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Cervical Cancer Prevention: The Journey Started Long Back…… Still Goal Not Achieved

Over last century remarkable progress has been made in the diagnosis and treatment of cervical cancer. Early stages of cancer cervix are now treatable via number of surgical approaches including nerve sparing surgery, fertility sparing surgery, minimal access surgery as well as advances in radiation oncology treatments. All these advances have improved cure rates, survival rates and most important the quality of life in these patients. **"But have these advances improved the clinical scenario of cancer cervix in India?"**

In current Indian clinical practice majority of cases of cancer cervix have advanced stage at time of diagnosis. According to Globocon 2012 the incidence of cancer cervix in India is around 22 cases per 1 lakh women cumulating to around 1,22,000 cases per year. India contributes around 25% of new cases of carcinoma cervix worldwide.[1] The mortality rate for cervical cancer is also high in India causing death of 1 woman every 8 minutes exceeding even the maternal mortality rate of India.

Are we improving??

Sadly speaking the answer is no. While every case of cancer cervix is preventable, over 20 years the Indian cancer registries show only modest decrease of around 3.4% with incidence rate.[2] The Indian statistics raise the important question **"Where have we gone wrong?"** To get to the answer we need to understand the biology of cancer cervix as well as social and financial factors in our country.

The most important causative factor for cancer cervix is Human Papilloma virus (HPV). **"Cervical cancer does not and will not develop in the absence of the persistent HPV infection".** Dr Herold Zur Hausen was awarded the prestigious Nobel Prize in Medicine in 2008 for this breakthrough discovery. HPV infection though spontaneously resolves in majority of women, persisting infection with high risk HPV genotypes in few women predisposes them to risk of developing cancer.

HPV infection causes gradual change in cervical epithelium from normal to premalignant, finally developing invasive malignancy over the period of years. During all these years screening grants us the opportunity to identify these women and treat them before invasive malignancy develops. Though Dr George Papanicolaou had demonstrated effective screening technique in year 1940 and the test was routinely used by year 1943; we as a nation still have failed to provide routine screening facilities to our women.

Cervical cancer screening - still a missed opportunity for India, why???

There are many techniques for cervical cancer screening like cytology (Pap smear or liquid based cytology), visual inspection with acetic acid (VIA), visual inspection with acetic acid & Lugol's iodine (VILI) and recently introduced HPV DNA analysis. Tests like cytology, HPV DNA requires more finances and trained manpower, while others like VIA or VILI requires less resources and can even be done by paramedics or trained health workers.

Numerous studies have been done about different screening methods along with their applicability as per country's needs and available resources. Most of developed countries have routine screening with cytology as part of health program. Many of recent studies have supported use of VIA as a cost effective screening method for underdeveloped or developing countries.[3] Our neighboring country like Bangladesh have also established national screening program with VIA as a screening method. Study by Shankarnarayan et al from rural India have demonstrated that even a single round of screening for human papillomavirus (HPV) could dramatically reduce the incidence of advanced cervical cancer and cervical-cancer mortality within 8 years far more than a single conventional cytologic test or visual inspection of the cervix with acetic acid (VIA).[4]

To do is more important than how to do in regards to cervical cancer screening

Till now India does not have a government sponsored mandatory cervical cancer screening program. Indian government had started opportunistic screening program which received a poor response and have failed to make any difference. The main reason for failure of opportunistic screening was its

inability to reach the low socioeconomic and predominantly rural population where the incidence of cancer cervix is maximum.[5] To start and implement effective screening program is a challenge with any approach, given that the estimated proportion of women screened within the past 5 years in developing countries is only 5% .[6] The essential reasons for failure are lack of political will, lack of awareness about screening and lack of resources. Hurdles of finances, motivation and manpower can be tackled, nothing is impossible. Simultaneously, after diagnosis appropriate treatment facilities are also required.

It is the need of time to make screening mandatory, may it be linked with, for example any of essential document like AADHAR, beneficial schemes like MA YOJANA or with incentives. If we look at patients with cancer cervix presenting GCRI over one year, 60%-70% were from rural area and low socioeconomic strata and more than 90% were in advanced stage. Special focus needs to be given to women from these rural areas and low socioeconomic strata where the disease is more prevalent.

The awareness programs have a key role and it can be through plays, exhibitions or electronic media etc. Even health care providers need to be sensitized for screening strategies and training. The awareness programs need to be sustained as well as to have coverage to reach all women. The adolescent girls also need to be educated through health education programs through schools and communities. There should be emphasis to control cofactors like use of tobacco in these education programs.

With the solid scientific information about its safety and efficacy, is it time to include HPV vaccine in universal immunization program??

Historically India was the country to enlighten importance of universal vaccination for diseases like polio. The pulse polio campaign, one of largest successful immunization campaign was implemented in India. But in case of HPV vaccine even after two decades of being launched and more than a decade after been approved for use in India, it is still not included in universal immunization program of government of India. Different surveys suggest that HPV vaccine that can prevent cervical cancer has been tragically underused, less than 5% of women in India vaccinated with HPV vaccine and predominantly from private sector.

Though there are many controversies regarding HPV vaccine, such as safety, benefit in long term immunity and cost factors [(6)], similar controversies were also raised with polio vaccine program. Study of HPV vaccine in adolescent girls in Punjab state have already suggested efficacy and cost effectiveness.[8] Out of two vaccines preventing malignancies, Hepatitis B vaccine is already included in immunization program, now it is time to look into larger picture of benefit and include HPV vaccine as well.

The journey have started long back, we need to target proper population to screen and for future include vaccination, only then we will reach the goal that have long been missed.

What can be the key weapon in fight to prevent cervical cancer?? VIA? Pap smear? HPV DNA test? or HPV vaccination? Actually screening and HPV vaccination are complimentary approaches and both together have the potential to eliminate cervical cancer.

Meaningful improvements in cancer prevention strategies will be required to prevent increase in number of cancer deaths over the next 20 years.

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Shri Madanmohan Ramanlal GCRI Luminary Oration Award - 2017

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Ahmedabad

How GCS-GCRI Enriched Me

Prologue: It is my great pleasure to receive Shri Madanmohan Ramanlal GCRI Luminary Oration Award which is envisaged as a Life-Time Award for its recipients. Shri Madanmohan Ramanlal was a karma-yogi, a philanthropist and a deeply religious man with highest priority on ethics and business morals. The award is given away to a senior GCRIan for his/her contribution to GCRI, to his/her discipline, science in general, professional organizations and society at large. It is said that it is awarded to a compassionate teacher who is a source of inspiration to generations of students. Seven GCRI Luminaries have adorned and embellished this recognition.

Introduction: When I try to link my contributions to the great institutions called Gujarat Cancer Society and Gujarat Cancer and Research Institute, words fail me for I know my littleness before these towering institutions. I start feeling like Poet Kalidas when he started describing Bhagvan ShriRam's Ancestry – Raghuvansh. He said in the 2nd Shlok of the 1st Sarg of his great poem (mahakavya) called Raghuvansham that, "What a family with Sun's brilliance and what am I with my petite intelligence who has embarked to sail the boundless ocean with a small raft!"

क्व सूर्यप्रभवो वंश: क्व चाल्पविषया मति:।
तितीर्षुर्दुस्तरं मोहादुडुपेनास्मि सागरम्॥

We are small and our contributions are also small, like that of the squirrel of Bhagvan ShriRam. When Bhagvan ShriRam was building a bridge over the ocean, a small squirrel also tried to add a few pinches of sand to it. Her small efforts were appreciated by Bhagvan ShriRam and it is said that the striae seen on her back represent the impressions of Bhagvan's fingers. I, too, am reminded of Shri Hiralal Bhagvati, the then General Secretary of GCS who appreciated me during one GCRI annual day function for my work at the Gujarat Vishvakosh and inspired me to publish a book on Cancer in Gujarati. So I will not dare to count my contributions to the organizations but would like to present what enriched me while I treaded their corridors. It is done to pay respect to the said organizations and put before you to pause, ponder and prosper yourselves with your experiences here.

See the accompanying picture (Figure 1). A lion, a snake and a crocodile are ready to prey on this boy whose rifle is away. What plan can you give the boy to save his life?

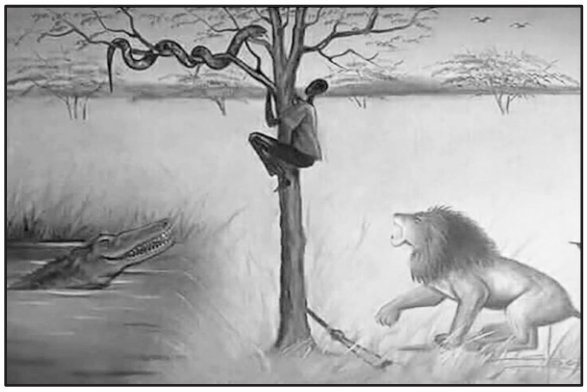

Figure 1: A scene from a story of an adventurer, a lion, a snake and a crocodile

One solution is to grasp the snake with one hand and fling it on the lion. It will scare the lion who may withdraw a bit. In the meantime, he may jump, take the gun and kill the lion. Thus he feeds the crocodile and walks away safely. But there is one more solution. He may be asleep and is having a nightmare. Wake him up so that he may be out of his frightful dream.

उत्तिष्ठत जाग्रत प्राप्य वरान्निबोधत।
क्षुरस्य धारा निशिता दुरत्यया दुर्गं पथस्तत्कवयो वदन्ति।।
(कठोपनिषद्, अध्याय १, वल्ली ३, मंत्र १४).

In Kathopanishad the Rishi has given us an advice. He wants us to discard sleep of ignorance and become aware (learn) to reach the life-goal that great souls have preached. But the path is as difficult as walking on the sharp edge of a dagger. Somebody (a teacher) shakes us from slumber but we have to learn, be aware and acquire knowledge ourselves, howsoever, it may be difficult and painful.

Example of Guru Dattatreya is quite handy in this regards. The young Dattatreya is famous in the Hindu texts as the one who started with nothing and without teachers, yet reached self-awareness by observing nature during his Sannyasi wanderings. He did not have formal disciples yet he is addressed to as Guru (a teacher). He learnt from his surroundings and circumstances. King Yadu asked him the secret of his happiness and the name of his Guru. He said that the

Atman (self) alone was his Guru, and yet, he had learned wisdom from 24 objects and individuals, who were, therefore, his teachers. Eight of the them were objects of Nature like the Earth, the water, the air, a fire, the sky, the Moon, the Sun and an ocean. Eleven were small creatures, birds and animals like a pigeon, a python, a moth, a bee, an elephant, a deer, a fish, a raven, a serpent, a spider and a beetle. Five were not learned persons, viz. a dancing-girl, a child, a maiden, an arrow-maker and a honey-gatherer. His message is simple. We must learn from all individuals, objects and circumstances irrespective of their stature or status. It is a great message of lifelong self-learning.

The Earth is unfalteringly productive and does its dharma (duty) though often it gets abused. It heals her wounds but continues to nourish. It teaches us forbearance and tolerance. A caterpillar is a lowly creature that accepts suffering of a closed cocoon but ultimately becomes a beautiful butterfly. Story of an arrow-smith (one who makes arrows) is quite enriching. He was so engrossed in his work that he did not notice that the King was passing by and he failed to rise in his respect. Such small incidences and creatures teach us a lot provided we are ready to observe, ponder and learn. Gandhiji has told us to learn as if we were never to die. Both these great souls have given us the counsel for lifelong self-learning.

We must remember that nothing or nobody can teach us, we only can learn. We can learn from individuals, groups, organizations, things, occasions, circumstances, thoughts, our reflections, subjects, disciplines etc. Our culture, attitude, resources, knowledge, imagination, environment and place of work are important sources as well as resources.

Lifelong Self Learning from Non-formal Teachers: Our non-formal teachers from whom we can learn are (1) the Nature, (2) the organizations where we work, (3) the disciplines we study and practice, (4) the occasions and circumstances we encounter, (5) persons and their formal or informal groups we work with or get acquainted to, (6) the print media like books, magazines, newspapers etc., (7 and 8) active and passive entertainment like games, films, dramas, pursuit of arts etc., (9) experiences, applications and work done as well as (10) critical observation of Formal Teaching Aids like Teachers, Schools, Books, Curriculum, Syllabus and Training. The process of self-learning is summarized in the accompanying figure-II. Of these I will discuss 4 important areas in the present context. They are summarized in the accompanying Table 1.

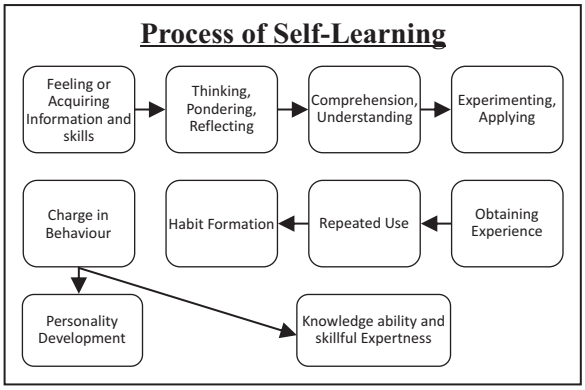

Figure 2: A process of self-learning

A. Organizations: The Gujarat Cancer Society (GCS) is an NGO whereas the Gujarat Cancer & Research Institute (GCRI) is a professionally run heath care organisation. Schools sensitised me to the need of service to the needy, communal harmony and humanity that threads all the different religious beads. It provided me an interesting opportunity for innovations in education.

The Gujarati Vishvakosh gave me opportunity to serve the Mother Tongue. It also provided me an opportunity in the field of health education. It improved my presentation style, made it more factual, precise, informative and narrative without unnecessary decorative adjectives. The Gujarat Vidyapith was a different experience with direct exposure to the Gandhian philosophy and its

Table 1 : My self-learning tools during my GCRI period

	A. Organisations	B. Circumstances	C. Subjects	D. Persons, Groups
1	GCS	Clinical Work - Care and Cure	Medicine	Doctors
2	GCRI	Conferences / Workshops etc.	Oncology	Patients and Relatives
3	Schools	Anchoring - Ceremonies, Programmes	Languages - Gujarati, English, Sanskrit	Co-Teachers
4	Gujarati Vishvakosh	Awareness and Advocacy	Education	Students
5	Gujarat Vidyapith Lexicon Gandhi-Darshan	Administration Unit, Research, Directorate (GCRI), Schools, Social Organisations	Research	Co-workers and Other Workers
6	Medical Associations - AMA, APA, APG, ISMPO, IACR-GSC	Institutional Politics - Progress and Hindrance, Success and Failures, Hope and Depressions, Struggle	Management, Administration, Leadership	Friends and Non - Friends ,Supporters, Jealous
7	Sadvichar Parivar (Evolving)	Encounter with Power - Political, Bureaucratic, GCS/GCRI	Expression	Government Servants - Political, Bureaucratic

implementation. The lexicon work led me into the words and their meanings. I realised that every word is a wallet of thoughts. Working for a dictionary brought in much clarity and exactness in thinking and understanding while attempting to decipher meanings of the words. It often reveals their hidden beauty, history, cultural trends apart from their origin and development.

Medical associations (Ahmedabad Medical Association-AMA, Ahmedabad and Gujarat Physicians' Associations-APA and APG, Indian Society of Medical and Paediatric Oncology-ISMPO and Indian Association Cancer Research-IACR-Gujarat Branch) helped me to develop professional leadership that is engaged in education of peers by organising scientific meets, drafting its scientific and academic agenda and by editing its journals. It gave me experience of leading peers and equals without any additional power. Working with such organisations fosters to lifelong self-learning and tendency towards fraternity building, provided one does not fall prey to the temptation of political power or ambitions. They have promoted honesty (who guards against the security guard?). They have also shown importance of physical fitness, clean professional image, neat and decent dress-code, public relations, good communication skills, understanding and fulfilling organisational needs, detailed and accurate documentation, ability to 'man the post' (discharging and transferring duties of the given post and position) and the last but not the least, change of the guards is a reality. All these qualities one learns from a security guard also! Both an office bearer of a social organisation and a security guard of any organisation serve and protect property that does not belong to them.

Gujarat Cancer Society (GCS) excels in the charity sector (NGO). It is a service organisation that works with compassion, love and care. Apart from medical services through its hospitals, it is engaged in awareness and advocacy programmes. It works proactively to serve the society. It thrives on human values and survives on philanthropic donations. I learnt the qualities of accountability to one's self and value-based activity for public good. What I have additionally learnt by my association with the organisation are – (1) Enthusiasm and dedication for the chosen charitable cause, (2) Team-working and social skills, (3) Communication skills, both oral and written, (4) Administrative and organisational skills, (5) Commercial or business awareness, as we are managing public money for a specified goal, (6) Pro-activity and flexibility, (7) Willingness to undertake tiring but necessary routine jobs, (8) Research and (9) Love for languages.

Gujarat Cancer and Research Institute (GCRI) is a teaching hospital promoting research. It is a semi-government organisation where administrative positions are impregnated with power and public accountability to fulfil the mission and vision of the organisation keeping core values intact. Its functioning imbibes professionalism and gives great lessons in science and management. Apart from medical services, formal and non-formal education and research, its activities include both awareness and advocacy. Activities are essentially scientific and hence carried out more dispassionately and are result oriented. It survives on service charges and government grant and hence there is an external accountability also. Though proactive in awareness programmes, its main beneficiaries (patients) have to come to its door-steps. It has taught me several important lessons in life, viz. (1) Mission, vision, ethics, and values of any establishment or team-work must be well defined and implemented by all stalk-holders including the employees, beneficiaries and the public. (2) Personnel ought to be treated equally and compensated fairly. (3) All programmes, policies, procedures, roles and responsibilities should be understood, followed and supported. (4) Diversity of origin and views are to be respected and endorsed. (5) Everyone involved can express one's view-points and have a say in decision-making. (6) Trust, teamwork and cooperation leading to high morale and zeal must prevail. (7) Optimistic, visionary and active leadership ought to be the norm at all levels. (8) High quality output is rewarded and recognized and poor performance is assisted to improve. (9) All values, standards, activities and endeavours should be of high quality fortified with continuous learning and improvisations. (10) Aims and purposes are successfully accomplished leading to ever-increasing contribution to the society and should lead to high organisational reputation. I also learnt that a modern hospital should provide coordinated care, be open to technology and workflow changes, make prices transparent, provide risk-based contracts and offer team-based care.

B. Circumstances and Occasions: They are our great teachers. Several situations provide opportunities to learn. Some of them are (1) clinical work (care and cure), (2) conferences and workshops, (3) anchoring ceremonies and functions, (4) awareness and advocacy programmes, (5) administration of clinical units and departments, research, GCRI-directorate etc. In my case, the schools and professional as well as social organisations also taught me a lot. (6) Institutional politics that lead to progress and hindrance, success and failures, hope and despair and, of course, struggle and (7) encounter with power, be it political, bureaucratic or local, i.e. GCS and GCRI.

Clinical activities teach us a lot and mould us into a humane human being. Love, compassion,

Table 2: Qualities of a good doctor and an ideal patient

No	Essential Qualities of a good doctor	Qualities Expected by the Patients	Qualities of an Ideal Patient
1.	Honesty	Professionalism	Time-keeping
2.	Forthrightness	Good Reputation	Planning
3.	Respectfulness	Strong Credentials	Preparation
4.	Healthy lifestyle	Sincerity	Courtesy
5.	No bias	Patience	Simplicity
6.	Knowledgeability	Openness, Responsiveness	Patience
7.	Well-Focused	Strong	Exactness
8.	Humane	Communication Skills	Prudence
9.	Skillfulness	Courteous	Faithful
10.	Empathy	Easy to Reach	Participation in decision making
11.	Confidence	Thoroughness	Loyal
12.	Accurate Documentation	Respect for other's Schedule	Primary study of ailment before-hand

warmth and satisfaction leading to happiness are both its virtues and principle rewards. In an academic environment, pure science and human values are combined at multiple levels and that becomes sometimes challenging. One needs to act on three fronts at a time, viz. clinics, academics and research. In our set-up, clinics take up most of the time available and often academics and research suffer. Our training for the latter two is inadequate also. We need to develop an aptitude for them. Often they are less rewarding. Self-satisfaction rather than material or any other obvious gain is the compensation. Clinical activity helped me to imbibe good qualities of fellow doctors and my patients (Table 2), too. I realised that a doctor who is timid, unfeeling, uncaring, deceptive, impolite, unfriendly, heartless, hasty or always in hurry is a bad doctor.

A good patient can help bring about the most significant change. They value doctor's services, follow treatment protocols to experience lasting results. They pay happily what the service is worth. They also refer their friends and stay under the same doctor's care because they understand its importance.

Professional Sociability: Scientific meetings like conferences and workshops, anchoring ceremonies and functions and awareness and advocacy activities have enriched me with professional sociability. They help us to develop qualities of good communication skills, development of affinity for and acceptance of diversity of thoughts and approaches, orientation towards the results and preplanning, generating everyone's progress and benefit, negotiating and persuading as well as updating and producing a change.

Administration, Management, Leadership: Important lessons were learnt when opportunities came to lead a clinical unit, research set-up, schools, social organisations, medical associations and an academic medical organisation. Lessons for so many good qualities were learnt in these situations. To name a few, allow me to list (1) cultural understanding, (2) an optimistic and encouraging attitude, (3) prioritization, (4) warmth, (5) competence, (6) empathy, (7) accountability, (8) honesty, (9) patience, (10) character, (11) flexibility, (12) effective decision making, (13) effective advocacy, (14) political skills, (15) total denunciation to animosity toward physicians, and (16) a firm grip on market trends. One should gather courage in maintaining independence and autonomy in decision making. One must be enterprising and staying three steps ahead to maximise returns for the mission he is working for. Though kind, loving and caring, One has to be strong in regulatory matters that require thorough compliance.

As a research administrator certain additional qualities are required. One must lead from the front, i.e. one has to be a performing scientist. He should be able to identify issues and should come out with innovative and practical solutions. Sme of the additional expertise are communication skills, team building, interpersonal skills; optimistic, confident and enthusiastic attitude, patient listening, connecting with everybody as well as sympathetic and rational concern for others' suffering that needs searching solutions.

Special Adverse Situations: They are mainly of 2 types, viz. institutional politics and an encounter with power. When 3 or more persons assemble and are engaged in fulfilling a common goal but have different

origins, desires, hidden aims and intentions to relish or exploit fruits of common success, politics will inevitably creep in. Gossip is its currency and shameless self-interest concealed in deceit is its driving force. Like any other employee anywhere else, crests and troughs of progress and hindrance, success and failures, hope and depressions as well strides of struggle were my experiences, too. My encounter with power included political, bureaucratic and hierarchical forces both within the organisations and outside. One's courage and conviction are often challenged, undermined or surmounted by physical, positional, legal or moral power.

Both the situations may turn out to be blessings in disguise. One must control emotions and seek and find other avenues to develop. It depends on ones hobby, area of interest, natural gift or aptitude. It is important to have one such past-time activity like interest in any art-form, social work, reading-writing-performing etc. They keep the fire in you burning and serve as an outlet valve of a pressure cooker when needed. In the process your development and contributions continue to nourish and flourish. In my case, the period was of over 12 years. It enriched me in the areas of linguistics and scientific literature, professional leadership and self-learning and peer-education. Do not get stuck up. Fight back. Exhibit the best performance and shine out. Remain useful to the organization and colleagues. If everything fails, quit and carry on in some other direction. All throughout one needs to control one's emotions. Table 3 summarizes a few methods to cope with the situation.

Avoiding an unpleasant situation is the simplest thing. Be away from or leave the scene. If one's presence is unavoidable, try to modify the situation. It requires tact. One may try to shift focus of attention to something other than the distressing thoughts and emotions. Change thoughts and responses to the situation. No hurried reactions or unwarranted responses. Only deep reflections are allowed. Find out someone sympathetic, loving and confidant (e.g. life partner or a very close friend) before whom one may give vent to boiling emotions. Be protective to their feelings, too. Trust a brighter future, be optimistic and try to see big and rosy futuristic picture. Always forgive the emotional triggers. Situations and not the men are bad. Be charitable in approach towards them. Even if severely hurt, forgive them. One must not have any grudge or animosity towards those who were seen as one's road-blockers. Often they act in the best interest, need and policy of the organisation. Love as usual. And of course, have faith and seek Devine guidance and protection.

C. Disciplines or Fields of Learning or Interest: We develop by our systematic pursuit of knowledge and skills in the fields of our formal and non-formal learning. They often constitute the core of our knowledge and principle means of livelihood. But they may also include areas of interest and hobbies. In my case, they were seven (Table 4). They have helped me to improve certain rewarding traits, some fully and some partially. They are summarised in the Table 5. Identifying issues, ability to solve them, courage to face them and do it for others without any selfish motive are some of the most important values one learns. They make the person fearless, truthful and useful. They promote innovations and creativity as well as ability to appreciate and evolve beauty and benevolence. They are often a good source of happiness and satisfaction.

D. Individuals and Groups: At GCRI and GCS, I have ample opportunity to meet and mingle with a variety of individuals – co-workers, beneficiaries and bystanders. They form main groups, viz. doctors, patients, co-teachers, students, paramedics, co-workers and co-contributors, friends, non-friends and foes as well as politicians and bureaucrats (Table-6). People think and behave differently when they are alone and when they are a part of a formal group (team or department) or a crowd. They give you different experiences, pleasant or otherwise, and by observing

Table 3: How to cope with a frustrating situation

No	Action/Response
1.	Avoid circumstances and situations
2.	Modify the situation and conditions
3.	Shift focus of attention
4.	Change beliefs and thoughts
5.	Change response
6.	Do not react right away
7.	Find a healthy outlet for emotions
8.	See the bigger picture
9.	Forgive emotional triggers
10.	Seek Divine guidance and blessings

Table 4: Disciplines or Fields of Learning or Interest

No.	Disciplines
1	Medicine
2	Oncology
3	Languages - English, Sanskrit, Gujarati
4	Education
5	Research
6	Management, Administration, Leadership
7	Study of Expressions

Table 5: Qualities developed by pursuing studies

No	Quality or Trait	No	Quality or Trait
1.	Identifying issues	9.	Reading the hidden thoughts
2.	Problem solving	10.	Innovation and creativity
3.	Keeping cool	11.	Fearlessness
4.	Facing crowd, crisis, conflict	12.	Beauty
5.	Thorough knowledge	13.	Truthful
6.	Acquiring skills and talents	14.	Usefulness
7.	Communication skills	15.	Benevolence
8.	Attending to details	16.	Character building

them from a distance, dispassionately, one learns a lot.

Co-teachers often induce a mission to the profession, promote knowledge. They are often very warm, creative and supportive. They demonstrate patience for the students with slow learning. They engage students with their effectiveness and communication skills. They know their students well and their cultural background. They demonstrate commitment to lifelong learning and become role models for life outside the working place with their hobbies. They impress us with their medical and clinical knowledge, skills, competence, clinical reasoning and productive relationships with students and supportive nature.

Our students are a life-time gift. They succeeded with their regularity and hard work. At an age beyond 30, but for the call of commitment and lure for learning, how can one bear the ravages of residency? They have taught me so many things - Politeness, inquisitiveness, constant readiness to learn new things, concepts and applications. Their exploring insight is a good quality to adopt. They might have forgotten the details of what I taught them, but have always remembered the importance of values in life, I often spoke, while going from one ward to the other. After having surpassed me in certain areas, they still love and remember me. My love and affection for them is everlasting as their progress and successes are my fulfilments.

Co-workers are co-contributors. I have observed and adored their over 100 qualities which I need to incorporate in my personality and behavior. They run in over 100 characteristics. I have tried to list the most commonly found among them. They are listed in the Table-VII.

Conclusion: Every one is a teacher and everything is a lesson, provided we observe, listen and learn. Observing, listening to and learning from every one and from everywhere will always enlighten us.

As we rise in the ladder, in the organization we tend to be alone with fewer friends. People come to see you more often with their problems and issues but less with pure love towards you. Not everyone will stay with you forever. Nor the things remain the same forever. Things change. Learn to walk alone. Not everyone who started with you will be able to finish with you. We tend to be lonely. Better be alone rather than lonely. Therefore, we must learn to tread alone on our chosen path.

Table 6: List and Qualities of Co-contributors observed and resourced for self-learning

No	Qualities	Departments
1	Capability and dependability	Accounts
2	Communication skill and ability	Administration, Management, Leaders
3	Enthusiasm, Creativity	Artist/Photographer
4	Gratification from job	Cleaners and sweepers
5	Health	Contractual workers
6	Honesty	Engineering
7	Learnability	House Keeping
8	Love and Care	Human Resource
9	Loyalty	Library
10	Never withering smile	Nursing
11	Obedience	Research
12	Politeness	Security
13	Punctuality	Service advisor
14	Team work	Stores and supplies
15	Work-ethics	Support technicians

Note: The Qualities and Departments are listed alphabetically and are not intended to match each other.

In long strides of life, we come across good and bad, friends and foes. We have to be like that proverbial swan, which discerns between water and milk and takes the latter only and feeds on pearls discarding the gravels. It is good to see or seek good and worthy in everything.

कृष्णस्यासीत्सखा कश्चित्ब्रह्मणो ब्रह्मवित्तमः ।
विरक्ता इन्द्रियार्थेषु प्रशान्तात्मा जितेन्द्रियः ॥

Sudama is introduced to us a poor brahmin. But that is not the reason why ShriKrishna loved him. He loved ShriKrishna as his friend, was knowledgeable, wise, dispassionate and satisfied with full self-control, calm and serene at heart. These qualities brought to him, his Lord's Love and blessings as well as eternal bliss and peace. Let us all be like him.

May I end with a slight modification of Longfellow's message, "Still achieving, Still pursuing; Learn, Labour, and My Friend, Wait"? (Original – Still achieving, still pursuing. Learn to labour and to wait.)

