VOLUME 6.0 | NOVEMBER 2024

DR. BHUBANESWAR BOROOAH CANCER INSTITUTE
TATA MEMORIAL CENTRE
DEPARTMENT OF ATOMIC ENERGY, GOVERNMENT OF INDIA

# BBCI EDGE

*A Science Magazine*


## Recent Advances in Oncology

das.drgaurav@gmail.com
bbciacademia@gmail.com
+ 0361 2800500
9957 033 199 / 212
www.bbcionline.org
A. K. Azad Road, Gopinath Nagar
Guwahati - 781016, Assam, India

DR B BOROOAH CANCER INSTITUTE

# ACADEMIC PROGRAMS

- MD Radiation Oncology
- DM Medical Oncology
- MCh Surgical Oncology
- MCh Head & Neck Surgery
- MCh Gynaecological Oncology
- DM Onco-Pathology
- PhD Programme
- PG Fellowship in Medical Oncology
- PG Fellowship in Onco-Pathology
- PG Fellowship in Gynecologic Oncology
- PG Fellowship in Adult Haematolymphoid Malignancy
- PG Fellowship in Head & Neck Oncology
- PG Fellowship in Surgical Oncology
- PG Fellowship in Oral Oncology
- PG Fellowship in Paediatric Oncology
- Merck International Fellowship
- MSc. Radiological Physics
- MSc. Cancer Biology
- MSc. Oncology Nursing
- Post Basic Diploma Oncology Nursing
- Certificate course in Palliative Medicine
- Certificate course in Cancer Epidemiology
- Certificate course in Preventive Oncology
- Masters in Hospital Administration
- Paramedical Courses / Certificate Courses
- Other Short Term Trainee


# BBCI EDGE

*A Science Magazine*

**Dr. Bhubaneswar Borooah Cancer Institute**
Tata Memorial Centre
A Grand-in-Aid Institute of Department of Atomic Energy,
Government of India

**Recent Advances in Oncology**
**Volume 6.0, November, 2024**

*editor-in-chief*
**Dr. Gaurav Das**
Professor, Department of Surgical Oncology
Dr. B. Borooah Cancer Institute, Guwahati

*dtp & design*
**Ph. Surachandra Singha**
SR. UDC
Dr. B. Borooah Cancer Institute, Guwahati

# Foreword

Dr. Bibhuti Bhusan Borthakur
Director
Dr. B. Borooah Cancer Institute

Medical science is a perpetually evolving and advancing science, which I believe is driven by the innate desire of humankind to live longer and to live better. In the process, it has attracted and subsumed numerous scientific and industrial innovations from other fields to suit its own needs, often leading to breakthroughs which were hitherto beyond imagination. In the absence of a check, this frenzy of inventions and innovations could easily reduce the status of a human to that of a lab animal. Happily, this check comes from the medical community, in the form of a culture to base clinical practices on a stringent framework of evidence which is derived from high fidelity clinical data, a culture which is religiously followed *sans* boundaries. The outcome is a harmonized ecosystem conducive to the growth of scientific and ethical medical practices.

I am very happy to introduce the reader to this issue of BBCI-EDGE, wherein the Editorial team has very effectively compiled articles showcasing medical technologies, some of which are truly mind boggling, along with recent advances in medical science and therapeutics. Importantly, the authors have presented an amalgamation of their own experiences with current knowledge on the subject. I am happy to note that a scaffold of evidence and ethics firmly supporting their work is readily perceptible, importantly because much of the work has been done at Dr B Borooah Cancer Institute. They are also pointers to the endeavors of the Institute, while offering a glimpse of the thoughts and aspirations of the authors.

Let me briefly share my own broad overview on the topics covered.

Ultrasound is a basic physical entity which has emerged as a versatile diagnostic and therapeutic tool, owing to phenomenal progress in electronics, software and application of artificial intelligence. It has diversified into multiple tracts, one of which is Point of Care Ultrasound (POCUS). This set of applications has been strengthened by assessment tools created from the parameters which have been extracted from repeated observations, based on their reliability and reproducibility. One such tool is VExUS, useful for the effective management of fluid balance in the critically ill patient.

Indocyanine Green (ICG) is a fluorescent compound which exhibits brilliance under infrared light. It is being increasingly used by surgical oncologists for intraoperative mapping of lymphatics, which is helpful both for removal of implicated nodes and conservation of the lymphatic basin. It has added precision to intraoperative staging and R0 resections.

Artificial Intelligence (AI) is creeping into almost every space, so also into oncology. Evidence based medicine together with

the huge body of robust data emerging from research, is creating an attractive ground for AI applications into clinical decision making. "Navya", a platform created by the National Cancer Grid for second opinion, creates AI driven clinical opinions which are subsequently vetted by domain experts. In the past few years it has helped many patients from across India with reliable opinion and guidance. AI opens up infinite possibilities awaiting to be explored.

Recent advances in understanding cell biology and cellular mechanisms have helped develop diagnostic tools based on molecular pathology which are useful for biological characterization of malignant cells and their cohabitants. Targeted therapies and immunotherapy are essentially based on these characteristics. These advances have also helped in effectively handling stem cells for transplant and regeneration, improving the conditions for wound healing, and in the thrilling arena of immunotherapy, to condition the body's own immune system to recognise and neutralize malignant cells. The recent development of indigenous CAR-T cell therapy jointly by Tata Memorial Centre and IIT Bombay has opened the door to an exciting future.

While technology does have a major role in these achievements, it is the committed efforts of surgeons and physicians to continuously improve the delivery of care, through innovative procedures and methods aimed to enhance precision, with tools and resources which may be available to them, trying to overcome obstacles which they experience, and sharing with their peers with brute honesty, which is the quintessential driver of progress in therapeutics. We are also gradually experiencing a gradient towards personalized medicine through regimens which are structured, sequenced or modified according to a person's biological attributes, supported by a growing body of evidence.

Cancer care must remain a continuum - with diagnosis and the bulk of treatment being addressed at specialized centers, whereas less complex care and oft-needed advice is available wherever the patient resides. Telemedicine and remote guidance are helpful, but a deep understanding of the needs of the region and the community is indispensable.

Ultimately, a vision which emerges from the confluence of dreams can be realized through the convergence of contributions of the community.

I take this moment to appreciate Dr Gaurav Das and the Editorial team for this issue of BBCI-EDGE. ■

# The Editorial Team

1. **Dr. Gaurav Das,** MCh (CI WIA). Professor, Surgical Oncology. Convenor GI HPB GU DMG. Lead Surgeon Musculoskeletal and Pediatric DMG, Dr. B. Borooah Cancer Institute. Dy Secretary & website-in-charge, NASO, Editor and website-in-charge, AONEI

2. **Dr. Jyoutishman Saikia,** MCh (AIIMS, New Delhi), Fellowship Breast Oncoplasty (ULHT, UK) and Thoracic Surgery Observership (Barcelona). Assistant Professor, Surgical Oncology, NCI-AIIMS (Jhajjar) and IRCH-AIIMS (New Delhi). Convenor (Thoracic Oncology), Oncology Forum (Delhi)

3. **Dr. Kaberi Kakati,** MS, Fellowship HN Oncology (BBCI), Fellowship Skull Base Surgery (TMH Mumbai), Associate Professor, Head and Neck Surgery. Lead Surgeon, Skull Base Surgery, Dr. B. Borooah Cancer Institute.

4. **Dr. Gautam Sarma**, MD. Associate Professor and in-charge, Radiation Oncology, AIIMS (Guwahati).

5. **Dr. Jyotiman Nath,** MD. Associate Professor, Radiation Oncology. Lead Radiation Oncologist, HN, GI HPB and GU Oncology. Dr. B. Borooah Cancer Institute. Executive member & Treasurer, AONEI

6. **Dr. Deepam Pushpam,** MD, DM (AIIMS, New Delhi). Associate Professor, Medical Oncology (AIIMS, New Delhi)

7. **Dr. Manasa K,** MD, Fellowship (IAP-PHO), Fellowship (BMT). Assistant Professor, Pediatric Hematology-Oncology & Stem Cell Transplant. Dr. B. Borooah Cancer Institute.

# Editorial

**Dr Gaurav Das**

It gives me immense pleasure to bring forward the sixth issue of BBCI EDGE A Science Magazine, an official publication from Dr. Bhubaneswar Borooah Cancer Institute. The journey, which started in 2020, has been gratifying so far. It boasts of a treasure trove of 120 articles in the past five issues. This speaks volume about the high level of participation by academicians who have made concerted efforts towards a successful venture.

The current issue has the theme of "Recent Advances". All the articles have been curated keeping this in mind. The "recentness" has varied connotations including global, national, regional and institutional. I have no doubt that the articles will engage the readership with diverse perspectives.

BBCI EDGE has evolved over time. It needs the support and care of a nurturing team. I am fortunate enough to have with me esteemed oncologists who joined this initiative in the capacity of an editorial team. There is a balanced representation from various specialties and institutions. This has enabled a robust system of critical review of all submitted articles.

I hope BBCI EDGE will see still better days with the enthusiasm of the oncology fraternity. My special thanks go to our Director, Dr. B. B. Borthakur and Deputy Directors, Dr. M. Bhattacharyya (Research), and Dr. Debabrata Barmon (Academics) for their continued support. Mr. Surachandra Ph. is the key person literally making this a beautiful publication with his creative DTP & Designing work.■

## Dr Kaberi Kakati

In the ever-evolving landscape of cancer rare, the convergence of innovation and collaboration stands as a beacon of hope. As we delve into the complexities of oncology, it becomes increasingly clear that the path to conquering cancer is not a solitary one. It is a journey that demands the collective expertise of clinicians, researchers, patients and caregivers.

The recent advancements in surgical and radiation technologies, targeted therapies and immunotherapy have revolutionized the way we approach cancer treatment. These breakthroughs are not just scientific triumphs but also testaments to the power of collaborative research. It is through the sharing of knowledge and resources that such monumental strides have been made.

However, the battle against cancer is far from over. The disease continues to pose significant challenges, with its ability to adapt and resist current treatments. This is where the role of innovation becomes crucial. We must foster an environment where creative solutions are encouraged and unconventional ideas are explored. Moreover, the importance of patient-centered care cannot be overstated. The voices of those who battle cancer must be heard, as their experiences can provide invaluable insights into the effectiveness of treatments and the areas that require more attention. The support networks play a pivotal role in bridging the gap between patients and healthcare providers, ensuring that the care delivered is not only clinically effective but also emotionally supportive.

As we look to the future, the oncology community must continue to embrace the spirit of innovation and collaboration. It is only by working together, across disciplines and borders, that we can hope to unlock the full potential of cancer research and care. In this context, this issue of BBCI EDGE focusing on recent advances in oncology is very apt. Let us unite in our efforts to create a world where cancer no longer signifies an end but marks the beginning of a journey towards healing and resilience. ■

## Dr Jyotiman Nath

*Shaping the Future of Oncological Care and Research in North East India with "BBCI EDGE"*

Greetings to the esteemed readers and contributors of "BBCI EDGE," dedicated to advancing oncological research and treatment. As a radiation oncologist and editor of this prestigious journal, I am delighted to share my vision for its future, with a particular focus on showcasing the remarkable work being done in North East India.

The mission of "BBCI EDGE" is to promote excellence in oncological research and foster collaboration and knowledge exchange among researchers and clinicians worldwide. In pursuit of this mission, I am committed to highlighting the unique contributions of our region, North-East India, to the global oncology community.

North-East India is home to a vibrant and diverse population and a burgeoning healthcare ecosystem that is increasingly recognized for its innovation and resilience. Yet, the oncological landscape in this region remains underrepresented in the broader academic discourse. Through "BBCI EDGE," we have an opportunity to change that narrative by providing a platform to showcase the groundbreaking research, clinical innovations, and community-based initiatives that are shaping the future of cancer care in North East India.

As radiation oncologists, we understand the importance of contextually relevant research and tailored treatment approaches that address the unique needs and challenges of our patients. By featuring studies and initiatives from North East India, "BBCI EDGE" can serve as a catalyst for collaboration and knowledge exchange, facilitating the adoption of best practices and the development of locally relevant solutions to improve cancer outcomes in our region and beyond.

Furthermore, I am committed to leveraging the collective expertise and resources of our global network of contributors to support capacity building and knowledge transfer initiatives in North East India. Whether through collaborative research projects, educational outreach programs, or professional development opportunities for local healthcare professionals, "BBCI EDGE" will actively engage with stakeholders in our region to strengthen oncological research and clinical care capabilities and promote sustainable, equitable access to high-quality cancer services.

In conclusion, the future of "BBCI EDGE" is not only about advancing oncological research but also about amplifying the voices and contributions of North East India to the global oncology community. By embracing collaboration, innovation, and inclusivity, we can elevate the standards of cancer care in our region and inspire positive change that resonates far beyond our borders. Long live 'BBCI EDGE'. ■

## Dr Manasa Kakunje

Oncology is a branch where doctors may sometimes not see favorable outcomes. Still, we continue to strive for better things. At the heart of oncology lies the patient. Advances in treatment must be paralleled by a commitment to holistic, patient-centered care that addresses not only the physical but also the emotional, psychological, and social needs of cancer patients. Palliative care, survivorship programs, and patient-reported outcomes should be integral components of oncology practice. Empowering patients through education and involving them in decision-making processes can significantly improve their quality of life and treatment satisfaction. The complexity of cancer necessitates a multidisciplinary approach, bringing together oncologists, surgeons, radiologists, pathologists, geneticists, and other healthcare professionals. Collaborative efforts are essential for translating research findings into clinical practice, developing comprehensive treatment plans, and advancing our understanding of cancer. Initiatives such as tumor boards and research consortia exemplify the power of teamwork in overcoming the multifaceted challenges of oncology. The journey of oncology is marked by remarkable progress, yet significant challenges remain. As we continue to push the boundaries of science and medicine, the integration of innovative technologies, collaborative efforts, and a steadfast focus on patient-centred care will be paramount. By embracing these principles, we can aspire to transform the cancer care paradigm and ultimately achieve better outcomes for patients.

With this journal we aim to improve collaborative efforts between different oncology branches, the multidisciplinary team as well as policy makers to promote advancements in the field of oncology to facilitate patient-centric approach.

*"To have striven, to have made the effort, to have been true to certain ideals – this alone is worth the struggle."*

– William Osler

# Contents

♦ Review Article

# Recent Advances in Head & Neck Oncology

*Tashnin Rahman*

*Professor, Department of Head & Neck Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

Head and neck surgical oncology is a challenging subspecialty. This branch has witnessed the integration of cutting edge technologies, right from diagnosis to surgical techniques and prognostication. Molecular markers, navigation systems, robotics, endoscopic platforms and altered reality techniques have revolutionized head and neck surgery.

**BIOPSY METHODS :**

There have been incremental gains to our conventional diagnostic methods for lesion visualization and biopsy. The backbone of our diagnostic modalities have been tissue sampling by biopsy. There has been an advent of brush biopsy, as a less invasive method to collect cellular samples. Goodson et al., in their work, demonstrated that the utilization of brush biopsy and liquid-based cytology as supplementary methods for the diagnosis of potentially malignant oral conditions.[1] This has resulted in dependable diagnoses that closely paralleled traditional histopathology assessment. This method allows mass screening and less invasive follow up. Liquid biopsy is another promising area of diagnosis and prognostication. With improving methods of detecting circulating DNA, we have witnessed the evolution of highly precise monitoring, recurrence detection and risk stratification systems, especially in virus based malignancies, like the HPV Positive Oropharyngeal cancer and the EBV based Nasopharyngeal cancers.[2] In a study by Zhang et al., a cohort of 50 patients with NPC stage II-IV, used the SE-iFISH technology for CTC detection before and after chemotherapy. They achieved a 92% CTC detection rate and demonstrated a higher CTC detection in more advanced stages. A decreased CTC count and chromosome 8 aneuploidy in CTC after chemotherapy was associated with tumor response.[3] Parallel to these advances, the evolving field of optical imaging has been used widely in recent times. Advanced optics using chemiluminescence and autofluoresence can accentuate subtle tissue alterations which improves the diagnostic precision and accuracy. In a recent meta-analysis by Moffa et al., showed that both these techniques have high sensitivity and high negative predictive value.[4] Thus, negative results in these modalities can safely rule out the need for invasive biopsy. Similarly, Narrow Band Imaging(NBI), has been extensively used in assessing mucosal lesions in head and neck. It has also been used recently in identifying primary tumour in cases of metastasis from unknown primary.[5]

**IMAGING TECHNOLOGY :**

**Photacoustic Imaging(PAI)** is an exemplary instance of the application of advanced imaging technology in the head and neck arena. PAI integrates ultrasound with laser-induced optical contrast to allow real time acquisition of high resolution images. This can furnish vital information about tumour vascularity and distribution of the blood vessels. Nishio *et al.,* demonstrated the potential of this technology by detecting lymph node metastasis by the synergistic use of PAI with anti-EGFR antibody-dye conjugate.[6] This is a prime example of molecular based imaging in head and neck. Exploring the potential of molecular imaging technologies, antibodies like cetuximab and panitumumab have been labelled with various radionuclides for non invasive imaging, allowing for therapy monitoring and personalized treatment planning.[7,8] The possibility of combining diagnostic and therapeutic potential of these theranostic strategies are currently being explored.

**Metabolomics**, that is, the examination of metabolic changes in the body, has seen newer advances in our field. MR spectroscopy and hyperpolarized MRI have found their use in head and neck diagnostics.[9,10] They allow the detection of shifts in metabolic profiles, thus distinguishing between benign and malignant lesions.

**Nanotechnology** has also been used to enhance the diagnostic yield in head and neck cancers. Engineered nanoparticles can target specific cancer markers, which allows early detection. These materials (phospholipid nanomicelles, gold nanoparticles, etc.) improve head and neck imaging by providing better contrast and enabling optical image guided surgery.[11]

**SURGICAL ADVANCES :**

**Exoscopic surgery** represents a new leap in scientific and technological advances in the surgical arena. This employs high definition cameras combined with advanced optics to offer magnified visualization of the surgical field in minimally invasive procedures.[12] Aided by 3D visualization, exoscopic systems allow the surgeons to access anatomically difficult areas with greater ease and accuracy. This reduces extensive tissue dissection and bleeding, which in turn, minimizes the ergonomic strain. Real time sharing of surgical field images also helps in teaching of head and neck trainees.[13] With these numerous advantages and the potential to optimize surgical outcomes, it is poised to play an important role in the future of head and neck surgery. European groups have been testing its applicability in oropharyngeal surgeries, where robot was the mainstay till date.[14]

**Augmented Reality(AR)**: By combining enhanced visualization with high precision, it has a tremendous potential in skull base surgeries. This approach provides the surgeons with an augmented, three dimensional view of the surgical field.[15] AR improves landmark identification, intraoperative navigation, and surgeon experience in trans-sphenoidal surgery, enhancing accuracy and efficiency. Moreover, AR technology enriches educational opportunities for students and trainees, providing immersive, practical learning experiences, as demonstrated in a recent study by Weeks et al.[16]

**MARGIN ASSESSMENT :**

A successful surgery is determined by the adequacy of the margins. In this regard, there have been attempts to leave no stone unturned to determine adequate and safe margins. Ravin et al, in their metaanalysis showed the efficacy of AB-dye conjugate imaging in achieving remarkable specificity and accuracy in tumor location and resection.[17] This technique utilized indocyanin dye in conjunction with fluorescence based imaging to facilitate precise delineation of tumours and improving margin safety. In line with this, De Wit et al.,[18] recently published the results of a Phase II trial focusing on EGFR-targeted fluorescence molecular imaging for intraoperative margin assessment in oral cancer patients. Their findings revealed100% sensitivity in detecting tumor-positive margins along with specificity of 85.9%, potentially paving the way for more precise tumor resection with reduced incidence of positive margins.

**RECENT TECHNOLOGY AT BBCI :**

1. **The Zeiss TIVATO 700 operating microscope *(Fig 1)*:** It offers significant benefits for head and neck surgery and microvascular reconstruction, enhancing surgical precision and outcomes. The Zeiss TIVATO 700's high-quality optics and 4K resolution provide practical and clear visualisation of delicate anatomical structures, crucial for intricate head and neck surgeries. It also allows stepless magnification and integration with fluoroscopy imaging.

2. **Luminis CO2 Laser *(Fig 2)*:** The Lumenis Carbon Dioxide (CO2) laser, specifically designed for use in head and neck oncologic surgery, offers several distinct features that enhance its utility and performance. It is equipped with AccuPulse Technology, SuperPulse Mode, AcuBlade Scanning Micromanipulator, etc. It has enabled transoral laser procedure in early carcinoma glottis cases.

3. **4k Endoscopic system(Karl Storz):** Equipped with 4k camera, monitor and recording devices, it has enabled anterior skull based and endoscopic sinus surgery procedures.

4. **Micromotor Drill System (Medtronics/Stryker):** This allows precise drilling in crucial areas in anterior skull base surgery for tumor removal and access.

5. **Temporal bone drilling system (Stryker):** Exclusively designed for lateral skull base procedures. We have been using it in lateral temporal bone resection.

6. Microdebrider syste, for sinonasal surgeries (Medtronics)

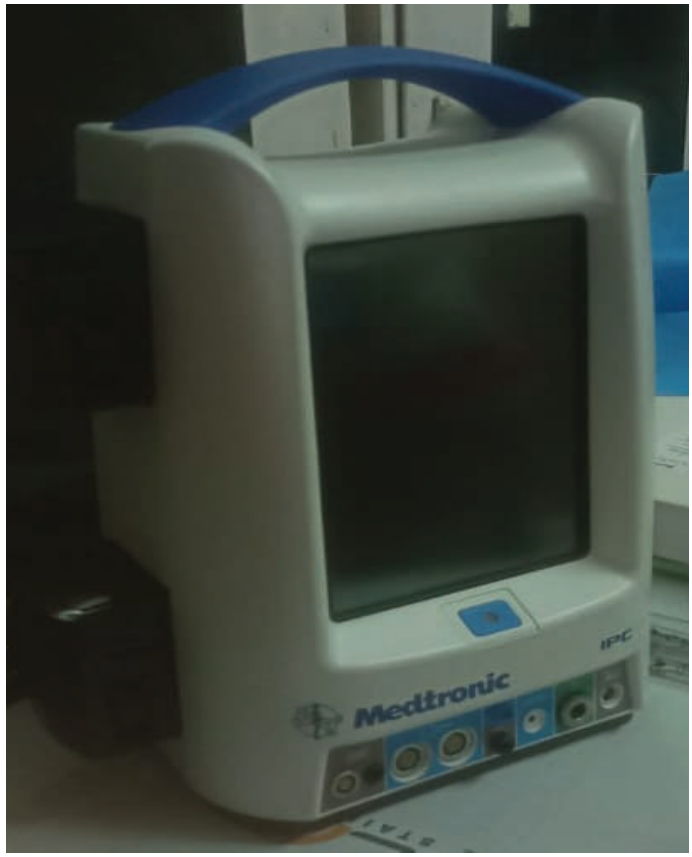
7. SPY-PHI System for ICG Angiography for parathyroid detection and vascularity.

Looking ahead, we would also like to integrate other modalities, including intraoperative nerve monitoring, robotic surgeries and image guided navigation system in out armamentarium in recent future. ■

*Figure 1*

*Figure 2*

*Micromotor drill system*




*Microdebrider*

**REFERENCES :**


1. *Goodson ML, Smith DR, Thomson PJ. Efficacy of oral brush biopsy inpotentially malignant disorder management. J Oral Pathol Med.2017;46(10):896-901.*
2. *Cabezas-Camarero S, Pérez-Segura P. Liquid Biopsy in Head and Neck Cancer: Current Evidence and Future Perspective on Squamous Cell, Salivary Gland, Paranasal Sinus and Nasopharyngeal Cancers. Cancers (Basel). 2022 Jun 9;14(12):2858. doi: 10.3390/cancers14122858. PMID: 35740523; PMCID: PMC9221064.*
3. *Zhang J., Shi H., Jiang T., Liu Z., Lin P.P., Chen N. Circulating tumor cells with karyotyping as a novel biomarker for diagnosis and treatment of nasopharyngeal carcinoma. BMC Cancer. 2018;18:1133. doi: 10.1186/s12885-018-5034-x.*
4. *Moffa A, Giorgi L, Costantino A, et al. Accuracy of autofluorescenceand chemiluminescence in the diagnosis of oral dysplasia andcarcinoma: a systematic review and meta-analysis. Oral Oncol.2021;121:1.*
5. *Di Maio P, Iocca O, De Virgilio A, et al. Narrow band imaging in head and neck unknown primary carcinoma: a systematic review and meta-analysis. Laryngoscope. 2020;130(7):1692-170*
6. *Nishio N, van den Berg NS, Martin BA, et al. Photoacousticmolecular imaging for the identification in head and neck cancer using an anti-EGFR antibody-dye conjugate.J Nucl Med. 2021;62(5):648-655.*
7. *Even AJG, Hamming-Vrieze O, van Elmpt W, et al. Quantitative assessment of Zirconium-89 labeled cetuximab using PET/CT imaging in patients with advanced head and neck cancer: a theragnostic approach. Oncotarget. 2017;8(3):3870-3880.*
8. *Wu J, Yuan Y, Tao XF. Targeted molecular imaging of head and neck squamous cell carcinoma: a window into precision medicine. ChinMed J. 2020;133(11):1325-1336.*
9. *Fujima N, Carlota Andreu-Arasa V, Barest GD, Srinivasan A, Sakai O. Magnetic resonance spectroscopy of the head and neck. Neuroimaging Clin N Am. 2020;30(3):283-293.*
10. *Mignion L, Acciardo S, Gourgue F, et al. Metabolic imaging usinghyperpolarized pyruvate-lactate exchange assesses response orresistance to the EGFR inhibitor cetuximab in patient-derivedHNSCC xenografts. Clin Cancer Res. 2020;26(8):1932-194.*
11. *Ruiz-Pulido G, Medina DI, Barani M, et al. Nanomaterials for thediagnosis and treatment of head and neck cancers: a review. Materials. 2021;14(13):3706.*
12. *Paderno A, Deganello A, Lancini D, Piazza C. Is the exoscope readyto replace the operative microscope in transoral surgery? Curr OpinOtolaryngol Head Neck Surg. 2022;30(2):79-86.*
13. *Rose AS, Kim H, Fuchs H, Frahm JM. Development of augmented-reality applications in otolaryngology-head and neck surgery.Laryngoscope. 2019;129(suppl 3):S1-S11.*
14. *Crosetti E, Arrigoni G, Manca A, Caracciolo A, Bertotto I, Succo G. 3D Exoscopic Surgery (3Des) for Transoral Oropharyngectomy. Front Oncol. 2020 Jan 31;10:16. doi: 10.3389/fonc.2020.00016. PMID: 32082996; PMCID: PMC7006030.*
15. *Thavarajasingam SG, Vardanyan R, Arjomandi Rad A, et al. The use of augmented reality in transsphenoidal surgery: a systematic review. Br J Neurosurg. 2022;36(4):457-47.*
16. *Weeks JK, Pakpoor J, Park BJ, et al. Harnessing augmented reality and CT to teach first-year medical students head and neck anatomy.Acad Radiol. 2021;28(6):871-87.*
17. *De Ravin E, Venkatesh S, Harmsen S, et al. Indocyanine greenfluorescence-guided surgery in head and neck cancer: a systematic review. Am J Otolaryngol. 2022;43(5):103570.*
18. *de Wit JG, Vonk J, Voskuil FJ, et al. EGFR-targeted fluorescencemolecular imaging for intraoperative margin assessment in oralcancer patients: a phase II trial. Nat Commun. 2023;14(1):4952.*

♦ Review Article

# Point of Care Ultrasound in Head and Neck Cancer Upper Airway Obstruction

*Siddhartha Basuroy[1], Kaberi Kakati[2], Sonai Dutta Kakati[3], Anupam Das[4] and Deeksha Sharma[5]*

*[1,5]Senior Resident, [2]Associate Professor, [4]Professor, Department of Head and Neck Oncology, and [3]Associate Professor, Department of Anesthesiology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

Upper airway obstruction is a well-recognized presentation in patients with advanced head and neck cancers.[1] It can be a life-threatening condition that may require an awake tracheostomy to relieve the symptoms.[2] Obstruction can occur anywhere in the upper airway, from the tongue, oropharynx, larynx, hypopharynx, thyroid, or due to other neck masses like lymph nodes.[3] Due to the anatomical location of these tumors, the presentation is often a 'cannot intubate, cannot oxygenate' situation which may require prompt action to secure the airway.[4] Prompt airway management may be a daunting task with potentially life-threatening complications, if not managed adequately.[5]

In a high-volume oncology center, tracheostomy is a relatively common emergency procedure that is done to relieve airway obstruction. However, in the presence of bulky neck nodes, deviated trachea, post-radiation fibrosis, lymphedema, and inability to position the patient adequately; it may lead to difficulty in palpating and localising the trachea.[6] Furthermore, disease related factors like subglottic extension and extra laryngeal extension may distort the airway anatomy , and may complicate tracheostomy tube insertion. As many of these tracheostomies require the securing of the airway very rapidly, any delay in localizing the trachea and subsequent tube insertion may lead to life-threatening complications resulting from hypoxia.

At present, the assessment for tracheostomy is essentially clinical. The availability of pre-tracheostomy cross-sectional imaging can go a long way in the planning and execution of a successful tracheostomy. However, many of these patients present to us without any prior investigation and a compromised upper airway. This can result in a daunting challenge for any head and neck cancer surgeon considering a tracheostomy due to altered airway anatomy, bleeding, and the severity of airway compromise.

Critical care medicine was one of the first disciplines to use the Ultrasonography for vascular and airway access.[7] With the advancements in technology, ultrasonography is now easily an available and portable radiological modality.

**Point of Care Ultrasound (POCUS)** is advanced diagnostic ultrasonography performed and interpreted by the attending physician as a bedside test.[7] In recent times, Sonographic airway assessment, especially in upper airway evaluation has been shown to outperform clinical assessment alone.[8] Airway assessment using POCUS usually focuses on three domains, namely, the anterior neck soft tissue thickness domain (TTD), anatomic position domain (APD), and oral space domain (OSD).[9] As far as surgical airway is concerned, anterior neck soft tissue thickness domain may play a major role.[10] Ultrasound measurements of the TTD that have been studied include the distance from skin to epiglottis (DSE), skin to anterior commissure of the vocal cords, skin to vocal cords, skin to thyroid cartilage, and skin to thyrohyoid membrane. [11]

Ultrasound outperforms visual inspection and digital palpation in the identification of the cricothyroid membrane.[12] One prior study demonstrated that ultrasound guidance during cricothyrotomy resulted in a five-fold improvement in correct tube placement among subjects with anatomy that was difficult to palpate.[13]

POCUS has been used as an aid in performing cricothyroidotomy.[14]

It has been suggested that the identification of cricothyroid membrane using a focussed ultrasound helps facilitate a faster and safer airway.[13] Ultrasound-guided cricothyroidotomy has been proven to have fewer periprocedural complications compared to the landmark identification method. Even though no study has attempted to replicate the same for tracheostomy, we expect that POCUS may similarly help us.

We have been using POCUS for rapid airway assessment in anticipated difficult tracheostomies, primarily on an experimental basis. There is no clear evidence about its usage in head and neck cancers. This ongoing prospective study explores the utility, advantages and the safety of POCUS in malignant upper airway obstruction.

The procedure is relatively simple and can be rapidly done after acquiring airway ultrasound assessment training. The learning curve, as per our experience is not extremely steep, given the relatively small area of interest. A linear probe with a frequency of around 10 MHz and a feld of view of 40 mm is adequate for head and neck POCUS. The patient is positioned in supine position. Infrahyoid neck ultrasound is performed in both, transverse and longitudinal views. The POCUS will be focussing on the following parameters:

1. Location of the trachea and midline
2. Estimating the thickness of any abnormal soft tissue overlying the trachea (from skin to anterior surface of trachea)
3. Estimating the level of tracheostomy or tracheal cut, by localising any subglottic disease
4. Location of cricothyroid membrane
5. Identifying any tracheal luminal narrowing or compression
6. Identification of any abnormal vessels Some of the possible applications of POCUS during an anticipated difficult tracheostomy has been summarised in *table 1.*

The interim analysis shows benefit in reducing the time duration and bleeding in anticipated difficult tracheostomies. It can also help us identify abnormal vessels and plan guided tissue biopsy at the same setting. Some of our findings have been depicted in *figures 1 and 2.*

*Table 1 : Hypothesised Utility of POCUS based on our experience*

| Condition | Utility |
|---|---|
| Anterior Neck Masses (Thyroid Malignancies etc.) | • Patency of the tracheal lumen at the planned tracheotomy site<br>• Identify the plane of least dissection<br>• Minimise bleeding |
| Laryngeal diseases with extralaryngeal extension | • Identify any significant tracheal extension<br>• In bilateral abductor cord palsies, to identify the possible etiology and confirm patency of trachea<br>• Plan the level of tracheotomy if there is extralaryngeal extension and the possibility of a total laryngectomy |
| Post Radiation Fibrosis | • To identify and localize the trachea in extensive fibrosis / edema |
| Revision trachostomy | • Identify the plane and to localize the trachea |

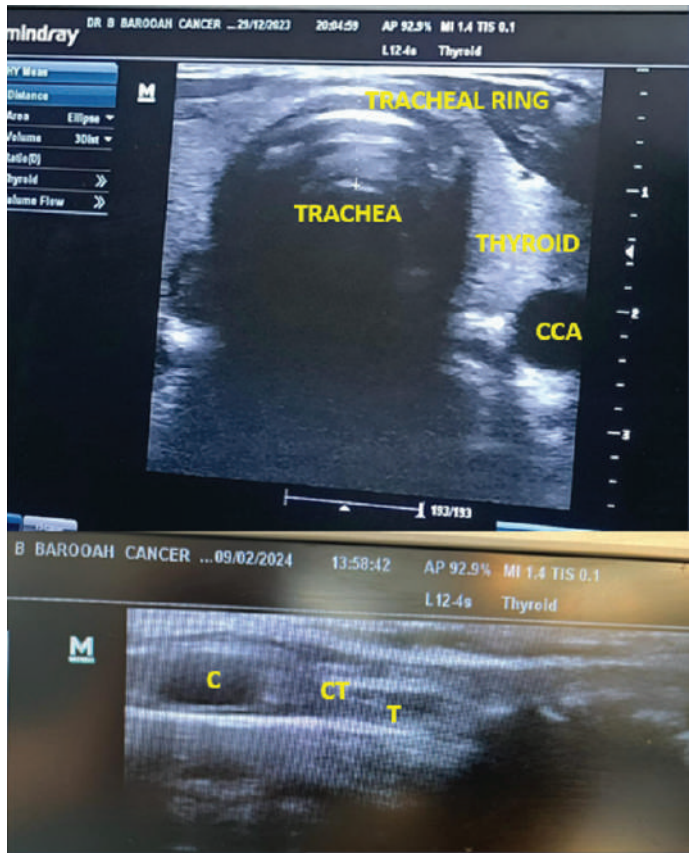



*Figure 1: Normal Sonographic Infrahyoid Anatomy.*

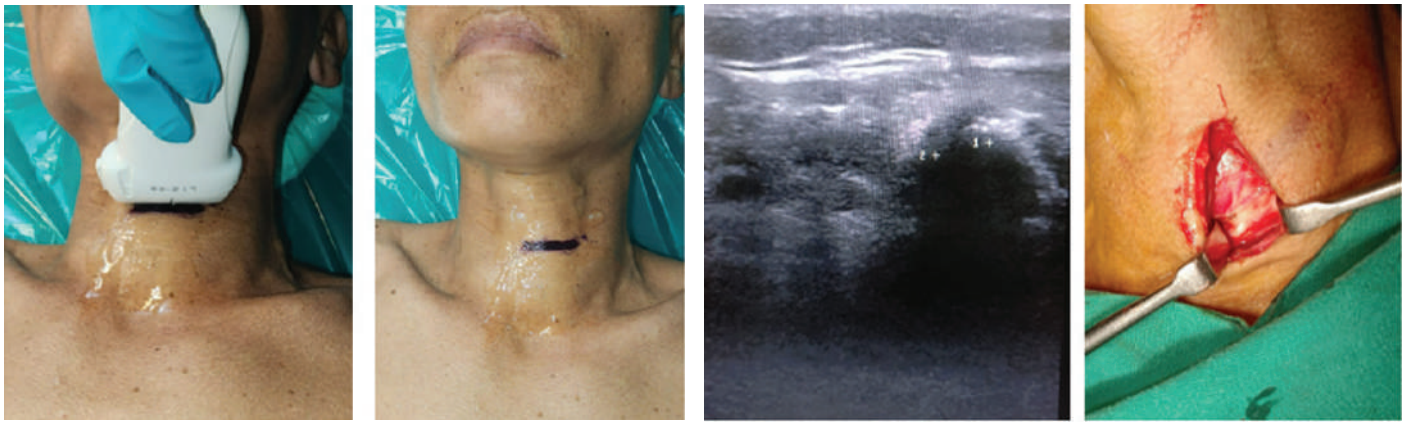


*Figure 2 : POCUS guided tracheostomy in a patient with Anaplastic Carcinoma of Thyroid.*

**REFERENCES:**


1. *Chen, K., Varon, J., & Wenker, O. C. (1998). Malignant Airway Obstruction: Recognition and Management. The Journal of Emergency Medicine, 16(1), 83–92. doi:10.1016/s0736-4679(97)00245-x.*
2. *Sagiv D, Nachalon Y, Mansour J, Glikson E, Alon EE, Yakirevitch A, Bachar G, Wolf M, Primov-Fever A. Awake Tracheostomy: Indications, Complications and Outcome. World J Surg. 2018 Sep;42(9):2792-2799. doi: 10.1007/s00268-018-4578-x. PMID: 29728730.*
3. *Hathiram, Bachi & Rai, Reema & Watve, Parag & Khattar, Vicky. (2010). Tracheostomy in Head and Neck Cancers. Otorhinolaryngology Clinics An International Journal. 2. 53-60. 10.5005/jp-journals-10003-1017.*
4. *Kwon YS, Lee CA, Park S, Ha SO, Sim YS, Baek MS. Incidence and outcomes of cricothyrotomy in the "cannot intubate, cannot oxygenate" situation. Medicine (Baltimore). 2019 Oct;98(42):e17713. doi: 10.1097/MD.0000000000017713. PMID: 31626153; PMCID: PMC6824795.*
5. *Cook TM, Woodall N, Harper J, Benger J, Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth 2011; 106: 632-42.*
6. *Sayoo C, Das AK, Das A, Rahman T, Das RJ, Das K. Redo Tracheostomy: Our Experience, Problems Encountered and How to Overcome Them. Indian J Otolaryngol Head Neck Surg. 2019 Dec;71(4):470-473. doi: 10.1007/s12070-019-01645-7. Epub 2019 Apr 8. PMID: 31750105; PMCID: PMC6838246.*
7. *Moore CL, Copel JA. Point-of-care ultrasonography. N Engl J Med 2011; 364: 749-57.*
8. *Gottlieb, M.; Holladay, D.; Burns, K.M.; Nakitende, D.; Bailitz, J. Ultrasound for airway management: An evidence-based review for the emergency clinician. Am. J. Emerg. Med. 2020, 38, 1007–1013.*
9. *Bhargava, V.; Rockwell, N.A.; Tawfik, D.; Haileselassie, B.; Petrisor, C.; Su, E. Prediction of Difficult Laryngoscopy Using Ultrasound: A Systematic Review and Meta-Analysis. Crit. Care Med. 2023, 51, 117–126.*
10. *Wu, J.; Dong, J.; Ding, Y.; Zheng, J. Role of anterior neck soft tissue quantifications by ultrasound in predicting difficult laryngoscopy. Med. Sci. Monit. 2014, 20, 2343–2350.*
11. *Bhargava V., Rockwell N.A., Tawfik D., Haileselassie B., Petrisor C., Su E. Prediction of Difficult Laryngoscopy Using Ultrasound: A Systematic Review and Meta-Analysis. Crit. Care Med. 2023;51:117–126. doi: 10.1097/CCM.0000000000005711.*
12. *Rai, Y.; You-Ten, E.; Zasso, F.; de Castro, C.; Ye, X.Y.; Siddiqui, N. The role of ultrasound in front-of-neck access for cricothyroid membrane identification: A systematic review. J. Crit. Care 2020, 60, 161–168.*
13. *Siddiqui, N.; Arzola, C.; Friedman, Z.; Guerina, L.; You-Ten, K.E. Ultrasound Improves Cricothyrotomy Success in Cadavers with Poorly Defined Neck Anatomy: A Randomized Control Trial. Anesthesiology 2015, 123, 1033–1041.*
14. *Neusa Lages, Diana Vieira, Joana Dias, Cláudia Antunes, Tiago Jesus, Telmo Santos, Carlos Correia, Ultrasound guided airway access, Brazilian Journal of Anesthesiology (English Edition), Volume 68, Issue 6, 2018, Pages 624-632, ISSN 0104-0014, https://doi.org/10.1016/j.bjane.2018.06.009.*

♦ Review Article

# Future of Personalized Medicine in Head and Neck Cancer

*Kaberi Kakati*

*Associate Professor, Department of Head and Neck Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

Head and Neck Cancer (HNC) ranks as the seventh most common cancer and is responsible for over 660,000 new diagnoses each year.[1] India is recorded as the country with the greatest incidence rates in Southeast Asia, where 80% of all instances of HNC are associated with tobacco consumption along with areca nut. The epidemiology of HNC has recently shown a changing trend with more incidence in younger people which is estimated to reach 30% of annual increase by 2030.[2] Despite advances in treatment, there has been a gradual increase in overall mortality, with five-year survival rates of approximately 40-45%. Current therapies for HNC include a multimodal approach that comprises surgical resection, radiation therapy and/or systemic therapy. Despite the mutational diversity, specific genetic mutations or biomarkers unique to HNC have not been universally identified. Also, unlike some other cancers (where certain mutations guide treatment decisions),HNC lacks a straightforward 'magic bullet'.

Personalised Medicine or Precision Medicine is an exciting frontier in the field of head and neck cancer which stratifies the patient according to the risk or expected response rate to achieve optimal individual treatment decision. Advances in genomics and molecular profiling allow us to tailor therapies based on individual tumor characteristics, ensuring that patients receive treatments optimized for their specific cancer subtype.[3]

**FUTURE PROSPECTS OF PERSONALISED MEDICINE IN HEAD AND NECK CANCER :**

1. Genomic testing/ Tumor sequencing : Human Papilloma Virus (HPV) infection is a known risk factor for HNC, especially oropharyngeal carcinoma. HPV related diagnoses showed detectable ctHPV16DNA.[4] This genetic data can predict that HPV-positive tumors often have a better prognosis and may respond differently to treatment compared to HPV-negative tumors. Epidermal growth factor receptor (EGFR) mutations are also common in HNC.[5] HPV infection has the potential to influence the expression of TMEM16A (11q13 gene amplification), in addition to affecting the EGFR, which has been identified as a possible co-biomarker for HPV positive cancers due to its phosphorylation. Other genetic mutations like PD-L1 expression, HER-2, BRCA-1,2 are also found to have association with HNC and identifying these targets can have implications for treatment, as they may respond differently to certain therapies. The chance of cancer recurrence may also be increased by specific genetic markers.

2. Epigenetic Biomarkers : Epigenetic Biomarkers are specific molecular modifications or patterns in the epigenome that can provide information on the incidence, progression, prognosis, or treatment response of a particular disease. These biomarkers are often used or diagnostic, prognostic, or predictive purposes. Hypermethylation of the DAPK, MGMT,MSP tumor suppressor gene (also known as CDKN2A or INK4a) are well documented in various cancers including HNC.[6] The detection of p16 gene hypermethylation is often used as a biomarker for the early diagnosis and prognosis of HNC.

3. miRNA Players : The miRNAs are tiny molecules, about 19–25 nucleotides long, which are like molecular conductors. They orchestrate gene expression by binding to specific messenger RNAs (mRNAs), either silencing them or fine tuning their activity. These miRNAs can be both heroes and villains. Depending on the context, they might act as cancer suppressors or oncogenes. Their behaviour varies across different cancer types and stages of tumorigenesis. HNC presents a fascinating opportunity to harness benefits of using miRNAs as innovative diagnostic tools. Given the diverse nature of HNC and the critical need for early and accurate detection, miRNAs have been extensively studied as potential aids in cancer detection, treatment prognosis, and evaluating the efficacy of treatments.[7] MiR-21 was first

discovered as a possible oncogenic miRNA in HNC. These OncomiRs are a subset of miRNAs associated with cancer and are linked to processes like carcinogenesis,malignant transformation, and metastasis.[8] Numerous studies have explored the potential of miRNAs as diagnostic indicators, indicating a plausible clinical utility for miRNA signatures specific to HNSCC in bodily fluids. The future of managing HNC holds enormous promise for the inclusion of miRNAs as revolutionary diagnostic tools in customized treatment.

