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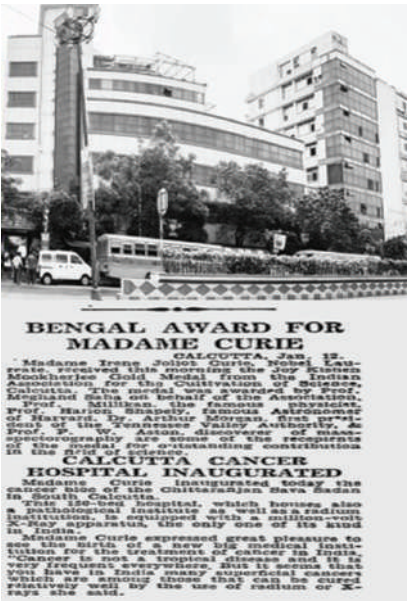
CNCI Bulletin

CHITTARANJAN NATIONAL CANCER INSTITUTE (KOLKATA)

(An Autonomous Body under Government of India, Ministry of Health & Family Welfare, Regional Cancer Centre)



BENGAL AWARD FOR MADAME CURIE

CALCUTTA, Jan. 15.

Madame Irene Joliot Curie, Nobel Laureate, received this morning the Prafulla Mookherjee Gold Medal from the Indian Association for the Cultivation of Science, Calcutta. The medal was awarded by Prof. Meghnad Saha on behalf of the Association.

Prof. Millikan, the famous physicist, Prof. Harkins, famous chemist of Harvard, Dr. Arthur Morgan, first president of the Tennessee Valley Authority, and Prof. F. W. Aston, discoverer of mass-spectrography are some of the recipients of the medal for outstanding contributions in the field of science.

CALCUTTA CANCER HOSPITAL INAUGURATED

Madame Curie inaugurated today the cancer block of the Chittaranjan Seva Sadan in South Calcutta.

This 120-bed hospital, which houses also a pathological institute as well as a radium institution, is equipped with a million-volt X-Ray apparatus, the only one of its kind in India.

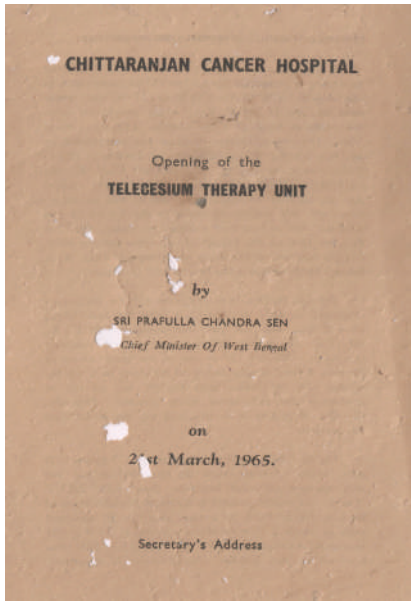
Madame Curie expressed great pleasure to see the birth of a new big medical institution for the treatment of cancer in India. "Cancer is not a tropical disease and it is very frequent everywhere. But it seems that you have in India many superficial cancers which are among those that can be cured relatively well by the use of radium or X-rays she said.

DIRECTOR'S MESSAGE

Dr. Jayanta Chakrabarti

Director,

Early detection is the primary weapon in the fight against cancer. Prompt medical intervention significantly reduces suffering and costs. However, despite widespread awareness, a crucial fact often goes unheeded: tobacco is the root cause of most cancers. This New Year, take a pledge to quit tobacco products, including cigarettes, bidis, and chewing tobacco. Make a commitment to a tobacco free lifestyle and invest in a healthier future.



CHITTARANJAN CANCER HOSPITAL

Opening of the

TELECESIUM THERAPY UNIT

by

SRI PRAFULLA CHANDRA SEN

Chief Minister Of West Bengal

on

21st March, 1965.

Secretary's Address

From Editors Desk

Dr. Suparna Mazumder,
Prof. & HOD, *Radiology*

Dear Readers,

Cancer care for India's diverse population -

Cancer poses a formidable challenge to healthcare systems worldwide, exacerbated by India's vast and heterogeneous population of 1.3 billion. The disease burden varies significantly across 29 states and 7 union territories, influenced by factors such as population genetics, environment, and lifestyle.

In low and middle-income countries, cancer patients often face poorer prognoses due to limited awareness, delayed diagnosis, and inadequate access to affordable healthcare services. India is no exception, with data from major centres revealing that most cancer patients seek medical attention at advanced stages.

Enhancing cancer awareness is crucial for promoting early detection and timely intervention. However, factors such as illiteracy, financial constraints, and myths perpetuate delayed health-seeking behaviour. Screening is a vital preventive measure, yet India's national program has been slow to implement, with limited availability of screening tests and underutilization of existing services.

Key challenges:

- Low awareness and delayed health-seeking behaviour
- Limited screening services and underutilization
- Inequitable access to affordable healthcare

Solutions:

- Enhance cancer awareness and education
- Expand screening services and promote utilization
- Improve access to affordable and quality healthcare

By addressing these challenges, India can reduce its cancer burden and improve outcomes for patients.

Dr. Jayasree Roy Chowdhury

(1934 -2024)

Eminent Oncologist and researcher Dr. Jayasree Roy Chowdhury passed away on December 3, 2024, at the age of 90. A distinguished figure in the field of oncology Dr. Roy Chowdhury served as the Director of Chittaranjan National Cancer Institute (CNCI). She was the daughter of renowned physician Dr. Subodh Mitra, the founder of CNCI, and the wife of renowned gynaecologist Dr. Nagen Roy Chowdhury. She was a rare combination of brain and beauty. Dr. Jayasree Roy Chowdhury distinguished herself academically, securing numerous scholarships throughout her MBBS course at Calcutta Medical College, which she completed in 1956. Following advanced training in tissue culture and virology at the prestigious Sloan Kettering Institute for Cancer Research in New York, she joined the renowned Chittaranjan National Cancer Research Centre in 1961.

Dr. Jayasree Roy Chowdhury made history as the Director of CNCI from 1977 to 1984, shattering glass ceilings as a female leader in a male-dominated field. Her exceptional administrative acumen and visionary leadership inspired a new generation of scholars. Under her guidance, students were empowered to pursue cutting-edge research, with many receiving opportunities to collaborate with international experts abroad."