Aberrant Glycosylation, a New Hallmark of Cancer has a Vital Translational Value

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Summary

As normal cell progress to neoplastic state, it acquires distinctive and complementary capabilities, which are called as the hallmark of cancer. In the course of noteworthy progress in cancer research, newer observations have modified the original formulation of the hallmark capabilities. Rising evidence supports vital role of altered glycosylation during all steps of tumor progression. Our data as well as other reports have documented aberrant glycosylation as a new hallmark of tumor proliferation, invasion, metastasis and angiogenesis. Protein glycosylation is the most widely observed and structurally diverse form of post-translational modifications after phosphorylation. It is the enzymatic process that produces glycosidic linkages of sachharides to other sachharides, proteins or lipids. Alterations in cell surface glycosylation particularly, terminal motifs may results in altered cell-cell adhesion, cell-matrix interactions, inter and intra- cellular signaling and cellular metabolism. We have reported that the understanding of biologically relevant aberrant glycosylation can serve as clinically importamt biomarker for various cancers. The review presented here symbolizes an ample overview of literature on translational glycobiology. The results also provide the evidence of aberrant glycosylation linked with other hallmarks of cancer leading to a conclusion that glycosylation is a new hallmark of cancer.

Keywords: Glycosylation, Sialyltransferase, Sialidase, Fucosyltransferase, Fucosidase

Hallmarks of Cancer

In 2000, a highly influential review article entitled "The hallmarks of cancer" was published by Hanahan and Weinberg which proposed six hallmarks of cancer that provides a logical framework for understanding the biology of cancer. It included sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis and resisting cell death. (Figure: 1a) [1] Almost after a decade they have reworked on the hallmarks of cancer and proposed another two emerging hallmarks: "Deregulating cellular energetics" and "Avoiding immune destruction" and two enabling characteristics: "Genome instability and mutation" and Tumor-promoting inflammation". (Figure: 1b) [2] The evidences indicate that tumorigenesis in humans is a multistep process and that these steps reflect genetic alterations that drive the progressive transformation of normal human cells into highly malignant derivatives. The hallmarks of cancer are characterized by functional capabilities that allow cancer cells to survive, proliferate and disseminate during tumorigenesis. Further, they have also proposed that refinement of these organizing principles will surly come in the foreseeable future which will continue in the remarkable conceptual progress in the hallmarks of cancer.

Glycosylation as a hallmark of cancer

Glycans exist as membrane-bound glycoconjugates or as secreted molecules, which become integral parts of the extracellular matrix. Changes in these glycan structures are associated with many physiological and pathological events such as cell growth, migration and differentiation. Consequently, aberrant glycosylation occurring in cancer cells influence cell proliferation, adhesion and motility as well as angiogenesis and metastasis.[3,4] Our laboratory is working on several aspects of glycosylation in cancer since 1985. Based on our experience, we have came to a conclusion that aberrant glycosylation interfere with almost all the steps involved in malignant transformation and therefore can be said as classic hallmark of cancer[5]. In support of this notion, several authors have also reported glycosylation as a new hallmark of cancer. [6,7] Glycosylation is not a template based process such as DNA, RNA or protein synthesis but is rather based on the balance achieved by the expression and activity levels of the different enzymes involved in the glycosylation process such as glycosyltransferases and glycosidases and on the availability of the nutrient resources and expression of enzymes responsible for their synthesis and interconversion.[8] The study of the changes in the enzymes associated with altered glycosylation provides new directions for understanding the molecular nature of cancer, cellular transformation and often new opportunities for identifying biomarkers of disease and developing interventional strategies for treatment of cancer.[9] Increased sialylation and fucosylation of cell surface glycoconjugates is among the key molecular changes associated with malignant transformation and cancer progression. Therefore the present review is mainly focused on clinical significance of aberrant glycosylation via altered sialylation (sialidases and sialyltransferases) and fucosylation (fucosidases and fucosyltransferases) in various cancers. In particular, aberrant protein glycosylation as a new hallmark of

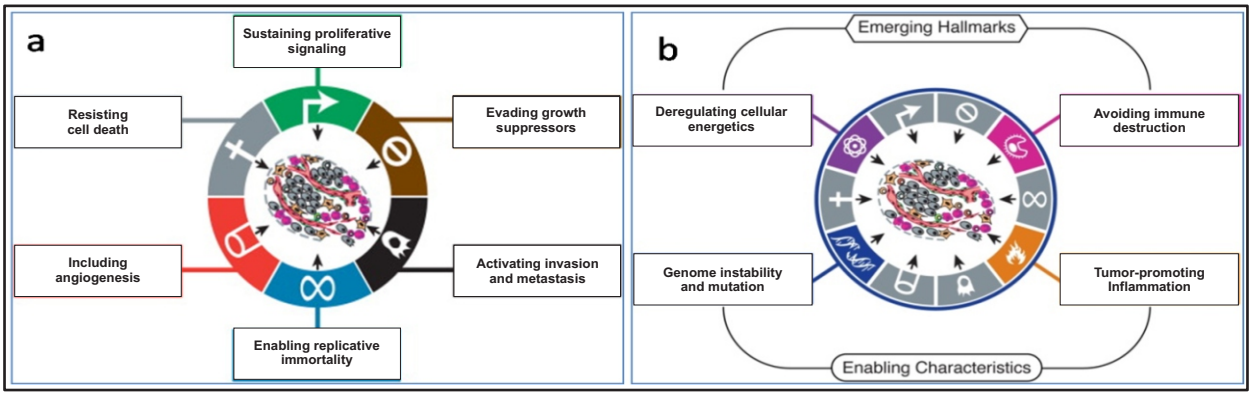

Figure 1: Hallmarks of Cancer (Reproduce from Hanahan and Weinberg RA, 2000,[1] 2011[2])

cancer will be conversed in relation with various human cancers.

Sialylation

Sialylation affects the half-lives of many circulating glycoproteins and plays a role in a variety of biologic processes such as cell-cell communication, cell matrix interaction, adhesion, and protein targeting. The transfer of sialic acids from CMP sialic acids to the acceptor carbohydrates is catalyzed by the sialyltransferase (ST) family. Aberrant sialylation in cancer cell is a characteristic feature associated with malignant properties including invasiveness and metastatic potentials.10 Sialic acid is linked either through α-2, 3 or α-2, 6 linkage to subterminal galactose or α-2, 8 linkage to another sialic acid forming polysialic acid catalyzed by specific ST. The different STs can be distinguished on the basis of oligosaccharide sequence used as acceptors and anomeric linkage formed with the penultimate sugar residue.[11, 12] Sialylation is governed by Sialyltransferases and sialidases. Sialic acids are transferred from a donor substrate to terminal positions of glycoprotein and glycolipid carbohydrate groups by STs.[13] STs are categorized into four families on the basis of the carbohydrate side chain they synthesize, namely ST3Gal (α2, 3-ST), ST6Gal (α2, 6-ST), ST6GalNAc and ST8Sia (α2, 8-ST).[14] On the other hand, their removal from glycan chains is catalyzed by sialidases. Sialidases also called neuraminidases (NEU) are glycosidases catalyzing the removal of α-glycosidically linked sialic acid residues from carbohydrate groups of glycoproteins and glycolipids. They are classified according to their major intracellular locations as intra-lysosomal, cytosolic, lysosomal membrane and plasma membrane associated NEUs. NEU1, NEU2 and NEU3 are known to be localized predominantly in the lysosomes, cytosol and plasma membranes, respectively and NEU4 is found in lysosomes or in mitochondria and endoplastic reticulum.[15] The amount and type of sialylation of tumor cell membrane depend on the activity of a number of different STs.[5] The activity of these enzymes affects the conformation of glycoproteins and therefore contributes to either increased recognition or masking of biologically relevant sites in molecules and cells.[15] Alterations in sialidase, STs and mRNA subtypes expression have been reported in various cancers.

Our laboratory has reported elevated sialidase activity in patients with OPC and oral cancer patients.[16] A study has observed alterations in different subtypes NEU1, NEU2 and NEU3 and NEU4 which was found to be correlated with cancer progression in various cancer cell lines.[15] NEU3 was also found to be up regulated in prostate cancer which plays a role in tumor progression through androgen receptor signaling.[17] In colon cancer, high expression of the sialidase NEU3 in cancer cells leads to protection against programmed cell death by modulation of gangliosides is documented.[18] In addition, NEU3 also plays a major role in maintenance of self-renewal and tumorigenic potential of colon cancer cells.[19] In various head and neck squamous cell carcinoma (HNSCC) cell lines, NEU3 has been reported to regulate the EGFR signaling through ganglioside modulation which is further associated with lymph node metastasis.[20] In colorectal cancer, NEU4 is implicated as an important player in control of sialyl Lewis antigen (sLe) expression and its impairment.[21] Our laboratory has reported significant over expression of sLe^X in malignant tissues as compared to adjacent normal tissues which is further associated with disease progression and poor prognosis of the patients.[10]

Earlier studies from our laboratory have reported altered enzyme activities of α-2, 3 and α-2, 6 STs in serum, saliva and tissue of patients with OPC and oral cancer patients and its significance in treatment monitoring. Figure 2 depicts levels of serum and salivary α-2, 3 and α-2, 6 ST in Pre treatment (PT), Complete responders (CR) and Non responders (NR) during post treatment follow-ups. It was observed that levels of serum and salivary α-2, 6 ST along with salivary α-2, 3 ST were significantly decreased in CR ($p=0.012$, $p=0.001$ and $p=0.010$ respectively) as

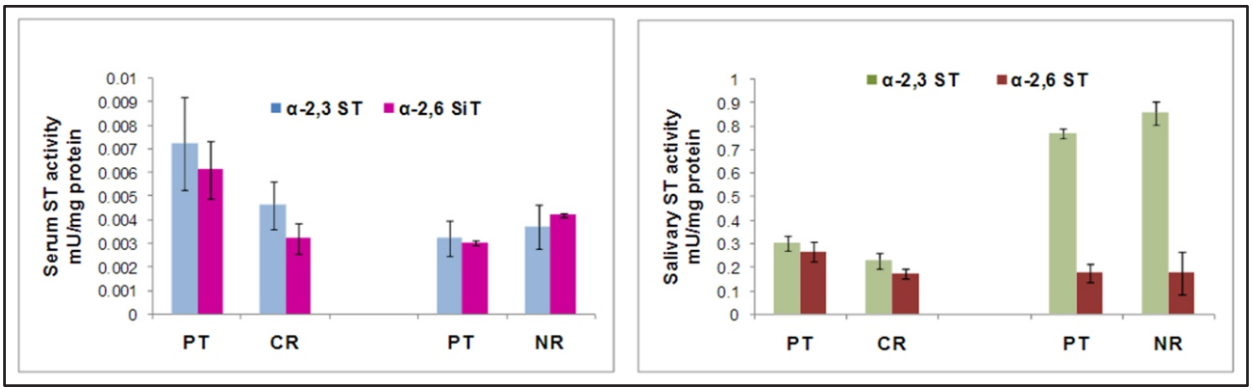

Figure 2: Levels of serum and salivary α-2, 3 and α-2, 6 ST in PT, CR and NR[22]

compared to PT levels. The levels of serum α-2, 6 ST were found to be significantly increased (p=0.024) in NR as compared to PT levels. The levels of serum α-2, 3 ST, serum and salivary α-2, 3 ST and α-2, 6 ST were also found to be increased in NR as compared to PT levels.[10,22]

During neoplastic transformation, the activity of the Golgi localized STs is usually increased and as a consequence, cancer cells express more heavily sialylated tumor associated carbohydrate antigen (TACA) at their surface. Various STs play role in formation of TACA in various cancers.[23] ST3GAL1 plays role in formation of sT antigen, ST3GAL4 in sLe^X formation, ST6GAL1 in CD75s and ST2H formation, ST6GALNAC1 in sTn antigen etc. The common glycan alterations observed in various cancers are increased $sLe^{x/a}$, increased Tn epitopes, increased sialyl Tn epitopes, increased sialyl T antigens and increased α-2,6 sialylation.[24] A study has reported ST3GAL1 as an independent adverse prognostic factor for recurrence and survival in clear cell renal cell carcinoma patients.[25] Further, it was observed that ST3GAL1 plays the major role in the T antigen sialylation, and its expression is associated with progression and recurrence in bladder cancer.[26]In cervical cancer, loss of ST6GAL1 has been showed to promote cell apoptosis and to inhibit the invasive ability of cancer cells.[27] Increased ST6GAL1 and subsequently elevated levels of cell-surface α 2, 6-linked sialic acids have found to be associated with metastasis and therapeutic failure in colorectal cancer.[28] In hepatocellular carcinoma, ST6GAL1 and ST8SIA2 regulation has been shown to affect unusual properties of invasion and chemosensitivity by modulating the PI3K/Akt signaling pathway.[29] Further, over expression of ST3GAL4 leads to SLe^X antigen expression in gastric cancer which in turn induces an increased invasive and aggressive phenotype.[30, 31] ST3GAL4 has also been reported as a biomarker for diagnosis and prognosis of multi drug resistance in acute myeloid leukemia.[32] In addition, elevated mRNA level of ST6GAL1 and ST3GAL4 are found to be positively associated with the high risk of pediatric acute lymphoblastic leukemia.[33] Hence, expression of STs are often found to be de-regulated in various cancers like colorectal, liver, gliomas, gastric and oral cancer.[10, 5] However, despite of increased amounts of evidence showing the involvement of STs and aberrant sialylation in cancer progression, therapeutic strategies to reduce aberrant sialylation lag behind.

Fucosylation

Fucosylation is one of the most common modifications involving oligosaccharides on glycoproteins and glycolipids. Fucosylation consists of transfer of fucose residue from GDP to N-glycans, O-glycans and glycolipids.[34] Fucosylation is catalyzed by a family of fucosyltransferase enzymes (FTs), consisting of 13 members, including FUT1 to 11, protein o-fucosyltransferase 1 (POFUT1) and protein o-fucosyltransferase 2 (POFUT2). FUTs promote attachment of fucose to N-, O- and lipid linked glycans through an α 1, 2- (by FUT 1 and FUT2), α 1, 3- (by FUT 3 to 7 and FUT 9 to 11), α 1, 4- (by FUT 3 and FUT5) and α 1, 6- (by FU8) linkage or directly link to the serine/ threonine residues of EGF-like or thrombospondin receptor (by POFUT 1 & 2).[35, 36] Fucosylated glycans can be generally divided into two subcategories, (i) core fucosylated and (ii) terminally fucosylated glycans.

Core Fucosylation: Core fucosylation is the addition of α 1-6 fucosyltransferases (encoded by FUT8). Up regulation of core fucosylation and the associated FUT8 gene has been observed in most cancers.[37] Importantly, in most of cancers the presence of core fucosylated glycans on the cell surface is largely mirrored by their presence, thereby demonstrating the potential for further use of specific protein glycoforms for early cancer detection.[38]

Terminal Fucosylation: Cell surface glycans frequently carry fucose residues in α 2-3 and/or α 2-4 linkage at the terminus of the N- and O- linked glycan structures, giving rise to the formation of specific

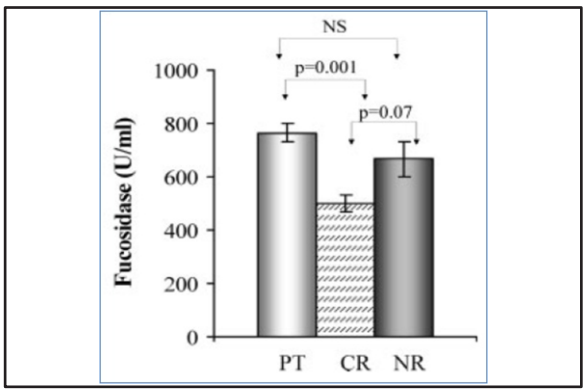

Figure 3: α-L-fucosidase between the untreated/pretreatment (PT) patients with OC and patients who achieved a CR or who had an NR[41]

Lewis blood group antigens, such as $Le^{x/y}$ and $Le^{a/b}$. Several FUTs are involved in the formation of Lewis antigens including those coded by FUT 1-7 and FUT 9[39] with FUT 3-7 and FUT 9 gene products known to produce the Lex structure. FUT 1-2 genes, on the other hand are involved in creating the precursor of H-antigen.[38]

Although fucosylation is essential for normal biological functions, alterations in fucosylation are strongly implicated in cancer and increasing metastatic potential. Alterations in fucosidase and fucosyltransferase expression have been reported in various cancers.

α-L-fucosidase (EC: 3.2.1.51) is a lysosomal enzyme that catalyzes the hydrolytic cleavage of terminal fucose residue that is involved in maintaining the homeostasis of fucose metabolism. The presence of fucosidases (FUCAs) is necessary for rapid turnover of N-glycans (including fucose) followed by reglycosylation and reinsertion of the proteins in plasma membrane.[40] Our earlier studies have documented serum a-L-fucosidase as a useful marker for close monitoring of patients during post–treatment follow-up. (Figure: 3) [41] Our pervious study has also reported significantly higher serum and salivary α-L-fucosidase activity in oral cancer patients as compared to controls.[42]

It has been observed that high FUCA expression alters the composition and decrease the quantity of cell surface fucosylation-associated molecules, thereby limiting the invasiveness of cancer cells in early-stage breast tumors.[43] So, the tumor cells expressing lower FUCA protein levels exhibit increased cell surface fucosylation, which enhances the malignant potential of the tumor cells in triple-negative breast cancer.[43] A study has reported that over expression of α-L-fucosidase 1 (FUCA1) suppressed the growth of cancer cells and induced cell death by protein defucosylation which is further involved in tumor suppression in several cancers.[44] In HNSCC, primary tumors exhibiting higher FUCA1 expression were found to be associated with significantly worse patient survival.[45] In adition, down-regulation of FUCA1 was also found to be correlated with increased aggressiveness of thyroid cancer.[46]

It has been demonstrated that altered expression of various FTs such as FUT3,[47] FUT4, 48 FUT6 ,[49, 50] FUT7, [51, 52] FUT8 [53, 54] mediate cancer cell migration and thereby metastasis, suggesting that altered fucosylation may play an important role in disease progression. Our laboratory has reported a significant decrease in FUT3 and FUT5 mRNA expressions in oral cancer patients.[22] Increased fucosylation has been established as a crucial character in invasive and metastatic properties of head and neck cancer stem cells.[55] In breast cancer high FUT8 protein expression was found to be correlated with lymphatic metastasis and stage status.[56] High expression of FUT8 was also found to be associated with poor survival which can be a significant and independent unfavorable prognostic factor in patients with potentially curatively resected non-small cell Lung Cancer.[57] Further, over expression of FUT8 was found to be associated with aggressive prostate cancer which can serve as a promising target to differentiate between aggressive and non-aggressive prostate tumors.[58] Moreover, altered levels of FUT8 were also significantly linked to the malignant behavior of proliferation and invasion in human hepatocarcinoma cell lines.[59] In addition, FUT4 was found to be associated with the proliferation and metastasis of breast cancer and which can serve as novel biomarker in the diagnosis and prognosis of breast cancer.[48] FUT3 mRNA over expression was found to be responsible for increased SLe^X biosynthesis leading to metastasis in colon carcinoma cell line whereas increased FUT7 levels were observed to be a significant indicator of poor prognosis.[60] The results documented here reveal the importance of monitoring fucosylation changes during various stages of cancer progression which can be helpful for early detection and management of cancer patients.

Our laboratory has long been keenly involved in studying clinical significance of glycosylation changes in various cancers. Our recent review has also summarized the correlation of altered glycosylation with other hallmarks of cancer.[5] Furthermore various studies which have documented alterations in sialylationa and fucosylation and its association with tumour burden, invasion and metastasis in a variety of cancers has strengthen our concept that glycosylation is a new hallmark of cancer progression.

Conclusion

Glycosylation is a posttranslational modification of proteins playing a major role in cell

signalling, immune recognition and cell-cell interactions. Aberrant glycosylation has been identified in almost every type of cancer due to significant modification/ alterations in sialylation and fucosyltion by altered expression of various enzymes involved in it. The current review summarizes various literatures including our data documenting clinical utility of altered expression of STs, sialidase, FUTs and fucosidase in various cancers. In nut shell, distinctive alterations in tumor-associated glycosylation may provide us a unique feature of cancer cells and therefore grant novel diagnostic and even therapeutic targets. This suggests that altered glycosylation has an important translational value in clinical setting. More interestingly, the development and progression of cancer results in the fundamental changes to the glycome; so, changes in glycosylation can be believed as a brand new hallmark of malignant transformation and a hallmark of translational value in cancer.

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A Retrospective Study of Definitive Radiotherapy in Locally Advanced Carcinoma of Uterine Cervix Treated Initially with Hypofractionation: A G.C.R.I. Experience

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Summary

Locally advanced carcinoma cervix represents a heterogeneous group of patients. Those considered unsuitable for curative treatment at the time of presentation are generally treated with hypofractionated radiotherapy. This study evaluates locoregional outcome, early and late toxicities of bladder, rectum and vagina in locally advanced carcinoma cervix patients treated with initial short course of palliative hypofractionated radiotherapy and subsequently followed by curative radiotherapy. Between 2013 and 2016, a total of 254 patients of locally advanced cervical carcinoma were initially treated to a dose of 30Gy in 10 fractions over 2 weeks. Fifty two out of 254 patients (20.5%) were identified who were subsequently treated with curative radiotherapy after being initially treated with palliative hypo-fractionated radiotherapy. Forty three of 52 patients (82.7%) were suitable for complete course of pelvic irradiation. Out of 43, 28 patients received brachytherapy boost and 15 patients received external beam radiotherapy boost. With a median follow-up of 19 months, 19 patients out of 40 (47.5%) had complete response, 10 (25%) had subjective symptomatic response initially and 11 (27.5%) had progressive disease. Patients receiving brachytherapy had disease free survival (15 months vs. 19 months; $p>0.05$) as compared to those received pelvic boost by external radiotherapy. In our study, 20.5% patients of locally advanced cervical carcinoma patients treated with initial short course hypofractionated palliative external beam radiotherapy became eligible for curative radiotherapy. These patients show a reasonably good survival and acceptable delayed toxicities and use of brachytherapy boost in selected subset of patients is encouraged. The data of this study correlates well with studies of similar nature done in the past.

Keywords: Locally advanced carcinoma cervix, Hypofractionated radiotherapy, Survival and Toxicities

Introduction

Radiation therapy plays an important role in carcinoma cervix stages II-IV.[1, 2] Treatment for carcinoma cervix stage IIIB is a combination of external beam radiation therapy and brachytherapy. Conventional external beam radiation delivering a dose of 1.8 to 2 Gy per fraction with standard pelvic portals and four field box technique has been established since last 3 decades. There have been attempts of several types of altered fractionation regimen to achieve highest probability of tumor control with lowest possible normal tissue damage.[3] This includes an optimal combination of total dose, dose per fraction, time interval between fractions, dose rate and overall treatment time, taking into account the biology of both tumor and acute and late reacting normal tissues. The basis of hypofractionation is delivering high dose per fraction (>22.5Gy) with reduced overall treatment time. This reduction in the total dose is needed so as to reduce acute normal tissue effects, given the high dose given in each fraction. The beneficial effect of reduction in overall treatment time is counteracted by high dose per fraction and hence the chances of late complication increase with increasing dose per fractionation. Various studies with split course radiation therapy have also practiced hypofractionation.[4] At few centres, hypofractionated radiotherapy has been delivered twice weekly or four days a week. Alteration in the fractionation has been attempted mainly to improve the local control at the same time decreasing the normal tissue complications.[5]

Carcinoma cervix stage IIIB includes a heterogeneous group of patients and some of these do not have good general condition and thus the extended 4-5 weeks of external radiation is not suitable. Short course of palliative hypofractionation schedules are preferred in this scenario due to short expected survival period. The focus of treatment is on symptomatic relief and survival in such patients is rarely studied. Some of these patients might show good subjective and objective improvement with palliative radiotherapy and become suitable for further curative radiotherapy with a possibility of long term survival.

Materials and Methods

Fifty-two out of 254 (20.5%) locally advanced carcinoma cervix patients, considered unsuitable for curative treatment at the outset, were initially treated with hypofractionated palliative external beam radiotherapy with total dose of 30Gy in 10 fractions over 14 days between 2013-2016.Median age of presentation was 49 years (range 34-74 years) and the mean duration of symptoms was 5 months (range 2-18 months). Table 1 enlists the characteristics of all patients included in the study.

Table 1: Patient Characteristics (n=52)

Characteristics	No.	%
*Tumor Extent		
Upper 1/3	10	19.2
Upper 2/3	28	53.8
Upto introitus	14	27
*Type of growth		
Infiltrative	27	51.9
Exophytic	16	30.8
Ulceroproliferative	9	17.3
*Parametrial involvement		
Unilateral upto pelvic wall	8	15.4
Bilateral upto pelvic wall	34	65.4
Frozen Pelvis	10	19.2
*Histopathology		
Well differentiated	19	36.5
Moderately differentiated	24	46.2
Poorly differentiated	9	17.3
*Stage		
IIIA	1	1.9
IIIB	49	94.2
IVA	2	3.9
*Imaging Features		
Tumor <4cm	9	17.3
Tumor >4cm	43	82.7
*Hydronephrosis	15	28.84
*Para-aortic node	2	3.8
*Rectal Infiltration	2	3.8

After staging and investigations they were considered for radiation therapy. Hypofractionated radiotherapy was considered because of extensive disease and poor general condition of patient, which made the patient unsuitable for curative radiotherapy. Patients were treated with standard parallel opposed pelvic portals with anterior-posterior and posterior-anterior field technique with total dose of 30 Gy in 10 fraction, 5 days a week, treated for 2 weeks. 2-3 weeks after completion of palliative hypofractionated radiation therapy, all patients were evaluated for disease response. Fifty-two patients out of 254 had more than partial response and were further treated with 20 Gy in 10 fractions and thus, these patients received external beam radiation therapy dose equivalent to 50 Gy employing 2 Gy per fraction regime. During radiation therapy, all patients were assessed for acute gastrointestinal, genitourinary and skin toxicity. Brachytherapy assessment was done after one week of completion of external radiotherapy. In 7 patients, brachytherapy was not feasible due to extensive local cervical growth and/or pelvic nodal disease and in 2 patients; persistent para-aortic nodes were present even after completion of external beam radiation therapy. These 9 patients were treated symptomatically. Forty-three patients out of 52(82.7%) were eligible for further completion of radiotherapy. Fifteen (34.9%) of 43 patients were not eligible for brachytherapy boost and thus, were treated with external pelvic boost 10 Gy to bring the total dose up to total dose of 60 Gy covering the uterus, cervix, vagina, paracervical and parametrium. Rest 28 patients were treated with brachytherapy boost. 25 patients of carcinoma cervix were treated with standard intracavitary brachytherapy with central uterine tandem and two vaginal ovoids delivering a dose of 15 Gy in 2 fractions to point A. Two patients of carcinoma vault were treated with Martinez Universal Perineal Implant Technique and one patient of carcinoma cervix received intracavitary with interstitial technique because parametrial disease may not be covered with standard intracavitary technique, delivering a dose of 16 Gy in 4 fractions to local disease area.

Follow-up

Patients were followed up at 4 weeks of completion of radiation therapy, monthly for 3 months, three monthly for the first year, 4 monthly for the second year and 6 monthly thereafter. At every follow-up patient were assessed for late reactions of skin, vagina, rectum and bladder.

Patients who had evidence of local disease at 6 weeks of completion of treatment were considered to have persistent disease. Patients were considered to have recurrence when disease was seen after initial complete response. Patients who had persistent disease or recurrence were considered to have loco-regional failures. Early and late reactions were assessed according to the RTOG scale. Statistical analysis was performed using SPSS for Windows and Kaplan Meier method was used for calculating the survival.[6]

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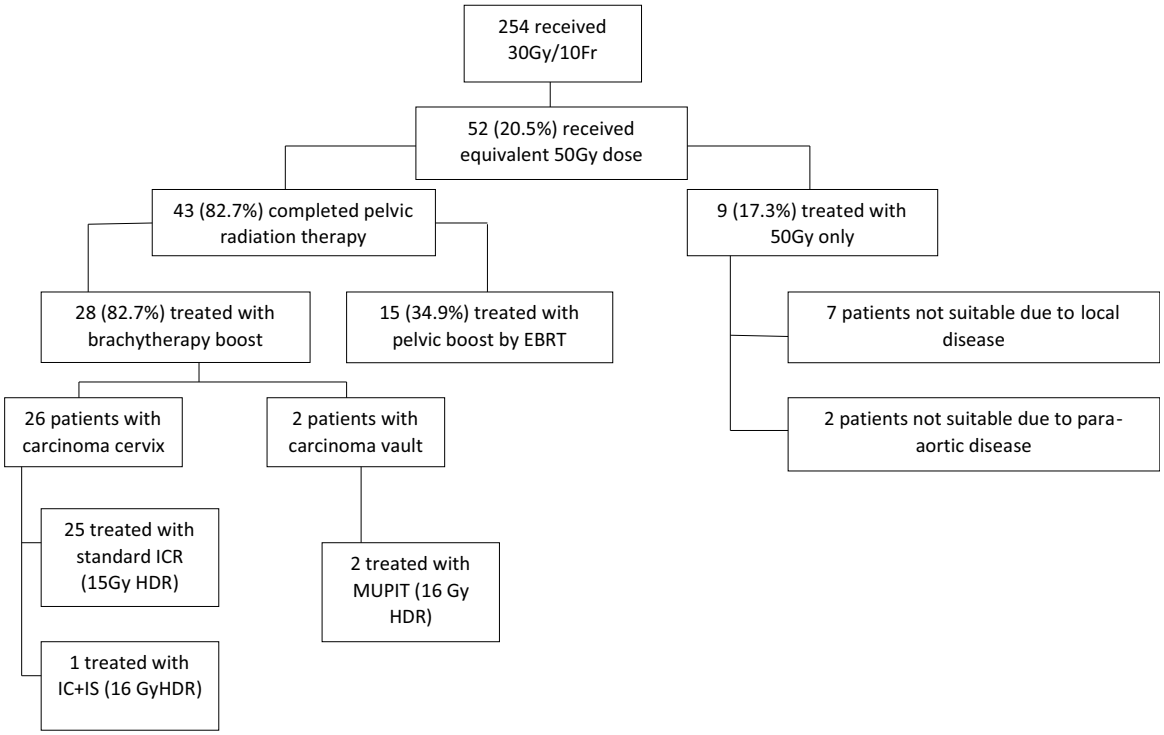

Figure 1: Schematic representation of treated patients

assessed according to the RTOG scale. Statistical analysis was performed using SPSS for Windows and Kaplan Meier method was used for calculating the survival.[6]

Results

A total of 254 patients of locally advanced carcinoma cervix patient were initially treated with hypofractionated palliative external beam radiation therapy with dose of 30 Gy in 10 fractions over a period of 2 weeks. Fifty-two patients out of 254 (20.5%) were considered for additional external pelvic radiotherapy of 20 Gy in 10 fractions, in view of more than partial response. A total of equivalent of 50Gy was received by these 52 patients. Forty-three of 52 (82.7%) patients were considered eligible for completion of pelvic radiation therapy with external beam radiotherapy and/or brachytherapy and 9 (17.3%) patients received external beam radiation therapy up to 50 Gy only due to no response. Twenty-eight of 43 (65.1%) patients completed pelvic radiation therapy by external pelvic radiation therapy boosted by brachytherapy, while 15 of 43 patients (34.9%) completed pelvic radiotherapy dose equivalent to 60 Gy.

