, the hazard ratio for graft loss was 2.1 (95% confidence interval [CI], 1.5 to 3.1) among patients with microvascular inflammation without evidence of an antibody-mediated response and 2.7 (95% CI, 2.2 to 3.3) among patients with antibody-mediated rejection. Patients with a diagnosis of probable antibody-mediated rejection had a higher risk of graft failure beyond year 5 after biopsy than those without rejection (hazard ratio, 1.7; 95% CI, 0.8 to 3.5). Patients with a diagnosis of either newly recognized microvascular inflammation phenotype had a higher risk of progression of transplant glomerulopathy during follow-up than patients without microvascular inflammation. Microvascular inflammation in kidney allografts includes distinct phenotypes,

with various disease progression and allograft outcomes. Our findings support the clinical use of additional rejection phenotypes to standardize diagnostics for kidney allografts.

25COASMA24:

Title: Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group

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Abstract: m In the EMPA-KIDNEY trial, empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, had positive cardiorenal effects in patients with chronic kidney disease who were at risk for disease progression. Post-trial follow-up was designed to assess how the effects of empagliflozin would evolve after the discontinuation of the trial drug. In the active trial, patients with chronic kidney disease were randomly assigned to receive either empagliflozin (10 mg once daily) or matching placebo and were followed for a median of 2 years. All the patients had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area or an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Subsequently, surviving patients who consented were observed for 2 additional years. No trial empagliflozin or placebo was administered during the post-trial period, but local practitioners could prescribe open-label SGLT2 inhibitors, including open-label empagliflozin. The primary composite outcome was kidney disease progression or cardiovascular death as assessed from the start of the active-trial period to the end of the post-trial period. Of the 6609 patients who had undergone randomization in the active trial, 4891 (74%) were enrolled in the post-trial period. During this period, the use of open-label SGLT2 inhibitors was similar in the two groups (43% in the empagliflozin group and 40% in the placebo group). During the combined active- and post-trial periods, a primary-outcome event occurred in 865 of 3304 patients (26.2%) in the empagliflozin group and in 1001 of 3305 patients (30.3%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.72 to 0.87). During the post-trial period only, the hazard ratio for a primary-outcome event was 0.87 (95% CI, 0.76 to 0.99). During the combined periods, the risk of kidney disease progression was 23.5% in the empagliflozin group and 27.1% in the placebo group; the risk of the composite of death or end-stage kidney disease was 16.9% and 19.6%, respectively; and the risk of cardiovascular death was 3.8% and 4.9%, respectively. There was no effect of empagliflozin on death from noncardiovascular causes (5.3% in both groups). In a broad range of patients with chronic kidney disease at risk for progression, empagliflozin continued to have additional cardiorenal benefits for up to 12 months after it was discontinued.

25COASMA25:

Title: Low-Dose Yellow Fever Vaccine in Adults in Africa

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Abstract: Yellow fever vaccine is highly effective with a single dose, but vaccine supply is limited. The minimum dose requirements for seroconversion remain unknown.In this double-blind, randomized, noninferiority trial in Uganda and Kenya, we assigned adults with no history of yellow fever vaccination or infection to receive vaccination with the Institut Pasteur de Dakar 17D-204 yellow fever vaccine at a standard dose (13,803 IU) or at a fractional dose of 1000 IU, 500 IU, or 250 IU. The primary outcome was seroconversion at 28 days after vaccination with each fractional dose as compared with the standard dose, evaluated in a noninferiority analysis. Seroconversion was defined as an antibody titer at day 28 that was at least four times as high as the antibody titer before vaccination, as measured by a plaque reduction neutralization test. We conducted noninferiority analyses in the per-protocol and intention-to-treat populations. Noninferiority was shown if the lower boundary of the 95% confidence interval for the difference in the incidence of seroconversion between the fractional dose and the standard dose was higher than −10 percentage points. RESULTS
A total of 480 participants underwent randomization (120 participants in each group). The incidence of seroconversion was 98% (95% confidence interval [CI], 94 to 100) with the standard dose. The difference in the incidence of seroconversion between the 1000-IU dose and the standard dose was 0.01 percentage points (95% CI, −5.0 to 5.1) in the intention-to-treat population and −1.9 percentage points (95% CI, −7.0 to 3.2) in the per-protocol population; the corresponding differences between the 500-IU dose and the standard dose were 0.01 percentage points (95% CI, −5.0 to 5.1) and −1.8 percentage points (95% CI, −6.7 to 3.2), and those between the 250-IU dose and the standard dose were −4.4 percentage points (95% CI, −9.4 to 0.7) and −6.7 percentage points (95% CI, −11.7 to 1.6). A total of 111 vaccine-related adverse events were reported: 103 were mild in severity, 7 were moderate, and 1 was severe. The incidence of adverse events was similar in the four groups. A yellow fever vaccination dose as low as 500 IU was noninferior to the standard dose of 13,803 IU for producing seroconversion within 28 days.

25COASMA26:

Title: Highly Pathogenic Avian Influenza A(H5N1) Virus Infections in Humans

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Abstract: Highly pathogenic avian influenza A(H5N1) viruses have caused widespread infections in dairy cows and poultry in the United States, with sporadic human cases. We describe characteristics of human A(H5N1) cases identified from March through October 2024 in the United States. We analyzed data from persons with laboratory-confirmed A(H5N1) virus infection using a standardized case-report form linked to laboratory results from the Centers for Disease Control and Prevention influenza A/H5 subtyping kit. Of 46 case patients, 20 were exposed to infected poultry, 25 were exposed to infected or presumably infected dairy cows, and 1 had no identified exposure; that patient was hospitalized with nonrespiratory symptoms, and A(H5N1) virus infection was detected

through routine surveillance. Among the 45 case patients with animal exposures, the median age was 34 years, and all had mild A(H5N1) illness; none were hospitalized, and none died. A total of 42 patients (93%) had conjunctivitis, 22 (49%) had fever, and 16 (36%) had respiratory symptoms; 15 (33%) had conjunctivitis only. The median duration of illness among 16 patients with available data was 4 days (range, 1 to 8). Most patients (87%) received oseltamivir; oseltamivir was started a median of 2 days after symptom onset. No additional cases were identified among the 97 household contacts of case patients with animal exposures. The types of personal protective equipment (PPE) that were most commonly used by workers exposed to infected animals were gloves (71%), eye protection (60%), and face masks (47%). In the cases identified to date, A(H5N1) viruses generally caused mild illness, mostly conjunctivitis, of short duration, predominantly in U.S. adults exposed to infected animals; most patients received prompt antiviral treatment. No evidence of human-to-human A(H5N1) transmission was identified. PPE use among occupationally exposed persons was suboptimal, which suggests that additional strategies are needed to reduce exposure risk.

25COASMA27:

Title: Embolization of the Middle Meningeal Artery for Chronic Subdural Hematoma

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N Engl J Med 2025;392:855-864, VOL. 392 NO. 9

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Abstract: Patients receiving standard treatment for chronic subdural hematoma have a high risk of treatment failure. The effect of adjunctive middle meningeal artery embolization on the risk of treatment failure in this population remains unknown. We randomly assigned patients with symptomatic chronic subdural hematoma to undergo middle meningeal artery embolization as an adjunct to standard treatment (embolization group) or to receive standard treatment alone (control group). Either surgical or nonsurgical standard treatment had been chosen for each patient before randomization. The primary efficacy outcome was a composite of the following events: recurrent or residual chronic subdural hematoma (measuring >10 mm) at 180 days; reoperation or surgical rescue within 180 days; or major disabling stroke, myocardial infarction, or death from neurologic causes within 180 days. The primary safety outcome was a composite of major disabling stroke or death from any cause within 30 days.

25COASMA28:

Title: Oral Infigratinib Therapy in Children with Achondroplasia

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N Engl J Med 2025;392:865-874, VOL. 392 NO. 9

DOI**: https://doi.org/10.1056/NEJMoa2411790**

Abstract: Achondroplasia is a genetic skeletal condition that results in disproportionately short stature and medical complications throughout life. Infigratinib is an orally bioavailable

FGFR1–3 selective tyrosine kinase inhibitor in development for achondroplasia. In this phase 2 dose-finding study, we evaluated the safety and efficacy of oral infigratinib in children with achondroplasia between the ages of 3 and 11 years. A total of 72 children were enrolled in five sequential cohorts to receive daily infigratinib at doses of 0.016 mg per kilogram of body weight (cohort 1), 0.032 mg per kilogram (cohort 2), 0.064 mg per kilogram (cohort 3), 0.128 mg per kilogram (cohort 4), and 0.25 mg per kilogram (cohort 5) for 6 months, followed by 12 months of extended treatment in which the dose in cohorts 1 and 2 could be escalated to the next ascending level at months 6 and 12. The primary safety outcome was the incidence of adverse events that led to a decrease in the dose or discontinuation of infigratinib. The primary efficacy outcome was the change from baseline in the annualized height velocity. During treatment, all the children had at least one adverse event, most of which were mild or moderate in severity; none resulted in treatment discontinuation. In cohort 5, an increased annualized height velocity was observed, which persisted throughout the duration of the study, with a mean change from baseline at 18 months of 2.50 cm per year (95% confidence interval [CI], 1.22 to 3.79; P=0.001). The mean change from baseline in height z score was 0.54 (95% CI, 0.35 to 0.72) relative to an untreated achondroplasia reference population at 18 months; the mean change from baseline in the upper-to-lower body segment ratio was −0.12 (95% CI, −0.18 to −0.06). The administration of oral infigratinib did not result in any apparent major safety signal and increased the annualized height velocity and z score and decreased the upper-to-lower body segment ratio at 18 months of treatment in cohort 5.

25COASMA29:

Title:Blinatumomab in Standard-Risk B-Cell Acute Lymphoblastic Leukemia in Children

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Abstract: B-cell acute lymphoblastic leukemia (B-cell ALL) is the most common childhood cancer. Despite a high overall cure rate, relapsed B-cell ALL remains a leading cause of cancer-related death among children. The addition of the bispecific T-cell engager molecule blinatumomab (an anti-CD19 and anti-CD3 single-chain molecule) to therapy for newly diagnosed standard-risk (as defined by the National Cancer Institute) B-cell ALL in children may improve outcomes. We conducted a phase 3 trial involving children with newly diagnosed standard-risk B-cell ALL who had an average or higher risk of relapse. Patients were randomly assigned to receive chemotherapy alone or chemotherapy plus two nonsequential 28-day cycles of blinatumomab. The primary end point was disease-free survival. The data and safety monitoring committee reviewed the results from the first interim efficacy analysis, which included 1440 patients who had undergone randomization (722 to chemotherapy alone and 718 to blinatumomab and chemotherapy) and recommended early termination of randomization. At a median follow-up of 2.5 years, the estimated 3-year disease-free survival (±SE) was 96.0±1.2% with blinatumomab and chemotherapy and 87.9±2.1% with chemotherapy alone (difference in restricted mean survival time, 72 days;

95% confidence interval, 36 to 108; P<0.001 by stratified log-rank test). The estimated 3-year disease-free survival among patients with an average relapse risk was 97.5±1.3% with blinatumomab and chemotherapy and 90.2±2.3% with chemotherapy alone; among those with a higher relapse risk, the corresponding values were 94.1±2.5% and 84.8±3.8%. Cytokine release syndrome, seizures, and sepsis of grade 3 or higher were rare during blinatumomab cycles, but the overall incidence of nonfatal sepsis and catheter-related infections was significantly higher among patients with an average relapse risk who had been assigned to receive blinatumomab and chemotherapy than among those assigned to receive chemotherapy alone. Adding blinatumomab to combination chemotherapy in patients with newly diagnosed childhood standard-risk B-cell ALL of average or higher risk of relapse significantly improved disease-free survival.

25COASMA30:

Title: Pulmonary Vein Isolation With Optimized Linear Ablation vs Pulmonary Vein Isolation Alone for Persistent AF The PROMPT-AF Randomized Clinical Trial

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Abstract: Success rates of pulmonary vein isolation (PVI) are modest for persistent atrial fibrillation (AF). Additional linear ablation beyond PVI has not been proved superior to PVI alone in randomized trials. Ethanol infusion of the vein of Marshall (EIVOM) facilitates ablation at the mitral isthmus and may lead to improved effectiveness of a linear ablation strategy. Objective To determine whether linear ablation with radiofrequency energy combined with EIVOM added to PVI improves sinus rhythm maintenance compared with PVI alone in patients with persistent AF. Design, Setting, and Participants The PROMPT-AF trial is an investigator-initiated, multicenter, open-label, randomized trial involving 12 tertiary hospitals in China. A total of 498 patients aged 18 to 80 years, with AF persisting for more than 3 months, undergoing first-time AF ablation, were enrolled and randomized from August 27, 2021, to July 16, 2023. Interventions Patients were randomized to undergo PVI alone or PVI plus EIVOM and linear ablation (intervention). The latter group first underwent EIVOM, followed by PVI and linear ablation of the left atrial roof, mitral isthmus, and cavotricuspid isthmus. Main Outcomes and Measures The primary end point was freedom from any documented atrial arrhythmias lasting more than 30 seconds, without the use of antiarrhythmic drugs within 12 months. Secondary outcomes included freedom from atrial arrhythmia recurrence, AF, atrial arrhythmia recurrence after multiple procedures, and documented atrial tachycardia or atrial flutter with or without antiarrhythmic drugs; AF burden; and improvement in quality of life. Patients were monitored with wearable single-lead electrocardiographic (ECG) patches, worn for 24 hours a week, supplemented by symptom-triggered ECGs and Holter monitoring. Results Among 498 randomized patients, 495 (99.4%) were included in the primary analysis (mean age, 61.1 years [SD, 9.7] years, 361 male [72.9%]). After 12 months, 174 of 246 patients (70.7%) assigned to undergo PVI plus EIVOM and linear ablation and 153 of 249 patients (61.5%) assigned to undergo PVI alone remained free from atrial arrhythmias without taking antiarrhythmic drugs (hazard ratio, 0.73;

95% CI, 0.54-0.99, P = .045). The intervention effect was consistent across all prespecified subgroups. The comparison of secondary outcomes did not demonstrate significant results.Conclusion Among patients with persistent AF, linear ablation combined with EIVOM in addition to PVI significantly improved freedom from atrial arrhythmias within 12 months compared with PVI alone.

25COASMA31:

Title: Oral Glucose-Lowering Agents vs Insulin for Gestational DiabetesA Randomized Clinical Trial

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Abstract: Importance Metformin and glyburide monotherapy are used as alternatives to insulin in managing gestational diabetes. Whether a sequential strategy of these oral agents results in noninferior perinatal outcomes compared with insulin alone is unknown.Objective To test whether a treatment strategy of oral glucose-lowering agents is noninferior to insulin for prevention of large-for-gestational-age infants. Design, Setting, and Participants Randomized, open-label noninferiority trial conducted at 25 Dutch centers from June 2016 to November 2022 with follow-up completed in May 2023. The study enrolled 820 individuals with gestational diabetes and singleton pregnancies between 16 and 34 weeks of gestation who had insufficient glycemic control after 2 weeks of dietary changes (defined as fasting glucose >95 mg/dL [>5.3 mmol/L], 1-hour postprandial glucose >140 mg/dL [>7.8 mmol/L], or 2-hour postprandial glucose >120 mg/dL [>6.7 mmol/L], measured by capillary glucose self-testing). Interventions Participants were randomly assigned to receive metformin (initiated at a dose of 500 mg once daily and increased every 3 days to 1000 mg twice daily or highest level tolerated; n = 409) or insulin (prescribed according to local practice; n = 411). Glyburide was added to metformin, and then insulin substituted for glyburide, if needed, to achieve glucose targets. Main Outcomes and Measures The primary outcome was the between-group difference in the percentage of infants born large for gestational age (birth weight >90th percentile based on gestational age and sex). Secondary outcomes included maternal hypoglycemia, cesarean delivery, pregnancy-induced hypertension, preeclampsia, maternal weight gain, preterm delivery, birth injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal intensive care unit admission. Results Among 820 participants, the mean age was 33.2 (SD, 4.7) years). In participants randomized to oral agents, 79% (n = 320) maintained glycemic control without insulin. With oral agents, 23.9% of infants (n = 97) were large for gestational age vs 19.9% (n = 79) with insulin (absolute risk difference, 4.0%; 95% CI, −1.7% to 9.8%; P = .09 for noninferiority), with the confidence interval of the risk difference exceeding the absolute noninferiority margin of 8%. Maternal hypoglycemia was reported in 20.9% with oral glucose-lowering agents and 10.9% with insulin (absolute risk difference, 10.0%; 95% CI, 3.7%-21.2%). All other secondary outcomes did not differ between groups. Conclusions and Relevance Treatment of gestational diabetes with metformin and additional glyburide, if

needed, did not meet criteria for noninferiority compared with insulin with respect to the proportion of infants born large for gestational age.

25COASMA32:

Title: Early Restrictive vs Liberal Oxygen for Trauma PatientsThe TRAUMOX2 Randomized Clinical Trial

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Abstract: Importance Early administration of supplemental oxygen for all severely injured trauma patients is recommended, but liberal oxygen treatment has been associated with increased risk of death and respiratory complications. Objective To determine whether an early 8-hour restrictive oxygen strategy compared with a liberal oxygen strategy in adult trauma patients would reduce death and/or major respiratory complications. Design, Setting, and Participants This randomized controlled trial enrolled adult trauma patients transferred directly to hospitals, triggering a full trauma team activation with an anticipated hospital stay of a minimum of 24 hours from December 7, 2021, to September 12, 2023. This multicenter trial was conducted at 15 prehospital bases and 5 major trauma centers in Denmark, the Netherlands, and Switzerland. The 30-day follow-up period ended on October 12, 2023. The primary outcome was assessed by medical specialists in anesthesia and intensive care medicine blinded to the randomization. Interventions In the prehospital setting or on trauma center admission, patients were randomly assigned 1:1 to a restrictive oxygen strategy (arterial oxygen saturation target of 94%) (n = 733) or liberal oxygen strategy (12-15 L of oxygen per minute or fraction of inspired oxygen of 0.6-1.0) (n = 724) for 8 hours.Main Outcomes and Measures The primary outcome was a composite of death and/or major respiratory complications within 30 days. The 2 key secondary outcomes, death and major respiratory complications within 30 days, were assessed individually. Results Among 1979 randomized patients, 1508 completed the trial (median [IQR] age, 50 [31-65] years; 73% male; and median Injury Severity Score was 14 [9-22]). Death and/or major respiratory complications within 30 days occurred in 118 of 733 patients (16.1%) in the restrictive oxygen group and 121 of 724 patients (16.7%) in the liberal oxygen group (odds ratio, 1.01 [95% CI, 0.75 to 1.37]; P = .94; absolute difference, 0.56 percentage points [95% CI, −2.70 to 3.82]). No significant differences were found between groups for each component of the composite outcome. Adverse and serious adverse events were similar across groups, with the exception of atelectasis, which was less common in the restrictive oxygen group compared with the liberal oxygen group (27.6% vs 34.7%, respectively). Conclusions and Relevance In adult trauma patients, an early restrictive oxygen strategy compared with a liberal oxygen strategy initiated in the prehospital setting or on trauma center admission for 8 hours did not significantly reduce death and/or major respiratory complications within 30 days.

25COASMA33:

Title: Changes in Patient Care Experience After Private Equity Acquisition of US Hospitals

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Abstract: Importance Private equity acquisitions of health care facilities have rapidly increased over the past decade. However, little is known about the effects of private equity acquisitions of US hospitals on patient care experience. Objective To evaluate whether the acquisition of hospitals by private equity firms was associated with changes in measures of patient-reported experience compared with matched control hospitals from 2008 through 2019. Design, Settings, and Participants This cohort study identified 73 US hospitals newly acquired by private equity firms and 293 matched control (nonacquired) US hospitals from 2008 through 2019. An event study, difference-in-differences design was used to evaluate changes in patient experiences measures from 3 years before to 3 years after private equity acquisition. Main Outcomes and Measures The primary outcomes were 2 global measures of patient-reported care experience from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, which included patients' overall hospital rating and willingness to recommend the hospital. Secondary outcomes included the 7 other HCAHPS measures encompassing clinical process, communication, and environmental measures. Results There were 73 private equity–acquired hospitals and 293 matched control hospitals. The percentage of patients rating hospitals as a 9 or 10, on a scale of 0 to 10, decreased at private equity–acquired hospitals (65.0% before acquisition and 65.2% after acquisition) when compared with control hospitals (66.2% to 69.2%) during the postacquisition period relative to the preacquisition period with a difference-in-differences estimate of −2.4 percentage points (95% CI, −3.9 to −0.9). In addition, the percentage of patients who would definitely recommend the hospital also decreased at private equity–acquired hospitals (66.9% before acquisition and 65.5% after acquisition) compared with control hospitals (68.2% to 69.3%) with a difference-in-difference estimate of −2.1 percentage points (95% CI, −3.6 to −0.7). For both of these global measures of patient experience, the difference between private equity–acquired and control hospitals increased over time and was largest in year 3 after acquisition (−5.2 percentage points [95% CI, −8.8 to −1.5] and −4.4 percentage points [95% CI, −8.0 to −0.70] for each measure, respectively). For secondary measures of patient care experience, there was a decrease in patient-reported responsiveness of hospital staff at private equity–acquired hospitals compared with control hospitals (−1.3 percentage points [95% CI, −2.4 to −0.2]), but no differential change across other measures of clinical process, communication, and environment. Conclusions and Relevance Patient care experience worsened after private equity acquisition of hospitals. These findings raise concern about the implications of private equity acquisitions on patient care experience at US hospitals.

25COASMA34:

Title:Screening for Osteoporosis to Prevent FracturesA Systematic Evidence Review for the US Preventive Services Task Force

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Abstract: Importance: Fragility fractures result in significant morbidity. To review evidence on osteoporosis screening to inform the US Preventive Services Task Force.Data Sources PubMed, Embase, Cochrane Library, and trial registries through January 9, 2024; references, experts, and literature surveillance through July 31, 2024. Study Selection Randomized clinical trials (RCTs) and systematic reviews of screening; pharmacotherapy studies for primary osteoporosis; predictive and diagnostic accuracy studies. Data Extraction and Synthesis Two reviewers assessed titles/abstracts, full-text articles, study quality, and extracted data; when at least 2 similar studies were available, meta-analyses were conducted. Main Outcomes and Measures Hip, clinical vertebral, major osteoporotic, and total fractures; mortality; harms; accuracy. Results Three RCTs and 3 systematic reviews reported benefits of screening in older, higher-risk women. Two RCTs used 2-stage screening: Fracture Risk Assessment Tool estimate with bone mineral density (BMD) testing if risk threshold exceeded. One RCT used BMD plus additional tests. Screening was associated with reduced hip (pooled relative risk [RR], 0.83 [95% CI, 0.73-0.93]; 3 RCTs; 42 009 participants) and major osteoporotic fracture (pooled RR, 0.94 [95% CI, 0.88-0.99]; 3 RCTs; 42 009 participants) compared with usual care. Corresponding absolute risk differences were 5 to 6 fewer fractures per 1000 participants screened. The discriminative accuracy of risk assessment instruments to predict fracture or identify osteoporosis varied by instrument and fracture type; most had an area under the curve between 0.60 and 0.80 to predict major osteoporotic fracture, hip fracture, or both. Calibration outcomes were limited. Compared with placebo, bisphosphonates (pooled RR, 0.67 [95% CI, 0.45-1.00]; 6 RCTs; 12 055 participants) and denosumab (RR, 0.60 [95% CI, 0.37-0.97] from the largest RCT [7808 participants]) were associated with reduced hip fractures. Compared with placebo, no statistically significant associations were observed for adverse events. Conclusions and Relevance Screening in higher-risk women 65 years or older was associated with a small absolute risk reduction in hip and major fractures compared with usual care. No evidence evaluated screening with BMD alone or screening in men or younger women. Risk assessment instruments, BMD alone, or both have poor to modest discrimination for predicting fracture. Osteoporosis treatment with bisphosphonates or denosumab over several years was associated with fracture reductions and no meaningful increase in adverse events.

25COASMA35:

Title: Intra-Arterial Tenecteplase Following Endovascular Reperfusion for Large Vessel Occlusion Acute Ischemic Stroke: The POST-TNK Randomized Clinical Trial

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Abstract: Importance The impact of adjunctive intra-arterial tenecteplase administration following near-complete to complete reperfusion by endovascular thrombectomy (EVT) for acute ischemic stroke is unknown. Objective To assess the efficacy and adverse events of adjunctive intra-arterial tenecteplase in patients with large vessel occlusion stroke who had achieved near-complete to complete reperfusion (defined as a score on the expanded Thrombolysis in Cerebral Infarction [eTICI] scale of 2c to 3) after EVT. Design, Setting, and Participants Investigator-initiated, randomized, open-label, blinded outcome assessment trial implemented at 34 hospitals in China among 540 patients with stroke due to proximal intracranial large vessel occlusion within 24 hours of the time they were last known to be well, with an eTICI score of 2c to 3 after EVT, and without prior intravenous thrombolysis. Recruitment took place between October 26, 2022, and March 1, 2024, with final follow-up on June 3, 2024. Interventions Eligible patients were randomly assigned to receive intra-arterial tenecteplase (n = 269) at 0.0625 mg/kg or no intra-arterial thrombolysis (control group; n = 271). Main Outcomes and Measures The primary efficacy outcome was freedom from disability, defined as a score of 0 or 1 on the modified Rankin Scale (range, 0 [no symptoms] to 6 [death]) at 90 days. The primary safety outcomes were death at 90 days and symptomatic intracranial hemorrhage within 48 hours. Results A total of 539 participants (99.8%) completed the trial (median age, 69 years; 221 female [40.9%]). The proportion with a modified Rankin Scale score of 0 or 1 at 90 days was 49.1% (132/269) in the intra-arterial tenecteplase group and 44.1% (119/270) in the control group (adjusted risk ratio, 1.15 [95% CI, 0.97-1.36]; P = .11). Ninety-day mortality was 16.0% and 19.3% (adjusted hazard ratio, 0.75 [95% CI, 0.50-1.13]; P = .16), respectively. The proportions of symptomatic intracranial hemorrhage were 6.3% and 4.4% (adjusted risk ratio, 1.43 [95% CI, 0.68-2.99]; P = .35), respectively. Conclusions and Relevance In patients with acute ischemic stroke due to large vessel occlusion presenting within 24 hours of time last known to be well and who had achieved near-complete to complete reperfusion after EVT, adjunctive intra-arterial tenecteplase did not significantly increase the likelihood of freedom from disability at 90 days.

25COASMA36:

Title: Intra-Arterial Urokinase After Endovascular Reperfusion for Acute Ischemic Stroke: The POST-UK Randomized Clinical Trial

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Abstract: Importance Persisting or new thrombi in the distal arteries and the microcirculation have been reported to limit the benefits of successful endovascular thrombectomy for patients with acute ischemic stroke. It remains uncertain whether intra-arterial thrombolysis by urokinase following near-complete to complete reperfusion by thrombectomy improves outcomes among patients with ischemic stroke due to large vessel occlusion. Objective To assess the efficacy and adverse events of intra-arterial urokinase

after near-complete to complete reperfusion by thrombectomy for acute ischemic stroke due to large vessel occlusion. Design, Setting, and Participants This investigator-initiated, randomized, open-label, blinded–end point trial was implemented at 35 hospitals in China, enrolling 535 patients with proximal intracranial large vessel occlusion presenting within 24 hours of time last known well, who achieved near-complete or complete reperfusion by endovascular thrombectomy and did not receive intravenous thrombolysis prior to the procedure. Recruitment took place between November 15, 2022, and March 29, 2024, with final follow-up on July 4, 2024. Interventions Eligible patients were randomly assigned to the intra-arterial urokinase group (a single dose of intra-arterial 100 000 IU urokinase injected in the initial target territory; n = 267) or control group (without intra-arterial thrombolysis; n = 267). Main Outcomes and Measures The primary efficacy outcome was the percentage of patients achieving survival without disability (modified Rankin Scale score of 0 or 1) at 90 days. The primary safety outcomes were mortality at 90 days and incidence of symptomatic intracranial hemorrhage within 48 hours. Results A total of 535 patients were enrolled (median age, 69 years; 223 [41.8%] female) and 532 (99.6%) completed the trial. The percentage of patients with survival without disability at 90 days was 45.1% (120/266) in the intra-arterial urokinase group and 40.2% (107/266) in the control group (adjusted risk ratio, 1.13 [95% CI, 0.94-1.36]; P = .19). Mortality at 90 days (18.4% vs 17.3%, respectively; adjusted hazard ratio, 1.06 [95% CI, 0.71-1.59]; P = .77) and incidence of symptomatic intracranial hemorrhage (4.1% vs 4.1%, respectively; adjusted risk ratio, 1.05 [95% CI, 0.45-2.44]; P = .91) were not significantly different between groups. Conclusions and Relevance Among patients with acute ischemic stroke due to large vessel occlusion, adjunct intra-arterial urokinase after near-complete to complete reperfusion by endovascular thrombectomy did not significantly increase the likelihood of survival without disability at 90 days.

25COASMA37:

Title: Palliative Care Initiated in the Emergency DepartmentA: Cluster Randomized Clinical Trial

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Abstract: Importance The emergency department (ED) offers an opportunity to initiate palliative care for older adults with serious, life-limiting illness.

Objective To assess the effect of a multicomponent intervention to initiate palliative care in the ED on hospital admission, subsequent health care use, and survival in older adults with serious, life-limiting illness. Design, Setting, and Participants Cluster randomized, stepped-wedge, clinical trial including patients aged 66 years or older who visited 1 of 29 EDs across the US between May 1, 2018, and December 31, 2022, had 12 months of prior Medicare enrollment, and a Gagne comorbidity score greater than 6, representing a risk of short-term mortality greater than 30%. Nursing home patients were excluded. Intervention A multicomponent intervention (the Primary Palliative Care for Emergency Medicine intervention) included (1) evidence-based multidisciplinary education; (2) simulation-based

workshops on serious illness communication; (3) clinical decision support; and (4) audit and feedback for ED clinical staff. Main Outcome and Measures The primary outcome was hospital admission. The secondary outcomes included subsequent health care use and survival at 6 months. Results There were 98 922 initial ED visits during the study period (median age, 77 years [IQR, 71-84 years]; 50% were female; 13% were Black and 78% were White; and the median Gagne comorbidity score was 8 [IQR, 7-10]). The rate of hospital admission was 64.4% during the preintervention period vs 61.3% during the postintervention period (absolute difference, −3.1% [95% CI, −3.7% to −2.5%]; adjusted odds ratio [OR], 1.03 [95% CI, 0.93 to 1.14]). There was no difference in the secondary outcomes before vs after the intervention. The rate of admission to an intensive care unit was 7.8% during the preintervention period vs 6.7% during the postintervention period (adjusted OR, 0.98 [95% CI, 0.83 to 1.15]). The rate of at least 1 revisit to the ED was 34.2% during the preintervention period vs 32.2% during the postintervention period (adjusted OR, 1.00 [95% CI, 0.91 to 1.09]). The rate of hospice use was 17.7% during the preintervention period vs 17.2% during the postintervention period (adjusted OR, 1.04 [95% CI, 0.93 to 1.16]). The rate of home health use was 42.0% during the preintervention period vs 38.1% during the postintervention period (adjusted OR, 1.01 [95% CI, 0.92 to 1.10]). The rate of at least 1 hospital readmission was 41.0% during the preintervention period vs 36.6% during the postintervention period (adjusted OR, 1.01 [95% CI, 0.92 to 1.10]). The rate of death was 28.1% during the preintervention period vs 28.7% during the postintervention period (adjusted OR, 1.07 [95% CI, 0.98 to 1.18]). Conclusions and Relevance This multicomponent intervention to initiate palliative care in the ED did not have an effect on hospital admission, subsequent health care use, or short-term mortality in older adults with serious, life-limiting illness.

25COASMA38:

Title: Antiretroviral Drugs for Treatment and Prevention of HIV in Adults: 2024 Recommendations of the International Antiviral Society–USA Panel

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JAMA. 2025;333(7):609-628.
doi: https://doi.org/10.1001/jama.2024.24543
Abstract: Importance New data and new antiretroviral drugs and formulations continue to become available for the prevention and management of HIV infection. Objective To provide updated recommendations for HIV treatment and clinical management and HIV prevention. Methods A panel of volunteer expert physician scientists were appointed to provide updated consensus recommendations for 2024. Relevant evidence in the literature since the last report was identified from PubMed and Embase searches (which initially yielded 3998 unique citations, of which 249 were considered relevant); from ongoing monitoring of the literature by the panel members; from data submitted by product manufacturers; and from studies presented at peer-reviewed scientific conferences between June 2022 and October 2024. Findings Antiretroviral therapy continues to be recommended for all individuals with HIV. For most people with HIV, initial regimens composed of an integrase strand transfer inhibitor (InSTI), specifically bictegravir or dolutegravir, with 2 (and

in some cases 1) nucleoside or nucleotide reverse transcriptase inhibitors are recommended. Recommendations are made for those with particular clinical circumstances, such as pregnancy and active opportunistic diseases, as well as for those unable to take InSTIs. Regimens may need to be changed for virologic failure, adverse effects, convenience, or cost, among other reasons. Long-acting injectable therapy is available for those who prefer not to take daily oral medications and for people struggling with adherence to daily therapy. Recommendations are provided for laboratory monitoring, management of substance use disorders and weight changes, as well as use of statins for cardiovascular disease prevention. For HIV prevention, oral (daily or intermittent) and injectable long-acting medications are effective options for people at increased likelihood of HIV exposure. Further, new tools for maintaining health and well-being among people with HIV, such as doxycycline postexposure prophylaxis to avert sexually transmitted infection, and strategies to treat substance use disorders, are recommended. Disparities in HIV acquisition and care access are discussed and solutions proposed. Conclusions New approaches for treating and preventing HIV offer additional tools to help end the HIV epidemic, but achieving this goal depends on addressing disparities and inequities in access to care.

25COASMA39:

Title: Camrelizumab vs Placebo in Combination With Chemotherapy as Neoadjuvant Treatment in Patients With Early or Locally Advanced Triple-Negative Breast Cancer The CamRelief Randomized Clinical Trial

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JAMA. 2025;333(8):673-681.
doi: https://doi.org/10.1001/jama.2024.23560
Abstract: Importance Preferred neoadjuvant strategies for early or locally advanced triple-negative breast cancer include a 4-drug chemotherapy regimen containing anthracyclines, cyclophosphamide, taxanes, and platinum. Blockade of the programmed death receptor 1/ligand-1 (PD-1/PD-L1) pathway may improve efficacy of classic neoadjuvant chemotherapy. Camrelizumab, an anti–PD-1 antibody, has showed antitumor activity in advanced triple-negative breast cancer. Objective To evaluate the efficacy and adverse events of camrelizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy for patients with early or locally advanced triple-negative breast cancer. Design, Setting, and Participants This randomized, double-blind, phase 3 trial enrolled patients from 40 hospitals in China between November 25, 2020, and May 12, 2023 (data cutoff: September 30, 2023). A total of 441 eligible patients were enrolled. Interventions Patients were randomized in a 1:1 ratio to receive either camrelizumab 200 mg (n = 222) or placebo (n = 219) combined with chemotherapy every 2 weeks. The chemotherapy included nab-paclitaxel (100 mg/m^2) and carboplatin (area under the curve, 1.5) on days 1, 8, and 15 in 28-day cycles for the first 16 weeks followed by epirubicin (90 mg/m^2) and cyclophosphamide (500 mg/m^2) every 2 weeks for 8 weeks. Main Outcomes and Measures The primary end point was pathological complete response (defined as no invasive tumor in breast and lymph nodes [ypT0/Tis ypN0]). Results Among 441 females randomized (median age, 48 years),

the median (range) follow-up duration from randomization was 14.4 (0.0-31.8) months. Pathological complete response was achieved in 126 patients (56.8% [95% CI, 50.0%-63.4%]) in the camrelizumab-chemotherapy group and 98 patients (44.7% [95% CI, 38.0%-51.6%]) in the placebo-chemotherapy group (rate difference, 12.2% [95% CI, 3.3%-21.2%]; 1-sided P = .004). In the neoadjuvant phase, adverse events of grade 3 or higher occurred in 198 patients (89.2%) in the camrelizumab-chemotherapy group and 182 (83.1%) in the placebo-chemotherapy group; serious adverse events occurred in 77 patients (34.7%) in the camrelizumab-chemotherapy group and 50 (22.8%) in the placebo-chemotherapy group, with fatal adverse events occurring in 2 patients (0.9%) in the camrelizumab-chemotherapy group.
Conclusions and Relevance Among patients with early or locally advanced triple-negative breast cancer, the addition of camrelizumab to neoadjuvant chemotherapy significantly improved pathological complete response.