4. Gene Silencing and Editing : These techniques represents potential strategies in comprehending HNC. It involves suppression of specific genes critical to neoplasm growth and identifies therapeutic targets to develop novel treatments. CRISPR/ Cas9 and RNA interference (RNAi) or post-transcriptional gene silencing (PTGS) are novel approaches in this context. CRISPR/Cas9 is a revolutionary gene-editing technology, which aims to specifically target genetic alterations that drive tumor growth. While RNAi or PTGS can provide a temporary knockdown of targeted mRNA, achieving a permanent knockout of the relevant genes is possible via gene editing techniques. Studies have reported positive outcomes have been seen in HR-HPV HNC by employing E6- and/or E7-targeting short hairpin RNAs (shRNA)or small interfering RNAs (siRNAs).[9] Oncogenes E6 and/or E7 have been significantly inhibited by these strategies. By tailoring the RNAi method to target specific genetic alterations present in HNC in individual patients, personalized treatments can be developed. The use of sequence-specific siRNAs or shRNAs against unique molecular targets in the cancer cells of each patient can enhance treatment effectiveness and reduce off-target effects.

5. Stem Cell therapies : Personalized treatment for HNC can be developed based on the identification and understanding of specific markers and downstream pathways associated with cancer stem cells (CSCs) and other therapeutic targets. The presence of specific markers like CD44, Bmi-1, FoxM1, and ALDH in CSCs provides potential targets for therapy.[10] Studies are targeted on creating drugs or therapies that target these markers, aiming to inhibit CSC activity, diminish self-renewal, and potentially sensitize CSCs to alternative treatments or novel therapeutic approaches. Targeting transcription factors like brachyury or SOX2, which play critical roles in regulating CSCs in certain HNCs, can also be investigated to develop targeted therapies that suppress CSC proper ties and enhance sensitivity to chemotherapy or radiotherapy.[11] Also, it has been reported that COX-2 promotes the maintenance of CSCs, and inhibiting this enzyme resulted in decreased expression of CSC-associated genes and reduced sphere formation in hypopharyngeal cancer. Patients with tumors showing elevated COX-2 expression might benefit from COX-2 inhibitors, potentially in combination with other standard therapies.[12]

6. Radiomics and Machine Learning : Radiomics is a method used to define tumor characteristics and involves extracting extensive data from clinical images. The diagnostic prediction of radiomics in HNSCC includes pathological subtypes, pre-treatment staging, tumor differentiation from inflammation or necrosis, tumor status prediction after treatments and early recurrences. Various prediction models/ nomogram have been esigned by combining the radiomics and Machine Learning (ML) to predict tumor aggressiveness and hold promise as an additional non-invasive diagnostic tool for HNC pre-treatment. This aids in tailoring and delivering precision treatment.[13]

**CONCLUSION :**

Personalized medicine has the potential to revolutionize the way we think about cancer care. However, a potential challenge to the wide spread adoption of personalized cancer medicine is the cost and this may limit their availability to those who can afford them, leading to a potential inequality in access to care. Nevertheless, personalised Cancer Care is expected to bring significant benefits to cancer patients. ■

**REFERENCES :**


1. *Gormley, M.; Creaney, G.; Schache, A.; Ingarfield, K.; Conway, D.I. Reviewing the Epidemiology of Head and Neck Cancer: Definitions Trends and Risk Factors. Br. Dent. J. 2022, 233, 780–786.*
2. *Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLO BOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.*
3. *Tinhofer I, Braunholz D, Klinghammer K. Preclinical models of head and neck squamous cell carcinoma for a basic understanding of cancer biology and its translation into efficient therapies. Cancers Head Neck. 2020;5(1):9.*
4. *Tanaka H, Suzuki M, Takemoto N, et al. Performance of oral HPV DNA, oral HPV mRNA and circulating tumor HPV DNA in the detection of HPV-related oropharyngeal cancer and cancer of unknown primary. Int J Cancer. 2022;150(1):174-186.*
5. *Dou S, Zhang L, Wang C, et al. EGFR mutation and 11q13 amplification are potential predictive biomarkers for immunotherapy in head and neck squamous cell carcinoma. Front Immunol. 022;13(March): 1-7.*
6. *Yang H, Zhou L, Yang F, Chen J, Wang Y. Prognostic value of O6-methylguanine-DNA methyltransferase hypermethylation and expression in head and neck cancer: a systematic review and meta analysis. edicine. 0033472 2023;102(14):E33472.*
7. *Kabzinski J, Maczynska M, Majsterek I. Microrna as a novel bio marker in the diagnosis of head and neck cancer. Biomolecules. 2021; 11(6):844.*
8. *Chang SS, Jiang WW, Smith I, et al. MicroRNA alterations in head and neck squamous cell carcinoma. Int J Cancer. 2008;123(12):2791 2797.*
9. *Li C, Johnson DE. Liberation of functional p53 by proteasome inhibition in human papilloma virus-positive head and neck squamous cell carcinoma cells promotes apoptosis and cell cycle arrest. Cell Cycle. 2013;12(6):923-934.*
10. *Yu SS, Cirillo N. The molecular markers of cancer stem cells in head and neck tumors. J Cell Physiol. 020;235(1):65-73.*
11. *Shimoda M, Sugiura T, Imajyo I, et al. The T-box transcription factor Brachyury regulates epithelial-mesenchymal transition in association with cancer stem-like cells in adenoid cystic carcinoma cells. MC Cancer. 2012;12(1):1-15.*
12. *Saito S, Ozawa H, Imanishi Y, et al. Cyclooxygenase-2 expression is associated with chemoresistance through cancer stemness property in hypopharyngeal carcinoma. Oncol Lett. 2021;22(1):533.*
13. *Wang H, Song B, Ye N, et al. Machine learning-based multipara metric MRI radiomics for predicting the aggressiveness of papillary thyroid carcinoma. Eur J Radiol. 2020;122:108755.*

♦ Review Article

# Revolutionizing Wound Healing

*Sumanjit S. Boro[1], and Saif Ahmad[2]*

*[1]Associate Professor, and [2]Junior Resident, Department of Reconstructive and Burns Surgery. All India Institute of Medical Sciences, Guwahati*

**INTRODUCTION:**

Wounds are discontinuity in the tissue most commonly epithelium arising due to injury from a variety of causes ranging from trauma, all kinds of surgeries including cancer surgeries, burns, pressure, infection, diabetes and vascular diseases. Often more than one cause is seen. Wounds can be superficial involving epidermis and dermis or deep involving subcutaneous tissues, underlying muscles and bones. Chronic non-healing wounds predispose patients to serious complications and can result in amputations and sepsis. There have been constant advancements in the development of dressing materials for wounds. The underlying objectives are to promote healing as early as possible with minimal to no tissue loss or scarring. Dressing materials should provide moisture, absorb any exudate, provide a barrier to infection while maintaining oxygenation and vascular supply.

**WOUND HEALING PASSES THROUGH FOLLOWING PHASES:**

1. **Hemostasis:**
   Immediately after injury, there is vasoconstriction followed by platelet activation and aggregation. This activates the coagulation cascade leading to formation of fibrin mesh which stabilizes the platelet plug and forms a thrombus. This ultimately leads to cessation of bleeding.

2. **Inflammation:**
   Cytokines released from platelets and local injured tissue cause inflammatory cells like WBCs to start moving towards the area of insult which is aided by increased vascular permeability. Phagocytic cells clear off the area from tissue debris and micro-organisms. Classic signs of inflammation like pain, swelling, surrounding erythema and locally increased temperature are well marked during this phase.

3. **Proliferation:**
   As inflammation settles, there is release of platelet derived growth factor and vascular endothelial growth factor. Fibroblasts migrate to the wound site and proliferate. These fibroblast produce type III collagen, glycosaminoglycan and proteoglycan. New blood vessels and epithelial cells form as a result of local growth factors. Fibroblasts differentiate to myofibroblasts causing wound contraction. All these are components of granulation tissue which functions as rudimentary tissue.

4. **Remodeling:**
   In the final phase there is maturation of previously laid tissues. Type III collagen is replaced by type I collagen and reorganized along the tension lines. The final tensile strength of the wound can reach up-to 80% of the uninjured strength.

**WOUND HEALING AND DEPENDENT FACTORS:**

Generally, wounds in the head and neck region heal faster than in the lower limb. Underlying conditions like diabetes, cardiovascular disease, poor nutrition, steroids, NSAIDs, smoking, chemotherapy, radiotherapy and immunocompromised states are associated with delayed wound healing. Alcohol intake being associated with nutritional deficiency due to poor eating habits and decreased immune response leads to delayed wound healing.

Local factors like hypoxia, vascular compromise, necrotic tissue, infection and foreign body cause delayed wound healing.

**BRIEF OF TYPES OF DRESSING MATERIALS:**

**A) Traditional Dressing:**

History of wound care can be dated back to 2200 BCE in ancient Mesopotamia which suggested that honey, oil, animal fat, wine and vinegar were used in wound care. Use of gauge as a dressing material has been firmly established by 5th century BCE which represented a pure cotton cloth.

**GAUZE:**

They absorb exudates and fluid in the wound bed. They require frequent change and stick to the wound causing trauma and pain when removed. They shed fibers and residue in the wound bed causing foreign body reaction. A subtype of this dressing called "wet to dry bandage" involves application of wet dressing and allowing it to dry in the wound. This has been described as providing mechanical debridement of devitalized tissue and bacteria when removed. However, this has shown higher bacterial contamination, wound disruption due to non-selective debridement and vasoconstriction due to evaporational cooling. Impregnated gauze containing iodine, zinc and bismuth were introduced for their antimicrobial effect.

*Fig. 1: Gauze*

**TULLE DRESSING:**

Tulle dressing is designed to promote healing by providing a moist environment and minimizing trauma on removal. It is made up of fine cotton gauze or mesh impregnated with substances like paraffin, chlorhexidine or other antiseptics. These are not ideal for exudative or infected wounds. Commercially available dressing includes Bactigras, Jelonet and Paratulle. Occasionally they can cause maceration due to excessive moisture retention.

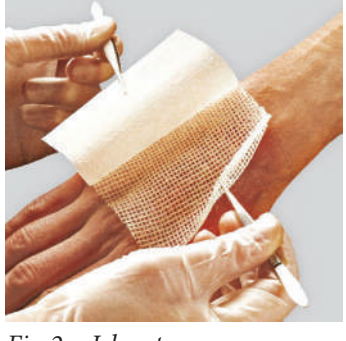


*Fig. 2a: Jelonet*

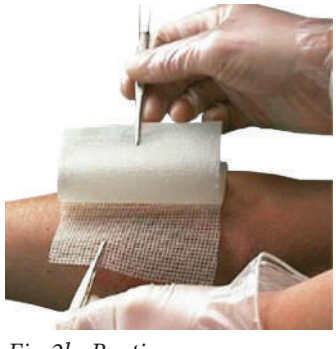


*Fig. 2b: Bactigras*

**TRANSPARENT FILMS:**

These are thin and translucent dressing materials made from polyurethane or other synthetic materials. They provide a moist environment and ensure gaseous exchange while preventing bacterial contamination. Being transparent they allow easy monitoring of the wound. They are easy to adapt and remove causing minimal trauma and pain. Due to their limited absorption capability, they are not suitable for exudative wounds. Commercially available ones include Tegaderm, Opsite, Bioclusive etc. They are suitable for superficial wounds, surgical sites, IV cannula and catheter sites.

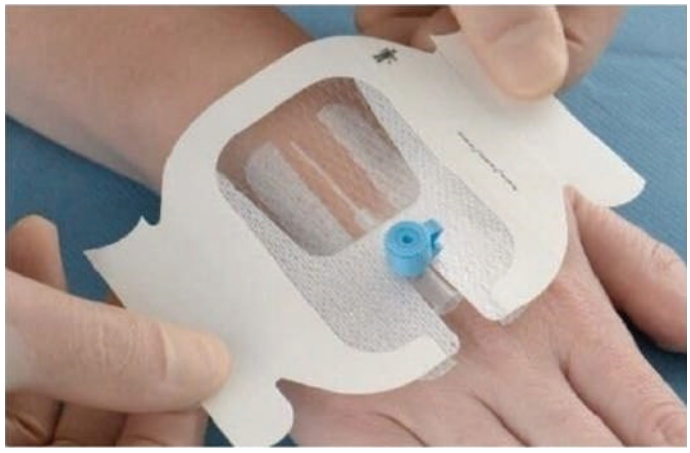


*Fig. 3: Tegaderm*

**HYDROCOLLOIDS:**

Hydrocolloid dressings are made up of an inner hydrophilic polymer layer of carboxymethylcellulose, alginate, pectin and gelatin. This layer absorbs water and exudates from the wound bed and swells up while maintaining a moist environment. The outer layer is waterproof and commonly made of polyurethane acting as a barrier to pathogens. Hydrocolloids promote autolytic debridement and are suitable for pressure sores and traumatic wounds. They are not preferred for infected wounds due to their occlusive property. They are used for non-infected wounds with mild exudate. Examples of this are Tegasorb, Comfeel and Duoderm.

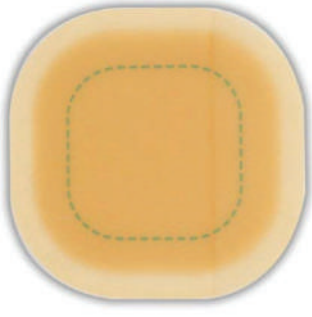


*Fig. 4: Duoderm*

*Fig. 5: Comfeel*

**HYDROGEL:**

Hydrogel has similar hydrophilic material as the inner layer of hydrocolloid but it is less resistant to bacterial contamination due to lack of the outer water-resistant layer. It also promotes

autolytic debridement. They are semi-occlusive dressing and usually require frequent changing. Hydrogel is suitable for dry and necrotic wounds, pressure ulcers, donor sites after skin grafting and partial thickness burns. Examples are Intrasite gel applipak and Mckesson hydrogel.

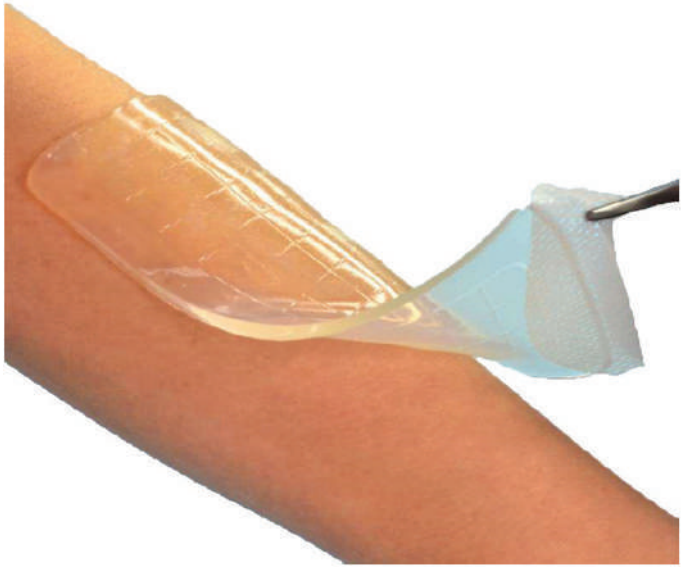


*Fig. 6: Hydrogel Dressing*

**HYDROFOAMS:**

These are highly absorbable polyurethane dressing designed to absorb excess exudate from the wound while maintaining moisture for optimal healing. Hydrofoam dressings require less frequent replacement, minimizing wound disruption and infection risk. This dressing is more comfortable for the patients with high exudate. Examples are Allevyn and Hepilex.

*Fig. 7: Allevyn Hydrofoam*

**HYDROFIBERS:**

Hydrofibres are advanced wound care dressing made primarily by carboxymethylcellulose in the form of non-woven fibers that transform into gel when in contact to wound exudate. They also usually contain Silver as an antibacterial agent. Apart from providing suitable conditions for wound healing like moisture, it is also atraumatic on removal (preferable in moderate to heavily exudative wound). Examples are Biatain alginate, Aquacel Ag, Durafiber etc. Very commonly used in India.


*Fig. 8: Biatain Ag*

**TISSUE ENGINEERED SKIN SUBSTITUTES:**

These are made by innovative methods involving cell isolation from a small biopsy. These cells like keratinocytes and fibroblasts are then cultured and seeded on biocompatible scaffolds made from natural or synthetic materials. Growth factors and antimicrobials are used in the process. After a series of testing and sterilization the matured skin substitute is prepared for grafting on the patient's wound.

**TYPES OF SKIN SUBSTITUTES:**

**a. Epidermal substitute:**

These are primarily composed of keratinocytes primarily focused on replacing the outermost layer of skin that is epidermis. This is suitable for superficial burns and partial thickness wounds. Examples are Epicel and Myskin.

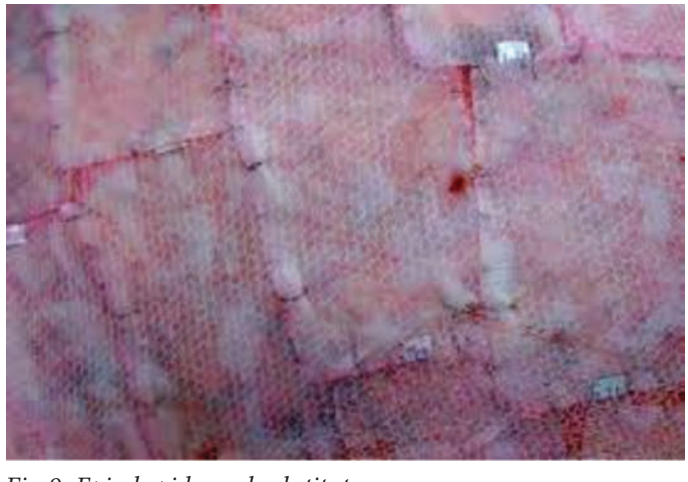


*Fig. 9: Epicel epidermal substitute*

**b. Dermal Substitute:**

These are intended to replace the deeper layer of skin which is dermis. They contain collagen, hyaluronic acid and also fibroblast to form the dermal matrix. They are used in full thickness burns and deep wounds. Examples are Alloderm, Integra, Matriderm, Dermacell AWM. These are very commonly used in the western world, even in India also they are used frequently. Limiting factor for these products are its cost, should be considered on patient-to-patient basis.

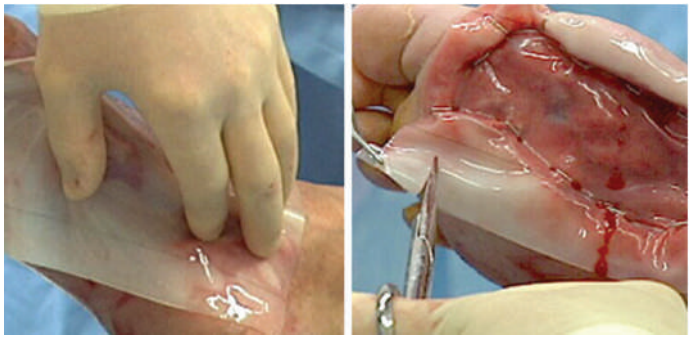


*Fig. 10: Integra Dermal Substitute*

**c. Composite substitute:**
Designed to mimic full thickness skin they contain both epidermal and dermal components . This includes a bilayer structure of both keratinocytes and fibroblasts, which is used for non-healing ulcers Examples are Apligraf and Orcel.

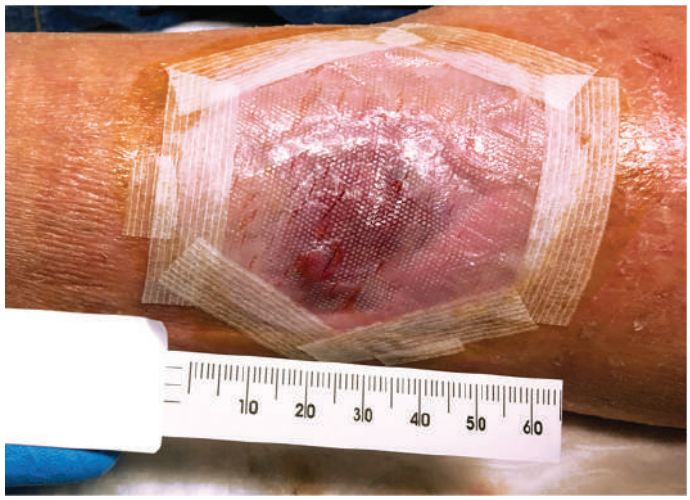


*Fig. 11: Apligraf composite skin substitute*

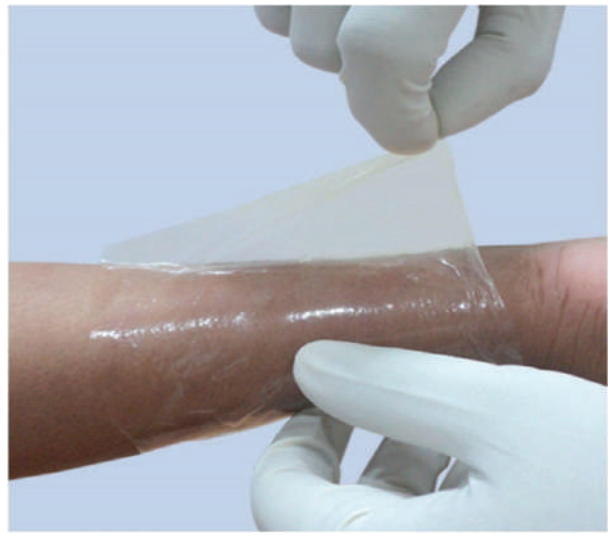
**MEDICATED DRESSINGS:**
For more effective wound healing dressing materials were combined with compounds. They offer targeted therapeutic benefits for complex wounds. Based on the nature of loaded compounds they can be called bioactive dressings or can be named under different categories of drug loaded dressings.

**BIOACTIVE DRESSINGS:**
They participate in the healing process by releasing and attracting biological agents that accelerate tissue repair.

For example, collagen dressing acts as a scaffold for new cell growth at the same time attracting fibroblasts and keratinocytes. Growth factor dressings are infused with substances like Platelet derived growth factors which stimulate cell proliferation, angiogenesis and granulation tissue.

Colgen MM, Colgen Matrix, Colgen W are different types of collagen dressings. Each of these have different properties like promoting granulation tissue, providing 3D structural support and antimicrobial activity in order.

[A]



[B]

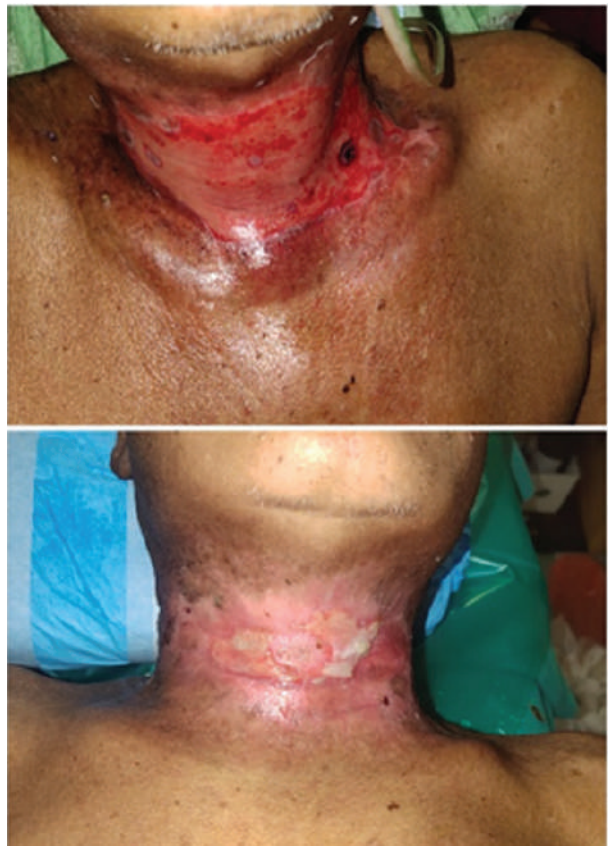


*Fig.12: [A] Collagen dressing; [B] a cancer patient with severe radiation dermatitis-upper picture (below picture is one week after collagen dressing application-the patient able to complete his full radiation dose subsequently).*

**DRUG LOADED DRESSINGS:**
***Antimicrobial Dressing:*** This type of dressing can incorporate Silver, Iodine or Chlorhexidine which is used mostly for infected wounds.

***Anti-inflammatory Dressing:*** They are loaded with agents like corticosteroids and NSAIDs. It is used for acute and chronic inflammatory wounds.

***Analgesic Dressings:*** They are used to manage pain at wound site with the help of agents like lidocaine and hydrogels.

There are dressings that prevent biofilm formation by the bacteria which helps to manage infection and promote healing.

***Composite Dressings:*** They are multi-layered wound care products which are suitable for a variety of wounds. The outer polyurethane waterproof layer prevents infection and allows gaseous exchange. The middle layer is made up of highly absorbent material that retains wounds exudate and protects from mechanical stress. The inner layer is non-adherent for a traumatic removal. This dressing is more versatile and comfortable, its high cost is a disadvantage. Examples are Combiderm and Alldress.

*Fig. 13: Alldress Composite Dressing*

***3-Dimensional Printed Wound Dressing:*** It's the latest advancement in wound care technology creating customized dressings tailored to patient specific needs. It can be designed to fit the exact shape and size of the wound and incorporate bioactive agents and medications as needed.
3D printing creates intricate structures similar to natural extracellular matrix providing scaffold for tissue regeneration. Its porous structure allows management of wound exudate and gaseous exchange. They can be produced in less time and reduce delay in wound care. Materials used for 3D printing include biopolymers like polylactic acid, polycaprolactone and hydrogels like alginate, hyaluronic acid. In addition to this it could be collagen based or cellulose based.

**CONCLUSION:**

Recent advancements in wound dressing technologies have revolutionized the field of wound care, offering more effective, personalized, and targeted solutions for patients. From bioactive dressings to 3D-printed options, these innovations are improving healing outcomes, reducing complications, and enhancing patient comfort. ■

**REFERENCES/SOURCES:**

*-Fig 1: Gauze: https://goldenhorsemedicalsupplies.com/cdn/shop/products/GPS42_800x.jpg?v=1501901941*
*-Fig 2 (a) -Jelonet: https://www.uslmedical.co.nz/slir/w1140-h860-q80/4104/*
*-Fig 3 (b)-Fig Bactigras: https://www.sssaustralia.com.au/Images/ProductImages/Original/1354256_1.jpg*
*-Fig 3-Tegaderm: https://m.media-amazon.com/images/I/41UUEPE7IlL.jpg*
*-Fig 4-Duoderm : https://d11qgm9a5k858y.cloudfront.net/vklfz784g17vcqqhljq6ep98gr3a*
*-Fig 5-Comfeel: https://www.medicalproductssupplies.com/cdn/shop/products/coi3213bx_large_2x.jpg?v=1576134774*
*-Fig 6-Hydrogel:https://medicare-wounddressing.com/Uploads/products/2021-05-24/en-Gel-hydrogel-dressing.jpg*
*-Fig 7-Allevyn hydrofoam:https://www.paramedicshop.co.za/cdn/shop/products/Allevyn.jpg?v=1610445648*
*-Fig 8-Biatain Ag: https://medicalmonks.com/wp-content/uploads/2016/04/coloplast_9622.jpg*
*-Fig 9-Epicel epidermal substitute: https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcSYbKcoyExr7jjE6TZx9ZylRQ2SrbZRsdvFPQ&s*
*-Fig 10: Integra dermal substitute: http://www.ilstraining.com/bmwd/images/bmwd_chronic_app_05NEW.jpg*
*-Fig 11: Apligraf composite substitute: https://apligraf.com/images/2-2-last-C.png*
*-Fig 12 (a): Collagen dressing: https://5.imimg.com/data5/SELLER/Default/2021/11/XQ/IA/AC/9082765/collagen-film-dressing.JPG*
*-Fig-13: Alldress composite dressing: https://shop.mysupply360.com/ecomm_images/items/medium/mol-265329.jpg*

♦ Review Article

# VeXUS Score : POCUS for the Assessment of Systemic Venous Congestion

*Sonai Dutta Kakati*

*Associate Professor, Department of Anesthesiology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

One of the most important factor for delayed recovery from major surgery is the excessive fluid accumulation. Proper evaluation of fluid status is an important aspect of management and outcome in patients with septic shock, congestive heart failure, acute renal failure, severe lung disease and post operative patients who have undergone major surgery. Excessive fluid administration just by looking at the vitals and blood pressure can be harmful as it can accumulate in the interstitial space and lead to venous congestion in not only peripheries, but also different organs. This leads to renal dysfunction, hepatic congestion, hypoperfusion of gut mucosa, pulmonary oedema leading to reduced perfusion in alveolar capillary exchange barriers of lungs leading to ventilation perfusion mismatch and acute kidney injury and increased mortality in critically ill patients[1]. Deresuscitation is as equally important as resuscitation with fluids after the major critical illness of hemodynamic instability is over[2].

Ultrasound (USG) has played an important role in the bedside assessment of fluid requitements and responsiveness in critically ill patients and the commonly used parameter is assessing the inferior vena cava (IVC) diameter and the IVC collapsibility and distensibility index.

The IVC might be dilated in various euvolemic conditions, pulmonary hypertension, valvopathies, and also as a normal physiologic variance in trained athletes. Estimating fluid status only from the IVC ignores the amount of congestion in other vital organs such as the lungs, liver, kidneys and gastrointestinal tract.

**VeXUS Score (**The venous excess ultrasound score**),** has been recently proposed as a composite criteria performed by ultrasound that gives a grading of the hepatic vein, portal vein and intrarenal venous system congestion using Doppler ultrasonography.

**THE BASIC PRINCIPLES OF VEXUS SCORE :**

Venous congestion can be first appreciated in the IVC: its size increases proportionally to CVP until it reaches its maximum dilation. Pressure is then transmitted in a retrograde fashion through the veins to the abdominal organs.

The basic principle being as one moves away from the heart, the venous pulse weakens, resulting in undulating and phasic flow in the smaller veins. This may not be same in case of right ventricular failure or intravascular volume overload or significant liver and portal vein abnormalities as it then congests the venous compartment and limits venous compliance. The pulsations are then transmitted back into the smaller veins, dampening the venous pulse. These abnormalities becomes severe as systemic congestion increases. The Pulsatility Index quantifies the degree of pulsatility. Pulsatility index can be calculated by the formula as: Pulsatility Index = Flow max.- Flow min./Flow max.

Flow-max is measured as the distance between the baseline and the peak of the wave and Flow-min is measured as the distance between the baseline and the trough of the wave. A pulsatility index of less than 30% is normal; between 30 and 49% denotes mild portal vein abnormality; and greater than 50% indicates severe portal vein abnormality. This pulsatility index can reach 100% with severe systemic congestion, resulting in a visibly pulsating portal vein.

The Venous Excess Ultrasonography Score (VExUS) is a 4-step protocol that not only evaluates the presence of congestion in the IVC, but also assesses the severity of congestion in three target organs: the liver, the gut and the kidneys. The VExUS scores range from 0 to 3, with higher scores indicating more severe abnormalities in venous blood.

The following steps are followed while calculating the VExUS score by USG.

**Step 1: IVC Assessment :**
**Interpretation of IVC Measurements:**
Evaluate the size and collapsibility of the IVC.

If the maximum IVC diameter is <2cm, then there is no significant venous congestion (at least cardiac related). The ***VExUS score is 0***.

If IVC is >2cm then proceed to the next steps.

**Step 2: HEPATIC Vein Doppler Assessment:**
***Acquiring the Hepatic Vein View with Ultrasound:***
There are three hepatic veins: the right, middle, and left hepatic veins. Any of these veins can be used to evaluate for hepatic vein Doppler patterns but the middle and right hepatic are usually the most accessible since the Left hepatic vein view can be obscured by bowel/ stomach gas.

***Interpretation of Hepatic Vein Doppler findings:***
The hepatic vein Doppler is composed of a systolic (S wave) and diastolic (D wave). As venous congestion increases, there will be alterations of these waves with typical patterns:

Flow in the suprahepatic veins is normally pulsatile, reflecting the pressure in the right atrium. It includes two anterograde waves - a larger systolic wave (S) and a smaller diastolic wave (D) - and a retrograde A wave (atrial systole). These three waves correspond to the jugular pulse's A, X and Y waves. When the pressures increase in the right atrium, the A wave becomes more prominent and the S wave decreases in amplitude, to the point where in patients with severe congestion the S wave inverts its flow and merges with the A wave.

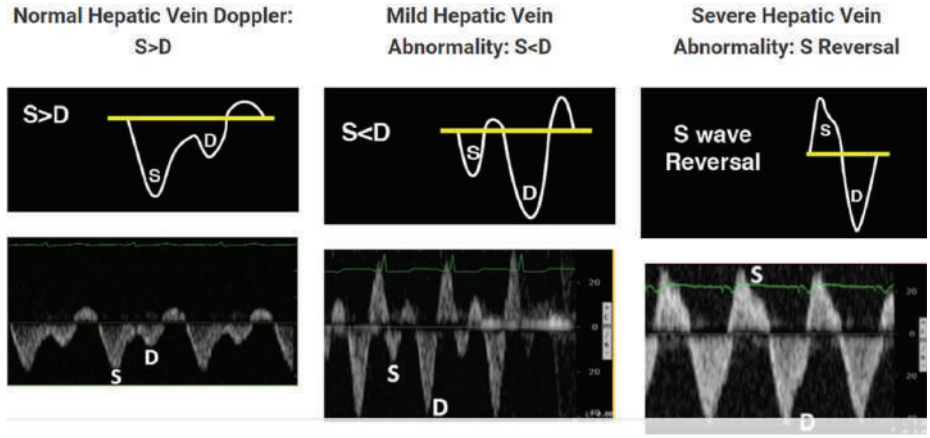



*Fig. 1 : Hepatic vein doppler flow.*

**Step 3 Portal Vein Doppler Assessment:**
We use a pulsed doppler to record flow in the portal vein at the mid-axillary line, aligning the probe with the vessels. A convex probe is preferred, with a vascular renal/hepatic profile. The flows are recorded in expiration, avoiding displacement of the sample volume, of a minimum of 2 to 3 continuous beats to secure a reliable examination, with electrocardiographic (ECG) recording.

The flow in the portal vein is normally continuous or slightly fluctuating and hepatopetal, with velocities of 20–30 cm/s. Since it is separated and buffered by the hepatic sinusoids of the venous system, its flow becomes altered with increased levels of congestion, constituting a more specific marker.

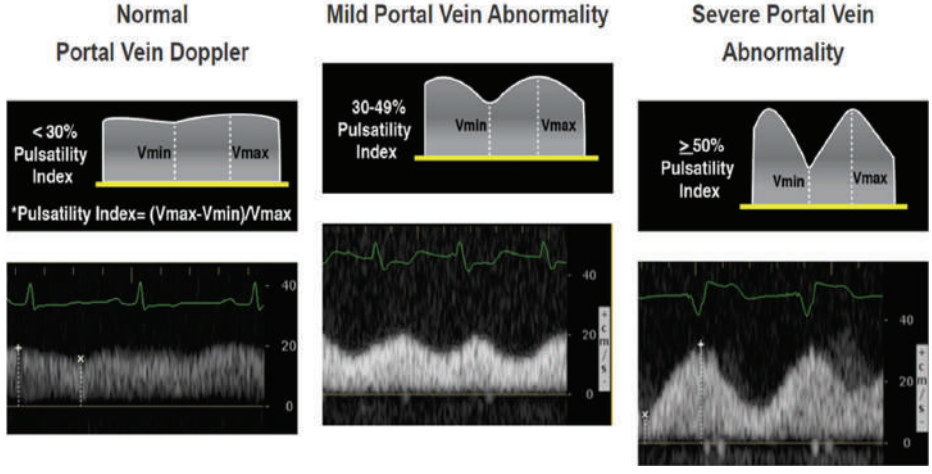



*Fig. 2 : Portal vein doppler*

**Step 4 Renal flow Doppler Assessment:**
Renal flow often includes the artery (positive, always pulsatile) and vein (under zero line), as they run parallel, more difficult to obtain as intrarenal veins are fairly small and the patient's breathing patterns may limit your views and creates confusion. This flow is normally continuous but becomes pulsatile in the presence of increased congestion. It initially becomes discontinuous until two waves are distinguished (S and D, biphasic discontinuous pattern). In the presence of severe congestion, the S wave decreases to the point of disappearing, and we observe a monophasic discontinuous pattern with only the D wave.

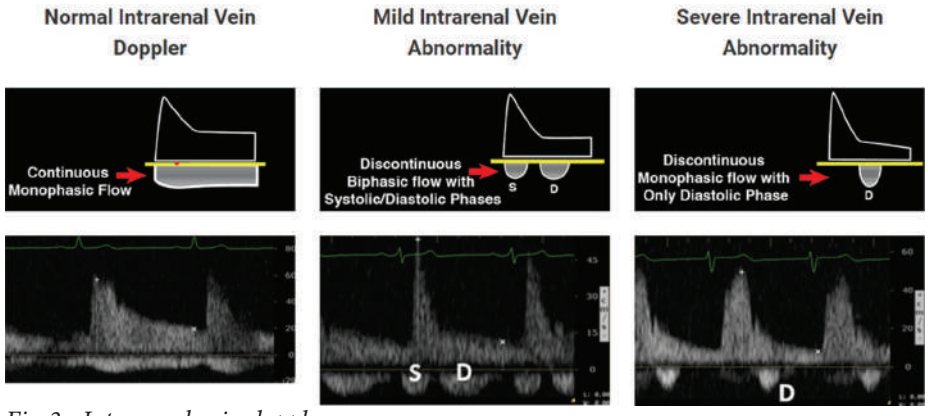



*Fig. 3 : Intrarenal vein doppler.*

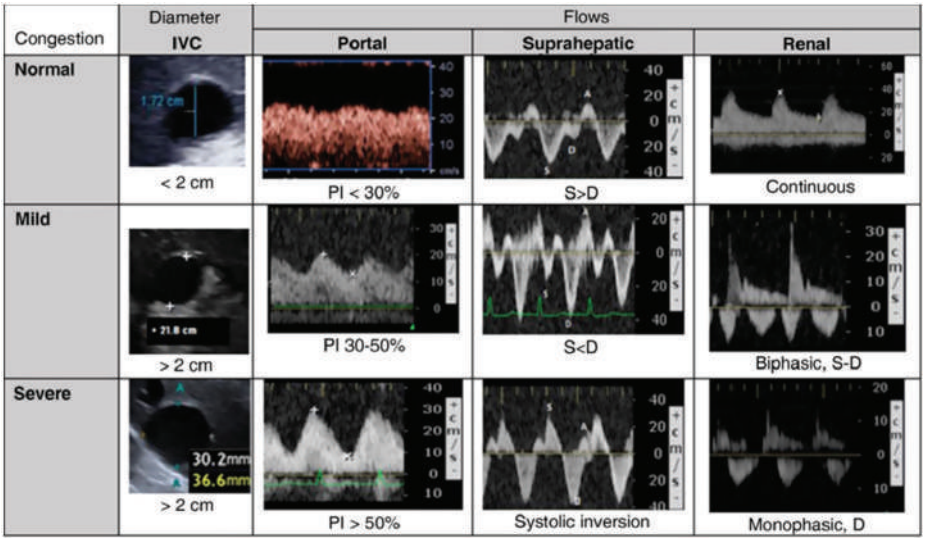



*Fig. 4 : Interpretation of VeXUS Score.*

The VExUS score ranges from Grades 0-3. In Grade 0, a non-dilated IVC (< 2 cm) indicates that no congestion is present. In Grades 1-3, the IVC diameter is > 2 cm. In Grade 1, a dilated IVC and any combination of normal or mildly abnormal flow patterns (but no severe features) indicates mild congestion. In Grade 2, a dilated IVC and one severely abnormal flow pattern indicates moderate congestion. In Grade 3, a dilated IVC and two or more severely abnormal flow patterns indicates severe congestion.

*Table 1 : Interpretation of VExUS Score:*

| Grade | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| | IVC<2cm | IVC>2cm | IVC>2cm | IVC>2cm |
| | No Congestion | Combo of Normal or Mildly Abnormal Patters Mild Congestion | One severely congestion pattern Moderate congestion | At least two severely congestion patterns Severe Congestion |

**DISCUSSION:**

Proper fluid management is one of the essential aspect of patient's outcome.[3] Now the concept is changing from liberal or restrictive fluid strategy to giving fluids according to dynamic test of fluid responsiveness that is individualised for each patient. This leads to a significant variation in practice amongst clinicians with regards to the physiological parameters to monitor fluid status and subsequently guide management.[4]

Ultrasound can play an important role in assessing fluid overload and systemic venous congestion. Assessment can be done via echocardiography, with the assessment of ventricular function and the estimation of pressures, lung ultrasound (B lines, pleural effusion) and the assessment of organ congestion, with the VExUS (Venous Excess Ultrasound Score) protocol.

This score was initially described by Beaubien-Souligny *et al.* in 2020, from a post-hoc analysis correlating ultrasound grading parameters with risk in development of AKI in cardiac surgery patients. The protocol assessed multiple sites of venous congestion, including the IVC, hepatic veins, portal veins and intrarenal veins. By assessing congestion in these multiple sites, the VExUS score was validated. The study used statistical analyses to determine the risk of acute kidney injury associated with normal, mild and severe VExUS grades. They found a higher VExUS grade was correlated with a higher risk of acute kidney injury. VExUS Grade 3 performed better than the traditional CVP (Central Venous Pressure) measurement in the prediction of acute kidney injury in this patient population.[5]

A strong correlation has been found between VExUS and right atrial pressure in a diverse patient population.[6] VExUS parameters can be easily obtained and can be used as an objective marker to help the clinician adjust the intravenous fluids and decongestive therapy.[7] Although a novel score, it was found to be reliable and reproducible and interpretable by clinicians with diverse backgrounds.[8]

VeXUS has been used perioperatively to assess the patient's intravascular status especial in major cardiac surgery, sepsis, renal failure, respiratory failure, obesity and in acute heart failure to avoid complications such as pulmonary oedema and acute kidney injury across various set ups from emergency to operating room and intensive care unit.[9] A combined grading of IVC, hepatic vein, and portal vein reliably demonstrated venous congestion and aid in the clinical decision to perform fluid removal in cardio renal syndrome in ICU.[10] Although not significantly associated with MAKE30, venous Doppler abnormalities suggestive of venous congestion were associated with higher mortality in critically ill patients with severe AKI.[11]

Apart from assessing venous congestion, VeXUS score has been used to guide interventions such as diuretic administration, ascites drainage, haemofiltration, and dialysis Intervention based on VExUS scores has resulted in a reduction of the score, indicating successful management of venous congestion.[12] It has also enabled physicians to monitor the effectiveness of the therapeutic strategy of management of hyponatremia, where the differential diagnosis between cerebral salt wasting and syndrome of inappropriate antidiuretic hormone secretion (SIADH) in critical patients can be challenging.[13] Despite the increasing interest, the incidence of high VEXUS score in the general ICU population is low and few studies have explored the validity of the score in a wider setting.[14]

While VExUS will not likely provide much information on the need for fluid, it may provide stop points to fluid resuscitation and identify patients who are likely to tolerate and benefit from fluid removal. The association between VExUS score and mortality in, intensive care unit (ICU) admission, or rapid response team activation within 24 hours among septic patients presenting to the ED(emergency department) has been studied and it was found that in septic patients presenting in emergency, higher VExUS scores were significantly associated with higher odds of mortality, ICU admission, or rapid response team activation within 24 hours, independent of lactate value and systolic blood pressure. And they found the VExUS scoring system an important tool for early identification of critically ill septic patients and risk stratification.[15]

**LIMITATIONS:**

It cannot be applied to certain clinical conditions such as in arteriovenous malformations, thin, healthy people as they may have portal vein pulsatile flow without venous congestion. Cirrhosis and non-alcoholic fatty liver disease patients may have a non-pulsatile portal vein despite severe venous congestion due to the lack of pressure transmission from the right atrium through the liver sinusoid. Renal parenchymal disease may affect the intrarenal Doppler venous waveforms. Right atrial compliance may prevent hepatic vein changes even in severe tricuspid regurgitation. Even though it gives us an idea of volume status, it cannot identify the cause. Hence, It has been recommended that the VExUS score should not be used alone, but rather as an adjunct.