Dr. Jayasree Roy Chowdhury achieved notable academic milestones, earning her Ph.D. in 1964 and subsequently her (link unavailable) from the University of Calcutta in 1968, recognizing her ground-breaking research on "Ergastoplasm and Ribosome in Human Cancer Cell Biology." Her distinguished career spanned various esteemed roles, including examiner for postgraduate degrees at multiple universities. Dr. Roy Chowdhury's prolific publication record boasts over 150 papers. She was a founding member of the Indian Academy of Cytologists and the Academy of Cancer Chemotherapy. Her contributions were acknowledged through prestigious awards, including the Raja Ravi Varma Singh of Kalsia Memorial Cancer Research Award (1966, 1972) and the Dr. Ambo Pashpati Nath Research Award (1977).

She was a versatile individual, beyond her medical career, she was an accomplished athlete, demonstrating expertise in swimming, javelin throw and lawn Tennis. Additionally, she showcased exceptional talent in classical dance and a deep appreciation for music. Her memory will continue to motivate us to make a difference.

Liquid Biopsy: A Revolutionary Diagnostic Tool

Dr. Srabani Chakrabarty,
Specialist, Gr - 1,
(Laboratory Services)

Liquid biopsies are non-invasive blood tests that detect circulating tumour cells (CTCs) and fragments of tumour DNA that are shed into the blood from the primary tumour and from metastatic sites.

Liquid biopsy is a minimally invasive alternative to surgical biopsy for tumour molecular profiling. These are blood-based biomarkers that can detect

- the circulating tumour cells (CTCs)
- fragments of tumour DNA (ctDNA) / cell-free DNA (cfDNA)
- Exosomes and micro vesicles that are shed into the blood from the primary tumour and from metastatic sites.
- Tumour educated platelets (TEPs)

Tracing its roots to 1869, T.R. Ashworth first described the presence of epithelial cells in the blood of a woman in metastatic breast cancer that were similar in appearance to her primary tumor cells. Presence of cell-free DNA in human blood was first described by Mandel and Metais in 1948.

Subsequently in the years of 2002 and 2003, Thiery and Steeg discovered the formation mechanisms of CTC. In 2007, CTC has been recommended as a new biomarker by ASCO.

The paradigm of cancer diagnosis has evolved beyond solely relying on morphological parameters, now encompassing more and more diagnostic algorithms supported by immunohistochemical and molecular alterations at the DNA, mRNA, miRNA, and a proteomic level.

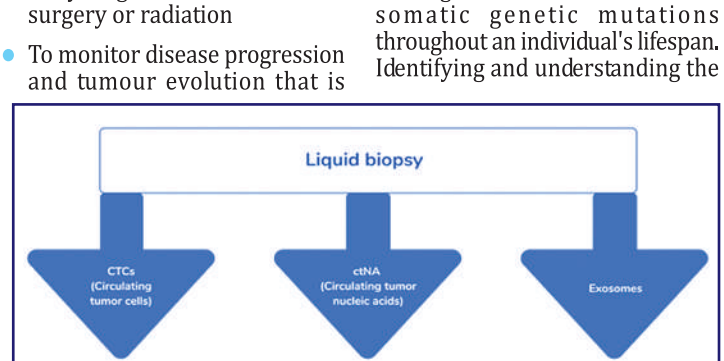
Liquid biopsy can be done from blood, serum / plasma, urine, CSF, saliva and body fluids. Blood can be sampled in EDTA tubes but the plasma has to be isolated and stored at -80-degree within one hour of collection. The extraction is preferably done on the same day. However, it is stable in plasma at -80-degree C. ctDNA has a very short half-life ranging from 15 minutes to few hours.

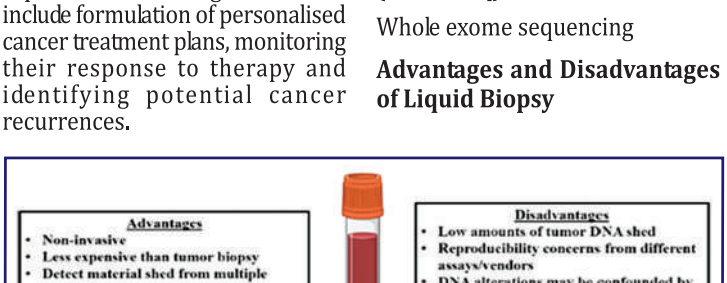
Indications of Liquid Biopsy

- Identifying patients who have early-stage cancer amenable to surgery or radiation
- To monitor disease progression and tumour evolution that is development of tumour resistance
- Aiding the physician explore other options of treatment when the patient is resistant to treatment
- Provide alternative biopsy strategies for cases where tissue acquisition from the primary site is challenging or infeasible, or when the origin of metastatic disease remains undetermined
- Additionally, it provides an alternative method for biopsy when the quantity of tissue obtained in a biopsy sample is limited and traditional molecular genotyping is required.
- To monitor residual disease in patients with known mutation in primary tumour.
- Provide prognostic information.
- Determine the risk of recurrence after treatment
- Determine treatment selection based on the presence of biomarkers
- Determine mechanisms of resistance, disease progression and identification of newer treatment

CTCs represent the clones within the tumour that have the metastatic potential. In cancer patients, only a small portion of cfDNA (usually 0.01-5%) is shared within the bloodstream by tumour cells. These cells usually only last for 1-2.4 hours in the circulation prior to destruction by the immune system and a small fraction can survive and cede distant metastatic sites.

The majority of cancers arise through the accumulation of somatic genetic mutations throughout an individual's lifespan. Identifying and understanding the somatic alteration in a patient's tumour can be critical to several aspects of cancer diagnosis. These include formulation of personalised cancer treatment plans, monitoring their response to therapy and identifying potential cancer recurrences.





As the tumour progresses, they often acquire additional genetic alterations. These acquired changes can significantly impact the effectiveness of therapeutic interventions, including chemotherapy and targeted therapies. Furthermore, metastatic lesions frequently harbour unique genomic characteristics that may not be detectable in the corresponding primary tumour. This inter-tumour heterogeneity is not only observed between patients but also within individual patients, with metastases at different sites exhibiting distinct genomic profiles.

Consequently, the analysis of the resected primary tumour alone even with potential re-evaluation based on biopsies of accessible metastases, may not provide a comprehensive understanding of the tumour's genomic landscape. This limitation can significantly hinder optimal treatment decision-making, emphasizing the need for more comprehensive approaches to tumour characterization.

The methods which enable detection of cfDNA and somatic mutations and have been used in different types of cancers are:

Next generation sequencing (NGS)

Droplet digital polymerase chain reaction (ddPCR)

Amplification

Magnetics (BEAMing)

Tagged-amplicon deep sequencing (TAm-Seq)

Cancer personalized profiling by deep sequencing (CAPP-Seq)

Whole genome sequencing (WGS)

Whole genome bisulfite sequencing (WGBS-Seq)

Whole exome sequencing

Advantages and Disadvantages of Liquid Biopsy

Is this the end of tissue biopsies?