25COASMA40:

Title: Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial

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Abstract: Importance For hospitalized critically ill adults with suspected sepsis, procalcitonin (PCT) and C-reactive protein (CRP) monitoring protocols can guide the duration of antibiotic therapy, but the evidence of the effect and safety of these protocols remains uncertain. Objective To determine whether decisions based on assessment of CRP or PCT safely results in a reduction in the duration of antibiotic therapy.Design, Setting, and Participants A multicenter, intervention-concealed randomized clinical trial, involving 2760 adults (≥18 years), in 41 UK National Health Service (NHS) intensive care units, requiring critical care within 24 hours of initiating intravenous antibiotics for suspected sepsis and likely to continue antibiotics for at least 72 hours.
Intervention From January 1, 2018, to June 5, 2024, 918 patients were assigned to the daily PCT-guided protocol, 924 to the daily CRP-guided protocol, and 918 assigned to standard care. Main Outcomes and Measures The primary outcomes were total duration of antibiotics (effectiveness) and all-cause mortality (safety) to 28 days. Secondary outcomes included critical care unit data and hospital stay data. Ninety-day all-cause mortality was also collected. Results Among the randomized patients (mean age 60.2 [SD, 15.4] years; 60.3% males), there was a significant reduction in antibiotic duration from randomization to 28 days for those in the daily PCT-guided protocol compared with standard care (mean duration, 10.7 [SD, 7.6] days for standard care and 9.8 [SD, 7.2] days for PCT; mean difference, 0.88 days; 95% CI, 0.19 to 1.58, P = .01). For all-cause mortality up to 28 days, the daily PCT-guided protocol was noninferior to standard care, where the noninferiority margin was set at 5.4% (19.4% [170 of 878] of patients receiving standard care; 20.9% [184 of 879], PCT; absolute difference, 1.57; 95% CI, −2.18 to 5.32; P = .02). No difference was found in antibiotic duration for standard care vs daily CRP-guided protocol (mean duration, 10.6 [7.7] days for

CRP; mean difference, 0.09; 95% CI, −0.60 to 0.79; P = .79). For all-cause mortality, the daily CRP-guided protocol was inconclusive compared with standard care (21.1% [184 of 874] for CRP; absolute difference, 1.69; 95% CI, −2.07 to 5.45; P = .03). Conclusions and Relevance Care guided by measurement of PCT reduces antibiotic duration safely compared with standard care, but CRP does not. All-cause mortality for CRP was inconclusive.

25COASMA41:

Title: 2024 Update of the RECOVER-Adult Long COVID Research Index

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Abstract: Importance Classification of persons with long COVID (LC) or post–COVID-19 condition must encompass the complexity and heterogeneity of the condition. Iterative refinement of the classification index for research is needed to incorporate newly available data as the field rapidly evolves. Objective To update the 2023 research index for adults with LC using additional participant data from the Researching COVID to Enhance Recovery (RECOVER-Adult) study and an expanded symptom list based on input from patient communities. Design, Setting, and Participants Prospective, observational cohort study including adults 18 years or older with or without known prior SARS-CoV-2 infection who were enrolled at 83 sites in the US and Puerto Rico. Included participants had at least 1 study visit taking place 4.5 months after first SARS-CoV-2 infection or later, and not within 30 days of a reinfection. The study visits took place between October 2021 and March 2024. Exposure SARS-CoV-2 infection. Main Outcomes and Measures Presence of LC and participant-reported symptoms. Results A total of 13 647 participants (11 743 with known SARS-CoV-2 infection and 1904 without known prior SARS-CoV-2 infection; median age, 45 years [IQR, 34-69 years]; and 73% were female) were included. Using the least absolute shrinkage and selection operator analysis regression approach from the 2023 model, symptoms contributing to the updated 2024 index included postexertional malaise, fatigue, brain fog, dizziness, palpitations, change in smell or taste, thirst, chronic cough, chest pain, shortness of breath, and sleep apnea. For the 2024 LC research index, the optimal threshold to identify participants with highly symptomatic LC was a score of 11 or greater. The 2024 index classified 20% of participants with known prior SARS-CoV-2 infection and 4% of those without known prior SARS-CoV-2 infection as having likely LC (vs 21% and 5%, respectively, using the 2023 index) and 39% of participants with known prior SARS-CoV-2 infection as having possible LC, which is a new category for the 2024 model. Cluster analysis identified 5 LC subtypes that tracked quality-of-life measures. Conclusions and Relevance The 2024 LC research index for adults builds on the 2023 index with additional data and symptoms to help researchers classify symptomatic LC and its symptom subtypes. Continued future refinement of the index will be needed as the understanding of LC evolves.

25COASMA42:

Title: Use of menopausal hormone therapy before and after diagnosis and ovarian cancer survival—A prospective cohort study in Australia

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International Journal of Cancer, Vol. 156, Issue-2
Doi- **https://doi.org/10.1002/ijc.35154**
Abstract: Menopausal hormone therapy (MHT) use before ovarian cancer diagnosis has been associated with improved survival but whether the association varies by type and duration of use is inconclusive; data on MHT use after treatment, particularly the effect on health-related quality of life (HRQOL), are scarce. We investigated survival in women with ovarian cancer according to MHT use before and after diagnosis, and post-treatment MHT use and its association with HRQOL in a prospective nationwide cohort in Australia. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) and propensity scores to reduce confounding by indication. Among 690 women who were peri-/postmenopausal at diagnosis, pre-diagnosis MHT use was associated with a significant 26% improvement in ovarian cancer-specific survival; with a slightly stronger association for high-grade serous carcinoma (HGSC, HR = 0.69, 95%CI 0.54–0.87). The associations did not differ by recency or duration of use. Among women with HGSC who were pre-/perimenopausal or aged ≤55 years at diagnosis (n = 259), MHT use after treatment was not associated with a difference in survival (HR = 1.04, 95%CI 0.48–2.22). Compared to non-users, women who started MHT after treatment reported poorer overall HRQOL before starting MHT and this difference was still seen 1–3 months after starting MHT. In conclusion, pre-diagnosis MHT use was associated with improved survival, particularly in HGSC. Among women ≤55 years, use of MHT following treatment was not associated with poorer survival for HGSC. Further large-scale studies are needed to understand menopause-specific HRQOL issues in ovarian cancer.

25COASMA43:

Title: Association between immune checkpoint inhibitor and cytomegalovirus infection: A pharmacovigilance study based on the adverse event reporting system

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International Journal of Cancer, Vol. 156, Issue-2
Doi- **https://doi.org/10.1002/ijc.35155**
Abstract: Immune checkpoint inhibitor (ICI)-induced adverse events due to excessive immune stimulation are problematic in immunotherapy. The activation of viral infection triggered by ICI-induced dysregulated immunity has been proposed; however, this association remains inconsistent. This study investigated the association between ICI administration and cytomegalovirus (CMV) infections, a pathogen linked to immune abnormalities and reactivation, using the Food and Drug Administration Adverse Event Reporting System. We used the crude data set and immunocompromise-free data set from the fourth quarter of 2012 to 2023. The disproportionality between CMV infection and ICI was analyzed using reporting odds ratio (ROR) and information component (IC) methodologies. Disproportionality between ipilimumab and nivolumab combination case and CMV infection was observed in the crude (ROR: 2.83, 95% confidence interval [CI]: 2.32–3.47; IC: 1.48,

95% CI: 1.14–1.73) and immunocompromise-free data set (ROR: 1.76, 95% CI: 1.33–2.33; IC: 0.80, 95% CI: 0.33–1.14), whereas disproportionality between other ICI and CMV infection was not observed in the immunocompromise-free data set. Multiple sensitivity analyses and time-scan analysis also revealed the consistent disproportionality between ipilimumab and nivolumab combination cases and CMV infection, regardless of the host's immune status. While further research is warranted to validate our findings, these results highlight new insights into ICI-induced viral infections and suggest the importance of considering the possibility of CMV infections during ipilimumab and nivolumab combination therapy, regardless of the host's immune status.

25COASMA44:

Title: Impact of accelerated biological aging and genetic variation on esophageal adenocarcinoma: Joint and interaction effect in a prospective cohort

Renjia Zhao, Huangbo Yuan, Shuaizhou Chen, Kelin Xu, Tiejun Zhang, Zhenqiu Liu, Yanfeng Jiang, Chen Suo, Xingdong Chen

International Journal of Cancer, Vol. 156, Issue-2

Doi: **https://doi.org/10.1002/ijc.35161**

Abstract: Accelerated biological aging may be associated with increased risk of esophageal adenocarcinoma (EAC). However, its relationship with genetic variation, and its effect on improving risk population stratification, remains unknown. We performed an exposome association study to determine potential associated factors associated with EAC. To quantify biological age and its difference from chronological age, we calculated the BioAge10 and Biological Age Acceleration (BioAgeAccel) based on chronological age and nine biomarkers. Multivariable Cox regression models for 362,310 participants from the UK Biobank with a median follow-up of 13.70 years were performed. We established a weighted polygenic risk score (wPRS) associated with EAC, to assess joint and interaction effects with BioAgeAccel. Four indicators were used to evaluate their interaction effects, and we fitted curves to evaluate the risk stratification ability of BioAgeAccel. Compared with biologically younger participants, those older had higher risk of EAC, with adjusted HR of 1.79 (95%CI: 1.52–2.10). Compared with low wPRS and biologically younger group, the high wPRS and biologically older group had a 4.30-fold increase in HR (95% CI: 2.78–6.66), at meanwhile, 1.15-fold relative excess risk was detected (95% CI: 0.30–2.75), and 22% of the overall EAC risk was attributable to the interactive effects (95% CI: 12%–31%). The 10-year absolute incidence risk indicates that biologically older individuals should begin screening procedures 4.18 years in advance, while youngers can postpone screening by 4.96 years, compared with general population. BioAgeAccel interacted positively with genetic variation and increased risk of EAC, it could serve as a novel indicator for predicting incidence.

25COASMA45:

Title: Malignant salivary gland tumors of the tongue: A multicenter REFCOR study

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International Journal of Cancer, Vol. 156, Issue-2

Doi- **https://doi.org/10.1002/ijc.35167**

Abstract: Salivary carcinomas of minor salivary glands are very infrequent tumors. When located in the tongue, the therapeutic strategy may comprise upfront surgery, which may be debilitating, and/or (chemo-)radiotherapy. The aim of this study was to identify the prognostic factors of salivary carcinomas of the tongue in a population-based cohort. This retrospective multicentric study, based on the "Réseau d'Expertise Français sur les Cancers ORL Rares" (REFCOR), included all the patients with a salivary carcinoma of the tongue, diagnosed between January 2009 and December 2018. Dubious slides were reviewed by REFCOR expert pathologists to ensure diagnostic accuracy. Treatment was performed in accordance with national REFCOR recommendations. From 28 centers, 103 patients were included in this study. Median age at diagnosis was 63 years, and 60.2% were female. Tumors were adenoid cystic carcinomas (41.7%), mucoepidermoid carcinomas (30.1%), and other adenocarcinomas (28.2%). Primary treatment was surgical for 61.2% of them. Five-year overall survival (OS) and event-free survival (EFS) rates were 84.7% and 38.6%, respectively. In multivariable analysis, EFS was significantly worse in case of nonsurgical treatment, alcohol consumption, and glossotonsillar sulcus involvement. N-positive status was the only significant prognostic factor for OS in multivariable analysis. Salivary carcinomas of the tongue represent a heterogeneous group of rare tumors, with a high risk of recurrence. In this national cohort, surgery was associated with better EFS and N-status was the main independent prognostic factor for OS.

25COASMA46:

Title: Aflatoxin exposure is associated with an increased risk of gallbladder cancer

Amit Yadav, Pankaj Gupta, Parikshaa Gupta, Amol N. Patil, Chandan K. Das, Harish Hooda, Deepa Thakur,

International Journal of Cancer, Vol. 156, Issue-2

Doi-**https://doi.org/10.1002/ijc.35171**

Abstract: Gall bladder cancer (GBC) is common among the socioeconomically deprived populations of certain geographical regions. Aflatoxin is a genotoxic hepatocarcinogen, which is recognized to have a role in the pathogenesis of hepatocellular carcinoma. However, the role of aflatoxin in the pathogenesis of GBC is largely unknown. We determined serum AFB1-Lys albumin adduct (AAA) levels as a marker of aflatoxin exposure in the patients with GBC and compared to those without GBC. The relationship of AAA levels to cytogenetic (TP53mutation&HER2/neu amplification) and radiological characteristics of the tumor was assessed. We included GBC cases (n = 51) and non-GBC controls (n = 100). Mean serum AAA levels were higher in the GBC group (n = 51) than those without GBC (n = 100) (26.1 ± 12.2 vs. 13.1 ± 11.9 ng/mL; p < .001). HER2/neu expression was associated with higher AAA levels compared to those with equivocal or negative expression (43.9 ± 3 vs. 28.6 ± 10 vs. 19.3 ± 7 ng/mL; p < .001). Older age (age >50 years) (odds ratio [OR] = 3.2 [CI: 1.3–8.2]; p = .013), positive Helicobacter pylori serology (OR = 5.1 [CI: 1.4–17.8]; p = .012), presence of GS (OR = 5 [CI: 1.5–16.9]; p = .009) and detectable AAA levels (OR = 6.8 [CI: 1.3–35.7]; p = .024) were independent risk factors for the presence of the GBC among all study subjects. Among patients harboring GS, older age (age >50 years) (OR = 4.5 [CI: 1.3–

14.9]; p = .015), female gender (OR = 3.8 [CI: 1.2–12.5]; p = .027), presence of multiple GS (OR = 21.9 [CI: 4.8–100.4]; p < .001) and high serum AAA levels (OR = 5.3 [CI: 1.6–17.3]; p = .006) were independent risk factors for the presence of the GBC. Elderly age >50 years (OR = 2.6 [CI: 1.3–5.2]; p = .010) and frequent peanut consumption (OR = 2.3 [CI: 1.1–4.9]; p = .030) were independent risk factors for high serum AAA levels. The current study has implications for the prevention of GBC through the reduction of dietary aflatoxin exposure.

25COASMA47:

Title: Breast cancer survival analysis in the Republic of Mauritius by age, stage at diagnosis and molecular subtype: A retrospective cohort study

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International Journal of Cancer, Vol. 156, Issue-2

Doi: **https://doi.org/10.1002/ijc.35172**

Abstract: Breast cancer is by far the leading cancer both in terms of incidence and mortality in the Republic of Mauritius, a Small Island Developing State (SIDS). However, few studies assessed its survival by age, stage at diagnosis and molecular subtype. We identified 1399 breast cancer cases newly diagnosed between 2017 and 2020 at the Central Health Laboratory, Victoria Hospital. Cancers were categorized into five molecular subtypes: (1) luminal A, (2) luminal B Her2 negative, (3) luminal B Her2 positive, (4) Her2 enriched and (5) Triple negative. The net 1 and 3-year survival were estimated for different age groups, staging at time of diagnosis and molecular subtype. We also estimated the excess hazards using a multivariate Cox proportional hazards model. While early stage at diagnosis (stage 1 [44.4%] and stage 2 [20.1%]) were most common compared to late presentation (Stage 3 [25.4%] and stage 4 [10.1%]), luminal B Her2 negative (36.7%) was the most frequent molecular subtype. The net 1- and 3-year breast cancer survival rates were 93.9% (92.3–95.4) and 83.4% (80.4–86.4), respectively. Breast cancer three-year survival rates were poorest among the youngest patients (<50 years), 77.1% (70.7–83.5), those diagnosed with stage 4 (28.5% [17.1–39.9]) and cancer with a triple negative molecular subtype (71.3% [63.3–79.3]). Emphasis on a national breast cancer screening programme, down staging breast cancer at diagnosis and systematic molecular subtyping of all breast tissues could be pivotal in improving breast cancer survival outcomes in the Republic of Mauritius.

25COASMA48:

Title: Polymorphisms within autophagy-related genes as susceptibility biomarkers for pancreatic cancer: A meta-analysis of three large European cohorts and functional characterization

Fernando Gálvez-Montosa, Giulia Peduzzi, José Manuel Sanchez-Maldonado, Rob ter Horst,

International Journal of Cancer, Vol. 156, Issue-2

Doi: **https://doi.org/10.1002/ijc.35196**

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with patients having unresectable or metastatic disease at diagnosis, with poor prognosis and very short survival. Given that genetic variation within autophagy-related genes influences

autophagic flux and susceptibility to solid cancers, we decided to investigate whether 55,583 single nucleotide polymorphisms (SNPs) within 234 autophagy-related genes could influence the risk of developing PDAC in three large independent cohorts of European ancestry including 12,754 PDAC cases and 324,926 controls. The meta-analysis of these populations identified, for the first time, the association of the $BID_{rs9604789}$ variant with an increased risk of developing the disease ($OR_{Meta} = 1.31$, $p = 9.67 \times 10^{-6}$). We also confirmed the association of $TP63_{rs1515496}$ and $TP63_{rs35389543}$ variants with PDAC risk ($OR = 0.89$, $p = 6.27 \times 10^{-8}$ and $OR = 1.16$, $p = 2.74 \times 10^{-5}$). Although it is known that BID induces autophagy and TP63 promotes cell growth, cell motility and invasion, we also found that carriers of the $TP63_{rs1515496G}$ allele had increased numbers of FOXP3+ Helios+ T regulatory cells and CD45RA+ T regulatory cells ($p = 7.67 \times 10^{-4}$ and $p = 1.56 \times 10^{-3}$), but also decreased levels of CD4+ T regulatory cells ($p = 7.86 \times 10^{-4}$). These results were in agreement with research suggesting that the $TP63_{rs1515496}$ variant alters binding sites for FOXA1 and CTCF, which are transcription factors involved in modulating specific subsets of regulatory T cells. In conclusion, this study identifies BID as new susceptibility locus for PDAC and confirms previous studies suggesting that the TP63 gene is involved in the development of PDAC. This study also suggests new pathogenic mechanisms of the TP63 locus in PDAC.

25COASMA49:

Title: SIAH3 is frequently epigenetically silenced in cancer and regulates mitochondrial metabolism

Verena E. Deutschmeyer, Nico A. Schlaudraff, Sara K. Walesch, Janine Moyer, Anna M. Sokol,

International Journal of Cancer, Vol. 156, Issue-2

Doi: **https://doi.org/10.1002/ijc.35202**

Abstract: Of the seven in absentia homologue (SIAH) family, three members have been identified in the human genome. In contrast to the E3 ubiquitin ligase encoding SIAH1 and SIAH2, little is known on the regulation and function of SIAH3 in tumorigenesis. In this study, we reveal that SIAH3 is frequently epigenetically silenced in different cancer entities, including cutaneous melanoma, lung adenocarcinoma and head and neck cancer. Low SIAH3 levels correlate with an impaired survival of cancer patients. Additionally, induced expression of SIAH3 reduces cell proliferation and induces cell death. Functionally, SIAH3 negatively affects cellular metabolism by shifting cells form aerobic oxidative phosphorylation to glycolysis. SIAH3 is localized in the mitochondrion and interacts with proteins involved in mitochondrial ribosome biogenesis and translation. We also report that SIAH3 interacts with ubiquitin ligases, including SIAH1 or SIAH2, and is degraded by them. These results suggest that SIAH3 acts as an epigenetically controlled tumor suppressor by regulating cellular metabolism through the inhibition of oxidative phosphorylation.

25COASMA50:

Title: Optimizing treatment sequence for inoperable locally advanced breast cancer: Long-term outcomes of surgery first versus neoadjuvant chemotherapy in a real-world setting

Bowen Liu, Yu Song, Ying Xu, Qiang Sun, Yidong Zhou, Yan Lin

International Journal of Cancer, Vol. 156, Issue-2

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Abstract: Locally advanced breast cancer (LABC) is challenging with limited treatment options. This study investigates the feasibility and long-term outcomes of upfront surgery compared to neoadjuvant chemotherapy (NAC) in a real-world cohort. This retrospective study analyzed 243 inoperable LABC patients (excluding T3N1M0) that underwent upfront surgery (n = 187) or NAC (n = 56) in matched groups. Disease-free survival (DFS) and overall survival (OS) are primary outcomes. Secondary outcomes included NAC response rate and subgroup analyses based on age, tumor stage, and treatment response. Survival was estimated using Kaplan–Meier methods with log-rank tests for comparisons. Cox proportional hazards models were used for subgroup analyses. With a median follow-up of 60.9 months, no significant difference emerged in 5-year OS (upfront surgery: 89.6%, NAC: 81.9%, p = .12) or 5-year DFS rates (73.0% vs. 67.1%, p = .24). Subgroup analyses revealed upfront surgery offered significantly better OS for patients under 60 (HR = 0.32; 95% CI: 0.10–0.96; p = .0429) and stage IIIA disease (HR = 0.22; CI: 0.06–0.86; p = .03). Upfront surgery showed a trend towards improved OS for tumors under 5 cm (HR = 0.37; 95% CI: 0.13–1.03; p = .056). Patients with progressive disease (PD) or stable disease (SD) after NAC had significantly worse DFS (HR = 0.27; 95% CI: 0.09–0.79; p = .017) and OS (HR = 0.09; 95% CI: 0.02–0.48; p = .004) compared to responders. Upfront surgery may be viable for LABC patients, particularly younger patients, those with stage IIIA disease, or smaller tumors. NAC response can inform treatment decisions. These findings highlight the need for personalized LABC treatment considering patient characteristics and NAC response.

25COASMA51:

Title: Nationwide registry-based trial of risk-stratified cervical screening

Laila Sara Arroyo Mühr, Jiangrong Wang, Sadaf S. Hassan, Emel Yilmaz, Miriam K. Elfström, Joakim Dillner

International Journal of Cancer, Vol. 156, Issue-2

Doi-**https://doi.org/10.1002/ijc.35142**

Abstract: In well-screened populations, most cervical cancers arise from small groups of women with inadequate screening. The present study aims to assess whether registry-based cancer risk assessment could be used to increase screening intensity among high-risk women. The National Cervical Screening Registry identified the 28,689 women residents in Sweden who had either no previous cervical screening or a screening history indicating high risk. We invited these women by SMS and/or physical letter to order a free human papillomavirus (HPV) self-sampling kit. The Swedish national HPV reference laboratory performed extended HPV genotyping and referred high-risk HPV-positive women to their regional gynecologist. A total of 3691/28,689 (12.9%) women ordered a self-sampling kit and 10.0%

(2853/28,689) returned a sample for testing. Participation among women who had never attended screening was low, albeit improved. Up to 22.5% of women in other high-risk groups attended. High-risk HPV types were detected in 8.3% of samples. High-risk HPV-positive women (238/2853) were referred without further triaging and severe cervical precancer or cancer (HSIL+) in histopathology were detected in 36/158 (23%) of biopsied women. Repeat invitations gave modest additional participation. Nationwide contacting of women with high risk for cervical cancer with personal invitations to order HPV self-sampling kits resulted in high yield of detected CIN2+. Further efforts to improve risk-stratified screening strategies should be directed to improving (i) the precision of the risk-stratification algorithm, (ii) the convenience for the women to participate and, (iii) ensuring that screen-positive women are followed-up.

25COASMA52:

Title: Combined inhibition of RAD51 and CHK1 causes synergistic toxicity in cisplatin resistant cancer cells by triggering replication fork collapse

Julia Mann, Kathrin Niedermayer, Johannes Krautstrunk, Lena Abbey, Lisa Wiesmüller, Roland P. Piekorz, Gerhard Fritz

International Journal of Cancer, Vol. 156, Issue-2

Doi: **https://doi.org/10.1002/ijc.35164**

Abstract: The therapeutic efficacy of the anticancer drug cisplatin is limited by acquired drug resistance. Cisplatin forms DNA crosslinks, that, if not removed, lead to replication stress. Due to this, the DNA damage response (DDR) gets activated regulating cell cycle arrest, DNA repair, cell death or survival. This makes DDR components promising targets for the development of new therapeutic approaches aiming to overcome acquired drug resistance. To this end, cisplatin-resistant bladder cancer cells were analyzed regarding their sensitivity to combination treatments with selected pharmacological DDR inhibitors. Synergistic cytolethal effects were achieved after combined treatment with low to moderate doses of the non-genotoxic RAD51-inhibitor ($RAD51_i$) B02 and CHK1-inhibitor ($CHK1_i$) PF477736. This effect was also found in cisplatin resistant tumor cells of other origin as well as with other $RAD51_i$ and $CHK1_i$. Combined treatments promoted decelerated replication, S-phase blockage, accumulation of DNA strand breaks, DDR activation and stimulation of apoptotic cell death as compared to mono-treatment, which is independent of the expression of RAD51, CHK1, and PrimPol. Based on these data, we suggest combined inhibition of RAD51 and CHK1 to overcome acquired cisplatin resistance of malignant cells. We propose that the molecular mechanism of this synergistic toxicity relies on a simultaneous inactivation of two key DNA damage tolerance pathways regulating replication fork restart, thereby circumventing the activation of alternative compensatory mechanisms and, in consequence, eventually effectively triggering apoptotic cell death by replication fork collapse.

25COASMA53:

Title: Uncovering possible silent acquired long QT syndrome using exercise stress testing in long-term pediatric acute lymphoblastic leukemia survivors

Audrey Harvey, Maxime Caru, Cecilia Gonzalez Corcia, Émilie Bertrand, Vincent Gagné,

International Journal of Cancer, Vol. 156, Issue-2
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Abstract: An example of chemotherapy-induced cardiotoxicity in cancer survivors is acquired long QT syndrome (aLQTS), which may cause serious yet preventable life-threatening consequences. Our objective was to identify and characterize childhood acute lymphoblastic leukemia (ALL) survivors with possible aLQTS using maximal exercise testing. In this cross-sectional study with exploratory analysis, a total of 250 childhood ALL survivors were evaluated for abnormal QT interval prolongation using the McMaster cycle exercise test. A total of 198 survivors (102 males; 96 females), having reached their V̇O2 peak (mean 32.1 ± 8.4 mL/kg/min; range 15.5–57.8 mL/kg/min), were included in our analyses. Two survivors were excluded for possible congenital LQTS. QT intervals were corrected for heart rate using the Bazett, Fridericia, and Rautaharju formulas at rest (supine, sitting, and standing positions), at the end of each stage of the CPET, and at 1, 3, and 5 minutes into the recovery period. The corrected QT (QTc) of borderline (n = 37) and long QT survivors (n = 20) was significantly longer than normal survivors (n = 141) at rest, exercise, and recovery. Out of 57 survivors presenting an abnormal QTc prolongation, 40 survivors (70%) showed no QT interval anomalies at rest but developed various anomalies during exercise. No significant differences were found between the groups for any of the measured clinical characteristics or cardiac parameters. The standardization of exercise testing in the regular follow-up of oncology patients is necessary for appropriate cardiac prevention and surveillance to enhance the health and quality of life of the ever-increasing number of cancer survivors.

25COASMA54:

Title: Enhanced pharmacological activities of AKR1C3-activated prodrug AST-3424 in cancer cells with defective DNA repair

Fanying Meng, Tianyang Qi, Xing Liu, Yizhi Wang, Jibing Yu, Zhaoqiang Lu, Xiaohong Cai, Anrong Li, Don Jung, Jianxin Duan

International Journal of Cancer, Vol. 156, Issue-2
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Abstract: AST-3424 is a novel and highly tumor-selective prodrug. AST-3424 is activated by AKR1C3 to release a toxic bis-alkylating moiety, AST 2660. In this study, we have investigated the essential role of DNA repair in AST-3424 mediated pharmacological activities in vitro and in vivo. We show here that AST-3424 is effective as a single therapeutic agent against cancer cells to induce cytotoxicity, DNA damage, apoptosis and cell cycle arrest at G2 phase in a dose- and AKR1C3-dependent manner in both p53-proficient H460 (RRID:CVCL_0459) and p53-deficient HT-29 cells (RRID:CVCL_0320). The combination of abrogators of G2 checkpoint with AST-3424 was only synergistic in HT-29 but not in H460 cells. The enhanced activity of AST-3424 in HT-29 cells was due to impaired DNA repair ability via the attenuation of cell cycle G2 arrest and reduced RAD51 expression. Furthermore, we utilized a BRCA2 deficient cell line and two PDX models with BRCA deleterious mutations to study the increased activity of AST-3424. The results showed that AST-3424 exhibited enhanced in vitro cytotoxicity and superior and durable in vivo anti-

tumor effects in cells deficient of DNA repair protein BRCA2. In summary, we report here that when DNA repair capacity is reduced, the in vitro and in vivo activity of AST-3424 can be further enhanced, thus providing supporting evidence for the further evaluation of AST-3424 in the clinic.

25COASMA55:

Title: FHL2 expression by cancer-associated fibroblasts promotes metastasis and angiogenesis in lung adenocarcinoma

Ryu Kanzaki, Steven Reid, Paulina Bolivar, Jonas Sjölund, Johan Staaf, Sara Larsson,

International Journal of Cancer, Vol. 156, Issue-2

Doi: **https://doi.org/10.1002/ijc.35174**

Abstract: Cancer-associated fibroblasts (CAFs) contribute to the progression of lung cancer. Four and a half LIM domain protein-2 (FHL2) is a component of focal adhesion structures. We analyzed the function of FHL2 expressed by CAFs in lung adenocarcinoma. Expression of FHL2 in fibroblast subtypes was investigated using database of single-cell RNA-sequencing of lung cancer tissue. The role of FHL2 in the proliferation and migration of CAFs was assessed. The effects of FHL2 knockout on the migration and invasion of human lung adenocarcinoma cells and tube formation of endothelial cells induced by CAF-conditioned medium (CM) were evaluated. The effect of FHL2 knockout in CAFs on metastasis was determined using a murine orthotopic lung cancer model. The prognostic significance of stromal FHL2 was assessed by immunohistochemistry in human adenocarcinoma specimens. FHL2 is highly expressed in myofibroblasts in cancer tissue. TGF-β1 upregulated FHL2 expression in CAFs and FHL2 knockdown attenuated CAF proliferation. FHL2 knockout reduced CAF induced migration of A110L and H23 human lung adenocarcinoma cell lines, and the induction of tube formation of endothelial cells. FHL2 knockout reduced CAF-induced metastasis of lung adenocarcinomas in an orthotopic model in vivo. The concentration of Osteopontin (OPN) in CM from CAF was downregulated by FHL2 knockout. siRNA silencing and antibody blocking of OPN reduced the pro-migratory effect of CM from CAF on lung cancer cells. In resected lung adenocarcinoma specimens, positive stromal FHL2 expression was significantly associated with higher microvascular density and worse prognosis. In conclusion, FHL2 expression by CAFs enhances the progression of lung adenocarcinoma by promoting angiogenesis and metastasis.

25COASMA56:

Title: Effect of anesthetic technique on antitumor immunity in patients undergoing surgery for gall bladder cancer: A prospective randomized comparative study

Ankit Sharma, Lata Kumari, Brajesh Kumar Ratre, Maroof Ahmad Khan, Sunil Kumar,

Doi: **https://doi.org/10.1002/ijc.35179**

Abstract: There is a paucity of literature regarding the effect of anesthetic techniques on antitumor immunity, especially in gall bladder malignancies. We designed a study to compare the effect of propofol-based total intravenous anesthesia and sevoflurane-based general anesthesia—on antitumor immunity, including tumor growth factor-β (TGF-β), T-helper cell

profile, and inflammatory markers. A pilot prospective randomized trial was conducted in 64 patients undergoing surgery for gall bladder malignancy under general anesthesia in a tertiary specialty cancer hospital. Adult cancer patients of ASA physical status I-III fulfilling the inclusion criteria were randomized to either group S (sevoflurane-based general anesthesia) or group T (propofol-based total intravenous anesthesia). Preoperative (morning of surgery) and postoperative (24 h and 1 month after surgery) blood samples were obtained. Demographic profile and preoperative parameters were comparable between both groups. There was a statistically significant difference in the postoperative value of TGF-β (higher in group T). There was a statistically significant difference in postoperative interleukin-17A value (indicative of TH17 cells), and it was found to be higher in group S. Propofol-based TIVA increases serum TGF-β levels. At the same time, Sevoflurane modulates T-helper cells-based immunity to increase TH17 cells in patients with gall bladder cancer. Multiple larger studies will be required to validate the results and provide useful recommendations.

25COASMA57:

Title: Benefit of adjuvant chemotherapy on recurrence free survival per consensus molecular subtype in stage III colon cancer

Simone van de Weerd, Arezo Torang, Inge van den Berg, Veerle Lammers, Saskia van den Bergh,

International journal of Cancer, vol-156, no.2

Doi- **https://doi.org/10.1002/ijc.35120**

Abstract: The consensus molecular subtype (CMS) classification divides colon tumors into four subtypes holding promise as a predictive biomarker. However, the effect of adjuvant chemotherapy on recurrence free survival (RFS) per CMS in stage III patients remains inadequately explored. With this intention, we selected stage III colon cancer (CC) patients from the MATCH cohort (n = 575) and RadboudUMC (n = 276) diagnosed between 2005 and 2018. Patients treated with and without adjuvant chemotherapy were matched based on tumor location, T- and N-stage (n = 522). Tumor material was available for 464 patients, with successful RNA extraction and CMS subtyping achieved in 390 patients (surgery alone group: 192, adjuvant chemotherapy group: 198). In the overall cohort, CMS4 was associated with poorest prognosis (HR 1.55; p = .03). Multivariate analysis revealed favorable RFS for the adjuvant chemotherapy group in CMS1, CMS2, and CMS4 tumors (HR 0.19; p = .01, HR 0.27; p < .01, HR 0.19; p < .01, respectively), while no significant difference between treatment groups was observed within CMS3 (HR 0.68; p = .51). CMS subtyping in this non-randomized cohort identified patients with poor prognosis and patients who may not benefit significantly from adjuvant chemotherapy.

25COASMA58:

Title: Family history and genetic risk score combined to guide cancer risk stratification: A prospective cohort study

Chen Ji, Wenjing Ge, Chen Zhu, Fang Shen, Yuhui Yu, Guanlian Pang, Qiao Li, Mingxuan Zhu,

International journal of Cancer, vol-156, no.3

Doi-**https://doi.org/10.1002/ijc.35187**

Abstract: Family history (FH) of cancer and polygenic risk scores (PRS) are pivotal for cancer risk assessment, yet their combined impact remains unclear. Participants in the UK Biobank (UKB) were recruited between 2006 and 2010, with complete follow-up data updated until February 2020 for Scotland and January 2021 for England and Wales. Using UKB data (N = 442,399), we constructed PRS and incidence-weighted overall cancer PRS (CPRS). FH was assessed through self-reported standardized questions. Among 202,801 men (34.6% with FH) and 239,598 women (42.0% with FH), Cox regression was used to examine the associations between FH, PRS, and cancer risk. We found a significant dose–response relationship between FH of cancer and corresponding cancer risk ($P_{trend} < .05$), with over 10 significant pairs of cross-cancer effects of FH. FH and PRS are positively correlated and independent. Joint effects of FH of cancer (multiple cancers) and PRS (CPRS) on corresponding cancer risk were observed: for instance, compared with participants with no FH of cancer and low PRS, men with FH of cancer and high PRS had the highest risk of colorectal cancer (hazard ratio [HR]: 3.69, 95% confidence interval [CI]: 3.01–4.52). Additive interactions were observed in prostate and overall cancer risk for men and breast cancer for women, with the most significant result being a relative excess risk of interaction (RERI) of 2.98, accounting for ~34% of the prostate cancer risk. In conclusion, FH and PRS collectively contribute to cancer risk, supporting their combined application in personalized risk assessment and early intervention strategies.