**CONCLUSION :**

The VExUS score is a strong tool to be considered for the assessment and management of fluid status in our patients. ■

**REFERENCES :**


1. *Messmer AS, Zingg C, Müller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid Overload and Mortality in Adult Critical Care Patients-A Systematic Review and Meta-Analysis of Observational Studies. Crit Care Med. 2020 Dec;48(12):1862-1870. doi: 10.1097/CCM.0000000000004617. PMID: 33009098*
2. *Malbrain MLNG, Martin G, Ostermann M. Everything you need to know about deresuscitation. Intensive Care Med. 2022 Dec;48(12):1781-1786. doi: 10.1007/s00134-022-06761-7. Epub 2022 Aug 6. PMID: 35932335; PMCID: PMC9362613*
3. *Makaryus R, Miller TE, Gan TJ. Current concepts of fluid management in enhanced recovery pathways. Br J Anaesth. 2018 Feb;120(2):376-383. doi: 10.1016/j.bja.2017.10.011. Epub 2017 Nov 24. PMID: 29406186*
4. *Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. Br J Anaesth. 2015 May;114(5):767-76. doi: 10.1093/bja/aeu452. Epub 2015 Jan 13. PMID: 25586725.*
5. *Beaubien-Souligny, W., Rola, P., Haycock, K. et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J 12, 16 (2020). https://doi.org/10.1186/s13089-020-00163-w*
6. *Longino, A., Martin, K., Leyba, K. et al. Correlation between the VExUS score and right atrial pressure: a pilot prospective observational study. Crit Care 27, 205 (2023). https://doi.org/10.1186/s13054-023-04471-0*
7. *Clinical applications of the venous excess ultrasound (VExUS) score: conceptual review and case series. Rola P, Miralles-Aguiar F, Argaiz E, et al. Ultrasound J. 2021;13:32*
8. *Longino, A.A., Martin, K.C., Leyba, K.R. et al. Reliability and reproducibility of the venous excess ultrasound (VExUS) score, a multi-site prospective study: validating a novel ultrasound technique for comprehensive assessment of venous congestion. Crit Care 28, 197 (2024). https://doi.org/10.1186/s13054-024-04961-9*
9. *Singh K, Carvalho R. Perioperative venous excess ultrasound score (VExUS) to guide decongestion in a dilated cardiomyopathy patient presenting for urgent surgery. Cureus. 2021;13:e20545. doi: 10.7759/cureus.20545*
10. *Bhardwaj V, Vikneswaran G, Rola P, Raju S,Bhat RS, Jayakumar A, et al. Combination of Inferior Vena Cava Diameter, Hepatic Venous Flow, and Portal Vein Pulsatility Index: Venous Excess Ultrasound Score (VEXUS Score) in Predicting Acute Kidney Injury in Patients with Cardiorenal Syndrome: AProspective Cohort Study. Indian J Crit Care Med 2020;24(9):783–789*
11. *Beaubien-Souligny W, Galarza L, Buchannan B, Lau VI, Adhikari NKJ, Deschamps J, Charbonney E, Denault A, Wald R. Prospective Study of Ultrasound Markers of Organ Congestion in Critically Ill Patients with Acute Kidney Injury. Kidney Int Rep. 2023 Dec 29;9(3):694-702. doi: 10.1016/j.ekir.2023.12.018. PMID: 38481488; PMCID: PMC10927464*
12. *Wong A, Olusanya O, Watchorn J, Bramham K, Hutchings S. Utility of the Venous Excess Ultrasound (VEXUS) score to track dynamic change in volume status in patients undergoing fluid removal during haemodialysis - the ACUVEX study. Ultrasound J. 2024 Mar 27;16(1):23. doi: 10.1186/s13089-024-00370-9. PMID: 38538806; PMCID: PMC10973283*
13. *Varudo R, Pimenta I, Blanco JB, Gonzalez FA. Use of venous excess ultrasound (VExUS) score in hyponatraemia management in the critically ill patient. BMJ Case Rep. 2022;15:e246995. doi: 10.1136/bcr-2021-246995*
14. *Andrei, S., Bahr, PA., Nguyen, M. et al. Prevalence of systemic venous congestion assessed by Venous Excess Ultrasound Grading System (VExUS) and association with acute kidney injury in a general ICU cohort: a prospective multicentric study. Crit Care 27, 224 (2023). https://doi.org/10.1186/s13054-023-04524-4*
15. *Rolston D, Li T, Huang H, Johnson A, van Loveren K, Kearney E, Pettit D, Haverty J, Nelson M, Cohen A. 204 A Higher Initial VExUS Score Is Associated with Inferior Outcomes in Septic Emergency Department Patients. Annals of Emergency Medicine. 2021 Oct 1;78(4):S82.*

♦ Editorial Report

# Recent Advances in the Department of Surgical Oncology

*Gaurav Das*

*Professor, Department of Surgical Oncology, Convenor of GI HPB GU DMG and Lead Surgeon, Bone and Soft tissue and Paediatric DMGs.*

**INTRODUCTION:**
The Department of Surgical Oncology in BBCI takes care of solid organ cancers in systems other than the Head and Neck and the Gynaecological divisions, for which separate teams have existed for a long time in the Institute. This article highlights a few key developments in the last two years.

**THE DISEASE MANAGEMENT GROUPS (DMGS):** Since August 2023, BBCI consolidated the cancer care services into dedicated working groups called Disease Management Groups (DMGs).

**The currently functioning DMGs are:**

1. Head and Neck DMG
2. Thoracic DMG (including stomach)
3. Gastrointestinal and genitourinary (GI GU) DMG
4. Breast DMG
5. Gynaecological DMG
6. Bone and soft tissue (BST) & Neurological (Neuro) DMG
7. Paediatric oncology DMG
8. Adult haematolymphoid DMG

The Department of Surgical Oncology is primarily responsible for services in DMG numbers 2,3,4,6 and 7 from the list above. *Table 1* gives a general overview of a few variables in the pre-DMG and post-DMG eras. The breast conservation rate shows improvement. Although the use of perforator-based flaps for breast oncoplasty was prevalent since 2019 itself, the Institute witnessed a milestone this year with the use of a free flap whole breast reconstruction for the first time.

In the thoracic DMG, the number of esophagectomies performed has seen a rise and the majority of the procedures are performed by minimally invasive approaches. The Institute has procured a Video Mediastinoscope and its incorporation into the evaluation of lung cancer is one key development.

There are three MIS systems, including two full HD and one with 4K and ICG mode capabilities. Apart from that, there is a portable handheld SPY-PHI © ICG system and a handheld gamma camera system for various utilities. Sentinel node biopsy procedures for cN0 breast, penile cancer and extremity malignant melanomas are routinely being done.

In the GI DMG, the conversion rate of laparoscopic rectal cancer surgery is a meagre 1.7%. Improvement of MIS rates is expected with acquisition of technical expertise in MIS among surgical residents and consultants. There is now an in-house MIS Skill Lab with functional endo-trainers to enable this. There is a dedicated stoma nurse running a daily outpatient and inpatient consultation clinic besides teleconsultation. BBCI is also a high-volume centre for pancreatic resections.

There is a leap in the number of limb salvage surgeries performed in the Institute, with 31 procedures in the past 10 months. This includes reconstructions using endoprosthesis and autologous bone reconstructions after extracorporeal radiation (ECRT) and vascularized pedicled or free fibula, and internal hemipelvectomies. The bone and soft tissue DMG receives a high number of patient referrals from across the state of Assam and rest of North East Region (NER). A dedicated team of physiotherapists, an occupational therapist and a psychological counsellor addresses key issues in standardized rehabilitation programmes.

The volume and complexity of paediatric cancer surgeries in the Institute has been a welcome change. The skillsets and knowhow of the paediatric anaesthesia and postoperative nursing teams have seen a notable transformation. Patients as young as infants

are now being operated at BBCI. Vascular access in terms of chemoport (Babyport) and Hickman's line is routinely being performed for solid and haematological malignancies of paediatric age group.

*Table 1: A few notable comparative variables between the pre-DMG and post-DMG eras.*

| Variables | Pre-DMG (Oct. 2022 to July 2023) (10 months) | Post DMG (Jan. 2024 to Oct.2024) (10 months) |
|---|---|---|
| **Breast DMG** | | |
| Total major surgeries | 207 | 200 |
| Breast conservation rate | 25.1% | 30.5% |
| **Thoracic DMG** | | |
| Esophgectomies | 48 | 54 |
| MIS rate | 92.5% | 90.7% |
| Radical Gastrectomies | 58 | 43 |
| MIS rate | 12.1% | 23.2% |
| **GI DMG** | | |
| Rectal cancer surgeries | 61 | 60 |
| MIS rate | 37.7% | 41.7% |
| Conversion rate | 8.2% | 1.7% |
| Sphincter preservation rate | 85.2% | 86.7% |
| Whipple's surgery | 9 | 25 |
| **BST DMG** | | |
| Limb salvage surgeries | 11 | 31 |
| **Paediatric Oncology DMG** | | |
| Major surgeries | 8 | 24 |

DMGs undergo periodic audits and peer reviews and the major issues including non-compliance and treatment deviations are addressed dynamically with the support of the social workers and KEVAT (patient navigator) teams.

**NEW EQUIPMENT:**

The following new appliances were added to the armamentarium of the surgical team:

1. Three MIS systems (two full HD and one 4K with ICG mode capabilities)
2. One intraoperative USG machine with finger probe
3. One intraoperative radiofrequency ablation (RFA) machine
4. One handheld SPY-PHI © system
5. One handheld gamma camera system
6. One hyperthermic intraperitoneal chemotherapy (HIPEC) machine
7. One nano-aerosolized chemotherapy (NAC) machine
8. One trans-anal endoscopic platform, TEO © system
9. One intraoperative endoscopy system
10. Three sets of advanced retractor systems
11. One Video Mediastinoscope system
12. One dedicated Operating Room (OR) for breast DMG

**BEGINNING OF THE HIPEC PROGRAMME:**

The first case of cytoreduction surgery with hyperthermic intraperitoneal chemotherapy (CRS HIPEC) was performed in the Institute on 12/09/2022 for a 52-year-old lady with adenocarcinoma of transverse colon with peritoneal disease (peritoneal cancer index, PCI score of 7/39) and ovarian metastases. The intraperitoneal chemotherapeutic agent used was mitomycin C and hyperthermia of 41 to 42◦C was achieved for 90 minutes. The patient is disease-free on imaging at last follow up (October 2024), although she had three metachronous isolated recurrences, namely in the left subdiaphragmatic area (treated with SBRT and systemic treatment) and in the left inguinal canal (treated with surgery on two occasions, and adjuvant radiotherapy on the second occasion, and systemic treatment).

*Table 2 : Shows the list of patients who were taken up for CRS HIPEC from the GI DMG till date.*

| Sl No | Age/ Sex | Primary diagnosis | Co-morbidities | Date of CRS HIPEC | Duration | PCI score and CC score | Agent | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 52/F | Ca colon | No | 12/09/2022 (closed technique) | 7 hours | 6/39, CC0 | MMC | Alive without disease (25 months) |
| 2 | 45/M | DSRCT peritoneum | No | 08/02/2023 (closed technique) | 6.5 hours | 16/39, CC0 | Cisplatin | Alive with disease (18 months) |
| 3 | 50/F | Ca ovary | HTN, hypothyroid | 14/06/2023 | 8 hours | 6/39, CC0 | Cisplatin | Alive with disease (16 months) |
| 4 | 49/F | Ca appendix | HTN | 05/06/2024 (Laparoscopic CRS HIPEC) | 8.5 hours | 4/39, CC0 | Oxaliplatin | Alive without disease (5 months) |
| 5 | 67/M | Ca rectosigmoid | Pulmonary (past history of pneumonia, CT findings of GGO, mild pleural effusion) | 16/08/2024 | 10 hours | 15/39, CC0 | Oxaliplatin | 30-day mortality (Ventilator-associated pneumonia) |
| 6 | 53/F | Pseudomyxoma peritonei | No | 28/10/2024 | 9 hours | 24/39, CC0 | Oxaliplatin | Normal postoperative recovery |

*Ca = Carcinoma, DSCRT = Desmoplastic Small Round Cell Tumour, HTN = Hypertension, GGO = Ground Glass Opacities, PCI = Peritoneal Cancer Index, CC = Completeness of Cytoreduction score, MMC = Mitomycin C*

The number of patients who underwent cytoreductive surgery (CRS) alone (without HIPEC) are far more than the list above. This is because the evidence for HIPEC in the age of effective systemic agents in combination for colorectal malignancies with peritoneal disease across the entire PCI range is not proven beyond doubt.

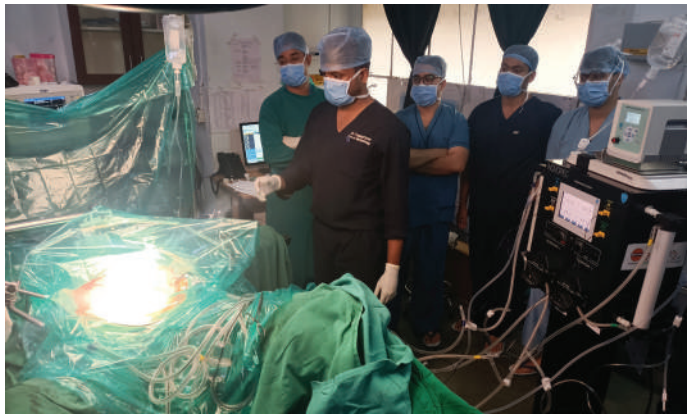


*Figure 1 : HIPEC being delivered.*

**THE ENHANCED RECOVERY AFTER SURGERY (ERAS) PROGRAMME:**

The ERAS programme has been adopted in one surgical unit of the GI DMG for colorectal cancers from April 2024. The first audit was done at 6 months of completion of the programme. ERAS team comprised of anaesthetists, a surgical consultant and residents of the unit, stoma-care nurse, nutritionist and physiotherapist. Protocols were drafted prior to enrolment of patients. Pre-designed proforma was used to check compliance of every parameter.

There were 22 patients till September 2024. The median age of patients was 56 years (range 13 to 77 years) with male : female ratio of 9:13. The most common comorbidities were hypertension (27.3%) and diabetes mellitus (22.7%). The surgeries were performed by one consultant & six resident surgeons and included low-anterior-resection (7), hemicolectomy (6), total-proctocolectomy (2), extra-levator-abdominoperineal-excision (2), abdominoperineal-resection (1), multi-visceral resection (2), beyond-TME (1) and sigmoidectomy (1). Minimally invasive surgery (MIS) was done in 50% patients.

The compliance for pre-operative counselling, prehabilitation & nutritional intervention was 100%. Median Apfel score was 2 and palanosetron use was 100%. Preoperative pregabalin use was 59.1%. Opioid-sparing analgesia was possible in 77.3%. The compliance for low-molecular-weight-heparin use (95.5%), pre-operative oral antibiotic (95.5%) and mechanical-bowel-preparation (81.2%) was high. Pre-operative glucose-loading was done in 81.2%. Use of epidural analgesia was 86.3% and intermittent muscle relaxant use was 27.3%. Immediate on-table extubation was feasible in 77.3% patients.

An abdominal drain was avoided in 59.1%. Nasogastric tube was omitted in 90.9%. Diversion-stoma was avoided in 63.6%. Deep-vein-thrombosis prophylaxis had 100% compliance. Either goal-directed or net-zero-fluid-balance was achieved in 100% patients.

The median duration of Foley's-catheter use was 1 day. The median ICU stay was 1 day (range 0-9 days). The median hospital stay was 5 days (range 3-14 days). The 30-day morbidity rate was 13.6% (diversion-stoma creation due to anastomotic leak).

The colorectal ERAS programme has subsequently included a total of 30 patients till date (31st October, 2024).

**ERAS** programme for gastric cancer surgery has been designed as a student thesis subject and it will be commenced after IEC approval.

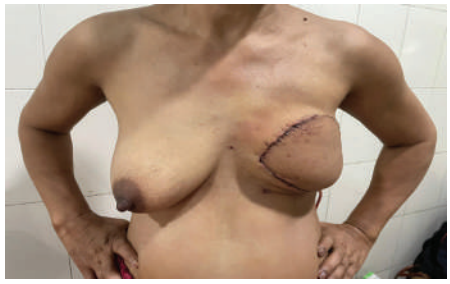
**CONCLUSION:**

The pursuit of excellence is a product of experience gained over time and adoption of evolving evidence-based practice and technology.

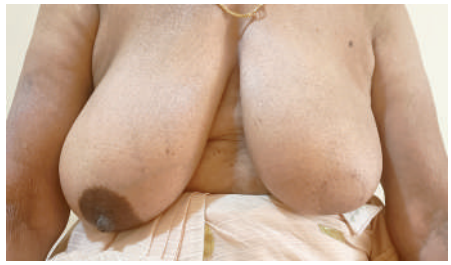
**ACKNOWLEDGEMENTS:**

*Dr. Abhijit Talukdar, Dr. Deep Jyoti Kalita, Dr. Shivaji Sharma, Dr. Pompi D. Buragohain (all consultants of Department of Surgical Oncology), Dr. Partha S Roy, Dr. Jyotiman Nath, Dr. Kaushik J Kataki, Dr. Rukmini Bezbaruah (all members of GI GU DMG), Dr. A. K. Kalita (convenor of BST Neuro DMG), Dr. Munlima Hazarika, Dr. Mouchumee Bhattacharyya, Dr. Manasa K, Dr. Suhani Barbhuiyan, Dr. Lopamudra Kakoti, Dr. Sakshi Gupta, Dr. Rashmisnata Barman, Dr. Amrita Talukdar, Dr. Nilanjana Howbora, Dr. Barnali Kakati and Dr. Debabrata Barmon (all members of Paediatric Oncology DMG), Dr. Tridip J Borah, Dr. Swaraj Sonowal, Dr. Sonai D Kakati, Dr. Anupam Das, Dr. Dokne Chintey, Dr. Marie Ninu, Dr. Yogapriyan, Dr. Tammanna Baktier, Dr. Twist Lahon, Dr. Kamal Deka, Mrs. Yumnam Piyainu, Dr. Rakesh Mohapatra, Dr. Kunal Deka, Dr. Tushar Deka, Dr. Prakharangshu, Mrs. Chandamita Barua and Ms. Dimi Ingtipi (other members of GI DMG, ERAS Colorectal team, CRS HIPEC team and BST rehabilitation team).* ■

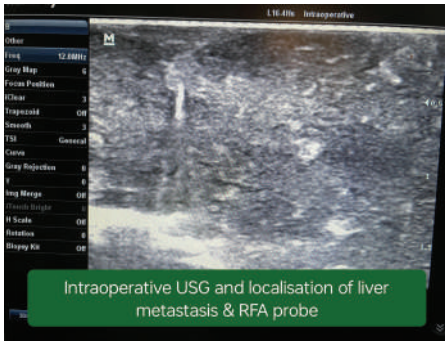
# Photo Gallery



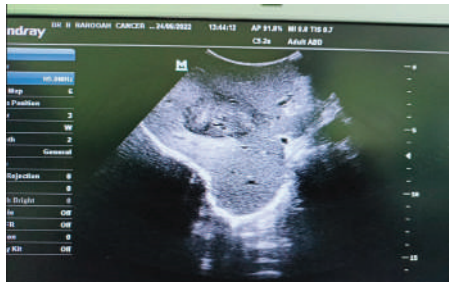
*First case of Whole Breast Reconstruction PC: Dr. Pompi D. B., Dr. P. Reddy*



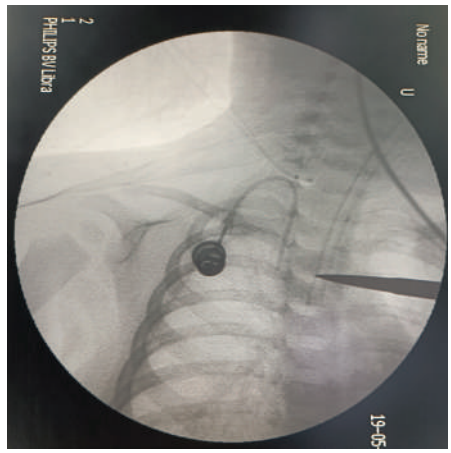
*Five year follow up of Grisotti flap*

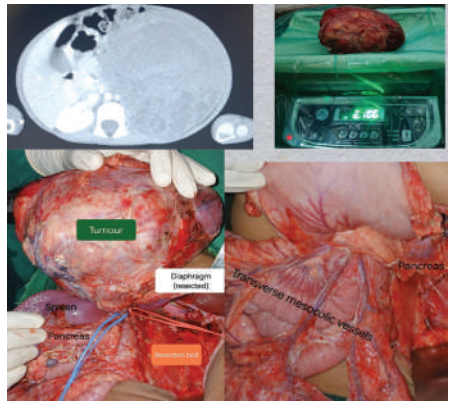




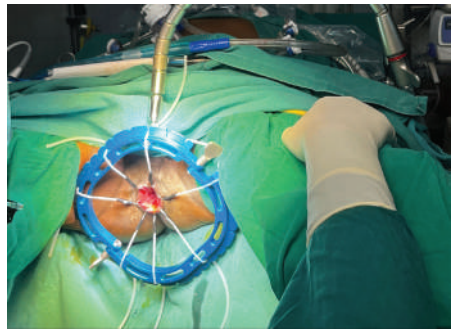
*Intraoperative localization of liver SOL for parenchyma-preserving hepatic resection*



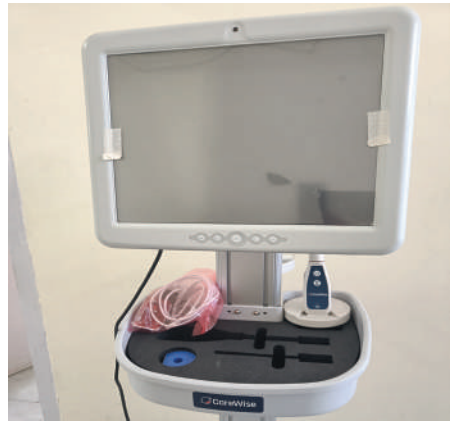

*Chemoport inserted in an infant*



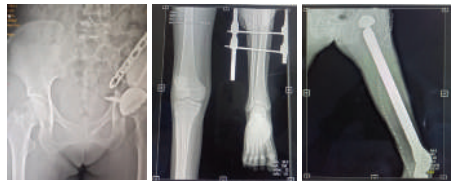

*Left radical nephrectomy for a large Wilm's tumour in a 4 year old child*



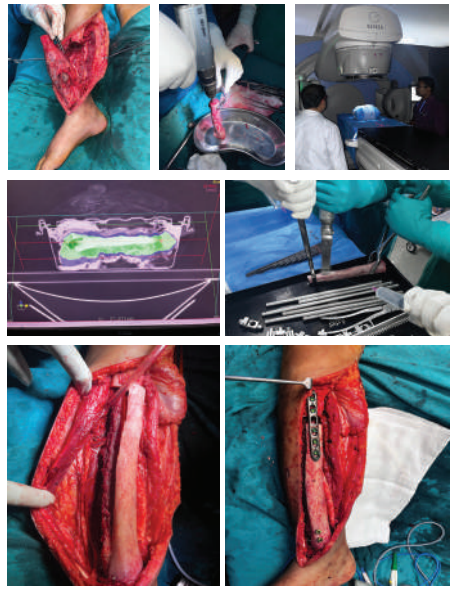
*Minimally invasive colorectal surgery (Laparoscopic Intersphincteric Resection)*



*The hand-held gamma camera system*



*a] Left Type IV internal hemipelvectomy and reconstruction, b] Rotationplasty type A1, c], Total Femur Resection and Modular Endoprosthesis reconstruction*



*a] Intercalary resection of Ewing's sarcoma of the distal shaft of the right tibia, b] Preparation of bone for ECRT, c] Bone within a sterile container being made ready for delivery of ECRT, d] Treatment planning for ECRT, e] Lateral osteotomy for docking of vascularized free fibula, f] Vascularized free fibula inserted in the trough in the tibia (modified Capanna technique) and g] Fixation done with cortical screws and plate with a 1 cm lengthening.*

♦ Case Report

# Spontaneous Ventilation Uniportal Video-Assisted Lung Metastasectomy (Tubeless VATS)

*Swaraj Sonowal[1], Gaurav Das[2], Dokne Chintey[3], Anupam Das[4], Tridip Borah[5], Akash Guha[6], and Kunal Deka[7]*

*[1,3,5] Associate Professor, [4] Professor and Head, Department of Anesthesiology Critical Care and Pain, Dr. B. Borooah Cancer Institute, Guwahati*
*[2] Professor, [6]Assistant Professor, and [7]Senior Resident, Department of Surgical Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**
Uniportal Video-Assisted Thoracoscopic Surgery (VATS) is a popular approach for resection of lung metastasis due to its minimally invasive nature and quicker recovery time. The choice of the word "tubeless" pertains to the avoidance of the following tubes: endotracheal tube, intercostal drainage tube(s) and Foley's catheter. This case also highlights the anesthetic technique avoiding muscle relaxants, utilizing laryngeal mask airway (LMA) for airway management and regional analgesia for postoperative pain control.

**CASE PRESENTATION:**
**Patient Information:** A 38-year-old gentleman without any co-morbid illness had undergone a laparoscopic right hemicolectomy in May 2023 at BBCI. The final histopathological examination (HPE) report showed a 6 cm × 5.5 cm × 3.5 cm ascending colon tumour of stage pT3N0 *(stage II)*. The lymph nodal status was 0/17 (all nodes negative). It was a moderately differentiated adenocarcinoma and R0 resection was achieved. There was no lymphovascular invasion (LVI) or perineural invasion (PNI) and preoperative serum CEA level was 5.09 ng/ml. He did not present with any obstructive symptoms. A disease management group (DMG) decision was taken for observation. After a disease-free interval (DFI) of 12 months, he was found to have a solitary nodule in the right lung upper lobe of size 8 mm in diameter. The nodule was enhancing after contrast administration. *(Fig. 1)*. The serum CEA level was 1.32 ng/ml and abdominal imaging was normal.

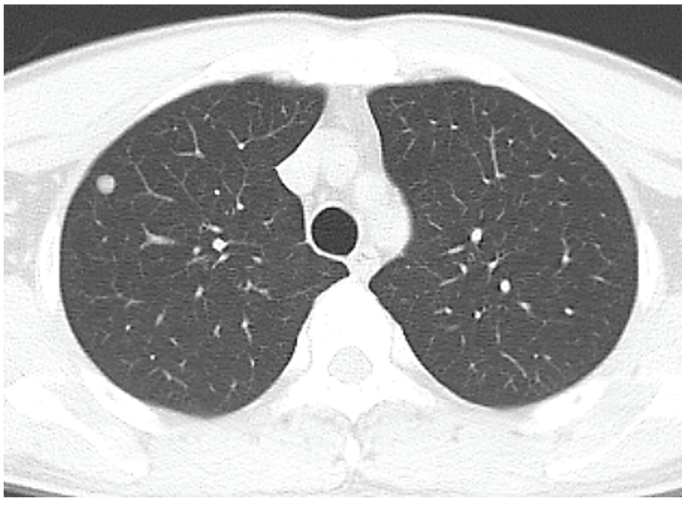


*Fig. 1 : The right upper lobe lung nodule (metastasis).*

**PREOPERATIVE ASSESSMENT :**
Preoperative evaluation included a thorough history and physical examination, with no contraindications for general and regional anesthesia. The patient's baseline vital signs were stable, and laboratory results were within normal limits.

**ANESTHETIC TECHNIQUE :**
1. **Induction and Airway Management:**
   - The patient was induced with intravenous agents

(propofol and fentanyl), and airway management was achieved using a size 4 LMA to ensure adequate ventilation while avoiding muscle relaxants.

2. **Analgesia:**
   - A thoracic epidural was placed at the T7-T8 interspace, and intercostal nerve blocks were administered at the 3rd, 4th, and 5th ribs on the right side to enhance analgesia. Local anesthetic (ropivacaine) was used for epidural and (bupivacaine) for intercostal blocks.

3. **Monitoring:**
   - Depth of anesthesia was monitored using Bispectral Index (BIS) technology, maintaining values between 40 and 60 throughout the procedure.

**INTRAOPERATIVE COURSE :**

The patient was positioned in the left lateral decubitus (right side up), with the operating surgeon, camera assistant and scrub nurse on the right side, the second assistant on the left side and the monitor (single) on the left side head end. Only a 4 cm access port incision in the right 4th intercostal space in the anterior axillary line was used to do the surgery (uniportal VATS). The positioning of the incision to match the location of the lung lesion enabled direct palpation of the lesion using the index finger. Multiple firings of roticulating endo-GIA stapler blue cartridges 45 mm were used to do the lung metastasectomy (wedge resection). On table assessment was done to verify that the small lesion (8 mm size) was within the resected specimen. Leak test using saline in the thoracic cavity ensured that there was no air leak. The wound was closed in layers. The duration of surgery was 90 mins and there was minimal blood loss (< 5ml).

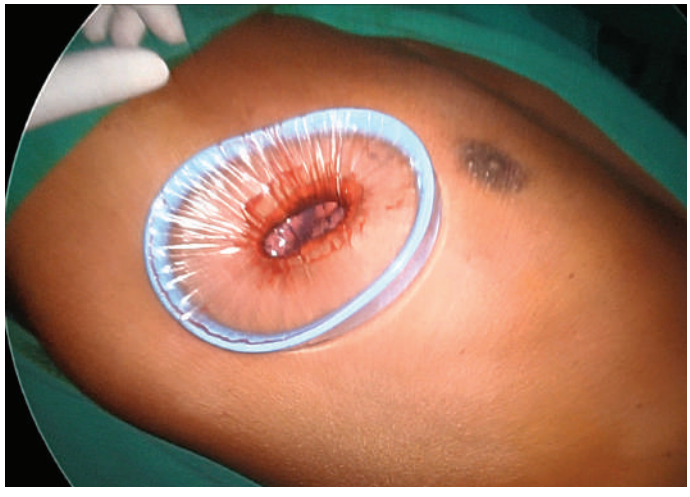


*Fig. 2 : Uniportal Access*

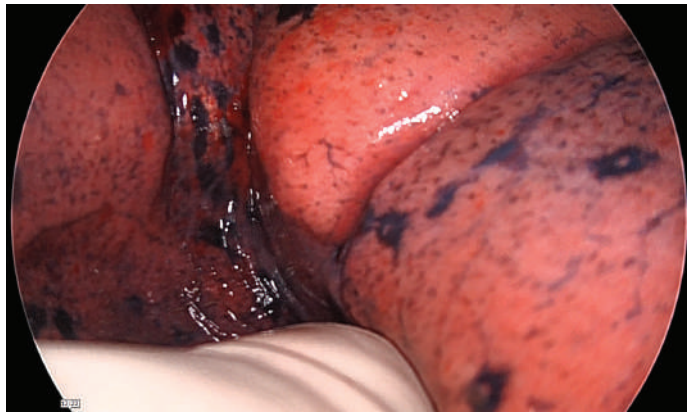


*Fig. 3: Localization of metastasis by palpation*

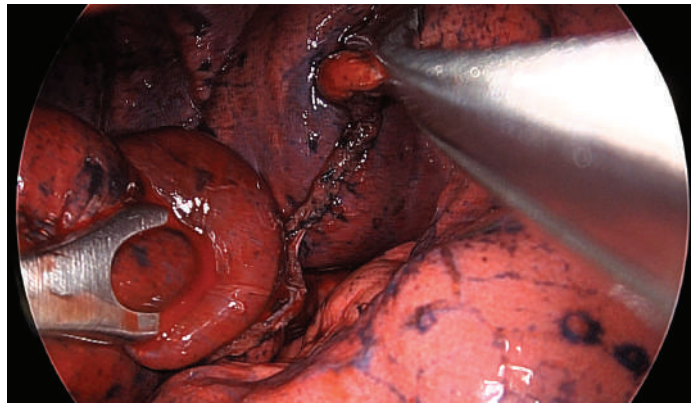


*Fig. 4: Stapling*

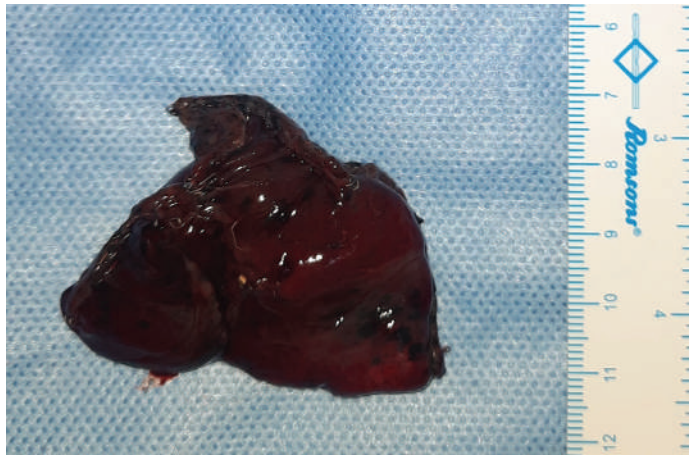


*Fig. 5: Specimen*

**POSTOPERATIVE CARE :**

Post-surgery, the patient was transferred to the recovery unit, where he was closely monitored. Thoracic epidural analgesia provided effective pain control, allowing him to ambulate normally within 3 hours postoperatively. He took a normal oral feed within a few hours of surgery.

**DISCHARGE :**

He was discharged within 24 hours of surgery (single day discharge, SDD) with stable vital signs and adequate pain control with an oral analgesic (paracetamol).

**FOLLOW UP :**
The patient has completed 5 months of follow up after the metastasectomy and is doing well.

**PATIENT'S PERSPECTIVE :**
The patient was glad to have such a curtailed hospital stay (1 day) which reduced his treatment-related expenses. His pain score by Visual Analogue Scale (VAS) was 0/10 all though-out the immediate postoperative period and at subsequent follow ups.

**DISCUSSION :**
Spontaneous ventilation video-assisted thoracoscopic surgery (VATS) for pulmonary metastasectomy represents an innovative approach that combines the benefits of minimally invasive techniques with the use of advanced anesthesia methods. This discussion highlights the implications of utilizing a laryngeal mask airway (LMA), thoracic epidural anesthesia, and intercostal nerve blocks in enhancing patient outcomes during this procedure.

The choice of spontaneous ventilation, particularly with the application of an LMA, offers several advantages. Unlike traditional general anesthesia requiring endotracheal intubation, the LMA facilitates easier airway management and minimizes the risk of complications associated with intubation. Additionally, spontaneous ventilation maintains a patient's physiological respiratory patterns, which can lead to improved gas exchange and reduced airway trauma. This is especially pertinent in patients with compromised pulmonary function due to metastatic disease. This case underscores the feasibility of performing uniportal VATS lung metastasectomy with a focus on multimodal analgesia and airway management without muscle relaxants. The use of LMA has been shown to be effective for maintaining airway patency in thoracoscopic procedures, reducing the need for endotracheal intubation and allowing for spontaneous ventilation.[1, 2]

Furthermore, the incorporation of thoracic epidural anesthesia provides significant pain relief while preserving respiratory mechanics. By effectively managing intraoperative pain, we reduce the need for systemic opioids, thereby minimizing potential respiratory depression. This multifaceted approach not only enhances intraoperative stability but also promotes quicker postoperative recovery. Patients benefit from less postoperative pain, reduced incidence of pulmonary complications, and shorter hospital stays, aligning with the goals of enhanced recovery after surgery (ERAS) protocols.

The use of intercostal nerve blocks complements the thoracic epidural by providing targeted analgesia to the thoracic region. This combination of regional techniques further contributes to effective postoperative pain management, allowing for earlier mobilization and improved overall recovery trajectories. Given that adequate pain control is crucial for optimal respiratory function post-surgery, these techniques can significantly mitigate the risk of atelectasis and other respiratory complications. Thoracic epidural analgesia combined with intercostal nerve blocks has been documented to provide superior postoperative pain relief, minimizing opioid consumption and enhancing recovery.[3,4]

However, this approach is not without challenges. The selection of appropriate patients is critical, as not all individuals with lung metastases may be suitable candidates for spontaneous ventilation VATS. Factors such as tumor location, size, and the extent of pleural involvement must be carefully evaluated. Additionally, the proficiency of the surgical and anesthesia teams in managing this technique is essential to ensure safety and efficacy.

**CONCLUSION :**
Spontaneous ventilation VATS for pulmonary metastasectomy utilizing LMA, thoracic epidural anesthesia, and intercostal nerve blocks represents a promising strategy that can enhance patient outcomes. ■

**REFERENCES :**


1. *Ferson DZ, Nesbitt JC, Nesbitt K, Walsh GL, Putnam JB Jr, Schrump DS, Johansen MJ, Jones RL, Roth JA. The laryngeal mask airway: a new standard for airway evaluation in thoracic surgery. Ann Thorac Surg. 1997 Mar;63(3):768-72. doi: 10.1016/s0003-4975(97)00007-6. PMID: 9066399.*
2. *Liu J, Liang H, Cui F, et al. Spontaneous versus mechanical ventilation during video-assisted thoracoscopic surgery for spontaneous pneumothorax: a randomized trial. J Thorac Cardiovasc Surg 2022; 163: 1702–1714.*
3. *Doyle E, Bowler GM. Pre-emptive effect of multimodal analgesia in thoracic surgery. Br J Anaesth. 1998 Feb;80(2):147-51. doi: 10.1093/bja/80.2.147. PMID: 9602575.*
4. *Guerra-Londono CE, Privorotskiy A, Cozowicz C, Hicklen RS, Memtsoudis SG, Mariano ER, Cata JP. Assessment of Intercostal Nerve Block Analgesia for Thoracic Surgery: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Nov 1;4(11):e2133394. doi: 10.1001/jamanetworkopen.2021.33394. PMID: 34779845; PMCID: PMC8593761.*

♦ Review Article

# Endoscopic Colorectal Polypectomy

*Dibyajyoti Deka*

*Senior Resident, Department of Surgical Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**Colorectal Cancer** (CRC) is the third most diagnosed malignancy and second deadliest cancer in the world[1] causing almost 900,000 deaths annually.[1-2] The lifetime risk of developing CRC is ≥4.0%.[3]

The carcinogenesis process of CRC includes four pathways: adenoma–carcinoma pathway, serrated neoplastic pathway, inflammatory pathway, and de novo pathway.[1,3,4] The first two pathways account for the vast majority and arise from colorectal polyps. The conventional adenoma–carcinoma pathway leads to ~70% of sporadic CRC.[2-3]

Colonoscopy has been shown to be an effective modality to prevent CRC development. Previous studies have shown a 60%-90% reduction in CRC incidence after screening colonoscopy.[4-6] CRC reduction is achieved by detecting and removing adenomas, which are precursors of CRC. Most colorectal polyps detected during colonoscopy are small, benign, and easily resected by skilled endoscopists. A significant number of resected polyp turns out to be malignant. It is essential for endoscopists to identify features of malignant polyps at the time of the index colonoscopy and manage them appropriately.

**Basic Techniques of Colorectal Polypectomy** [8]

Endoscopists should have the appropriate skills to conduct a colorectal polypectomy. First, looping on the colonoscope should be unwound by shortening before performing polypectomy; otherwise, colonoscope manipulation would be paradoxical and troublesome. Second, endoscopists should position the polyp at 5-6 o'clock on the monitor because the instrument exits the colonoscope channel at 5 o'clock *(Figure 1)*. Finally, the base of the polyp, particularly that of a pedunculated polyp, should lie opposite to gravity. Polyp stretching by gravity improves the visualization of the polyp base, and this maneuver prevents blood pooling at the resected site *(Figure 1)*.

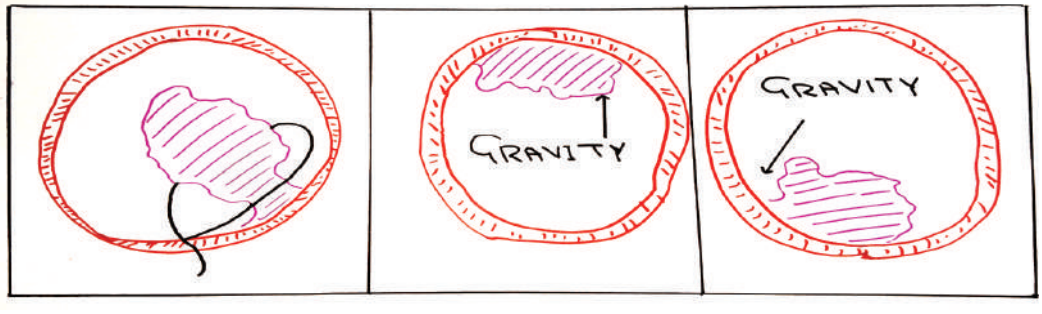



*Figure 1 : Difficult polypectomy, manoeuvre to prevent blood pooling.*

**DIFFERENT TECHNIQUES OF COLONOSCOPIC POLYPECTOMY :**

**A]** **Cold Forcep Polypectomy** - The simplest method for polypectomy is cold forceps removal. Cold forceps polypectomy was the technique of choice for small polyps, particularly polyps 1 to 3 mm in size[9] Advantages to cold forceps polypectomy include avoiding risk associated with electrocautery and an almost negligible risk of colonic perforation[10] One challenge associated with cold forceps polypectomy is that after the initial bite, minor bleeding can obscure the polypectomy field.

**B]** **Hot Forceps Polypectomy** - Hot forceps polypectomy preferred for polypectomies for polyps 3-6 mm in size,In hot forcep polypectomy only the tip of the polyp is grabbed in the forceps. The small polyp is pulled into the colon lumen to create a tent-like effect and electrocautery is applied to destroy the polyp base

while preserving the polyp tissue inside the forceps as a histological specimen.[11]

C] **Snare Polypectomy** - Snare polypectomy was found to be the preferred method for removal of polyps 1 cm or greater in size in a survey of common gastroenterology practices.[12] A snare is a self-contained metal ring that is opened over the polyp and then closed entrapping polyp tissue for resection by closing the ring.

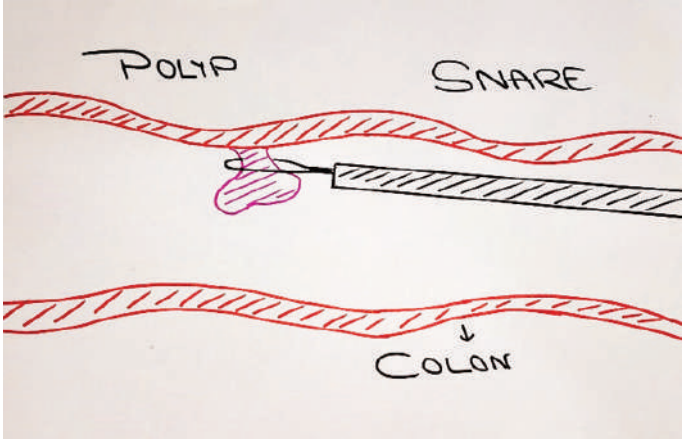



*Figure 2 : Snare polypectomy*

D] **Endoscopic Mucosal Resection** - Endoscopic Mucosal Resection (EMR) can be performed on sessile polyps 2 cm in size or larger. EMR involves submucosal injection (often of saline) creating a cushion for the polyp and then hot snaring the polyp either en bloc (all together) or piecemeal (multiple snarings). EMR can provide resection down to the muscularis propria.[13-15] Endoscopic Submucosal Dissection (ESD) is another technique of endoscopic resection (ER).

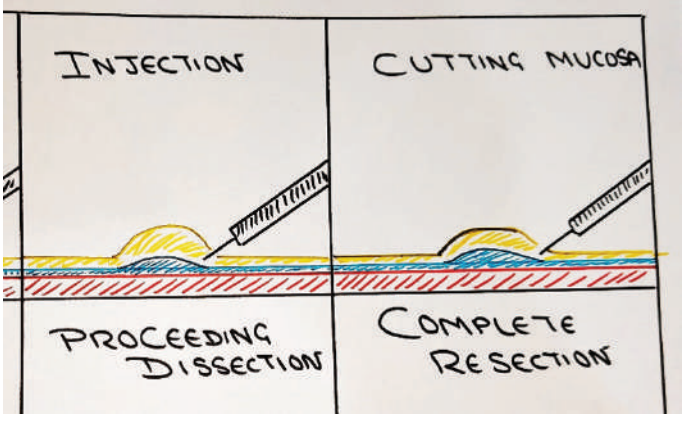



*Figure 3 : Endoscopic submucosal resection*

**ONCOSURGEONS PERSPECTIVE :**

Malignant polyps comprise 12% of resected polyps.[16] It is essential for endoscopists to identify features of malignant polyps at the time of the index colonoscopy and manage them appropriately by marking the polypectomy site, resecting them in entirety instead of piecemeal, and referring the patient for surgical evaluation .

It is always better if high risk polyps are referred to a surgical oncologist for further management.

**High Risk Features –**

1- Patient with polyp whose age is above 50 years.
2- Patient has family history of CRC.
3- Polyp of size more than 1 cm.
4- Sessile polyp.
5- Multiple polyp.

All high risk polyps showed be considered potentially malignant until proven otherwise.

Patient must be advised Endoscopic Ultrasound (EUS) or a MRI to appreciate the depth of Invasion. Although EUS is better modality but MRI is preferred because of easy availability , non-invasive , and additional advantage of detecting Lymph nodal involvement.

**Endoscopic resection is contraindicated if –**

1- Tumour invading beyond lamina propria.
2- Suspicious nodal involvement.

If there are no contraindication then endoscopist can proceed for endoscopic resection. ER is adequate treatment for the following:

1- Tumour is well differentiated.
2- No lympho vascular invasion.
3- Margin more than 2 mm
4- No extension of invasive cancer to the stalk.

If any one of the above feature is positive then patient undergoes radical surgery.