Tissue biopsy will remain as the gold standard. Liquid biopsies are recommended when tissue biopsy is difficult or when primary site of disease is unknown. Many challenges still remain to make liquid biopsy a reality in the clinic.

Oral Sub mucous Fibrosis: Etiopathogenesis and Treatment Strategies

Dr. Rajdeep Guha,
Specialist Gr-I
Dept. of Head & Neck Oncology

Oral Sub mucous Fibrosis (OSMF) is characterized by abnormal distribution of collagen in the oral connective tissue. It is a common precancerous condition in the Asian countries and causes significant compromise in the quality of life of patients by restricting mouth opening and causing symptoms such as burning of mouth, ulceration and xerostomia in the oral cavity.

Etiopathogenesis:

Inflammation and Autoimmunity contribute to OSMF. Also, nutritional deficiency such as beta carotene, iron, vitamin C and zinc has been observed. Higher levels of copper is seen which may be responsible for increased lysyl oxidase activity (LOX) which may explain cross-linkages of collagen and elastin. Hypermethylation of Wnt Inhibitory factor 1 (WIF1) and p16 gene has also been observed.

Betel nut chewing is the most important risk factors for OSMF. Arecolin is the major compound which initiates the process of OSMF. LOX is upregulated by arecolin and it also increases cell proliferation rate and total reactive oxygen species and DNA damage.

Arecolin activates TNF alpha which stimulates cell inflammation. This initiates wound healing reaction which reduces MMP (matrix metalloprotinase) and increases TIMP (tissue inhibitors of metalloproteinases). The degradation of extracellular matrix is thus slowed down. The inflammation causes cell expression of bFGF (beta fibroblasts growth factor) and TGF beta 1 (transforming growth factor beta 1) causing collagen deposition and converting fibroblast to myofibroblasts which is responsible for collagen production and wound contracture. Normally, myofibroblasts undergo apoptosis after wound healing, but in OSMF, this process is hampered.

Arecolin also causes increased production of ROS (reactive oxygen species) which causes cell senescence and DNA breaks. The inflammation and ROS leads to increase of TGF beta which stimulates CTGF (Connective tissue growth factor) which promotes fibroblasts mediated deposition of extracellular matrix.

The copper then causes the cross linkage of collagen and hardens the mucosa causing the limitation of mouth opening. Commercially available Areca nuts contain a high amount of copper.

Other risk factors include tobacco and alcohol consumption.

Classification:

The clinical classification of OSMF includes Stage I: Faucial bands only, Stage II: Faucial and buccal bands and Stage III: Faucial, buccal and labial bands.

The Functional classification includes Stage A: Mouth opening > 20mm, Stage B: mouth opening 11-19mm, Stage C: Mouth opening < 10mm.

Histological classification includes Group I: Very Early - features which includes fine fibrillary collagen network. Group II: Early - Juxtra epithelial hyalinisation with presence of young fibroblasts and presence of inflammatory cells and keratinisation of epithelium. Group III: Advanced - Juxtra epithelial hyalinisation with discernible collagen bundles and presence of mature fibroblasts and atrophic epithelium with loss of rete pegs. Group IV: Advanced - hyalinisation of collagen with scarce or absent fibroblasts, with extensive fibrosis of blood vessels and eliminating melanocytes. Total loss of rete pegs with mild to moderate atypia.

Malignant potential:

OSMF is considered to be premalignant for SCC. The hypermethylation of WIF1 and p16, and the presence of long non coding RNA are considered to be contributing to malignant transformation. However, the mechanism of transformation from OSMF to OSCC remains unclear. Persistent inflammation, collagen deposition, growth factors, cytokine secretions caused by arecolin are all considered contributing to malignant transformation. TGF beta contributes to metastasis and chemo resistance. TNF alpha contributes to malignant transformation, invasion and metastasis. MMPs contribute to malignant transformation and cancer progression.

Tissue hypoxia resulting from the collagen deposition and resultant capillary blockage may also be a contributory factor for malignant transformation.

Lab experiments with topical application of arecolin on SD rats and BALB/C mice confirms its malignant potential.

Various studies report malignant transformation rate to vary from 7-30%. About a third of OSMF patients would be having OSCC.

Treatment strategies:

Corticosteroids like hydrocortisone, triamcinolone, dexamethasone and betamethasone as well as anti inflammatory cytokines like interferon gamma ameliorate inflammation and decrease collagen formation. Enzymatic drugs like collagenase, hyaluronidase and chymotrypsin reduce the viscosity extracellular matrix and improve trismus and fibrosis. Supplementation of vitamins and minerals improve the burning sensation and ulceration. However, no standard guidelines are currently available for treatment and high quality clinical studies are required to have and effective treatment strategy.

Therapeutic non invasive treatment includes stretching devices which can improve mouth opening from 10.5mm to 14mm on an average within a span of 3 to 6 months and also helps to maintain the bite size as reported in various studies. A protocolized exercise programme has been seen to improve mouth opening up to 29mm interincisal distance over a period of 1y. However, the devices are unsuitable for people who have severe periodontitis or have edentulous ridges in which case it may lead to pain and soft tissue injuries. 3D printing technology may be used to customise such devices for patients with better compliance.

Surgical intervention is required in patients having mouth opening less than 20mm. Cutting the fibrotic bands using various instruments viz. blades, lasers, electrocautery have all been tried with varying success. The raw area would require to be covered by a well vascularised flap to prevent post surgical contracture eg. fat flap, tongue flap, nasolabial flap, mandibular muco-periosteal flap, palatal flap and platysmal myocutaneous flap have all been used. They have been found to be more effective than split skin graft and fresh human amnion grafts. The surgery may be combined with coronoidectomy and may be used in addition to local vasodilators and anti inflammatory materials.