25COASMA59:

Title:Impact of organized and opportunistic screening on excess mortality and on social inequalities in breast cancer survival

Marie Poiseuil, Florence Molinié, Tienhan Sandrine Dabakuyo-Yonli, Isabelle Laville,

International journal of Cancer, vol-156, no.3

Doi: **https://doi.org/10.1002/ijc.35173**

Abstract: In most developed countries, both organized screening (OrgS) and opportunistic screening (OppS) coexist. The literature has extensively covered the impact of organized screening on women's survival after breast cancer. However, the impact of opportunistic screening has been less frequently described due to the challenge of identifying the target population. The aim of this study was to describe the net survival and excess mortality hazard (EMH) in each screening group (OrgS, OppS, or No screening) and to determine whether there is an identical social gradient in each groups. Three data sources (cancer registry, screening coordination centers, and National Health Data System [NHDS]) were used to identify the three screening groups. The European Deprivation Index (EDI) defined the level of deprivation. We modeled excess breast cancer mortality hazard and net survival using penalized flexible models. We observed a higher EMH for “No screening” women compared with the other two groups, regardless of level of deprivation and age at diagnosis. A social gradient appeared for each group at different follow-up times and particularly between 2 and 3 years of follow-up for “OrgS” and “OppS” women. Net survival was higher for “OrgS” women than “OppS” women, especially for the oldest women, and regardless of the deprivation level. This study provides new evidence of the impact of OrgS on net survival

and excess mortality hazard after breast cancer, compared with opportunistic screening or no screening, and tends to show that OrgS attenuates the social gradient effect.

25COASMA60:

Title: Pelvic inflammatory disease and risk of borderline ovarian tumors: A national population-based case–control study in Sweden

Sarah Jonsson, Håkan Jonsson, Eva Lundin, Christel Häggström, Annika Idahl

International journal of Cancer, vol-156, no.3

Doi: **https://doi.org/10.1002/ijc.35180**

Abstract: The resemblance between fallopian tube cells and serous borderline ovarian tumors (BOTs) suggests a potential origin link, with salpingitis proposed as a contributing factor in the pathogenesis of BOT. This study aimed to explore the potential association between pelvic inflammatory disease (PID) and the risk of developing BOT. A national population-based case–control study in Sweden included women with BOT between 1999 and 2020 and 10 matched controls. Data from nationwide registers were analyzed using conditional logistic regression, adjusting for age, residential district, educational level and parity. Among 4782 cases and 45,167 controls, 2.0% of cases and 1.3% of controls had a history of PID. Previous PID was associated with an increased risk of BOT overall (aOR, 1.48; 95% CI, 1.19–1.85). Significant association was observed with serous tumors (aOR, 1.76; 95% CI, 1.36–2.29), while not with mucinous tumors (aOR, 0.95; 95% CI, 0.60–1.49). A dose–response relationship between number of PID episodes and serous BOT risk was noted ($P_{trend} < .001$). This study demonstrates that PID is associated with increased risk of serous BOT, with a dose response relationship. The study highlights the potential serious implications of upper reproductive tract infections and inflammation. This underscores the need for further investigation of biological mechanisms and possible impact of PID on serous BOT development.

25COASMA61:

Title:Occupational exposure to radiofrequency electromagnetic fields and brain tumor risk: Application of the INTEROCC job-exposure matrix

Maxime Turuban, Hans Kromhout, Javier Vila, Miquel Vallbona-Vistós, Frank De Vocht,

International journal of Cancer, vol-156, no.3

Doi: **https://doi.org/10.1002/ijc.35182**

Abstract: Radiofrequency electromagnetic fields (RF-EMF, 100 kHz to 300 GHz) are classified by IARC as possibly carcinogenic to humans (Group 2B). This study evaluates the potential association between occupational RF-EMF exposure and brain tumor risk, utilizing for the first time, a RF-EMF job-exposure matrix (RF-JEM) developed in the multi-country INTEROCC case–control study. Cumulative and time-weighted average (TWA) occupational RF-EMF exposures were estimated for study participants based on lifetime job histories linked to the RF-JEM using three different methods: (1) by considering RF-EMF intensity among all exposed jobs, (2) by considering RF-EMF intensity among jobs with an exposure prevalence ≥ the median exposure prevalence of all exposed jobs, and (3) by considering RF-EMF intensity of jobs of participants who reported RF-EMF source use. Stratified conditional

logistic regression models were used, considering various lag periods and exposure time windows defined a priori. Generally, no clear associations were found for glioma or meningioma risk. However, some statistically significant positive associations were observed including in the highest exposure categories for glioma for cumulative and TWA exposure in the 1- to 4-year time window for electric fields (E) in the first JEM application method (odds ratios [ORs] = 1.36, 95% confidence interval [95% CI] 1.08, 1.72 and 1.27, 95% CI 1.01, 1.59, respectively), as well as for meningioma for cumulative exposure in the 5- to 9-year time window for electric fields (E) in the third JEM application method (OR = 2.30, 95% CI 1.11, 4.78). We did not identify convincing associations between occupational RF-EMF exposure and risk of glioma or meningioma.

25COASMA62:

Title:Circulating tryptophan–kynurenine pathway metabolites are associated with all-cause mortality among patients with stage I–III colorectal cancer

Victoria Damerell, Niels Klaassen-Dekker, Stefanie Brezina, Jennifer Ose, Arve Ulvik, Eline H. van Roekel,

International journal of Cancer, vol-156, no.3

Dio: **https://doi.org/10.1002/ijc.35183**

Abstract: Alterations within the tryptophan–kynurenine metabolic pathway have been linked to the etiology of colorectal cancer (CRC), but the relevance of this pathway for prognostic outcomes in CRC patients needs further elucidation. Therefore, we investigated associations between circulating concentrations of tryptophan–kynurenine pathway metabolites and all-cause mortality among CRC patients. This study utilizes data from 2102 stage I–III CRC patients participating in six prospective cohorts involved in the international FOCUS Consortium. Preoperative circulating concentrations of tryptophan, kynurenine, kynurenic acid (KA), 3-hydroxykynurenine (HK), xanthurenic acid (XA), 3-hydroxyanthranilic acid (HAA), anthranilic acid (AA), picolinic acid (PA), and quinolinic acid (QA) were measured by liquid chromatography–tandem mass spectrometry. Using Cox proportional hazards regression, we examined associations of above-mentioned metabolites with all-cause mortality, adjusted for potential confounders. During a median follow-up of 3.2 years (interquartile range: 2.2–4.9), 290 patients (13.8%) deceased. Higher blood concentrations of tryptophan, XA, and PA were associated with a lower risk of all-cause mortality (per doubling in concentrations: tryptophan: HR = 0.56; 95%CI:0.41,0.76, XA: HR = 0.74; 95%CI:0.64,0.85, PA: HR = 0.76; 95%CI:0.64,0.92), while higher concentrations of HK and QA were associated with an increased risk of death (per doubling in concentrations: HK: HR = 1.80; 95%CI:1.47,2.21, QA: HR = 1.31; 95%CI:1.05,1.63). A higher kynurenine-to-tryptophan ratio, a marker of cell-mediated immune activation, was associated with an increased risk of death (per doubling: HR = 2.07; 95%CI:1.52,2.83). In conclusion, tryptophan–kynurenine pathway metabolites may be prognostic markers of survival in CRC patients.

25COASMA63:

Title:Life's Essential 8, genetic susceptibility, and risk of incident pancreatic cancer: A prospective cohort study

Zhuo Wu, Liangtang Zeng, Zhou Fang, Yuan Yuan, Yu Zhou, Rufu Chen

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Doi: **https://doi.org/10.1002/ijc.35184**

Abstract: The association between the American Heart Association (AHA) Life's Essential 8 (LE8) and the risk of pancreatic cancer (PC) remains unclear. Our goal was to assess the relationships between LE8, genetic susceptibility, and PC risk. This cohort consisted of 234,102 participants from the UK Biobank. The components of LE8 include diet, nicotine exposure, sleep, physical activity, blood glucose, body mass index, blood lipids, and blood pressure. LE8 is classified into three categories: low cardiovascular health (CVH), moderate CVH, and high CVH. Measurements were made using Cox proportional risk models to estimate impact of associations between LE8, genetic susceptibility, and incidence of PC in participants. Compared to participants with low LE8 scores, those with moderate and high LE8 scores had a 53% (HR, 0.47; 95% CI, 0.39–0.57) and 70% (HR, 0.30; 95% CI, 0.22–0.41) lower risk of developing PC, respectively. Interestingly, among individuals with high genetic risk, high LE8 scores were associated with greater benefits (HR, 0.24; 95% CI, 0.15–0.40), whereas the protective effect was weaker among those with low genetic risk (HR, 0.40; 95% CI, 0.21–0.75). Participants with a high LE8 score and a low polygenic risk score (PRS) had the lowest risk of PC (HR, 0.19; 95% CI: 0.11–0.33). Furthermore, we observed a significant additive interaction between LE8 and PRS. A higher LE8 score is associated with a lower risk of PC, especially for participants with a high PRS. These findings have important implications for participants most genetically predisposed to PC and for targeted strategies for PC prevention.

25COASMA64:

Title: Does use of anal cytology as a triage test improve the performance of high-risk human papillomavirus screening in gay and bisexual men for anal cancer prevention?

Fengyi Jin, I. Mary Poynten, Richard J. Hillman, Carmella Law, Monica Molano,

International journal of Cancer, vol-156, no.3

Doi: **https://doi.org/10.1002/ijc.35185**

Abstract: Anal high-risk human papillomavirus (HRHPV) testing-based anal cancer screening gay and bisexual men (GBM) is associated with high sensitivity, but low specificity. We report the potential role of triage use of anal cytology with HRHPV testing in detecting 12-month persistent anal high-grade squamous epithelial lesions (HSIL) in a cohort of GBM in Sydney, Australia. Participants were GBM from the Study of the Prevention of Anal Cancer (SPANC) who underwent annual anal HPV testing, cytology, and high-resolution anoscopy (HRA)-guided histology. The sensitivity and specificity of five screening algorithms based on HRHPV test results with triage use of anal cytology (atypical squamous cells of undetermined significance (ASCUS) and atypical squamous cells, cannot exclude HSIL (ASC-H) used as referral thresholds) were compared to these of HRHPV testing and anal cytology alone. A total of 475 men who had valid HRHPV, cytological, and histological

results at both baseline and first annual follow-up visits were included, median age 49 years (inter-quartile range: 43–56) and 173 (36.4%) GBM with human immunodeficiency virus. Of all triage algorithms assessed, two had comparable sensitivity with HRHPV testing alone in detecting persistent anal HSIL, but ~20% higher specificity and 20% lower HRA referral rates. These two algorithms involved the immediate referral of those with HPV16 and for those with non-16 HRHPV either immediate or delayed (for 12 months) referral, depending on cytology result at baseline. Triage use of anal cytology in GBM testing positive for anal HRHPV increases specificity and reduces referral rates while maintaining high sensitivity in detection of HSIL.

25COASMA65:

Title:Use of chemotherapy and loco-regional therapy in stage IA triple-negative breast cancer and their association with oncologic outcomes: A cancer registry study

André Pfob, Irina Surovtsova, Daria B. Kokh, Baden-Württemberg Cancer Registry (BWCR), Joerg Heil, Maggie Banys-Paluchowski,

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Abstract: We aimed to evaluate the role of adjuvant chemotherapy and loco-regional therapy for stage IA (pT1, pN0) triple-negative breast cancer (TNBC) in a real-world setting. We identified patients with pT1, pN0 TNBC diagnosed between 2009 and 2021 within the Baden-Württemberg cancer registry (BWCR), Germany. Overall survival (OS) was assessed using Kaplan–Meier statistics and multivariate Cox regression models (adjusted for age, use of chemotherapy, local therapy (breast conserving therapy [breast conserving surgery + radiotherapy] vs. mastectomy), and tumor histologic subtype). A total of 1231 patients with a median follow-up of 45.9 months were identified: 1.0% (12 of 1231) with pT1mi stage, 9.5% (117 of 1231) with pT1a, 23.7% (292 of 1231) with pT1b, and 65.8% (810 of 1231) with pT1c. Multivariate Cox regression analysis revealed no significant influence for the use of chemotherapy on OS in pT1b patients (HR 0.90, 95% CI 0.43–1.90). For pT1c patients with Grade 1–2 tumors, the use of chemotherapy was not significantly associated OS (HR 1.01, 95% CI 0.48–2.11) but breast conserving therapy was associated with improved OS (HR 0.41, 95% CI 0.18–0.93). For pT1c patients with Grade 3 tumors, the use of chemotherapy (HR 0.51, 95% CI 0.33–0.78) as well as breast conserving therapy (HR 0.42, 95% CI 0.23–0.76) was associated with OS. This data suggests that OS in stage IA TNBC is strongly influenced by local therapy rather than the use of chemotherapy, except for pT1c patients with Grade 3 tumors. Larger studies with longer-term follow-up are welcomed to fully inform this discussion.

25COASMA66:

Title: Performance of visual inspection, partial genotyping, and their combination for the triage of women living with HIV who are screen positive for human papillomavirus: Results from the AIMA-CC ANRS 12375 multicentric screening study

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Abstract: The WHO recommends the use of human papillomavirus (HPV) testing for primary cervical cancer (CC) screening because of its high sensitivity. However, triage is desirable to correctly identify HPV+ women who have high-grade lesions (CIN2+) and require treatment. The ANRS-12375 study was conducted in Côte d'Ivoire, Burkina Faso and Cambodia to assess the performance, feasibility and benefits of different triage options for detecting CIN2+ lesions: partial (HPV16 and HPV16/18/45) and extended genotyping, visual inspection (VIA) alone and VIA combined with partial genotyping. VIA was performed by gynecologists. The sensitivity, specificity, and diagnostic likelihood ratio (DLR) of each triage option for detecting CIN2+ lesions with histology as a reference standard were calculated. Of the 2253 women living with HIV (WLHIV) included, 932 (41%) were HPV+. A CIN2+ lesion was identified in 105 (13%) of the 777 participants with histopathology results. The sensitivity of VIA as a triage test for CIN2+ patients was 89%, while that for extended genotyping was 89%, that for HPV16/18/45 partial genotyping was 51%, and that for HPV16 partial genotyping was 36%. The specificities for these tests were 45%, 29%, 72%., and 85%, respectively. Combining VIA and/or partial genotyping positivity slightly increased the sensitivity (94%) at the cost of lower specificity (28%). There was significant intersite heterogeneity ($p = .04$). Among the three triage tests with a sensitivity ≥85%, the VIA had the highest specificity and positive likelihood ratio ($p < .001$). VIA and extended genotyping, whether independent or combined, are good triage options with high sensitivity for identifying WLHIV needing treatment for CIN2+.

25COASMA67:

Title: The risk of treatment-related toxicities with PD-1/PD-L1 inhibitors in patients with lung cancer

Hao Hu, Qian Zhu, Hua Tang, Si-Cai Zhang, Yan-Ze Huang, Ya-Fang Wang, Zhi-Yong Xu, Xiong-Wen Yang, Ji-Hua Zheng, Chang-Ying Guo

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Doi-**https://doi.org/10.1002/ijc.35195**

Abstract: The risk of treatment-related toxicities with programmed cell death 1 and its ligand (PD-1/PD-L1) inhibitors in patients with lung cancer is unclear and inconclusive. PubMed, EMBASE, and the Cochrane Library databases were systematically searched without language restrictions from inception to May 31, 2024 to identify Phase 3 randomized controlled trials of lung cancer comparing PD-1/PD-L1 inhibitors versus placebo/best supportive care (alone or in combination with nontargeted chemotherapy) that had available data regarding treatment-related adverse events (TRAEs) or incidence and sample size. Random-effect models were employed to study the pooled relative risk (RR) and 95% confidence intervals (CIs). Finally, 36 trials, involving 19,693 participants, fulfilled the inclusion criteria. PD-1/PD-L1 inhibitors significantly augmented the likelihood of developing all-grade (RR, 1.03; 95% CI, 1.01–1.04, $p < .01$) and grade ≥3 TRAEs (RR, 1.16; 95% CI, 1.10 to 1.23, $p < .01$). PD-1/PD-L1 inhibitors substantially augmented the odds of developing treatment-related serious adverse events (SAEs) (RR, 1.48; 95% CI, 1.27–

1.71, p < .01) and fatal adverse events (FAEs) (RR, 1.42; 95% CI, 1.11–1.82, p < .01). Subgroup analyses indicated that the RR of SAEs and FAEs were generally consistent, regardless of treatment type, tumor type, treatment setting, PD-1/PD-L1 inhibitors type and study design. The most common causes of FAEs were respiratory failure/insufficiency (33.3%), cardiac events (16.1%), and hematological disorders (10.1%). We demonstrated that PD-1/PD-L1 inhibitors were significantly correlated with higher possibility of developing treatment-related toxicities, especially SAEs and FAEs, compared with placebo/best supportive care controls.

25COASMA68:

Title: 14-3-3σ restricts YY1 to the cytoplasm, promoting therapy resistance, and tumor progression in colorectal cancer

Amol Lonare, Kumarkrishna Raychaudhuri, Sanket Shah, Gifty Madhu, Anoushka Sachdeva, Sneha Basu, Rahul Thorat, Sanjay Gupta, Sorab N. Dalal

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Doi-**https://doi.org/10.1002/ijc.35176**

Abstract: 14-3-3σ functions as an oncogene in colorectal cancer and is associated with therapy resistance. However, the mechanisms underlying these observations are not clear. The results in this report demonstrate that loss of 14-3-3σ in colorectal cancer cells leads to a decrease in tumor formation and increased sensitivity to chemotherapy. The increased sensitivity to chemotherapy is due to a decrease in the expression of UPR pathway genes in the absence of 14-3-3σ. 14-3-3σ promotes expression of the UPR pathway genes by binding to the transcription factor YY1 and preventing the nuclear localization of YY1. YY1, in the absence of 14-3-3σ, shows increased nuclear localization and binds to the promoter of the UPR pathway genes, resulting in decreased gene expression. Similarly, a YY1 mutant that cannot bind to 14-3-3σ also shows increased nuclear localization and is enriched on the promoter of the UPR pathway genes. Finally, inhibition of the UPR pathway with genetic or pharmacological approaches sensitizes colon cancer cells to chemotherapy. Our results identify a novel mechanism by which 14-3-3σ promotes tumor progression and therapy resistance in colorectal cancer by maintaining UPR gene expression.

25COASMA69:

Title: Cytokine-armed vaccinia virus promotes cytotoxicity toward pancreatic carcinoma cells via activation of human intermediary CD56^{dim}CD16^{dim} natural killer cells

Ruonan Wang, Mengwen Hu, Isis Lozzi, Cao Zhong Jing Jin, Dou Ma, Katrin Splith, Jörg Mengwasser, Vincent Wolf,

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Doi-**https://doi.org/10.1002/ijc.35209**

Abstract: Pancreatic ductal adenocarcinoma (PDAC) remains a particularly aggressive disease with few effective treatments. The PDAC tumor immune microenvironment (TIME) is known to be immune suppressive. Oncolytic viruses can increase tumor immunogenicity via immunogenic cell death (ICD). We focused on tumor-selective (vvDD) and cytokine-

armed Western-reserve vaccinia viruses (vvDD-IL2 and vvDD-IL15) and infected carcinoma cell lines as well as patient-derived primary PDAC cells. In co-culture experiments, we investigated the cytotoxic response and the activation of human natural killer (NK). Infection and virus replication were assessed by measuring virus encoded YFP. We then analyzed intracellular signaling processes and oncolysis via in-depth proteomic analysis, immunoblotting and TUNEL assay. Following the co-culture of mock or virus infected carcinoma cell lines with allogenic PBMCs or NK cell lines, $CD56^{+}$ NK cells were analyzed with respect to their activation, cytotoxicity and effector function. Both, dose- and time-dependent release of danger signals following infection were measured. Viruses effectively entered PDAC cells, emitted YFP signals and resulted in concomitant oncolysis. The proteome showed reprogramming of normally active core signaling pathways in PDAC (e.g., MAPK–ERK signaling). Danger-associated molecular patterns were released upon infection and stimulated co-cultured NK cells for enhanced effector cytotoxicity. NK cell subtyping revealed enhanced numbers and activation of a rare $CD56^{dim}CD16^{dim}$ population. Tumor cell killing was primarily triggered via Fas ligands rather than granule release, resulting in marked apoptosis. Overall, the cytokine-armed vaccinia viruses induced NK cell activation and enhanced cytotoxicity toward human PDAC cells in vitro. We could show that cytokine-armed virus targets the carcinoma cells and thus has great potential to modulate the TIME in PDAC.

25COASMA70:

Title: Detection of anti-EBV TCR CDR3s associated with better outcomes for EBV-positive, Ugandan cases of Burkitt lymphoma

Rahul Jain, Taha I. Huda, Srijit Paul, Andrea Chobrutskiy, Boris I. Chobrutskiy, Madeline C. Baker, Nandini Goel, George Blanck

International journal of Cancer, vol-156, no.3

Doi- **https://doi.org/10.1002/ijc.35212**

Abstract: Burkitt lymphoma (BL) has a tight association with Epstein–Barr virus (EBV), especially in sub-Saharan Africa. While the relationship between BL and EBV is well documented, the relationship between the anti-EBV adaptive immune response, particularly in sub-Saharan African cases, and disease course, has not been substantially investigated. An analysis of T-cell receptor (TCR) complementarity determining region-3 (CDR3) sequences, reported here, from EBV-positive, Ugandan BL tumor samples revealed a correlation between the presence of anti-EBV CDR3s and improved overall survival probabilities. Furthermore, chemical complementarity assessments demonstrated higher complementarity for TCR CDR3s and EBV epitopes in the cases where there had been a detection of the anti-EBV CDR3 AA sequence matches in the BL tumor samples. Overall, the results reported here raise the question of whether EBV targeted immunotherapy would lead to better BL outcomes?

25COASMA71:

Title: Recurrent cervical cancer detection using DNA methylation markers in self-collected samples from home

Mirte Schaafsma, Rianne van den Helder, Constantijne H. Mom, Renske D. M. Steenbergen, Maaike C. G. Bleeker, Nienke E. van Trommel
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Doi- **https://doi.org/10.1002/ijc.35143**
Abstract: Early detection of recurrent cervical cancer is important to improve survival rates. The aim of this study was to explore the clinical performance of DNA methylation markers and high-risk human papillomavirus (HPV) in cervicovaginal self-samples and urine for the detection of recurrent cervical cancer. Cervical cancer patients without recurrence (n = 47) collected cervicovaginal self-samples and urine pre- and posttreatment. Additionally, 20 patients with recurrent cervical cancer collected cervicovaginal self-samples and urine at time of recurrence. All samples were self-collected at home and tested for DNA methylation and high-risk HPV DNA by PCR. In patients without recurrent cervical cancer, DNA methylation levels decreased 2-years posttreatment compared to pretreatment in cervicovaginal self-samples ($p < .0001$) and urine ($p < .0001$). DNA methylation positivity in cervicovaginal self-samples was more frequently observed in patients with recurrence (77.8%) than in patients without recurrence 2-years posttreatment (25.5%; $p = .0004$). Also in urine, DNA methylation positivity was more frequently observed in patients with recurrence (65%) compared to those without recurrence (35.6%; $p = .038$). Similarly, high-risk HPV positivity in both cervicovaginal self-samples and urine was more frequent (52.6% and 55%, respectively) in patients with recurrence compared to patients without recurrence (14.9% and 8.5%, respectively) ($p = .004$ and $p = .0001$). In conclusion, this study shows the potential of posttreatment monitoring of cervical cancer patients for recurrence by DNA methylation and high-risk HPV testing in cervicovaginal and urine samples collected at home. The highest recurrence detection rate was achieved by DNA methylation testing in cervicovaginal self-samples, detecting 77.8% of all recurrences and, specifically, 100% of the local recurrences.

25COASMA72:

Title: The transcriptional landscape and clinico-biological characterization of human endogenous retroviruses in esophageal squamous cell carcinoma

Xinrui Shi, Minyi Lu, Xukun Li, Jiaqi Li, Siqi Bao, Caifeng Jia, Hongyan Chen
International journal of Cancer, vol-156, no.3
Doi-**https://doi.org/10.1002/ijc.35147**
Abstract: Human endogenous retroviruses (HERVs) are emerging as critical elements in host genomic regulation. Aberrant HERV transcription has been implicated in developmental and tissue-specific aging and pathological processes. In this study, we presented a comprehensive locus-specific characterization of the HERV expression landscape in esophageal squamous cell carcinoma (ESCC). We demonstrated the transcriptional diversity among patients and identified 12 clinically relevant HERVs in the SCH cohort, which were experimentally validated by Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR) in the CAMS cohort. ESCC patients were stratified into three HERV-based subtypes ($HERV^{high}$, $HERV^{median}$ and $HERV^{low}$) with distinct clinical and biological characteristics. The $HERV^{high}$ subtype was associated with worse survival, increased CD4+ T cells infiltration and decreased metabolic activity, whereas the $HERV^{low}$ subtype was characterized by

abundant CD8+ T cells, increased metabolic activity, and better survival. The HERV-based tumor subtyping was further robustly validated by RNA sequencing and RT-qPCR in two additional external cohorts. Our findings demonstrate the clinical significance of HERVs for tumor subtyping and prognosis, provide insights into the functional role of HERVs and a valuable resource for developing novel biomarkers and therapeutic targets in ESCC.

25COASMA73:

Title: Anxiety and depression in cancer patients and survivors in the context of restrictions in contact and oncological care during the COVID-19 pandemic

Daniela Doege, Julien Frick, Rachel D. Eckford, Lena Koch-Gallenkamp, Michael Schlander, Baden-Württemberg Cancer Registry, Volker Arndt

International journal of Cancer, vol-156, no.4

Doi- **https://doi.org/10.1002/ijc.35204**

Abstract: Treatment modifications and contact restrictions were common during the COVID-19 pandemic and can be stressors for mental health. There is a lack of studies assessing pandemic-related risk factors for anxiety and depression of cancer patients and survivors systematically in multifactorial models. A total of 2391 participants, mean age 65.5 years, ≤5 years post-diagnosis of either lung, prostate, breast, colorectal cancer, or leukemia/lymphoma, were recruited in 2021 via the Baden-Württemberg Cancer Registry, Germany. Sociodemographic information, pandemic-related treatment modifications, contact restrictions, and anxiety/depression (Hospital Anxiety and Depression Scale, HADS) were assessed via self-administered questionnaire. Clinical information (diagnosis, stage, and treatment information) was obtained from the cancer registry. Overall, 22% of participants reported oncological care modifications due to COVID-19, mostly in follow-up care and rehabilitation. Modifications of active cancer treatment were reported by 5.8%. Among those, 50.5% had subclinical anxiety and 55.4% subclinical depression (vs. 37.4% and 45.4%, respectively, for unchanged active treatment). Age <60 years, female sex, lung cancer, low income, and contact restrictions to peer support groups or physicians were identified as independent risk factors for anxiety. Risk factors for depression were lung cancer (both sexes), leukemia/lymphoma (females), recurrence or palliative treatment, living alone, low income, and contact restrictions to relatives, physicians, or caregivers. The study demonstrates that changes in active cancer treatment and contact restrictions are associated with impaired mental well-being. The psychological consequences of treatment changes and the importance for cancer patients to maintain regular contact with their physicians should be considered in future responses to threats to public health.

25COASMA74:

Title:Association between family history with lung cancer incidence and mortality risk in the Asia Cohort Consortium

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Doi-**https://doi.org/10.1002/ijc.35191**

Abstract: Family history of lung cancer (FHLC) has been widely studied but most prospective cohort studies have primarily been conducted in non-Asian countries. We assessed the association between FHLC with risk of lung cancer (LC) incidence and mortality in a population of East Asian individuals. A total of 478,354 participants from 11 population-based cohorts in the Asia Cohort Consortium were included. A Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). A total of 7,785 LC incident cases were identified. FHLC (any LC subtype) was associated with an increased risk of LC incidence (HR = 1.45, 95% CI = 1.30–1.63). The positive association was observed in men and women (HR = 1.44, 95% CI = 1.26–1.66 in men; HR = 1.47, 95% CI = 1.22–1.79 in women), and in both never-smokers and ever-smokers (HR = 1.43, 95% CI = 1.18–1.73 in never-smokers; HR = 1.46, 95% CI =1.27–1.67 in ever-smokers). FHLC was associated with an increased risk of lung adenocarcinoma (HR = 1.63, 95% CI: 1.36–1. 94), squamous cell carcinoma (HR = 1.88, 95% CI: 1.46–2.44), and other non-small cell LC (HR = 1.94, 95% CI: 1.02–3.68). However, we found no evidence of significant effect modification by sex, smoking status, and ethnic groups. In conclusion, FHLC was associated with increased risk of LC incidence and mortality, and the associations remained consistent regardless of sex, smoking status and ethnic groups among the East Asian population.

25COASMA75:

Title: Postmarketing adverse events of tamoxifen in male and female patients with breast cancer

Chengjie Ke, Maohua Chen, Li Lin, Yaping Huang

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Doi-**https://doi.org/10.1002/ijc.35193**

Abstract: Tamoxifen (TAM), a selective estrogen receptor (ER) modulator, has received approval for use in patients with breast cancer (BC) exhibiting positive ER expression. Given the widespread clinical use of TAM, a comprehensive real-world study of its adverse events (AEs) is warranted. The database for analysis, sourced from the Food and Drug Administration Adverse Event Reporting System (FAERS), covers the period from the first quarter of 2014 to the third quarter of 2023. A disproportionality analysis was conducted to quantify the correlation between TAM and AEs. Subgroup analyses were performed to identify differences between BC AEs in males and females receiving TAM, aiming to assess the risk factors of male BC AEs. Total 4890 reports indicated BC, with 91 and 4190 specifically linked to AEs in male and female patients with BC, respectively. Male-specific AE was libido decreased (reporting odds ratio [ROR]: 43.33), and female-specific AE was uterine disease, including sarcoma uterus (ROR: 519.51), endometrial cancer (ROR: 131.26), uterine polyp (ROR: 40.83), endometriosis (ROR: 11.39), among others. A notably higher risk of AEs in male patients with BC was observed in individuals aged >65 years ($\chi^2 = 20.83$, $p < .001$). Male patients with BC had a relatively higher risk of hospitalization ($\chi^2 = 4.83$, $p = .03$) and a lower risk of deaths ($\chi^2 = 5.32$, $p = .02$). Theses finding may assist healthcare professionals in recognizing the TAM-associated AEs and understanding gender differences, potentially improving safety in clinical applications.

25COASMA76:

Title: Potentially functional variants of PARK7 and DDR2 in ferroptosis-related genes predict survival of non-small cell lung cancer patients

Huilin Wang, Hongliang Liu, Xiaozhun Tang, Guojun Lu, Sheng Luo, Mulong Du, David C. Christiani, Qingyi Wei

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Abstract: Ferroptosis, a form of regulated cell death, is characterized by iron-dependent lipid peroxidation. It is recognized increasingly for its pivotal role in both cancer development and the response to cancer treatments. We assessed associations between 370,027 single-nucleotide polymorphisms (SNPs) within 467 ferroptosis-related genes and survival of non-small cell lung cancer (NSCLC) patients. Data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial served as our discovery dataset, while the Harvard Lung Cancer Susceptibility Study used as our validation dataset. For SNPs that remained statistically significantly associated with overall survival (OS) in both datasets, we employed a multivariable stepwise Cox proportional hazards regression model with the PLCO dataset. Ultimately, two independent SNPs, PARK7 rs225120 C>T and DDR2 rs881127 T>C, were identified with adjusted hazard ratios of 1.32 (95% confidence interval = 1.15–1.52, p = .0001) and 1.34 (95% confidence interval = 1.09–1.64, p = .006) for OS, respectively. We aggregated these two SNPs into a genetic score reflecting the number of unfavorable genotypes (NUG) in further multivariable analysis, revealing a noteworthy association between increased NUG and diminished OS (p_{trend} = .001). Additionally, an expression quantitative trait loci analysis indicated that PARK7 rs225120T genotypes were significantly associated with higher PARK7 mRNA expression levels in both whole blood and normal lung tissue. Conversely, DDR2 rs881127C genotypes were significantly associated with lower DDR2 mRNA expression levels in normal lung tissue. Our findings suggest that genetic variants in the ferroptosis-related genes PARK7 and DDR2 are associated with NSCLC survival, potentially through their influence on gene expression levels.

25COASMA77:

Title: Profound primary prevention of liver cancer following a natural experiment in China: A 50-year perspective and public health implications

Jian-Guo Chen, Thomas W. Kensler, Jian Zhu, Yuan-Rong Zhu, Jin-Bing Wang, Jian-Hua Lu, Alvaro Muñoz, John D. Groopman

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Doi- **https://doi.org/10.1002/ijc.35198**

Abstract: Liver cancer causes upwards of 1 million cancer deaths annually and is projected to rise by at least 55% over the next 15 years. Two of the major risk factors contributing to liver cancer have been well documented by multiple epidemiologic studies and the hepatitis B virus (HBV) and aflatoxin show a synergy that increases by more than 8-fold the risk of liver cancer relative to HBV alone. Using the population-based cancer registry established by the Qidong Liver Cancer Institute in 1972 and aflatoxin-specific biomarkers, we document

that reduction of aflatoxin exposure has likely contributed to a nearly 70% decline in age-standardized liver cancer incidence over the past 30 years despite an unchanging prevalence of HBV infection in cases. A natural experiment of economic reform in the 1980s drove a rapid switch from consumption of heavily contaminated corn to minimally, if any, contaminated rice and subsequent dietary diversity. Aflatoxin consumption appears to accelerate the time to liver cancer diagnosis; lowering exposure to this carcinogen adds years of life before a cancer diagnosis. Thus, in 1990 the median age of diagnosis was 48 years, while increasing to 67 years by 2021. These findings have important translational public health implications since up to 5 billion people worldwide might be routinely exposed to dietary aflatoxin, especially in societies using corn as the staple food. Interventions against aflatoxin are an achievable outcome leading to a reduction in liver cancer incidence and years of delay of its nearly always fatal diagnosis.

25COASMA78:

Title: Comparative sequencing study of mismatch repair and homology-directed repair genes in endometrial cancer and breast cancer patients from Kazakhstan

Ying Zheng, Natalia Vdovichenko, Peter Schürmann, Dhanya Ramachandran, Robert Geffers,

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Doi- **https://doi.org/10.1002/ijc.35215**

Abstract: Endometrial cancer has been associated with pathogenic variants in mismatch repair (MMR) genes, especially in the context of the hereditary Lynch Syndrome. More recently, pathogenic variants in genes of homology-directed repair (HDR) have also been suggested to contribute to a subset of endometrial cancers. In the present hospital-based study, we investigated the relative distribution of pathogenic MMR or HDR gene variants in a series of 342 endometrial cancer patients from the Oncology Clinic in Almaty, Kazakhstan. In comparison, we also sequenced 178 breast cancer patients from the same population with the same gene panel. Identified variants were classified according to ClinVar, ESM1b, and AlphaMissense prediction tools. We found 10 endometrial cancer patients (2.9%) carrying pathogenic or likely pathogenic variants in MMR genes (7 MSH6, 1 MSH2, 2 MUTYH), while 14 endometrial cancer patients (4.1%) carried pathogenic variants in HDR genes (4 BRCA2, 3 BRCA1, 3 FANCM, 2 SLX4, 1 BARD1, 1 BRIP1). In the breast cancer series, we found 8 carriers (4.5%) of pathogenic or likely pathogenic variants in MMR genes (2 MSH2, 2 MSH6, 4 MUTYH) while 12 patients (6.7%) harbored pathogenic or likely pathogenic HDR gene variants (5 BRCA1, 3 BRCA2, 1 BRIP1, 1 ERRC4, 1 FANCM, 1 SLX4). One patient who developed breast cancer first and endometrial cancer later carried a novel frameshift variant in MSH6. Our results indicate that MMR and HDR gene variants with predicted pathogenicity occur at substantial frequencies in both breast and endometrial cancer patients from the Kazakh population.