**TATTOOING :**

India ink is the preferred identification agent for tattooing polyps[17] because the ink is phagocytosed by macrophages giving the site an almost permanent easily detected marking. Other dyes like indigo carmine and methylene blue are too rapidly resorbed to be useful. Commercially available India ink is a sterile carbon based dye suspended in stabilizing particles and diluted in normal saline to a 1:100 concentration.[18] India ink is injected through an injection needle and targeted to the submucosal layer . Common practice is to place a tattoo on more than one side of the lesion in either a two or a four quadrant manner. Injecting at an oblique angle tangential to the colon wall can avoid penetration of the colon wall which can result in inflammation and a diffuse staining of the peritoneum thereby obscuring the surgeon's view during operation.[19-20] To ensure proper ink placement, a double injection technique has been described in which 1 mL of saline is first injected creating a submucosal bleb.[21] Once the saline bleb is made, the needle is left in place, the saline syringe is changed to an India ink syringe and about 0.1 to 0.2 mL of tattoo ink is then injected into the bleb space.[22-23] After tattooing the polyp site, the endoscopist should also include in the report the distance of the site from the anal verge in centimeters to aid in future localization. *[FIG 4]*

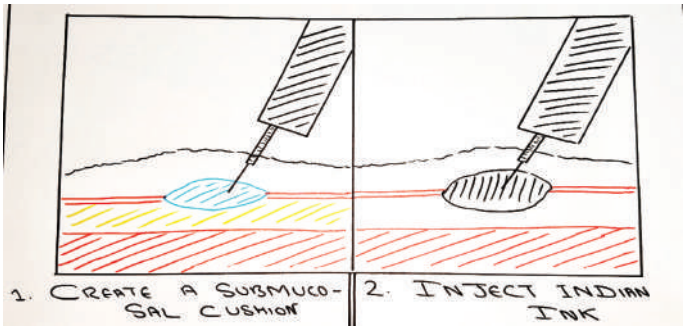



*Figure 4 : Tattoing post polypectomy*

**CONCLUSION :**

Endoscopic polypectomy is a continuously evolving therapy that has been remarkable at reducing the risk of colorectal cancer. Mastery of this highly advanced technique requires learning about the available instruments and polypectomy methods. Colorectal oncosurgeon's must be thoughtful and proficient in techniques such as snaring, injection, tattooing, and all other tools related to polypectomy. ■

**REFERENCES :**


1. *Keum N, Giovannucci E.. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol 2019;16:713–32.*
2. *Dekker E, Tanis PJ, Vleugels JLA. et al. Colorectal cancer. Lancet 2019;394:1467–80*
3. *Siegel RL, Miller KD, Fuchs HE. et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.*
4. *Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329:1977-1981*
5. *Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty.*
6. *Gallegos-Orozco JF, Gurudu SR. Complex colon polypectomy. Gastroenterol Hepatol (N Y). 2010;6:375-382*
7. *Ngamruengphong S, Pohl H, Haito-Chavez Y, Khashab MA. Update on Difficult Polypectomy Techniques. Curr Gastroenterol Rep. 2016;18:3.*
8. *Pattarajierapan S, Takamaru H, Khomvilai S. Difficult colorectal polypectomy: Technical tips and recent advances. World J Gastroenterol 2023; 29(17): 2600-2615*
9. *Singh N, Harrison M, Rex DK. A survey of colonoscopic polypectomy practices among clinical gastroenterologists. Gastrointest Endosc. 2004;60:414–418*
10. *Rex DK. Preventing colorectal cancer and cancer mortality with colonoscopy: what we know and what we don't know. Endoscopy. 2010;42:320–323*
11. *Williams CB. Small polyps: the virtues and the dangers of hot biopsy. Gastrointest Endosc. 1991;37:394–395*
12. *Singh N, Harrison M, Rex DK. A survey of colonoscopic polypectomy practices among clinical gastroenterologists. Gastrointest Endosc. 2004;60:414–418*
13. *Conio M, Repici A, Demarquay JF, Blanchi S, Dumas R, Filiberti R. EMR of large sessile colorectal polyps. Gastrointest Endosc. 2004;60:234*
14. *Moss A, Bourke MJ, Tran K, Godfrey C, McKay G, Chandra AP, Sharma S. Lesion isolation by circumferential submucosal incision prior to endoscopic mucosal resection (CSI-EMR) substantially improves en bloc resection rates for 40-mm colonic lesions. Endoscopy. 2010;42:400–404.*
15. *Sakamoto N, Osada T, Shibuya T, Beppu K, Matsumoto K, Mori H, Kawabe M, Nagahara A, Otaka M, Ogihara T, et al. Endoscopic submucosal dissection of large colorectal tumors by using a novel spring-action S-O clip for traction (with video) Gastrointest Endosc. 2009;69:1370–1374.*
16. *Zhang QW, Teng LM, Zhang XT, et al. Narrow-band imaging in the diagnosis of deep submucosal colorectal cancers: a systematic review and meta-analysis. Endoscopy 2017;49:564-80*
17. *Lightdale CJ. India ink colonic tattoo: blots on the record. Gastrointest Endosc. 1991;37:99–100.*
18. *Ginsberg GG, Barkun AN, Bosco JJ, Burdick JS, Isenberg GA, Nakao NL, Petersen BT, Silverman WB, Slivka A, Kelsey PB. Endoscopic tattooing: February 2002. Gastrointest Endosc. 2002;55:811–814*
19. *Shatz BA, Thavorides V. Colonic tattoo for follow-up of endoscopic sessile polypectomy. Gastrointest Endosc. 1991;37:59–60*
20. *Hellmig S, Stüber E, Kiehne K, Kosmahl M, Fölsch U. What do we really know about the long-term safety of colonic tattooing? Gastrointest Endosc. 2005;61:186–187.*
21. *Sawaki A, Nakamura T, Suzuki T, Hara K, Kato T, Kato T, Hirai T, Kanemitsu Y, Okubo K, Tanaka K, et al. A two-step method for marking polypectomy sites in the colon and rectum. Gastrointest Endosc. 2003;57:735–737*
22. *Raju GS. What is new in tattooing? Custom tattooing. Gastrointest Endosc. 2004;59:328–329; author reply 329. [PubMed] [Google Scholar]*
23. *Matsushita M, Takakuwa H, Matsubayashi Y. Effective endoscopic tattooing technique. Gastrointest Endosc. 2004;60:165–166.*

♦ Original Article

# ICG in the Current Practice of Oncology

*Jayavarmaa*

*Senior Resident, Department of Surgical Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

Indocyanine green dye (ICG) usage in field of oncology is evolving. Broadly, the role of ICG can be divided into two categories-lymphatic mapping with sentinel node biopsies, and intraoperative assessment of perfusion.

**HISTORY :**

ICG was first approved for diagnostic use in humans in 1956 and had a long history of usage in ophthalmology, heart and vascular surgery, cosmetic and reconstructive surgery, oncologic surgery, and cardiology. Fluorescein was previously employed in surgical applications due to the ability to view the produced fluorescence with the naked eye and without the usage of a specialized camera. ICG, on the other hand, has the benefit of greater vision of deeper tissues than fluorescein and has recently gained popularity. ICG is safe with very minimal complications and tolerated very well which has been established in numerous studies.[1]

**ABOUT THE DYE :**

- Indocyanine green dye is a lyophilized green powder containing 25 mg of ICG dye, with no more than 5% sodium iodide, which is reconstituted with sterile water and administered by various routes *(Table 1).*
- ICG dye undergoes no significant extrahepatic or enterohepatic recirculation, and there is negligible renal, peripheral, lung, or cerebrospinal uptake of the dye. Excretion occurs after uptake by the hepatic parenchymal cells and is secreted entirely into the bile.[2]
- Contraindications to the use of ICG were established as iodine allergy, pregnancy, liver disease, uremia, and a previous anaphylactic reaction to a dye injection.
- There is no correlation of adverse reactions to the dose of ICG used.[3]
- The dose varies according to the application.[4]

**HOW DOES IT GLOW?**

When bound to proteins in plasma or in lymph fluid, indocyanine green absorbs light in the near-infrared region at 806 nm and emits fluorescence (light) at a slightly longer wavelength, with peak emission at 830 nm. Fluorescence imaging devices provide external energy as near infrared light for ICG to absorb, resulting in excitation of the ICG and the emitted light (fluorescence) is transferred from the field of view to an image on a monitor. These optical properties of indocyanine green are utilized in fluorescence imaging of the micro and macro vasculature, blood flow and tissue perfusion, the extrahepatic biliary ducts, and for lymphatic mapping of lymph nodes and lymphatic vessels.[5]

**ROUTES OF ADMINISTRATION OF ICG AND THEIR CLINICAL APPLICATION[6]**

| Route of administration | Intended use | Clinical application |
|---|---|---|
| Intravenous | Perfusion assessment | Gastric conduit perfusion (esophagectomy), Flap perfusion (reconstructive surgery, Colon perfusion (Colectomy) |
| Intravenous | Biliary drainage | Cholangiography |
| Peritumoral | Lymph node mapping | Sentinel lymph node biopsy (Breast carcinoma, Penile carcinoma, endometrial carcinoma) |
| Groin nodal injection | Lymphography | Chyle leak localization, Thoracic duct mapping |

*Emerging indication - Localize parathyroid gland in thyroidectomy surgeries.[7]*

**INTERNATIONAL SOCIETY FOR FLUORESCENCE GUIDED SURGERY (ISFGS) DOSING CHART [8]**

| PROCEDURE | INJECTION TYPE | USUAL DOSAGE | INJECTION TIME | FIRST ICG DETECTION | ICG DURATION |
|---|---|---|---|---|---|
| Colorectal resection and Esophagectomy | Intravenous (I.V) | 3-3.5ml + 10 cc saline flush | Intraoperatively | 30-60 sec after injection | Arterial and Venous phase, min |
| Para-thyroidectomy | I.V | 0,0.2-1ml + 10 cc saline flush | After identification of suspected parathyroid adenoma | 30 sec | Min |
| Cervical/ Endometrial Cancer | Cervical submucosa and deep into stroma (1cc each) | 1mL at quandrants 3 and 9 (2.5 mg/mL) | Prior to dissection & insertion of uterine manipulator | At start of procedure | Stable during surgery. Slowly diffuses through lymphatics |
| Vulvar Cancer | Peritumoral | 1 mL | At start of procedure | Min after Injection | Remains stable during surgery. Slowly diffuses through lymphatics |
| Breast Cancer | Subcutaneous into peri-areolar region in each quadrant | 1 mL 2.5mg/mL) | At start of procedure | 5-10 min after injection | Remains stable during surgery. Slowly diffuses through lymphatics |
| Immediate Breast Reconstruction | I.V | 3 mL (2.5 mg/mL) + 10 cc saline flush | Before, during & after reconstruction | 45 sec after injection | Arterial & venous phase, mins |

**ADVERSE EFFECTS:**
Adverse reactions to ICG are very rare with severe reactions occurring in 0.05% to 0.07%, moderate reactions in 0.2%, and mild reactions in 0.15% of the exposed patients.[3,9]

- Reactions may be due to sodium iodide or to the molecule itself. The following mechanisms have been proposed [3]
  1. Non-allergic histamine release.
  2. IgE-mediated hypersensitivity (immediate reaction).
  3. Complement activation (by disruption of the endothelial lining of blood vessels after the administration of IG).
  4. Release of other inflammatory mediators.
- ICG is relatively safe with a low risk of adverse effects at a dose of 0.1 mg to 0.5 mg/mL/kg for human use.[10]

**EVIDENCES TO SUPPORT ICG USE** :
Many retrospective studies and prospective studies have evaluated identification rates of sentinel nodes after ICG

**Sentinel lymph node biopsy (SLNB) in breast cancers**
ICG has been approved by FDA for lymphatic mapping in breast cancer. Studies in early breast cancer initially suggested higher sentinel node detection rate than technetium nano colloid.

Recent meta-analysis of 12 non randomized trials, ICG was equal to or better than radioactive colloid in localizing sentinel lymph-nodes and tumor positive sentinel nodes.[11]

**DSNB in Penile Cancer**
ICG guided inguinal lymph node dissection can improve number of nodes retrieved and reduced the lymph-node non-compliance rates without increased complication rates and therefore can be recommended in selected penile cancer patients during dynamic sentinel lymph-node biopsy with radiocolloid dye or alone.[12]

**Colorectal Anastomosis**
Many studies have confirmed that use of ICG decreases the use of anastomotic leak (AL), but very few RCT are available to substantiate this fact. Recent meta-analysis of 4 RCT have established that use of ICG during rectal cancer surgery could reduce the rate of AL. (9% vs 13.9% p=0.03). [13]

**Gastric conduit perfusion after esophagectomy**
Ng et al.[14] reported the proposed recommendations developed from an expert panel for the use of ICG-NIR fluorescence in thoracic and esophageal procedures. The expert panel was composed of 12 thoracic and gastrointestinal surgeons from Asian-Pacific countries, and these recommendations were formulated during a consensus meeting to adopt, optimize, and standardize the use of this technique in thoracic and esophageal surgery, including the indications, the route of administration, the dose required, and the contraindications, based on the most

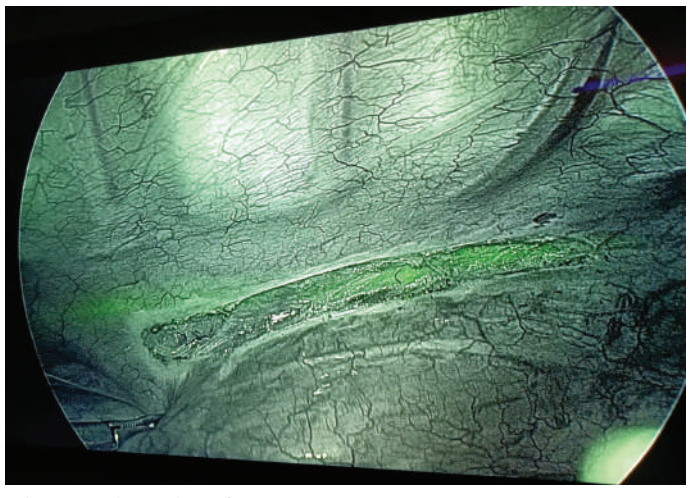
current surgical literature.

**Gynecologic Oncology**
Established use in lymphatic mapping and sentinel node mapping. Identification rates being better than conventional blue dye and colloid dye in endometrial cancer.[15] NCCN guidelines and European Society of Gynecologic Oncology guidelines also established role of ICG in sentinel node identification in endometrial cancer.

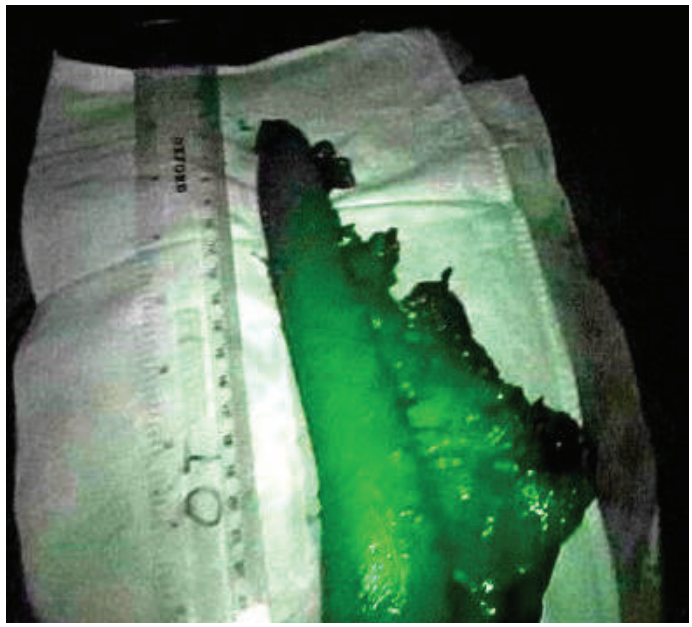
**Others uses:**
1. Early ovarian cancers, results are preliminary
2. Ureteral assessment, minimizing ureteral injury

**Thoracic duct identification and chlye leak identification during esophagectomy**
Injection of ICG either in inguinal lymph-node or mesentery prior to or during abdomen part of esophagectomy can identify thoracic duct during thoracoscopic mobilization of esophagus aid in preventing the thoracic duct injury and in case of inadvertent injury, intraoperative identification of leaks is possible.[16,17]

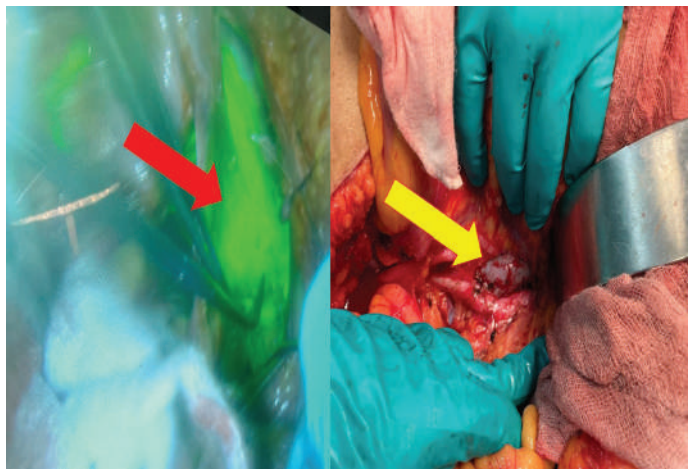
**OUR INSTITUTE EXPERIENCE :**
At present we are using ICG in our institution in following areas
1. SLNB for breast cancers - validation study with dual dye technique (methylene blue and ICG)
2. Dynamic sentinel node biopsy in carcinoma penis (validation study done)
3. Sentinel node biopsy identification in melanoma of foot (2 cases done till now)
4. Gastric conduit perfusion after minimally invasive esophagectomy (35 patients till now study is going on and sample is being recruited)
5. Thoracic duct identification during esophagectomy (35 patients till now)
6. Before doing colorectal anastomosis in low anterior resection for carcinoma rectum (for perfusion of proximal colon).
7. Delineation of tracheobronchial tree by intratracheal nebulization.



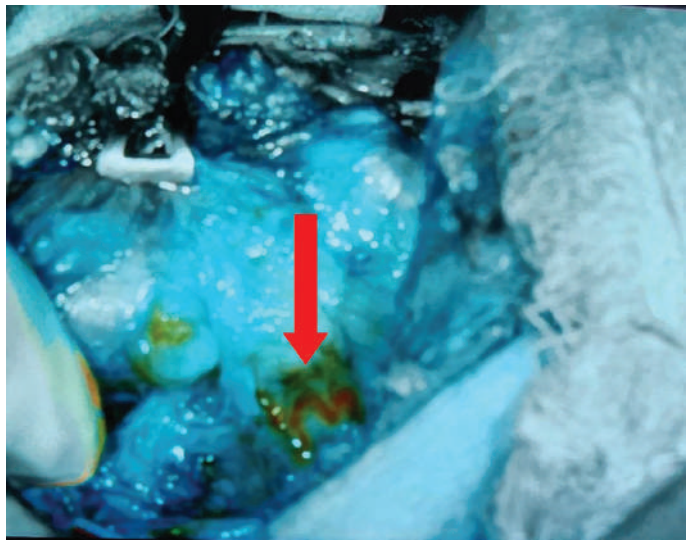
*Thoracic duct identification*



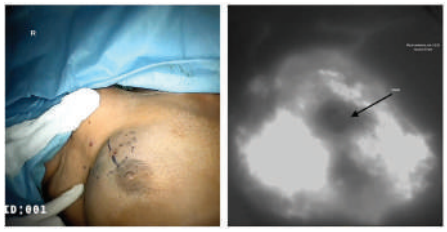
*Gastric conduit perfusion after esophagectomy*



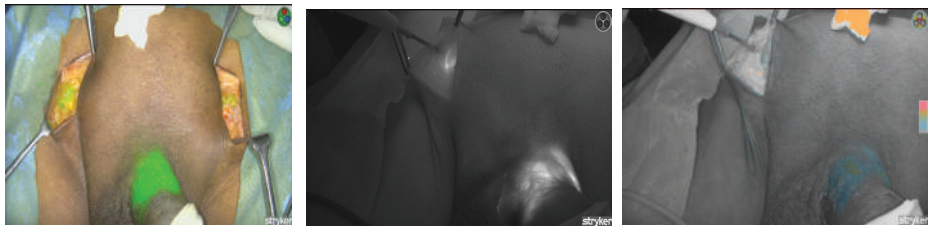
*Sentinel lymph node identification in endometrial cancer*



*Identification of Para-thyroid during thyroidectomy*



*ICG based SLNB in a case of breast cancer. PC : Dr. Pompi D. B.*



*a] Overlay mode, b] DSNB with ICG in a case of penile cancer, contrast mode and c] CSF (Colour Segmented Fluorescence) mode. PC: Dr. Shivaji Sharma*

**CONCLUSION :**

ICG is now being used widely in many fields of oncology and its scope is expanding. ■

**REFERENCES :**


1. *Tamburini N, Chiozza M, Maniscalco P, Resta G, Marino S, Quarantotto F, et al. Application of Indocyanine Green Enhanced Fluorescence in Esophageal Surgery: A Mini Review. Front. Surg (2022). 9:961856.*
2. *Kumagai Y, Hatano S, Sobajima J, Ishiguro T, Fukuchi M, Ishibashi KI, et al. Indocyanine green fluorescence angiography of the reconstructed gastric tube during esophagectomy: efficacy of the 90-second rule. Dis Oesophagus (2018) 31 (12):1–4.*
3. *Hope-Ross M, Yannuzzi LA, Gragoudas ES, et al. Adverse reactions due to indocyanine green. Ophthalmology. 1994;101(3):529–533.*
4. *Pollmann, L.; Juratli, M.; Roushansarai, N.; Pascher, A.; Hölzen, J.P. Quantification of Indocyanine Green Fluorescence Imaging in General, Visceral and Transplant Surgery. J. Clin. Med. 2023, 12, 3550.*
5. *US Food and Drug Administration. Highlights of prescribing information: Information about spy agent green. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211580s000lbl. pdf. Accessed June 20, 2023.*
6. *Rao Thammineedi S, Shukla S, Syed N, Raj Saksena A, Chyau Patnaik S, Reddy Ramalingam P. Scope of Real Time Fluorescence Imaging in Esophagectomy. Esophageal Surgery - Current Principles and Advances. IntechOpen; 2023*
7. *Spartalis E, Ntokos G, Georgiou K, Zografos G, Tsourouflis G, Dimitroulis D, Nikiteas NI. Intraoperative Indocyanine Green (ICG) Angiography for the Identification of the Parathyroid Glands: Current Evidence and Future Perspectives. In Vivo. 2020 Jan-Feb;34(1):23-32. doi: 10.21873/invivo.11741. PMID: 31882459; PMCID: PMC6984100.*
8. *International society of fluorescence guided surgery guidelines. August 2023.*
9. *Obana A, Miki T, Hayashi K, et al. Survey of complications of indocyanine green angiography in Japan. Am J Ophthalmol. 1994;118(6):749–53.*
10. *Alander JT, Kaartinen I, Laakso A, Pätilä T, Spillmann T, Tuchin VV, et al. A review of indocyanine green, fluorescent imaging in surgery. International Journal of Biomedical Imaging. 2012; 2012:940585.*
11. *Sugie T, Ikeda T, Kawaguchi A, Shimizu A, Toi M. Sentinel lymph node biopsy using indocyanine green fluorescence in early-stage breast cancer: a meta-analysis. Int J Clin Oncol. 2017 Feb;22(1):11-17. doi: 10.1007/s10147-016-1064-z. Epub 2016 Nov 19. PMID: 27864624.*
12. *Yuan P, Xie Y, Xu R, Li Y, Yao K, Liu J, Yan B, Jiang S, Lu Q, Chen Q, Zang H, Xiong W, Tang Y, Hu S, Wang L. Efficacy of indocyanine green fluorescence-guided inguinal lymph node dissection for penile cancer: a randomised trial. BJU Int. 2024 Apr;133(4):442-450. doi: 10.1111/bju.16231. Epub 2023 Dec 13. PMID: 37983593.*
13. *Lucarini A, Guida AM, Orville M, Panis Y. Indocyanine green fluorescence angiography could reduce the risk of anastomotic leakage in rectal cancer surgery: a systematic review and meta-analysis of randomized controlled trials. Colorectal Dis. 2024 Mar;26(3):408-416. doi: 10.1111/codi.16868. Epub 2024 Jan 21. PMID: 38247221.*
14. *Ng CS, Ong BH, Chao YK, et al. Use of indocyanine green fluorescence imaging in thoracic and esophageal surgery. Ann Thorac Surg 2023; 115:1068–76.*
15. *Zapardiel I, Alvarez J, Barahona M, Barri P, Boldo A, Bresco P, Gasca I, Jaunarena I, Kucukmetin A, Mancebo G, Otero B, Roldan F, Rovira R, Suarez E, Tejerizo A, Torrent A, Gorostidi M. Utility of Intraoperative Fluorescence Imaging in Gynecologic Surgery: Systematic Review and Consensus Statement. Ann Surg Oncol. 2021 Jun;28(6):3266-3278. doi: 10.1245/s10434-020-09222-x. Epub 2020 Oct 23. PMID: 33095359.*
16. *Yang F, Gao J, Cheng S, Li H, He K, Zhou J, Chen K, Wang Z, Yang F, Zhang Z, Li J, Zhou Z, Chi C, Li Y, Wang J. Near-infrared fluorescence imaging of thoracic duct in minimally invasive esophagectomy. Dis Esophagus. 2023 Jan 28;36(2):doac049. doi: 10.1093/dote/doac049. PMID: 35849094.*
17. *Barbato G, Cammelli F, Braccini G, Staderini F, Cianchi F, Coratti F. Fluorescent lymphography for thoracic duct identification: Initial experience of a simplified and feasible ICG administration. Int J Med Robot. 2022 Jun;18(3):e2380. doi: 10.1002/rcs.2380. Epub 2022 Feb 9. PMID: 35120398.*

♦ Original Article

# SBRT for Abdominal Malignancies in Resource Limited Settings

*Saswati Datta [1], Jyotiman Nath[2], Apurba Kalita[3], Mouchumee Bhattacharyya[4], Bhaveswar Yadav[5], Pranjal Goswami[6], Yanpothung Yanthan[7], Jahnabi Das[8], and Kaushik J. Kataki[9]*

*[1]Jr. Resident, [2]Associate Professor, [3,4]Professor, [5,6]Medical Physicist, [7,8,9]Assistant Professor, Department of Radiation Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION:**

Stereotactic Body Radiation Therapy (SBRT) is a method of external beam radiotherapy (EBRT) that accurately delivers a high irradiation dose to an extracranial target in one or a few treatment fractions.[1]

The principles and techniques of SBRT were adapted from cranial stereotactic radiotherapy/radiosurgery in the mid-1990s, thanks to groundbreaking work at the Karolinska Hospital in Sweden. This approach was rapidly embraced and advanced further in Japan and Germany.[2-3]

Stereotaxy is a form of neurosurgery that uses a mechanical head frame and a precise 3dimensional (3D) coordinate system to align and direct surgical instruments. SRT uses the methods of stereotactic neurosurgery to locate and target malignant and benign brain lesions before the delivery of radiation therapy. In 1994, Lax et al. in Sweden applied this 3D approach to the targeting of extracranial tumours. They constructed a combined body frame-abdominal compressing device and devised a method for the placement of external fiducial markers that could be indexed to the internal target.[1] In 1998, Uematsu et al. developed a frameless "focal unit" which combines a linear accelerator (Linac), computed tomography (CT) scanner, and X-ray simulator (X-S). Treatment of 66 primary and metastatic lung carcinomas by this technique resulted in only 2 cases of local progression.[5]

The radiobiological basis for SBRT mirrors that of SRS; administering a few fractions of large doses over a relatively short treatment duration leads to a more powerful biological effect. Clinical outcomes of SBRT for both primary and metastatic diseases are comparable to those of surgery, with minimal side effects. Additionally, the reduced number of treatment fractions makes SBRT more convenient for patients and potentially a more cost-effective option compared to traditional radiation therapy. [6-7]

SBRT was initially reserved for patients with unresectable or medically inoperable tumours, particularly in a palliative intent to reduce pain or other symptoms. Major oncology treatment guidelines have recommended SBRT as the primary treatment modality in various malignancies, including lung and pancreas, in select groups of patients. As long as dosimetric constraints are adhered to, SBRT is generally well tolerated.[9]

**THE SBRT PROCEDURE :**

SBRT, particularly the thoracic and abdominal, must overcome four hurdles: (i) patient positioning, (ii) internal organ motion, (iii) target volume shrinkage or expansion and (iv) subclinical malignant involvement not identifiable on the images available at treatment planning. Proper patient positioning, target localization, and management of breathing related motion are essential to ensure the tight planning margins of SBRT. SBRT uses various imaging techniques to delineate lesions, use dose calculation algorithms, monitor patient immobilization, and use positioning devices and image guidance systems to ensure safety and reliability. Recent SBRT-ready machines integrate several state-of-the-art RT capabilities (IGRT, immobilization, and respiratory motion solution technology) into a single machine. On completion of pretreatment simulation, the Gross Tumour Volume (GTV) is outlined in each slice where the lesion appears. A Clinical Target Volume (CTV) is applied to account for the microscopic extension of the lesion, although the CTV and GTV are considered equal in the case of metastases. The final Planning Target Volume (PTV) has margins (3-5 mm) to correct for inaccuracies in the delivery system. The PTV is generally encompassed by the 75-95% isodose line. SBRT may use a single treatment fraction ("radiosurgery") or up to

5 fractions.

Geometrical uncertainties, which can be machine-related (e.g. laser misalignment) or patient related (e.g. target volume definition, setup errors, organ motion), are handled by applying safety margins. In addition, basing nodal RT portals on vascular rather than bony anatomy can significantly reduce average tissue irradiation. IGRT enables automatic correction of patient position through translation and rotation of the treatment couch based on measurements provided by the imaging system. The most common image guidance system for obtaining volumetric patient geometry information is 3D-cone-beam-CT (CBCT). It has become standard equipment on many modern linear accelerators.

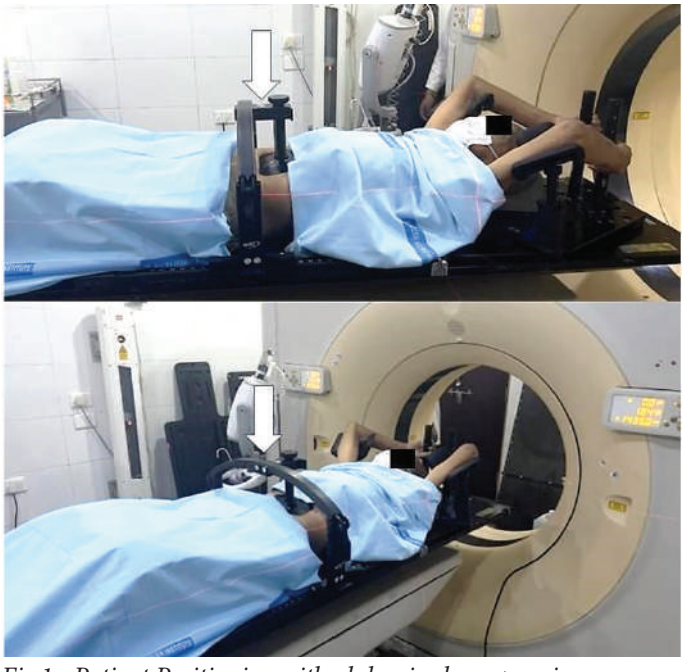


*Fig 1 : Patient Positioning with abdominal compression.*

Despite massive technological development in treatment planning and verification, the main hurdle in delivering high-dose radiation with SBRT in abdominal malignancies is organ motion, like in thoracic malignancies. The organ motion leads to significant uncertainties of the dose received by too many critical structures nearby. Although various technologies have emerged to combat organ motion like DIBH, and DEBH; however, the gold standard should be the integration of four-dimensional CT (4D-CT) planning with gated treatment delivery. However, mere absence of 4D-CT can never be a contraindication of doing SBRT in select cases of abdominal malignancies. Use of abdominal compression *(Fig 1)* is a popular immobilization technique for both thoracic and abdominal radiotherapy. Many literatures are available for the use of abdominal compression devices with or without other modalities like DIBH or 4DCT for radiotherapy of abdominothoracic malignancy. Although abdominal compression has no significant impact on setup error, it may reduce imag matching times in addition to the reduction in radiation to normal tissues. This decrease in time from image acquisition to treatment can help improve treatment accuracy as it minimizes the opportunity for intrafraction motion and increases the likelihood that the image represents the patient's position during treatment.[10]

In this article, we present a few cases of abdominal malignancies treated with SBRT, where motion management was taken care of by abdominal compression since respiratory gating was not available during the initial implementation days. Abdominal compression techniques attempt to constrain the patient to perform relatively shallower chest wall breathing instead of diaphragmatic breathing (the former is associated with less motion).

Therefore, we in the Department of Radiation Oncology, Dr BBCI, started using abdominal compression to perform abdominal SBRT in select patients until the department was fully equipped with a 4D-CT scanner recently.

*Table 1: Few cases of abdominal malignancies treated with SBRT using abdominal compression.*

| Sl No. | AGE | SEX | DIAGNOSIS | TECHNIQUE | DOSE | REMARKS | Severe TOXICITY |
|---|---|---|---|---|---|---|---|
| 1. | 74 | Male | Ca Head of Pancreas | SBRT to Primary | 30Gy/5# | SD at 20 Months FU | None |
| 2. | 70 | Male | Ca Sigmoid Colon with Hepatic Mets | SBRT to the Mets | 45Gy/5# | PR of the Hepatic secondary at12month FU | None |
| 3. | 82 | Male | Periampullary Ca | SBRT to Primary | 33Gy/5# | SD at 6- month FU | None |
| 4. | 58 | Female | HCC | SBRT to Primary | 40 Gy/5# | Disease Progression at 2 months | None |
| 5. | 59 | Male | Ca Esophagus with isolated PA node | SBRT to PA Node | 40 Gy/8 # | PR at 9 months | None |
| 6. | 77 | Female | Ca Head of Pancreas | SBRT to Primary | 40 Gy/5 # | SD at 9 months | None |
| 7. | 78 | Male | Hepatic Mets | SBRT to Hepatic Mets | 45Gy/5# | Lost to FU | None |
| 8. | 66 | Female | Hepatic Mets (Primary CA Colon) | SBRT to Hepatic Mets | 45Gy/5# | SD of the Hepatic secondary at 6month FU | None |
| 9. | 72 | Male | Distal Cholangiocarcinoma | SBRT to primary | 33Gy/5# | SD at 3-month FU | None |

*SBRT: Stereotactic Body Radiotherapy, SD: Stable Disease, FU: Follow Up, Gy: Grey, Mets: Metastasis, CA: Cancer, HCC: Hepatocellular Carcinoma, PA: Para-aortic.*

*Table 1* depicts a few initial patients of abdominal malignancies, both primary and metastatic, treated with SBRT using abdominal compression and immobilization. The indication for taking the primary malignancies like pancreatic carcinoma was either medically inoperable or patients' unwillingness to undergo surgery.

For SBRT, the patients were immobilized supine on a universal base plate. Abdominal compression was applied with the help of a base plate mountable device *(Fig 1)*. Compression was increased till the patient could bear the pressure.

CT images with adequate intravenous contrast were acquired in three phases for pancreatic tumour cases: the arterial, venous and portal. For other sites, only a delayed abdominal phase CT was acquired in the Phillips Brilliance Big Bore CT simulator. The slice thickness of CT images was 1mm. The images were then transferred to Eclipse 5.0 treatment planning system and target volume delineation was done with the help of multimodality image fusion.

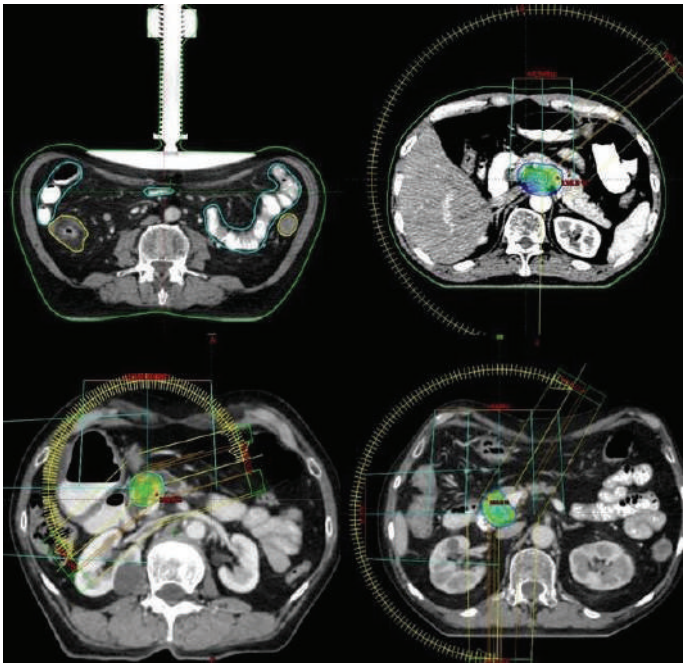


*Fig 2 : Axial Images of SBRT dosewash*

SBRT plans were generated using multiple coplanar beams using FFF beams *(Fig 2)*. Different planning parameters were used as per various sites. The treatment plan was normalized such that 100 % of the target volume was conformally covered by prescription isodose (80 to 90%).

To account for low dose spillage, the Dose Gradient Index (GI) was evaluated where the ratio of the Volume of 50% of the prescription dose isodose to the Volume of the PTV must be no greater than R50% where the value R50% is taken from RTOG 0813.

Conformity Index was calculated as per the RTOG formula, which is the ratio between the volume of the reference isodose and the target volume. The ideal value is 1. The gradient score Index (CGIg) was also evaluated. The ideal value is 50- 100. The accepted global max was 130%.

Treatment planning evaluation involved reviewing treatment plans for PTV, including adequate dose coverage and proper falloff gradients, and reviewing dose/volume statistics. The organs at risk (OARs) considered were the liver, kidney, spinal cord, stomach, duodenum and bowel. Normal tissue constraints that were followed for acceptance of the plan were: Liver- Mean dose <5 Gy; 50% of Volume should receive <4Gy and 70 % of Volume should receive <2.5Gy, for Kidney 75% of Volume of each kidney <5Gy, Spinal cord – max dose <5 Gy Stomach, Duodenum and other bowel – V15Gy<9cc, V 25Gy<3cc, V33 Gy< 1cc etc.

Tumour's response was classified according to the RECIST criteria in version 1.1. PET Response Criteria in Solid Tumours (PERCIST) were used to evaluate metabolic response in patients who underwent PET scans after SBRT. Toxicities were reported according to the RTOG/EORTC scoring system, 5–6 weeks post-SBRT and three months post-SBRT. Late toxicities were scored after a 6-month from SBRT according to the SOMA (symptoms, objective, management, analytic) scoring system. None of the patients had acute or chronic grade 3 or 4 toxicities.

**Conclusion :**

Delivering SBRT to areas with higher organ motion, like the thorax and abdomen, is a real challenge. A 4D-CT-based treatment plan and gated treatment delivery are standard for this precise treatment. However, most institutions are not equipped with all these newer technologies. Until a year back, our institute was not equipped with a functioning 4D CT scanner. Therefore, using abdominal compression was found suitable for implementing the SBRT procedure in select patients in such resource-constrained situations. Here, we have shared our initial experience of treating a few abdominal primary and secondary tumours with SBRT using abdominal compression as an immobilization device to reduce organ motion.

While the limitations of infrastructure, expertise, and financial resources may seem daunting, but customized approaches can effectively leverage SBRT's precision and reduced treatment duration to benefit patients. ■

## REFERENCES :


1. *Guckenberger M, Andratschke N, Alheit H, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol. 2014;190(1):26-33. doi:10.1007/s00066-013-0450-y*
2. *Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol. 1994;33(6):677-683.*
3. *Uematsu M, Shioda A, Tahara K, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer. 1998;82(6):1062-1070.*
4. *Wulf J, Hädinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. Radiother Oncol. 2000;57(2):225-236.*
5. *Almaghrabi, M.Y., Supiot, S., Paris, F. et al. Stereotactic body radiation therapy for abdominal oligometastases: a biological and clinical review. Radiat Oncol 7, 126 (2012).*
6. *R. D. Timmerman, "An overview of hypofractionation and introduction to this issue of seminars in radiation oncology," Semin. Radiat. Oncol. 18, 215–222 (2008)*
7. *I. S. Grills, V. S. Mangona, R. Welsh, G. Chmielewski, E. McInerney, S. Martin, J. Wloch, H. Ye, and L. L. Kestin, "Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer," J. Clin. Oncol. 28, 928–935 (2010)*
8. *Song, C.W., Kim, MS., Cho, L.C. et al. Radiobiological basis of SBRT and SRS. Int J Clin Oncol 19, 570–578 (2014)*
9. *National Comprehensive Cancer Network - Home [Internet]. NCCN. Available from: https://www.nccn.org/home*
10. *Chu KY, Cooke R, Van Den Heuvel F, Mukherjee S, Hawkins MA. Impact of abdominal compression on setup error and image matching during radical abdominal radiotherapy. Technical Innovations & Patient Support in Radiation Oncology.2019 Dec 1;12:28–33.*

♦ Review Article

# Interstitial Brachytherapy for Extremity Soft Tissue Sarcomas

*Abhinandan Das[1], Rudrasankar C.[2], Manthan Thakkar[3], Y. Yanthan[4], Kaushik J. Kataki[5], A. K. Kalita[6], Jyotiman Nath[7], Tapashi Das[8], Bhaveshwa Yadav[9], and Pranjal Goswami[10]*

*[1,8]Sr. Resident, [2]Jr. Resident, [4,5]Assistant Professor, [6]Professor and Head, [7]Associate Professor, [9,10] Medical Physicist, Department of Radiation Oncology, [3]Senior Resident, Department of Surgical Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

Soft tissue sarcomas (STS) are rare malignancies that can develop in various locations, including the extremities, trunk, and head and neck. They have diverse pathological subtypes, histological grades, and clinical courses. Surgery is the primary treatment, often supplemented by radiation and chemotherapy to improve outcomes and while preserving integrity of structure/limbs. For extremity STS, limb-sparing surgery with or without radiation has become gold standard, achieving local control rates of about 85-90% and curative rates of 50%. Key factors influencing recurrence, include tumor histology, stage, location, and resection margins.[1,2]

**RADIATION THERAPY TECHNIQUES:**

Radiation therapy for soft tissue sarcomas (STS) includes preoperative or postoperative external beam radiation therapy (EBRT) and brachytherapy (BT).

While interest in brachytherapy declined as conformal EBRT became popular in the mid-nineteenth century, recent technical advancements have revitalized it. Historically, treatment planning was labor-intensive, relying on manual calculations. However, sophisticated dosimetric planning and computerized systems have transformed the field, enabling precise, patient-specific dosimetry that enhances treatment effectiveness and safety.[3]

For extremity STS, brachytherapy can deliver high doses directly to tumors while minimizing damage to surrounding organs. Interstitial brachytherapy (IBRT) is commonly used as adjuvant therapy after surgery or as a monotherapy for recurrent tumors when re-resection is not feasible, aiming to preserve limb function. The American Brachytherapy Society (ABS) has established guidelines on BT in sarcoma management, including techniques, doses, and expected outcomes.[3]

Despite its advantages, BT adoption is limited due to concerns about technical execution and patient selection.

**INDICATIONS FOR ADJUVANT RADIATION THERAPY**

Patient and tumor characteristics that warrant consideration for adjuvant radiation therapy (RT) for STS, particularly in the context of brachytherapy, include tumor size greater than 5 cm, high histological grade, invasion into or deeper than the superficial fascia, locally recurrent tumors, and close margins etc.

*Table 1: Patient selection for BT.*

| Grade | Size and margin | Preferred treatment |
|---|---|---|
| Intermediate/ High grade | <10 cm and negative margin | BT Alone |
| Intermediate/ High grade | >10 cm, and negative margin | BT + EBRT |
| Low grade | >5 cm, deep | BT + EBRT |
| All grades | Close margin | BT + EBRT |
| Recurrent | - | BT + EBRT |
| Re irradiation | - | BT Alone |

**SPECIAL CONSIDERATIONS/TUMOR LOCATIONS:**
The location of a STS significantly influences treatment options, including surgical approaches and radiation therapy strategies. It affects the geometry for BT procedures and the proximity of OARs to target volumes.

BT represents a proven approach for extremity/trunk STS with the best outcomes noted in the extremity. However, in areas with decreased blood flow, like the distal extremities (e.g., hands and feet), acral lesions are less favorable for BT. EBRT should be considered due to risks of wound complications, difficulties dosimetry.

**PROCEDURE, PLANNING, AND DOSE OF BRACHYTHERAPY**
The fundamental principle of radiotherapy is to deliver an optimal dose to the target while minimizing exposure to healthy tissues. Similarly, interstitial brachytherapy aims to provide a high dose to the tumor bed following en bloc resection while protecting OARs. A successful brachytherapy plan relies on effective implantation. Modern brachytherapy planning systems adhere to the principles of the Paris system, established by Pierquin and Dutreix in the 1960s, which emphasize:

1. Active sources should be arranged parallel and straight.
2. Source lines should be equidistant.
3. Line or plane on which the midpoints of the sources lie should be at right angles to the axis of each source.
4. Adjacent sources should be equidistant.[4]

In practice the spacing between adjacent sources should be between 8 to 12 mm. A minimum of two source planes should be utilized for thickness greater than 12 mm. Consideration of the target volumes shape is essential when selecting source forms and arrangements.

