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Designed by: Rushi C Patel, Head, Department of Educational Graphics & Medical Photography, GCRI, Ahmedabad, India.
Radiotherapy (Radiation Oncology)

Radiotherapy (RT) is the treatment of neoplastic disease by ionizing radiation. It is also useful in the treatment of certain benign diseases. Radiation alone can be delivered with a radical intent in a curative setting in early stage of the disease. Its combination with surgery can vary diversely from being delivered during (intraoperative), before (neoadjuvant) or after resection (adjuvant), or with systemic therapy, sometimes for organ preservation (such as in larynx, breast, urinary bladder, anal canal etc). Moreover, it can provide symptomatic relief in cancers that are locally advanced or disseminated, by reducing or eliminating pain from bone metastases etc. in 60% of cases. RT also has an effect on the dissemination of the tumor in that local/regional therapies are, in effect, ‘stopping metastases at their source’. More recently, the possibility of the abscopal effect has been raised on the basis of a remission in out-target lesions after localised RT.

History of Radiotherapy

After the discovery of X-rays in 1895 by Wilhelm Conrad Roentgen, the scenario changed rapidly, for their role in the treatment of malignant and benign diseases. Antoine Henri Becquerel started to study the phenomenon of radioactivity and the natural sources of radiation. In 1898, Maria Sklodowska-Curie and her husband Pierre Curie discovered radium as a source of radiation. Three years later, Becquerel and Curie reported on the physiologic effects of radium rays. Period from 1930 to 1950, was characterised by continuous scientific progress to treat patients affected by deep cancers. This era (also known as Orthovoltage era) was mainly characterised by the use of the radium-based interstitial irradiation (brachytherapy) and by the development of super voltage X-ray tubes able to deliver energy from 50 kV to 200 kV. The second one, the introduction of electron beam therapy, an useful therapeutic option able to deliver higher and variable energies for treating tumors up to a depth of 5 centimetres. The studies, which were conducted during the successive three decades (Megavoltage era), were also committed to the production of more and more innovative radio-therapeutic devices capable of treating cancers in the deep tissues. This period saw the introduction of the Cobalt teletherapy, producing high-energy γ-rays, and of more potent electron linear accelerators (also known as LINACS), able to deliver megavoltage X-rays. The new devices were able to deliver a higher dose of energies than the previous ones, making possible the treatment of deeper tumors with a greater skin sparing. Due to the difficulties of managing these sources and thus the perilousness of excessive radiation within the tissue surrounding cancer, innovative multi-field plans of irradiations were designed. Another important progress in radiotherapy was achieved by the end of the 1990s when the introduction of more sophisticated computer planning systems allowed the development of a 3D conformal radiotherapeutic device (Stereotactic Radiation Therapy), able to treat in a more proficient and safer way with the aid of multileaf collimators (MLC). RT techniques have changed significantly over the past few decades due to the improvements in engineering and computing, evolving from conventional irradiation using simple treatment fields towards highly conformal RT techniques, such as Intensity-Modulated Radiotherapy (IMRT), Intensity-Modulated Arc Therapy (IMAT) and Stereotactic Radiotherapy (SRT, SRS), which aim to improve the outcome by escalating the dose to the target and minimizing the toxicity to normal tissue and critical organs. So, nowadays, certain tumors (i.e. breast and prostate cancer) receive shorter courses of RT as a secure and well-tolerated alternative to the longer conventional schemes; this often holds an enormous advantage for patients and also for healthcare costs. Indeed, high-precision extremely hypo-fractionated RT has been called virtual surgery, since in many situations it can have a radical curative effect locally that's almost like surgery. From the biological point of view, such a high
dose per fraction induces different radiobiological mechanisms of cell killing and thereby introducing a novel concept of Radioablation. Technological advances have mainly been the outcomes of integration of imaging information in every phase of the treatment, from the point of simulation to planning to treatment delivery. Indeed, Treatment Planning Systems (TPS) provide sophisticated image registration and fusion algorithms. Moreover, treatment planning optimization is becoming more radiobiology-oriented, integrating local radiation damage models. At present, the precise identification of target volumes for treatment planning is particularly grounded on the fusion of radiological/metabolic imaging, like Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET), with Computed Tomography (CT) scan simulation. Tumor localisation immediately prior to and through treatment delivery by means of image-guided techniques is becoming crucial for clinical practice and a fundamental prerequisite for high-precision RT. As a part of comprehensive RT treatment process, Adaptive RT (ART) techniques make it possible to alter the treatment plan during the course of RT so as to account for anatomical and biological changes.

Novel Techniques in Radiotherapy

A. Treatment techniques: state of the art

1- Intensity-Modulated Radiotherapy(IMRT): Intensity modulation was introduced in the early 1990s as a further refinement in the delivery of Three-Dimensional Conformal Radiation Therapy (3D-CRT). IMRT was made possible by the use of computer-controlled MLCs and mMLCs and advanced treatment planning optimization algorithms that are able to create the desired dose variation inside the radiation field. As opposed to standard planning techniques, where the dose distribution can only be modified by means of a trial and error approach (changing for instance the field weight, angle and shape), with IMRT, the radiation oncologist designates the doses and dose/volume constraints for the tumor and the surrounding normal organs and the TPS determines the optimal fluence of each field leading to a tailored dose distribution (inverse planning). In the past, IMRT was usually delivered using a conventional LINAC with a static field geometry. Developments in IMRT techniques have focused on reducing treatment times with arc therapy by converting multiple static field IMRT into continuously rotating gantry intensity modulation.

2- Stereotactic Body Radiotherapy(SBRT): SBRT is very much a technology-driven treatment modality. SBRT systems are capable of delivering very conformal treatment plans with a steep dose gradient outside the target. This technique makes possible the delivery of a secure, sound and proficient treatment across a wide range of anatomic locations, in proximity to critical organs, and even adjacent to or within prior RT fields. Essential requirements for SBRT are the veritableness of target delineation, and thus the implementation of inter- and intra-fraction tumor motion compensation strategies (especially for tumors within the lung and in the upper abdomen). The wider availability of in-room imaging and advanced treatment delivery systems means that more institutions are now offering SBRT. At present, there are a variety of systems available for SBRT.

3- Particle beam therapy: Proton therapy has been used internationally for cancers of the eye, base of skull and spine, particularly in paediatric patients. Indeed, proton therapy in children has been shown to have a lower incidence of vision and hearing impairment, of neurocognitive degeneration and of second cancers, than is the case with other RT modalities. Moreover, heavy particles, such as Carbon ions, are particularly indicated for severely radio-resistant tumors because their biological effectiveness is greater than that of photons and protons. According to the Particle Therapy Co-Operative Group (PTCOG, www.ptcog.com), which constantly updates the statistics on cancer treatment with particle therapy, ten carbon ion therapy facilities are in operation to date (July 2017). The National Institute of Radiological Sciences Chiba, Japan, has been treating cancer with high-energy carbon ions since 1994, with almost greater than 10,000 patients treated by August 2016 and, thus, is the centre with the greatest experience in carbon ion treatment worldwide. For the first time, at the National Centre for Oncological Hadron therapy in Pavia, Italy, carbon ions delivered with active scanning together with breathing synchronisation and rescanning modalities have been used to treat patients with tumors of the liver and pancreas.

B. Tumor localisation in treatment planning

As mentioned earlier, the more precise radiation delivery becomes, the more important it is to accurately identify the extension of both the tumor mass and also the normal tissue and critical organs involved in the neoplastic degeneration. This is essential so as to optimize irradiation geometry by delivering the radiation dose to the tumor itself while minimizing the dose delivered to surrounding tissue and organs at risk (OARs). The integration of radiological/metabolic imaging, like MRI and PET, with the CT scan simulation can provide useful information for accurately visualizing the tumour
volume. PET with different tracers has made it possible to acquire metabolic information and identify the foremost radio resistant sub-volumes within the tumor. Automatic or semiautomatic (needing manual revision) segmentation algorithms can speed up the delineation of OARs and they offer reliability and repeatability in delineating the structures.

C. Tumour localisation in treatment delivery

1- Image Guided Radiotherapy (IGRT):
Technological innovations have made possible the direct integration of imaging technology into the radiation treatment device to augment the precision and accuracy of radiation delivery by controlling the delivery of the dose within the body. A broad range of IGRT modalities are now available and usually used. There are several methods for localizing the target during each and every treatment fraction: by localizing surrogates, including implanted fiducial markers, external surface markers or anatomical features (through planar imaging, fluoroscopy, kilovoltage CT (kV-CT) or megavoltage CT (MV-CT), MRI, ultrasound and x-ray imaging, electromagnetic localisation, optical surface imaging and then on. Depending on the imaging methods used, the IGRT systems may broadly be divided into radiation based, non-radiation based and hybrid systems. Of all soft-tissue based IGRT techniques, cone beam CT (CBCT) is the most widely used. It consists of acquiring multiple projection radiographs (for head and neck imaging ~350, for thoracic/pelvic imaging up to 600) before the RT fraction and within a gantry rotation of 180°–360°. A volumetric image with high spatial resolution and sufficient soft-tissue contrast is reconstructed and registered to the reference planning CT to figure out the true target position. Translational and rotational positioning errors are often corrected online before Irradiation. To mitigate the consequences of tumor motion because of respiration on image quality and registration uncertainty, CBCT are often acquired in conjunction with breath-hold strategies or during a respiratory triggered approach (4D-CBCT). Moreover, ultrafast ‘snapshot’ volume imaging is ready to be deployed clinically.

2- Breathing adaptive radiotherapy: Real-time monitoring of patient position significantly reduces intra-fraction movement, due either to physiological movement as in the case of the prostate, or due to respiration when tumors are located in the lung or upper abdomen. Electromagnetic technologies such as implanted radiofrequency markers have been successfully used for the prostate. Marker-based real-time image guidance has been in clinical use within the CyberKnife systems for over a decade. For its use to become widespread, real-time IGRT will probably need markerless solutions. A variety of kilovolt-based and MV-based possibilities have been proposed. Cine MRI, which is available with the new MRI-guided radiation therapy systems, is able to provide non-invasive target localisation during RT treatment.

3- Adaptive Radiotherapy (ART): The term ART usually pertains to: 1) modifying the treatment plan during a course of RT to account for temporal variation in anatomy (e.g. tumor shrinkage, weight loss, internal motion or change of OARs), 2) adoption of the delivered dose based on early tumor response and 3) adaptation of the treatment strategy based on early response (e.g. adding chemotherapy or hypoxic sensitizers). ART is very much dependent on the anatomical information provided by IGRT. An appealing approach is the integration of molecular imaging in to anatomical information with the aim of identifying radiation-resistant regions within the tumor, such as clonogen density, proliferation or hypoxia, as different tumor regions have different radiosensitivity, which may make a heterogeneous dose distribution desirable in order to obtain greater tumor control.

D. Biological advances in tumor targeting

The efficacy of RT is restricted by the intrinsic radio-resistance of tumor cells, which suggests an increased risk of local tumor recurrence, therefore there is urge to overcome radio-resistance and improve radio-sensitivity explains why there is such great interest in identifying new molecules that have a synergistic effect with radiation. One way to enhance the efficacy of RT that is already in use is to give chemotherapy or targeted agents concomitantly in order to modify the radio-sensitivity of the tumor cells at the molecular level. This field of radiation and cancer biology is rapidly expanding to provide a selective improvement within the tumor response to radiation, including T-cell checkpoint inhibitors, hypoxic radiosensitizers and cytotoxins, antiangiogenic agents, DNA repair inhibitors, signal transduction blockers, chemokine inhibitors and oxygen metabolism modifiers. Thus, there is a huge gap between the many exciting ideas emerging from pre-clinical studies in modern radiation and tumor biology and the lack of clinical trials testing these new concepts. Furthermore the Immunotherapy field offers exciting prospects along with Radiotherapy. Identifying biomarkers that can predict the sensitivity or resistance of tumors to radiation therapy and the risk of developing toxicity is another promising area of the research. In radiation oncology, ‘omics’ could even be able to predict the treatment response by screening for genetic polymorphism or by genetic polymorphism analysis, and assessing the potential of
epigenetic factors, post translational modification, signal transduction and metabolism. An example within the plethora of ‘omics studies’ was published recently: a patient-specific molecular signature of radiation sensitivity to identify the optimum RT dose; a gene expression-based radiation sensitivity index and the linear quadratic model to derive the genomic-adjusted radiation dose (GARD).^{26}

**Conclusion**

As can be seen, radiotherapy has undergone tremendous progress over years in terms of improved technology which leads to exact target localization, highly conformal dose delivery with powered image guidance and breath hold techniques too. With this all tools, we can give long term survival with reduction of late side effects which ultimately leads to better quality of life. But, we need to be very cautious in selecting patients for the highest technology and we also need highly skilled professionals to deliver such treatments.

**References**


Uro-pathogens Isolated and its Antibiotic Sensitivity in Cancer Patients in a State Cancer Institute of Gujarat

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Summary
Urinary tract infection (UTI) is common cause of nosocomial infection in hospital. There is increased morbidity due to prolong catheterization and immunocompromised status in cancer patients. Most of UTIs are treated empirically, which may lead to frequent misuse of antibiotics. So, knowledge of infection epidemiology and their resistance pattern in institute will help physicians to select optimal empirical treatment in cancer patients. Retrospective analysis of the culture and sensitivity was performed for one year. Standard procedures were followed for culture and sensitivity. The identification and sensitivity testing were performed by automated ID and AST system. Bacteria isolated from Enterobacteriaceae group in non-catheterized urine sample (NCU) shows sensitivity to amikacin followed by gentamicin, imipenem and nitrofurantoin. Whereas, isolates from catheterized urine sample (CU) are sensitive to amikacin, followed by nitrofurantoin, gentamicin, imipenem, etc. Non-lactose fermenting Gram negative bacilli isolated from NCU have showed sensitivity to gentamicin followed by amikacin, meropenem etc. Similarly, non-lactose fermenting Gram negative bacilli from CU are sensitive to amikacin, gentamicin, piperacillin/ tazobactam, etc. Funguria was due to Candida spp. which showed sensitivity to amphotericin -B, caspofungin, 5-fluorocytocin, etc. UTI is a burden on health care leading to morbidity and increased stay in hospital. Since it is the second most common quality indicator for HAI, guidelines for prevention must be strictly adapted.

Keywords: Urinary tract infection, Non-catheterized urine, catheterized urine, Cancer, Antibiotic susceptibility, Vitek-2 compact.

Introduction
Urinary tract infections (UTI) can be an infection of kidney, ureters, bladder or urethra, and usually presents with fever and burning micturition. The bacteria spread to the bladder from urethra (ascending infection) and the infection spread can also occur through hematogenic route and lymphatic route (descending infection). Mid-stream urine is sterile and germ free in normal person.

UTI is second most common cause of hospital acquired infections and it account for 20-30%.1,2 Annually, worldwide more than 150 million people suffer from UTI.2,3 In different parts of India prevalence rate ranges from 15 to 30 %. E. coli is most common and predominant pathogen causing UTI.4 Gram positive bacteria like Enterococcus, Staphylococcus especially coagulase negative staphylococci and Streptococcus agalactiae are also responsible for UTI.5 There is female predominance which is suggested by different clinical studies.

In cancer patients there are symptoms of fever, burning micturition, chills and rigors and there is increased morbidity due to catheterization as well as immunocompromised status, and they land up in bacteriuria or candiduria.1

Most of UTIs are treated empirically, which may lead to frequent misuse of antibiotics.1 So, knowledge of infection, epidemiology, causative agents and their resistance pattern in institute will help physicians to select optimal empirical treatment. Extensive use of antimicrobial agents has extensively resulted in development of antibiotic resistance, which has become a major health problem. The antibiotic resistance pattern varies from place to place and even in short period of time.6,7 Therefore, this retrospective data analysis aims at knowing the causative organisms of UTI, their antibiotic sensitivity and recommend the ideal antibiotics for the treatment for patients.

Methods and Materials
This retrospective observational study was carried out in Department of Microbiology of The Gujarat Cancer Research Institute, a State Cancer Center of India. Analysis of the culture and sensitivity was performed for one year from June 2018 to June 2019. Approval of Institutional review board was taken for this study and there were no ethical issues related to this study.

Urine was collected in cases having symptoms of urinary tract infections after giving proper instructions to collect mid-stream urine and urine from catharized urine tube after having taken sterile precautions. Patient’s details and demographic details were noted. There were 1210 urine samples which were from both types of collection. Semi-Quantitative method was used to report significant bacteriuria. In the laboratory the standard procedures were followed for culture and sensitivity. The identification and sensitivity testing were performed by automated ID and AST system from Vitek-2 compact, from the company Biomerieux.