25COASMA79:

Title: Oligometastatic non-small cell lung cancer: Impact of local and contemporary systemic treatment approaches on clinical outcome

Marcel Wiesweg, Claudia Küter, Johannes Schnorbach, Julius Keyl, Martin Metzenmacher,
International journal of Cancer, vol-156, no.4
Doi-**https://doi.org/10.1002/ijc.35199**
Abstract: Oligometastatic (OMD) non-small cell lung cancer (NSCLC) is a distinct but heterogeneous entity. Current guidelines recommend systemic therapy and consolidation with local ablative therapy (LAT). However, evidence regarding the optimal choice of multimodal treatment approaches is lacking, in particular with respect to the integration of immunotherapy. This real-world study identified 218 patients with OMD NSCLC (2004–2023, prespecified criteria: ≤5 metastases in ≤2 organ systems) from three major German comprehensive cancer centers. Most patients had one (72.5%) or two (17.4%) metastatic lesions in a single (89.9%) organ system. Overall survival (OS) was significantly longer with a single metastatic lesion (HR 0.54, p = .003), and female gender (HR 0.4, p < .001). Median OS of the full cohort was 27.8 months, with 29% survival at 5 years. Patients who had completed LAT to all NSCLC sites, typically excluding patients with early progression, had a median OS of 34.4 months (37.7% 5-year OS rate) with a median recurrence-free survival (RFS) of 10.9 months (13.3% at 5 years). In those patients, systemic treatment as part of first-line therapy was associated with doubling of RFS (12.3 vs. 6.4 months, p < .001). Despite limited follow-up of patients receiving chemo-immunotherapy (EU approval 2018/2019), RFS was greatly improved by adding checkpoint inhibitors to chemotherapy (HR 0.44, p = .008, 2-year RFS 51.4% vs. 15.1%). In conclusion, patients with OMD NSCLC benefitted from multimodality approaches integrating systemic therapy and local ablation of all cancer sites. A substantial proportion of patients achieved extended OS, suggesting a potential for cure that can be further augmented with the addition of immunotherapy.

25COASMA80:

Title: Clinically validated HPV assays offer comparable long-term safety in primary cervical cancer screening: A 9-year follow-up of a population-based screening cohort

Anja Oštrbenk Valenčak, Kelsi R. Kroon, Danijela Fabjan, Jana Mlakar, Katja Seme,
International journal of Cancer, vol-156, no.4
Doi-**https://doi.org/10.1002/ijc.35200**
Abstract: Molecular testing for human papillomaviruses (HPV) is gradually replacing cytology in cervical cancer screening. In this longitudinal population-based cohort study, 4140 women 20 to 64 years old attending organized screening were tested at baseline by five different screening methods and followed for 9 years. To assess long-term safety, the cumulative risks of CIN2+/CIN3+ were estimated after a negative baseline result obtained by conventional cytology and four clinically validated HPV assays: Hybrid Capture 2 (hc2), RealTime High Risk HPV assay (RealTime), cobas 4800 HPV Test (cobas_4800), and Alinity m HR HPV (Alinity). HPV-negative women at baseline had a substantially lower risk for CIN2+ compared to those with normal baseline cytology: 0.84% (95% CI, 0.46–1.22), 0.90% (95% CI, 0.51–1.29), 0.78% (95% CI, 0.42–1.15), and 0.75% (95% CI, 0.39–1.11) for hc2, RealTime, cobas_4800, and Alinity, respectively, compared to 2.46% (95% CI, 1.88–3.03) for cytology. No differences were observed between HPV assays in longitudinal sensitivity (range: 86.21%–90.36%) and negative predictive values (range: 99.54%–99.70%)

for CIN2+ in women ≥30 years, but were significantly different from cytology ($p < .05$). The 9-year cumulative risk of CIN2+ differed significantly between HPV genotypes, reaching 32.1% (95% CI, 14.5–46.1) for HPV16, 24.9% (95% CI, 4.7–40.8) for HPV18/45, 27.2% (95% CI, 14.6–37.8) for HPV31/33/35/52/58, and 8.1% (95% CI, 0.0–16.7) for HPV39/51/56/59. Four clinically validated HPV assays showed comparable safety and better assurance against precancerous lesions than cytology, but some important differences were identified in the performance characteristics of HPV assays impacting the referral rate. Information about the HPV genotype is valuable for guiding further clinical action in HPV-based screening programs.

25COASMA81:

Title: Therapy adherence after interdisciplinary tumour board discussion is associated with improved outcome in soft tissue sarcoma: A Charité Comprehensive Cancer Centre analysis

Annika Strönisch, Daniel Rau, Silvan Wittenberg, David Kaul, Georgios Koulaxouzidis,

International journal of Cancer, vol-156, no.4

Doi- **https://doi.org/10.1002/ijc.35201**

Abstract: Centralising soft tissue sarcoma (STS) treatment in expert centres and implementing comprehensive therapy concepts through interdisciplinary tumour boards (ITB) has led to significant treatment progress. However, our knowledge on the implementation of the ITB recommendations and its impact on patient outcome is limited. In this retrospective analysis, we examined a cohort of 222 adult patients (pts) with primary STS who were presented to the ITB of the Charité Comprehensive Cancer Centre between 2015 and 2020. In localised disease ($n = 188$), resection was recommended in 71% ($n = 134$) of pts. The treatment modalities chemotherapy with or without regional deep hyperthermia, and radiotherapy were recommended in 37% ($n = 69$), 26% ($n = 48$) and 52% ($n = 97$), respectively. Complex multidisciplinary concepts were established in 29% ($n = 54$) including ≥3 treatment modalities. Only partial adherence, either by choice of patient or treating physician, was associated with a higher risk of both progression (HR 4.0 95%-CI 1.6–9.7 $p < .01$) and mortality (HR 5.3 95%-CI 1.7–16.4 $p < .01$). Pts inable to follow the ITB recommendations due to complications or rapid progression showed a high-risk profile with increased mortality and progression rates (HR 18.1 95%-CI 8.5–38.2 $p < .001$; HR 21.5 95%-CI 8.5–54.7 $p < .001$). To our knowledge, this represents the first German Comprehensive Cancer Centre analysis of therapy adherence in STS. It provides further real-world evidence that full adherence to ITB recommendations and the ability to adhere to them are of prognostic value for patient outcome and underlines the importance of interdisciplinary decision-making and treatment planning for STS patients.

25COASMA82:

Title: A new treatment approach of toripalimab in combination with concurrent platinum-based chemoradiotherapy for locally advanced cervical cancer: A phase II clinical trial

Jie Chen, Jinming Shi, Yuanjie Cao, Chen Li, Junyi Li, Zhiyong Yuan

International journal of Cancer, vol-156, no.4
Doi- **https://doi.org/10.1002/ijc.35206**

Abstract: This study investigated the efficacy and safety of toripalimab in combination with concurrent platinum-based chemoradiation in patients with untreated locally advanced cervical cancer. Eligible patients received toripalimab 240 mg once every 3 weeks in combination with concurrent platinum-based chemoradiotherapy, followed by the maintenance of toripalimab once every 6 weeks up to 1 year. The primary endpoint was objective response rate (ORR). Secondary endpoints included 2-year and 3-year progression-free survival (PFS) rates, 3-year overall survival (OS) rate, and safety. Biomarker analysis of PD-L1 expression and genomic mutational analysis by next-generation sequencing were conducted, as well as PD-L1 expression on tumor biopsies. A total of 82 patients were enrolled. The median follow-up was 21 months (range, 5.2–44.5 months). The ORR and disease control rate were both 87.8% among the 82 patients. Median PFS and OS were not reached. A trend toward longer PFS was observed in the populations with a PD-L1 combined positive score ≥10, low tumor mutation burden and loss of heterozygosity in human leukocyte antigen (HLA LOH) detected populations. A total of 37 patients experienced treatment-related adverse events, of which 17 (20.7%) patients experienced grade 3 or higher adverse events. Collectively, toripalimab plus concurrent platinum-based chemoradiotherapy showed promising antitumor efficacy with acceptable safety profiles in patients with untreated locally advanced cervical cancer.

25COASMA83:

Title: Ninjurin1 deficiency differentially mitigates colorectal cancer induced by azoxymethane and dextran sulfate sodium in male and female mice

Chin-Hee Song, Nayoung Kim, Ryoung Hee Nam, Soo In Choi, Jae Young Jang, Eun Hye Kim,

International journal of Cancer, vol-156, no.4
Dio-**https://doi.org/10.1002/ijc.35225**

Abstract: This study investigated the role of Ninjurin1 (Ninj1), encoding a small transmembrane protein, in colitis-associated colon tumorigenesis in relation to sex hormones. Male and female wild-type (WT) and Ninj1 knockout (KO) mice were treated with azoxymethane (AOM) and dextran sulfate sodium (DSS), with or without testosterone propionate (TP). At week 2 (acute colitis stage), Ninj1 KO exhibited an alleviation in the colitis symptoms in both male and female mice. The M2 macrophage population increased and $CD8^+$ T cell population decreased only in the female Ninj1 KO than in the female WT AOM/DSS group. In the female AOM/DSS group, TP treatment exacerbated colon shortening in the Ninj1 KO than in the WT. At week 13 (tumorigenesis stage), male Ninj1 KO mice had fewer tumors, but females showed similar tumors. In the WT AOM/DSS group, females had more M2 macrophages and fewer M1 macrophages than males, but this difference was absent in Ninj1 KO mice. In the Ninj1 KO versus WT group, the expression of pro-inflammatory mediators and Ho-1 and $CD8^+$ T cell populations decreased in both female and male Ninj1 KO mice. In the WT group, M2 macrophage populations were increased by AOM/DSS treatment and decreased by TP treatment.

However, neither treatment changed the cell populations in the Ninj1 KO group. These results suggest that Ninj1 is involved in colorectal cancer development in a testosterone-dependent manner, which was different in male and female. This highlights the importance of considering sex disparities in understanding Ninj1's role in cancer pathogenesis.

25COASMA84:

Title: Early circulating tumor DNA changes predict outcomes in head and neck cancer patients under re-radiotherapy

Florian Janke, Florian Stritzke, Katharina Dvornikovich, Henrik Franke, Arlou Kristina Angeles,

International journal of Cancer, vol-156, no.4

Doi-**https://doi.org/10.1002/ijc.35152**

Abstract: Local recurrence after radiotherapy is common in locally advanced head and neck cancer (HNC) patients. Re-irradiation can improve local disease control, but disease progression remains frequent. Hence, predictive biomarkers are needed to adapt treatment intensity to the patient's individual risk. We quantified circulating tumor DNA (ctDNA) in sequential plasma samples and correlated ctDNA levels with disease outcome. Ninety four longitudinal plasma samples from 16 locally advanced HNC patients and 57 healthy donors were collected at re-radiotherapy baseline, after 5 and 10 radiation fractions, at irradiation end, and at routine follow-up visits. Plasma DNA was subjected to low coverage whole genome sequencing for copy number variation (CNV) profiling to quantify ctDNA burden. CNV-based ctDNA burden was detected in 8/16 patients and 25/94 plasma samples. Ten additional ctDNA-positive samples were identified by tracking patient-specific CNVs found in earlier sequential plasma samples. ctDNA-positivity after 5 and 10 radiation fractions (both: log-rank, $p = .050$) as well as at the end of irradiation correlated with short progression-free survival (log-rank, $p = .006$). Moreover, a pronounced decrease of ctDNA toward re-radiotherapy termination was associated with worse treatment outcome (log-rank, $p = .005$). Dynamic ctDNA tracking in serial plasma beyond re-radiotherapy reflected treatment response and imminent disease progression. In five patients, molecular progression was detected prior to tumor progression based on clinical imaging. Our findings emphasize that quantifying ctDNA during re-radiotherapy may contribute to disease monitoring and personalization of adjuvant treatment, follow-up intervals, and dose prescription.

25COASMA85:

Title: Identification and evaluation of a serum micro RNA panel to diagnose colorectal cancer patients

Lui Ng, Ryan Wai-Yan Sin, David Him Cheung, Carlos King-Ho Wong, Cindy Lo-Kuen Lam,

International journal of Cancer, vol-156, no.4

Doi- **https://doi.org/10.1002/ijc.35175**

Abstract: Screening plays a crucial role in the early detection of colorectal cancer, greatly reducing mortality rates. The objective of this study was to identify a non-invasive diagnostic method utilizing serum microRNA expression for the diagnosis of colorectal cancer patients.

The study consisted of three stages. In the first stage, 129 patients with colorectal cancer and 129 normal subjects were recruited as the training set for the development of a blood miRNA panel. The second stage involved recruiting 200 patients from each group as the validation cohort. Finally, a blinded study was conducted in the third stage, with 260 patients recruited to determine the predictive value of our miRNA panel. Serum samples were prospectively collected from colorectal cancer patients and normal subjects between 2017 and 2021 at Queen Mary Hospital in Hong Kong. Quantitative PCR was utilized to detect the serum levels of candidate microRNAs, and a multiple linear regression model was employed to formulate a serum microRNA panel for diagnosing colorectal cancer patients. The performance of the panel was evaluated using ROC analysis. Our study showed that the values of three pairs of serum microRNAs, namely miR-106b-5p/miR-1246, miR-106b-5p/miR-16 and miR-106b-5p/miR-21-5p, exhibited statistically significant differences between colorectal cancer patients and normal subjects. A serum microRNA panel formulated from these three pairs of microRNAs demonstrated high accuracy in diagnosing colorectal cancer patients from normal subjects, with an AUC of approximately 0.9. The serum miRNA test proved to be a feasible and promising non-invasive biomarker for the diagnosis of colorectal cancer patients in comparison to normal subjects.

25COASMA86:

Title: Soluble CD206 in metastatic renal cell carcinoma: Relation to clinical–biochemical parameters and patient outcome

Kasper Munch Lauridsen, Holger Jon Møller, Mie Wolff Kristensen, Niels Fristrup, Frede Donskov,

International journal of Cancer, vol-156, no.4

Doi-**https://doi.org/10.1002/ijc.35194**

Abstract: The mannose receptor (MR/CD206) is a marker of M2-like tumor-associated macrophages. Membrane CD206 can be shed, releasing the receptor as a soluble protein (sCD206), which can be measured in serum. Here, we investigated the biomarker potential of sCD206 in patients with metastatic renal cell carcinoma (mRCC). Serum sCD206 was measured by an enzyme-linked immunosorbent assay in 88 mRCC patients and 20 healthy controls (HCs). At diagnosis, serum sCD206 was elevated in patients with intermediate-risk mRCC according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk score, compared to both HCs and patients with favorable MSKCC risk score. Furthermore, sCD206 levels correlated with both sCD163 and C-reactive protein. Soluble CD206 levels decreased after treatment initiation ($p < .0001$ at 5 weeks) but with a tendency toward elevated levels at time of progression, compared to baseline ($p = .06$). In univariate survival analysis, high levels of serum sCD206 at baseline was a significant risk factor associated with reduced overall survival (hazard ratio [HR] = 1.37, 95% confidence interval: 1.12–1.67, $p = .002$). Stratified by clinical risk scores, increased sCD206 was still a statistically significant risk factor of overall mortality ($p < .01$) in the intermediate-risk group by both the MSKCC (HR = 1.48) and the newer International Metastatic RCC Database Consortium (IMDC) score (HR = 1.53). Furthermore, addition of sCD206 as a dichotomized variable to the IMDC risk score enabled separation of the intermediate-risk group into two groups with survival

comparable to those with favorable and poor risk, respectively. Overall, sCD206 is a potential add-on biomarker for mRCC patients in the intermediate-risk group of the current clinical risk scores.

25COASMA87:

Title: Safety and efficacy of pegcetacoplan treatment for cold agglutinin disease and warm antibody autoimmune hemolytic anemia

Eloy Roman, Bruno Fattizzo, Merrill Shum,

Blood (2025) 145 (4): 397–408.
Doi- https://doi.org/10.1182/blood.2023022549

Abstract: Cold agglutinin disease (CAD) and warm antibody autoimmune hemolytic anemia (wAIHA) are rare autoimmune hemolytic anemias characterized by red blood cell destruction, largely attributable to complement activation resulting in intravascular and extravascular hemolysis. Pegcetacoplan is a subcutaneously administered C3-targeted therapy, which may be suitable for treating CAD and wAIHA. In this open-label phase 2 study, analyses were conducted in 2 cohorts, 1 for patients with CAD and the other for those with wAIHA. In each cohort, patients were randomly assigned to receive pegcetacoplan 270 mg/d or 360 mg/d for up to 48 weeks. Safety end points included the incidence and severity of treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESI). Efficacy end points included change from baseline in hemoglobin (Hb), lactate dehydrogenase, absolute reticulocyte count, haptoglobin, indirect bilirubin, and functional assessment of chronic illness therapy (FACIT)-fatigue scale. Thirteen of 13 (100%) and 10 of 11 (91%) patients with CAD and wAIHA, respectively, experienced at least 1 TEAE. Ten patients had at least 1 serious AE; none were considered related to pegcetacoplan. The only treatment-related AESIs were injection site reactions. Pegcetacoplan increased Hb levels, reduced hemolysis, and increased FACIT-fatigue scale scores in the first weeks; at week 48 the median (interquartile range) change from baseline Hb for the CAD and wAIHA total groups was 2.4 (0.90-3.00) and 1.7 g/dL (−1.40 to 2.90), respectively, and improvements in hemolysis and FACIT-fatigue scale scores were maintained. This study demonstrated that pegcetacoplan is generally well tolerated and suggests it can be effective for patients with CAD and wAIHA.

25COASMA88:

Title: Ex vivo venetoclax sensitivity predicts clinical response in acute myeloid leukemia in the prospective VenEx trial

Sari Kytölä, Ida Vänttinen, Tanja Ruokoranta,

Blood (2025) 145 (4): 409–421.
Doi-https://doi.org/10.1182/blood.2024024968

Abstract: The B-cell lymphoma 2 inhibitor venetoclax has shown promise for treating acute myeloid leukemia (AML). However, identifying patients likely to respond remains a challenge, especially for those with relapsed/refractory (R/R) disease. We evaluated the utility of ex vivo venetoclax sensitivity testing to predict treatment responses to venetoclax-azacitidine in a prospective, multicenter, phase 2 trial. The trial recruited 104 participants

with previously untreated (n = 48), R/R (n = 39), or previously treated secondary AML (sAML) (n = 17). The primary end point was complete remission or complete remission with incomplete hematologic recovery (CR/CRi) rate in ex vivo sensitive trial participants during the first 3 therapy cycles. The key secondary end points included the correlations between ex vivo drug sensitivity, responses, and survival. Venetoclax sensitivity was successfully assessed in 102 of 104 participants, with results available within a median of 3 days from sampling. In previously untreated AML, ex vivo sensitivity corresponded to an 85% (34/40) CR/CRi rate, with a median overall survival (OS) of 28.7 months, compared with 5.5 months for ex vivo resistant patients (P = .002). For R/R/sAML, ex vivo sensitivity resulted in a 62% CR/CRi rate (21/34) and median OS of 9.7 vs 3.3 months for ex vivo resistant patients (P < .001). In univariate and multivariate analysis, ex vivo venetoclax sensitivity was the strongest predictor for a favorable treatment response and survival. This trial demonstrates the feasibility of integrating ex vivo drug testing into clinical practice to identify patients with AML, particularly in the R/R setting, who benefit from venetoclax..

25COASMA89:

Title: Conserved helical motifs in the IKZF1 disordered region mediate NuRD interaction and transcriptional repression

Tianyi Zhang, Yi-Fang Wang, Alex Montoya

Blood (2025) 145 (4): 422–437.

Doi- https://doi.org/10.1182/blood.2024024787

Abstract: The transcription factor (TF) Ikaros zinc finger 1 (IKZF1) is essential for B-cell development, and recurrently mutated in human B-cell acute lymphoblastic leukemia (B-ALL). IKZF1 has been ascribed both activating and repressive functions via interactions with coactivator and corepressor complexes, but the relative abundance of IKZF1-associated coregulators and their contribution to IKZF1-mediated gene regulation are not well understood. To address this, we performed an unbiased identification of IKZF1-interacting proteins in pre-B cells and found that IKZF1 interacts overwhelmingly with corepressors and heterochromatin-associated proteins. Time-resolved analysis of transcription and chromatin state identified transcriptional repression as the immediate response to IKZF1 induction. Transcriptional repression preceded transcriptional activation by several hours, manifesting as a decrease in the fraction of transcriptional bursts at the single-molecule level. Repression was accompanied by a rapid loss of chromatin accessibility and reduced levels of histone H3 lysine 27 acetylation (H3K27ac), particularly at enhancers. We identified highly conserved helical motifs within the intrinsically disordered region of IKZF1 that mediate its association with the nucleosome remodeling and deacetylase (NuRD) corepressor complex through critical “KRK” residues that bind the NuRD subunit retinoblastoma binding protein 4 (RBBP4), a mechanism shared with the TFs FOG1, BCL11A, and SALL4.

25COASMA90:

Title: Cryo-EM structure of the human native plasma coagulation factor XIII complex

Sneha Singh, Gregor Hagelueken, Deniz Ugurlar

Blood (2025) 145 (4): 438–449.

Doi- https://doi.org/10.1182/blood.2024025369
Abstract: The structure of human coagulation factor XIII (FXIII), a heterotetrameric plasma protransglutaminase that covalently cross-links preformed fibrin polymers, remains elusive until today. The heterotetrameric complex is composed of 2 catalytic FXIII-A and 2 protective FXIII-B subunits. Structural etiology underlying FXIII deficiency has so far been derived from crystallographic structures, all of which are currently available for the FXIII-A_2 homodimer only. Here, we present the cryogenic electron microscopy (cryo-EM) structure of a native, human plasma–derived FXIII-A_2B_2 complex at 2.4 Å resolution. The structure provides detailed information on FXIII subunit interacting interfaces as the 2 subunits interact strongly in plasma. The native FXIII-A_2B_2 complex reveals a pseudosymmetric heterotetramer of 2 FXIII-B monomers intercalating with a symmetric FXIII-A_2 dimer forming a "crown"-like assembly. The symmetry axes of the A_2 and B_2 homodimers are twisted relative to each other such that Sushi domain 1 interacts with the catalytic core of the A subunit, and Sushi domain 2 with the symmetry related A′ subunit, and vice versa. We also report 4 novel mutations in the F13A1 gene encoding the FXIII-A subunit from a cohort of patients with severe FXIII deficiency. Our structure reveals the etiological basis of homozygous and heterozygous pathogenic mutations and explains the conditional dominant negative effects of heterozygous mutations. This atomistic description of complex interfaces is consistent with previous biochemical data and shows a congruence between the structural biochemistry of the FXIII complex and the clinical features of FXIII deficiency.

25COASMA91:

Title: Imetelstat: a new addition to the therapeutic landscape of lower-risk MDS

Yasmin Abaza,Amy E. DeZern

Blood (2025) 145 (5): 469–474.
Doi-https://doi.org/10.1182/blood.2024025702

Abstract: Anemia is the most prevalent cytopenia in lower-risk myelodysplastic neoplasms (LR-MDS). There is a paucity of drugs for red blood cell transfusion dependence (RBC-TD), and erythropoiesis-stimulating agents (ESAs) are the mainstay of therapy in many centers. Imetelstat, an oligonucleotide telomerase inhibitor, was recently approved for adults with RBC-TD LR-MDS who are ineligible for or failed prior ESA therapy. Although not yet approved worldwide, here we spotlight the current data for imetelstat and where it may fit in the therapeutic landscape of LR-MDS.

25COASMA92:

Title: A phase 1 study of the amino acid modulator pegcrisantaspase and venetoclax for relapsed or refractory acute myeloid leukemia

Yuchen Liu, Dominique R. Bollino, Osman M. Bah,

Blood (2025) 145 (5): 486–496.
Doi-https://doi.org/10.1182/blood.2024024837

Abstract: Glutamine dependency has been shown to be a metabolic vulnerability in acute myeloid leukemia (AML). Prior studies using several in vivo AML models showed that depletion of plasma glutamine, induced by long-acting crisantaspase (pegcrisantaspase

[PegC]) was synergistic with the B-cell lymphoma-2 (BCL-2) inhibitor venetoclax (Ven), resulting in significantly reduced leukemia burden and enhanced survival. Here, we report a phase 1 study of the combination of Ven and PegC (VenPegC) for treating adult patients with relapsed or refractory AML, including patients who had previously received Ven. The primary end points were the incidence of regimen-limiting toxicities (RLTs) and the maximum tolerated dose (MTD). Twenty-five patients received at least 1 PegC dose with Ven, and 18 efficacy-evaluable patients completed at least 1 VenPegC cycle; 12 (67%) had previously received Ven. Hyperbilirubinemia was the RLT and occurred in 60% of patients treated with VenPegC; 20% had grade ≥3 bilirubin elevations. MTD was determined to be Ven 400 mg daily with biweekly PegC 750 IU/m^2. The most common treatment-related adverse events of any grade in 25 patients who received VenPegC included antithrombin III decrease (52%), elevated transaminases (36%-48%), fatigue (28%), and hypofibrinogenemia (24%). No thromboembolic or hemorrhagic adverse events or clinical pancreatitis were observed. The overall complete remission rate in efficacy-evaluable patients was 33%. Response correlated with alterations in proteins involved in messenger RNA translation. In patients with RUNX1 mutations, the composite complete remission rate was 100%..

25COASMA93:

Title: Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a TP53 mutation

Anita Kumar, Jacob Soumerai, Jeremy S. Abramson

Blood (2025) 145 (5): 497–507.
Doi- nhttps://doi.org/10.1182/blood.2024025563

Abstract: TP53-mutant mantle cell lymphoma (MCL) is associated with poor survival outcomes with standard chemoimmunotherapy. We conducted a multicenter, phase 2 study of zanubrutinib, obinutuzumab, and venetoclax (BOVen) in untreated patients with MCL with a TP53 mutation. Patients initially received 160 mg zanubrutinib twice daily and obinutuzumab. Obinutuzumab at a dose of 1000 mg was given on cycle 1 day 1, 8, and 15, and on day 1 of cycles 2 to 8. After 2 cycles, venetoclax was added with weekly dose ramp-up to 400 mg daily. After 24 cycles, if patients were in complete remission with undetectable minimal residual disease (uMRD) using an immunosequencing assay, treatment was discontinued. The primary end point was met if ≥11 patients were progression free at 2 years. The study included 25 patients with untreated MCL with a TP53 mutation. The best overall response rate was 96% (24/25) and the complete response rate was 88% (22/25). Frequency of uMRD at a sensitivity level of 1×10^{-5} and uMRD at a sensitivity level of 1×10^{-6} at cycle 13 was 95% (18/19) and 84% (16/19), respectively. With a median follow-up of 28.2 months, the 2-year progression-free, disease-specific, and overall survival were 72%, 91%, and 76%, respectively. Common side effects were generally low grade and included diarrhea (64%), neutropenia (32%), and infusion-related reactions (24%). BOVen was well tolerated and met its primary efficacy end point in TP53-mutant MCL. These data support its use and ongoing evaluation.

25COASMA94:

Title: Bivalent CD47 immunotoxin for targeted therapy of T-cell acute lymphoblastic leukemia

Jihong Ma, Zhaohui Wang, Danielle Mintzlaff

Blood (2025) 145 (5): 508–519.
Doi- https://doi.org/10.1182/blood.2024025277

Abstract: CD47 is overexpressed on the surface of many types of cancer cells, including T-cell acute lymphoblastic leukemia (T-ALL) cells. In this study, we have developed a diphtheria toxin (DT)–based bivalent anti-human CD47 immunotoxin (bi-CD47-IT) for the targeted therapy of $CD47^+$ cancers using a unique DT-resistant yeast Pichia pastoris expression system. Bi-CD47-IT demonstrated compelling in vivo efficacy in multiple T-ALL cell line–derived xenograft (CDX) and patient-derived xenograft (PDX) mouse models. Bi-CD47-IT significantly prolonged the median survival of the tumor-bearing mice and highly effectively depleted the T-ALL blast cells in the peripheral blood, spleen, liver, bone marrow, brain, and spinal cord in the T-ALL CDX and PDX mouse models. Bi-CD47-IT cured 60% of tumor-bearing mice in a T-ALL Molt-4 CDX mouse model. Because CD47 is also expressed on normal tissues, including red blood cells and lymphocytes, specificity is a concern. We thus analyzed the in vitro binding avidity and hemagglutination of bi-CD47-IT in human red blood cells, finding no binding or hemagglutination. We further performed a toxicity study of bi-CD47-IT in humanized mice, which showed that bi-CD47-IT transiently depleted the human lymphocytes for ∼4 weeks after the 10-day treatment. No clinical adverse events were observed. As a result, bi-CD47-IT appears to possess the "optimal" binding avidity, with effective binding to human $CD47^+$ T-ALL tumor cells, no binding to human red blood cells, and weak binding to human lymphocytes. We believe that bi-CD47-IT is a promising and safe therapeutic drug candidate for the targeted therapy of $CD47^+$ cancers.

25COASMA95:

Title: Development of hyperdiploidy starts at an early age and takes a decade to complete

Mehmet K. Samur, Anil Aktas Samur

Blood (2025) 145 (5): 520–525.
Doi-https://doi.org/10.1182/blood.2024025250

Abstract: Nearly half of patients with multiple myeloma (MM) have hyperdiploidy (HMM) at diagnosis. Although HMM occurs early, the mutational processes before and after hyperdiploidy are still unclear. Here, we used 72 whole-genome sequencing samples from patients with HMM and identified pre- and post-HMM mutations to define the chronology of the development of hyperdiploidy. An MM cell accumulated a median of 0.56 mutations per megabase before HMM, and for every clonal pre-HMM mutation, 1.21 mutations per megabase accumulated after HMM. This analysis using mutations before and after hyperdiploidy shows that hyperdiploidy happens after somatic hypermutation. Prehyperdiploidy mutations are activation-induced cytidine deaminase and age/clock-like signature driven, whereas posthyperdiploidy mutations are from DNA damage and APOBEC.

Interestingly, the first hyperdiploidy event occurred within the first 3 decades of life and took a decade to complete. Copy number changes affecting chromosomes 15 and 19 occurred first. Finally, mutations before initiating event affected chromosomes at different rates, whereas post–initiating event mutational processes affect each chromosome equally.

25COASMA96:

Title:Soluble B-cell maturation antigen levels for disease monitoring in oligosecretory and nonsecretory relapsed multiple myeloma

Daisuke Ikeda, Shuichi Aikawa, Chiho Misono

Blood (2025) 145 (5): 526–532.

Doi-https://doi.org/10.1182/blood.2024026028

Abstract: Soluble B-cell maturation antigen (sBCMA) is elevated on multiple myeloma (MM) cells. We investigated whether sBCMA levels correlated with other myeloma tumor volume indicators and its utility in monitoring oligosecretory/nonsecretory (O-S/Non-S) MM. In 115 patients with newly diagnosed MM, sBCMA was compared with M-protein levels, bone marrow plasma cells (BMPCs), circulating tumor cells (CTCs), and total diffusion volume (tDV; estimated by whole-body diffusion-weighted magnetic resonance imaging) at diagnosis. sBCMA levels increased significantly with International Staging System stage, chromosome 1q21 gain/amplification, and CTC levels. sBCMA also correlated strongly with %BMPC ($r = 0.65$) and moderately with tDV ($r = 0.55$) and paraprotein levels (involved immunoglobulin in IgG and IgA subtypes, $r = 0.44$ and 0.4; involved free light-chain levels in light-chain-only MM, $r = 0.61$, all $P < .05$). Longitudinal changes in sBCMA were consistent with disease status in both 17 O-S/Non-S and other secretory MM cases. Furthermore, sBCMA levels increased as early as 6 months prerelapse in almost all O-S/Non-S relapsed patients. Thus, sBCMA correlates strongly with total tumor volume in MM, as assessed using different modalities. We suggest that sBCMA is useful, not only for monitoring responses in patients with O-S/Non-S MM but also for early relapse detection and prediction.

25COASMA97:

Title: A bulge uridine in the HIF2α IRE allows IRP1 but not IRP2 to selectively regulate HIF2α expression and ensuing EPO levels

De-Liang Zhang, Hayden Ollivierre,

Blood (2025) 145 (5): 533–542.

Doi-https://doi.org/10.1182/blood.2024025246

Abstract: Iron regulatory proteins (IRP1 and IRP2) play a pivotal role in maintaining cellular iron homeostasis by binding to iron-responsive elements (IREs) of target messenger RNAs and regulating the expression of these iron-related genes. Mice and humans who lack functional IRP1 develop erythrocytosis due to erythropoietin (EPO) overproduction, whereas those who lack IRP2 develop microcytic anemia, believed to result from iron deficiency of erythroblasts. Here, we discovered that IRP2 deficiency reduced the expression of hypoxia-inducible factor 2α (HIF2α) and its transcriptional target, EPO, thereby compromising the stress erythropoiesis response to generate red blood cells upon anemia. The distinct

consequences of IRP2 and IRP1 on EPO result from the higher binding affinity of the HIF2α IRE for IRP1 than IRP2. This difference in binding affinity arises from a bulge uridine in the upper stem of HIF2α IRE that impairs the ability of IRP2 to bind the IRE. These results reveal that IRP1 and IRP2 play distinct roles in erythropoiesis and unveil an unsuspected IRE binding preference that contributes to the divergent phenotypes observed in IRP1- and IRP2-deficient mammals.

25COASMA98:

Title: Venetoclax Plus Gilteritinib for FLT3-Mutated Relapsed/Refractory Acute Myeloid Leukemia

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Journal of Clinical Oncology, Volume 40, Number 35
Doi- https://doi.org/10.1200/JCO.22.00602

Abstract: The FMS-related tyrosine kinase 3 (FLT3) inhibitor gilteritinib is standard therapy for relapsed/refractory FLT3-mutated ($FLT3^{mut}$) acute myeloid leukemia (AML) but seldom reduces $FLT3^{mut}$ burden or induces sustained efficacy. Gilteritinib combines synergistically with the BCL-2 inhibitor venetoclax in preclinical models of $FLT3^{mut}$ AML.
This phase Ib open-label, dose-escalation/dose-expansion study (ClinicalTrials.gov identifier: NCT03625505) enrolled patients with FLT3 wild-type and $FLT3^{mut}$ (escalation) or $FLT3^{mut}$ (expansion) relapsed/refractory AML. Patients received 400 mg oral venetoclax once daily and 80 mg or 120 mg oral gilteritinib once daily. The primary objectives were safety, identification of the recommended phase II dose, and the modified composite complete response (mCRc) rate (complete response [CR] + CR with incomplete blood count recovery + CR with incomplete platelet recovery + morphologic leukemia-free state) using ADMIRAL phase III–defined response criteria. Sixty-one patients were enrolled (n = 56 $FLT3^{mut}$); 64% (n = 36 of 56) of $FLT3^{mut}$ patients had received prior FLT3 inhibitor therapy. The recommended phase II dose was 400 mg venetoclax once daily and 120 mg gilteritinib once daily. The most common grade 3/4 adverse events were cytopenias (n = 49; 80%). Adverse events prompted venetoclax and gilteritinib dose interruptions in 51% and 48%, respectively. The mCRc rate for $FLT3^{mut}$ patients was 75% (CR, 18%; CR with incomplete blood count recovery, 4%; CR with incomplete platelet recovery, 18%; and morphologic leukemia-free state, 36%) and was similar among patients with or without prior FLT3 inhibitor therapy (80% v 67%, respectively). The median follow-up was 17.5 months. The median time to response was 0.9 months, and the median remission duration was 4.9 months (95% CI, 3.4 to 6.6). FLT3 molecular response ($< 10^{-2}$) was achieved in 60% of evaluable mCRc patients (n = 15 of 25). The median overall survival for $FLT3^{mut}$ patients was 10.0 months. The combination of venetoclax and gilteritinib was associated with high mCRc and FLT3 molecular response rates regardless of prior FLT3 inhibitor exposure. Dose interruptions were needed to mitigate myelosuppression.