**THE INTERSTITIAL IMPLANT PROCEDURE**
The interstitial brachytherapy procedure involves placing catheters during the surgical excision of STS. The target volume encompasses a volume of tissue rather than merely a surface, especially when dealing with gross residual tumors. Surgical and radiation oncologists collaboratively define the tumor bed and target volume during surgery, taking into account the preoperative clinical and radiological findings, postoperative bed and establishing recommended margins for the clinical target volume (CTV).

**KEY STEPS INCLUDE:**

A) Determining the number of planes of implantation and the number of catheters required to adequately treat the desired volume.

B) Placing interstitial needles in a parallel and equidistant arrangement within a single transverse plane to ensure appropriate coverage of the CTV. Hollow needles are inserted through the skin and tissue, with a recommended distance of 1-2 cm from the incision to the catheter entry point.

C) Replacing rigid steel needles with flexible plastic catheters for brachytherapy, ensuring proper positioning of drain tubes.

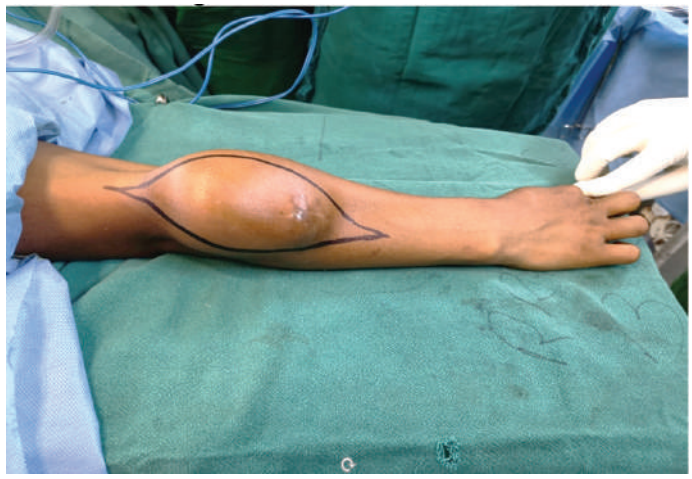
**ADVANTAGES OF INTRAOPERATIVE PLACEMENT**

1. Tumor Visibility: direct visualisation of extent of the primary tumor and the post surgical tumor bed.

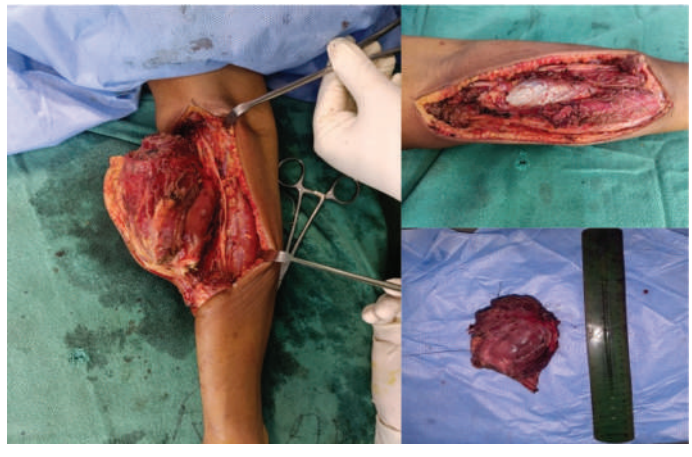
2. Anatomical Considerations: Careful placement of catheters considers critical structures such as bones, blood vessels, and nerves.

**CHALLENGES**
Bony anatomy may restrict catheter placement, and caution is necessary to avoid damage to arteries, veins, and nerves. Techniques such as mapping nerve pathways and utilizing spacers (e.g., Gelfoam) can mitigate risks. Radio-opaque markers or clips are employed to delineate the tumor bed and critical structures for enhanced identification during treatment planning.

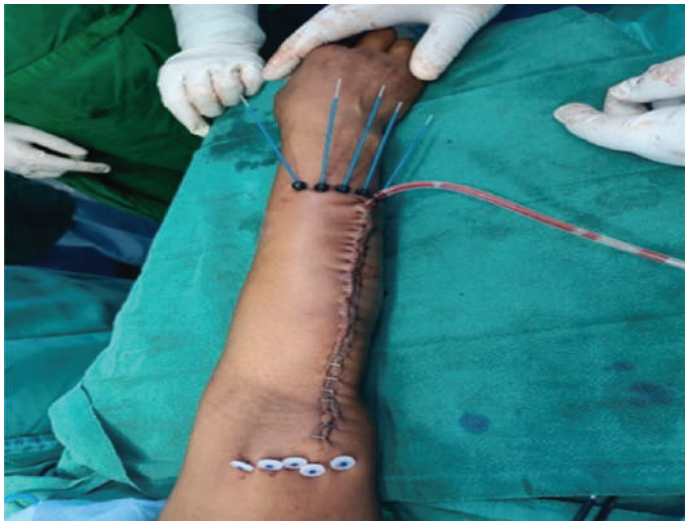
D) Obtain CT planning images to confirm isodose coverage after prescription, following the Paris system rules and optimization.



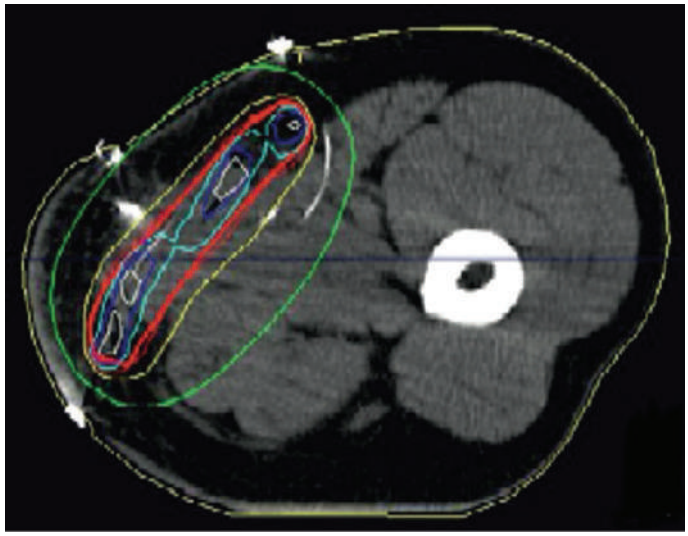
*A. Marking the tumor extent before the surgery.*



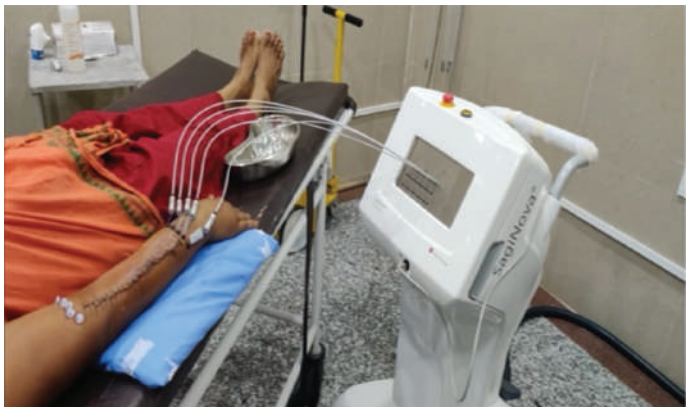
*B. Direct visualisation of the post operative bed.*



*C. A single plane interstitial brachytherapy implant, after suturing and drain placement.*



*D. CT planning image (transverse section) illustrating the isodose distribution following the prescription of 41, in accordance with Paris system guidelines and optimization. Observe the sufficient coverage of the postoperative bed (red line: 100% isodose) and the protection of the skin from high doses (green line: 50% isodose).*



*E. Brachytherapy catheters connected to the machine in treatment room*

## CATHETER PLACEMENT TECHNIQUES

Catheter placement techniques for interstitial brachytherapy are crucial for configuration and dosimetry.

1. Placement Orientation: Catheters can be positioned parallel or perpendicular to the incision, with crossed configurations being beneficial in certain cases. Parallel catheters are generally fewer and longer, ideal for conforming to the extremity's shape.

2. Spacing: Catheters should be spaced 1-1.2 cm apart to ensure effective dosimetry. Single-plane implants require closer spacing than multiplane implants to avoid scalloping of the prescription isodose.

3. Impact of wound closure: The suturing process can affect catheter alignment due to tissue movement, necessitating careful coordination to ensure optimal CTV coverage.

## CATHETER STABILIZATION

Effective stabilization techniques are essential for ensuring accurate dosimetry and treatment efficacy. External devices, such as fixing buttons, can be employed to anchor catheters to the skin surface for additional stability.

## CATHETER CARE AND LOADING

Key considerations for catheter care and loading in interstitial brachytherapy include:

1. ***Post-Placement Assessment:*** After catheter placement and wound closure, verifying correct catheter positioning is critical, maintaining a space of approximately 0.5 cm between catheter buttons and the skin to accommodate postoperative swelling.

2. ***Orientation:*** Catheters should be oriented to facilitate easy insertion of the radiation source, ensuring smooth operation during treatment.

3. ***Drain Management:*** The ABS guidelines recommend keeping drains in place until brachytherapy is completed and catheters are removed, to prevent accidental displacement and reduce seroma formation risk.

**Internal Leaders and Dummy Ribbons in Brachytherapy Catheter Management**

1. ***Internal Leaders:*** Brachytherapy catheters often include internal leaders to prevent stretching during insertion, ensuring proper placement.

2. ***Dummy Ribbons:*** Prior to simulation, dummy ribbons are inserted into catheters to stabilize their position until the source is loaded, allowing for more accurate dosimetry.

These strategies enhance treatment accuracy and effectiveness by ensuring that catheters remain in their intended positions throughout the procedure.

## SIMULATION AND TREATMENT PLANNING

***Simulation Timing:*** Simulation is conducted on days 4 or 5 post-surgery to ensure adequate wound healing.

***Planning Preference:*** CT-based planning is preferred for accuracy.

**CTV Delineation:**

- Pre-operative imaging is utilized for planning.
- The surgical bed is outlined using radio-opaque markers.

**Dose Regimen and Prescription:**

| Modality | Total dose | Fractionation |
|---|---|---|
| As Monotherapy | 30–54 Gy in 2–4.5 Gy fractions<br><br>NCCN: 36Gy/10# | BID |
| As Boost | 12–20 Gy in 2–4.5 Gy fractions | BID |

- Basal dose points are set at 0.5 cm from the implant plane, aiming for 85% reference isodose coverage of the CTV.

**Treatment Planning:**

- A computerized HDR stepping source treatment planning system (TPS) generates dwell times and positions, followed by geometric optimization for ideal CTV coverage.

**Quality Evaluation:**

- Implant quality is assessed using Dose Volume Histogram parameters (D90, V100, V150).

**Dose Limitations:**

- High doses (150% and above) to bones, nerves, and vessels should be minimized.
- The dose at the surgical incision should be kept below 100% of the prescribed dose.
- Skin dose should not exceed two-thirds of the prescribed dose.

**Source Loading Precautions:**

- Source loading should avoid placing sources within 5 mm of the skin surface to limit the risk of skin toxicities.

## POST-TREATMENT CARE

**Key considerations include:**

1. ***Wound Care:*** Patients should be educated on proper care for surgical sites and catheters, emphasizing the importance of keeping the area clean and dry to prevent infection. Also to avoid movements which can cause excessive bending or kinking of the catheters.

2. ***Monitoring for Complications:*** Rates of wound complications can vary significantly, influenced by factors such as tumor stage, treatment modality, and prior therapies. Proactive management and timely intervention strategies can minimize complications.

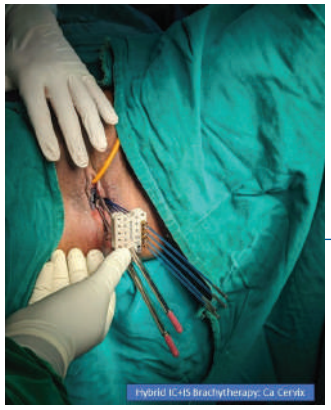
Here is a summary of few cases of extremity STS cases treated with BT in our department using the Eckert and Ziegler SagiNova HDR brachytherapy unit with a Cobalt-60 radionuclide source.

| Case No | Age/ Sex | Diagnosis | Treatment details | Brachytherapy protocol | Outcome |
|---|---|---|---|---|---|
| 1 | 38y, Female | Poorly differentiated high grade synovial sarcoma right forearm | Wide local excision followed by interstitial BT on post op day 4 | 36 Gy in 9 fractions (HDR Brachytherapy) twice daily regimen. | The treatment was well-tolerated, with successful primary intention healing of the surgical scar and no complications. |
| 2 | 28y, Male | Recurrent spindle cell sarcoma of the right leg, post-operative and post-radiotherapy (EBRT) | Wide local excision followed by interstitial BT on post op day 4 | 36 Gy in 9 fractions (HDR Brachytherapy) twice daily regimen. | The treatment was well-tolerated, with successful primary intention healing of the surgical scar and no complications. |
| 3 | 24y, Female | Recurrent dermatofibrosarcoma protuberant of right calf, post operative spindle cell sarcoma of the right leg, post-operative | Wide local excision followed by interstitial BT on post op day 6 | 36 Gy in 9 fractions (HDR Brachytherapy) twice daily regimen. | The treatment was well-tolerated, with successful primary intention healing of the surgical scar and no complications. |

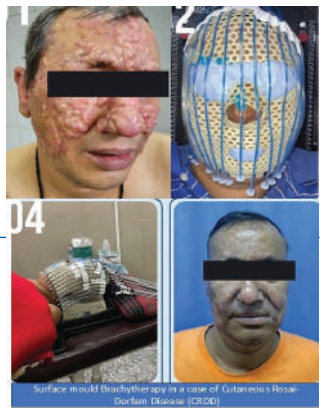
## CONCLUSION:

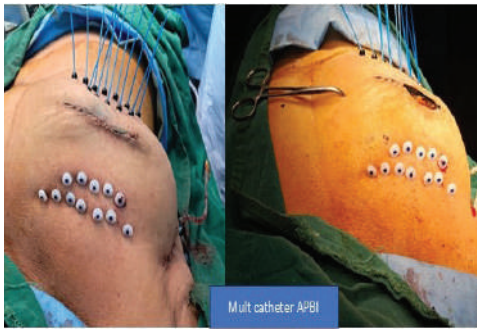
With appropriate patient selection, interstitial brachytherapy can be safely integrated into the postoperative management of extremity sarcomas. By adhering to the recommendations set forth by the American Brachytherapy Society (ABS), this approach does not compromise wound healing or cause additional treatment-related complications and can enhance therapeutic outcomes. ■

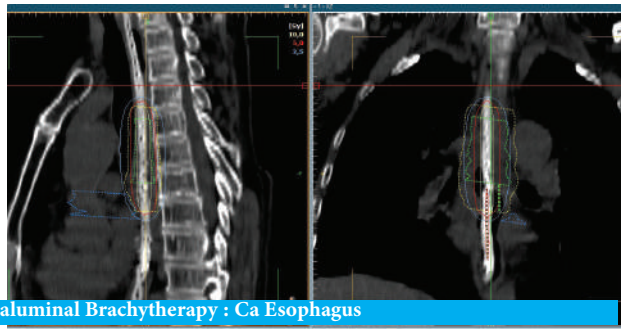
## OTHER BRACHYTHERAPY SERVICES :







Intraluminal Brachytherapy : Ca Esophagus

## REFERENCES:


1. *Neugebauer, J., Blum, P., Keiler, A., Süß, M., Neubauer, M., Moser, L., & Dammerer, D. (2023). Brachytherapy in the Treatment of Soft-Tissue Sarcomas of the Extremities-A Current Concept and Systematic Review of the Literature. Cancers, 15(4), 1133. https://doi.org/10.3390/cancers15041133*
2. *Brennan MF, Hilaris B, Shiu MH, et al. Local recurrence in adult soft-tissue sarcoma. A randomized trial of brachytherapy. Arch Surg 1987;122:1289-1293.*
3. *Medhi PP, Mahantshetty U, Goswami S, Momin FJRM. Brachytherapy. In: Principles & Practice of Oncology. 1st ed.*
4. *Campbell SR, Shah C, Scott JG, Mesko N, Nystrom L, Kolar M, et al. American Brachytherapy Society (ABS) consensus statement for soft-tissue sarcoma brachytherapy. Brachytherapy. 2021;20(6):1200–18. doi:10.1016/j.brachy.2021.05.011.*
5. *Pierquin B, Dutreix A, Paine CH, Chassagne D, Marinello G, Ash D. The Paris system in interstitial radiation therapy. Acta Radiol Oncol. 1978;17(1):33–48. doi:10.3109/02841867809127689.*

♦ Review Article

# Advancement in CAR-T Cell Therapy for Glioblastoma

*Jahnabi Das[1], Jyotiman Nath[2], Yanpothung Yanthan[3] and Kaushik J. Kataki[4]*

*[1,3,4]Assistant Professor, [2]Associate Professor, Department of Radiation Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION:**

Glioblastoma multiforme (GBM) represents 14.5% of all central nervous system tumours and 48.6% of malignant central nervous system tumours, making it one of the most aggressive cancers and the most frequent malignant primary tumour of the brain and central nervous system. GBM patients have a relatively low median overall survival (OS) of approximately 15 months. [1,2]

**MOLECULAR PARADIGM OF GBM :**

In the nomenclature of GBM, the "multiforme" denotes the heterogeneity of the tumour. The term "multiforme" was eliminated from the WHO classification system in its revised 4th edition in 2016. The typical glioblastoma IDH-wildtype CNS WHO grade 4 presentation is necrosis and/or microvascular growth. It has also been noted that IDH-wildtype astrocytomas behaved similarly to glioblastomas, even though they were classified as grades 2 or 3 according to histopathological standards (i.e., no necroses or microvascular growth). In light of this, genetic changes such as EGFR amplification, TERTp mutations, chromosomal gain, and chromosome loss that may be indicative of aggressive behaviour were evaluated. Therefore, even in the absence of glioblastoma histology, an IDH-wildtype diffuse astrocytoma with at least one of these molecular characteristics permits a diagnosis of glioblastoma IDH-wildtype CNS WHO grade 4. If the molecular signature is not consistent with a glioblastoma, one should consider testing for BRAF alterations, histone mutations (H3 K27- and H3 G34-mutant diffuse gliomas) or methylation profiling.

In addition, IDH-wildtype gliomas should also be tested for H3 K27 and H3 G34 mutations. Patients ≥ 55 years at diagnosis with no immunoreactivity for IDH1 R132H can be diagnosed as glioblastoma IDH-wildtype CNS WHO grade 4 if histopathological features of glioblastomas are present, the tumour is not located in the midline and there is no history of earlier low-grade glioma. Gliosarcoma, giant cell glioblastoma and epithelioid cell glioblastoma are still registered subtypes of glioblastomas. The term "glioblastoma multiforme" thus should not be used.[3]

Efforts to link this disease with environmental and occupational exposures have been mostly inconclusive. Ionizing radiation is a confirmed risk factor for glioma, often seen years after therapeutic radiation for another condition. Other exposures, such as vinyl chloride, pesticides, smoking, and certain industrial activities, have been loosely linked to glioma development. However, electromagnetic fields, formaldehyde, and cell phone radiation have not been proven to cause glioma. Certain genetic diseases like neurofibromatosis and Li-Fraumeni syndrome increase glioma risk, though less than 1% of glioma patients have a known hereditary disease.[4]

Since 2005, the conventional treatment for glioblastoma has involved surgery, radiation, and alkylating chemotherapy. For patients under 70, the standard regimen includes maximal surgical resection, followed by concurrent temozolomide (TMZ) and radiation therapy (RT). Clinical studies indicate that the two-year survival rate is 26.5% with RT and TMZ, compared to 10.4% with RT alone. After five years, 97% of patients receiving only RT and 89% of those receiving combined treatment had died.[5] The poor prognosis of GBM patients receiving standard therapy has caused focus to turn toward other cutting-edge treatments, like immunotherapy particularly CAR-T cell therapy, offer new hope in the fight against this devastating disease.

The immune system can detect and destroy tumour cells through immunosurveillance. However, some tumour cells evade this process and develop into tumours. Tumour immunotherapy aims to overcome the immune resistance of these cells to treat the tumour. Immunotherapy methods include vaccines, oncolytic virus therapies, checkpoint inhibitors, and adoptive T cell therapies. Recently, tumour immunotherapy has advanced

rapidly, showing promising results in various cancers such as lung cancer, kidney cancer, and melanoma.[6]

Through immunosurveillance, the immune system may identify and eliminate tumour cells. Nonetheless, certain tumour cells manage to evade immune surveillance and progressively transform into tumour lesions. Tumour immunotherapy aims to treat tumours by overcoming the immunological resistance exhibited by tumour cells. Vaccines, checkpoint blocking, oncolytic virus treatments, and adoptive T cells are all included in immunotherapy. Recent years have seen a rapid evolution of tumour immunotherapy, which has demonstrated encouraging outcomes in treating a range of tumours, including melanoma, kidney cancer, and lung cancer.[6]

The primary approach for directly recruiting T cells is through adoptive lymphocyte transfer. This involves training, amplifying, and activating autologous T cells in vitro to target tumour cells before transferring them back into the patient's body. These genetically modified T cells, such as tumour-infiltrating lymphocytes, cytokine-induced killer cells, TCR-engineered T cells, and CAR T-cell therapies, enhance tumour immunity by specifically targeting cancer cells. Often, immune therapies are combined with other treatments for improved clinical outcomes. CAR T-cell therapy, in particular, has made significant advancements in treating glioblastoma (GBM). However, challenges remain, and further research is needed to overcome these obstacles and explore future directions in this promising field of therapy.

**UNDERSTANDING CAR-T CELL THERAPY:**

Chimeric Antigen Receptor T (CAR-T) cell therapy is a form of immunotherapy that harnesses the power of the body's own immune system to target and destroy cancer cells. In CAR-T therapy, T cells from a patient's own immune system are genetically engineered to express a synthetic receptor called a chimeric antigen receptor (CAR) on their surface. Fig 1 shows structure of the T cell receptor (TCR) containing TCR-CD3 complex.

Chimeric antigen receptors (CARs) are engineered receptors made up of an extracellular part that recognizes antigens, often derived from antibodies. This part is connected to intracellular signalling domains through spacer and transmembrane domains. These receptors have evolved through different generations, incorporating costimulatory domains and activation signals to improve their signalling activity (Fig 2). When T cells are equipped with CARs, they gain the ability to recognize and destroy cancer cells selectively.[7]

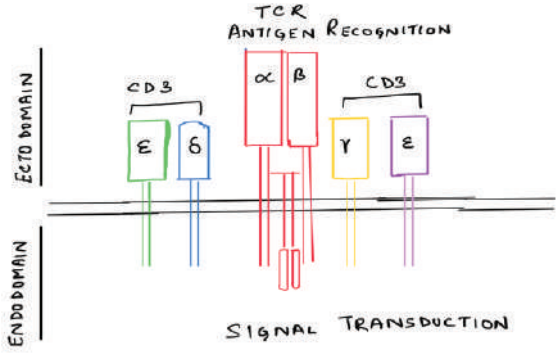



*Fig 1. T cell receptor (TCR) containing TCR-CD3 complex*

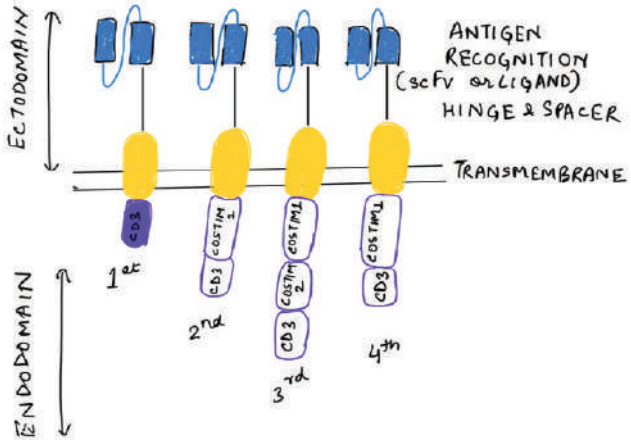



*Fig 2: 1st to 4th generation design of chimeric-antigen receptor (CAR). The ectodomain of CAR is composed of an antigen-binding region, a hinge, and a spacer. The transmembrane portion links the ectodomain to intracellular endodomain.*

**Targeting GBM with CAR-T Cells:**

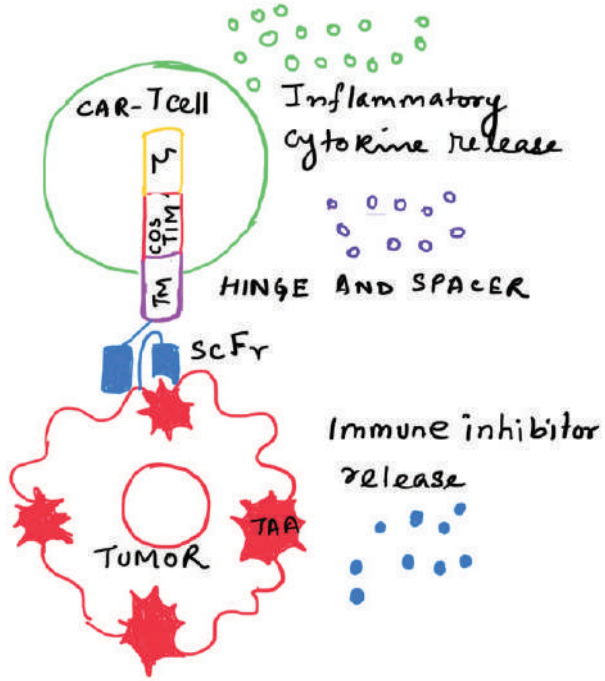



*Fig 3: Mechanism of CAR t-cell therapy. CAR T cell use the ScF domain of the CAR to recognize and bind to the tumour associated antigen (TAA) on the tumour cell surface. This binding activates CAR-T cell signalling through the CD3 which elicit cytotoxic functions by producing performing, granzyme and cytokine.*

CAR-T cell therapy holds promise for GBM treatment by targeting specific antigens expressed on the surface of glioblastoma cells. These antigens, such as EGFRvIII, IL13Rα2, and B7-H3, are often overexpressed in GBM tumours, making them ideal targets for CAR-T cell therapy (Fig 3).

EGFR is a receptor tyrosine kinase (RTK) known for its role in cancer development, particularly in glioblastoma (GBM). A common mutation, EGFRvIII, occurs in approximately 45% of GBM patients, resulting in constitutive activation of signaling pathways like RTK/RAS/AKT. Despite being specific to GBM and absent in normal tissues, inhibitors targeting EGFRvIII have shown limited effectiveness due to signaling bypass mechanisms. Consequently, there's interest in developing EGFRvIII-CAR T-cell therapy. O'Rourke et al. conducted the first human study, administering EGFRvIII-CAR T cells intravenously to 10 recurrent GBM patients.[8] While the treatment demonstrated safety and some tumour response, targeted antigen downregulation was observed.Currently, there are six EGFRvIII-CAR T cell clinical trials ongoing with two in combination with chemotherapy.[9]

Interleukin-13 receptor alpha 2 (IL13Rα2) is overexpressed in over 75% of GBM tumours, correlating with aggressive growth and poor prognosis. In gliomas, IL13Rα2 binds to IL-13 with higher affinity than IL13Rα1, sequestering IL-13 away from its pro-apoptotic signaling pathway. This specificity to GBM and enhanced binding affinity has made IL13Rα2 the primary target for CAR T-cell therapy in GBM. Initial clinical trials administering IL13Rα2-specific CAR T cells post-surgically showed promising results, with a median overall survival of 11 months and a 7.5-month regression period, but challenges such as antigen loss and limited T cell persistence have been observed. Strategies to enhance CAR T-cell efficacy targeting IL13Ra2 are being explored, including combination therapies with immune checkpoint inhibitors like nivolumab and ipilimumab in ongoing clinical trials (NCT04003649).[10]

HER2, also known as ERBB2, belongs to the EGFR family and is associated with poor survival in GBM patients due to elevated protein levels. While EGFRvIII is specific to GBM, HER2 is overexpressed in various cancers such as breast, ovarian, and GBM, as well as in some normal tissues, raising safety issues.

Liu et al.[11] demonstrated that reducing the strength of interaction between scFv and HER2 could enhance the selective binding of CAR T cells to tumour tissue over normal tissue in preclinical cancer models. This presents an effective approach for targeting antigens that aren't exclusive to solid tumours. Regarding GBM, researchers at Baylor College of Medicine conducted a clinical trial (NCT01109095) to assess the safety and effectiveness of HER2-specific CARs utilizing virus-specific T cells (CAR-VSTs).[12]

New targets such as Chlorotoxin, B7H3, EPHRIN TYPE A receptor 2, and CD70 have emerged as promising antigenic targets for GBM CAR T cell therapy. These targets are currently undergoing clinical evaluation, with results eagerly anticipated. Chlorotoxin, a peptide derived from scorpion venom, has shown specificity for GBM cells. B7H3 is a cell surface protein overexpressed in GBM, making it a potential target for CAR T cell therapy. EPHRIN TYPE A receptor 2 is involved in cell signalling and has been implicated in GBM progression. CD70, a member of the tumour necrosis factor (TNF) receptor family, is also being explored as a target for CAR T cell therapy in GBM. Continued research into these novel targets holds promise for advancing the treatment of GBM.

Numerous clinical trials are underway to evaluate the safety and efficacy of CAR-T cell therapy in GBM patients. These trials explore various aspects of CAR-T therapy, including different target antigens, CAR designs, and treatment protocols. Early results from some of these trials have shown promising responses and survival benefits in subsets of patients.

*Table 1: Clinical trials of CAR T-cell therapy in glioblastoma*

| Study Title | Study Location | Status | Target Antigen | Clinical Trial ID |
|---|---|---|---|---|
| Investigating CART-EGFRvIII Combined with Pembrolizumab in Glioblastoma | University of Pennsylvania, Philadelphia, USA | Completed | EGFRvIII | NCT03726515 |
| Clinical Trial for EGFRvIII-targeted CAR T Cell Therapy in Malignant Gliomas | National Institutes of Health Clinical Center, Bethesda, USA | Completed | EGFRvIII | NCT01454596 |
| Genetically Modified T-Lymphocyte Immunotherapy for High-Grade Malignant Glioma | City of Hope Medical Center, Duarte, USA | Completed | IL13Rα2 | NCT00730613 |
| Evaluating CAR-T Cells Targeting HER2 in Glioblastoma Patients | Houston Methodist Hospital, Houston, USA | Completed | HER2 | NCT01109095 |
| Efficacy and Safety Study of Brain-targeting EGFRvIII-CAR T Cells for Glioblastoma with Leptomeningeal Disease | Jyväskylä Central Hospital, Jyväskylä, Finland; University of Oulu, Oulu, Finland; Apollo Hospital, New Delhi, India | Active, not recruiting | EGFRvIII | NCT05063682 |

| Study Title | Study Location | Status | Target Antigen | Clinical Trial ID |
|---|---|---|---|---|
| Genetically Modified T-cell Therapy for Recurrent or Refractory Malignant Glioma | City of Hope Comprehensive Cancer Center, Duarte, USA | Active, not recruiting | IL13Rα2<br>B7-H3 | NCT02208362<br>NCT05241392 |
| Safety and Efficacy Study of Anti-B7-H3 CAR-T Cell Therapy for Recurrent Glioblastoma | Beijing Tiantan Hospital, Beijing, China | Recruiting | B7-H3 | NCT05345180 |
| Investigating B7-H3 CAR-T Therapy for Recurrent or Refractory Glioblastoma | Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China | Recruiting | B7-H3 | NCT05094456 |
| Autologous CAR-T Cells Targeting B7-H3 for Recurrent or Refractory Glioblastoma | Lineberger Comprehensive Cancer Center, Chapel Hill, USA | Recruiting | B7-H3 | NCT05650728 |
| Clinical Trial of B7-H3 Chimeric Antigen Receptor T Cells for Recurrent Glioblastoma Multiforme | Stanford Cancer Institute, Palo Alto, USA | Recruiting | B7-H3 | NCT04385163 |
| CAR-T Cells with Chlorotoxin Targeting MMP2+ Glioblastoma | City of Hope Medical Center, Duarte, USA | Recruiting | Chlorotoxin | NCT05241379 |

**CHALLENGES AND FUTURE DIRECTIONS:**

Despite the progress, challenges remain in the development and optimization of CAR-T cell therapy for GBM. These challenges include:

(A) The immune privilege of the brain presents physical and cellular obstacles to CAR-T-cell homing. The blood-brain barrier, consisting of endothelial cells, astrocyte end-feet, and pericytes, forms a formidable barrier. Additionally, at the post-capillary venules, a perivascular space harbors antigen-presenting cells (APCs) crucial for reactivating T cells to traverse the glia limitans.

(B) The immunosuppressive tumour microenvironment (TME) is comprised of pro-tumoural myeloid cells, immunosuppressive cytokines / chemokines, and checkpoint molecules, collectively hindering CAR-T-cell efficacy and activation.

(C) Hypoxia within glioblastoma (GBM) creates a hostile environment, severely limiting oxygen and nutrient availability for CAR-T cells.

(D) Prolonged antigen exposure leads to CAR-T-cell exhaustion, compromising their functionality over time.

(E) Inter- and intra-tumoural heterogeneity pose significant challenges in designing CAR constructs and selecting target antigens, complicating the development of effective therapies.

**CONCLUSION:**

CAR-T cell therapy represents a promising approach in the treatment of glioblastoma, offering new hope for patients with this aggressive form of brain cancer. Continued research and clinical trials are essential to further explore the potential of CAR-T therapy and bring effective treatment. The table below gives a comprehensive overview of immunotherapeutic strategies tested in patients with Glioblastoma Multiforme (GBM). This table highlights the strengths and weaknesses of each strategy, along with specific examples of immunotherapies applied to GBM patients.

In the battle against Glioblastoma Multiforme (GBM), the quest for effective treatments continues to evolve, with promising modalities emerging beyond the confines of conventional therapy. While CAR T cell therapy shines brightly on the forefront, our table reveals a constellation of innovative approaches waiting to be harnessed. From the precision of antibodies to the potential of vaccines, the adaptability of immunotherapy, and the potency of adoptive effector cell transfer, the arsenal against GBM expands. These strategies offer not just hope, but tangible pathways toward improved outcomes for patients. As we navigate this complex landscape, it becomes increasingly evident: the future of GBM treatment lies not in singular solutions, but in the orchestration of diverse immunotherapeutic strategies, each contributing its unique brilliance to illuminate the path towards conquering this formidable disease. ■

## REFERENCES:


1. *Koshy M, Villano JL, Dolecek TA, Howard A, Mahmood U, Chmura SJ, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries. J Neurooncol. 2012 Mar;107(1):207–12.*
2. *Tran B, Rosenthal MA. Survival comparison between glioblastoma multiforme and other incurable cancers. J Clin Neurosci Off J Neurosurg Soc Australas. 2010 Apr;17(4):417–21.*
3. *Torp SH, Solheim O, Skjulsvik AJ. The WHO 2021 Classification of Central Nervous System tumours: a practical update on what neurosurgeons need to know—a minireview. Acta Neurochir (Wien). 2022;164(9):2453–64.*
4. *Alifieris C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. Pharmacol Ther. 2015 Aug;152:63–82.*
5. *Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJB, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009 May;10(5):459–66.*
6. *Jackson CM, Choi J, Lim M. Mechanisms of immunotherapy resistance: lessons from glioblastoma. Nat Immunol. 2019 Sep;20(9):1100–9.*
7. *Li L, Zhu X, Qian Y, Yuan X, Ding Y, Hu D, et al. Chimeric Antigen Receptor T-Cell Therapy in Glioblastoma: Current and Future. Front Immunol [Internet]. 2020 Nov 3 [cited 2024 May 31];11. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2020.594271/full*
8. *O'Rourke DM, Nasrallah MP, Desai A, Melenhorst JJ, Mansfield K, Morrissette JJD, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med. 2017 Jul 19;9(399):eaaa0984.*
9. *Google Docs [Internet]. [cited 2024 May 31]. car t cell in gbm. Available from:https://docs.google.com/document/d/1UDPFwxjLKQ_TWuvM0y6Z3IHr95jpDuItkJwtuX4raw8/edit?ouid=111795257640473863566&usp=docs_home&ths=true&usp=embed_facebook.*
10. *IL13Ra2-CAR T Cells With or Without Nivolumab and Ipilimumab in Treating Patients With GBM - Full Text View - ClinicalTrials.gov [Internet]. [cited 2024 Jun 6]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04003649*
11. *Liu X, Jiang S, Fang C, Yang S, Olalere D, Pequignot EC, et al. Affinity-Tuned ErbB2 or EGFR Chimeric Antigen Receptor T Cells Exhibit an Increased Therapeutic Index against Tumors in Mice. Cancer Res. 2015 Sep 1;75(17):3596–607.*
12. *Ahmed N, Brawley V, Hegde M, Bielamowicz K, Kalra M, Landi D, et al. HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma: A Phase 1 Dose-Escalation Trial. JAMA Oncol. 2017 Aug 1;3(8):1094–101.*

♦ Review Article

# HER2 dual ISH DNA Probe Cocktail Assay in Breast Cancer

*Moumita Sengupta[1], Anupam Sarma[2], Shiraj Ahmed[3], Lopamudra Kakoti[4], Sakshi Gupta[5], and Rukmini Bezbaruah[6]*

*[1]DM Resident, [2]Professor and Head, [3]Professor, [4]Associate Professor, [5,6]Assistant Professor,Department of Oncopathology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

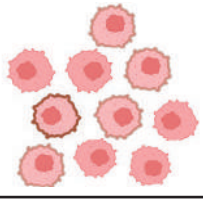
Broadly neoplastic breast lesion is classified morphologically into in situ and invasive and further into ductal and lobular. The literature published by Perou *et al* in 1999, transformed dramatically the method of classification of breast carcinoma and introduced four molecular subclasses: ER positive (Luminal A) and (Luminal B), HER-2/new positive, Basal-like-Triple Negative.[1] HER2 gene over expression and amplification is the characteristic features of 15-20% invasive breast carcinoma.[2]

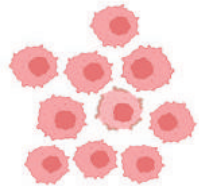
HER2 gene is located on chromosome 17q12 and comprises of membrane receptor that dimerize and phosphorate to enable signal transduction from cell exterior to nucleus.[3] HER2 is considered both prognostic and predictive biomarker. HER2 positive tumours behave more aggressively with incidence of metastasis than HER2 negative counterpart. But on the other hand HER2 positivity predicts likelihood of responding to HER2 targeted therapy.[4,5] Thus HER2 testing is routinely performed for all newly diagnosed breast cancers in both upfront setting as well as in post neoadjuvant setting for re characterization in case of disease progression.[6]

**HER2 STATUS ASSESSMENT: INTRODUCTION OF HER2 DUAL ISH DNA PROBE COCKTAIL ASSAY :**

Combination of immunohistochemistry [IHC] and in situ hybridization [ISH] technique is recommended by American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.[7] IHC detects the HER2 protein expression on the cell membrane of breast cancer cells, while ISH detects the presence of gene amplification using locus specific probe [HER2] and centromeric probe [CEP17].[8] IHC slide interpretation is the initial step of the HER2 testing workflow. Completeness of membrane staining, intensity of staining and percentage of cells in which the staining is identified are the three main parameters of HER2 IHC scoring.

