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Editorial

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Focusing on Oral Cancer Biology: Is this Only the Hope?

India tops in the prevalence of oral cancer in the world.[1] There is no significant change in treatment modalities over the past decades. Surgery, radiation and chemotherapy are still the main approach to treat oral cancer patients. Disappointingly, no considerable improvement in outcome of oral cancer patients is observed in recent decades because patients still frequently develop locoregional recurrences, distant metastases and second primary tumours.[2]

Growing complexity of oral cancer

It has been documented that the higher incidence of oral cancer is due to widespread habits of tobacco consumption in complex patterns particularly smokeless tobacco in the Indian population. According to Global Adult Tobacco Survey, India (2009-2010), 46.2% males and 11.3% females were tobacco users in Gujarat. If we focus on incidence of tobacco users developing oral cancer, it is not proportionate to the numbers consuming tobacco. This implies that all tobacco habituates do not develop oral cancer and also underlies the importance of genetic predisposition. It has been reported that approximately, 20% patients develop this malignancy without definite etiologic risk factors suggesting the role of additional risk factors.[3] There is growing evidences which suggest that human papilloma virus (HPV) contributes to increased risk of oral cancer, along with alcohol and tobacco use. However, the incidence of HPV associated oral cancer widely varies across the different regions of India.[4] Apart from this, herpes, epstain-bar virus (EBV) etc. also observed to play role in oral carcinogenesis. Thus, etiology of oral cancer is getting complex day by day. It was also observed that HPV associated oral cancers has more favorable prognosis and response to treatment than tobacco associated oral cancers. The association of treatment outcome with multifaceted etiology signifies the complexity of the underlying biology of oral carcinogenesis.

Rich cancer biology, but; poor oral cancer biology?

Major investments in basic science have created an opportunity for significant progress in clinical medicine. Researchers have discovered hundreds of genes that harbor variations contributing to cancer, identified genetic variability in patient's responses to treatments, and begun to target the molecular causes of cancer. Basic science also offers screening methods for certain cancers (HPV testing in cervical carcinoma, prostate specific antigen (PSA) levels for prostate cancer etc.) which lead to drastic decrease the incidence of various cancers. This approach of using molecular targets for screening and diagnosis of cancer is successful for other malignancies because of the great understanding of fundamental biology. Unlike other cancers, there are no specific screening and diagnostic tests that can help in screening and early diagnosis of oral cancer patients. It is thus of paramount importance to put further efforts into better understanding the biology of oral cancer to develop screening and diagnostic tests which will ultimately aid in early detection of oral cancer patients. This will facilitate to improve treatment outcome and hence eventually aid in decreasing the mortality rate.

Also, the understanding of cancer biology has led to the development and validation of several target-selective agents referred as targeted therapies with improved efficacy against chemotherapy (table 1). In addition, scientists have developed diagnostic tests based on genetics or other molecular mechanisms to better predict patient's responses to targeted therapy. For example, clinicians now commonly use diagnostic test to determine which breast tumors overexpress the human epidermal growth factor receptor type 2 (HER2), which is associated with a worse prognosis but also predicts a better response to the medication; trastuzumab. Finally, this helps to develop personalized medicines.

However, the clinical use of targeted agents is still lagging behind in the case of oral cancer due to lack of understanding of the underlying biology involved in oral cancer progression.

Molecular signatures of oral cancer

Oral carcinogenesis is a highly complex multifocal process that takes place when squamous epithelium is affected by environmental carcinogens which leads to several genetic alterations. "Field cancerization" refers to the potential of cancer cell to development at multiple sites and it has been observed during the development of oral cancer. It is evident that oral cancer develops over many years, and during this period, there are multiple sites of neoplastic transformation occurring throughout the oral cavity.[12] The multiplicity of the oral carcinogenesis process makes it difficult to interrupt the progression of cancer through surgical removal.

Table 1: list of targeted therapies in various cancers

Molecular targeted therapy	Cancers	Authors
EGFR-tyrosine kinase inhibitor	NSCLC Pancreatic cancer	Rosell et.al., 2012[5] Troiani et al., 2012[6]
Anti-EGFR monoclonal antibody	Colorectal carcinoma	Debucquoy et al., 2010[7]
B-Raf inhibitors	Melanoma	Lott, 2011[8]
Anti VEGF monoclonal antibody	Metastatic cancers of the Lung, Colon and Kidney	Kerr, 2004[9]
Proteasome inhibitor	Multiple myeloma	Mahindra et al., 2012[10]
Histone deacetylase inhibitor	Cutaneous lymphoma	Lansigan and Foss, 2010[11]

In the past years, several investigators have made efforts to study biology of oral cancer. Hence, understanding of the fundamental mechanisms behind oral cancer has improved, but this has also lead to a greater appreciation for the complexity of this disease process. Many studies have been published on this subject, however, data are still controversial. The study of oral cancer is particularly challenging as no single alteration is reported in every oral cancer patient. These genetic and biological heterogeneity of oral cancer has hampered the development of new strategies for screening, early diagnosis, prevention and treatment.

Genetic and molecular advances have revealed several genes and pathways involved in the development and progression of oral cancer. In general, cancer arises through the accumulation of genetic and epigenetic changes in genes acting in cancer-associated signaling pathways, causing the acquisition of cancer-related phenotypes including limitless replicative potential, self-sufficiency in growth signals, insensitivity to anti-growth signals, ability to evade apoptosis, invasion and metastasis, and angiogenesis.[13] Oral cancer gains limitless replicative potential through abrogation of the p53 and retinoblastoma (Rb) pathways that disturb cell cycle regulation. It may be further supported by telomerase reverse transcriptase (TERT) expression leads to immortalization. Moreover, oral cancer becomes independent from growth factors by alterations in the epidermal growth factor receptor (EGFR) signaling pathway.[14] Oral cancer may escape from the growth inhibitory transforming growth factor-β (TGFβ) pathway through somatic mutation or chromosome loss of key genes. This pathway seems to be interconnected to the nuclear factor-κB (NF-κB) pathway.[13] Then PI3K–PTEN–AKT pathway is frequently activated in oral cancers through somatic mutations and genetic changes.[13] Further, MMPs as well as VEGF expressions also support the progression of oral cancer through providing the capacity of invasion and metastasis. Hence, oral cancer is complex multifactorial disease impacting nearly all hallmarks of cancer. Therefore, multi-faceted molecular evaluation may logically be required to estimate the changes related to early, intermediate and late end points like prognosis and treatment outcome. Thus, there is much more that needs to be understood before we are able to make a significant impact on oral cancer management.

The malignancy is usually preceded by premalignant lesions like leukoplakia, erythroplakia and oral submucous fibrosis. According to the type of lesion, the transformation rate varies from 0 to 20% in 1–30 years.[15] However, there is dearth of understanding to identify which precancerous lesion will turn into malignancy. Our laboratory is constantly looking for markers which can help to delineated high risk patients with these precancerous lesions. Progressive increase in glycosylation from healthy individuals to patients with oral precancerous lesions to oral cancer patients is observed.[16-18] This observation might be useful in early identification of high risk precancerous lesions. Recent discovery of better prognosis of HPV positive oral cancer patients as compares to HPV negative oral cancer patients is a ray of hope in oral cancer management.[19] However, appropriately powered, well designed studies should be conducted in future to address important clinical issues of HPV status in oral cancer in terms of clinical outcome and treatment response. In addition, saliva, a non-invasive tool is a mirror of human health. Among all the malignancies, oral cancer is one such malignancy where saliva examination for detection can show the greatest benefit because of its direct contact with oral cancer lesions.[15] Our laboratory has observed that several biomarkers are elevated in saliva of oral cancer patients compared to controls.[15,17] Thus, in-depth analysis of these salivary biomarkers has a great potential to be clinically useful noninvasive biomarkers for screening, diagnosis and treatment monitoring of oral cancer patients. Further, interest in cisplatin-based neoadjuvant chemotherapy has recently been emerged by its benefits for survival in locally advanced oral cancer patients. Recently, Perrone et al., (2010) suggested that the loss of function of mutant p53 proteins may predict a significant low pathologic complete remission rate

and suboptimal response to cisplatin- based neoadjuvant chemotherapy in patients with oral cancer[20]. However, the association of p53 status and cispaltin cytotoxicity depends on several other factors, like tumor cell type, the presence of other genetic alterations etc. further studies on such genetic alterations are required to determine the role of p53 in cisplatin cytotoxicity.

Now-a-days, multi-institutional clinical trials are being conducted to investigate the utility of molecular targeted therapy compared to conventional cytotoxic chemotherapy for the treatment of oral cancer patients.[2] Most of the targeted agents mentioned in table 1, including those targeting EGFR receptors, VEGF and VEGFR, Raf, and proteasome, are also deregulated in oral cancer, thus may provide potential therapeutic benefits for oral cancer patients. Thus, it is clear that better understanding of the molecular and biological profile of oral cancer should facilitate the development of more efficient targeted therapies. Current clinical trials with targeted agents in oral cancer are likely to bring promising directions decreasing the risk of tumor recurrence and improving survival of patients with oral cancer.

In conclusion, understanding the oral cancer biology today will certainly improve oral cancer screening, diagnostics and treatment modalities of tomorrows; the only anticipated remedy to strengthen fight against oral cancer.

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Shri R. J. Kinarivala Research Oration Award

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Potential Role of Curcumin in Cervical Cancer

Cervical cancer is the second most common cancer amongst women. Out of the estimated 5,10,000 new cases occurring globally annually, a 50% mortality rate is seen in them. India accounts for 132082 new cases, with a mortality of 74118 cases every year. In most cases the etiology for cervical cancer is associated with persistent infection with high risk HPVs. The most common high risk HPVs being HPV16 and 18. Most cervical cancer cases present at an advanced stage of disease when the cure rate is poor and the patients are unable to tolerate the toxic effects of radiotherapy and chemotherapy. Hence, there is a need for drugs that can decrease the toxicity of radiotherapy and chemotherapy.

Carcinogenesis is a multistep process involving genetic and epigenetic changes. One-third of all cancer deaths are preventable and diet is closely linked to cancer prevention. Epidemiological and experimental research has centered the attention on dietary phytochemicals to be developed as cancer chemopreventive agents. These phytochemicals are capable of inhibiting transformation, hyperproliferation, invasion, angiogenesis and metastasis of various tumors, thus halting, delaying or reversing the process of carcinogenesis. Out of the many such explored molecules curcumin (diferuloylmethane), a polyphenolic phytochemical obtained from the dietary spice turmeric which is the rhizome of Curcuma longa is widely studied. It primarily consists of various curcuminoids including curcumin-77%, demethoxycurcumin-17% and bisdemethoxycurcumin-3%. It is a well known chemopreventive agent that inhibits cancer cell proliferation by arresting them at various phases of the cell cycle, depending upon the cell type. It also has anti-oxidant, anti-inflammtory and anti-tumorigenesis activity, with no or very low pharmacological toxicity. Curcumin reduces overall cancer formation and metastasis. It can suppress the cell growth pathways by inhibiting cellular protein kinases such as PKC, JNK, EGF receptor kinase, leading to growth inhibition. It also blocks the NF-κB cell survival pathway and inhibits C-Jun/AP1 function, MAPK, Growth Factor receptor protein kinase, cyclin D1, and inflammatory cytokines. One of the important mechanisms of prevention of carcinogenesis by curcumin is downregulation of several cytochrome P-450 enzymes and induction of phase II metabolizing enzymes such as glutathione S-transferase. Its anti-angiogenic effect is due to inhibition of VEGF receptor and angiopoietins.

Curcumin induces apoptosis through both mitochondrial dependent as well as mitochondrial independent mechanisms. In most cells, curcumin sequentially induces activation of caspase-8, cleavage of BID, loss of mitochondrial membrane potential, opening of transition pores, release of cytochrome C, caspase-9 activation, caspase-3 activation and cleavage of PARP. It inhibits anti-apoptotic genes BCL-XL, BCL-2 and IAPs.

In vivo studies in animal models of chemical and radiation induced prostatic cancer, hepatic cancer, esophageal cancer, breast cancer and neuroblastoma, suggest that curcumin may provide a valuable tool for the development of therapeutic combination in these cancers. Curcumin abolishes the induction of NF-κB binding to the DNA, blocks IKK activation, IκBa phosphorylation and degradation as well as NF-κB P65 translocation into the nucleus. By this mechanism it overcomes the resistance conferred by NF-κB activation seen by some anti cancer agents such as cisplatin, vincristin and 5-fluorouracil. Curcumin inhibits COX-2 and LOX, thus inhibiting inflammation. The combination of curcumin with cisplatin resulted in a synergistic anti-tumor activity by decreasing the expression of C-MYC, BCL-XL, c-IAP-2, NIAP, XIAP in human hepatic cancer cell lines. In our laboratory it has been shown that curcumin augments apoptosis mediated by cisplatin in Hep-2 cell lines, sensitizes vinorelbine induced apoptosis in human lung squamous carcinoma cell line H520. However, curcumin does not affect normal cells. It directly competes with the ATP binding site of MDR pump by inhibiting the drug efflux and

increases the intracellular concentration of chemotherapeutic agents. By inhibiting glutathione synthase, it also interferes in the functioning of MDR drug efflux pump, which requires a steady supply of glutathione. The molecular targets of curcumin are similar to those of cancer therapeutics and hence, curcumin is likely to induce apoptosis in cancer cells. Curcumin has been shown to augment the cytotoxic effects of chemotherapeutic drugs including doxorubicin, tamoxifen, cisplatin, campothecin, daunorubicin, vincristin, and melphalan. It also contributes to the reversal of resistance to adriamycin by suppressing the P-glycoprotein expression through inhibition of the PI3K/ Akt/ NF-κB signalling cascade.

Radiation activates NF-κB and induces expression of COX-2, TNF, BCL-2, which in turn mediate radio-resistance in the long run. Curcumin has been shown to sensitize prostate tumor cells to radiation through down-modulation of NF-κB regulated BCL-2 expression. Curcumin mediated radio-sensitisation may also be mediated by effects on EGFR signaling pathway and downstream MEK phosphorylation of ERK 1 and 2. It potentiated radiation induced reactive oxygen species (ROS) generation leading to sustained ERK 1 and 2 activation which is required for radio-sensitisation. The significant radio-sensitisation achieved by low dose of curcumin at clinically relevant dose (2-6 Gy) has implications for improving radiation therapy in radio-resistant tumors such as the tumors of the uterine cervix. Curcumin has been studied for its chemopreventive, chemosensitizer and radiosensitizer potential in a wide variety of cancers, in both preclinical studies and in clinical trials. It regulates diverse molecular targets. It does not cause any toxicity. Clinical trials with curcumin have been reported for colorectal carcinoma, urinary bladder, uterine cervical intraepithelial neoplasia, oral leukoplakia, melanoma, etc. These studies suggest that curcumin has chemopreventive action in these cancers. It is observed that there is no treatment related toxicity with oral dosage of upto 10,000 mg/day. Beyond 8,000 mg/day the bulky volume of the drug is unacceptable to the patients. Dosage of 12,000 mg/day is associated with mild gastrointestinal side effects and that too after a prolonged use for 3 months. The serum concentration usually peaks at 1-2 hrs after oral intake of curcumin and gradually declines within 12 hrs. Thus developing curcumin as an adjunct to standard chemotherapy and radiotherapy is an important goal. It may offer a therapeutic advantage in the clinical management of various refractory tumors over other standard modalities.

The reason why cancer therapies might fail and tumors develop relapse is because these strategies do not target rare tumor cells or so-called cancer stem cells. It is believed that these cancer stem cells are often resistant to chemotherapy and radiation, and treatments that substantially reduce tumor mass by removing proliferating tumor cells often fail to target these stem cells and cure patients completely with certain cancers. In this context, curcumin seems to offer an ideal agent because over the last two decades, significant evidence has indicated anticancer potential of curcumin. In fact, it is very encouraging to notice that unlike many "targeted" chemotherapeutic drugs that suffer from toxicity and resistance concerns, curcumin by itself can target several of these molecular targets/pathways without any associated toxicity or resistance. In fact, newer data suggest that in addition to its chemopreventive ability, curcumin can sensitize many human cancers to chemotherapy and radiation, by increasing apoptosis as well as afford protection against the toxicity of these treatment regimens. Data from both in vitro and in vivo studies have supported the potential chemosensitizing ability of curcumin in multiple cancers and has provided evidence for curcumin's use singly or as an adjunct to current chemotherapeutic drugs. In addition, curcumin also suppressed the paclitaxel-induced expression of several antiapoptotic (XIAP, IAP-1, IAP-2, BCL-2, and BCL-XL), proliferative (Cox-2, c-myc, and cyclin D1),and metastatic (VEGF, MMP-9, and ICAM-1) proteins. Generation of ROS and activation of the JNK pathway is a frequent manifestation of pro-apoptotic ability offered by many chemotherapeutic drugs. Data suggest that NF-κB may contribute to cisplatin-induced chemoresistance in cervical cells and highlights the potential applicability of combination therapy with NF-κB inhibitors such as curcumin in this scenario. Curcumin is also shown to downregulate taxol-induced activation of NF-κB and phosphorylation of serine/threonine kinase Akt in cervical cells and embryonic kidney cells.

Curcumin may be an ideal adjunct for radiation therapy if it has radiosensitizing properties. In support of this, it has been demonstrated that pretreatment of two cervical cancer cell lines HeLa and SiHa with curcumin prior to ionizing radiation resulted in radiosensitization of cancer cells but had no effect on normal human fibroblasts. Such effects of curcumin were due to its ability to sensitize cancer cells for increased production of ROS, which in turn led to activation of ERK1 and ERK2. These data provide a novel mechanism of curcumin mediated radio-sensitization and suggest that curcumin may be an effective radio-sensitizer in cervical cancer. In a pilot study we studied the role of curcumin as a radio and chemo sensitizer.[37] advance cervical cancer patients

were recruited for this study. Their cervical scrapes/ cervical exfoliated cells were collected at base line (untreated cases), at 1 month and at 6 months post treatment. They received external radiotherapy for 27 days along with weekly carboplatin and brachytherapy, along with curcumin or placebo, which was continued for 3 months. After completion of treatment, samples of cervical scrapes were collected. All the samples i.e. at base line, 1 month follow up, at 6 months follow up were evaluated for the presence of HPV. If positive for HPV, then the viral load and expression of proteins PCNA and p16INK4a was done. No statistically significant change in any of the markers was found between those receiving curcumin and placebo.

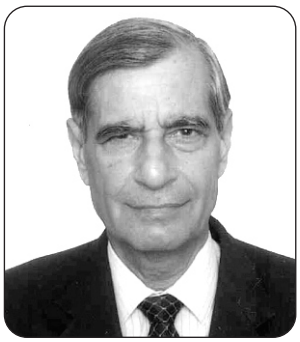
Curcumin is considered as a pleiotropic molecule interacting with multiple signaling pathways. The molecular basis of anti-carcinogenic and chemopreventive activity of curcumin is attributed to its effect on diverse targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators, and cellular signaling molecules. Chemosensitization has been observed in several cancers of the breast, colon, liver, lung, prostate, bladder, cervix, ovary, head and neck, etc. Similar studies have also revealed that this agent can sensitize a variety of tumors to gamma radiation. How curcumin acts as a chemo-sensitizer and radio-sensitizer has also been studied extensively. For example, it downregulates various growth regulatory pathways and specific genetic targets including genes for NF-κB, Stat-3, Cox-2, Akt, antiapoptotic proteins, growth factor receptors, and multidrug-resistance proteins. Although it acts as a chemo-sensitizer and radio-sensitizer for tumors in some cases, curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy induced toxicity. The protective effects of curcumin appear to be mediated through its ability to induce the expression of antioxidant enzymes.

Although, studies have established that curcumin is safe and well tolerated in animals and humans, it is still not approved as a chemotherapeutic agent because of its poor bioavailability. Hence, numerous strategies have been designed to overcome the limitations of curcumin, which includes the use of natural and synthetic analogues.

Bisdemethoxycurcumin was identified to be more active than curcumin for its anticarcinogenic property. Similarly demethoxycurcumin and the synthetic analogues of curcumin such as FLLL11 and FLLL12 were found to be more potent than curcumin in various cancer cell lines. Bioavailability as well as the biological activity of curcumin is improved by the use of piperine as an adjuvant (it increased the bioavailability upto 2000%) liposomal and nanoparticle based formulations. Furthermore, the anti tumor activity of paclitaxel was greatly enhanced by liposomal curcumin. It is also interesting to note that curcumin loaded into solid lipid nanoparticles significantly enhanced its bioavailability. Use of a curcumin-based, anticancer therapeutic strategy would also allow use of lower doses of chemotherapeutic drugs and radiation but still achieve much higher antitumor efficacy and yet lower toxicity and resistance in the management of variety of human cancers. Thus combining curcumin with current chemotherapy and/or radiation may also reduce the need for palliative surgery in some instances. These effects combined with its ability to prevent depression, fatigue, neuropathic pain, lack of sleep, and lack of appetite, all symptoms that are induced by cancer and cancer treatment, makes curcumin an ideal agent for cancer patients.

"Let food be thy medicine and medicine be thy food."
Hippocrates

Shri Madanmohan Ramanlal GCRI Luminary Award



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50 Years of the Gujarat Cancer and Research Institute: Past, Present and Future

I have tried to incorporate the progress of the Gujarat Cancer and Research Institute (GCRI) over 50 years in my today's talk. The foundation of this institute was laid on 26 January 1962 by Shree Mehdi Nawaz Jung, Governor of Gujarat. At that time, New Civil Hospital Campus had 1500 beds with multiple specialties. Cancer patients were treated as a part of general surgery. It was proposed to have a separate hospital exclusively for treatment of cancer patients. Hence that was the begining of Cancer Hospital. In 1964, it was a small beginning in the giant campus of 1500 beds New Civil Hospital, Ahmedabad.

In 1965, M P Shah Cancer Hospital was started, with a team of dedicated doctors in their field including Dr B K Sinha as surgeon, Dr N L Patel as radiologist, Dr Tapan Hazare as radiotherapist, Dr M T Bhatia as anaesthetist and Dr Sehgal as pathologist. It required dedication of staff, support of public, donation and inflow of patients for survival.

This gave us stimulus to be **"firsts"** in developing the latest anaesthesia techniques at GCRI. Our aim was to achieve recognition as most advanced postgraduate institute in the medical world of India and abroad. The Indian Society of Anesthesiologists (ISA) awarded "Rukamani Pandit Research Award" to GCRI in 1985 for research on Laryngeal Mask Airway. More awards followed with introduction of newer drugs like Etomidate, Propanidid and Epidural and Nerve block techniques. First ventilators were introduced in GCRI way back in 1968 and thereafter we had IPPV ventilators like "Siemen 800" in every theater of GCRI. First epidural anaesthesia was practiced for operative and postoperative analgesia at GCRI in 1973 after my return of one year training in King's College and Hospital, London. First ICU, first Day Stay Unit and first postoperative ward were started in GCRI around that time.