25COASMA99:

Title: Direct-Acting Antivirals as Primary Treatment for Hepatitis C Virus–Associated Indolent Non-Hodgkin Lymphomas: The BArT Study of the Fondazione Italiana Linfomi

Michele Merli

Journal of Clinical Oncology, Volume 40, Number 35
Doi-https://doi.org/10.1200/JCO.22.00668

Abstract: Purpose We prospectively treated patients with hepatitis C virus (HCV)–associated indolent lymphomas with genotype-appropriate direct-acting antivirals (DAAs) with the aim to evaluate virologic and hematologic outcomes. No prospective studies in this setting have been published so far. Methods FIL_BArT is a prospective, multicenter, phase II trial that evaluated genotype-appropriate DAAs in untreated HCV-positive patients with indolent lymphomas without criteria for immediate conventional antilymphoma treatment. The primary objective was sustained virologic response, whereas the main secondary objectives were overall response rate of lymphoma and progression-free survival. Results Forty patients were enrolled, including 27 with marginal zone lymphoma. Median age was 68 years. Extranodal sites were involved in 14 cases (35%). Main genotypes were 1 in 16 patients and 2 in 21 patients. All patients received genotype-guided DAAs: 17 ledipasvir/sofosbuvir, eight sofosbuvir plus ribavirin, and 15 sofosbuvir/velpatasvir. All patients achieved sustained virologic response (100%). DAAs were well tolerated, with only two grade 3-4 adverse events. Overall response rate of lymphoma was 45%, including eight patients (20%) achieving complete response and 10 (25%) partial response, whereas 16 exhibited stable disease and six progressed. With a median follow-up of 37 months, two patients died (3-year overall survival 93%; 95% CI, 74 to 98) and three additional patients progressed, with a 3-year progression-free survival of 76% (95% CI, 57 to 87). Conclusion HCV eradication by DAAs was achieved in 100% of HCV-positive patients with indolent lymphomas not requiring immediate conventional treatment and resulted in non-negligible rate of lymphoma responses. Treatment with DAAs should be considered as the first-line therapy in this setting.

25COASMA100:

Title: Twenty-Year Benefit From Adjuvant Goserelin and Tamoxifen in Premenopausal Patients With Breast Cancer in a Controlled Randomized Clinical Trial

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Abstract: Purpose To assess the long-term (20-year) endocrine therapy benefit in premenopausal patients with breast cancer. econdary analysis of the Stockholm trial (STO-5, 1990-1997) randomly assigning 924 premenopausal patients to 2 years of goserelin (3.6 mg subcutaneously once every 28 days), tamoxifen (40 mg orally once daily), combined goserelin and tamoxifen, or no adjuvant endocrine therapy (control) is performed. Random assignment was stratified by lymph node status; lymph node–positive patients (n = 459) were

allocated to standard chemotherapy (cyclophosphamide, methotrexate, and fluorouracil). Primary tumor immunohistochemistry (n = 731) and gene expression profiling (n = 586) were conducted in 2020. The 70-gene signature identified genomic low-risk and high-risk patients. Kaplan-Meier analysis, multivariable Cox proportional hazard regression, and multivariable time-varying flexible parametric modeling assessed the long-term distant recurrence-free interval (DRFI). Swedish high-quality registries allowed a complete follow-up of 20 years.
In estrogen receptor–positive patients (n = 584, median age 47 years), goserelin, tamoxifen, and the combination significantly improved long-term distant recurrence-free interval compared with control (multivariable hazard ratio [HR], 0.49; 95% CI, 0.32 to 0.75, HR, 0.57; 95% CI, 0.38 to 0.87, and HR, 0.63; 95% CI, 0.42 to 0.94, respectively). Significant goserelin-tamoxifen interaction was observed (P = .016). Genomic low-risk patients (n = 305) significantly benefitted from tamoxifen (HR, 0.24; 95% CI, 0.10 to 0.60), and genomic high-risk patients (n = 158) from goserelin (HR, 0.24; 95% CI, 0.10 to 0.54). Increased risk from the addition of tamoxifen to goserelin was seen in genomic high-risk patients (HR, 3.36; 95% CI, 1.39 to 8.07). Moreover, long-lasting 20-year tamoxifen benefit was seen in genomic low-risk patients, whereas genomic high-risk patients had early goserelin benefit. This study shows 20-year benefit from 2 years of adjuvant endocrine therapy in estrogen receptor–positive premenopausal patients and suggests differential treatment benefit on the basis of tumor genomic characteristics. Combined goserelin and tamoxifen therapy showed no benefit over single treatment. Long-term follow-up to assess treatment benefit is critical.

25COASMA101:

Title: Development and Validation of the PREMMplus Model for Multigene Hereditary Cancer Risk Assessment

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Abstract: Purpose With the availability of multigene panel testing (MGPT) for hereditary cancer risk assessment, clinicians need to assess the likelihood of pathogenic germline variants (PGVs) across numerous genes in parallel. This study's aim was to develop and validate a clinical prediction model (PREMMplus) for MGPT risk assessment.vMaterials and Methods**v**PREMMplus was developed in a single-institution cohort of 7,280 individuals who had undergone MGPT. Logistic regression models with Least Absolute Shrinkage and Selection Operator regularization were used to examine candidate predictors (age, sex, ethnicity, and personal/family history of 18 cancers/neoplasms) to estimate one's likelihood of carrying PGVs in 19 genes (broadly categorized by phenotypic overlap and/or relative penetrance: 11 category A [APC, BRCA1/2, CDH1, EPCAM, MLH1, MSH2, MSH6, biallelic MUTYH, PMS2, and TP53] and eight category B genes [ATM, BRIP1, CDKN2A, CHEK2, PALB2, PTEN, RAD51C, and RAD51D]). Model performance was validated in nonoverlapping data sets of 8,691 and 14,849 individuals with prior MGPT ascertained from clinic- and laboratory-based settings, respectively. Results
PREMMplus (score ≥ 2.5%) had 93.9%, 91.7%, and 89.3% sensitivity and 98.3%, 97.5%, and 97.8% negative-predictive value (NPV) for identifying category A gene PGV carriers in

the development and validation cohorts, respectively. PREMMplus assessment (score ≥ 2.5%) had 89.9%, 85.6%, and 84.2% sensitivity and 95.0%, 93.5%, and 93.5% NPV, respectively, for identifying category A/B gene PGV carriers. Decision curve analyses support MGPT for individuals predicted to have ≥ 2.5% probability of a PGV. Conclusion PREMMplus accurately identifies individuals with PGVs in a diverse spectrum of cancer susceptibility genes with high sensitivity/NPV. Individuals with PREMMplus scores ≥ 2.5% should be considered for MGPT.

25COASMA102:

Title: Phase I Trial of MCARH109, a G Protein–Coupled Receptor Class C Group 5 Member D (GPRC5D)–Targeted Chimeric Antigen Receptor T-Cell Therapy for Multiple Myeloma: An Updated Analysis

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Journal of Clinical Oncology, Volume 43, Number 5
Doi- https://doi.org/10.1200/JCO-24-01785

Abstract: MCARH109 is a first-in-class G protein–coupled receptor, class C, group 5, member D (GPRC5D)-targeted chimeric antigen receptor (CAR) T-cell therapy for patients with relapsed/refractory multiple myeloma. This phase I clinical trial included 17 patients and determined that MCARH109 is safe at a maximum tolerated dose of 150 × 10^6 CAR T cells. In this updated analysis, no new serious adverse events were reported at a median follow-up of 37 months. Overall, 12 (71%) of 17 patients responded, including seven (70%) of 10 patients previously treated with B-cell maturation antigen-targeted therapy. The median duration of response was 8.6 months (95% CI, 5.7 to not reached [NR]) with two patients sustaining a stringent complete response at the time of last follow-up, 32 months and 41 months, respectively. The median overall survival (OS) was NR and the 3-year OS estimate was 59% (95% CI, 40 to 88). Possible GPRC5D loss via immunohistochemistry was observed in 6 (60%) of 10 patients at relapse. High-dimensional spectral cytometry–based immune profiling associated an activated T-cell phenotype at apheresis with a response to MCARH109.

25COASMA103:

Title:OPAR: A Randomized Trial of Partial Breast Irradiation in Five Fractions Once Daily for Early Breast Cancer

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Journal of Clinical Oncology,Volume 43, Number 5
Doi-https://doi.org/10.1200/JCO.24.00600

Abstract: Purpose Previous studies suggest that external-beam partial breast irradiation (PBI) delivered twice a day can lead to increased adverse cosmesis (AC). The objective of our trial was to determine whether two regimens for PBI given once daily over 1 week resulted in acceptable AC to inform a phase III trial. Methods-Patients age ≥50 years with invasive breast cancer or ductal carcinoma in situ, ≤3 cm in size treated by lumpectomy with negative axillary nodes were randomly assigned to external-beam PBI of 30 Gy or 27.5 Gy, each given in five fractions once daily. The primary outcome was AC (fair or poor) by

photographic assessment at 2 years. Secondary outcomes included AC assessed by nurse at 2 years, by patient self-assessment at 3 years, and late toxicity. On the basis of a 17% risk of AC with whole-breast irradiation, the upper bound of a two-sided 90% CI, 23% was set as the tolerance margin (OPAR, ClinicalTrials.gov identifier: NCT02637024). Results In total, 142 patients were randomly assigned to 30 Gy and 139 to 27.5 Gy. The median follow-up was 5 years. The mean age was 65 years, and the mean tumor size was 1.2 cm. Both schedules met acceptability criteria by photographic assessment (AC, 12.1% [90% CI, 8.2 to 17.6] for 30 Gy and 15.2% [90% CI, 10.8 to 21.1] for 27.5 Gy) and by nurse assessment. AC by patient self-assessment exceeded the 90% CI for the 30 Gy regimen. At 5 years, 16 (11.3%, 90% CI, 7.6 to 16.4) patients treated with 30 Gy and eight (5.8%, 90% CI, 3.3 to 9.9) patients treated with 27.5 Gy were observed to have grade 2 or more late toxicity. Conclusion-According to the study design, 30 Gy and 27.5 Gy resulted in acceptable cosmetic outcomes. In light of recent studies, a lower dose was chosen for the phase III trial.

25COASMA104:

Title: Trastuzumab Duocarmazine in Pretreated Human Epidermal Growth Factor Receptor 2–Positive Advanced or Metastatic Breast Cancer: An Open-Label, Randomized, Phase III Trial (TULIP)

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Journal of Clinical Oncology, Volume 43, Number 5
Doi- https://doi.org/10.1200/JCO.24.00529

Abstract: Purpose-Human epidermal growth factor receptor 2 (HER2)–targeted therapy is standard of care for HER2-positive (HER2+) breast cancer, but most patients develop progressive disease with persistent HER2 expression. No definitive treatment guidance currently exists beyond second line. Trastuzumab duocarmazine (T-Duo) is a third-generation, HER2-targeted antibody-drug conjugate that demonstrated efficacy and acceptable safety in phase I studies of heavily pretreated patients with HER2+/HER2-low breast cancer. Methods In this open-label, randomized, phase III trial, T-Duo was compared with physician's choice (PC) in patients with unresectable locally advanced/metastatic HER2+ breast cancer with progression during/after ≥2 HER2-targeted therapies or after trastuzumab emtansine (T-DM1). The primary endpoint was progression-free survival (PFS) by blinded independent central review. Results In total, 437 patients were randomly assigned 2:1 to T-Duo (n = 291) or PC (n = 146). The median age was 56.0 years (range, 24-86); most patients (93.6%) had metastatic disease. The median time from diagnosis of metastatic disease to trial entry was 3.5 years; the median number of prior HER2-targeted therapies in metastatic setting was three. The median PFS was 7.0 months (95% CI, 5.4 to 7.2) with T-Duo versus 4.9 months (95% CI, 4.0 to 5.5; hazard ratio [HR], 0.64 [95% CI, 0.49 to 0.84]; P = .002) with PC. PFS benefit was maintained across most predefined subgroups. The median overall survival (first analysis) was 20.4 (T-Duo) versus 16.3 months (PC; HR, 0.83 [95% CI, 0.62 to 1.09]; P = .153). Objective response rate was 27.8% (T-Duo) versus 29.5% (PC); other efficacy end points—clinical benefit rate, duration of response, and reduction in target lesion measurement—tended to favor T-Duo. Grade ≥3 treatment-emergent adverse events occurred in 52.8% (T-Duo) versus 48.2% (PC). Conclusion Treatment with T-Duo

was manageable, but tolerability was affected by prevalent ocular toxicity, leading to a higher discontinuation rate in the T-Duo arm. T-Duo significantly reduced the risk of progression in patients with advanced HER2+ breast cancer who have progressed during/after ≥2 HER2-targeted therapies or after T-DM1.

25COASMA105:

Title: Quality of Treatment Selection for Medicare Beneficiaries With Cancer

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Journal of Clinical Oncology, Volume 43, Number 5
Doi- https://doi.org/10.1200/JCO.24.00459

Abstract: Purpose The Medicare part D Low-Income Subsidy (LIS) improves access to oral cancer drugs, but provides no assistance for clinician-administered/part B drugs. This analysis assessed the association between LIS participation and receipt of optimal cancer treatment. Methods We investigated initial systemic therapy using SEER-Medicare data (2015-2017) and National Comprehensive Cancer Network (NCCN) Evidence Blocks (EB) as the standard for treatment recommendations. We included cancer clinical scenarios wherein (1) ≥one treatment was optimal (higher efficacy and safety scores) versus other treatments; (2) identifiable in SEER-Medicare (eg, not defined by clinical data unavailable in registry data or claims); and (3) both EB and ASCO Value Framework agreed regarding optimal treatment. We fit logistic regression models to assess the association between receipt of systemic therapy (v no therapy) and patient and provider characteristics. Contingent on receipt of treatment, we modeled the likelihood of receiving a treatment ranked (by EB scores) within the highest or lowest quartile for that cancer type. Results Nine thousand two hundred and ninety patients were included across 11 clinical scenarios. Fifty-seven percent (5,336) of patients received any systemic therapy and 43% (3,954) received no systemic therapy. Compared with non-LIS participants, LIS participants were less likely to receive any systemic therapy versus no systemic therapy (odds ratio, 0.64 [95% CI, 0.57 to 0.72]). Contingent on receiving systemic therapy, LIS participants received treatment ranked within the worst quartile 24.8% of the time, compared with 21.9% of non-LIS patients (adjusted prevalence difference, 4.3% [95% CI, 0.5 to 8.2]). Conclusion LIS participants were less likely to receive systemic therapy at all and were more likely to receive treatments that receive low NCCN EB scores.

25COASMA106:

Title: SWOG S1815: A Phase III Randomized Trial of Gemcitabine, Cisplatin, and Nab-Paclitaxel Versus Gemcitabine and Cisplatin in Newly Diagnosed, Advanced Biliary Tract Cancers

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Journal of Clinical Oncology, Volume 43, Number 5
Doi- https://doi.org/10.1200/JCO-24-01383

Abstract: Purpose SWOG S1815 was a randomized, open label phase III trial, evaluating gemcitabine, nab-paclitaxel, and cisplatin (GAP) versus gemcitabine and cisplatin (GC) in

patients with newly diagnosed advanced biliary tract cancers (BTCs). Methods Patients with newly diagnosed locally advanced unresectable or metastatic BTC, including intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) and gallbladder carcinoma (GBC), were randomly assigned 2:1 to either GAP (gemcitabine 800 mg/m^2, cisplatin 25 mg/m^2, and nab-paclitaxel 100 mg/m^2 intravenously once per day on days 1 and 8 of a 21-day cycle) or GC (gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 intravenously once per day on days 1 and 8 of a 21-day cycle). Results Among 452 randomly assigned participants, 441 were eligible and analyzable, 67% with ICC, 16% with GBC, and 17% with ECC. There was no significant difference in overall survival (OS) between GAP versus GC. Median OS with GAP was 14.0 months (95% CI, 12.4 to 16.1) and 13.6 months with GC (95% CI, 9.7 to 16.6); hazard ratio (HR), 0.91 (95% CI, 0.72 to 1.14); P = .41. Median progression-free survival (PFS) was similar between groups with median PFS for GAP being 7.5 months (95% CI, 6.4 to 8.5) versus 6.3 months for GC (95% CI, 4.4 to 8.2); HR, 0.89 (95% CI, 0.71 to 1.12); P = .32. In exploratory subset analyses, the OS and PFS benefits of GAP versus GC treatment were greater in locally advanced disease compared with metastatic disease, although not statistically significant (interaction P = .14 for OS and P = .17 for PFS). Moreover, GAP versus GC showed greater improvement in PFS among participants with GBC than those with ICC or ECC (interaction P = .01), but not OS (interaction P = .28). Conclusion The addition of a taxane in the GAP regimen to the standard gemcitabine-cisplatin regimen did not improve OS in newly diagnosed BTC. More toxicity was encountered with GAP versus GC.

25COASMA107:

Title: Atezolizumab Plus Chemotherapy With or Without Bevacizumab in Advanced Biliary Tract Cancer: Clinical and Biomarker Data From the Randomized Phase II IMbrave151 Trial

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Journal of Clinical Oncology, Volume 43, Number 5
Doi- https://doi.org/10.1200/JCO.24.00337

Abstract: Purpose Biliary tract cancers (BTCs) harbor an immunosuppressed tumor microenvironment and respond poorly to PD-1/PD-L1 inhibitors. Bevacizumab (anti–vascular endothelial growth factor) plus chemotherapy can promote anticancer immunity, augmenting response to PD-L1 inhibition. Patients and Methods This randomized, double-blind, proof-of-concept phase II study enrolled patients (n = 162) with previously untreated advanced BTC (IMbrave151; ClinicalTrials.gov identifier: NCT04677504). Patients were randomly assigned 1:1 to receive cycles of atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) or atezolizumab plus placebo once every 3 weeks until disease progression or unacceptable toxicity. All patients received cisplatin (25 mg/m^2) plus gemcitabine (1,000 mg/m^2; cisplatin plus gemcitabine [CisGem]) on days 1 and 8 once every 3 weeks for up to eight cycles. Stratification of patients was by disease status, geographic region, and primary tumor location. The primary end point was progression-free survival (PFS). No formal hypothesis testing was performed. Exploratory correlative biomarker analysis was undertaken using transcriptome analysis (n = 95) and mutation profiling (n = 102) on baseline tumor

samples. Results Between February and September 2021, 162 patients were enrolled. Median PFS was 8.3 months in the bevacizumab arm and 7.9 months in the placebo arm (stratified hazard ratio [HR], 0.67 [95% CI, 0.46 to 0.95]). Median overall survival (OS) was 14.9 and 14.6 months in the bevacizumab and placebo arms, respectively (stratified HR, 0.97 [95% CI, 0.64 to 1.47]). The incidence of grade 3 or 4 adverse events was 74% in both arms. High VEGFA gene expression was associated with improved PFS (HR, 0.44 [95% CI, 0.23 to 0.83]) in the bevacizumab arm versus placebo. Conclusion In unselected patients with advanced BTC, adding bevacizumab to atezolizumab plus CisGem modestly improves PFS but not OS. High VEGFA gene expression may represent a predictive biomarker of benefit from atezolizumab/bevacizumab, warranting further investigation.

25COASMA108:

Title: Outcomes After Brexucabtagene Autoleucel Administered as a Standard Therapy for Adults With Relapsed/Refractory B-Cell ALL

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Abstract: Purpose-On the basis of the results of the ZUMA-3 trial, brexucabtagene autoleucel (brexu-cel), a CD19-directed chimeric antigen receptor T-cell therapy, gained US Food and Drug Administration approval in October 2021 for adults with relapsed/refractory (R/R) B-cell ALL (B-ALL). We report outcomes of patients treated with brexu-cel as a standard therapy. Methods We developed a collaboration across 31 US centers to study adults with B-ALL who received brexu-cel outside the context of a clinical trial. Data were collected retrospectively from October 2021 to October 2023. Toxicities were graded per American Society for Transplantation and Cellular Therapy guidelines for cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Results At the time of data lock, 204 patients had undergone apheresis and 189 were infused. Median follow-up time was 11.4 months. Forty-two percent of patients received brexu-cel in morphologic remission and would have been ineligible for participation in ZUMA-3. After brexu-cel, 151 achieved complete remission (CR), of which 79% were measurable residual disease (MRD) negative remissions. Median progression-free survival (PFS) was 9.5 months and median overall survival was not reached. Grade 3-4 CRS or ICANS occurred in 11% and 31%, respectively. In multivariable analysis, patients receiving consolidative hematopoietic cell transplantation (HCT; hazard ratio, 0.34 [95% CI, 0.14 to 0.85]) after brexu-cel had superior PFS compared with those who did not receive any consolidation or maintenance therapy. Conclusion Similar to ZUMA-3, high rates of MRD-negative CR were observed after brexu-cel treatment for R/R B-ALL. The use of HCT as consolidation after brexu-cel resulted in improved PFS.

25COASMA109:

Title: JCCG ALL-B12: Evaluation of Intensified Therapies With Vincristine/Dexamethasone Pulses and Asparaginase and Augmented High-Dose Methotrexate for Pediatric B-ALL

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Journal of Clinical Oncology, Volume 43, Number 5
Doi-https://doi.org/10.1200/JCO.24.00811
Abstract: Purpose The JCCG ALL-B12 clinical trial aimed to evaluate the effectiveness of unvalidated treatment phases for pediatric ALL and develop a safety-focused treatment framework. Patients and Methods Patients age 1-19 years with newly diagnosed B-ALL were enrolled in this study. These patients were stratified into standard-risk (SR), intermediate-risk (IR), and high-risk (HR) groups. Randomized comparisons assessed the effectiveness of vincristine (VCR)/dexamethasone pulses in the SR group, evaluated the effects of L-asparaginase (ASP) intensification in the IR group, and compared standard consolidation including block-type treatment with experimental consolidation with high-dose methotrexate (HD-MTX) intensified with VCR and ASP in the HR group. Results Of 1,936 patients enrolled, 1,804 were eligible for the experimental treatment. The overall 5-year event-free survival and overall survival rates were 85.2% (95% CI, 83.5 to 86.8) and 94.3% (95% CI, 93.1 to 95.3), respectively. The cumulative incidence of relapse and postremission nonrelapse mortality was 13.2% (95% CI, 11.6 to 14.8) and 0.6% (95% CI, 0.3 to 1.0), respectively. Random assignment in the SR group showed no significant benefit from pulse therapy. In the IR group, ASP intensification had limited effects. In the HR group, standard block therapy and HD-MTX yielded equivalent outcomes. Conclusion The ALL-B12 trial achieved favorable outcomes in a nationwide cohort by stratifying treatment on the basis of risk and balancing treatment intensity. This study not only demonstrated that existing standard of care can be further refined but also indicated that improvement in outcomes with intensified chemotherapy has reached a plateau.

25COASMA110:

Title: Phase II Trial of Enfortumab Vedotin in Patients With Previously Treated Advanced Head and Neck Cancer

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Journal of Clinical Oncology, Volume 43, Number 5
Doi-https://doi.org/10.1200/JCO.24.00646
Abstract: Purpose Despite advances in immunotherapy, unresectable recurrent/metastatic head and neck cancer (HNC) carries a poor prognosis, and effective treatments are needed. As nectin-4 is widely expressed in HNC, enfortumab vedotin (EV), a nectin-4–directed antibody-drug conjugate, was explored in HNC in EV-202 (ClinicalTrials.gov identifier: NCT04225117). Methods This open-label, multicohort, phase II study evaluated intravenous EV 1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle. In the HNC cohort, eligible patients had recurrent/metastatic HNC and had received platinum-based therapy for locally advanced/metastatic disease and a PD-1/PD-L1 inhibitor. The primary end point was investigator-assessed confirmed objective response rate (ORR) per RECIST version 1.1. Secondary end points were investigator-assessed duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS); overall survival (OS); and safety. Results
The primary analysis included 46 patients; all received EV (median follow-up, 9.3 months).

Most patients (52.2%) had ≥3 previous lines of systemic therapy in the metastatic setting. Confirmed ORR was 23.9%, DCR was 56.5%, and median DOR was not reached (median DOR was 9.4 months at a later data cutoff [median follow-up, 11.3 months]). Median PFS and OS were 3.9 and 6.0 months, respectively. Treatment-related adverse events (TRAEs) occurring in >20% of patients were alopecia (28.3%), fatigue (26.1%), and peripheral sensory neuropathy (23.9%). Sixteen patients (34.8%) experienced grade ≥3 TRAEs; anemia and decreased neutrophil count occurred in ≥1 patient (both n = 2; 4.3%). Conclusion EV demonstrated antitumor activity in heavily pretreated HNC. Safety was consistent with the known safety profile of EV; no new safety signals were identified. These data support further evaluation of EV for advanced HNC not amenable to definitive local therapy.

Surgical Oncology

25COASMA1

Title: Profile of haemostasis and coagulation in patients with peritoneal carcinomatosis undergoing cytoreductive surgery with hyperthermal chemotherapy,

Diego Cuenca Apolo, Antonio Puppo Moreno, Cristóbal Muñoz Casares, Javier Padillo Ruíz,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109497,
https://doi.org/10.1016/j.ejso.2024.109497.

Abstract: One-third of patients with peritoneal carcinomatosis undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) present alterations in conventional coagulation test results. However, perioperative coagulation has not been systematically investigated in these patients. This study aimed to investigate hemostatic changes in such patients. This prospective observational study included patients with peritoneal carcinomatosis who underwent CRS-HIPEC. Variables of conventional coagulation and rotational thromboelastometry (ROTEM) parameters of patients who underwent CRS-HIPEC at baseline (time 0, T0: before surgery) were compared with those of healthy blood donors (HBD). Blood samples were collected at baseline (T0), 2-h (T2), and 72-h (T72) after surgery. 44 patients who underwent CRS-HIPEC and 40 HBDs were included. At T0, patients who underwent CRS-HIPEC presented with lower hemoglobin levels and elevated C-reactive protein, fibrinogen, factor XIII (FXIII), and D-dimer levels than HBDs. At T2, significant decreases in hemoglobin, platelet count, fibrinogen, and FXIII levels were observed. In contrast, D-dimer and von Willebrand factor levels increased. Regarding ROTEM parameters, in the postoperative period, increased clotting time in thromboelastometry with extrinsic activation, and maximum clot firmness in thromboelastometry with fibrin contribution, along with a significant decrease in maximum clot firmness in thromboelastometry with extrinsic activation without a hyperfibrinolysis pattern, were observed. Platelet function, as assessed using the platelet function assay, was normal. CRS-HIPEC causes coagulopathy secondary to a pronounced platelet drop, worsening of fibrinogen and FXIII levels, and impaired clot firmness as evidenced by ROTEM. A proinflammatory status was ubiquitously observed.

Keywords: Coagulation; Peritoneal carcinomatosis; Cytoreductive surgery; Coagulopathy; Thromboelastometry; ROTEM

25COASMA2

Title: Indocyanine green highlights the lymphatic drainage pathways, enhancing the effectiveness of radical surgery for mid-low rectal cancer: A non-randomized controlled prospective study,

Wenlong Qiu, Gang Hu, Shiwen Mei, Yuegang Li, Jichuan Quan, Huiyong Niu, Lan Mei, Shangkun Jin,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109520,
https://doi.org/10.1016/j.ejso.2024.109520.

Abstract: Fluorescence-guided lymphadenectomy (FLND) using indocyanine green (ICG) has emerged as a promising technique to enhance the accuracy of lymphadenectomy in rectal

cancer surgery. Effective lymphadenectomy is crucial for improving prognosis in patients with advanced rectal cancer, but it remains technically challenging and controversial. This prospective nonrandomized controlled study was conducted involving 129 patients underwent laparoscopic surgery, and 64 patients assisted by FLND. Patients received submucosal ICG injections before surgery to facilitate FLND. Lymph nodes were categorized as station 251, station 252, or station 253 based on their anatomical locations. The effectiveness of FLND was evaluated by comparing the number of harvested and metastatic lymph nodes between the FLND and control groups. The FLND group demonstrated a significantly higher median number of harvested station 253 lymph nodes compared to the control group (2.0 vs. 1.0, P = 0.007). The FLND cohort had a shorter postoperative hospital stay (6 days vs. 8 days, P < 0.001) and similar rates of postoperative complications compared to the control cohort. The study found no significant differences in the median number of harvested station 251 (10.0 vs. 11.0, P = 0.872) and station 252 (6.0 vs. 5.0, P = 0.369) lymph nodes between the groups. Univariate and multivariate analyses indicated that FLND significantly increased the harvested lymph node count. Radical surgery assisted by FLND significantly improves the accuracy and yield of lymphadenectomy in mid-low rectal cancer, enhancing surgical outcomes and patient prognosis. Future advancements in fluorescence imaging and related technologies hold promise for further improving the clinical effectiveness of this technique.

Keywords: Mid-low rectal cancer; Indocyanine green; Radical surgery; Lymphatic drainage pathways

25COASMA3

Title: Evaluating the perioperative risks in esophageal resection and reconstruction for esophageal carcinoma among elderly patients: A retrospective propensity score matching analysis,

Ji Yong Kim, Jae Kwang Yun, Hyeong Ryul Kim, Seung-Il Park, Yong-Hee Kim,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109542,
https://doi.org/10.1016/j.ejso.2024.109542.

Abstract: With the global aging, the number of elderly candidates for esophageal resection is increasing. However, studies on esophagectomy in elderly patients have yielded conflicting results, and individuals over 75 years old are frequently excluded from studies on esophageal cancer. This study aimed to analyze perioperative and survival outcomes post-esophagectomy in elderly patients using propensity score matching (PSM). Patients with esophageal carcinoma who underwent esophagectomy (2006–2020) were studied. A 1:2 PSM was performed, with matching variables, including operational approach, type of operation, Charlson Comorbidity Index without age score, clinical stage, and treatment modality. Perioperative and survival outcomes were compared between the age groups. After PSM, 91 elderly and 182 non-elderly patients were analyzed. The postoperative in-hospital mortality rate was identical for both groups at 1.1 %. The non-elderly group had a significantly higher 4-week discharge rate (91.8 % vs. 84.6 %, p = 0.032). There were no significant differences in overall postoperative complications (p = 0.886). Grade III–IV complications occurred in 16.5 % of elderly and 8.8 % of non-elderly patients, with no significant difference

(p = 0.092). The 5-year overall survival rate was significantly lower in the elderly group (47.3 % vs. 69.8 %, p = 0.022), while the 5-year recurrence-free survival rate showed no significant difference (45.7 % vs. 63.6 %, p = 0.119). Elderly patients undergoing esophagectomy were similar to non-elderly patients in overall complications and in-hospital mortality. Despite a tendency for increased severity of complications and a significantly lower 4-week discharge rate, esophagectomy remains acceptable for elderly patients.

Keywords: Esophageal carcinoma; Complications; Elderly patient; Esophageal resection; Esophageal reconstruction; Esophagectomy

25COASMA4

Title: Multimodal prehabilitation to improve functional abilities and reduce the chronic inflammatory response of frail elderly patients with gastric cancer: A prospective cohort study,

Yuqi Sun, Yulong Tian, Zequn Li, Shougen Cao, Xiaodong Liu, Hongding Han, Lei Han, Lingxin Kong,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109563,
https://doi.org/10.1016/j.ejso.2024.109563.

Abstract: Population ageing and cancer burden are important global public health problems that pose unprecedented threats to health systems worldwide. Frailty is a common health problem among elderly patients with cancer. In recent years, the use of prehabilitation to improve frailty has received widespread attention. Few studies have addressed the specific physiologic effects of prehabilitation on patients undergoing surgery. Frail elderly patients (aged at least 65 years) who underwent elective primary surgery for gastric cancer between September 2022 and October 2023 were included in this single-centre prospective cohort study and were categorized into multimodal prehabilitation or ERAS standard care groups. Prehabilitation, including physical and respiratory training, nutritional support and psychosocial treatment, was provided at least two weeks before gastrectomy. The primary outcome was functional status. Secondary outcomes included changes in indices of lipid metabolism, oxidative stress and chronic inflammation. Over a 13-month period, 137 participants were assessed for eligibility, and 110 patients (prehabilitation 55, ERAS 55) were analysed. Compared with the baseline, patients in the prehabilitation group exhibited increased physical capacity before the operation (mean 6-min walk test change +28 m; P < 0.001). After prehabilitation intervention, inflammation-related indicators (NLR, PLR, SII and CRP) improved, and proinflammatory cytokine production (IL-5, IL-6, IL-1β, IL-10 and TNF-α) decreased. After surgery, the increase in IL-6 was reduced in the prehabilitation group (P = 0.036). Moreover, prehabilitation was associated with alleviating oxidative stress as determined by the levels of MDA (P = 0.005). Multimodal prehabilitation can play a beneficial role in improving functional abilities by reducing chronic inflammation, improving lipid metabolism, and attenuating oxidative stress.

Keywords: Multimodal prehabilitation; Frail elderly patients; Functional capacity; Mechanism

25COASMA5

Title: Adjuvant chemotherapy for node-negative gastric adenocarcinoma after neoadjuvant chemotherapy and gastrectomy: A propensity score matched analysis study,

Enoch Wong, Sivesh K. Kamarajah, Fadi Dahdaleh, Samer Naffouje, Victoria Kunene, David Fackrell, Ewen A. Griffiths,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109506,
https://doi.org/10.1016/j.ejso.2024.109506.

Abstract: The long term survival of patients undergoing curative resection for gastric cancer remains poor owing to high recurrence rates. The use of adjuvant chemotherapy in node positive gastric cancer to prolong survival and prevent recurrence is widely accepted. However, the role for adjuvant chemotherapy in node negative gastric cancer is less clear, particularly in the era of neoadjuvant chemotherapy. To determine the association of adjuvant chemotherapy with survival in patients undergoing pathologically node negative gastric cancer resection, following neoadjuvant chemotherapy. We examined a national cancer database containing patients who had undergone neoadjuvant chemotherapy and pathologically node negative curative gastrectomy. We divided these patients into those who had undergone adjuvant chemotherapy versus those who had not. Using a propensity score matched analysis, we analyzed the survival of these patients between the 2 groups. 5309 patients who had undergone curative gastrectomy were identified from the database and 806 of these patients were given adjuvant chemotherapy. Following propensity score matched analysis, patients who had been given adjuvant chemotherapy had an increased median survival of 150 vs 125 months (5-year 68 % vs 62 %, $p < 0.001$). There is a small, but statistically significant survival benefit for adjuvant chemotherapy in patients with node negative gastric cancer who had undergone neoadjuvant chemotherapy. Further studies are required to examine the role of adjuvant chemotherapy in this subset of patients.

Keywords: Neoadjuvant chemotherapy; Outcomes; Gastrectomy; Adjuvant chemotherapy

25COASMA6

Title: Salvage surgery for oesophageal cancer: The need for more intensive surveillance,

Rand Abdulrahman, Natallia Kharytaniuk, Nuha Birido, Orla Monaghan, Jan Sorensen, Brian O'Neill,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109548,
https://doi.org/10.1016/j.ejso.2024.109548.