*Table 1: HER2 IHC is scored using a three-tiered system [ 2018 ASCO/CAP guideline] [7]*

| Score | Completeness of membrane staining | Intensity | Percentage of cells in which staining is identified | | Control |
|---|---|---|---|---|---|
| 3+ | Circumferential membrane staining that is complete | Intense | >10% of tumor cells |  | Batch controls and on slide controls show appropriate staining |
| 2+ | Complete membrane | Weak to moderate | >10% of tumor cells |  | |

| Score | Completeness of membrane staining | Intensity | Percentage of cells in which staining is identified | | Control |
|---|---|---|---|---|---|
| 1+ | Incomplete membrane | faint/ barely perceptible | >10% of tumor cells |  | Batch controls and on slide controls show appropriate staining |
| 0 | No staining is observed or Membrane staining that is incomplete | faint/barely perceptible | <10% of tumor cells |  | |

In the case of an equivocal result (score 2+), ISH is used as a reflex test. Fluorescent in situ hybridization [FISH] technique is considered gold standard for detection of HER2 gene amplification using fluorescent labelled HER2 and centromeric probe.[9] But this technique needs special instruments for processing and evaluation & expertise for its interpretation. Bright field in situ hybridization technique has been introduced to overcome these difficulties. Dual ish DNA probe cocktail assay [DDISH] is the latest version of its which has been approved by US Food and Drug Administration (FDA) for detection of HER2 gene amplification in the year 2020.[10]

*Table 2: Comparison of IHC and ISH technique.*

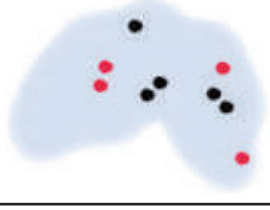
| | FISH/ DDISH | IHC |
|---|---|---|
| **Assessment** | Number of HER2 gene copies | Level of HER2 protein expression |
| **Site of interpretation** | Nucleus | Cell membrane |
| **Methodology** | labelled DNA probe | Antibody and detection system |

**PRINCIPLES OF DDISH PROCEDURE :**

The HER2 Dual ISH DNA Probe Cocktail comprises of HER2 probes (labeled with the hapten dinitrophenyl or DNP) and Chromosome 17 probes (labeled with the hapten digoxigenin or DIG). The probes are sketched to detect amplification of the HER2 gene in invasive breast carcinoma. Post incubation with hydroxyquinoxaline-labeled mouse anti-DNP primary antibody and mouse anti-hydroxyquinoxaline horseradish peroxidase secondary antibody conjugate, the silver precipitate is deposited in the nuclei due to hybridization reaction. A black dot represents a single copy of HER2 gene. On the other hand nitropyrazole-labeled anti-DIG primary antibody adheres to the DIG hapten on the CEP17 probe. Red precipitate is visualised as anti-hapten primary antibody hybridize with the mouse antinitropyrazole conjugated to the alkaline phosphatase enzyme. Counterstaining is done along with Haematoxylin and eosin stain followed by evaluation by light microscope under 60 x objectives.[11]

**ENUMERATION OF THE SISH AND RED ISH SIGNALS TO DETERMINE HER2 GENE STATUS :**

A minimum of 40 tumour nuclei needs to be counted and average HER2 and CEP17 signals and their ratio is calculated. If needed additional 20 tumour nuclei will be analysed.

| Signals | Enumeration | Signals | Enumeration |
|---|---|---|---|
|  | Counting of overlapping nuclei is not recommended |  | Count as 2 black (HER2) and 2 red (Chr17) signals. |
|  | No signals - not included in signal counting |  | Count as 1 black (HER2) and 2 red (Chr17) signals. The black signal is a "doublet". Count two adjacent signals of same color only if the distance between the signals is equal to or greater than the diameter of a single signal. |

| Signals | Enumeration | Signals | Enumeration |
|---|---|---|---|
|  | Only one colour signal - not included in signal counting |  | Small SISH clusters can only be estimated by using the size of a single signal as reference. Use stromal cells to estimate signal size (smaller cell). For instance, this cluster could be estimated as 6 SISH signals - adding the other 2 single signals yields a total count of 8. Count as 2 red signals. Note on scoring sheet that clusters are present for HER2. |
|  | Signals outside the nucleus - - not included in signal counting |  | Estimate the large cluster. Here, the cluster can be estimated as 12 black signals - adding the other 4 single signals yields a total count of 16. Count red signals as 2 copies of Chr17. Note on scoring sheet that clusters are present for HER2. |
|  | Count as 1 black (HER2) and 1 red (Chr17) signa |  | A red signal close to a black signal should be counted as one red signal and one black signal. This may require enumeration at 60x objective to discern. Therefore, count as 4 black (HER2) and 2 red (Chr17) signals. |

**INTERPRETATION OF D-DISH[12] :**

| Interpretation | HER2/ CEN17 ratio | HER2 copy number/ nuclei | CerbB2 IHC score |
|---|---|---|---|
| **Amplification** | **≥ 2** | **≥ 4** | **Any score** |
| | **≥ 2** | **<4** | **3+** |
| | **<2** | **≥ 6** | **2+ or 3+** |
| | **<2** | **≥ 4 and <6** | **3+** |
| **No amplification** | <2 | <4 | Any score |
| | ≥ 2 | <4 | 0 to 2+ |
| | <2 | ≥ 6 | 0 to 1+ |
| | <2 | ≥ 4 and <6 | 0 to 2+ |

**QUALITY CONTROL :**

**Preanalytical**
- Cold ischaemia time<1 hours
- Fixative - 10% neutral buffer
- Fixation time : 6-72 hours

**Analytical**
- Evaluate both H&E and IHC slide to locate invasive focus [ target area]
- Internal control [ fibroblast, lymphocytes]
- Look for tumor heterogeneity

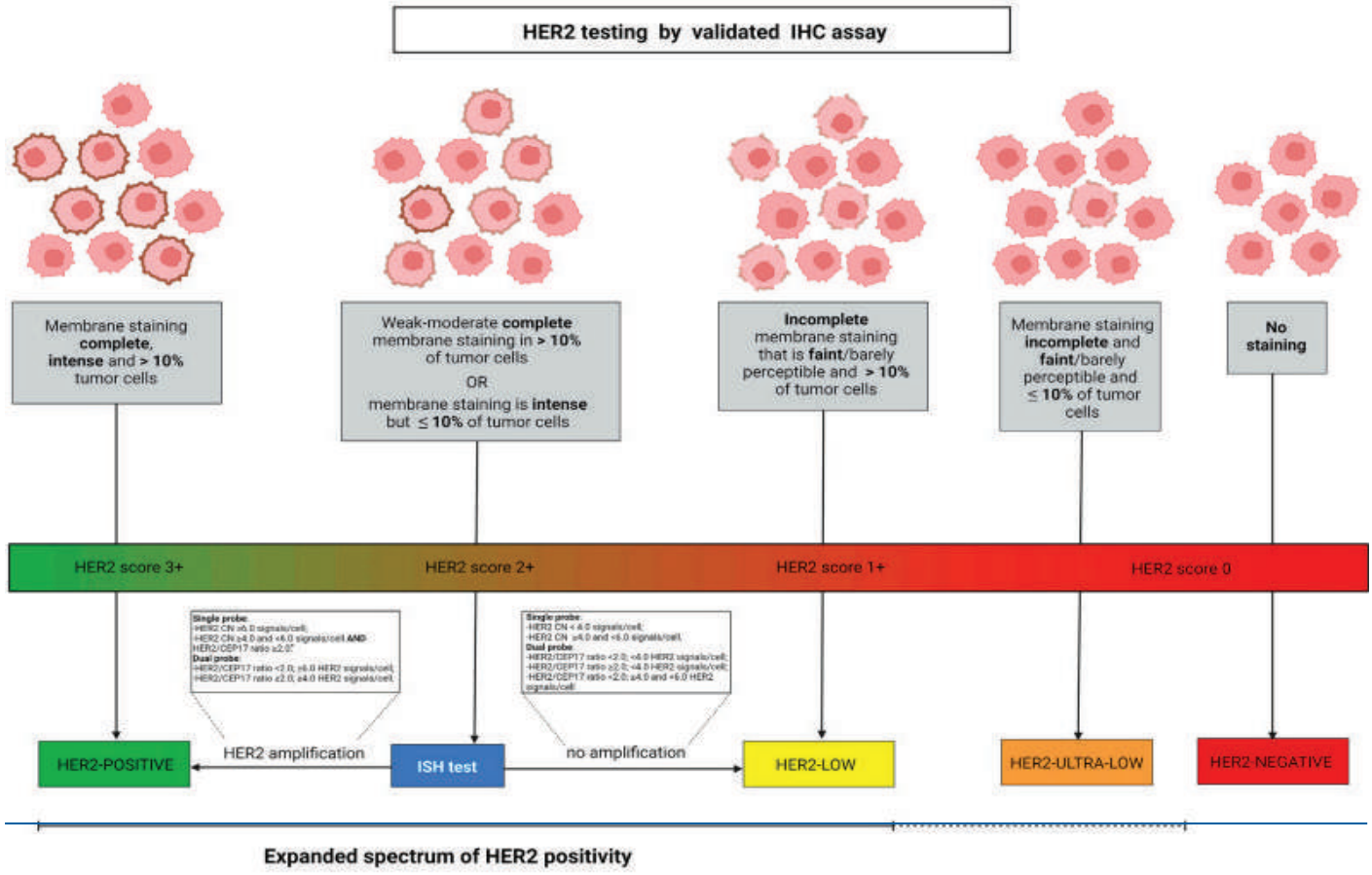
**Postanalytical**
- Final report [ considering both IHC and DDISH] should be conveyed to surgical oncologist

**DISCUSSION :**

Breast carcinoma is extremely heterogenous in terms of tumour morphology, prognosis and response to therapy.[13] Traditional clinical [age] and pathological [tumor size and grade] fails to assign them in different risk categories. Identification of HER2 oncogene and discovery of HER2 targeted therapy is the major revolution in this context. Anti HER2 monoclonal antibodies [trastuzumab and pertuzumab] drastically improve the life expectancy in HER2 positive breast carcinoma.[14] A novel anti-HER2 antibody-drug conjugate (ADC) is the newest addition in the existing lists. In patient with residual disease after neoadjuvant therapy, Ado-trastuzumab-emtansine (T-DM1) is approved in adjuvant setting. DESTINY-Breast 03 trial proposed another HER2 directed ADC Trastuzumab-deruxtecan (T-DXd) with an appreciable progression free survival.[15]

Tumours with low levels of HER2 expression (i.e. IHC 1+ or 2+ with negative ISH), is considered as HER2 "low. Among IHC score 0 tumours, a substantial proportion of cases shows incomplete and faint staining in ≤10% of tumour cells.[16]

This group is considered as HER2 "ultra low". Several translational research studies are applying different classes of monoclonal antibodies in HER2-low and HER2 ultralow breast cancer.[17]




DDISH is completely automated methodology for detection of HER2 gene status using bright field microscopy. Excellent correlation with morphology and prompt detection of both intermixed and clustered heterogeneity are the key attractive features of this newly introduced technique.[18] Quantification of average CEP17, and HER2 signals and assessment of the HER2:CEP17 ratio almost corroborate with FISH with minimal discordant.[19,20]

Rathi *et al* conducted a study to evaluate the concordance of the latest D-DISH assay versus FISH in Tata Memorial Hospital, Mumbai.[21] They successfully validated the latest version of D-DISH assessment as a substitute for FISH for rapid detection of HER2 gene status. They also documented perfect agreement and good interobserver reproducibility among four pathologist [Concordance of 98.65% and a Cohen κ value of 0.97] Misclassification may be attributed by smaller [tiny dust like] HER2neu signals and larger CEP17 [large blotchy] signals. Ability of simultaneous examination of both histomorphology and DDISH slides, provision of review the slides in future and ease to examine in bright field microscope overshadow its disadvantages. Adoption of this newly emerging technique in routine diagnostic services for assessment of HER2 status may substitute FISH in future.

Exact stratification of all possible HER2 associated breast lesions needs morpho-molecular approach including both immunohistochemistry and in situ hybridization platforms. Different trials are highlighting the major switch in the concept of delivery of care in breast carcinoma patient and collaborative approach of oncopathologists, medical oncologist and surgical oncologist in taking appropriate therapeutic decision in different HER2 entities [HER2 amplified, HER2low and HER2 ultralow]. ■

## REFERENCES:


1] *Perou CM, Jeffrey SS, Van de Rijn M, Rees CA, Eisen MB, Ross DT et al . Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc Natl Acad Sci U S A 1999 Aug 3;96(16):9212-7.*

2] *Seshadri, R., Firgaira, F. A., Horsfall, D. J., McCaul, K., Setlur, V., and Kitchen, P. (1993). Clinical Significance of HER-2/neu Oncogene Amplification in Primary Breast Cancer. The South Australian Breast Cancer Study Group. Jco 11, 1936–1942.*

3] *Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177–182.*

4] *Ghosh J, Gupta S, Desai S, et al. Estrogen, progesterone and HER2 receptor expression in breast tumors of patients, and their usage of HER2-targeted therapy, in a tertiary care centre in India. Indian J Cancer. 2011;48(4):391–396.*

5] *Wang J, Xu B. Targeted therapeutic options and future perspectives for HER2-positive breast cancer. Signal Transduct Target Ther. 2019;4(1):1–22.*

6] *Press MF, Kim GN, Khoshchehreh M, Ma Y, Slamon DJ. HER2 testing in the era of changing guidelines. In: Hurvitz S, McCann K, eds. HER2-Positive Breast Cancer. St Louis, MO: Elsevier Inc.; 2018:13–39.*

7] *Wolff, A. C., Hammond, M. E. H., Allison, K. H., Harvey, B. E., Mangu, P. B., Bartlett, J. M. S., et al. (2018). Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Jco 36, 2105–2122.*

8] *Pauletti, G., Godolphin, W., Press, M. F., and Slamon, D. J. (1996). Detection and Quantitation of HER-2/neu Gene Amplification in Human Breast Cancer Archival Material Using Fluorescence In Situ Hybridization. Oncogene 13 (13), 63–72.*

9] *Press, M. F., Slamon, D. J., Flom, K. J., Park, J., Zhou, J. Y., and Bernstein, L. (2002). Evaluation of HER-2/neu Gene Amplification and Overexpression: Comparison of Frequently Used Assay Methods in a Molecularly Characterized Cohort of Breast Cancer Specimens. J. Clin. Oncol. 20 (20), 3095–3105.*

10] *US Food and Drug Administration. VENTANA HER2 Dual ISH DNA Probe Cocktail—P190031. FDAhttps://www.fda.gov/medical-devices/recentlyapproved-devices/ventana-her2-dual-ish-dna-probe-cocktail-p190031. Accessed February 5, 2023.*

11] *Ventana HER2 Dual ISH DNA Probe Cocktail assay [package insert]. Published July 27, 2020. Accessed December 18, 2022. https://diagnostics. roche. com/global/en/products/tests/ventana-her2-dual-ish-dna-probe-cocktail-assay. Html*

12] *Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO-CAP guideline update [published online June 7, 2023]. Arch Pathol Lab Med. 2023.*

13] *Filho, O. M., Viale, G., Stein, S., Trippa, L., Yardley, D. A., Mayer, I. A., et al. (2021). Impact of HER2 Heterogeneity on Treatment Response of Early-Stage HER2- Positive Breast Cancer: Phase II Neoadjuvant Clinical Trial of T-DM1 Combined with Pertuzumab. Cancer Discov. 11, 2474–2487.*

14] *Dieci, M. V., and Miglietta, F. (2021). HER2: a Never Ending story. Lancet Oncol. 22, 1051–1052.*

15] *Cortes, J., Kim, S. B., Chung, W. P., Im, S. A., Park, Y. H., Hegg, R., et al. (2021). LBA1 - Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients (Pts) with HER2+ Metastatic Breast Cancer (mBC): Results of the Randomized Phase III DESTINY-Breast03 Study. Ann. Oncol. 32, S1287–S1288.*

16] *Banerji, U., van Herpen, C. M. L., Saura, C., Thistlethwaite, F., Lord, S., Moreno, V., et al. (2019). Trastuzumab Duocarmazine in Locally Advanced and Metastatic Solid Tumours and HER2-Expressing Breast Cancer: a Phase 1 Dose-Escalation and Dose-Expansion Study. Lancet Oncol. 20, 1124–1135.*

17] *Denkert, C., Seither, F., Schneeweiss, A., Link, T., Blohmer, J.-U., Just, M., et al. (2021). Clinical and Molecular Characteristics of HER2-Low-Positive Breast Cancer: Pooled Analysis of Individual Patient Data from Four Prospective, Neoadjuvant Clinical Trials. Lancet Oncol. 22, 1151–1161.*

18] *Kosa C, Kardos L, Kovacs J, Szollosi Z. Comparison of dual-color dualhapten brightfield in situ hybridization (DDISH) and fluorescence in situ hybridization in breast cancer HER2 assessment. Pathol Res Pract. 2013;209(3): 147–150.*

19] *Gao FF, Dabbs DJ, Cooper KL, Bhargava R. Bright-field HER2 dual in situ hybridization (DISH) assay vs fluorescence in situ hybridization (FISH): focused study of immunohistochemical 2þ cases. Am J Clin Pathol. 2014;141(1):102–110.*

20] *Troxell M, Sibley RK, West RB, Bean GR, Allison KH. HER2 dual in situ hybridization: correlations and cautions. Arch Pathol Lab Med. 2020;144(12): 1525–1534.*

21] *Rathi A, Sahay A, Shet TM, Patil, Desai SB. Validation of Dual-Color Dual In Situ Hybridization for HER2/neu Gene in Breast Cancer. Arch Pathol Lab Med. 2024 Apr 1;148(4):453-460.*

♦ Review Article

# Artificial Intelligence in Gynaecologic Oncology

*Karthik Chandra Bassetty[1], Debabrata Barmon[2], Upasana Baruah[3], and Dimpy Begum[4]*

*[1] Senior Resident, [2]Professor and In-charge, [3]Professor, and [4] Associate Professor*
*Department of Gynaecology Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

## INTRODUCTION:

"Artificial Intelligence" (AI) is a digitalised computer-based system that seeks to replicate the human brain's critical analysis capacity using various algorithms.[1] The purpose of this review article is to briefly discuss the components and role of AI in Gynaecology Oncology.

## EVOLUTION OF AI:

The evolution of AI has been illustrated in *Figure 1*.

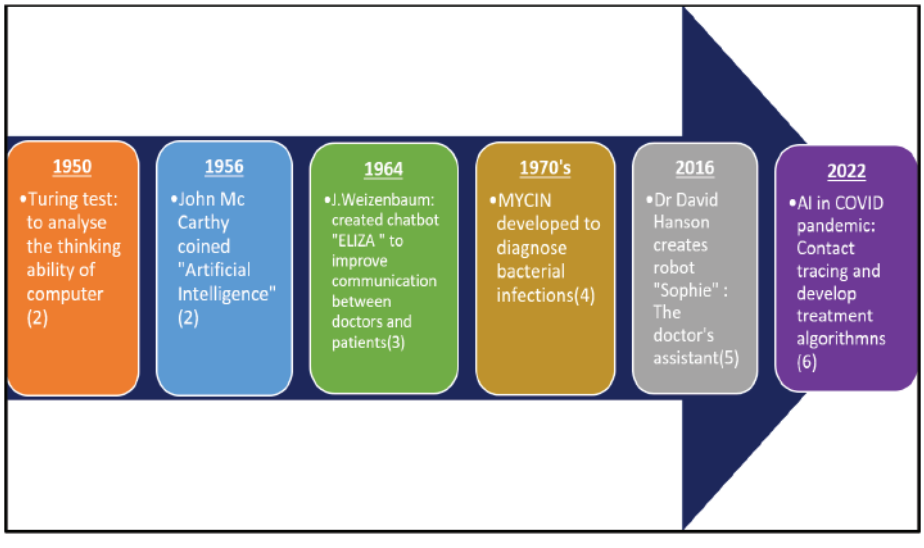



*Figure 1: Figure showing the evolution of AI.*

## COMPONENTS OF AI:

In the "conventional system" trained doctors based on their experience recognise various patterns in diagnostic tests to reason out and draw their conclusions to reach the final diagnosis. Traditional computer programming necessitates a programmer (human) to code in a specific set of instructions (program) and then modify the program till the computer analyses the data as desired to produce the required outcome. This becomes extremely challenging in medical science due to the complexity of diseases and varied presentations.

Machine learning is an alternative to this process wherein the computer is fed with the input and the desired output, and it returns a program which maps the inputs to the output. After fine-tuning this program (training and validation) a new set of data is provided and the cost/loss function (difference between outcome and desired outcome) is computed. The machine keeps on learning and evolving till it gets its predictions right. Once this goal is achieved the machine is considered "trained". The examples of well-known machine learning programs are Logistic regression, support vector machines and Random Forests. [7]

Deep Learning (DL) is based on the mesmerizing structure of the human brain with its intercalated neural network. It is a specialised form of machine learning based on Artificial/Convoluted Neural Networks (ANN/CNN) with interconnecting units called artificial neurons between them.[8] Deep learning is used in various image and speech recognition applications. [9]

This entire spectrum which includes

machine learning, deep learning and generative AI comes under the purview of artificial intelligence is shown in *Figure 2.*

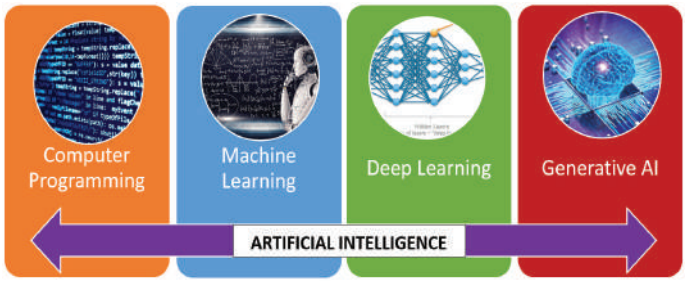



*Figure 2: Components of artificial intelligence- It includes computer programming, machine learning, deep earning and generative AI.*

## APPLICATION OF AI IN GYNECOLOGY ONCOLOGY:

The advent of AI in Gynaecology Oncology has been promising. Its application has been extensively studied in cervical cancer screening. In the subsequent sections, we will discuss the areas wherein AI has been tested.

### 1) Cancer Screening :

To achieve the WHO goal of cervical cancer elimination by 2030 we need to screen at least 70% of all eligible women by a high-performance test.[10] AI can help to circumvent the drawbacks of cytology/visual inspection with acetic acid (interobserver variation and requirement of specialised trained personnel) and Human papillomavirus testing (limited availability and requirement for specialised laboratories) and colposcopy (subjective interpretation).[11]

The use of Digital colposcopy/ Visual inspection with deep learning technology could help to increase the accuracy of automated image diagnosis.[12] With the advent of novel algorithms, the sensitivity of various AI-based diagnostics has surpassed 90% since 2018.[13] A study done in Costa Rica achieved an Area Under Curve (AUC) of 0.91 for cervical image analysis which was higher than the diagnostic accuracy of traditional cytology, liquid-based cytology and even HPV DNA detection techniques.[14]

The "EVA system"(combination of a digital colposcope, mobile application and online portal application) from MobileODT is one such device (shown in *Figure 3*) which utilised AI to perform Automated Visual Examination (AVE) and has a sensitivity of 97.7% and specificity of 85% in women of reproductive age group[15]. This translates into earlier and more effective treatment of lesions using minimally invasive procedures like thermal ablation reducing the need for unnecessary biopsies.[16]

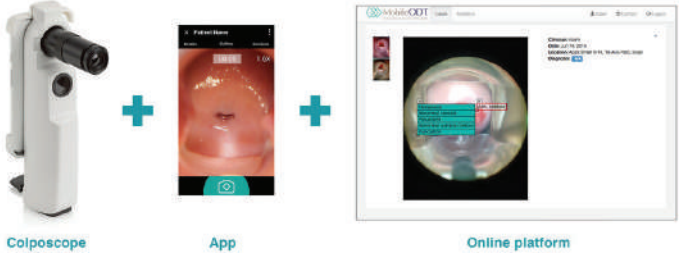



*Figure 3: EVA system consisting of the colposcope, mobile application and online platform which uses the AI-based diagnostic system to assess the cervix during cervical screening.*

### 2) Cancer Patients:

Various studies have evaluated the application of AI in gynaecological cancers as shown in *Figure 4.*

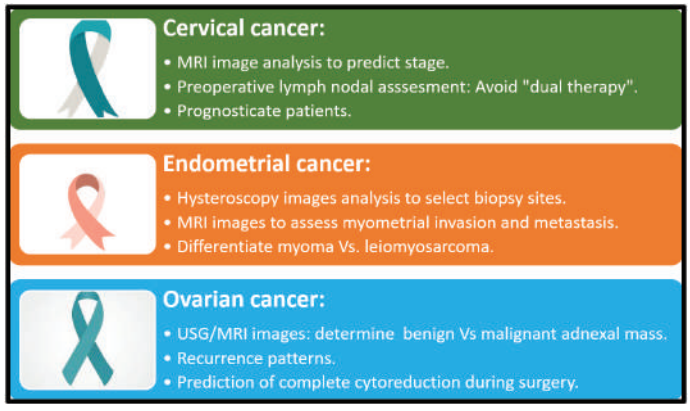



*Figure 4: Figure showing the application of AI in gynaecological cancers*

### 3) Others :

The use of AI in the perioperative period and research setting has been depicted in *Figure 5.*

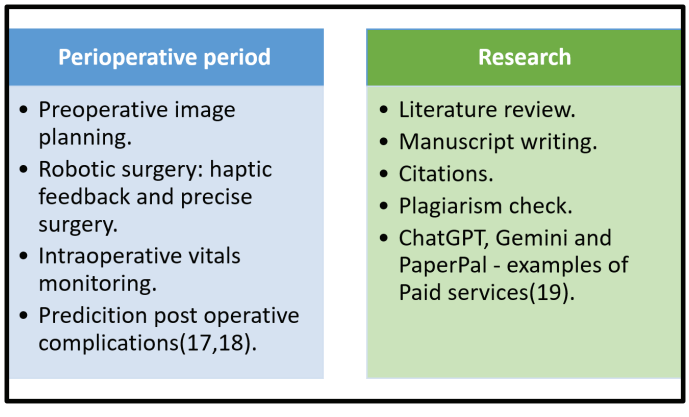



*Figure 5: Figure showing the application of AI in the perioperative period and research setting.*

## PROS AND CONS OF AI:

AI has shown promise in analysing diagnostic images to determine disease status and increase the speed of analysis while reducing the errors in diagnosis which are the main drawbacks with human interpretations owing to the ever-growing workload

on health care professionals. In most of the studies, the performance of AI was comparable to that of human experts.[20] The use of AI in research has the potential to manage extensive datasets and help to improve the quality of a research paper.

The main drawback of above-described AI applications was that they used a small dataset of patients in single institutes.[21] Most of the studies lacked external validation due to the smaller data set used and hence could not be applicable to certain populations or were making incorrect predictions for certain groups. AI-based systems thus might struggle to predict outcomes in cases where a lot of uncertainty or multiple outcomes are possible.

A common problem encountered is the limited clinical knowledge of deep learning scientists and the limited technical knowledge of clinical experts during the development of the AI model. The need of the hour is to address the importance of data privacy as the development of AI-based systems requires large data sets which has to be anonymised.[22] This data management process needs to be addressed to keep the data unadulterated as wrong data sets can lead to improper training of AI systems which can have disastrous implications for patients.[23]

Often these data sets are not available for testing nor can a particular AI be used on other diagnostic systems which leads to the lack of generalisability and reproducibility. Non generalisation of results occurs due to underlying patient population differences, socioeconomic differences and disease burden between centres where the AI system was developed.[24] As most of the AI systems do not share their source code hence the reproducibility in another institution or with a different image generator might not work as well as it had done during the testing phase.

Legal responsibility has also been a topic of debate due to the split up of responsibility across the design of the model, the human-machine interaction and the AI-driven human decision.[25] Another common problem with AI is the "hallucination effect" wherein despite the propensity of the system to introduce errors, the generated results appear trustworthy despite being factually incorrect.[26] This has been demonstrated in the use of ChatGPT in the research field. Moreover, the free version of ChatGPT incorporates information up to 2021 only.[27] A study showed AI-derived content is of limited depth, contains factual errors and fabricates references thereby resulting in a formula-based language of the manuscript.[28] This has led to the prohibition of the utilisation of AI systems by educational institutions including schools and universities to prevent misuse of AI technology.[29]

**WHAT DOES THE FUTURE HOLD ? :**

Various machine learning platforms such as those offered on the online site "Kaggle" provide data sets for data scientists and machine learning practitioners to develop more accurate prediction models.[30] This helps to constantly improve the AI-based devices to further streamline the diagnosis process. Multicentre studies both at a national and international level can help in the creation of robust algorithms.[31] A shared platform wherein data scientists and clinical experts can pool their expertise can help streamline this process.

**POSSIBLE APPLICATION OF AI IN OUR INSTITUTE :**

As of date the role of AI has been externally validated in cervical cancer screening. This allows us to extend our screening outreach programmes to remote areas wherein a healthcare worker can use the AI-based system to analyse the cervical images and follow the treatment algorithm provided. This can also be applied to the Papanicolaou (PAP) smear which is prepared by a technician and read by an AI-based application. As the AI app has a provision for uploading to an online platform the concerned doctor can also provide his expertise when needed. In Kenya, this has been tried on a trial basis as shown in *Figure 6*. This technological advancement can be a game changer for our country where the cervical screening rates are quite dismal.


*Figure 6: Slide digitization equipment, including (1) laptop computer with access to the slide-management platform, (2) slide scanner, (3) mobile-network router, and (4) Papanicolaou test microscopy slide Image source: Holmstöm et al., JAMA Network Open 2021.*

**CONCLUSION:**

The use of AI is an exciting domain towards practical solutions. ■

## REFERENCES:


1. *Amisha, Malik P, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. J Fam Med Prim Care. 2019 Jul;8(7):2328–31.*
2. *McCarthy J. EPISTEMOLOGICAL PROBLEMS OF ARTIFICIAL INTELLIGENCE. In: Webber BL, Nilsson NJ, editors. Readings in Artificial Intelligence [Internet]. Morgan Kaufmann; 1981 [cited 2024 Jul 27]. p. 459–65. Available from: https://www.sciencedirect.com/science/article/pii/B9780934613033500350*
3. *An Overview of Chatbot Technology | SpringerLink [Internet]. [cited 2024 Jul 27]. Available from: https://link.springer.com/chapter/10.1007/978-3-030-49186-4_31*
4. *Shortliffe EH, Davis R, Axline SG, Buchanan BG, Green CC, Cohen SN. Computer-based consultations in clinical therapeutics: Explanation and rule acquisition capabilities of the MYCIN system. Comput Biomed Res. 1975 Aug 1;8(4):303–20.*
5. *Parviainen J, Coeckelbergh M. The political choreography of the Sophia robot: beyond robot rights and citizenship to political performances for the social robotics market. AI Soc. 2021 Sep 1;36(3):715–24.*
6. *Bindra S, Jain R. Artificial intelligence in medical science: a review. Ir J Med Sci. 2024 Jun;193(3):1419–29.*
7. *Machine Learning in Fetal Cardiology: What to Expect - PubMed [Internet]. [cited 2024 Jul 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/31910421/*
8. *A typology of reviews: an analysis of 14 review types and associated methodologies - Grant - 2009 - Health Information & Libraries Journal - Wiley Online Library [Internet]. [cited 2024 Jul 27]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1471-1842.2009.00848.x*
9. *Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. Commun ACM. 2017 May 24;60(6):84–90.*
10. *Global strategy to accelerate the elimination of cervical cancer as a public health problem [Internet]. [cited 2024 Jul 27]. Available from: https://www.who.int/publications/i/item/9789240014107*
11. *Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin Number 131: Screening for cervical cancer. Obstet Gynecol. 2012 Nov;120(5):1222–38.*
12. *Xue P, Ng MTA, Qiao Y. The challenges of colposcopy for cervical cancer screening in LMICs and solutions by artificial intelligence. BMC Med. 2020 Jun 3;18(1):169.*
13. *Huang W, Sun S, Yu Z, Lu S, Feng H. Chronic Cervicitis and Cervical Cancer Detection Based on Deep Learning of Colposcopy Images Toward Translational Pharmacology. Front Pharmacol [Internet]. 2022 May 27 [cited 2024 Jul 27];13. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.911962/full*
14. *Ahmed SR, Befano B, Lemay A, Egemen D, Rodriguez AC, Angara S, et al. REPRODUCIBLE AND CLINICALLY TRANSLATABLE DEEP NEURAL NETWORKS FOR CANCER SCREENING. Res Sq. 2023 Mar 3;rs.3.rs-2526701.*
15. *MobileODT. Automated Visual Evaluation (AVE) explained: Everything you need to know about the new AI for cervical cancer screening [Internet]. MobileODT. 2019 [cited 2024 Jul 27]. Available from: https://www.mobileodt.com/blog/everything-you-need-to-know-about-ave-automated-visual-examination-for-cervical-cancer-screening/*
16. *EVA COLPO | MobileODT [Internet]. [cited 2024 Jul 27]. Available from: https://www.mobileodt.com/products/eva-colpo/*
17. *Hassan AM, Rajesh A, Asaad M, Jonas NA, Coert JHenk, Mehrara BJ, et al. Artificial Intelligence and Machine Learning in Prediction of Surgical Complications: Current State, Applications, and Implications. Am Surg. 2023 Jan;89(1):25–30.*
18. *Bhattacharya K, Bhattacharya N, Kumar S, Yagnik VD, Garg P, Choudhary PR. Artificial Intelligence in Predicting Postoperative Surgical Complications. Indian J Surg [Internet]. 2024 May 9 [cited 2024 Jul 27]; Available from: https://doi.org/10.1007/s12262-024-04081-2*
19. *Zawacki-Richter O, Marín VI, Bond M, Gouverneur F. Systematic review of research on artificial intelligence applications in higher education – where are the educators? Int J Educ Technol High Educ. 2019 Oct 28;16(1):39.*
20. *Brandão M, Mendes F, Martins M, Cardoso P, Macedo G, Mascarenhas T, et al. Revolutionizing Women's Health: A Comprehensive Review of Artificial Intelligence Advancements in Gynecology. J Clin Med. 2024 Feb 13;13(4):1061.*
21. *Shen WC, Chen SW, Wu KC, Hsieh TC, Liang JA, Hung YC, et al. Prediction of local relapse and distant metastasis in patients with definitive chemoradiotherapy-treated cervical cancer by deep learning from [18F]-fluorodeoxyglucose positron emission tomography/computed tomography. Eur Radiol. 2019 Dec;29(12):6741–9.*
22. *Acharya UR, Sree SV, Kulshreshtha S, Molinari F, En Wei Koh J, Saba L, et al. GyneScan: an improved online paradigm for screening of ovarian cancer via tissue characterization. Technol Cancer Res Treat. 2014 Dec;13(6):529–39.*
23. *Explainable AI: A Review of Machine Learning Interpretability Methods - PMC [Internet]. [cited 2024 Jul 27]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7824368/*
24. *Shrestha P, Poudyal B, Yadollahi S, E Wright D, V Gregory A, D Warner J, et al. A systematic review on the use of artificial intelligence in gynecologic imaging - Background, state of the art, and future directions. Gynecol Oncol. 2022 Sep;166(3):596–605.*
25. *Bleher H, Braun M. Diffused responsibility: attributions of responsibility in the use of AI-driven clinical decision support systems. AI Ethics. 2022;2(4):747–61.*
26. *Xiao Y, Wang WY. On Hallucination and Predictive Uncertainty in Conditional Language Generation. In: Merlo P, Tiedemann J, Tsarfaty R, editors. Proceedings of the 16th Conference of the European Chapter of the Association for Computational Linguistics: Main Volume [Internet]. Online: Association for Computational Linguistics; 2021 [cited 2024 Jul 27]. p. 2734–44. Available from: https://aclanthology.org/2021.eacl-main.236*
27. *Guillen-Grima F, Guillen-Aguinaga S, Guillen-Aguinaga L, Alas-Brun R, Onambele L, Ortega W, et al. Evaluating the Efficacy of ChatGPT in Navigating the Spanish Medical Residency Entrance Examination (MIR): Promising Horizons for AI in Clinical Medicine. Clin Pract. 2023 Dec;13(6):1460–87.*
28. *Yazdani A, Costa S, Kroon B. Artificial intelligence: Friend or foe? Aust N Z J Obstet Gynaecol. 2023;63(2):127–30.*
29. *ChatGPT banned from New York City public schools' devices and networks [Internet]. [cited 2024 Jul 27]. Available from: https://www.nbcnews.com/tech/tech-news/new-york-city-public-schools-ban-chatgpt-devices-networks-rcna64446*
30. *B. N, Velchamy I. Evaluation of machine learning based optimized feature selection approaches and classification methods for cervical cancer prediction. SN Appl Sci. 2019 Jun 1;1.*
31. *Pergialiotis V, Pouliakis A, Parthenis C, Damaskou V, Chrelias C, Papantoniou N, et al. The utility of artificial neural networks and classification and regression trees for the prediction of endometrial cancer in postmenopausal women. Public Health. 2018 Nov;164:1–6.*

♦ Review Article

# Recent Advances in Medical Oncology

*Partha S. Roy*

*Professor, Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION:**

The last decade has witnessed significant advancement in the field of medical oncology with our better understanding of cancer biology, advances in diagnostics, and improvement in cancer therapeutics. Huge additions to our knowledge of cancer biology at the molecular and genetic level with the advancements in genomic technologies have opened the door to a potential 'golden era' of cancer treatment, where personalized therapies are crafted for individual patient using drugs that target specific markers/molecular pathways on cancer cells, or even re-educate the body's immune system has resulted in a paradigm shift in oncological care.[1] In addition, the latest development in the field of immune-oncology with manipulations of immune checkpoints and adoptive cell therapies has paved new paths for cancer management.[2]

Following advances in specific treatment areas that have recently shown promising results in clinical trials and/or in clinical practice are:

- Precision medicine
- Immunotherapy [immune checkpoint inhibitors (ICI's), chimeric antigen receptor T-cell therapy (CAR-T)]
- Radiotherapy [systemic radiotherapy with infusing or injecting radioisotopes, proton beam therapy (PBT)]
- Oncolytic virus therapy (cancer vaccines)
- Combined approaches

**PRECISION MEDICINE AND TARGETED THERAPIES:**

Precision or personalized medicine is a strategy that allows the selection of specific treatments based on the patient's genetic or genomic changes that may occur in an individual's tumor. The goal of precision medicine is simply to deliver the right treatment to the right patient at the right dose and the right time. This inherent variability of cancer imparts itself to the emerging field of precision medicine also known as personalized medicine, which is a strategy tailored for each patient's tumor genetic or genomic makeup.

Advances in molecular medicine have been crucial in precision medicine. Key advancements in precision oncology include the identification of predictive biomarkers for treatment response and the advances of targeted therapies directed against specific molecular targets. Examples of predictive biomarkers in medical oncology include mutations in the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC), that predicts sensitivity to EGFR tyrosine kinase inhibitors (TKIs).[3] Targeted therapies exploit vulnerabilities unique to cancer cells, such as aberrant signaling pathways or overexpressed growth factor receptors, while sparing normal cells from collateral damage.[4] Examples of targeted therapies include small molecule inhibitors (TKIs), monoclonal antibodies, and antibody-drug conjugates, which selectively target oncogenic drivers such as BRAF mutations in melanoma or HER2 amplification in breast cancer.[5,6] Recent developments in omics technologies have focused on a more precise approach for precision therapy.[7] There are now numerous biomarkers needed for treatment assessment in patients with lung cancer, breast cancer and various other malignancies. Examples of few US FDA approved biomarkers for specific tumours are: HER2/neu expression (ERBB2) for breast cancer, EGFR L858R mutation for NSCLC, BCR-ABL1 fusion for chronic myeloid leukemia, KIT expression for gastrointestinal stromal tumour (GIST), BRAF V600E mutation (melanoma, lungs cancer, colon cancer), 17p deletion for endometrial cancer, etc., and this number will continue to increase as new molecularly defined subsets are identified.

In breast cancer, specific druggable mutations have been identified. Since the FDA approval of trastuzumab in 1998, the treatment options for patients with HER2-positive breast cancer have undergone a significant shift in the field of precision medicines. Various drugs have been approved by the FDA, and there are other prospective new drugs in the pipeline that have exhibited a good clinical function in HER2-positive breast cancer.

Recently, lung cancer, after several decades of choosing platinum-based doublets for every patient, has undergone a transformation integrating precision medicine. When diagnosing a patient, measuring

EGFR mutation [US FDA approved EGFR targeted agents approved during last decade are afatinib (2013), osimertinib (2015) and dacomitinib (2018)], and ALK or ROS1 fusions [recently US FDA approved ALK/ROS1 inhibitors are ceritinib (2014), alectinib (2015), brigatinib (2017) and lorlatinib (2021)], will help determine whether a tyrosine kinase inhibitor (TKI) should be used in lieu of cytotoxic chemotherapy.[8] When considering patients who are diagnosed with NSCLC, these biomarkers may alter treatment decisions in approximately 50% of patients to biologic agents instead of cytotoxic chemotherapy.

The discovery of several non-overlapping driver mutations and tyrosine kinase (TK) inhibitors in NSCLC and melanoma led to assays of alterations conducted by polymerase chain reaction (PCR) enabling these biomarkers to be used for treatment decisions in solid tumors, which signified the potential of molecular profiling.

Many targeted therapies have been approved by the FDA in the past several decades for the treatment of a variety of cancer types with specific genetic, genomic, or epigenetic alterations paired to specific targeted therapies (as illustrated in the table).

*Table: List of approved targeted therapies (approved in last decade)*

| Drug | Primary targets | Drug category | Cancer Type (FDA approved/year) | Indications |
|---|---|---|---|---|
| Ado-trastuzumab emtansine | ERBB2 | Antibody-drug conjugate (ADC) | Breast cancer, 2013 | HER2+ breast cancer |
| Belantamab mafodotin-blmf | BCMA | ADC | Multiple myeloma, 2020 | Multiple myeloma |
| Brentuximab vedotin TNFRSF8 | TNFRSF8 | ADC | Lymphoma, 2011 | cHL; sALCL; PTCL |
| Enfortumab vedotin-ejfv | Nectin-4 | ADC | Urothelial cancer, 2019 | Urothelial cancer |
| Fam-trastuzumab deruxtecan-nxki | ERBB2 | ADC | Breast cancer, 2019 | HER2+ breast cancer |
| Gemtuzumab ozogamicin | CD33; DNA | ADC | Leukemia, 2000 | CD33-positive AML |
| Ibritumomab tiuxetan | CD20 | ADC | Lymphoma, 2002 | Relapsed NHL |
| Inotuzumab ozogamicin | CD22 | ADC | Leukemia, 2017 | ALL |
| Polatuzumab vedotin-piiq | CD79b | ADC | Lymphoma, 2019 | DLBCL |
| Sacituzumab govitecan-HZIY | TOP1 | ADC | Breast cancer, 2020 | mTNBC |

Despite the remarkable progress in precision oncology, challenges remain, including the need for improved biomarker validation, the development of effective combination therapies, and the emergence of resistance mechanisms. Additionally, access to comprehensive genomic profiling and targeted therapies may be limited by factors such as cost, insurance coverage, and geographic location. [9,10]

**IMMUNO-ONCOLOGY ADVANCEMENTS:**

Key advancements in cancer immunotherapy include the development and expansion of immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and cancer vaccines in clinics. Unlike traditional treatments such as chemotherapy and radiation that directly target cancer cells, immunotherapy harnesses the body's immune system to recognize and combat cancer by selectively attacking cancer cells, often sparing normal cells from the collateral damage associated with traditional treatments. The recent development of immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment and has improved patient survival. Immunotherapy has emerged as a revolutionary approach in cancer therapy, representing a paradigm shift in the treatment of various malignancies.[11,12,13] ICIs specific for checkpoint proteins, such as CTLA-4, PD-L1 or PD-1, have been approved for the treatment of several cancer types, including NSCLC, melanoma, head-neck cancer, bladder cancer, renal cell cancer, and, some lymphomas. This approach has demonstrated the potential for prolonged and durable responses in some patients. In recent years, immunotherapy has witnessed rapid advancements, leading to innovative approaches that are transforming the landscape of cancer treatment.[14]

Immune checkpoint inhibitors by targeting inhibitory pathways such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), unleash the antitumor immune response, leading to durable tumor regression and prolonged survival in subsets of patients.[15,16,17] Notable examples include pembrolizumab and nivolumab, which have been approved for the treatment of melanoma and other skin cancers, as well as NSCLC, breast, endometrial, kidney, esophageal, and various other malignancies. Recently, PD-L1 expression (tumor proportion score ≥ 50%) has proven to be effective in enriching patients with lung cancer who may benefit from immunotherapy (pembrolizumab) instead of chemotherapy.[18]

Clinically approved antibodies against PD-L1/PD-1 have demonstrated therapeutic efficacy across a range of human cancers (as illustrated in the table).[19,20]

*Table 2: List of approved immunotherapy agents in recent years.*

| Drug | Primary targets | Drug category | Cancer type (FDA approved, Year) | Indications |
|---|---|---|---|---|
| Atezolizumab | PD-L1 | Monoclonal antibody (MoAb) | Urothelial ca; Lung ca; Breast ca; Hepatocellular ca; Melanoma (2016) | Urothelial ca; NSCLC; SCLC; TNBC; HCC; Melanoma |
| Avelumab | PD-L1 | MoAb | Skin ca; Urothelial ca; Kidney ca (2017) | MCC; Urothelial ca; RCC |
| Daratumumab | CD38 | MoAb | Multiple myeloma (2015) | Multiple myeloma |
| Durvalumab | PD-L1 | MoAb | Urothelial ca; Lung ca (2017) | Urothelial ca; NSCLC; ES-SCLC |
| Ipilimumab | CTLA4 | MoAb | Melanoma; Kidney ca; Colorectal ca; Hepatocellular ca; Lung ca (2011) | Melanoma; RCC; CRC; HCC; NSCLC with no EGFR or ALK genomic tumor alterration; Malignant pleural mesothelioma |
| Nivolumab | PD1 | MoAb | Melanoma; Lung ca; Kidney ca; Lymphoma; Colorectal ca; Urothelial ca; Hepatocellular ca; Esophageal ca; Head and Neck ca (2014) | Melanoma; NSCLC; SCLC; Malignant pleural mesothelioma; RCC; cHL; HNSCC; CRC; HCC; Urothelial ca; Esophageal SCC |
| Obinutuzumab | CD20 | MoAb | Leukemia; Lymphoma (2013) | CLL; Follicular lymphoma |
| Pembrolizumab | PD1 | MoAb | Melanoma; Lung ca; Head and neck ca; Lymphoma; Urothelial ca; Gastric ca; Esophageal ca; Cervical ca; Hepatocallular ca; Skin ca; Kidney ca; Endometrial ca (2014) | Melanoma; NSCLC; SCLC; HNSCC; cHL; PMBCL; Urothelial ca; PD-L1 expressing gastric ca, esophageal ca, or cervical ca; HCC; MCC; cSCC; RCC; Endometrial ca; TMB-H cancer; MSI-H or dMMR solid cancer |
| Tafasitamab-cxix | CD19 | M0Ab | Lymphoma (2020) | DLBCL |

Another significant advancement in cancer immunotherapy is CAR-T cell therapy, a form of adoptive cell therapy that involves engineering patients' T-cells to express chimeric antigen receptors targeting tumor-specific antigens.[21] CAR-T cell therapy has demonstrated remarkable efficacy in hematologic malignancies, particularly in patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL).[22] Following successful clinical trials and FDA approval, T-cell engineering has recently gained attention. Approved CAR-T cell therapies such as axicabtagene ciloleucel and tisagenlecleucel have ushered in a new era of personalized cancer treatment, offering hope to patients with otherwise dire prognoses.[23] Since 2017, the US FDA has approved six CAR-T therapies for hematological malignancies such as lymphoma, certain leukemias, and, most recently, multiple myeloma (axicabtagene ciloleucel for large B-cell lymphoma, 2017; tisagenlecleucel for B-cell ALL and NHL, 2017; brexucabtaagene autoleucel for MCL and ALL, 2020; lisocabtagene maraleucel for B-cell NHL, 2021; idecabtagene vicleucel for multiple myeloma, 2021; ciltacabtagene autoleucel for multiple myeloma, 2022).[24,25,26]

In addition to checkpoint inhibitors and CAR-T cell therapy, cancer vaccines have emerged as a promising strategy for stimulating antitumor immune responses and preventing cancer recurrence. Notable examples include the human papillomavirus (HPV) vaccine, which has proven highly effective in preventing HPV-related cervical and oropharyngeal cancers.[27] While early cancer vaccine trials showed limited efficacy, recent advancements in vaccine design and delivery have reinvigorated interest in this approach.[28] Overall, the rapid pace of advancements in cancer immunotherapy holds promise for transforming the treatment landscape and improving outcomes for patients with cancer. The most advanced virus therapy so far is talimogene laherparepvec (T-VEC), a modified herpes simplex virus.[29] T-VEC is approved by NICE (2016) for some unresectable melanomas patients. However, challenges remain, including identifying predictive biomarkers of response, managing immune-related adverse events, and overcoming mechanisms of resistance. [30]

Additionally, the field of medical oncology has witnessed few notable advances in recent years, for example:

1. Sotorasib, first-ever KRAS inhibitor approved (2021) for undruggable advanced NSCLC in patients who have already received at least one other treatment. [31]

2. Approval of Lu-PSMA-617 therapy for advance/ metastatic prostate cancer. [32]

3. The US FDA has given the accelerated approval in 2021 to the immunotherapy drug pembrolizumab (combining the IO with standard treatments), for patients with advanced esophageal and/or gastric cancer. [33]

4. Trastuzumab deruxtecan (a breast cancer targeted therapy) showed its efficacy in advanced lung cancer driven by the HER2 protein. [34]

5. Non-operative management of rectal cancer after total neoadjuvant therapy (TNT) for patients with locoregionally advanced rectal cancer (LARC), who achieve a complete clinical response (cCR) to neoadjuvant therapy - studies are now evaluating surveillance alone (i.e., non-operative management) for those who achieve a complete clinical response (cCR) to neoadjuvant therapy (NAT) (March 2024). [35]

6. The addition of novel checkpoint inhibitor toripalimab plus gemcitabine and cisplatin in metastatic nasopharyngeal carcinoma (2023) has became the new standard of care (2023). [36]

7. The FDA has approved lifileucel, the first treatment for cancer that uses immune cells called tumor-infiltrating lymphocytes (TILs). Lifileucel is the first cellular therapy to be approved for a solid tumor (unresectable or metastatic melanoma after progression on a PD-1 inhibitor and a BRAF inhibitor, March 2024). [37]