Mile stones : Progress of GCRI

In 1968, Government of India started National Cancer Control Program and Wahi Commission visited us to include GCRI in this program. Thus, yearly grant was sanctioned for GCRI under this program.

In 1966, MP Shah Cancer Institute was under Government of Gujarat. The staffs were under direct control of the superintendent, New Civil Hospital, Ahmedabad. All the doctors were appointed as teachers in B J Medical College, Ahmedabad. Accordingly all the doctors of GCRI were appointed teachers and examiners of Gujarat University as soon as all relevant formalities were completed.

In 1972, M P Shah Cancer Hospital was transformed to Gujarat Cancer and Research Institute under leadership of the medical director Dr T B Patel. New teaching and training methods were adapted. Postgraduate students were given practical training on patients or on dummies as required. Our training program of MD and DA in anaesthesia, were very popular and made every student proud to be a GCRI post graduate.

From 1984 onwards, Pain Conferences and training programs in pain management were held regularly, every year. Indian Society for the Study of Pain, which is an Indian Chapter of International Association for the Study of Pain, was started in 1986 at Ahmedabad and Varansi. This gave a new direction to study pain control and related research projects in India. Recognisation of GCRI as most advanced "Pain Relief Centre" was achieved and maintained thereafter.

ICMR project on home care of terminal cancer patients in rural area, under care of primary health center of Bavla and Oudh-Pirana, was sanctioned for 3 years. It was based on research on terminal cancer pain in patients of rural areas of Gujarat. Eighty percent of patients attending GCRI, were from rural area of Gujarat. They were visited by ICMR appointed staff and were treated at home for their pain. Free oral morphine tablets and other medicines were collected by relatives from nearby primary health center. Some of the conclusions of this ICMR study were as follows-

1. Drugs like oral morphine tablets should be delivered to terminal cancer patient at primary health center.

2. Oral morphine tablets should be given free of cost by goverment of India to patients through regional cancer centers throughout India.
3. Oral morphine tablets and other analgesic drugs like Fentanyl transdermal patch should be allowed to be dispensed from chemist shops against duplicate prescription of a registered medical practitioner. We are glad to note these conclusions were later adopted by government of India on recommendation of members of parliaments of Gujarat.

Vasna Project was started as a training center for relatives of terminal cancer patients. Care givers were trained to take care of these patients at home. In western world, the concept of Hospice is very popular. In India due to shortage of indoor hospital beds,curable and acute diseases are given priority.Vasna center is established to provide Hospice Care to terminal cancer patients having severe pain or symptoms. Later on they are treated at home by 'Home Care Team'. This is possible in India because of strong family support and social culture. Hon. Shri R Venkatraman, President of India, inaugurated Vasna Hospice Center on 4 April 1988.

Indian Association of Palliative Care was established in 1994 at Ahmedabad and Varansi. Training in palliative care and International conferences of palliative care were sponsored by W.H.O. all over the India. In 1995, 2nd International Conference of Palliative care was held at GCRI on 6 - 7 February1995. Dr Twycross and Ms Gillian Burn, WHO trainers in Palliative Care, conducted several training workshops in GCRI for doctors and nurses. WHO sent Dr Pamela Sutton to GCRI for three months to train nurses for diploma in palliative care and training of relatives for Home Care of terminal cancer patients

During my tenure, as Head, Department of Anaesthesia for about 30 years at GCRI, we tried to achieve following goals:

1. WHO included a chapter on "Home care of terminal cancer patient" as an alternative to costly hospital care till death, which was popular in Europe.
2. Dr Jan Stjerward, WHO chief for cancer care, visited Ahmedabad several times during 1980-90s.
3. WHO sponsored Miss Sally Wimbles, senior nurse to Ahmedabad for a period of one year to initiate nurses' training programs in palliative care at GCRI. WHO also sponsored repeated visits of Matron Mrs Gillian Burn (Gillyben) to GCRI to help us in establishing home care programs for terminal cancer patients.
4. Oral Morphine tablets were supplied by WHO to all recognized regional cancer centers for advanced cancer patients.
5. Government also sanctions budget for pain relief and palliative care, home care of terminal cancer patients and to develop Hospice at Vasna Center, as WHO training center of palliative care. WHO is running similar International Training Center at Calicut in Kerala.
6. Government's priority is to spend medical budget on infective and curative patients. This should not affect the care of terminal cancer patients.

Future-Post Modi era

1. Restriction of funds through government health care program will continue due to inflation.
2. Advice through telemedicine or mobile phone and follow up of patients is possible for those coming from far of places of India or even Gujarat.
3. Day care units need to be encouraged to cut down the cost of hospitalization.
4. Home care programs of incurables is need of time to minimize suffering, cost and to improve quality of life of cancer patients.
5. Cost of medicines, doctors and nurses will get higher in future; hence day stay unit's cancer treatment needs to be encouraged.
6. Vasna unit can act as centralized unit for providing training of relatives, volunteers, doctors and nurses. It should be developed as treatment center for terminal cancer patients
7. Vasna unit can also be used for teaching center for MD in palliative care and other courses for nurses, consultant doctors and family physicians, in palliative care.
8. Terminal cancer care patients should be provided proper care while still living in their home, through a well-established "Home Care Plan"

Acknowledgement: I am thankful to the Director, Gujarat Cancer and Research Institute and Oration Committee for awarding me "Shree Madanmohan Ramaniklal Luminary Oration" award for the year 2014.

I am also very thankful to all doctors of department of anaesthesiology for their kind help and guidance in preparation of this talk. I am also thankful to department of photography for supporting me in collecting photographs and documents for this presentation.

Dr. T.B. Patel Oration Award

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Challenges in Oncology: Professionalism, Ethics and Practice

Cancer is a major cause of morbidity and mortality in developing and developed countries alike. The diagnosis of cancer often leads to catastrophic personal health expenditures. Such expenditures can ruin entire family's stability, especially when combined with an absence of what are seen as acceptable services. India spends less than 1.5% of its GDP on health for central and state government funded health care out of a total of 4% public + private spend on health care. To add to problem is poor public health expertise, inadequate medical and health professional education.

The doctors are reluctant to take responsibilities for rising medical cost. In some countries sometimes doctors receives payment up to 27% percentage of health care spending as physician fee. There have been reports of over-diagnosis and overtreatment in cancer, where complex treatment advised and more expensive treatment executed, however the results do not prove to be superior. In 2010, medical errors are reported to cause death in nearly 50,000 patients in USA as reported in the journal 'Health Affairs'. It was attributed to problem in teaching in hospitals and health system recognized the cultural change across all phases of medical education for patient safety.

In 2013, ASTRO Conference dedicated a plenary session for choosing the treatment wisely such as, in women less than 50 years of age with early stage breast cancer 'do not' initiate whole breast radiotherapy as part of conservative therapy without considering short treatment course and 'do not' initiate management of low-risk prostate cancer without discussing active surveillance etc. etc.

There has been always ethical dilemma arise when there is an internal dissonance between what should be done and what is being done. It should be questioned what is right for the patient. Is it that is decided by guidelines invented by committee in one environment? Not necessarily the new is always better. Therefore judgement for an individual is necessary and accordingly skills applied. Generally it is notices that there is lack of good doctors in basic medicine. The ethical dilemma is further expanded due to new century advances related to 'site and sub-site specialization' of medicine, faculty reward systems, application of 'Publish or Perish' and generational gaps. The holistic approach of medicine reduced to traces with coning of vision. It can be seen that development are limited only to urban population (private super-specialties) however, rural population largely ignored. The application of new technology many-a-times is oriented to paying capacity and capita generation rather than improvising healthcare.

Due to rapid advances in technology, the whole system veering towards technology oriented rather than clinical oriented management. Clinician immediately jumps to CT/MRI rather than clinical judgment. In the process, although the efficiency increased but critical thinking and reasoning is almost obsolete. As new technology largely dependent on pressure of peers and economic consideration of industry, it may not be always superior. Public sector recognizes that fewer than 5% patients need specialized technology in treatment of cancer, yet there is a dramatic increase in the state-of-art-radiation oncology practices clustered around urban and essentially high paying capacity population. There is profound influence of a market economy with perverse financial incentives threatens to reduce the medical profession to a lowest common denominator. If physician practice recast as a profit center rather than a group of healers, will lead to erosion of patients' TRUST!

The medical graduate and physician of the 21stcentury are expected to possess basic competencies of effective communication, basic clinical skills of using science to guide Diagnosis, Management, Therapeutics and Prevention, the social and community health care, moral reasoning and ethical judgment and Professionalism and role recognition. A profession has been defined as an occupation that regulates itself through systematic, required training and collegial discipline; that has a

base in technical, specialized knowledge; and that has a service rather than a profit orientation, enshrined in its code of ethics. Therefore professional should be bearing (a) technical skill and craftsmanship, renewed by continuing education (b) a sense of social responsibility (c) knowledge of history, literature and the arts (d) personal integrity and grace of humility and (e) faith in the meaning and value of life. The professional should not be dishonest, greedy and self serving.

In the modern education system there is gradual disintegration of education community, disappearance of the master clinician, loss of role models and loss of mentors. It is known that individuals from different generations eschew different goal. We should be aware, that current individuals are no less professional or altruistic than their predecessors. Their core of professionalism remains intact, it is the duty of teachers to hit the core and guide them. Administrators need to focus on revitalizing profession giving attention to faculty development, system of evaluation providing strong institutional support.

In India, Veda's are ancient hymns, prayers and teachings which based mostly on religious and moral codes. Those are also the supernaturalistic sources of the ancient Indian medicine. These describe healing methods, references to disease, injuries, fertility, sanity and health. These are Indian naturalistic medicine dating 1st century AD and beyond. We all remember the 'Hippocratic oath', while the oath also exists in Charaka Samhita. According to this oath, physicians swear to speak only the truth, not to cause another person's death/injury, speak words that are gentle, eat no meat on the day of surgery, not to carry arms etc.

What we need to do:

- To think about our conduct as educationists and role models for our peers and students.
- To think about updating ourselves with regard to our skills.
- To look towards pragmatic medicine (such as in socialist health care health delivery in the open market).
- The Americans have realized the folly of over treating and are now going back to pragmatic oncology practice, that has its origins in Britain, Canada and Australia and other countries where health care is a government and societal responsibility and largely out of commercial interests.
- It is so much more relevant in India given out economic and social framework to provide reasonable and affordable health care.

We are still the "Good Doctor"

We are the chosen ones!!
Still the most noble profession!!
Still the most hard working people!!

"No one should have to choose between medicine and other necessities. No one should have to use the emergency room every time a child gets sick. And no one should have to live in constant fear that a medical problem will become a financial crisis."

Brad Henry

Searching Inroads in Triple-Negative Breast Cancer

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Summary

Triple-negative breast cancer (TNBC) is a unique type of breast cancer, which lacks the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) on the cell surface. Current literature reveals that TNBC itself is not a single disease and it has many molecular subtypes with variable prognosis. It is akin to non Hodgkin's lymphoma, which also bears a negative terminology; likewise TNBC includes different sub entities. There are two broad subtypes of TNBC (basal like and non-basal like) defined either by gene expression profiling or by immunohistochemistry (IHC) markers. Basal like TNBC express basal markers like CK5/6, CK14, CK17 and epithelial growth factor receptor (EGFR). Consistent with its more aggressive biology this BC subtype very often manifests itself as an interval cancer diagnosed between screening mammograms. More than 90% of BLBCs/TNBCs exhibit an invasive ductal histology and high histological grade. Anthracycline and taxane based chemotherapy is still standard of care however limited data are available for its impact on overall outcome of TNBC. Dose dense chemotherapy has been tried and it improves pathological complete remission (CR) but whether it translates into survival advantage is still controversial. Platinum compounds have theoretical advantage of being more effective in TNBC however clinical data regarding optimal use of platinum compounds in TNBC is still lacking. The majority of studies indicate a negative impact of a triple negative (TN) or basal like (BL) phenotype on patient prognosis. Peak risk of recurrence occurs within the first 3 years after initial treatment of the disease with the majority of deaths occurring in the first 5 years, and after diagnosis of metastatic disease, a significantly shorter survival was observed in both BL and TNBC. Till date, there are many unresolved issues related to prognosis and therapeutics of TNBC which need to be addressed.

Keywords: Breast cancer, Triple negative, Basal like, EGFR

Triple-negative breast cancer (TNBC) is a unique type of breast cancer, which lacks the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) on the cell surface. Targeted therapies directed against these receptors are not effective in this subset.[1] Biologically; TNBC is associated with a more aggressive clinical course and worse clinical outcomes than its non-TNBC counterpart. A recent cohort study of 1601 patients with breast cancer demonstrated that those with TNBC had a greater risk for systemic recurrence and death than did those with non - TNBC. These events occurred mostly within the first 5 years after diagnosis, as the risk for systemic recurrence for patients with TNBC peaked at 3 years and declined rapidly afterwards, whereas non - TNBC patients' risk for recurrence was constant.[2] Patients with TNBC have a higher rate of visceral metastasis and their tumors are more likely to harbor abnormalities in the p53 and BRCA1 genes compared with patients with non-TNBC.[3,4,5] Current literature reveals that TNBC itself is not a single disease and it has many molecular subtypes with variable prognosis. It is akin to non Hodgkin's lymphoma, which also bears a negative terminology; likewise TNBC includes different sub entities.

Molecular heterogeneity of TNBC subtypes

TNBC is not a single disease. There are two broad subtypes of TNBC (basal like and non-basal like) defined either by gene expression profiling or by immunohistochemistry (IHC) markers. In most cases, they are negative for ER, PR and HER-2 and are positive for cytokeratins (CK) 5/6 and epithelial growth factor receptor (EGFR). Although, the majority of cases of basal like breast cancer (BLBC) are triple-negative, 5-15% are not. TNBC tumors are histologically heterogeneous and may include infiltrating ductal carcinoma (basal-like and non-basal-like) and other subtypes such as medullary, squamous, and apocrine.[6,7] However, BLBC and TNBC overlap significantly and in day to day usage the term TNBC is commonly understood to include BLBC.

Basal like TNBC express basal markers like CK 5/6 and EGFR. All BLBC are not TNBC some of them express ER and Her2/neu. Non-basal TNBC has a better prognosis. Basal like subset comprises 10-20% of all tumors and approximately 50-75% of TNBC, it has a distinct cell type of origin or developmental stage of arrest. More than 50% of tumor are Tp53 mutated, highly proliferative and BRCA1-associated/defective homologous recombination mediated DNA repair.[6,7]

Divergences between TNBC and BLBC

The term 'basal-like' (BL) stems from the resemblance of its expression pattern to the one observed among normal basal/myoepithelial cells of the breast, which comprise high molecular-weight basal CKs (CK5/6, CK14, CK17), vimentin, p-cadherin, aB crystalline, caveolins 1 and 2, as well as the EGFR.[7] Consequently, it has been indicated that BLBCs arise from the outer (basal) layer of normal breast ducts (i.e. myoepithelial cells) or perhaps more accurately originate from a stem cell precursor of basal myoepithelial cells. In contrast, luminal cancers may originate from a more differentiated luminal precursor cell. A number of subsequent reports support this hypothesis of increased expression of

keratin 14 in contrast to low expression of keratin 18 are characteristics of cells carrying the potential to self-renew and differentiate into both luminal and myoepithelial cells.[8,9,10,11]

BLBCs commonly express an 'embryonic stem-cell signature'. BLBCs exhibit well-established characteristics of epithelial-mesenchymal transition, such as loss of epithelial characteristics and acquisition of a mesenchymal phenotype. BLBCs frequently express a CD44+/CD242 phenotype which has been associated with a 'stem-cell' phenotype.[8,12,13] Despite the common understanding that BLBC carries unfavorable (and therefore clinically relevant) prognostic features, no widely accepted and clinically usable (i.e. robust, reproducible and standardized) assay is currently available to define BLBC status, and there is good but imperfect concordance between the TNBC and BLBC demonstrating that heterogeneity within groups defined by either one of the above classification methods poses a significant limitation to each method. A retrospective analysis of the WSG AM 01 high-risk breast cancer (BC) trial, 33% of 66 TNBCs were clustered as BL by k-clustering of 24 protein expression profiles 44% of TNBCs were completely negative for all measured basal markers (EGFR, CK5 and 17, vimentin, c-kit).[8,14]

Scientific efforts have aimed for an identification of IHC markers in conjunction with TNBC status hypothesizing that TNBC is a heterogeneous entity with BLBC representing only one presumable subtype. For instance, EGFR expression may be found among 57% of BL but only 8% of non-BLBC cases.[15] Nielsen et al indicated a so-called 'five-marker method' triple negative (TN) and either EGFR or CK5/6 positive, which identified gene expression based BLBC with a sensitivity of 76% and a specificity of 100%.[16] Conversely, only 85% of TN tumors were truly BL. Recently, in a retrospective analysis of 3744 cases, 17% and 9% stained as TN and BL (by the five-marker method). Recent evidence indicates that several further divergent pathways may be active within TNBC. O Sparano et al identified that expression of growth factor receptor-bound protein[7] (a key element in cell signaling, motility and migration) was lower among TNBCs and significantly associated with outcome in multivariate analysis.[17]

In summary, divergences of BL and TNBC may explain existence of two distinct subtypes within the TN phenotype, i.e. gene expression-based BL versus a normal-like subtype as defined by Sorlie et al[8,18] or an IHC based basal marker-positive versus a multiple marker-negative subtype.[8,19] Most importantly, while the predicted impact of conventional ER, PR and HER-2 measurements in the clinical setting are relatively clear, the clinical significance of molecular class remains to be determined. Non-BL TNBCs may carry a more favorable prognosis and increased chemotherapy sensitivity; however, to date, there is no convincing evidence that stratification into molecular classes leads to more appropriate treatment recommendations and should yet be considered investigational.[8,10,18,20,21]

Epidemiological profile and risk factors

The epidemiological risk factors for TNBC compared with non-TNBC appear to differ significantly. Overall, the prevalence of TNBC in large unselected breast cancer patient cohorts is 11–20 %, whereas in selected cohorts of patients with advanced BC or patients of African-American ethnicity, TNBC may be diagnosed among as many as 23–28% of all patients. The close correlation with African-American ethnicity seems to be independent of an increased frequency of obesity in this patient population or age.[22] Risk factors for TNBC include high parity, young age at the time of first birth, lack of breast-feeding, use of oral contraceptives (in women <40 years old), younger age at diagnosis (<50 years), African-American ethnicity, Hispanic ethnicity, lower socioeconomic status, increased body weight and metabolic syndrome (particularly high blood glucose, high triglyceride, or low HDL levels)[23,24]

Imaging

Rare scientific data indicate that a reduced incidence of micro calcifications and peritumoral DCIS represent typical mammographic characteristics. Consistent with its more aggressive biology, this BC subtype very often manifests itself as an interval cancer, i.e. diagnosed between screening mammograms.[8,25,26] Furthermore, unifocality, mass lesion type, smooth mass margin, rim enhancement, persistent enhancement pattern, and very high intratumoral signal intensity on T2-weighted MR images are typical features associated with TNBC. MRI carries a particular potential to predict response to neoadjuvant chemotherapy in TNBC.[8,27,28] Furthermore, TN breast tumors show enhanced 2-[fluorine-18] fluoro-2-deoxy-Dglucose (FDG) uptake allowing for detection of TNBC with a high sensitivity by using FDG–positron emission tomography (PET).[29]

Histological appearance of BLBC/TNBC

More than 90% of BLBCs/TNBCs exhibit an invasive ductal histology and high histological grade, present with high mitotic index and carry central necrotic zones and pushing borders as well as a conspicuous lymphocytic infiltrate. Additional characteristics of BLBC are frequent metaplastic elements and medullary/atypical medullary features.

Recent reports confirm that very aggressive metaplastic tumors are BL by expression analysis.[30]

Prognosis

TNBC accounts for a disproportionate number of breast cancer deaths; the majority of studies indicate a negative impact of a TN (on the basis on data of thousands of patients) or BL (defined by a few molecular studies) phenotype on patient prognosis. In numerous randomized trials patients with TN or BL tumors treated by anthracyclines and taxanes experience a significantly decreased survival compared with patients with other tumor types. [8,10,34,35] Importantly, the prognostic effect of TNBC is independent of poor grade, nodal status, tumor size and treatment.[32] The aggressiveness of TNBC is further indicated by the fact that the peak risk of recurrence occurs within the first 3 years after initial treatment of the disease with the majority of deaths occurring in the first 5 years, and after diagnosis of metastatic disease, a significantly shorter survival was observed in both BL and TNBC. Conversely, the risk for late recurrences (i.e. beyond 5 years of diagnosis) is decreased by 50% compared with HR-positive disease. However, differences between TNBC and non-TNBC regarding overall survival (OS) wear off in 10 years of follow-up.[8,19,33]

Although the association between TNBC/BLBC and a less favorable prognosis has been clearly established, the effect on risk of local and distant recurrence remains less clear. Several studies have supported a significantly increased rate of visceral versus bone metastasis among patients with TNBC compared with non-TNBC. In the largest report to date, data on 12858 patients indicate an increased risk for lung [odds ratio (OR) 2.27] and brain (OR 5.32) metastasis as first site of recurrence and lower risk for bone recurrence (OR 0.23) in patients with TNBC. CNS metastasis occurs in 6%-46% particularly pronounced among young patients with node positive disease.[8,10,34,35]

Identification of new prognostic markers in TNBC

Clinicians from the UK[36] have robust data to support routine assessment of basal cytokeratins and androgen receptors, in addition to traditional pathologic parameters (tumor size and lymph node status), in women with triple-negative breast cancer. This additional information yields useful prognostic information that can help guide treatment decisions. Triple-negative breast cancer is a high risk breast cancer that lacks the benefit of specific therapy that targets these proteins. To identify prognostic markers that might signal more aggressive behavior of these specific tumors, the researchers examined a series of 1,944 well characterized invasive breast carcinomas with a median clinical follow up of 56 months. Among 1,726 informative cases, 282 (16.3%) were of the triple-negative phenotype and formed the basis of the study. Most triple-negative tumors, Rakha et al reported, were grade 3 ductal carcinomas of no specific type. The absence of androgen receptor expression, seen in 234 triple-negative tumors (87%), was associated with higher histological grade, development of recurrences and distant metastasis. Higher grade was also associated with loss of E-cadherin expression and positive expression of basal cytokeratins, P-cadherin, p-53, and EGFR. Interestingly, basal phenotype, as defined by the expression of CK5/6 and/or CK14 in 10% or greater of tumor cells, was detected in 55.7% of triple-negative tumor in the lymph node-negative subgroup (63% of cases), basal phenotype was the sole prognostic marker identified in this subgroup, in these tumors, basal phenotype was associated with a poorer outcome, and thus, can define a group of patients that may benefit from a more aggressive therapeutic intervention.[36]

Impact of Chemotherapy in BLBC/TNBC

In the largest study to date regarding this issue, Liedtke et al[37] examined the association between the TNBC and response to several regimens of neoadjuvant chemotherapy as well as OS in 1118 patients with early-stage BC. Again, although an increased pathological complete remission (pCR) rate was observed for TNBC, patients in the TNBC subgroup showed decreased survival rates compared with non-TNBC. Interestingly; patients experiencing pCR following neoadjuvant chemotherapy had an excellent OS regardless of receptor expression; in contrast, patients who had residual invasive carcinoma after completion of neoadjuvant chemotherapy had a significantly shorter OS associated with TNBC compared with non - TNBC. This clearly demonstrates that the poor OS of TNBC is derived from the fraction of patients with chemo resistant disease unfortunately representing >50% of TNBC. This observation underscores two important issues. First, novel diagnostic tools need to be developed allowing for the identification of those patients that are not sensitive to existing chemotherapies and are in need of alternative treatment options. Secondly and consequently, these patients require the development of novel therapeutic tools. [8,37,38]

Tumor grade as a predictive marker for chemo sensitivity in TNBC

Recently, a multigene index representing a genomic correlates genomic grade index (GGI) of histological tumor grade has been established. High GGI is predictive of response to chemotherapy across

all BCs, but since most TNBCs have high GGI, its predictive value within this subset is limited.[8,40]

Also, a subgroup of TNBC shows resistance to taxane and anthracycline containing chemotherapy despite high grade indicating that some TNBCs carry additional molecular features overriding the increased chemo sensitivity generally associated with a high tumor grade. For instance, newer data support a presumable association between response to chemotherapy and the extent of the local immune reaction within the TN tumor indicating tumor-infiltrating lymphocytes and level of tumor cell apoptosis as predictive markers of response to neoadjuvant chemotherapy.[8,40]

Although, TN and BL status as predictive markers for chemotherapy sensitivity, I-SPY trial [8,41] is a multicenter trial designed specifically to identify predictive markers for both pCR and survival among women with locally advanced BC and it is the first trial comparing the predictive value of TNBC and BL status. Recent analyses by Esserman et al[8,42] demonstrated that patients with TNBC as well as BLBC can expect similarly favorable pCR rates of 33% and 34%, respectively, following anthracycline–taxane based neoadjuvant chemotherapy, which are significantly increased compared with those in HR-positive/luminal disease.