Survival

Forty-three patients were assessed for further follow-up. At four weeks after completion of radiotherapy, 32 patients out of 43 had completely relieved bleeding per vaginum, 21 patients were relieved of white discharge per vaginum and symptomatic relief in abdominal pain was seen in 26 patients. Sixteen (37.2%) patients achieved complete response, 8 (18.6%) patients had more than partial response, 3 (7%) patients had less than partial response and 16 (37.2%) patients had stable clinical disease.

At 3 months, 3 patients were lost to follow-up and so, 40 patients were assessed for further follow-up. Complete locoregional response was achieved in 25 of 40 patients (62.5%) but 1 patient eventually developed bone metastasis, so complete response was achieved in 24 (60%) patients, while 12 patients (30%) had stable central disease and 3 patients had local progression of disease.

Median follow up was 19 months (range 8-48 months). Ten (25%) had subjective symptomatic response initially and eventually these patients developed central progressive disease and 11 (27.5%) had progressive disease involving bone metastases (2), para-aortic nodal disease (3), vesico-vaginal fistula (1), rectovaginal fistula (1), liver metastases (1) and loco-regional progressive disease (3). Nineteen (47.5%) of 40 patients had complete response. Out of 5 patients with distant metastasis 2 patients had loco-regional complete response, so 21(52.5%) had loco-regional response. Out of these 19 patients who achieved complete response till the last follow up, 16 had achieved brachytherapy boost and 3 patients received external pelvic boost.

Mean disease free survival for entire cohort was 17.5 months. Patients receiving brachytherapy had disease free survival of 15 months and those who

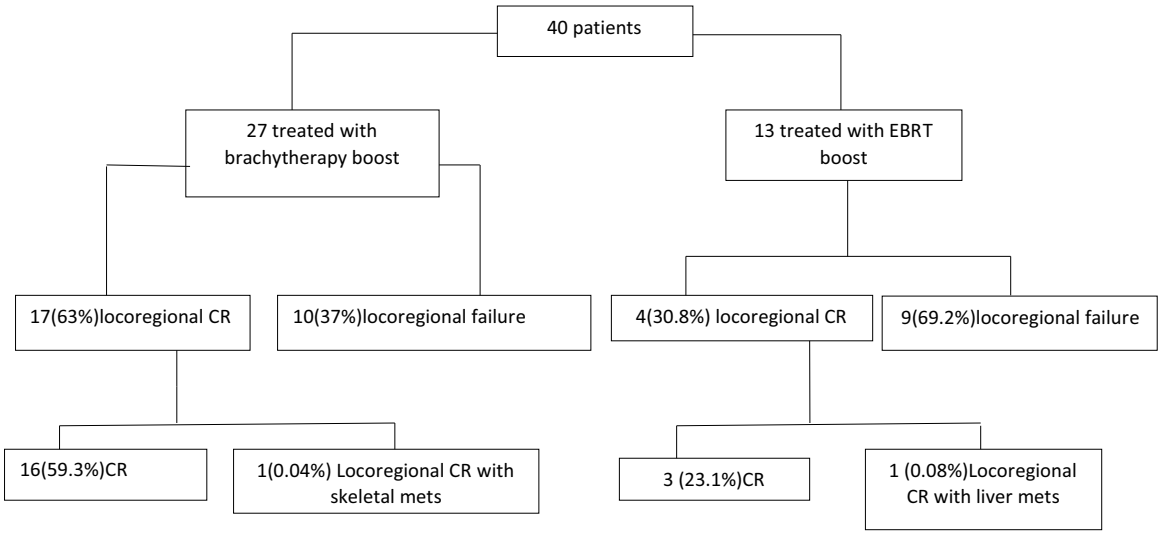

Figure 2: Treatment response in each arm

did not receive brachytherapy but completed pelvic dose by external beam radiotherapy up to total dose of 60Gy had disease free survival of 19 months($p > 0.05$). Other factors like age, stage and use of chemotherapy had no impact on DFS ($P > 0.05$).

Acute Reactions

Twenty of 43 (47%) patients developed grade I skin reaction, 6 patients (14%) had grade II skin reaction and 1 patient had grade III skin reaction in the form of confluent moist desquamation and were treated with gentian violet 1%. All these patients were managed conservatively. Thirty five of 43 patients (81.4%) developed acute gastrointestinal reaction during radiotherapy. Out of these 7 patients had grade I reaction, 23(53.5%) patients had grade II reaction, 4 patients had grade III reactions and 1 patient had grade IV reaction. They were treated with anti-motility agents and plenty of oral fluids orally. Two patients required patient admission and use of parenteral fluids and antibiotics but all the patients completed the planned radiation therapy. Two of 43 patients developed grade I proctitis, 34 (79.1%) patients developed grade II proctitis, and 7 (16.3%) patients developed grade III proctitis. These patients were managed successfully with anti-inflammatory agents. Sixteen of 43 patients (37.2%) developed genitourinary complications during the treatment. Out of these patients 9 patients had grade I and 7 patients developed grade II reactions. All were treated with plenty of oral fluids and managed conservatively. (Table 2)

Table 2: Acute reactions during the course of Radio-chemotherapy

Site	Grade I	Grade II	Grade III	Grade IV	Total
Skin	20	6	1	-	27
Gastointestinal	7	23	4	1	35
Rectal	2	34	7	-	43
Genito-urinary	9	7	-	-	16

Late Reactions

Five (12.5 %) of 40 patients developed late rectal reactions. Two patients had grade I, 2 patients had grade II and 1 patient had grade III rectal toxicities. The mean duration of symptoms was 2 months with a range of 1-5 months. Proctoscopy revealed telengiectasia in the rectum and all these patients were initially treated with anti-inflammatory, purgative, oral hemostatic drugs and use of liquid diet. Non-responders were treated with sucralfate enema and steroid retention enema and no patient required colostomy. Late bladder reactions were observed in 2 of 40 (5 %) patients. One patient had grade II and 1 patient had grade III cystitis. All the patients were managed conservatively. Late vaginal complication

Table 3: Late reactions in organs at risk

Site	Grade I	Grade II	Grade III	Grade IV	Total
Bladder	-	1	1	-	2
Rectum	2	2	1	-	5
Vagina	-	34	7	-	43

was observed in 16 of 40 patients (40%). Four of 16 patients had vaginal synechia, 3 patients had vaginal narrowing, while 9 patients had vaginal stenosis and 7 of 9 patients had vulval edema along with vaginal stenosis.(Table 3)

Discussion

Carcinoma cervix is one of the most common gynecological malignancies in India but large number of patients present at late stages. Patients with carcinoma cervix with extensive local disease at presentation with fair to poor general condition and those who cannot withstand 5 weeks of standard treatment were considered for hypofractionated irradiation.

Radiation therapy is an effective palliative treatment modality for patients with locally advanced cervical carcinoma. Although no standard regime has been established, usually short course hypofractionated schedules are preferred where local disease is extensive and unsuitable for conventional fractionation. Since the expected survival period is poor in this group of patients, the focus of treatment is on symptomatic relief and survival is rarely studied. Some of these patients might show good subjective and objective improvement with palliative irradiation. Those patients who responded with near complete or more than partial response can be considered for full dose of radiation to pelvic region with a curative intent for a possibility of long term survival.

Review of literature suggests several high-dose fractionation schedules with external beam which have been used for palliation purpose. Meoz and coworkers described satisfactory palliation with single doses of 1000cGy combined with misonidazole, delivered every 3 to 6 weeks for a total of 3000 cGy although complications in the long-term survivors were relatively high (15%).[7] Spanos and associates reported on a phase II study of daily multifraction split-course irradiation in 142 patients (50% with recurrent or metastatic disease in the pelvis only and 50% with associated extra-pelvic metastases).[8]

Irradiation consisted of 370 cGy per fraction given twice daily for two consecutive days, repeated at 3- to 6-week intervals for a total of three courses, aiming to a total tumor dose of 4440 cGy, the dose was based on linear quadratic equation considerations of acute and late effects assuming α/β ratio of 10 for acute and 4 for late effects. Occasionally this regimen was combined with an intracavitary insertion (4500 mgh), blocking the midline for the last 1440cGy external dose. Eighty-three (59%) of the 142 evaluable patients received three courses of radiation; 29 (20%) received only one course. Complete response was noted in 15 (10.5%) of the treated patients and partial response in 32 (22.5%). For patients completing three courses of irradiation, the complete response plus partial response rate was 45%. Twenty-seven patients survived more than 1 year and only two cases of grade 3 toxicity (lower GI) were recorded. There was a significant decrease in the incidence of radiation toxicity reported in this study as compared to study done by Spanos and Meoz et al[9] in 46 patients, which reported 11% grade III toxicity and 19% Grade IV toxicity. Protocol was treating with 1000 cGy fractions given every 4 weeks for a total of 3000 cGy combined with misonidazole (4 g/m2 administered 4 to 6 hours before irradiation).The RTOG multiple daily fraction study has been expanded to a phase III protocol randomizing between a short (2 week) or a longer (4 week) rest period between the split course of irradiation.[10] In present studies 15 of 43 patients were treated with 30 Gy in 10 fractions, followed by 20 Gy in 10 fractions with gap correction of 2-3 weeks between two fractionation schedules and after 2-3 weeks those patients who were not suitable for brachytherapy were treated with 10 Gy in 5 fractions to a total dose of 60 Gy delivered at 2 Gy per fraction regimen.

Four of 13 (30.8%) patients had loco-regional complete response till last follow-up, while 2 patients were lost to follow-up. Partial response was noted in 5 (38.5%) patients without grade III or IV toxicities. Thus, complete plus partial response rate was 69.2% with acceptable toxicities. Occasionally, brachytherapy procedures cannot be performed because of medical reasons, unusual anatomic configuration of the pelvis, extensive local lesion and the inability to identify the cervical canal. These patients can be treated with higher doses of external-beam irradiation alone. Castro and co-workers reported 118 patients with invasive cervical carcinoma treated with 5000-6000 cGy delivered to the whole pelvis with four-field box technique and additional doses with reduced AP-PA portals to complete the 7000cGy tumor dose.[11] No pelvic tumor control was obtained below 5000 cGy, but disease control and survival were significantly enhanced with higher doses. The complications, however, also increased. Ulmer and Frischbier[12] treated 150 patients up to 8000 cGy to central pelvis and 6000 cGy to pelvic wall in 6 weeks by rotational technique with external beam irradiation alone. They reported 80% tumor control and 6 patients developed grade II and 6 patients developed grade III complications. Similar study by Akine and associates treated 104 of 2701 patients with carcinoma of the uterine cervix with external beam irradiation alone by AP-PA or four-field box techniques up to 5000 cGy to the whole pelvis followed by additional doses with reduced portals to deliver a total of 6080 cGy in 6 weeks, 7230 cGy in 7.5 weeks, and 8050 cGy in 8 weeks with a daily dose of 190 cGy or 200 cGy.[13] The local tumor control rate was 27% for stage II, 19% for stage III, and 15% for stage

Table 4: Comparison of similar studies done in past with present study

Incidence of Pelvic Failures				
Author	**Stage**	**External Beam Only**	**External Beam and Intracavitary**	**p-Value**
Hanks et al[18]	III	33/38 (86%)	55/109 (50%)	0.0002
Montana et al[19]	III	14/35 (40%)	12/37 (32%)	0.6725
Coia et al[15]	I,II,III	53%	22%	<0.01
Present study	III,IV	9/13 (69%)	10/27 (37%)	>0.05

IVA disease with increased late complications. Some of the patients required surgical treatment for managing complications. In our study, 13 patients, who were not suitable for brachytherapy boost, were treated by external pelvic boost to a total dose of 60 Gy. 30.8% achieved complete locoregional response in stage IIIB-IVA with acceptable toxicity.

Coia and co-workers, in an analysis of 565 patients with various stages of cervical carcinoma treated in the Patterns of Care Study, reported 4-year survival rate as 67% and 36% and pelvic tumor control rate as 78% and 47% in patients who received brachytherapy and those who had no intracavitary applications respectively.[14] The present study reported complete response rate of 59.3% (16 of 27 patients) and 23.1% (3 of 13 patients) and loco-regional control rate of 63% (17 of 27) and 30.8% (4 of 13) in patients who received brachytherapy compared with those who had no brachytherapy applications, but treated with external boost instead, respectively.

Hanks and associates[15] and Montana[16] reported a higher incidence of central pelvic recurrences in patients with stage III cervical carcinoma treated with external beam irradiation alone than in patients receiving brachytherapy in addition to external beam irradiation. This is in accordance with the results of this study, in which patients who received brachytherapy boost had locoregional failure rate of 37% (10 of 27) and those receiving external pelvic boost had loco-regional failure rate 69.2% (9 of 13). Table 4 showing the comparison of various studies is shown below.

Mary et al. and associates treated 62 women with advanced carcinoma cervix IIIB with standard pelvic portals to a total dose of 39Gy in 13 fractions followed by intracavitary brachytherapy and 48 patients completed the planned treatment.[17] 5-year disease free survival was 59% and the overall survival was 50% at the mean follow-up of 40 months. 44% (21) developed acute gastrointestinal toxicity of which 5 patients had grade III and one patient had grade IV reaction. 21% patients developed acute genitourinary complications. 27% (13) had late rectal reactions of which 5 had grade III reactions and 20% had late bladder complications. Another similar study done by Sharma et al had shown 13.7% (41 of 300) locally advanced cervical carcinoma treated with initial short course hypofractionated palliative external beam radiotherapy (8-30 Gy in 1-10 fractions) become eligible for curative RT.[18] 13.7% (41) patients showed >50% of disease regression after palliative radiotherapy treated up to total dose of 50 Gy employing 2 Gy per fraction regime. Thirty of 41 patients underwent subsequent intracavitary brachytherapy (7 Gy in 3 fraction to point A) was performed if the patients were found suitable. After median follow-up was 17 months, 19 patients had progressive disease, 7 had partial response and 15 had complete response to treatment. Patients receiving intracavitary brachytherapy had better disease-free survival (20 months vs 7 months; p = 0.002) as compared to those who did not receive it. Grade 3 or more late rectal and bladder toxicity was seen in 4

Table 5: Comparison of similar studies with the present study

Author	**No. of pts.**	**Total dose**	**Treatment algorithm**	**Follow-up (months)**	**Response**	**Acute toxicity**	**Late toxicity**
Muckadenet al.[17]	62	39Gy/13 # f/b ICR	-	Mean- 40	5-yr DFS-59% OS- 50%	GI-44% GU-21%	Bladder-20% Rectal- 27%
Sharma et al.[18]	300	30Gy/110# F/b response evaluation - 50Gy given f/b ICR	13.7% pts received upto 50Gy and 73.2% pts. had ICR	Median-17	CR -15 pts. PR -7 pts. Progression-19 pts. ICR DFS- 20 months NO ICR- 7 months	-	Bladder-6.7% Rectal -13%
Present Study	254	30 Gy f/b 20 Gy then either brachy or pelvic external boost	20.5% received 50 Gy and 82.6% completed treatment, 65% pts ICR	Mean-19	21 of 40 locoregional CR Brachy DFS-15 months	GI- 81.4% GU- 37.2%	Bladder- 5% Rectal-12.5%

patients and 2 patients respectively. A comparison of 3 studies of similar nature done in past, including the present study is presented in table 5.

Conclusion

In our study, about 20.5% of locally advanced cervical carcinoma patients treated with initial short course hypofractionated palliative external beam radiation therapy (30Gy/10Fr/2weeks) became eligible for curative radiation therapy. Patients, who responded well to therapy and had near complete disease regression after completion of hypofractionated radiation therapy, were considered for curative radiation therapy to improve the disease free and overall survival. These patients exhibited a reasonably good survival with acceptable delayed toxicity. Use of brachytherapy is encouraged in such patients since it leads to improved survival in those patients whose loco-regional disease has shown good response with initial external radiotherapy. However, in that subset of patients with loco-regional disease up to lateral pelvic wall even after equivalent 50Gy, which could not be covered with tandem and ovoids can be treated with small pelvic field to incorporate the disease site.

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Prognostic Significance of TP Expression in Tumor Cells and Associated Stromal Cells in Patients with Colorectal Cancer

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Summary

Thymidine phosphorylase (TP) plays essential role in the nucleotide salvage pathway. TP has been described as a promoter of tumor growth and metastasis by inhibiting apoptosis and induction of angiogenesis. Many studies showed association of TP expression with response to 5-FU based therapy and prognosis in colorectal cancer (CRC) patients. Hence, the study aimed to evaluate TP protein expression in CRC patients and further its correlation with clinicopathological parameters and prognosis.TP protein expression was examined in a total 143 primary CRC patients by immunohistochemistry. Statistical analysis was performed using SPSS software. TP showed cytoplasmic and/or nuclear staining in tumor cells. It also showed expression in associated stromal cells. No significant association of TP protein expression was observed with relapse-free survival (RFS) or overall survival (OS) in total patients. While, in early stage patients, a trend of reduced RFS and OS was observed in patients with low stromal TP expression (P=0.085) and low nuclear TP expression (P=0.086), respectively as compared to their respective counterparts. Further, a positive intercorrelation of cytoplasmic TP expression was noted with nuclear TP (P<0.001) and stromal TP expressions (P=0.089). Thus TP protein expression in tumor cells might have impact on stromal cells in tumor microenvironment and it would be helpful in predicting prognosis in early stages of CRC patients.

Keywords: Thymidine phosphorylase, immunohistochemistry, prognosis, colorectal cancer

Introduction

Thymidine phosphorylase (TP) is involved in pyrimidine metabolism in the cell. TP gene, located on chromosome 22q13.33,[1] encodes a protein that catalyzes the phosphorylation of thymidine or deoxyuridin to thymine or uracil and also forms a catalytic product 2-deoxyribose-1-phosphate. Thus, it is essential for the nucleotide salvage pathway that recovers pyrimidine nucleosides formed during RNA or DNA degradation.[2] TP and its catalytic product, 2-deoxy-D-ribose-1 phosphate act as angiogenic factors via induction of endothelial cell migration and tube formation.[3] Thus, TP is also known as platelet-derived endothelial cell growth factor (PD-ECGF).[4] Moreover, it seems to impart resistance to apoptosis during hypoxia.[3] The role of TP has been described as a promoter of tumor growth and metastasis by inhibiting apoptosis and induction of angiogenesis.[5]

On the other side, TP also plays an important role in 5-Fluorouracil (5-FU) metabolism by catalyzing the conversion of 5-FU into 5-fluoro-2-deoxyuridine (5-FUDR), which is the first step of 5-FU activation in tumor cells, consequently leading to inhibition of DNA synthesis.2 Moreover, TP is also involved in the conversion of capecitabine to 5-FU. Capecitabine is transformed to FU via three-step enzymatic cascade. The final step, which is conversion of 5-deoxy-5-fluorouridine to FU, is catalyzed by TP.[6,7]

Thus, TP is having a dual function in predicting clinical outcome of patients. Its neoangiogenetic activity in tumors may promote tumor growth and thus may lead to poor prognosis, while it may predict good prognosis because of its role in activation of 5-FU. Several studies demonstrated the association of low TP expression with better outcome and improved response to 5-FU therapy in CRC patients.[8-10] Moreover, several reports have showed the role of high TP expression as a predictor of better prognosis and response to capecitabine therapy in CRC[11] and gastric cancer.[12] Moreover, TP expression is observed not only in tumor epithelial cells, but it also seems to be expressed in the interstitia by stromal cells such as macrophages, monocytes and fibroblasts, as well as in endothelial cells.[13] Han et al showed the association of high tumor TP and low stromal TP expressions with better outcome and response to capecitabine/docetaxel chemotherapy in NSCLC.[14] Further, Mitselou et al in CRC showed that high cytoplasmic TP expression in tumors was associated with better survival.[15] These contradictory reports suggest the differential role of TP in tumor cells than stroma. Hence, present study evaluated immunohistochemical localization of TP and further its association with clinicopathological parameters and prognosis in CRC patients.

Materials and Methods

Patients

A total of 143 untreated patients with histologically confirmed CRC were enrolled in this study. Written consent of the patients who underwent surgery at the Department of Surgical Oncology was

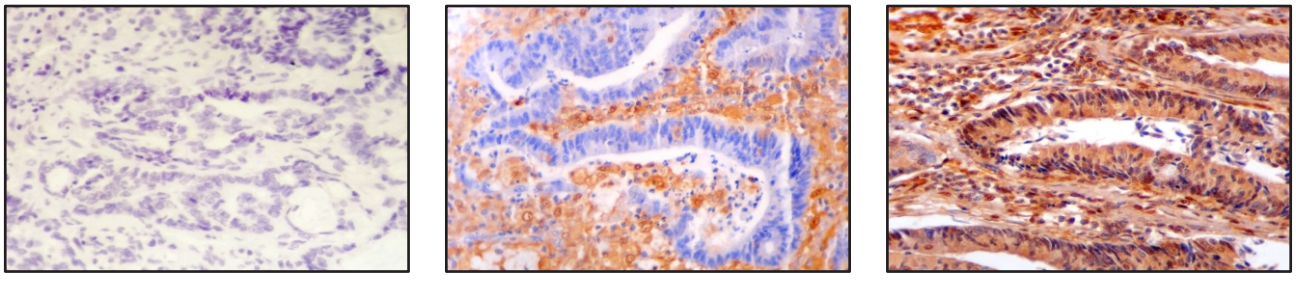
Table 1: Treatment and survival analysis of CRC patients

Characteristics	N (%)
Treatment (N=143)	
Surgery alone	24 (17)
Surgery+Chemotherapy	67 (47)
Surgery+Chemotherapy+Radiotherapy	46 (32)
Surgery+Radiotherapy	06 (04)
Chemotherapeutic treatment (N=113)	5
5-FU alone (5-FU intravenous or oral capecitabine)	66 (58)
5-FU+oxaliplatin [5-FU+OX (FOLFOX or CAPOX)]	47 (42)
Recurrence/Metastasis (N=101)	
Absent	82 (81)
Present	19 (19)
Disease status (N=114)	
Alive	86 (75)
Dead	28 (25)
Adjuvant treatment (RFS: N=83)	
Single drug: 5-FU	55 (66)
Combined drug: 5-FU+OX	28 (34)
Adjuvant treatment (OS: N=94)	
Single drug: 5-FU	60 (64)
Combined drug: 5-FU+OX	34 (36)

obtained, prior to collection of paraffin-embedded tumor tissue blocks. The detailed clinical history (age, gender, anatomic site, TNM stage, hisopathological findings) was noted from the case files maintained at the Medical Record Department of the institute. Pathologic staging was performed according to TNM classification with World Health Organization (WHO) Grading System. Sixteen percent of patients had stage I, 45% had stage II, 36% had stage III and only 3% had stage IV disease. Primary treatment offered to all patients was surgery or surgery followed by adjuvant chemotherapy and/or radiotherapy. Out of 143, 113 patients were treated with chemotherapeutic regimen. The main chemotherapeutic treatment included were 5-FU and leucovorin, oral Capecitabine, or in combination with Oxaliplatin. The patients were followed for a minimum period of 36 months or until death within that period. Complete follow-up details were obtained in 114 CRC patients and were included for overall survival (OS) analysis, out of which 25% of patients died within the follow-up period. Out of 114 patients, 13 patients who died due to persistent disease were not included for relapse-free survival (RFS) analysis. Therefore, 101 patients were evaluated for RFS. Survival analysis was also performed in the subgroups of patients with early stage and advanced stage according to disease stage; as well as in the subgroups of colon cancer and rectal cancer patients according to tumor site. Further, to evaluate the predictive efficacy of TP on survival according to adjuvant treatment, patients were subgrouped into those treated with 5-FU alone and those treated with combined 5-FU plus oxaliplatin (5-FU+OX) irrespective of RT. In relation to adjuvant treatment, out of 101, 83 patients were included for RFS; and out of 114, 94 patients were included for OS analysis (Table 1).

TP protein expression by immunohistochemistry

Immunohistochemistry was performed to detect TP protein expression in primary tumors of CRC patients. Briefly, 4 µm thick sections were cut from the formalin fixed paraffin embedded tumor tissue blocks. The immunohistochemical staining was carried out using primary mouse monoclonal TP antibody (P-GF.44C: GTX23151, GeneTex, Inc.; dilution- 1:100) and Mouse and Rabbit specific HRP/DAB (ABC) Detection IHC kit from Abcam, as per manufacturer's protocol recommendations. Antigenicity was retrieved by heating the tissue sections in 10mM tri-sodium citrate buffer (pH-6.0) solution for 20 minutes in a pressure cooker prior to



(a) (b) (c)

Figure 1: Representative photomicrographs showing staining of TP (40x)
(a)Negative staining of TP in rectal adenocarcinoma
(b)Cytoplasmic and nuclear in tumor cells and stromal staining of TP in colon adenocarcinoma
(c)Stromal staining of TP in rectal adenocarcinoma

application of the primary antibody. All sections were scored independently by two independent researchers in a blinded fashion. The staining intensities and the percentage of positive cells were separately assessed for all primary tumor tissues (N=143). Modified histoscore (H-score) method was used to combine the staining intensity and percentage of TP expressing cells.[16] More specifically, the staining intensity was assessed with a four-point scale from negative (0), weak (1), moderate (2) and strong intensity (3). The extent of the staining was expressed as percentage of positive cells (0-100%) by 10% intervals. The final histoscore was counted by multiplying the intensity level by percentage of positive cells resulting in a value between 0 and 300.

Statistical analysis

The data was statistically analyzed using the Statistical Package for Social Sciences (SPSS) software version 17 (SPSS Inc., USA). Two-tailed χ^2 test was used to assess the associations of TP protein expression with clinicopathological parameters. Correlation between two parameters was calculated using Spearman's correlation coefficient (r) method. RFS and OS were calculated using Kaplan-Meier estimates and the difference in survival curve was calculated using Log rank test. P value ≤ 0.05 was considered to be significant.

Results

TP exhibited cytoplasmic and/or nuclear expression in tumor cells. It also showed stromal expression predominantly in fibroblasts and inflammatory cells. The total immunoreactivity of TP in tumor cells (cytoplasmic/nuclear) and/or stroma was 96% (137/143) of total CRC patients. For statistical evaluation, cytoplasmic, nuclear and stromal expressions were scored independently and compared separately. Cytoplasmic TP expression in tumor cells was observed in 41% (58/143) of patients, nuclear TP expression in tumor cells was present in 22% (31/143) of patients. However, stromal TP immunoreactivity was observed in majority of the patients (91%, 130/143). The median H-score value of each cytoplasmic, nuclear and stromal TP expression was used as cut-off value to divide the patients into low (<median H-score) and high (≥ median H-score) expression groups, respectively. Figure 1 shows the representative photomicrographs for TP staining.

Correlation of TP protein expression with clinicopathological parameters

A significant higher cytoplasmic expression was observed in adenocarcinoma patients as compared to mucinous/signet ring cell carcinoma patients (P=0.018), while nuclear TP expression was found to be significantly higher in colon cancer patients as compared to rectal cancer patients (P=0.041). Additionally, a significant higher stromal TP expression was observed in patients with negative nodal status (P=0.031), early stage (P=0.028) and adenocarcinoma (P=0.004) as compared to their respective counterparts. Moreover, a trend of higher cytoplasmic (P=0.058) and nuclear TP expression (P=0.055) as well as a trend of lower stromal TP expression (P=0.087) was noted in patients with older age group as compared to younger age group. (Table 2).

Association of TP protein expression with survival

In total patients, Kaplan-Meier univariate survival analysis showed that TP protein expression was not significantly associated with RFS or OS. However, when patients were subgrouped according to tumor stage, in early stage patients, a trend of reduced RFS was observed in patients with low stromal TP expression (21%, 5/24) as compared to those with high stromal TP expression (7%, 3/43; Log rank=2.960, df=1, P=0.085) (Figure 2). Similarly, a trend of reduced OS observed in the patients having low nuclear TP expression (19%, 11/58) as compared to those with high nuclear TP expression (0%, 0/14; Log rank=2.942, df=1, P=0.086) (Figure 3). Additionally, no significant difference in the incidence of disease relapse or death was found in the subgroup of advanced stage, colon cancer and rectal cancer patients. Further, TP protein expression was not significantly associated with RFS or OS in the subgroup of patients treated with 5-FU alone or those treated with 5-FU plus oxaliplatin based treatment (data not shown).

Intercorrelation of TP cytoplasmic, nuclear and stromal TP expression

Spearman's correlation analysis revealed that cytoplasmic TP expression was significantly positively correlated with nuclear TP expression (r=+0.602, P<0.001). Further, a trend of positive correlation of cytoplasmic TP expression was noted with stromal TP expression (r=+0.143, P=0.089). However, no significant association was observed between nuclear TP and stromal TP expression (r=+0.062, P=0.464).