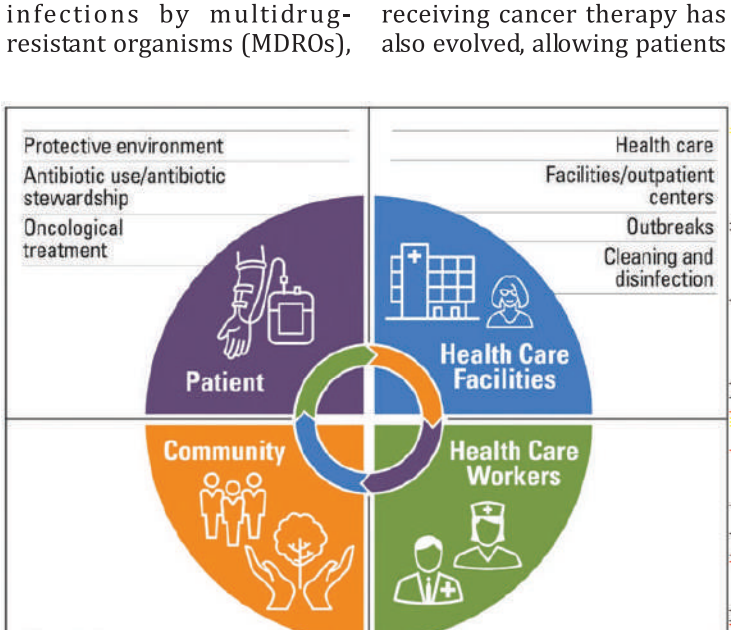
Infection Control Practices in Oncology Centre: An Update

Dr. Subhranshu Mandal,
Associate professor and
Specialist Microbiologist
Dept. of Laboratory Medicine

Hippocrates (circa 460-377 BCE) originally recognized the effects of our surroundings on human diseases in his treatise On Airs, Waters, and Places, attributing illness to characteristics of climate, water, modes of life, and nutrition.Two thousand years later, in the 1800s, Ignaz Semmelweis (1818?1865 CE) documented the effects of environmental control through hand hygiene on clinical outcomes, achieving a dramatic decrease in puerperal mortality with the widespread use of aseptic techniques, in which practitioners cleaned their hands with chlorine solution in between patients.

Although it took decades before the medical community accepted this discovery, infection control practices have changed medicine, improved patients' outcomes, and become the law of the land.For immunocompromised patients, infection control strategies are a fundamental part of modern oncologic care and comprise a multilevel approach, including the patient, the healthcare environment, the community, and healthcare workers. Guidelines for infection control and prevention (ICP) in patients with hematologic or oncologic malignancies are centered on recommendations for hematopoietic cell transplant (HCT) recipients and have typically been based on principles of hand hygiene, air quality, barrier isolation (eg, the use of gowns, gloves, masks, and eye protection, depending on the type of exposure), endogenous flora suppression by prophylactic antibiotics, and the prevention of device-related infections (eg, central venous catheters and urinary catheters). An equally relevant aspect of ICP for patients with cancer is the recognition of higher rates of colonization and infections by multidrug-resistant organisms (MDROs), such as vancomycin-resistant Enterococcus (VRE), methicillin-resistant Staphylococcus aureus (MRSA), and multidrug-0resistant Gram-negative bacilli (MDR?GNB), and Clostridium difficile compared with the general patient population. Well-known risk factors associated with the transmission of these MDROs include: hematologic malignancy; neutropenia; frequent contact with the health care environment; multiple and/or prolonged hospitalizations; devices, including urinary catheters and central lines; as well as changes in the microbiome driven by the use of antimicrobial agents and chemotherapy. Moreover, intestinal colonization with VRE and extended-spectrum β lactamases (ESBL) Escherichia coli has been associated with an increased risk ratio (RR) of developing bloodstream infection (BSI) with these organisms.

Therapies in oncology have evolved rapidly over the last few years. At the same pace, supportive care for patients receiving cancer therapy has also evolved, allowing patients to safely receive the newest advances in treatment on both inpatient and outpatient basis. The recognition of the role of infection control and prevention (ICP) in the outcomes of patients living with cancer has been such that it is now a requirement for hospitals and involves multidisciplinary groups. Some unique aspects of ICP for patients with cancer that have gained momentum over the past few decades include catheter-related infections, multidrug-resistant organisms, community-acquired viral infections, and the impact of the healthcare environment on the horizontal transmission of organisms. Furthermore, as the potential for infections to cross international borders has increased, alertness for outbreaks or new infections that occur outside the area have become constant. As the future approaches, ICP in immuno-compromised hosts will continue to integrate emerging disciplines such as outpatient cancer care and the entailed infection control practices (including up-to-date immunizations & community outbreaks), the role of antibiotic stewardship, and the use of whole-genome sequencing (WGS) for outbreak investigations, have great applications in ICP for patients living with cancer. However, there is no clear consensus or guidance on the variety of ICP strategies; recommendations for these practices are mainly center-adapted.



Important Aspects of Infection Control and Prevention in Patients Living with Cancer.

The growth of the infection control discipline has played a vital role in the progress of cancer treatments, allowing patients to undergo new therapies safely. The application of current recommendations to cancer care and other healthcare environments must follow local patterns of infections; must continuously be reevaluated; and requires a multidisciplinary team, including infection control practitioners, physicians, nurses, and administrators, as well as a space for patients to voice their concerns. A good ICP program depends on current and open communication within the institution to ensure constant guidance on evolving infection control practices, especially those that cover the needs of the immuno-suppressed patient.

Langerhans cell histiocytosis: A rare case diagnosed in one year old female child

Dr. Srabanti Hajra
Specialist Grade I
Dept. of Pathology

Langerhans cell histiocytosis (LCH)is a disorder of proliferation of dendritic cells or histiocytes characterized by accumulation of Langerhans cells and other inflammatory cells including eosinophils, giantcells, histiocytes and neutrophils. Langerhans cells have characteristic indented nuclei and slightly eosinophilic cytoplasm. They contain a Tennis racket shaped, intracytoplasmic organelle calledBirbeck's granule - identified by electron microscopy. Diagnostic IHC markers include Langerin (CD 207), CD 1a, S100 protein.

LCH can be divided into three major categories on the basis of type and extent of the organ involvement. Solitary bone involvement, multiple bone involvement (with or without skin involvement), or multiple organ involvement (bone, liver, spleen, and others).

The cases with solitary bone involvement, which represent the most common variety, have been traditionally referred to as eosinophilic granuloma. Yong adults are most commonly affected. Any bone can be involved, with the possible exception of the hands and feet. The most common sites are the cranial vault, jaw, humerus, rib, and femur. Most lesions appear as well-circumscribed, punched out radiolucent lesion. In flat bones, Langerhans cell histiocytosis can have an aggressive pattern of bone destruction reminiscent of Ewing sarcoma or lymphoma.

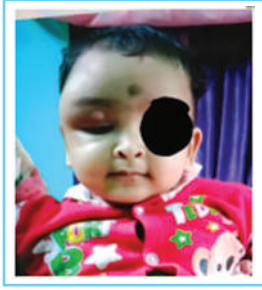
The treatment may include observation, surgery, radiotherapy, or chemotherapy, depending on the extent of the disease. Many solitary lesions regress following biopsy. The long-term prognosis, particularly for solitary lesions, is excellent.