Effectiveness of anthracyclines and cyclophosphamide

Patients with HER-2 overexpressing and/or topoisomerase-IIa-abnormal BCs are especially sensitive to anthracycline based chemotherapy and derive the most pronounced benefit from anthracycline-containing chemotherapy; results on the efficacy of anthracycline-based regimens in patients with TNBC remain controversial. A recent meta-analysis of four studies investigating anthracycline-containing regimens versus cyclophosphamide–methotrexate–5-fluorouracil (CMF) showed that although the benefit from anthracyclines was pronounced among patients with HER-2-positive disease, patients with TNBC still experienced a substantial 23% reduction in the risk of disease relapse (P = 0.11).[8,42,43] In the neoadjuvant setting, anthracycline-based regimens both with and without taxanes in this group are similarly efficacious. For instance, pCR rates after 4-6 courses of cyclophosphamide–epirubicin–5-fluorouracil (CEF) were 17% for patients with TNBC. Berrada et al,[44] studying 823 patients receiving six cycles of CEF or no chemotherapy identified p53+/BLBC as one subgroup deriving particular benefit from this chemotherapy. Similarly, as enhanced response rates to anthracyclines may be achieved by increasing either dose intensity/density of the applied chemotherapy, an increase in the pCR rate from 13% to 47% by intensifying conventional neoadjuvant FE100C chemotherapy to E70C700 mg/m2 (d1+8) in combination with standard 5-FU (d1-5) has been reported.[8,44]

The WSG AM 01 trial 14 randomly assigned patients with more than nine involved lymph nodes to receive either dose-dense conventional chemotherapy (i.e. 4xEC followed by 3xCMF q2w) or a rapidly cycled tandem high-dose regimen (i.e. 2xEC q2w followed by 2x Epirubicin 9 Cyclophosphamide 3000 + Thiotepa 400 q3w). In this study, young patients with TNBC and/or grade 3 tumors derived greater benefit from the rapidly cycled tandem approach than from the dose-dense conventional regimen. The high-dose approach lead to 5-year event-free survival rates as high as 71% in patients with TNBC compared with only 26% in TNBC patients treated with conventional dose-dense chemotherapy.[8,14]

A retrospective analysis from the MA5 trial randomly assigning patients to receive either CMF or CEF adjuvant chemotherapy indicated an increased 5-year DFS for the former (71% versus 51%, respectively) among patients with BLBC; the test for interaction between BL phenotype and treatment arm reached borderline significance (P = 0.06) indicating that patients with TNBC may not derive a particular benefit from anthracyclines. Although these retrospective results challenge the role of anthracyclines in adjuvant therapy for TNBC/BLBC, additional data will be needed for final clarification of this issue.[8,45]

Impact of taxanes

To date, there are limited data from randomized clinical trials investigating the impact of implementing taxanes into the adjuvant setting in patients with TNBC. Hayes et al illustrated that patients with either TN or HER-2-positive BC derived the greatest benefit from the addition of four cycles of paclitaxel to four cycles of escalating doses of doxorubicin combined with a fixed dose of cyclophosphamide (AC) in 3170 node-positive patients.[46] Similarly, Citron et al showed that the same dose-dense schedule, particularly benefited patients with ER-negative tumors at an overall relative reduction in the hazard of recurrence of 32% and 19% for ER-negative and ER positive BCs, respectively. [47] However, this difference by ER status did not reach statistical significance. In the results of the trial comparing conventional 4xAC followed by 4xpaclitaxel every 3 weeks versus 4xAC followed by 12xpaclitaxel weekly, particular benefit of weekly paclitaxel was obtained for TNBC (5-year DFS 87% versus 79%, HR = 0.59, P = 0.037). This is in line with

recent data regarding weekly paclitaxel after four cycles of AC indicating that the benefit of paclitaxel every week (but not docetaxel) compared with paclitaxel q3w was pronounced in the TNBC and HR+/HER-2 subgroups.

In patients with metastatic TNBC resistant to anthracycline based or taxane-based chemotherapy, Rugo et al[48] reported improved progression-free survival (PFS 4.1 versus 2.1 months) and overall response rate (ORR 27% versus 9%) for the novel microtubule-stabilizing agent ixabepilone in combination with capecitabine compared with capecitabine alone as current standard in this situation. Similarly, in the neoadjuvant setting, a 26% pCR rate was observed among patients with TNBC. As a consequence of these data, the PACS 08 trial49 has been designed as a randomized phase III trial evaluating the benefit of a sequential CEF100 and ixabepilone chemotherapy compared with CEF100 followed by three cycles of docetaxel in the adjuvant treatment of patients with TNBC.

Role of platinum containing agents

The association of TNBC with BRCA1 mutations and dysfunctional DNA repair may indicate an increased sensitivity to DNA-damaging agents i.e. platinum agents. A recent preclinical study demonstrated that over expression of p63 (a p53-related transcription factor) and p73 (p53 associated as well) is common among TN cases and associated with increased sensitivity to cisplatin. The results are promising. However, clinical data regarding the use of platinum agents in TNBC are still limited.[8,50,51]

Molecular Targeted therapy in TNBC

PARP (poly-ADP-ribosome-polymerase) inhibitors

Single-strand DNA breaks are usually removed by base excision repair, of which PARP-1 represents one of the central components. In the absence of PARP, single-strand breaks may degenerate to double-strand breaks, which cannot be repaired in BRCA1-mutated cells. Preclinical evidence indeed indicates BRCA1-null cells to be particularly sensitive to PARP1 inhibitors. Furthermore, pretreatment with a PARP inhibitor can enhance the effect of cisplatin chemotherapy in vitro in preclinical models using BC cell lines. Consequently, a number of clinical trials are currently being conducted with PARP inhibitors either alone or in combination with platinum based chemotherapy, some of which have already provided promising results. Results of two very important clinical trials implementing PARP inhibitors in patients with metastatic BC have recently been reported. These phase II results are promising, but will need to be validated in larger possibly phase III trials.[8,52,53]

EGFR Inhibitors

TNBC is strongly associated with EGFR expression. A body of preclinical data supports a synergistic effect of EGFR inhibition with chemotherapy showing improved efficacy compared with chemotherapy or targeted therapy alone. On the basis of the available evidence, there is little reason to believe that either single-agent cetuximab or a small-molecule tyrosine kinase inhibitor of EGFR will show substantial single-agent activity in patients with TNBC. Efforts to examine the effect of EGFR-targeted treatments on chemotherapy sensitivity are currently being conducted. Until the results of these clinical trials are presented, it remains unknown whether EGFR-targeted agents add any value to the therapy for TNBC.[8,52]

Multityrosine kinase inhibitors

The multityrosine kinase inhibitor dasatinib is a small molecule that has recently been approved for the treatment of bcr-abl mutated chronic myeloid leukemia resistant to imatinib. In vitro evidence supports the use of this small molecule, particularly in subgroup of BLBC in which several tyrosine kinase receptors such as stem-cell factor receptor c-kit is over expressed and/or mutated. A single phase II study evaluating single-agent dasatinib in patients with advanced TNBC reported modest activity, with a partial remission among two and a clinical benefit among six patients (overall clinical benefit rate 9.3%); however, a discontinuation of therapy and dose reductions weaken the results of the study.[8,53]

Antiangiogenic agents

Antiangiogenic therapy provides a further candidate mechanism for improving treatment efficacy in patients with TNBC. For instance, Linderholm et al. reported increased levels of vascular endothelial growth factor (VEGF) in patients with TNBCs which were associated with shorter RFS in patients with TNBC compared with those with non-TNBC. Also, VEGF-2 has been reported by the same group as a prognostic factor among patients with TNBC indicating vascular pathways as one very interesting mechanism for targeting this BC subtype.[54]

Recently, a particular association between VEGF signaling and chromosome organization related to gene gains in 6p21–22 in the TNBC phenotype was shown which may represent potential pathway targets in this subtype. The monoclonal anti-VEGF antibody bevacizumab in combination with weekly paclitaxel caused a significant increase in response rates and PFS in all subgroups with metastatic BC. The study of bevacizumab in adjuvant

therapy in TNBC was designed to investigate the effect of adding bevacizumab to adjuvant chemotherapy in TNBC. However, PFS and response rate do not predict major OS improvements when adding bevacizumab to chemotherapy treatment.[55]

Unresolved Issues

Role of protracted maintenance therapy in TNBC following standard adjuvant:

After the complétion of adjuvant chemotherapy, TNBC patients are usually kept under observation. In endocrine responsive disease, 5-10 years of extended hormonal therapy is usually prescribed while in Her.2 positive disease one year of trastuzumab used routinely. Is protracted therapy is beneficial for the suppression and eradication of malignant clone? There are data of efficacy of metronomic chemotherapy in metastatic settings, however data in adjuvant settings are still lacking.

Evaluating the role of prophylactic cranial irradiation:

Brain can be a sanctuary site for metastatic disease, as commonly used chemotherapy has negligible CNS penetration. Prophylactic cranial irradiation (PCI) has definitive role in haematological malignancies. It has proven role in small cell lung cancer. However there are no robust data of its role in breast cancer in general and TNC in particular. Given the substantial risk of brain metastasis and the associated dismal outcome innovative clinical trial concepts such as prophylactic cranial irradiation at least in patients with chemotherapy resistant tumors, may be justified although controversial till date.

Optimizing the role of dose dense chemotherapy:

There is evidence that patients with TNBC derive particular benefit from dose-dense (weekly or biweekly) and other intensified chemotherapy regimens with standard agents, although the best strategy to select patients for these more toxic and cost-intensive therapies remains to be defined.[8]

Incorporation of cisplatin in adjuvant/neoadjuvant settings of TN/BL breast cancer:

BRCA1 and several proliferation mechanisms play a crucial role in therapy response of TNBC/BLBC and are discussed to mediate sensitivity to DNA-damaging agents (platinum, alkylating agents). There is no specific guideline for use of platinum compounds in the TNBC. Anthracycine and taxanes are used routinely. TNBC has aggressive clinical course and worse clinical outcome. It is sensitive to taxane and anthracycline containing regimens in the preoperative setting; they are nevertheless associated with poorer long-term outcomes.

Identifying patients as unresponsive to chemotherapy:

There are patients who do not benefit sufficiently from standard chemotherapy and so improved strategies required for early recognition of responders and non responders which may include novel imaging techniques like PET and/or MRI may be reevaluated in the context of TN disease.[8]

Alteration of chemotherapy in poor responders to NACT:

Patients who do not achieve complete pathological remission have a rather poor outcome and alternative and/or additional chemotherapy options should be evaluated.

To recognize distinct molecular features to stratify distinct BC subtype:

It seems to be reasonable that the poor outcome observed among patients with TNBC can be partly attributed to BL tumors within this clinically defined subgroup; however, to date, there is no consensus regarding the methodology for defining BLBC and clinical consequences for this subtype remain unclear. There is an urgent need to identify distinct molecular features to stratify distinct BC subtypes with patients with the TN disease in order to improve identification, sub grouping, and treatment of patients with TNBC.

Establishing novel targeted therapies:

If TNBC/BLBCs are not ER/PR driven, not HER family driven, and no other specific and common driver is identified, then what is the target and how can we move past conventional chemotherapy while better identifying those who do benefit from it? Novel targeted therapies e.g. PARP, EGFR, c-kit and VEGF inhibitors alone or in combination with chemotherapy are currently under investigation and have shown promising results in numerous phase II trials. Still clinically useful, targeted agents are not available.

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"Formerly, when religion was strong and science weak, men mistook magic for medicine; now, when science is strong and religion weak, men mistake medicine for magic."

Thomas Szasz

Impact of Intervention on the Quality of Life of Advanced Stage Cancer Patients

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Summary

The aim was to study the change in quality of life (QOL) of patients of advanced cancer between the first visit and third visit to the Department of Pain and Palliative Medicine. Patients referred to pain and palliative department for supportive and symptomatic treatment were selected. All these patients had advanced and metastatic cancer and patients undergoing no anti-cancer treatment whatsoever were only selected. Questionnaire QLQ-C15 PAL by EORTC was used. The questionnaire was filled out on the patient's first visit and third visit by the counsellor. The change in QOL was noticeable in all patients. There was significant improvement in all aspects that were measured. Most patients came every 15 days, thus the time difference between the first visit and third visit was approximately a month. Advanced cancer patients can achieve good palliation in symptoms and an improvement in quality of life through dedicated efforts by an ardent palliative care team.

Keywords: Palliative care, Quality of life, EORTC, QLQ-C15 PAL, Post-intervention

Introduction

Health related quality of life is multi-dimensional and includes physical, social, psychological and spiritual dimensions. It can only truly be determined by the patient. This makes it highly subjective and difficult for doctors to assess. Palliative care is aimed at improving quality of life of patients and family. This is done through pain relief, symptomatic relief, psychological relief and nutritional support. Quality of life in advanced stage cancer patients is broad-ranged, it takes into consideration a person's physical health, psychological state, level of independence, social relationships and personal beliefs.

Quality of life is not given the same importance in India as it is given in the western culture. The level of illiteracy and poverty is responsible for the negligence towards QOL. Illiteracy also makes it difficult for doctors and counsellors to get patients to fill out questionnaires, thus translation and explanation in the regional language is necessary. This study is aimed at evaluating the effect of psychological counselling and pain relief on quality of life in advanced cancer patients. Many quality of life scales have been developed by various groups like The McGill Quality of Life Questionnaire[1], The Functional Assessment of Cancer Therapy (FACT) scale[2] and QLQ-C15 PAL by European Organization for Research and Treatment of Cancer (EORTC).[3]

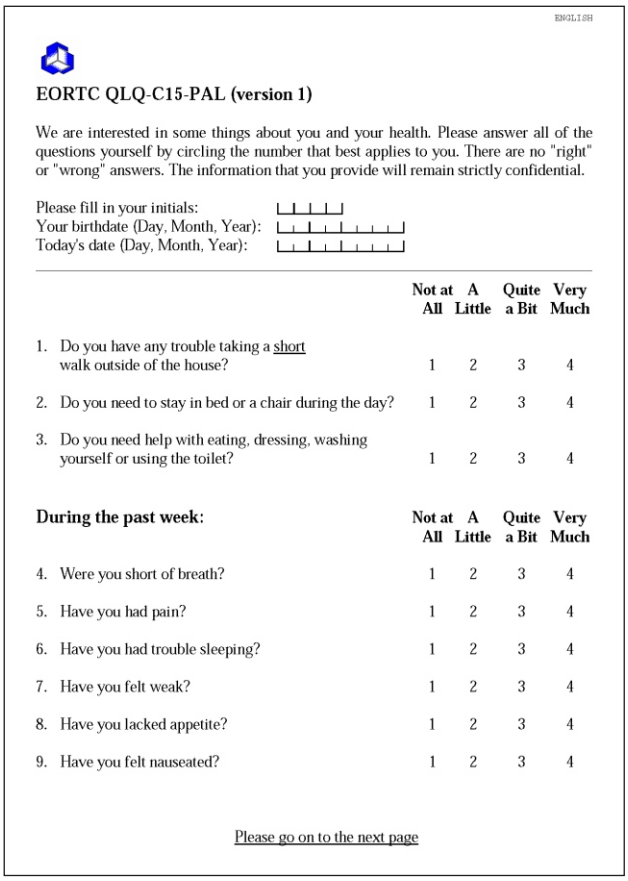
We have used the QLQ-C15 PAL by EORTC for this study. QLQ-C15 PAL is developed by the EORTC specially to study the quality of life of patients undergoing palliative care. Although studying quality of life is difficult in such circumstances, it gives the doctors a better understanding of all the aspects of a patient's life. With this complete understanding the doctors are able to manage the patient's treatment better, which is very crucial in advanced stage patients.

Materials and methods

Patients attending the Pain and Palliative Department in GCRI, Ahmedabad, for the first time were selected for this study from 10/1/2014 to 30/6/2014. As per the EORCT criteria, only patients with advanced, incurable and symptomatic cancer with no ongoing anti-cancer treatments like chemotherapy, radiotherapy, or palliative surgery were selected. Most patients had a life expectancy of two or more months. There were 70 such patients who fit this criteria during the study's duration. Patients fitting these criteria were made to fill out the questionnaire to evaluate their quality of life. The questionnaire used for this study was QLQ-C15 PAL by EORTC. This questionnaire is four point scaled. It consists of 15 questions, all covering different aspects which determine the quality of life.

They were asked to fill out the same questionnaire on their first consultation and third consultation, These visits were roughly a month apart as the patients visit every fifteen days.

The QLQ C15 PAL covers several different aspects of a patient's life which help us determine the quality of life. It covers areas like pain, insomnia, hunger, etc. This questionnaire measures the physical functioning, emotional functioning and symptoms like insomnia, pain, fatigue, nausea, vomiting, dyspnoea, appetite loss and constipation. It is a four point scale as 1-not at all, 2-a little bit, 3-quite a bit and 4- very much. Given the illiteracy rate of our country, the patients were merely asked the questions by the psychologist in order to avoid error. Even literate patients were read out the questions to make sure they fully comprehend. The data were collected over duration of six months and analysed statistically using T-test and paired sample correlation.



ENGLISH

EORTC QLQ-C15-PAL (version 1)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Today's date (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4

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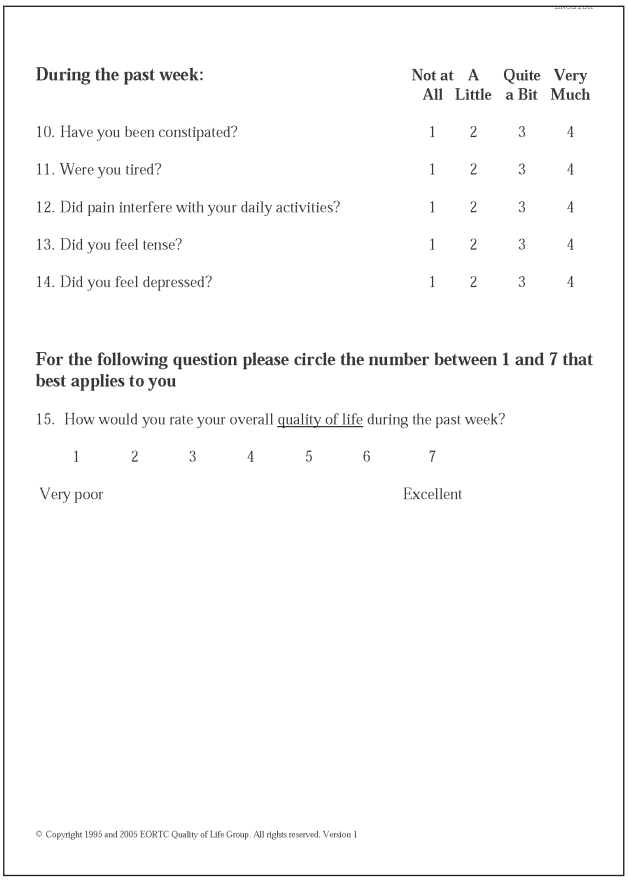

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following question please circle the number between 1 and 7 that best applies to you

15. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

Figure 1: EORTC QLQ - C15 - PAL

Results

Advanced and metastatic cancer patients referred to pain and palliative department during 10/1/2014 to 30/6/2014 and those who fit the eligibility criteria constitute the subject group of this study, there were 70 such patients. This was an assisted questionnaire and was filled out by the help of a counsellor. Out of all patients, 46 were male and 24 were female.

The patients were asked the questions in the local vernacular language and the counsellor filled out the questionnaire as per their response. The interventions used between the first and third visit were in the form of pain medication, mostly opioids, psychological counselling, nutritional advice, and general guidance. The QLQ C15 PAL questionnaire pre-intervention was filled out by 100 patients, but the post-intervention patients who completed the questionnaire were 70. Further analysis was done from these 70 questionnaires, and the results are as follows. We analysed the pre-intervention and post-intervention data for all the fifteen questions by using paired sample T-test. Questions 1-14 were rated on a scale of 1-4, whereas question 15 was rated on a scale of 1-7, as 1-very poor and 7-excellent.(Figure 2) The mean of each question pre-intervention and post-intervention is given, where N=70. We can see a decline in the mean of all questions post-intervention by at least 0.20 points. The standard deviation for each question is also given in this (Figure 2)

In Figure 3 we can see the correlation between the two results of each questions. We can see high correlation in questions 1-3, which are all related to physical functioning of the patient, which shows a medium level of improvement in these aspects. Questions 4-12 cover symptoms, which shows low correlation, which can be interpreted as a high level of improvement in these aspects. Questions 13-14 are related to emotional functioning, and they also show significantly low correlation, which means that improvement in emotional functioning was reported post-intervention. Question 15 was to measure the overall quality of life or global health status, there was very low correlation thus showing a drastic improvement in quality of life of patients post intervention.