8. Approval of amivantamab (EGFR targeted therapy) plus chemotherapy for advanced NSCLC with uncommon activating EGFR exon 20 insertion mutation based on the results of superior efficacy of the combination therapy in a phase 3 PAPILLON study (October 2023).[38]

9. Approval of eflornithine (an ornithine decarboxylase inhibitor) as maintenance therapy in patients with high-risk neuroblastoma who achieve at least a partial response to prior systemic agents and complete maintenance immunotherapy (January 2024).[39]

10. The treatment of CLL has evolved from traditional chemoimmunotherapy (CIT) to an increasing number of targeted and biologic approaches. Randomized trials have demonstrated superiority of covalent bruton tyrosine kinase inhibitors (cBTKis) over CIT, and second-generation compounds such as acalabrutinib and zanubrutinib appear to have a more favorable efficacy/ safety profile than ibrutinib. The noncovalent BTKi, pirtobrutinib, has shown impressive activity after failure of the cBTKis and is quite tolerable. The Bcl-2 inhibitor venetoclax plus a CD20, generally obinutuzumab, provides a high level of efficacy as initial treatment or after failure on a cBTKi, with many patients achieving a state of undetectable minimal residual disease. [40]

**CONCLUSION:**

The future of cancer treatment holds great promise, driven by a commitment to unraveling the intricacies of resistance, harnessing the power of the immune system, and advancing personalized therapeutic strategies. Through continuous research, collaboration, and the integration of cutting-edge technologies, immunotherapy and personalized medicine aims to redefine the paradigm of cancer care, offering hope for improved outcomes and a brighter future for patients facing this challenging disease. ■

## REFERENCES:


1. *Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009;458(7239):719-724. Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science. 2013;339(6127):1546-1558. Garraway LA, Verweij J, Ballman KV. Precision oncology: an overview. J Clin Oncol. 2013;31(15):1803-1805.*
2. *Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-489. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450-461. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379(1):64-73.*
3. *Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med. 2005;2(3):e73.29.*
4. *Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031-1037.*
5. *Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009;9(7):463-475.*
6. *Crimini, E.; Repetto, M.; Aftimos, P.; Botticelli, A.; Marchetti, P.; Curigliano, G. Precision medicine in breast cancer: From clinical trials to clinical practice. Cancer Treat. Rev. 2021, 98, 102223. Garraway, L.A.; Verweij, J.; Ballman, K.V. Precision Oncology: An Overview. J. Clin. Oncol. 2013, 31, 1803–1805.*
7. *Naito, Y.; Urasaki, T. Precision medicine in breast cancer. Chin. Clin. Oncol. 2018, 7(3), 29. Collins, F.S.; Varmus, H. A New Initiative on Precision Medicine. N. Engl. J. Med. 2015, 372, 793–795.*
8. *Schwartzberg L, Kim ES, Liu D, et al. Precision Oncology: Who, How, What, When, and When Not? 2017 ASCO Educational Book | asco.org/edbook.*
9. *Van Allen EM, Wagle N, Levy MA. Clinical analysis and interpretation of cancer genome data. J Clin Oncol. 2013;31(15):1825-1833.*
10. *Prasad V, Fojo T, Brada M. Precision oncology: origins, optimism, and potential. Lancet Oncol. 2016;17(2):e81-e86.*
11. *BorgersJ S W, Heimovaara J H, Cardonick E, Dierickx D, Lambertini M, Haanen J B A G, Amant F (2021) Immunotherapy for cancer treatment during pregnancy. Lancet Oncol 22(12):e550-e561.doi: 10.1016/S1470-2045(21)00525-8.*
12. *Rusch T, Bayry J, WernerJ, Shevchenko I, Bazhin AV (2018) Immunotherapy as an option for cancer treatment. Arch Immunol Ther Exp (Warsz);66(2):89-96.DOI: 10.1007/s00005-017-0491-5.*
13. *Trapani JA and Darcy PK, (2017) Immunotherapy of cancer. Aust Fam Physician, 46(4):194-199.*
14. *Ma W, Pham W, Li T (2022) Cancer neoantigens as potential targets for immunotherapy. Clin Exp Metastasis. 39(1):51-60. doi: 10.1007/s10585-021-10091-1.*
15. *Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450-461.*
16. *Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell. 2015;161(2):205-214.*
17. *Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355.*
18. *Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387:1540-1550.*
19. *Zahavi D, Weiner L. Monoclonal Antibodies in Cancer Therapy. Antibodies 2020, 9, 34.*
20. *Finn OJ. Human Tumor Antigens Yesterday, Today, and Tomorrow. Cancer Immunol. Res. 2017, 5, 347–354.*
21. *June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379(1):64-73.*
22. *Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.*
23. *Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439-448.*
24. *Al-Haideri M, Tondok SB, Safa SH, Maleki AH, et al. CAR-T cell combination therapy: The next revolution in cancer treatment. Cancer Cell Int. 2022, 22, 365.*
25. *Sengsayadeth S, Savani BN, Oluwole O, Dholaria B. Overview of approved CAR-T therapies, ongoing clinical trials, and its impact on clinical practice. EJHaem 2022, 3, 6–10.*
26. *Muthukutty P, Woo HY, Ragothaman M, Yoo SY. Recent Advances in Cancer Immunotherapy Delivery Modalities. Pharmaceutics 2023, 15, 504. https://doi.org/ 10.3390/pharmaceutics15020504.*
27. *Joura EA, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-723.*
28. *Palucka K, Banchereau J. Dendritic-cell-based therapeutic cancer vaccines. Immunity. 2013;39(1):38-48.*
29. *Ribas A et al. (2017). Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy. Cell, Vol 170, 1109.*
30. *Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168(4):707-723.*
31. *Skoulidis F., Li B. T., Dy G. K., Price T.J., et. Al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. N Engl J Med 2021;384:2371-81.*
32. *Sartor O., de Bono J., Chi K. N., Fizazi K., et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2021;385:1091-103.*
33. *Janjigian YY, Kawazoe A, Yañez P, Li N, et al. Combined PD-1 and HER2 blockade for HER2-positive gastric cancer. Nature. 2021 December; 600(7890): 727–730.*
34. *Li B-T, Smit EF, Goto Y, Nakagawa K, et al. Trastuzumab Deruxtecan in HER2-Mutant Non–Small-Cell Lung Cancer. N Engl J Med 2022;386:241-51.*
35. *Verheij FS, Omer DM, Williams H, et al. Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial. J Clin Oncol 2024; 42:500.*
36. *Mai H-Q, Chen Q-Y, Chen D, Hu C, et al. Toripalimab Plus Chemotherapy for Recurrent or MetastaticNasopharyngeal Carcinoma. JAMA. 2023 Nov 28; 330(20): 1961–1970.*
37. *Warner AB, Corrie PG, and Hamid O. Tumor-Infiltrating Lymphocyte Therapy in Melanoma: Facts to the Future. Clin Cancer Res 2023;29:1835–54.*
38. *Zhou C, Tang KJ, Cho BC, Liu B, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med 2023;389:2039-51.*
39. *Oesterheld J, Ferguson W, Kraveka JM, et al. Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score-Matched Survival Outcome Comparisons. J Clin Oncol 2024; 42:90.*
40. *Cheson BD and Sharman JP. Current Approaches and Novel New Agents in the Treatment of Chronic Lymphocytic Leukemia. JCO Oncology Practice. June 2004.*

♦ Review Article

# Recent Advances in Paediatric Oncology

*Munlima Hazarika[1], Manasa Kakunje[2], and Suhani Borbhuiyan[3]*

*[1]Professor and Head, [2,3] Assistant Professor, Department of Medical Oncology and Pediatric, Dr. B. Borooah Cancer Institute, Guwahati*

Every year, approximately 40000 children are diagnosed with cancer globally. Progress in Pediatric Oncology is one of the biggest success stories in oncology in the last millennium with over 80% cure rate. These improvements in survival were largely because of therapy intensification, especially for high-risk subgroups of patients, along with advances in supportive care. Outcomes of relapse/refractory cases are still a signifcant challenge. Molecular diagnostic advances have resulted in numerous breakthroughs in the diagnosis and treatment of childhood cancer with introduction of immunotherapy and targeted therapies along with cytotoxic chemotherapy, which are associated with many long-term side efects.

## ADVANCES IN THE CARE OF HEMATOLOGIC MALIGNANCIES:

### 1. Acute Lymphoblastic Leukemia (ALL)

ALL is the most common pediatric cancer, with 5 year overall survival (OS) above 90%. Although most children with ALL respond to traditional chemotherapy, mortality of relapsed/ refractory patients are still very high. However, targeted therapies for B-ALL have provided new promising options for patients with R/R disease.

Outcome of Philadelphia chromosome-positive (Ph+) ALL has improved after introduction of targeted Tyrosine Kinase Inhibitors like Imatinib and Dasatinib.

The development of new immunotherapy led to prolonging OS and disease-free survival (DFS) in pediatric patients with Ph- R/R B-ALL. Blinatumomab, a bispecific antibody that binds CD19+ on B cells and CD3+ on T cells, proved its effectiveness in achieving Minimal Residual Disease (MRD) status, which allows qualification for hematopoietic stem cell transplantation (HSCT). Inotuzumab Ozogamicin (InO) is monoclonal antibody conjugated to Calicheamicin with CD22 on B cells as a target showing improved remission rate in CD22+ R/R B-ALL in adults. The pediatric clinical trials are going on for proper dose for children, which would limit the toxicities like post-HSCT sinusoidal obstruction syndrome associated with it.

Another immunotherapy, which is used as bridge to HSCT, is CD19 chimeric antigen receptor (CAR) T-cells therapy, which involves genetically modifying a patient's T-cells with fusion proteins that lead them to kill cancer cells, regardless of the patient's MHC. The only CAR T-cell therapy approved by the FDA for use in the treatment of R/R B-cell precursor ALL in pediatric patients is Tisagenlecleucel.

### 2. Acute Myeloid Leukemia (AML)

AML is a hematopoietic disease presented by clonal expansion of myeloid stem cells, characterised by high relapse rate (25–30%). Although molecular landscape of AML is still not understood completely, the TARGET project identified mutation of KIT and FLT3, two specific genes that are distinctly mutated in pediatric AML.

FLT3 mutation is present in 30% of the patients with newly diagnosed AML and bear poor prognosis. FLT3 inhibitors include Sorafenib, Sunitinib, Midostaurin and Lestaurtnib. Most of the FLT3 inhibitors show better result if used with cytotoxic chemotherapy. The therapy For pediatric cases with KIT gene change includes combination of multikinase inhibitor Dasatinib and multi-agent chemotherapy .

The targets for immunotherapy are different for pediatric patients than their adult counterpart. For instance, CD123 is over-expressed in adult AML but not in pediatric. Whereas blasts of pediatric AML show high expressions of CLEC12A and CD33. Thus, this combination can be selected as targets in pediatric AML. CAR T cells therapy is another option for pediatric patients with high risk AML.

DOT1L and Bromodomain and Extra-Terminal Domain (BET) family of proteins are two other targets identified recently. For cases of NPM1 mutant AML, using DOT1L inhibitors combined with MLL inhibitors gave positive results. Mutations in the MLL gene appear in 18% of pediatric cases more so in infants. VTP50469, a novel inhibitor of Menin MLL interaction is found to be useful against many target genes like HOXA, and MEIS1, and reducing neoplasm transformation.

3. **Chronic Myeloid Leukemia (CML)**

CML constitutes about 2–3% of leukemias in pediatric patients under 15 years. Children and adolescents usually have more aggressive course of disease compared to adult. Although treatment of CML started with hematopoietic stem cell transplantation, the current first line therapy includes Tyrosine Kinase Inhibitors - first-generation TKI Imatinib, second-generation Dasatinib, Nilotinib and third-generation Bosutinib. Stem cell transplantation is considered as a third-line treatment for most pediatric CML. However, search is going on for therapy guidelines adapted specially for children.

4. **Hodgkin's lymphoma (HL)**

HL is the most commonly diagnosed lymphoid malignancy in adolescents (aged 15–19 years), derived from B cell and characterised by presence of binucleated giant cells known as Reed Sternberg cell. Several risk factors like EBV infection or mutations in NF-κB pathway genes can cause the development of this disease. HL has long-term survival rates of more than 90% after treatment with chemotherapy alone or combined with radiotherapy (RT).

In pediatric HL patients CD30 and NF-κB have been identified as potential biomarkers, and therapeutic targets. CD30 is mainly expressed on HRS cells and it's over expression leads to activation of transcription factors NF-κB.

Treatment of HL constitute risk adapted therapy. HL has long-term survival rates of more than 90% after treatment with chemotherapy alone or combined with radiotherapy (RT). In favourable-risk pediatric patients, RT is omitted. For relapsed/refractory (R/R) HL treatment is based on salvage chemotherapy, high dose chemotherapy (HDCT), followed by autologous stem cell transplantation (auto SCT).

Targeted therapy of pediatric Hodgkin lymphoma comprises of monoclonal antibodies, signal transduction inhibitors, immunotherapy, and epigenetic agents (histone deacetylase (HDAC) inhibitors). A commonly used anti-CD30 antibody–drug conjugate, involved in inducing apoptosis of HRS cells, is Brentuximab vedotin (Bv), which currently comprises, alongside with chemotherapy, first line treatment in advanced stage HD. Nivolumab(PD 1 Blocker) is another monoclonal antibody used in pediatric HL. Treatment of pediatric HL may also include the use of Bortezomib which selectively inhibits the 26S proteasome stabilizing the NF-κB inhibitor. Vorinostat and Panobinostat are two histone deacetylase inhibitors which are tried to treat pediatric HL that are involved in cell cycle arrest and apoptosis. Moreover, HDAC inhibitors have been shown to interact synergistically with proteasome inhibitors to induce apoptosis.

5. **Non-Hodgkin's Lymphoma (NHL)**

Non-Hodgkin lymphoma (NHL) refers to cancers of mature lymphoid cells. Approximately 60% of all pediatric NHL are B cell origin. The most common pediatric B-NHLs are Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and primary mediastinal B-cell lymphoma (PMBCL). Currently, NHL treatment is based on chemotherapy with the addition of immunotherapy with special emphasis on CNS directed therapy. Both DLBCL and BL are treated with similar aggressive protocols in pediatric age group with incorporation of Rituximab, an anti CD20 monoclonal antibody, into frontline therapy. In the LMB-96 study, the group with PMBCL had a 5-year EFS of just 66%, which was significantly inferior to the outcome of DLBCL (EFS 85%). The outcome of PMBCL improved with the use of DA-R-EPOCH chemo protocol with EFS and OS being 72% and 82% at a median follow-up of 27 months in a phase II trial by EICNHL Group.

## ADVANCES IN THE CARE OF SOLID TUMOURS IN CHILDREN:

Solid tumours constitute 30% of all pediatric malignancies of which cancers of brain are the commonest (26%). Other common types include Neuroblastoma (15%), Rhabdomyosarcoma (7%), Wilms tumor (6%), Ewing sarcoma (8%), Retinoblastoma (5%), and other miscellaneous tumours. The cure rates of most of these tumours have improved by more than 50% during last few decades due to better understanding of their molecular and cellular basis.

1. **Neuroblastoma (NBL):**

NBL is a tumour of neural crest cells and comprises 6–7% of all neoplasms in children aged 0–14 and accounts for almost 15% of all pediatric cancer deaths with an overall 5-year survival rate of less than50%. The prognosis of high-risk NBL is very poor despite high dose chemotherapy and autologous stem cell transplantation. But currently the prognosis has significantly improved due to the use of immunotherapy. The outer cell membrane of NBL cells express high level of GD2 ganglioside. Dinutuximab is the first approved anti-GD2 monoclonal antibody which has improved the survival of high risk NBL significantly.

Another potential target for high risk NBL in future is the Bromodomain and Extra Terminal (BET) family of proteins. They regulate the expression of the MYCN genes, which is found in more than 50% of the high risk NBL. Recent research has shown that selective inhibition of the BET proteins led to downregulation of the MYCN genes as well as bcl2 gene causing cytotoxicity.

2. **Brain Tumour:**
Malignancies of brain are the most common solid tumours in children of which low-grade gliomas (pLGG) are the commonest. Although surgery and radiotherapy are the mainstay of treatment, this may not always be possible for tumours of inaccessible sites and possibility of long-term adverse effects. Pediatric LGG is associated with the upregulation of the RAS-mitogen-activated (RAS/MAPK) pathway making it a target for their treatment. Pediatric high-grade gliomas have extremely poor prognosis. Although many targeted therapies are tried in different clinical trials, none of the therapies successfully extended the OS.

Another common pediatric brain tumour is medulloblastoma (MB) accounting for almost 20% of all childhood CNS malignancies. The standard treatment for MB is surgical intervention, radiotherapy, and chemotherapy. These tumours are currently classified into four groups using molecular expression (WNT, SHH, Gr3, Gr4) and most of the clinical trials are going on to develop targeted therapy based on hedgehog pathway inhibitors. Bevacizumab shows promising result due to the high expression of VEGF. NMYC gene inhibition is another potential research area. Currently high dose CT followed by autologous stem cell rescue has shown promising result in high-risk MB.

3. **Osteogenic Sarcoma (OGS):**
OGS is the most common bone malignancy in children with overall 5-year survival rate of below 70% in various studies. Current standard of care for OGS is Surgery and chemotherapy; Doxorubicin, Cisplatin, High dose Methotrexate and Ifosphamide being the most active chemotherapy agents. Other additional and experimental treatments in metastatic or progressive disease consist of "targeting the bone microenvironment (Bisfosfonates), tyrosine kinase receptor (e.g., Sorafenib, Pazopanib), and intracellular signaling molecules (Dasatinib).

Mifamurtide, an immunostimulant used as an additional and complementary drug to conventional chemotherapy has shown to lower the risk of progression around 5 times than the control group. No other immunotherapy has demonstrated efficacy against OGS.

Cabozantinib, MET/VEGRF2 inhibitor, has shown promising results in unresectable and relapsed Osteosarcoma and Ewing sarcoma in Phase II of CABONE trial (NCT02243605).

4. **Ewing's Sarcoma:**
Ewing sarcoma is characterized by the balanced translocation of EWSR1 and a gene of the E-26 transformation-specific (ETS) family, most commonly FLI1 in 90% of patients. The 5-year relative survival rate for Ewing sarcoma is on average 61% with very dismal outcome in metastatic and relapse/ refractory cases. Due to extraordinarily low mutational burden, therapeutic targets for Ewing's sarcoma are limited to EWSR1-ETS transcription factor or its downstream targets. In an ongoing clinical trial (NCT02657005) involving R/R Ewing's sarcoma combination of standard CT and TK216, which inhibits the interaction between the EWS-FLI1 protein and RNA helicase A, a key mediator of oncogenicity in Ewing sarcoma, has shown promising result. EWS-FLI1 fusion protein was found to upregulate the expression of SLFN11, which leads to increased sensitivity to temozolomide and PARP inhibitors in addition to camptothecins. In a phase l clinical trial (SARC025) addition of Talazoparib or Niraparib (selective PARP inhibitors) to Irinotecan and Temozolomide showed promising result.

5. **Rhabdomyosarcoma (RMS):**
Rhabdomyosarcoma constitute 3% of all pediatric cancers. Current risk stratification is based on tumour genomics in addition to the site of the primary tumour, extent of surgical resection, presence of metastasis. Genetically, RMS is divided into fusion positive (FP) or negative (FN) disease, depending on the presence or absence of a balanced translocation between PAX-FOXO1. FP is associated with worse outcomes.

Low and intermediate risk patients without metastases treated with frontline multi-modality therapy have excellent outcomes. Hence the focus has been on lowering Cyclophosphamide doses and reducing treatment-related toxicity (myelosuppression, infectious complications, and infertility) without compromising efficacy.

However, management of high-risk, metastatic and relapse/ refractory disease still hold therapeutic challenge. A randomized European Soft Tissue Sarcoma Group (EpSSG) study demonstrated improved survival with the addition of weekly vinorelbine and daily low-dose Cyclophosphamide maintenance to standard therapy with a 77.6% 5-year disease-free survival rate compared with 69.8% in patients who did not receive maintenance therapy.

In another trial (COG ARST0921), patients with first relapse or refractory RMS were randomized to receive bevacizumab, a monoclonal antibody to VEGF, or the mTOR inhibitor temsirolimus, both given with a vinorelbine and cyclophosphamide chemotherapy backbone. Temsirolimus resulted in a 6-month progression-free survival rate of 69.1% with a 47% objective response rate compared with 54.6% and 28%, respectively, in the bevacizumab arm. The addition of temsirolimus to frontline therapy is now being studied in patients with intermediate-risk RMS (ClinicalTrials.gov NCT02567435).

Phosphodiesterase type 5 (PDE5) overexpression has also been observed in Rhabdomyosarcomas. A recent study in the University Children's Hospital of Tuebingen,

Germany has shown that Sildenafil (PDE5 inhibitor), when combined with chemotherapeutic drugs like Doxorubicin, have increased their cytotoxic effects while potentially reducing side effects.

**6. Wilm's Tumour:**

Wilms tumour is the most common renal cancer in the pediatric age group mainly seen in below 5 years of age with excellent 5 - year survival of 90%. Hence targeted therapy and immunotherapy are usually not considered in Wilm's Tumour.

The research in Wilms tumour immunotherapy is going on in three fields- inhibition of the COX-2 pathway (to inhibit tumour immune escape), chimeric antigen receptor (CAR)-T cell therapy (Glypican-3, EGFR, and B7-H3), and multi–tumour associated antigen (TAA)-specific cytotoxic T lymphocytes (CTL) therapy. Targeted therapy research is mainly focused on the Insulin-like growth factor 2 (IGF2) pathway, anti-angiogenesis (especially concerning the VEGF pathway), PI3K signalling pathway, and some miRNAs as a targeted drug with preliminary report showing promising result.

**CONCLUSION:**

Cancer is one of the leading causes of death in children despite of improvement in cure rate in all types of cancers during the last millennium. Targeted therapies and molecular approaches have opened a new door to lower toxicity and long-term side effects and more studies are needed to establish their safety and efficacy in children. ◆

**REFERENCES:**


1. *Katarzyna Adamczewska-Wawrzynowicz1 . Anna Wiącek2 . Aleksandra Kozłowska2 . Klaudia Mikosza, Lidia Szefler, Weronika Dudlik, Shreya Dey, Noel Varghese, Katarzyna Derwich; Modern treatment strategies in pediatric oncology and hematology; Discover Oncology (2023) 14:98 | https://doi.org/10.1007/s12672-023-00658-7*

2. *Erin Butler, Kathleen Ludwig, Holly L. Pacenta, Laura J. Klesse, Tanya C. Watt, Theodore W. Laetsch; Recent Progress in the Treatment of Cancer in Children; ca cancer j clin 2021;71:315–332, volume 71 | number 4 | july/august 2021*

3. *Bleijs, M.; Pleijte, C.; Engels, S.; Ringnalda, F.; Meyer-Wentrup, F.; van deWetering, M.; Clevers, H. EWSR1-WT1 Target Genes and Therapeutic Options Identified in a Novel DSRCT In Vitro Model. Cancers 2021, 13, 6072.*

♦ Review Article

# Haploidentical Stem Cell Transplantation

*Asif Iqbal*

*Associate Professor, Department of Hematolymphoid Malignancy, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION:**

Stem cell transplantation (SCT) is a curative treatment modality for many hematological malignancies, immunological disorders and some solid tumors. Among the allogenic SCTs, HLA disparity has been one of the crucial barriers to successful outcomes. Haploidentical donor (HID) SCTs have been developed where HLA identical donors (related or unrelated) are unavailable. The long-term prognosis of these patients was guarded due to the high proportion of graft rejection, and graft-versus-host disease (GVHD). Various procedures have been adopted over the years to tackle the alloreactive T-cells. While ex-vivo depletion of alloreactive T-cells was developed, and is still in practice, it is associated with higher risks of non-relapse mortality and risks of relapse[1]. The prospect of using unmanipulated T-cell replete grafts is very exciting. The use of anti-thymocyte globulin (ATG) is one such strategy. One of the most promising and practice changing therapeutic intervention was the use of high-dose cyclophosphamide post-transplantation (PTCy)[2]. From India's standpoint, cost is an important issue for the successful implementation of any therapeutic intervention. In this regard, PTCy is cost affective and hence, an attractive option. In a vast country with multiple isolated ethnic communities, India's unrelated donor registry is often insufficient to cater to the demands of MUD searches[3]. Acquiring stem cells from international registries is costly. As a result, haploidentical donors are the best choice for patients needing stem cell transplantation, and after PTCy, the numbers have increased manifold among its approximately 150 active centers. The 2 year overall survival for HID SCTs has been reported between 38% to 64% while in USA, the estimated 3 yr OS among patients > 18yrs in HID SCTs is 56.6% across all disease groups. It should be noted that in USA, the median age of patients undergoing HSCT is higher, and HID SCTs were carried out in large proportion of patients with HSCT-CI > 34-6.

**REVIEW OF LITERATURE:**

Haploidentical SCT is defined as transplantation of stem cells that involves partially mismatched HLA antigens between recipient and donor, and atleast 1 haplotype matched for HLA-A,B, and DRB1. Historically, HID SCTs are associated with a high incidence of graft failure, GVHD, and early mortality. The pivotal study by Luznik et al. demonstrated that use of high dose cyclophosphamide post transplantation can kill the alloreactive T-cells that are responsible for graft rejection, and GVHD, while preserving the non-alloreactive T-cells2. In that study, a non-myeloablative conditioning regimen consisting of Cyclophosphamide 14.5mg/kg/d on D-6,-5, Fludarabine 30mg/m²/d on D -6 to -2, TBI 200cGy on D-1 followed by bone marrow infusion, Cyclophosphamide 50mg/kg/d on D+3,+4, MMF and tacrolimus starting D+5 was used. Patients with high-risk hematologic malignancies and PNH up to age 70 yrs were included in that study. The cumulative incidence of grades[3-4] aGVHD was 6%, and graft failure occurred in 13%. The incidence of non-relapse mortality (NRM) was 15%, which was much lower than historical controls, and deaths due to infections only accounted for in 6% of patients. However, the incidence of relapse at 1 yr was 51%, which may be attributed to improved NRMs resulting in more patients at risk of relapse, and the fact that only high-risk malignancies were accrued in the study. Despite an overall survival of 36% at 2yrs after transplantation, this study paved the way for a new idea on tackling the problem of GVHD in HID SCTs.

The reduced cost of the application and the fact that haploidentical donors are readily available have led to the widespread adoption of this approach. However, the concerns of increased relapses were confirmed in a few other studies also[7-9]. Subsequently, some modifications were applied to the existing protocol, which can be divided into two types: change in intensity of conditioning, and use of PBSC instead of BM grafts.

In the subsequent studies with post-transplant cyclophosphamide, myeloablative conditioning was compared with reduced intensity conditioning to address the concerns for increased relapse rates. In a meta-analysis conducted among 20 studies, all except one from the Western world, there was no difference in OS (HR = 0.95; P = 0.32) among the patients who received MAC regimens from those who received RIC regimens10. In the same study, the incidence of relapses was lower (HR=0.7, P=0.001), and PFS was increased (HR=0.86, P= 0.002) with MAC regimens. However, NRM remained lower with RIC regimens (HR = 1.24, P=0.002). When PBSCs were compared with BM grafts, OS (HR = 1.05, P= 0.61), PFS (HR = 0.95, P= 0.52), and NRM (HR = 1.14, P= 0.13) were not different. The relapse rates were lower with PBSC grafts. The rates of aGVHD and cGVHD were higher with PBSC grafts, but the rates of graft failure were lower. A study from India where 100% of patients received PBSC grafts with PTCy showed 38% TRM, with 19% relapse-related deaths. 2 yr OS was 38%. Cumulative incidences of aGVHD and cGVHD were 19% and 38% respectively[11]. Another Indian study on leukemic children undergoing HID SCTs with MAC and PTCy showed NRM of 20%, 2 yr OS of 64.3%[12]. CMC Vellore published the data on the largest cohort of haploidentical transplants in India[5]. In majority, the source of the graft was GSF-stimulated peripheral blood. All the patients received PTCy along with tacrolimus and MMF for GVHD prophylaxis. 2 yr OS was found to be 40%. Factors identified to have adverse effects on survival were old age, late stage at diagnosis, non-myeloablative conditioning, and the presence of documented bacterial and fungal infections.

Supportive care remains the most important aspect of the management of patients undergoing SCTs. While infective complications are the biggest concern. Studies show that in India, infections are the most important cause of TRM and NRM[5,13]. Systemic problems that occur following engraftment, multiple drug interactions and toxicities, and immune reconstitution are also important concerns. Antibiotic, antiviral, and antifungal prophylaxis, prophylaxis against seizures, and sinusoidal obstruction syndrome are standard of care. There are institutional protocols for agents approved for the above indications[14]. For example, Letermovir offers a significant reduction in risk of CMV infection, and is better suited for prophylactic use than ganciclovir or foscarnet because of tolerability[15]. Similarly, defibrotide prophylaxis results in significant lowering of incidences of SOS in high risk patients[16]. Virus specific cytotoxic T-lymphocytes are used to treat and eradicate infections caused by CMV, BK, JC, and EBV in immunocompromised SCT recipients[17]. Though most of these CTLs are on trials, their successful implementation across centres in United States have had them on the brink of FDA approval. These conditions are not related to type of grafts, or conditioning regimen used, but cause mortalities. However, all agents may not be available in most countries, or are too expensive, limiting their use as prophylaxis. There are other SOPs in place, mostly regarding type and duration of immunosuppressants, use of G-CSF and other growth factors, and transfusion guidelines that differ from place to place. All practices, related or unrelated to grafts influence the outcomes of SCTs.

**HID SCTs IN USA:**

The data are obtained from CIBMTR database, and other relevant articles. For simplicity, we have focussed on the results on adult patients only. The annual number of stem cell transplants in US is steadily increasing. In 2021, more than 20,000 1st transplants were carried out across 178 centres of US, out of which 8295 were allogeneic. Stratifying by the type of graft, Matched unrelated donor (MUD) forms the largest group with 44% of all allogeneic SCTs, followed by haploidentical donor (23%). By the source of graft, peripheral blood forms > 90% of grafts in patients > 18yrs of age with matched donors (related or unrelated). In HID SCTs, bone marrow grafts were used comparatively more often (20%). Stratifying by disease, AML forms the largest disease group accounting for 40% of HID SCTs followed by MDS/MPN (23%). The number of HID SCTs for lymphoid malignancies is declining because of rapid progress in cellular adoptive immunotherapies. So far, six CAR-T cells have been approved by FDA, and there are more than 50 under various stages of trials[18]. Unfortunately, most of the success has been with B-lymphoid malignancies. Antigen escape, modest anti-tumor activity, severe life-threatening toxicities, and limited tumor infiltrations are barriers to CAR-T treatment in other hematologic malignancies and solid tumors[18,19]. By the type of conditioning regimen used, RIC regimens have been traditionally more often used than MAC regimens in HID SCTs[20]. The conditioning regimens also depend on the type and severity of the disease, and the performance status of patients under treatment. When compared, the disease subtypes have maintained similar proportion throughout the last decade. But, the proportion of MAC regimens has increased gradually over the last decade[4,20]. For example, in 2014, 202 out of 575 HID SCTs (35.1%) were MAC, which increased to 596 out of 1475 in 2018 (40.4%), to 800 out of 1901 in 2021 (42%). The number of HID SCTs as a whole, and proportionately increased numbers of MAC regimens point towards an improved acceptance of HID SCTs across all centres. Since 2013, the number of patients with HCT-CI more than 5 has increased while the number of HCT-CI = 0 has decreased, indicating sicker, older and more frail patients have been taken up for HID SCTs than before. In 2013, 25% of patients with HCT-CI = 0 and 15% of patients with HCT-CI ≥ 5 had undergone allogeneic SCTs. In 2021, these numbers are 20% and 18% respectively. This is likely due to better survival outcomes following improved GVHD prophylaxis and supportive care across all centres. In the last decade, more number of patients with higher comorbidities (HCT-CI ≥ 3) have undergone allogeneic SCTs with PTCy based GVHD prophylaxis (48%) than any other form of GVHD prophylaxis. In 2021, PTCy based GVHD prophylaxis accounted for 91% of all HID SCTs in USA. Between 2018 - 2020, GVHD related deaths following HID SCTs have decreased (5% due to aGHVD and 7% due to cGVHD), while relapse of the primary disease has been the major cause of mortalities (50% of deaths beyond 100 days of transplant). Among others, this might be the most important explanation for the increasing use of MAC regimens in HID SCTs. Among the MAC regimens, Bu-Flu based protocols are the most commonly used regimens in myeloid neoplasms (AML, MDS, MPN). Use of PK guided fractionated busulfan has been one of the key contributors that have led to the safe implementation of MAC regimens in elderly

and frail patients[21]. Among the RIC regimens, Flu-Mel based or TBI based protocols are used in myeloid neoplasms. In lymphoid neoplasms, TBI based protocols are used in both MAC and RIC regimens. There are a few centres that have promoted thiotepa in place of TBI in adult ALL, but general usage is scarce.

**HID SCTs IN INDIA:**

India is a geographical hotspot for genetic diseases and single-gene hematological disorders. The curative treatment in most of them is an allogeneic SCT. Unfortunately, most patients will not undergo transplants due to the following reasons: lack of financial resources, lack of suitable donors, and lack of facilities and trained personnel near their home[22]. This has changed in the last decade due to the increased number of centers capable of performing allogeneic SCTs in most major cities and in a few tier-2 ones. However, lack of suitable donors remains a concern. The national marrow registry is not strong enough to find donors in most cases, and getting stem cells from an International registry is very costly. Hence, HID SCTs increased manifold, and post PTCy, haploidentical donors became the highest source of grafts in India. To maintain uniformity, we have included data of adult patients.

Nataraj et al[23] evaluated a single center experience from South India that used unmodified John Hopkin's protocol for all its HID SCTs. The cases were recorded from 2012 to 2019. All patients had AML. The cumulative incidences of aGVHD and early mortality were high. But the survival curves flattened out after 1 year, and the patients maintained a relapse-free survival after a median follow-up of 4 years.

Batra et al11 analyzed 21 patients of acute and chronic myeloid leukemia who underwent HID SCTs from 2014 to 2019 in one center from North India. TRM was 38% and 2 yr was 38%. Sepsis was the cause in most of the deaths.

Garg et al[24] analyzed their center's HID SCTs performed between 2015 to 2019. There were 50 patients who underwent HID SCTs for both benign and malignant disorders. All patients received peripheral blood derived stem cells and PTCy with MMF and tacrolimus for GVHD prophylaxis. Cumulative incidences of aGVHD and cGVHD were 28% and 6% respectively. 2 yrs OS was 43% and 42% were alive after a median follow up of 50 months.

Sharma et al[26] analyzed their center's HID SCTs performed between 2010 to 2019, 64 patients underwent HID SCTs. All conditions were malignant. They found that the 2 yr OS was 21.7% which was significantly inferior than the OS of the MSD group (52.6%). All patients had PTCy based GVHD prophylaxis. Both MAC and RIC regimens were used. The incidences of GVHD were comparable in MAC vs RIC and MSD vs HID SCT groups.

George et al[5] published the largest data on HID SCTs from India. It was also a single center retrospective analysis where 257 patients who underwent HID SCTs from 2010 to 2020 were studied. Graft source was predominantly G-CSF mobilized peripheral blood stem cells, and median cell dose was kept high (10 x 106 CD34/kg). All patients received PTCy based GVHD prophylaxis. In the last year, r-ATG was also added to the prophylaxis regimen. Grade 2-4 aGVHD was seen in 24.3% and extensive cGVHD was seen in 15%. 90% of high grade GVHD were steroid refractory. Across the cohort, 2 yr OS was 40.5%. When stratifying into two halves (2010 – 2015) and 2016 – 2020), the 2 yr OS was significantly lower in the former (35.8% vs 43.6%). In multivariate analysis, older age, late stage disease, nonmyeloablative conditioning regimen, presence of documented bacterial and fungal infections, and presence of aGVHD were found to affect the overall survival.

*Table 1 : Indian series of SCTs.*

| Study | No of patients | Regimen (MAC/ RIC) | GVHD prophylaxis | Outcomes |
|---|---|---|---|---|
| Batra et al[11] | 21 | RIC | PTCy + Others | 2yr OS 38%, TRM 38%, Relapse 19% |
| Uppuluri et al[12] | 19 | RIC | PTCy + Others | 2yr OS 68.4%, TRM 30%, aGVHD 68% |
| Garg et al[24] | 50 | MAC 76%<br>RIC 24% | PTCy + Others | Graft failure 30%, aGVHD 28%, 2 yr OS 43% |
| Sharma et al[25] | 44 | MAC 50%<br>RIC 50% | PTCy + Others | 3yr OS and RFS in RIC 58.5% and 53.2%, respectively, and 3yr OS and RFS in MAC 59.4% and 53.1%, respectively |
| Sharma et al[26] | 64 | MAC 31.2%<br>RIC 69% | PTCy + Others 45, PTCy + ATG 9, Others 10 | Gr 2-4 aGVHD 26.8%, 5yr OS 21.7% |
| George et al[5] | 257 | RIC 42.4% | PTCy + others 89%, PTCy + ATG 11%, | Gr 3-4 aGVHD 23.9%, extensive cGVHD 15.4%, 2yr OS 34.2%, |
| Nataraj et al[23] | 36 | RIC 100% | PTCy + MMF/Tacro | aGVHD and cGVHD were 32.6% and 15.2% respectively. Day 100 survival was 67% and 2 yr OS 50% |


*Fig 1: Data points on India map*

**DISCUSSION:**

Haploidentical stem cell transplantation has been increasing throughout the globe. PTCy has been a unifying feature in all. Other methods of T-cell depletion (graft manipulation, atg) are still in use in USA, but the numbers are smaller, and the indications have become limited. When ATG was compared with PTCy, PTCy was marginally better in preventing cGVHD and deaths in the multivariate analysis[9]. It was expected that inhibiting T-cells to reduce GVHD will also reduce graft versus leukemia (GVL) effect, but the heightened relapse rates were also due to a marked decrease in early deaths. Various modifications were made on the original protocol developed by the John Hopkin's group, such as using myeloablative conditioning, using G-CSF mobilized peripheral blood as stem cell source, and modifying the dose of cyclophosphamide. However the idea of successful conduct of allogeneic SCTs using unmanipulated haploidentical grafts has made SCTs available to virtually every patient. And because of the low cost involved in PTCy when compared to other forms of T-cell depletion, like depletion of αβ-T cells, or selection of CD34+ cells, or even ATG, it is an attractive option to resource-limiting nations like India. Use of PTCy has been successfully employed in HLA matched transplants also, but the results are less convincing than in haploidentical transplants.

When the general practice of HID SCTs in USA and India are compared, some striking differences are observed. In USA, the most common cause of death is relapse of the primary disease. Primary disease is an important cause of early deaths also, second only to organ failure[4]. This has been addressed and the conditioning regimens have gradually become more intense. Both PBSC and marrow grafts are used in HID SCTs. With current regimens, GVHD, both acute and chronic have been controlled. Long term survival outcomes of HID SCTs are now marginally inferior to matched donor transplants. PTCy is almost universally adopted across all centres. In recent years, older, and sicker patients are also enrolled in HID SCT programs.

In India, graft failure, aGVHD, and infections are still the leading cause of mortalities. Across all centres, early deaths are high. RIC regimens are used more frequently. PBSCs comprise more than 90% of the source of grafts. PTCy is used universally, but a significant proportion received PTCy + ATG. The average age of patients in HID SCTs are much lower. No studies have indicated the comorbidity indices of the patients selected, but it is expected that only fit patients have been transplanted[5,27]. The 2 yr OS of HID SCTs in USA and the cumulative 2 yr OS in India across the studies are 56% and 43%, respectively.

**ADDRESSING THE POSSIBLE PROBLEMS[4,5,10,21,28]**

We will place the most probable root causes of the problems, and suggest solutions in a numbered manner. All SCT centers have SOPs for treatment schedules, and to manage complications.

1. Outcomes of stem cell transplantation don't only depend on the SCT facility, but on the entire health care infrastructure. For example, India has 150 active SCT centres in 2023. An average Indian center performs 25-50 transplants in a year. An average center in USA performs 250 SCTs in one year, with better outcomes, while managing maximum data, and fewer errors. MD Anderson Cancer Center performed 750 SCTs last year. At any given time, MDACC treats 70-100 SCT patients indoor, maintaining each appointments, chemotherapy schedules, stem cell transfers, managing donors, and running financial options for the patients. USA is blessed to have a gamut of mid level health care workers: pharmDs, physician assistants, APNs, counsellors, that work to maintain constant patient contact and counselling, data collection, collecting medical history from previous appointments, running errands, dispensing drug prescriptions to their local GPs, and ensuring compliance. They form a beautiful blend between nurses and physicians, and ensures that there is no gap in communication and understanding and same is relayed to the patients. To my knowledge, this level of skilled and dedicated health care workers is absent elsewhere.

2. Indian health care is a mix of public and private hospitals. While 90% of SCTs happen in private hospitals, the greater majority of Indian patients go to public hospitals. Because the cost of an SCT in India, though markedly less when compared to US, is beyond reach for the most. This results in a wide gap in the demand and supply of the service. To make the treatment available to most, and to run a program that manages itself, the costs of SCTs are brought down by many private hospitals. Personnel, tests, equipments, that are deemed "unnecessary" would be removed from the system. And this would compromise the quality of service, and eventual outcomes.

3. Among the technical part, conditioning protocols involved in HID SCTs could be improved. Evidences favor MAC regimens. Myeloablative conditioning, or atleast more intense RIC regimens could be used. MDACC has adopted a PK-guided time sequential Busulfan dosing for allogeneic SCTs in myeloid neoplasms. This has brought down the organ failures involved with MAC regimens, and they can administer MAC to most patients.

4. 97% of Indian patients and donors are seropositive for CMV. Reactivation following SCT is very common. CMV disease is lethal in half of its victims. It is therefore of prime importance to start empirical therapy after CMV is detected by PCR. However, while ganciclovir is myelosuppressive and toxic to the graft, foscarnet and cidofovir is extremely toxic to the kidneys. CMV reactivation is an important and frequent complication following SCTs and India need a better solution to the problem. Letermovir is a safe drug and is approved for prophylaxis against CMV. Unfortunately, it is unavailable in India. More advanced forms of treatments like virus specific cytotoxic T- lymphocytes (CTLs) are also unavailable in India.

5. Infection is the key cause of mortalities in many Indian studies. We observed that Indian patients harbour multidrug resistant organisms. Antibiotic stewardship programs have been unsuccessful so far, and in a country with gap of awareness among practitioners, and where most of the drugs are available over the counter, injudicious use of high-end antibiotics is prevalent. Novel strategies to debug the patients before they undergo conditioning should be developed. Levofloxacin prophylaxis does not work in Indian patients, as the gram negative bacilli prevalent here are often resistant to fluoroquinolones.

6. We have observed some variations in the CD34 cell dose among the Indian centers performing HID SCTs. Except CMC, Vellore, other centers have kept the cell dose below 6 x 106/kg. Since all centers are exclusively using G-CSF mobilized peripheral blood as the stem cell source, and PTCy as GVHD prophylaxis, a high dose of CD34 cells could be beneficial.