Discussion

In current study, several patterns of TP imunoreactivity could be distinguished in primary tumors of CRC patients. Predominant stromal pattern was observed in 91% of patients; along with cytoplasmic (41%) and nuclear (22%) immunoreactivity in tumor cells. In stroma, TP was predominantly expressed in fibroblasts and inflammatory cells. Accordingly, van Triest et al reported that TP immunoreactivity was observed in

Table 2: Correlation of TP protein expression with clinicopathological parameters in CRC patients (N=143)

Characteristics	N	TP protein expression					
		Tumor				Stromal	
		Cytoplasmic		Nuclear			
		Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)
Age (years)							
<52	68	46 (68)	22 (32)	58 (85)	10 (15)	23 (34)	45 (66)
>52	75	39 (52)	36 (48)	54 (72)	21 (28)	36 (48)	39 (52)
		χ^2=3.622, r=+0.159, **P=0.058**		χ^2=3.712, r=+0.161, **P=0.055**		χ^2=2.957, r=-0.144, **P=0.087**	
Gender							
Female	58	35 (60)	23 (40)	44 (76)	14 (24)	23 (40)	35 (60)
Male	85	50 (59)	35 (41)	68 (80)	17 (20)	36 (42)	49 (58)
		χ^2=0.033, r=+0.015, **P=0.857**		χ^2=0.348, r=-0.049, **P=0.559**		χ^2=0.104, r=-0.027, **P=0.750**	
Tumor site							
Colon	69	37 (54)	32 (46)	49 (71)	20 (29)	25 (36)	44 (64)
Rectum	74	48 (65)	26 (35)	63 (85)	11 (15)	34 (46)	40 (54)
		χ^2=1.872, r=-0.114, **P=0.174**		χ^2=4.193, r=-0.171, **P=0.041**		χ^2=1.390, r=-0.099, **P=0.241**	
Tumor size							
T2	36	23 (64)	13 (36)	31 (86)	05 (14)	13 (36)	23 (64)
T3	95	53 (56)	42 (44)	71 (75)	24 (25)	39 (41)	56 (59)
T4	12	09 (75)	03 (25)	10 (83)	02 (17)	07 (58)	05 (42)
		χ^2=2.026, r=+0.002, **P=0.980**		χ^2=2.183, r=+0.075, **P=0.374**		χ^2=1.839, r=-0.096, **P=0.256**	
Nodal status							
Negative	90	55 (61)	35 (39)	74 (82)	16 (18)	31 (34)	59 (66)
Positive	53	30 (57)	23 (43)	38 (72)	15 (28)	28 (53)	25 (47)
		χ^2=0.281, r=+0.044, **P=0.599**		χ^2=2.176, r=+0.123, **P=0.142**		χ^2=4.652, r=-0.180, **P=0.031**	
TNM stage							
Early (I+II)	88	54 (61)	34 (39)	72 (82)	16 (18)	30 (34)	58 (66)
Advanced (III+IV)	55	31 (56)	24 (44)	40 (73)	15 (27)	29 (53)	26 (47)
		χ^2=0.351, r=+0.050, **P=0.557**		χ^2=1.647, r=+0.107, **P=0.202**		χ^2=4.850, r=-0.184, **P=0.028**	
Tumor differentiation							
Well	29	17 (59)	12 (41)	22 (76)	07 (24)	12 (41)	17 (59)
Moderate/Poor	114	68 (60)	46 (40)	90 (79)	24 (21)	47 (41)	67 (59)
		χ^2=0.010, r=-0.008, **P=0.920**		χ^2=0.130, r=-0.030, **P=0.721**		χ^2=0.000, r=+0.001, **P=0.988**	
Histologic type							
Adenocarcinoma	103	55 (53)	48 (47)	78 (76)	25 (24)	35 (34)	68 (66)
Mucinous/Signet ring cell	40	30 (75)	10 (25)	34 (85)	06 (15)	24 (60)	16 (40)
		χ^2=5.577, r=-0.197, **P=0.018**		χ^2=1.459, r=-0.101, **P=0.230**		χ^2=8.048, r=-0.237, **P=0.004**	

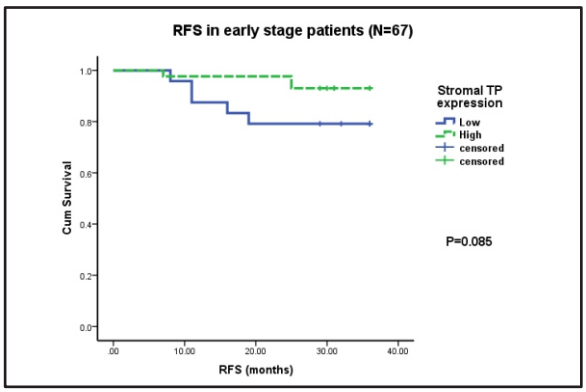


Figure 2: Kaplan-Meier survival curve for RFS in relation to stromal TP protein expression in early stage patients (N=67)

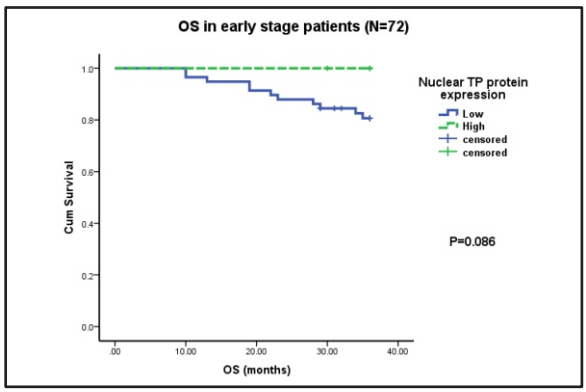


Figure 3: Kaplan-Meier survival curve for OS in relation to nuclear TP protein expression in early stage patients (N=72)

44% of the tumor epithelial cells with a cytoplasmic or perinuclear staining pattern, while staining of the infiltrating cells (mostly fibroblast and plasma cells) was observed in 94% of the samples in CRC.[9] Another study in CRC by Mitselou et al showed cytoplasmic and nuclear TP expression in 89.8% and 43.3% of tumor cells, respectively, whereas stromal TP expression was observed in all 100% of patients.[15] On the other side, high tumor TP expression and high stromal TP expression were observed in 38% and 49% of the patients, respectively in advanced CRC.[17] Liakakos et al reported that 31.8% of patients showed cytoplasmic and nuclear staining in tumor cells and 60.6% of patients showed positive expression in stromal fibroblasts in gastric cancer patients.[18] Similarly, in breast cancer patients, TP expression was observed in 43.3% of cancer cells, while 70% of patients showed TP positive inflammatory cells in cancer tissue.[19] In NSCLC, cytoplasmic expression and in some cases both cytoplasmic and nuclear staining was observed in all 100% of patients with high expression in 43% of patients, while stromal TP expression was observed in 93% of patients with high expression in 53% of patients.14 On the other side, TP expression was observed to be high in 83% of infiltrating cells (macrophages and lymphocytes) in colon cancer patients, whereas TP staining was detected in only 5% of tumor epithelium.[20] Similarly in patients with gastric cancer, only 10% of the tumors were positive for TP, whereas 54% of the infiltrating cells (predominantly macrophages) showed TP expression.[21] Yang et al reported TP immunoreactivity in tumor cells with cytoplasmic and/or nuclear staining pattern and in tumor-associated macrophages with total positive TP expression observed in 78.6% of breast cancer patients.[22] In present study, the high incidence of stromal TP expression as compared to TP expression (cytoplasmic and nuclear) in tumor cells may partly be explained due to angiogenic role of TP in tumor microenvironment. Additionally, it may suggest that tumor associated stromal (TAS) cells might be the main source of overall TP levels in the tumor tissue.

In relation to clinicopathological parameters, present study revealed that higher cytoplasmic and nuclear TP expressions in tumor cells were associated with older age group. Moreover, cytoplasmic TP and stromal TP expressions were significantly higher in adenocarcinoma patients as compared to mucinous/signet ring cell adenocarcinoma; and, high stromal TP expression was associated with younger age and early stage patients. Also an association of higher nuclear TP expression in tumor cells was noted in patients with colon cancer as compared to patients with rectal cancer. Contrary to our results, Lindskog et al reported that rectal cancer patients exhibited higher tumor TP expression as compared to colon cancer in metastatic CRC.[3] Similarly, Lindskog et al in stage III CRC patients showed that patients with rectal cancer had significantly higher TP expression in mucosa and tumors compared with patients having colon cancer.[23] Takebayashi et al in CRC found that positive TP protein expression was associated with more advanced Dukes' stage, as well as with lymph node metastasis and extensive angiogenesis.[24] In addition, Bai et al described that TP positivity was sig¬nificantly greater in CRC patients with lymph node metastasis (P=0.013).[25] On the other side, no significant association of TP expression was observed with clinicopathological parameters in CRC.[10,26] Further, no correlation of TP intratumoral gene expression was observed with the clinicopathological parameters in CRC.[27] Besides CRC, in gastric cancer, Saito et al also reported no significant association of TP expression with clinicopathological parameters.[28] Han et al in NSCLC observed that TP expression in tumor cells and stroma was not associated with tumor histology, stage, or gender.[14] Further, in breast cancer, high TP expression was associated with lower tumor grade and negative p53 status.[22]

Since up and downregulation of TP expression plays a significant role in initiation and

growth of tumors affecting prognosis and therapeutic indices, present study explored the clinical utility of TP protein expression and observed no significant association of tumor TP (cytoplasmic and nuclear) or stromal TP expression with prognosis in total patients. However, in the subgroup of early stage patients, low stromal and low tumor nuclear TP expressions were associated with worse RFS and OS, respectively. In accordance with current results, low tumor TP expression correlated with poor prognosis as compared to high tumor TP expression in metastatic CRC.[3] Further, similar to present results, Yasuno et al in advanced CRC patients showed that high stromal TP expression was associated with a favorable prognosis in the group of patients who underwent curative resection, and also in the group receiving adjuvant 5-FU derivatives.[17] High TP expression was related to longer survival and increased response in CRC patients treated with capecitabine/oxaliplatin based therapy.[11] Ogawa et al showed association of low TP intratumoral gene expression with worse outcome, but particularly in the adjuvantly treated CRC patients with stage III disease.[27] Contrarily, high tumor TP levels have been shown to correlate with unfavourable clinical outcome,[9,24] and poor response to 5-FU 8 in CRC patients. Moreover, Bai et al demonstrated that overall clinical outcome and efficacy of 5-FU based chemotherapy were relatively poor in CRC patients with high TP expression levels.[25] Soong et al[10] demonstrated that low TP protein expression had no prognostic value in either stage II or stage III CRC patients when treated by surgery alone, whereas, it was associated with a trend for better survival in stage III CRC treated with 5-FU, explaining that TP expression might have different prognostic values depending on whether patients were treated with or without 5-FU chemotherapy. Further, Derwinger et al [13] showed that chemotherapeutic treatment may cause reduction in TP gene expression, whereas adjuvant radiotherapy causes a significant increase in TP expression in rectal cancer patients. Several studies have also confirmed the prognostic role of TP in other malignancies such as transitional cell carcinoma of the bladder, cervical cancer, and gastric carcinoma.[29] In gastric cancer patients, low TP expression was associated with poor prognosis[28] and lower response to capecitabine therapy.[30] Further, in breast cancer, high TP expression was significantly associated with better prognosis.[31] In advanced NSCLC, patients with high tumor TP expression tended to have better prognosis, whereas those with high stromal TP expression tended to have worse prognosis,[14] which is contrary to present results where both high tumor nuclear TP and high stromal TP expressions were associated with better prognosis in CRC patients. These discrepancies regarding prognostic role of TP may be explained by several factors such as different sample size, different experimental techniques, and use of varying antibodies and scoring methods.

The expression of TP in CRC has a dual function as it is mainly involved in nucleoside metabolism and in angiogenesis and hence it may play an important role in cancer chemotherapy as a target for antiangiogenic agents.[15] One theory proposed that high expression of TP is associated with poor prognosis in patients with CRC due to its angiogenic role, indicated by increased infiltration, growth, and tumor metastasis. On the other side, TP is involved in the metabolism of 5-FU, where it catalyses the conversion of 5-FU to 5-fluoro-2'-deoxyuridine (5-FUDR), which consequently leads to inhibition of DNA synthesis.[2] Therefore, another theory suggests that high TP expression in CRC tissues increases the intratumoral concentration of 5-FU [32] and thus improves the curative effect of 5-FU, which is important in the treatment of CRC and may lead to better survival.[33] Hence, correlation of higher TP (tumor nuclear and stromal) expression with better survival in the present study might follow the latter theory. Moreover, only the subgroup of early stage patients showed association of high stromal and high tumor nuclear TP expression with good prognosis suggesting the role of TP in early onset of the disease. Thus, TP expression could be considered as a prognostic factor in early stages of CRC.

Present results contributed to the elucidation of the relationship between tumor cells and stroma. In current study, when tumor cytoplasmic, tumor nuclear and stromal TP expressions were intercorrelated, tumor cytoplasmic TP expression was significantly positively correlated with tumor nuclear TP expression. Moreover, tumor cytoplasmic TP expression also showed a trend of positive correlation with stromal TP expression, suggesting the relationship between tumor cells and associated stromal cells.

Conclusion

TP protein expression in tumor cells might have impact on associated stromal cells in tumor microenvironment in CRC. Moreover, TP immunoreactivity might have a prognostic value in early onset of CRC patients and hence it could be useful biomarker in predicting prognosis in early stage of disease.

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Epithelial Mesenchymal Transition Markers in Breast Cancer

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Summary

Epithelial-mesenchymal transition (EMT) is defined by the loss of epithelial characteristics and the acquisition of a mesenchymal phenotype. It can be associated with increased aggressiveness, and invasive and metastatic potential in cancer. The aim of the study was to assess the occurrence of EMT in human breast tumors by evaluation of epithelial markers E-cadherin, α-catenin, γ-catenin and mesenchymal markers N-cadherin and fibronectin. These markers were evaluated by immunohistochemistry on paraffin embedded tumor tissue section of 100 patients with breast carcinoma. Among epithelial markers, loss of γ-catenin α-catenin and E-cadherin expression was noted in 83%, 70% and 46% of breast tumors, respectively. Loss of α-catenin expression was significantly higher in histologic grade III tumors, BR score 7 tumors with a trend of reduced disease free survival (DFS) and overall survival (OS). Among mesenchymal markers, gain of N-cadherin and fibronectin expression was noted in 87% and 24% of breast tumors, respectively. A trend of reduced OS was noted in N-cadherin and Fibronectin positive patients. Further, a significant positive correlation of PRL-3 with cytokeratin and N-cadherin and of Snail with Vimentin and N-cadherin was noted. In multivariate survival analysis apart from clinicopathological parameters, Vimentin expression emerged as a significant predictor of reduced DFS and OS. PRL-3 and Snail are found to be upstream regulators in triggering EMT in breast cancer and showed significant association with mesenchymal markers N-cadherin and vimentin. Vimentin can be used as a biomarker for predicting disease aggressiveness at diagnosis.

Keywords: EMT, Breast Cancer

Introduction

Breast cancer is a heterogeneous disease, which includes a wide range of histologic subtypes, a diversity of clinical behavior and patient outcome.[1] In breast cancer, epithelial mesenchymal transition (EMT) can be associated with increased aggressiveness, invasiveness and metastatic potential. Several oncogenic pathways (peptide growth factors, Src, Ras, Ets, integrin, Wnt/β-catenin, and notch) induce processes characteristic of EMT, such as down regulation of the cell adhesion molecule and gain of mesenchymal phenotype. EMT induces alterations in cell morphology characteristic which are associated with changes in the expression of several molecules. These molecules are often used as biomarkers to detect EMT.

PRL-3, a metastatic associated phosphatase acts as an upstream regulator of the PTEN–phosphoinositide 3-kinase (PI3K) signaling which activate transcription factor Snail and triggers EMT during tumor progression.[2] Activation of Snail downregulates epithelial markers E-cadherin, cytokeratin, α-catenin, γ-catenin and upregulates mesenchymal markers Vimentin, N-cadherin and fibronectin. Decreased expression of E-cadherin is thought to be the prototypical marker of EMT. Loss of E-cadherin contributes to EMT both by modulating cell–cell adhesion and by altering signaling through the sequestration of associated cytoplasmic proteins, including β-catenin. α-catenin is a linker molecule between E-cadherin and the actin cytoskeleton and play a role in regulating cell proliferation. γ-catenin has also nearly identical interaction with E-cadherin. Further, vimentin is a biomarker of mesenchymally-derived cells or cells undergoing an epithelial-to-mesenchymal transition during both normal development and metastatic progression. N-cadherin is a classical cadherin from the cadherin superfamily mediates interactions between cancer and stromal cells and overexpression in breast carcinoma correlates with invasiveness. Fibronectin is involved in cell adhesion, growth, migration, and differentiation. Cellular Fibronectin is assembled into the extracellular matrix, an insoluble network that separates and supports the organs and tissues of an organism. Fibronectin enhance tumorigenicity and resistance to apoptosis.[3]

Our previous study evaluated role of PRL-3 and Snail in determining down regulation of Cytokeratin and gain of Vimentin. It was demonstrated that Snail overexpression enhanced mesenchymal marker vimentin. Vimentin emerged as strong indicator of biologically aggressive breast cancer. In light of these findings, the present study evaluated additional molecules involved in EMT such as epithelial markers E-cadherin, α-catenin, γ-catenin and mesenchymal markers N-cadherin and fibronectin in breast cancer. Further these markers were correlated with established clinicopathological parameters and previously studied molecules of EMT such as PRL3, Snail, cytokeratin and vimentin.

Materials and Methods

Patients

This retrospective study, approved by institutional scientific and ethical committees,

included 100 breast cancer patients diagnosed and treated at the Gujarat Cancer & Research Institute (early stage [stage I+II, N=67] and advanced stage [stage III+IV, N=33]). Detailed clinical history, pathological and radiological findings, and treatment offered were recorded. Disease staging was done according to UICC TNM classification. The primary treatment offered to patients was neoadjuvant chemotherapy or surgery followed by adjuvant chemotherapy and/or radiotherapy (RT) and/or endocrine therapy. Disease status was assessed by clinical examination, radiological investigations and biochemical investigations.

Immunohistochemical localization

Immunohistochemical localization of epithelial markers E-cadherin, α-catenin, γ-catenin and mesenchymal markers N-cadherin and fibronectin was performed on formalin fixed paraffin embedded (FFPE) tissue blocks containing primary tumor and evaluated by Hematoxylin and Eosin (H&E) staining, on Ventana Benchmark XT autoimmunostainer using Ventana reagents (Ventana, USA). The tumor tissue blocks were obtained from the archives of the Department of Pathology of the institute. Four microns thin sections were cut on microtome (Leica, Germany) and taken on to 3-Aminopropyl triethoxysilane (APES) coated slides. Briefly, the protocol includes following steps of deparafinization using EZ solution, antigen retrieval for 60 minutes using retrieval solution CC1, and incubation with Ultra View DAB Inhibitor for 4 minutes, 100 µl of respective primary antibodies of E-cadherin (NCH-38, 1:75, Dako) at 37°C for 32 minutes, α-catenin (25B1, 1:50, Leica) at 37°C for 60 minutes, γ-catenin (11B6, 1:50, Leica) at 37°C for 32 minutes, N-cadherin (polyclonal, 1:100, Thermo scientific) at 37°C for 32 minutes, fibronectin (568, 1:100, Leica) at 37°C for 32 minutes, Ultra View HRP Multimer for 8 minutes, Ultra View DAB Detection kit for 8 minutes, counterstained with hematoxylin for 8 minutes and mounted with DPX.

Scoring

Two individual observers scored the sections. Cytoplasmic staining pattern was observed for fibronectin and membranous staining pattern for E-cadherin, α-catenin, N-cadherin, and γ-catenin.

Histoscore (H-score) was evaluated by multiplying percentage of the positive cells with the staining intensity for E-cadherin, α-catenin, γ-catenin, N-cadherin and fibronectin. H-score from 0 to 300 were evaluated where 0-50 was scored as negative (0), 51-100 as weak positive (1+), 101-200, as moderate positive (2+), and 201-300 as strong positive (3+). For statistical analysis, H-score 0 was scored as negative, and 1+, 2+ and 3+ were clubbed as positive.

Results

Patients' characteristics and outcome

This retrospective study included 100 patients, and more than 50% of patients had age >45 years, postmenopausal status, T2 tumor size, lymph node negative status, stage II disease, histological grade II tumors, invasive ductal carcinoma (IDC) and triple negative tumors (ER, PR and Her-2-neu negative). The maximum follow-up period was 96 months with a median follow-up was 62 months and 47% of patients developed metastasis or local recurrence and 19% of patients died due to cancer within the study period.

Epithelial markers

E-cadherin expression

Membranous expression of E-cadherin and loss of E-cadherin was noted in tumor tissue of 54% and 46% of breast cancer patients, respectively (Figure 1a, 1b). E-cadherin expression with H-score of 1+ was noted in 7%, 2+ in 38% and 3+ in 9% of patients.

E-cadherin expression in relation to clinicopathological parameters

E-cadherin expression when correlated with clinical and pathological parameters, no significant difference was observed between loss of E-cadherin expression and subgroups of age, menopausal status, tumor size, lymph node status, disease stage, histopathological subtypes, histological grade, BR score, ER, PR and Her-2-neu status. However, a trend of higher incidence of loss of E-cadherin expression was noted in patients with bone metastasis and brain metastasis as compared to patients with lung metastasis and multiple metastases. While one patient with ovary metastasis showed loss of E-cadherin expression. (Table 1)

E-cadherin expression in relation to survival analysis

According to Kaplan and Meier univariate survival analysis, with respect to DFS, a trend of higher incidence of disease relapse was noted in E-cadherin positive (52%, 28/54; 53.59 ± 3.15 months) than E-cadherin negative patients (41%, 19/46; 56.62 ± 3.47 months; Log rank=0.95, df=1, p=0.33). While with respect to OS, significantly higher incidence of death was noted in E-cadherin positive (26%, 14/54; 60.83 ± 2.55 months) than E-cadherin negative patients (11%, 05/46; 64.67 ± 2.58 months; Log rank =3.65, df=1, p=0.05). (Figure 1c)

α-catenin expression

Membranous expression of α-catenin and loss of α-catenin was noted in tumor tissue of 30% and 70% of breast cancer patients, respectively. (Figure

Table 1: Correlation of E-cadherin, α-catenin and γ-catenin expression with clinicopathological parameters, metastatic site, ER, PR and Her-2-neu

Parameters		Incidence of E-cadherin expression		Incidence of α-catenin expression		Incidence of γ-catenin expression	
	N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)
Age	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
≤45 years	37(37)	19(51)	18(49)	23(62)	14(38)	33(89)	04(11)
> 45 years	63(63)	27(43)	36(57)	47(75)	16(25)	50(79)	13(21)
Menopausal status	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
Pre-menopausal	35(35)	19(54)	16(46)	24(69)	11(31)	32(91)	03(09)
Post-menopausal	65(65)	27(42)	38(58)	46(71)	19(29)	51(78)	14(22)
Tumor size	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
T1 (≤ 2 cm)	07(07)	04(57)	03(43)	03(43)	04(57)	07(100)	00(00)
T2 (≥2cm to ≤5cm)	69(69)	33(48)	26(52)	49(71)	20(29)	54(78)	15(22)
T3 (≥5cm)	18(18)	08(44)	10(56)	15(83)	03(17)	17(94)	01(06)
T4 (any tumor size extended to chest wall or skin)	06(06)	01(17)	05(83)	03(50)	03(50)	05(83)	01(17)
Lymph node status	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
Negative	52(52)	26(50)	26(50)	35(67)	17(33)	42(81)	10(19)
Positive	48(48)	20(42)	28(56)	35(73)	13(27)	41(85)	07(15)
Disease stage	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
Stage I	02(02)	01(50)	01(50)	00(00)	02(100)	02(100)	00(00)
Stage II A + Stage II B	65(65)	33(51)	32(49)	48(74)	17(26)	53(82)	12(18)
Stage III A + Stage III B	31(31)	12(39)	19(61)	20(65)	11(35)	26(84)	05(16)
Stage IV	02(02)	00(00)	02(100)	02(100)	00(00)	02(100)	00(00)
Early (stage I and stage II)	67(67)	34(51)	33(49)	48(72)	19(28)	52(82)	12(18)
Advanced (stage III and stage IV)	33(33)	12(36)	21(64)	22(67)	11(33)	28(25)	05(15)
Histopathology	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
IDC	77(77)	32(42)	45(58)	53(69)	24(31)	65(84)	12(16)
IDC + DCIS	10(10)	07(70)	03(30)	08(80)	02(20)	08(80)	02(20)
Medullary carcinoma	03(03)	01(33)	02(67)	01(33)	02(67)	01(33)	02(67)
Papillary carcinoma	03(03)	01(33)	02(67)	02(67)	01(33)	02(67)	01(33)
Lobular carcinoma	05(05)	03(60)	02(40)	04(80)	01(20)	05(100)	00(00)
IDC + Mucinous carcinoma	02(02)	02(100)	00(00)	02(100)	00(00)	02(100)	00(00)
Histologic grade	75	36(48)	39(52)	55(73)	20(27)	63(84)	12(16)
Grade I	08(10)	03(37)	05(63)	02(25) **a**	06(75) **a**	06(75)	02(25)
Grade II	56(75)	26(46)	30(54)	43(77) **a**	13(23) **a**	47(84)	09(16)
Grade III	11(15)	07(64)	04(36)	10(91) **a**	01(09) **a**	10(91)	01(09)
BR score	80	37(46)	43(54)	55(70) **b**	25(30) **b**	67(84)	13(16)
4	01(01)	01(100)	00(00)	00(00) **b**	01(100) **b**	01(100)	00(00)
5	13(16)	07(54)	06(46)	06(46) **b**	07(54) **b**	09(69)	04(31)
6	24(30)	10(42)	14(58)	14(58) **b**	10(42) **b**	19(79)	05(21)
7	32(40)	14(44)	18(56)	27(84) **b**	05(16) **b**	29(91)	03(09)
8	09(12)	04(44)	05(56)	07(78) **b**	02(22) **b**	08(89)	01(11)
9	01(01)	01(100)	00(00)	01(100) **b**	00(00) **b**	01(100)	00(00)

Table 1: Correlation of E-cadherin α-catenin and γ-catenin expression with clinicopathological parameters, metastatic site, ER, PR and Her-2-neu (Continued)

Parameters		Incidence of E-cadherin expression		Incidence of α-catenin expression		Incidence of γ-catenin expression	
	N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)
ER	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
Negative	63(63)	32(51)	31(49)	43(68)	20(32)	54(86)	09(14)
Positive	37(37)	14(38)	23(62)	27(73)	10(27)	29(78)	08(22)
PR	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
Negative	71(71)	32(45)	39(55)	53(75)	18(25)	60(85)	11(15)
Positive	29(29)	14(48)	15(52)	17(59)	12(41)	29(78)	06(21)
Her-2-neu	100	46(46)	54(54)	70(70)	30(30)	83(83)	17(17)
Negative (0 and +1)	60(60)	28(47)	32(53)	42(70)	18(30)	50(83)	10(17)
Positive +2	18(18)	08(44)	10(56)	12(67)	06(33)	15(83)	03(17)
Positive +3	22(22)	10(45)	12(55)	16(73)	06(27)	18(82)	04(18)
Metastatic site	47	19(40)	28(60)	37(79)	10(21)	39(83)	8(17)
Local recurrence	04(09)	00(00)	04(100)	02(50)	02(50)	03(75)	01(25)
Bone	19(40)	10(53)	09(47)	15(79)	04(21)	15(79)	04(21)
Lung	10(21)	04(40)	06(60)	08(80)	02(20)	08(80)	02(20)
Brain	02(04)	01(50)	01(50)	01(50)	01(50)	01(50)	01(50)
Liver	05(11)	00(00)	05(100)	04(80)	01(20)	05(100)	00(00)
Ovary	01(02)	01(100)	00(00)	01(100)	00(00)	01(100)	00(00)
Multiple metastasis	06(13)	02(33)	04(67)	06(100)	00(00)	06(100)	00(00)

P value: a χ^2=11.36, r=-0.34, p=0.003, b χ^2=10.93, r=-0.32, p=0.05

2a, 2b). α-catenin expression with H-score of 1+ was noted in 4%, 2+ in 25% and 3+ in 1% of patients.

α-catenin expression in relation to clinicopathological parameters

α-catenin expression when correlated with clinical and pathological parameters, significantly higher incidence of loss of α-catenin expression was noted in histologic grade III tumors (91%, 10/11) than histologic grade II tumors (77%, 43/56) and histologic grade I tumors (25%, 02/08; χ^2=11.36, r=-0.34, p=0.003). Similarly, significantly higher incidence of loss of α-catenin expression was noted in patients with BR score 7 tumors (84%, 27/32) as compared to their respective counterparts (χ^2=10.93, r=-0.32, p=0.05). However, no significant difference was observed between α-catenin expression and subgroups of age, menopausal status, tumor size, lymph node status, disease stage, histopathological subtypes, ER, PR and Her-2-neu status.

Further, a trend of higher incidence of loss of α-catenin expression was noted in patients with multiple metastases, lung metastasis, liver metastasis and bone metastasis as compared to patients with local recurrence and brain metastasis.(Table 1)

α-catenin expression in relation to survival analysis

According to Kaplan and Meier univariate survival analysis, with respect to DFS, a trend of higher incidence of disease relapse was noted in α-catenin negative (53%, 37/70; 52.52 ± 2.78 months) patients than α-catenin positive patients (33%, 10/30; 60.76 ± 4.10 months; Log rank=3.12, df=1, p=0.07). While with respect to OS, similar incidence of death and mean OS was noted in α-catenin negative (20%, 14/70; 61.44 ± 2.15 months) and α-catenin positive patients (17%, 5/30; 65.30 ± 3.38 months; Log rank=0.24, df=1, p=0.62).