We can conclude by these results that advanced cancer patients see significant improvement in symptomatic relief such as pain, insomnia, loss of appetite and constipation, and in emotional functioning. There is little improvement seen in the physical functioning of terminal cancer patients post-intervention. This could be due to the fact that a significant amount of permanent damage has already occurred by the time these patients reach this stage of the disease.

		Mean	N	Std. Deviation	Std. Error Mean
Ques 1	Pre	2.41	70	1.028	.123
	Post	2.00	70	.799	.095
Ques 2	Pre	3.19	70	.786	.094
	Post	2.57	70	.714	.085
Ques 3	Pre	1.86	70	1.011	.121
	Post	1.69	70	.860	.103
Ques 4	Pre	1.73	70	.833	.100
	Post	1.34	70	.562	.067
Ques 5	Pre	3.30	70	.622	.074
	Post	2.26	70	.630	.075
Ques 6	Pre	3.00	70	.917	.110
	Post	1.66	70	.740	.088
Ques 7	Pre	3.14	70	.643	.077
	Post	2.50	70	.717	.086
Ques 8	Pre	2.84	70	.958	.114
	Post	2.47	70	.829	.099
Ques 9	Pre	1.63	70	.802	.096
	Post	1.30	70	.645	.077
Ques 10	Pre	2.09	70	.897	.107
	Post	1.44	70	.651	.078
Ques 11	Pre	3.13	70	.567	.068
	Post	2.57	70	.717	.086
Ques 12	Pre	3.19	70	.687	.082
	Post	2.51	70	.697	.083
Ques 13	Pre	2.90	70	.640	.077
	Post	2.30	70	.492	.059
Ques 14	Pre	2.97	70	.659	.079
	Post	2.31	70	.498	.059
Ques 15	Pre	3.07	70	1.094	.131
	Post	4.54	70	1.188	.142

Figure 2: Paired Samples Statistics

		N	Correlation	Sig.
Ques 1	Pre & Post	70	.706	.000
Ques 2	Pre & Post	70	.428	.000
Ques 3	Pre & Post	70	.730	.000
Ques 4	Pre & Post	70	.636	.000
Ques 5	Pre & Post	70	.133	.272
Ques 6	Pre & Post	70	.214	.076
Ques 7	Pre & Post	70	.251	.036
Ques 8	Pre & Post	70	.533	.000
Ques 9	Pre & Post	70	.331	.005
Ques 10	Pre & Post	70	.232	.053
Ques 11	Pre & Post	70	.323	.007
Ques 12	Pre & Post	70	.464	.000
Ques 13	Pre & Post	70	.327	.006
Ques 14	Pre & Post	70	.426	.000
Ques 15	Pre & Post	70	.204	.091

Figure 3: Paired Samples Correlations

There was a significant improvement in pain relief in all patients post-intervention which is essential for improving quality of life in terminal patients. We can also note a substantial improvement in symptomatic relief.

Emotional functioning improved drastically post-intervention as patients received psychological counselling and guidance. During counselling a lot of misconceptions were cleared which helped patients cope up with the disease and its side-effects better. Psychological effect of disease is over-looked in Indian culture, This study highlights the effects of counselling on the overall quality of life of the patient.

Discussion

Cancer has become the second leading cause of death in the world, taking the lives of nearly 8 million people each year. Advanced cancer patients all over the world are also increasing due to increase in the aging population.

The importance of palliative care is also growing and it is no longer given to the patient as a last resort. Nowadays palliative care starts with the diagnosis of the disease. It is also known as an extra layer of support.

Palliative care is provided by a team of doctors, psychologists, nutritionist, nurses and other specialists. It is a joint effort by everyone involved to improve the quality of life of a patient. Palliative care focuses on symptoms like pain, shortness of breath, loss of appetite, difficulty sleeping, constipation and depression.

It is important to assess the effect of palliative care on quality of life improvement. We do this by using questionnaires before palliative intervention and a month after the intervention to see the effect.

We used QLQ C15 PAL questionnaire by EORTC, which is designed to measure the quality of life in advanced stage patients. There is a criteria set by EORTC for selecting patients for a study using this questionnaire, the patient should have advanced metastatic cancer with no ongoing anti-cancer treatment. Thus it is used for palliative patients only, receiving only symptomatic relief.

It is a shorter version of QLQ C30 by EORTC, which was considered too long for the patients to fill out, hence they developed QLQ C15 PAL which is a shorter and direct version.[4]

QLQ-C30 is multidimensional, it measures many aspects like physical functioning, social functioning, emotional functioning, cognitive functioning and role functioning. Thus it was considered too long and sometimes complex, or too stressful for some individuals. Thus a shorter version of the same, QLQ-C15 PAL was developed, it may not cover as many aspects as its previous counterpart but it gives us a basic idea about the quality of life of advanced stage cancer patient, before and after intervention.

This questionnaire covers several topics like physical functioning, emotional functioning and symptoms like pain, insomnia etc.

This questionnaire was translated by EORTC in several languages and our regional language Gujarati was one of them. Even though the study was carried out in the local vernacular language, we faced communication problems with the patients.

The questions often had to be repeated and clarified several times to the patients. The point based rating system was not easily understood by the patients, and the counsellor had to simplify it for them. Another major problem faced during this study was the fact that many patients didn't return after their first visit to our clinic, and even if they did, they were missed due to the density of patients visiting our clinic. Many patients were also irregular and came after very long intervals and a few patients expired after the first visit. Thus, we had a lot of incomplete forms which could not be used.

Sometimes the patients couldn't talk due to disfigurement and their questionnaires were filled out with the help of their relatives who accompanied them. This would have been a major hurdle for us as we could have misunderstood the responses, but as this questionnaire was point based, the patients could communicate through signs.

A trained counsellor was made to fill out the questionnaire in order to maintain uniformity, thus giving us more reliable results.

Majority of the patients reported improvement in quality of life in all most all aspects. There was a significant improvement in emotional functioning.

As this questionnaire is developed in Europe, its reliability on Indian patients was a concern, but we found that it was easily applicable and suitable for Indian patients.

Indians are extremely religious, which goes a long way to provide support in such situations. We also have a very close-knit society which can contribute a lot to the quality of life of the patient. Thus all these factors were considered while assessing the quality of life.

Conclusion

The diagnosis of cancer is a major psychological trauma not only for the patient but also the family, thus support is needed from day one. The role of palliative care is not at the end of life, but the current concept is that pain and palliative team should play an active role from the day of diagnosis.[5] Symptomatic relief and psychological support has to be provided along with other forms of treatment.

We can see noticeable change in the quality of life after palliative interventions in advanced cancer patients. During end-of-life care, the main focus is on making the patient comfortable and improving their quality of life. Death with dignity is also an important issue in palliative care, which can be achieved through making the patient as independent as possible and giving them emotional support. This is an important factor in improving quality of life.

We can also conclude that QLQ C15 PAL is accurate at measuring the difference in quality of life in terminal cancer patients pre-intervention and post-intervention.

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Burden of Infections in ICU: Strategies to Control

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Summary

Patients are admitted in Intensive Care Unit (ICU) for close monitoring and constant medical care with life threatening illness. This is a study analysis is to know the rates of infections occurring in patients admitted in ICUs (Medical, Surgical and Neuro Oncology) of the hospital and to come out with the strategies and guidelines to prevent infections. This is a laboratory based study analysis focusing on ICUs Infections. The method of study analysis included manual as well as computer assisted analysis (WHONET software). The study analysis was for one year (2013) a total of 238 patients were admitted with different malignancies like solid tumor and hematological malignancies in the ICUs. Overall infection rate in ICU was 43.69%. The data showed 92.3% infection in patients with interventional procedures, where as it was 47.1% in patients without interventions. Catheter associated blood stream infections in medical, surgical and neuro ICU was 16.04%, 42.85% and 46.15% respectively. The infection in peripheral line catheter was 23.3% and in central line catheters was 38.46%. Infections other than blood stream infections were called routine infections. Routine infections in medical, surgical and neuro ICU were 55.8%, 75% and 63.8% respectively. Amongst the gram positive cocci, staphylococcus aureus was 10.5% followed by coagulase negative staphylococcus (3.94%). Amongst the gram negative organisms 32.89% of Acinatobacter baumannii followed by Pseudomonas 27.6%, E. coli 14.47%, Klebseilla 11.8% and Enterobacter. 7.8% of Candida species of the fungi caused infection. The antibiotic sensitivity of the isolates shows the gram positive cocci in blood culture were resistant to ampicillin, gentamycin, ciprofloxacin, tigecycline, erythromycin, levofloxacin, penicillin G and ranged from 26% to 93%. The antibiotics sensitive to GPC were tigecycline, linezoid, tetracyclin, vancomycin and teicoplanin, which ranged from 60-93%. 60% of the MRSA causing infections were detected.

The GNBs were resistant to ampicillin, piperacillin/tazobactum (62%), cephalosporin group (66 to 85.7%), amikacin and gentamycin (48 and 52%), imipenem and meropenem (43 and 24%), ciprofloxacin, trimethoprim/sulfamethoxazole, aztreonam, cefazolin, tobramycin, ceftazidime showed resistance ranging from of 67 to 85.7%. The antibiotics which can be used for treatment are amoxicillin / clavulanic acid, meropenem, amikacin, aztreonam. The GNBs resistant to antibiotics were ESBL and Carbapenemase producers which inactivated the cephalosporin and carbapenem group of antibiotics. 72.7% of the E. coli and Klebsialla were ESBL producer and around 11.1% of the GNBs were carbapenemase producer. There is a growing concern about the bacteria developing resistance to the existing antimicrobial drugs as per the current study. Moreover the cost of the antibiotics like carbapenams, linezolid, vancomycin are too high. Therefore multidimensional approach including (1) Bundle (Care Bundle) of infection control interventions (2) Education (3) Surveillance (4) Performance feedback of infection control practices should be implemented to reduce the morbidity and mortality. Of all the strategies hand hygiene remains the corner stone in controlling healthcare associated infection.

Keywords: Intensive Care Unit, Infection prevention, Care Bundle

Introduction

Patients are admitted in Intensive Care Unit (ICU) for close monitoring and constant medical care with life threatening illness. Because of their already existing clinical conditions, common use of antibiotics, prevalence of multidrug resistant organisms, impaired immunity, other factors like patients on ventilators or central line catheterization or on urinary tract catheters, they are at high risk of infections.[1]

Estimates from National Nosocomial Infections Surveillance (NNIS) system, found approximately 1.7 million health care associated infections occurred in the United States Hospitals in 2002 with 24% of these infections in ICU, a rate of 13 per 1000 patient days. The complex care of an ICU patient relies upon the interaction of many individuals including physicians, nurses and support staff[2] The intension of this study analysis is to know the rates of infections occurring in patients admitted in ICUs (Medical, Surgical and Neuro Oncology) of the hospital and to come out with the strategies and guidelines to prevent infections.

Methods (Data Collection)

This is purely a laboratory based study analysis focusing on ICUs of the hospital including medical, surgical and neuro oncology. The method of study analysis included manual method from daily data entry registers as well as computer assisted analysis (WHONET software).

Results

During the study analysis from January to December 2013 (one year) a total of 238 patients were admitted with different malignancies like solid tumor and hematological malignancies in the ICUs. Highest number of patients (78) belonged to age group 51-75 year and there was male preponderance. Other patients included belonged to other age groups like 0-16 years (31) , 17-30 (67), and 31-50 (61). Overall infection rate in ICU was 43.69%. There was an observation that the infection in the month of July was maximum (15.59%) followed by 11% in January and 10% in December. The infection rate fluctuated from 4.58% to about 9% in the other months (Figure 1).

The data showed that there was a 92.3% infection in patients with interventional procedures,

where as it was 47.1% in patients without any interventions (Table-1). Catheter associated blood stream infections in medical, surgical and neuro ICU was 16.04%, 42.85% and 46.15%, respectively. There are two modes of catheter insertion in patients receiving therapy, like peripheral and central catheters. It was found that infection in peripheral line catheter was 23.3% and in central line catheters was 38.46%. Infections other than blood stream infections were called routine infections. Routine infections in medical, surgical and neuro ICU were 55.8%, 75% and 63.8%, respectively (Figure 2).

Figure 3 shows the different types of bacteria and fungi grown from different samples received in the laboratory from ICUs. Amongst the gram positive cocci, Staphylococcus Aureus was 10.5% followed by Coagulase negative Staphylococcus (3.94%), S. Haemolyticus, Enterococcus and Staphylococcus epidermidis. Amongst the gram negative organisms 32.89% of Acinatobacter baumannii followed by Pseudomonas 27.6%, E. coli 14.47%, Klebseilla 11.8% and Enterobacter. Amongst the fungi species of candida (7.8%) were grown which were causing infection.

The antibiotic sensitivity of the isolates is given in Figures 3-6. It was observed that most of the gram positive cocci in blood culture (Figure 4) were resistant to antibiotics like ampicillin, gentamycin, ciprofloxacin, tigecycline, erythromycin, levofloxacin, penicillin G which ranged from 26% to 93%. The antibiotics which were sensitive to gram positive cocci were tigecycline, linezoid, tetracyclin, vancomycin and teicoplanin, and sensitivity ranged from 60-93%. Whereas the isolates from routine samples showed a range of resistance which was less when compared to blood culture samples (Figure 5).60% of the Staphylococci were Methicillin resistance (MRSA).

The gram negative bacilli isolated from different samples of patients admitted in ICU showed that they were resistant to ampicillin, piperacillin/tazobactum (62%), cephalosporin group (66 to 85.7%), amikacin and gentamycin (48 and 52%), imipenem and meropenem (43 and 24%), ciprofloxacin, trimethoprim/sulfamethoxazole, aztreonam, cefazolin, tobramycin, ceftazidime showed resistance ranged of 67-85.7%.

The antibiotics which can be preferred are amoxicillin/ clavulanic acid, meropenem, amikacin, aztreonam (Figures 6A, B and 7A, B). The gram negative bacilli which where resistant to antibiotics were ESBL and carbapenemase producers and they inactivated the cephalosporin and carbapenem group of antibiotics. It was seen that 72.7% of the E. coli and Klebsialla were ESBL producer and around 11.1% of the GNBs were carbapenemase producer.

Discussion and Conclusion

The cancer patients are compromised hosts who have an increased risk of infectious complications due to impairment of host defense mechanism. The patients with malignancies were admitted in ICUs for post operative complications like septicemia, leakages or leukemia patients on chemotherapy with breathlessness, tachycardia, consolidation, ascites. It was observed that most of the patients were elderly. The overall burden of infection rate was approximately 43% the reason for fluctuation of infection rate throughout the year was not clear. It was found that in the month of July 2013 (monsoon season) the infection rate was highest (15.5%) and this may be probably because of increased humidity.

Catheter associated blood stream infection were 16.04, 42.85 and 46.15% in medical, surgical and neuro oncology ICUs. These infections were not calculated according to the catheter per days. The most common organism isolated was Staphylococcus aureus and 60% of them were MRSA. Amongst the gram negative bacilli the most common bacilli causing infection was Acinetobacter baumannii (32.89%). Other GNBs isolated in order of rate of isolation were Pseudomonas spp., E. coli, Klebsiella and Enterobacter. Whereas the study conducted by Tao et al[4] showed the same results but the isolation of Acinetobacter baumannii was 19.1% and only difference in their study was that they focused on device related infections.

Thus it is concluded that antibiotic resistance in ICU is more prevalent than in general hospital ward.[2] Resistance rate to most bacterial pathogen are increasing. The cause of resistance is multi factorial, but one of the most critical and possible reason is antibiotic misuse. There is a growing concern about the bacteria developing resistance to the existing antimicrobial drug as per the current study. Moreover the cost of the antibiotic like carbapenamase, linezolid, vancomycin is too high. Therefore multidimensional approach including 1. Bundle (Care Bundle) of infection control interventions 2. Education 3. Surveillance 4. Performance feedback of infection control practices should be implemented to reduce the morbidity mortality. Of all the strategies hand hygiene remains the corner stone in cross health care associated infection prevention.

What is a bundle?

A bundle is a structured way of improving processes of care and patient outcomes. It is a small straightforward set of practices - generally three to five - that, when performed collectively, reliably and continuously, have been proven to improve patient outcomes.

Who can use the bundles?

Table 1: Prevalence of infections in patient interventions

Sr. No.	Interventional Infection			Sr. No.	Non-Interventional Infection		
		Total	Culture Positive			Total	Culture Positive
1	Tracheostomy tube	18	18	1	Sputum	24	16
2	Endotracheal Tube	7	7	2	Pus Swab	13	10
3	Central line	6	4	3	CSF	17	2
4	ICD	3	2	4	Pleural fluid	9	1
5	Tips	4	4	5	Peritoneal Fluid	1	1
6	Stent	1	1	6	BAL	2	1
				7	Nasopharyngeal swab	2	1
				8	Rectal swab	2	1
	Total	39	36 (92.3%)		Total	70	33 (47.1%)

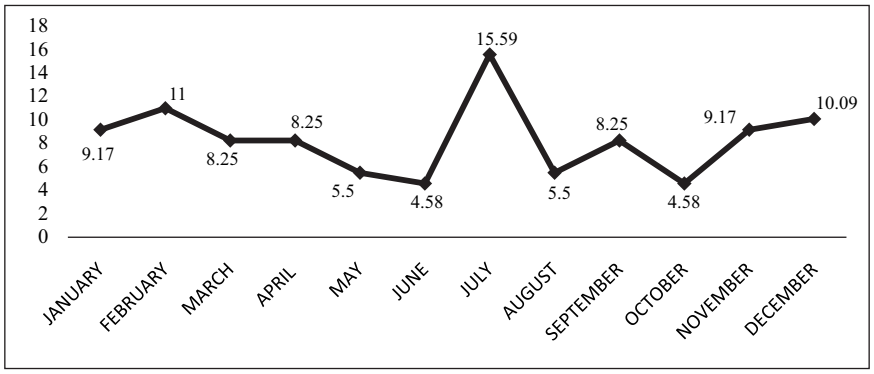

Figure 1: Trend of infections in the year 2013 (%)

