Volume 19 Number 2 October 2017 ISSN 2320-1150

Gujarat Cancer Society Research Journal

www.gcriindia.org Official Journal of Gujarat Cancer Society, Ahmedabad, India

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Gujarat Cancer Society
Research Journal

ISSN 2320-1150

Volume 20 Number 2 October 2017

Address for correspondence:

The Editors,
Gujarat Cancer Society Research Journal
The Gujarat Cancer and Research Institute
GCS Journal Office, Research Wing,
Asarwa, Ahmedabad 380016
Gujarat, India
gcsjournal2012@gmail.com

(Formerly Published as GCS Research Bulletin)

Gujarat Cancer Society
Research Journal

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Editorial

Pandya Shashank J
Professor and Head, Department of Surgical Oncology
Corresponding author : drsjpandya@gmail.com

Breast Cancer: An Age of Smaller Resections

Surgical resection was one of the first effective treatments for breast cancer and continues to play a critical role in the treatment of this disease. Amultimodality treatment is now considered the standard of care, involving a coordinated effort of the surgeon with the medical and radiation oncologist to achieve the best possible outcome in each patient. Improvement in each of these disciplines can improve quality of life and overall survival of breast cancer patients. Most significant improvement in surgical management occurred in early stage breast cancer. Adoption of breast conservation surgery has allowed an advantage of better cosmetic outcome without compromising survival.

Breast cancer is the second most common cancer in the world. According to Globocan 2012,[1] it is the most frequent cancer among women with estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). Breast cancer ranks fifth common cause of death from cancer overall (5,22,000 deaths) and in women it is the most frequent cause of cancer death in less developed regions (3,24,000 deaths,14.3%) , and second in number in more developed regions (1,98,000 deaths,15.4%) after lung cancer. While the incidence has increased over the past decade, the mortality rate of breast cancer has gradually declined. This improved survival may stem from early detection as well as improved therapies.[2,3]

Historical aspect

The Greek physician Galen, in the second century AD, is considered to be one of the earliest advocates of surgical treatment, recommending wide excision of breast tumors. In 1867, C.H. Moore emphasized complete resection of breast and also stated that palpable axillary nodes should also be removed. In 1877 Banks supported Moore's concepts and advocated the resection of non palpable axillary lymph nodes as well. In 1894 Halsted and Meyer reported superior locoregional control rates after radical resection. They established 'Radical mastectomy' as a state of art, which consisted of en bloc resection of the breast, the pectoralis muscles, and the axillary contents (level I to III nodes, long thoracic nerve and thoracodorsal neurovascular bundle). During Halsted era, initial presentation of profoundly advanced tumors was the norm. In 1948 Patey and Dyson proposed 'modified radical mastectomy' with preservation of pectoralis major muscle with equivalent local control and less morbidity.

The National Surgical Adjuvant Breast and Bowel Project B-04 conducted by Bernard Fisher and coinvestigators proposed postoperative radiotherapy for control of local tumor recurrence, laying the groundwork for breast conservation therapy (BCT). .Since the 1970's, considerable progress has been made in the integration of surgery, radiation and chemotherapy to achieve locoregional control, to increase survival and to increase possibility of breast conservation.[4]

Current operative management

Optimal management of a patient with breast cancer includes establishing a pathologic diagnosis prior to any definitive treatment. A good core needle biopsy provides histopathological diagnosis, tumor grade with hormonal and HER2 receptor status.[5] This information is critical for optimal decision making regarding treatment options, most importantly neoadjuvant chemotherapy prior to operative intervention.[5]

After the diagnosis of breast cancer is established, patients are evaluated for further staging work up. Standard of care includes bilateral mammography to identify any suspicious areas in either breast that will impact surgical management. Laboratory values that will assist in treatment recommendations include complete blood count, liver function tests and alkaline phosphatase. Additional imaging studies to evaluate for metastatic disease are obtained depending on signs and symptoms of the patient, as well as the clinical stage at presentation. A bone scan is indicated if the patient has localized bony pain or elevated alkaline phosphatase, chest imaging is indicated for pulmonary symptoms, and abdominal imaging by computerized tomography is indicated for abnormal liver functional tests or abdominal symptoms.

After staging workup, multidisciplinary team decision is made for definitive management of the patient. Those patients with evidence of advanced disease are typically managed medically with preoperative chemotherapy, prior to any definitive surgical management. Locoregional (operative) control of breast cancer remains the mainstay of treatment. Surgical treatment should allow the

patient's involvement in the decision-making process. Definitive surgical management typically involves breast conservation (BCT) or mastectomy. There are two required components for BCT. First, tumors must be resectable with a pathologically clear margin, that is, a surrounding margin of breast parenchyma without disease. Secondly, patients undergoing partial mastectomy typically receive whole breast irradiation to achieve local control in the breast. Tumor size must be sufficiently small relative to the entire breast, such that the appearance of the breast is cosmetically acceptable following partial mastectomy. Additionally, all suspicious findings on imaging must be resectable with the partial mastectomy.

Contraindications to BCT include: [6]

Absolute:

1. Radiation therapy during pregnancy
2. Diffuse suspicious or malignant appearing microcalcification
3. Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result
4. Diffusely positive pathological margins

Relative:

1. Prior radiation therapy to the chest wall or breast
2. Active connective tissue disease involving the skin
3. Tumor > 5cm
4. Positive pathologic margin
5. Women with a known or suspected genetic predisposition to breast cancer

From the 2014 society of surgical oncology-American society for radiation oncology consensus guidelines recommended negative margin as "no ink on the tumor". Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy.[7]

Mastectomy is indicated for the curative resection of tumors (i.e., absence of metastatic disease) not amenable to BCT, and for those patients that do not want to consider conservation even though they meet criteria. In addition to resection of the primary tumor, all invasive breast cancers require assessment of axillary lymph nodes for tumor invasion. The sentinel lymph nodes represent the first group of nodes at risk for invasion. Sentinel lymph node biopsy (SLNB) is an important evolution in the management of axilla. SLNB assesses axilla during lumpectomy or at the time of mastectomy and has replaced routine axillary lymph node dissection (ALND) in clinically node-negative axilla. Injection of a dye and/or radio-isotope into the breast allows the surgeon to identify the first ("sentinel") lymph node draining the tumor basin. In American college of Surgeons Oncology Group (ACOSOG) Z10 trial, no significant differences were seen in the rate of sentinel node identification with the use of blue dye alone, radiocolloid alone or the combination of the two.[8] During SLNB care should be taken to excise any palpable abnormal nodes intraoperatively because lymph nodes that contain a heavy tumor burden may not take up the mapping agent. Involvement of axillary nodes is considered regional disease and is usually followed by complete axillary node resection.[9] Nodal status provides critical staging information necessary for the proper selection of adjuvant therapy. Furthermore, negative findings after a properly performed SLNB allow a patient to avoid the potential for significant morbidity after axillary dissection, particularly lymphedema and sensorimotor nerve damage.[10] Presence of isolated tumor cells (ITC)(<0.2 mm deposits) and micrometastases(>0.2-<2 mm) in sentinel lymph node do not increase locoregional or distant recurrence rate if not followed by ALND , so routine use of serial sections and IHC to detect ITC or micrometastases is not warranted.

In situ breast cancer is a neoplasm that is completely limited within its basement membrane. This early neoplasm can be derived from a duct or lobule and is, therefore, referred to as lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS).

LCIS requires special consideration, as it is considered a marker for the future development of invasive breast cancer. There are no clinical or mammographic abnormalities associated with the lesion and diagnosis is usually incidental following breast biopsy for other indications. The risk of developing invasive cancer is low, and if it occurs, histology tends to be favorable. For this group of women, LCIS is managed by active surveillance without additional intervention. Alternatively, hormonal therapy can be administered for the purpose of breast cancer prevention. The potential adverse reactions of these medications must be considered and balanced with the presumed risk reduction. Surgical excision biopsy is only required if there is a discordance between the pathology and imaging, and the presence of pleomorphic LCIS in a core needle biopsy.

In contrast to LCIS, the diagnosis of DCIS requires treatment for local control at the time of diagnosis. With the development of techniques for the earlier diagnosis of breast cancer, DCIS is the only diagnosis in approximately 15% of newly diagnosed breast cancer patients. This finding must be addressed, as the survival rates for treated DCIS are near 100%, but the development of invasive disease occurs in up to 30% of patients with untreated DCIS.[11] Treatment options include breast conservation with

partial mastectomy and radiation, or total mastectomy. Although DCIS is often found in conjunction with an invasive carcinoma, treatment for the invasive component takes precedence and dictates both surgical and medical management. In contrast to management of invasive disease, those patients with DCIS usually do not require axillary dissection, as axillary nodal involvement in patients with pure DCIS is unusual. Selective use of SLNB includes all patients who undergo mastectomy and in patients who undergo BCT with palpable mass, solid mass or a lesion >25 mm on imaging, intermediate or high risk DCIS, age under 55 years.[12] Adjuvant hormonal therapy is indicated in hormone positive status.(Tamoxifen for 5 years)

Multimodality Management

Starting in the mid-twentieth century, most notably in the lab of Bernard Fisher, early chemotherapeutic agents were being analyzed for use in the preoperative setting. The use of neoadjuvant chemotherapy (NACT) represents a crucial improvement in breast cancer therapy, addressing the systemic aspect of this disease. NACT is indicated for locally advanced tumors or inflammatory breast cancer. Locally advanced breast cancer which require NACT includes those that invade the chest wall or skin (T4) or have spread to the axillary nodes (N2 /N3).[13] Treatment typically includes NACT, surgery, radiotherapy and +/- hormonal treatment. A recent extension of these principles is the use of chemotherapy to downstage tumors in initially operable cases to avoid mastectomy and make BCT feasible. NACT is indicated for tumors meeting all criteria for breast conservation except for tumor size.

Patients on NACT should undergo routine response evaluation in form of clinical and imaging assessment. Patients with operable breast cancer experiencing progression of disease should be taken promptly for surgery. Patients who most likely to be converted to BCT are those with unicentric, higher grade, HER2+ or triple negative cancers, as such cancers respond dramatically to chemotherapy. Pathologic complete response(pCR) is defined as the absence of residual invasive cancer in the breast and axilla following preoperative therapy. pCR is associated with better long term outcomes, lower risk of cancer recurrence than with presence of residual disease. Preoperative clipping of lesion is helpful in these patients who develop pCR to guide local resection. pCR in the breast range from 15 to 40%. Despite these only 25 to 30 % of the patients can be converted into BCT candidate.[14] This is a reflection of both the difficulty of assessing the extent of residual viable tumor and often patchy nature of response.

In the era of multimodality management, there is a significant role of adjuvant chemotherapy, radiotherapy and hormonal therapy according to final histopathological stage and menopausal status of the patient to improve overall and disease free survival. As stated previously adjuvant whole breast irradiation is the cornerstone of BCT.

Recent Updates:

Oncoplastic Breast Surgery

It involves operative breast cancer therapy with a concomitant focus on breast reconstruction.[15] Plastic surgery techniques utilized include breast augmentation and reduction, flaps, implants, and expanders, on both the diseased and the normal breast if necessary to achieve the desired symmetry. Indications are still widely debated, but appropriate candidates are those that have sufficient residual breast after the oncological resection to facilitate the necessary reconstruction.[16]

Avoidance of ALND in Positive Sentinel Nodes

Traditionally, a positive SLNB represents an absolute mandate for a complete axillary dissection. However, ACOSOG Z0011 clinical trial states that in patients with up to 2 positive SLNs there may not be added benefit with ALND.[17] AMAROS (After mapping of axilla :radiotherapy or Surgery) trial states that in patients with positive sentinel node, RT to axillary and supraclavicular fields instead of ALND give equal DFS and lower risk of lymphedema.[18]

Role of SLNB in LABC after NACT

The accuracy of sentinel node biopsy in patients with clinically evident axillary nodal metastases at presentation who receive NACT with resolution of clinically apparent adenopathy has been studied in two multi institutional prospective studies(ACOSOG Z1071 and SENTINA study).[19,20] They state that ALND should remain the standard approach for these patients unless three or more sentinel nodes are identified.

Conclusion

Surgical intervention is currently definitive cure of breast cancer. Recent advances in multimodality management has made possible the upsurge of breast conservation therapy possible and extensive resections performed by Halstead and his predecessors has become history only. Breast conservative surgery with oncoplastic procedure has enhanced the acceptance with excellent cosmetic results. SLNB technique has significantly refined the management of axilla. Though multimodality treatment has improved overall and disease free survival and breast conservation rate, continued improvements in early diagnosis via breast imaging, advanced prognostic tests, patient-specific molecular

diagnosis, and the development of targeted chemotherapeutic agents should be the priority to get further better results. By doing so, breast cancer therapy will become more focused, increasing efficacy and reducing complications of all the treatment disciplines. This will move the bar closer to the ultimate goal of transforming breast cancer into an easily targeted, readily manageable disease.

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Shri Madanmohan Ramanlal GCRI Luminary Award - 2016

Dr Kirti M Patel
MD

Dean, GCS Medical College
Former Hon. Deputy Director and Unit Chief Medical Oncology,
GCRI, Ahmedabad

My Professional Career: Last Four Decades

It is a common experience that when we meet our friends, we feel delighted. When we meet our guides, elders, mentors and advisors, we feel proud to be with them. Today, this is an opportunity that I sincerely express my highest regards and love for all of you as all that I could do would never have possible without continuous support from all of my mentors, friends and faculty members. I believe that they have not only loved me but considered me capable of doing what we wanted to accomplished. They made me responsible for doing my best and helped me continuously. This is in a way empowerment or trust but in my heart, I feel it like an extension for benevolent ownership.

It is needless to narrate to this augustus gathering that we all are the committed fellow travellers on the path of healing. The speciality of oncology is one of the most sought after during last four decades as the prevalence of several cancers showed unprecedented rise. Each day adds new chapters of magnitude, identification, management and cure of various pathologies. The science of medicine is expanding at a galloping speed. Oncology, too, has developed and continues to show new paths at a significant pace. New perspectives, new technologies and new therapies have really advanced the capacity of medical fraternity. What was difficult, or even impossible, before four decades, has been tackled as a routine health care procedure today.

The year 1971, when the state initiated a mission in the name of Gujarat Cancer Research Institute, is today a historical landmark and has certainly seen spectacular progress in the years till today. With this scientific research gains, we also find novel institutional philosophy, refined organizational aptitudes and improved infrastructure. Combined together, these changes contribute to overall better management and health care in our mission of healing. The focus now encompasses prevention, cure and rehabilitation effectively.

Yes, I did mention 1971 in the beginning because soon after these pioneering days, it was my good luck to undergo my residency period at this prestigious institute. These years of 1973 to 1976 have a visible impact on my career as an onco-physician. These were the years when new modalities of diagnosis and care were emerging. Since then, it is amazing that each day has contributed to plan, implement and review new projects and initiatives at our Institute. The department of medicine, in pace with all around development, made its own contribution which reflects in large number of post graduate studies and a series of other clinical and academic activities. This was to synchronise with the changes and researches in medical sciences all over the globe.

The grand journey of the professional career in academics started in 1977 for me and today after 40 years of this journey on the path of science, academics, management and teamwork, a kaleidoscopic view of these years generates a sense of satisfaction and provides a boost for the journey ahead. This entire journey is not like a student reading through several authentic text books, mugging important points for, say, NEET or PG entrance examination. It is a real learning through a teamwork that requires being together and sharing dreams. For example, a 40 bedded hospital of 1971 required a small family of co-workers and today's 600 plus bedded hospital has all features comparable to a building up of a metro. It includes judicious use of latest technology, required structural additions, recruiting and training of various faculties and expanding the horizons of in-built research. This is like transforming a township into an inevitable and consumer oriented metro.

Being a native of Usmanpura, suburb of greater Ahmedabad, it has been natural to see this metamorphosis our suburb has gone through paramount growth and development in last half a century. It allowed me to visualize the development and have a tuning with all hi-tech innovations. A specific mention here may be about the tuning of academics with university regulations, fraternity

expectations and ethics or research on centre stage when I worked for university, medical association or medical council. It is clear and simple that the symphony needs these essential instruments in the well tuned orchestra.

All these happen to be the petals of a magnificent lotus of medical world. These relatively diverse organizations have a core of oneness, being supportive to the objectives of human health care through education, discipline, ethics and research. They make you learn about various odds and evens while working together. Being a teacher allows you to be a learner too. A learner has a capacity for nurturing mutual binding through his awareness of all these organizations. Whether it is Indian Medical Association or Gujarat Cancer Society Association, it is like an effort to understand our own family members. Young and elders, ambitious and sober, dynamic and easy to go and such characters get together and continue to forge your personality as an outcome.

Essentially, one who reads books learns theory. One who practices the theory turns out to be a skilled physician but one who associates himself with his own fraternity builds up a social domain to be a good family member of the great medical fraternity. The liaison with medical association starting with a non-significant membership to various posts of responsibilities definitely groom anyone and this happened in parallel to the senior posts in the ladder of teaching profession. By the time a professor's orientation started, a chance permitted me to be a president for the association. This is very honestly speaking allowed me to work for uniting the different aspects of a larger design for excellence. This can lead to a mutual development. This is more identified when one starts with being an executive member and happens to ride a post of president at the state or higher than that. Even a participation in various events trains you to problem solving. They improve the communication, the connectivity and generate compassion for the fellow travellers, actually making a student of human endeavour. This equally applies to organizing a mega conference or even drafting a schedule for the scientific event or identifying the menu to entertain the guests at dinner. The importance is imbibed in a sense of satisfying the most of our own family members and feeling oneness that invariably caters happiness to all.

Extending all these learning to an application as running a teaching Institute provides a unique opportunity. This was in 2009 when management of Gujarat Cancer Society selected me as dean of GCS medical college, A dream of mine..... A teacher needs to be transformed in a matrix of a manager and an academician. The keyword in all these phases, as I said earlier, is empowerment and trust. I believe that goodwill and common sense are the real qualities to make the tasks easier and graceful.

GCS medical college, in its seven years of being has marked substantial development. The milestones can be described in terms of the opportunities generated for the undergraduate and postgraduate education, The time does not allow me for further details but the fact remains that we are the key player for the course of DM (Oncology) and Mch (oncology) at GCRI the premier Institute. Now about 90 students secured DM course, itself talks about the history.

My respected patrons and friends, the achievements are the mirror of success and are the means to build a future. Apart from medical acumen and organizational capacity, what is required most today, is the "humane" aspect of the success. A medical professional, in all possibilities, is the best person to run the show, if this vital aspect is to underline. By genesis, a medical professional, more so if he is a teacher also, is a reviewer, reader and learner. He is trained for inspection, palpation, percussion and auscultation. He is trained to face emergencies that are life threatening and he is bound to take decisions in critical moments. These qualities, I am sure, are rare and vital for any Institutional management. These are the characteristics that form the basis of human relationships. The ultimate outcome is good "humane" governance. Do we need robots and machines that are not, by training, prepared to sympathise a patient, empathise a medico and feel the climate of organisational harmony? It can be justifiably said that a doctor, a medical expert, with his head and heart, is the best manager. What is required is a real support and unconditional respect for this noble profession. This requires an opportunity to be provided and certainly he will turn up as the best administrator, manager, leader and fellow traveller in this absolutely human endeavour. Hear, I would like to quote Sir Willam Osler "A doctor is a student till his death, when he fails to be a student, he dies". For my fellow medical brothers and sisters I shall repeat that we are from the society, by the society and for the society. Sensitization of social needs and responding to social obligations is our duty. This requires being with the community whenever the chance permits. This will lead to community awareness, involvement and participation. Fortunately enough, the Almighty provided me to work with and govern some of the social, cultural and religious organizations. This experience allows one to interact and understand the community at large. Meeting and interacting with people across the social strata is not the destiny of all. We need to seek all opportunities to meet poor and wealthy, villagers and urbanites, literates and illiterates, old and young, women and children, just to get sensitized. One might say that we, the doctors, do

come in their contact and interact. It is true but mostly when we meet they are patients and their relatives. This is but a sample of the community in need. To be with the healthy, non-patient and larger part of the community will certainly help us understand their expectations much more. One is unlikely to have complete idea without working in villages, slums or for that matter, community at large. Once we understand them, we are sure to be more committed to our mission of healing. This stage of being with and understanding each other is the base with which community has always identified a physician as a person next to God.

When on one hand, the society makes us divine and truly respects us, it may provide shock and criticism when a misunderstanding is generated. To balance these emotional conflicts, the unanimous commitment by all members of the fraternity has to be booked. This demands ethical commitment to the professional etiquettes. It is common that all of us have some differences and no two persons are unique but a core concern for the patient will undo all such differences. Working with different community organizations provides a real concern for our fellow brother. It provides a chance to learn the strength, the weakness, the opportunity and the challenges on either side.