γ-catenin expression

Membranous expression of γ-catenin and loss of γ-catenin was noted in tumor tissue of 17% and 83% of breast cancer patients. (Figure 3a, 3b) γ-catenin expression with H-score of 1+ was noted in 2%, 2+ in 9% and 3+ in 6% of patients.

γ-catenin expression in relation to clinicopathological parameters

γ-catenin expression when correlated with clinical and pathological parameters, no significant

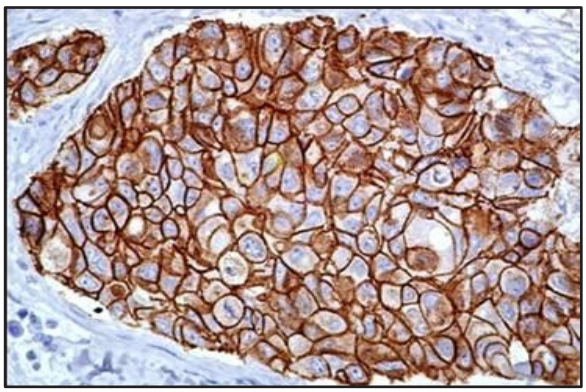

Figure 1a: Membranous staining E-cadherin expression (score 3+) in breast carcinoma.

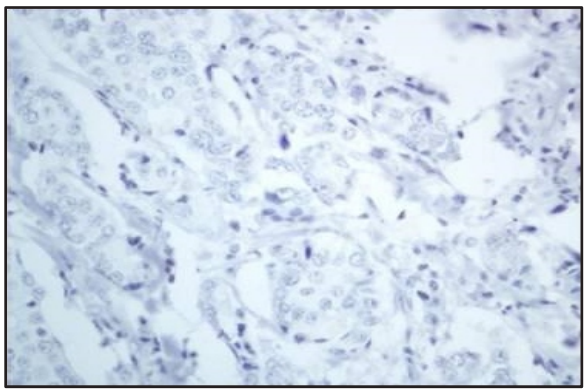

Figure 1b: Loss of E-cadherin expression in tumor cells of breast carcinoma.

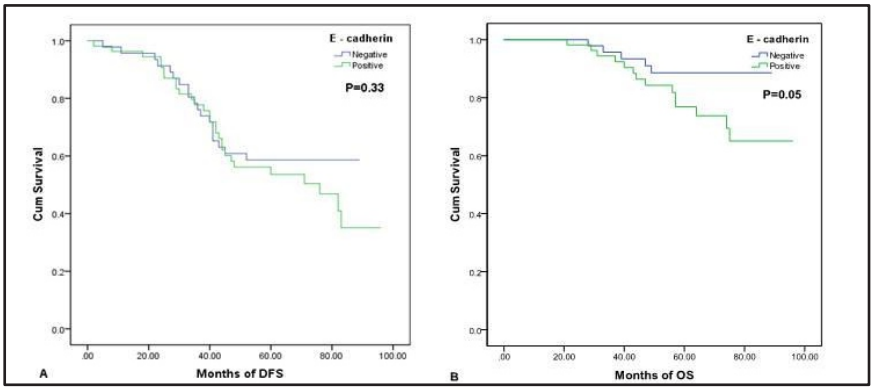

Figure 1c: Kaplan - Meier survival curves showing reduced DFS and OS in E-cadherin expressing breast carcinoma.

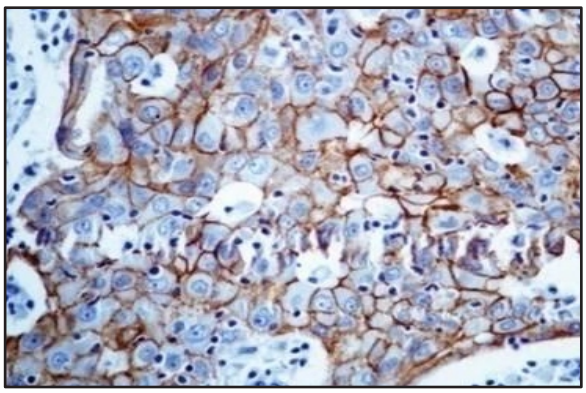

Figure 2a: Membranous staining α-catenin expression (score 3+) in breast carcinoma.

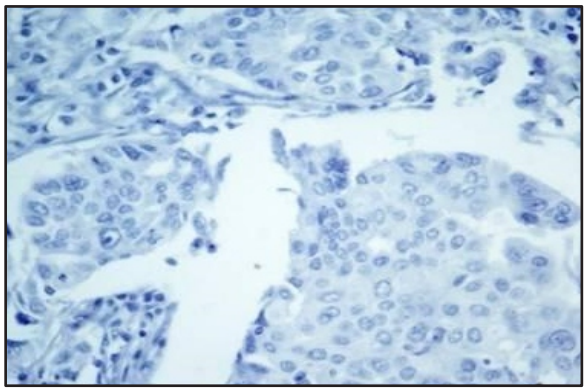

Figure 2b: Loss of α-catenin expression in tumor cells of breast carcinoma.

difference was observed between γ-catenin expression and subgroups of age, menopausal status, tumor size, lymph node status, disease stage, histopathological subtypes, histological grade, BR-score, ER, PR and Her-2-neu status.

A trend of higher incidence of loss of γ-catenin expression was noted in patients with multiple metastases, liver metastasis, lung metastasis, bone metastasis and local recurrence as compared to patients with and brain metastasis. (Table 1)

γ-catenin expression in relation to survival analysis

According to Kaplan and Meier univariate survival analysis, with respect to DFS, similar incidence of disease relapse and mean months DFS was noted in γ-catenin negative (47%, 39/83; 54.03 ± 2.57 months) and γ-catenin positive patients (47%, 08/17; 59.70 ± 5.47 months; Log rank=0.13, df=1, p=0.71). While with respect to OS, similar incidence of death and mean months OS was noted in γ-catenin negative (19%, 16/83; 62.15 ± 2.01 months) and γ-catenin positive patients (18%, 03/17; 64.76 ± 4.32 months; Log rank=0.04, df=1, p=0.83).

Mesenchymal markers

N-cadherin expression

Membranous expression of N-cadherin was noted in tumor tissue of 87% of breast cancer patients (Figure 4a), with H-score of 1+ in 08%, 2+ in 48% and 3+ in 31% of patients.

N-cadherin expression in relation to clinicopathological parameters

N-cadherin expression when correlated with clinical and pathological parameters, no significant difference was observed between N-cadherinexpression and subgroups of age, menopausal status, tumor size, lymph node status, disease stage, histopathological subtypes, histological grade, BR-score, ER, PR and Her-2-neu status.

A trend of higher incidence of N-cadherin expression was noted in patients with multiple metastases, local recurrence and brain metastasis as compared to patients with lung metastasis, bone metastasis and liver metastasis. (Table 2)

N-cadherin expression in relation to survival analysis

According to Kaplan and Meier univariate survival analysis, with respect to DFS, similar incidence of disease relapse and mean months DFS was noted in N-cadherin negative (54%, 7/13; 55.38 ± 6.15 months) and N-cadherin positive patients (46%, 40/87; 54.94 ± 2.52 months; Log rank=0.16, df=1, p=0.68). While with respect to OS, a trend of higher incidence of death and mean OS was noted in N-cadherin positive (21%, 18/87; 62.54 ± 1.99 months) than N-cadherin negative patients (8%, 1/13; 63.00 ± 4.43 months; Log rank=1.04, df=1, p=0.30).

Fibronectin expression

Cytoplasmic expression of fibronectin was noted in tumor tissue of 24% of breast cancer patients (Figure 4b), with H-score of 1+ in 3%, 2+ in 18% and 3+ in 3% of patients.

Fibronectin expression in relation to clinicopathological parameters

Fibronectin expression when correlated with clinical and pathological parameters, no significant difference was observed between fibronectin expression and subgroups of age, menopausal status, tumor size, lymph node status, disease stage, histopathological subtypes, histological grade, BR-score, ER, PR and Her-2-neu status.

A trend of higher incidence of fibronectin expression was noted in patients with local recurrence, brain metastasis and lung metastasis as compared to patients with bone metastasis and liver metastasis.

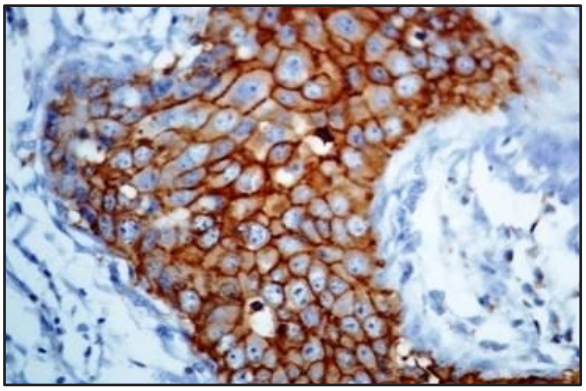

Figure 3a: Membranous staining γ-catenin expression (score 3+) in breast carcinoma.

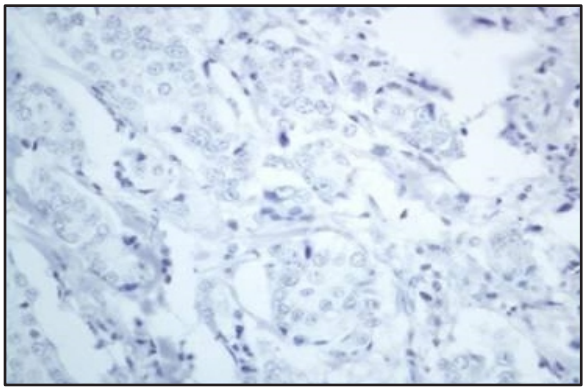

Figure 3b: Loss of γ-catenin expression in tumor cells of breast carcinoma.

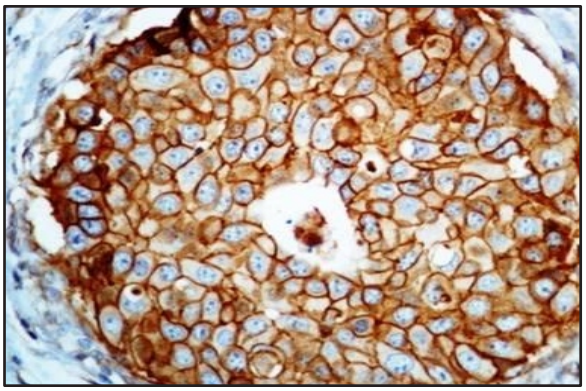

Figure 4a: Membranous staining N-cadherin expression (score 3+) in breast carcinoma.

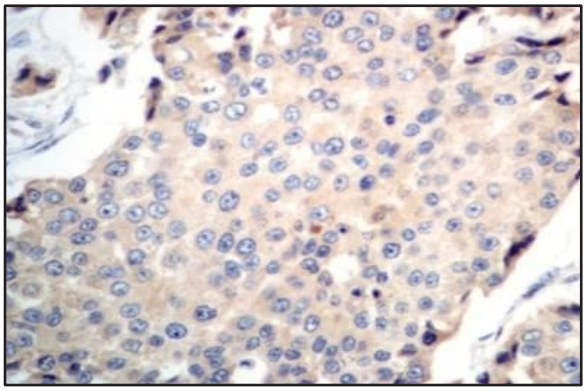

Figure 4b: Cytoplasmic staining Fibronectin expression (score 2+) in breast carcinoma.

Table 2: Correlation of N-cadherin and Fibronectin expression with clinicopathological parameters, metastatic site, ER, PR and Her-2-neu

Parameters		Incidence of N-cadherin expression		Incidence of Fibronectin expression	
	N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)
Age	100	13(13)	87(87)	76(76)	24(24)
≤45 years	37(37)	04(11)	33(89)	28(76)	09(24)
> 45 years	63(63)	09(14)	54(86)	48(76)	15(24)
Menopausal status	100	13(13)	87(87)	76(76)	24(24)
Pre-menopausal	35(35)	02(06)	33(94)	28(80)	07(20)
Post-menopausal	65(65)	11(17)	54(83)	76(76)	24(24)
Tumor size	100	13(13)	87(87)	07(100)	00(00)
T1 (≤ 2 cm)	07(07)	00(00)	07(100)	51(74)	18(26)
T2 (≥2cm to ≤5cm)	69(69)	09(13)	60(87)	15(83)	03(17)
T3 (≥5cm)	18(18)	03(17)	15(83)	03(50)	03(50)
T4 (any tumor size extended to chest wall or skin)	06(06)	01(17)	05(83)	76(76)	24(24)
Lymph node status	100	13(13)	87(87)	42(81)	10(19)
Negative	52(52)	06(11)	46(89)	34(71)	14(29)
Positive	48(48)	07(15)	41(85)	76(76)	24(24)
Disease stage	100	13(13)	87(87)	02(100)	00(00)
Stage I	02(02)	00(00)	02(100)	52(80)	13(20)
Stage II A + Stage II B	65(65)	08(12)	57(87)	21(68)	10(32)
Stage III A + Stage III B	31(31)	05(16)	26(84)	01(50)	01(50)
Stage IV	02(02)	00(00)	02(100)	76(76)	24(24)
Early (stage I and stage II)	67(67)	08(12)	59(88)	22(67)	11(33)
Advanced (stage III and stage IV)	33(33)	05(15)	28(85)	76(76)	24(24)
Histopathology	100	13(13)	87(87)	76(76)	24(24)
IDC	77(77)	12(16)	65(84)	58(75)	19(25)
IDC+DCIS	10(10)	00(00)	10(100)	07(70)	03(30)
Medullary carcinoma	03(03)	00(00)	03(100)	01(33)	02(67)
Papillary carcinoma	03(03)	00(00)	03(100)	03(100)	00(00)
Lobular carcinoma	05(05)	00(00)	05(100)	05(100)	00(00)
IDC+ Mucinous carcinoma	02(02)	01(50)	01(50)	02(100)	00(00)
Histologic grade	75	11(15)	64(85)	54(72)	21(28)
Grade I	08(10)	00(00)	08(100)	07(88)	01(12)
Grade II	56(75)	08(14)	48(86)	39(70)	17(30)
Grade III	11(15)	03(27)	08(73)	08(73)	03(27)
BR score	80	11(14)	69(86)	59(74)	21(26)
4	01(01)	00(00)	1(100)	01(100)	00(00)
5	13(16)	00(00)	13(100)	10(77)	03(23)
6	24(30)	04(17)	20(83)	16(67)	08(33)
7	32(40)	05(16)	27(84)	24(75)	08(25)
8	09(12)	02(22)	07(78)	08(89)	01(11)
9	01(01)	00(00)	01(100)	00(00)	01(100)

Table 2: Correlation of N-cadherin and Fibronectin expression with clinicopathological parameters, metastatic site, ER, PR and Her-2-neu (Continued)

Parameters		Incidence of N-cadherin expression		Incidence of Fibronectin expression	
	N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)
ER	100	13(13)	87(87)	76(76)	24(24)
Negative	63(63)	07(11)	56(89)	44(70)	19(30)
Positive	37(37)	06(16)	31(84)	32(87)	05(13)
PR	100	13(13)	87(87)	76(76)	24(24)
Negative	71(71)	09(13)	62(87)	56(79)	15(21)
Positive	29(29)	04(14)	25(86)	20(69)	09(31)
Her-2-neu	100	13(13)	87(87)	76(76)	24(24)
Negative (0 and +1)	60(60)	05(08)	55(92)	48(80)	12(20)
Positive +2	18(18)	05(28)	13(72)	13(72)	05(28)
Positive +3	22(22)	03(14)	19(86)	15(68)	07(32)
Metastatic site	47	07(15)	40(85)	33(70)	14(30)
Local recurrence	04(09)	00(00)	04(100)	02(50)	02(50)
Bone	19(40)	05(26)	14(74)	13(68)	06(32)
Lung	10(21)	02(20)	08(80)	06(60)	04(40)
Brain	02(04)	00(00)	02(100)	01(50)	01(50)
Liver	05(11)	00(00)	02(40)	04(80)	01(20)
Ovary	01(02)	00(00)	01(100)	01(100)	00(00)
Multiple metastasis	06(13)	00(00)	06(100)	06(100)	00(00)

Fibronectin expression in relation to survival analysis

According to Kaplan and Meier univariate survival analysis, with respect to DFS, a trend of higher incidence of disease relapse and mean months DFS was noted in fibronectin positive (58%, 14/24; 55.08 ± 4.79 months) patients than fibronectin negative patients (43%, 33/13; 54.97 ± 2.68 months; Log rank=0.60, df=1, p=0.43). While with respect to OS, a trend of higher incidence of death and mean OS was noted in fibronectin positive (25%, 6/24; 61.00 ± 3.96 months) than fibronectin negative patients (17%, 13/76; 63.10 ± 2.05 months; Log rank=0.84, df=1, p=0.35).

Epithelial and Mesenchymal markers expression in relation to treatment

Patients expressing loss of E-cadherin expression treated with FAC alone and CMF with adjuvant treatment showed better overall survival as compared to patients treated with FAC with adjuvant treatment. This difference was statistically significant (Log rank=4.56, df=1, p=0.03). (Table 3a)

Other epithelial and mesenchymal markers expression were not found as an independent predictor of treatment response in relation to DFS and OS (Table 3a, 3b).

Intermarker correlation

These markers were intercorrelated with each other and also with previously studied markers such as PRL3, Snail, cytokeratin and Vimentin. A significant positive correlation was noted between E-cadherin and γ-catenin expression (χ^2 =6.62, r=0.25, p=0.01); E-cadherin and Cytokeratin expression (χ^2 =15. 93, r=-0.39 p=0.001); γ-catenin and fibronectin expression (χ^2 =19.01, r=0.436, p=0.001); N-cadherin and cytokeratin expression (χ^2 =19.01, r=0.436, p=0.001); N-cadherin and PRL-3 expression (χ^2 = 7.07, r=0.26, p=0.007); N-cadherin and Snail expression (χ^2 =17.54, r=0.41, p=0.0001); cytokeratin and PRL-3 expression (χ^2=6.38, r=0.25, p=0.01); Vimentin and Snail expression (χ^2 =4.16, r=0.20, p=0.04).

Correlation of markers with molecular subtypes of breast cancer

EMT markers were correlated with molecular subtypes of breast cancer viz. Luminal A (N= 30), Luminal B (N= 20), Triple Negative (N= 30) and Her-2-neu positive (N= 20). In relation to epithelial markers, loss of γ-catenin expression was higher in triple negative breast cancer patients while loss of cytokeratin was higher in Her-2-neu positive breast cancer. Similarly, with mesenchymal markers, gain of

Table 3a: E-cadherin, α-catenin and γ-catenin expression in relation to treatment offered to the patient

	Treatment offered	N	Remission N (%)	Relapsed N (%)	Alive N (%)	Dead N (%)
E-cadherin expression						
Negative	CMF, CMF+TMX, CMF+TMX+RT	2	02(100)	00(00)	02(100)	00(00)
	FAC	5	05(100)	00(00)	05(100)	00(00)
	FAC+TMX, FAC+RT+TMX	38	19(50)	19(50)	33(87)	05(13)
Positive	CMF, CMF+TMX, CMF+TMX+RT	12	07(58)	05(42)	10(83)	02(17)
	FAC	9	05(56)	04(40)	08(89)	01(11)
	FAC+TMX, FAC+RT+TMX	31	12(39)	19(61)	20(65)	11(35)
			Log rank=1.60, df=1, p=0.20		Log rank=4.56, df=1, p=0.03*	
α-cateninexpression						
Low/no	CMF, CMF+TMX, CMF+TMX+RT	8	05(63)	03(37)	07(88)	01(12)
	FAC	10	06(60)	04(40)	09(90)	01(10)
	FAC+TMX, FAC+RT+TMX	50	20(40)	30(60)	38(76)	12(24)
High	CMF, CMF+TMX, CMF+TMX+RT	6	04(67)	02(33)	05(83)	01(17)
	FAC	4	04(100)	00(00)	04(100)	00(00)
	FAC+TMX, FAC+RT+TMX	19	11(58)	08(42)	15(79)	04(21)
			Log rank=2.07, df=1, p=0.10		Log rank=2.37, df=1, p=0.62	
γ-catenin expression						
Negative	CMF, CMF+TMX, CMF+TMX+RT	9	06(67)	03(33)	08(89)	01(11)
	FAC, FAC+TMX, FAC+RT+TMX	71	35(49)	36(51)	56(79)	15(21)
Positive	CMF, CMF+TMX, CMF+TMX+RT	5	03(60)	02(40)	04(80)	01(20)
	FAC, FAC+TMX, FAC+RT+TMX	12	06(50)	06(50)	10(83)	02(17)
			Log rank=0.90, df=1, p=0.76		Log rank=0.04, df=1, p=0.82	

p value ≤ 0.05 is significant df= degrees of freedom

Table 3b: N-cadherin and Fibronectin expression in relation to treatment offered to the patient

	Treatment offered	N	Remission N (%)	Relapsed N (%)	Alive N (%)	Dead N (%)
N-cadherin expression						
Negative	CMF, CMF+TMX, CMF+TMX+RT	1	01(100)	00(00)	01(100)	00(00)
	FAC	1	01(100)	00(00)	01(100)	00(00)
	FAC+TMX, FAC+RT+TMX	11	04(36)	07(64)	10(90)	01(10)
Positive	CMF, CMF+TMX, CMF+TMX+RT	13	08(62)	05(38)	11(85)	02(15)
	FAC	13	09(69)	04(31)	12(92)	01(08)
	FAC+TMX, FAC+RT+TMX	58	27(47)	31(53)	43(74)	15(24)
			Log rank=0.02, df=1, p=0.88		Log rank=1.16, df=1, p=0.28	
Fibronectin expression						
Low/no	CMF, CMF+TMX, CMF+TMX+RT	13	09(69)	04(31)	11(85)	02(15)
	FAC	11	09(82)	02(18)	11(100)	00(00)
	FAC+TMX, FAC+RT+TMX	50	23(46)	27(54)	39(78)	11(22)
High	CMF, CMF+TMX, CMF+TMX+RT	01	00(00)	01(100)	01(100)	00(00)
	FAC	03	01(33)	02(67)	02(67)	01(33)
	FAC+TMX, FAC+RT+TMX	19	08(42)	11(58)	14(74)	05(26)
			Log rank=0.22, df=1, p=0.63		Log rank=0.55, df=1, p=0.45	

p value ≤ 0.05 is significant df= degrees of freedom

Table 4: Intercorrelation of different markers

		α-catenin expression	γ-catenin expression	N-cadherin expression	Fibronectin expression	Cytokeratin expression	Vimentin expression	PRL3 expression	Snail protein expression
E-cadherin	r value	0.16	0.25	0.12	0.14	0.39	0.04	0.14	0.07
	P value	0.09	0.01*	0.23	0.15	0.0001*	0.66	0.16	0.46
α-catenin	r value		0.16	0.18	0.14	0.16	-0.06	0.09	0.03
	P value		0.09	0.06	0.15	0.09	0.52	0.34	0.72
γ-catenin	r value			0.09	0.36	0.08	-0.13	0.00	-0.17
	P value			0.34	0.0001*	0.41	0.18	0.95	0.09
N-cadherin	r value				0.14	0.43	0.17	0.26	0.41
	P value				0.14	0.0001*	0.08	0.007*	0.0001*
Cytokeratin	r value						0.08	0.25	0.18
	P value						0.41	0.011*	0.06
Vimentin	r value							0.06	0.20
	P value							0.52	0.04*

*p value ≤ 0.05 is significant

N-cadherin expression was higher in triple negative breast cancer patients and gain of vimentin expression was higher in Her-2-neu positive breast cancer patients. (Table 5)

Multivariate survival analysis

Multivariate survival analysis by Cox regression model with forward stepwise (likelihood ratio) method was carried out by including the markers of present and previous studies. In the analysis, lymph node positive status was entered at step 1 and vimentin expression entered at step 2 for predicting reduced disease free survival, and vimentin expression entered at step 1 and lymph node positive status entered at step 2 for predicting poor overall survival. (Table 6)

Discussion

EMT is a complex process that converts epithelia into migratory mesenchymal cells. PRL-3, a metastasis associated phosphatase up-regulates transcription factor Snail which further down-regulates expression of epithelial markers E-cadherin, cytokeratin, α-catenin, γ-catenin and gain of mesenchymal markers vimentin, N-cadherin, fibronectin, which are major effectors in the EMT pathway.[4] In breast cancer, the present study evaluated epithelial markers E-cadherin, α-catenin and γ-catenin and mesenchymal markers N-cadherin and Fibronectin and compared with previously studied EMT molecules PRL-3, Snail, Cytokeratin and vimentin. Among epithelial markers, loss of γ-catenin expression (83%) was higher than α-catenin (70%), E-cadherin (46%) and Cytokeratin (32%) expressions. Among mesenchymal markers gain of N-cadherin expression (87%) was higher than Fibronectin (24%) and vimentin (17%) expressions.

Further, our study observed higher incidence of loss of γ-catenin expression (83%) than other studies on breast cancer and oral cancer that reported its loss of expression in the range of 50% to 60% [5,6] and 40% to 52% [7,8,9] respectively. Loss of γ- catenin expression did not show significant correlation with clinicopathological parameters in the present study and in the study of Sirvikoz et al[6], however, a strong association with high grade tumors was demonstrated in renal carcinoma.[10] In relation to survival analysis, loss of γ-catenin was associated with reduced DFS and OS in the present study and in renal carcinoma.[10] Contrary to that decreased expression of γ- catenin correlated with poor survival in the study of Shimazui et al in renal carcinoma.[11]

Regarding α-catenin expression, its loss was noted in 70% of breast carcinoma patients and in various human malignancies including breast carcinoma where Rimm et al observed loss of α-catenin expression in 81% of tumor tissue.[12] In renal carcinoma and prostate carcinoma, loss of α-catenin expression was noted in 72% 10 and 40% [13,14] of tumors, respectively. Further, our study demonstrated no association of loss of α-catenin expression with clinicopathological parameters, however, higher incidence of relapse and death was seen. Similarly, association of loss of α- catenin and β- catenin expression with poor prognosis was also found in invasive breast carcinoma [15], and in renal cell carcinoma.[10,11]

Furthermore, E-cadherin is most widely studied epithelial marker and its loss of expression was found in 46% of breast carcinoma patients. This finding was in accordance with several studies where loss of E-cadherin was seen in range of 25% to 54% in breast tumors.[16,17,18,19,20] Further, significant correlation was not observed between loss of E-cadherin expression and clinicopathological

Table 5: Correlation of molecular subtype of breast cancer with EMT markers

Markers	Luminal A 30(30)	Luminal B 20(20)	Triple negative 30(30)	Her-2-neu positive 20(20)
E-cadherin expression				
Negative	13(43)	07(35)	15(50)	11(55)
Positive	17(57)	13(65)	15(50)	09(45)
	χ^2 =1.90, r=-0.10 p=0.59			
α- catenin expression				
Negative	19(63)	14(70)	23(77)	14(70)
Positive	11(37)	06(30)	07(23)	06(30)
	χ^2 =1.27, r=-0.07, p=0.73			
γ-catenin expression				
Negative	21(70)	17(85)	29(97)	16(80)
Positive	09(30)	03(15)	01(03)	04(20)
	χ^2 =7.74, r=-0.16, p=0.05*			
N-cadherin expression				
Negative	03(10)	06(30)	02(07)	02(10)
Positive	27(90)	14(70)	28(93)	18(90)
	χ^2 =6.75, r=0.059, p=0.08			
Fibronectin expression				
Negative	23(77)	15(75)	25(83)	13(65)
Positive	07(23)	05(25)	05(17)	07(35)
	χ^2 =2.23, r=0.05, p=0.52			
Cytokeratin expression				
Negative	08(27)	07(35)	07(27)	10(50)
Positive	22(73)	13(65)	23(76)	10(50)
	χ^2 =4.48, r=-0.11, p=0.21			
Vimentin expression				
Negative	27(90)	19(95)	23(76)	14(70)
Positive	03(10)	01(05)	07(24)	03(30)
	χ^2 =6.33, r=0.22, p=0.09			
PRL3 protein expression				
Negative	12(40)	04(20)	08(27)	06(30)
Positive	18(60)	16(80)	22(73)	14(70)
	χ^2 =2.54, r=0.07, p=0.46			
Snail protein expression				
Negative	13(43)	10(50)	13(43)	10(50)
Positive	17(57)	10(50)	17(57)	10(50)
	χ^2 =0.42,r=-0.029, p=0.93			

*p value ≤ 0.05 is significant

Table 6: Multivariate survival analysis including all parameters

Patients	Step	Variables	Wald statistic	df	p Value	Exp (B)	95% CI for Exp(B)	
							Lower	Upper
DFS	1	Lymph node	14.37	1	0.001	4.05	1.96	8.36
	2	Vimentin	13.33	1	0.001	3.93	1.88	8.22
OS	1	Vimentin	9.58	1	0.002	4.54	1.74	11.84
	2	Lymph node	8.72	1	0.003	5.54	1.79	17.26

parameters in the present study. This observation was in accordance with the findings of Acs et al, [21] Lipponen et al [22] and Kowalski et al.[19] In univariate survival analysis, it was observed that patients with loss of E-cadherin had significantly lower incidence of disease relapse as compared to patients with E-cadherin expression which was in discordance with findings of Siitonen et al[23] and Guriec et al.[24] The reason could be E-cadherin antibody was used which recognizes all forms of E-caherin, 120 KD (transmembrane glycoprotein), 82 KD (extracellular protein) and 40 KD (cytoplasmic protein truncated form). Several MMPs have been implicated in the extracellular cleavage and shedding of unique E-cadherin fragment (80 KD).[25] Siitonen et al have used HECD-1 antibody which recognise 120 KD protein of E-cadherin which shown association of reduced E-cadherin expression was associated with shortened DFS (p=0.027).[23] Also, Guriec et al have shown loss of E-cadherin m-RNA expression associated with reduced DFS and OS.[24]

Regarding mesenchymal markers, this study demonstrated membranous N-cadherin expression in 87% of breast tumors, which was in accordance with study by Rezaei et al where N-cadherin expression was noted in 82% of the breast tumors.[26] However, other two studies demonstrated N-cadherin expression only in 52% and 40% of breast tumors, respectively.[18,27] Instead of membranous staining, Soler et al, observed cytoplasmic N-cadherin expression in tumors of patients with breast cancer.[28] Our study in association with other two studies observed no association of N-cadherin expression with clinicopathological parameters and hormone receptors.[27,28] While a positive correlation of membranous N-cadherin expression with high histological grade, lymph node positive status and hormone receptors negative status was found in the study of Hanan et al.[18] Moreover, an association of N-cadherin expression with worse prognosis was observed by Han et al and Wheelock et al [29,30] however, this trend was not observed by Soler et al and Nakajima et al[28,31] and in the present study.