There were 1067 urine samples which were
Table 1: Prevalence rate of UTI

<table>
<thead>
<tr>
<th>Type of sample</th>
<th>Total samples</th>
<th>Significant growth</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCU</td>
<td>1067</td>
<td>319</td>
<td>29.8</td>
</tr>
<tr>
<td>CU</td>
<td>143</td>
<td>63</td>
<td>44.05</td>
</tr>
<tr>
<td>Total samples</td>
<td>1210</td>
<td>382</td>
<td>31.5</td>
</tr>
</tbody>
</table>

Table 2: Age and gender wise prevalence of UTI (%)

<table>
<thead>
<tr>
<th>Age groups (yrs.)</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCU</td>
<td>CU</td>
<td>NCU</td>
</tr>
<tr>
<td>0-14</td>
<td>13.9 (6/43)</td>
<td>0</td>
<td>17.46 (6/34)</td>
</tr>
<tr>
<td>15-44</td>
<td>23.68 (27/114)</td>
<td>75 (6/8)</td>
<td>28.24 (61/216)</td>
</tr>
<tr>
<td>45-60</td>
<td>29.52 (31/105)</td>
<td>63.64 (7/11)</td>
<td>31.02 (103/332)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>47.25 (43/91)</td>
<td>42.86 (6/14)</td>
<td>31.82 (42/132)</td>
</tr>
<tr>
<td>Total</td>
<td>30.31 (107/353)</td>
<td>57.58 (19/33)</td>
<td>29.7 (212/714)</td>
</tr>
</tbody>
</table>

Table 3: Department wise prevalence of UTI (%)

<table>
<thead>
<tr>
<th>Department</th>
<th>OP</th>
<th>IP</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCU</td>
<td>CU</td>
<td>NCU</td>
</tr>
<tr>
<td>Gynecology</td>
<td>31.12 (107/343)</td>
<td>46.67 (14/30)</td>
<td>31.86 (43/135)</td>
</tr>
<tr>
<td>Surgery</td>
<td>48.11 (51/106)</td>
<td>56 (7/8)</td>
<td>38.75 (31/80)</td>
</tr>
<tr>
<td>Medicine</td>
<td>28.26 (26/92)</td>
<td>66.67 (2/3)</td>
<td>14.21 (26/183)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>25.93 (7/27)</td>
<td>0</td>
<td>8.33 (4/48)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>66.67 (12/18)</td>
<td>100(1/1)</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>Neurology</td>
<td>5 (3/16)</td>
<td>50 (1/2)</td>
<td>36.36 (4/11)</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>66.67 (2/3)</td>
<td>0</td>
<td>33.33 (1/3)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>34.38 (208/605)</td>
<td>56.82 (25/44)</td>
<td>24.03 (111/462)</td>
</tr>
</tbody>
</table>

Table 1: Prevalence rate of UTI collected from non-catheterized patients and 143 were catheterized patients. All ID AST reports were generated by using WHONET software and analyzed. The data was then converted into excel and charts and figures were created.

Out of total 1210 processed samples, there were 1067 (88.18%) non-catheterized urine (NCU) and 143 (11.82%) catheterized urine (CU). Table 1 shows the infection rate of UTI in both the type of samples. Age and gender wise prevalence of UTI is described in table 2. Table 3 shows department wise prevalence of UTI in cancer patients. Table 4 shows distribution of isolated pathogens isolated in UTI.

The pathogenic Gram-negative bacilli of Enterobacteriaceae group in NCU shows sensitivity to amikacin (65.3%) followed by gentamicin (53.5%), imipenem (46.7%), nitrofurantoin (41%), aztreonam (36.4%), piperacillin/tazobactam (33.2%), trimethoprim/sulfamethoxazole (32.8%), cefepime (31.3%). Whereas, isolates from CU are sensitive to amikacin (46.9%), followed by nitrofurantoin (43.5%), gentamicin (31.2%), imipenem (31%), etc. (Table 5)

As per table 6 the non-lactose fermenting Gram negative bacilli isolated from NCU have shown sensitivity to gentamicin (46.5%) followed by amikacin (46.2%), meropenem (45.8%), cefepime (42.9%), imipenem (41.9%), etc. Similarly, non-lactose fermenting Gram negative bacilli 15(3.93%) from CU are sensitive to amikacin (69.2%), gentamicin (50%), piperacillin/tazobactam, ceftazidime, cefepime equally showed 41.7% sensitivity, and imipenem showed 36.4%.

Gram-positive cocci isolated from NCU

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Table 4: Distribution of pathogens isolated in UTI

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>MSU</th>
<th>CU</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOTAL (n=319)%</td>
<td>TOTAL (n=63)%</td>
<td>Grand Total (n=382)%</td>
</tr>
<tr>
<td><strong>GNB(LF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>131</td>
<td>19</td>
<td>150</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>56</td>
<td>13</td>
<td>69</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella sp.</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total GNB(LF)</strong></td>
<td>208</td>
<td>36</td>
<td>244</td>
</tr>
<tr>
<td><strong>GNB(NLF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>17</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Pseudomonas sp.</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Sphingomonas paucimobilis</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Acinetobacter baumpf.</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acinetobacter junii</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas putida</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Proteus rettgeri</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Salmonella sp.</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total GNB(NLF)</strong></td>
<td>55</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td><strong>GPC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>11</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Staphylococcus hominis</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus xylosus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total GPC</strong></td>
<td>23</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td><strong>FUNGUS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>14</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>13</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total Fungus</strong></td>
<td>33</td>
<td>9</td>
<td>42</td>
</tr>
</tbody>
</table>

showed same sensitivity (55.9%) to linezolid and teicoplanin, followed by nitrofurantoin (54.5%), trimethoprim/sulfamethoxazole (50%), vancomycin (48.5%), etc. And those that isolated from CU are sensitive to trimethoprim/sulfamethoxazole (100%) followed by teicoplanin (50%), vancomycin (20%), penicillin G (16.7%), nitrofurantoin (16.7%) etc.

When compared with other non-lactose fermenting bacilli like Acinetobacter spp, Burkholderia sp, Shingomonas and Salmonella, the antibiotic sensitivity of Pseudomonas species was little different. On the whole (Table 8) there was less sensitivity to all the anti-pseudomonal drugs.

Funguria was due to Candida species like Candida albicans and Non-albicans (C. Glabrata and C. tropicalis) was present. They were 77.8-93.9% sensitivity to amphotericin-B, 75-88.9% sensitive to caspofungin, 89.3 – 100 % sensitive to 5-flurocytocin, 85.7-86.4 to fluconazole, 87.5-88.9 % sensitive to micafungin and 88.9-93.9% to voriconazole. (Table 9)

**Discussion**

UTI is the most common bacterial infection among the patients admitted in the hospital. In the present retrospective study1210 urine samples were analyzed. There was 29.9% and 44.06 % NCU and CU samples respectively which showed infection. According to Sarasu et al and Vyawahara et al had
Table : Percentage sensitivity of tribe Enterobacteriaceae

<table>
<thead>
<tr>
<th>Antibiotic name</th>
<th>NCU  (n=55)</th>
<th>CU  (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td>20.9</td>
<td>10</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>33.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>13.4</td>
<td>0</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>31.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Imipenem</td>
<td>46.7</td>
<td>31</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>36.4</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>15.8</td>
<td>12.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>6.7</td>
<td>0</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>32.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>41</td>
<td>43.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>53.5</td>
<td>31.2</td>
</tr>
<tr>
<td>Amikacin</td>
<td>65.3</td>
<td>46.9</td>
</tr>
</tbody>
</table>

Table 6: Percentage sensitivity of NLF

<table>
<thead>
<tr>
<th>NLF</th>
<th>% Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>33.3</td>
</tr>
<tr>
<td>Ticarcillin/Clavulanic acid</td>
<td>33.3</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>22.5</td>
</tr>
<tr>
<td>Cefepime</td>
<td>42.9</td>
</tr>
<tr>
<td>Imipenem</td>
<td>41.9</td>
</tr>
<tr>
<td>Meropenem</td>
<td>45.8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>46.5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>46.2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>26.7</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Table 7: Percentage sensitivity of GPC

<table>
<thead>
<tr>
<th>GPC</th>
<th>% Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>20.6</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>41.7</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>12.1</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>50</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>54.5</td>
</tr>
<tr>
<td>Linezolid</td>
<td>55.9</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>48.5</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>55.9</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>38.2</td>
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</table>

Table 8: Percentage sensitivity of Pseudomonas spp

<table>
<thead>
<tr>
<th>PSEUDOMONASspp</th>
<th>% Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>19.2</td>
</tr>
<tr>
<td>Ticarcillin/Clavulanic acid</td>
<td>23.1</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>14.8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>32.1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>27.6</td>
</tr>
<tr>
<td>Meropenem</td>
<td>31</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>34.5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>42.9</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>19.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Table 9: Percentage sensitivity of FUNGUS

<table>
<thead>
<tr>
<th>Fungus</th>
<th>% Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Fungal name</td>
<td>NCU</td>
</tr>
<tr>
<td>AmphotericinB</td>
<td>93.9</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>75</td>
</tr>
<tr>
<td>5-Fluorocytosine</td>
<td>89.3</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>86.4</td>
</tr>
<tr>
<td>Micafungin</td>
<td>87.5</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>93.9</td>
</tr>
</tbody>
</table>

et al for NCU. Whereas in the study done by Vyawahara et al there was male preponderance.

E. Coli was the common isolated uropathogen from NCU as well as CU. Though other common organisms causing infections was Klebsiella and Enterobacter (LF). Amongst non-lactose ferments were Pseudomonas, Acinetobacter spp, Burkholderia, Proteus, Sphingomonas. Amongst the GPO, we had Enterococcus and Staphylococcus commonly isolated from both type of sample. Similar results were shown by other workers like Sarasu et al for NCU and the results of catharized urine was similar to the study of Vyawahara et al.

It is also concluded that the Enterobacteriaceae organisms were sensitive to amikacin, gentamicin, and piperacillin/tazobactam. The carbapenem antibiotics sensitivity (46%) to Gram negatives was reduced when compared to other study (79%). Quinalones were less effective. GNBs were ineffective to Beta-lactams and beta-lactamase inhibitor (BL-BLIs). GNBs showed MDR to Cephalosporin group of antibiotics in both NCU and CU.

Gram positive cocci showed sensitivity to linezolid and teicoplanin followed by nitrofurantoin, trimethoprim/sulfamethoxazole, vancomycin in NCU and CU. Most of the GN Bacilli (Enterobacteraceae) are ESBL, Carbapenemase, MBL producers and thus, resistance to many antibiotics. Carbapenem-resistant Enterobacteriaceae are of particular concern as they
are increasingly reported globally and few treatment options are available for these types of infections. Acinetobacter spp. strains resistant to carbapenems have increased in prevalence and present a serious treatment challenge to clinicians. Therefore, drug of choice still recommended is amikacin and nitrofurantoin as there is clinical clearance of pathogens. It is also recommended to stop usage of quinolones for three months and suppress its use.

Conclusions

UTI is a burden on health care services leading to morbidity and increased stay in hospital. In our study UTI is more common in female patients and more prevalence is seen in 45-60 year age group. The most common bacteria responsible is Escherichia coli in both NCU and CU. Constant surveillance is essential to monitor emergence of antimicrobial resistance in these organisms. Since it is the second most common quality indicator of HAI, guidelines for prevention must be strictly adapted.

References

Accurate prescribed dose delivery is very important for each patient undergoing radiation treatment in order to avoid over or under dosing. One way of verifying the delivered dose is through in-vivo dosimetry i.e. measuring the patient dose during treatment. In in-vivo dosimetry silicon diodes are used to measure the entrance dose in radiotherapy. Two diode detectors from IBA Dosimetry used in this study were tested, calibrated and corrected in order to be accepted for treatment verification. The corrections of varying field sizes, source-to-surface distances, temperature and angle of incidence have been reported. This work investigates the feasibility of performing routine quality control protocol using in vivo dosimetry for two dimensional (2D) and three dimensional conformal radiotherapy (3D-CRT) treatments. For each radiation field used in treatment a measured dose on the patient skin and calculated dose from treatment planning system were compared using a 5 % tolerance. The maximum entrance dose deviation was observed to be 4.1 % for all the considered 10 cases. It can detect potential errors in accurate dose delivery to the patient.

Keywords: In-vivo dosimetry, Diode, Radiotherapy

Introduction
The purpose of radiotherapy treatment is to deliver radiation dose to various malignant or non-malignant targets efficiently, accurately and safely. Normally the quality assurance program have been introduced to verify the accurate performance of all the components of radiotherapy together with treatment planning, imaging modality to treatment execution. As the number of radiation incidences reported due to human errors, separate patient dose verification (in-vivo) is required during the actual treatment delivery in external beam radiotherapy (EBRT).1-4

In early 1980s the silicon diodes were first introduced for in-vivo dosimetry with proper buildup cap based on type and beam quality. Silicon diode offers many advantages like instantaneous read out, high sensitivity, simple instrumentation and robustness. Though, silicon diode with buildup cap response to various influencing factors that need to be corrected for field size, source to surface distance, temperature and angle of incidence. The selection of proper build up cap is important for entrance dose measurements as the dosimeter below significantly attenuates the dose by the buildup cap material. The entrance dose measurement often performed for limited fractions.

Nowadays p-type diode is preferred over n-type because of accumulated dose rate over its life time. Over a period of time diode sensitivity decreases due to accumulated dose and is more evident in n-type diodes compared to p-type diodes.5 During exposure the rate of electron hole pairs production increases with increase in dose rate. At higher dose rate, large charge carriers will escape recombination process compared to lower dose rate. Hence diode sensitivity depends on dose rate.6 The p-type diodes have very limited dose rate dependence with a higher doping level.7-9 The diode detector after significant use accumulates dose may show increase in response with increase in dose rate.10

In this paper, we will be discussing how we established in-vivo dosimetry technique using p-type diodes by measuring various correction factors at our center.

Material and Method
The measurements were carried out on a Elekta Synergy linac, providing a 6 MV photon beam. Two identical diodes from IBA Dosimetry [EDP-10/5143 and EDP-10/5144 detectors (p-type silicon diodes)] with hemispherical buildup cap with DPD-12 (emX) electrometer were tested for entrance dose measurements. The diode detectors for in-vivo dosimetry are available commercially in two forms, cylindrical and flat design with buildup cap of different thickness and nature. The detectors used in our study offers flat design for easy placement on skin, diameter of active area is 1.6 mm, sensitivity as 100 nC/Gy and sensitivity variation with temperature (SVWT) is 0.25%/°C. High density materials like stainless steel and epoxy (thickness 1 g/cm²) are used in order to reduce the physical thickness of the buildup cap. Buildup cap is accountable for optimized low field perturbation, minimized field size and directional dependencies, and low temperature dependence. Before using the diode in actual dosimetry, one should always measure the diode response as a function of energy in which it is used. These diodes were calibrated against an ion chamber (FC65) from Scanditronix Wellhofer in a 6 MV photon beam.
As a reference condition, the diode was fixed on a solid water phantom having dimensions 30 x 40 x 40 cm³. The diode was set at a distance of 100 cm from linac focus. The field size was set to 10 x 10 cm² at 0° gantry angle. The ion chamber was kept and exposed below the phantom surface at depth of maximum dose as shown in Figure 1. Apart from calibration factor, other correction factors for various field sizes, source to surface distances, temperature and gantry angles were determined. The diode was connected to a dedicated channel on DPD-12 (emX) electrometer from Scanditronix Wellhofer. The electrometer was then connected to a computer having DPD12-pc software. Before starting the actual measurement, dark current drift and any offset were measured and corrected.

**Diode Calibration:**

The diode calibration factor (F) is the ratio of adsorbed dose measured with the ion chamber \( D_{en} \) and the meter reading of the diode \( M_{en} \) under reference conditions (Figure 1).

\[
F = \frac{D_{en}}{M_{en}}
\]

**Field size dependence:**

The diode was kept on a solid phantom at SSD=100 cm. For a number of square fields ranging from 3 x 3 cm² to 40 x 40 cm² meter-readings (response) were measured. The field size dependence correction factor (\( F_{FS} \)) was calculated using the following formula.

\[
F_{FS} = \frac{M_{en}(FS)}{D_{en}}
\]

Where \( M_{en} \) is the entrance dosimeter reading for reference field size. \( D_{en} \) is the dose at depth of maximum (1.5 cm) for reference field size. The dose variation is not measured directly but calculated from previously measured output ratios.

**SSD dependence:**

The diode was kept on the surface of phantom. The SSD correction factor \( F_{SSD} \) was measured at different SSD’s covering the range from 80 cm to 120 cm.

The SSD dependence correction factor is given by

\[
F_{SSD} = \frac{M_{en}(SSD)}{D_{en}}
\]

\( F_{SSD} \) accounts for dose rate dependency of diode, insufficient buildup and effect of source to diode distance and source to chamber distance.

**Angular dependence:**

The angular dependency of diode is because of diode buildup and phantom scatter. \( F_{\text{gantry}} \) is the ratio of reading at beam axis during calibration to central beam axis. In axial dependency of beam axis rotates in plane perpendicular to the cable and during tilt the beam axis rotates in the plane of the cable.

The angular dependence correction factor is given by

\[
F_{\text{gantry}} = \frac{R(\Theta=0)}{R(\Theta)}
\]

**Temperature correction factor:**

The temperature correction factor is given by

\[
F_{\text{temp}} = \frac{R(T_{\text{cal}})}{R(T)}
\]

Where T is the room temperature and \( T_{\text{cal}} \) is the diode calibration temperature.

If \( F_{\text{temp}} \) is less than 0.4 % per °C then temperature correction factor is not required.