This is essential as the regulating bodies, may it be medical council or university or the government or even judiciary, are interested in ethical, updated and essential management of the medical education and its application. As an example, a University provides and frames a system of scaling, assessing and evaluating the level of knowledge and performance of a medico. The medical council, at the same time, is concerned with the orientation of the medico for the ethics and researches apart fro his knowledge and skills. Working with these monitoring and guiding systems, one is expected to help his own academics in the right direction. How can an academician be thought of in his best form in absence of discipline, updating of knowledge, ethical commitment and humane care while working with an ailing person and suffering community?

My dear friends, I am not here to provide any sermons but my experience compels me to tell that we all are passing through a great sequence of community awareness and many changes related to the same. The values are being redefined and so are the morals. The global village touches every life. The cross cultural ideas are shared very fast. Information technology has already changed the behaviours. The health care is transformed to an industry. The next generation is computer savvy. The physical work and the hardships of life are eased by and large. These provide opportunities to win if applied in right direction. The nation claims of good days ahead and there is no reason to doubt. The only care to be taken is to move in the right direction. This is crucial because an energy pushed in wrong direction can be a catastrophe. We decide and pray that all of us will have a vision for the right.

In this context, the million dollar question is related to the gadgets replacing the human skills and mind. I think there will be an enhanced need for supporting the sentiments – of a family, of a patient, of a community, of an institutional milieu. This will necessitate a paradigm shift in Medical Education. Classroom teaching has been a core activity and will be required to be replaced to some extent by interactive, skill based, need based training. The behavioral science, communication skills and competency matrix will have to be part of the training. It will help saying a quote that "Today's teacher is trained by yesterday's teachers and he/she trains tomorrow's doctor". This identifies limitations and need for updating teaching technology and contents to make them contextual.

I am sure that each one on the platform of medical education will realize the challenge as it has a power to change the entire scenario of health care provision. In the era of universal health care Coverage, the role of our fraternity has to be outstanding, vital and all encompassing. The basics of medical skills and opened wings of hi-tech health care need to be supplementary for the coverage of a large population that is to be served. Last but not the least, the human face of Health Care has to be more visible so that the society continues to look at this noble profession with the respect that has been since ages.
Hear I would like to quote Mother Teresa.."You can do what' I cannot do, I can do what you cannot do but together we can do great things".

At this prestigious award ceremony, I heartily thank one and all who helped me during last four decades of my professional career in one way or the other. I sincerely thank my seniors, guides, mentors, friends and philosophers for accepting me with whatever capacities I have and supporting through their very positive attitudes and concerns. I thank all those who are here today and also those unable to remain present but are in my heart, in same way I am in their heart. They shall continue to support and bless me in my all endeavors. That's my 'prathana'.

Randomized Study of Oral Misoprostol for Cervical Ripening before Intracavitary Brachytherapy for Carcinoma Uterine Cervix

Anand Mridul[1], Parikh Ankita[2],Patel Sonal Shah[3],Suryanarayan U[4]
Junior Lecturer[1], Associate Professor[2], Assistant Professor[3], Professor and Head of Department[4]
Department of Radiotherapy
Corresponding author : drankitaparikh@yahoo.com

Summary

Intracavitary brachytherapy forms an integral part of treatment of carcinoma cervix and the complications arising out of the procedure are partly related to the difficulties in cervical dilatation. This study aims to evaluate the efficacy of oral misoprostol in facilitating this transcervical procedure as a part of intracavitary brachytherapy and reduce the complications of the procedure. A total of 100 patients of carcinoma cervix stage II and III were included in the study who underwent external beam radiotherapy followed by intracavitary brachytherapy. These were randomly assigned to the study group and the placebo group. Study group received 400 microgram of misoprostol orally, three hours before the procedure. The procedure was evaluated for the amount of bleeding, size of the initial hegar dilator, grading of the procedure as easy, moderate or difficult, subjective perception of rigidity of cervix and subjective difficulty level of tandem insertion. With regard to bleeding, no significant difference was found in both the arms (Chi square test-0.285). Other parameters measured like ease of dilation and the average no. of hegar dilator used were found to be insignificant. Administration of misoprostol 400 micrograms for cervical ripening for tandem application facilitates the transcervical procedure, increases tolerability and decreases the complications of procedure in this study.

Keywords : Carcinoma cervix, Misoprostol, Brachytherapy, Tandem application

Introduction

The treatment of carcinoma cervix comprises of external beam radiotherapy and brachytherapy. Both modalities supplement each other and in general, external radiotherapy followed by brachytherapy is practiced in most of the cases. Brachytherapy as a form of conformal dose escalation helps in the reduction of pelvic recurrences since it allows higher dose to the target area while reducing dose to other organs at risk.[1,2]

The efficacy of brachytherapy in carcinoma cervix largely depends on the correct application of the afterloading applicator. Due to previous radiotherapy, residual disease or postmenopausal changes, the negotiation of cervical os becomes difficult. It may lead to complications like bleeding, perforation, pain, infection or abscess formation.Cervical ripening before transcervical procedure has shown to reduce the complications during the various obstetric and gynaecological procedures.[3-5] Misoprostol has been used for this purpose in pregnant and nonpregnant women. It is the best suited prostaglandin due to a number of advantages like short half life, few side effects, easy dose titration and is relatively cheap. A single dose of misoprostol 400 microgram before the intervention sublingually or intravaginally has shown to give the best efficacy.[6]

The aim of this study is to evaluate the efficacy of 400 microgram of oral misoprostol to facilitate tandem application during transcervical procedure as a part of brachytherapy in the treatment of carcinoma cervix.

Methods

This study was conducted prospectively between february 2015 and april 2015 at the radiation oncology department of Gujarat Cancer Research Institute, Ahmedabad. A total of 100 patients of carcinoma cervix stage II & III who underwent External beam radiotherapy followed by intracavitary brachytherapy were eligible for the study after taking informed consent of the patient. Pain was assessed by the visual analogue scale (0= no pain, 1-5=minimal pain , 6-10=severe pain) and The International Federation of Gynecology and Obstetrics classification was used for clinical staging.[7,8] Patients were randomly assigned to the study group and the placebo group. Study group received 400 microgram of misoprostol orally, 3 hours before the procedure. Placebo group received a vitamin tablet.

The procedure was evaluated for the amount of bleeding, which was graded as either absent (no bleeding), minor (bleeding not requiring any intervention), moderate (bleeding that stops by application for 5 minutes), or heavy (bleeding that stops by suturing or pressure application for 2 hours). Sizes of maximum hegar dilators were recorded. The procedure was graded subjectively as easy, moderate or difficult by the physician. All the applications were performed by the same physician.

Intracavitary brachytherapy was performed after external beam radiotherapy and those patients with break in the treatment, delay or any other discrepancy in the treatment plan were excluded. The patients were treated on high dose rate Ir-192 afterloading system with a reference dose at 0.5 cm.The applicator consisted of Fletcher Suit applicaton with a tandem of adjustable length and two ovoids.

Results

Out of 100 patients, two patients were lost to

treatment and thus excluded from the statistical analysis. 45 patients had received misoprostol and 53 patients had received placebo. Patient characteristics with regard to age are summarized in table 1.Mean age in the study group was 48.1 years ±8.3 years and that of control group was 47.77 ±7.5 years(Student t-test).The difference was found to be insignificant(p-0.160).In regard to stage vise distribution, out of all patients, 39.79% belonged to stage II and 60.20% belonged to stage III and the difference was found to be insignificant.

With regard to bleeding, no significant difference was found in both the arms (Mantel haezel test p value -0.663) as shown in table no. 2.The other parameter measured included ease of dilatation. Out of 98 applications done, 88.8% were subjectively found to be easy and 11.2% were found to be difficult. The difficult cases were distributed almost equally between the two arms. Test of significance(Mantel-Haenszel test) was applied and the difference was found to be insignificant (p value-0.554).This is shown in table 3.

All the patients were initially assessed by uterine sounding followed by the hegar dilator, to assess the dilatation of the patient. 24% of the study arm and 28.3% of the control arm patients required further dilation.Those patients in whom uterine sounding was feasible in reaching the os, no further dilatation was done and a hegar dilator no. 3-3.5 sufficed. In patients who needed dilation, it was done using increasing diameter of hegar dilator and the largest admittable hegar was noted. The data is shown in table 5 and Figure 1.

Discussion

Intracavitary Brachytherapy and external beam radiotherapy (EBRT) are supplemental methods to each other in the radical treatment of cervical cancer. The application of intracavitary brachytherapy as a part of treatment of carcinoma cervix plays an important role in the pelvic control.[9-11]

In particular, optimised intracavitary treatment plays a significant role in the tumor control. But in practice, there are certain clinical conditions which lead to difficulty in proper application. Brachytherapy in old age is one such example.[10] Due to cervical atrophy, there is distorted uterocervical anatomy and insertion of applicator becomes difficult. Previous external radiotherapy also leads to fibrosis. Due to advent of high dose brachytherapy applications, there is all the more need of efficient and correct application to decrease the complication rate.[12] The complications encountered during the brachytherapy application is mainly related to the difficulty of cervical dilatation. These can cause difficulties in sounding and

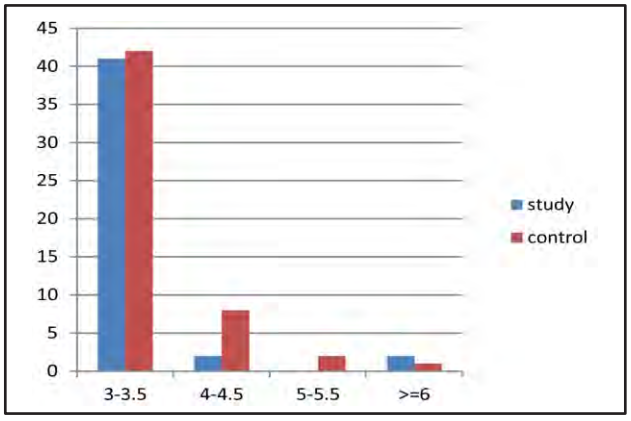

Figure 1: Bar diagram showing the distribution of sizes of hegar dilators in study and control group

Table 1: distribution of patients in control and study arm

misoprostol	No.	Mean	Std. Deviation	Std. Error Mean
Yes	45	48.1333	8.34647	1.24422
No	53	47.7736	7.50293	1.03061

Table 2 : Bleeding incidences in both the arms

	Misoprostol		Control	
	No.	%	No.	%
None	17	37.77	20	37.73
Mild	18	40	20	37.73
Moderate	10	25	13	24.52
Total	45	100	53	100

Table 3 : Ease of insertion in both the arms

	Misoprostol	Control		
	No.	%	No.	%
Easy	39	86.66	48	90.56
Difficult	6	13.33	5	9.5
Total	45	100	53	100

Table 4 : Requirement for dilation in misoprostol and control arm

	Misoprostol		Control	
	No.	%	No.	%
Required	11	24.5	15	28.3
Not required	34	75.5	38	71.7
Total	45	100	53	100

Table 5 : Distribution of various dilator sizes in both the arms

Size of Hegar Dilator	Misoprostol	Control	TOTAL
3-3.5	41	42	83
4-4.5	2	8	10
5-5.5	0	2	2
>= 6	2	1	3
Total	45	53	98

dilating the cervix, leading to under dosing of the tumor and delivery of more than optimal dose to the surrounding normal tissues. Therefore there is a need for an effective cervical priming agent which can be used before the procedure to facilitate the same.[13]

Misoprostol is a stable, orally active synthetic prostaglandin E1 analogue which is used for prophylaxis of peptic ulcer.Misoprostol has several advantages over other priming agents, such as osmotic dilator, other prostaglandins and mifepristone . In studies done by Perrone et al, misoprostol led to significant cervical dilatation ($p<0.01$) as compared to placebo.[14] In obstetric procedures, there is enough evidence that use of misoprostol helps in the ease of procedure, reduces pain and leads to cervical dilation.[14,15] However, there is limited data in case of gynecologic conditions and non-pregnant females. Several studies showed that the intravaginal misoprostol increases cervical dilatation, reduced the need for cervical dilatation and complications.[15,16,17] In a single institute study done by kimia Cepni et al at Istanbul, Turkey showed that the administration of 400 microgram of oral misoprostol for cervical priming before tandem application in cervix carcinoma facilitates the procedure, increases tolerability and decreases the complication rates. They showed that in the study group, the procedure was found to be significantly easy ($p<0.001$) , average size of initial hegar dilator was significantly ($p<0.017$) higher and in the control arm, pain score was significantly higher ($p<0.001$).

In our study, parameters like ease of dilation, average size of initial hegar dilator inserted, ease of insertion, side effects like bleeding or any other adverse effects were compared between the study and control group and it was found that there is no significant difference between the two groups.

Conclusion

Brachytherapy forms an important mode of treatment in carcinoma cervix and the greater conformality achieved by it relies on accurate application. The results of our study are statistically insignificant as far as various parameters like ease of dilation, ease of insertion ,size of hegar dilator and side effects are concerned.This is in contradiction to the one study done before. To further validate the use of misoprostol, a cervical priming agent which is proved to be effective in various gynaecological and obstetric procedures,we need more number of studies with greater number of patients.

(Authors declared - No Conflicts of Interest)

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Impact of PET-CT on Target Volume Delineation and Staging in Head and Neck Cancer

Anand Mridul[1], Bhattacharya Jigna[2], Vyas Rakesh K[3], Goyal Sumit[2], U.Suryanarayan[4], Rachh Swati[2*], Sinha Omprakash[5*]
Junior Lecturer[1], Assistant Professor[2], Director and Professor[3], Professor and Head[4], Radiation Safety Officer[5]
Department of Radiotherapy
Department of Nuclear Medicine*
Corresponding author : jignabhattacharya@gmail.com

Summary

Contrast Enhanced Computed Tomography is the imaging of choice in head and neck malignancies. This study is undertaken to evaluate the impact of Hybrid PET-CT scan on target volume delineation and staging and compare it to CT alone volumes in head and neck cancers. A total of 25 patients of squamous cell carcinoma of oropharynx (n = 20) and hypopharynx (n = 5) were included.FDG-PET and CECT scan were performed in a single session as a part of radiotherapy treatment planning for Intensity modulated radiotherapy. Hybrid PET/CT imaging led to a change in 7 out of 25 patients, i.e. 28% as compared to CT alone in our study.The mean primary GTV volumes on PET-CT and CT were significantly different (PET-CT_GTV : 32.42 ± 15.92 cc vs. CT_GTV : 28.52 ± 15.08). The difference between the two target volumes was statistically significant (p =0.004). Recurrence patterns following IMRT show that most of them are in the high-dose region. Thus, PET-CT has the advantage of functional imaging apart from anatomical detailing. These biological target volumes (gross tumor volume delineated on PET) canbe included in the radiotherapy planning in head and neck cancers and could potentially be used for higher boost to the primary site.

Keywords: PET-CT scan, Head and neck cancers, Staging

Introduction

Most of the patients of head and neck cancers have locally advanced stage primary disease with nodal metastasis and are treated with Chemotherapy and radiotherapy. With the paradigm shift in the treatment of radiotherapy from conventional to conformal techniques, IMRT has shown benefits in delivering higher dose to the target and reducing the toxicities, leading to improvement in locoregional control in these patients.[1, 2] Imaging modalities like CT,MRI and PET have been used to assist in the target delineation, which is the most crucial segment for IMRT. CT is the principal modality used for delineating gross tumor volume but nowadays functional and metabolic imaging, PET-CT using Flurodeoxyglucose as a molecular probe for glucose metabolism in cancer cells has been demonstrated to have high accuracy for detection of many tumour types.[3]

The purpose of this study was to evaluate the potential impact of hybrid PET-CT on Gross Tumour Volume and Staging and comparing it with the CT alone volumes.

Methods and Materials

Twenty five patients with primary carcinoma of the oropharynx, and hypopharynx who had 18FDG-PET/CT scan as a part of their work-up were included in this observation study done from August 2013 to October 2015 in the department of radiation oncology and nuclear medicine, after review was done by the ethical committee. The candidates were selected for radiotherapy after obtaining their informed consent about using their PET-CT images for study. Inclusion criteria were patients having histology proven squamous cell cancer of oropharynx and hypopharynx, stage II-IVA and those have not received any prior chemotherapy and radiotherapy for head and neck cancer. Detailed history and work-up was done including endoscopic evaluation and biopsy. The clinical stage was defined according to the 2010 American Joint Committee on Cancer (AJCC) classification.

Steps included preparation of immobilization device and a hybrid FDG-PET was performed on the same couch after giving 10 mCi (370 MBq) of FDG intravenously to each patient. Post injection patients were kept in dark area and instructed to take plenty of water to reduce bladder radiation dose. After an hour, patient was asked to void the bladder and taken for the PET/CT . FDG-PET imaging was performed on Discovery 600 GE Scanner which combines a light speed 16 slice CT in line with PET (Bismuth Germanate Oxide crystal). The slice thickness was 3.75 mm. The obtained images were reconstructed using algorithm, yielding axial, sagittal and coronal slice. An experienced nuclear medicine specialist prospectively evaluated all FDG-PET images, using corresponding CT images to optimize anatomic orientation.

Target volumes were defined according to the guidelines of ICRU report number. 62 by a radiation oncologist, taking the help of nuclear medicine personnel. CT-scan was used for the information thus delineating CT_GTV.The interpretation of the 18F-FDG PET images was performed in conjunction with

the CT images to help localize the metabolically active foci and differentiate physiologic from pathologic foci of 18F-FDG uptake to form PET_GTV. Once the original CT and PET contours were completed (CT_GTV and PET_GTV), now PET target margins were taken into consideration in redefining the CT contours to create a final contour that represented a union of CT and PET-defined targets (PET-CT_GTV), creating a composite volume. Thus the three parameters defined were CT defined GTV (CT_PET defined GTV (PET_GTV) and union of PET and CT contours (PET-CT_GTV).

Results

In our study, 25 patients were enrolled belonging to different age groups with primaries of various subsites of oropharynx and hypopharynx. Figure 1represents the age-vise distribution of all the patients with range 35-66 years and majority belongs to age groups 45-55 years. Figure 2 shows the stage vise distribution of patients according to CT alone (before PET) and after PET-CT (after PET).Figure 3 depicts the site vise distribution of the patients.

The volume of GTV as defined by CT alone, PET alone and PET/CT combined for all patients is mentioned in the Table 1.In our study, GTV- PET alone volumes were smaller than GTV-CT alone volumes but co-registration increased the GTV such that PET-CT_GTV was larger and closer to the CT-GTV values . PET-CT_GTV was smaller than CT-GTV in 20 out of 25 cases (80%) and greater than CT-GTV in 5 out of 25 cases. (20%). In general CT-GTV was closer to PET-CT GTV as compared to PET alone.The mean CT-GTV, PET-GTV and PET-CT_GTV volume were 28.52 15.08 , 19.35 9.31 and 32.42 15.92 cc. respectively. This is shown in Table 2 and pictorially depicted in Figure 5 and Figure 6. Student t-test was performed as a test of significance between the CT_GTV and PET-CT_GTV and was found to be significant.(p=0.004).

Hybrid PET/CT imaging led to a change in staging (as compared to CT alone staging) in 7 out of 25 patients, i.e. 28%. Out of these 7 patients, Upstaging was seen in 5 patients and the remaining 2 were downstaged. In the rest of 18 patients i.e. 72% there was no change in the staging.Figure 7 and tables 3 and 4 show the same. Figure 8 shows the change in Gross tumor volume as seen on CT alone, PET alone and combined PET-CT images.