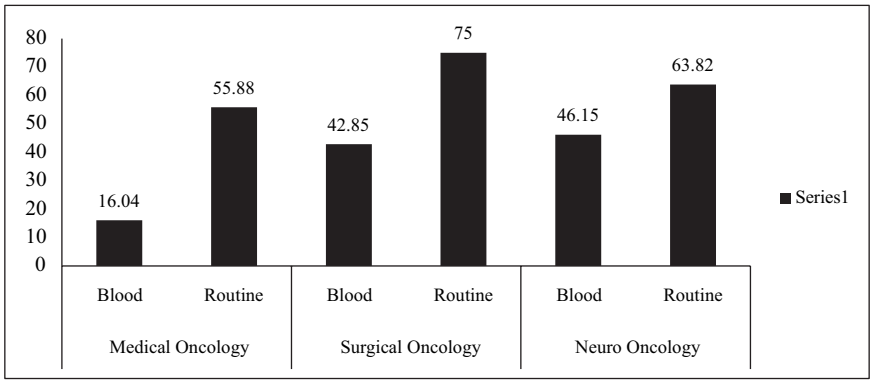

Figure 2: Infections in ICU-2013

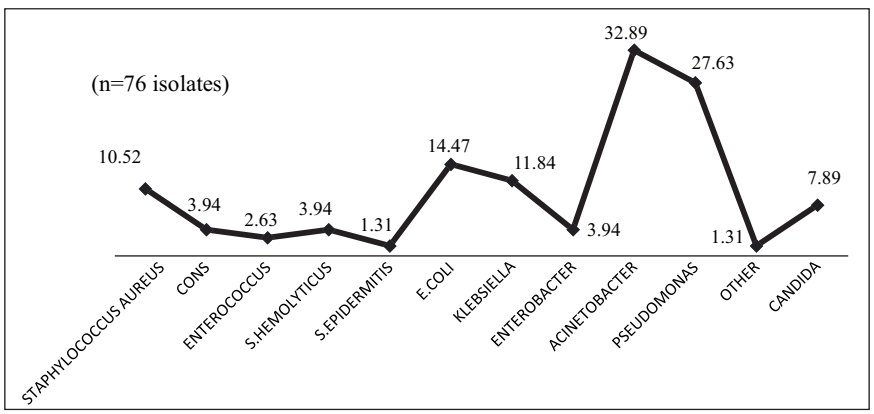

Figure 3: Type of organisms isolated in ICUs

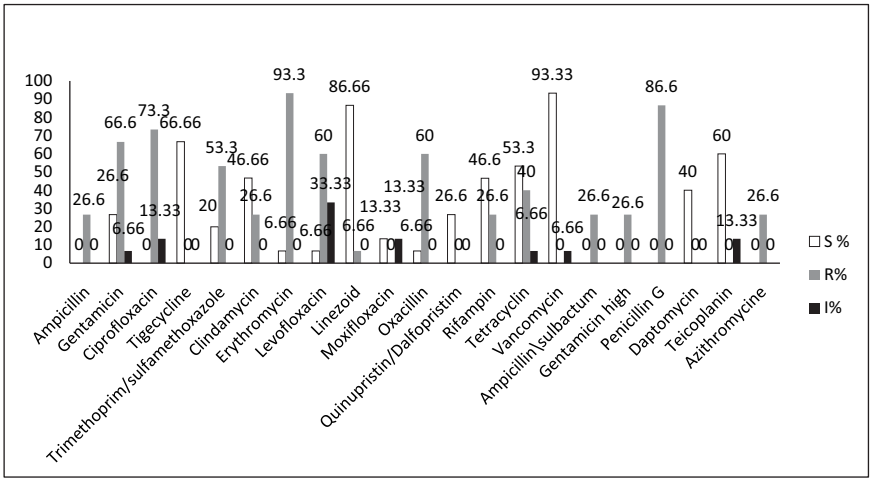

Figure 4: Antibiotic sensitivity of GPC in blood cultures

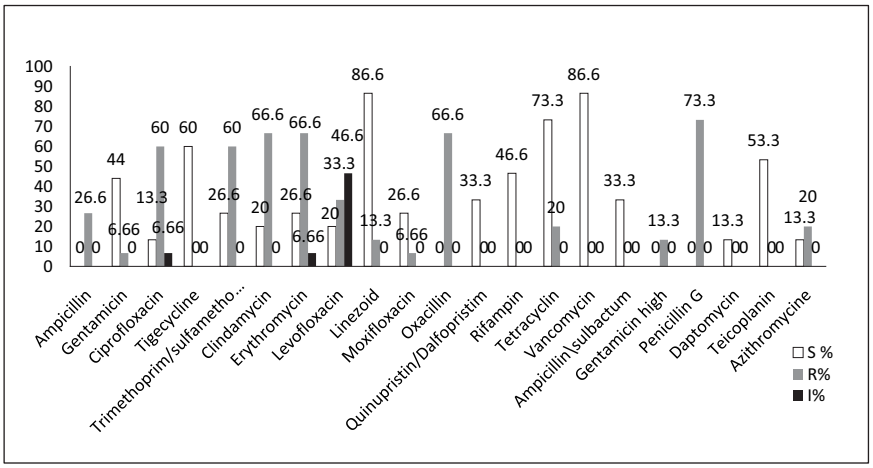

Figure 5: Antibiotic sensitivity of GPC in routine cultures

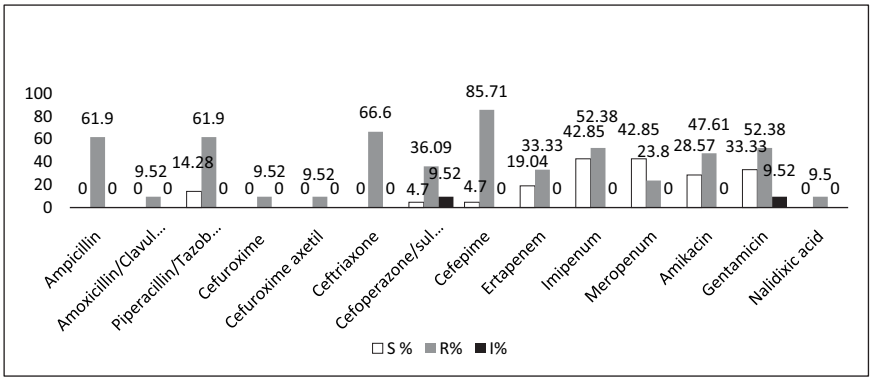

Figure 6A: Antibiotic sensitivity of GNB in blood cultures

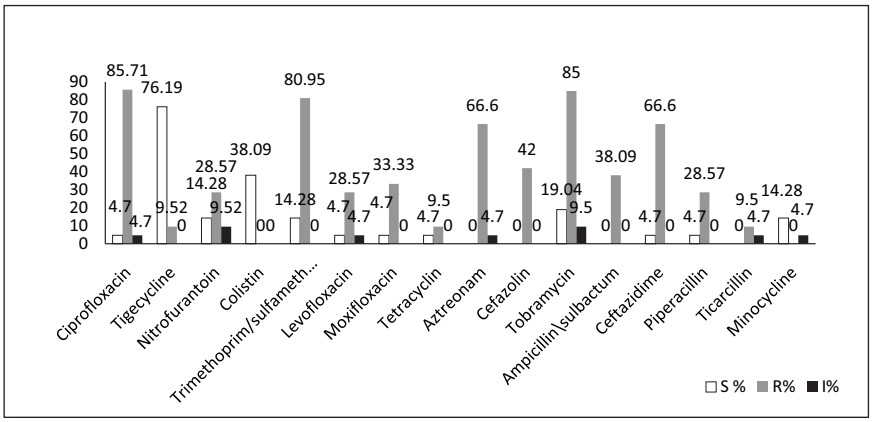

Figure 6B: Antibiotic sensitivity of GNB in blood cultures

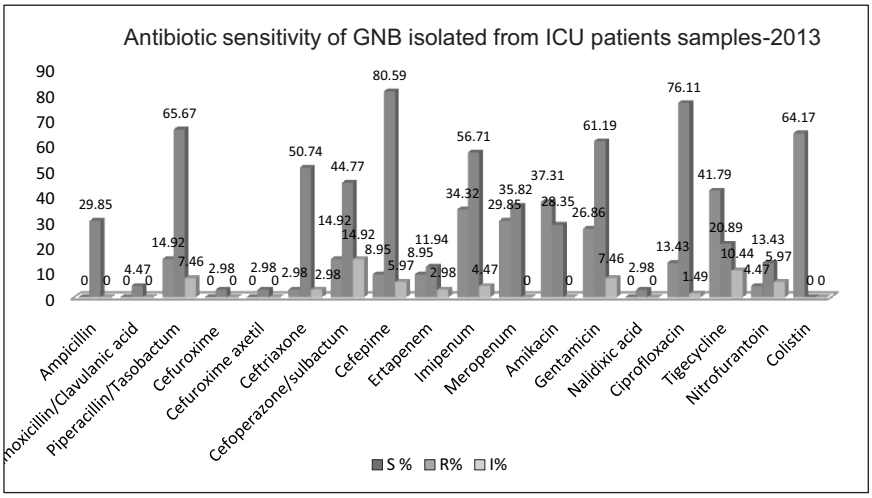

Figure 7A: Antibiotic sensitivity of GNB in routine cultures

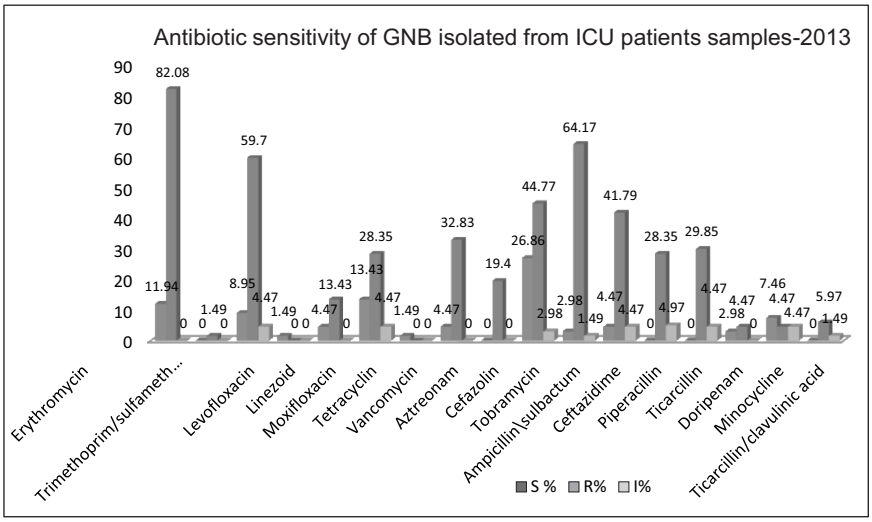

Figure 7B: Antibiotic sensitivity of GNB in routine cultures

Anyone (guidelines created by secretary, HICC of the hospital, implemented by the in charge Doctor and Head nurse and followed by staff nurses) in the clinical setting with the agreement of the clinical team and Quality Improvement Leads can use the bundles.

Types of Bundles?

- Preventing contamination when taking a sample for blood culture
- Preventing catheter associated urinary tract infection - Acute settings
- Preventing catheter associated urinary tract infections - Community settings
- Preventing infections when inserting and maintaining a central vascular catheter (CVC)
- Preventing the transmission of Clostridium difficult
- Preventing infections when inserting and maintaining a peripheral vascular catheter (PVC)
- Preventing surgical site infections (SSI)

Acknowledgement: The authors thank Junior Research Fellows Roshani Patel, Riddhi Khara and Anuj Patel who were associated in the generation of data from the clinical laboratory services.

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Breaking Bad News: When, How, How much?

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Communication is the art of transmitting information, ideas and attitudes from one person to another. It is the process of meaningful interaction among human beings.

All of us have faced a situation where we find ourselves caught in trouble while talking to patients and their relatives!!!!! It is especially true when we as doctors have to tell for the first time that "they have got a cancer" or "their cancer is no longer curable"!
Hence in this article we have tried to focus such different scenarios and discuss whether or not to convey them about their disease status and if it is necessary, how it should be communicated? Before we proceed to discussion let us see few things about communication.

"Communication like tumors; can be benign or malignant"

Malignant communication destroys the hope and leaves them traumatized. While good communication aims at

- Reducing uncertainty
- Enhancing relationship
- Giving the patients and family a direction in which to move
- Preventing conspiracy of silence
- Preventing unrealistic expectations

The basic message we want to convey here is "No matter what happens to you, we will not desert you"or "You may be dying but you are still important to us". Communication is both verbal as well as nonverbal. Nonverbal communication is very important as it occupies the major part of communication.
For example:

- Our facial expression
- Eye contact
- Posture (sitting / standing)
- Pitch/pace of voice
- Touch

All verbal and nonverbal communication signal/short interest/disinterest and our attitude towards them. Basic aim of this article is to make everyone aware and to make this job easier for all of us.

Scenario 1

A 45 year old, male patient diagnosed with cancer of Esophagus, living with his wife and two unmarried daughters, comes to OPD with USG abdomen showing liver metastasis. He is unable to read his report. He is anxious about his daughters' marriage. He asks you what it is. "I will be fine no!? Since I have no complains at present and after stenting I am also able to eat well." How will you deal with it? Will you tell the truth/ hide it?

Discussion

Breaking bad news is the art of medicine. Bad news is always bad news however well it is said. But if said poorly, it will hamper the well being of patient, impair quality of life and future contact of patient with healthcare system will be thwarted.

Most of the time in efforts to protect patients from uncomfortable and distressing facts, Doctors and Nurses frequently censor their information giving in mistaken belief that what some-one does not know does not harm them. This misguided albeit, well intentioned assumption, and is made at all stages of the disease trajectory.

Our first instinct here would be to tell the patient that everything will be fine. Do not worry. But is it good in this scenario? Will it benefit patient and their relative? NO! Here patient needs to know the truth so as to make some arrangements for his family. To spend few last quality days with the family and saying something to his family members, which is important to him.

There is a SPIKES PROTOCOL for breaking bad news:[1,2]

S - setting up an interview
P - assessing patient's perception
I - obtaining patients' Invitation
K - giving knowledge and information to patient
E - addressing the patient's emotions with empathetic response
S - strategy and summary

After taking required time out for interview, here we will assess how much patient knows and how much he wants to know. We may say initially that report does not look so good though it is good that he is not having any complains at present. This is a warning shot, which will prepare the patient mentally. Now, based on the response if patient wants to know more we will tell him truth. But to give him empathetic support we will tell him that we will be with you all the time, and though disease is no longer curable, medicines are available to reduce suffering. We will

try to build up a realistic hope of having as much comfortable life as possible and to make preparations for daughters' wedding.

Scenario 2

A 14 years old boy having Ewing's sarcoma and lung metastasis brought by his parents to your OPD. They have tears in their eyes. What will be next? This is our only child and we have not missed a single appointment.
How will you communicate with parents?

Discussion

This is more sensitive issue. It is always difficult to talk with parents of pediatric patients. Here actually they have some idea about their child's disease status, though they have not heard it from doctors. Despite continuous treatment their child is not getting better and actually symptoms are worsening. All they need here is empathetic support and someone to listen their story. Active listening with nods in between and few words of support is all that they need. One can give them reassurance by saying them that we are with you and take optimum efforts to reduce his suffering. Child may not be told about prognosis. Our aim should be to give the family support and realistic hope to have good time together, however small time is left.

Scenario 3

Collusion – A situation where relatives do not want doctor to tell anything to patient.

A very common scenario in Asian culture. Where there is generally a head in the family who takes all the decision. And he is afraid patient will not be able to take the news. He/She will take most health related decisions on behalf of patients, which actually hampers patient's autonomy. While on positive note, collusion may protect the loved one from the psychological burden, but may damage patients' faith in doctor and healthcare system on long run.

Discussion

Collusion is inevitable in certain cultures and certain contexts. The imperative to provide culturally competent care (care that includes a set of behaviors, attitudes and polices that enables individuals and families from diverse cultural groups to reach their own health goals) involves a better understanding of issues of collusion and its multiple manifestations across cultures. Here, before we decide whether to tell the patient the truth or not, it is important to listen to care-givers' worries. Firstly, we need to understand families' concerns of not wanting to cause any more hurt to the patient. If patient is already depressed and/or suicidal it is better not to tell the patient. It can be postponed to subsequent meetings. Otherwise after listening to care givers worries, they should be told that it will be difficult for doctors & hospital staff to be untruthful to patient. They can be reassured and truth can be gently disclosed. Here things are situation dependent.

Is it always necessary to Break Bad News to patient?

One of the most difficult ethical dilemmas that health care professionals working in oncology settings face is whether, when, how and how much to tell cancer patients about their diagnosis and prognosis. However, there is evidence from UK that a substantial minority of patients (13%) prefers to "leave it up to the doctor" or "to have information only if it is good"[3].

It is the duty of Palliative Care physicians to handle this delicate and difficult situation. We need to understand patient's background, culture, education, social status and psychology before taking up the issue of Breaking Bad News. Control of pain and other distressing symptoms takes priority. This requires two to three visits of patients and care givers in Palliative Care OPD. Sometimes, our patients don't have such time left, when they are referred to us. This makes situation very complicated. Education of patient about their disease, involving them in decision making and empowering them about their treatment right at the stage of diagnosis, helps us to tell them about their disease status. Early reference to Department of Pain and Palliative Medicine solves lots of problem.

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Meig's Syndrome - A Diagnostic Dilemma

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Summary

Meig's syndrome is a benign condition with 100% cure rates. However this condition mimics advanced ovarian malignancy, causing diagnostic dilemma to the treating doctor. It is a rare condition and seen only in 1% cases of ovarian fibroma. The raised CA125 levels seen in our set of cases add to the diagnostic dilemma. Post operatively both ascites and pleural effusion in both our patients resolved completely. Follow up of both the patients is uneventful till date. Thus showing life expectancy after surgical removal of the tumor mirrors that of the general population.

Keywords: Meig's syndrome, Ovarian fibroma, Raised CA 125

Introduction

Meigs's syndrome is the triad of ovarian fibroma with ascites and pleural effusion. It is a rare but well known syndrome. Pleural effusion and ascites resolve with successful resection of the ovarian tumor. Although Meig's syndrome mimics a malignant condition, it is a benign disease and has a very good prognosis if properly managed. Life expectancy after surgical removal of the tumor mirrors that of the general population.

We report 2 cases mimicking epithelial ovarian tumor with significantly raised serum CA125 in postmenopausal women. Both of which ultimately turned out to be Meig's syndrome.

Case 1

Sixty years old menopausal female came with complains of abdominal distention, decrease appetite and bloating of abdomen for one week. On per abdomen examination, there was a mobile, non tender, firm to hard mass corresponding to 22-24 week size uterus arising from pelvis. On per vaginum and per rectal examination 8x10 cm hard mass posterior to uterus projecting in Pouch of Douglas (POD) was felt, uterus was felt separately from the mass. On investigation chest x-ray revealed right sided gross pleural effusion (Figure1). Computerized tomography abdomen-pelvis showed 11x10 cm sized heterogeneously enhancing soft tissue density lesion arising from pelvis. Mild ascites and gross right pleural effusion noted. CA125 was 1246 IU/ml and CEA was 2.2 ng/ml. Pleural and ascitic fluid cytology was negative for malignancy. Ultrasound guided biopsy was done thrice which was repeatedly negative. Risk of malignancy index was 11,214 (Risk of malignancy index >250 is suspicious of malignancy).

Patient developed breathlessness, hence intercostal tube was inserted on the right side which drained 1000 ml fluid. As biopsy was inconclusive, exploratory laparotomy was planned. There was a solid mobile tumour on left side. Correct intraoperative histologic assessment of an ovarian mass is crucial to select an appropriate surgical procedure and avoid under- and over-treatment of the patient so tumor was removed and sent for frozen section which reported as benign spindle cell tumor of ovary, fibroma - thecoma type. Right side ovary and uterus were normal.The other abdominal organs were found to be normal.Total abdominal hysterectomy with right salpingo-oophorectomy was done and abdomen closed in layers, thus avoiding a radical surgery for the patient. Final histopathology report revealed fibroma of left ovary. Pleural effusion subsided gradually after the removal of the tumor. Intercostal tube drain was nil by 9th postoperative day (Figure 2) and was removed on 10th postoperative day. Patient was discharged on 12th postoperative day.

Case 2

A 53 years multiparous, postmenopausal female presented with complain of abdominal distention for 1 month. On examination clinical findings were similar to case 1. Computerized tomography scan of abdomen and pelvis and tumor marker were suggestive of advanced malignancy. Risk of malignancy index was 22,887. Hence pleural and ascitic fluid cytology was done but was negative. Ultrasound guided biopsy was done twice which was negative for malignancy. Thus the diagnosis for Meig's syndrome was suspected. Intercostal tube insertion was done to relieve breathlessness, which drained 900 ml of fluid. Exploratory laparotomy with right ovarian mass removal and total abdominal hysterectomy with left salpingo-oophorectomy was done. Intraoperative 20x12 cm size solid mass on left side adherent posteriorly to small bowel was found. Per operative frozen section was reported as spindle cell tumor favouring fibroma. Opposite side ovary, uterus and other abdominal organs were grossly normal on inspection. Moderate ascites was there. Final histopathology report was fibroma left ovary (Figure 3). Ascites and effusion was clear within 3 days of surgery. Thus diagnosis of Meig's syndrome was confirmed. Patient was discharged on 10th postoperative day.

Discussion

In 1937, Meigs' and Cass described 7 cases of ovarian fibromas associated with ascites and pleural effusion.[1] This syndrome has been named after Meigs' and must fulfill the minimal criteria of pleural effusion, solid ovarian tumor and clearing of effusion after removal of the tumor.

Ovarian fibroma is found in 2-5% of surgically removed ovarian tumors, and Meig's syndrome is observed in about 1%.[2] Ascites is present in 10-15% of those with ovarian fibroma and pleural effusion in 1%, especially with large lesion.[3,4] Meigs suggested that the fluid in the abdomen originated from the edematous fibroma that can leak fluid. A discrepancy between the arterial supply to large mass of tumor tissue and its limited venous and lymphatic drainage may contribute to stromal edema and transudation.[5] Other proposed mechanisms are direct pressure on surrounding lymphatics or vessels, hormonal stimulation and tumor torsion. [6,7]

Conclusion

Meig's syndrome is a purely benign condition with almost 100% cure after surgery. Thus postmenopausal woman presenting with ascites, mobile solid ovarian mass, raised CA125 with negative ascitic, pleural fluid cytology and with repeatedly negative ultrasound guided biopsy should raise the suspicion of Meig's syndrome. Raised CA125 is an associated finding seen in some cases of Meig's, but not to forget CA125 is again a very nonspecific tumor marker.

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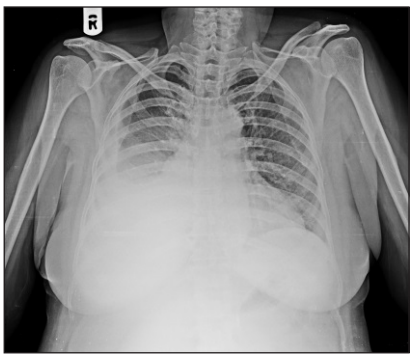

Figure 1: Pre-operative chest X-ray with gross effusion

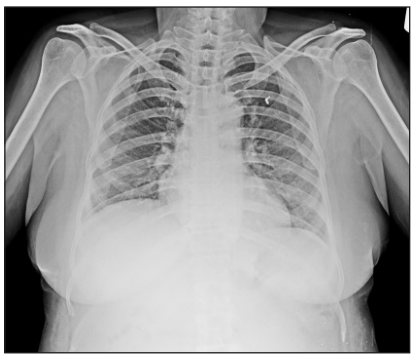

Figure 2: Post-operative chest X-ray with clear lung fields on 10th postoperative day

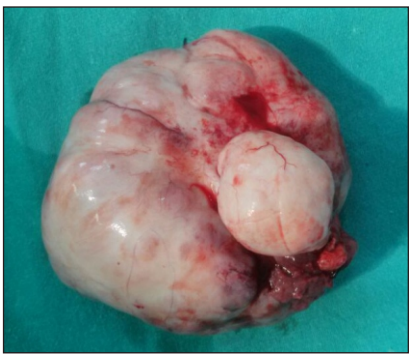

Figure 3: Specimen of ovarian tumor

As seen in our set of cases, ovarian tumor in postmenopausal females with ascites and raised CA125 suggested advanced malignancy. The coincidence of Meigs syndrome with an elevated CA125 levels has been described in the published literature in only 28 cases and in 15 cases the ovarian tumor was fibroma.[7] It has been suggested that serum elevation of CA125 antigen in patients with Meigs syndrome is caused by mesothelial expression of CA125 rather than byfibroma.[7] Mechanical irritation by the huge ascites and ovarian tumor might be the cause.

Meig's syndrome is found to be more frequent in elderly women, hence forms a very important differential diagnosis for malignancy. Thus postoperative follow up of ourpatients make usconclude that surgery is curative and life expectancy is similar to general population.

Malignant Mixed Mullerian Tumour of the Ovary- A Diagnostic Dilemma

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Summary

Malignant mixed Mullerian tumour (MMMT) of ovary or ovarian carcinosarcoma is an aggressive neoplasm of post-menopausal females. Histologically, it is comprised of both epithelial and sarcomatous components. Prognosis is poor and is largely dependent on stage and optimal cytoreduction, and partly on age and characteristic of sarcomatous component. Taxane and platinum combination is the most widely used chemotherapeutic regimen. We present here a case of MMMT in a postmenopausal female who presented to us with ovarian mass and colonic involvement.

Keywords: Malignant mixed Mullerian tumour, Pathology, Diagnosis, Prognosis, Chemotherapy

Introduction

Malignant mixed Mullerian tumour (MMMT) or ovarian carcinosarcoma, comprises approximately 1-4% of all ovarian malignancies. MMMT is an aggressive tumour with poor overall survival rate. Here, we describe a patient of MMMT who posed a diagnostic and management challenge.

Case Report

A 45 years old postmenopausal woman presented to us with complaints of progressive abdominal pain and lump lower abdomen since two months. Her obstetric history suggested four uneventful pregnancies – all healthy live births. She had no past history of surgery, irradiation or exogenous estrogen or hormonal therapy. On examination, her vitals were stable and abdominal examination revealed a large mass in her lower abdomen extending above umbilicus. Per-speculum and bimanual examination revealed mass in the right adnexa. Investigations showed normal baseline laboratory parameters. Serum CA-125 was elevated (379 U/ml). Sonography of the abdomen and pelvis showed a lesion of heterogenous echogenecity in the pelvis with involvement of both the ovaries. Uterus, liver, pancreas and gall-bladder were all normal. On computerized tomography (CT) of the abdomen and pelvis, a large mass lesion of size 18x15x19 cm was visualized, arising from the pelvis, adherent to uterus and extending upwards into lower abdomen with involvement of both the ovaries. Anteriorly, the mass was displacing urinary bladder. Posteriorly, it was displacing rectum, rectosigmoid junction and sigmoid colon with luminal compromise and there was loss of fat plane between the mass and sigmoid colon. Mild free fluid was present. The patient was taken up for laparotomy with a probable diagnosis of ovarian malignancy. At laparotomy, mild ascites was present and a mass of around 23x18x65 cm was seen adherent to uterus and sigmoid colon. En-bloc removal of mass was done with total abdominal hysterectomy, left salpingo-oophorectomy, part of large intestine with lower colorectal anastomosis. Optimal cytoreduction and no residual disease present. The operative and post-operative periods remained uneventful and the patient was discharged on 16th post-operative day. Subsequently, she received six cycles of carboplatin and paclitaxel. Patient was on regular follow up for 6 months then she developed recurrent pelvic mass. She took only one cycle of ifosfamide and doxorubicin and did not report for further treatment.