Regarding Fibronectin expression, gain of cytoplasmic expression of Fibronectin was noted in 24% of breast tumors of the present study which was quite low as compared to study of Swiatoniowask et al who reported low, intermediate and high Fibronectin expression in 51.6%, 29% and 19.4% of breast tumors, respectively.[32] Further, no significant correlation was noted between Fibronectin expression and clinicopathological parameters, ER, PR and Her-2-neu status except a trend of reduced DFS and OS. Studies on Fibronectin expression in breast cancer are few and conflicting. Swiatoniowask et al have reported correlation of Fibronectin with histological grade but not with DFS and OS.[32] Contrary to this Takei et al revealed no association of Fibronectin expression with lymph node metastasis or tumor size, however, found as an independent predictor of relapse-free survival in invasive breast carcinoma.[33]

With respect to molecular subtypes, our study observed trend of higher incidence of loss of γ-catenin and gain of N-cadherin in triple negative breast carcinoma while loss of cytokeratin and gain of vimentin in Her-2-neu positive tumors, which suggests EMT molecules involved are uncommon in different molecular subtypes of breast cancer.

Further markers when intercorrelated, among epithelial markers, a significant positive correlation of E-cadherin was noted with γ-catenin and cytokeratin. Among mesenchymal markers, a significant positive correlation was noted between N-cadherin and vimentin. Further, epithelial markers when correlated with mesenchymal markers, a significant positive correlation were noted between cytokeratin and N-cadherin, and γ-catenin and fibronectin. Similarly, Maureen et al have noted strong positive associations of three basal keratins with vimentin in breast cancer.[34] However, no such correlation was noted between E-cadherin and N-cadherin by Nakashima et al in lung cancer.[35] Contrary to that an inverse correlation of E-cadherin expression with N-cadherin and vimentin was found in pancreatic carcinoma[31] and with only N-cadherin in breast cancer.[36]

Furthermore, PRL-3 an EMT initiator showed significant positive correlation with N-cadherin and cytokeratin in the present study. Such type of correlation has not been observed in any study till now. While Wang et al reported PRL-3 over expression enhanced the expression of Snail and mesenchymal marker fibronectin.[4] Up-regulation of Snail, together with other transcriptional events, likely lead to down-regulation of the epithelial markers E-cadherin, γ-catenin, and integrin β. Snail not only represses epithelial genes but also stimulates mesenchymal gene transcription leading to disease aggressiveness. [2,4,18,37] Further, a significant positive correlation of Snail was noted with vimentin and N-cadherin in our study and with study Hanan et al.[18] Therefore, the findings of present study confirmed that Snail enhances EMT in breast carcinoma.

Additionally, multivariate analysis by cox regression forward stepwise regression model strengthened our previous findings that among EMT markers vimentin emerged as significant prognostic factor for predicting poor DFS and OS in breast cancer.

Conclusion

Thus, PRL-3 and Snail are found to be upstream regulators in triggering EMT in breast

cancer which was confirmed by a positive correlation of PRL-3 with N-cadherin and Snail with N-cadherin and vimentin. Further, vimentin expression emerged as a biomarker for predicting reduced DFS and OS in breast cancer that can be evaluated with other predictive parameters to identify candidates in whom of EMT inhibitors needed to revert EMT.

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Febrile Neutropenia in Hematological Malignancies: Clinical and Microbiological Profile and Outcome

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Summary
Febrile neutropenia (FN) is considered a medical emergency. Patients with hematological malignancies (HM) commonly experience FN. Broad spectrum antibiotics have to be started empirically to prevent complications. This study attempts to highlight the common infectious agents, their antibiotic sensitivity pattern and outcome in HM like acute myeloid leukemia (AML). Since sporadic data exist from India, this study can be a useful guide for oncologists managing FN in India and building institutional antibiotic policy. In this study, 44 patients with HM, diagnosed and treated for FN episodes with positive blood culture from April 2015 to march 2016 at GCRI, Ahmedabad were analyzed. Blood cultures of patients during febrile episodes were collected from central venous catheters and peripheral blood. Majority of the patients (84%) with FN episodes had absolute neutrophil count (ANC) less than 100/mm3. Eighty four percent patients developed FN between post chemotherapy day 6 to 10. The most common organisms isolated were gram-negative bacilli (80%), with Escherichia coli (48%) being the most frequent pathogen. All Escherichia coli were sensitive to colistin (100%), whereas sensitivity pattern to other antibiotics was as follows: 95%, 50%, 15%, 5% to tigecyclin, amikacin, meropenem, piperacillin-tazoactum respectively. Second most common organisms isolated were Acinetobacterbaumanniiand Klebsiellapneumoniae (14%). Sensitivity pattern of Acinetobacterbaumannii to piperacillin-tazoactum, meropenum, amikacin, levoflox was 100%, 100%, 83%, 16% respectively. Sensitivity of Klebsiellapneumoniae to colistin, tigecyclin, amikacin, meropenum was 100%, 50%, 33%, 16%. Overall mortality was 30%.In AML, there is high risk of developing FN on 2nd week post chemotherapy and when ANC is less than 100/mm3. Most common cause of FN is gram negative septicemia with most common organism is Escherichia coli. Sensitivity of microorganisms to various antibiotics is very predictable. Thus, one can start antibiotic empirically according to institutional sensitivity pattern and then therapy should be tailored to the most appropriate antibiotics according to the bacterial culture results.
Keywords: Acute myeloid leukemia, Febrile neutropenia, Gram negative bacilli, Antibiotics sensitivity.

Introduction

Febrile neutropenia (FN) is considered a medical emergency. It leads to prolonged hospital stay, increases the cost of treatment, morbidity and mortality. With the use of empiric antibiotics and availability of broad spectrum antibiotics, aggressive chemotherapeutic regimens can be used and the mortality due to FN has gradually reduced from 75% to <10%. Patients with hematological malignancies (HM) commonly experience FN. Broad spectrum antibiotics have to be started empirically to prevent complications. This study attempts to highlight the common infectious agents, their antibiotic sensitivity pattern and outcome in HM like acute myeloid leukemia (AML). Since sporadic data exist from India, this study can be a useful guide for oncologists managing FN in India and building institutional antibiotic policy.

Methods and Materials

This is a retrospective cohort study conducted at medical oncology department of tertiary care center from April 2015 to March 2016 (12 months). In this study, 44 patients with HM, diagnosed and treated for febrile neutropenic episodes with positive blood culture were analyzed. Blood cultures of patients during febrile episodes were collected from central venous catheters (CVC) and peripheral blood.CVC was inserted in all patients except 1 patient with APML.

All diagnosed cases of HM admitted in the ward were started on treatment as per the standard protocol.[1-4] GCSF was given only in patients with AML during consolidation as a prophylaxis. It was not given during induction chemotherapy.FN was diagnosed in the occurrence of a single oral temperature of ≥ 101°F or 100.4°F for more than 1 hour, along with an absolute neutrophil count (ANC) ≤500/µl or ≤1000/µl with predicted rapid decline over next 48 hours.[7]

Laboratory Parameters:

All febrile patients were evaluated for relevant history, physical examination, complete haemogram and other relevant investigations. Microbiological cultures of blood from peripheral vein, central line were sent in patients diagnosed as FN. Sputum, stool and/or pus cultures were done when clinically indicated.

All patients received piperacillin-tazobactum, amikacin and fluconazole empirically. Antibiotics were modified according to culture reports available within 4 to 5 days. Vancomycin was

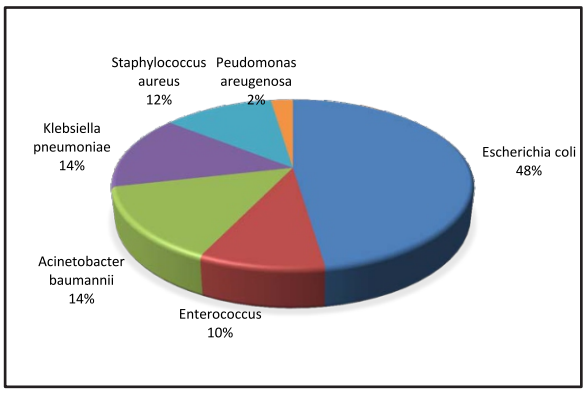

Figure 1: Most common organism isolated was Escherichia coli

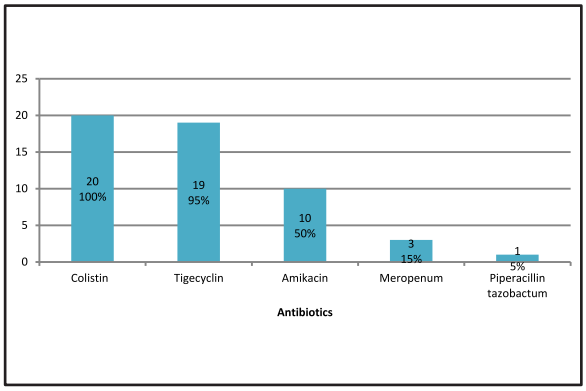

Figure 2: Sensitivity of Escherichia coli to antibiotics

administered additionally to the patients, who had persistent fever, hypotension, suspected central line infection, mucositis or pneumonia. Amphotericin B was initiated empirically in patients in whom fever persisted despite antibiotics on day 4 or 5, in sinusitis with suspected fungal infection, pleuritic chest pain or chest X-ray suggested presence of fungal ball or halos. Culture positivity, organism isolated, antibiotic sensitivity and outcome of FN were recorded for all patients.

Results

In our study 44 patients, 27 male and 17 female were included (Table 1). Out of 44 patients 42 patients had AML, 1 had acute promyeloblasic leukemia and 1 had aplastic anemia. Fifty nine percent of patients developed neutropenia within 48 hours of initiation of chemotherapy. Eighty four percent of the patients with FN episodes had ANC less than 100/cumm. Eighty four percent of patients developed FN between post chemotherapy days 6 to 10. The most common organisms isolated were gram-negative bacilli (GNB) (80%), with Escherichia coli (48%) being the most frequent pathogen followed by Acinetobacterbaumannii(14%), and Klebsiellapneumoniae (14%), Staphylococcus aureus(12%), Enterococcus (10%), Peudomonasaeruginosa(2%)(Figure 1).All Escherichia coli were sensitive to colistin (100%),

Table 1: Characteristics of the patients

Patient Characteristics	N
Gender	
Male	27
Female	17
Age(Years)	
1 -20	22
20 -50	22
>50	None
Diagnosis	
AML	42
APML	1
Aplastic Anemia	1
Type of Treatment	
Induction	35
Consolidation	8
TIS	1
Clinical Event	
LRTI	11
Neutropenic Diarrhea	6
Not Known	27

Table 2: Comparison with other studies

Study	Gram -ve Septicemia	Most Common Organism	Mortality
Rudrapatna S[14]	63%	E. coli	14%
Kalaskar P[15]	60%	E. coli	-
Ghosh I[6]	56%	Gram –ve bacilli	8%
Advani SH[7]	-	E.coli	
Our Study	80%	E. coli	30%

whereas sensitivity pattern to other antibiotics was as follows: 95%, 50%, 15%, 5% to tigecyclin, amikacin, meropenem, pipercillin-tazoactum respectively (Figure 2). Second most common organisms isolated were Acinetobacterbaumannii and Klebsiellapneumoniae (14%). Sensitivity pattern of Acinetobacter baumannii to pipercillin-tazoactum and meropenem was 100% while it was 83% and 16% to amikacin and levoflox respectively. Sensitivity of Klebsiella pneumonia to colistin was 100% while sensitivity of tigecyclin, amikacin and meropenum was 50%, 33%, 16% respectively. Sensitivity of Staphylococcus

aureus to tigecyclin was 100%, to vancomycin and linezolid it was 80% and to teicoplanin it was 60%. Sensitivity of Enterococcus to tigecyclin, linezolid, teicoplanin was 100%, however for vancomycin it was 75%. No patient required removal of CVC. Overall mortality was 30%, all attributed to septicemia.

Discussion

This study was undertaken to review the clinical profile, antibiotic sensitivity pattern, and outcome of treatment in FN with HM patients.

We found FN to be most common in AML patients on chemotherapy. Similar incidence was also seen in other studies.[6] This high incidence of FN in acute myeloid leukemia could be attributed to the use of intensive chemotherapy leading to prolonged and profound neutropenia, which increases the risk of infection. Similar to other studies FN more occurred during induction chemotherapy, than during consolidation and maintenance chemotherapy commonly.[7] In this study, majority of the patients had prolonged neutropenia (>7 days) and with associated morbidity and mortality, which was in concordance to other studies.[8]

Therapy for AML in India is complicated by 65% culture positive infections.[9] Inwestern countries, while infections with GNB predominated during 1970 and 80, a predominant shift to gram positive cocci (GPC) infections has been reported in later years.[10] This is usually attributed to frequent use of indwelling CVCs and the use of fluoroquinolone prophylaxis which suppresses the aerobic GNB colonizing the GIT but fails to suppress the microaerophilic GPC.[11,12] In developing countries like India GNB septicemia is predominantthat can be due to fluroquionolone resistant organisms.[13-15](Table 2)

Our retrospective data was analyzed to document culture and susceptibility pattern in patients with FN, so that first-line antibiotic policy can be reviewed with reassurance of better surveillance in the treatment paradigm of HM. Gram negative infection with Escherichia coli is the most prevalent type of infection but showing considerable sensitivity to the current first-line antibiotic cover making this choice the most effective strategy. Overall mortality in this study was 30% in spiteof starting sensitive antibiotics according to culture which can be explained by associated fungal infections or polymicrobial infections or in vivo resistance or many times refractory disease. In our study only 12% cases with MRSA were identified, 80% of which were vancomycin susceptible.

Cancer patients on chemotherapy are significantly predisposed to FN due to immune deficiency mediated either by the underlying malignancy and/or anticancer chemotherapy and mucosal breach due to chemotherapy. This is reflected by the fact that nearly 80% of these infections are due to endogenous flora. With the present menace of antibiotic resistant "superbugs," judicious use of available antibiotics is the need of an hour. The strength of our study is that it is a large single institutional study which has taken into account the FN in HM. Though observational, it can go a long way in transforming the health policies and antibiotic policies in our tertiary care oncology center. Since sporadic data exist from this part of the world, this study can be a useful guide for oncologists managing FN in India and building institutional antibiotic policy. As our study is a large single institutional retrospective study, selection bias could not be excluded. Further multi-centric studies are needed to validate these findings.

Conclusion

In AML, there is high risk of developing FN on second week post chemotherapy and when ANC is less than 100/mm^3. Most common cause of FN is gram negative septicemias with commonest organisms are Escherichia coli and Acenatobacterbaumanni which have reasonable sensitivity to our empirical first line antibiotics. Sensitivity of microorganisms to various antibiotics is very predictable. Thus, one can start antibiotic empirically according to institutional sensitivity pattern and then therapy should be tailored to the most appropriate antibiotics according to the bacterial culture results.

Conflict of interest:
None

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An Audit of Malignant Melanoma Patients Treated in Three Years at a Single Institute: Our Regional Cancer Centre Experience

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Summary

Malignant melanoma is skin malignancy with very minor subset of presentation. It is a rare malignancy but forming major contribution from skin cancer related mortality and morbidity. The cell of origin is melanocyte and thus present in all areas of epidermis and in parts of eye and upper respiratory, gastrotintestinal and genitourinary tracts. We aimed at analyzing this rare group of patients presenting at our hospital with detailed analysis including clinical features, presentation, diagnosis, management and response and follow up. The present study of series of 27 patients presenting to Gujarat Cancer & Research Institute is a mixed subgroup of various presentation of this rare disease at different sites with different presentation and management also offered according to each individual case accordingly.

Keywords: Malignant melanoma, regional cancer centre, audit

Introduction

Malignant Melanoma (MM) is a rare cutaneous malignancy. The paradox is, though it represents a minority of all cancers, it is a major contributor of skin cancer related morbidity and mortality. The estimated age-standardized incidence of melanoma has been 22 in 100,000 people and has risen greater than 10-fold in the recent decades.[1] Various studies have established the excessive sun exposure as a strong risk factor, especially during childhood in the fair skinned population belonging to low socio-economic class living in the tropical areas. The prime aim of the treatment is to identify the lesion as early as possible and to excise it with adequate margins without causing significant mutilation to the patient, as the excisional surgeries alone have been shown to be adequate for early or thin lesions. The Malignant Melanoma is relatively resistant to chemotherapy and radiotherapy. Their role in the adjuvant settings are yet unproven.

Aims and Objectives

The present study is aimed at analyzing the patients diagnosed and treated for MM of various sites between 2012 to 2014 at the Gujarat Cancer & Research Institute (GCRI), Ahmedabad, Gujarat, India. GCRI is a Regional Cancer centre in the western India and receives the patient flow from Gujarat, Rajasthan and Madhya Pradesh which are the geographic regions lying near the Tropic of Cancer and having dry and hot weather conditions for the major part of the year and majority of the people belonging to the low socio-economic class working as farmers, farm labourer, labourers at construction sites and other menial manual labors done in heat sun-exposed conditions. Since MM is asymptomatic in presentation, it goes unnoticed by the patient for a long time resulting in the delay in presenting to a clinician. Further, the rarity of it and its overlapping picture with many benign conditions poses diagnostic challenges to the local clinicians of the rural areas. MM has many peculiarities in the etiopathogenesis, nodal and distant metastasis, prognostic factors and the treatment approaches. We also have a limited data on the epidemiology and the outcomes of MM this part of the country. Through this study, we aim at identifying the different patterns of presentation of MM which is very rare disease and how differently they are managed at different sites reflecting difference in their prognosis too.[2]

Methods and Materials

The current study is analysis of 27 patients diagnosed with Malignant Melanoma (MM) of various sites and treated by various modalities at our institute between 2012 and 2014. Their data were obtained from the Medical Records Department of the institute and analyzed to identify the demographic pattern, the various modalities of the treatment taken by them. The medical record files of the patients were studied to determine the Progression Free Survival (PFS), Loco-regional control (LRC) and the time duration of development of the distant metastasis. Later on, they were telephonically contacted to find out the outcome in terms of Overall Survival (OS).

A total of 27 diagnosed cases of the Malignant Melanoma (MM) were treated at the GCRI between 2012 and 2014. Of these, 14 patients were males and 13 were females, making the sex predilection almost equal. The median age group of presentation was 51-60 years with more than half of the total patients belonging to this age group (n=15). Very few patients belonged to the two extremes of the age groups with only 5 patients in the age group between 31 – 50 years

and just 1 patient in the advanced age of 71+ years group. All the patients were then analyzed for their presentation, treatment received, response, and relapse and survival pattern.

Results and Analysis

The patients contacted if possible and otherwise their files collected from medical record department were studied in detail. Seventy seven percent (n=21) of the patients presented with primary lesion over skin followed by those of rectum/anal canal (n=4), eye/orbit/uveal tract (n=1), breast (n=1). Only one patient had lymph node metastasis at the time of presentation. 88.9% (n=24) patients were treated with the surgical excision of the primary lesion. Following it, 40.7% (n=11) patients underwent adjuvant radiotherapy. Similar number of patients were treated with the chemotherapy (n= 11) of with the agents used were taxanes (n=2), dacarbazine (DTIC) (n=2), Platins (n=3), Imatinib (n=1) and Temozolamide (n=3). No patient showed progression during the treatment. Only 1 patient died during the course of the treatment. Only 4/27 patients are surviving and disease free in December 2017.

One patient (56/M) in the cohort had the MM of the choroid of the left eye. It was diagnosed in November 2010. He had underwent Enucleation for the same following which no adjuvant treatment was taken and had disease free survival (DFS) of 4 years. Then, he developed a recurrent lesion which was 4.5 cm in the greatest dimension and was eroding the bone of the orbit on the Computed Tomography (CT) scan. The surgery done this time was left sided exenteration following which he was treated with adjuvant radiotherapy 50 Gy/25# with single anterior field on cobalt till January 2015. Patient was disease free for 1.5 years when he developed brain metastasis (5.5 X 3.8 X 5.4 cm greatest dimension of the lesion in left high parietal region) for which, he was given whole brain radiotherapy (WBRT) in May, 2016. Then, patient got diagnosed with biopsy proven liver metastasis in August, 2016. Since then, patient is on maintenance temozolamide therapy.

One patient (70/F) had got MM of the left breast. It was 3 cm lesion in the greatest dimension, located in the peri-areolar region. On the presentation itself, the patient had 3.7 X 2.7 cm nodal mass in the left axilla. She was treated with the primary surgery of left sided modified radical mastectomy. On histopathological examination, it was staged as pT2N3; stage III C. Patient has been lost to follow up since surgery and could not be contacted even telephonically so the current disease status could not be found out.

Four patients had MM of anal canal and rectum. In 2 patients initially the patient was given neoadjuvant chemotherapy with two three cycles of combination of paclitaxel and carboplatin following which abdominoperineal resection with colostomy was done. One of the patient had histopathological findings revealing the tumor size to be 1.5 cm in greatest dimension with depth of invasion 0.6 cm infiltrating muscularis externa, involving 2/3rd of the wall thickness but less than ½ circumference of anal canal. All three perianal lymph nodes were free of the disease. It was followed by adjuvant radiotherapy 50gy/25# delivered through anteroposterior/posteroanaterior portals. The patient is disease free till now and on regular follow up. Another patient of the MM of rectum had presence of liver metastases on presentation and patient was kept on temozolamide following which patient survived for 8 months. Rest two patients were of lesion on anal canal treated with curative radiotherapy and chemotherapy (60Gy/30#) with no lesion at follow up till date.

Maximum patients (n=21) had MM of the skin, mainly appendages like thumb, toe or heel. Seventy six percent (n=16) patients developed skin metastasis at distant sites like the anterior abdominal wall. The mean greatest dimension of the lesion was 3.6 cm on the histopathological examination following the primary surgical excision. Only 1 patient developed lung metastasis. MM of the skin as the primary site had less preponderance for the distant metastasis. Table 1 shows glimpse of all patients presenting at different sites with their treatment approach and behavior pattern.

Discussion

Malignant Melanoma WHO Code 8720 is a potentially preventable but a highly fatal form of skin cancer. MM arises from the neural crest of the embryo and during the development; they migrate to various locations such as basal layer of epidermis and the uveal tract. The most common site of presentation is the skin and mucous layer which are the sun-exposed anatomic sites, but due to this migration, it can also affect the sites like the central nervous system (e.g. meninges and uveal tract), the aero-digestive and genitourinary tracts (eg. nasopharynx, oral cavity and vagina).

The excessive sun-exposure has been established as a strong causative agent. Other risk factors being atypical dysplastic melanocytic naevi (moles) (>15 atypical naevi associated with 3 to 20 fold raised risk of developing MM), patients receiving immunosuppressive therapy following organ transplantation (3-fold risk), extensive treatment with PUVA (Psoralens and UVA therapy), changes in moles during pregnancy, genetic predisposition associated with chromosome 1, 6 and 9 and the

Table 1: Pattern of presentation and management of malignant melanoma at different sites

Patient No	Age	Sex	Diagnosis	Surgery	CT	RT	Metastases	Remarks	Alive (A) Or Dead (D)
1	56	M	MM Choroid	Enucleation 2010Exenteration 2014	TMZ	Adjuvant RT 50 Gy/25# Jan 2015 WBRT May 2016	Brain Liver	-	D
2	48	M	MM Rectum	APR HPE: Invovling 2/3rd thickness	2-3 cycles NACT (Paclitaxel Carboplatin)	Adjuvant RT 50 Gy/25#	nil	Disease free on regular follow up	A
3	52	M	MM Rectum	APR HPE: 3/3 LN positive	2-3 cycles NACT (Paclitaxel Carboplatin)	Adjuvant RT 50 Gy/25#	nil	-	D
4	61	M	MM Rectum	-	-	-	Liver	Survived for 8 months	D
5	60	F	Anal canal	-	TMZ	Curative RT 60 Gy/30#	-	Disease free on regular follow up	A
6	63	F	Skin	RND	TMZ	Adjuvant RT	nil	Disease free and on regular follow up	A
7	50	M	Skin	-	-	WBRT 30Gy/10#	Brain Liver	Survived for 1 year	D
8	58	M	Skin	Excision	Imatinib	30Gy/10# local site	Anterior abdominal wall	-	D
9	65	F	Skin	Excision of thumb	DTIC	Adjuvant RT	Skin	Disease free on regular follow up	A
10	55	M	Skin	Excision of great toe	Platin	Adjuvant RT	Skin	-	D
11	60	M	Skin	Excision	Platin	-	Skin	-	D
12	55	F	Skin	Excision	-	Adjuvant	Skin	-	D
13	60	F	Skin	Excision	-	Adjuvant	Skin	-	D
14	45	F	Skin	Excision	-	Adjuvant	Skin	-	D
15	60	F	Skin	Excision	DTIC	-	Skin	Best supportive care	D
16	45	F	Skin	Excision	-	Adjuvant	Skin	-	D
17	60	F	Skin	Excision	-	-	Skin	-	D
18	55	F	Skin	Excision	-	-	Skin	-	D
19	70	F	Skin	Excision	Platin	Adjuvant	Lung	-	D
20	55	F	Skin	Excision	-	-	Skin	-	D
21	60	M	Skin	Excision	-	-	Skin	-	D
22	85	M	Skin	Excision	-	-	Skin	-	D
23	40	M	Skin	Excision	-	-	Skin	-	D
24	55	M	Skin	Excision	-	-	Skin	-	D
25	40	M	Skin	Excision	-	-	Skin	-	D
26	60	M	Skin	Excision	-	-	Liver	-	D
27	70	F	MM Breast	Left MRM HPE: T2N3	-	-	-	Patient could not be contacted	Not known

NACT: Neo Adjuvant Chemotherapy
APR: Abdomino Perineal resection
WBRT: Whole Brain Radiotherapy
MRM: Modified Radical Mastectomy
DTIC: Dacarbazine
RND: Radical Neck Dissection

inherited conditions like Xeroderma Pigmentosum and radiation treatment for the childhood cancer. 'Red hair phenotype' i.e. light skin pigmentation, red or blond hair colour, high density freckling and light eye colour (green, hazel, blue) has elevated risk of developing MM. There is preclinical evidence that Vitamin D confers protection against the malignant transformation of melanocytes, though, low levels of it along with excessive sun-exposure can lead to MM.

There are four major subtypes of MM : Superficial Spreading Melanoma-70% cases, Nodular Melanoma - 15 % cases, Acral Lentiginous Melanoma -10% cases, Lentigo Maligna Melanoma - 5% cases, having precursor lesion of melanoma in situ called Hutchinson's freckle which manifests as a relatively large (>3 cm), flat, tan-colored with different shades of brown and is present for >5 years. Other less common variants are amelanotic melanoma, spitzoid melanoma, desmoplastic melanoma and pigment synthesizing (animal-type) melanoma aka melanocytoma.[3] Differential diagnosis of MM having similar clinical picture as it are Basal Cell Papilloma (seborrhoeic keratosis), pigmented basal cell carcinoma, thrombosed angioma, pyogenic granuloma and dermatofibroma. Melanocytoma may be confused with other cutaneous melanocytic proliferations, such as common blue nevus, cellular blue nevus, malignant blue nevus and Spitz nevus.

Dermatoscopy or epiluminescence microscopy is used for diagnosis of the primary lesion aided by the imaging of the local site. Investigations for the metastatic disease include CT scan of chest and abdomen, full blood count, renal, liver and bone profile; and LDH should be individually tailored in view of the presence of the symptoms. The staging is done according to the 8th edition of the AJCC TNM classification and the treatment is decided accordingly. The screening tools for the early detection of MM include most commonly the 'The Ugly Duckling Sign Concept" based on the patient self-examination ABCDE criteria i.e. asymmetry (A), border irregularity (B), colour variability (C), diameter greater than 6 mm(D) and elevation or enlargement(E). [4,5]

The most important prognostic factor was the tumor depth of invasion. More than 1mm depth of invasion was associated with poor prognosis due to high risk metastasis. Other factors being ulceration, satellitosis and presence of metastasis at the time of diagnosis. For the patients with the documented nodal metastases, the most crucial prognostic feature was the number of the involved lymph nodes, but primary tumor ulceration and the microscopic and macroscopic burden of the nodal disease was significant on the multivariate analysis. Patients with skin, subcutaneous and distant nodal metastases fared better than those with visceral metastases. Patients with thinner lesions may still be at risk of nodal disease and may benefit from Sentinel Lymph node biopsy, if the primary lesion is ulcerated, is associated with satellitosis or is Clark Level IV or V.

The prime aim of the treatment is to identify the lesion as early as possible and to excise it with adequate margins without causing significant mutilation to the patient, as the excisional surgeries alone have been shown to be adequate for early or thin lesions. The MM is relatively resistant to chemotherapy and radiotherapy. Their role in the adjuvant settings are yet unproven. Though, the metastatic disease spread through haematogenous route to liver, brain or lungs have to be given an attempt of chemotherapy. Also, few studies have been conducted to show the role of adjuvant radiotherapy in incompletely excised disease or extra capsular nodal disease.