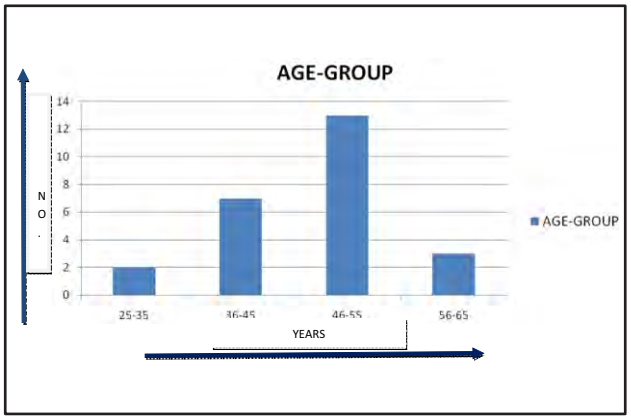

Figure 1: Age wise distribution of patients

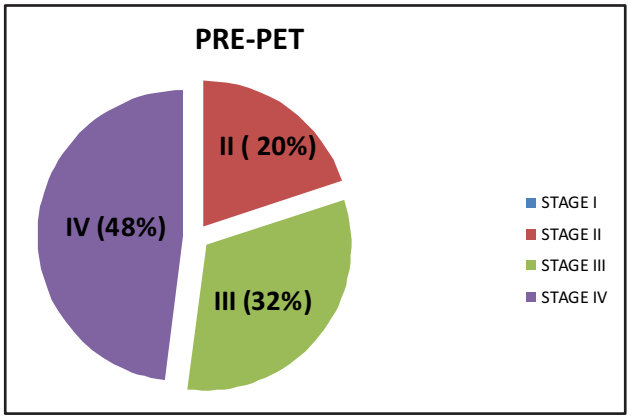

Figure 2: Stage wise distribution (CT only)

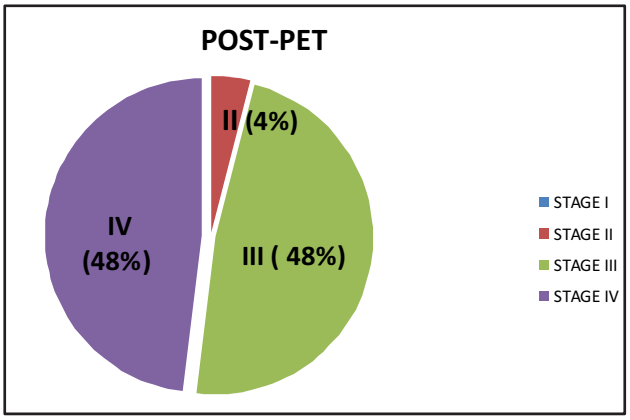

Figure 3: Stage wise distribution (PET-CT)

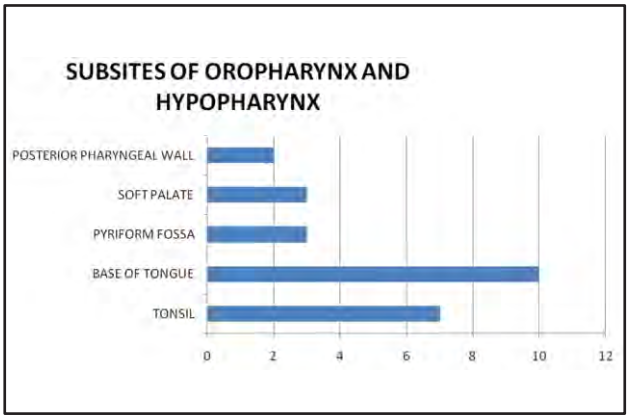

Figure 4: Site wise distribution

Table 1: GTV's (cc) defined by CT alone, PET alone and PET-CT

No.	Site	CT_GTV(cc.)	PET_GTV(cc.)	PET-CT_GTV(cc.)
1.	Ca tonsil	8.81	8.6	13.06
2.	Ca Base of tongue	28.81	20.98	33.74
3.	Ca Base of tongue	22.55	25.27	22.06
4.	Ca Base of tongue	42.24	29.12	43.41
5.	Ca leftpyriform fossa	35.95	19.74	42.02
6.	Ca tonsil	37.06	20.83	39.51
7.	Ca soft palate	6.96	3.3	8.92
8.	Ca tonsil	31.01	34.21	45.48
9.	Ca Soft palate	50.09	28.31	57.01
10.	Ca Tonsil and Soft palate	58.48	31.91	55.04
11.	Ca Tonsil	26.75	14.98	31.71
12.	Ca Base of tongue	65.79	29.63	73.26
13.	Ca Base of tongue	30.21	25.26	43.70
14.	Ca Pyriform sinus	40.52	15.06	42.14
15.	Ca Base of tongue	22.47	11.99	34.05
16.	Ca Base of tongue	24.08	15.26	36.46
17.	Ca Tonsil & base of tongue	23.16	33.37	23.51
18.	Ca posterior pharyngeal wall	28.46	27.73	37.49
19.	Ca Pyriform fossa	9.76	6.9	14.50
20.	Ca Soft palate	37.46	15	21.92
21.	Ca Tonsil	27.76	28.12	28.16
22.	Ca Base of Tongue	24.20	11.82	27.05
23.	Ca Base of tongue	9.24	12.85	11.38
24.	Ca base of tongue	14.16	10.18	16.28
25.	Ca posterior pharyngeal wall	7.06	3.5	8.8

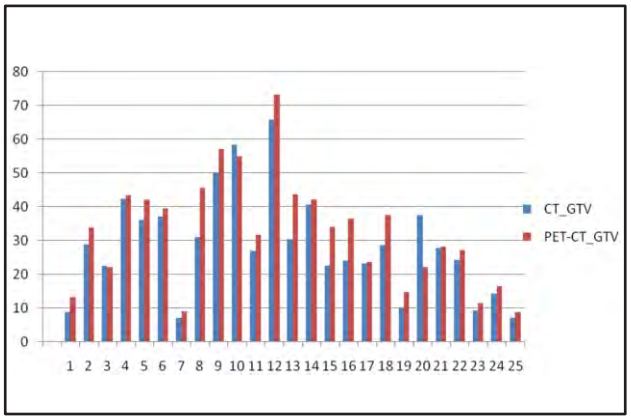

Figure 5: Bar chart showing the comparison of CT_GTV and PET-CT_GTV in all patients

Table 2: Comparison of various target volumes (*All values are in cc.)

*Target volumes	Mean	S.D.	Median	Range
CT_GTV	28.52	15.08	27.76	7.06-65.79
PET_GTV	19.35	9.31	19.74	3.3-29.64
PET-CT_GTV	32.42	15.92	33.74	8.92-43.41

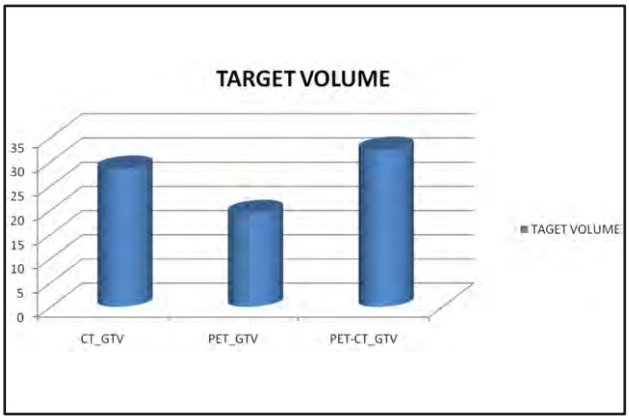

Figure 6: CT_GTV, PET_GTV and PET-CT_GTV

Table 3: Upstaging - Seen in 5 out of 25 patients. (20%)

Case No.	Site	CT-Staging	PET-CT Staging
2	Ca Base of tongue	T2N0 (II)	T3N1 (III)
5	Ca Pyriform fossa	T2N1 (III)	T4aN1(IV)
6	Ca Tonsil	T2N0 (II)	T2N1(III)
8	Ca Tonsil	T2N0 (II)	T3N2b (IV A)
11	Ca Tonsil	T2N0(II)	T2N1(III)

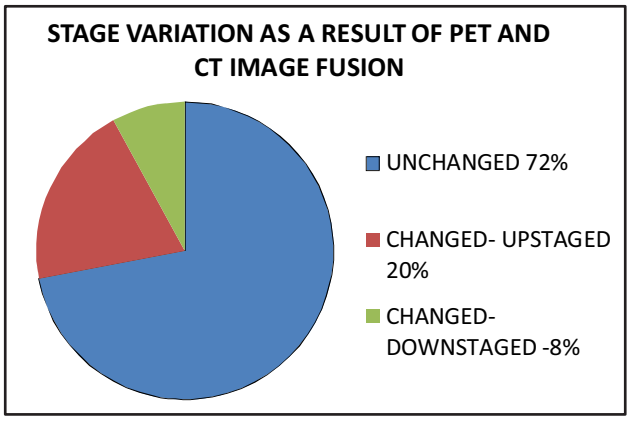

Figure 7: Pie-Chart showing Changes in TNM staging

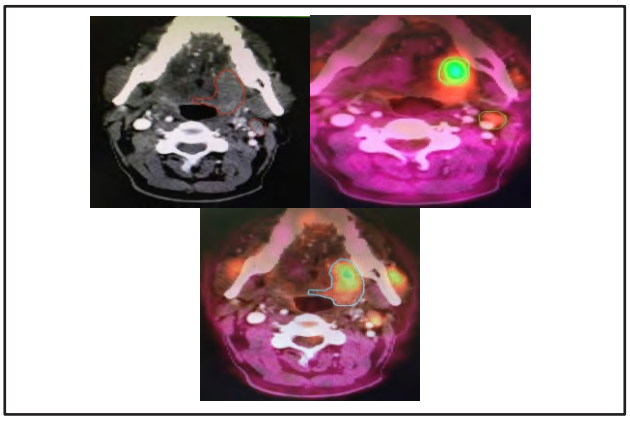

Figure 8: GTV delination in a case of ca tonsil (a) Gross tumor volume on CT scan (b) Gross tumor volume on PET scan (c) Gross tumor volume on fusion of PET-CT scan

Table 4: Down staging- Seen in 2 out of 25 patients (8%)

Case No.	Site	CT-Staging	PET-CT Staging
19	Ca Pyriform fossa	T2N2c (IV A)	T2N1 (III)
23	Ca Base of tongue	T3N2c(IV A)	T3N1 (III)

Discussion

FDG-PET is increasingly being used in the practice of radiation oncology. The main impact of PET in head and neck region lies in it's superior diagnostic accuracy, as compared to MRI or CT for nodal disease. 4The use of PET-CT influences both tumor and nodal volume delineation, as compared to CT, thence variating the staging. The advantage of PET/CT fusion has been already reported for staging and RT planning of non-small cell lung cancer and other tumor locations such as esophagus, rectum, anal canal and pancreas.5 However, studies for the role of PET/CT imaging for staging and RT treatment planning for head and neck carcinoma are limited.[6]

In this study, we studied the comparison of CT_GTV (GTV as seen on CT alone images) with PET-CT _GTV (i.e. GTV obtained by fusion of CT and PET images) PET/CT alters the delineation of GTV by considering the PET information in addition to that available from CT alone. In our study, GTV-PET alone volumes were smaller than GTV-CT alone volumes but co-registration increased the GTV such that PET-CT_GTV was larger and closer to the CT-GTV values. PET-GTV was smaller than CT-GTV in 20 out of 25 cases i.e. 80% and larger than CT-GTV in 5 out of 25 cases i.e. 20%, which was statistically significant (p value-0.015). A Study done by Heron et al. showed that in a group of 21 patients, there is a significant decrease (p=0.002) of PET-based GTV as compared to CT-GTV.[7] In another study by Paulino et al in 40 patients, PET-GTV was smaller in 75% of patients with median 16.9 cc. difference between PET-GTV and CT-GTV. Seperate study by Ciernik et al found that the GTV was reduced by more than 25% in 33% of patients of head and neck cases.[8] In all these studies, the similar finding of having smaller PET-GTV may be related to the inability of PET to identify areas of necrosis inside the tumor, due to lack of FDG uptake of the necrotic tissue. These areas of necrosis are easily seen by CT, hence resulting in greater GTV.

However the best and accurate method of GTV determination is it's correlation with the surgical pathological sample. A study done by Daisne et al compared the GTV identified by various imaging Modalities (CT, PET-CT and MRI) with the pathology specimens and they found that tumor volume delineated on FDG PET were by far the closest to the reference volume assessed from the surgical specimens. Regarding the specificity, it was quoted that the FDG-PET was more specific than MRI or CT.[9] However, contrasting reports from Wang et al. in 28 patients, it was concluded that FDG PET could improve the staging accuracy of oral cavity or oropharyngeal and laryngeal squamous cell carcinomas, but only when used in addition to CT or MR imaging.[10]

There is often debate about the margin used for PET positive target volume. Neither the optimal threshold or the margin of the PET-defined CTV have been defined. In our study, we used 40% of the SUV as the tumor threshold similar to what has been proposed for lung and head and neck cancers.Other methods include percentage of the maximal signal intensity, absolute standard uptake value, auto-contouring of the areas above a certain threshold or ratio of background signal have been used.[11]

There is insufficient data as yet to allow confidence in removing the PET negative areas from standard radiotherapy target delineation. However studies show that extension of conventionally defined targets to include PET-positive volumes is justified. Thus, CT is still considered the standard for treatment planning volumes and PET can be used for greater

target delineation to avoid the geographical misses. How the greater tumor volumes translate into better locoregional control and the reduction in recurrences at the initial tumor site with the help of complex planning like IMRT, needs to be evaluated in the prospective studies.

Since PET provides information regarding the biologically active area within the tumor, it can aid in clinical decisions. With the advent of adaptive radiotherapy, using the fusion of PET and CT images during the course of radiotherapy is a promising approach to changing dose distributions and can be utilised for dose escalation strategies.

Conclusion

The present study states that functional information in the form of FDG-PET/CT images can improve the GTV delineated on CT alone,highlight the unknown areas of disease and alters the staging. These areas can be used for dose escalation with the technique of simultaneous integrated boost. More prospective clinical studies are needed for ascertaining the impact of the incorporation of PET information as an adjuvant for radiotherapy planning and usage of highly conformal and biologically effective treatment.

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Human Papilloma Viruses (HPV) and Human Cancers: Experience from a Regional Cancer Research Centre, Gujarat

Goswami Parijath[1], Pandya Shashank J[1]*, Patel Shilpa M[1#]
Professor and Head[1]
Microbiology Department
Department of Surgical Oncology*
Department of Gynaecological Oncology[#]
Corresponding author : bannuhyd@yahoo.co.in

Summary

To detect the etiological role of HPVs in patients with head and neck cancers from tissues. A total of 363 (100 head and neck cancers, and 263 cervical cancer patients) patients were included in the study and tissue biopsy was taken for histopathology and molecular studies by multiplex PCR. Out of 100 cases of Head & Neck cancers, the HPV was detected in 20% of cases. High risk HPV 16 was detected in 35% of SCC of oral & oropharyngeal cancers. 65% of other types of HPV were detected like; HPV-33 (15%), HPV-39 (5%), HPV-45 (10%), HPV-52 (20%) and HPV-58 (15%). Among Cervical cancer patients, overall 57.41% of the patients showed presence of HPV. HPV was found in 71.4% , 43.4%, and 2.27% in Cervical cancer, CIN and Control groups respectively. Out of 263 cervical cancers, positivity of different HPV types were, HPV-16 (60%), HPV-18 (2.85%), HPV-45 (1.42%), HPV-52 (0.71%), HPV-35 (2.14%) and HPV-39 (0.71%) of the 196 cases studied. It was also observed that in 69.73% of lesions single type genome was detected while in 30.52% cases there was mixed genotypes of HPV was seen. Different HPV types detected were HPV16, 33, 39, 45, 52 and 58 in Head & Neck carcinomas. There was no 100% co-relation of HPV as a sole etiological agent in the genesis of the squamous cell carcinoma. Oral cancers occurred typically in more than 50 yrs, chronic drinkers and smokers. Some studies suggest that 15% - 25% of the oropharyngeal cancers are associated with HPV-16. In cervical cancers apart from different types of HPV detected, it was also observed that in single patient multiple HPV types were found.

Keywords: HNSCC, biopsy, Head and neck squamous cell carcinoma, Cerivical Cancer, Human Papilloma Virus (HPV)

Introduction

Epidemiologic studies have shown that the association of Human genital papillomavirus (HPV) with cervical cancer is strong, independent of other risk factors, and consistent in several countries. There are more than 20 different cancer-associated HPV types, but little is known about their geographic variation.[1]

Links between human papillomaviruses (HPVs) and cervical cancer were first suspected almost 30 years ago. HPV oncogenes that are expressed in these cells are involved in their transformation and immortalization, and are required for the progression towards malignancy. Epidemiological studies have underlined that HPVs are the main aetiological factor for cervical cancer.[2] Human papillomavirus (HPV) spread by skin-to-skin contact. HPV can infect surfaces of the skin, lining of the mouth, tongue, throat, tonsils, vagina, penis, cervix, and anus. Most people who get HPV won't have any signs or symptoms and spread the disease without even knowing.Human papillomavirus (HPV) now causes the majority of oropharyngeal cancers in the United States, and the incidence is rising, especially among men. Men are twice as likely as women to develop oropharyngeal cancers that are linked to HPV, according to new data presented at the recent annual meeting of the American Association for the Advancement of Science (AAAS). They are not only more likely to become infected with oral HPV infection than women, but the research also showed that once they become infected men (~37%) are less likely to clear these infections than women, further contributing to their cancer risk. Oral sex is the main risk factor for oral HPV infection. These differences in sexual behavior across age cohorts explain the differences that we see in oral HPV prevalence and in HPV-related oropharyngeal cancer across the generations and why the rate of this cancer is increasing.[3] HPV-positive head and neck cancer is a distinct and growing disease entity with strong ties to sexual behaviors and oral HPV infection.

Human papilloma virus belongs to the family papovaviridae and papilloma virus. The papilloma viruses produce in their host benign epithelial tumors like papillomas and warts. They are double stranded circular super coiled DNA molecule and have a molecular weight of 5000 kD. Genital HPV types have been subdivided into low-risk types, which are found mainly in genital warts, and high–risk types, which are associated with cervical and head and neck cancers. The number of high risk types varies from 13 to 19 and only 11 HPV types , like 16,18,31,33,35,39,45,51,52,56 and 58 are consistently classified as entailing high risk types.[5]

The aim of the study is to know the prevalence of HPV infection and its various types in cancers of head and neck and uterine cervix.

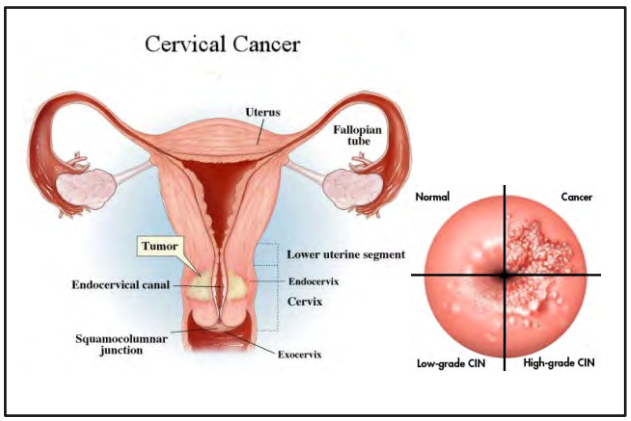

Figure 1 : Cervical Cancer

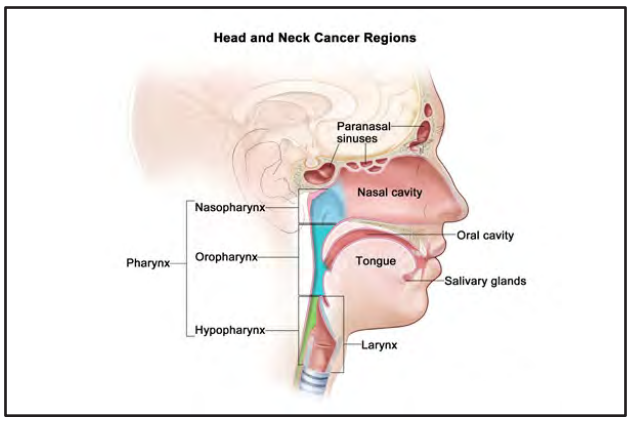

Figure 2 : Head and Neck Cancer

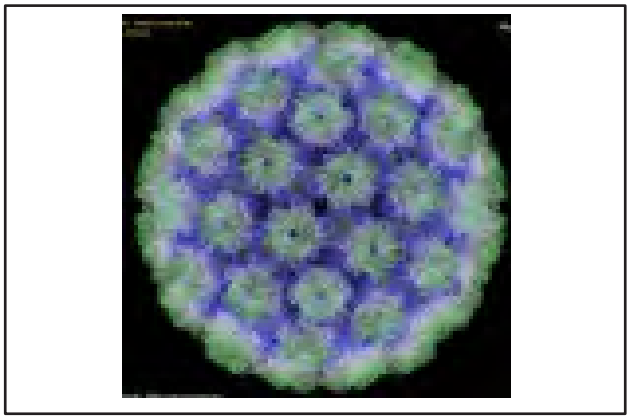

Figure 3: Human Papilloma Virus

Materials and Methods

The microbiology department worked with Gynaec oncology and surgical oncology departments since the year 2000 and the focus was to know the type prevalence of the HPV in head and neck and cervical cancer.

Subjects

A total of 363 (100 head and neck cancers, and 263 cervical cancer patients) patients were included in the study. A patient detail along with history was taken. Patients who were clinically suspected as head and neck cancers and cervical cancers were subjected for biopsy and the tissue sample was sent for histological and molecular studies. The procedures followed were in accordance with the ethical standard and approved by institute ethical committee and Institutional review board. Patient's written consent was taken and detailed history of the patient was recorded. Demographic data including age, gender, habits, history obstetric and menstrual history in female as well as clinical data of tumor site and histological type were obtained. The head and neck cancers patients were classified as non alcohol drinkers, alcohol drinkers, smokers and non smokers, tobacco chewers and non chewers.