After determining correction factors to account for these effects, the measured signal can be converted to measured dose using the following formula.

\[
\text{Measured dose (Gy)} = \text{Diode reading} \times F \times F_{FS} \times F_{SSD} \times F_{\text{gantry}} \times F_{\text{temp}}
\]

**In-vivo measurements:**

The diode was used in regular measurements to verify the entrance dose with treatment planning system (TPS) calculated in patients treated with two fields (breast treatment), three fields (oesphagus) and box technique (cervix) with the isocenter at the surface of the patient.
In clinical routine the patient was set-up in the proper treatment position as planned on treatment planning system. The diode was fixed on patient skin at the central beam axis. The reading was then multiplied by calibration factor and other suitable correction factors to get the measured dose. The measured dose and treatment planning system calculated dose was compared for deviation. A thorough investigation of treatment plan need to be performed provided the deviation exceeds the acceptance level of 5%. At next treatment session, the in-vivo dosimetry was then repeated by carefully measuring SSD and verifying the correct position of dosimeter. If we repeat the procedure for more sessions, skin dose increases due to beam attenuation by diode and reduction in dose at depths.

**Results**

**Field Size Correction factor:**

Figure 2 shows the comparison of field size correction factors for various square field sizes. For 6MV photons, the field size correction factors for two identical diodes are found to be comparable for all considered field sizes. Table 1 lists the field size correction factors for various field sizes for two diodes. For the 6 MV photon beam, the $F_{SS}$ for the EDP-10/5143 diode are 0.9108 and 1.0854 for the field size of 3 x 3 cm$^2$ and 40 x 40 cm$^2$ respectively, while the $F_{SS}$ for the EDP-10/5144 diode are 0.9136 and 1.0853 for the field size of 3 x 3 cm$^2$ and 40 x 40 cm$^2$ respectively.

---

**Table 1: Field size correction factors as a function of field size**

<table>
<thead>
<tr>
<th>Field Size (cm$^2$)</th>
<th>EDP-10/5143</th>
<th>EDP-10/5144</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 x 3</td>
<td>0.9108</td>
<td>0.9136</td>
</tr>
<tr>
<td>5 x 5</td>
<td>0.9485</td>
<td>0.9487</td>
</tr>
<tr>
<td>7 x 7</td>
<td>0.9749</td>
<td>0.9754</td>
</tr>
<tr>
<td>10 x 10</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>12 x 12</td>
<td>1.0083</td>
<td>1.0100</td>
</tr>
<tr>
<td>15 x 15</td>
<td>1.0259</td>
<td>1.0254</td>
</tr>
<tr>
<td>17 x 17</td>
<td>1.0310</td>
<td>1.0327</td>
</tr>
<tr>
<td>20 x 20</td>
<td>1.0390</td>
<td>1.0405</td>
</tr>
<tr>
<td>25 x 25</td>
<td>1.0479</td>
<td>1.0496</td>
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<tr>
<td>30 x 30</td>
<td>1.0604</td>
<td>1.0614</td>
</tr>
<tr>
<td>35 x 35</td>
<td>1.0729</td>
<td>1.0738</td>
</tr>
<tr>
<td>40 x 40</td>
<td>1.0854</td>
<td>1.0853</td>
</tr>
</tbody>
</table>

**Table 2: SSD correction factors for two types of identical diode detectors measured for field size 10 x 10 cm$^2$**

<table>
<thead>
<tr>
<th>SSD (cm)</th>
<th>$F_{SS}$ (EDP-10/5143)</th>
<th>$F_{SS}$ (EDP-10/5144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>0.95013</td>
<td>0.95438</td>
</tr>
<tr>
<td>81</td>
<td>0.95327</td>
<td>0.9627</td>
</tr>
<tr>
<td>82</td>
<td>0.95575</td>
<td>0.95993</td>
</tr>
<tr>
<td>83</td>
<td>0.95912</td>
<td>0.96776</td>
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<tr>
<td>84</td>
<td>0.9617</td>
<td>0.96578</td>
</tr>
<tr>
<td>85</td>
<td>0.96514</td>
<td>0.97357</td>
</tr>
<tr>
<td>86</td>
<td>0.96661</td>
<td>0.96983</td>
</tr>
<tr>
<td>87</td>
<td>0.96956</td>
<td>0.97843</td>
</tr>
<tr>
<td>88</td>
<td>0.97108</td>
<td>0.97409</td>
</tr>
<tr>
<td>89</td>
<td>0.97487</td>
<td>0.98265</td>
</tr>
<tr>
<td>90</td>
<td>0.97673</td>
<td>0.9803</td>
</tr>
<tr>
<td>91</td>
<td>0.98012</td>
<td>0.98831</td>
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<tr>
<td>92</td>
<td>0.98138</td>
<td>0.98388</td>
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<tr>
<td>93</td>
<td>0.98331</td>
<td>0.99188</td>
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**Figure 2:** Comparison of field size correction factors for two diode detectors as a function of field size.
SSD Correction factor:

Table 2 lists the SSD correction factors for change in SSD for two identical silicon diode detectors. For 6-MV photons, the $F_{SSD}$ for the EDP-10/5143 diode are 0.95013 at SSD of 80 cm and 1.04366 at SSD of 120 cm, while $F_{SSD}$ for the EDP-10/5144 diode are 0.95438 at SSD of 80 cm and 1.05125 at SSD of 120 cm.

Angular dependence correction factor:

Figure 3 shows the dependence of diode for various angles. Directional response of diode from angles -45° to +45° for both axial and tilt is less than 3%. Table 3 provides the angular dependence factors.

Temperature correction factor:

The diode response due to change in temperature is shown in figure 4. The diode response is linearly increasing with temperature.

In-vivo dosimetry was conducted in 10 patients and the maximum entrance dose deviation was observed to be 4.1% for all the considered cases.

Discussion

The discrepancies between the planned and measured dose should be analyzed and reported to the radiation oncologist and radiation technologist who treat the patient. After measuring the entrance dose ($D_e$), the expected dose ($D_r$) computed from treatment planning system (TPS) was compared using the formula $(D_r - D_e) \times 100 / D_e$. 

In in-vivo dosimetry the accepted deviation level considered to be 5%. For the results to be effective and more realistic, we used 5% and 10% two sets of tolerances. The radiation technologist will check for setup error, SSD, any treatment parameter etc, if the deviation is greater than 5% but less than 10%. The physicist will observe for the reading consistency during the next treatment and investigate the cause of deviation. As the reported error for wedged field is more than 8%, we have not included the wedged fields in our study. Some observations are comparable to the literature.

The diode sensitivity decreases as function of angle between the symmetry axis of diode and the beam axis. The angular dependence of diode may be of importance when oblique radiation beams are used. It has been observed for the first time with no supporting document that if the angle is more than 45°, the dose comparison will show more than 5% deviation. Hence, oblique radiation with more than 45° angle is not included in our study.
It has been observed that the temperature can affect the diode response.\textsuperscript{10,21-23} The sensitivity of p-type diodes increases with increase in temperature after an accumulated dose.\textsuperscript{22} But the temperature correction factor variation with temperature is linear in our study. As the treatment time is short, the diode kept on the patient skin cannot reach the thermal equilibrium. Hence, in-vivo dosimetry, the temperature correction factors measured at room temperature are used.

**Conclusion**

In-vivo entrance dose measurements have been proved to be a very useful tool for the verification of dose delivered to a given patient. During the patient treatment serious errors like incorrect selection of daily dose, selection of wrong beam energy, error in wedge selection, setup errors and changes in machine output can be rectified during the subsequent fractions.

Accurate absorbed dose can be obtained from diode signal by applying calibration and proper correction factors. There is a need to implement it on phantom first and verify whether diode system provide accurate dose.

The in-vivo dosimetry results using diodes are available in real time. In-vivo dosimetry is a useful technique for quality control in radiotherapy and increasing treatment accuracy.

**References**

What is the Endpoint in Trying to Save a Patient's Life?

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Understanding and Accepting Death
For understanding death, we should be clear about a simple fact of our existence on this planet. The being is the unconsciousness and is the reality of existence. The body is collected in the womb first and then throughout life till death. The being occupies the place in the fetus inside the womb and that being leaves the body when the person dies. The being doesn’t die with each cycle of life and death. It will be alive and free for long time before it occupies any other womb. You are a being and the body is something you have collected; the body is not you. So at the moment of reading this article, understand yourself as a being inside the body. And as you will leave this body at the time of death the being will persist and the body will perish. This is just like undressing yourself, just assume it as undressing the whole body. This might seem awkward at the moment but this will start making sense when you start becoming aware. Considering that cycle, can you imagine that each one of us has lived somewhere in between 100-10,000 lives, repeating this cycle again and again. Doesn’t it feel boring to do that over and over again? What is the point?

At the time of death, a person is no longer so much connected to his body, his family members, his wealth, his possessions, his qualifications, etc. You can understand this if you have stuck in fearful situations in life, where you no longer care for anything that you possess, your degrees, your wealth and even the people around you. In those times, you just want yourself to be safe and at ease. Death is a kind of an extension of an experience like that. You must have heard stories of fearless people; some of them might be quite fearful and attached to materialistic things in life, but just one near-death incident makes them fearless. They give up all their possessions and switch to a basic lifestyle. The famous book titled, The Monk Who Sold His Ferrari, conveys a similar message.

Just by understanding the simple concept of death as a very important part of life, you might start to think about the importance of death in our existence and stop running from it. The corollary can be day and night, happiness and sorrow, sleep-wake cycle and many more. Do you think night, sorrow and sleep are the important parts of existence? Definitely yes! But there are some ignorant out there, who do not understand the real meaning of life, and those are people who feel there should always be happiness, no sorrows. Can you live in places where there are very short night times? Some work alcohols feel there should not be any sleep. But in the case of death, people think that is the end of existence. It is not so. What if we know that your long life span of seventy years is just a pop-up phenomenon and then we each one of us will be dead for a very long time before we’re alive again? Existence is like that only: life-death-life-death-life. The cycle goes on with an increasing level of consciousness with each life and death cycle until the moksha is achieved. Looking at life with this viewpoint, death doesn’t seem that bad.

Is there anyone out there who is willing to accept death? Very few. Most of us are not even willing to lose our mobiles, forget about life. But from a spiritual and psychological view of life, acceptance in life is one of the major factors that help one to go through the tough times. The treating doctor, relatives of the patient and the patient himself; all of them have a different perspective on how they look at dying. Well, most of the time, we feel the patient’s relatives are often the worst affected and relatives think for the physician as it is like any other dying patient for the doctor. Doctors can understand how the relatives feel because all of the doctors have their loved ones, but relatives can’t think like doctors. Amid all this emotional drama, we never really think for the dying, we just consider his physical and emotional pain as his suffering. Here comes the role of an aware medical professional who understands death, accepts it as the real possibility of our existence of the planet, and can become a “bridge” between the family and dying. An aware being can do a lot for the dying which is well beyond the imagination of an unaware being.

What are we trying to achieve by putting in more and more resources and avoiding death? What are we aiming for? Are we trying to fight nature and conquer death? What is the endpoint in trying to save a patient’s life? We are constantly pushing our boundaries of death as science is advancing. Why is that we’re not ready to accept death? Should we start accepting deaths? What is right and what is wrong? Should we stop trying to save every life? We need to find answers to these questions and decide on a case.
by case basis as to where it will be the right step to put in the effort, energy, and resources, and where it is a waste and all the efforts will just prolong the morbidity and extend suffering.

In the real case scenario, there is no definite answer to these questions. But it can be concluded that there are a majority of patients that can be treated without any second thought and some of which we’re sure of the mortality. The middle area of the grey zone is one that gives a challenge to the clinicians. In some of these cases, we might need to give in some days to understand the disease, body and the life within and decide when it is the right time to stop. This is where we need to choose what the right approach is. This will demand awareness of the physician in analyzing the situation as to how it is rather than how it looks like.

I can give an example of my personal experience here. There was a two years old child with a malignant liver tumor with extensive involvement of the liver. Surgical resection was not possible and liver transplantation was the only option available. Mother didn’t match the blood group with son and father who had the same blood group as that of the son, refused to donate a segment of the liver for his son. The patient was listed in the cadaveric graft waiting list. While waiting, we completed neoadjuvant chemotherapy and in the meantime, father agreed to become a donor. Serum markers and CT scans showed a good response to chemotherapy. As we planned for the operation, the baby developed cough and fever and lost some weight. So the patient was declared unfit for anaesthesia and we questioned if we will ever be able to transplant him. We worked on to give him more of comfort, and peace, rather than lots of medical interventions. Idea was to assess if the body is good enough to support the life within or not. If the body isn’t able to support the life, it will leave soon. So we decided to observe the child over a week to ten days, so we know how he’s doing, without much intervention. We treated cough, fever, gave him high calorie, high protein diet so as to give a last attempt to look if we could do something better for the child while at the same time getting prepared for the fatality. Parents were explained and consent was taken for no resuscitation in case of a fatal event. Everything was going on well, but one morning after 5 days later, the patient’s mother informed that the child is a bit lazy. His serum levels of alpha feto protein were out the same day and were highly elevated. I counselled the parents to take the baby home and give him palliative care. But just a few hours after that, the child aspirated while the mother was giving sips of water. The child was not resuscitated, no attempt at intubation or cardio-pulmonary resuscitation was made.

How do I see this death? The most unusual event was that life within the body left perfectly at the time when we stopped trying. This means we tried until the right time. As soon as we realized that he might not be able to tolerate the operation, we tried to keep the baby in as much comfort as possible. Also, by not doing a cardio-pulmonary resuscitation, we didn’t prolong the suffering of the child. The parents were satisfied that they tried their best, the baby didn’t suffer, and I as a clinician felt so fulfilled from inside to take the right decision at the right time. I am not saying that this was the only right decision for the baby. There could be many decisions depending on the circumstances. But as per my understanding of the circumstances at the time, I feel we did the right thing for the child. Life is a learning process, we should always try to decrease the pain and suffering of ourselves and everyone around us. I could do a little help for the child and relatives. In the future, maybe I would grow more and help more. Just keep trying!

If we come to terms with the realization of the simple fact that healthcare workers are only human beings and medical science has not reached a level beyond the creator of the universe, acceptance of reality is much easier. Understanding and awareness of death by the clinician is very helpful. An aware clinician will be able to judge when to start the treatment and when to stop trying. His awareness will also be very helpful for the colleagues and his patients. He will never think of death as his failure. It is always the intention and the efforts which matter. No human being has ever been or will ever be able to conquer death!

Suggested Reading:
3. The Monk who sold his Ferrari by Robin Sharma.

“Death is not a calamity, it's a natural process of life." 
Sadhguru Jaggi Vasudev.
Primary Ovarian Carcinoma Presenting as Breast Lump

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Summary
Metastases to breast from EOC account for 0.03-0.6% of malignant breast cancers. A 62 year old women presented with lump 6x4 cm mass in upper outer quadrant of right breast. Biopsy revealed invasive ductal carcinoma. CT abdomen and pelvis showed metastatic deposits in omentum, diaphragmatic surface of liver, pelvis and bowel mesentery. Uterus and both adnexal regions appeared normal. Her CA125 was 1918 U/ml, CEA and CA19-9 were within normal range. Biopsy with IHC of omental deposits revealed metastatic papillary adenocarcinoma, primary from ovary, positive for CK7, WT1, PAX8 and negative for GCDFP15, Mammaglobin, Calretinin and CEA. A review of breast biopsy with IHC showed metastasis from ovary and was positive for PAX8 and WT1. Patient underwent standard neo-adjuvant chemotherapy followed by interval debulking. She recurred 5 months after first line treatment and received various second line chemotherapy.

Keywords: Breast metastasis, Ovarian cancer, IHC, Chemotherapy

Introduction
Around three fourth of patients with epithelial ovarian carcinoma (EOC) are diagnosed in advanced stage (FIGO 3/4) at the time of presentation. Ovarian epithelial cancers spread primarily by exfoliation of cells through peritoneal cavity manifesting as peritoneal carcinomatosis (85%). However a minority spread by lymphatic or hematogenous route resulting in distant metastasis. In this regard, metastases to breast from EOC are rare and account for 0.03-0.6% of malignant breast cancers. Nevertheless, their detection and distinction from breast carcinoma is of huge clinical importance because the treatment and prognosis differ significantly. This case report demonstrates a rare case of breast metastases with advanced ovarian cancer where patient initially presented as breast lump.

Case Report
A 62 year old women presented to surgical OPD (November 2017) with complain of lump in right breast since 4 months. On examination, there was 6x4 cm mass in upper outer quadrant of right breast which was firm, nontender and fixed to underlying tissue. Abdominal examination revealed moderate free fluid and pelvic examination there was fornical fullness due to ascites. Mammography showed 5x3 cm lesion in upper outer quadrant and 2x1.7 cm lesion in outer inferior quadrant of right breast. Biopsy of breast lesion revealed invasive ductal carcinoma. Her metastatic workup included CT chest, abdomen and pelvis which revealed 48x31 mm and 25x15 mm lesions involving right breast. There were few enlarged nodes in right axilla, largest measuring 14x10 mm. Metastatic deposits were seen in omentum (largest 5x4 cm), diaphragmatic surface of liver (6x5 cm), pelvis and bowel mesentery (4x3 cm). Uterus and both adnexal regions appeared normal. Her CA125 was 1918 U/ml, CEA and CA19-9 were within normal range.

Biopsy with immunohistochemistry (IHC) of omental deposits revealed metastatic serous papillary adenocarcinoma, primary from ovary (genital origin) which was positive for CK7, WT1, PAX8 and negative for GCDFP15, Mammaglobin, Calretinin and CEA (Figure 1). With this new evidence, a review...
of breast biopsy with IHC was done which suggested metastasis from ovary and was positive for PAX8 (Figure 2) and non specific stained for WT1.