Abstract: There is currently no consensus on the role, method or frequency of surveillance following curative treatment of oesophageal cancer; re-investigation largely relying on symptom triggers which may delay detection of recurrence and impact survival. We hypothesised that intensive surveillance with endoscopy and imaging was more likely to detect recurrent or new cancer at a curable stage and this study examined the outcomes of this surveillance policy. A prospective database of curatively treated oesophageal carcinoma patients was interrogated for patients with new or recurrent disease detected on surveillance and amenable to salvage surgery. Surveillance was by clinic visits and endoscopy/biopsy 3-monthly to 3 years, 6-montjhly to 5 years and yearly thereafter while computerised

tomography (CT) was performed 6-monthly for the first 3 years, annually to 5 years, and subsequently as indicated. Of 205 patients treated with curative intent, 24 (11.7 %) underwent salvage surgery for 27 incidences of new or recurrent cancer. The median and 5-year survival was 51.8 months and 45.8 %, which was not inferior to the entire cohort of patients treated for cure, which was 30.2 months and 32.6 % respectively (p = 0.498).Intensive surveillance identified almost 12 % of patients with recurrent or second primary cancer amenable to salvage surgery, with a non-inferior outcome to the remaining cohort. Further studies will refine surveillance intervals, techniques and follow-up duration for oesophageal cancer as for other GI malignancies.

25COASMA7

Title: Risk reducing mastectomy in Norwegian BRCA1/2 carriers,

Hanne Kjensli Hyldebrandt, Astrid Tenden Stormorken, Valeria Vitelli, Lovise Mæhle, Ellen Schlichting,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109571,
https://doi.org/10.1016/j.ejso.2024.109571.

Abstract: Risk reducing mastectomy (RRM) is an option for women with pathogenic germline variants in BRCA1 or BRCA2 (BRCA1/2). This study investigates and compares RRM-uptake among Norwegian BRCA1/2 carriers from 2008 to 2021, temporal trends, and incidence of breast cancer (BC) after surgery. BRCA1/2 carriers without prior breast or ovarian cancer, tested at Oslo University Hospital between January 1st, 2008 and December 31st, 2021 were included in the study. Data on RRM was obtained from The Norwegian Patient Registry. RRM-uptake, time from genetic testing (GT) to RRM, and RRM-uptake 2- and 5-years post-GT was calculated for all carriers, according to gene and age at GT. RRM-uptake was compared for those tested in 2008/2009 versus 2015/2016. BC diagnoses post-RRM was collected from The Cancer Registry of Norway. In total, 1237 BRCA1/2 carriers were included, 679 (54.9 %) BRCA1 and 558 (45.1 %) BRCA2. Six hundred and four (48.8 %) had chosen RRM, 370 (54.5 %) BRCA1 and 234 (42.0 %) BRCA2 ($p < 0.001$). Mean age at RRM was 40.1 for BRCA1 and 44.6 for BRCA2 ($p < 0.001$). Mean time from GT to RRM was 2.3 years for BRCA1 and 3 years for BRCA2 ($p < 0.001$). Women tested in 2015/2016 were 2.6 times more likely to choose RRM compared to those tested in 2008/2009. Two out of the 604 (0.3 %) had developed BC post-RRM. Nearly half of BRCA1/2 carriers had chosen RRM, with increasing uptake since 2008. Compared to BRCA2 carriers, more BRCA1 carriers chose RRM, were operated at a younger age and sooner after GT. Post-RRM BC incidence was low.

Keywords: BRCA1; BRCA2; Risk-reducing mastectomy; Breast cancer; Prevention

25COASMA8

Title: CT-radiomics and pathological tumor response to systemic therapy: A predictive analysis for colorectal liver metastases. Development and internal validation of a clinical-radiomic model,

Angela Ammirabile, Lara Cavinato, Carola Anna Paolina Ferro, Francesco Fiz, Matteo Stefano Savino

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109557,
https://doi.org/10.1016/j.ejso.2024.109557.

Abstract: The standard treatment of colorectal liver metastases (CRLM) is surgery with perioperative chemotherapy. A tumor response to systemic therapy confirmed at pathology examination is the strongest predictor of survival, but it cannot be adequately predicted in the preoperative setting. This bi-institutional retrospective study investigates whether CT-based radiomics of CRLM and peritumoral tissue provides a reliable non-invasive estimation of the pathological tumor response to chemotherapy. All consecutive patients undergoing liver resection for CRLM at the two institutions were considered. Only patients with a radiological partial response or stable disease at chemotherapy and with a preoperative/post-chemotherapy CT performed <60 days before surgery were included. The pathological response was evaluated according to the tumor regression grade (TRG). The tumor (Tumor-VOI) was manually segmented on the portal phase of the CT and a 5-mm ring of peritumoral tissue was automatically generated (Margin-VOI). The predictive models underwent internal validation. Overall, 222 patients were included; 64 had a pathological response (29 %, TRG1-3). Two-third of patients displaying a radiological response (111/170) did not have a pathological one (TRG4-5). For TRG1-3 prediction, the clinical model performed fairly (Accuracy = 0.725, validation-AUC = 0.717 95%CI = 0.652–0.788). Radiomics improved the results: the model combining the clinical data and Tumor-VOI features had Accuracy = 0.743 and validation-AUC = 0.729 (95%CI = 0.665–0.798); the full model (clinical/Tumor-VOI/Margin-VOI) achieved Accuracy = 0.820 and validation-AUC = 0.768 (95%CI = 0.707–0.826). CT-based radiomics of CRLM allows an insightful non-invasive assessment of TRG. The combined analysis of the tumor and peritumoral tissue improves the prediction. In association with clinical data, the radiomic indices outperform standard radiological and clinical evaluation.

Keywords: Radiomics; Computed tomography; Colorectal liver metastases; Neoadjuvant chemotherapy; Pathological response; Tumor regression grade

25COASMA9

Title: Dissection of RET p.M918T-driven progression of hereditary vs. sporadic medullary thyroid cancer,

Andreas Machens, Kerstin Lorenz, Frank Weber, Henning Dralle,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109549,
https://doi.org/10.1016/j.ejso.2024.109549.

Abstract: Whether inherited in the context of multiple endocrine neoplasia 2B at germline level or acquired in a lifetime, all RET p.M918T (RET c.2753T>C) mutations should activate the RET tyrosine kinase receptor alike, with similar degrees of medullary thyroid cancer (MTC) progression when disparities in disease onset and multifocal growth are accounted for. This cross-sectional analysis of RET p.M918T-driven progression of hereditary MTC (33 patients) vs. sporadic MTC (36 patients) sought to explore this hypothesis. Patients with hereditary disease were significantly younger at thyroidectomy (medians of 10 vs. 57 yrs.) and featured significantly more often multifocal growth (69 vs. 14 %) with more thyroid tumor foci (medians of 2 foci vs. 1 focus) than patients with sporadic disease. Although the former had 3.6-fold smaller primary thyroid tumor diameters (medians of 5 vs. 18 mm) and

twice as many neck nodes dissected (medians of 66.5 vs. 32 nodes) than the latter, extrathyroid tumor extension (42 vs. 36 %), node metastasis (64 vs. 77 %), distant metastasis (33 vs. 17 %), and biochemical cure rates (45 vs. 35 %) were fairly comparable, as was the number of dissected node metastases (medians of 7 vs. 8 involved nodes). Sensitivity analyses, with breakdown of patients by tumor multifocality and nodal status, corroborated these findings. RET p.M918T-driven progression of MTC is similar in hereditary and sporadic disease, barring earlier development and more frequent multifocal growth of hereditary MTC. This makes a compelling case for referral of patients with RET p.M918T-driven MTCs to specialist surgical centers.

Keywords: Medullary thyroid carcinoma; RET proto-oncogene; Extrathyroid extension; Lymph node metastases; Distant metastases; Biochemical cure

25COASMA10

Title: Prime suspect or collective responsibility: Impact of specific lymph node station dissection on short- and long-term outcomes among locally advanced gastric cancer patients after neoadjuvant chemotherapy,

Katarzyna Sędłak, Marcin Kubiak, Zuzanna Pelc, Radosław Mlak, Sebastian Kobiałka, Magdalena Leśniewska,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109545,
https://doi.org/10.1016/j.ejso.2024.109545.

Abstract: Lymphatic route is the main pathway for gastric cancer (GC) spread, and lymph node (LN) involvement is a major prognostic factor after curative resection. The aim of this study was to assess the outcomes of specific LN station dissection. Patients with locally advanced (cT2-4N0-3M0) GC who underwent multimodal treatment between 2013 and 2023 were included in the study. Patients who had not undergone gastrectomy, had early (cT1) or metastatic GC, who had undergone multiorgan resections, palliative care, had died before the end of curative-intent planned treatment, or had incomplete clinical or pathological information were excluded. The primary endpoint was the development of serious complications, and the secondary outcome was OS. Mulivariable analysis revealed, that among patients who received neoadjuvant chemotherapy (NAC), it was observed that station 10 lymphadenectomy was associated with a higher risk of serious postoperative complications. (27.6 % vs 8.7 %; OR = 3.28) Among the no-NAC group, it was observed that station 13 lymphadenectomy was associated with a higher risk of serious postoperative complications. (57.1 % vs 13.2 %; OR = 6.96). Among the NAC group, a lower risk of death was observed in patients with station 8 (HR = 0.53) or 11 lymphadenectomy (HR = 0.53). While D2 lymphadenectomy remains crucial, particularly in in high-volume, experienced GC centers, the necessity of a more extensive D2+ lymphadenectomy is not supported by our findings. Moreover, we aimed to highlight the importance of tailored surgical approaches and emphasize the significance of LN station dissection in influencing both short-term complications and long-term survival outcomes.

25COASMA11

Title: Short- and long-term outcomes of vaginal, laparoscopic, and robotic-assisted surgery in "oldest old" endometrial cancer,

Giorgio Bogani, Francesco Raspagliesi, Mario Malzoni, Ilaria Cuccu, Giuseppe Vizzielli, Giovanni Scambia,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109568,
https://doi.org/10.1016/j.ejso.2024.109568.

Abstract: To assess the safety and long-term effectiveness of minimally invasive approach in managing "oldest old" endometrial cancer patients. This is a retrospective cohort, multi-institutional study. Consecutive patients, treated between 2000 and 2020, with apparent early-stage endometrial cancer patients, aged ≥85 years. Surgery-related outcomes of robotic-assisted, laparoscopic, and vaginal surgery were compared. Survival was evaluated in patients with at least 3-year follow-up data. Charts of 82 endometrial cancer patients "oldest old" were retrieved. Intermediate-high and high-risk endometrial cancer patients accounted for 26 (31.7 %) and 17 (20.7 %), respectively. In total, 12 (15 %), 45 (55 %), and 25 (30 %) patients underwent robotic-assisted, laparoscopic, and vaginal surgery, respectively. Looking at surgery-related outcomes, robotic-assisted surgery correlated with a longer operative time ($p < 0.001$) and longer length of hospital stay ($p = 0.002$) in comparison to laparoscopic and vaginal approaches. Overall, seven (8.5 %) conversions from the planned approach occurred. The surgical approach did not influence disease-free survival ($p = 0.6061$) and overall survival ($p = 0.4950$). Via multivariate analysis, only serosal/adnexal invasion correlated with the risk of death (HR: 3.752, $p = 0.038$). All three minimally invasive approaches are safe and effective methods for managing endometrial cancer in the oldest old population. Chronological age, per se, should not be considered a contraindication for receiving minimally invasive surgery.

Keywords: Endometrial cancer; Robotic-assisted; Laparoscopy; Vaginal hysterectomy; Minimally invasive hysterectomy

25COASMA12

Title: Perspectives of the medical oncologist regarding adjuvant chemotherapy for pancreatic cancer: An international expert survey and case vignette study,

N.C. Biesma, M.U.J.E. Graus, G.A. Cirkel, M.G. Besselink, J.W.B. de Groot, B. Groot Koerkamp,

European Journal of Surgical Oncology,Volume 51, Issue 3,2025,109544,ISSN 0748-7983,
https://doi.org/10.1016/j.ejso.2024.109544.

Abstract: Adjuvant chemotherapy improves survival in patients with resected pancreatic ductal adenocarcinoma (PDAC). The decision to initiate chemotherapy involves both patient and physician factors, decision-specific criteria, and contextual considerations. This study aimed to assess medical oncologists' views on adjuvant chemotherapy following pancreatic resection for PDAC. An online survey and case vignette study were distributed to medical oncologists via the Dutch Pancreatic Cancer Group (DPCG), International Hepato-Pancreato-Biliary Association (IHPBA) and related networks. A total of 91 oncologists from 14 countries participated, 46 % of whom treated more than 40 new PDAC patients annually,

with a median experience of 15 years. Significant discrepancies were noted in their recommendations for adjuvant chemotherapy across case vignettes. In patients over 70, 17 % advised against chemotherapy, while 31 % said age was not a factor. Oncologists with less than 10 years of experience and those in non-academic settings were less likely to recommend adjuvant therapy. While 87 % agreed mFOLFIRINOX is the preferred adjuvant treatment, consensus on individual cases was lacking. The recommended interval between surgery and chemotherapy ranged from 3 to 26 weeks, with varying reasons for withholding treatment, primarily due to postoperative recovery and performance status. Our study revealed substantial variation among oncologists in counseling on adjuvant chemotherapy after PDAC resection. This emphasizes the need for more patient involvement in decision-making and improving shared decision-making.

25COASMA13

Title: Minimal invasive surgery protects against severe postoperative complications regardless of body composition in patients undergoing colorectal surgery,

Thaís T.T. Tweed, Stan Tummers, Evert-Jan G. Boerma, Nicole D. Bouvy, David P.J. van Dijk, Jan H.M.B. Stoot,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109561,
https://doi.org/10.1016/j.ejso.2024.109561.

Abstract: For many colorectal cancer patients, primary surgery is the standard care of treatment. Further insights in perioperative care are crucial. The aim of this study is to assess the prognostic value of body composition for postoperative complications after laparoscopic and open colorectal surgery. From January 2013 to 2018 all consecutive patients who underwent surgery for colorectal cancer were enrolled in this study. Patients with a preoperative CT-scan <90 days before surgery were included. All CT-scans were obtained retrospectively, and body composition was analysed using a single transverse slice at the level of the third lumbar vertebra (L3) within the Slice-O-Matic-software. The studied outcome measure was the occurrence of major postoperative complications (Clavien-Dindo grade ≥3b). A total of 1213 patients were included in the final analyses. Multivariable analyses showed that patients with low-skeletal muscle mass Z-score (OR 0.67, 95 % CI 0.45–0.97, p = 0.036) or a high visceral adipose tissue Z-score (OR 1.56, 95 % CI 1.06–2.29, p = 0.023) were significantly associated with an increased risk of developing major postoperative complications after open surgery. In the laparoscopic group, all six body composition parameters were not significantly associated with an increased risk of developing a major postoperative complication. In this study, open colorectal surgery in patients with either low skeletal muscle mass or high visceral adipose tissue mass was associated with increased risk of postoperative complications. Laparoscopic surgery did not show this correlation. This demonstrates the importance of using minimal invasive surgery in colorectal cancer patients and implementing this as standard care.

Keywords: Laparoscopic surgery; Body-composition; Sarcopenia

25COASMA14

Title: Fluorescent Nanobodies for enhanced guidance in digestive tumors and liver metastasis surgery,

Łukasz Mateusiak, Sarah Hakuno, Eveline S.M. de Jonge-Muller, Sam Floru, Cornelis F.M. Sier,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109537,
https://doi.org/10.1016/j.ejso.2024.109537.

Abstract: Fluorescence molecular imaging, a potent and non-invasive technique, has become indispensable in medicine for visualizing molecular processes. In surgical oncology, it aids treatment by allowing visualization of tumor cells during fluorescence-guided surgery (FGS). Targeting the urokinase plasminogen activator receptor (uPAR), overexpressed during tissue remodeling and inflammation, holds promise for advancing FGS by specifically highlighting tumors. This study explores the extended use of Nanobody-based (Nb) anti-uPAR tracers, evaluating their receptor binding, ability to visualize and demarcate colorectal (CRC) and gastric cancer (GC), and detect localized (PC) and metastatic (PC-M) pancreatic carcinoma. First, the receptor structure interactions of Nb15, which binds specifically to the human homologue of uPAR, were characterized in vitro to deepen our understanding of these interactions. Subsequently, Nbs 15 and 13—where Nb13 targets the murine uPAR homologue—were labeled with the s775z fluorescent dye and validated in a randomized study in mice (n = 4 per group) using orthotopic human CRC, GC, and PC models, as well as a mouse PC-M model. Nb15, which binds to the D1 domain of uPAR and competes with urokinase's binding fragment, showed rapid and specific tumor accumulation. It exhibited higher tumor-to-background ratios in CRC (3.35 ± 0.75) and PC (3.41 ± 0.46), and effectively differentiated tumors in GC (mean fluorescence intensity: 0.084 ± 0.017), as compared to control Nbs. Nb13 successfully identified primary tumors and liver metastases in PC-M models. The tested fluorescently-labeled anti-uPAR Nbs show significant preclinical and clinical potential for improving surgical precision and patient outcomes, with Nb15 demonstrating promise for real-time surgical guidance.

Keywords: Nanobodies; Urokinase plasminogen activator receptor; Fluorescence-guided surgery; Fluorescence molecular imaging; Liver metastasis

25COASMA15

Title: Breast cancer outcomes in women with ovarian cancer and a pathogenic germline BRCA mutation,

Quratul Ain, Rachel L O'Connell, Parinita Swarnkar, Terri McVeigh, Angela George, Marios K Tasoulis,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025, 109380,
https://doi.org/10.1016/j.ejso.2024.109380.

Abstract: Women with ovarian cancer (OC) and a pathogenic variant in the BRCA1 or BRCA2 genes are at increased risk of developing breast cancer (BC). Evidence for long term outcomes in these patients who undergo bilateral risk reduction mastectomy (RRM) after ovarian cancer is sparse. The aim of this study was to analyse the long-term breast cancer-related outcomes of patients who have been diagnosed with ovarian cancer and found to have

BRCA1 or 2 pathogenic variants. Local approval was granted. The hospital clinical genetics database was interrogated to identify women who have been diagnosed with OC and a germline BRCA1/2 pathogenic variant between January 2010–March 2020. Patient demographics, OC treatment as well as any BC related information was analysed. 148 women were diagnosed with OC and a pathogenic variant in BRCA1/2 in the study period. 47 patients were excluded as they did not have treatment at our institution. 101 patients were included. The median age at diagnosis of OC was 52 years (IQR 46–61). Eighty-four (82 %) were FIGO stage 3 or 4 OC. At a median follow-up of 63 months (IQR 39–94), 55 (54.4 %) women had been diagnosed with a recurrence of ovarian cancer and 38 (37 %) women have died. Twenty-one (21 %) women were diagnosed with BC. 13 (12.9 %) had BC before OC, 4 after and 4 synchronous with OC. Of the remaining patients who did not have BC, 6 underwent bilateral risk reduction mastectomy (RRM) after treatment for OC. Risk of disease recurrence and death due to stage 3 and 4 ovarian cancer remained high in this time period. RRM can be undertaken in carefully selected patients, however we would recommend reserving this for women who have favourable OC disease prognosis.

25COASMA16

Title: Comparing efficacy and safety of transanal vs. laparoscopic total mesorectal excision for middle and low rectal cancer: Updated meta-analysis,

Xiao Zhang, Jiang Chen, Feng He, Wenchun Du, Xianhe Li, Xianhao Yu,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109559,
https://doi.org/10.1016/j.ejso.2024.109559.

Abstract: This study aimed to compare the efficacy and safety of transanal total mesorectal excision (TaTME) with laparoscopic total mesorectal excision (LaTME) in patients with middle and low rectal cancer. A comprehensive search of PubMed, Embase, and Cochrane databases was conducted to identify studies evaluating TaTME and LaTME from inception to June 2023. An additional search update was conducted in November 2024 to capture recently published studies. A total of 24 studies (3 randomized controlled trials and 21 observational studies) involving 3443 patients were included. Meta-analysis assessed key outcomes, including circumferential resection margin (CRM) positivity, R0 resection rate, completeness of mesorectal excision, conversion to open surgery, and postoperative complications. TaTME was associated with a significantly lower positive rate of CRM (odds ratio [OR] = 0.68, 95 % confidence interval [CI] = 0.49–0.94), a higher R0 resection rate (OR = 1.74, 95 % CI = 1.17–2.59), and a reduced incidence of conversion to open surgery (OR = 0.16, 95 % CI = 0.10–0.26) compared to LaTME. Completeness of ME was comparable between the two groups (OR = 1.29, 95 % CI = 0.85–1.96). There was no significant difference in postoperative complications (OR = 0.80, 95 % CI = 0.62–1.03) or 30-day mortality (OR = 0.42, 95 % CI = 0.12–1.47). TaTME demonstrates superior outcomes in terms of CRM positivity, R0 resection, and conversion rates compared to LaTME, with comparable safety profiles and no significant differences in postoperative complications or 30-day mortality. These findings support TaTME as a viable surgical approach for middle and low rectal cancer.

Keywords: Rectal cancer; Transanal; Laparoscopic; Total mesorectal excision; Meta-analysis

25COASMA17

Title: Immunotherapy-extended survival in patients with recurrent pulmonary pleomorphic carcinoma following surgery,

Wakako Nagase, Yujin Kudo, Jun Matsubayashi, Satoshi Takahashi, Kotaro Murakami, Hideyuki Furumoto,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109565,
https://doi.org/10.1016/j.ejso.2024.109565.

Abstract: Pulmonary pleomorphic carcinoma is a relatively rare and aggressive subtype of non-small cell lung cancer (NSCLC), with a poor prognosis and early recurrence, and is resistant to conventional therapies. This study investigated the efficacy of immune checkpoint inhibitors (ICIs) in improving the survival outcomes of patients with pulmonary pleomorphic carcinoma with postoperative recurrence. We conducted a retrospective analysis of 71 patients with pulmonary pleomorphic carcinoma who underwent pulmonary resection at Tokyo Medical University Hospital between 2008 and 2022. Clinicopathological data, programmed cell death ligand 1 (PD-L1) expression, and postoperative recurrence treatment outcomes were reviewed. Among the 71 patients with pulmonary pleomorphic carcinoma, the 5-year overall survival (OS) rate was 48.6 %, and high PD-L1 expression (28-8 clone) was observed in 87 %. The median recurrence-free survival (RFS) was 19.4 months, and postoperative recurrence occurred in 38 patients (54 %). Treatment after recurrence was administered to 24 patients (63 %), and immunotherapy was administered to 10 patients (26 %). In patients treated with ICI, the overall response rate (ORR) was significantly higher (50 %) compared to those treated without ICI (7 %). The median survival time after relapse was notably longer in the ICI-treated group (83.9 months), compared to the non-ICI group (10.1 months).ICIs significantly improve survival outcomes in patients with recurrent pulmonary pleomorphic carcinoma, particularly in those with high PD-L1 expression. Early postoperative recurrence and rapid progression have been observed, making therapeutic intervention challenging. Close follow-up is crucial, and ICIs become a pivotal treatment option for managing this highly aggressive cancer.

Keywords: Pulmonary pleomorphic carcinoma; Non-small cell lung cancer; Immune checkpoint inhibitors; Immunotherapy; PD-L

25COASMA18

Title: Learning curve for robot-assisted Mckeown esophagectomy in patients with thoracic esophageal cancer,

Ligong Yuan, Tianci Zhang, Xianning Wu,

European Journal of Surgical Oncology, Volume 51, Issue 3, 2025, 109516,
https://doi.org/10.1016/j.ejso.2024.109516.

Abstract: Robot-assisted minimally invasive esophagectomy (RAMIE) is an effective but technically demanding procedure. The learning curve of RAMIE has been studied to help guide training and to ensure its safe implementation.We retrospectively analyzed the first 83

consecutive patients with thoracic esophageal cancer who underwent robot-assisted minimally invasive Mckeown esophagectomy (RAMIE-MK) between May 2021 and August 2023, all performed by a single surgeon. A cumulative sum (CUSUM) analysis was applied to generate the learning curve of RAMIE-MK, based on total operation time. The learning curve was divided into two phases based on the CUSUM analysis: Phase I, the initial learning phase (cases 1–27) and Phase II, the proficiency phase (cases 28–83). When comparing the proficiency phase with the initial phase, we observed a significant decreased trends in total operation time (329.6 ± 71.0 min vs 221.3 ± 33.5 min, P＜0.001). No significant differences were found in other clinicopathological characteristics. For a surgeon experienced in open and thoracolaparoscopic esophagectomy, and who also received systematic robot-assisted thoracic surgery training on animals, a total of 27 cases were required to gain technical proficiency in RAMIE-MK.

Keywords: Esophageal cancer; Robot-assisted; Mckeown

25COASMA19

Title: Evolution of breast cancer management after mediastinal hodgkin lymphoma: Towards a breast- conserving approach,

Jihane Bouziane, Pierre Loap, Kim Cao, Lea Pauly, Alain Fourquet, Youlia Kirova,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109555,
https://doi.org/10.1016/j.ejso.2024.109555.

Abstract: To analyse the clinical and histological characteristics of breast cancers (BC) occurring after Hodgkin lymphoma (HL), as well as their outcome with particular attention to the effectiveness and safety of breast-conservative surgery with radiation therapy (RT). This is a retrospective study of 218 patients who developed stage 0 to III BC after treatment for mediastinal HL between 1951 and 2022. Comprehensive demographic, clinical, and therapeutic data were collected for HL and BC, as well as survival and locoregional control. Statistical analyses were performed using R software version 4.1.1. The median age at HL diagnosis was 24 years [7–79]. BC appeared at a median age of 47 years [22–86], with a median interval of 21 years [5–51] after HL. Locoregional treatment included mastectomy in 117 (56.0 %) and lumpectomy in 92 (44.0 %), with postoperative RT in 99 patients (47.6 %). Isocentric lateral decubitus irradiation (ILD) was performed for 48 patients treated by tumorectomy (63.2 %). With a median follow-up of 29.7 years after HL and 7.7 years after BC, the 5-year overall survival (OS) and locoregional control rates were resp. 89.2 % and 86.4 % for invasive, and 100 % for in situ cancers. The 5-year metastasis-free survival rate was 87.4 % [95 % CI: 82.7–92.4 %]. No late sequelae was reported.Breast-conserving surgery, combined with appropriate RT, can be considered in the treatment of BC after HL despite prior thoracic irradiation. This approach provides comparable outcomes in terms of local control and survival while reducing the risk of long-term complications associated with mastectomy.

Keywords: Mediastinal hodgkin lymphoma; Breast cancer; Breast conserving surgery with radiotherapy; Re-irradiation

25COASMA20

Title: Integrating tumour and lymph node radiomics features for predicting disease-free survival in locally advanced esophageal squamous cell cancer after neoadjuvant chemotherapy and complete resection,

Bo Zhao, Ya-Qi Wang, Hai-Tao Zhu, Xiao-Ting Li, Yan-Jie Shi, Ying-Shi Sun,

European Journal of Surgical Oncology,Volume 51, Issue 3,2025,109547,
https://doi.org/10.1016/j.ejso.2024.109547.

Abstract: To investigate the utility of combined tumour and lymph node (LN) radiomics features in predicting disease-free survival (DFS) among patients with locally advanced esophageal squamous cell carcinoma (ESCC) after neoadjuvant chemotherapy and resection.
We retrospectively enrolled 176 ESCC patients from January 2013 to December 2016. Tumour and targeted LN segmentation were performed on venous phase CT images. Models were constructed using LASSO Cox regression: a clinical model, a clinical-tumour radiomics model, and a clinical-tumour-LN radiomics model. Model fitting was evaluated using Akaike information criterion and likelihood ratio (LR), while performance was assessed using Harrell's concordance index (C-index) and time-dependent receiver operating characteristic analysis.The clinical model included clinical stage and neutrophil-to-lymphocyte ratio (NLR). Integration of tumour features significantly improved prognostic accuracy (clinical-tumour model vs. clinical model, LR: 17.84 vs. 11.84, P = 0.049). Subsequent integration of LN features further augmented model performance (clinical-tumour-LN model vs. clinical-tumour model, LR: 24.48 vs. 17.84, P = 0.009). The final model included clinical stage, NLR, two tumour features (Conventional_mean and GLZLM_HGZE), and one LN feature (GLCM_entropy). The C-index was 0.68 for the training set and 0.70 for the test set. The nomogram based on these features effectively stratified patients into high- and low-risk groups (P < 0.001).The clinical-tumour-LN model, integrating clinical stage, NLR, and radiomics features, outperformed simpler models in predicting DFS among ESCC patients after neoadjuvant chemotherapy and resection. This underscores the potential of radiomics data to enhance prognostic models, offering clinicians a more robust tool for assessment.

Keywords: Esophageal squamous cell carcinoma; Computed tomography; Disease-free survival; Radiomics

25COASMA21

Title: Patterns of recurrence after esophagectomy following neoadjuvant immunochemotherapy in patients with thoracic esophageal squamous cell carcinoma,

Qiuying An, Ping Zhang, Hongyan Wang, Zihan Zhang, Sihan Liu, Wenwen Bai, Hui Zhu, Chanjun Zhen,

European Journal of Surgical Oncology, Volume 51, Issue 3,2025,109546,
https://doi.org/10.1016/j.ejso.2024.109546.

Abstract: To explore the recurrence pattern and risk factors associated with the relapse of thoracic esophageal squamous cell carcinoma (TESCC) among patients who received esophagectomy following neoadjuvant immunochemotherapy (NICT). A total of 191 TESCC patients who received esophagectomy following NICT were retrospectively reviewed from 2019 to 2022. The first recurrence patterns were assessed. The postoperative recurrence-free

survival (RFS) was determined using the Kaplan–Meier method. Multivariate recurrence risk factor analysis was performed using the logistic regression model. As of the December 31, 2023 follow-up, 66 patients experienced recurrence, with a median time to recurrence of 10.8 months (1.2–37.3 months). The recurrence pattern included locoregional recurrence (LR), distant recurrence (DR), and LR + DR, accounting for 69.7 %, 16.7 %, and 13.6 %, respectively. Locoregional lymph node (LN) predominated the pattern of postoperative recurrence (40/66), particularly in the mediastinal station 2R (17.5 %) and 4R (16.5 %). The 2-year RFS rates for groups with dissected LN stations of ≤6, 7–9, and 10–14 were 50.5 %, 72.3 %, and 63.5 %, respectively (P = 0.04). Similarly, the 2-year RFS rates for groups with dissected LNs of <15, 15–29, and ≥30 were 49.7 %, 61.6 %, and 71.6 %, respectively (P = 0.28). Furthermore, tumor length >5 cm, the T-stage evaluation as clinically stable disease, dissected LN stations ≤6, and the ypN2–3 stage were unfavorable factors for postoperative failure in patients. The major pattern of LR may be LN recurrence after NICT in TESCC patients, particularly in the station 2R and 4R. In addition, less than 6 LN dissection stations or less than 15 LNs are not recommended.

Keywords: Esophageal squamous cell carcinoma (ESCC); Neoadjuvant immunochemotherapy (NICT); Esophagectomy; Recurrence pattern; Recurrence risk factor

25COASMA22

Title: A wellness resource guide for residents and fellows,

Vanessa A. Hortian,

Seminars in Colon and Rectal Surgery,Volume 36, Issue 1,2025,101083,
https://doi.org/10.1016/j.scrs.2025.101083.

Abstract: Surgical training requires resilience and grit, as well as sacrifice. Each stage of training presents a set of unique challenges. Studies have shown that training is associated with burnout, attrition, and even cases of suicide. This article describes training-associated challenges that can lead to burnout and attrition and provides a resource guide to aid in maintaining well-being and humanity while navigating the journey of surgical training.

Keywords: Fellow; Resident; wellbeing; burnout; resilience

25COASMA23

Title: Returning to the operating room,

Alexis D. Desir, Emina H. Huang,

Seminars in Colon and Rectal Surgery, Volume 36, Issue 1,2025,101084,
https://doi.org/10.1016/j.scrs.2025.101084.