Tumor specimens

Two fresh tumor specimens (head and neck cancers and cervical cancers) were collected from different sites of upper respiratory tract like oral cavity, oropharynx, hypopharynx, and cervix in sterile normal saline for molecular studies and in formalin for histopathology. Tissue in saline was stored at -20^{0}C until processed and tissue in formalin was processed for haematoxylin and eosin staining for histopathology diagnosis. Approximately 25 mg of tissue was taken from the tumor specimen for the extraction of the HPV DNA and placed in a 1.5 ml micro centrifuge tube and 300 ul lyses solution was added. Then vortexed it and incubated for 5 mins at 65^{0}C and then centrifuged for 7-10 secs. 20 ul of sorbent was added to each tube, incubated tube for 3 mins at room temperature. Then centrifuged tubes for 30 secs at 5000 g. Then supernatant was discarded without disturbing the pellet. 500ul of washing solution was added to the tubes and centrifuged for 30 secs at 10,000 g. Again supernatant was removed. Then incubated for 5 mins. at 65^{0}C and vortexed periodically. Pellet was re-suspended with 100 ul of DNA elution buffer. Later incubated for 5 min at 650C and centrifuged for 1 min at 12000 g. And finally supernatant containing the desired DNA was available for amplification. Extracted DNA was stored at -20^{0}C until processed.

Ready to use multiplex PCR kit (Sacace Biotechnologies, Italy, supplied from Biotron, India) which contains PCR master mix, buffer red, hot start polymerase, primers directed against region of HPV high risk group and low risk HPV types. Master Mix was prepared according to kit instructions. 15 ul of prepared master mix and 10 ul of extracted DNA were added to each PCR reaction tube. Then 25 PCR cycles were run using following protocol: Soaking for 15 mins at 95^{0}C followed by denaturation 95^{0}C for 15 mins (1 cycle), annealing at 63^{0}C for 30 secs (42 cycles), and final extension at 72^{0}C for 1cycle for 1 min. Later, gel electrophoresis was done using 1.2%

agarose gel. Analysis of results based on the presence or absence of specific bands of amplified DNA in agarose gel was noted.

Statistical analysis

Statistical analysis: Prevalence of HPV infection is expressed as the number of cases with a positive test result divided by the total number of cases tested. Comparisons of prevalence rates by patients a characteristic was performed using chi-square testing.

Factors associated with HPV status were selected on cross-tabulation and logistic regression modeling. Cross-tabulation was analyzed by the use of the chi-square test or Fisher's exact test, wherever appropriate. A logistic regression model was used to determine the effect of multiple factors on HPV status. Results are summarized as ORs and corresponding 95% CIs.For all statistical analysis, a P value of < 0.05 was consider significant.Statistical analysis was performed using SPSS (SPSS Inc, Chicago, IL version 13) and Epi-Inf(version 3) statistical software.

Results

Head and neck cancer patients

During the one year and five month study (August 2009 to January 2011) 100 patients suffering with oral cancer were included in the study. The characteristics of the population studied showed that there was male preponderance (4:26:1), 69% of the cases were more than 50 years and 31% patients were less than 50 years, 58% belonged to urban area and 42% were from rural area, 35% were tobacco non-chewers and 65% were tobacco chewers. Observation showed that 61% of them were smokers while 39% were non smokers. Contrary to their tobacco related habits, majority of the patients (87%) were nonalcoholic while only 13% were alcoholics.Human papilloma virus was detected in 20% (20/100) of the patients. Distribution of HPV prevalence with respect to demographic data showed that 90% (18/20) were males, 75% (15/20) were more than 50 years and belonged to urban areas, were tobacco chewers and 60% were smokers. It was also observed that 75% (15/20) of the patients who had HPV virus were non-alcoholics. (Table 1)

The sites of the cancers were divided into oral cancer, oropharyngeal cancer & Head & neck cancer for the convenience of study purpose. Oral cancer occurs in the oral cavity which includes lip, tongue and hard palate, and oropharyngeal cancer includes soft palate,base of the tongue, tonsils & places around. The histopathology of the tissue biopsy showed that almost all were squamous cell carcinomas.

On the whole, detection of HPV types by multiplex PCR was 20% (20/100). High risk HPV-16was detected in 35 % (7/20) in sqaumous cell carcinomas of oral and oropharyngeal cancers. Other HPV types detected were 65% (13/20). Out of which, HPV-33 was in 15%, HPV-39 was in 5%, HPV-45 was in 10%, HPV-52 was in 20% and HPV-58 was in 15% of the cases.

HPVs in oral cavity lesions

Out of the 73 cases of squamous cell carcinomas of oral cavity, HPV-16 and 33 was detected in 6.84 % (5/73), whereas in the non-malignant cases also we did found 81.8 % (7/11) of different high risk HPV types. The breakup of these high risk HPV types in non - malignant cases showed that 9.09 %(1/11) was HPV-39, 18.18 % (2/11) were HPV – 45, 27.27 % (3/11) were HPV-52 and HPV-58.

HPVs in oro-pharyngeal lesions (n=5)

We found high risk HPV types in 100 % of the cases. In one case there was detection of two types of HPV type (HPV-16 & 52). The high risk types found were HPV-16 (50%), HPV-33 (40%). There were no HPV types detected in non-malignant lesions in oro-pharynx.

HPVs in cancers of mandible, thyroid and maxilla (Head and Neck)

There was no HPV detected in either SCC nor non-malignant cases. (Table 2)

Cervical cancer patients

A total of 263 women suffering with different cervical lesions were enrolled (2006 to 2008) in the study. Histopathology of the lesions showed that out of 263 biopsies, 196 patients had cervical cancers, 23 of them had CIN and 44 patients were taken as control group who had no visible clinical lesions of Cervix and these patients had disease other than cervical lesions like ovarian cancer and in whom hysterectomy was recommended.

Multiplex PCR showed that in 57.41% (151/263) of patients had presence of HPV DNA. Around 71.4% of patients with cervical cancer, 43.4% of patients with CIN and 2.27% of control group had presence of HPV DNA.(Figure 4) Histopathologically, the cervical lesions were squamous cell carcinomas (well, moderately and poorly differentiated), adenocarcinomas, neuroendocrine tumors, inflammation, necrosis and benign lesions. It was noted that in poorly differentiated SCC lesions the incidence of HPV was 75%, followed by 73.98% of moderately differentiated carcinoma and in 25% of well differentiated SCC. In benign lesions also there was detection of HPV in the range of 33 to 90 %. (Figure 5) The prevalence of HPV infection in invasive lesions was 47.82%. In CIN-I it was 40%, in CIN –II it was 100%, CIN-III it was 66.66% and in HSIL it was 50%. There was a single case of wart and there was no

presence of HPV present. (Figure 6)

In non-malignant lesions like inflammation of cervix, HPV – 16 was detected in 33.3% cases, HPV-45 in 11.11% cases. In necrotic lesions HPV-16 was detected in 66.6% and in benign lesion, HPV-16 was 33.3% and HPV-18 in 5.55 %. (Figure 7)

Detection of different HPV types

Different types of Human papilloma virus detected were, HPV 16 in 60%, HPV 18 in 2.85%, HPV 45 in 1.42%, HPV 52 in 0.71%, HPV 35 in 2.14% and HPV 39 in 0.71% of the 196 cases studied. It was also observed that in 69.73% of disease, single type genome was detected while in 30.52% cases there was mixed genotypes of HPV.

Discussion

HPV and Head and Neck cancers

The incidence of Head and Neck cancers varies widely around the world and also within population. Oral and oropharyngeal cancer contributes 3-5% in Europe while this figure in parts of South East Asia reaches up to 40-50 %. Around 80-90% of head and neck cancer cases are associated with risk factors such as smoking, betel nut chewing or tobacco chewing and alcohol abuse.[8] Recent studies have clearly established HPV as a definitive risk factor for oral pharyngeal cancer and it is now a well defined entity with well known characteristics that include young age, good performance status, male gender, non-smoking or non – drinking status and high risk sexual behavior.[7] We procured the data for the prevalence rates of head and neck cancers from the community oncology department of our institute and it is 33%, 33.65% and 34.26% in 2009, 2010 and 2011 respectively and there has always been a male preponderance (2.92:1). We included 100 patients suffering with head and neck cancers in our study. The

Table 1: Characteristics of the head and neck cancer study population grouped by HPV status

Characteristic	Total (n=100)		HPV-positive group (n=20)		HPV-negative group (n=80)		Unadjusted OR*	
	No.	%	No.	%	No.	%	OR(CIs)**	P value
Sex								
Male	81	81	18	90	63	79	2.42 (0.51-11.5)	0.263
Female	19	19	2	10	17	21		
Age at diagnosis (yrs.)								
> 50	69	69	15	75	54	68	1.44 (0.47-4.40)	0.518
< 50	31	31	5	25	26	32		
Geographical area								
Urban	58	58	15	75	43	54	1.18 (0.37-3.77)	0.772
Rural	42	42	5	25	17	46		
Tobacco exposure(Chewing)								
Chewers	35	35	5	25	30	38	0.55 (0.18-1.68)	0.298
Non-chewers	65	65	15	75	50	62		
Smoking								
Non smoker	61	61	8	40	53	66	0.33 (0.12-0.93)	0.035
Smoker	39	39	12	60	27	44		
Alcohol intake								
Non Alcohol drinkers	87	87	15	75	72	90	0.33 (0.09-1.10)	0.084
Alcohol drinkers	13	13	5	25	8	10		

*OR : Odd ratio **CI : Confidence Interwal

Table 2: Histopathology & HPV detection from biopsies of Head & Neck cancer

					HPV types(n=20)					
Sr. No	**Site of Biopsy**	**Histopathology**	**Total**	**Positive**	**16****	**33****	**39**	**45**	**52**	**58**
1	Oral cancers	SCC*	73	5	4	1	0	0	0	0
		Non-Malignant	11	9	-	-	1	2	3	3
2	Oropharyngeal	SCC	5	6	3	2	-	-	1	-
		Non-Malignant	4	0	-	-	-	-	-	-
3	Head & Neck cancer like mandible, thyroid, maxilla	SCC	7	0	-	-	-	-	-	-
		Non-Malignant	0	0	-	-	-	-	-	-
		Total	100	20	7(35%)	3(15%)	1(5%)	2(10%)	4(20%)	3(15%)

*Squamous cell carcinoma, ** Type 16 & 33 is a high risk HPV.

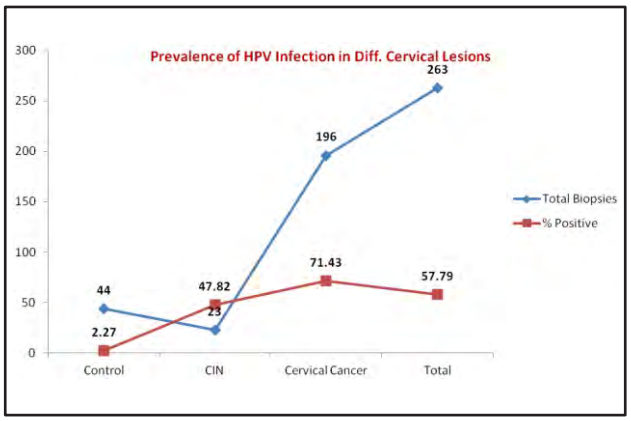

Figure 4 : Prevalence of HPV Infection

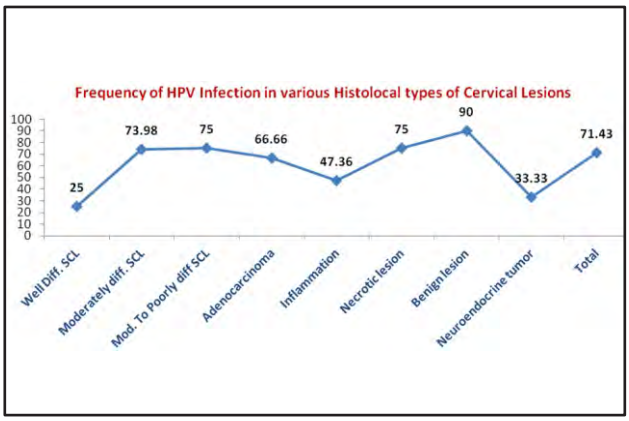

Figure 5 : Frequency of HPV Infection

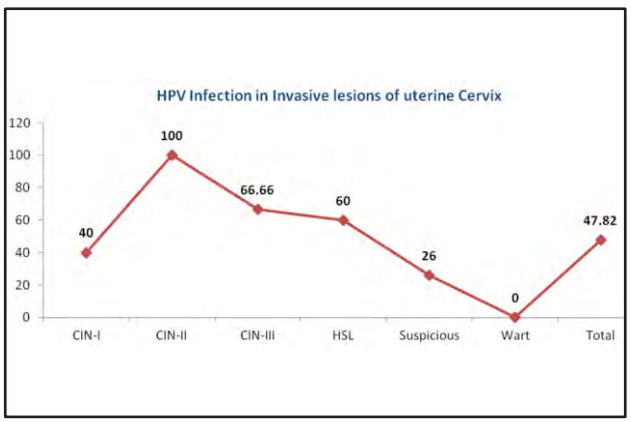

Figure 6 : HPV Infection in Invasive Cancer Cervix

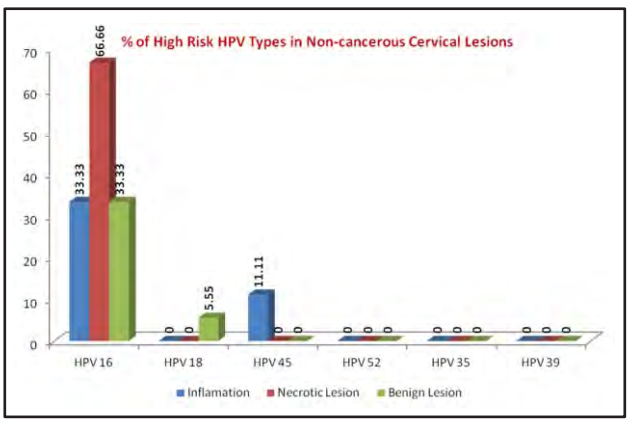

Figure 7 : Percent of high risk HPV types in Non-cancerous Cervical Lesions

observations showed that there was male preponderance (4.26:1).The study showed 69% of the patients were above the age of 50 years. A report by Jeanne Erdann[9] states that these patients belong to age group of 60-65 years who were chronic alcoholics and smokers. We observed that the conventional risk factors like smoking (61%), tobacco chewing (65%) and age more than 50 yrs were the contributory factors for the development of oropharyngeal cancers. In our study HPV was detected in 20% of the cases which is nearer to some studies conducted elsewhere. The study conducted by Sarnath et al,[10] showed that the detection of HPV was 34% in patients less than 50 yrs which was quite high when compared to our study. HPV-positive oropharyngeal cancers comprise a distinct molecular, clinical, and pathologic disease

that has a markedly improved prognosis. HPV 16 in our study was prevalent in 35% of the cases while in Pilch H et al study[4] showed that HPV 16 was predominant viral type in 45.3% of the cancers.

There is a strong association between HPV and oropharyngeal cancers and our findings suggest that HPV-positive oropharyngeal cancer arising from buccal mucosa and tongue have etiological association with high-risk HPV-16. In contrast to HPV-negative oropharyngeal cancers we have seen that they have distinct pathology, risk factors like tobacco chewing, associated with smoking. An etiological link between HPV and non-oropharyngeal tumors is less firmly established. The predominance of oncogenic high-risk viral types (HPV 16, 18, 31, 33) in HNSCC (16,52) previously identified as the major HPV types in cervical carcinomas argues for a potential analogue role for these viruses in development of malignancy in the upper airway. The means by which HPV is transmitted to the upper airway is unclear. Although oral HPV infections are rare in newborn children of infected mother prior to sexual activity, infections increase after onset of sexual activity. Epidemiologic studies of cervical cancers have clearly demonstrated that high-risk type mucosa-tropic HPVs are transmitted by sexual contact. Although HPV presence in head and neck cancers has not yet been convincingly linked to the specific sexual practices such as oral sex. HPV positivity has been linked to the number of sexual partners in three case-control studies. Therefore this may be another reason for the low identification of HPV types in our group of patients.

HPV and Cervical Cancers

Human papilloma virus, a sexually transmitted is increasingly implicated in the pathogenesis of cervical cancers. Pilch et al, in their retrospective study used consensus primers mediated PCR followed by DNA sequencing and found 73.4% HPV DNA prevalence in paraffin embedded tissues from cervical carcinomas[11] Other studies reported detection of ranging from 50% to 90%. In our prospective study, we used primers directed to all the high risk HPV genotypes by multiplex PCR in biopsy samples from the clinically diagnosed cervical cancers. There was overall the prevalence of HPV in 71.43% of cases. Detection of HPV 16 is higher in our study than when compared to other studies. We found HPV 16 in 90% of the cases and HPV 18 in 3.1% , where as in other studies HPV 16 was detected in in squamous cell carcinoma and HPV 18 dominated in adenocarcinomas in 60.9% of cases. Other high risk HPV types detected in our study were HPV 35, 39, 45 and 52 in few cases of SCC, where as other studies didn't report other high risk type of HPVs. The results of the study conducted by Xavier Bosch et al were almost similar to our study. They found HPV DNA 93% of tumors. HPV 16 was present in 50% of specimen, HPV 18 in 14%, and HPV 31 in 5%. As with them the HPV 18 prevalence was 56% and was predominantly present in adenocarcinomas, which is similar to that of our study where our finding was 60.9%.[12]

Conclusion

There has been a shift in the aetiopathogeness of the head and neck tumors. HPV positive oropharyngeal cancer is recognized as a distinct subset of head and neck squamous cell carcinoma with a good prognostic association in the treatment outcome which is independent of age, status, tumor differentiation, and gender or patient's habits. It was obvious from the study which we undertook that the overall detection of HPV-DNA in tumorigenic tissue was 20% of which HPV-16 accounted for 35%. In rest of the patients it can be hypothetically stated that the other risk factors like age more than 50 years, old habits of smoking or chewing tobacco or the betel nut may have attributed to tumourogenesis. More studies on the tumourbiology, and oncogenes (useful markers) combining with HPV status will give a different direction for the precise treatment of individual cases.

It is a known fact that cervical cancer is closely associated with HPV virus and is more prevalent in the developing world and screening with PAP test is not sufficient as many pre cancer lesions go un noticed and un treated. Epidemiological studies have shown that the association of genital human papillomavirus (HPV) with cervical cancer is strong, independent of other risk factors, and consistent. There are more than 20 different cancer-associated HPV types, but little is known about their geographic variation. Extensive study on geographical distribution has not yet been done around the world.

Therefore, looking into the presence of the high risk HPV types in Head & Neck cancers as well as cervical cancers, it can be authenticated that the human papilloma virus is the initiating factor for the development of cancers, along with the other contributing factors like hygienic conditions, multiple sex partners, eating habits (chewing tobacco and betel nut) and age factors are contributing to the development of cancers in human beings.

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Time Trends of Breast Cancer Incidence of Two Periods in Ahmedabad Urban Agglomeration Area

Shah Janmesh[1], Shah Anand[1], Patel Himanshu[2], Pandya Vishruti[3], Joshi Geeta[4]*
Assistant Professor[1], Medical Record Officer[2], Jr. Statistical Assistant[3], Professor and Head[4]
Department of Palliative Medicine*, Department of Community Oncology
Corresponding author : janmesh.shah3@gmail.com

Summary
Breast cancer is the leading female cancer across the globe. It was thought that due to higher rural population in India, leading female cancer is cervical cancer. But as years passes and due to the effect of urbanization breast cancer scenario in India is also changing. To see this trend in Ahmedabad urban area, Age Adjusted Rates (AAR) of breast cancer is compared of two periods 1990-94 and 2007-11. The data of Population Based Cancer Registry is used for comparison. It is seen that speed of increasing the breast cancer in second period is almost double than the previous period. More cases from early age group (15-34) are seen in later period (2007-11) compared to earlier years (1990-94).
Keywords: Breast cancer, Ahmedabad Urban, Trend, Comparison

Introduction

As the world is developing, shift is seen from communicable diseases to non communicable diseases. Cancer is a rising problem all over the world both in males and females. Cancer is not just a physical disease; it is a loss to the nation. Physical, social, economical every aspect is affected by the disease. An estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compared with 12.7 million and 7.6 million, respectively, in 2008[1]. In females of urban area, the leading cause of morbidity and mortality amongst all cancers is breast cancer. Ahmedabad also has its cancer registry to keep an eye on the incidence of all the cancers including breast cancer. The aim was to study and compare the trend of Breast cancer during 1990-1994 and 2007-2011. The main objectives were:

(1)To study and compare age group wise trends for cancer of breast during 1990–1994 and 2007-2011 among the Ahmedabad urban agglomeration area.[2] To study overall trend of breast cancer during 1990–1994 and 2007-2011 among the Ahmedabad urban agglomeration area.