Multiple bone lesions can be accompanied by proptosis, diabetes insipidus, chronic otitis media, or a combination of these conditions, historically referred to as Hand-Schuller-Christian disease.

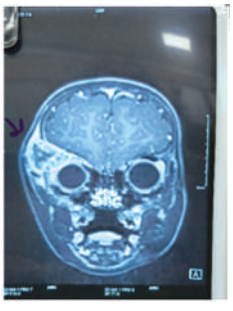
This form is characterized by a prolonged clinical course, often marked by alternating episodes of regressions and recrudescences, although the eventual outcome is favorable is most cases. By contrast, Letterer-Siwe disease- the development of Langerhans cell histiocytosis in multiple organ systems- follows a more aggressive clinical course.

Langerhans cell histiocytosis should be regarded as a neoplastic disease. Recently, it has been shown that a relatively high percentage of cases of Langerhans cell histiocytosis harbor BRAF V600E mutations, resulting in activation of the MAPK pathway.

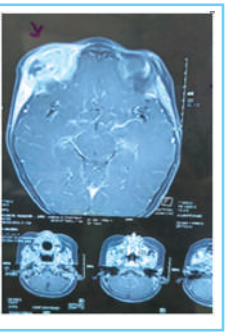
The differential diagnosis of Langerhans cell histiocytosis of bone at the microscopic level includes osteomyelitis and the osseous manifestations of Rosai- Dorfman disease.



One year old female child presented withfeverandsudden onset orbital and frontotemporal swelling in the right side for 15 to 20days. The swelling was painful and rapidly increasing in size.
On examination, no other swelling was present in the body. Hepatosplenomegaly was not detected.
Routine blood examination was within normal limits.

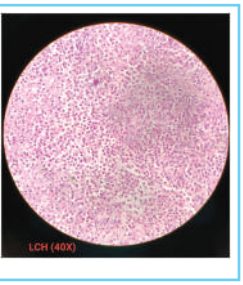


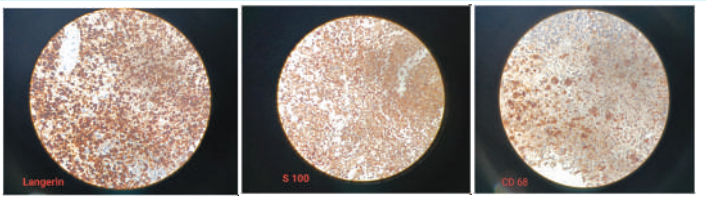
Radiology: MRI showed a lobulated heterogeneously enhancing lesion in the right frontal and periorbital region with bone destruction, intracranial epidural extension and intraorbital extracaval involvement. No obvious parenchymal lesion is noted in brain.



Section shows numerous "Langerhans cells" having folded or indented nuclei, fine nuclear chromatin, inconspicuous nucleoli, moderate amount of slightly eosinophilic cytoplasm. Plenty of eosinophils, neutrophils and histiocytes are seen in the background.

BIOPSY FROM THE LESION (H & E STAIN) : 40 X





IMMUNOHISTOCHEMISTRY shows
I. LANGERIN: POSITIVE (strong and diffuse)
II.S100: POSITIVE (strong and diffuse)
III.CD68: POSITIVE (patchy)

Flash Radiotherapy: An Innovative Advancement in Radiation Oncology

Atanu Kumar
Physicist, ***Dept. of Medical Physics,***

Radiotherapy has long been a critical weapon in the fight against cancer. Since the discovery of X-rays in 1895, ionizing radiation has been employed in cancer treatment for over 120 years, benefitting countless patients.With thecontinuous advancement of modern radiotherapy technology, new radiotherapy methods such as intensity modulated radiation therapy, helical tomotherapy and proton therapy have gradually emerged.Although these emerging radiation modalities can relieve radiation induced toxicity to a certain extent, the therapeutic effect is still relatively limited.FLASH-radiotherapy is another innovative radiotherapy technique that can achieve ultra-high dose rate (UHDR) with a mean dose rate greater than 40 Gy/s within a delivery time of less than 200 mS. A significant number of preclinical studies have proven the effectiveness ofFLASH RT, which reduces the toxicity to normal tissue while achieving comparabletumour control efficacy to conventional radiotherapy.This innovative method promises to deliver radiation doses with unprecedented speed and precision, potentially reducing side effects and improving patient outcomes.

The Fundamental Concept

Flash radiotherapy funda-mentally differs from conventional radiation treatments by delivering an entire radiation dose in less than a second - typically in milliseconds contrasting with traditional radiotherapy which administers radiation over several minutes. So,the key distinction lies in the ultra-rapid dose delivery. This dramatic reduction in treatment time can have significant implications for patient care and treatment effectiveness.

Scientific Mechanisms

The biological mechanisms behind flash radiotherapy's potential advantages are still being researched, but early studies suggest several promising hypotheses. The extremely rapid dose delivery appears to exploit differences in how healthy and cancerous tissues respond to radiation.

Basically, the principle of flash radiotherapy is constructed upon an effect known as the 'flash effect'. Early experimental outcom-esuggests that when exposed at ultra-high dose rates, tissues differ in their behaviour towards the radiation. Tumour cells are highly susceptible to lethal damage caused by radiation, on the other hand, normal cells present an apparent mechanism of protection, thus reducing toxicity.

It has been observed for long time that oxygen can enhance radiation damage to the cell. It can increase the radiosensitivity of cell by a factor of 2.5 to 3 where environment changes from hypoxic to aerobic. There are several hypotheses trying to explain the flash effect. Among them the most prominent and testable one is the 'Oxygen Depletion Hypothesis'. Thisessentially suggests that at ultra high dose rates, there is a fast and profound depletion of oxygen unlike conventional dose rateswhere the fast resupply of oxygen from nearby blood capillaries does not result in this steep depletion of oxygen, henceproviding the advantage of normal tissue protection. In case of tumours which arepresumed to beless oxygenated, the difference is less pronounced and therefore the tumour control is maintained.

Technological Requirements

Implementing flash radiotherapy demands sophisticated technological infrastructure. Specialized linear accelerators capable of delivering extremely high dose rates are essential. These machines must:

- Generate ultra-high radiation doses
- Maintain pinpoint accuracy
- Provide real-time imaging and tracking
- Ensure patient safety during millisecond-level treatments

Current research focuses on developing more robust and precise delivery systems that can consistently meet these demanding specifications. Various platforms for FLASH RThave been demonstrated by using electrons generated by linear accelerator, X-rays generated in a synchroton facility, protons using an isochronous cyclotron and a synchrotron, as well as helium and carbon ions generated using asynchroton.