Patient was planned for standard neo-adjuvant chemotherapy (carboplatin and paclitaxel). Post chemotherapy (3 cycles), her CA-125 was 390 U/ml and mammography showed a 2x1.7 cm residual lesion in upper outer quadrant of right breast. Her post chemotherapy CT of abdomen and pelvis revealed multiple metastatic deposits in pelvis, largest measuring 46x32 mm in right side and 41x24 mm on left side. There was mild omental infiltration ans mild ascites. Rest abdomen was normal. After a thorough tumor board discussion, patient was planned for interval debulking with simple right mastectomy. After the informed consent, patient underwent total abdominal hysterectomy with left salpingo-oophorectomy and right ovarian mass (5x4cm) removal with pelvic peritonectomy, total omentectomy and resection of cancer deposits. She was subsetopically cytoreduced with residual disease along inferior surface of bilateral hemidiaphragm and between fundus of stomach and spleen. Thus, right mastectomy was abandoned. She further received 3 cycles of adjuvant chemotherapy. Her post treatment CT revealed 12x18 mm residual lesion in right breast with no residual disease in abdomen and pelvis. Her CA-125 levels were 38.43 U/ml. Patient was kept under observation following which she recurred within 5 months. Her CA-125 level raised to 143 U/ml and CT showed 7.5 x 3.5 cm lesion in pelvis abutting the rectum, metastatic infiltration at subdiaphragmatic surface of lower bowel, serosa in right iliac fossa and surface of sigmoid colon. Bilateral lung fields showed multiple metastatic deposits. She was started on second line chemotherapy with gemcitabine followed liposomal doxorubicin and oral etoposide successively till December 19.

Discussion

Breast cancer is one of the commonest primary malignancies in women, yet metastasis to breast are rare. A study by Hadju and Urban with 4,051 breast cancer women found an overall incidence of primary gynecologic cancers metastatic to breast of 0.17%, with only 0.07% of metastatic from primary ovarian cancer.

In contrast to primary breast cancers, metastasis to breast generally are solitary, superficial, firm, well-circumscribed and multinodular. Furthermore, the most common location of metastasis is upper outer quadrant of breast seen in 62% of patients. Our patient also presented with a firm, well defined nodule in upper outer quadrant of right breast. The majority metastasis are unilateral solid cancer, however bilateral, inflammatory and ductal carcinoma in situ-like presentation has also been described. DeLair et al evaluated 85 patients with nonmammary metastases to breast and found that the most common type of metastasis was primary ovarian serous epithelial carcinoma followed by melanoma and sarcoma, respectively. The above patient also had a primary ovarian serous papillary adenocarcinoma metastasizing to breast.

Breast metastasis from a primary ovarian cancer generally is diagnosed an average of 2 years after initial diagnosis of ovarian cancer. However our patient had breast metastasis at initial presentation not only and was being first evaluated as primary breast malignancy.

In mammographic evaluation, metastatic cancersto breast are frequently well-circumscribed, non-calcified dense masses and lack speculation, microcalcifications and architectural distortion. The breast metastasis generally lacks a characteristic morphologic pattern and may have overlapping morphology with primary breast cancer which can make the diagnosis difficult. However, IHC is helpful as certain markers like PAX8, WT-1 (85%) have been generally found positive in ovarian carcinoma but are negative in primary breast malignancies. Bhargava et al reported that mammaglobin and GCDFP-15 were positive in 93.1% and 84.5% of primary breast cancers but not in breast metastasis.

Secondary breast involvement from an ovarian cancer suggests advanced stage disease and has been reported with a poor prognosis in most of studies. Micha et al found that after detection of metastatic breast disease from ovarian primary cancer, survival ranged from 13 days to 3.5 years, with most dying within 1 year. However, Karam et al reported 10 cases of metastatic breast cancer and noted that median overall survival after breast metastasis in ovarian cancer was 26 months, suggesting that metastatic breast cancers from ovarian cancer are not associated with a poor prognosis. Our patient had completed primary treatment for ovarian cancer, had received various second line of chemotherapy and is still alive after 20 months of initial diagnosis of breast metastasis (December 19).

Breast metastasis should be distinguished from primary breast cancers to avoid any unnecessary surgical procedures as it influences the management and prognosis. Klein et al found 1-year survival rate of 40% for patients with ovarian cancer who also had breast metastasis, as opposed to 4-year survival rate of 75% for patients with primary breast cancer. Ovarian metastasis to breast should be treated as a systemic disease, with appropriate chemotherapeutic agents. Mastectomy of breast mass is likely best reserved for patients who are unresponsive to systemic therapy and require palliation.
Conclusion: EOC with breast metastasis is a rare diagnosis. It carries grave prognosis, therefore differentiation with primary breast malignancy is essential. Given the similarities between breast and ovarian cancer morphology, IHC markers are helpful in making a distinct diagnosis.

Conflicts of interest: There were no conflicts of interest.

References
A Case Report on Synchronous Adult Granulosa Cell Tumour and Endometrial Cancer

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Summary
Granulosa cell tumours (GCTs) are a rare type of ovarian cancer, representing only 2-5% of all ovarian malignancies. They are mainly estrogen secreting tumour. These tumours can be diagnosed either by ovarian cancer symptoms or endometrial pathologies. The estrogenic effect of the tumour gives rise to an abnormal uterine bleeding pattern. We report a case of GCT associated with endometrial carcinoma. The aim is to review the clinical features of GCT, along with its prognosis, treatment and follow-up recommendations, given in the available literature.

Keywords: Granulosa cell tumour; Endometrial cancer; Postmenopausal bleeding.

Introduction
Granulosa cell tumour (GCT) comprises 5% of all ovarian malignancies but accounts for 70% of malignant sex-cord-stromal tumours. GCT is of two variety, juvenile (5%) and adult (95%) type. The adult type occurs more commonly in post-menopausal woman with a mean age of 50-54 years. Symptoms of GCT are abdominal pain, abdominal distention due to large tumour size (average diameter of 12 cm), abnormal vaginal bleeding and secondary amenorrhoea. GCT produces estrogen resulting in an abnormal uterine bleeding pattern- menorrhagia, metrorrhagia and post-menopausal bleeding. Prolonged exposure of estrogen to endometrium results in endometrial hyperplasia and endometrial adenocarcinoma. The provisional diagnosis was endometrial carcinoma with ovarian tumour (possibility of GCT). The patient underwent staging laparotomy. Intraoperatively, a solid cystic right adnexal mass of about 10x11x9 cm was found, uterus was bulky, left adnexa, rest of the pelvis and abdominal viscera appeared to be normal. Frozen section of mass was suggestive of granulosa cell tumour of the right ovary. Total abdominal hysterectomy, left salpingo-oophorectomy, bilateral pelvic lymph node dissection (BPLND), infracolic omentectomy and multiple peritoneal biopsies were performed. Ascitic fluid cytology was negative for malignant cells. The final histopathology revealed well – differentiated, micro follicular, insular, solid pattern GCT of right ovary (10 x 9 cm) with mitosis of 1-2 /10 HPF and capsular infiltration without capsular breach. It also showed well-differentiated endometroid adenocarcinoma of the uterus, lesion measuring 5x4.5x1.8 cm and myometrial invasion of < 50 % without lymph vascular permeation. Lower uterine segment, cervix, left adnexa, bilateral pelvic lymph nodes, peritoneal biopsies and omentum were free of tumour. FIGO stage of GCT was stage IC2 and carcinoma endometrium stage IAG1. After tumour board discussion, she received 6 cycles of adjuvant chemotherapy (carboplatin and paclitaxel) for GCT stage IC2. After consultation with radiotherapist patient was kept on observation for endometrial cancer stage IAG1. She is on regular follow up and disease free till date (34 months).

Discussion
GCT is the most common estrogen producing ovarian tumour. The adult type GCT is responsible for
abnormal vaginal bleeding, breast tenderness and pelvic pain. GCT can be solid (28%) or cystic tumour (30%). They are usually unilateral but bilateral occurrence can occur in 10% cases. They usually have a favourable outcome because of low grade with indolent growth. Radiologically, adult GCT presents as a solid large mass measuring up to 12 cm in diameter, with the multicystic appearance or solid tumour with heterogeneous echogenicity. So, whenever the patient presents with large, unilateral, solid, cystic, adnexal mass associated with abnormal bleeding per vagina, differential diagnosis can be GCT, primary endometrial cancer metastasising to the ovary, primary ovarian cancer with metastasis to the uterus and synchronous epithelial ovarian and endometrial cancer. On microscopy, call-exner bodies, nuclear grooves and coffee bean nuclei are pathognomic diagnostic features of GCT. Microfollicular, trabecular, solid, tubular, diffuse and water-silk patterns are histological pattern seen in GCT. Endometrial hyperplasia is reported in 25-50% of cases. Low-grade endometrial adenocarcinoma develops in approximately 10% of patients of GCT. They are usually well-differentiated, and detected in an early stage with favourable prognosis as seen in our case. Diagnostic work up includes imaging, tumour marker - inhibin B and, endometrial biopsy. Serum inhibin has 89% sensitivity with 100% specificity to diagnose recurrent disease and should be used when available. In our case, inhibin B testing was not done due to non-availability of this testing in our institute and patient could not afford to get it done outside. We followed the patient with clinical examination, USG, and CA-125 (which was increased pre-operatively). The most important prognostic factor in ovarian GCT is stage. Other prognostic factors are mitotic activity, DNA ploidy and S-phase fraction. Surgery remains the cornerstone of the treatment. Comprehensive staging surgery should be done to establish the real extent of disease. Staging laparotomy with total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies and peritoneal cytology should be performed in whom child bearing is completed. As there is no evidence that nodal dissection has improved the survival rate, so, BPLND is not recommended in surgical staging of GCT. Suspicious nodes should be excised or sampled. In our case bilateral lymph node dissection was carried out as it is recommended in the management of the endometrial cancer. Approximately 75% of GCT are diagnosed in stage I A-C, 20% stage II, 8% stage III and 6% stage IV of tumour disease. In GCT five-year survival with early disease (I A or I B) is 96% and no adjuvant treatment is required. However, patients with, stage I C with poor prognostic factors (large tumour size, high mitotic index or tumour rupture), stage III and IV are candidates for adjuvant platinum-based chemotherapy because of increased risk of relapse. Lifelong follow-up with clinical examination, ultrasound, and inhibin B measurement is recommended as GCT is known for late recurrences.

Ethical issues: None

Abbreviation
GCT: Granulosa Cell Tumour, BPLND: Bilateral pelvic lymph node dissection

References
3. Yim GE, Kim YT: Granulosa cell tumor of the ovary: time to launch a new prospective trial. JGynecol Oncol 2011; 22:143-144
Summary
Pituitary adenomas include over 90% of para-sellar and sellar mass. Intracranial chondrosarcoma is a rare neoplasm. It is seen in approximately 0.15% of all intracranial tumours and 6% of all tumours of base of skull. We report a rare case of intracranial chondrosarcoma originating from para-sellar region. This case denotes the importance of keeping chondrosarcoma as one of the differential diagnoses of para-sellar and sellar mass and also studies the role of cytotoxic chemotherapy in such tumour.

Keywords: Chondrosarcoma, Para-sellar region, Chemotherapy.

Introduction
About 90% of the para-sellar and sellar mass are pituitary adenomas. The remaining 10% include other tumours originating from pituitary gland like craniopharyngiomas, pituitary carcinomas, and astrocytoma and tumours of non-pituitary origin like meningiomas, germ cell tumours, chondrosarcomas, chordomas, and metastatic lesions. Non-adenomatous sellar lesions can be easily confused with pituitary adenomas because of similar location and appearance on neuroimaging. Intracranial chondrosarcoma is a rare neoplasm. It is seen in approximately 0.15% of all intracranial tumours and 6% of all tumours of skull base.

Intracranial chondrosarcoma can occur at any age but is commonly found in the age group of 30 to 50 years. It is seen equally in males and females. We report a rare case of intracranial chondrosarcoma originating from para-sellar region. This case stresses the importance of keeping chondrosarcoma as one of the differential diagnoses for para-sellar and sellar mass and elucidate role of chemotherapy in such tumours.

Case Report
Twenty seven year old female was referred to the department of medical oncology to seek second opinion for role of chemotherapy in residual/recurrent chondrosarcoma of para-sellar region. On examination she was conscious oriented and had right eye ptosis and diplopia with no other obvious neurological deficit. Her past case records were studied for presenting features at the time of primary presentation, investigations done and past treatment taken.

In August 2017 she presented to government hospital, Baroda with complaint of pain in right side of face and jaw since last 2 months with 1 month history of difficulty in mastication. Oral and dental examinations were normal. There was no history of galactorrhea, diabetes insipidus, amenorrhea or headache. She had taken oral analgesic as advised by dentist but had no symptomatic relief. Later magnetic resonance imaging (MRI) of brain was done and demonstrated a 4.2x4.4x4.8 cm lobulated extra-axial space occupying lesion in right para-sellar region with several calcifications, patchy areas of enhancement with mild extension in suprasellar and prepontine cisterns. (Figure1). Blood investigations showed no significant abnormality.

She underwent right sided fronto-temporal craniotomy with near total excision of tumour mass in September 2017. Post surgery patient was discharged on 3rd day with no neurological deficit and in conscious state. Histopathology of excised mass
(Figure 2) showed tumour composed of lobules of hyaline cartilage rimmed by bony trabecula, morphologically foci of myxoid change, calcification and enchondral ossification with no evidence of cytological atypia, mitosis, necrosis suggestive of low grade mesenchymal neoplasm. Immunochemistry showed tumour cells positive for S100 and Vimentin and negative for EMA and AE1 revealing a diagnosis of low grade chondrosarcoma.

One month later she developed right eye ptosis with diplopia. Follow up MRI brain (Figure 3) was done which revealed 3.9x3.2 cm lesion in para-sellar region with pituitary gland not seen separately suggestive of residual/recurrent chondrosarcoma.

She was treated with 65Gy/30 fractions postoperative cranial radiotherapy by volumetric arc therapy (VMAT) technique in November 2017 at Baroda. She had persistent ptosis and diplopia even after radiotherapy. MRI brain two months after radiotherapy showed 3.1x2.6 cm residual mass in para-sellar region. She was started on chemotherapy with VAC/IE (Vincristine, Adriamycin, Cyclophosphamide and Ifosfamide, Etoposide) for 3 alternating cycles with growth factor support till May 2018 which were well tolerated. Post chemotherapy MRI brain (Figure 4) revealed same sized mass in para-sellar region as before starting chemotherapy and with persistent ptosis and diplopia. Patient was then referred to our center for second opinion.

At our institute diagnosis was reconfirmed and histopathological review and immunohistochemistry revealed low grade chondrosarcoma. Fresh MRI brain (Figure 5) showed presence of 3.4x3.2x4 cm mass involving suprasellar and right para-sellar region. Review of literature was done for role of chemotherapy in chondrosarcoma of para-sellar region. In view of debatable role of chemotherapy in this condition, patient was asked to follow up in neurosurgery department. The patient has been kept under close follow up in view of non-progressive disease and as per the record, patient last attended hospital in December 2019.

Review of Literature

Chondrosarcoma is a rare form of bone sarcoma marked by chondroid matrix production. The incidence rate is approximately 0.2 per one lakh person and more commonly seen in third and fifth decade of life without any gender predilection. They may arise anywhere in the body. They may arise anywhere in the body.

Intracranial chondrosarcomas of the skull base are seen in 1% of the total chondrosarcomas, and in approximately 6% of entire skull base tumours. Endocranial chondrosarcomas originate more commonly from the base of skull than skull vault. This may be due to difference in embryonic development pattern. Bones of skull base develop by enchondral ossification while skull vault bones develop by intramembranous ossification. Chondrosarcoma of the skull base is considered to originate from remnants of endochondral mesenchymal tissues. In a review study on intracranial chondrosarcoma by Korten et al, common locations were petrous bone (37%), occipital bone and clivus (23%), sphenoid bone (20%), frontal, ethmoidal and parietal bones (14%) and dural tissue (6%).

Common clinical presentations of intracranial chondrosarcomas observed in various studies are history of headaches, facial pain,
chondrosarcoma and is dedifferentiated (Grade III). Grade I chondrosarcoma need to be differentiated from enchondroma. It has a slightly higher cell density and more cellular atypia compared to enchondroma. Grade II chondrosarcoma is more cellular than grade I. The tumor cells are large and have irregular and hyperchromatic nuclei. Grade III chondrosarcoma is hypercellular with enlarged and hyperchromatic cell nuclei resulting in fusiform pattern. This grading system is important because of its prognostic value. 

Skull base chondrosarcomas mostly have low-grade histology. These tumors are locally aggressive with low risk of metastases resulting in therapeutic challenges. Immuno-histochemical markers such as vimentin, cytokeratin, and S100 help to differentiate chondrosarcoma from chordoma. Chordomas do not express vimentin and chondrosarcomas are negative for cytokeratin expression. S-100 protein expression is present in both.

Intracranial chondrosarcoma is mostly treated with surgical resection when feasible. Surgery may be followed by adjuvant radiation and/or chemotherapy to improve recurrence rates and overall survival. Few studies in literature show chemotherapy may be effective in mesenchymal chondrosarcoma and in dedifferentiated chondrosarcoma. Chemotherapy in general had minimal benefit in grade I chondrosarcoma, and is not considered as standard of care in adjuvant/neoadjuvant setting. However, it can be considered in the locally advanced or metastatic setting. In general, minimal objective responses were seen in different studies with regimens frequently used in other soft tissue and bone sarcomas, i.e. anthracycline, ifosfamide, cisplatin and gemcitabine in combinations.