Methods

A hospital based study was done using secondary data collected from different sources like hospitals, laboratory, clinics etc. of Ahmedabad urban agglomeration by field workers of Population Based Cancer Registry (PBCR). Females of more than 15 years were taken as study population. Those cases whose mandatory information was not available were excluded. Data was cleaned, compiled and analyzed by community oncology department of Gujarat Cancer Research Institute (GCRI). Data was also sent to and verified by National Cancer Registry Programme (NCRP).

The data on breast cancer was collected in 2 periods.
1. The first period: from 1990 to 1994
2. The second period: from 2007 to 2011

Age Adjusted Rate (AAR) of breast cancer was calculated for both the periods and was used for comparison of trends. Statistical test like ANOVA was performed in Epi info7 software.

Table 1: AAR of breast cancer of consecutive years of two periods

Age Groups		15-34		35-64		65+		All age Groups	
First Period	Second Period	First Period	Second Period	First Period	Second Period	First Period	Second Period	First Period	Second Period
1990	**2007**	0.81	1.28	14.05	16.1	3.63	5.75	19.9	25
1991	**2008**	1.34	1.12	11.72	15.4	4.37	5.52	18.6	24
1992	**2009**	1.15	1.28	11.86	18.3	4.26	5.6	18.2	28
1993	**2010**	0.54	1.54	13.91	17.6	5.01	6.03	20.1	28
1994	**2011**	0.85	1.58	13.25	17.5	6.51	6.09	21.4	28
Slope		-0.07	0.1	0.06	0.08	0.64	0.1	0.45	0.98
p - value		0.033		0.0006		0.0721		0.0002	

Results

Below table shows the age adjusted rate of breast cancer among the first period (1990-94) and second period (2007-2011). It is clearly visible from Table 1 that AAR is increasing during both the periods, however the speed of increase in second period (0.98) is almost double than the first period (0.45). Apparently the speed of rise (determined by slope) is higher in second period as compared to the first period, but it is not statistically significant at p value 0.06.

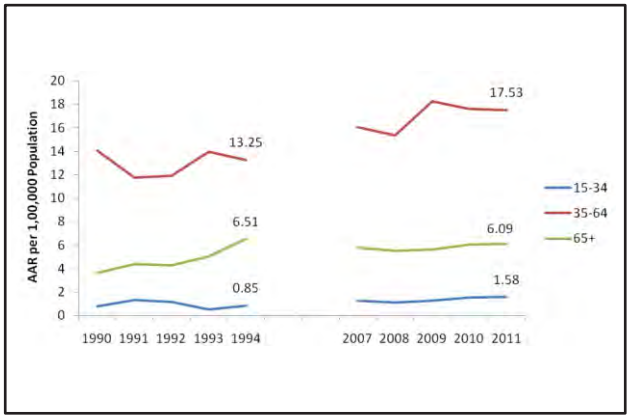

Figure 1: Age wise trend of breast cancer (1990-94, 2007-11)

This figure shows the age wise trend of Age Adjusted Ratio (ARR) per 100000 populations. On comparing the graph of both the periods we can see that with time span AAR had been nearly double among the 15-34 age group, whereas among 65+ age group the AAR remains the same. AAR of 35-64 years had increase from 13.25 to 17.53 between two time periods.

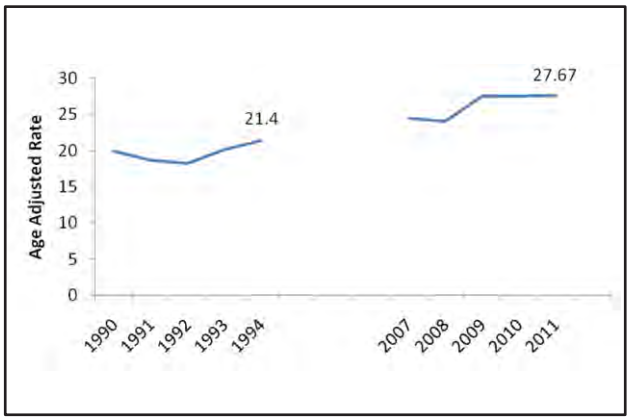

Figure 2: Trend of Cancer Breast

The above figure shows the overall Age adjusted ratio for breast cancer for both the periods, the rate has increased from 21.4 to 27.67 per 100000 population. As a whole the AAR had increased by nearly 6 points but on considering age specific AAR (Graph 1), significant rise was seen in early age (15 – 34 years) group.

Discussion

In a study done by Pink initiative in major cities like Mumbai, Delhi, Bengaluru, Bhopal, Kolkata, Chennai, Ahmedabad etc.; Trend of Ca. Breast was increasing and Ca. breast accounts for 25% to 32% of all female cancers[2] which is also seen in this study. Similar finding were also seen in other studies.[3,4]

Conclusion

It is seen that the trend of Ca. Breast is increasing over the years. The most common age group to be affected is from reproductive age group (35-64 years). Though overall AAR of breast cancer is significantly increased, AAR of breast cancer in elderly females is almost the same in both the period.

Recommendation

More efforts should be done on Breast cancer awareness and self breast examination, training of medical officer for screening cancers, integrated cancer control services with MCH activities. Development of health infrastructure and manpower, establishment of cobalt unit, chemotherapy units which will reduces out of pocket expenditure of rural population, palliative centre, diagnostic kits to be provided and planning and implementation of cancer screening camps. Establishment of regional cancer centers and biopsy centers, increasing State government participation, involvement of NGO on the model of public private partnership. We can take this study of Ahmedabad as a pilot (representative) study for all the metro cities of India.

Acknowledgement:

1. National Cancer Registry Programme, Bangalore
2. Indian Council of Medical Research
3. Population Based Cancer Registry- Ahmedabad Urban Agglomeration Area
4. The Gujarat Cancer & Research Institute, Ahmedabad

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Assessment of Salivary Lactate Dehydrogenase Activity in Oral Squamous Cell Carcinoma

Patel Jayendrakumar B[1], Patel Kinjal R[2], Patel Shruti R[2] , Patel Kinjal D[3], Patel Prabhudas S[4]
[1]Senior Scientific Officer[1], Juniour Research Assistant[2], Junior Research Fellow[3], Professor and Head[4]
Department of Cancer Biology
Corresponding author : jayendra_p@rediffmail.com

Summary

Oral cancer is a major health burden in India. Therefore, it is important and necessary to apply the vast knowledge about salivary biomarkers for screening of oral cancer. Hence, aim and objective of the study were to evaluate salivary lactate dehydrogenase (LDH) and its isoenzyme activities in healthy individuals and oral cancer patients. Blood and saliva samples were collected from 20 healthy individuals and 25 oral cancer patients. Total LDH activities from serum and saliva samples of the subjects were analyzed by spectrophotometric method. Isoenzymes of LDH were separated using polyacrylamide gel disc electrophoresis and gels were analyzed using densitometer. Statistical analyses were carried out by SPSS software (version 15). Salivary LDH activity was found to be increased in oral cancer patients as compared to controls. Based on tumor sites, it was also observed that mean salivary LDH activity was higher in patients with buccal mucosa as compared to the patients with base of tongue. Receiver operating characteristic curve analysis revealed that salivary LDH activity can discriminate between controls and oral cancer patients. Salivary LDH activity was also higher in oral cancer patients with moderately differentiated tumor than patients with well differentiated tumor. All the five isoenzymes of salivary LDH were higher in oral cancer patients than controls.

The present study suggested that the measurement of salivary LDH activity is simple and noninvasive technique which may be helpful in screening and as early diagnostic markers for oral squamous cell carcinoma.

Keywords: Lactate Dehydrogenase, Saliva, Oral Cancer

Introduction

Oral cancer is significant component of the global burden of cancer. It is also a significant disease globally with an estimated 390,000 new cases worldwide accounting for 2% to 3% of all malignancies.[1] However, oral cancer is the most common malignancy in developing than in developed countries. India has been identified as one of the high risk countries where 77,000 new oral cancer cases were reported which constitute one third of world burden and seems to be still rising making it a major health problem.[2] It was also reported that tobacco is the major risk factor found to be associated with oral cancer.[3-4]

Oral squamous cell carcinoma is one of the most common epithelial malignancies with significant morbidity and mortality rates worldwide. In spite of diagnostic and therapeutic advances over the decades, the disease still remains a challenge for medical professionals with the five year survival rate being 30%-50%.[5-6] Recent observations indicate that the clinical and histological appearance of oral mucosa may not truly depict the damage occurring at the genetic level. For that, it is necessary to gather information from DNA's, RNA's and proteins present in the saliva. Salivary DNA represents the genetic information of the hosting human body, the oral microbiota and the infecting DNA-viruses. Salivary RNA provides information on the rates of transcription of the host genes and those of oral microbiota. Salivary proteins represent genetic information and help to understand the translational regulation of the host body and the oral microbiota. In addition, saliva is also useful in detection of markers such as cell cycle markers (p16, p53 etc), growth factors (epidermal growth factor, transforming growth factor etc), cell surface markers, oxidant and antioxidants.[7] Currently, more than 2400 salivary proteins have been identified, but it is expected that this number will increase in the near future.[8]

Lactate dehydrogenase (LDH) is an enzyme which is most commonly found in animals, plants, and prokaryotes. LDH has medical significance because it is found extensively in body tissues, such as blood cells and heart muscle. LDH releases during tissue damage, thus it can play a role as a marker of common injuries and disease. LDH is an enzyme that transfers a hydride from one molecule to another. There are four distinct enzyme classes of LDH and each one acts on either D-lactate (D-lactate dehydrogenase) or L-lactate (L-lactate dehydrogenas). Two are cytochrome c-dependent enzymes and two are NAD(P)-dependent enzymes.[9,10] Functional LDH is tetramers in homo or hetero form. Each tetramer is composed of M and H protein subunits encoded by the LDHA and LDHB genes, respectively. LDH-1 is composed of four H protein subunits, which is most commonly present in the heart and in red blood cells. LDH-2 is composed of three H and one M protein subunit which is most commonly present in the reticuloendothelial system. LDH-3 is composed of two H and two M protein subunits, which is generally present in the lungs. LDH-4 is composed of one H and three M protein subunits, which is commonly present in the kidneys, placenta, and pancreas. LDH-5 is composed of four M protein subunits, which is most commonly present in the liver and striated muscle. Various studies have been reported increased levels of LDH and its isoenzymes levels from serum sample of

cancer patients. It was also observed that serum LDH isoenzymes determination in carcinoma has been found to be useful in diagnosis as well as an important prognostic parameter. Therefore, characterization of a malignant disease by molecular markers is expected to improve the overall understanding of variations in the clinical course of individual patient and help to estimate their prognosis. Moreover, targeting the molecular markers linked to the malignant transformation may provide a non surgical therapeutic approach. There are many established molecular markers in malignancy, but there is far less knowledge on salivary biomarkers in development of oral carcinoma. Considering this, the aim of present study is to evaluate salivary LDH activity in healthy individuals and oral cancer patients.

Materials and Methods

Subjects for Study

The study was approved by the institutional review board. Prior consent was taken from all subjects. The present study recruited 25 cases with histopathologically confirmed oral carcinoma who attended the outpatient's department of the Gujarat Cancer and Research Institute, Ahmedabad, India. Twenty healthy individuals were included who were blood donors and accompanied patients seeking treatment at the Institute. The inclusion criterion for the controls was the absence of prior history of cancer or precancerous conditions and any major illness in past. The socio-demographic details, detailed history of tobacco habit and clinical details were collected. Oral cancer patients were further classified according to the sites of cancer as base of tongue and buccal mucosa.

Collection and Processing of Samples

A subject was requested to spit 5 ml of saliva in sterile falcon tube. All possible care was taken so that cough or mucous should not come along with saliva sample. The falcon tube was immediately kept in ice bucket until processing. Further saliva sample was centrifuged at 7500 rpm for 15 minutes at 4 degree centigrade. Supernatant of saliva was collected for LDH analysis and stored at -70^{o}C for analysis of rest of the markers.

Analysis of Lactate Dehydrogenase and its Isoenzymes

Analysis of LDH activity was done by spectrophotometric method.[11] The separation of LDH isoenzymes was performed by electrophoretic method described by Dietz and Lubrano.[12] This method utilizes vertical electrophoretic technique in a specialized glass column instead of conventional plate electrophoresis. PAGDE method is a modified method of PAGE for separation of isoenzymes for their qualitative as well as quantitative analysis. The protein content in saliva was estimated according to the method of Lowery et al.[13]

Statistical Analysis

Statistical analysis of data was carried out using the SPSS statistical software (Version 15). Student's 't' test was performed to compare LDH enzyme activities between subjects. Receiver operating characteristic(ROC) curves were constructed to evaluate the discriminatory efficacy of the LDH enzyme levels between the subjects. P values <0.05 were considered statistically significant.

Results

LDH activity, total protein (TP) and ratio of LDH/TP from saliva samples of healthy individuals and oral cancer patients are shown in Figure 1. Salivary LDH activity was found higher in oral cancer patients than in controls. There was no significant difference in salivary total protein levels between healthy individuals and oral cancer patients. Oral cancer patients showed increased ratio of salivary LDH/TP as compared to healthy individuals. Present study also evaluated serum LDH levels from healthy individuals and oral cancer patients. Serum LDH activity were comparable between healthy individuals (116±29.0 IU/L) and oral cancer patients (114.3±29.1 IU/L) (Table 1).

In present study, LDH activity in major sites of buccal mucosa and base of tongue were estimated. Table 1 shows salivary LDH activity, salivary TP, ratio of salivary LDH/TP and serum LDH activity in healthy individuals and in patients with squamous cell carcinoma of buccal mucosa and tongue. Mean salivary LDH activity and salivary LDH/TP ratio of oral cancer patients having squamous cell carcinoma of buccal mucosal was found to be higher than those having squamous cell carcinoma of tongue. However total serum LDH activity and salivary TP levels were comparable between squamous cell carcinoma of tongue and buccal mucosa patients.

Table 1 showed LDH activity in oral cancer patients with well and moderate tumor differentiation. In oral cancer patients with moderately differentiated tumour higher mean salivary LDH activity was found than those of patients with well differentiated tumors. Rest of biomarkers were comparable between well and moderately differentiated tumors of oral squamous cell carcinoma.

ROC curve analysis was performed using SPSS statistical software for evaluation of sensitivity and specificity. As shown in Figure 2, ROC curve for salivary LDH activity revealed that it had good discriminating power between oral cancer patients and healthy individuals. But rest of biomarkers could not discriminate between oral cancer patients and

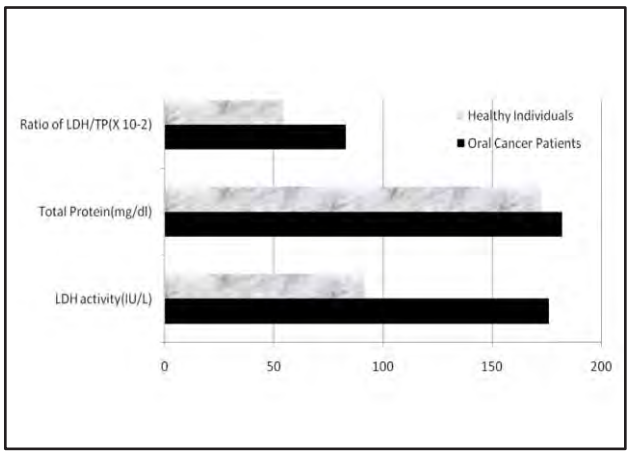
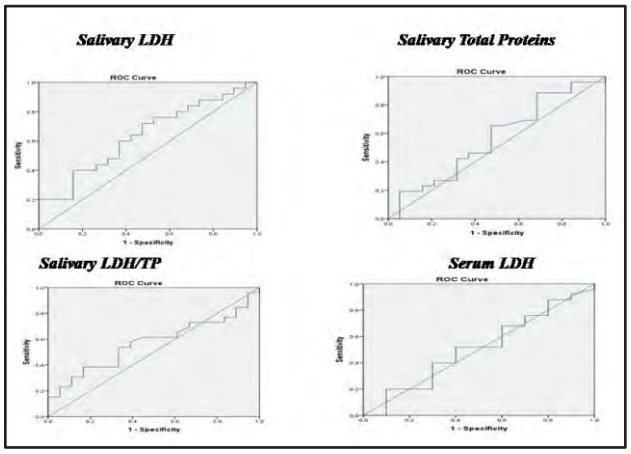


Figure 1: Comparison of mean salivary LDH activity, total protein levels and ratio of LDH/TP in healthy individuals and oral cancer patients



Biomarkers	Area under curve	Std. Error	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Salivary LDH	.636	.084	.126	.471	.801
Salivary TP	.565	.089	.462	.391	.738
Salivary LDH/TP	.571	.087	.431	.401	.740
Serum LDH	.510	.111	.927	.292	.728

Figure 2: ROC curve for comparison of salivary LDH activity, salivary total protein, salivary LDH/TP ratio and serum LDH activity between controls and oral cancer patients

healthy individuals.

LDH isoenzymes were separated in column of PAGE apparatus. Each gel containing the separated isoenzymes were analyzed in densitometer and band densities of all the five isoenzymes were measured (Figure 3). Activity of each isoenzyme was calculated by dividing the density with total LDH activity for the particular sample. Densitometric analysis revealed that all the five salivary LDH isoenzymes activities was higher in oral cancer patients as compared to controls, as shown in Figure 4. Hence, evaluation of isoenzyme activities of salivary LDH suggested that all the five isoenzymes were higher in oral cancer patients than controls.

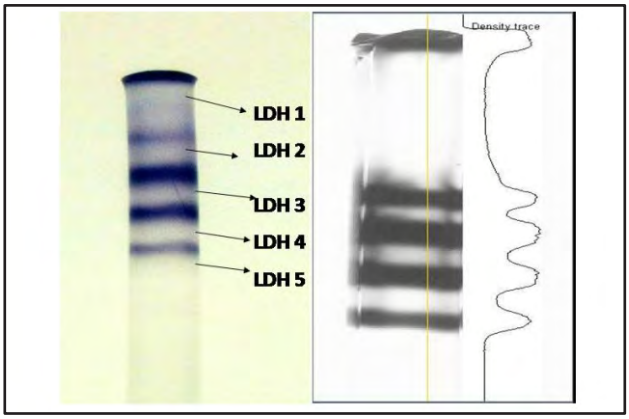


Figure 3: Representative pattern of polyacrylamide gel showing separation of five isoenzymes of LDH

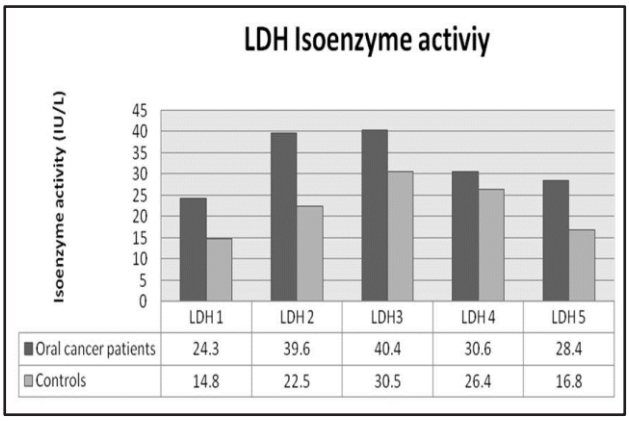


Figure 4: Mean salivary LDH isoenzyme activities in oral cancer patients and controls

Table 1: Comparision of biomarker levels with sites and tumor differentiation of squamous cell carcinoma

	Salivary LDH activity(IU/L) Mean±SE	Salivary Total Proteins(mg/dl) Mean±SE	Salivary LDH/TP ratio Mean±SE	Serum LDH activity (IU/L) Mean±SE
Healhty Individuals	91.4±13.8	172±16.0	0.537±0.01	116±29.0
Bucal Mucosa Cancer Patients	227.1±89.8	192.3±19.0	0.71±0.13	100.4 ±20.6
Tongue Cancer Patients	74.6 ±14.7	156.0 ±18.3	0.99 ±0.68	128.1 ±37.5
Well Differentiated Tumor	139.3 ±32.9	188.7 ±22.5	0.97±0.40	118.8 ±27.8
Moderately Differentiated Tumor	298.1 ±150.4	188.1 ±32.2	0.91 ±0.2	131.6 ±24.1

Table 2: Review of literature regarding LDH activity in oral precancerous condition and oral cancer

Sr no.	Inferences	Sites of Diseases	References
1.	Salivary LDH is more significant biomarker for leukoplakia.	Oral Leukoplakia	Dhivyalaxmi et al; 2014[15]
2.	Salivary LDH levels can be used as supportive biomarker for oral squamous cell carcinoma along with other salivary markers.	Oral cancer	Shpitzer et al; 2009[16]
3.	Salivary LDH estimation can prove to be vulnerable substitute to serum LDH as a biochemical marker.	Oral cancer	Joshi et al; 2012[17]
4.	LDH is none significantly higher in oral squamous cell carcinoma patients in comparison with acute leukemia patients.	Oral cancer	Merza et al; 2010[18]
5.	75% of whole salivary LDH originates from extra salivary gland source from which the major source is the shedded oral epithelial cells.	Oral cancer	Nagler et al; 2001[14]
6.	Salivary LDH levels are consistently higher in oral pre cancerous conditions and cancer. Hence it could be future marker.	Oral precancerous conditions and oral cancer	Shetty et al; 2012[19]
7.	The present salivary analysis for LDH enzyme revealed an overall altered salivary LDH enzyme level in oral leukoplakia and oral squamous cell carcinoma patients.	Oral leukoplakia and oral cancer	Patel et al; 2015[10]

Discussion

An array of unsolved questions exists in the fight against cancer. Rapid industrial development is leading to changes in the life styles of people leading to increase in the incidence of tumors particularly those which are related to oral cavity. Oral cancer is leading type of cancer in India. Early detection and disease management can drastically increase the overall survival rate in patients with oral cancer. A number of biomarkers are available for detection of oral cancer. For many years blood is used as a useful source of various biomarkers specifically for detection of oral cancer. Since the blood collection procedure has some drawbacks, it is important to look for a better and reliable source for presence of biomarkers. Saliva is used since 1990's as a potential diagnostic tool for various diseases. Major advantages of saliva for its use as diagnostic tool includes its composition, non invasiveness, ease of collection, less contamination, reduced patient discomfort etc.