Abstract: Returning to the operating room after birth-related leave presents significant challenges for female surgeons, who are often navigating the demands of parenthood alongside rigorous work schedules. This manuscript explores the multifaceted hurdles faced by these surgeons, including physical, mental, financial, and professional impacts. The physically demanding nature of surgery, coupled with hormonal changes, breastfeeding challenges, and sleep deprivation, exacerbates the difficulties of postpartum recovery. Additionally, female surgeons are at higher risk for postpartum depression and anxiety, which can hinder their performance in the operating room. Professionally, trainees may face

changes in relationships with co-residents, potential delays in graduation, and evolving career priorities as they balance surgical training with family responsibilities. The manuscript emphasizes the need for flexible, supportive environments in surgical programs to better accommodate new mothers. By recognizing these challenges and adopting policies that prioritize wellness, the surgical community can help ensure that female surgeons successfully reintegrate into their careers without compromising their health or professional development.
Keywords: Birth-related leave; Female surgeons; Postpartum recovery; Breastfeeding; Work-life balance

25COASMA24
Title: Ergonomics and body wellness during surgery: A review and practical guide,
Basil Karam, Ian Soriano,
Seminars in Colon and Rectal Surgery, Volume 36, Issue 1,2025,101085,
https://doi.org/10.1016/j.scrs.2025.101085.
Abstract: Work-related musculoskeletal disorders (WRMSDs) are highly prevalent among surgeons, contributing to chronic pain, reduced operative efficiency, and premature career attrition. The increasing adoption of minimally invasive and robotic-assisted surgical techniques has introduced distinct ergonomic challenges that necessitate targeted interventions. This review examines the impact of surgical ergonomics on surgeon well-being, outlining key risk factors, prevalence data, and preventive strategies. A structured approach to optimizing posture, instrument handling, operating room configuration, and intraoperative microbreaks is presented.. The integration of ergonomic principles into surgical practice is essential for enhancing surgeon longevity, optimizing performance, and ensuring sustainable career progression.
Keywords: Surgical ergonomics; Work-related musculoskeletal disorders; Surgeon wellness; Minimally invasive surgery; Robotic surgery

25COASMA24
Title: What it takes to be a surgeon today,
Celine Soriano, Terrah Paul Olson,
Seminars in Colon and Rectal Surgery, Volume 36, Issue 1,2025,101080,
https://doi.org/10.1016/j.scrs.2025.101080.
Abstract: A long career in surgery requires prioritizing surgeon well-being. Burnout is prevalent in surgery, and is tied to job dissatisfaction, mental illness, and adverse patient outcomes. Individual and institutional factors, such as protection of identity, boundary setting, supportive workplace culture and communities, and creative re-structuring of work models can alleviate burnout and optimize surgeon wellness. This can allow surgeons today to thrive in the profession and enjoy life outside of it.
Keywords: Surgeon wellbeing; Surgical culture; Non-traditional work models

25COASMA25
Title: Thriving through career challenges: Building and maintaining resilience,
Najjia N. Mahmoud,

Seminars in Colon and Rectal Surgery, Volume 36, Issue 1,2025,101082,
https://doi.org/10.1016/j.scrs.2025.101082.
Abstract: The focus on interventions to prevent burnout has shifted over the past five years from those exclusively aimed at the personal circumstances and personalities of surgeons and other healthcare workers, to approaches that affect the systems we work within. Systemic factors that create psychological stress, anxiety, feelings of helplessness, and moral injury have proven to be serious instigators and compounders of burnout. Additionally, strategies that contribute to enhancing engagement and building resiliency are widely recognized as essential to creating an environment where a physician may not only thrive, but survive the inevitable personal and professional challenges that arise. This chapter explores how resilience is best supported to survive not only the serious systemic issues that create moral injury and burnout, but personal issues that arise that can negatively impact a wonderful career. Interventions aimed at increasing engagement and promoting resiliency include those that contemplate strategies for individuals, healthcare institutions, and national organizations. Reviewing information supporting a range of interventions is important to understanding how to implement change meaningfully. Prevention of burnout and identification of factors boosting resilience should start early in training with modeling and messaging from mentors, and should incorporate individualized stress management strategies. Critically, however, the most compelling data for building resilience requires structural re-organization of institutions to align their values and processes with those of physicians and allied providers. Advocating for changes at the institutional and national level that preserve our relationships with our patients and colleagues, provide time for reflection and for outside interests that recharge and restore, should be a common goal and imperative for healthcare reform.
Keywords: Burnout; Resilience; Engagement; Stress management; Wellbeing; Moral injury

25COASMA26
Title: Coaching as a resource for the modern surgeon,
Sharon L. Stein,
Seminars in Colon and Rectal Surgery, Volume 36, Issue 1,2025,101086,
https://doi.org/10.1016/j.scrs.2025.101086.
Abstract: Surgical coaching is becoming more prevalent over the last ten years. The practice of surgical coaching is widely variant, from technical coaching to developmental and remedial coaching. However, the premise behind coaching remains the same, to continue to foster the growth and development of news skills for the surgeon. This chapter reviews some of the data on coaching, as well as information on types of coaching. It also reviews some of the cultural biases that limit the acceptance of coaching by surgeons.
Keywords: Coaching; Professional development; Wellness; Surgical coaching; Sustaining behavioral changes; Growth oriented; Coaching for surgeons

25COASMA27
Title: The joys of a surgical career and beyond,
Patricia Roberts,
Seminars in Colon and Rectal Surgery, Volume 36, Issue 1,2025,101087,

https://doi.org/10.1016/j.scrs.2025.101087.
Abstract: In 2017, my Presidential address to the American Society of Colon and Rectal Surgeons was titled “the joys of a surgical career.” The address examined the continuum of a long surgical career, and particularly the four stages including the initial education and training to become a colon and rectal surgeon, early career, mid career and late career. This paper builds on that address and specifically looks at ways to continue to thrive and to find joy in the clinical practice of surgery and beyond.
Keywords: Surgical career; Joy; Thriving; Colon and rectal surgery

25COASMA28

Title: Is endoscopic submucosal dissection safe in the management of early-stage colorectal cancers?,

Metincan Erkaya, Attila Ulkucu, Kamil Erozkan, Brogan Catalano, Daniela Allende, Scott Steele,
The American Journal of Surgery,Volume 241,2025,116159,
https://doi.org/10.1016/j.amjsurg.2024.116159.
Abstract: Endoscopic submucosal dissection (ESD) is increasingly being adopted for the treatment of early-stage colorectal cancer (CRC) lesions.We retrospectively analyzed patients with early-stage CRC treated between 2015 and 2023, using ESD and colectomy databases, categorizing them into three groups: ESD only (n = 24), oncological colorectal resection (OCR) only (n = 90), and OCR after ESD (n = 59). We compared pathological and oncological outcomes among these groups.The OCR after ESD group demonstrated higher non-granular lesions, and deeper submucosal invasion compared to ESD only group. The primary OCR group showed higher 2-year overall survival compared to ESD-only group (98.9 % vs 85.6 %, p = 0.01), with no colorectal cancer-related mortality in any of the groups. Notably, 2-year disease-free survival rates were comparable across all groups (93.8 % ESD only, 88.0 % primary OCR only, and 97.8 % for OCR after ESD, p = 0.27).The current study highlights feasibility the promising potential and oncologic safety of ESD in carefully selected patients with early malignant lesions.
Keywords: Colorectal cancer; Endoscopic submucosal dissection; Oncologic colorectal resection; Early-stage; Overall survival rate; Pathological outcomes

25COASMA29

Title: Analysis of intestinal ostomy content on TikTok: The role of social media in countering fear and stigma,

Meghan E. Linz, Mulin Xiong, Haley C. Lanser, Albert T. Young, Monica James,
The American Journal of Surgery, Volume 241,2025,116136,
https://doi.org/10.1016/j.amjsurg.2024.116136
Abstract: Ostomates suffer from multiple comorbidities and social stigma, which can be especially debilitating in young patients. TikTok has become a popular platform for this population to establish a community and gain resources. This study aims to characterize intestinal ostomy videos on TikTok.The top 50 videos for search terms “ileostomy,” “colostomy,” “ostomy,” and “stoma” were queried on TikTok. Information was compiled

regarding the videos' creators, content type, overall sentiment, and viewer engagement.A total of 113 videos amongst 38 creators garnered 52,021,700 likes and 370,983 comments. Most videos focused on education (45.5%) and personal stories (22.7%). Creators were predominantly young females (82.0%), with minimal input from healthcare professionals (3% of videos). Sixty-nine (61%) of videos had responses with further questions.Our study reveals a gap between interest and availability of professional educational material regarding intestinal ostomies. Addressing this deficiency may improve patient acceptance, bystander understanding, and its negative stigma.

Keywords: TikTok ostomy"; "TikTok education"; "Colostomy"; "Intestinal ostomy"; "Ostomy stigma"

25COASMA30

Title: Weight loss outcomes and associated factors after metabolic bariatric surgery: Analysis of routine clinical data in Scotland,

Beatrice Leyaro, Lyz Howie, Kevin McMahon, Abdulmajid Ali, Raymond Carragher,

The American Journal of Surgery, Volume 241,2025,116151,
https://doi.org/10.1016/j.amjsurg.2024.116151.

Abstract: Bariatric surgery is a cornerstone intervention for individuals with severe obesity, offering substantial and sustainable weight loss.This retrospective cohort study included 186 patients with obesity and Type2 diabetes who underwent sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) between 2009 and 2020 at University Hospital Ayr. Optimal clinical response weight loss was defined as excess weight loss (%EWL) ≥50 % or total weight loss (%TWL) ≥20 %.At 2-years post-surgery, 43.6 % achieved ≥50 %EWL, and 44.1 % achieved ≥20%TWL, with 31.8 % maintaining this at 5-years. Depending on the definition used, between 11.2 % and 45.9 % of patients experienced recurrent weight gain. BMI had significant positive association with %TWL but negative with %EWL ($p < 0.05$). RYGB had significantly higher %TWL compared to SG ($p < 0.05$).Most patients experienced weight loss which was maintained over time, however recurrent weight gain was noted. Pre-surgery BMI was significantly associated with weight changes.

Keywords: Total weight loss; Excess weight loss; Bariatric surgery; Gastric bypass; Sleeve gastrectomy

25COASMA31

Title: A personalized smartphone app for a surgery residency: Is it useful?,

Crystal Zhang, Katrina Thede, Robert Dorenbusch, Andrew Ehrsam, Jonathan Saxe,

The American Journal of Surgery, Volume 241,2025,116117,
https://doi.org/10.1016/j.amjsurg.2024.116117.

Abstract: Access to schedules, protocols, and learning materials needs to be convenient and fast. Smartphones have become the default pathway for information access. The purpose of this study was to understand the impact of a smartphone application (app) on residency workflow and education.After app development, a survey was conducted before and after implementation using Likert scales.Student's t-test was used for analysis.Pre-app, 76 % of faculty did not know the resident on call compared to 50 % post implementation ($p < 0.01$).

Pre-app, management algorithms required internet search; post-app no searching was required ($p < 0.05$). Post-app, a printed call schedule became unnecessary and hospital operator calls decreased from daily to occasionally for residents and almost never for faculty ($p < 0.01$).A smartphone application has proven to be beneficial for consolidating resources and workflow to improve resident training and patient care.

25COASMA32

Title: Surgical opioid prescription and the risk of opioid initiation among opioid-naive households,

Mujtaba Khalil, Selamawit Woldesenbet, Muhammad Musaab Munir, Zayed Rashid,

The American Journal of Surgery, Volume 241,2025,116029,
https://doi.org/10.1016/j.amjsurg.2024.116029.

Abstract: We sought to investigate the association between surgical opioid prescriptions and the risk of opioid initiation among opioid-naive spouses.Patients who underwent surgery for breast or gastrointestinal cancer were identified from the IBM Marketscan database. Multivariable regression analysis was performed to examine the association between surgical opioid prescription and opioid initiation among opioid-naïve patient spouses.Among the 9365 individuals included in the analytic cohort, 77.9 % (n = 7300) filled a perioperative opioid prescription. Of note, spouses of patients who received a surgical opioid prescription (6.7 % vs. 4.5 %; $p < 0.001$) were more likely to begin using opioids. On multivariable analysis, surgical opioid prescription was associated with 61 % (1.61, 95%CI 1.28–2.03) higher odds of opioid initiation among opioid-naïve spouses.Surgical opioid prescriptions are associated with an increased risk of opioid initiation among opioid-naive spouses. These findings underscore the importance of counseling on safe opioid use, storage, and disposal for the family.

Keywords: Surgical opioids; Opioid misuse; Household risk; Spouse; Children

25COASMA33

Title: Global gender representation among presidents of cardiothoracic surgery societies,

Mariam Shariff, Ashish Kumar, John Stulak,

The American Journal of Surgery,Volume 241,2025,116064,
https://doi.org/10.1016/j.amjsurg.2024.116064.

Abstract: Females continue to be underrepresented in academia. An analysis of gender representation among presidents of cardiothoracic surgery societies worldwide was performed.A comprehensive search was performed to identify cardiothoracic surgical societies present worldwide and divided by regions. Respective Society's official webpage was searched to extract data on past and present presidents. Gender was determined and verified via publicly available online profiles. Proportions and respective 95 % confidence interval(CI) were calculated using Binomial exact calculation.A total of 34 cardiothoracic surgery societies were identified globally, of which only 16 provided information on past presidents in the public domain. A total of 563 past and current society presidents were identified. Women constituted only 16 [2.84 %; 95 % confidence interval: 1.63 %; 4.57 %]

presidents. The first-ever women president was appointed in the year 2007 by the STSA during the 54th Annual meeting.Stark lag persists in gender representation of presidential roles among the cardiothoracic societies globally.
Keywords: Gender; Cardiothoracic surgery; President; Cardiothoracic societies

25COASMA34

Title: Frailty is associated with poor outcomes in midlife trauma patients,

Colette Galet, Colleen Bloeser, Jacklyn Engelbart, Patrick Ten Eyck, James Torner, Dionne Skeete,

The American Journal of Surgery, Volume 241,2025,116157,
https://doi.org/10.1016/j.amjsurg.2024.116157.

Abstract: The impact of frailty on outcomes in midlife trauma patients (50–64 y) remains understudied. We evaluated the impact of frailty on midlife trauma patients' outcomes.This is a retrospective cohort study using TQIP 2021 data. Demographics, injury and hospital information, comorbidities, complications, mortality, and discharge disposition were extracted. Frailty was scored using the modified frailty index-5. Multivariate analyses were performed. $P < 0.001$ was considered significant.In 2021, 5.1 % midlife trauma patients were frail. On multivariate analysis adjusting for demographics, insurance status, injury severity score, vitals on arrival, and mode of transportation, frailty was associated with increased risk of death (OR = 2.27 [2.01–2.57]), longer hospital and ICU stay (MR = 1.46 [1.43–1.49] and MR = 1.30 [1.24–1.36]), and discharge requiring higher level of care (OR = 2.11 [2.01–2.22]).Our data support the need for preventative efforts regarding frailty in midlife adults.
Keywords: Frailty; Trauma; Midlife adults; TQIP

25COASMA35

Title: Exploring the impact of surgeon-reported gender on palliative care utilization in geriatric trauma patients,

Morgan J. Hopp, Paul T. Kang, Jacob J. Strand, Wil L. Santivasi, Alexzandra K. Hollingworth,

The American Journal of Surgery, Volume 241,2025,116177,
https://doi.org/10.1016/j.amjsurg.2024.116177.

Abstract: Geriatric trauma research increasingly supports the use of Palliative Care (PC). We surveyed trauma surgeon for perspectives on PC usage. Significant gender differences were identified, necessitating post-hoc investigation.A post-hoc gender comparative analysis was completed on data collected from a national survey of trauma surgeons investigating decision-making and barriers to PC consults for geriatric trauma.Sixty-four members responded (2.8 %). Women surgeons identified reason for a PC consult as: "when trauma team does not agree with patient/family wishes" ($p = 0.009$), "different members of the team do not agree on the plan of care" ($p = 0.023$) and "additional patient/family support needed" ($p = 0.023$). Women respondents more commonly reported PC consultation barriers as: "Patient/family misconception of PC" ($p = 0.001$), "concern that patient/family will lose hope" ($p = 0.014$) while men more commonly responded "no barriers to PC consults in my practice" ($p = 0.029$).The identified gender differences in PC consultation use and barriers

provides interesting data to support further studies specifically investigating these observations.

Keywords: Physician gender; Gender difference; Woman surgeon; Palliative care; Trauma surgeon

25COASMA36

Title: Clinical impacts of utilizing ceftriaxone and metronidazole versus piperacillin/tazobactam in patients diagnosed with complicated diverticulitis,

Will Carns, Richard Arndt, Sara Ausman, Jason Beckermann, Kristin C. Cole, Erin Gruber, Megan Schleusner,

The American Journal of Surgery, Volume 241,2025,116195,
https://doi.org/10.1016/j.amjsurg.2025.116195.

Abstract: The optimal antibiotic regimen to empirically treat complicated diverticulitis has not been well established in guidelines.A 5-year retrospective cohort study was conducted with 322 patients admitted to Mayo Clinic hospitals for complicated diverticulitis. Outcomes for 89 patients treated with ceftriaxone and metronidazole were compared to 233 patients treated with piperacillin/tazobactam. Patients were included if they received one of the treatment options for at least 96 h during hospital admission and did not receive any other diverticulitis antibiotic treatment regimen for at least 96 h.Ceftriaxone and metronidazole was found to be non-inferior to piperacillin/tazobactam for the combined primary outcome of 30-day readmission or all-cause mortality (21.4 % vs 15.9 %, P = 0.12). No significant differences were found for 30-day antibiotic failure (P = 0.30) or 90-day Clostridioides difficile infection rate (P = 0.96). Patients who received oral antibiotic therapy in the 7 days prior to admission were found to have increased risk of mortality or readmission and antibiotic failure.Ceftriaxone and metronidazole showed non-inferior outcomes to piperacillin/tazobactam for treating complicated diverticulitis.

25COASMA37

Title: The role of combining interim and final analysis by using endoscopic and radiologic methods in total neoadjuvant treatment,

Kamil Erozkan, David Liska, Ayda Oktem, Ali Alipouriani, Lukas Schabl, Michael A. Valente,

The American Journal of Surgery, Volume 241,2025,116104,
https://doi.org/10.1016/j.amjsurg.2024.116104.

Abstract: We aim to compare the relative performance of flexible sigmoidoscopy (FS), rectal magnetic resonance imaging (MRI), and their combinations during interim (i) and final (f) analysis to evaluate concordance with complete response (CR) following total neoadjuvant treatment (TNT) in rectal cancer.Patients who opted TNT and underwent restaging with FS and MRI between 2015 and 2022 were evaluated. Concordance between the assessment methods and CR was analyzed using the weighted-κ test.A cohort comprising 208 patients revealed CR rate of 42.3 %. When evaluating individual methods, fFS alone demonstrated the most heightened sensitivity (68.2 %) for CR detection, with a moderate level of concordance (κ = 0.46). Only the combinations of iFS-fFS and fFS-fMRI reached a

comparable level of concordance to that achievable by fFS alone. Among the available diagnostic tools, the combination of final MRI and FS still appears to offer the highest concordance with CR, with relatively higher sensitivity. Additionally, interim MRI may not add significant clinical value and could be omitted.
Keywords: TNT; Restaging; Interim analysis; Final analysis; Flexible sigmoidoscopy; MRI

25COASMA38
Title: Clinician perspectives on the perioperative roles and responsibilities of anesthesia, surgery, and primary care,
Donna Ron, Madison M. Ballacchino, Alexandra Briggs, Stacie G. Deiner,
The American Journal of Surgery, Volume 241,2025,115948,
https://doi.org/10.1016/j.amjsurg.2024.115948.
Abstract: Although high-risk older patients benefit from a multidisciplinary approach to perioperative care, the specific roles and responsibilities of the clinicians involved have yet to be adequately characterized.Qualitative analysis of semi-structured interviews with four anesthesia preoperative clinic providers, seven surgeons, and nine primary care providers in northern New England.The analysis revealed both distinct and overlapping roles and responsibilities. Anesthesia providers were described as a “safety net” and surgeons as “captain of the ship”, in charge of getting “all the ducks in a row” to avoid surgery delays and cancellations. Primary care providers saw themselves as the “quarterback”, ensuring care continuity and consideration of patient psychosocial factors.While all have a shared responsibility for facilitating patient-centered decision-making and a safe perioperative course, each discipline has different areas of focus and expertise. Role clarification can help optimize the distribution of responsibilities and enhance perioperative communication and collaboration.
Keywords: Perioperative care; Preoperative assessment; Geriatric surgery; Multidisciplinary care; Care transitions; Primary care; Anesthesia; Surgery

25COASMA39
Title: Mediation analysis identifies causal factors that lead to increased rates of kidney transplant failure in patients with peripheral vascular disease,
Johnathan Torikashvili, Melissa A. Kendall, Tyler Zander, Rajavi Parikh, Paul C. Kuo, Emily A. Grimsley,
The American Journal of Surgery,Volume 241,2025,116190,
https://doi.org/10.1016/j.amjsurg.2025.116190.
Abstract: This study aims to identify causal mediators of one-year kidney transplant failure in patients with peripheral vascular disease.Standard Transplant Analysis and Research database was queried for adults who underwent kidney transplantation from 1987 to 2021. Multi-organ transplant, prior transplant, and living donor kidneys were excluded. Causal mediation analysis with 2000 percentile bootstrapping interactions identified mediators of one-year kidney transplant failure.212,259 patients were included: 16,215 with and 196,044 without peripheral vascular disease. Causal mediators of one-year kidney transplant failure are Kidney Donor Profile Index (proportionate mediation [PM] 17 %, $p < 0.01$, E-value =

1.20), pre-transplant dialysis (PM 19 %, p < 0.001, E-value = 1.17), recipient total serum albumin (PM 2 %, p = 0.003, E-value = 1.05), and donor hypertension (PM 1 %, p = 0.017, E-value = 1.04).Several causal mediators increase rates of one-year kidney transplant failure in patients with peripheral vascular disease. Understanding these mediators can improve pre-transplant assessments and post-transplant outcomes.

Keywords: Peripheral vascular disease; Kidney transplant failure; Mediation analysis

25COASMA40

Title: Variation in commercial prices for thyroidectomy and parathyroidectomy at US hospitals,

Samuel J. Enumah, David C. Chang, Nancy L. Cho, Carrie E. Cunningham, Gerard M. Doherty,

The American Journal of Surgery, Volume 241,2025,116072,
https://doi.org/10.1016/j.amjsurg.2024.116072.

Abstract: The 2021 Hospital Price Transparency Rule mandated hospitals to publicly disclose their service prices to improve competition and lower healthcare costs. Our aim was to characterize commercial price variation for thyroidectomy and parathyroidectomy. We performed a national cross-sectional study of hospital price variation in 2022 and 2023 using the Turquoise Health dataset. Our main outcomes were within- and across-hospital 90th-to-10th percentile commercial price ratios and a high commercial-to-Medicare (1.5) price ratio. We performed logistic regressions to identify hospital factors associated with a high commercial-to-Medicare price ratio.For 16,794 unique commercial rates across 564 facilities, within-hospital price ratios ranged from 2.0 to 2.4, and across-hospital price ratios ranged from 2.7 to 4.1. High market concentration and five-star hospital rating were associated with high commercial-to-Medicare price ratios compared to low market concentration and three-star hospital rating, respectively.Notable variation exists within and across hospitals signaling facilities have negotiated different payments from insurance companies for the same service. Quality may be a modifiable factor to increase hospital revenue and improve care for patients.

Keywords: Thyroid; Parathyroid; Endocrine; Price; Transparency; Quality; Health economics

25COASMA41

Title: REBOA in patients with high-grade liver injury may be associated with worse outcomes,

Wei Huang, Naveen Balan, Feifei Jin, Yu Cheng Chiu, Demetrios Demetriades,

The American Journal of Surgery, Volume 241,2025,116174,
https://doi.org/10.1016/j.amjsurg.2024.116174.

Abstract: Although controversial, resuscitative endovascular balloon occlusion of the aorta (REBOA) has been used to manage liver injuries. This matched cohort study evaluated outcomes in severe liver injuries treated with REBOA or without REBOA.Trauma Quality Improvement Program database study. Patients with high-grade liver injuries (IV and V) treated with REBOA were propensity score matched (1:2) with similar patients managed

without REBOA. Outcomes included mortality and complications.252 patients treated with REBOA were matched with 503 patients managed without REBOA. Overall mortality was significantly higher in the REBOA group [57.9 % vs. 35.2 % ($p < 0.001$)]. The REBOA group patients had higher blood product transfusion requirements.REBOA use in patients with high-grade liver injuries may be associated with poorer outcomes.

Keywords: REBOA; Liver injury; Mortality; Outcome

25COASMA42

Title: Barriers to perioperative palliative care across Veterans Health Administration hospitals: A qualitative evaluation,

Emily E. Evans, Sarah E. Bradley, C. Ann Vitous, Cara Ferguson, R. Evey Aslanian, Shukri H.A. Dualeh,

The American Journal of Surgery,Volume 241,2025,116063,
https://doi.org/10.1016/j.amjsurg.2024.116063.

Abstract: Palliative care remains widely underused for surgical patients, despite a clear benefit for patients with life-limiting illness or nearing the end-of-life.Interviews exploring end-of-life care among critically-ill surgical patients were conducted with providers from 14 pre-specified Veterans Affairs (VA) hospitals. Data were analyzed iteratively through steps informed by inductive and deductive descriptive content analysis.Six major domains were identified. At the patient and family level, barriers included managing expectations and goal-discordant care. At the provider-level, knowledge of and attitudes towards palliative care and provider role and identity were frequently cited barriers. At the system-level, participants identified institutional resources and culture as significant barriers.While providers recognize the importance of palliative care and end-of-life care, obstacles to its use exist at various levels. Identification of these barriers highlights areas to focus future efforts to improve the quality of palliative and end-of-life care for Veterans.

Keywords: palliative care; End-of-life care; Veterans; Veterans health; Surgical critical care

25COASMA43

Title: Sublobar or lobar resection in early-stage peripheral non-small cell lung cancer less than 2cm: A meta-analysis for randomized controlled trials,

Lei Wang, Jianming Zhou, Shengjie Jing, Bin Liu, Jin Fang, Tao Xue,

The American Journal of Surgery, Volume 241,2025,116069,
https://doi.org/10.1016/j.amjsurg.2024.116069.

Abstract: The aim of our study was to investigate whether sublobar resection is non-inferior to lobar resection in early-stage non-small cell lung cancer less than 2 cm.This is a meta-analysis for randomized controlled trials. Databases including PubMed, Web of Science, EMBASE and Cochrane Central Register were searched up to June 3, 2023. The primary outcome was 5-year survival, and the secondary outcomes were 5-year disease-free survival, cancer-related mortality, recurrence rate, postoperative lung function and perioperative events.A total of 5 studies enrolling 2035 patients were included. Sublobar resection was found to be non-inferior to lobar resection concerning the 5-year survival rate, 5-year disease-free survival rate and cancer-related mortality. However, sublobar resection was associated

with higher recurrence rate and less reduction of postoperative lung function.Sublobar resection was non-inferior to lobar resection in terms of survival outcomes and was associated with better postoperative lung function.

Keywords: Non-small cell lung cancer; Lobar resection; Sublobar resection; Segmentectomy; Wedge resection

25COASMA44

Title: The critical role of tumor size in predicting lymph node metastasis in early-stage colorectal cancer,

Attila Ulkucu, Metincan Erkaya, Ekin Inal, Emre Gorgun,

The American Journal of Surgery, Volume 241,2025,116152,
https://doi.org/10.1016/j.amjsurg.2024.116152.

Abstract: Main purpose of this study is to investigate impact of tumor size on risk of lymph node metastasis (LNM) in pT1-stage colorectal cancer (CRC), focusing on colon, rectosigmoid junction, and rectum.Patients diagnosed with primary pT1 CRC between 2015 and 2019 were selected from National Cancer Database, utilizing International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes. We analyzed factors influencing LNM using uni- and multivariate analysis, then isolated tumor size to study its impact on LNM.In this study of 27,649 pT1-stage tumor patients, we found that 10 % of colon, 16 % of rectosigmoid junction, and 13 % of rectum were LNM+. The study had 14,339 males (51.97 %). Mean age was 64.9 (±11.7). In multivariate analysis, sample was adjusted by excluding confounding factors, isolating impact of tumor size on LNM. Analysis for only tumor size, patients with colon tumors >45 mm had 53 % increased odds of LNM (95 % CI [1.06, 2.23], p = 0.03), whereas tumor size did not significantly affect LNM in rectosigmoid and rectum cases, with odds ratios of 2.05 (95 % CI [0.82, 5.09], p = 0.12) and 1.62 (95 % CI [0.97, 2.71], p = 0.065) respectively, for tumors ≥45 mm compared to those <15 mm.
This investigation refines predictors of LNM, crucial for tailoring organ-sparing strategies in early-stage CRC management. While tumor size is significant determinant of LNM in colon cancer, early rectal and rectosigmoid cancers may be associated with lower risk of LNM.

Keywords: Colorectal neoplasms; Neoplasm size; Lymphatic metastasis; Lymph nodes; Pathology; Risk factors; Multivariate analysis

25COASMA45

Title: Economics of emergency laparoscopic cholecystectomy at an Australian tertiary centre in the post COVID-19 era,

Raymond Hayler, Sam Hanna, Andrea Boerkamp, Yijun Gao, Sam T. Alhayo, Michael L. Talbot,

The American Journal of Surgery, Volume 241,2025,116158,
https://doi.org/10.1016/j.amjsurg.2024.116158.

Abstract: Laparoscopic cholecystectomy (LC) is a common operation performed worldwide. Indications include acute cholecystitis (AC), with a trend of increasing complexity post-COVID-19. We aim to evaluate the health expenditure on LC at an Australian tertiary centre.

A retrospective chart review was performed for all LC between July 1, 2022–June 30, 2023 collecting demographics, costs and wait times and comparisons performed between elective and emergency LC.125 patients underwent emergency and 78 elective LC. There was no difference between age, sex or ASA. 67 patients (53.6 %) had emergency LC within their booking priority category. Average cost for emergency LC was $12,689.90 with a median stay of four days, compared to $7181.10 and one day for elective ($p < 0.01$). Operative related costs were the majority with emergency LC higher ($4866.5, 38.4 % v $3957.6, 55.1 % $p = 0.02$). The largest cost disparity was nursing costs ($2193.7, 17.3 % v 648.3, 9 % $p < 0.01$).Costs are likely driven by access to emergency theatre time and increased length of stay. A semi-emergency theatre model could save costs.

25COASMA46

Title: Gender variations in 30-day outcomes following cholecystectomy in patients with biliary acute pancreatitis,

Nicholas Stevens, Ghazi-Abdullah Saroya, Alain Elian, Saad Shebrain,
The American Journal of Surgery, Volume 241,2025,116034,
https://doi.org/10.1016/j.amjsurg.2024.116034.

Abstract: Biliary acute pancreatitis (BAP) can be associated with severe morbidity and mortality. This study aims to evaluate whether gender is associated with worse 30-day postoperative outcomes following cholecystectomy for BAP.Patients in the ACS-NSQIP database (2014–2017) with a diagnosis of BAP who underwent cholecystectomy were stratified into two groups: male and female. Patients' demographic characteristics, perioperative data, and 30- day outcomes between the two groups were compared using univariate and multivariable analyses.4158 (1556 male, 2602 female) patients were examined. Male gender was found to have significantly higher rates of both serious and overall morbidity. On multivariable analysis, male gender was an independent predictor of serious morbidity. No difference in mortality between the two groups was noted.Male gender is associated with an increased rate of morbidity after cholecystectomy in patients with BAP, however there is no difference in mortality between the male and female genders.

Keywords: Acute pancreatitis; Biliary pancreatitis; Gallstone pancreatitis

25COASMA47

Title: Changes in the surgical management of melanoma and measures to implement change,

Laurence E. McCahill,
The American Journal of Surgery, Volume 241,2025,116129,
https://doi.org/10.1016/j.amjsurg.2024.116129.

Abstract: Cutaneous malignant melanoma has traditionally been a surgically managed disease. Recent clinical trials highlight major shifts in surgical management of this disease, emphasizing a multidisciplinary approach.Clinical trials evaluating the role of completion lymph node dissection (CLND) in the management of sentinel lymph node positive patients and more recent trials evaluating the impact of neoadjuvant immunotherapy on patients presenting with clinically advanced but surgically resectable melanoma are reviewed, as well

as ongoing trial evaluating surgical margins.Both DeCOG and MSLT-II trials confirmed that CLND is no longer standard management of the sentinel node positive patient. CLND offers no melanoma-specific survival benefit. Associated surgical morbidity justifies a surveillance and observation approach, combined with adjuvant therapy. Patients presenting with clinically advanced surgically resectable disease are best served by neoadjuvant therapy. This approach demonstrates significantly improved melanoma-specific survival compared to upfront surgery, underscoring the need for rapid adoption by surgeons.Changes in surgical management of melanoma have been dramatic and offer patients improved outcomes though both reduction in the magnitude of surgery, as well as improved disease specific survival for patients with advanced surgically resectable disease.

25COASMA48

Title: Radiofrequency ablation of Bethesda category III thyroid nodules with benign molecular testing: Preliminary findings from a single institution,

Young Jae Ryu, Shawn Y. Hsu, Eric J. Kuo, Rachel Liou, Catherine M. McManus, James A. Lee,

The American Journal of Surgery, Volume 241,2025,115929,
https://doi.org/10.1016/j.amjsurg.2024.115929.

Abstract: The efficacy of radiofrequency ablation (RFA) in treating thyroid nodules with indeterminate cytology remains less studied. The objective of this study was to determine the efficacy of RFA in treating nodules with Bethesda III that have been molecularly profiled benign (BIII-MPN).We included prospectively enrolled patients who underwent RFA for benign and BIII-MPN thyroid nodules. Primary outcome measures were volume reduction ratio (VRR), symptom score (range 0–10), and cosmetic score (range 0–3) at 1, 3, 6, and 12 months after RFA, as well as complication rates. A total of 258 nodules in 192 patients were included (benign: 238 in 174; BIII-MPN: 20 in 18). The median VRR differed insignificantly, whereas symptom and cosmetic score improvements were similar between two cohorts. BIII-MPN thyroid nodules were associated with lower rates of infection and temporary voice change.Our preliminary findings suggest that RFA may be a feasible management option for BIII-MPN thyroid nodules. However, appropriate will be important to address the important risk of potentially missed malignancies.

Keywords: Radiofrequency ablation; Thyroid nodule; Atypia of undetermined significance; Molecular testing

25COASMA49

Title: Trainee-initiated dictations of endocrine surgeries: Implications for education and reimbursement,

Daniel M. Chopyk, Theresa N. Wang, David E. Weirich, Stephanie Paras, Barbra S. Miller, John E. Phay,

The American Journal of Surgery,Volume 241,2025,115947,
https://doi.org/10.1016/j.amjsurg.2024.115947.

Abstract: Our university-based surgery department recently transitioned to attending-only authorship of operative reports. We performed a mixed-methods investigation to determine if

trainee-initiated endocrine surgical reports were associated with under-coding of specific procedures.Endocrine operations performed from July 2020 to June 2022 were identified from billing data. Pre- and post-policy RVU distributions and note modification history were reviewed to determine how often trainees captured billable differentiators over attending note modification.714 operations and 1138 billed procedures were identified. Parathyroidectomy alone showed greater mean RVUs with attending-only reports attributable to attending practice change in coding for intraoperative parathyroid hormone monitoring. Trainees were more likely to miss coding modifier 22 but RVU losses were prevented by attending note modification.Trainee-initiated operative reports were not associated with RVU losses for endocrine operations compared to attending-only reports. Trainee dictation can be improved by emphasizing education on procedural billing differences and surgical reasoning.

Keywords: Relative value units (RVUs); Thyroidectomy; Parathyroidectomy; Adrenalectomy; Modifier 22

25COASMA50

Title: Risk factors and outcomes of cardiac arrest in pediatric traumatic brain injury patients,

Irim Salik, Sima Vazquez, Nisha Palla, Norbert Smietalo, Richard Wang, Monica Vavilala, Jose F. Dominguez,

The American Journal of Surgery,Volume 241,2025,116087,
https://doi.org/10.1016/j.amjsurg.2024.116087.

Abstract: Cardiac arrest (CA) in pediatric traumatic brain injury (pTBI) is associated with morbidity. Our objective is to investigate the incidence, risk factors, and outcomes for CA following pTBI. The Kid Inpatient Database (KID) was queried for patients with pTBI. Patients who experienced CA were identified. Demographics, comorbidities, hospital course, and complications were compared between patients who developed CA and who did not. Risk factors for CA were explored using multivariate analysis.CA patients were more likely to have hypertension, hypertrophic cardiomyopathy, and heart defects ($p < 0.01$). CA was more likely in patients with subdural bleeding, cerebral edema, herniation, coma, or mechanical ventilation ($p < 0.001$). CA patients had higher odds of vasopressor and transfusions, tracheostomy, percutaneous endoscopic gastrotomy ($p < 0.001$), and mortality ($p < 0.01$). Mechanical ventilation, cerebral edema, heart, vasopressor use, and transfusions were associated with CA on multivariate analysis.Risk factors for CA in pTBI patients include severity of injury and underlying cardiovascular abnormalities. CA was associated with morbidity and resource utilization in pTBI patients.

Keywords: Pediatric critical care; Cardiac arrest; Traumatic brain injury; Risk factors; Healthcare resource utilization

25COASMA51

Title: Variation in lymph node assessment after pancreatic cancer resection: Patient, surgeon, pathologist, or hospital?,

Muhammad Musaab Munir, Selamawit Woldesenbet, Mujtaba Khalil, Muhammad Muntazir Mehdi Khan,

The American Journal of Surgery, Volume 241,2025,116067,
https://doi.org/10.1016/j.amjsurg.2024.116067.
Abstract: We sought to define individual contributions at the patient, surgeon, pathologist, and hospital levels on lymph node assessment after pancreatic cancer resection. SEER-Medicare beneficiaries who underwent pancreatic cancer resection were identified. Multi-level multivariable regression was performed to assess the proportion of variance explained by patient, surgeon, pathologist, and hospitals on lymph node assessment (≥12 versus <12). 2872 patients underwent pancreaticoduodenectomy by 646 distinct surgeons and 1063 distinct pathologists across 308 hospitals. Patient-related characteristics contributed the most to the variance in adequate lymph node assessment (71.0 %). After accounting for all explanatory variables in the full model, 5.5 % of the residual provider-level variation was attributed to the pathologist, 35.2 % to the surgeon, and 59.3 % to the hospital.Patient-to-patient variation was the greatest underlying contributor to variations in adequate lymph node assessment related to pancreatic cancer surgery. Variation among hospitals was greater than among surgeons or pathologists.
Keywords: Lymph node; Variance; Oncologic care; Patient characteristics

25COASMA52

Title: Balancing risks of surgical complications and positive margins for patients with invasive lobular carcinoma of the breast and elevated BMI: An institutional cohort study,

Israel Falade, Kayla Switalla, Astrid Quirarte, Molly Baxter, Daniel Soroudi, Harriet Rothschild,
The American Journal of Surgery, Volume 241,2025,116073,
https://doi.org/10.1016/j.amjsurg.2024.116073.
Abstract: The risks of postoperative complications in breast cancer patients vary by patient and tumor characteristics. Elevated BMI and invasive lobular carcinoma (ILC) increase risks of surgical complications and positive margins, respectively.We retrospectively analyzed patients with BMI ≥30 kg/m2 from an institutional ILC database. The primary outcome was surgical complication rate by procedure type. The secondary outcome was positive margin rates by surgical approach, stratified by T stage.Of 154 analyzed patients, standard BCS, lumpectomy with oncoplastic closure, and simple mastectomy had the lowest complication rates (18.2 %, 17.0 %, 11.8 %). Oncoplastic reduction mammoplasty and mastectomy with aesthetic closure had the highest rates (35.5 %, 33.3 %). The overall positive margin rate was 28.5 %, significantly higher in BCS vs. mastectomy (37.4 % vs. 15.0 %, p = 0.003). Oncoplastic surgery significantly reduced positive margin rates in BCS.In this study, 23.4 % of patients experienced surgical complications, with higher rates in oncoplastic/reconstructive approaches. However, oncoplastic surgery reduced positive margins, highlighting the importance of balancing risks for optimal surgical planning.