Clinical Applications and Potential

Initial research has shown promising results across multiple cancer types, with particular potential in:

Brain tumors,Pediatric cancers, tumors in the vicinity of radiosensitive critical structures, andchallenging anatomical locations.

Early clinical trials have demon-strated remarkable outcomes, including:

- Reduced inflammation in surrounding tissues
- Decreased long-term tissue damage
- Potentially shorter overall treatment protocols
- Enhanced patient tolerance

Challenges and Limitations

Despite its potential, flash radiotherapy is not without challenges. Critical considerations include:

- Limited long-term clinical data
- Complex technological requirements
- High initial equipment costs
- Need for specialized training
- Uncertainty about optimal protocols for different cancer types

Current Research Landscape

Multiple research institutions worldwide are actively investigating flashradiotherapy. Those institutions are conducting comprehensive studies to understand the technique's full potential, refine delivery methods and establish standardized protocols.

Dosimetry

The success of FLASH-RT broadly depends upon the implementation of accurate dosimetry system.There are not yet validated and standardized protocols for UHDR(Ultra High Dose Rate) beam dosimetry for FLASH-RT as detectors for dosimetry and beam monitoring have not been fully established. However,a joint Task Group (TG-359) has been recently formed by the AAPM(American Association of Physicists in Medicine)to review the uncertainty in determining the dose and need for standardization in dosimetry for FLASH beams to be used in experiments, research and potentially in pre-clinical applications.They willassess the suitability of radiation measurement equipment (ion chambers, film, diodes, Faraday cap,TLD/OSLD, Cherenkov dosimeter etc) for FLASH mode.

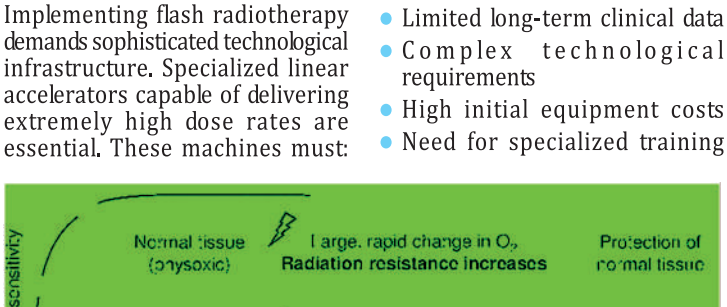
Future Outlook

The future of flash radiotherapy looks promising. As technological capabilities advance and more clinical data become available, this technique could become a standard treatment option. Researchers anticipate significant improve-ments in:

- Treatment precision
- Patient comfort
- Recovery times
- Overall cancer management strategies

Conclusion

Flash radiotherapy represents a paradigm shift in cancer treatment, offering the potential to deliver effective tumor control with significantly fewer side effects. While challenges remain, ongoing research and technological innovations are paving the way for its broader adoption. As this revolutionary approach transitions from the laboratory to the clinic, it holds the promise of transforming oncology and improving outcomes for countless cancer patients worldwide.



Primary Low Grade Conjunctival Follicular Lymphoma (Adult-Type) Mimicking Nodular Anterior Scleritis in a Child with Arthrogryposis: A Case Report

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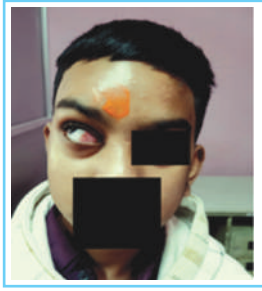
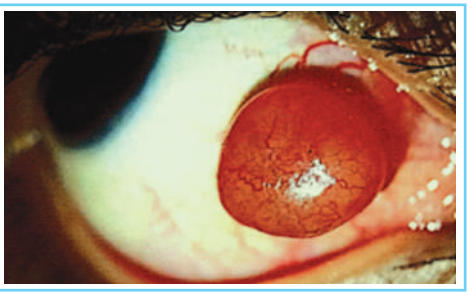
Non-Hodgkin lymphoma (NHL) are malignant lymphoid tumours arising as clonal proliferations of either B or T-lymphocytes, or less commonly NK cells. Periocular lymphoma represents only 2% of all extra nodal sites, with primary conjunctival lymphomas accounting for 25-30% of all lymphomas in this region with male predominance.





CASE REPORT:

A 11-year-old boy, a known case of Arthrogryposis, torticollis, metopic craniosynostosis, fifth toe nail hypoplasia with mild dysmorphism presented to an Eye Specialist with complained of redness, mild discomfort and progressive fleshy swelling over the medial canthus of the right eye for last five months.

Due to protracted symptoms and prolonged history, he was treated

as nodular anterior scleritis with Steroid, anti-inflammatory and antibiotic eye drops. As symptoms failed to improve an excisional biopsy of the right conjunctival lesion was performed.

HPE s/o ill-defined nodule composed of small to intermediate size lymphoid cells having dispersed nuclear chromatin and irregular nuclear margin admixed with few centroblastic cells (2-4/HPF). On IHC, CD 20 & PAX5 positive lymphoid cells, expressing BCL 2, BCL 6, CD 23, IgM &IgD. Negative for CD5, CD 10 & Cyclin D1, CD 3 & CD 5 marked background T Lymphoid cells. Ki67 index is about 8-10%:

Classic Follicular Lymphoma, WHO Grade 1-2.

Once the patient was referred to our centre, routine blood investigations and staging work up was done. Whole Body PET CT scan revealed, no metabolically active residual lesions at the surgical site or elsewhere in right eye or anywhere in the body. Contrast Enhanced MRI Brain & Orbit suggested no abnormality. No involvement of Bone marrow in aspiration and biopsy report.

In view of Unilateral localized completely resected disease without any systemic involvement,he was kept on watchful surveillance, as review of literature also supported this approach.

Discussion

Conjunctival lymphoma has been classically described as a painless, nodular lesion with salmon-pink or fleshy patches at the fornix or bulbar conjunctiva. Patients can be asymptomatic or can suffer ocular irritation with redness. The indolent course of the disease often results in delay in diagnosis. Studies have reported conjunctival lymphomas masquerading as chronic follicular conjunctivitis and scleritis. Therefore, lymphoma should be considered in the case of an atypical presentation of conjunctivitis or scleritis that does not respond to antibiotic and anti-inflammatory therapy. In such cases, a conjunctival excisional biopsy should be performed.