Prognosis in patients with intracranial chondrosarcoma depends on multiple factors like histological subtype, extent of tumor resection, previous treatment received (surgery or radiation therapy), and use of postoperative radiation therapy. Studies have shown local recurrence to be the most important predictor for adverse outcomes.

With chemotherapy, no significant objective responses were observed in studies of intracranial chondrosarcoma. Objective response rate was found to be dependent on the histological type in the study by Italiano et al, with low grade chondrosarcoma having 11.5% objective response and median progression-free survival of 4.7 months for all grades. In the same study, cytotoxic chemotherapy had responses in 31% of the patients with mesenchymal type and in 20% of the patients with dedifferentiated type.

In contrast to conventional chondrosarcoma, dedifferentiated chondrosarcomas are high grade. They are locally aggressive with greater risk of metastasis. They are generally treated with regimens used for osteosarcomas. Mesenchymal type of chondrosarcoma also have an aggressive behavior and is treated with chemotherapy regimens similar to Ewing sarcoma.

Mortality rate is lowest among patients with Grade I chondrosarcoma. The overall 5-year mortality rate of patients with intracranial chondrosarcoma reported in study was 11.4%, and the mean survival time was 53.7 months.

Conclusion

Chondrosarcoma should be considered as a differential diagnosis for intracranial tumors, especially when located at the skull base (para-sellar region). Therapy should include extensive surgical excision, followed by radiotherapy. Chemotherapy has limited role in treatment, as chemo-sensitivity of these tumors is low.

References:

8. Gay E, Sekhar LN, Rubinstein E et al: Chordomas and chondrosarcomas of the cranial base: Results
and follow-up of 60 patients. Neurosurgery 1995;36:887–897
Hepatocellular carcinoma (HCC) is commonest primary tumor of liver as well as the fourth leading reason of carcinoma related death worldwide. The most frequent sites of extra hepatic metastases of HCC are lungs, regional lymph nodes, kidney, adrenal and bone marrow. While skull metastases from HCC are rare, metastasis to scalp and skull on presentation of HCC are reported very rarely in the literature. Here we report rare case of HCC presented as asymptomatic metastatic lesion in the scalp and skull in a chronic hepatitis B patient. Excision of the scalp lesion was performed and on histopathology revealed metastatic Adenocarcinoma. Immunohistochemistry (IHC) report confirmed metastasis from HCC. On further investigation, two liver lesions with periportal nodes and left adrenal metastasis were detected and patient was started on sorafenib. After progression on sorafenib, regorafenib was started; ultimately he died after two months. 

Keywords: Hepatocellular Carcinoma, Skull Metastasis, Metastatic Adenocarcinoma

Introduction

HCC is commonest primary tumor of liver as well as predicted to be 6th most commonly diagnosed carcinoma, while 4th leading reason of cancer related deaths worldwide. HCC may occur in association with chronic hepatitis caused by hepatitis B (HBV) or hepatitis C (HCV) viral infections which are common causes of hepatic cirrhosis. HCC is commonly occurring in the 6th to 7th decade of life. Extra hepatic metastases are seen in 55-65% of patients with HCC. Commonest sites of extra hepatic metastases of HCC are pulmonary metastasis (35-65%), common hepatic, periportal nodes (15–39%) but rarely to bones (1.5–15%). The incidence of skull metastases from HCC is very rare (0.4–1.6%). We report a rare case of asymptomatic metastatic lesion in the scalp and skull from HCC.

Case Report

A 49 year old adult male patient visited the neurosurgery department at our hospital with a painless scalp lump along midline of vertex region which he noticed accidentally 2 months back. Then he noticed that it was growing in size very quickly. According to him, no history of head trauma as well as no past history of medical illness was present except for chronic HBV related chronic liver parenchyma disease (on Tenofovir for last 3 years). Neurological and physical examination revealed painless, firm mass with restricted mobility, two in number, in the midline of scalp, larger anterior lesion around 70x50 mm; with no neurological deficits or other obvious abnormalities.

His initial laboratory reports revealed hemoglobin: 15.4 g/dl, hematocrit: 45.5, white blood cell count 6400, platelets: 186000, prothrombin time (INR): 0.9, blood glucose: 98mg/dl, aspartate transaminase: 107 u/l, alanine transaminase: 44 u/l, alkaline phosphatase: 220 IU/L, albumin: 3.9gm/dl, globulin: 3.1gm/dl, total bilirubin: 0.67 mg/dl and normal renal function test. HBsAg was confirmed positive. alpha feto protein (AFP) was normal (16 ng/ml).

Ultrasonography of the abdomen revealed mild hepatomegaly with diffuse altered echo texture of liver. MRI brain with contrast showed large mixed intensity lesions (two in number) in midline in relation to parietal bone. The lesions were lytic in nature being hypo intense on T2W/FLAIR image with intralesional hyper intense area with iso to hypo intense on T1W image. Anterior lesion was larger measuring 71x51 mm in size. Both lesions showed intra as well as extra cranial component.

Excision of the scalp lesions was performed, and histopathological examination revealed metastatic adenocarcinoma. Meanwhile patient was given whole brain radiotherapy. Subsequently IHC report was positive for AE1, hepatocytes (Heppar), Glypican, with TTF1-, confirming metastatic HCC. On further workup with CECT (abdomen) two liver lesions (37x45 mm, 23x22 mm), few periportal lymph nodes (13x8 mm) with large (66x48 mm) left adrenal metastasis was noted, hence treatment was started with oral sorafenib. After 5 months of progression free interval on sorafenib, patient presented with backache for which CECT abdomen pelvis thorax was performed and new bony lytic lesion at D7 vertebra.
with soft tissue component of size 27x30 mm with increased abdominal lymphadenopathy were seen. Patient was given radiotherapy to local site for palliation of symptoms. Later patient was started on regorafenib and he died after 2 months.

**Discussion**

HCC is one of the most common malignancies worldwide; its occurrence is high in the area where HBV or HCV infections are endemic or commonly seen. Cirrhosis related HCC is most commonly due to HCV (25-75%) followed by HBV (15-50%), chronic alcohol consumption related (5-35%), hemochromatosis as well as idiopathic (5%).

Commonest sites of metastasis from HCC are lungs, loco regional nodes and adrenals. Its extra hepatic presentation usually occurs in cases with advanced intrahepatic tumor growth. In our case report the patient was having scalp and skull lesion with asymptomatic liver lesion with normal bilirubin and normal AFP.

Yanase et al group studied postmortem autopsy results of around 4000 patients of hepatocellular carcinoma from Japan and they also reported rare occurrence of bony metastasis as well as very rarely reported metastasis of HCC to cranium in very few patients (<5%), which correlated with rare incidence of extra hepatic metastatic pattern of HCC given in the literature.

Hsieh et al also reported few cases of HCC metastasized to skull that had mean age of fifty seven years. Six patients also had associated multifocal involvement of skull bones. Most of them presented as a lump in the skull region, some of them had mild pain along with swelling. On skull imaging most of them had lytic bony lesions.

Kuratsu et al also recorded a case of HCC with central nervous system metastases (cranial bones) that had shown high serum AFP. On contrary, in our reported case AFP was in normal range. There are very scanty data on imaging characteristic pattern and of HCC with cranial or skull metastasis. Kuratsu et al reported typical MRI findings of the cranial metastasis as lytic as well as expansile bony lesions, which were iso intense on T1 in few cases while hypo intense on T2 in some cases relative to cerebral white matter.

Guo et al reported one adult male patient of HCC who presented with single, painless midline lump in vertex region of cranium. He had no past history of medical illness. Brain CT demonstrated a hyper vascular enhancing lesion associated with lytic bony lesion in high parietal and occipital area, MR imaging of brain demonstrated lytic as well contrast enhancing bony lesion. On CT abdomen-pelvis revealed a large hepatic mass, without any metastatic lesion elsewhere. Laboratory test revealed normal liver function tests but serology report was HBsAg+, with raised AFP value. He had undergone craniotomy with total excision of lump. On histopathological examination, metastatic lesion from HCC was confirmed. His primary tumor was treated with Transcatheter arterial chemoembolization (TACE) using chemotherapy (Pirimicrubin + Carboplatin + Floxuridine), with lipiodol as well as gelatin sponge. Ultimately, he died due to acute respiratory distress syndrome (ARDS).

Like our case report, Goto et al reported a 56-year-old male with skull and vertebral metastasis from HCC which presented as with occipital mass. Contrast CT demonstrated lytic hyper vascular enhancing lesion of cranial bone with a solitary large hepatic tumour. MRI revealed multiple dorsal vertebral metastatic lesions. On serology he was positive for both HBsAg and anti HBC antibody, with normal liver functions tests. Finally confirmation of HCC with solitary primary lesion with metastatic lesion in the cranium and dorsal vertebrae was made. He was treated with TACE to primary hepatic lesion and radiotherapy for bony lesions.

For treating bony metastatic lesion of the cranium, multidisciplinary team management involving medical oncologist, surgical oncologist, radiation oncologist and palliative medicine expert should be considered to alleviate the pain, to decrease suffering from neurocognitive dysfunction and to improve or maintain quality of life.

**Conclusion**

There are only few case reports about skull and scalp metastasis from HCC. Even if infrequent, this should be considered among differential diagnoses during evaluation and workup and accordingly further complete evaluation should be considered. Management must be planned according to disease extent on individual basis for symptomatic treatment, improving quality of life and for optimum survival.

**References**


Sentinel Lymph Node Biopsy in Early Breast Cancer: An Institutional Experience from GCRI for the Year 2018-19

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Summary
Sentinel lymph node biopsy is the standard of care for management of node negative axilla in early breast cancer. Objectives of present study were to share our institutional experience, to analyze factors predicting presence of positive non sentinel axillary nodes, to analyze factors predicting axillary node metastasis. This was an observational study of prospectively managed data of sentinel lymph node biopsy in early breast cancer for the year 2018-2019. Total 168 procedures were performed. SPSS statistics version 25 was utilized for statistical analysis. Overall sentinel node identification rate was 95.2% (160/168). There was no statistically significant difference between blue dye method alone or dual technique (p=0.736). Sentinel lymph node biopsy after lumpectomy (n=40, success rate=92.5%) did not affect sentinel node identification (p=0.352). Median of sentinel nodes was four (1–13). Only 35.7% patients had positive non sentinel axillary nodes after having positive sentinel nodes. Presence of three or more positive sentinel nodes (80% vs. 29.7%), positive non blue non-radioactive node (suspicious enlarged node) (66.7% vs. 30.6%) were associated with high chance of finding positive non sentinel axillary nodes. Hence it may be concluded that dual method is standard of care for sentinel lymph node biopsy, but in resource constraint center blue dye technique can be utilized. In selected patients axilla may be preserved even after positive one or two sentinel nodes. Factors like hormone receptor negative status, tumor biology other than IDC, age>50 years, grade 1 tumor and T1 tumor size are associated with high chance of negative SLNs.

Keywords: Sentinel lymph node biopsy, Axillary lymph node dissection, Early breast cancer, Radiocolloid, Methylene blue

Introduction
Sentinel lymph node biopsy (SLNB) is the standard of care for management of node negative early breast cancer. It prevents morbidities like lymphedema, sensory neuropathy, shoulder dysfunction, and seroma formation associated with axillary lymph node dissection (ALND). Main objectives of present study were to audit and share our institutional experience of SLNB, to study factors associated with extra positive nodes (other than SLNs) in ALND, to study factors associated with axillary nodal involvement in present patients’ cohort.

Materials and Methods
Patients
This study presents the experience of SLNB in early breast cancer from February 2018 to July 2019 from a prospectively managed data in The Gujarat Cancer & Research Institute. SLNB was done in all clinicoradiologically node negative axilla. In those patients who had clinicoradiologically suspicious N1 node, ultrasound guided fine needle aspiration cytology (FNAC) was done and SLNB was done only if FNAC came negative or FNAC was not possible due to very small size of node. Total 168 SLNBs were performed during the study period, 117(69.6%) by dual technique (radiocolloid + methylene blue dye) and 51(30.4%) by only blue dye technique (methylene blue dye). Only blue dye technique was done only when radiocolloid was not available in nuclear medicine department or due to other logistic issues. Out of 168 patients, SLNs were identified in 160 patients. From this 160 patients, sentinel lymph nodes were sent for frozen section analysis in 154 patients and in 6 patients nodes were sent directly for final histology examination.

Blue dye method
Two to five ml of one percent W/V methylene blue dye was injected aseptically after painting and draping in periareolar region intradermally or subdermally based on surgeon’s preference. The injection site was massaged for five minutes. Then first, an axillary incision (in breast conservative surgery) or superior flap incision at its lateral aspect (in case of mastectomy) was put and dissection was done towards the axilla. Once the blue lymphatic got identified, it was traced to reach blue axillary node. (Figure 1) After removing first blue node, other blue nodes were searched in nearby area and were removed. Utmost care was taken not to injure intercostobrachial nerve. The whole procedure was completed by 15 to 20 minutes after putting skin incision; as more delay may cause blue dye to reach second echelon lymph nodes which increases unnecessary more lymph node removal.

Radiocolloid method
Aseptically prepared filtered 99mTc sulfur colloid (filtered with 0.22μ Millipore filter) (total 0.4
ml) was injected in periareolar region intradermally. The total injected dose was 400-500 uCi for the same day surgery (2-3 hours before surgery) and approximately 800-1200uCi, if the surgery was planned next day (16-24 hours before surgery). Usual precautions like gentle shaking of the syringe prior to injection were taken to avoid the clumping of colloidal particles together. After injecting, each site was massaged for one to two minutes to facilitate lymphatic flow. Bleb formation at the injected site confirms the proper injection technique. Sequential dynamic or static images were taken to identify the sentinel node by gamma imaging. (Figure 2) Sentinel node localization by probe and surface marking was done after proper identification of sentinel node by gamma probe in the department of nuclear medicine. During surgery, the highest radioactive (hot) sentinel lymph node removed first. Other radioactive nodes were searched by gamma probe and removed till the radioactivity of the axillary bed was less than ten percent of the highest radioactive sentinel lymph node. (Figure 3)

Any enlarged hard suspicious non blue non-radioactive nodes were also removed, as diseased node might not take dye or radiocolloid if it was studded with disease or lymphatics were blocked by the tumor cells.

For patients who presented after lumpectomy from outside our institute and had scar at upper outer quadrant, blue dye and radiocolloid were injected at upper and outer side of the scar. In such cases to prevent obscuring of the radioactive sentinel lymph nodes by background radioactivity of injection site, the skin of radiocolloid injection site were excised if required.

**Intraoperative frozen section evaluation**

Frozen section analysis was done as per the recommendation provided by the College of American Pathologist. All sentinel lymph nodes sent for frozen section were submitted entirely. Sentinel lymph nodes were bisected along the longitudinal axis and 2mm thick multiple slices were submitted. Imprint smears were also taken in all large lymph nodes. Two slides were prepared from each slice of tissue. Sections were stained with Hematoxylin and Eosin. The entire procedure took 15-20 minutes.

**Statistical Analysis:**

SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY) was utilized for statistical analysis. Frequencies in descriptive statistics was used to calculate mean, median and range. Pearson Chi-square test was applied as a test of significance. Multivariate analysis was done by logistic regression method. P value <0.05 was considered significant.

**Results**

In present series, 99.4 % (167/168) patients were female and one patient was male. Median age of patients was 52 years (range: 28 -82 years).(Figure 4) Out of 168 SLNB procedures; 111 patients got spared of any radical axillary treatment [ALND or radiotherapy(RT)], 50 patients underwent ALND and 7 patients received radiotherapy to axilla [Figure 5]. Breast conservative surgery was done in 43.5 % (73/168) patients. Median node yield was four (range-1 to 13) in SLNB and 15(range- 8 to 27) in ALND. (Figure 6)
Node identification rate

Total 117 cases were done by dual technique and 51 cases were done by blue dye technique only. Overall node identification rate in our study was 95.2% (160/168). In blue dye only technique the SLN identification rate was 96.1% (49/51) while by dual technique it was 94.9% (111/117; p=0.736). Although this was not quantified in present study, it was experienced that in dual technique it was easier and faster to identify sentinel nodes (blue and hot nodes), which took more time and more dissection in blue dye technique alone.

As study institute is a tertiary cancer care institute, many patients came after undergoing breast lump excision outside the institute. SLNB was also done in such cases if axilla was node negative. In present study 23.8% (40/168) such cases underwent SLNB. SLN identification rate in these patients was 92.5% (37/40) [p = 0.35 {when comparing with SLN identification rate of non-lumpectomy patients which was 96.1% (123/128)}].

Rate of positive non sentinel nodes in ALND specimen and factors affecting it

Out of 42 patients who underwent ALND for positive SLN, only 15 patients (35.7%) had extra positive nodes in ALND specimen, which means that 64.3% patients had undergone unnecessary ALND. Factors like more than two positive SLNs, positive non blue non radioactive suspicious node, extranodal extension in SLNs, LVI in primary tumor and their effect on presence of extra positive nodes in ALND was analyzed. Presence of more than two positive SLNs was significantly associated with high chance of presence of extra positive nodes in ALND and positive non blue non radioactive SLN was showing trend towards it (Table 1).