Pathological Findings

Gross Examination: A greyish white to brown mass was identified arising from right adnexa measuring 23x18x65 cm with irregular borders, variegated appearance and necrotic cut surface. It was adherent to fundus and right lateral wall of uterus, anterior lip of cervix and serosal wall of sigmoid colon (Figure 1).

Microscopic Details: Microscopy of the tumour showed presence of both carcinomatous as well as sarcomatous components indicative of malignant mixed mullerian tumour of ovary stage-IIB as per FIGO classification (Figure 2-4). Tumour had a sarcomatous component of >90% and mitotic figures were >10 per high power field with 100% homogenous component. Immunohistochemical staining revealed positivity for epithelial marker (EMA) suggestive of carcinomatous component as well as for vimentin, desmin, actin and CD10 suggestive of sarcomatous component. Tumour was involving serosa while muscular layer of colon was free. Tumour extends to involve fundus and right lateral wall of uterus, anterior lip of cervix. Left fallopian tube and left ovary were unremarkable.

Discussion

MMMT of the ovary is a rare malignant neoplasm with an aggressive clinical course and carries a poor prognosis. MMMT most commonly arise from either uterus or ovary, although they may

develop anywhere along the female genital tract and rarely in the peritoneum. Proposers of metaplastic theory suggest that epithelial cells transform into sarcomatoid ones.[1] On the contrary, other workers have shown presence of epithelial-like characteristics in both kinds of tumour cells.[2-4] The high recurrence rates again points towards some other mechanism and need for further studies in relation to tumour molecular characteristics to guide development of targeted therapies.

Clinically, MMMT is a malignancy of post-menopausal females between fifth to seventh decades of their lives. Presentation is similar to ovarian adenocarcinoma. Histologically, MMMT is a biphasic tumour composed of both carcinomatous and mesenchymal components which may be either homologous or heterologous to ovary. The morphologic heterogeneity poses difficulty in accurate diagnosis.[1-3] Diagnosis is confirmed by immunohistochemical staining demonstrating both carcinomatous and sarcomatous components and also by electron microscopy.[4] Prognosis of this tumour is overall poor. Relationship of poor prognosis with presence of heterologous component is controversial. Some workers have not found this to be associated with worse prognosis.[4-7] Also, the extent, percentage and mitotic activity of sarcomatous component have not been found to impart an aggressive behaviour in mesenchymal predominant tumour.[1,2,8,9] Other clinical and histopathogical parameters such as age of the patient, tumour size, laterality, vascular invasion, histologic type and grade of carcinomatous component, necrosis and amount of necrosis were not found to be associated with poor outcome in several studies .[4,5,8-12](Table 1) The sarcomatous component in our patient was more than 90% which, as per some workers, is indicative of poor prognosis.

Because of rarity of disease no standard treatment has been recommended. Role of optimal cytoreduction in epithelial ovarian carcinoma is well established; however in ovarian MMMT the results are not always good. In a review of 27 patients, a benefit of optimal surgical cytoreduction has been reported in patients with advanced malignancy – 2-year survival of 52% with cytoreduction versus 14% without.[6] Sood et al also demonstrated improved outcome with surgical cytoreduction in 47 patients (25 months versus 8 months).[8] Similarly, Rutledge et al reported a benefit of optimal cytoreduction with median survival of 25 months in comparison to 16 months in the suboptimal group.[13] Duska et al showed an increase in disease free interval,but not in overall survival with optimal cytoreduction.[14] In another retrospective series, Cicin et al reported improved survival in optimally debulked patients.[15] Similarly, Brown et al reported longer median survival in patients with optimal debulking (14.8 versus 3.1 months).[10] However, it has also been suggested that surgery for MMMT can be difficult and associated with high morbidity.[8] Surgical stage has been shown to provide prognostic information and better survival is seen in patients with lower stage of the disease.[4-6,8]

There is no consensus on the optimal chemotherapeutic regimen in MMMT.Multiple regimens have been evaluated with modest response rates. The trials are difficult to evaluate due to small number of patients, retrospective nature of series, multiple treatment regimens and occasional use of radiation therapy. Review of literature does seem to support the use of platinum based chemotherapy

Table 1: Factors predicting poor outcome of ovarian MMMT

Study	Year	No. of patients	Variables analysed	Factors significantly predictive of outcome
Chang et al [5]	1995	37	FIGO stage, type of SC,grade, type and % of CC	FIGO stage
Sood et al[8]	1998	40	FIGO stage, status of surgical debulking, type of SC, adjuvant treatment, preoperative CA-125	Stage, type of SC
Ariyoshi et al[4]	2000	23	Stage,tumour size, histologic type of CC and SC, mitotic count,vascular invasion,residual tumour size, P53,Ki67 immunochemistry	FIGO stage
Harris et al[11]	2003	40	Stage, type of SC, status of surgical debulking	Stage ,type of SC
Brown et al[10]	2004	65	FIGO stage, status of surgery debulking, type of SC	Status of surgical debulking
Kunkel et al[9]	2012	47	Stage, histologic type of CC and SC,mitotic count, % of SC, vascular invasion, size, laterality, necrosis,tumour outside ovary, degree of surgical debulking	Tumour outside ovary, stage
Jernigan et al[12]	2013	47	Age, preoperative CA 125, stage, cytoreduction, type of surgery	Age, stage, residual disease (>1cm)

CC = Carinomatous component; SC = Sarcomatous component.

regimens with a 68% overall response rate in the platinum group compared with 23% response rate in the non-platinum containing regimens.[6,10,11,16,17] In a retrospective study of 28 MMMT cases treated with platinum and paclitaxel, Duska et al reported 16 patients with complete response and six patients with partial response with overall median survival of 27.1 months.[14] In the study by Rutledge et al with 27 patients, 11 received platinum and ifosfamide, whereas 16 received platinum and taxane combination. Although the overall survival was improved with the use of ifosfamide and cisplatin, there was no significant advantage for advanced stage subgroup.[13] Leiser et al reported 40% complete and 23% partial response in patients treated with platinum and taxanecombinations.[17] A pilot study by Crotzer et al evaluated the safety and activity of ifosfamide, cisplatin and mesna showed median overall survival of 21 months was reported in eight patients with acceptable toxicity.[18] The best overall survival of 46 months was recently reported in 10 patients with advance disease, all of whom underwent aggressively debulking surgery followed by platinum based combination therapy.[19] On the basis of available literature, we started platinum and taxane based chemotherapy in our patient.

Conclusion

MMMT of the ovary is a very aggressive tumour usually diagnosed at an advance stage. Survival depends on stage and partially on histological type. Management recommendations are inadequate due to rarity of disease, retrospective nature of studies and non-uniformity of treatment. Despite aggressive treatment, women with MMMT of ovary have increased risk of death. The poor prognosis associated with this rare malignancy emphasizes the need for collaborative prospective studies targeted to better understand the molecular pathogenesis and to develop newer targeted therapies to improve patient's survival.

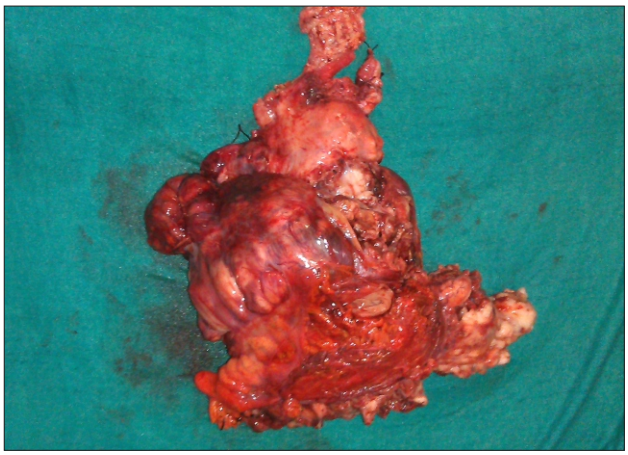

Figure 1: Gross specimen of resected heterogenous ovarian mass with uterus and fallopian tubes

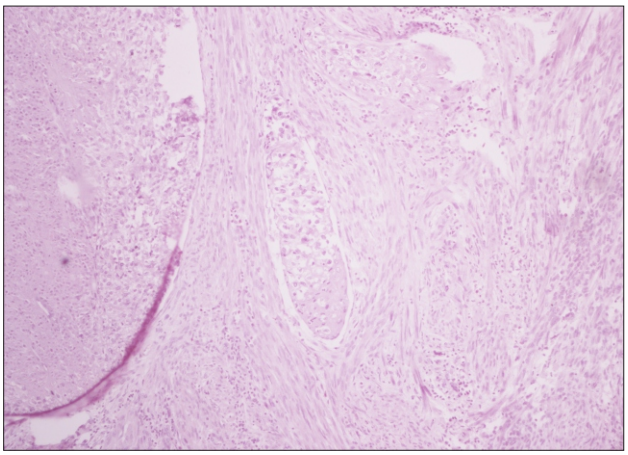

Figure 2: Microscopic view of the tumour specimen showing epithelial component in a malignant stroma (H&E stain, 10x)

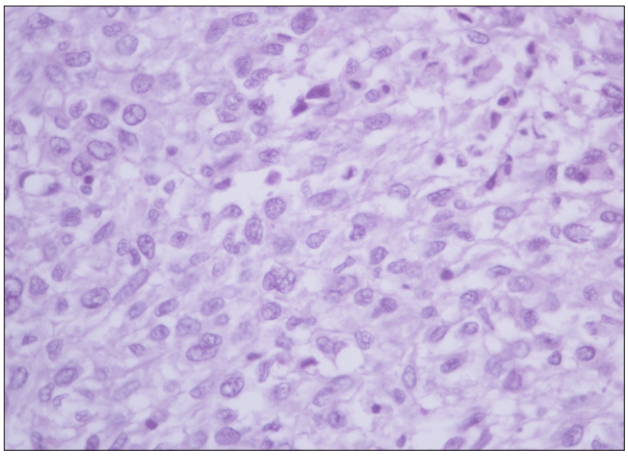

Figure 3: High power view of the tumour showing solid sheets of epithelial cells with well-defined cell borders (H&E stain, 40x)

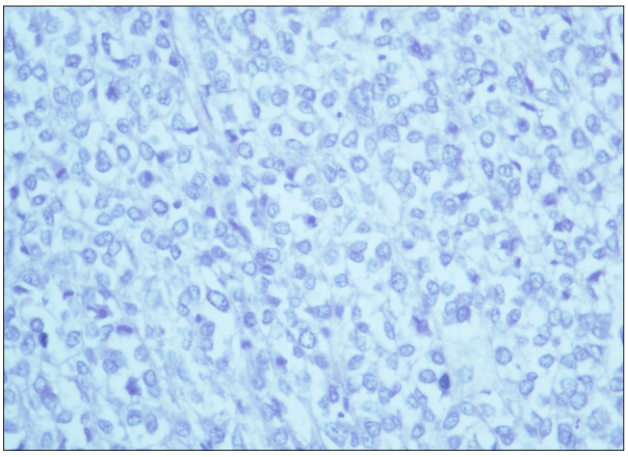

Figure 4: High power view of the tumour showing diffuse staining of fascicles of spindle cells (H&E stain, 40x)

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Anaesthetic Management of a Child with a Large Wilms' Tumour-A Case Report

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Summary

This case report describes the anaesthetic management of a male child with a right sided Wilms' tumour (post chemotherapy) aged 7 years and weighing 25 kg. Patient presented with severe abdominal pain and rise in temperature. Patient had enlarged tense abdomen, tachypnoeia, pallor and hypertension. Here we describe the important role of anaesthesiologist in the perioperative management of surgical resection of Wilms' tumour in a child which includes preoperative optimization, management of intraoperative and postoperative complications.

Keywords : Wilms' tumour, Paediatric patient, Anaesthetic management

Introduction

Nephroblastoma or Wilms' tumor is the most common malignant renal tumor in children. It accounts for approximately 5–6% of the neoplasms in children and is rare in the adult population.[1] There are dramatic improvements in survival due to advances in anaesthetic and surgical management, radiation therapy and chemotherapy.[2]

Case Report

A seven year old male child weighing 25 kg was admitted in our institute with eight days history of sudden onset of abdominal pain and fever. By paediatric oncology department chemotherapy was started (actinomycin D, vincristine, doxorubicine). As tumour was chemoresistant, surgical resection was planned.

Patient presented with severe abdominal pain, fever, breathlessness and hypertension. On examination patient was pale and breathless, had temperature-102^{0}F, pulse (P)-140/min, blood pressure (BP)-170/130 mm Hg. In respiratory system there was decreased air entry in right basal zone. Cardiovascular system was showing tachycardia and central nervous system was normal. Patient's abdomen was grossly distended with dilated veins. There was no history of hematuria and vomiting, previous surgery, anaesthesia, blood transfusion, any other illness and any developmental anomalies. All blood investigations were normal except, haemoglobin-4.3gm/dl, total count- 18,600/cmm and chest x-ray was showing elevated right dome of diaphragm with clear lungs. In ECG there was T inversion in chest leads, 2D Echo was normal, urinary venyllylmandellic acid was 1.2mg/24 hr, pulmonary function tests were showing restrictive stage COPD, CT abdomen and pelvis was showing large mass of 16×16×24 cm arising from upper and mid pole of right kidney, infiltrating right lobe of liver, stretching inferior vena cava and renal hilar vessels. Ultrasonography guided biopsy was showing Wilms' tumour with predominant epithelial component. Cardiologist advised tab clonidine (0.1mg) twice a day and tab metoprolol (12.5mg) twice a day. Infection was controlled with antibiotic and antipyretic in a week. With packed cell transfusion Hb was raised from 4.3gm/dl to 9gm/dl.

After preoperative optimization, written informed consent of patient's relative was taken for high risk surgery and anaesthesia, peroperative excessive blood loss and post operative ventilatory support. Outcome of anesthesia was explained to relatives. Morning antihypertensive doses were given two hours before surgery with a sip of water. In the operation room all the monitors were applied which showed: P-118/min, BP-150/120 mm Hg, respiratory rate 28/min and temp 99^{0}F. Intravenous line was secured with 20 G peripheral venous cannula. Ringer lactate was started. Inj cefuroxime 500 mg, inj ranitidine 1mg/kg and inj ondansetron 0.2 mg/kg were given intravenously. Inj Glycopyrrolate 0.004 mg/kg, inj fentanyl 2 mcg/kg were given intravenously five minutes before induction of anaesthesia. After three minutes of preoxygenation, patient was induced with inj thiopentone sodium 5 mg/kg, inj atracurium hydrochloride 0.5 mg/kg intravenously and patient was intubated with endotracheal tube no. 5.5 in semisitting position as patient was not able to sleep in supine position due to large abdominal mass. Anaesthesia was maintained with O2+ N2O + sevoflurane + atracurium. Central venous catheter was inserted in right basilic vein. Patient's extremities were wrapped in cotton wool to prevent heat loss.

During intraoperative period temperature, pulse, BP, ECG, SpO2, EtCO2, CVP, blood loss, urine output and Ryle's tube aspirate were monitored. Due to tumor spillage, total three litre of blood was lost and BP fell down to 60/38 mm Hg. So noradrenaline infusion at the rate of 8 mcg/min was started. Volume

replacement was done with 1400 ml of packed cells (PCV), 500 ml haemacele, 300 ml fresh frozen plasma (FFP), 300 ml platelet rich plasma (PRP), two litre RL and one litre normal saline. During laprotomy, a tumor arising from right kidney was pushing the liver upwards and bowel to one side. Renal vein was clamped and debulking of tumor was done. Haemostasis was achieved. Total duration of surgery was 5 hours. Urine output was 70 ml at the end of operation.

Before the abdominal closure 500 mg paracetamol infusion was started and repeated eight hourly for two days. Patient was shifted to ICU and was put on elective mechanical ventilation with inj atracurium 6 mg/hr and inj fentanyl 12 mcg/hr. Inotropic support with noradrenaline infusion was continued till normalization of BP. Arterial blood gas report was showing acidosis. Hb was 3.1 mg/dl with TC- 8800/cmm3 and PC- 60,000/cmm3 which was corrected with 2 units of PCV, 2 units of PRP, 2 units of FFP (each unit containing 125 ml). On first postoperative day infusion of inj dexmeditomidine was started at the rate of 0.25mcg/kg/hr and atracurium and fentanyl infusions were stopped. On second postoperative day patient was extubated. As Hb level and PC were low and prothrombin Time (International Normalised Ratio) was high, inj Vit K 10 mg IV once a day, PCV, PRP and FFP were given till complete correction of coagulation profile. Due to coagulation abnormality surgical wound drain was around 600-700ml per day for five days. Total eight units PCV, 12 units FFP , six units PRP were infused in ICU. Urine output was maintained with IV fluids and inj lasix. Multiple ABG (arterial blood gas) reports were showing CO2 retention and acidosis. Patient was kept on BIPAP (Biphasic positive airway pressure) intermittently for five days. Potassium and magnesium were supplemented to correct their lower levels. On the 10th post operative day, all blood investigations and X-Ray chest were normal. Patient was shifted to ward with 20 kg body weight on 11th post operative day.

Discussion

Wilms' tumour is the most common malignant renal tumour in children. It is usually unilateral but bilateral in some patients. It is associated with birth defects including urinary tract abnormalities, absence of iris and hemihypertrophy.[1] Patient presents with abdominal swelling, abdominal pain, fever, leucocytosis, vomiting, biood in urine and hypertension. Wilms' tumour may secrete increased amounts of renin causing hypertension and it is corrected after removal of tumor. Before nephrectomy plasma renin activity levels are found significantly higher.[3]

Our patient presented with large abdominal swelling associated with abdominal pain, fever, leucocytosis and hypertension. We tried to normalize BP before surgery using tab clonidine and tab metoprolol. Due to large abdominal tumour, patient had breathing difficulties and was not able sleep in supine position. So we induced him in semi sitting position with pillows under the occipital region and shoulder.

Preoperative chemotherapy decreases tumour size resulting in easier surgeries with significantly fewer incidences of tumour rupture and a favourable stage distribution.[4] But unfortunately our patient was chemo-resistant. A rupture of Wilms' tumour puts the patient at risk of haemorrhage and peritoneal dissemination of the tumour. So surgical intervention by surgeon who is experienced in the removal of such a fragile tumour is imperative. In our case, there was tumour spillage per-operatively and resulted in massive blood loss which needed multiple blood transfusions. Guideline for massive blood transfusion was strictly followed.[5]

Kosloske et al reported a case of intraperitoneal rupture of Wilms' tumour. Right nephrectomy was followed by chemotherapy and radiotherapy. There was no metastatic tumour after two years of completion of chemotherapy.[6]

Patient had coagulation abnormalities and acidosis in the post operative period. Patient needed BIPAP intermittently and 10 days stay in ICU. Post operative acidosis is observed in patients after major abdominal surgeries. Operation length, estimated blood loss and saline infused are higher in acidotic patientts. ICU stay is also significantly higher in acidotic group of patients .[7]

Caudal epidural analgesia was not used as proper positioning of patient was not possible due to large abdomen preoperatively and abnormal coagulation profile and hypotension postoperatively. Analgesia was provided with inj fentanyl and inj paracetamol as both are safe. NSAIDS may worsen the preexisting renal dysfunction. Dexmeditomidine was used in lower dose.

Conclusion

High mortality is seen with surgical resection of a large Wilms' tumour due to preoperative hypertention, massive blood loss and shock. Succesful management of such patient requires preoperative optimization of patient, an adequate preoperative preparation, selection of appropriate anaesthetics technique and agent and careful postoperative management. Surgical expertise in paediatric malignant tumour resection is also equally important.

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"If insurance companies paid for lifestyle-management classes, they would save huge sums of money. We need to see that alternative medicine is now mainstream."

Deepak Chopra

Summaries of Published Articles

01. Association between p53 gene variants and oral cancer susceptibility in population from Gujarat, West India

Kinjal R Patel, Bhairavi N Vajaria, Rasheedunnisa Begum, Franky D Shah, Jayendra B Patel, Shilin N Shukla, Prabhudas S Patel

Summary

p53 gene variants i.e. 16 bp duplication in intron 3, Arg72Pro in exon 4 and G>A in intron 6 have been reported to modulate susceptibility to various malignancies. Therefore, the present study evaluated the role of these p53 polymorphisms in oral cancer susceptibility in a population from Gujarat, West India. Method: Genotype frequencies at the three p53 loci in 110 controls and 79 oral cancer cases were determined by the PCR-RFLP method. Results: Heterozygous individuals at exon 4 showed protection from developing oral cancer. Homozygous wild and heterozygous individuals at intron 3 and those heterozygous at exon 4 in combination appeared to be at lowered risk. Furthermore, carriers of the 16 bp duplication allele at intron 3, proline allele at exon 4 and G allele at intron 6 were protected from oral cancer development. Conclusion: p53 polymorphisms, especially Arg72Pro in exon 4 could significantly modify the risk of oral cancer development in Gujarat, West Indian population.