Saliva is the only biofluid that resides in the oral cavity which might contain shed epithelial cells when the tumor is present. Since several findings suggests that presence of LDH in whole saliva is only due to the shed epithelial cells,[14] it becomes clear that salivary LDH could play a dramatic role in detection of oral cancer as an advanced and cost effective diagnostic tool. Table 2 displays summarized review of literature regarding salivary LDH activities. In the present study, total salivary LDH activity and total salivary proteins were measured and both were found to be higher in oral cancer patients than the healthy individuals, whereas, total serum LDH activity was comparable between oral cancer and healthy individuals. This can be because the fact that serum is systemic, which is not in direct contact with the shedding epithelial cells of oral mucosa while saliva remains in direct contact with the malignant cells. Among the various sites of oral cavity, buccal mucosal cancer showed elevated values of salivary total LDH activity. This could be because 75% salivary LDH activity is due to the cells that are shed during tumorogenesis. [14,20] Total salivary LDH activity from tongue cancer patient had high level but not as high as that of buccal mucosa. It was also observed that mean salivary LDH activity was higher in patients with moderately differentiated tumor as compared to patients with well differentiated tumor. These results may be due to different morphology of cancerous cell which are being shed from well and moderately differentiated tumors.

Study of isoenzymes of LDH may provide important information about the expression of different isoforms of LDH. Moreover, the isoforms expression can reveal a better knowledge of the genetic background of LDH expression. Since LDHA gene plays a key role in tumor proliferation, expression of LDH2, LDH3, LDH4 and LDH 5 is important to study. In the present study, all the five isoenzymes of LDH were separated and it was found that all the isoenzyme activities were higher in oral cancer patients as compared to healthy controls, which strongly supports the fact that LDHA gene is responsible for tumor proliferation. Shpitzer et al have reported that cancer related changes in salivary tumour markers may be used as a diagnostic tool for diagnosis, prognosis and post-operative monitoring.[16] Joshi et al have observed that salivary LDH estimation can prove to be valuable substitute to serum LDH as biochemical marker.[17] Gorogh et al have reported that gradual changes in the percentage distribution of LDH isoenzymes may represent a useful parameter of

disease activity in patients with squamous cell carcinoma.[21]

Conclusion

The present study has shown altered salivary LDH activities in oral cancer patients. These results indicate that salivary LDH can be useful in understanding the pathogenesis of oral cancers. It was also suggested that analysis of salivary LDH activity is a simple and non-invasive technique which may be useful in screening and as an early diagnostic markers for oral cancer patients. Further study with large number of patients can corroborate these significant results.

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Dialogue, Discussion and Debate

Voralia Meera
Store Officer,
Department of Store and Purchase
Corresponding author : voraliam@gmail.com

वृन्दे वृन्दे तत्त्वचिन्तानुवादः ।
वादे वादे जायते तत्त्वबोधः ॥

Whenever learned people assemble, there is dialogue, discussion or debate as they think and deliberate on important issues. And every dialogue, discussion or debate adds to our understanding of fundamentals.
Do you know the difference between dialogue, discussion and debate?

Not all such interactions are fruitful. Watch these three scenarios.....
"I Love you"..."I love you too" It is a dialogue that results into a marriage.
"I like you but why do you..."..."I like you, too but because you..." It is a discussion that sustains and matures the marriage.
"I hate you and I am right"..."I am right, that is why I dislike you." The debate ends in a divorce.

All the three has its own value. Do we recognise dialogue if we heard it in our work place? To go through this question I would first like to distinguish dialogue from the other form of communication- debate and discussion.

Debate is combative and seeks to be victorious; it wants to express itself and say it is better than you. We always learn through controversy. Nothing grasps our attention and sharpens our minds more than controversy. Many leaders became such by participating in debates and public forums. Thus, debate always plays with our mind constantly up to the victorious finish. Better examples of political leaders in debate at election time.

While discussion can be described as debate trying to play nice much like debates, it is interested in advocating its view points and in challenging those of others. Real communications starts in both directions when a healthy discussion takes place.
In George Bernard Shaw's play, Saint Joan hears voices from the God. The King is annoyed.
King: "Oh, Your voices, your voices. Why don't the voices come to me? I am king, not you."
Joan: "They do come to you but you do not hear them. You have not sat in the field in the evening listening for them. When the angelus rings, you cross yourself and have done with it; but if you pray with your heart you would hear the voices as well as I do."
Here is the best example of discussion going on between King and John.

Dialogue on the other hand, seeks to find a shared connection. It is not concerned with winning or losing rather it aspires to listen more deeply understand more fully, and build a collective point of view.

When diversity of personality and opinion present moments of conflict and tension, dialogue steps in and mediates the conversation back to the renewed sense of connection.

A great workplace fosters dialogue and encourages a diverse perspective. After all, these are very elements that lead to growth and innovation. The issue being raised here today rest in the assumption that dialogue is rather enemic in organizations and I would content that if it is practised so little, it is because it is understood so little. Let's explore some of the principles that make dialogue so valuable in a workplace. As one engages in a dialogue, it is asked that they-
-suspend judgements
-listen
-inquire
-explore assumptions

When we suspend our judgement, we temporarily silence our thoughts and open our capacity to engage as listeners, Greater inquiry into others viewpoints helps us better understand those we work alongside and afford us the opportunity to adopt the new ways of thinking. When we explore our assumptions, we encounter unchallenged ideas, unchecked biases and patterns of thought that influences and possibly inhibit us workspace engagement.

Dialogue is also however a very challenging undertaking, becoming aware of personal assumptions is tough work. It places us in a position of measuring the consistency between our words and our actions and realizing that their alignments may not be as linear as we believe. Inevitably, the practice of dialogue ask us to conside that our opinions are not always correct, and that others may have more effective methods for approaching situations. Doing this is neither natural nor cathartic, but growth is rarely comforting.

When we speak with the eye contact, with correct posture, with good gesture and with full of confidence dialogue occurs.
"I would say to this house, as I said to those who have joined this Government. 'I have nothing to offer but blood, toil, tears and sweat'."
The world's best dialogue delivered by Winston Churchill.

What so ever we think about these three super words, they are equally important in our life. We need to dialogue with ourselves sometime to understand our own thoughts, we have to discuss our strengths and weaknesses with our own soul and finally we need to differentiate what is good and what is bad for us. Isn't it so? Think about it.

(Inspired by and reference taken from the blog of Mr. Joseph Alonzo
https://www.greatplacetowork.com/blog/587-the-difference-between-debate-discussion-and-dialogue)

Bleomycin induced Flagellate Erythema: A Rare and Unique Drug Rash

Patil Rakesh[1], Panchal Harsha[2], Parikh Sonia[3], Jain Preetam[1], Vala Ekta[1], Patkar Salil[1], Ranjan Alok[1]
Resident[1], Professor [2], Associate Professor[3]
Department of Medical and Pediatric Oncology
Corresponding Author : drharshapanchal@gmail.com

Summary

Bleomycin has been used most commonly in the treatment of Hodgkin's lymphoma, certain germ cell tumors and for the sclerosis of recurrent pleural effusions. Bleomycin toxicity predominantly affects the skin and lungs. Skin toxicity includes Raynaud's phenomenon, hyperkeratosis, nail-bed changes and palmoplantar desquamation. Flagellate erythema is an unusual rash occurring specifically during bleomycin use. In the present study, we report a case of bleomycin-induced flagellate erythema in a patient with Hodgkin's lymphoma (HL). A 45-year-old male was diagnosed with stage IV Hodgkin's lymphoma and treated with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy. After 3 months from the initiation of treatment, the patient subsequently developed a generalized pruritus and erythematous linear rash that was most prominent on the trunk, and upper and lower extremities. The patient was commenced on a short course of low-dose oral prednisolone, 20 mg daily, and antihistaminics. Consequently, bleomycin was withheld from the patient's treatment regimen. The present study describes the case, along with a review of the associated literature.

Keywords: Bleomycin, skin toxicity, Flagellate erythema

Introduction

Bleomycin is a chemotherapeutic antibiotic. Its mode of action is to block DNA uptake of thymidine in the S-phase of the cell cycle. Since it was first developed in Japan in 1966,[1] it has been used most commonly in the treatment of Hodgkin's lymphoma, certain germ cell tumors (GCT) and for the sclerosis of recurrent pleural effusions.[2] Bleomycin is inactivated in the majority of tissues by an enzyme, bleomycin hydrolase, which cleaves the ammonia group from bleomycin. This enzyme is active in all tissues, with the exception of skin and lung tissue, which may account for these being the most common sites of toxicity.

Reported dermatologic adverse effects of bleomycin include Raynaud's phenomenon, hyperkeratosis, nail-bed changes and palmoplantar desquamation. Flagellate erythema is an unusual rash that appears as 'whip-like' linear streaks and occurs specifically during bleomycin use. Bleomycin-associated flagellate erythema has been reported since 1970 ;[3–5] however, with the declining use of bleomycin, this adverse reaction has become much less common in practice. In the present study, we report a case of bleomycin-associated flagellate erythema with a review of the associated literature.

Case Report

In August 2016, 45yrs old male patient was diagnosed with stage IV B hodgkins lymphoma in accordance with Ann Arbor classification6 at GCRI, Ahmedabad. Computed tomography (CT) scan of neck, thorax, abdomen and pelvis suggestive of non bulky bilateral submental, para-aortic and inguinal lymph nodes. Submental lymph node biopsy and immune histochemistry confirmed classic hodgkin's lymphoma. Bone marrow biopsy suggestive of marrow involvement by hodgkin's lymphoma.

Patient was started on ABVD chemotherapy with intravenous administration of adriamycin 25mg/m^2, bleomycin 10units/m^2, vinblastine 6mg/m^2 and dacarbazine 375mg/m^2 on day 1 and day 15. Treatment was intended to be repeated at 28 days. After 3 months from the start of treatment, when fourth course day 1 was due, the patient developed a generalized pruritus and erythematous linear rash that was most prominent on the trunk and upper and lower extremities. Patient was referred to skin specialist and given antihistaminics.

The patient then revisited clinic for ABVD treatment on day 15, and the rash in which the patient appeared to have been whipped over multiple body areas was observed. Patient complained of generalized pruritus followed by pigmentation. Physical examination showed the appearance of an erythematous popular rash on the whole body,with moderate pigmentation, with evidence of dermatographia (Figure 1). There were no scales or lichenification, and the patient's vital signs were normal. Laboratory tests showed a white blood cell count of 5,800/mm^3 (normal range, 4,000–11,000/mm^3) (segmented neutrophils, 70%; lymphocytes, 24%; and eosinophils, 3%), hemoglobin levels of 13.9 g/dl (normal range, 13.0–16.0 g/dl), a platelet count of 313,000/mm^3 (normal range, 150,000–450,000/mm^3), serum LDH levels of 208 U/l (normal range, <190 U/l) and C-reactive protein levels of 5.35 mg/dl (normal range, <0.75 mg/dl). Prothrombin time and activated prothrombin time were within normal range.

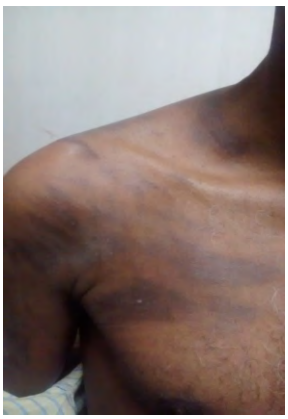

Figure A

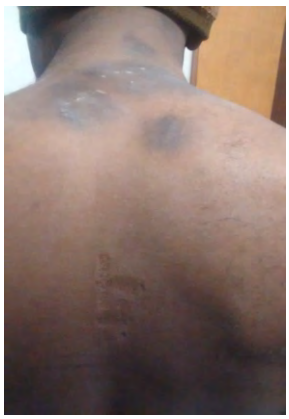

Figure B

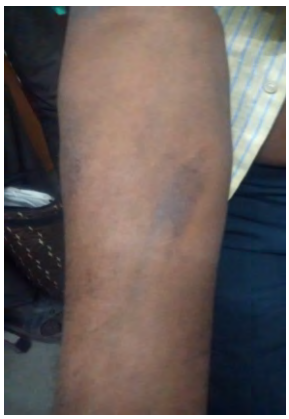

Figure C

Figure 1 : Multiple,well-dermarcated, erythematous patches in a linear configuration on (A) the shoulder, (B) the back, and (C) the arm.

Given the patient's clinical history and the gross appearance of the lesions, the diagnosis was most compatible with a severe bleomycin-induced flagellate erythema reaction. Patient was given fourth course, day 15 of chemotherapy with adriamycin, vinblastine and dacarbazine. Bleomycin of day 15 was omitted because increase in lesions on continuation of bleomycin and severity of lesions affecting most of trunk and both limbs.The patient was commenced on a short course of oral prednisolone, 20 mg daily, and antihistamine. The itching sensation was improved, but moderate hyperpigmentation remained.

Consequently, bleomycin was withheld from the treatment regimen. Disease evaluation was done after fourth course of chemotherapy with positrone emission tomography (PET-CT) scan. The disease was under complete remission. Patient was planned for two additional courses of chemotherapy, AVD.

Discussion

Diverse cutaneous reactions to bleomycin therapy are common in the literature, and are reported as having an incidence of 8 to 20% in patients receiving cumulative doses >100 units. Bleomycin is associated with numerous dermatological toxicities, such as alopecia, skin ulceration (predominantly plantar-palmar), eczematous changes, erythematoid bulla, sclerodermoid lesions, nail-bed changes and Raynaud's phenomenon.[7] Flagellate erythema is a less common cutaneous toxicity of bleomycin, but is one with a strikingly characteristic presentation.

The development of flagellate erythema appears to be dose-independent, and flagellate erythema is considered to be a reaction specific to bleomycin and is independent of the route of administration or type of malignant disease being treated. The lowest reported dose with systemic dermatologic complications is 15 units given intravenously.[8] Another report of low-dose bleomycin causing flagellate erythema involved the intrapleural administration of 30 units of bleomycin for the treatment of mesothelioma.[9] Flagellate erythema may also occur at a dose of <15 units intracutaneously.[10]

Several hypotheses regarding the cause of hyperpigmentation have been proposed. It has been proposed that the linear lesions are induced by rubbing or scratching the skin, which causes the drug to leak out of blood vessels. Alternatively, it has been suggested that accumulation of bleomycin in the skin causes a subsequent fixed drug eruption, due to the direct effects of bleomycin on the keratinocytes. Histopathologically, the lesions have shown a spectrum of morphological findings, including urticarial hypersensitivity reaction,[4] localized increase in melanogenesis from hyperactive and enlarged melanocytes, inflammatory oncotaxis[8] and lymphocytic vasculitis.[11]

The course of bleomycin-induced flagellate erythema is varied. The majority of patients initially develop generalized pruritus several hours to several weeks following the administration of bleomycin. Erythematous linear streaks eventually progress to the typical flagellate hyperpigmentation.[8,9,12,13] Onset of the characteristic lesions can occur anywhere from 1 day to 9 weeks after bleomycin administration.[14] There does not seem to be a characteristic distribution as cases have shown involvement of the face, trunk and extremities. Dermatographia is present to a limited extent and the role of scratching in producing the linear shape of the lesions has been debated.[15] However, studies have shown the clear appearance of linear streaks in the absence of direct trauma.[5] The majority of cases are reversible following cessation of bleomycin; however, persistence of hyperpigmented streaks for ≤1 year after treatment has been reported.[8,9,12]

There is no specific treatment for flagellate erythema, which usually has a self-limited course of several weeks to months, as long as bleomycin is subsequently avoided, although permanent hyperpigmentation in affected areas is not unusual. Occasionally, topical corticosteroids with or without oral corticosteroids are required. Re-exposure to bleomycin may cause further extension or recurrence of this rash and should be stopped.[16]

Vennepuredy et al[17] case study, 27 yr old woman, stage IIB hodgkin's lymphoma, developed severe bleomycin induced flagellar erythema after 2nd cycle day 15 of ABVD chemotherapy. They withheld bleomycin, treated with topical steroids and low dose steroids. Her rash improved. Rest chemotherapy continued with AVD. Ahitagni Biswas et al;[18] did a similar case study on patient with stage IIB hodgkin's lymphoma with bleomycin induced flagellar erythema at AIIMS, New Delhi. They also omitted bleomycin and treated with topical and oral steroids. In both cases rash was improved very significantly followed by post inflammatory hyperpigmentation.

Conclusion

In summary, the present study describes a patient with flagellate erythema following bleomycin administration. Despite the declining use of bleomycin, clinicians should be aware of this very rare but peculiar cutaneous manifestation. Severe rash may warrant cessation of the drug. Lack of detoxifying enzymes for bleomycin in the skin makes it a vulnerable site for the adverse effects of bleomycin.

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Minimal Residual Disease Detection in Splenic Marginal Zone Lymphoma by Flow Cytometry and Cytogenetic Techniques

Vora Hemangini H[1], Raiya Birva N[2],Trivedi Pina J[3], Patel Dharmesh M[4], Patel Prabhudas S[5]
Brahmbhatt Beena K[6],Parikh Sonia K[7]*
Associate Professor[1], Research Assistant [2], Senior Scientific Officer[3], Research Assistant[4],
Professor and Head of Cancer Biology[5], Assistant Professor[6], Associate Professor[7]
Department of Cancer Biology
Department of Medical Oncology*
Corresponding author : ihcgcri@hotmail.com

Summary

Splenic marginal zone lymphoma (SMZL) is rare indolent B-cell lymphoma and affects elderly people. As a rare disease, with no randomized prospective trials, there is no standard of care for SMZL so far. Spleenectomy has been considered as the treatment of choice, however, it is a major surgical procedure with significant morbidity especially in elderly patients. It has been observed that after successful treatment SMZL cases do relapse. To detect residual disease in peripheral blood or bone marrow flowcytometric immunophenotyping and advanced cytogenetic techniques are considered to be sensitive enough. Here, we described minimal residual disease (MRD) detection in a case of SMZL.

Keywords : MRD, SMZL, Flow Cytometry, FISH

Introduction

Splenic marginal zone lymphoma (SMZL) is a B-Cell lymphoproliferative disorder accounts for <2% of all lymphoid malignancies and has a five year overall survival of approximately 70%. The diagnosis of SMZL mainly relies on either spleen histology or bone marrow histology with cell morphology and immunophenotype in blood and bone marrow.[1,2] Minimal residual disease (MRD) assessment is the identification of residual malignant cells which cannot be detected by morphology. MRD detection has now become standard diagnostic care for leukemia and lymphoma to identify patients who requires intensive treatment. In recent years, multiparameter flow cytometry immunophenotyping, FISH and molecular techniques are used to detect MRD. The sensitivity of multiparameter flow cytometric immunophenotyping and FISH analysis is 10^{-4}, and of polymerase chain reaction is 10^{-5} for identification of malignant cells among the population of normal cells in peripheral blood or bone marrow to detect MRD. Here we report MRD detection in peripheral blood of patient with SMZL by multiparameter flowcytometric, cytogenetic and FISH analyses.

Case Report

A 71 year old man a known case of SMZL referred from private practitioner to GCRI for MRD detection. The patient has persistent complaints after initial treatment, however, the hemogram was normal. Therefore, peripheral blood of the patient was subjected to morphologic, flowcytometric, and conventional cytogenetics with FISH analysis for MRD detection. A panel for low grade B-cell neoplasms (CD45, CD19, CD20, CD22, CD23, CD25, FMC-7, BCl-2, CD5, CD10 and CD11c; Table 1) by flowcytometric analysis and deletion of chromosome 7q by FISH was evaluated.