Analysis of various factors and axillary lymph node involvement

Total 52 patients (31%) had positive axillary node in present study in final histology. On comparing ultrasonography findings with final axillary node status, overall accuracy of sonography was 65.9% with sensitivity of 21.2% and specificity of 86.1% (Table 2).

In total 154 patients, frozen section analysis of SLNs was done. In 153 patients there was concordance between frozen report and final histology report of SLNs, while in one patient frozen report of SLNs was negative but final histology report of SLNs came out to be positive, so this patient was given axillary radiotherapy. Accuracy of frozen section analysis was 99.4% (153/154) and sensitivity was 97.8% (44/45).
Table 1: Factors associated with presence of positive non sentinel nodes in ALND specimen

<table>
<thead>
<tr>
<th>Factor</th>
<th>% of cases with extra positive nodes</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive SLNs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 SLNs positive</td>
<td>80% (4/5)</td>
<td>0.028</td>
</tr>
<tr>
<td>&lt;=2 SLNs positive</td>
<td>29.7% (11/37)</td>
<td></td>
</tr>
<tr>
<td>Status of non blue non radioactive SLN:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>66.7% (4/6)</td>
<td>0.087</td>
</tr>
<tr>
<td>Negative/not identified</td>
<td>30.6% (11/36)</td>
<td></td>
</tr>
<tr>
<td>ENE in SLN:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>37.5% (6/16)</td>
<td>0.850</td>
</tr>
<tr>
<td>Absent</td>
<td>34.6% (9/26)</td>
<td></td>
</tr>
<tr>
<td>LVI in primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>30% (6/20)</td>
<td>0.461</td>
</tr>
<tr>
<td>Absent</td>
<td>40.9% (9/22)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Comparison of ultrasonography finding of axilla and final (histological) axillary status

<table>
<thead>
<tr>
<th>USG status of axilla</th>
<th>Final histological status of axilla</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological/metastatic node</td>
<td>Positive (11)</td>
<td>(True Positive) 16 (False Positive)</td>
</tr>
<tr>
<td>Benign node</td>
<td>41 (False Negative)</td>
<td>99 (True Negative)</td>
</tr>
</tbody>
</table>

Table 3: Univariate analysis of various factors and their impact on final axillary status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sub characteristics</th>
<th>Axilla positivity rate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;=50</td>
<td>40.3% (31/77)</td>
<td>23.1% (21/91)</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T stage</td>
<td>Tis</td>
<td>0% (0/1)</td>
<td>14.3% (5/35)</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>14.3% (5/35)</td>
<td>37.5% (42/112)</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>14.3% (5/35)</td>
<td>37.5% (42/112)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>11.8% (2/17)</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td></td>
<td>Tx</td>
<td>11.8% (2/17)</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td>Multicentric disease</td>
<td>Present</td>
<td>33.3% (4/12)</td>
<td>30.8% (48/156)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease histology</td>
<td>Favorable (medullary, mucinous, papillary, DCIS, tubular)</td>
<td>0% (0/11)</td>
<td>0% (0/3)</td>
</tr>
<tr>
<td></td>
<td>Metaplastic carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ILC</td>
<td>0% (0/11)</td>
<td>0% (0/3)</td>
</tr>
<tr>
<td></td>
<td>IDC</td>
<td>0% (0/11)</td>
<td>0% (0/3)</td>
</tr>
<tr>
<td>Grade</td>
<td>1</td>
<td>18.8% (3/16)</td>
<td>46.7% (28/60)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>46.7% (28/60)</td>
<td>30% (21/71)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>30% (21/71)</td>
<td>0% (0/21)</td>
</tr>
<tr>
<td>Lymphovascular Invasion</td>
<td>Present</td>
<td>38.6% (27/70)</td>
<td>25.5% (25/98)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perineural invasion (PNI)</td>
<td>Present</td>
<td>42.9% (6/14)</td>
<td>29.9% (46/154)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone/Her 2 receptor status</td>
<td>HR+Her2-</td>
<td>37.1% (23/62)</td>
<td>45.9% (17/37)</td>
</tr>
<tr>
<td></td>
<td>HR+Her2+</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>HR-Her2+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR-Her2-</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Unknown</td>
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</table>

Patient and tumor characteristics and their effect on positive axillary status was analyzed. (Table 3 and 4) On univariate analysis, factors like age <=50, higher T stage, invasive ductal carcinoma biology, high grade, and positive hormone receptor status were significantly associated with more chance of positive axillary lymph node, while lymphovascular invasion showed trend towards positive axillary status. On multivariate analysis, hormone receptor positive status was significantly associated with positive axillary node, while age <50 and high T stage showed trend towards positive axillary status.

Discussion

Median age of breast cancer in U.S. is 62 years, while in present study it was 52 years. This suggests that there is an unmet need to identify those factors which put Indian women at a risk to get breast cancer ten years earlier.

Axillary lymph node status is one of the most important prognostic factors in breast cancer. Sentinel lymph node biopsy has replaced axillary lymph node dissection in node negative early breast cancer, as lower morbidity with comparable survival can be achieved with SLNB."

Nonsurgical assessment of the axilla is not promising, different imaging modalities like
Table 4: Multivariate analysis of factors affecting axillary lymph node status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence Interval of odds ratio</th>
<th>p value</th>
</tr>
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Table 5: Results of ultrasonography findings of present study and study by Hwang et al

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<td>Accuracy</td>
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<tr>
<td>Sensitivity</td>
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</tr>
<tr>
<td>Specificity</td>
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<tr>
<td>Positive predictive value</td>
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<tr>
<td>Negative predictive value</td>
<td>70.7%</td>
<td>81.7%</td>
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ultrasonography, magnetic resonance imaging, and positron emission tomography/computed tomography have been proven to be of limited value in cN0 axilla. In present study also, ultrasonography was of limited help with better specificity but poor sensitivity (Table 5).

In present study cohort, sentinel node identification rate was 95.2%. There was no significant difference with either blue dye alone method or dual tracer method. Combined use of both tracers appears to be complementary, minimizing the false negative rate (FNR) in most but not all studies. In American college of Surgeons Oncology Group (ACOSOG) Z0010 trial also there was no significant differences in the rate of sentinel node identification with the use of blue dye alone, radiocolloid alone, or dual technique. In systemic review by American Society of Clinical Oncology (ASCO), use of dual technique was associated with an almost significant trend toward fewer FNRS. However in situations like surgeons with limited experience, prior breast or axillary surgery, obese patient, and after neoadjuvant therapy, dual technique should be used as there is high chance of low identification rate and high FNR with single technique. Another important finding in present study was successful application of SLNB in patients who had undergone previous diagnostic excision biopsy of breast lump, there was no statistically significant difference of lymph node identification between patients who underwent lumpectomy vs. no lumpectomy prior to SLNB [92.5% (37/40) vs. 96.1% (123/128) respectively, p=0.35]. Other studies also have demonstrated similar findings and shown feasibility of SLNB for such patients. One thing that should be taken care in such patients is that patients who had lump in upper outer quadrant of breast, should be injected tracer at outer expect of the excision scar as lymphatics might have been broken at the scar site which might hamper lymph flow if tracer injected at periareolar region or at inner site of the scar.

Theoretically, DCIS (Ductal carcinoma in situ) is a noninvasive disease and it doesn’t spread by lymphovascular route. However, according to one metaanalysis, up to 26% of the patients diagnosed by needle biopsy may harbor invasive or microinvasive disease on final histopathology. Multiple factors like palpable mass, mammographic size>4 cm, high grade, age <55 years, diagnosis on smaller core biopsy needle, and multicentricity may predict an increased risk of invasive or microinvasive component in the final specimen. Also patients who undergo mastectomy for DCIS should undergo SLNB, as chance of SLNB is lost if final histopathology suggest
invasive disease. In present series, four patients had cTis (three had DCIS and one had paget’s disease), out of which in final histological examination only one patient had DCIS, rest all had invasive or microinvasive disease. One reason for this finding is that, screening mammography is not common in our country, and majority of our patients with DCIS have a palpable mass, which put them into a high risk of having invasive or microinvasive disease.

Median sentinel node retrieval in present series was four (range 1-13). Wong et al19 in their prospective multi institutional study, suggested that single sentinel node identification was associated with higher FNR (14.3%) as compared to multiple sentinel nodes retrieval (4.3%). In their study, use of blue dye injection alone was the only factor independently associated (p<0.0001) with identification of a single SLN. Chagpar et al15 in their multi-institutional prospective study, retrieved median two SLNs (range 1-18), with more than three nodes removed in 17.9% patients. They suggested that FNR decreases with multiple SLNs identification, they also suggested that though most of the patients will have three or fewer SLNs identified, if more than three SLNs are identified, these SLNs should be removed because there is a significantly higher FNR associated with limiting SLN biopsy procedures to three SLNs. All blue, hot (more than ten percent radioactivity of the highest radioactive node), nodes at the end of blue lymphatics, and suspicious enlarged hard nodes should be sampled as sentinel nodes.

Multiple studies have shown that only approximately 40% of patients with a positive sentinel lymph node had residual disease in the axilla.16,17 In present series, only 35.7% (15/42) patients had extra positive nodes in ALND specimen other that positive sentinel nodes. Presence of more than two positive SLNs was strongly associated with presence of extra positive nodes, while presence of positive non blue non-radioactive node was showing trend towards presence of extra positive nodes. Changsri et al18 noticed that presence of extranodal extension (ENE) and size of the metastatic deposit in SLNs were associated with presence of residual disease in axilla. Turner et al19 noticed presence of peritumoral lymphovascular invasion (LVI), size of primary tumor, ENE in SLNs as predictor of positive non sentinel lymph nodes.

Many trials studied avoidance of axillary dissection after positive SLNs. According to ACOSOG Z-0011 trial,20 completion ALND can be avoided in patients with T1 or T2 breast cancer with one or two positive SLNs undergoing breast conservative surgery and SLNB followed by whole breast irradiation. In present series, total 49 patients have positive SLNs, out of which 16 (32.7%) patients were fulfilling Z0011 criteria and they could have been spared of further axillary treatment. After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial21 compared axillary dissection vs. axillary radiotherapy after positive sentinel nodes by SLNB. There was no difference between disease free survival and overall survival. In present study, seven patients were given axillary radiotherapy instead of axillary dissection after positive sentinel nodes. The AMAROS trial showed axillary radiation to be an acceptable alternative to ALND in patients who have positive sentinel node(s) but do not meet the Z0011 criteria. For those who meet the Z0011 criteria, axillary radiation is likely to add morbidity without any added benefit. After the results of above mentioned trials on avoidance of completion ALND, many centers across the world have decreased the practice of completion ALND and intraoperative frozen section nodal assessment after SLNB.22,23 In present series also we had started decreasing the use of intraoperative evaluation of sentinel nodes during last three months by not sending frozen section analysis in six cases, with the plan of giving axillary radiation if sentinel nodes comes positive, in accordance with AMAROS trial.

On univariate evaluation of factors affecting lymph node involvement, factors like young age<50, higher T stage, invasive ductal carcinoma (IDC) biology, high tumor grade, and positive hormone receptor status were significantly associated with positive axilla, while lymphovascular invasion showed trend towards positive axillary status. Tumor biology like medullary, mucinous, papillary, DCIS, tubular, metaplastic carcinoma, invasive lobular carcinoma have significantly less lymph node involvement. On multivariate evaluation, hormone receptor positive status was the only factor significantly associated with positive axillary involvement, while young age (<50) and high T stage showed trend towards more axillary metastasis. In accordance to the present study, Oliveira Filho HR et al24 reported that molecular subtype luminal A(ER and PR positive and Her-2 negative), larger tumors, younger patient’s age, and the presence of LVI have the highest likelihood of axillary lymph node metastasis in early breast cancer, while triple negative subtype is predictive of a lower incidence of axillary lymph node metastasis regardless of patient’s age or tumor size. They also reported in their results that patients with triple negative tumors had approximately a 90% lower chance of developing lymph node metastasis compared to those with luminal A tumors[OR=0.11; 95% CI 0.01-0.88; p=0.01]. Ashutkar et al25 also reported that ER and PR negative tumor, favorable histological type and grade I tumors have low probability of axillary involvement. From these
results, it appears that in invasive ductal carcinoma histology, hormone receptor positive disease has more propensity for locoregional spread while hormone receptor negative disease has more propensity for systemic spread.

Though in present series higher grade (grade 2 > grade 1) and higher T stage (T2 > T1) showed significant lymph node involvement in univariate analysis, grade 3 tumors and T3 stage tumors showed decreased lymph node involvement than grade 2 and T2 stage respectively. To find the reason, subgroup analysis was done. According to subgroup analysis of grade, there were significantly more hormone receptor positive tumors in grade 2 than in grade 3 subgroup (76.3% vs. 52.2% respectively; p=0.005) and in present series hormone receptor positive status was the only factor which was strongly associated with axillary lymph node involvement by both univariate and multivariate analysis. So this could be the reason of why grade 2 tumors had more lymph node involvement as compared to grade 3 tumors. On other hand, for T stage, the number of patients with T3 tumors (11.8%) was small in present series, it appears that T3 tumors only with low probability of lymph node metastasis might remain clinicoradiologically node negative and were able to undergo SLNB. Also 41.2% (7/17) of T3 tumors had biology other than invasive ductal carcinoma (biology other than IDC had low chance of lymph node metastasis ) and other 41.2% (7/17) T3 tumors were grade 3 (grade 3 tumors showed low lymph node metastasis as compared to grade 2 tumors). Because of above mentioned reasons, there might be low lymph node involvement in T3 than T2 tumors in present series, but it is not justifiable to generalize this finding and to conclude that T3 tumors are associated with low chance of lymph node spread, a larger cohort needs to be analyzed to reach final conclusion.

Conclusion
Sentinel lymph node biopsy is standard of care for the management of node negative early breast cancer. Ultrasonography has good specificity but poor sensitivity to assess axillary status. SLNB can be performed after lumpectomy. Dual method is standard of care for SLNB, but in resource constraint centre, blue dye technique can be utilized. Role of intraoperative frozen section is decreasing after Z0011 and AMAROS trial results. Chances of extra positive axillary nodes (other than SLN) are high when 3 or more SLNs are positive or non blue non radioactive node is positive, so in selected patients axilla may be preserved even after positive one or two sentinel nodes. Factors like hormone receptor negative status, tumor biology other than IDC, age >50 years, grade 1 tumor and T1 tumor size are associated with high chance of negative SLNs.

Abbreviations:
ACOSOG- American College of Surgeons Oncology Group
ALND- Axillary lymph node dissection
AMAROS- After Mapping of the Axilla: Radiotherapy or Surgery
ASCO- American Society of Clinical Oncology
DCIS- Ductal carcinoma in situ
ER- Estrogen Receptor
FNAC- Fine needle aspiration cytology
FNR- False negative rate
HR- Hormone receptor
IDC- Invasive ductal carcinoma
LVI- Lymphovascular invasion
PNI- Perineural invasion
PR- Progesteron receptor
RT- Radiotherapy
SLN- Sentinel lymph node
SLNB- Sentinel lymph node biopsy
W/V- Weight by volume

Competing interests: None

References


**Diffuse Large B-Cell Lymphoma of the Uterine Cervix: A Rare Case and Review of Literature**

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Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat, India.
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**Summary**
Extra nodal Non Hodgkin’s Lymphoma of the genital tract accounts for less than 1% of all the NHLs. Most commonly involves the ovary followed by cervix, vulva and vagina in descending order. Most of the genital tract lymphomas present in early stage and Diffuse Large B Cell Lymphoma (DLBCL) is the most common histology. Indolent lymphomas can also present with primary genital tract involvement. Diagnosis is confirmed by histopathology and immuno-histochemistry. PET is used for staging and assessment of bone marrow. There are no standard treatment guidelines for this entity and management is based grossly on the principles of management of nodal lymphomas. Here we present a case of DLBCL of uterine cervix presenting with obstructive uropathy, who underwent haemodialysis and percutaneous nephrostomy followed by one cycle of chemotherapy and succumbed to severe febrile neutropenia.

**Keywords:** Diffuse large B Cell Lymphoma, Extranodal, Genital tract, Uterine cervix

**Introduction**
Extra nodal Non Hodgkin's lymphoma (NHL) of the genital tract accounts for less than 1% of all NHLs. Isolated gynaecological NHL involves the ovary in 59% of the cases, uterine cervix in 15.5%, vulva in 7.5% and vagina in 6%. Most common histology is Diffuse Large B cell lymphoma (DLBCL)-37%, followed by follicular lymphoma (FL). Median age of diagnosis is 46 years (range 20-85 years). Majority of these tumours present in early stage i.e. Stage I-69.2%, stage II-22.7%, stage III and IV-8.1%. Therapeutic approach to these tumours is not standardised but based on general principles of treatment of NHL. Here we present a rare case report of primary diffuse large B cell lymphoma of the uterine cervix.

**Case Report**
A 68-year-old, post-menopausal female with no known co-morbidities came to our institute with a history of post menopausal bleeding since 15 days. Her clinical pelvic examination revealed transversely enlarged, globular uterine cervix with an open os with a mass seemingly within the endo-cervix. Examination of the para-metrium revealed involvement bilaterally till the pelvic wall making it FIGO stage IIIB. A punch biopsy of the endo-cervical mass was performed which was morphologically suggestive of poorly differentiated carcinoma. Immuno-histochemistry (IHC) revealed presence of Lymphocyte common antigen (LCA), PAX8, PAX5, CD20, BCL2 and MUM1 and negative for AE1 and BCL2. MIB1 was 70-80%.