Asian Pacific J Cancer Prev 2013, 14 (2), 1093-1100

02. Evaluation of Serum and Salivary Total sialic acid and Alpha-L-Fucosidase in Patients with Oral Precancerous Conditions and Oral Cancer

Bhairavi N Vajaria, Kinjal R Patel, Rasheedunnisa Begum, Franky D Shah, Jayendra B Patel, Shilin N Shukla, Prabhudas S Patel

Summary

We compared serum and salivary total sialic acid/total protein (TSA/TP) ratios and a-L-fucosidase activity in patients with oral precancerous conditions (OPCs) and oral cancer to better understand the utility of saliva, in monitoring early changes occurring during oral cancer progression. A cross-sectional study of 100 oral cancer patients, 50 patients with OPC, and 100 controls was performed. Serum and salivary TSA/TP ratios and α-L fucosidase activity were significantly higher in OPC and oral cancer patients compared to the controls. Also, levels were higher in controls and oral cancer patients with tobacco habits as compared to those without tobacco habits. Salivary TSA/TP ratio and α -L-fucosidase activity were elevated with higher magnitude than serum levels. These results suggest that a larger study may prove the use of these saliva biomarkers as a noninvasive method for detecting early changes occurring during oral carcinogenesis

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology 2013, 115; 764-771

03. A Review on Genetic Susceptibility Towards Oral Cancer Risk Among Indian Population

Patel Kinjal R, Vajaria Bhairavi N, Begum Rasheedunnisa, Patel Prabhudas S

Summary

Oral cancer is the major health burden in India. Recently an increasing trend of oral cancer incidence especially in the younger population are reported from Gujarat, the western part of India, which is mainly due to different forms of tobacco consumption. Moreover, not allthe tobacco habituates develop oral cancer; this disparity is mainly attributed to differences in genetic susceptibility of the individuals. Therefore, the association of genetic polymorphism with etiology of oral cancer needs to be explored thoroughly. In the studies on genetic polymorphism and oral cancer risk among Indian, it is observed that the most commonly studies genes for oral cancer risk assessment include carcinogen metabolizing enzymes. Apart from this, genetic polymorphism in cell cycle related and DNA repair gens are much explored in recent years. Studies representing single polymorphism may remain insufficient to validate an association between gene polymorphism and oral cacner risk. However, there is a great dearth of reports from India focusing on gene –gene and gene environment association. Thus, studies that concomitantly consider multiple genetic and environmental factors involved in oral carcinongenesis are needed not only to establish the contribution of these factors to oral cancer development but also to understand their putative interactions. The data generated might be helpful in construction of genetic risk profiles which will help to delineate the individuals that are at higher risk of developing this disease. Identifying molecular markers associated with individual's vulnerablility to oral cancer due to tobacco exposure might prove to be useful as early indicators of risk. Such molecular markers may be ultimately useful for preventive purposes and risk assessment of oral cancer.

Gujarat Cancer Society Research Journal. 2013;15: 10-17

04. Gene Polymorphism, Tobacco Exposure and Oral Cancer Susceptibility- A Study From Gujarat, West India

Ragini D Singh, Haridas N, Franky D Shah, Jayendra B Patel, Shilin N Shukla, Prabhudas S Patel

Summary

Polymorphic variability in the enzymes involved in biotransformation of tobacco-related pro-carcinogens plays an important role in modulating oral cancer susceptibility. CYP1A1*2A, CYP1A1*2C, GSTM1 and GSTT1 polymorphisms were determined in 122 oral carcinoma cases and 127 controls from Gujarat, West India using PCR-based methods. The results revealed that the polymorphic variants of CYP1A1 gene did not show association towards oral cancer risk. The GSTM1 and GSTT1 null genotypes were found to be over-represented in patients than controls, suggesting a moderate increase in risk of oral cancer. The oral cancer risk was significantly increased in the patients having either alone or concurrent deletion of GSTM1 and GSTT1. The results also suggested significant association between tobacco habits, especially chewing, variant genotypes of CYP1A1, GSTM1 and GSTT1 and oral cancer risk. Our data have provided evidence that GST polymorphism modified the susceptibility to oral cancer and individuals with variant genotypes of the three genes with tobacco habits are at significant risk of developing oral cancer.

Oral Disease 2014; 20: 84-93

05. Prevalence of High-Risk Human Papillomavirus Type 16 And 18 in Oral and Cervical Cancers in Population from Gujarat, West India

Kinjal R Patel, Bhairavi N Vajaria, Rasheedunnisa Begum, Ava Desai, Jayendra B Patel, Franky D. Shah, Shilin N Shukla, Prabhudas S Patel

Summary

Oral and cervical cancers are major malignancies in men and women, respectively, in India. This study evaluated occurrence of human papillomavirus (HPV) 16 and 18 infections in oral and cervical cancers to estimate HPV-associated burden of these cancers in the population from Gujarat, West India. A total of 97 malignant oral carcinoma tissues and 52 cervical carcinoma tissues were analyzed by type-specific PCR for the presence of HPV type 16 and 18 infections. None of the oral cancer patients revealed the presence of HPV type 16 and 18 infection. In cervical cancer, 31 (59.6%) patients were infected with HPV 16 and 18. Of these 31 HPV-positive cervical cancer patients, 28 (90.3%) were infected with HPV 16 and 3 (9.7%) were infected with HPV 18. CONCLUSION: The results suggested that HPV 16 and 18 do not play an important role in oral carcinogenesis in the population from Gujarat, West India. However, HPV16 is highly prevalent in the cervical cancer patients, which may be considered for planning of prevention programs such as screening and vaccination in women from this region.

J Oral Pathol Med 2014; 43: 293-297

06. Significance of glycosyltransferases: ST3GAL1, FUT3, FUT5 and FUT6 transcripts in oral cancer.

Bhairavi N Vajaria, Kinjal R Patel, Rasheedunnisa Begum, Franky D Shah, Jayendra B Patel, Geeta M Joshi, Prabhudas S Patel

Summary

Oral carcinogenesis process is frequently accompanied by alterations in glycosylation, regulated by sialyltransferase (ST) and fucosyltransferase (FUT) enzymes. The study aimed to assess ST3GAL1, FUT3, FUT5, and FUT6 mRNA expression by semi-quantitative reverse transcriptase PCR in 50 oral cancer and 50 adjacent normal tissues. The results indicated increased ST3GAL1 mRNA levels in malignant tissues as compared to adjacent normal tissues. A significant decrease in FUT3 and FUT5 transcripts was observed in malignant tissues as compared to adjacent normal tissues. Survival analysis of FUT3 transcript levels depicted significant lower survival with values above cutoff. The levels of ST3GAL1 and FUT6 were found to be higher in metastatic tissues as compared to the non-metastatic tissues and were also higher in advanced disease as compared to the early disease. The results indicated potential clinical utility of ST3GAL1, FUT3, FUT5, and FUT6 transcript levels in oral cancer pathogenesis.

Glycobiology Insights 2014; 4 :7-14.

Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, Lugli A, Zlobec I, Hartmann A, Bifulco C, Nagtegaal ID, Palmqvist R, Masucci GV, BottiG,Tatangelo F, Delrio P, Maio M, Laghi L, Grizzi F, Asslaber M, D'Arrigo C, Vidal-Vanaclocha F, Zavadova E, Chouchane L, Ohashi PS, Hafezi-Bakhtiari S, Wouters BG, Roehrl M, Nguyen L, Kawakami Y, Hazama S, Okuno K, Ogino S, Gibbs P, Waring P, Sato N, Torigoe T, Itoh K, Patel PS, Shukla SN, Wang Y, Kopetz S Sinicrope FA, Scripcariu V, Ascierto PA, Marincola FM, Fox BA, Pagès F. J Pathol. 2014 Jan;232:199-209.

The American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TNM staging system provides the most reliable guidelines for the routine prognostication and treatment of colorectal carcinoma. This traditional tumour staging

summarizes data on tumour burden (T), the presence of cancer cells in draining and regional lymph nodes (N) and evidence for distant metastases (M). However, it is now recognized that the clinical outcome can vary significantly among patients within the same stage. The current classification provides limited prognostic information and does not predict response to therapy. Multiple ways to classify cancer and to distinguish different subtypes of colorectal cancer have been proposed, including morphology, cell origin, molecular pathways, mutation status and gene expression-based stratification. These parameters rely on tumour-cell characteristics. Extensive literature has investigated the host immune response against cancer and demonstrated the prognostic impact of the in situ immune cell infiltrate in tumours. A methodology named 'Immunoscore' has been defined to quantify the in situ immune infiltrate. In colorectal cancer, the Immunoscore may add to the significance of the current AJCC/UICC TNM classification, since it has been demonstrated to be a prognostic factor superior to the AJCC/UICC TNM classification. An international consortium has been initiated to validate and promote the Immunoscore in routine clinical settings. The results of this international consortium may result in the implementation of the Immunoscore as a new component for the classification of cancer, designated TNM-I (TNM-Immune).

"Music is therapy. Music moves people. It connects people in ways that no other medium can. It pulls heart strings. It acts as medicine."

Macklemore

Summaries of Presentations at Clinical Meetings

01. Lung and Skeletal Metastases in Patients with Differentiated Thyroid Carcinoma and Evaluation of Response to Radioiodine Therapy

Rachh Swati
Department of Nuclear Medicine

Summary

The most common site of metastases in differentiated thyroid carcinomas (DTCs) is the lungs followed by bone. In our study, we aimed to determine the ratios of lung and skeletal metastases in patients with DTCs and response to radioiodine therapy. A total 500 patients with DTCs who were admitted in the radioiodine therapy ward were included in the study. High doses of ^{131}I were administered to the patients with lung and bone metastases. Responses to therapy were evaluated with ^{131}I scans and stimulated thyroglobulin levels were examined at least 6 months to 1 year after therapy. Lung metastases were detected in 46 (9.2%) of 500 patients with DTCs. The primary tumors in these patients were histological classified as papillary 35 (76.1%), follicular 11 (23.9%). 31 (67.4%) patients have documented lung metastasis only, 14 (30.4%) patients had lung and skeletal metastasis and 1(2.3%) patient had lung, liver and kidney metastasis. 28 out of total 46 patients with complete follow up data in which we evaluated the response of therapy, complete response to therapy was obtained in 4 (14.3), partial response was obtained in 13 (46.4%) and no response could be obtained in 11 (39.3%). Skeletal metastases were detected in 35 (7.0%) of 500 patients with DTCs. The primary tumors in these patients were histological classified as papillary 13 (37.1%) and follicular 22 (62.9%). 21 patients have documented skeletal metastasis only (58.3%). Seventeen out of total 35 patients with complete follow up data in which we evaluated the response of therapy, complete response to therapy was obtained in 3 (18.8%), partial response was obtained in 4 (25%) and no response could be obtained in 10 (62.5%). Although lung and skeletal metastases from DTCs are rare, those are more common in advanced ages and males. Patients with only lung/skeletal metastasis has good prognosis. High doses of ^{131}I therapy may be partially beneficial in these patients. Thus repetition of therapy is frequently required.

02. Molecular Insight in to Drug Resistance to Imatinib in Ph+ CML: Multifactorial Approach

Rawal Rakesh M.
Division of Medicinal Chemistry and Pharmacogenomics

Summary

Chronic myeloid leukaemia (CML) is a myeloproliferative disease of stem cell origin. It is characterized by the Ph chromosome, product of reciprocal translocation between chromosome 9 and 22 which produce constitutively activated Bcr-Abl fusion protien that is causative in CML. Imatinib, TKIs target Bcr-Abl and block its tyrosine kinase activity, has led to the significant prolongation of life and remission in a majority of patients, but relapses are an increasing problem. Acquisition of ABL kinase mutations, Clonal evolution of the gene, quiescent stem cell, Drug exporter and importers and plasma protein bindings are known to be major mediators of clinical resistance. It has been hypothized that imatinib-resistant leukemic cells emerge from CML stem cells that acquire resistance even before exposure to BCR–ABL targeted agents such as imatinib. In-vitro screening of Ph+ CML cells have been treated with circulating levels of Imatinib at different time intervals using patient's plasma receiving Imatinib. Mutational and gene expression analysis was done by ASO and RT-PCR, respectively. Residual resistant cells those harbouring the mutant clone reappeared and repopulated after 72 hours suggestive of presence of a clone harbouring more than one mutation. Clones harbouring mutation at Imatinib binding site repopulates at faster rate as compared to other mutations. MDR-1 gene is inducible in a dose and time dependent manner. Imatinib resistant mutations are present at the time of diagnosis goes in favour of it substantiating the fact that few of the myeloid leukemic cells harbor one or more than one mutation at or near Imatinib binding site which ultimately determines its prognosis.

03. Metastatic Behaviour of Subtypes in Locally Advanced Breast Cancer

Nagpal Puneet
Department of Radiotherapy

Summary

Breast cancer is by far the most frequent cancer among women in developed world as well as in urban India. In developing countries, major chunk of patients have locally advanced or metastatic disease at the time of diagnosis. the study intended to see the association of locally advanced breast carcinoma patients based on their subtypes with the different sites of metastasis. A total of 200 randomly selected locally advanced carcinoma breast patients were studied retrospectively (from 1st January - 31st December 2010). Patients were tested for their ER/PR/HER 2

NEU status at the start of the treatment. Patients were provided treatment as per their requirement. Patients were then kept on follow up till they develop any local or distant failures. Bone was the most common site of metastasis in all the subtypes of breast carcinoma except triple negative subtype. Keeping Luminal A/B as the reference there was an increased rate of metastasis in Luminal HER and HER2 enriched subtypes at all the sites viz. brain, bone, liver and lung. HER2 Enriched subtype patients had around 25-28% of metastasis at all the sites with slight lesser incidence of brain metastasis (21%).

04. PET CT- How It Helped in Management of Gynaecological Malignancy

Pawar Ashwini
Department of Gynaecologic Oncology

Summary

To study role of PET CT (Positron Emission Tomography) in diagnosis and management of gynaecological malignancies in primary and recurrent setting. A retrospective analysis was done of 56 cases to study role of PET CT in the management of different gynecological malignancies in the patients registered for treatment in department of gynaec-oncology at Gujarat Cancer and Research Institute, Ahmedabad from June 2011 to December 2013. PET scan was indicated for pre-treatment (staging), to confirm recurrence, and to monitor therapeutic response. Out of 56 cases of PET done: carcinoma cervix-23, carcinoma endometrium-9, carcinoma ovary-20 , carcinoma vulva -1 , carcinoma vagina -2, GTN-1, PET scan was negative in 37 % of patients where CT scan was suspicious, which changed the therapeutic modality and prevented further unnecessary interventions. In cases clinically suspected of recurrence, where CT scan was negative, PET-CT was able to pick up malignancy in 78% cases. 9 patients with recurrence and inconclusive CT scan but negative PET CT scan were kept on follow up, thus reducing further morbidity and cost. PET-CT, a non invasive modality has been shown effective in identification of malignant tissue in different primary and metastatic tumor types. It can detect lesions otherwise missed or misinterpreted on conventional morphological imaging studies including CT-scan.It is possible that the addition of PET-CT to gynaecologist's imaging armamentarium may improve both outcomes and costs by altering management strategies in indicated cases of primary and recurrent setting.

05. A Retrospective Analysis of Neuroendocrine Tumor of Pancreas- A Single Institute Study

Sundaram Pillai K
Department of Surgical Oncology

Summary

Pancreatic NET are a sub group of GEP-NETs (gastro-entero-panceratic tumor) with unique tumor biology, natural history and clinical management. The study includes NET of pancreatic origin referred to GCRI during the period from January 2008 to December 2010. In this study of 70 patients, 61(87.14%) were non functional. In this study, male: female ratio is 4:1. Approximately 77% of PETs were advanced on presentation (57% metastatic and 20% locally advanced). 20 patients had disease resectable on presentation (11 non functional + 9 functional). These 20 patients belong to stage I and II of TNM staging system. Only 4 out of 40 metastatic disease had locally resectable tumor of whom 2 underwent distal pancreatectomy and pancreatico-duodenectomy each. In the absence of randomized control trial and prospective studies, we hope this case series will help to guide the management of NET pancreas.

06. Need of Antibody Screening

Kusumgar Rima
Blood Bank

Summary

Antibody screening is used to detect red cell antibodies in patients' serum. Approximately 5% of patients have a positive antibody screening due to IgG antibodies, IgM antibodies or both. Most clinically significant allo-antibodies are IgG antibodies that react best at 37°C and are formed as a result of previous exposure via transfusion or pregnancy. Examples include antibodies to Rh, Kell, Kidd, and Duffy red cell antigens. IgM antibodies are usually not clinically significant (except for ABO antibodies) but are a source of in-vitro serologic difficulty that may delay transfusion. Antibody screening has been performed to detect unexpected circulating antibodies to red cell antigens in the recipient's or donor's serum before transfusion, to determine the presence of anti-D antibody in maternal blood, to evaluate the need for Rh immune globulin administration, to aid diagnosis of acquired hemolytic anemia. Allo-immunisation to red cell Ags is current problem in transfusion medicine. Additional testing of blood donors for Rh and Kell Ag should be implemented as a routine to prevent as far as possible incidence of alloimmunisation which would be cost effective to provide compatible blood to allo-immunised patients extended blood typing should be implemented for some categories of polytransfused patients as well. This strategy is one step ahead to improve the safety of blood transfusion with optimal blood grouping.

07. Incidence of Hepatitis Delta Virus Infection among HBsAg Positive in Cancer Patients

Lunagaria Rahul

Department of Microbiology

Summary

Hepatitis delta virus (HDV) is a delta agent that is deformed and incomplete RNA virus whose replication and expression is dependent on the presence of HBsAg. HDV and Hepatitis B virus (HBV) co-infection is well known to induce a spectrum of acute and chronic liver diseases which further advance to cirrhosis, fulminant hepatitis and hepatocellular carcinoma (HCC). The delta antigen is primarily expressed in liver cell nuclei and only occasionally present in serum. Anti-delta IgM antibodies appear in serum 2-3 weeks after the infection and can be identified by ELISA method. Delta RNA sequences have been cloned and DNA probes have been developed for rapid identification of delta particles in circulation but the method is costly. In this study evaluation of prevalence of Hepatitis Delta Virus super-infection among Hepatitis B Surface Antigen (HBsAg) positive in cancer patients was detected by ELISA method. Detection of HBeAg and Anti-Hbc IgM in HBsAg positive cancer patients was also done. 5043 blood samples from Feb'13 to April'13 were processed for HBsAg and 150 samples were positive for HBsAg. Those 150 samples for anti-HDV IgM, HBeAg and Anti-HBc IgM were also tested. Out of 150 HBsAg positive samples, all samples were negative for anti-HDV IgM, 54 (36%) were positive for HBeAg and 38 (25%) were positive for anti-HBc IgM.

08. MR Spectroscopy- Role in Oncology

Bhardava Vishalkumar H
Department of Radiodiagnosis

Summary

MR spectroscopy (MRS) is newer technique in imaging era. MRS provides an insight of chemical composition of tissue and helps in localizing and characterizing tissue. In our setting of oncology it is precious and better tool. It helps in characterization of the mass lesion. It helps determine the grade of malignancy, provides target site for biopsy. It gives differential from primary mass from metastasis. Overall invaluable tool in oncology setting.

09. Cytogenetic Analysis of Acute Lymphoblastic Leukemia Patients

Patel Dharmesh M
Department of Cell Biology Division

Summary

The Cytogenetic findings play a pivotal role in the diagnosis, treatment, and prognosis of ALL patients. Therefore, aim of the present study was to evaluate significance of cytogenetic studies at the time of clinical presentation and diverse cytogenetic changes with favorable, intermediate and unfavorable prognosis of ALL patients. 273 ALL patients were enrolled for the study. There were 193 (70.7%) males and 80 (29.3%) were females. Their age range was 4 months to 75 years. ALL patients underwent chemotherapy as per protocol MCP841. Philadelphia positive ALL patients were additionally treated with IM (Imatinib mesylate). Various clinical and cytogenetic parameters were compared between (i) cytogenetic categories (ii) cytogenetic risk groups (iii) FAB classification and (iv) Immunophenotype (IPT) sub groups. In terms of chromosomal patterns,54.6% patients were normal and 45.4% patients showed abnormal chromosomal patterns viz., t(9;22) [n=27], t(9;22) with hyperdiploid (2n+) [n=10], (2n+) [n=26], (2n-) [n=20], and miscellaneous other anomalies [n=41]. The overall survival was significantly higher in 2n+ group, intermediate for 2n-, normal karyotype, sole t(9;22) and miscellaneous grops and shorter for 2n+ with t(9;22).The analysis of the karyotypic abnormalities may enable risk stratification of ALL patients to ascertain the precise events that take place in the genesis of ALL, it may enhance the clinical applications of risk factors and anti leukaemic agents, and to identify treatment regimens that might boost the generally low cure rates of ALL with high risk. Such an approach may identify patients who could benefit from newer therapeutic approaches.

10. Infiltration of T Cell Subsets in Oral Squamous Cell Carcinoma and Oral Leukoplakia.

Brahmbhatt Birva V
Immunohistochemistry and Flowcytometry Division

Summary

Alteration of local T cell immune response is often observed in Oral Squamous Cell Carcinoma (OSCC). Further, tumor infiltrating T cells are frequently associated with patient's clinical outcome. However, their role in premalignant conditions is still unclear. This study has been planned to observe T cell subsets during the oral carcinogenesis. The proportion of T cell subsets (Cytotoxic, Helper and Regulatory T cells) infiltrated in tissue of OSCC (N=100), Hyperplasia (N=23) and Dysplasia (N=20) patients were evaluated and compared by immuno-histochemistry. High number of tumor infiltrating T cells was observed in tumor stroma, followed by tumor margin and tumor nest. The ratio of Regulatory T cells to Cytotoxic and Helper T cells was found elevated in tumor nest as compared to tumor stroma and tumor margin. In relation to clinicopathological parameters, significantly low number of Cytotoxic T cells in tumor stroma was observed in patients with $\leqslant$ 45 years of age and in stage III disease as compared to their respective counter parts. Similarly, low number of Cytotoxic T cells in tumor margin was

observed in patients with ⩽45 years of age and in males as compared to their respective counter parts. Further, significantly low number of helper T cells tumor stroma and tumor margin was seen in patients with neural invasion as compared to patients without neural invasion. Also, a trend of high number of regulatory T cells in tumor nest was observed in histological grade III tumors as compared to grade I and II. In contrast, low number of regulatory T cells in tumor stroma and tumor margin was seen in histological grade III tumors than grade I and II. With respect to disease status, a trend of high incidence of disease relapse and death along with reduced DFS and OS was seen in patients with high number of regulatory T cells and elevated regulatory to cytotoxic T cells ratio in tumor nest and tumor stroma. Further, T cells infiltration was increased in step wise manner from hyperplasia to dysplasia to carcinoma and an increased regulatory to cytotoxic T cells ratio in dysplasia patients was associated with increased risk for developing squamous cell carcinoma. An altered local immune response was observed in patients with OSCC and dysplasia. High regulatory to cytotoxic T cells ratio in tumor stroma was indicator of poor prognosis of OSCC. Also, number of regulatory T cells in dysplasia may plays a critical role during oral carcinogenesis.

11. Role of Counselor in Palliative Care

Dayma Natvar B
Department of Pain and Palliative Medicine

Summary

Department of Pain & Palliative Medicine was started 3 ½ years back at GCRI with the support of JivDaya Foundation. First time a counselor started attending palliative care patients. In palliative care counselor has a very important role to play. He does counseling regarding stage of the disease, its prognosis, Psycho-Social issues, Spiritual issues, and financial issues. He helps doctors and staff nurse in managing difficult symptoms by giving psychological support to patient and care givers. Cancer as a disease and its treatment is a difficult journey for patients and their relatives, counselor with his empathetic and caring approach makes this journey as comfortable as possible. Encourages them to improve their quality of life in their own scenario.