Morphologic assessment showed a normal differential count with few atypical lymphocytes having moderate amount of cytoplasm and occasional cells having villous projections. The marker panel and their clone used for flow cytometric analysis are mentioned in Table 2. Approximately 2,75,000 cells were acquired, out of them 18% of CD19 positive B-cells were gated that express CD45, CD20, CD23, FMC7, Bcl2, CD11c, SIgM and Lambda. The immunophenotype was compatible with SMZL (Figure 1).

The conventional cytogenetic study with unstimulated blood lymphocyte culture showed non analyzable 4 metaphases (Figure 2), which is usually not observed in lymphoma patients suggesting aggressiveness of the disease. Stimulated blood culture showed 46, XY karyotype (Figure 3). In FISH analysis, deletion 7q probe (Vysis) was used and a total of 203 inter phase cells were scored. Of them, deletion of 7q31 region was observed in 15% (31 cells) cells, loss of chromosome 7 in 2% cells (4 cells) and no deletion of chromosome 7 in 83% cells (168 cells, Figure 4). Based on these findings, the further management of the patient will be decided by the clinician.

Discussion

This study tried to detect MRD in SMZL patient by flowcytometric and cytogenetic analyses. SMZL does not harbor a specific immunophenotype and hence flow cytometry should be tailored to

Table 1: Comparison of markers in five low grade B-cell neoplasms

	CD5	CD10	Cd11	CD19	CD20	CD22	CD23	CD25	FMC7
SMZL	-	-	±	+	+	+	-	±	+
HCL	-	-	+	+	+	+	-	+	+
SLL	+	-	-	+	+	-	+	-	-
PLL	±	-	-	+	+	±	-	-	+
HCL – hairy cell leukemia, MCL- mantle cell lymphoma, PLL-prolymphocytic leukemia, SMZL-splenic marginal zone lymphoma, SLL-small lymphocytic lymphoma									

Table 2: Antibody Panel for MRD detection

Marker	**CD45**	**CD5**	**CD10**	**CD11c**	**CD19**	**CD20**	**Cd22**
Clone	2D1	L17F12	HI1oa	S-HCL3	ST25c1	L27	S-HCL-1
Marker	**CD23**	**CD25**	**FMC7**	**bcl2**	**Kappa**	**Lambda**	
Clone	EBVcS5	2A3	FMC7	Bcl2/100	Poly	Poly	

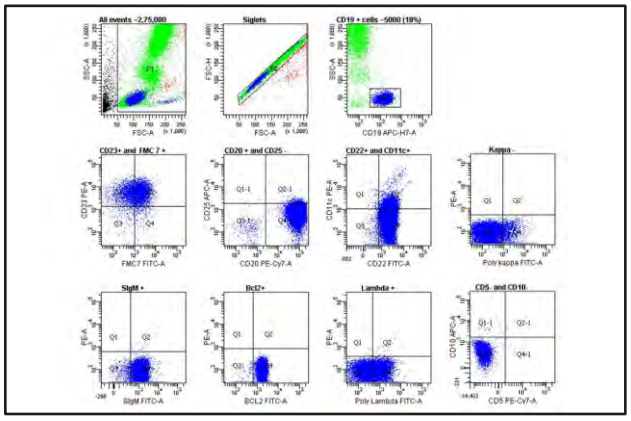

Figure 1: Dot plots of markers expression on CD19 gated abnormal cells by flow cytometry.

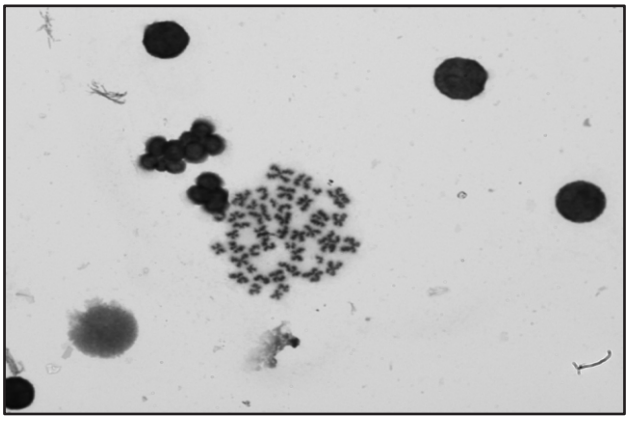

Figure 2: Metaphase seen in unstimulated blood lymphocyte culture.

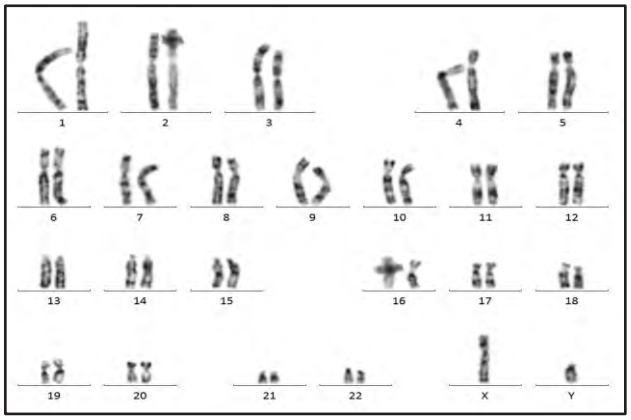

Figure 3: Stimulated blood culture showed 46, XY karyotype.

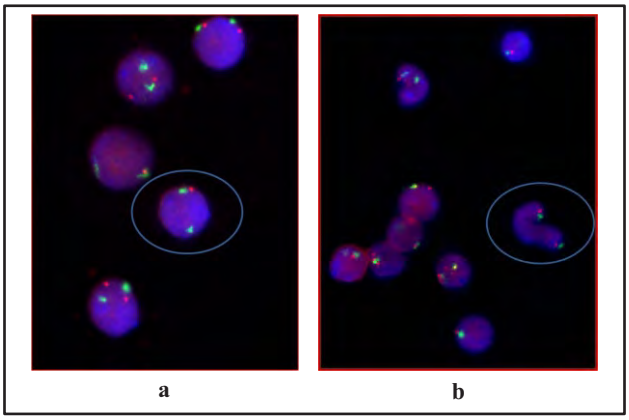

Figure 4a: 2G1O (2 Green 1 Orange) indicates 7q31 deletion.
Figure 4b: 1G1O (1 Green 1 Orange) indicating monosomy 7 or deletion 7.

exclude other subtypes. Phenotypically SMZL express SIgM, CD19, CD20, CD22, FMC-7, BCl-2 CD45, may or may not express CD11c and do not express CD5, CD23, CD10, CD103. In this patient, 18% of CD19 positive abnormal B-cells were found in peripheral blood which expressed CD45, CD20, CD23, FMC7, Bcl2, CD11c, SIgM and Lambda and confirmed as SMZL phenotype. It has been noted that CD23 or CD5 can be positive in 20-30% of SMZL cases.[3]

The most common cytogenetic abnormality involves allelic loss at 7q21-32 or translocation involving this region and kappa chain on chromosome 2 in 40-45% of SMZL cases.[3-6] By FISH analysis, abnormalities of chromosome 7 is seen in 17% of cells included deletion of 7q31 region in 15% cells and complete loss in 2% cells. Further, unstimulated blood lymphocyte culture showed non analyzable 4 metaphases which also suggests disease aggressiveness. It has been shown that deregulation of CDK6 gene located on 7q22 contribute to pathogenesis of SMZL.

By both the methods equal number of abnormal cells was identified and combining these two methods increased the sensitivity of detection of MRD in this patient. Therefore, in low grade lymphoma MRD determination should be enrolled as standard of care to identify persistence of residual tumor cells which are undetectable using conventional diagnostic procedures.

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Extraskeletal Osteosarcoma Arising from Kidney: A Case Report

Soni Himanshu[1], Pateliya Mehul[2], Rathava Jitendra[2]
Associate[1], Resident[2]
Corresponding author : himanshucsoni@yahoo.com

Summary

Osteosarcoma is a highly aggressive malignant mesenchymal origin tumour most commonly arising from bone. Extraskeletal osteosarcoma is a very rare entity with very few reported cases worldwide. We hereby report of case encountered by us, a 65 year old male patient presenting with lump in right lumbar region. On CT scan study there was a large densely calcified mass lesion seen involving right Kidney without attachment to bone. Multiple pulmonary metastases were also noted most of which were showing internal calcification / ossification. We suspected extraskeletal osteosarcoma arising from right kidney, which was confirmed on histopathology examination. This was a very rare location demonstrating extraskeletal visceral origin of osteosarcoma.

Key words: Extraskeletal osteosarcoma, CT Scan, X-Ray

Introduction

Extraskeletal osteosarcoma is a rare entity. Very few reported cases exist worldwide amounting to 4 % of osteosarcoma. It is malignant lesion with mesenchymal origin with osteoid or chondroid calcification matrix within.

By definition a lesion is termed as extraskeletal osteosarcoma if it has the above histological findings and if the lesion is not arising from bone or periosteum. Amongst all soft tissue sarcomas this entity occurs in less than 1.2 % of cases.[1]

It occurs in 5th to 7th decade of life, commonly in males. Like all sarcomatous lesions, these tumours also metastasize to lungs frequently, so lung should be actively searched for metastasis. Positive associations are history of trauma or past radiotherapy.[2] However our case was not associated with such a history.

The key role of imaging is to characterise the lesion and delineate the limits of the lesion. An early diagnosis of malignancy is important before lung metastasis has developed. The definitive treatment includes resection of the lesion followed by chemotherapy or radiotherapy or localised metastatectomy.

Case Report

Fourty four years old male patient had presented to our hospital with complains of pain in right lumbar region and blood in urine. On examination he was pale with fair built. Local examination revealed a large hard consistency palpable mass in right lumbar region suspected to be arising from kidney. Initial X-ray KUB, revealed a large soft tissue density mass lesion in the region of right kidney with internal dense calcification. Right renal shadow was not seen separately from the mass (Figure. 1a). Chest radiograph revealed multiple soft tissue rounded opacities of varying sizes more in right lung field. Few of the right lung lesions showed internal calcification (Figure. 1b). The patient was advised for CT scan thorax, abdomen and pelvis with bowel preparation. Plain CT study was done followed by IV post contrast study with non ionic iodinated contrast. Non contrast computed tomography (NCCT) revealed a heterogeneous attenuation soft tissue density lesion replacing upper pole and interpolar region of right kidney. It was a densely calcified ill defined lesion with infiltrative soft tissue component (Figure. 2a).The soft tissue component showed heterogeneous enhancement on post contrast study (Figure. 2b & 2c). It was not seen in continuity of surrounding bones. Indistinct fat planes of the lesion were appreciated with right crus of diaphragm and right psoas muscle. The lesion was infiltrating right renal hilum encasing right renal vessels. Mild ascites and few tiny retroperitoneal nodes were seen in paracaval region. Bone window image showed the dense calcification/ossification (Figure. 2d). Contrast enhancing computed tomography (CECT) of lung revealed multiple soft tissue density lesions of varying sizes in both lung fields (Figure. 3a), most of the pulmonary lesions were showing calcification within soft tissue component (Figure. 3b).

Diagnosis of malignant renal mass was considered. Howsoever, renal cell carcinoma was unlikely with such dense calcification, our next tentative diagnosis was of osteosarcoma arising from right kidney as the mass is showing internal dense calcification/ossification and the pulmonary metastasis were showing internal calcification which is typical for osteosarcoma. Biopsy of the lesion was performed which showed osteosarcoma as etiology. We believe ours is one of the rare cases of extraskeletal osteosarcoma arising from a visceral retroperitoneal structure. Patient was lost to follow up after the metastatic work up which showed advanced stage of the disease.

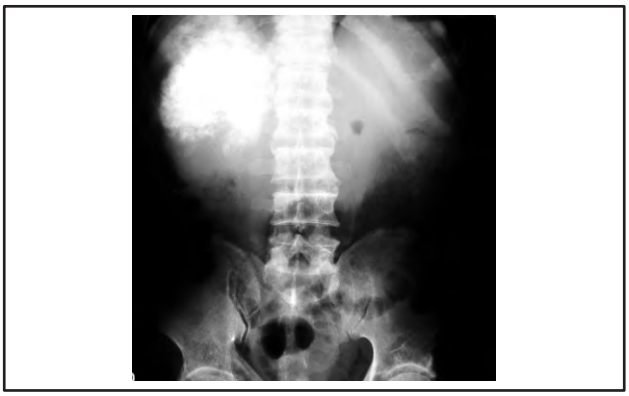

Figure 1a: X ray KUB showing a densely calcified lesion in right lumbar region replacing right renal shadow.

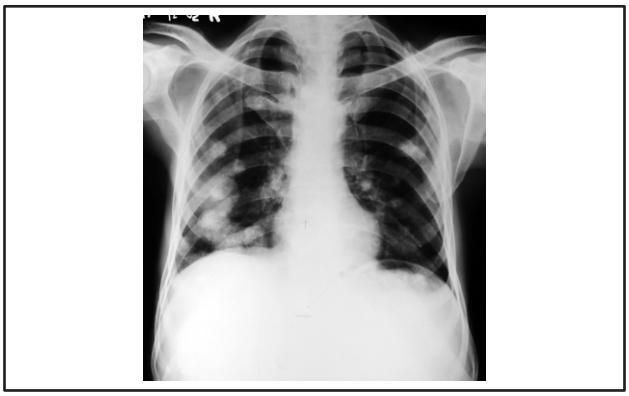

Figure 1b: Chest X-ray PA view showed multiple soft tissue opacities more in right lung field some of which showing calcification, consistent with metastasis.

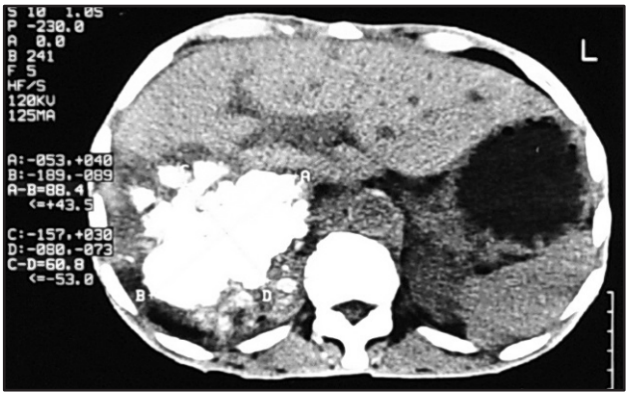

Figure 2a: Axial plain CT scan shows densely calcified lesion arising from upper pole of right kidney.

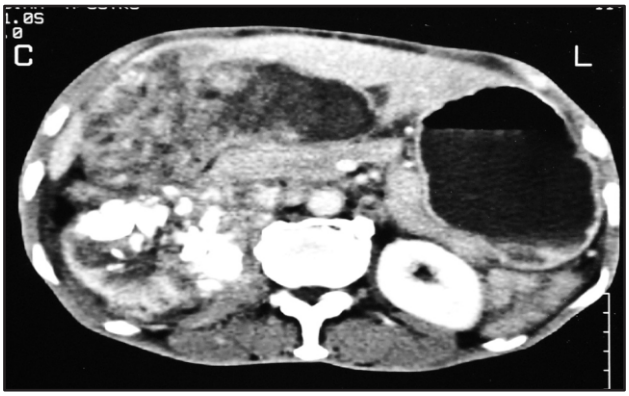

Figure 2b and 2c: Axial post contrast CT scan shows densely calcified lesion with inhomogeneous enhancement and ill defined walls involving upper pole of right kidney. [Figure. 2c is caudal to 2b]

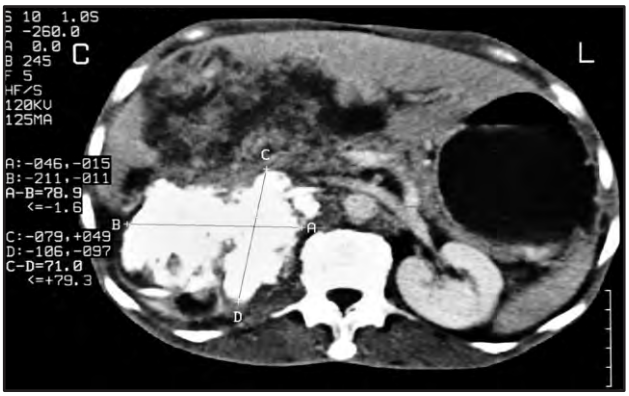

Figure 2c

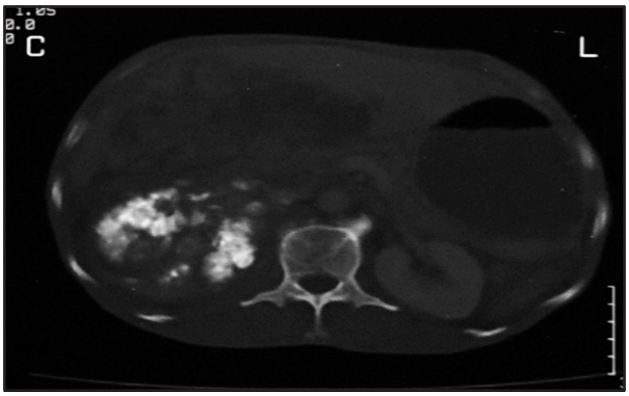

Figure 2d: Axial CT image in bone window shows dense calcification/ossification within right renal mass lesion.

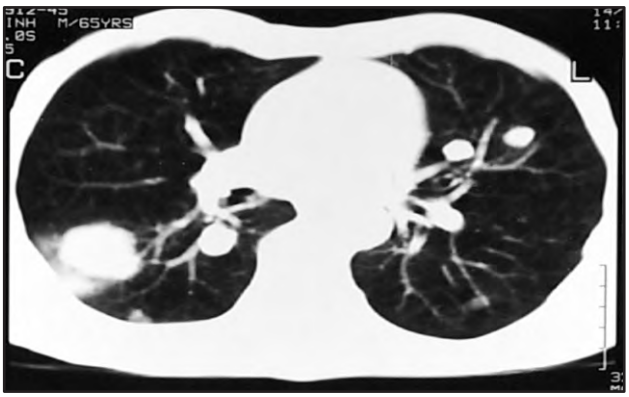

Figure 3a: Axial contrast enhanced computed tomography (CECT) image at right pulmonary artery level in lung window settings reveals multiple soft tissue density lesions in both lung fields.

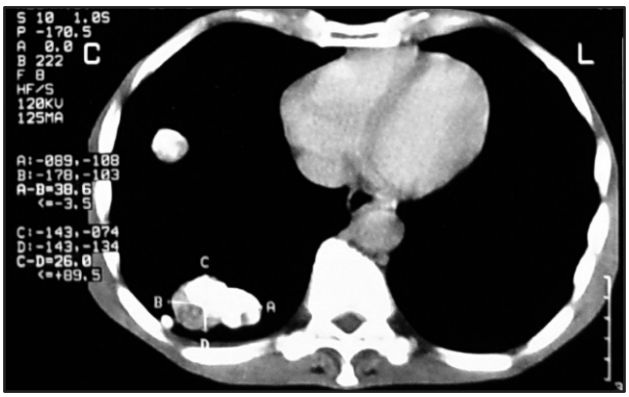

Figure 3b: Axial contrast enhanced computed tomography (CECT) image at left ventricular level in mediastinal window settings reveal soft tissue density lesions with calcification in most of the pulmonary lesions.

Discussion

Extraskeletal osteosarcoma is malignant mesenchymal origin tumour with osteoid or chondroid calcification matrix within and such tumour shouldn't be arising from bone or its periosteum. It is a rare malignancy reported cases amount to less than 4 percentage of all osteosarcoma. The incidence is less than 1 % amongst all soft tissue sarcomas In our knowledge only 20 cases have been recorded so far of renal osteosarcoma.[3] Prognosis is very poor with poor mean survival rate even with surgical resection, chemotherapy and radiotherapy offered as curative or palliative treatment. It occurs more commonly in older age as opposed to classical osteogenic osteosarcoma. The peak incidence is noted in 5th to 7th decade with male predominance. Lower limb is a more common site amongst the extremities. Other sites where extraskeletal osteosarcoma has been reported are upper limbs, pleura and retroperitoneum. Lee JSY et al observed that thigh and gluteal regions are the most common sites in lower limb.[4] Although visceral organ involvement is rare, it has been reported to occur in kidney, breast, lung, heart, thyroid and urinary bladder.