Diagnosis of DLBCL was established. Viral markers for HIV (Human immunodeficiency virus), HbsAg (Hepatitis B surface antigen), HCV (Hepatitis C virus) were negative. She had Haemoglobin of 8.2, liver function was normal. Her serum creatinine level on presentation was 3.39 which raised to 9.64 within a week’s time. She had to undergo a couple of sessions of haemo-dialysis followed by placement of percutaneous nephrostomy in view of moderate hydro-uretero-nephrosis on the left side. Post procedurally the creatinine level was down trending and she could undergo evaluation with whole body Positron emission tomography (PET) alone without computed tomography (CT) which revealed a large conglomerated mass lesion in lower abdomen and pelvic region involving mesentery, encasing bowel loops in mid line and left iliac fossa, uterus, cervix upper vagina, infiltrating the posterior wall of bladder and encasing both ureters causing proximal hydro-uretero-nephrosis. Size of the lesion was 10.3x9.3x1.2 cm with SUV max of 31.2. Few para rectal nodes were present of about 1x1 cm with SUV max of 5.6. There was a conglomerated lymph nodal mass involving para-aortic, left common iliac and left external iliac region of size 4.7x3.2 cm with SUV max 32.8. In the mediastinum a left hilar node of 1.3x0.7 cm was present with SUV max of 32.8. In the mediastinum a left hilar node of 1.3x0.7 cm was present with SUV max of 6.4. Multiple bilateral lung infiltrates were present, largest measuring 1.7x1.7 cm with SUV max of 12.6. She was Ann Arbor stage IV with IPI (International Prognostic Index) of 5 falling in poor risk category. She was started on chemo-immunotherapy as her cardiac reserve was normal. She was given rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone (R-miniCHOP with 50% dose reduced cyclophosphamide, adriamycin, vincristine). She developed grade IV febrile neutropenia post first cycle of chemotherapy and succumbed to pneumonitis.
Discussion
The question whether this is a primary lymphoma of the uterine cervix or secondary extra nodal involvement remains. Extra nodal involvement is seen in one in every four cases of Non Hodgkin's Lymphoma. Female genital tract as a site of extra nodal involvement is seen in 1-1.5% of the cases. Primary Non Hodgkin's lymphoma of the uterine cervix accounts for 0.12% of all cases. In view of major bulk of the disease and metabolic activity residing within the cervix and para aortic nodes and the presenting symptom and sub centimetric hilar nodes, an assumption of primary from the cervix was made. In either case this is a rare presentation and hence has been reported. Predominant symptoms of genital tract extra-nodal NHL are dysfunctional uterine bleeding, cervical or pelvic mass and pain in descending order. Early stages can present without symptoms, 'B' symptoms are rare compared to nodal DLBCL. Our patient presented with bleeding per vaginum and obstructive uropathy akin to squamous cell carcinoma of the cervix. For the lymphoma of uterine cervix, lack of involvement of mucosa, sparing of stroma and junctional zone are characteristic. Uterine cervix lymphomas should be distinguished from sarcoma, poorly differentiated carcinoma, neuroendocrine tumours, malignant melanoma, malignant mixed Mullerian tumour, extra-osseous Ewing's and chronic cervicitis. From the reports in literature, therapeutic approach ranged from surgery with adjuvant radiotherapy for localised disease to adjuvant chemotherapy for advanced disease to systemic chemotherapy alone. Over the last few years, immuno-chemotherapy combination regimens have established efficacy. The therapeutic value of surgery is limited besides providing histological diagnosis. Few reports state that for localised NHL with aggressive histology offering radiotherapy post chemotherapy does not seem to offer any benefit in progression free or overall survival. Few reports quote that many patients achieve prolonged progression free survival with combination of chemotherapy and involved field radiotherapy. Cure rates are good in patients with limited disease (5-year PFS of 80-85%) where- as approximately a 50% 5-year PFS of can be observed in patients with advanced disease. The treatment regimen of choice is CHOP chemotherapy combined with Rituximab, a mono-clonal anti-CD20 antibody. Central nervous system prophylaxis with intrathecal methotrexate has been used by few in literature. As in nodal DLBCL role of autologous bone marrow transplant has no role in first remission but indicated for relapsed, refractory disease.
Conclusion
Primary DLBCL of the uterine cervix is a rare disease. There are no standard guidelines for the management. Majority of reports in literature used PET scan for staging, chemo-immunotherapy as primary treatment, involved field radiotherapy and CNS prophylaxis have been used in few reports. More case reports or series with long term follow up may shed light regarding standard management of this entity.

Acknowledgements
I thank Dr Ashini Shah, Assistant Professor, Oncopathology for providing me with the slide images.

References
We report a case of orbital metastasis as initial presentation of breast cancer in a 47-year-old woman. Patient presented with proptosis of left eye and loss of vision over 2 months in her left eye with diminution of vision in the right eye. Magnetic resonance study (MRI) reported extraconal nodular lesions in both orbits. On examination, nipple retraction in left breast and few skin nodules over chest wall were noted. Biopsy from the chest wall nodule reported invasive lobular carcinoma of breast. Diagnosis was confirmed by biopsy of right orbital lesion. Initial treatment with orbital radiotherapy resulted in gradual improvement of local symptoms which was followed by hormonal treatment and bisphosphonates with palliative intent. The orbital metastasis is a rarely encountered condition. The most prevalent primary disease remains carcinoma breast. Possibility of orbital metastasis should be considered in a patient with a diagnosis of breast cancer presenting with relevant orbital symptoms.

Keywords: Orbital metastasis, Carcinoma breast, Invasive lobular carcinoma

Introduction

The orbit is an uncommon site for metastasis, accounts for metastatic involvement in 1 to 3% of cancer patients. Breast carcinoma accounts for 29% to 70% of all the cancers with orbital metastases. Majority of the orbital metastases are detected in patients with previously diagnosed breast cancer and denovo presentation of breast carcinoma with orbital metastasis is infrequent. Orbital metastases from breast carcinoma may involve extraocular muscles, fat, or bone and preservation of visual function and quality of life are vital goals. Histopathological evaluation of the affected orbital tissue confirms the diagnosis. Metastatic involvement of orbits by breast cancer is reported only in a few studies mostly with invasive lobular breast cancer (ILC). Here, we report a patient with metastatic involvement extraconal orbit by breast carcinoma and briefly review the relevant literature on orbital metastasis of breast carcinoma.

Case Report

A 47-year-old woman presented with exophthalmos, decreased visual acuity and left orbital pain (Figure 1). She also reported of few skin nodules over chest wall. Clinical examination revealed nipple retraction and in the left breast. Ophthalmologic examination revealed absence of perception of light in left eye and reduced visual acuity in right eye. MRI of the orbits revealed few extraconal lesions in both orbits with diffuse involvement of extraocular muscles (Figure 2). Brain MRI did not reveal any abnormality. FDG avid lesions in the left breast, left axilla, bilateral intra orbital–extraconal regions, and multiple lesions in axial skeleton on PET/CT suggested metastatic disease in the orbit and bone. Biopsy from the chest wall nodule reported invasive lobular carcinoma of breast. ER/PR (estrogen receptor/progesterone receptor) stained strongly positive and the specimen was negative for Her-2 neuexpression. Biopsy from right orbital lesion revealed proliferation of atypical cells with pleomorphic nuclei in scant eosinophilic cytoplasm suggestive of metastatic carcinoma (Figure 3). In view of impending loss of vision in right eye, the orbital lesions were irradiated with the use of external beam radiotherapy, with a total dose of 30 Gy delivered to the tumor in 10 fractions. She was asymptomatic for bone disease. Eye symptoms improved notably on both side during the following weeks. Though she had lost vision in left eye at diagnosis itself, vision in the right eye could be salvaged. Patient was put on Letrozole and bisphosphonates (for bone disease) as palliative treatment in absence of any visceral crisis at the end of radiation. Skin lesions responded remarkably. The patient remains considerably free from ocular symptoms 3 months after radiotherapy (Figure 4). She continues to receive Letrozole, bisphosphonates and eye care for left eye along with artificial tears and ointment.

Discussion

Longer survival of patients with metastatic disease and diagnostic advances probably have led to increasing occurrence of orbital involvement in breast cancer. Majority of the orbital metastases are detected in patients with previously diagnosed breast cancer, many a times, along with additional systemic metastases. About 12-31% of patients are newly diagnosed cancer cases. Probability of additional systemic involvement remains high. Breast carcinoma is the most prevalent cancer that metastasises to orbit. Other primary cancers with
orbital metastatic involvement comprise lung carcinoma, prostatic carcinoma, renal cell carcinoma and melanoma. Unlike other primaries, bilateral metastases can be seen in 15-20% of breast carcinoma cases. Yet, overall, orbit remains a rare site even for breast cancer metastasis and particularly, site of initial presentation. Orbital metastasis may present with symptoms like proptosis, double vision, decreased visual acuity, pain, chemosis, ptosis, or orbital bony involvement. Orbital metastases from breast cancer frequently involve fat or extraocular muscles. Enophthalmos, secondary to scirrhus infiltration of orbit is rare. Exclusion of the alternative diagnoses like granulomatous, vasculitis, endocrine, and immunologic disorders remain relevant. Histopathological examination of the affected orbital tissue confirms the diagnosis. Estrogen and progesterone receptor and Her2-neu expression by immunohistochemically assessment of the biopsy specimen is warranted for diagnosis as well as steering the treatment plan.

As extensive metastatic involvement in other organs is frequent in the setting of orbital breast metastases, workup for additional metastases should be carried out. Multidisciplinary team involving medical oncologist, radiation...
oncologist, and ophthalmic surgeon may enable formulation of most appropriate treatment plan. Treatment of metastatic breast cancer involves hormonal therapy, targeted therapy or chemotherapy, determined by the systemic burden of disease and immunohistochemistry. Enucleation does not offer any advantage in view of progression of disease or overall survival.

External beam radiotherapy remains the most important component of treatment. Radiotherapy allows control of tumor growth, preservation of visual function, reduction of proptosis and exposure keratopathy and better patient comfort. Exposure keratopathy is treated with frequent use of artificial tears and ointment. Temporary tarsorrhaphy can be considered failing conservative options. Palliative tumor resection may be appropriate in few select patients to address pain, diplopia, and proptosis where other measures fail. Five-year overall survival with metastatic breast cancer is 21%. With diagnosis of metastatic involvement of orbits by breast carcinoma, median survival is 22 months.

Conclusion

Possibility of orbital metastases should be perceived if pertinent orbital symptoms are noted in a patient with breast cancer. Metastatic lesions in the orbit are rare and often are associated with additional systemic metastases from breast cancer. So, the best possible management requires involvement of a multidisciplinary team.

Acknowledgement

We thank Dr. Ami Shah and Dr. Viral Bhanvadiya, Department of Ocular pathology, M & J Institute of Ophthalmology, Ahmedabad for providing images of pathology slides.

References

## Panel Discussion at the Clinical Meetings

(July 2019 to December 2019)

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Panel Discussion at the Clinical Meetings

(July 2019 to December 2019)

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Data Presentation for Morbidity, Mortality at Clinical Meetings

(July 2019 to December 2019)

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<td>3.</td>
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<td>26.10.19</td>
<td>Pegu Farista</td>
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<td>Maru Bhumi</td>
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<td>28.12.19</td>
<td>Solanki Kinjal</td>
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## Presentations at the Clinical Meetings

(July 2019 to December 2019)

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<th>Speaker/Department</th>
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<td>Kausadikar Shripad Medical Oncology</td>
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<td>K. Sangeetha Gynaecologic Oncology</td>
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<td>Darji Mona Matron Gr.I</td>
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<td>Procalcitonin Versus c –reactive Protein: Usefulness as Biomarker of Sepsis in ICU Patient</td>
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<td>Targeting KRAS in Metastatic Colorectal Cancer: Current Strategies &amp; Emerging Opportunities</td>
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About the Journal and Instructions to Authors

About the Journal

Gujarat Cancer Society Research Journal is a biannually (April and October) peer-reviewed journal published by the Gujarat Cancer Society (formerly published as GCS Research Bulletin). The journal's full text is available online at http://www.cancerindia.org

Scope of the Journal

The Journal intends to cover basic, clinical, clinico-basic research and medical education carried out by the staff of the Gujarat Cancer Society and Gujarat Cancer and Research Institute related to human well being including ethical and social issues in the field of Oncology. The Journal gives preferences to original scientific papers, case reports, anecdotal reports and mini reviews. It may comprise invited review articles, publish oration speeches and work presented in the clinical meetings and the journal clubs. Hence it will continue to serve as an academic-research bridge between the basic sciences and the applied sciences, viz. various disciplines of medicine within and outside GCS-GCRI.

Authorship Criteria

Authorship credit should be based only on contributions any of the three components mentioned below:
1. Concept and design of study or acquisition of data or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content; and
3. Final approval of the version to be published. Each contributor should have participated sufficiently in the work to take public responsibility for appropriate portions of the content of the manuscript. The order of contributors should be based on the extent of contribution towards the study and writing the manuscript.

Review Process

The submitted manuscripts not meeting with the Instructions to Authors would be returned to the authors for technical correction, before they undergo editorial / peer-review process. The editors will review all submitted manuscripts initially for suitability for formal review. Manuscripts with insufficient originality, serious scientific or technical flaws, or lack of a significant message will be rejected before proceeding for formal peer-review. Manuscripts that are unlikely to be of interest to the Gujarat Cancer Society Research Journal readers are also liable to be rejected at this stage itself. Manuscripts that are found suitable for publication in Gujarat Cancer Society Research Journal are sent to expert reviewer/s.

The journal follows a double-blind review process, wherein the reviewer/s and authors are unaware of each other's identity. Every manuscript is also assigned to a member of the editorial team, who based on the comments from the reviewer/s takes a final decision on the manuscript.

The comments and suggestions (acceptance/ rejection/ amendments in manuscript) received from reviewer/s are conveyed to the corresponding author. If requisite, the author is requested to provide a point by point response to reviewers' comments in a separate sheet and submit a revised version of the manuscript with the changes duly highlighted in different color. This process is repeated till reviewers and editors are satisfied with the manuscript. Manuscripts accepted for publication are copy edited for grammar, punctuation, print style, and format. Page proofs are sent to the corresponding author. The corresponding author is expected to return the corrected proofs within two days.

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Contents of the Gujarat Cancer Society Research Journal are covered by copyright. Gujarat Cancer Society Research Journal does not accept any responsibility for the statements made by the authors. The Editorial Board has the right to introduce such changes in the articles as may be considered necessary for effectiveness of communication.

Plagiarism

Plagiarism is considered by the Gujarat Cancer Society Research Journal as serious professional /scientific /publication misconduct. Each manuscript submitted to the Gujarat Cancer Society Research Journal shall be subjected to thorough plagiarism check with professional plagiarism detection software as well as scrutiny by the editorial team before processing the manuscript, every time. Authors are themselves responsible to ensure that a submitted manuscript is free from plagiarism. Authors and reviewers are advised to be careful to maintain high ethical standards as per existing international norms.

Ethics

Do not use names and initials of patient or hospitals numbers, especially in illustrative material. When informed consent for the same has been taken from the patient, it should be mentioned in the manuscript. Any report of experimental investigation on human subjects must contain evidence of informed consents by the subjects and of approval by the institutional ethics committee.

Units and abbreviations

Avoid abbreviations in the title and abstract. All unusual abbreviations should be fully explained at their first occurrence in the text. All measurements must be in metric units, preferably with corresponding SI units in...
parentheses. No periods, no plural form (eg. '10 cm' not '10 cms').

**Name of Drugs**
Use only generic names of drugs. In case trade names (Proprietary drugs) are used, the manufacture should be identified clearly.

**Submission of Manuscripts**
All manuscripts must be submitted on gcsjournal2012@gcriindia.org along with scanned IRC approval letter duly addressed to the editors. One hard copy of the same along with covering letter through the Head of the department should be submitted.

By submitting the manuscript to Gujarat Cancer Society Research Journal, the authors agree that the work is original and free from plagiarism. It has not been submitted for publication/ is not under consideration for publication at another Journal. The journal expects that authors would authorize one of them to correspond with the journal for all matters related to the manuscript. The manuscript must be submitted with contributors' form signed by all the contributors.

**Manuscript Format**
Manuscript submitted using Microsoft Word, Font Times Roman, Paper size A4, Margin 2.5 cm from all four sides for Windows is preferred. Images should be submitted as JPEG file.

Manuscripts reporting clinical studies should, where appropriate, contain a statement that they have been carried out with ethical committee approval.

All manuscripts should include the following sections, in order. All sections are mandatory unless designated "optional":
- Title page
- Summary
- Main text
- Abbreviations
- Acknowledgments (optional)
- Contributions (optional)
- Competing interests
- References
- Tables
- Figures

**Types & size of manuscripts**
1. **Original article:** The text of original articles amounting to up to 3000 words (excluding summary, references and Tables) should be divided into sections with the headings Summary (unstructured - max. 200 words), Key-words, Introduction, Material and Methods, Results, Discussion, Conclusion, References (maximum up to 25), Tables and Figure legends.