Up to 20% of patients with primary conjunctival lymphoma will develop systemic disease, although this may be months, or even years later. Clinical clues to the presence or future risk of systemic lymphoma in patients with conjunctival disease include location of the tumour (fornix or mid-bulbar conjunctiva higher risk) and increasing number of discrete tumours.

2 types of low-grade B-cell NHL arising in the conjunctiva, include extranodal marginal B-cell lymphoma (EMZL)and follicular lymphoma (FL), while the two high-grade types are diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma(MCL).Conjunctival EMZL spreading down the nasal cavity to the lacrimal sac is reported. This is an indication for imaging, particularly in patients who report nasal congestion, difficulty breathing or epiphora. Lymphoma of the ocular adnexae (LOA) is very rare in children.

Histopathologically, such lesions can be RLH, EMZL, or FL.

The distinction between RLH and FL usually requires a combination of light microscopy, IHC, and gene rearrangement studies. The follicles in RLH vary in size and shape and are widely separated.

In FL, the follicles tend to be more closely packed together and are similar in size and shape, with absent intervening mantle zones compared with RLH.The general IHC profile of positivity is similar for RLH and FL except for BCL-2, which is present in B cells in the follicles of FL but not RLH. Additional

Table 1. Differences in morphological and clinical features with outcomes between pediatric type follicular lymphoma and usual (conventional) follicular lymphoma.

Feature	Pediatric-type follicular lymphoma	Usual follicular lymphoma
Age	Majority under 25 years old	Rarely in those aged <30 years
Sex	Male predominance (male:female of 10:1)	Equal male and female incidence
Stage at presentation	Localized disease (stage I/II)	Majority present with advanced stage
Extra-nodal involvement	Rare, and its presence clouds the diagnosis	Commonly present, especially in the bone marrow
Microscopic features	Aggregates of atypical blastoid cells in a follicular pattern with a starry sky pattern	Various degrees of centrocytes and centroblasts
Immunophenotypic and cytogenetic	Lack of *BCL2* expression and absence of *BCL2* and *BCL6* rearrangement	Strong expression of *BCL2* in addition to other B-cell antigens t(14;18) present in 85% of the cases *BCL6* rearrangement present in 15% of the cases
Genetic profile	Lack of mutations in epigenetic modifier genes *MAP2K1* and *IRF8* mutation	Presence of mutations in epigenetic modifier genes at considerable frequencies
Outcome and prognosis	Curable disease with favorable outcomes and negligible risk of relapse	Relapsing-remitting disease

studies such as PCR studies for immunoglobulin gene rearrangement are usually necessary to confirm the presence of a monoclonal population that favors a diagnosis of FL, especially in children, where FL is often BCL-2 negative.

FL typically demonstrates densely packed multinodular follicles. The follicular population (centrocytes, centroblasts and immunoblasts) are uniformly atypical. Prognosis worsens with greater proportion of centroblasts/HPF.

The tissue contains IgA, IgD and IgM expressing CD20+ B cells, macrophages, CD21+& CD23+ follicular dendritic cells, as well as some CD3+ T cells in the surrounding areas. The CD21 and CD23 positivity highlighted the presence of an expanded follicular dendritic cell meshwork.

A Pediatric type of conjunctival follicular lymphoma has also been reported, though very rare. Pediatric type follicular lymphoma can be differentiated from adult type, as described in the table 1.

The management of conjunctival lymphoma is varied and tailored to the type of lymphoma, degree of dissemination and patien-tspecific factors. Management options include wait & watch, regional radiotherapy, chemotherapy and targeted therapies.

The mainstay of treatment in localized high grade conjunctival disease is with EBRT. Intralesional injections of interferon alpha-2b have also been reported. Alternatively, some studies demonstrated spontaneous regression of low-grade conjunctival lymphomas. Watchful waiting remains an option, as low-grade conjunctival lymphomas rarely metastasize. Chemotherapy is indicated with systemic involvement. A recent case series with paediatric follicular lymphoma suggested that in patients who are candidates for complete tumor excision, observation alone after excision can result in a good outcome.

The prognosis of LOA is determined by the grade of histology, TNM stage, and age of the patient. Conjunctival lymphoma has a good prognosis, with a 66% 5-year PFS and a 76% 5-year OS.

Conclusions

A case of follicular lymphoma in a paediatric patient is documented in this report. Follicular lymphoma of theconjunctiva in the paediatrics age group is rare and could be easily mistaken for a morecommon entity such as RLH. High suspicion of such tumors in children iswarranted to provide necessary early treatment. Failing to do so will have a detrimental effect on themorbidity and mortality of the child.

Global Progress in Research Driven Cancer Care in 2024 and Way Forward

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Cancer incidence is expected to rise significantly particularly in lower and middle income countries but the pace of bringing novel technologies to patients is uneven in different countries due to differences in testing rates, adoption of research driven therapies and lack of infrastructure to deliver advanced therapies.

In 2024, the U.S. Food and Drug Administration (FDA) hasmore than 50 approvals for cancer indications for patients with different cancers. These includeLifileucel, the first tumor-infiltrating lymphocyte-based cellular immunotherapeutic for patients with advanced melanoma; Tarlatamab-dlle, a new bispecific T-cell engager for the treatment of small cell lung cancer that simultaneously binds the DLL3 protein on cancer cells and the CD3 protein on T cells; Nogapendekin alfa inbakicept-pmln, the first IL-15 receptor agonistfor BCG-unresponsive non-muscle invasive bladder cancer ; Imetelstat, the first direct inhibitor of telomerase; Afamitresgene autoleucel, the first T-cell receptor gene therapy for synovial sarcoma; Denileukindiftitox , the first toxin fusion protein to target IL-2; Zolbetuximab-clzb , the first claudin 18.2-targeting therapy ; Revumenib, the first menin inhibitor; Zanidatamab-hrii, the first HER2-targeting bispecific antibody targeting treatment for biliary tract cancer; Tovorafenib, for the treatment of children with relapsed or refractory pediatric low-grade glioma harboring the BRAF fusion or rearrangement or BRAF V600 mutation; Repotrectinib, for the treatment of children with solid tumors having NTRK gene fusion alteration, and Eflornithine to reduce the risk of relapse in high-risk neuroblastoma, to name a few. Other approvals include several AI-based tools, molecularly targeted therapeutics and immuno-therapeutics and imaging agents as well as Invitae, a blood based panel for 47 genes linked to hereditary cancer; Shield, a liquid biopsy test for the early detection of colorectal cancer. Many emerging issues gotaddressedin 2024 in areas such as- developing targeted therapies for sarcomas utilizing sequencing?based reclas-sification, predicting treatment response via gut microbiome, overcoming ovarian cancer's resistance to immunotherapy, overcoming resistance to fibroblast growth factor receptor 2 (FGFR2) inhibitors in biliary tract cancers,extra-chromosomal DNA (ecDNA) in treatment resistance, antibody drug conjugates including design of IgA antibodies to target driver genes like KRAS,NK cell based vaccines, turn Tregs against solid tumors, bacteria-based delivery system for oncolytic viruses, use of "mini-colons" to examine cancer initiation, understanding molecular differences in Hodgkin lymphomas between young adults compared with over 60 to design precision medicine ,etc. Apart from personalized neoantigen cancer vaccines showing promise in clinical trial (for head and neck squamous cell carcinoma and pancreatic cancer), 2024 also seen"Cancer Vaccine Launch Pad" initiative that expect mRNA based cancer vaccine trial to be completed by 2027, whereas Russia already confirmed vaccines being available from 2025.Recent cutting edge developments also include urine tests to detect cancer. completion of INTERLACE trial showing a short course of chemotherapy before standard treatment reduced the risk of death and relapsein cervical cancer, proteomic based test to screen 18 early stage cancers, drug (Anastrozole) in prevention of breast cancer, algorithm (Sybil) to forecast lung cancer risk from low-dose CT scanand machine-learning algorithm to identify a small set of extracellular vesicle proteins to detect early-stage pancreatic, ovarian, and bladder cancers.