Pathogenesis of extraskeletal osteosarcoma is poorly understood however positive correlation has been observed with history of trauma or radiotherapy at the tumour site. Prognosis depends on the histological differentiation of tumour and presence of metastasis. Most of the well differentiated tumours have better prognosis but it was observed by Arai H et al that such well differentiated tumours following resection can recur at same site with dedifferentiation also, making the overall prognosis worrisome in most cases.[5] Poor prognosis is seen when the size of primary mass lesion is equal or more the 5 cm or distal metastasis is present at initial presentation.[6] Diagnosis depends on the following criteria: (1) uniform morphological pattern of sarcomatous tissues that excludes the possibility of mixed malignant mesenchymal tumor, (2) osteoid, cartilage or bone production by neoplastic cells, and (3) exclusion of an osseous origin.[7] The role of histopathology and immunohistochemistry is significant when osteosarcoma arises from rare location.

Role of imaging is to detect organ of origin, presence of internal calcification/ossification and to exclude their origin from adjacent bone or its periosteum. This can be accomplished accurately by a CT scan or MRI. Periosteal origin can be appreciated with MRI more accurately and helps in ruling out skeletal osteosarcoma.

Most early cases of extraskeletal osteosarcoma can still be surgically excised. Imaging helps to delineate the boundaries of the lesion which aids in surgery. In our case the lesion was adherent to liver and extended beyond the perinephric spaces. This excluded surgical excision as a first line treatment.

Another important role of imaging is to assess distant site for metastasis. Lee JSY, et al observed in their review study of 40 cases that 65 % of their patients had distant metastasis of which 81% had metastasized to lung. Hence it is prudent to scan the lungs. Our case had lung metastasis right at the time of presentation. More number of lung metastases were seen on CT scan than with radiograph and calcification within the metastasis was also better appreciated in some. Calcification / ossification within pulmonary metastasis help to suggest diagnosis of osteosarcoma as primary etiology. Metastasis of extraskeletal osteosarcoma can also spread to soft tissues, bones, liver, peritoneum or adrenal glands. Most of these metastatic lesions show calcification/ ossification within just like the primary tumour.

Like for any renal mass lesion the differential diagnosis to be considered are adult type of Wilm's tumour, sarcomatous renal cell carcinoma and metastasis. Biopsy remains the definitive means of diagnosis to differentiate the above differentials.When extraskeletal osteosarcoma involves extremities, the most important differential is myositis ossificans. It can be differentiated with help of CT scan, ultrasound as well as MRI by the demonstration of 'zone phenomenon'. Ossification in peripheral location is pathognomic of myositis ossificans. Ossification in extraskeletal osteosarcoma would be more in the centre. Ultrasound is a better modality to suggest myositis ossificans at the earliest. Howsoever biopsy is the gold standard investigation to differentiate extraskeletal osteosarcoma and myositis ossificans, when biopsy is taken in maturation phase.[8]

The mode of treatment for renal Osteosarcoma is found to be equivocal. Hence by common consensus local excision followed by chemotherapy should be considered in all cases. Renal osteosarcoma are found to be more responsive to chemotherapy when multiple drug regimes are used. Howsoever it is less chemosensitive or radiosensitive in comparision to its classical skeletal variety. It has been observed that extraskeletal is neither chemosensitive nor radiosensitive.[9] On the other hand, it was observed by Goldstein- Jackson SY et al in 2005 in their retrospective study of 17 patients that good survival rates were observed when patients were treated like classical osteosarcoma.[10] Prognosis is bad even with chemotherapy or after surgical excision. Poor mean survival rates of 8 to 22 months have been observed. Our case presented in advanced stage. The patient did not accept any form of treatment.

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Summaries of Presentations at Clinical Meetings

How Immunotherapy and Targeted Agents are Changing the Practice in Lung Cancer

Jain Preetam Kumar
Medical Oncology

Summary

At present, survival rate of metastatic lung cancer is poor with 5 yr survival rate being less than 5%. The use of molecular targeted therapies has improved median overall survival in a limited group of NSCLC patients whose tumors harbor specific genetic alterations. In particular, the checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) ,programmed death-1 (PD-1) and Programmed death ligand1 (PDL-1) pathway have shown durable clinical responses with manageable toxicity. PD-1 inhibitors (Nivolumab, pembrolizumab) are new treatment option for patients with advanced Non small cell lung cancer who progress on previous systemic therapy.PD-L1 expressions in the tumor is associated with an increased likelihood of response to agents against same. One has to be vigilant about immune related adverse event caused by these agents along with rapid intervention for optimal management

A Case Report on Medical Pleurodesis in Patient with Recurrent Pleural Effusion.

Kumari Puja
Palliative Medicine

Summary

A 30 yrs old female, diagnosed with metastatic Breast cancer, having breathlessness due to bilateral pleural effusion. She was treated with medical pleurodesis caused by tetracycline 1200 mg in each pleura. Patient was relieved of symptoms and pain. A case report describing medical pleurodesis is presented here with.

Our Experience of GCRI Statistics Based on Hospital Based Cancer Registry (HBCR) Data for Year 2014-15

Shah Anand
Community Oncology

Summary

This presentation will provide brief idea about GCRI statistics, leading cancer sites among males and females, proportion of tobacco related cancers as well as proportion of cancers diagnosis based on diagnostics method and spread of cancer. All the malignant registered cancer cases at GCRI are included in hospital based cancer registry; each case has been entered in the NCRP software given by NCDIR, Bangalore. Total 38,102 malignant cases were registered in year 2014-15 at GCRI. Out of total 61.6% were male patients. Mouth cancer alone attributes 20% of cancer among males. Tobacco related cancers were among the leading cause of cancer among males. Every year tobacco related cancers are on rise. 51% of male patients and 44.8% of the female patients, who are registered at GCRI at least once, do not take any form of treatment here which is alarming.

Psychological Distress in Women Afflicted by Gynaecological Malignancy : A Prospective Study

Kenkre Mangirish
Gynecologic Oncology

Summary

Aim is to determine the proportion of women suffering from gynaecological malignancies afflicted to psychological distress and to determine the factors associated with psychological distress interms of demographic details, tumour pathology and mode of treatment. Study was conducted in the department of gynaecologic oncology from Feb 1 to March 31 2017 wherein 120 patients were included. Patients were presented with a hospital anxiety and depression scale to assesss the psychological change in terms of anxiety and depression. Depression and anxiety was observed in 55% and 53.4% of the patients. Depression was most frequently associated with carcinoma of vulva and cervix. Depression was seen in the age group of 40-60 years so was anxiety. Postmenopausal women had a higher affliction rate for depression. Psychological disturbances are more frequent in advanced malignancies and prolonged course of illness. Depression was more common in patients receiving radiotherapy. Psychological distress was seen to be significantly associated with with stage, duration of disease, age, menopausal status and treatment strategy. Reducing psychological symptoms is a desirable outcome , improving the quality of life as well as to optimise the body's immunological response to cancer. A partnership between psychiatry and oncology is necessary to combat the above mentioned issues.

Knowledge and Practices of Health Care Workers Regarding Needle - Stick injury in a Tribal Setting of Rajnandgaon, Chhattisgarh, India

Christian Arpit
Hospital Infection Control Department

Summary

Needle Stick Injuries (NSIs) in healthcare settings are a global issue. Percutaneous injuries, caused by needle sticks and other sharps, are a serious

concern for all Health Care Workers and pose a significant risk of occupational transmission of blood borne pathogens. The incidence of NSI is considerably higher than current estimates, because of gross under reporting and hence a low injury rate should not be interpreted as a nonexistent problem. The present study was carried out to determine the occurrence of NSI among various categories of HCWs. The present prospective cross sectional study was carried out at the 400 bedded Government Medical College Hospital, Rajnandgaon, Chhattisgarh, India during period from November 2015 to August 2016. Out of total (180) study participants, 18 were doctors, 142 nurses and 20 lab technicians from different clinical departments/wards of the hospital. Data was collected by using a predesigned pretested questionnaire. The first part of the questionnaire contained information on background characteristics and second part contained the questions regarding knowledge and practices about NSI. Out of 180 HCW, 149 (82.78%) were females and, 31 (17.22%) were males. Majority of the subjects were nurses (78.89%). 92.2% subjects were aware of the Needle Stick Injury (NSI). 85% of the subjects knew that certain diseases can be spread through NSI. Almost all of them were using disposable/auto disabled syringes and needles at the hospital. Re-capping of used needle was practiced by 35.5% subjects. 63.8% subjects gave history of NSI in the last one year. Most chances of getting NSI were found to be while working in the Obstetrics and Gynecology Department (29.4%). 68.9% of the study subjects were immunized completely against Hepatitis B. We reported 2.3% (22/940 HCW) of NSI. Out of which, 18 (81.81%) were females and 4 (18.18%) were males, 10(45%) were Nurses, 7(31,81%) were Class IV employees, 3(13.63%) were Technician and, 2(9.09%) were Doctors. 73% of HCW were vaccinated against Hepatitis B Virus, whereas 27% were not. They were having low anti Hbs Titer level. They were advised to take booster dose. There was gap between the knowledge and use of preventive measures. There is a need to address this gap by organizing on job training, retraining at regular intervals, workshops for HCWs regarding hazards, preventive measures and post-exposure prophylaxis for NSIs. Preventing NSI should be an essential part of any blood borne pathogen prevention strategy in the work place. Even though there is awareness about NSI, it is observed in 0.1% of cases the HCW don't report. We have well established protocol to tackle the needle stick injuries which is been strictly followed.

Presentations at the Clinical Meetings

(January 2017 to June 2017)

Sr. No.	Date	Speaker/Department	Title
1	28.01.2017	Jain Preetam Kumar Medical Oncology Unit-I	How Immunotherapy and Targeted Agents are Changing the Practice in Lung Cancer
2	11.02.2017	Bhagat Maitri Radiotherapy	Comparison of Hypofractionated External Radiotherapy vs. Conventional Radiotherapy in Post MRM Breast Cancer Cases
3	25.02.2017	Kumari Puja Pain & Palliative Medicine	A Case Report on Medical Pleurodesis in Patient with Recurrent Pleural Effusion
4	25.03.2017	Shah Anand Community Oncology	Our Experience of GCRI Statistics Based on Hospital Based Cancer Registry (HBCR) Data for Year 2014-15
5	08.04.2017	Kenkre Mangirish Gynec Oncology Unit-IV	Psychological Distress in Women Afflicted by Gynaecological Malignancy : A Prospective Study
6	22.04.2017	Christian Arpit Hospital Infection Control	Knowledge and Practices of Health Care Workers Regarding Needle - Stick InjuryiIn A Tribal Setting Of Rajnandgaon, Chhattisgarh, India
7	27.05.2017	Mittal Lalchand Medical Oncology Unit-II	A Study of Use of Long Term Venous Access Catheters and Devices in Cancer Patients at GCRI
8	10.06.2017	Gajjar Kinjal Tumor Biology	Clinical Utility of 5-FU Metabolic Enzymes in Colorectal Cancer

Journal Club/Guest Lecture/ Review Lecture Presentations

(January 2017 to June 2017)

Sr. No.	Date	Presenter/Department	Topic	Authors	Citation
1	25.02.2017	Kenkre Mangirish, Gynacological Oncology Unit-II	Chemoradiotherapy Followed by Consolidation Chemotherapy Involving Paclitaxel and Carboplatin and in FIGO Stage IIIB/IVA Cervical Cancer Patients	Mabuchi S, Isohashi F, Okazawa M, et al	Journal of Gynecological Oncology 2017; 28:e15
2	25.03.2017	Sukhadeve Ankit, Radiology Department	Thermal Ablation of Colorectal Lung Metastases: Retrospective Comparison Among Laser-Induced Thermotherapy, Radiofrequency Ablation and Microwave Ablation	Nour-Eldin NA, Exner S, Al-Subhi M, et al	Int J Hyperthermi 2017; 3:1-10
3	22.04.2017	Jha Rohit, Head & Neck Unit-II	A Prospective Multicenter Clinical Feasibility Study of A New Automatic Speaking Valve for Postlaryngectomy Voice Rehabilitation	Lansaat L, de Kleijn BJ, Hilgers FJ, et al	Eur Arch Otorhinolaryngo 2017;274:1005-1013
4	13.05.2017	Khoja Jasmin, Physiotherapy	A Study of Common Impairements following Modified Radical Mastectomy	Kaya T, Karatepe AG, Günaydn R, et al	South Med J. 2010;103:37-41
5	27.05.2017	Rajvik Kruti, Immunohaematology Lab	Predictive Biomarker Profiling of > 6000 Breast Cancer Patients Shows Heterogeneity in TNBC, With Treatment Implications	Millis SZ, Gatalica Z, Winkler J, et al	Clin Breast Cancer 2015;15:473-481
6	24.06.2017	Raval Pankaj, Microbiology Department	Persistence of Zika Virus in Body Fluids - Preliminary Report	Paz-Bailey G, Rosenberg ES, Doyle K, et al	N Engl J Med. 2017

Case Presentations for Morbidity, Mortality at Clinical Meetings

(January 2017 to June 2017)

Sr. No.	Date	Presenter/Department	Case Discussion
1	28.1.2017	Bhardwaj Abhishek Anesthesiology	Morbidity & Mortality Data Presentation of surgical & Medical Departments
2	28.1.2017	Bohra Murtaza Medical Oncology	Clinical & Microbiological Characteristics of perianal infection in adult patient with leukemia
3	25.2.2017	Kumar Suresh Anesthesiology	Morbidity & Mortality Data Presentation of surgical & Medical Departments
4	25.2.2017	Chakraborty Amit Surgical Oncology	Discussion on operated case of Carcinoma Esophagus – Post CT + RT
5	25.03.2017	Kumar Suresh Anesthesiology	Morbidity & Mortality Data Presentation of surgical & Medical Departments
6	25.03.2017	Shukla Hemkant Surgical Oncology	Post Hepatectomy- Morbidity
7	22.04.2017	Chirmade Pushpak Medical Oncology	AML with Bombay Blood Group: an interesting case scenario
8	27.5.2017	Bhardwaj Abhishek Anesthesiology	Morbidity & Mortality Data Presentation of surgical & Medical Departments
9	27.5.2017	Verma Hemkant Pediatric surgery	Case Morbidity -Displaced Hickmen Catheter
10	24.06.2017	Bhardwaj Abhishek Anesthesiology	Morbidity & Mortality Data Presentation of surgical & Medical Departments
11	24.06.2017	Krishnakumar Rohan Gynecologic Oncology	Post Operative 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, Journals Master List. The journal's full text is available online at http://www.gcriindia.org

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

- Title Page (Font size: 12)
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- 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	%		

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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;
4. The name of the department(s) and institution(s) to which the work should be attributed;
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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
- Numerals at the beginning of the sentence spelt out

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.

Identify precisely all drugs and chemicals used, including their generic names, their manufacturer's name, city and country in parenthesis, doses, and routes of administration.

Results: 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.

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

Bio-Medical Engineering Department

Christian Princy,
Gujarat Cancer and Research Institute

Over the last decade the changing healthcare environment has required hospitals and specifically Biomedical Engineering to critically evaluate, optimize and adapt their operations. The focus is now on new technologies, changes to the environment of care, support requirements and financial constraints. Rapidly changing technology coupled with the financial impact of organized health care, has required hospital Biomedical engineering organizations to augment their traditional operational and business models to increase their role in developing enhanced clinical applications utilizing new and evolving technologies.

The bio-medical engineering (BME) department was started in 2013 in Gujarat Cancer and Research Institute. This field of engineering has started 15 years back in Gujarat and now has evolved on a large scale. Initially, when the hospital was established, there was a single electronics engineer who was looking after all imaging equipment because there was no existence of bio-medical engineering field.

The first bio-medical engineer was appointed in the year 2007-08.At present there are four bio-medical engineers (B.E) (one head of the department, other three junior BME's) and two theatre technicians (Diploma) and one clerk looking after the record keeping work for the routine maintenance of the medical equipment.

We have one apprentice from Industrial Training Institute (ITI)every year and we, bio-medical engineers, train them for our routine day to day technical as well as documentation work so that they can get both the exposures which can be helpful for their carrier.Shri Dayal C. Arora joined as chief physicist in 1970's and is still working and guiding us in all our routine maintenanceof bio-medical equipment.

Introduction

Biomedical engineering is the application of engineering principles and design concepts to medicine and biology for healthcare purposes (e.g. diagnostic or therapeutic). This field seeks to close the gap between engineering and medicine, combining the design and problem solving skills of engineering with medical biological sciences to advance health care treatment, including medical diagnosis, monitoring, and therapy. Biomedical engineering has only recently emerged as its own study, as compared to many other engineering fields. Such an evolution is common as a new field transitions from being an interdisciplinary specialization among already-established fields, to being considered a field in itself. Much of the work in biomedical engineering consists of research and development, spanning a broad array of subfields (see below). Prominent biomedical engineering applications include the development of biocompatible prostheses, various diagnostic and therapeutic medical devicesranging from clinical equipment to micro-implants, common imaging equipment such as MRIsand EKGs, regenerative tissue growth, pharmaceutical drugsand therapeutic biological.

Role of a Bio-Medical Engineer

- Handling and maintenance of all the medical equipment
- Evaluation of safety, efficiency, and effectiveness of biomedical equipment
- Train clinicians and other personnel on the proper use of equipment
- A biomedical engineer may design instruments, devices, and software, bringing together knowledge from many technical sources to develop new procedures, or conducting research needed to solve clinical problems. They often serve a coordinating function, using their background in both engineering and medicine. In industry, they may create products where an in-depth understanding of living systems and technology is essential. They frequently work in research and development or in quality assurance.
- Procurement of equipment's (which includes inviting quotations/tenders for purchasing new equipment's/machines & preparing comparison chart for the same.
- Coordinating with the technical specifications submitted by the head of various departments for all the new equipment and machinery.
- Preparing the submission, purchase orders, agreement, devising letters and all sort of documentation work related to procurement and maintenance of medical equipment.
- Evaluating the equipment and machinery on the basis of its initial cost as well as its operating cost: since many times, the high maintenance & operating cost of the equipment turns out to be

much higher than the initial cost.
- Inspection of incoming equipment, machinery and doing pre-acceptance checks before official acceptance and payment.
- Maintaining records like equipment history, setting standards and ensuring their compliance. Maintaining the equipment to the best of its performance by organizing a planned maintenance program for all equipment and attending to emergency breakdowns and repairs.
- Arranging for training programs for personnel in clinical engineering department as well as the end users.
- Advising and providing expertise to the medical staff and administration.
- Maintaining equipment inventory for all existing and incoming equipment. Active involvement in the activities of the hospital's safety committee and checking safety hazards.
- Monitoring contract services viz. A.M.C. and C.M.C.
- Keeping record of the spares/consumable items.
- Carry out inspection and repairs of the equipment/machine at company site or at the hospital site.
- Attending the training programs, technical conferences, and medical exhibitions which can be helpful for pursuing the knowledge of the latest technology evolving in the field of healthcare for medical equipment.

Training Program
- Since, 2001, Bio-Medical Engineering students from all the engineering colleges of Gujarat are getting the exposure and training related to the operation, clinical Application, Merits-demerits and technical aspects of an individual medical equipment of various departments.
- Nursing students, ITI apprentices, diploma students of instruments and mechanics and bio-medical engineering students are also getting trained under bio-medical engineering department.

Other activities at the department and staff training

- Have undergone training for the linear accelerator at St.Cathrina Hospitals, The Netherlands in 2013.
- Have undergone EOE 1 technical training at Crawley, UK in 2015 for the newly purchased Linear Accelerator Model : Synergy
- Training for the low energy linear accelerator at Beijing, China in 2017

Future Directions

We propose
- Trained apprentice/ITI Personnel who can help and can assist the Field Service Engineer continuously for the troubleshooting and replacements of the spares ina Medical Equipment.
- To have enough manpower who can dedicatedly do the tender work and purchase work for the procurement of medical equipment.
- Software which can help us to maintain the daily routine records and maintenance data so that we can save the time.

THE GUJARAT CANCER SOCIETY
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Smt Bhartiben S. Parikh
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Shri Om Prakash Kohli

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Shri Prashant Kinarivala
Shri Kshitish Madanmohan
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Shri Prashant Kinarivala

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Health & Family Welfare Dept.
Dr. Jayanti S Ravi, IAS
Principal Secretary, PH & ME &
Commissioner of Health Services
Govt. of Gujarat
Shri. Milind Torawane, IAS
Secretary to Govt. of Gujarat
Finance Dept (Expenditure)
Dr. Bharat Amin
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Directorate General of Health Services
Ministry of Health & Family Welfare
Director (IF)
Ministry of Health & Family Welfare
Govt. of India

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Gujarat Cancer Society
Shri Kshitish Madanmohan
Secretary, Gujarat Cancer Society
Dr. D. D. Patel
Member, Gujarat Cancer Society
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Government of India
Director (IF), Ministry of Health,
Government of India

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Dr. R K Vyas

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2017
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Bio-Medical Engineering Department Services at GCRI

Troubleshooting of Anaesthesia Trolley

Fault finding in Linear Accelerator

Measuring the voltage from the SMPS
of a Linear Accelerator

Troubleshooting of Laboratory Equipments