2. **Case report:** It should have maximum limit up to 1000 words (excluding Summary and references) and should have the following headings: Summary (unstructured - max. 200 words), Keywords, Introduction, Case report, Discussion, Reference (max. up to 10), Table and Figure legends.

3. **Review article:** It should have summary (max. 200 words), Introduction/Historical Background, Discussion, Conclusion, References, Tables, Figure and Legends.

4. **Short communication:** The length of it should not exceed 1000 words and References 10.

**Note:** Discussion and conclusion can be combined in one section. Please do not add numbers before subtitles. Write subtitles and headings in sentence case.

**Title Page**
Include in the title page the manuscript title, author’s name(s), affiliations, and corresponding author’s phone/fax number and/or email. The name of the department(s) and institution(s) to which the work should be attributed.

**Title:** Use sentence format; only the first word and proper nouns should be capitalized.

**Authors:** The list of authors and contributors should conform to the guidelines set out by the International Committee of Medical Journal Editors. Provide full names of all authors. Eg: *Write surname before the first name* and initials of middle name (Patel Rajesh K) with institutional affiliation.

**Language and grammar**
- Uniformly American English
- Abbreviations spelt out in full for the first time
- Numerals from 1 to 10 spelt out
- Numerals at the beginning of the sentence spelt out

**Summary:** A structured abstract must be included with each original scientific manuscript with 4 clearly identifiable elements of content: rationale (goals of the investigation), methods (description of study subjects, experiments, and observational and analytic techniques), results (major findings), and conclusions. Except for the rationale, these sections should be preceded by headings (i.e., Methods, Results, and Conclusion). **Summary** should not contain citations to references, any images or math equations.

**Keywords:** Submit 5 keywords with the summary.

**Research manuscript sections (Font size: 12):** This should comprise of Introduction (comprising of Aims and Objectives), Materials and Methods, Results, Discussion with Conclusions. Cite every Reference, Figures and Tables mentioned in the text in Arabic numerals (e.g. 1,2,3).

**Introduction/Aims and Objective**
Briefly place the study in a broad context and highlight why it is important. Define the purpose of the
study or observation and its significance, including specific hypotheses being tested. Review carefully current state of the study research field citing key publications. Finally, briefly mention the main aim of the work and highlight the main conclusions.

**Materials and Methods**

Describe precisely your selection of the observational or experimental subjects (patients, including controls). Identify the methods, apparatus (including manufacturer’s name and address in parenthesis), and procedures in sufficient detail to allow others to reproduce the method. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited. Identify precisely all drugs and chemicals used, including their generic names, their manufacturer’s name, city and country in parenthesis, doses, and routes of administration.

**Results**

Provide a concise and precise description of the only important observations of experimental results, their interpretation as well as the conclusions that can be drawn. Do not repeat in the text all the data in the tables, and figures. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Avoid duplication and repetition of data in figures and tables. Specify the statistical methods used to analyze the data.

**Discussion**

Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible and limitations of the work highlighted. Future research directions may also be mentioned. This section may be combined with results.

**Conclusions**

This section is not mandatory, but can be added to the discussion.

**Tables** (Font size: 12)

Type each “Table” double-spaced on a separate sheet. Number “Tables” consecutively in Arabic numerals (e.g. 1, 2, 3) in the order of their first citation in the text and supply a brief title, which should be shown at the top of each table.

**Figures and Legends** (Font size: 12)

All “Figures” must be submitted on separate sheet, in JPEG finished format that is ready for reproduction. Figures should be numbered consecutively in Arabic numerals (e.g. Figure 1, 2, 3) according to the order in which they have been first cited in the text. If photographs of persons are used, the subjects or patients must not be identifiable.

**Legends** (Font size: 12)

Present the legends for figures on separate sheet (Font size: 12) using double-spacing with Arabic numerals corresponding to the Figures.

**Acknowledgements** (Font size: 9)

State contributions that need to be acknowledged.

**References** (Font size: 12):

References on separate sheet and must be numbered in order of appearance in the text. Identify references in the text in numerals in superscript and parenthesis. Omit month and issue number. List all authors, but if the number is six or more, list first three followed by et al. The references should be cited according to the Vancouver agreement (International Committee of Medical Journal Editors). Authors must check and ensure the accuracy of all references cited. Abbreviations of titles of medical periodicals should conform to the latest edition of Index Medicus. Some examples are shown below:

**Standard Journal**


**Online journal article**


**Chapter in a book**


**Online book or website**


**In press**


**Referees**

Generally, submitted manuscripts are sent to two experienced referee from our panel. The contributor’s may submit names of two to five qualified reviewers who have had experience in the subject of the submitted manuscript, but not associated with the same institution(s) as contributors nor have published manuscripts with the contributors in the past 10 years.
Contributors' Form

( to be modified as applicable and one signed copy attached with the manuscript)

Journal Title:
Manuscript Title:
Manuscript type: Original article / Review article / case report / short communication / letter to editor
Manuscript Number:

I/we certify that

1. I/we have participated sufficiently in contributing to the intellectual content, concept and design of this work or the analysis and interpretation of the data (when applicable), as well as preparation of the manuscript, to take public responsibility for it and have agreed to have my/our name listed as a contributor.

2. We surrender the rights to the corresponding author to make necessary changes as per the request of the journal, do the rest of the correspondence on our behalf and he/she will act as the guarantor for the manuscript on our behalf.

3. The manuscript is original work or compilation, without fabrication, plagiarism and fraud.

4. The manuscript neither is currently under consideration elsewhere nor will be submitted elsewhere for publication unless a final decision is made by Editors of journal as it is not acceptable

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3                                               ___________________________________   ____________________                 ____________________
4                                               ___________________________________   ____________________                 ____________________

(Up to 4 contributors for case report/ short communication / review)

5                                               ___________________________________   ____________________
6                                               ___________________________________   ____________________

(Up to 6 contributors for original studies)

Corresponding author: ____________________________
Mailing address: __________________________________
Phone: __________________________ Email: __________________________
Introducing M.Sc Medical Physics at GCRI

Pelagade Satish M  
Associate Professor  
Department of Medical Physics  
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat, India.  
Corresponding Author: satish.pelagade@gcriindia.org

The Gujarat Cancer & Research Institute, Ahmedabad is introducing M.Sc Medical Physics (Two Years) full time post graduate programme for the first time in Gujarat from June 2020. The course is affiliated to Gujarat University, Ahmedabad and recognized by Atomic Energy Regulatory Board (AERB), Mumbai.

Medical Physics is the application of physics to medicine. Ionizing radiation finds extensive applications in medicine, industry and research. With greater accent on radiation based diagnosis and treatment, there is a growing need of well-trained Medical Physicists in India and abroad. M.Sc in Medical Physics is a three years postgraduate course including one year compulsory internships. Its primary objective is to provide students a thorough background needed to pursue a career as Medical Physicist. Qualified candidates are eligible for RSO certification from AERB.

Medical Physicists are concerned with three areas of activity: clinical service and consultation, research and development and teaching.

Clinical Service and Consultation  
Medical Physicists are heavily involved with responsibilities in areas of diagnosis and treatment, often with specific patients. In radiation oncology departments, one important example is the planning of radiation treatment for cancer patients, using either external radiation beam or internal radioactive sources. An indispensable service is the accurate measurement of the radiation output from radiation sources employed in cancer therapy. In the specialty of Nuclear Medicine, physicists collaborate with physicians in procedures utilizing radio-nuclides for delineating internal organs and determining important physiological variables, such as metabolic rates and blood flow. Other important services are rendered through investigation of equipment performance, organization of quality control in imaging systems, design of radiation installations, and control of radiation hazards. The Medical Physicist is called upon to contribute clinical and scientific advice and resources to solve the numerous and diverse physical problems that arise continually in many specialized medical areas.

Research and Development  
Medical Physicists play a vital and often leading role on the medical research team. In cancer, they work primarily on issues involving radiation, such as the basic mechanisms of biological change after irradiation, the application of new high energy machine to patient treatment, and the development of new techniques for precise measurement of radiation. Significant computer developments continue in the area of dose calculation for patient treatment and video display of this treatment information. Particle irradiation is an area of active research with promising biological advantages over traditional photon treatment.

Medical Physicists are also involved in the development of new instrumentation and technology for use in diagnostic radiology. These include the use of magnetic and electro-optical storage devices for the manipulation of x-ray images, quantitative analysis of both static and dynamic images using digital computer techniques, radiation methods for the analysis of tissue characteristics and composition, and the exciting new areas of computerized tomography and magnetic resonance imaging for displaying detailed cross-sectional images of the anatomy. Medical Physicists are also engaged in research and development on imaging procedures utilizing infrared and ultrasound sources.

Teaching  
Medical physicists have a central position between clinic, technology development and science. Totally novel medical applications of physics in medicine continue to emerge. Medical Physicists have the opportunity to contribute more, owing to specific and high-level scientific attitude, to the development of the cancer cures of the future. Often medical physicists have faculty appointments at universities and colleges, where they help to train future medical physicists, resident physicians, medical students, and technologists who operate the various types of equipment used to perform diagnosis and treatment. They also conduct courses in medical physics and radiotherapy technology for a variety of graduate and undergraduate students.
Infrastructure and Facilities

The Institute is having Seven Linear Accelerators (with photon and or electron beams), One Telecobalt Unit, Two HDR Brachytherapy Unit, One Simulator, One CT-Simulator, Three Treatment Planning Systems and Adequate dosimetry/monitoring instruments. Apart from the equipments, the Institute has all basic amenities required for teaching including seminar hall, classrooms, library and audio visual teaching aids useful in effective teaching. The library has more than 3810 books, 68 national and international journals, internet facilities and access to proquest medicine.

Intake Capacity

Ten students per year

Duration of Course

The duration of the course shall be on full time basis for a period of three years from the commencement of the academic term (two years of degree programme with one year compulsory internship). The internship should be carried out in Gujarat Cancer & Research Institute or its associated institutes or in any AERB recognized internship centers. The degree will be conferred by Gujarat University, Ahmedabad.

Eligibility for Admission

Candidates who have passed final year of B.Sc., Science stream of examination in first class with Physics as major subject by a recognized university within India and the candidates who are in their final year/semester also may apply, subject to the condition that they have to produce the course completion certificate with first class at the time of admission to the course.

Admission Criteria

Every year, announcement of the course will appear in Gujarati and English news papers as well as on the website of GCRI (www.cancerindia.org). Admission will be given based on the merit list with weightage of personal interview as well as marks in graduation degree.

Fee Structure

For Boys: Rs.13500/- and for Girls Rs.12000/- per semester per student. The other fee such as University Examination fee has to be paid separately as per Gujarat University Regulations. The hostel accommodation charges are to be paid separately as per Gujarat University norms.

Contact

Dr. Shashank Pandya, Course Director
Dr. Satish Pelagde, Course Coordinator for further information on
Phone: +91-79-22688252, 22688066
Fax: + 91-79-22685490,
E-mail: medicalphysicsgcri@gmail.com
Information Brochure and Syllabus will be available on our website www.cancerindia.org from June 2020.
The Cancer Biology Department (Research Wing) was established in 1980 with three research laboratories. Today, it has flourished into six well equipped world class research laboratories, each having competent and enthusiastic team working on state-of-the-art research activities through various cancer research projects. The area of interest are particularly in the field of molecular epidemiology, cytogenetic, genomics, proteomics, epigenomics, stem cell research, bioinformatics, medicinal and pharmacogenomics. The Department has earned national and international fame through its more than 300 research projects, more than 400 research papers published in peer reviewed national and international journals and honours/ awards achieved at national and international forums.

Academics Activities: 
Apart from research, the Cancer Biology Department is also indulged in Academics Activities. It is also affiliated to Gujarat University (Life Sciences and Medical Microbiology) and M.S. University (Biochemistry) for PhD degree courses. Involved in educational activities such as dissertations to post graduate students of M.Sc., M.Pharm. and M.Phil. (both within and outside Gujarat), observership to postgraduate students from science and allied science and permitting Ph.D. students of many universities to perform their partial Ph.D. work at Cancer Biology Department.

In addition to the above academic activities, the Department has been involved in two new academic activities

2. Cancer Biology Finishing School

M.Sc. Cancer Biology (Life Science) 
From the year 2013, the Department has introduce the new course, M.Sc. Cancer Biology (Life Science), for the first time in India, in affiliation with Gujarat University, Ahmedabad. This MSc. Cancer Biology course is 2 Years Full Time Course and specifically designed for students who wish to acquire advanced education and training in biological sciences, pertaining to a disease that affects a large proportion of the global population. The course aims specific orientation on cancer, providing training in the modern practical, academic and research skills that are useful in academia and industry. The programme will culminate with a research project that investigates the molecular and cellular basis of cancer biology under the close guidance of active cancer research scientists. Through a combination of lectures, small-group seminars and practical classes, students will apply the knowledge gained towards translational research and development of new therapies. It will open avenues in Academics, and Research Institutes, Pharmaceutical Industries and Diagnostic Laboratories catering technology development, stem cell research, translational research, etc, and as Post-doctoral students in India and abroad to further advance their knowledge in the subject.

Eligibility for M.Sc. in Cancer Biology 
Graduates in one of the disciplines of Biological Sciences including Biochemistry, Microbiology, Biotechnology and Zoology of Gujarat University or any other University recognized as equivalent.

Admission Criteria for M.Sc. in Cancer Biology 
At the start of each academic year, announcement of the course will appear in Gujarati and English news papers as well as on the website of GCRI (www.cancerindia.org).

Admission will given based on the merit list with weightage of personal interview as well as marks in graduation degree.

Admission Procedure: Central Admission at Gujarat University Every Year. Each year total of 20 students will be admitted. Reservation of seats for candidates belonging to SC/ST/SEBC/PH etc. in both the categories will be as per rules of Gujarat University.

Fee structure is as follows:
• For Boys: Rs. 13500/- and for Girls Rs.12000/- per semester, per student.
• An examination fee of Rs. 500/- per semester is collected along with the examination form.
• The convocation fee is charged as per Gujarat University rules.
• Fees once paid shall not be refunded under any circumstances.
Cancer Biology Finishing School

Cancer Biology Finishing School Programme is a 4 months (16 weeks) **Full Time, Certification Course** run by Cancer Biology Department at The Gujarat Cancer & Research Institute, Ahmedabad, Gujarat, supported by Department of Science and Technology, Government of Gujarat, through Gujarat State Biotechnology Mission (GSBTM) under Gujarat Biotechnology Policy, 2016-21.

The opportunities in the fields of molecular biology and the potential to use this information in diagnostic procedures are escalating. With this in mind, the aim of Cancer Biology Finishing School Programme is to provide fundamental knowledge and training of molecular biology tools and its scientific concepts relevant to cancer biology.

The objective is to equip the aspiring students enrolled in Cancer Biology Finishing School Programme with all above-mentioned biotechnology facilities. The students enrolled in Finishing School Programme will be taught through lectures related to basic and advanced Genomics, Proteomics and Cytogenetic technologies. The medium of teaching will be English. Internal assessment of the students will be done by faculty members. The practical conducted during the course will be pertaining to recent molecular based biotechnologies useful in oncology. Relevant hands on practical training will comprise of DNA and RNA extraction from various biological fluids, quantification using various methods, qRTPCR, ddPCR, Immunohistochemistry, Flow cytometry, Microarray, Next generation sequencing (NGS), FISH, etc. They will also be actively involved in seminars, assignments, industrial/ research centre visit, personal interaction of students with eminent scientists, etc. Apart from teaching they will gain knowledge on fundamentals of Bioinformatics and Biostatistics, special emphasis will remain to nurture the students in the field of oncology, clinical research and cancer research.

Eligibility for Cancer Biology Finishing School

- Minimum 50% in following disciplines:
  - MSc Biological Sciences (Life Science, Biotechnology, Microbiology,
  - Biochemistry, Zoology, etc.) from recognized UGC University
  - BSc/MSc with MLT from recognized institute
  - Candidates who have pursued MBBS, MD, BDS, MDS, B.Pharm/M.Pharm

Intake Capacity and Admission Criteria for Cancer Biology Finishing School

Twice a year, 20 students will be admitted per batch

Announcement of admission of the course will appear in Gujarati and English news papers as well as on the website of GCRI (www.gcriindia.org). Admission will be given based on the merit list with weightage of personal interview.

Application form is available on GCRI website (www.gcriindia.org) and from the HR department of the Institute.

Fee Structure for Cancer Biology Finishing School

- **Science/Pharmacy students:** Rs.10,000/
- **Medical/Dental students:** Rs. 25,000/

Fees once paid shall not be refunded under any circumstances.

Certificate will be issued to the candidates only after successful completion of the course.
THE GUJARAT CANCER SOCIETY
OFFICE BEARERS 2019-2020

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Hon’ble Governor
Shri Acharya Devvrat

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Govt. of Gujarat

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Gujarat Cancer Society

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Govt. of Gujarat

Shri. Roopwant Singh, IAS
Secretary to Govt. of Gujarat

Nominated by
Gujarat Cancer Society

Finance Dept. (Expenditure)
Govt. of Gujarat

Shri. Kshitish Madanmohan
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Gujarat Cancer Society

Dr. Bharat Amin
Consultant Surgeon

Nominated by
Govt. of Gujarat

Former Director, GCRI

Dy. Director, GCRI
Dr. Pariseema Dave

Past Director
Dr. Shilin N Shukla

Director, GCSMCH & RC
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CEO, COC, Vasna
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