7. PTCy and atg are both effective forms of in-vivo T-cell depletion. However, combining them is not necessarily better in controlling GVHD, unless in special situations like HID SCTs in Thalassemia/ Sickle cell disease/ second transplant for Aplastic anemia, etc. Combining both forms are associated with a heightened risk of viral infections, and could contribute to increased early mortality rates

8. HID SCTs may require long term immunosuppression. The standard 6-month oral immunosuppressants doesn't work in most patients. Since continuing immunosuppressants mean frequent opd visits, frequent phlebotomies, blood biochemistry, drug levels, and because these facilities may not be available in the patient's hometown, and the patient is stuck in the city for longer duration of time than initially counselled, the physician is tempted to taper off immunosuppressants prematurely. Often these patients would come back with extensive GVHD, and not infrequently succumb to it. ■

## REFERENCES:


1. *Anasetti C, Beatty PG, Storb R, et al. Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. Hum Immunol, 1990;29(2):79-91*
2. *Luznik L, O'Donell PV, Symons HJ, et al. HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide. Biol Blood Marrow Transplant, 2008;14(6):641-650*
3. *Maiers M, Halagan M, Joshi S, et al. HLA match likelihoods for Indian patients seeking unrelated donor transplantation grafts: a population-based study. Lancet Hematol, 2014;1(2):57-63*
4. *Bolon YT, Atshan R, Allbee-Johnson M, Estrada-Merly N, Lee SJ. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2022.*
5. *George B, Kulkarni U, Lionel S, et al. Haploidentical transplantation is feasible and associated with reasonable outcomes despite major infective complications_A single center experience from India. Transplant Cellular Therapy, 2021;28:451-458*
6. *Philip C, George B, Ganapule A, et al. Acute Myeloid Leukemia: challenges and real world data from India. Br J Haematol, 2015;170:110-117*
7. *Wang Y, Wu DP, Liu QF, et al. Low-dose post-transplant cyclophosphamide and anti-thymocyte globulin as an effective strategy for GVHD prevention in haploidentical patients. J Haem Oncol, 2019;12:88*
8. *McCurdy SR, Fuchs EJ. Comparable Outcomes for Hematologic Malignancies after HLA-Haploidentical Transplantation with Post-transplantation Cyclophosphamide and HLA-Matched Transplantation. Adv Haematol, 2015;431923*
9. *Nagler A, Kanate AS, Labopim M, et al. Post transplant cyclophosphamide versus anti-thymocyte globulin for graft vs host disease prevention in haploidentical transplantation for adult acute lymphoblastic leukemia. Haematologica, 2020;106(6):1591-1598*
10. *Arcuri LJ, Hamerschlak N, Rocha V, et al. Outcomes after Haploidentical Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide: A Systematic Review and Meta-Analysis Comparing Myeloablative with Reduced-Intensity Conditioning Regimens and Bone Marrow with Peripheral Blood Stem Cell Grafts. Transplant Cellular Therapy, 2021;782e1-782e7*
11. *Batra A, Kalaiyarasi JP, Kannan K, et al. Haploidentical stem cell transplantation in Leukemia: Experience from a cancer center in India. Indian J Haematol Blood Transfus, 2021;37(3):463-471*
12. *Uppuluri R, Sivasankaran M, Patel S, et al. Haploidentical Stem Cell Transplantation in Children with Benign Disorders: Improved Survival and Cost-Effective Care Over 15 Years from a Single Center in India. Indian J Haematol Blood Transfus, 2019; 35(3):426-430*
13. *Khattry N, Laskar S, Sengar M, et al. Long term clinical outcomes of adult hematolymphoid malignancies treated at Tata Memorial Hospital: an institutional audit. Indian J Cancer 2018;55(01):9–15*
14. *Fu S, Majhail NS. Supportive care in alternative donor transplantation. Seminars Haematol, 2016; 53(2):129-136*
15. *Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic cell transplantation. N Eng J Med, 2017; 377:2433-2444*
16. *Corbacioglu S, Aggarwal S, Topaloglu O, et al. A systematic review of studies of defibrotide prophylaxis for veno-occlusive disease/sinusoidal obstruction syndrome. Transplant Cellular Therapy, 2020;26(3):133*
17. *Prockop SE, Shahid S, et al. Viral cytotoxic T-lymphocytes: from bench to bedside. Gene Cellul Immunother Cancer, 2022: 269-290*
18. *Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J, 2021;11(4):69*
19. *Appelbaum JS, Milano F. Haematopoietic stem cell transplantation in the era of engineered cell therapy. Curr Hematol Malig Rep, 2018;13(6):484-493*
20. *McCurdy S, Luznik L. Relapse after allogeneic transplantation with post-transplant cyclophosphamide: shattering myths and evolving insight. Blood Rev, 2023:101093*
21. *AlAtrash G, Kidwell KM, Thall PF, et al. Reduced intensity vs myeloablative conditioning with fludarabine and PK-guided busulfan in allogeneic stem cell transplantation for patients with AML/MDS. Bone Marrow Tranplant, 2019;54(8): 1245-1253*
22. *Jaiswal SR, Chakrabarti S. Haploidentical transplantation in children with acute leukemia: the unresolved issues. Adv Hematol, 2016:346762*
23. *Nataraj KS, Prabhu S, Bhat S, et al. Hematopoietic stem cell transplant outcomes in patients with acute myeloid leukemia from a tertiary care center in South India. Biol Blood Marrow Transplant, 2020;26(03):S123–S124*
24. *Garg A, Trivedi M, Raj A, et al. Haploidentical stem cell transplantation: half match but more hope- single center experience from west India. Indian J Hematol Blood Transfus, 2023:s12288-023-01722-6*
25. *Sharma SK, Choudhary D, Doval D, et al. Myeloablative versus reduced intensity conditioning regimens for allogeneic hematopoietic stem cell transplant for acute myeloid leukemia and myelodysplastic syndrome: a retrospective analysis. Indian J Hematol Blood Transfus 2020; Doi: 10.1007/s12288-020-01386-6*
26. *Sharma SK, Choudhary D, Doval D, et al. Hematopoietic stem cell transplant for hematologic malignancies: experience from a tertiary care center in northern India and review of Indian data. South Asian J Cancer 2022;11(1):62–67*
27. *Sharma A, George B, Subhash C, et al. Summary of the highlights of ASTCT meeting by the iNDUS BMT group in Chennai, India. Ind J Hematol Blood Transfus, 2019;35(3): 409-415*
28. *28. Okamoto, S, Iida, M, Hamad, N, et al. (2023). American Society of Transplantation and Cellular Therapy International Affair Committee: Report of the third Workshop on Global Perspective to Access to Transplantation at the 2022 Tandem Meeting. Transplant Cellular Therapy (7), 410–417.*

♦ Review Article

# Paediatric Hematopoietic Stem Cell Transplantation

*Manasa Kakunje[1], Munlima Hazarika[2], Asif Iqbal[3], Ranjita Sarma[4], and Suhani Barbhuiyan[5]*

*[1,5]Assistant Professor, [2]Professor and Head, [3]Associate Professor, Department of Medical Oncology; [4]Associate Professor, Department of Transfusion Medicine, Dr. B. Borooah Cancer Institute, Guwahati*

Hematopoietic stem cell transplant (HSCT) has emerged during the past 6 decades as an increasingly successful option to cure a variety of malignant and nonmalignant disorders in children. HSCT has been performed in humans since the late 1950s, with significant success first noted in the 1970s.[1] Pediatric hematopoietic stem cell transplant (HSCT) has undergone significant advancements in recent years globally, but addressing the specific needs in regions like Northeast India remains a challenge.Many of the pediatric malignancies have high rates of cure and stem cell transplantation is one of the treatment modalities for a variety of pediatric malignancies like Relapsed/Refractory Acute Lymphoblastic Leukemia,Acute Myeloid Leukemia (High risk or relapsed),Hodgkin's Lymphoma(Relapsed /refractory),Juvenile Myelomonocytic Leukemia(based on cytogenetic mutations involved),Chronic Myeloid Leukemia (TKI resistance/poor response to TKI), solid tumors like High risk Neuroblastoma,Metastatic retinoblastoma Retinoblastoma and a variety of benign hematological disorders like inherited bone marrow failure syndromes,secondary aplastic anemia , immune deficiency disorders like Severe combined immunodeficiency disorder,Chronic Granulomatous disease, Hemophagocytosis Lymphohistiocytosis, Wiskott Aldrich syndrome among varied other conditions .Many of these inherited marrow failure syndromes and immune disorders can predispose these children to different kinds of malignancies.[2]

One of the key advancements in pediatric HSCT is the refinement of conditioning regimens. These regimens, which prepare the patient's body for receiving the transplanted stem cells, have become more tailored and less toxic over time.[2] This reduces the risk of complications and improves outcomes, particularly in pediatric patients who may be more vulnerable to the side effects of intensive treatments. Also, various techniques like graft manipulation have significantly reduced the incidences of Graft versus host disorder in patients undergoing haploidentical transplantation.[3,4]

There have been improvements in donor selection and availability. With the advent of techniques such as haploidentical transplantation, more patients who lack matched related or unrelated donors now have options for undergoing HSCT. This is crucial in regions like Northeast India where finding suitable donors can be challenging due to limited registries and genetic diversity.

Another significant advancement is the use of novel stem cell sources such as umbilical cord blood and haploidentical donors. These sources offer advantages in terms of availability and reduced risk of graft-versus-host disease (GVHD), a common complication of HSCT.[3] However, the adoption of these techniques may require infrastructure is currently lacking in Northeast region.Lack of access to graft manipulation techniques along with the high financial burden makes haploidentical stem cell transplant still inaccessible to majority of the patients requiring it.

Drugs like Blinatumomab and Inotuzumab , which help to get the patients into remission(MRD/Measurable residual Disease becomes negative ) make transplant more feasible in patients with refractory disease by acting as a bridge to transplant.[5] Due to the high cost of these drugs and lack of funding to support such intensive treatments, there is currently limited access to

these among the patients who require them .

Advances in supportive care have improved the management of complications post-transplant, leading to better overall survival rates and quality of life for pediatric patients. Supportive care pre-, during and post-HCT is of critical importance in reducing adverse drug effects, organ toxicity, infectious complications and ultimately non-relapse mortality.[3] This includes better infection control strategies, improved nutritional support, better access to allied services like pediatric intensive care, pediatric surgery, pediatric gastroenterology, pediatric pulmonology, pediatric cardiology, pediatric endocrinology, pediatric nephrology, laboratory support, pain and palliative medicine, Medical Social Worker team and also enhanced psychosocial support for patients and their families.Not to forget the most important part of the team which is the trained nursing team to look after the patients round the clock.The pediatric hematopoietic stem cell transplant unit has to be well equipped with the support of all the allied branches for the best possible outcomes during and post HSCT. It is imperative to keep complications during Pediatric HSCT and long-term complications minimum as these children have their lives ahead of them post-transplant and also, they undergo treatment receiving high intensity drugs at a time when their organs are at a developing stage.[6]

There are still unmet needs in Northeast India and similar regions. Access to specialized pediatric HSCT centres, trained healthcare professionals, and advanced technologies and other resources like conditioning drugs and drugs for management of GVHD remains limited in many areas. Addressing these disparities requires a multi-faceted approach involving investment in healthcare infrastructure, training programs for healthcare professionals, and increased awareness about the benefits of HSCT among patients and families.

The 5 Bedded Hematopoietic Stem Cell Transplant unit at Dr BBCI has been set up and Inaugurated on 30th may 2023 with the support of funding from H T Parekh Foundation.The unit has 5 HEPA filtered rooms, cryopreservation unit, platelet agitator and other basic amenities required for HSCT. The blood bank team ,laboratory services, anesthesia and the nursing team and all other supporting teams have gone beyond their limits in making the unit functional and catering to pediatric age group including the challenging task of stem cell apheresis of children weighing 10kg. Continued support from various funding sources as well as continuous efforts from the whole team is required to farther in terms of the number as well as progress in terms of types of hematopoietic stem cell transplants being done.

*Pictures : Peripheral Blood stem cells being infused to different children in Dr BBCI HSCT unit*

Most importantly due to lack of awareness among the population and lack of social support there is a high rate of abandonment of treatment and many parents of pediatric patients requiring HSCT refuse treatment. There is a need to create a well-knit social support system for these families to tackle the social and psychological needs of this intense treatment requiring long term commitment from the family as well as the healthcare system. A total of 11 pediatric age group cancer patients have undergone Stem Cell Transplantation from August 2023 to October 2024. The 90 day mortality was 0%. The success rate was 90.1%

**CONCLUSION :**

In conclusion, while there have been significant advancements in pediatric HSCT globally, there is a need for tailored strategies to address the specific challenges faced in regions like Northeast India. This requires collaborative efforts from healthcare providers, policymakers, and the community to ensure that all pediatric patients have access to life-saving transplant therapies. ■

**REFERENCES :**


1. *Copelan EA, Manookian A, Nasrabadi AN, Asadi M;, Pentz RD, Alderfer MA, et al. Children's Lived Experiences of Hematopoietic Stem Cell Transplantation [Internet]. Vol. 354, Bone Marrow Transplant. 2006. Available from: http://pedsinreview.aappublications.org/Downloadedfrom*
2. *Thakkar D, Rastogi N, Yadav S. Pediatric hematopoietic stem cell transplantation - What a pediatrician should know ? Journal of Pediatric Critical Care. 2018;5(3):51.*
3. *Katsanis E, Hanley PJ, Simpson RJ. Editorial: Advances in Pediatric Hematopoietic Cell Therapies and Transplantation. Vol. 10, Frontiers in Pediatrics. Frontiers Media S.A.; 2022.*
4. *Bethge WA, Eyrich M, Mielke S, Meisel R, Niederwieser D, Schlegel PG, et al. Results of a multicenter phase I/II trial of TCRαβ and CD19-depleted haploidentical hematopoietic stem cell transplantation for adult and pediatric patients. Bone Marrow Transplant. 2022 Mar 1;57(3):423–30.*
5. *Sasaki K, Kantarjian HM, Ravandi F, Short NJ, Kebriaei P, Huang X, et al. Sequential Combination of Inotuzumab Ozogamicin (InO) with Low-Intensity Chemotherapy (Mini-hyper-CVD) with or without Blinatumomab Is Highly Effective in Patients (pts) with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia (ALL) in First Relapse. Blood. 2019 Nov 13;134(Supplement_1):3806–3806.*
6. *Gupta VG, Bakhshi S. Pediatric Hematopoietic Stem Cell Transplantation in India: Status, Challenges and the Way Forward: Based on Dr. K. C. Chaudhuri Oration 2016. Vol. 84, Indian Journal of Pediatrics. Springer India; 2017. p. 36–41.*

♦ Special Report

# Multiplex Lateral Flow Assay

*Rashmisnata Barman[1], and Amrita Talukdar[2]*

*[1,2]Associate Professor, Department of Microbiology, Dr. B. Borooah Cancer Institute, Guwahati*

The RESIST-5 O.K.N.V.I. assay as an in vitro diagnostic test for detecting five common carbapenemases provided rapid and accurate results in a short time, indicating that this method could provide an innovative solution for early detection, resulting in appropriate antimicrobial treatment in the clinical field.

The dissemination of carbapenem-resistant organisms is a serious global threat to human public health with few treatment options for infected patients due to their coresistance to other β-lactam antimicrobials.[1,2] Notably, the genes encoding carbapenemases, which were reported to be one of the major mechanism for carbapenem resistance, are mostly located on mobile genetic elements such as transposons, plasmids and genomic islands. Thus, horizontal transfer of these genes frequently occurs among bacterial species.[3] Therefore, carbapenemase-producing (CP) organisms, including Enterobacterales and glucose non-fermenting bacilli (GNFB), have become widespread in several countries, including India.

The rapid and accurate detection and identification of carbapenemases to prevent further dissemination and to address adequate antimicrobial treatment of infected patients in the clinical field remain a challenge.[4] Among the diverse types of carbapenemases, the five most prevalent enzymes in Enterobacterales and GNFB isolates include KPC variants of Ambler class A, three metallo-β-lactamases (MBLs) of Ambler class B (NDM, VIM and IMP-variants) and OXA48-like-variants of Ambler class D.[5] For identifying and characterizing the variable types of carbapenemases, several diagnostic tools, such as culture-based methods using resistant phenotypes and molecular biology-based methods using gene amplification, have been widely used in clinical microbiology laboratories.[6-8] However, culture-based phenotypic methods are labor intensive and time consuming and the molecular method needs expensive equipment and high expertise. Recently, multiplex immunochromatographic lateral flow assays for detecting and characterizing carbapenemases were developed[9,10] and the RESIST-5 O.K.N.V.I. assay (CORIS BioConcept, Gembloux, Belgium) with membrane technology of colloidal gold nanoparticles was introduced to identify five targeted carbapenemase genes in a single test without specialized equipment within 15 min.

RESIST-5 O.K.N.V.I. Assay The RESIST-5 O.K.N.V.I. assay (CORIS BioConcept, Gembloux, Belgium) is a new immunochromatography test composed of two lateral-flow cassettes (one cassette for VIM and IMP and the other cassette for OXA-48-like, KPC and NDM) for identification of five targeted carbapenemases *(Figure 1)*.

These tests are based on a membrane technology with different colloidal gold nanoparticles. A nitrocellulose membrane is sensitized with each monoclonal antibody directed against OXA-48-like, KPC, NDM, VIM and IMP carbapenemases and their variants. *Figure 1.* Two lateral-flow cassettes. Each cassette contains one sensitized strip. The first cassette contains a nitrocellulose membrane sensitized with monoclonal antibody directed against NDM carbapenemase ("N" line), KPC carbapenemase ("K" line) and OXA-48-like carbapenemase ("O" line) and a control capture reagent ("C" line) and the other cassette contains a nitrocellulose membrane sensitized with monoclonal antibody directed against IMP carbapenemase ("I" line) and VIM carbapenemase ("V" line) and a control capture reagent ("C" line). (B).


*Figure 1 :*

**CONCLUSION:**

Screening for these resistance gene can guide the clinician in rational antibiotic prescription and more targeted therapy. ■

## REFERENCES :


1. *Nordmann P and Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. Clin Microbiol Infect 2014;20:821-30.*
2. *Patel G and Bonomo RA. "Stormy waters ahead": global emergence of carbapenemases. Front Microbiol 2013;4:48.*
3. *Aguirre-Quiñonero A and Martínez-Martínez L. Non-molecular detection of carbapenemases in Enterobacteriaceae clinical isolates, J Infect Chemother 2017;23:1-11.*
4. *Glupczynski Y, Evrard S, Ote I, Mertens P, Huang TD, Leclipteux T, et al. Evaluation of two new commercial immunochromatographic assays for the rapid detection of OXA-48 and KPC carbapenemases from cultured bacteria. J Antimicrob Chemother 2016;71:1217-22.*
5. *Glupczynski Y, Jousset A, Evrard S, Bonnin RA, Huang TD, Dortet L, et al. Prospective evaluation of the OKN K-SeT assay, a new multiplex immunochromatographic test for the rapid detection of OXA-48-like, KPC and NDM carbapenemases. J Antimicrob Chemother 2017;72:1955- 60.*
6. *Papadimitriou-Olivgeris M, Vamvakopoulou S, Spyropoulou A, Bartzavali C, Marangos M, Anastassiou ED, et al. Performance of four different agar plate methods for rectal swabs, synergy disk tests and metallo-βlactamase Etest for clinical isolates in detecting carbapenemase-producing Klebsiella pneumoniae. J Med Microbiol 2016;65:954-61.*
7. *Lee SY, Octavia S, Chew KL. Detection of OXA-carbapenemase-producing Enterobacteriaceae with chromID CARBA SMART screening plate. Pathology 2019;51:108-10.*
8. *Glupczynski Y, Evrard S, Huang TD, Bogaerts P. Evaluation of the RESIST-4 K-SeT assay, a multiplex immunochromatographic assay for the rapid detection of OXA-48-like, KPC, VIM and NDM carbapenemases. J Antimicrob Chemother 2019;74:1284-7.*
9. *Greissl C, Saleh A, Hamprecht A. Rapid detection of OXA-48-like, KPC, NDM, and VIM carbapenemases in Enterobacterales by a new multiplex immunochromatographic test. Eur J Clin Microbiol Infect Dis 2019; 38:331-5.*
10. *Rösner S, Kamalanabhaiah S, Küsters U, Kolbert M, Pfennigwerth N, Mack D. Evaluation of a novel immunochromatographic lateral flow assay for rapid detection of OXA-48, NDM, KPC and VIM carbapenemases in multidrug-resistant Enterobacteriaceae. J Med Microbiol 2019;68: 379-81.*

♦ Review Article

# Telemedicine in Ostomy Management

*Yumnam Piyainu*

*Enterostomal Therapist, Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION :**

Nursing is both an art and a science. For the wound, ostomy, and continence (WOC/ET) nurses, teaching, and supporting the ostomy patient is the example of this. Telemedicine uses information and telecommunications technology to transfer medical information for diagnosis, therapy, and education. The information may include medical images, live two-way audio and video, patient medical records, output data from medical devices, and sound files.

The telemedical interaction may involve two-way live audio and video visits between patients and medical professionals, sending patient monitoring data from the home to the clinic, or transmitting a patient medical file from a primary care provider to a specialist.

**SELECTION SERVICES:**

In assessing the needs of the identified population, the type of services to be provided are evaluated. Serving the ostomy patient is a new frontier. When evaluating services traditionally provided to the ostomy patient, the practitioner must assess which services might be provided from a distance an considered the essential tasks to be accomplished both before and after surgery *(Table - I).*

*Table 1: Items to consider before providing services from a distance.*

| | |
|---|---|
| 1 | Physical, Psychologic, Mental, and Emotional status |
| 2 | Cultural, Social, and Philosophic attitudes |
| 3 | Sensory perception |
| 4 | Experience (Past) |
| 5 | Current meaning of the event |
| 6 | Interest and motivation |
| 7 | Actual knowledge |
| 8 | Environment |
| 9 | Presence and attitudes of others |

*From Hampton BG, Bryant RA, Editors : Ostomies and continent diversions : nursing managements' St. Louis, 1992, Mosby.*

Many of these tasks can be carried out during the initial interview with the patient and a family member, a care giver, or a significant other.

Post-operative interventions such as education, counselling, and follow up care can be accomplished by telemedicine. Live video equipment acts as a "television came" to allow both parties instant access to information. A question-and-answer session can be performed as it would be in person. The camera helps in viewing the patients care environment, and assess skin and stoma condition and function, as well as accurate pouching system placement. Observing the patient on multiple occasions in the home or in a clinic space that is geographically convenient will accelerate patient learning a possibly prevent problems.

One area that does not appear to be conducive to telemedicine is preoperative stoma site selection and marking. The process of selecting and accurately marking a stoma site requires a hands-on approach.

**SELECTING THE APPOPRIATE PATIENT :**

The first step in a telehealth program is identifying the appropriate patient. Not all patients should receive telemedicine

services. Technology is a great tool, but it does not always apply to every situation and patient. Although no hard and fast rules currently exist from the governing bodies, *Table 2* suggests guidelines.

*Table 2 : Guidelines to consider in selecting patients for Telemedicine Services.*

| | |
|---|---|
| 1 | The patient and / or the caregiver should be alert and oriented to diminish the potential for confusion. |
| 2 | The patient should have good cognition and hearing |
| 3 | A significant other or a caregiver should be present for all or most encounters |
| 4 | The patient or caregiver should demonstrate comfort with technology |
| 5 | Patients who do not have local access to a WOC practitioner or have developed a bond to the Telemedicine practitioner or have developed a particular bond to the Telemedicine practitioner would be good candidates. |

*Modified from Telemedicine Reimbursement Guidelines for Medicare Recipients. (n.d.), website : www.fcc.gov/e-file/ecfs.*

**PERFORMING THE TELECONSULTATION :**

After selecting and enrolling the appropriate patient into the program, the visit process can begin. First and foremost, the clinician must obtain consent. The language of the current patient consent form must be checked. Does it contain a photography clause? If not, a separate consent for video and photography must be obtained.

*Table 3 : Steps to a successful Telemedicine consultation.*

| | |
|---|---|
| 1 | Activate the equipment as directed by the manufacturer |
| 2 | Greet patient as per routine. Encourage the operator of the equipment in the remote location to focus the camera on the patient's face at the beginning of the call. Acknowledge the patient and all parties present. Then ask whatever questions are pertinent. Now focus the camera on the patient's abdomen. |
| 3 | Discuss issues at hand and allow time for comments and discussion. Initial visits, until everyone is comfortable with the technology, may be lengthy |
| 4 | Give clear, concise camera directions, such as "move to the middle of abdomen," or "toward the head Avoid using words like "up" and "down." these can be misleading and end up frustrating everyone. |
| 5 | Take photo stills of each visit for records, research, and reference. Save these photos to the patient file. |
| 6 | Proceed with instructions, moving the camera back to the patient's face so the feeling of an in-person encounter is created |
| 7 | Close the visit with a plan and a schedule for follow-up. |

**PATIENT RESPONSE :**

The success of the program can be greatly influenced by how the program is explained to those who participate. Patient responses range from excitement to fear and skepticism. Many patients have a concern about privacy. The patient must be assured that all routine privacy regulations will be maintained.

**SELECTING THE TECHNOLOGY :**

The device of choice is the tele-video patient monitoring system. This tool allows live, real-time transmission of voice and video from the user to the monitoring station or clinician and allows visualization of the patient and the clinical situation. Such support can increase patient independence and self-confidence. Being able to see the situation rather than just hearing about it can be a tremendous asset for both the patient and the health care provider.

**ASSESSING NEEDS :**

Telemedicine has proven to be a great teaching tool. A telemedicine camera provided to the patient at discharge can make teaching in the home more effective. The cameras are page sent home with the patient like any other piece of durable medical equipment. The patient and/or the home care nurse schedule a time for a joint visit, and the patient is seen in the home environment. This is a great advantage for the homebound patient or patients in rural areas with limited access to health care services. It is useful to imagine being able to watch the patient perform his or her ostomy care in the home environment. How much easier would it be to observe technique and identify problems? As the patient progresses or tries a new pouching system, the camera could be activated for follow-up and monitoring. Solutions to problems could be achieved so much faster.

If the patient population is not homebound, or if a large portion of the patient population travels a great distance to receive services, virtual clinic may be the best use of telemedicine. A virtual clinic can exist anywhere. It may be a room at the local community centre or in a senior citizen housing facility. In the virtual clinic mode, a room is set up as the receiving station where patients are seen. By setting the area aside, privacy is ensured. Regularly scheduled appointments are planned. The number of cameras required is generally limited to one (decreasing the financial investment) and the "clinic" can be staffed by a registered nurse or licensed practical nurse and perhaps an office assistant or clerk. At regular times the system is activated and the patients seen, assessed, taught, or treated as necessary.

**CHOICES OF TELEMEDICINE SYSTEMS :**

Telemedicine technology is rapidly evolving. Cell phones can capture transmit pictures and will soon be telehealth- capable. Video and voice transmission can be sent over the phone lines quite well. The only infrastructure that is required to turn any telemedicine system on is a phone line and an electrical outlet. Are the lines and cables needed

available in the space planned, or will they have to be installed? Although high-speed Internet access can enhance the system, it is not an essential component.

The use of off-the-shelf software can be considered, rather than custom designs, to keep costs low. The cost of training time for the staff and the IT department's time in implementing the program must be figured in.

**CONCLUSION:**

The future of telemedicine is endless. For the WOC/ET nurse, this technology can be used to record and evaluate patient technique and provide follow-up care. Telemedicine gives new meaning to the phrase, "Reach out and touch someone!" ■

**REFERENCES :**


1. *American Telecare, Inc. (n. d), website:www.americantelecare.com.*
2. *American Telemedicine Association (1999): Report to Congress on Telemedicine, website; www.atmeda.org/news/newres.htm.*
3. *Health Insurance Portability and Accountability Act of 1966*
4. *(HIPPA). Website: (www.fcc.gov/e-file/ecfs).*
5. *HomMed,Inc.(n.d.), website: www.HomMed.com*
6. *Joint commission on Accreditation of Healthcare Organizations (JCAHO): 2001-2002 Comprehensive accreditation manual for home care. Oakbrook Terrace,III,2002, Author.*
7. *Retrieved from website: www.Motion-Media.com*
8. *Telemedicine Reimbursement Guidelines for Medicare*
9. *Recipients (n.d.), website: www.fcc.gov/e-file/ecfs.*

♦ Review Article

# Apheresis Technology

*Karabi Kuli[1], Chandana Kalita[2], and Ranjita Sharma[3]*

*[1]Assistant Professor, [2]Medical Officer, [3]Associate Professor, Department of Transfusion Medicine , Dr. B. Borooah Cancer Institute, Guwahati*

**INTRODUCTION:**

Apheresis is a medical procedure that involves the separation and removal of specific components of the blood while returning the remainder back to the donor or patient. The term comes from the Greek word "aphairesis," meaning "to take away" and it was first used in 1914 by Able, Rowntree, and Turner. This technique plays a vital role in collection of blood component from donors as well in therapeutic procedures in certain medical conditions.

Based on the targeted blood component, apheresis can be categorized into Plasmapheresis, plateletpheresis, leukapheresis, Erythrocytapheresis, Granulocytapheresis as well as may include few specialized therapeutic apheresis procedures like extracorporeal photopheresis, Immunoadsorbtion Low-density lipoprotein (LDL) apheresis etc.

**PRINCIPLE:**

Apheresis procedure requires a specialized instrument where separation of blood elements is performed by centrifugation or membrane filtration or elutriation or in combinations. Most apheresis instruments use centrifugation method where centrifugal force separates the blood into its components based on differences in specific gravity. In filtration method, a membrane surface with pores or a bundle of hollow fibres is used that sieves the desired blood components from healthy donors or allows therapeutic removal of abnormal plasma constituents. In some systems, elutriation is also used, where two opposing forces— centrifugal force that pushes heavier elements away from the centrifuge center and pump withdrawal force that pulls the elements to the centrifuge center. Combination of both centrifugation and filtration has been incorporated in few instruments, as it increases the plasma collection efficiency.

**ANTICOAGULATION IN APHERESIS :**

During an apheresis procedure, extracorporeal blood has to be anticoagulated prior to its contact extensively with the tubing sets. The most commonly used anticoagulant is ACD-A [ Acid citrate dextrose -A] which acts by binding to Calcium ion and thereby preventing its participation in the coagulation cascade. The advantage of ACD-A is due to its regional anticoagulation with minimal residual effect. However, complications may happen in citrate-based anticoagulation too, primarily due to the physiologic effect of hypocalcemia. Prophylactic Oral calcium supplementation or continuous intravenous Calcium infusion, in high volume processing is often required to counteract the symptoms.

Heparin based anticoagulation is usually not preferred due to its systemic effect. Its use is limited to high blood flow procedures [membrane filtration based plasmapheresis, LDL apheresis, extracorporeal photopheresis] and combined citrate/heparin therapy in pediatric apheresis. Then there is always the risk of hemorrhagic episodes and development of Heparin induced Thrombocytopenia.

**VASCULAR ACCESS :**

Both therapeutic and donor apheresis procedure requires adequate venous access to achieve the optimum inlet flow rate and efficient returning of blood to the donor/patient. Peripheral venous access using large bore needle of 17 gauge or larger is preferable, whenever possible, because of the risks associated with Central venous catheter placement especially in healthy donor procedures. It has also been demonstrated that ultrasound guided peripheral access reduces use of CVC by 20%.

It may be necessary to insert CVC in patients where peripheral access is difficult due to the underlying disease condition, previous IV insertions, multiple apheresis and hypovolemia. Rigid, large diameter, shorter and preferably double lumen Central veinous catheters are apt for apheresis procedure to

withstand the negative pressure, minimize resistance and allowing a single line for draw and return respectively.

**IMPLEMENTATION OF APHERESIS SYSTEM IN BBCI:**
The spectra optia apheresis system was acquired by our institute in the year 2021 through a comprehensive evaluation. Further to tackle the rising number of procedures, another system was added recently. This is a fully automated, continuous flow, centrifugation based apheresis system with a Leukoreduction system chamber. This multi component cell separator has various protocols that can collect/remove platelets, granulocytes, plasma, and Peripheral blood stem cell/mononuclear cells.

The system can also be used for therapeutic plasma exchange as well as red cell exchanges. As all available automated systems, prepackaged product specific disposable sets of sterile bags and tubings are used.

The first plateletpheresis procedure for single donor platelet was performed on 17/05/2022 in our institute with a collection of 162 SDP in the first year. In the succeeding year, 423 donor plateletpheresis was done marking a significant rise and > 900 procedures has been done so far this till date. There has been also a notable increase in voluntary SDP donors as seen over the years. The shift towards single donor platelet has been a necessity for the multi-transfused patients as well as the hematopoietic stem cell transplant patients. There has been also a notable increase in voluntary SDP donors as seen this year.

Few procedures related complications have been encountered during donor plateletpheresis usually hematoma, mild symptoms of hypocalcemia and a rare complain of dizziness. Prophylactic oral calcium is used in most procedures depending on the donor physiology and duration of the procedure.

**Advantages of single-donor component separation by Apheresis :**

| Patient Related | Donor Related |
|---|---|
| 1. Reduced risk of alloimmunisation and transfusion - transmitted infections due to reduced donor exposure.<br><br>2. Reduced risk of febrile non-haemolytic transfusion reaction, alloimmunization and cytomegalovirus transmission due to provision of leukureduced blood component.<br><br>3. Better quality product. | 1. Reduced donor adverse reaction.<br><br>2. Less venous injury due small needle technology |

The spectra optia machine possesses an automated interface management (AIM] system which continuously manages the separated component layers using an optical detection technology. This helps in efficient removal of the targeted components without solely relying on the user. It has a user-friendly touchscreen graphical interactive display and also is a safely transportable instrument. These features have been quite helpful in our procedures especially for peripheral blood stem cell collection.

The first PBSC harvest was done on 30th December ,2022 and so far,26 PBSC harvest procedures have been conducted including 6 allogenic cases. In all the procedures for both adult and pediatric, only single vein access technique has been used through central venous catheter insertion. Low weight pediatric cases do require blood priming in view of the extracorporeal volume. Continous IV calcium infusion throughout the procedure is routinely practiced to counteract hypocalcemia. Beside two cases, where repeat next day procedure was required, adequate doses were harvested for all the procedures. The stem cell product hematocrit and platelet count were found to be acceptable.

Indication of therapeutic apheresis among our patients has been met rarely as observed till now. Only a single procedure of therapeutic leukapheresis was conducted on a case of AML with symptomatic hyperleukocytosis. Reduction of >1 lakh in TLC was observed after processing of 1. 5 times the total blood volume.


*Apheresis Machine*

**CONCLUSION:**

Incorporation of the current apheresis system has proven to be an essential technology in blood component collection by enhancing the efficiency and safety as well as quality of products. Effort to enhance our apheresis service is ongoing and our immediate future plan focus on starting donor granulocytapheresis procedures in BBCI.

Apheresis technology makes a tailored approach to manage the patient's blood requirement as well to the therapeutic needs. ■

**REFERENCES:**

1. *Lee G, Arepally GM. Anticoagulation techniques in apheresis: from heparin to citrate and beyond. J Clin Apher. 2012;27(3):117-25. doi: 10.1002/jca.21222. Epub 2012 Apr 24. PMID: 22532037; PMCID: PMC3366026.*
2. *AABB-Apheresis-Principles-and-Practice-3rd-Edition*
3. *Salazar E, Garcia S, Miguel R, Segura FJ, Ipe TS, Leveque C. Ultrasound-guided peripheral venous access for therapeutic apheresis procedures reduces need for central venous catheters. J Clin Apher. 2017 Aug;32(4):266-269. doi: 10.1002/jca.21493. Epub 2016 Aug 10. PMID: 27509232.*
4. *Rossi's Principles of Transfusion Medicine, Sixth Edition*

♦ Editorial Report

# Prioritizing Cancer Care in North-East India

*Jyoutishman Saikia*

*Assistant Professor, Department of Surgical Oncology, NCI-AIIMS, Jhajjar*

The North-Eastern (NE) part of India has always been a very welcoming place for tourists but unfortunately, cancer, an unwelcome guest has rooted itself in these regions for many decades. Data collected from 11 population-based cancer registries (PBCR) from 2012-2016 (which covered 35% population) identified the NE region as the area with the highest number of new cases of cancers detected per year.[1] This has created panic among government agencies catering to community levels on approval and implementation. As per the GLOBACON 2020, newly diagnosed cancer cases in India have risen to 1.3 million with 0.8 million annual deaths[2] This is a nearly 20% increase in both incidence and mortality from the last 8 years, emerging as a significant public health problem.

Lip and oral cavity cancers are reported to be the leading cause of cancer death among males.[3] Compared to the rest of the country, the NE region deserves special attention being the cancer capital of India. Cancers of the oesophagus, hypopharynx, stomach, lung, liver and cervix were higher than the rest of the nation. Most of these cancers have been attributed to some identifiable risk factors which include esophageal cancer (betel nut chewing, spicy and hot beverages), stomach cancer (fermented and smoked foods, alkali intake), lung cancer (tobacco smoking and second-hand smoke), liver (heavy smoking and drinking, intravenous drug use and hepatitis B/C infection), gall bladder cancer (impure water, salmonella typhi infection and adulterants in edible oil), nasopharyngeal cancer (smoke, Epstein–Barr virus and nitrosamine-containing food), breast cancer (mostly unknown, other include genetic, usual hormonal risk factors and lifestyle modifications), carcinoma cervix (human papillomavirus 16 and 18 infection).[1] Unfortunately, this region also has a high incidence of tobacco smoking and smokeless tobacco use.[4]

An analysis by the ICMR-NCDIR identified that the projected rise of new cancer cases in India from 2020 to 2025 is expected to be around 12.8%.[5] If we look at the currently available healthcare resources, there are only a handful of dedicated cancer-treating facilities in each of these eight NE states which makes these treatment centres overwhelmingly burdened by new cases daily. To add to this, only 11 Atomic Energy Regulatory Board (AERB) licensed, nuclear medicine facilities exist in this NE region, which is less than 2% of the available facilities in India.[6] Similar is the state of other diagnostic and treatment facilities. With the growing developments in oncology, medical treatment has become unaffordable for the common people where the majority of the population (81.6%) is in rural areas.[7] Although the government has launched many schemes, facilities are not available in local areas. Many of these patients have to travel to the rest of the country in search of adequate cancer treatment increasing their out-of-pocket expenses. The question arises that how can we fight back with limited treatment facilities and human resources?

Exploring about the validity of cancer prevention, a study of nearly 12000 participants followed up for 14 years with adherence to cancer prevention guidelines for obesity, diet, physical activity, and alcohol consumption found a significant impact on reducing cancer mortality.[8] Evidence-based guidelines from The National Cancer Institute suggested that a reduction in relative risk of 15% is seen for all-cause mortality among heavy smokers subjected to intensive clinical cessation interventions.[9] They have observed that methods like counselling by a health care professional or a simple advice from a physician can greatly reduce the smoking rates, besides drug deaddiction therapy.[10] According to the National Family Health Survey 2020-21 among women, cervical screening for cancer rates is as low as <1% and breast examination for cancer <0.5% in many of these NE states which is much below the national rates (1.9% and 0.9 % respectively) and far below those of developed countries 11. For a successful screening program, a lot of resources are required and above all, if such a program

would have been extensively implemented, huge demands are likely to arise from repeated screening for cancers, such as those of the breast, cervix, and oral cavity.[12] Most states will unlikely be able to cater to these needs. Hence, primary prevention seems to be the most important cancer prevention strategy. Primary prevention is neither easy, it also comes at a cost. It demands a planned approach with strategies to reduce the cancer burden on both individuals and society.[13] Looking back at the identified risk factors in this NE region, diet seems to take a very strong place which is also highly influenced by individual culture and beliefs. So, changing to less carcinogenic dietary practices would require health education as one of its prime pillars. Education can start at school and community level.[14] Public awareness along with participation of non-governmental organisations are crucial.[15] Active steps should be taken by the government in preventing food adulteration as people "die of bad food rather than no food".[16] Policies should be in place and implemented to reduce exposure to key environmental pollutants that are known carcinogens. The provision of safe drinking water and cost-effective methods for monitoring drinking water quality are utmost importance for cancer prevention.[17] Continued efforts should be in force to reduce tobacco and alcohol consumption. It is time to strengthen and widen cancer registration and registries, including the strengthening of death certification. Proper protection of workers from occupational hazards needs attention. Lots of importance needs to be given to construction areas also. The importance of regular physical activities in cancer prevention has been underestimated.[18] Outdoor areas should have walking and cycling tracks. Planning during the construction of living areas so that they should have secure spaces and facilities for exercise and leisure.[19] The government can strengthen the current health system by utilizing the community and rural health workers in prevention programs. Putting a focus on cancer research and scaling screening programs would lead the way forward.

Cancer prevention is a wholesome goal, which needs to be achieved through the efforts put forward by every citizen along with support from both the state and the central governments. With adequate zeal and enthusiasm, a lot can be done by bridging the knowledge gap, spreading awareness and promoting community-based approaches. While addressing cancer in the NE region, the prime focus should be on specific cancers prevalent in particular regions, where most resources can be focused to achieve maximum results within specified time periods. ■

**REFERENCES:**


1. *Shanker N, Mathur P, Das P, et al. Cancer scenario in North-East India & need for an appropriate research agenda. Indian J Med Res. 2021;154:27.*
2. *Cancer Today. Accessed January 22, 2024. https://gco.iarc.fr/today/fact-sheets-populations*
3. *Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-249.*
4. *Round S. TOBACCO SURVEY INDIA 2016-2017 | RepoRt.*
5. *Sathishkumar K, Chaturvedi M, Das P, et al. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. Indian J Med Res. 2022;156:598.*
6. *Nuclear Medicine | AERB - Atomic Energy Regulatory Board. Accessed January 22, 2024. https://www.aerb.gov.in/english/regulatory-facilities/radiation-facilities/application-in-medicine/nuclear-medicine1*
7. *Home | Government of India. Accessed January 22, 2024. https://censusindia.gov.in/census.website/*
8. *McCullough ML, Patel A V., Kushi LH, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. Cancer Epidemiol Biomarkers Prev. 2011;20:1089-1097.*
9. *Board PS and PE. Cigarette Smoking: Health Risks and How to Quit (PDQ®). PDQ Cancer Information Summaries. Published online December 22, 2023.*
10. *Lancaster T, Stead L. Physician advice for smoking cessation. Cochrane Database Syst Rev. 2004.*
11. *NFHS Project | International Institute for Population Sciences (IIPS). Accessed January 22, 2024. https://www.iipsindia.ac.in/content/nfhs-project*
12. *Sankaranarayanan R. Cancer prevention and care in India: An unfinished agenda. Lancet Oncol. 2014;15:554-555.*
13. *Mathur MR, Singh A, Dhillon PK, et al. Strategies for cancer prevention in India—Catching the 'low hanging fruits.' J Cancer Policy. 2014;2:105-106.*
14. *Barros A, Moreira L, Santos H, et al. "Cancer – Educate to Prevent" – High-School Teachers, the New Promoters of Cancer Prevention Education Campaigns. PLoS One. 2014;9:e96672.*
15. *Van Parijs LG. Public education in cancer prevention. Bull World Health Organ. 1986;64:917.*
16. *Haji A, Desalegn K, Hassen H. Selected food items adulteration, their impacts on public health, and detection methods: A review. Food Sci Nutr. 2023;11:7534-7545.*
17. *Morris RD. Drinking water and cancer. Environ Health Perspect. 1995;103:225.*
18. *Mctiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. Med Sci Sports Exerc. 2019;51:1252-1261.*
19. *Jurdana M. Physical Activity and Cancer Risk. Actual Knowledge and Possible Biological Mechanisms. Radiol Oncol. 2021;55:7.*

DR B BOROOAH CANCER INSTITUTE

# MILESTONES

| | | |
|---|---|---|
| 1973 | ◆ | Inauguration of Dr. B. Borooah Cancer Institute, Guwahati |
| 1979 | ◆ | First Tele-Cobalt Therapy Unit |
| 1980 | ◆ | Recognized by Govt. of India as Regional Cancer Centre (RCC) |
| 1989 | ◆ | Tripartite Agreement with Govt. of Assam; Department of Atomic Energy, Govt. of India and North-Eastern Council, Govt. of India |
| 1999 | ◆ | Nuclear Medicine Department |
| 2001 | ◆ | Dual Energy Linear Accelerator |
| 2003 | ◆ | Preventive Oncology, Palliative Medicine Services, PBCR, HRD Brachytherapy. |
| 2005 | ◆ | CT Simulation |
| 2006 | ◆ | Minimally Invasive Surgery |
| 2007 | ◆ | Linear Accelerator with IMRT & 3DCRT, 1.5 Tesla MRI |
| 2009 | ◆ | Physiotherapy and Occupational Therapy |
| 2010 | ◆ | Molecular Oncology Research Programme, HBCR |
| 2012 | ◆ | IGRT, MSc. Radiological Physics. |
| 2013 | ◆ | MD Radiotherapy |
| 2016 | ◆ | MCh. Surgical Oncology |
| 2017 | ◆ | DM Medical Oncology; Grant-in-Aid Institute of Dept. of Atomic Energy, 1973 Govt. of India and a unit of TMC, Mumbai |
| 2018 | ◆ | Skull Base and Micro Vascular Surgery, Diploma Oncology Nursing |
| 2019 | ◆ | LINAC with IMRT, IGRT, VMAT, 6XFFF; St. Jude India Child Care Centre; High Dose Radio-Isotope Therapy Ward. |
| 2020 | ◆ | MCh. in Head & Neck Surgery and Gynae. Oncology; DM in Onco-Pathology; Molecular Virology Laboratory; SRS. |
| 2021 | ◆ | SBRT; BMT; MSc. in Oncology Nursing; Masters in Health Administration; Journal of 'Annals Oncology Research and Therapy' Release of Oncology Text Book (First Edition) 'Principles and Practice of Oncology' |
| 2022 | ◆ | Allogenic Bone Marrow Transplantation, Release of Book "Triple 'C' in Cancer" for general public; Apheresis facility, Release of oncology book (First Edition) 'Principles and Practice of Common Cancers' and 'Fundamentals of Gynaecological Malignancy' published by Springer Nature, NABL Accreditation of Laboratory Services. |
| 2023 | ◆ | Bhabatron II Telecobalt Unit; 4 bedded Bone Marrow Transplant (BMT) Unit; Diagnostic Video Endoscopy System (Hopkin's); High Definition Minimally Invasive Surgery (MIS) System; Blood Irradiator 2000 and Mobile Van for Blood collection with Accessories. |
| 2024 | ◆ | PET-CT Scan Facility; Emergency Ward. |

# Coming Soon

Finalized site plan for Ancillary Building (New OPD) against Sanctioned DPR from DAE, GoI.

Dr. Bhubaneswar Borooah Cancer Institute, Guwahati