India has also joined the stride with homegrown CAR-T cell therapy,completing 10,000 genome' project and building India's first of its kind cancer genomic databaseand development of pro-oxidant drugs with resveratrol and copper to prevent metastasis in present year.It is to be observed how the upcoming R&D initiatives show translational benefit aimed to better patient care in 2025.

Reference: www.aacr.org

Is Oral Cancer the next Ticking Timebomb in Women?

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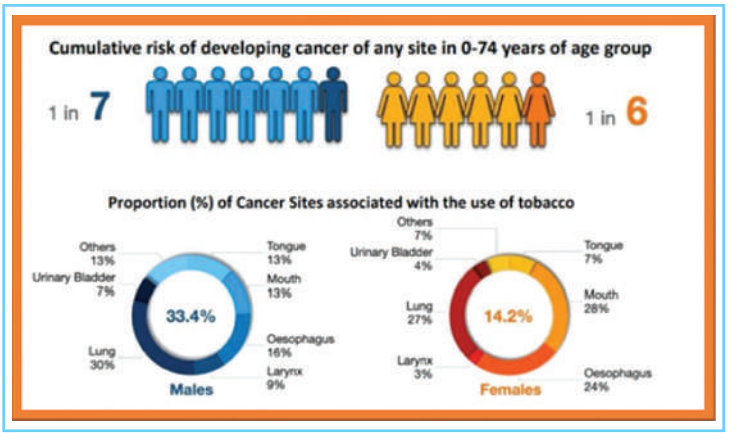
"Cancer is not a concentration camp, but it shares the quality of annihilation: it negates the possibility of life outside and beyond itself; it subsumes all living. The daily life of a patient becomes so intensely preoccupied with his or her illness that the world fades away." - a famous quote by bestselling author Siddhartha Mukherjee from his book The Emperor of all Maladies, reiterates the dark truth of a disease which burdens an affected individual and their family with financial, social and psychological implications.

In India, Head and Neck Cancers (HNC) contribute up to 3.9% of all new cancer cases and 3.7% of the total cancer deaths that occur in this country. As per recent statistics, India has still managed to retain its crown for contributing the highest number of Head and neck cancers (60%) worldwide.

The National Cancer Registry Program report of 2021-22, states that the highest relative proportion of tobacco related cancers was seen among 33.4% males and 14.2% in females. But it also highlights a fact which can be quite disturbing for the foreseeable future. It says that 1 in every 6 Indian women have the cumulative risk of developing cancer of any site between ages 0-74 along with an increasing trend of developing oral cancers of up to 35%, in contrast to 26% in males.



Courtesy: NCDIR 2021-22 Annual Report

Radiology: MRI showed a lobulated heterog-eneously enhancing lesion in the right frontal and periorbital region with bone destruction, intracranial epidural extension and intraorbital extracaval involvement. No obvious parenchymal lesion is noted in brain.

Factors causing increased incidence of oral cancer in women -

- The use of tobacco is directly associated with approximately 80% of oral cancers. It has been observed over the last few decades that young adults and women are increasingly getting addicted to and consuming smoked or smokeless tobacco products especially flavored cigarettes, khaini, gutkha and quid.
- In a meta-analysis article named 'The Hierarchy of Oral cancer in India' by Dr. Naik Balachandra, the causes of such behavioral and lifestyle changes were stated to be multifactorial: A) imitation of their peers B) low socio-economic status C) occupational stress D) Illiteracy E) associated with poor oral hygiene F) widespread and unchecked television and print media advertisements. After reviewing 66 years of English literature on oral cancers in India, he stated that at present, the male to female ratio of oral cancer incidences were almost equal at 1:1.
- Smokeless Tobacco especially Gutkha, a cheap and easily available product is being rampantly sold with a misleading narrative and deceptive advertising by the tobacco industry, of it being a safer alternative to smoking; with addicted peers endorsing and justifying the same. An estimated 200 million adults, including women are reportedly addicted to this deadly cocktail of carcinogens, where most consumers are unaware of its cancer-causing effects.
- India has been a part of the WHO Framework Convention on Tobacco Control (WHO FCTC) since February 27, 2005. While the COTPA Act of 2003 is India's primary legislation for tobacco control, it currently has no specific laws to implement Article 5.3 or prevent a child from getting access to a tobacco product. It is notable to state that at present,the Tobacco industry in India is the 2nd largest exporter of tobacco after the Republic of China.

Oral Cancer prevention and control are best achieved by increasing awareness /screening of the general population and early detection. Various government organizations and NGO's such as NCCP, NCRP and NPCDCS are at present focusing on screening, diagnosis, identification and addressing modifiable risk factors, tobacco cessation clinics, referral of pre-cancerous conditions and community level follow up of treated patients.

Cancer is the second most leading cause of death in women worldwide, anteceded only by cardiac disease; unless we act now, the timebomb will surelyimplode and we might soonlose our women and children to this dreadful and unforgiving disease.

CHITTARANJAN NATIONAL CANCER INSTITUTE (KOLKATA)

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