To come to the consensus of the adequate margins according to the thickness of the tumor, some studies were conducted. Regarding, the practice of the Elective Lymph Node Dissection (ELND), it's role is established only in the cases of proven lymph node metastasis. The surgeon should take the decision of ELND with a pinch of salt in unproven cases of LN metastasis as there is no proven survival benefit and it is associated with a high risk of lymphedema. The rate of melanoma-specific deaths in the biopsy group was 26.2% among patients who underwent immediate lymphadenectomy compared with 48.7% in the observation group who underwent delayed lymphadenectomy. For the advanced disease, where lymphoid infiltration into tumor and surrounding tissues is seen, spontaneous remissions are reported by use of Interferon alfa and interleukin-2 shown single-agent response rates of 15-20%.[6] For unresectable tumors, radiotherapy can prevent ulceration and bleeding. It can also be used in unresectable lymph node disease, painful subcutaneous or bone metastasis. High dose in single fraction or hypofractionated regimens have been used.

DTIC is the 'gold standard' chemotherapeutic agent against which all other agents are tested.[7] When used alone, it gives a partial response rates of about 20% and complete responses in 5 to 10%. Temozolamide[8] is a new alkylating agent with the advantage of giving 100% oral bioavailability and excellent penetration of the BBB (blood brain barrier) and CSF. It's effectiveness is equal to that of DTIC in the metastatic MM giving a median survival of 77 months v/s 64 months with TMZ and DTIC respectively. Also, TMZ has shown improvement in the quality of line in certain aspects. Other agents studied are vinca alkaloids, nitrosoureas and the most

recently taxanes. No survival advantage has been seen with combining immunotherapy with DTIC for the palliative setting. Isolated limb perfusion with melphalan with or without tumor- necrosis factor has been useful for peripheral lesions, especially lower limb, where primary lesion is unresectable or has extensive in-transit metastasis. Another peculiarity about MM is that the clinical use of immune checkpoint blocking antibodies such as ipilimumab or pembrolizum has shown great results in the treatment of the metastatic melanoma through the abscopal effect.[9] Our series of 27 patients with different presentation at different sites were individualized and tailored treatment accordingly.

Conclusion

Malignant melanoma is a rare skin malignancy but with different presentation and behavior at different sites. Each site behaves differently and should be thus managed according to individual site and staging for optimal results.

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Percutaneous Sclerotherapy for the Treatment of Aneurysmal Bone Cyst, What are the Outcomes?

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Summary

Aneurysmal bone cyst (ABC) shows onset in the first decades of life with incidence of 1.4/100,000 constituting about 1% of benign bone tumours. Management includes combinations of embolization, curettage with or without bone grafting, cementing of the cavity, reconstructive surgery but shows recurrence rates of 10 to 30%. Sclerotherapy is an interesting alternative to surgery with less recurrence. We report our experience using 3% polidocanol as sclerosant and describe the clinical and radiological results. We retrospectively reviewed 15 patients who underwent percutaneous sclerotherapy for the treatment of Aneurysmal bone cyst with polidocanol from 2015 to 2017. Repeated percutaneous injection of 30 mg/mL 3% polidocanol under fluoroscopic or CT guidance and general anaesthesia was the mainstay of treatment. Three injections were given at the interval of six weeks and maximum of four injections had been given if previous three failed to heal the lesion. Radiological assessments of the tumour combined with clinical assessment of the patient's symptoms were performed on an outpatient basis, usually 6–8 weeks after completion of a session of injections. The median number of injections per patient was 2 (1-4). 4 patients were cured by a single injection of polidocanol, whereas 1 patient required 4 injections. The efficacy of the method was 93.33%. Pain resolved (VAS = 0) in 14 patients (93.33%) by 3 months after injections and had convincing radiological sclerosis. One patient had persistent pain even after fourth injection and progression of disease, hence opted for scapulectomy. There were no cases of local recurrence, anaphylaxis, major adverse reactions or local necrosis at the injection site. Minor local inflammatory reactions were observed in 2 patients and resolved spontaneously. Sequential percutaneous administration of polidocanol is the standard treatment for Aneurysmal bone cyst at our institution as we have found it to be a safe, simple procedure with an excellent cure rate.

Keywords: Aneurysmal bone cyst, Percutaneous sclerotherapy, Polidocanol, efficacy

Introduction

Aneurysmal bone cyst (ABC) shows onset in the first decades of life with incidence of 1.4/100,000 constituting about 1% of benign bone tumours.[1, 2] It is mainly located in the metaphysis of the long bones and in the spine.[3-5] Many authors consider diagnostic biopsy imperative [6–10]. Secondary forms associated with benign or malignant tumour and differential diagnoses such as telangiectatic osteosarcoma need to be ruled out. Understanding of the pathogenesis is still evolving; however, the original description by Lichtenstein.[11] favouring hemodynamic disturbance is the most popular.[12, 13, 14] Management includes combinations of embolization, curettage with or without bone grafting, cementing of the cavity, reconstructive surgery but shows recurrence rates of 10 to 30%.[2,4,6,15] Sclerotherapy is an interesting alternative to surgery with less recurrence.[4, 5, 16, 17, 18, 19] We report our experience using a method of sclerotherapy using 3% polidocanol (hydroxypolyaethoxydodecan; available in 2 ml ampoules; 1 ml = 30 mg of polidocanol) and describe the clinical and radiological results.

Patients and Methods

We retrospectively reviewed 15 patients who underwent percutaneous sclerotherapy for the treatment of Aneurysmal bone cyst with polidocanol from 2015 to 2017 (Table 1). Diagnosis was based on the radiological characteristics of the lesion (plain radiographs and MRI scans) and histopathologically confirmed with J needle biopsy. Repeated percutaneous injection of 30 mg/mL 3% polidocanol under fluoroscopic or CT guidance and general anaesthesia was the mainstay of treatment. The lesion was punctured with a J needle and fluid was aspirated to verify proper positioning preceding infusion of the sclerosant. Aspiration of a significant amount of bloody fluid from the cavity was interpreted as a sign of remaining active disease. 3 injections were given at the interval of six weeks and maximum of four injections had been given if previous three failed to heal the lesion. The mean follow-up time was 20.2 (3–36) months. Radiological assessment of the tumour (to detect signs of cortical sclerosis, reduction of the volume and ossification of the cavity) combined with clinical assessment of the patient's symptoms (pain which was assessed by VAS score and swelling at the site of the lesion) were performed on an outpatient basis, usually 6–8 weeks after completion of a session of injections. Patients were allowed normal weight bearing and were followed until the lesion showed evidence of sclerosis and the symptoms subsided (defined as healing, which was the endpoint of treatment). Family and patient were informed of the advantages and risks of the procedure and written consent was obtained.

Results

The results are summarised in Table 2. The median number of injections per patient was 2 (1-4).

Table 1: Demographic data and tumour characteristics

Patient No	Gender	Age	Site
1	M	17	Calcaneum
2	F	12	Superior Pubic Rami
3	M	13	Proximal Humerus
4	M	18	Distal Femur
5	M	30	Calcaneum
6	M	11	Sacrum
7	F	16	Iliac Wing
8	M	19	Scapula
9	F	16	Proximal Humerus
10	M	19	Proximal Humerus
11	M	10	Proximal Tibia
12	F	9	Fibula
13	M	15	Proximal Femur
14	F	14	Sacrum
15	M	8	Proximal Humerus

Four patients were cured by a single injection of polidocanol, whereas 1 patient required 4 injections. The efficacy of the method was 93.33%. Only 1 patient had progressive disease despite repeated sclerotherapy for aneurysmal bone cyst of the scapula and proceeded to scapulectomy.

Pain resolved (VAS = 0) in 14 patients (93.33%) by 3 months after injections and had convincing radiological sclerosis. One patient had persistent pain even after fourth injection and progression of disease, hence opted for scapulectomy. Two patients are still on routine follow-up and their symptoms have clearly improved. Representative case is presented in Figure 1, depicting consolidation of the lesions after serial sclerotherapy. There were no cases of anaphylaxis, major adverse reactions or local necrosis at the injection site. Minor local inflammatory reactions were observed in 2 patients and resolved spontaneously. There were no cases of

Table 2: Outcomes of Sclerotherapy

Patient No	No of Injections	Post Procedure Complications	VAS Score	Follow Up Months
1	2	Nil	0	15
2	2	Nil	0	17
3	3	Nil	0	15
4	1	Nil	0	24
5	3	Local inflammation	0	26
6	1	Nil	0	3
7	2	Nil	0	14
8	4	Progression of disease, Scapulectomy	6	8
9	2	Nil	0	36
10	1	Nil	0	34
11	1	Nil	0	32
12	2	Nil	0	28
13	2	Nil	0	24
14	3	Local inflammation	0	16
15	2	Nil	0	12

Table 3: Review of Literature and Comparison of efficacy of Sclerotherapy

Study	Year	No of Patients	Efficacy
Rastogi et al	2006	72	97%
Varshney et al	2010	45	93.3%
Brosjo et al	2013	38	97%
Batisse et al	2015	19	94.7%
Current Study	2018	15	93.33%

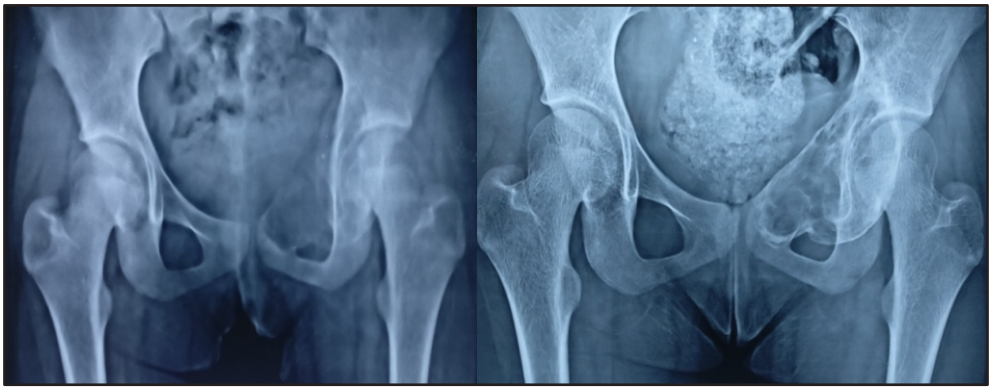

Figure 1: Aneurysmal bone cyst in the superior pubic rami of a 12-year old female patient, showing consolidation after 2 injections of polidocanol

infection or complex regional pain syndrome.
There was none case of local recurrence till last follow up.

Discussion

The optimal treatment method for Aneurysmal bone cyst is still being debated. Open curettage with or without bone grafting is a widely accepted mode of treatment but it is accompanied by a high recurrence rate of approximately 30% which can be reduced to 15% when a high-speed burr is used.[17] Wide en-bloc resection gives excellent results in terms of local control, which approximates 100%. Yet wide surgical margins are often not feasible as the lesion can be close to neurovascular structures. Furthermore, extensive surgery is associated with considerable morbidity. Cumulative data suggest a growth disturbance rate of about 10% after various surgical procedures. [20, 21, 22, 23] Embolization of the feeding arteries has also been suggested as an alternative with good results reported.[24] However the procedure is technically demanding and is not applicable to all cases as they often lack large afferent vessels. When used for the treatment of aneursymal bone cysts of the spine selective angiography is necessary to ensure that there is no risk of spinal cord ischemia. Thus it is usually regarded as supplement to surgery.[25]

Sclerosants, in general, act by direct damage to the endothelial lining triggering a coagulation cascade and thrombotic occlusion of blood vessels.[26,27] Several sclerosing agents have been used but an alcoholic solution of Zein was the most popular. Polidocanol has been used safely in the treatment of varicose veins, venous malformations of the head, neck and limbs, gastro-oesophageal varices, endoscopic injection of intestinal vascular malformations and hydrocele of the testis.[27,28] The use of polidocanol is a definite advancement over previous sclerotherapy regimens that relied on alcoholic zein solutions which were more toxic and had serious adverse effects after spill-out into nearby tissues.[2,4,28] Indeed, we observed only minor transient inflammatory reactions which are in line with previous studies [(16-19)].

In our hands and also in previous reports (16-19) it has an efficacy exceeding 90%. Furthermore, the treatment is simple and carries negligible risk of morbidity, there is no scar formation and it can be reliably performed as a day-care surgery. The method is applicable to all cases and does not require sophisticated technical equipment. Most importantly sclerotherapy is effective in the case of lesions of the pelvis and sacrum that are difficult to treat surgically due to the risk of heavy bleeding and other major complications. In our series all 4 patients who presented with tumour in this region healed uneventfully. (Table 3) The limitation of this study is small sample size and retrospective nature and no comparison group was used. So a multicenter study with a comparison group would be recommended for future studies.

Conclusion

Sequential percutaneous administration of polidocanol is the standard treatment for Aneurysmal bone cyst at our institution as we have found it to be a safe, simple procedure with an excellent cure rate. It allows minimally invasive treatment of deep, potentially damaging lesions where access is difficult for surgery. We recommend that sclerotherapy should be carried out after an appropriate assessment of the patient under aseptic conditions and fluoroscopic/ CT guidance. Prevention of extravasation is the key to avoiding complications.

Conflict of interest
None

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Hospice Care is Not Only for Maggoted wound care!

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Hospice care is a **philosophy** of caring that supports those nearing the end of life and in need of refuge. It is a system of caring specially designed to restore dignity and provide a sense of personal fulfillment to the dying. Hospice, is an opportunity to care when cure is not possible!

History of Hospice

The name was first applied to specialized care for dying patients by physician Dame Cicely Saunders, who began her work with the terminally ill in 1948 and eventually went on to create the first modern hospice, 'St. Christopher's Hospice' in 1967 at Sydenham, England.[1]

The modern-day American hospice movement began in 1974 with establishment of the Connecticut Hospice in New Haven.[1]

In India, the earliest facilities to deliver palliative care within cancer centers were established in some places like Ahmedabad, Bangalore, Mumbai, Trivandrum, and Delhi in the late 1980s and the early 1990s.[2] In Gujarat, a hospice started in 1988, with generous donation by Shri Rajendra Dwarkadas Thakor and was inaugurated be Shri R Ventkatraman, President of India, at Community Oncology Center, Vasna, Ahmedabad.

Hospice for 'Pain management'

Approximately 80% of currently diagnosed patients are identified in advanced stages and often suffer from moderate to severe pain.[3]

Patients under hospice care have better pain management. The hospice care team will evaluate patient's pain on every visit using pain rating scales. Morphine dosages and schedules are maintained by nurses, which helps managing patients' pain better. Treating the side effects of drugs immediately, improves their compliance. Not all patients experience pain at the end of life, but Pain management is one of the primary goals of hospice care. In hospice, their "TOTAL PAIN" is addressed, which has physical, social, psychological and spiritual dimensions. This helps relieve their pain to great extent and improving Quality of Life (QoL) of patient and family members.

Hospice for 'Symptom control'

Seale and Cartwright, in 1994, in their book on "The year before death" have mentioned that cancer patients have huge symptom burden towards end of life. This not only affects their QoL but is the main cause of worries and fear in caregivers. At hospice, symptoms are assessed by round the clock assessment and are managed with appropriate treatment. Good symptom control is achieved for in-patients in hospitals as well, But at hospice, such symptoms are managed without many interventions or subjecting patients to investigations. Non-pharmacological interventions, individualized care and better communication are the cornerstone of hospice care. The expert hospice team works closely with the patient, their family, and their doctor to diminish or eliminate these symptoms through the use of medications, companionship, emotional and/or spiritual counseling, and change in diet, education or other techniques.

Hospice for 'Wound care in head and neck cancer'

There are various domains affecting QoL of head and neck cancer patients. The first and foremost dimension, appearance and cosmoses were least attended and least complained domain in our patients.[4] Fungating wound, with or without maggots or foul smell, is the most distressing domain, affecting their self-esteem, dignity and social status. Wound care by expert nurses, improves their appearance, reduces foul smell, and helps re-establish their social image and status. General care, overall hygiene and cleanliness are important aspects of nursing care in hospice. This uplifts their moral and restores their value.

Hospice for 'Psycho-social support'

Psychosocial support of a patient and their family is a responsibility of hospice team. Supports are aimed at enhancing overall well-being for the patient and their family, strengthening their own skills and abilities, and using their own resources for overcoming challenges. It also involves attending to the emotional, psychological, social, spiritual, practical needs and wishes of the individual within the context of their community of family, friends, and neighbors.

To fully appreciate and provide such support, social workers, clinical counselors and mental health providers are the part of the team of hospice. This team helps patients and caregivers by providing information, assisting in decision making, and

resolving their issues which cause distress. Some interventions may be tangible or information based, such as giving information about disease status, treatment options, financial benefits or resources that has an impact on care of patient and caregiver.

Hospice for 'Spiritual Care'

Religion and spirituality has impact on health of cancer patients. Patients reporting greater overall religiousness and spirituality also reported better physical health, greater ability to perform their usual daily tasks, and fewer physical symptoms of cancer and treatment.[5] Contrary to Out-patient and hospital set up, at hospice there is enough time and opportunity to discuss this aspect of patients' life. His/her belief in God, existence issues and values of life are discovered. They are able to express their desire and wishes which are fulfilled, whenever possible. Patients having strong religious beliefs, which are usually found in our Indian set up, accept death easily. Religious get-together in hospice adds life to their days.

Hospice for 'End of Life Care'

Hospice care is for patients who have been given a terminal diagnosis and have less than six months to live if the illness runs its course, but receiving hospice care doesn't mean that death is imminent. Many patients live for more than 18 months after their cancer is advanced or declared incurable. Such patients can go home and get admitted to hospice as and when need arises. The earlier the patient receives hospice care, the more opportunity there is to stabilize their medical condition and living well when dying.

Towards the end of life and terminal stage, hospice provides shelter to dying patient and their family. A well informed patient, whose symptoms are controlled, and pain is relieved is a matter of satisfaction to caregivers. Frequent communication, understanding and guidance by hospice staff solve many issues of end of life. After understanding about the terminal stage, many families/patients prefer to go home. As per the study, 83% of patients choose to die at home amongst their loved ones![6] Hospice care focuses on caring, not curing, and neither hastens nor prolongs the dying process. Dying is a natural process in hospice.

Hospice to 'Empower caregivers'

Hospice is a family-centered concept of care and focuses as much on the grieving family as on the dying patient. It addresses their problems, stress and worries through communication and education. Caregivers are trained and empowered to take care of patients at home. Caregivers' meeting, training sessions for general care of patients, Ryle's tube feeding, nutrition, wound care and medications help them to become self-reliant and confident to face the situation. Sharing of experience and sufferings through caregivers' group activities helps them to change their attitude towards the disease and death.

Following the death of a loved one, hospice provides continuous support to family with individual counseling, grief support groups, workshops, social groups and literature.

Hospice - 'A continuum of care'

Hospice is actually an approach to care that goes to wherever the patient is: A well linked home care service is the requirement of hospice, so that patient and family continue to receive the same care and communication, even when patient wishs to be at home. Hospice's interdisciplinary team helps patients and families address their concerns and strengthen their connections. Receiving hospice care does not mean giving up hope. When given a terminal diagnosis, a well-established hospice and home care services, allow patients to live life as fully as possible until the end.

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Management of a Giant Leiomyoma Mimicking Ovarian Malignancy

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Summary

A giant uterine leiomyomas can be sometimes confused for ovarian neoplasm. 36 year old nulliparous woman presented with dull aching pain and lump abdomen. On examination, there was a fixed, hard abdominopelvic mass uptill umbilicus , extending upto bilateral pelvic walls, obliterating POD and compressing rectum. In CT scan, there was 35x16x13 cm multilobulated, heterogeneously enhancing lesion in pelvis. Her CA125 was 62.33mIU/ml while CE19-9, beta hCG and alpha-fetoprotein were normal. With provisional diagnosis of ovarian cancer, patient was planned for chemotherapy. Later, biopsy of mass with IHC revealed leiomyoma.To reduce size of mass and facilitate surgery, patient was given four 3.75 mg monthly injection of leuprolide which led to reduction in size with increased mobility. Intraoperatively, there was a large abdominopelvic mass indenting inferior surface of liver and displacing transverse colon, extending deep in POD and rectovaginal septum. Intra-operative blood loss was 400ml. Post-operative period was uneventful. Final histopathology revealed multiple subserosal and intramural fibroids. The mass weighed around 3.8 kg. Bilateral ovaries were normal. At 3 months follow up, patient was asymptomatic with no radiological evidence of recurrence.

Keywords: Giant leiomyoma, Mimicking ovarian tumor, Ureteric injury, GnRH analogues

Introduction

Leiomyoma is the most common benign tumour of the uterus and affects 20–40% of women.1 Due to contiguity of structures, a giant uterine leiomyomas can be sometimes be confused for an ovarian or retroperitoneal cysts or neoplasm. Here, we present a case of a woman with giant uterine leiomyoma, mimicking an ovarian malignancy, with its management.

Case Report

A 36 year old nulliparous woman presented to the Gynae oncology OPD in GCRI, with complaints of dull aching pain, lump in abdomen and constipation for 6 months. Her menstrual history was normal. On examination, there was moderate ascites and a hard abdominopelvic mass was palpable uptill umbilicus. In pelvic examination, the mass was fixed, extending upto the bilateral pelvic walls, obliterating pouch of doughlas, compressing rectum and appear dissecting the rectovaginal septum. Also there was a 2x2 cm nontender, hard nodular growth around the umbilicus which was painful only during menstruation. On CT scan, there was 35x16x13 cm multilobulated, heterogeneously enhancing soft tissue density lesion seen arising in pelvis, extending to hypogastrium, right lumbar and right hypochondrium. Lesion was displacing the bladder anteriorly and right ureters laterally with moderate hydronephrosis. Moderate ascites was present. Her CA125 was 62.33mIU/ml while levels of CE19-9, beta hCG and alpha-fetoprotein were normal. The provisional diagnosis of an ovarian malignancy was made and patient was planned for chemotherapy with tissue diagnosis, in view of anticipated inoperability. Ultrasound guided biopsy of mass revealed benign spindle cell lesion . Immunohistochemistry was positive for vimentin, desmin, calponin and negative for S-100 and beta catenin suggesting it to be leiomyoma.

To reduce the size of mass and facilitate surgery, patient was given 3.75 mg monthly injection of leuprolide with clinical assessment prior to each dose. After 4 doses, the mass was slightly reduced in size with significantly increased mobility and there was space between the mass and bilateral pelvic wall. The CT scan showed a nonsignificant reduction in size of the mass. Patient was planned for surgery with consent for myomectomy and if needed hysterectomy as she was nulliparous. The patient was not keen on childbearing and consented for hysterectomy. Intraoperatively, there was 40x30x15 cm abdominopelvic mass. Superiorly, it was indenting the inferior surface of liver and displacing upper ascending and transverse colon while inferiorly it was extending deep in Pouch of Douglas, rectovaginal septum and compressing rectum. The uterine anatomy was not be made out seperately. Bilateral infundibulopelvic ligaments were stretched and along with both ovaries were adherent to the mass (Figure 1). Bilateral ureters were splayed by the mass and bladder was pulled over it. There was around 10x8 cm encystic fluid collection over the mass (Figure 2). Considerint the high risk of of ureteric damage during surgery for a large mass, the ureters were dissected and secured on umbilical tape above pelvic brim. The moblisation of mass was only possible when bilateral infundibulopelvic ligaments were ligated and transected high up in mid-abdomen, thus sacrificing

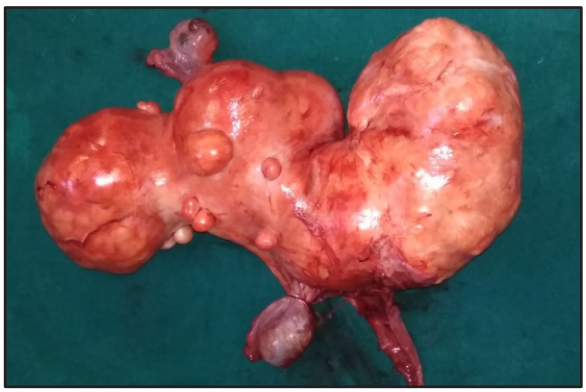

Figure 1 : Mass with bilateral tubes and ovaries

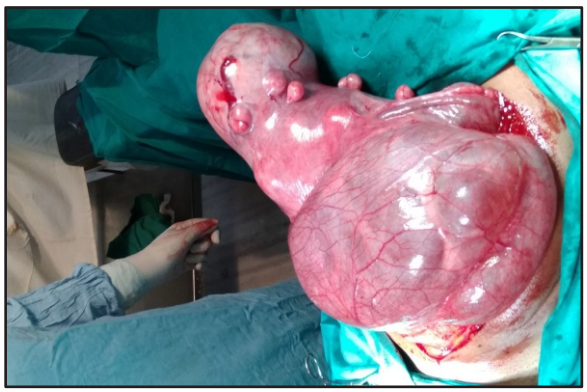

Figure 2 : Encystic fluid collection over the mass

both ovaries. The subcutaneous nodule around umblicus and skin was excised and send for histopathology. Intra-operative blood loss was 400ml and patient received one unit of packed cell RBCs. There was no injury to any viscera. The post-operative period was uneventful and patient was discharged on post operative day 5.

Final histopathology revealed 36.0x19.0x14.0 cms mass with multiple subserosal and intramural fibroids varying in diameter from 1.0 cm to 15 cms having white whorled firm cut surface. The mass weighed 3.8 kg. Bilateral tubes and ovaries were normal. Section from cyst wall shows calcification and fibroadipose tissue with no lining epithelium or evidence of malignancy. The subcutaneous nodule and overlying skin showed foci of endometriosis.

At 3 months follow up, the patient was asymptomatic and with no clinical and radiological evidence of recurrence. She was started on hormone replacement therapy in form of oral contraceptive pills.

Discussion

Leiomyomas can be asymptomatic but if neglected for a long time, they can reach an enormous size resulting in chronic pelvic pain, compression of contiguous structures like the bladder and the bowel resulting in bladder and bowel dysfunction.[2] They can lead to menstrual abnormalities especially with a coexisting intrauterine myoma. The leiomymas can be associated with multiple beningn pelvic diseases like endometriosis, pelvic inflammatory disease, adenomyosis etc. Our patient had a subcutaneous nodule with foci of endometriosis, which led to a disturbing periumblical tenderness during her menstruation, superimposed over her chronic pelvic pain.

Uterine leiomyomas has a remarkable potential to grow to an extreme size before causing symptoms, likely due to large volume of the peritoneal cavity, the distensibility of abdominal wall and slow growth rate of leiomyomas.The pathogenesis of fibroids is still unclear but it seems that hormonal stimulation by estrogen and possibly progesterone plays an important role.[3]

Leiomyoma masquerading as ovarian tumors impose a challenge to both the surgeon and radiologist and should always be in the list of differentials. [4-6] The presented case illustrates diagnostic difficulties, which may occur when rapid tumor enlargement and radiological and laboratory tests results imitate ovarian tumor. The patient had a large abdominopelvic mass which was fixed, hard in consistency with ascites. The CT scan showed a heterogeneously enhancing lesion with nonvisualisation of both ovaries and uterus seperatly.

A stepwise and a multidisciplinary approach in management of these cases is needed to achieve optimal results. The chosen approach should be individualized depending on various factors, including age, type and severity of symptoms, suspicion of malignancy, desire for future fertility and proximity to menopause. Surgery is most frequently preferred for management of giant leiomyomas.[7] Only the most experienced gynecologic surgeons should attempt such operation with intraoperative assistance from gynecologic oncology, gastro and urosurgeons.[8]

Intraoperatively, the patient should be positioned to allow adequate ventilation and reduce vena cava compression. The skin incision should allow easy manipulation of the mass and exploration of the upper abdomen. The surgical approach of these giant tumors concerns some intraoperative technical difficulty such as the increase of blood loss, any injury to adjacent organs due to dense intestinal adhesions or displacement of ureters because of huge mass within the pelvic cavity. Preoperative mechanical bowel preparation may decrease the risk of bowel injury and aid visualization.

Medical management (Gn-RH agonists) is efficient for small leiomyomas and in preoperative treatment to decrease tumors volume and blood loss before myomectomy or hysterectomy but is associated with high cost, loss of planes in leiomyoma

and increased recurrence risk. In the presented, case Gn-RH agonist (leuprolide) were given to reduce tumor size, facilitate operability and reduce post-operative morbidity.[9]

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Empowering Cancer Biology to Strengthen Fight against Cancer: National Conference on New Horizons in Cancer Biology

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Summary

In spite of a major endeavor of research and development to search new anticancer agents, cancer remains a major health problem and one of the leading causes of death worldwide. So, the need of the hour is basic research in Cancer Biology that could be translated into clinical practice. Also, it is equally important to take initiatives for having preventive medicine along with curative measures. The last few decades of basic research in Cancer Biology have created a broad base of knowledge that has been critical to strengthen fight against the disease. Knowledge gained from these studies deepens the understanding of cancer and produces insights that could lead to the development of new clinical interventions. In fact, many advances in the prevention, diagnosis and treatment of cancer would not have occurred without the knowledge that has come from investigating basic questions about the biology of cancer. Hence, to address some of these issues, the **"National Conference on New Horizons in Cancer Biology"** was organized during March 16-17, 2018 by Cancer Biology Department to have a fusion of basic eminent scientists along with clinical oncologists and academicians in order to bridge the collaborative efforts for solving many of their unresolved problems. The conference aimed to deliver novel insights into the complexity of Cancer Biology and cover the entire spectrum of various issues in cancer. Several distinguished experts were invited from renowned institutions around India. This article highlights primary features of this conference

Keywords: Cancer, Prevention, Conference

"National Conference on New Horizons in Cancer Biology" was organized by Cancer Biology Department under the auspices of The Gujarat Cancer & Research Institute (GCRI) and Gujarat Cancer Society (GCS) on March 16-17, 2018 at J B Auditorium, Ahmedabad Management Association, Ahmedabad. The conference was coordinated by Dr. Pina Trivedi, Cytogenetics Laboratory, Cancer Biology Department. The theme of the conference was Empowering Cancer Biology to strengthen fight against Cancer. As today cancer remains a major health problem and one of the leading causes of death worldwide, the need of the hour is basic research in cancer biology that could be translated into clinical practice, together with taking the initiatives for having preventive medicine along with curative measures. Hence, the conference has focused upon this concern by bringing together distinguished scientists from various parts of India and budding researchers to discuss and deliberate on the emerging trends and future prospects of prevention and treatment of cancer. The scientific programme included the keynote addresses and invited lectures of well-renowned and eminent scientists from 13 distinguished institutes all over India to share their noteworthy experiences and highly enlightening theories. The event also included oral presentations, technical talks, young scientist award oral presentations and poster presentations by PhD scholars and post-graduate students. There was a huge participation of students and faculties from different research and academic institutions reaching to more than 450 attendees and around 28 participating institutions.