25COASMA53

Title: Malignancy risk associated with radioactive iodine therapy for Graves' disease,

Sruthi Ramesh, Jason C. Fisher, Paige Curcio, Gary D. Rothberger, Jason Prescott, John Allendorf, Insoo Suh, Kepal N. Patel,
The American Journal of Surgery, Volume 241,2025,116075,
https://doi.org/10.1016/j.amjsurg.2024.116075.

Abstract: Radioactive iodine therapy (RAI) is a frequently chosen therapy for Graves' disease. The aim of this study was to determine whether RAI for Graves' disease increases the risk of thyroid malignancy.A retrospective analysis was performed of all Graves' disease patients who underwent thyroidectomy at a single institution between 2013 and 2022. Comparative analyses were performed with cohorts based on RAI therapy as the primary grouping variable.413 patients were identified, of which 38 received RAI prior to surgery. RAI treated patients were more likely to undergo surgery for known malignancy or indeterminate nodules. RAI patients were also more likely to have malignancies larger than 1 cm. Among RAI treated patients, those who developed malignancy were older at the time of Graves' diagnosis and received early RAI therapy.Use of RAI for treatment of Graves' disease increases the progression of thyroid carcinoma, but not the prevalence. Older age and early RAI therapy may be risk factors for malignancy in RAI treated patients.

Keywords: Graves' disease; Radioactive iodine; RAI; Hyperthyroidism

25COASMA54

Title: Re-operation following urgent and emergent colectomies: An investigation of indications and utility as a quality indicator,

Raisa Gao, Kayla Flewelling, Nicholas Stevens, Clayton Wyland, Theresa McGoff, Austin Brubaker, Laurence E. McCahill,
The American Journal of Surgery, Volume 241,2025,116081,
https://doi.org/10.1016/j.amjsurg.2024.116081.

Abstract: For urgent and emergent colectomies, return to the operating room is interpreted as a negative quality indicator. We sought to describe indications, procedures performed, and outcomes of patients undergoing reoperation after colectomy. Retrospective study of patients undergoing urgent and emergent colectomy with re-operation at a single institution from 2013 to 2023. Details of the patients and surgeries indexed.117 patients met the study criteria. Sepsis prior to surgery was noted in 29 % of patients, intraoperative vasopressors were used in 80 % and 52 % were left in gastrointestinal discontinuity. Among re-operations, 60 % of patients underwent a "planned second look", 17 % had a supportive procedure, and 23 % had an unplanned re-operation, the latter group most reflective of surgical complications. Patients undergoing urgent and emergent colectomies are very ill at presentation. Planned second look and supportive procedures account for most re-operations, suggesting the current utilization of re-operation as a quality indicator is flawed.

Keywords: Re-operation; Colectomy; Return to operating room

25COASMA55

Title: Does prophylactic tamsulosin use with ERAS protocol provide improvement after colorectal surgery?,

Kamil Erozkan, Mikhael Belkovsky, Michael Klingler, Lukas Schabl, Attila Ulkucu, Arielle Kanters,
The American Journal of Surgery,
Volume 241,2025,116127,
https://doi.org/10.1016/j.amjsurg.2024.116127.

Abstract: Early urinary catheter removal has been incorporated into Enhanced Recovery After Surgery (ERAS) pathways to aid faster recovery and minimize urinary tract infection. However, early catheter removal can result in urinary retention, which may lead to catheter reinsertion and a prolonged hospital stay. Tamsulosin, an alpha-blocking medication, effectively treats urinary retention in both men and women. Our study aims to compare urinary retention rates and short-term outcomes between patients treated with tamsulosin and those who were not.This retrospective cohort study included patients who underwent elective abdominopelvic colorectal procedures using the ERAS protocol between September 2020 and October 2023. After April 2022, postoperative 0.4 mg tamsulosin treatment was added to the ERAS protocol. Univariate analysis was used to compare demographics and perioperative treatment history. The control and tamsulosin groups were matched in a 2:1 ratio, using propensity scores. The primary outcomes were urinary retention and the length of hospital stay.The study included 2072 patients (1215 female, 58.6 %), with a mean age of 53.1 (±17.1) years. The initial univariate analysis was followed by propensity score matching, resulting in 344 patients in the tamsulosin group and 688 in the control group. The urinary retention rate was notably lower in patients who received tamsulosin during hospitalization (9.2 % vs. 4.7 %, $p = 0.01$). Furthermore, the length of hospital stay was shorter in patients treated with tamsulosin (5 vs. 4.2 $p < 0.01$).Postoperative prophylactic tamsulosin use decreases urinary retention rates and length of stay after colorectal surgery and should be considered complementary to ERAS protocols for improved recovery.

25COASMA56

Title: Development models to predict complication and prognosis following liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension,

Shilei Bai, Yizhe Dai, Pinghua Yang, Zhengqing Lei, Fuchen Liu, Zhao Yang, Fengwei Li, Yong Xia,
The American Journal of Surgery, Volume 241,2025,116172,
https://doi.org/10.1016/j.amjsurg.2024.116172.

Abstract: Postoperative complications are potential factors influencing the prognosis of patients with HCC combined with CSPH. This study aims to explore the risk factors affecting the occurrence of postoperative complications, investigate potential factors influencing long-term prognosis in these patients, and establish predictive models.From April 2018 to December 2021, a total of 190 patients with HCC combined with CSPH who underwent curative liver resection in our hospital were included, comprising 69 cases in the complication group and 121 cases in the non-complication group. LASSO-Logistic regression was employed to identify risk factors influencing postoperative complications and establish a predictive model. LASSO-Cox regression was used to determine prognostic

factors for long-term outcomes in patients with HCC combined with CSPH and establish a predictive model.LASSO regression selected variables including ALBI grade, preoperative ascites, major hepatectomy, and portal vein occlusion time >15 min. These variables were incorporated into logistic regression ($P < 0.05$) to establish a nomogram for predicting postoperative complications, with a C-index of 0.723. Results from the multivariable Cox regression analysis showed that postoperative complications, maximum tumor diameter, and microvascular invasion were risk factors for recurrence, while postoperative complications, maximum tumor diameter, microvascular invasion, and prealbumin were risk factors for overall survival. The C-index values for the respective nomograms were 0.635 and 0.734. The calibration curves and ROC curves demonstrated good performance for all three nomograms.The three nomograms achieved optimal predictive performance for postoperative complications, recurrence, and overall survival in patients with HCC combined with CSPH undergoing curative resection.

Keywords: Hepatocellular carcinoma; Portal vein hypertension; Nomogram; Postoperative complications; Prognosis

25COASMA57

Title: Impressions of inclusivity within orthopedic surgery: Differences amongst women, minority, and LGBTQIA medical students,

Katherine M. Gerull, Priyanka Parameswaran, Ling Chen, Cara A. Cipriano,

The American Journal of Surgery, Volume 241,2025,116051,
https://doi.org/10.1016/j.amjsurg.2024.116051.

Abstract: To better understand reasons for the underrepresentation of certain groups in orthopedic surgery, we investigated whether there were differences in medical students' perceptions of inclusivity in orthopedic surgery between (1) men and women, (2) White, Asian and URiM, and (3) LGBTQIA and non-LGBTQIA students.A one-time survey consisting of validated and/or previously used instruments measuring students' sense of belonging in orthopedics, prospective belonging uncertainty (an individual's worry that they will not fit in), stereotype threat (the effect of negative stereotypes on stereotyped group-members), and pluralistic ignorance (erroneously believing your beliefs are different than "typical" group-members).The survey was distributed at Loyola University, St. Louis University, University of Michigan, and Washington University in St. Louis.All medical students at these institutions were offered participation, and 441 medical students completed the survey (~20% response-rate).There was a lower sense of belonging for each of the following groups when compared to their majority-group peers: women (mean difference = 0.5, 95% CI 0.3–0.7, $p < 0.001$), Asian students (mean difference = 0.4, 95% CI 0.1–0.7, $p < 0.001$), URiM students (mean difference = 0.4, 95% CI 0.07–0.7, $p < 0.001$) and LGBTQIA students (mean difference = 0.4, 95% CI 0.07–0.6, $p = 0.003$). Medical students perceived that orthopedic faculty, residents, and the general public believe that men are better orthopedic surgeons than women, and that White surgeons are better surgeons than non-White surgeons. Women reported less confidence to succeed in orthopedics compared to "typical" peers (mean −0.5, SD 1.3), whereas men felt similar confidence compared to their peers (mean 0.1, SD 1.3; mean difference 0.6, 95% CI 0.4–0.9, $p < 0.001$).These differences

in belonging, prospective belonging uncertainty, stereotype threat, and pluralistic ignorance provide insight into how medical students perceive the inclusivity of orthopedics, which may ultimately play a role in the underrepresentation of minority groups.

Keywords: Orthopedic surgery; Medical student; Specialty selection; Diversity; Inclusion; Belonging

25COASMA58

Title: Physiologic readiness and subjective workload of performing operations: A prospective observational study of attending and trainee surgeons,

Kenneth Perrone, Michelle Earley, Graeme Rosenberg, Carla Pugh, Cindy Kin,
The American Journal of Surgery, Volume 241,2025,116175,
https://doi.org/10.1016/j.amjsurg.2024.116175.

Abstract: Physical health and perceived workload are determinants of career satisfaction and longevity for surgeons. The aim of this prospective observational study was to determine if biometric indicators of physical recovery among surgeons are associated with perceived workload during operations. The primary outcome was whether there was an association between surgeon self-assessment and a physiologic recovery score based on heart rate variability measured with a wearable biometric sensor. These associations were evaluated through mixed-effects regression models. Of the 66 participants, 29 were attending surgeons and 37 were surgical trainees across multiple surgical subspecialities. There was no association between recovery score and perceived workload for either trainees or attendings. Differences in self-assessment scores were identified between trainees based on gender and years in training, as well as for attendings based on years in practice. Additionally, recovery scores were higher for both junior trainees and attendings compared to their senior counterparts. These findings underscore the importance of awareness of differences in experience among surgeons and may reveal targets for improvement in performance and career satisfaction.

Keywords: Surgical performance; Heart rate variability; Biometric data; Readiness to perform

25COASMA59

Title: Soleus Muscle Necrosis Following Harvest of Fibula Free Flap: A Case Report and Retrospective Contrast CT Analysis,

Nuri, Takashi and Asaka, Akinori and Lee, Sooyeon and Otsuki, Yuki and Ueda, Koichi,
The Laryngoscope,Volume-135,Number-3,pages-1083-1085,
https://doi.org/10.1002/lary.31842,

Abstract: Soleus muscle necrosis is a rare complication following fibula free flap harvest for mandibular reconstruction. This report presents a case of soleus necrosis without compartment syndrome or infection and reviews the blood supply of the soleus muscle in 24 patients. Variations in the vascular anatomy of the soleus muscle, particularly reliance on the peroneal artery, may predispose to this complication. Clinicians should consider soleus muscle necrosis in patients with atypical donor site pain after fibula harvest.

Keywords: complication, donor morbidity, fibula flap, muscle, necrosis,

25COASMA60

Title: Allograft Nerve Repair of a Transected Recurrent Laryngeal Nerve With Voice and Singing Recovery,

Johnson, Ariel C. and Esch, Elena M. and Le, Elliot L.H. and Fink, Daniel S. and Iorio, Matthew L.,

The Laryngoscope, Volume-135,Number-3,pages-1086-1089,
https://doi.org/10.1002/lary.31861,

Abstract: Recurrent laryngeal nerve injuries can occur during thyroid and neck procedures or similar interventions. Immediate nerve repair when possible is preferred to both faciliate the repair and allow timely recovery of the muscle. Here, we report a case of transected left recurrent laryngeal nerve repaired by allograft nerve interposition with excellent return of speaking and singing voice with vocal cord function.

Keywords: hoarseness, nerve injury, nerve recovery, vocal cord recovery,

25COASMA61

Title: A Randomized Pilot Trial of Virtual Reality Surgical Planning for Head and Neck Oncologic Resection,

Nunes, Kathryn L. and Jegede, Victor and Mann, Derek S. and Llerena, Pablo and Wu, Richard and Estephan,

The Laryngoscope,Volume-135,Number-3,pages-1090-1097,
https://doi.org/10.1002/lary.31874,

Abstract: Objective Application of virtual reality (VR) for surgical planning may improve clinical outcomes for head and neck cancer (HNC) resection. There is a lack of randomized trials and meaningful metrics to assess such technological applications. Our objective was to evaluate the feasibility of a VR protocol for oncologic surgical planning and assess the impact on surgical outcomes. Methods A randomized controlled trial utilizing a VR Case Enhancement Protocol (VRCEP) versus standard of care (SOC) surgical planning was conducted. The primary endpoint was feasibility, defined as >80\% successful VRCEPs. Metrics included surgeon task-load burden (TLB) using the NASA Task-Load Index and “margin events,” defined as 'the need for defect-driven margins, positive frozen margins, and/or positive final margins.' Margin events were used to calculate a margin event score (MES) per case and margin event rate (MER) per cohort. Results Thirty-four patients were included in the final analysis (17 VRCEP, 17 SOC) with 94.4\% of eligible VRCEP cases completed (17/18). Surgeon TLB was unchanged with VRCEP. Cases undergoing VRCEP were associated with a lower mean MES (0.27 vs. 0.94, $p = 0.014$) and MER (11.6\% vs. 35.6\%, $p = 0.0041$). VRCEP was associated with decreased defect-driven margins (10\% vs. 53.3\%, $p = 0.032$). Although not statistically significant, positive frozen and final margin rates were lower in VRCEP. Conclusion Completion of the VRCEP was feasible with no significant increase in surgeon TLB appreciated. VRCEP yielded fewer MEs. Further investigation into the benefit of VR in HNC resection is warranted. Margin events may represent useful metrics for assessing novel surgical technologies.

Keywords: head and neck cancer, oral cancer, surgical margins, virtual reality, virtual surgical planning,

25COASMA62

Title: Impact of Adjuvant Interferon Therapy on Survival Outcomes for Cutaneous Melanoma With Parotid Involvement,

Kim, Erin and Raven, Sarah A. and Lenze, Nicholas R. and Farlow, Janice L. and McLean, Scott A.,

The Laryngoscope,Volume-135,Number-3,pages-1098-1104,
https://doi.org/10.1002/lary.31854,

Abstract: Objectives To determine the relative 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) outcomes for adjuvant interferon therapy in the treatment of head and neck cutaneous melanoma (HNCM) with parotid gland involvement. Methods A retrospective cohort study was conducted at a single tertiary care institution to analyze patients undergoing parotidectomy for cutaneous head and neck melanoma involving the parotid gland from 2000 to 2014. Time-to-event analyses were performed using Kaplan–Meier curves with log-rank p-values and Cox proportional hazards models. Results The sample consisted of 82 patients who underwent surgical resection of stage III HNCM with parotid involvement. The mean follow-up was 67.8 months (SD 65) after diagnosis. Twenty-one patients received adjuvant interferon therapy, 12 patients received adjuvant radiation therapy, and 49 patients received no adjuvant therapy. Crude 5-year OS rates were 95.0\% for interferon therapy, 33.3\% for adjuvant RT, and 40.4\% for no adjuvant therapy. Crude 5-year RFS rates were 75.2\%, 19.5\%, and 40.8\% respectively. In the fully adjusted model, adjuvant interferon therapy was associated with improved 5-year OS compared to adjuvant RT (HR 0.10, 95\% CI 0.011–0.837; p = 0.034). There was no significant association between adjuvant interferon therapy and 5-year RFS in the fully adjusted model. Conclusion Adjuvant interferon therapy for surgically resected stage III cutaneous melanoma with parotid gland involvement may be associated with improved survival outcomes. These findings support the growing evidence for the use of immunotherapy in melanoma, and potentially a unique role for when melanoma involves the lymphatic-rich parotid gland.

Keywords: head and neck neoplasms, immunotherapy, interferon, melanoma, parotid,

25COASMA63

Title: Patient-Initiated Communication After Parotidectomy,

Prince, Andrew D.P. and Oslin, Kimberly and Forner, David and Smith, Josh D. and Hershey,

The Laryngoscope,Volume-135,Number-3,pages-1105-1112,
https://doi.org/10.1002/lary.31852,

Abstract: Objectives We sought to study the incidence of patient-initiated communication after parotidectomy, identify patient and surgical factors associated with patient-initiated communication, and evaluate trends and possible areas for improvement. Methods A retrospective cohort study of patients who underwent parotidectomy without combined procedures from 2018 to 2022 in a single tertiary-care institution was performed. We reviewed all patient communications documented within the electronic medical record within 30 days of discharge. We categorized patient communications as requiring an action by the

surgeon, instruction by support staff, or reassurance. Results A total of 363 patients were included. Most patients were women (55.4\%), Caucasian (78.8\%), and had an average age of 56 years ± 16. We found 123 (33.9\%) patients initiated postoperative communications. Swelling (47.2\%) was the most common concern followed by wound concerns (15.4\%). Switching from planned inpatient to outpatient surgery increased (OR = 2.635; 95\% CI = 1.200–6.146, p = 0.026) propensity for postoperative communication. We found 31 (25.2\%) postoperative communications required an action by the surgeon, 40 (32.5\%) required instruction by the support staff, and the other 52 (42.3\%) required reassurance or clarification. Multivariate analysis showed swelling (OR = 6.5, CI = 2.2–19, p < 0.001), male sex (OR = 3.27, CI = 1.127–9.459, p = 0.029), previous smoking (OR = 3.468, CI = 1.181–10.185, p = 0.024), and cancer (OR = 6.862, CI = 1.757–26.804, p = 0.006) were predictive of requiring an action by the surgeon. Conclusions This is the first study to evaluate patient-initiated communication after parotidectomy and found it occurred 33.4\% of the time. We found significant opportunities to improve perioperative care, enhance patient satisfaction, and reduce the overall burden on medical personnel.

Keywords: head and neck, parotidectomy, postoperative communication,

25COASMA64

Title: Nasopharynx Cancer in the United States: Racial and Ethnic Disparities in Stage at Presentation,

Dee, Edward Christopher and Wang, Stephanie and Ho, Frances Dominique V. and Patel, Roshal R. and Lapen,

The Laryngoscope,Volume-135,Number-3,pages-1113-1119,
https://doi.org/10.1002/lary.31907,

Abstract: Introduction Although nasopharynx cancer (NPC) is rare in the United States, global epidemiology varies greatly. Therefore, understanding NPC disparities in the diverse US setting is critical. Methods and Materials Data from the National Cancer Database (NCDB, 2004-2021) identified patients with NPC; NCDB allows disaggregation by Asian American (AA) subgroups. Multivariable ordinal logistic regression adjusting for demographic and socioeconomic factors defined adjusted odds ratios (aORs). Results Of 15,862 patients, 11,173 (70.4\%) were male (median age 59). Commonest groups included 10,034 (63.3\%) White, 2,272 (14.3\%) Black, 1,103 (7.0\%) Chinese, 442 (2.8\%) Filipino, and 338 (2.1\%) Vietnamese patients. Prior to disaggregation, the proportion of stage IV disease at presentation was 43.2\% among White (ref), 50.0\% among Black (aOR 1.12, p = 0.012), 52.0\% among Native American (aOR 1.18, p > 0.05), 41.9\% among AA (aOR 0.97, p > 0.05), and 55.1\% among Native Hawaiian and Other Pacific Islander patients (aOR 1.47, p = 0.021). Upon disaggregation, the proportion of stage IV disease was the greatest (>50\%) among Black (50.0\%, aOR 1.12, p = 0.012), Laotian (61.5\%, aOR 2.21, p = 0.001), Hmong (73.2\%, aOR 2.92, p < 0.001), and Other Pacific Islander patients (60.9\%, aOR 1.83, p = 0.004); 44.2\% of Filipino patients also presented with stage IV disease (aOR 1.21, p = 0.033). Odds of presenting with advanced stage disease were lower among Chinese patients (35.7\% stage IV, aOR 0.72, p < 0.001). Conclusions Although most NPC patients were Chinese, White, or Black, stage IV disease at presentation was most common among

Hmong, Laotian, non-Hawaiian Pacific Islander, and Black patients. Efforts are needed to improve awareness of NPC among less canonically affected groups.
Keywords: cancer disparities, head and neck cancer, health services, nasopharyngeal cancer, nasopharynx cancer, racial disparities,

25COASMA65

Title: Safe distance from facial nerve for bipolar coagulation in parotid surgery—Animal study,

Stanković, Petar and Bette, Michael and Mandić, Robert and Hoch, Stephan and Stuck, Boris A. and Wilhelm, Thomas,
The Laryngoscope,Volume-135,Number-3,pages-1120-1126,
https://doi.org/10.1002/lary.31883,
Abstract: Objective Currently no data exist on what distance from facial nerve (FN) it is safe to perform bipolar cautery (BC) in parotid surgery, although frequently performed. Methods The degree of damage was measured using continuous intraoperative neuromonitoring (cIONM, NIM™ 3, Medtronic) in 16 Wistar rats. Amplitude drop of at least 50\% (A50) or a loss of signal (LOS) in the cIONM was defined as harmful; BC was performed in power range 20–60 W. Results BC ≤30 W did not cause LOS (0/14 nerves). When applying 35 W, A50 occurred at 4 mm from FN and LOS was noted in 1 of 5 nerves. BC at a power of 40 to 60 W demonstrated LOS in all nerves (12/12) at a 5 mm distance. Conclusion BC up to 30 W can be safely applied up to 3 mm distance from FN. 40 to 60 W should be avoided and used only at a distance of over 6 mm from FN.
Keywords: animal study, bipolar cautery, intraoperative neuromonitoring, facial palsy, cIONM,

25COASMA66

Title: Open Expansion Laryngoplasty for Combined Glottic and Subglottic Stenosis,

Laitman, Benjamin M. and Kominsky, Rachel and Gregory, Jill and Woo, Peak,
The Laryngoscope,Volume-135,Number-3,pages-1127-1131,
https://doi.org/10.1002/lary.31855,
Abstract: Expansion laryngoplasty is a new, combined procedure which can treat both glottic and subglottic stenosis simulataneously. This is a small case series showing how to perform this surgery as well as outcomes from a 15-year period.
Keywords: laryngotracheoplasty, open airway surgeryposterior glottic stenosissubglottic stenosis,

25COASMA67

Title: Improving Laryngeal Procedure Workflow: Moving From the Operating Room to the Outpatient Setting,

Huang, Jie Lily and Khalid, Hesham and Alvaran, Krizzia Angelaine Biaco and Hey, Shiying and Watson,
The Laryngoscope,Volume-135,Number-3,pages-1132-1142,
https://doi.org/10.1002/lary.31849,

Abstract: Objectives Laryngology disease burden is growing while theater capacity is falling. Over half a million patients are waiting for ENT care in England alone (1). The demand for laryngology services has continued to grow significantly, particularly post-COVID (2). Meanwhile, the number and efficiency of ENT theater lists are reduced (3). To tackle the growing backlog, NHS England has emphasized the need for innovative strategies by separating elective from emergency services and by increasing the resilience of elective delivery (4). The establishment of an office-based laryngology procedure clinic is a potential solution. Methods We offer a narrative review and audit of our experience in founding an in-office laryngology procedure service within a tertiary NHS center with the aim of streamlining this setup process for other interested ENT units. Results We outline an in-depth exploration of the personnel, equipment, and processes necessary to establish an in-office procedure clinic. Our experience showed that the procedure clinic functions well when implemented within the framework of existing ENT elective and emergency services. Although there is initial investment required in terms of money, effort, and time, our outcomes show that the clinical and economic benefits of the clinic outweigh the costs, also allowing for patients to access investigations and treatments reliably and efficiently. Conclusion Setting up a laryngology in-office procedure clinic within the NHS confers patient, organizational, and economic benefits. It provides a novel and resilient approach in addressing the growing backlog of patients awaiting laryngology care and should be popularized in the current health care environment.
Keywords: health policy, laryngeal electromyography, laryngology, quality improvement, voice disorders,

25COASMA68

Title: Quantifying Health Utility of Age-related Vocal Atrophy,

de Leon, Julio A. and Cvancara, David J. and Carlson, Abbey L. and Cheng, Alice and Rizvi, Zain H. and Giliberto,

The Laryngoscope,Volume-135,Number-3,pages-1143-1147,
https://doi.org/10.1002/lary.31850,

Abstract: Objective Age-related vocal atrophy (ARVA) negatively impacts voice and quality of life (QOL). This study aims to determine utility-based QOL in ARVA patients, correlate findings with traditional patient-reported outcome measures (PROMs), and generate utility-based inferences. Methods Forty ARVA patients were prospectively recruited from a tertiary care center. Health utility was measured using standard gamble, time trade-off, and visual analog scale, assessing participants' current health states relative to defined comparison states (blindness/death). Traditional PROMs (Voice Handicap Index-10 [VHI-10] and Voice-Related Quality of Life Scale [V-RQOL]) were also collected. Descriptive and paired statistics were performed to determine health utility, and Pearson correlation assessed the association between PROMs and health utilities. Results Mean health utility in ARVA was 0.84 ± 0.22, 0.88 ± 0.17, and 0.62 ± 0.25 using standard gamble, time trade-off, and visual analog scale, respectively. There were positive correlations between V-RQOL and time trade-off ($r = 0.66$; $p < 0.0001$) as well as with standard gamble ($r = 0.47$; $p = 0.002$). Participants with ARVA reported no difference in health utility impact between their voice impairment

and monocular blindness (Mean dif 10.9; 95\% CI –1.6, 23.5; p = 0.101). Patients with ARVA were willing to part with an average 4.6 ± 6.1 years of life to restore normal voice. Conclusions ARVA patients view their voice impairment as a significant health decrement, comparable to monocular blindness. These findings underscore the substantial impact of ARVA on QOL and highlight the need for continued research and new therapies.
Keywords: age-related vocal atrophy, health utility, patient reported outcome measures, standard gamble, time trade-off,

25COASMA69

Title: Improving Diagnostic Yield in Patients with Pulsatile Tinnitus: A Ten-Year Analysis,

Sismanis, Aristides and Coelho, Daniel,

The Laryngoscope,Volume-135,Number-3,pages-1148-1154,
https://doi.org/10.1002/lary.31838,

Abstract: Objectives To determine the yield of a comprehensive diagnostic algorithm for patients with pulsatile tinnitus (PT) and to review the common etiologies and present clinical pears for their diagnosis. Methods Retrospective chart review of patients with PT from 2013 to 2023. Charts were reviewed for demographic data (age, sex, BMI), side of PT (or bilateral), specialty clinic of initial evaluation, coexistent symptoms in addition to PT, and final diagnosis (or non-diagnosis). Clinical, audiometric, laboratory, and radiographic data were collected. Putative chart diagnoses were reviewed by the authors and deemed likely or unlikely to be the source of the patient's PT. Those with “unlikely” were grouped in the “idiopathic” cohort. The diagnostic algorithm is presented in detail. Results Two hundred and 90 patients were included for analysis. The overall diagnostic yield was 90.7\% for all patients and 95.6\% for those patients who completed the recommended workup – a substantial improvement over published rates. Twenty-nine etiologies were identified with the most common etiology was idiopathic intracranial hypertension (IIH). Twenty-one diagnoses comprised no more than 5\% of patients. Seventy-three patients (25.2\%) had more than one pathology as a potential source for their PT. Conclusions PT can present a diagnostic challenge to the clinician. The findings of this study, however, reveal that proper evaluation based on obtaining a thorough history, performing a physical examination, coupled with properly directed imaging studies and blood testing can accomplish a high diagnostic yield of at least one potential etiology.
Keywords: algorithm, diagnosis, intracranial hypertension, pulsatile tinnitus,

25COASMA70

Title: Predictors of Abnormal MRI Findings in Patients with Asymmetrical Sensorineural Hearing Loss,

Prayuenyong, Pattarawadee and Pitathawatchai, Pittayapon and Plodpai, Yuvatiya and Atchariyasathian,

The Laryngoscope,Volume-135,Number-3,pages-1155-1160,
https://doi.org/10.1002/lary.31841,

Abstract: Objective This study aimed to determine the predictive factors of abnormal MRI findings in patients with asymmetrical sensorineural hearing loss (ASNHL). Study Design A retrospective review of medical records. Setting A tertiary care hospital. Methods Patients with asymmetries of ≥10 dB in at least 1 frequency, who underwent an MRI study of the temporal bone or brain during 2019–2021, were included. Age, sex, clinical symptoms, past medical history, and audiometric parameters, including pure tone thresholds, speech reception thresholds, and speech discrimination scores, were retrieved from the electronic database. The MRI findings reported by radiologists were reviewed and extracted. Results Of 390 patients, 50 (12.8\%) patients had relevant abnormal MRI findings that could explain ASNHL. The most prevalent abnormal MRI finding was an internal acoustic canal (IAC) or cerebellopontine angle (CPA) tumor (n = 38; 76.0\%), with other notable abnormalities including labyrinthitis, stroke, mucocele, and epidermoid. Multiple logistic regression analysis highlighted that hearing asymmetry of 15 dB at 1000 Hz (OR = 4.8; 95\% CI 2.2–10.5) was a significant variable. The proposed predictor demonstrated 84\% sensitivity and 48\% specificity in detecting abnormal MRI findings. Conclusion A hearing asymmetry of 15 dB at 1000 Hz was an important clinical predictor of abnormal MRI findings in patients with ASNHL. This finding has the potential to serve as a referral guide for further MRI investigations.
Keywords: magnetic resonance imaging, sensorineural hearing loss,

25COASMA71

Title: Toward Intelligent Head Impulse Test: A Goggle-Free Approach Using a Monocular Infrared Camera,

Ouyang, Yang and Luo, Wenwei and Zhan, Yinwei and Wei, Caizhen and Liang, Xian and Huang,

The Laryngoscope,Volume-135,Number-3,pages-1161-1168,
https://doi.org/10.1002/lary.31848,

Abstract: Objectives To assess vestibular function, video head impulse test (vHIT) is taken as the gold standard by evaluating the vestibulo-ocular reflex (VOR). However, vHIT requires the patient to wear a specialized head-mounted goggle equipment that needs to be calibrated before each use. For this, we proposed an intelligent head impulse test (iHIT) setting with a monocular infrared camera instead of the head-mounted goggle and contributed correspondingly a video classification approach with deep learning to vestibular function determination. Methods Within the iHIT framework, a monocular infrared camera was set in front of the patient to capture test videos, based on which a dataset DiHIT of HIT video clips was set up. We then proposed a two-stage multi-modal video classification network, trained on the dataset DiHIT, that took as input the eye motion and head motion data extracted from the facial keypoints via HIT clips and outputted the identification of the semicircular canal (SCC) being tested (SCC identification) and determination of VOR abnormality (SCC qualitation). Results Experiments on this dataset DiHIT showed that it achieved the accuracy of 100\% in prediction of SCC identification. Furthermore, it attained predictive accuracies of 84.1\% in horizontal and 79.0\% in vertical SCC qualitation. Conclusions Compared with existing video-based HIT, iHIT eliminates goggles, does not require equipment calibration,

and achieves complete automation. Furthermore, iHIT will bring more benefits to users due to its low cost and ease of operation.

Keywords: acute vestibular syndrome, deep learning, head impulse test, semicircular canal, vestibular function assessment, video classification,

25COASMA72

Title: Exploring the Link between Serum Klotho and High-Frequency Hearing Loss in Older Adults,

Yan, Jingchao and Li, Ling and Ye, Qing and Huang, Taomin,

The Laryngoscope,Volume-135,Number-3,pages-1169-1176,
https://doi.org/10.1002/lary.31851,

Abstract: Objective Klotho is a protein with various biological functions, including anti-aging effects. Although research suggests Klotho plays a key role in auditory function, the relationship between serum Klotho levels and high-frequency hearing loss (HFHL) in older adults remains unclear. Methods We analyzed data from individuals aged 70–79 years participating in the 2009–2010 cycle of the National Health and Nutrition Examination Survey. Multivariate logistic regression models were employed to assess the relationship between serum Klotho levels and HFHL. Restricted cubic splines were utilized to evaluate linearity and examine the dose–response relationship. Additionally, we performed subgroup analyses to evaluate the consistency of this relationship across various subgroups. Results In this study of 422 elderly individuals aged 70–79 years (mean age 73.8 years, with 47.4\% male participants), the median serum Klotho concentration was 754.6 pg/mL. Multivariable logistic regression analysis consistently demonstrated that higher serum Klotho levels were associated with a reduced risk of HFHL across various models (ORs: 0.24–0.32, $p = 0.020$–0.028). Additionally, restricted cubic spline analysis confirmed a linear negative association between serum Klotho levels and HFHL risk, with a p-value for nonlinearity of 0.474. Subgroup analyses did not reveal any statistically significant interactions modifying this relationship. Conclusion Serum Klotho levels are inversely associated with the risk of HFHL.

Keywords: hearing loss, high frequency, National Health and Nutrition Survey, presbycusis, α-Klotho (Klotho),

25COASMA73

Title: The Impact of Sleep Deprivation on Video Head Impulse Test Results,

Keren, Shir and Hazan, Itai and Ungar, Omer J. and Peled, Chilaf and Gimmon, Yoav and Abu Freh,

The Laryngoscope,Volume-135,Number-3,pages-1177-1182,
https://doi.org/10.1002/lary.31857,

Abstract: Objective To investigate the association between sleep deprivation and vestibular dysfunction by Video Head Impulse Test (vHIT). Methods This prospective clinical trial explores the impact of acute sleep deprivation on the vestibular-ocular reflex (VOR) in medical residents. The study involved healthy physicians from diverse medical disciplines. Participants underwent vHIT assessments before and after a 26-h shift. The examinations focused solely on the right lateral semicircular canal. Participants further completed a

demographics and fatigue questionnaire, including the Fatigue Severity Scale (FSS) questionnaire and a Visual Analog Fatigue Score (VAFS). Results The study involved 30 medical residents. Participants experienced a statistically significant decrease in VOR gain in the right horizontal semicircular canal during a 26-h shift ($p < 0.01$). While the FSS and VAFS questionnaires showed no significant difference before and after the shift, the analysis of ΔVOR gain indicated a statistically significant increase associated with decreased sleep time during the shift ($p = 0.018$, 95\% Confidence Interval [0.08, 0.68]). The most substantial increase in ΔVOR occurred between 22–26 h of sleep deprivation. No significant differences were observed in ΔVOR between genders, ages, disciplines, department shifts versus emergency room shifts, or years of residency. Conclusion vHIT can be used as an objective, reliable screening tool for severe sleep deprivation among physicians. The decrease in the VOR gain may indicate that vestibular function is influenced by sleep deprivation. The clinical significance of these findings is still questioned, more studies may help to assess this effect.

Keywords: sleep deprivation, vestibular function, vestibular-ocular reflex (VOR), video head impulse test (vHIT),

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