12. Lymphoepithelioma - like Carcinoma of Breast

Jansari Trupti
Department of Pathology

Summary

Lymphoepithelioma-like carcinoma (LELC) is an undifferantiated carcinoma, it occurs in the organs that exclude nasopharynx, but has the same morphology as that of nasopharyngeal lymphoepithelioma. It has been described in several organs however it is rarely seen in the breast. It is a rare clinical entity with good prognosis. Due to the undifferentiated appearance of neoplastic cells and the presence of prominent lymphocytic infiltrate, LELC can wrongly be diagnosed as lymphoma and medullary carcinoma. Relationship with Epstein-Barr virus (EBV) has not yet been observed in the breast. Out of reported 16 cases 50%, 75% and 93.7% showed negativity for ER, PR and HER2 respectively. We present two such cases of LELC of the breast in a 39 year-old and 42 year-old woman with clinical, histological and immunohistochemical features and special emphasis on its differential diagnosis.

13. EMBRACE: An International Study on MRI-Guided Brachytherapy in Locally Advanced Cervical Cancer

Patel Neha
Radiotherapy Department

Summary

Major role of brachytherapy is due to rapid dose fall off. So far ,radiation dose and reporting of dose to normal critical organs have been assessed using point doses as mentioned in ICRU 38.Then came the new era of 3D treatment planning MRI with applicator in situ. Major advantage of it is,it can confirm the dose with regard to both volume (3D) and time (4D). This is an ongoing multicentre study in which 19 centres participated. Treatment schedule was EBRT planned by 3DCRT plus chemotherapy with brachytherapy by HDR. All institutions should follow GEC-ESTRO recommendations. Patients were treated in estimated treatment period from July 2008 to December 2013. Dose should be prescribed to D90 HRCTV (75-96 Gy) with dose constraints for D2cc for rectum, bladder and sigmoid as < 70-75 Gy, <95 Gy and <75 Gy. Assessment of outcome of disease, morbidity and QoL was done. As it is ongoing study, as per public release dated 20/4/13, 523 patients have been followed. It showed there was vaginal shortening and narrowing in upper vagina with rare severe vaginal side effects. From the result till date it is shown that it is possible to obtain local control rate over 90% of patients with application of very high dose to disease of over 90 Gy.[3] DCRT plus chemotherapy with MRI based adaptive brachytherapy in advanced disease results in local control rates over 90% with moderate rate of treatment related morbidities and better Qol.

Presentations at Clinical Meetings

(January 2014 to June 2014)

Sr. No.	Date	Speaker/Department	Title
1.	11.01.14	Rachh Swati Nuclear Medicine	Lung and Skeletal Metastasis in Patient with Differentiated Thyroid Carcinoma and of Response to Radioiodine Therapy
2.	25.01.14	Rawal Rakesh M Medicinal Chemistry and Pharmacogenomics	Molecular Insight into Drug Resistance of Imatinib in Ph+Chronic Myeloid Leukemia: Multifactoiral Approch
3.	08.02.14	Nagpal Punnet Radiotherapy	Metastatic Behaviour of Subtypes in Locally Advanced Brest Carcinoma
4.	22.02.14	Pawar Ashwini Gynecologic Oncology Unit-I	PET CT - How It Helped in Management of Gynaecological Malignancy
5.	08.03.14	Pillai Sundaram Surgical Oncology Unit-I	A Retrospective Analysis of Neuroendocrine Tumor of Pancreas - A Single Institute Study
6.	22.03.14	Kusumgar Rima Blood Bank	Need of Antibody Screening in Blood Bank at Oncology Hospital
7.	12.04.14	Lungaria Rahul Microbiology	Incidence of Hepatitis Delta Virus Infection among HBsAg Positive in Cancer Patients
8.	26.04.14	Bharvada Vishalkumar Radiology	MR Spectroscopy- Role in Oncology
9.	10.05.14	Patel Dharmesh Cell Biology Division	Cytogenetic Analysis of Acute Lymphoid Leukemia Patients
10.	14.06.14	Brahmbhatt Birva V Immuno-Histochemistry	Infiltration of T-cell Subsets in Oral Squamous Cell Carcinoma and Oral Leukoplakia
11.	28.06.14	Dayma Natvar B Pain and Pallative Medicine	Role of Counselor in Palliative Care
12.	28.06.14	Jansari Trupti Pathology	Lymphoepithelioma - like Carcinoma of Breast
13.	28.06.14	Patel Neha A Radiotherapy	An International Study on MRI Guided Brachytherapy in Locally Advanced Cervical carcinoma

Journal Club Presentations

(January 2014 to June 2014)

Sr. No.	Date	Presenter/ Department	Topic	Authors	Citation
1.	11.01.14	Modi Gaurang Medical Oncology Unit -I	Randomized Phase III Trial of Induction Chemotherapy with Docetaxel, Cisplatin, and Fluorouracil Followed by Surgery Versus Up-Front Surgery in Locally Advanced Resectable Oral Squamous Cel Carcinoma	Zhong Lp1, Zhang CP, Ren GX, Guo W, William WN Jr, Sun J et al.	Journal Of Clinical Oncology 2013; 31(6): 744-751
2.	08.02.14	Khanna Anju Gynecologic Oncology Unit-III	Fertility Preservation in Carcinoma Endometrium	Kesterson Jp1, Fanning J.	Journal of Gynecol Oncology. 2012 Apr; 23(2):120-124
3.	08.03.14	Saxena Mohit Medical Oncology Unit-III	Clinical Impact of Delaying Initiation of Adjuvant Chemotherapy in Patients with Breast Cancer	Gagliato Dde M1, Gonzalez-Angulo AM, Lei X, Theriault RL, Giordano SH, Valero V et al.	Journal Of Clinical Oncology 2013; 32(8): 735-744.
4.	12.04.14	Shah Kinna Anaesthesiology	A Review of Enhanced Recovery for Thoracic Anesthesia and Surgery	N. L. Jones, L. Edmonds, S. Ghosh and A. A. Klein	Anaesthesia 2013; 68:179–189
5.	10.05.14	Darji Mona Nursing	Types and Causes of Medication Errors from Nurse's Viewpoint	Shahid Beheshti Nursing and Midwifery Faculty,Iran J Nurs Midwifery	Res. 2013 May-Jun; 18(3): 228–231

Case Presentations for Morbidity, Mortality at Clinical Meetings

(January 2014 to June 2014)

Sr No	Date	Presenter/Department	Case discussion
1	25 .01.14	Kalsariya Chetna Anaesthesiology	Mortality and Morbidity Data Presentation of Surgical and Medical Departments
2	25.01.14	Sharma Mohit Surgical Oncology Unit-I	A Case of Hypoxic Respiratory Failure in Operated Case of Total Laryngectomy-Mortality
3	22.02.14	Modi Hardul Anaesthesiology	Mortality and Morbidity Data Presentation of Surgical and Medical Departments
4	22.02.14	Patel Ankit Medical Oncology Unit-I	A Case Report of Rituximab Induced Pure Red Cell Aplasia Succesfully Treated with IV Immunoglobulin
5	22.03.14	Kalsariya Chetna Anaesthesiology	Mortality and Morbidity Data Presentation of Surgical and Medical Departments
6	22.03.14	Yadav Dinesh Surgical Oncology Unit-VI	An Operated Case of Distal Gastrectomy with Septicaemia and Multiorgan Failure-Mortality
7	26.04.14	Modi Hardul Anaesthesiology	Mortality and Morbidity Data Presentation of Surgical and Medical Departments
8	26.04.14	Tadaiya Mahavir Surgical Oncology Unit-V	In Operated Case of Whipples Procedure - Septicaemia and Renal Failure-Mortality
9	26.04.14	Patel Dipika Anaesthesiology	Retrospective Data Analysis of Whipples Procedure Done in 2013
10	31.05.14	Kalsariya Chetna Anaesthesiology	Mortality and Morbidity Data Presentation of Surgical and Medical Departments
11	31.05.14	Patel Jigar Medical Oncology Unit -III	Methotrexate Induced Hypersensitivity Pneumonitis in a Case of T-cell ALL
12	28.06.14	Modi Hardul Anaesthesiology	Mortality and Morbidity Data Presentation of Surgical and Medical Departments
13	28.06.14	Bhanupriya H Anaesthesiology	An Inoperable Case of Carcinoma Larynx with Acute Renal Failure-Mortality

About the Journal and Instructions to Author

Gujarat Cancer Society Research Journal is a biannually (April and October), ISSN 2320-1150, peer-reviewed journal published by the Gujarat Cancer Society. **The journal is indexed with Index Coperinicus.**

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The Editorial Procss

A manuscript will be reviewed for possible publication with the understanding that it is being submitted to Gujarat Cancer Society Research Journal at that point in time and has not been published anywhere, simultaneously submitted, or already accepted for publication elsewhere. The journal expects that authors would authorize one of them to correspond with the journal for all matters related to the manuscript. On submission, editors 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 are 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.

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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. It may not be possible to incorporate corrections received after that period.

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6. Manuscript should have signature of the first author and unit head.

The following documents are required for each submission: (Font: Times New Roman)

- Title Page (Font size: 12)
- Title of manuscript (Font size: 16)
- Summary and Keywords (Font size: 9)
- Text (Introduction, Aims and Objectives, Materials and Methods, Results and Analysis, Discussion with Conclusions; Font size: 12).
- Tables (separate page, Number Arabic numerals (e.g. 1,2,3) as it comes in results) (Font size: 12)
- Figures and Illustration (separate page, JPEG format, Number Arabic numerals (e.g. 1, 2,3) as in results, if photographs of persons are used, the subjects or patients must not be identifiable).
- Legends to Figures and Illustration: Present the legends for illustrations separate page using double-spacing, with Arabic numerals corresponding to the Illustrations. (Font size: 12)
- References (separate page, Number references consecutively in the order in which they are first mentioned in the text. Identify references in the text in numerals in superscript and parenthesis; Font size: 12).
- Acknowledgement (Font size: 9)

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 should be expressed in SI units. Drug names Generic drug names should be used.

Abbreviations of units should conform to those shown below:

Decilitre	dl	Kilogram	kg
Milligram	mg	Hours	h
Micrometer	mm	Minutes	min
Molar	mol/L	Mililitre	ml
Percent	%		

Title Page

The title page should include

1. Type of manuscript (article/case report)
2. The title of the article, which should be concise, but informative; (Title case, not ALL CAPITALS, not underlined)
3. The name by which each contributor is known (Last name, First name and initials of middle name), with institutional affiliation;
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Language and grammar

- Uniformly American English
- Abbreviations spelt out in full for the first time

- Numerals from 1 to 10 spelt out
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Summary and Keywords: Summary no more than **250 (150 for Case Report)** words. Should have following headings: **Introduction** (state the purposes of the study or investigation), **Materials and Methods** (selection of study subjects/patients, observational and analytical methods), **Results** (give specific data and their statistical significance, where ever possible), and **Conclusion** (succinct emphasis of new and important aspects of the study or observations). Do not use symbols in the summary; rather, spell out what they stand for in full. Three to eight keywords must be included below the summary.

Text: This should consist of **Introduction (including 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: State the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent information and references, and do not review the subject extensively. Do not include data or conclusions from the work being reported.

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. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well-known. For new or substantially-modified methods, describe and give reasons for using them and evaluate their limitations.

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Results: Present your results in a logical sequence in the text, Tables, and Illustrations. Do not repeat in the text all the data in the Tables or Illustrations. Emphasize or summaries only important observations. Specify the statistical methods used to analyze the data. Restrict Tables and Illustrations to those needed to explain the argument of the paper and to assess its support. Where possible, use Graphs as an alternative to Tables with many entries. Do not duplicate data in Graphs and Tables.

Discussion: Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including the implications for future research. Relate the observations to other relevant studies.

Tables: Print 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.

Illustrations (Figures) and Legends for Illustrations: All Illustrations must be submitted in JPEG finished format form 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.
Present the legends for illustrations using double-spacing, with Arabic numerals corresponding to the Illustrations.

Acknowledgements: State contributions that need to be acknowledged.

References

A list of all the references cited in the text should be given at the end of the manuscript and should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in the text by Arabic numerals in superscript. 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. 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

You CH, Lee KY, Chey RY et al: Electrogastrographic study of patients with unexplained nausea, bloating, and vomiting. Gastroenterology 1980; 79:311-314

Online journal article

Miyamoto O, Auer RN. Hypoxia, hyperoxia, ischemia and brain necrosis. Neurology [serial online] 2000; 54:362-71. Available at: www.neurology.org. Accessed February 23, 2000.

Chapter in a book

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: Saunders, 1974: 457-472

Online book or website

Garrow A, Weinhouse GL. Anoxic brain injury: assessment and prognosis. In: Up To Date Cardiovascular Medicine [online] Available at: www.UpToDateInc.com/card. Accessed February 22, 2000.

In press

Lillywhite HB, Donald JA. Pulmonary blood flow regulation in an aquatic snake. Science. In press.

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Cosmetic Prosthetic Laboratory

Cosmetic prosthetic laboratory was started in 1975 under the leadership of plastic surgeon, Dr J R Jaju and an anaplastologist, Mr Deriln B Atkins (sculpture artist). He became an expert in making artificial prosthetic organs for the patients who lost their organs in diseases like cancer, burn, accident and for those who were born physically disabled after obtaining a degree in medical sculpting.

In August 1984, Ms Jyotika Soni was appointed as medical sculpture trainee in cosmetic prosthetic lab. After 18 months training, she was selected as assistant medical sculptor in cosmetic prosthetic lab. Since then prosthesis of patients was made in cosmetic prosthetic lab and between 1984 to 1985, 35 patients' prostheses were made. It continued to increase years after years.

From 2001, prostheses were made under the guidance of Dr Heman Jaju,. Up to 2012, 150 to 200 prostheses were made. After that patients were coming from Gujarat as well as from neighboring States. Prosthodontist, neuro surgeon, ophthalmologist, gynecologist, and physiotherapists as well social workers were sending the patients for making the prosthesis. At present we are working with one assistant medical sculptor and one trainee medical sculptor working but in future the department is likely to expand

The Prime Work of Prosthetic Department

1. **Prepare External Artificial Limbs and Organs**

Majority of the patients are of breast prosthesis followed by ear, eye, nose, fingers and toes made from either or silicone rubber and acrylic. Prosthesis helps to give proper shape and refashion with consideration to the age of the patient. Colors are also mixed and matched according to the skin tone. Before making prosthesis patients are explained about the procedure ie impression, mould making, modeling, mould cast either silicone or acrylic, color mixing and last finishing prosthesis. After examining the patient, front and side view photographs are being taken. Patient has to undergo all these process and finally the prosthesis is prepared. Patients are given appointment and privacy is maintained. Patient's psychological feelings are considered and he/she must be satisfied with the shape and color of the prosthesis. Cosmetic prosthesis is not new, but silicone gel which is used in it is new. It is soft, smooth, looks like natural skin and gives a successful and satisfactory result.

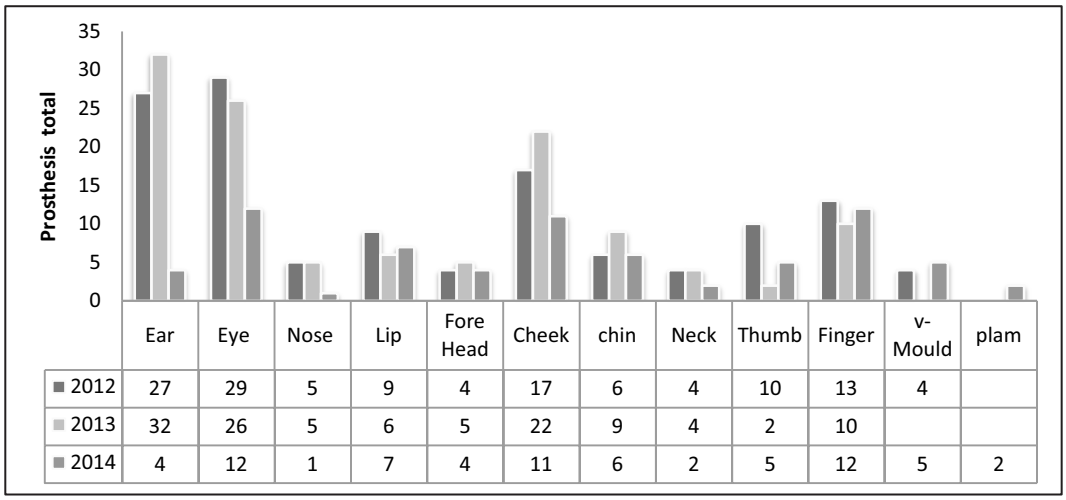
2. Training Programe at Prosthetic Department

Since 2006, students from various dental, paraplegia and nursing colleges from all over the state are being trained at the department as listed below:

2006 Government Dental College, Civil Hospital, Ahmadabad

2009 - 2014 Ahmedabad Dental College, Rancharda

Total Prosthesis: 2012- 2014



	Ear	Eye	Nose	Lip	Fore Head	Cheek	chin	Neck	Thumb	Finger	v-Mould	plam
2012	27	29	5	9	4	17	6	4	10	13	4	
2013	32	26	5	6	5	22	9	4	2	10		
2014	4	12	1	7	4	11	6	2	5	12	5	2

2010 Karnavti Dental College, Uvarsad

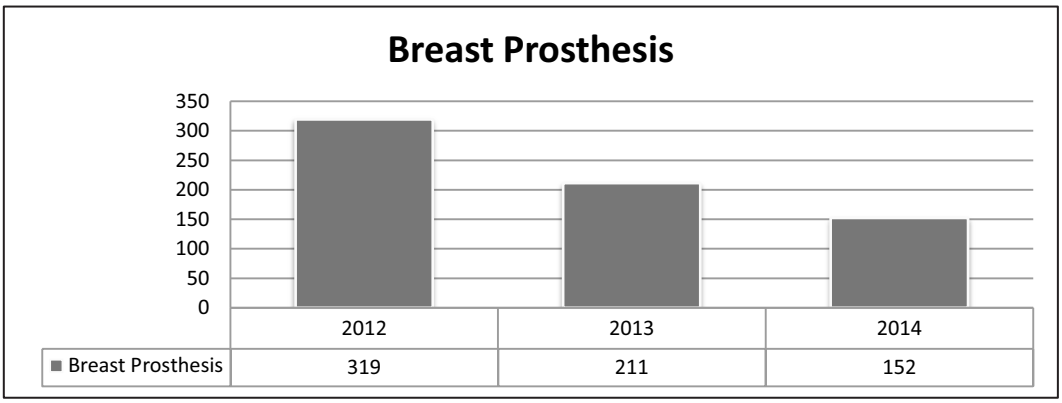
2011 P.G.D.R P. B.M Institute Of Mental Health Ahmedabad.

2012 Government P and O College, Civil Hospital Ahmedabad.

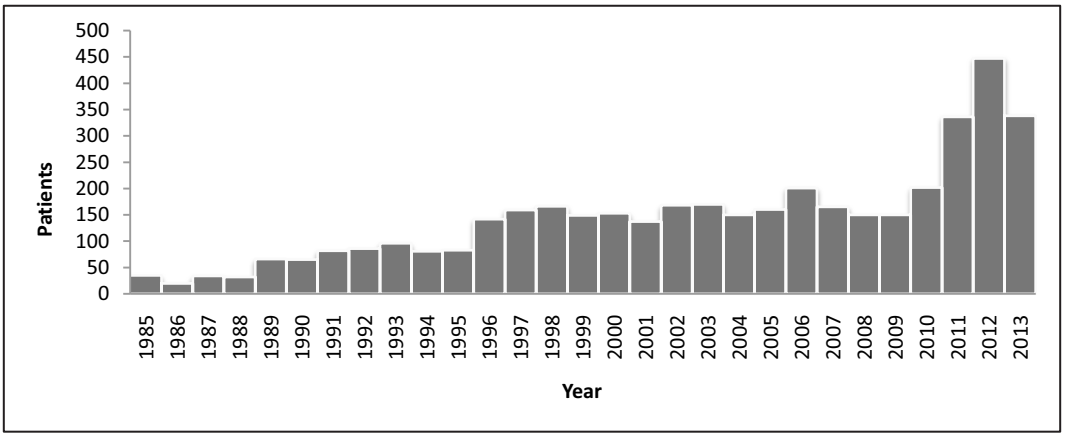
2013 College of Dental Science, Bopal

2014 D.D.I.T Faculty of Science, Nadiad

2014 Lily Karishma Uttra Calox Teachers University, Bopal



Total Prosthesis: 1985-2013



3. Other Activities at Prosthetic Department:

2001 Conference of plastic surgeon (GCRI) Prosthetic exhibition.
2003 Conference of spastic surgeon (mabicon)
2004 Innovation of prosthetic department-(K.M. Mehta)
2010 Awareness of breast cancer in convention of women
2013 Women development cell: Patient awareness poster exhibition

"Death is the liberator of him whom freedom cannot release, the physician of him whom medicine cannot cure, and the comforter of him whom time cannot console."

Charles Caleb Colton

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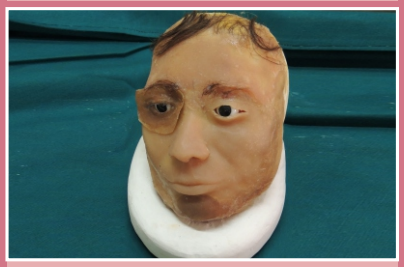
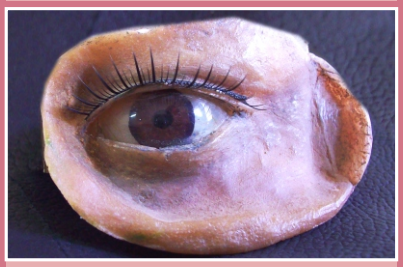


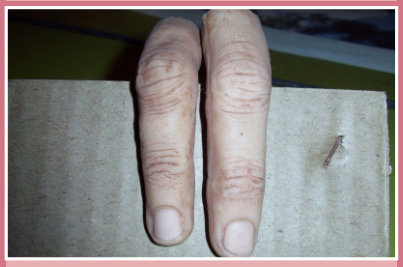
Silicone Mask



Acrylic Eye

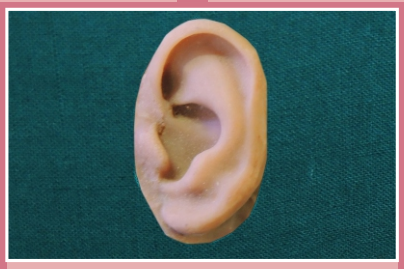
Prosthodontist Student Learn With Us

Acrylic Mask



Silicone Finger

Silicone Thumb



Silicone Ear