March 16, 2018

The first scientific session began at 9.00 am followed by welcome note of Dr. Pina Trivedi. The first session was chaired by Dr. Shashank Pandya (GCRI, Ahmedabad) and Dr. Kirti Patel (GCS Medical College, Hospital & Research Centre, Ahmedabad). The session included the keynote lectures by Dr. Shilin Shukla (GCRI, Ahmedabad) and Dr. T. Rajkumar (Cancer Institute, Chennai). Dr. Shilin Shukla shed light on the importance and coordination of cancer biology with clinical oncology in order to conquer cancer. Dr. T. Rajkumar also explained about the importance of molecular screening of breast cancer and uterine cervical cancers, thereby reinforcing the cancer prevention.

The second session was chaired by Prof. Meenu Saraf (Gujarat University, Ahmedabad) and Prof. Priti Mehta (Nirma University, Ahmedabad). Invited speakers Dr. Gopal Kundu (NCCS, Pune) and Dr. Subhash Chandra Gupta (BHU, Varanasi) enlightened the delegates with their in-depth knowledge on tumor micro-environment and its effect on different upcoming molecules for their utilization in cancer therapy.

The third session was introduced by Dr. Parijath Goswami (GCRI, Ahmedabad) and Dr. Hyacinth Highland (Gujarat University, Ahmedabad). The speaker Dr. Sorab Dalal (ACTREC, Navi Mumbai) gave highlight on chemo- and radio-

Figure 1 : Delegates participated in the conference

Figure 2 : Lamp lightning during the inauguration

Figure 3 : Group photo of Cancer Biology Lab Heads with the Dignitaries present in the conference

resistance resulting in tumor progression. The session also included three technical talks following the invited lecture. Dr. Mukesh Jaiswal from Agilent Technologies described about the evolving technologies in cancer genomics. The applications of Droplet Digital PCR in cancer diagnostics, prognosis and disease monitoring were detailed out by Dr. Abhijeet Dixit from BioRad Laboratories (India) Pvt. Ltd. The third technical talk was delivered by Mr. Swapnil Walke of BD Biosciences explaining the advancements in Flow Cytometry for Cancer Biology. Simultaneously during the lunch session, 69 posters were displayed by research scholars and post-graduate students from various institutes, covering different aspects in the field of cancer research. The posters were viewed and judged by the senior faculties of various state universities and there were fruitful discussions and suggestions from the judges, which will certainly help the students for their future research work. Also, the MSc Cancer Biology students presented a model explaining about the symptoms, causes of cancer formation and also the display the work carried out in various labs of cancer biology department.

The post-lunch session (fourth session) was chaired by Prof. N.K. Jain (Gujarat University, Ahmedabad) and Dr. Neeta Shrivastava (PERD Centre, Ahmedabad). Invited speaker Dr. Madhumita Roy (CNCI, Kolkata) described about the consequence of isothiocyanates over conventional chemotherapy in cervical cancer. The following lecture by Dr. Ajai Kunnumakkara (IIT, Guwahati) focused upon the oral squamous cell carcinoma by explaining the role of AKT kinase isoforms and that silencing of these isoforms inhibits proliferation and survival of oral cancer cells.

The following session (fifth session) was introduced by Dr. Archana Mankad (Gujarat University, Ahmedabad) and Prof. Jigna Shah (Nirma University, Ahmedabad). Invited speaker Dr. Franky Shah (GCRI, Ahmedabad) discussed about the clinical significance of upcoming Vitamin D signaling pathway in breast cancer. The second lecture by Dr. Madhvi Joshi (GBRC, Gandhinagar) who elucidated upon hereditary breast and ovarian cancer patients and the frequent mutations found in these patients. The scientific programme of Day 1 was concluded by the sixth session which was chaired by Dr. B. K. Jain (M G Science Colege, Ahmedabad) and Dr. Neeraj Jain (CHARUSAT, Changa). The session included oral presentations by Dr. Dharmesh Patel (Cytogenetics Lab, GCRI), Dr. Jyoti Sawhney (Pathology Department, GCRI) and Dr. Kruti Rajvik (Immunohematology Lab, GCRI).

Inaugural function took place after the scientific sessions of the day. The Chief Guest of the programme was Dr. Jayanti Ravi, IAS. Dr. Hemangini Vora (Immunohematology Lab, GCRI) coordinated the inaugural function. Dr. Prabhudas Patel (Dept. Cancer Biology, GCRI) felicitated the dignitaries present. Padmashri Dr. D.D. Patel and Padmashri Dr. P.M. Shah were felicitated by the Cancer Biology Department. The event was carried forward with an inspirational speech by Dr. Jayanti Ravi. She explicated about the importance of research in healthcare. Madam declared about the health passports to be issued to people of Gujarat. She emphasized that young science students should choose research as career objective. She explained

about tremendous scope of research in science. Madam finally concluded her speech by congratulating the department for organizing the conference. The abstract book of the conference was released by Shri Prashant Kinariwala (General Secretary, GCS) and Archival Vistas volume II was released by Shri Kshitishbhai Madanmohan (Secretary, GCS). Archival Vistas is assembled petals of projects, publications, presentations, awards, honors and achievements of Cancer Biology Department (Research Wing) during the period of 2008-2017. The book was meliculously compiled by Dr. Hemangini Vora, Associate Professor at Cancer Biology Department. Finally, vote of thanks was delivered by Dr. Pina Trivedi. The inauguration was concluded by national anthem and was followed by dinner of all the delegates.

March 17, 2018

The first session on Day 2 of the conference was chaired by Prof. Manjunath Ghate (Nirma University, Ahmedabad) and Dr. Manish Nivsarkar (PERD Centre, Ahmedabad). Invited speaker Dr. Mukul Jain (ZRC, Ahmedabad) methodically explained about the novel and potent tankyrase inhibitor in cancer therapy. Following lecture by Dr. Kiran Kalia (NIPER, Ahmedabad) detailed out about various pathways in epithelial cancers and the cross-talks amongst them. This was followed by another session that was chaired by Dr. Rajen Tankshali (GCRI, Ahmedabad) and included the third keynote lecture by Dr. Pankaj Chaturvedi (TMH, Mumbai) who brilliantly discussed about the ways to conquer oral cancer.

The next session was chaired by Prof. R.J. Verma (Gujarat University, Ahmedabad) and included lectures by Dr. Babu Rao Vundinti (NIIH, Mumbai) and Dr. Dhanlaxmi Shetty (ACTREC, Navi Mumbai) who explained to the delegates about the role of cancer cytogenetics and mutations in hematological malignancies. The session was concluded by technical talk from Dr. Umang Patel for Qiagen India Pvt. Ltd. who discussed the use of real time PCR in oncogenetics and personalized health care.

The post-lunch session was chaired by Dr. Bhupesh Yagnik (K K Shastri Science College, Ahmedabad) and Dr. Harshang Pandya (M G Science College, Ahmedabad). The session included 12 young scientist award oral presentations that were divided into faculty and student category. There were 7 presenters in the faculty category and 5 presenters in student category. The conference was concluded with the award announcements and valedictory function by Dr. Trupti Trivedi. Finally, Dr. Prabhudas Patel made the closing remarks by appreciating the organizing committee and Cancer Biology Department for working hard to make the conference a grand success.

Summaries of Presentations at Clinical Meetings

Comparison of three different OT table height for intubation in trainees – An Ergonomics view

Kantesariya Vidhi
Anaesthesia department

Summary

The aim was to evaluate the effect of different OT table height on intubation time, success rate, and laryngeal view grading and posture discomfort. The study included seventy five patients divided into three groups (25 in each) according to patient's forehead at the level of intubator's nipple line (group N), xiphisternum (group X) and umbilicus (group U). An Observation for time to intubate, success, discomfort in ventilation & intubation and posture was made. From left sided photographs- neck & knee flexion, distance from intubator's eye to heel of scope was noted. Study reveals that table height at nipple level make intubation less time consuming ($p= 0.001$) and with comfortable posture and better laryngeal view. Distance from trainee's eyes to heel of scope was more in group N (p value < 0.001). Trainees tended to crouch towards patient's mouth with bended posture in group U and group X than group N. Higher OT table height can provide much better laryngeal view with less discomfort and less time consuming intubation. Trainees must be taught and prefer to set OT table height at nipple level making them erect and comfortable in posture.

Keywords: Intubation, OT table height, Ergonomics

Surgical Outcome of carcinoma lung and carcinoma esophagus operated in last 1 year in our unit

Bansal Vishal
Surgical Oncology BT Unit II

Summary

Carcinoma lung and carcinoma esophagus are the two major thoracic malignancies performed in our unit. The best cure or disease free survival is by surgical resection. Within last 1 year we have performed 21 esophagectomies and 11 lung resections (lobectomy/ pneumonectomy). We analysed the post operative outcome in these patients. Out of 21 esophagectomies performed, only 1 patient died post operatively while the remaining 20 patients are on regular follow up and are disease free. The average lymph node yield was 14. Out of 11 lung resections 2 patients died postoperatively and 2 patients developed recurrence while remaining 7 patients are on regular follow up and are disease free. Video assissted thoracoscopic mobilisation of esophagus was done in 4 patients. Minimal access approach has been helpful in reducing post operative complications and decreased hospital stay. We have now started doing thoracoscopic lung resections. Hopefully in future with robotic assisstance we may be able to further improve the outcome.

Recent Molecular Markers in Breast Cancer – A Case-Control Study

Patel Kinjal
Molecular Oncology Laboratory-4

Summary

In a case-control study, we analyzed genetic determinants of vital genes involved in cell homeostasis (DNA repair, p53), molecules of vitamin D signaling, iASPP and MMPs. Our findings suggest that XRCC1, APEX1 and p53 gene variants can modify breast cancer risk independently or in combination with other genotypes. Association of distinct polymorphisms with aggressive breast cancer phenotype and poor prognostic markers explains their involvement in pathophysiology of breast cancer and disease prognosis. Further, serum levels of 25(OH) D may influence breast cancer risk and might be associated with poor disease prognosis. Imbalance in vitamin D metabolizing enzymes CYP27B1 and CYP24A1 and presence of VDR gene polymorphisms, might be responsible for altered vitamin D signaling pathway in breast cancer. Contribution of iASPP in breast cancer causation and involvement of iASPP and MMPs in breast cancer progression offers potential drug targets for breast cancer treatment. Thus, comprehensive analysis of these molecular markers may help to identify "At risk" population for early detection and prevention of breast cancer, to identify newer drug targets for treatment, targeted use of vitamin D analogues in combination with chemotherapeutic agents and possible markers for prognostication.

Advances in Digital Breast Tomosynthesis

Pateliya Mehul
Radiology Department

Summary

Breast cancer is a progressive disease and early detection enables improved prognosis. Mammography can reduce breast cancer mortality by 30% or more. Despite the success of mammography, overall sensitivity is limited by the presence of dense fibro glandular breast tissue, which can obscure an underlying early cancer detection. Specificity is also reduced by the presence of overlapping fibro glandular tissue, which can mimic the appearance of early cancer. The Food and Drug Administration (FDA) first approved DBT in 2011, and multiple studies have shown that DBT is effective in both screening and diagnostic settings. Digital breast tomosynthesis (DBT) has rapidly emerged as an important new imaging tool that reduces the masking effect of overlapping fibro glandular tissue, thereby improving breast cancer detection. This article will review key features of DBT including technique, clinical implementation, and benign and malignant imaging findings. We will also present the benefits of DBT in screening, diagnostic workup, and image-guided biopsy.

Role of CRS+HIPEC in Colorectal Cancer with Peritoneal Carcinomatosis

Puj Ketul
Surgical Oncology

Summary

Peritoneal seedings of a colorectal tumor represent the second most frequent site of metastasis (after the liver). Generally these patients are treated with palliative chemotherapy and targeted therapy with poor prognosis. In the era of multimodality treatment, Cytoreductive Surgery + Hyperthermic Intraperitoneal Chemotherapy (CRS+HIPEC) have shown promising results in terms of disease free survival and overall survival. Considering significant morbidity with this procedure a strict selection criteria [based on peritoneal cancer index (PCI) and Peritoneal Surface Disease Severity Score (PSDSS)] should be followed. Dutch randomized controlled trial (Verwaal V.J et al, Cancer J 2009;15: 212–215) has shown median survival of 12.6 months in chemotherapy only group(standard arm) vs. 22.2 months in CRS+HIPEC + adjuvant chemotherapy group(experimental arm)(p=0.028). The 6-year survival was only 5% in the standard arm and 20% in the experimental arm. After that many publications has shown a median survival of 32 to 47 months with CRS+HIPEC. Cooperation between medical and surgical oncologists represents an unmet need in oncology when it comes to patients with colorectal cancer with peritoneal carcinomatosis . Multidisciplinary team approach is needed to get best outcome for these patients and get best results from CRS+HIPEC.

Detection of EGFR mutation in lung cancer patients using liquid biopsy: GCRI experience

Raval Apexa
Stem Cell Biology lab

Summary

Lung cancer is one of the most fatal malignancy amongst all malignancies. Having the important role in lung cancer, the detection of EGFR gene mutations are being carried out in diagnostics. Four exonic mutations (exon 18, 19 &21: TKI sensitive; exon 20: TKI resistant) are known for EGFR gene. The cell free DNA was extracted from the blood i.e. liquid biopsy- a non invasive way to obtain sample. The qualitative Realtime PCR associated with mutant enrichment method was done to check the presence of seven different mutations. Total 165 patients were collected in 2016. The major histologic type was Adenocarinoma (62%). Majority of the patients were young (54%), female (60%), and they were either smokers / having the direct exposure to the smoke (50%). From 165 patients EGFR mutations were detected in 42 patients. The TKI resistant and sensitive mutations are present in equal proportion (21%). Exon20 insertion is the highest mutation observed followed by exon 19 deletion. The patients with active smoke exposure showed higher rate of exon 20 insertion (16%) compared to exon 19 deletion (8%). While in passive smokers exon19 deletion (14%) and exon21L858R (14%) mutation exon20 insertion (12%) were observed. The high concordance (84%) was obtained between FFPE and cell free DNA samples suggesting as a useful tool for early detection of specific EGFR gene aberrations. Thus, liquid biopsy can be considered as latest weapon against cancer.

Institutional Repository: A New Digital Asset of Information Resources

Kalita Nuri
Library and Information Services

Summary

The modern age of Information Industry may be characterized by new ways of knowledge creation, managing, sharing and dissemination because it is merged with the information and communication technology. Earlier Library collection was limited to print documents like books; journals etc and most of the collections can be acquired through purchase and as complimentary offers. Now information media has moved to areas like digital, intellectual, computer, smart phone and digital asset. The Institutional repository is a new concept of digital library collection. It plays a very important role in harvesting, centralizing, preserving, and making accessible institution's intellectual property in a single window to the wider users. For this, Libraries are creating institutional repositories by collecting various types of Intellectual outputs to make them accessible to their users. The GCRI has initiated to introduce Institutional Repository to their Faculty members, Academicians, Research scholars, Students and Resident doctors. IR provides the possibility to standardise the Institutional records. The role, focus, domain and benefits and implementation of IRs in GCRI will be outlined in the proposed presentation.

Evaluation of incompletely staged ovarian malignancy: a study from State Cancer Centre in India

Makhija Amrita
Gynaecological Oncology

Summary

Incomplete initial surgery complicates subsequent management of ovarian tumors. This study aimed to study demographic and clinical factors associated with incompletely staged ovarian tumor patients. Twenty four patients were included in this study. Mean age of patients was 43.9 years. 72% of patients had abdominal pain as initial complaint. 54% patients were operated using a tranverse incision. Six patients were operated laparoscopically. Omentectomy and lymphadenectomy was not done in most of the patients. The final histopathology was serous in 62.6%, mucinous in 2, borderline malignancy in 4, endometroid in 1 and granulosa cell tumor in 2. Sixteen patients were subjected to chemotherapy; two patients were observed and rest underwent staging procedures. Ovarian masses with high suspicion of malignancy should be managed by gynec-oncologists.

Presentations at the Clinical Meetings

(July 2017 to December 2017)

Sr. No.	Date	Speaker/Department	Title
1	08.07.2017	Kantesariya Vidhi Anaesthesia	Comparison of three different OT table height for intubation in trainees – An Ergonomics view
2	22.07.2017	Bansal Vishal Surgical Breast and Thorax Unit-II	Surgical Outcome of carcinoma lung and carcinoma esophagus operated in last 1 year in our unit
3	12.08.2017	Patel Kinjal Molecular Oncology Lab	Recent Molecular Markers in Breast Cancer – A Case-Control Study
4	26.08.2017	Pateliya Mehul Radiology	Advances in Digital Breast Tomosynthesis
5	23.09.2017	Puj Ketul Surgical Oncology Unit-III	Role of CRS+HIPEC in Colorectal Cancer with Peritoneal Carcinomatosis
6	14.10.2017	Raval Apexa Stem Cell Biology	Detection of EGFR Mutation in Lung Cancer Patients Using Liquid Biopsy : GCRI Experience
7	28.10.2017	Kalita Nuri Library	Institutional Repository: A New Digital Asset of Information Resources
8	23.12.2017	Makhija Amrita Gynaec Oncology Unit-III	Evaluation of Incompletely Staged Ovarian Malignancy: A Study from State Cancer Centre in India

Journal Club/Guest Lecture/ Review Lecture Presentations

(July 2017 to December 2017)

Sr. No.	Date	Presenter/Department	Topic	Authors	Citation
1	22.07.2017	Merja Manthan Orthopedic Oncology	Surgical Management of Pelvic Sarcomas with Internal Hemipelvectomy: Oncologic and Functional Outcomes	Salunke AA, Shah J, Warikoo V, et al	J Clin Orthop Trauma 2017;8:249-253
2	26.08.2017	Samanta Satarupa Pathology Department	Head and Neck Cancers-Major Changes in the AJCC Eighth Edition Cancer Staging Manual	Lydiatt WM, Patel SG, O'Sullivan B, et al	CA Cancer J Clin 2017;67:122-137
3	09.09.2017	Poddar Pabashi Gynaecological Oncology	Controversies in Borderline Ovarian Tumours	Seong SJ, Kim DH, Kim MK, et al	J Gynecol Oncol 2015;470:343-349
4	23.09.2017	Kusumgar Rima Blood Bank	Automated Nucleic Acid Amplification Testing in Blood Banks: An Additional Layer of Blood Safety	Chigurupati P, Murthy KS	Asian J Transfus Sci 2015;9:9-11
5	28.10.2017	Agrawal Prerak Radiotherapy	Elucidating the Role of Chest Wall Irradiation in 'Intermediate-Risk' Breast Cancer: The MRC/EORTC SUPREMO Trial	Kunkler IH, Canney P, van Tienhoven G, et al	Clin Oncol (R Coll Radiol) 2008;20:31-34
6	11.11.2017	Varma Priya Cytogenetic Lab	Chronic Myeloid Leukemia in India	Ganesan P,Kumar L.	J Glob Oncol 2016;3:64-71
7	25.11.2017	Patel Priyanka Medical Unit III	Adjuvant Capacitabine for Breast Cancer after Preoperative Chemotherapy-CREATE-X Trial	Masuda N, Lee SJ, Ohtani S, et al	N Engl J Med 2017;376:2147-2159
8	09.12.2017	Anand Mridul Radiotherapy	The Vienna Applicator for Combined Intracavitary and Interstitial Brachytherapy of Cervical Cancer: Clinical Feasibility and Preliminary Results	Dimopoulos JC, Kirisits C, Petric P, et al	Int J Radiat Oncol Biol Phys 2006; 66:83-90.
9	23.12.2017	Trivedi Trupti Clinical Carcinogenesis Lab	A Clinical Perspective on the 2016 WHO Brain Tumor Classification and Routine Molecular Diagnostics	van den Bent MJ, Weller M, Wen PY, et al	Neuro Oncol 2017;9:614-624

Case Presentations for Morbidity, Mortality at Clinical Meetings

(July 2017 to December 2017)

Sr. No.	Date	Presenter/Department	Case Discussion
1	22.7.2017	Dr Abhishek Bhardwaj Anesthesiology	Morbidity Mortality Data Presentation of Surgical & Medical Departments
2	22.7.2017	Dr. Salil Medical Oncology	Post Interventional Management of Pts Treated at GCRI for Obstructive Jaundice
3	26.8.2017	Dr. Twinkal Patel Anesthesiology	Morbidity Mortality Data Presentation of Surgical & Medical Departments
4	26.8.2017	Dr. Tapan Singh GI - Surgical Oncology	A Case of Periampullary Ca undergone Whipple's Procedure
5	23.9.2017	Dr. Mohit Rathod Anesthesiology	Morbidity Mortality Data Presentation of Surgical & Medical Departments
6	23.9.2017	Dr. Nikhil Garg Surgical Oncology (H&N)	A Case of Ca Buccal Mucosa Undergone CR + Flap
7	28.10.2017	Dr. Twinkal Patel Anesthesiology	Morbidity Mortality Data Presentation of Surgical & Medical Departments
8	28.10.2017	Dr. Honey Parekh Medical Unit-II	Pelvic Actinomycosis- A benign condition masquerading Malignancy
9	25.11.2017	Dr. Twinkal Patel Anesthesiology	Morbidity Mortality Data Presentation of Surgical & Medical Departments
10	25.11.2017	Dr. Manthan Paediatric Oncology	A Case of an Infant Operated for Right Supra-renal Teratoma
11	23.12.2017	Dr. Mohit Rathod Anesthesiology	Morbidity Mortality Data Presentation of Surgical & Medical Departments
12	23.12.2017	Dr. Mayur Surgical Oncology GI I	A Case of Cytoreductive Procedure for Pseudomyxoma Peritoni With Carcinomatosis

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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- Title of manuscript (Font size: 16)
- Summary and Keywords (Font size: 9)
- Text (Introduction, Aims and Objectives, Materials and Methods, Results and Analysis, Discussion with Conclusions; Font size: 12).
- Tables (separate page, Number Arabic numerals (e.g. 1,2,3) as it comes in results) (Font size: 12)
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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.

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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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Department of Nuclear Medicine

Tiwari Rasna,
Gujarat Cancer and Research Institute

Introduction

About us

The department of Nuclear Medicine at Gujarat Cancer and research Institute, Hospital is committed to improving health through excellence in patient care, research and education. Based on the knowledge about functions of the organs and nature of disease, we provide superb medical services for diagnosing and treating of variety of disease. To develop more effective strategies to conquer disease, we are actively pursuing biomedical research through close collaboration between physician and scientists. In addition, we manage training programs for future physicians and scientists, not only for intramural members but also for international applications. Two faculty members, one Health physicist, Four nuclear medicine technologists, two nursing and administrative members are working in patient care and research.

Patient Care

As we are one of the leading institute in the field of nuclear medicine and oncology research, we provide state of the art medical services in diagnosing and treating disease.

Diagnostic Imaging

- Using diverse radioactive tracers, nuclear medicine can visualize the status of disease and monitor effect of treatment through medical imaging in living body. For diagnostic imaging, we currently have 1 gamma camera and 2 PET/CT scanners.

1. PET

PET (positron emission tomography) is an imaging tool using positron-emitting radiotracers. Various PET tracers have been developed and are in use. With an adequate radiotracer, cancer lesions, viable myocardium and metabolic status of brain can be diagnosed. At present we can offer various PET traces with active support of radiopharmacy outside the state.

- 18F-FDG: For glucose metabolism.
- 18F-NaF: For Bone scan.

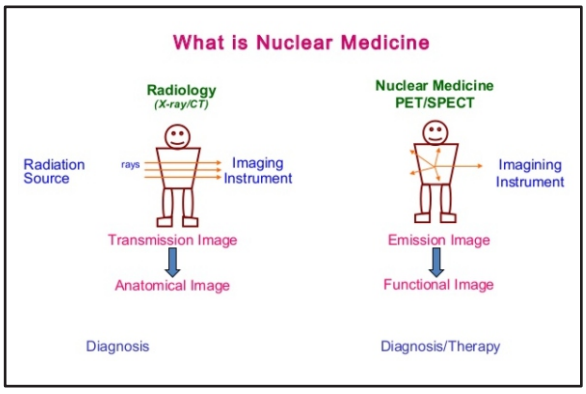
2. Gamma camera, SPECT, and SPECT/CT

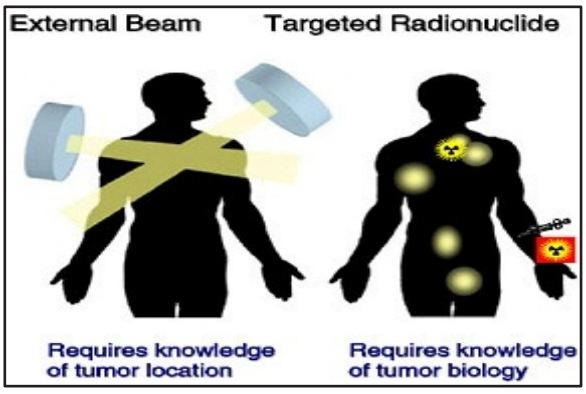
A gamma camera is a traditional imaging tool in nuclear medicine, using diverse radiotracer labeled with gamma-emitters such as ^{99m}TC, ^{201}Tl, ^{123}I, SPECT (single photon emission computed tomography) is a reconstructed gamma camera image to show 2-D tomographic images. A wide range of gamma camera imaging is available in our department.

- Bone scan.
- Myocardial perfusion SPECT (/CT).
- Brain perfusion SPECT (/CT).
- Thyroid scan
- Renal scan.
- Liver scan.
- Hepatobiliary scan.
- White blood cell scan (for infection).
- Parathyroid scan (SPECT/CT).
- Salivary gland scan
- Lymphangiography
- Spleen scan etc.

3. Radioisotope Therapy clinic

Radioisotope therapy is a kind of cancer therapy using radiopharmaceuticals that emit destruction radiation. Targeted radiopharmaceuticals can be accumulated in cancer tissue and destruct them by radiation. The Radioisotope therapy clinic of our





department has been in operation for more than 20 years. The most important target of radioisotope therapy is thyroid cancer and pain palliation for osseous metastatic lesion at present. However, we are trying to expand the scope of radioisotope therapy by developing novel therapeutic radiopharmaceuticals.
At present, clinics for outpatients and one therapy room are in operation for several diseases.

- Thyroid cancer
- Palliation of metastatic bone pain
- Lymphoma
- Neuroendocirne tumors etc.

4. Future Developments:

Short term Goals :

Government has approved of our cyclotron project leading us to make available more radio nuclides and focus on other mechanism of oncology imaging other than F18- FDG they are:

- ^{18}F-FP-CIT: For DA transporter
- ^{11}C-Methionine: For amino acid metabolism
- ^{11}C-Acetate: For fatty acid metabolism
- ^{11}C-PIB: For amyloidal plaques in Alzheimer's disease
- ^{68}Ga-RGD: For angiogenesis
- ^{15}N-Ammonia: For myocardial perfusion etc.

Long term Goal:

•Clinical Nuclear Medicine
- ★General nuclear Medicine
- ★PET oncology with new tracers.
- ★Nuclear cardiac imaging for ischemic heart disease and atherosclerosis.
- ★Neuroimaging for Alzheimer disease, vascular diseases and movement disorder.
- ★Radioisotope therapy.
- ★Innovative medical fusion imaging (PET/MRI).
- ★Translational research of molecular imaging.

•Radiochemistry.
- ★Development of new PET tracers for tumor using angiogenesis and hypoxia.
- ★Development of new PET tracers for ischemic heart disease.
- ★Development of 99mTc-based radipharmaceuticals.
- ★Development of therapeutic radiopharmaceuticals.
- ★Improvement in compounding methods (developing kits)

•Nuclear Medicine Physics
- ★Development of new imaging devices (PET/MRI, animal SPECT).
- ★Enhancement of image reconstruction(new algorithms).
- ★Tracer kinetics analysis for new imaging agents.
- ★Radiation dosimetry.

•Molecular Imaging and Nanomedicine.
- ★Reporter gene imaging for gene or protein expression.
- ★Gene therapy using radioisotope.
- ★Development of biomarkers for targeted imaging and therapy (miRNA, aptmer).
- ★Application of nanoparticle carriers in vivo.
- ★Cell trafficking imaging.

5. Research

We are pursuing many research programs not only for the purpose of academic development but also for the purpose of enhancing the quality of medical services. As one of the best research centers, our department has made every endeavor to develop innovative methods in diagnosis and therapeutics of diseases. As a result, we present research articles in the Annual Meeting of the Society of Nuclear Medicine in India and abroad every year.

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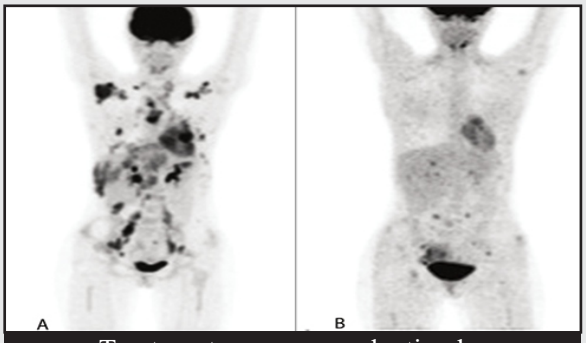

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