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PRESIDENT WRITES

Dear Fellows and Members,

Breast cancer is an important cause of morbidity and mortality. The issue of quality of life in treated patients is centre stage with this problem in particular. Radical and extended radical surgery have given place to conservation of the organ and lumpectomies. The day of the wit who quipped that it is difficult to distinguish between the excised specimen and the remaining part is mercifully past.

Early diagnosis and periodic mass screening, health education, self examination, mammogram and various other imaging modalities made a tremendous impact in the management of breast lesions. Balance and clinical good sense will be the need of the day for sound management of the problem. The vast amount of knowledge acquired about the biology of breast cancer is impressive. However, despite markers, advances in surgery, radiotherapy, chemotherapy and hormone therapy after an apparent quiet for a decade or more, secondaries show up on patients and pose problems of considerable magnitude. Long term disease-free state and good quality of life are the current goals of therapy.

This issue of our journal highlights the problem of breast cancer, its various dimensions and will be a complete update.

The new year 2006 is with us and I extend to you all good wishes for a prosperous year.



Dr. K. Jagadeesan,
President, IMSA



IMSA WEBSITE



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All fellows and members of IMSA can have **access** to the site and get information about its objectives, benefits to the fellows/members, chapters and their activities including seminars, refresher courses, rural CME's etc. and also IMSACON - a regular annual event of international standard; *application form for enrollment as fellow/member can also be downloaded. Fellows - members and even non fellows - members can have access to full text in the quarterly journal - JIMSA from July-Sept. 2003 onwards by putting their E-mail address under 'user name' and using the password 'UserJimsa'.*

IMSACON 2006 Lahore, Pakistan

Dear friends,

Annual Conference of International Medical Sciences Academy **IMSACON 2006** will be held on 3,4,5th November, 2006 at Lahore (Pakistan).

Dr. Shaheena Asif, Surgimed Hospital, Lahore is the organising Secretary.

- Theme** : "Update in Medical and Dental Sciences"
- Venue** : Lahore Hospital and Dental Medical College, Canal Bank North, Tulsapura, Lahore, 53400, Pakistan.
- Visa** : Visa is required for Pakistan and must be obtained before Travel. Please allow 3 months before conference date for application to be processed. During our conference IMSACON 2004 held in Mayo Clinic (USA) we had to experience difficulties in obtaining visa, because action was not taken in time. Therefore, please apply for visa well in time to avoid any unpleasant situation.

First information brochure can be seen on the IMSA website "www.imsaonline.com". The brochure contains all details about registration fee, registration form, details of hotel stay etc.

Non fellows accompanying the fellows of IMSA are welcome to participate. I shall request you to register for the conference early and participate with your spouse and enjoy the hospitality of the hosts.

In case participants intend to present paper in the Scientific Programme of the conference, they may send "Abstract" of the paper to the Organizing Secretary at Lahore with a copy to the Headquarter at New Delhi.

Interested persons should furnish the following information to the organizing secretary at Lahore Pakistan under intimation to the headquarter at New Delhi

1. they should send first four pages of their passport urgently to me through post or e-mail so that their visa applications can be facilitated by the Home Department in Pakistan. This process takes about 6-7 weeks, so all those who are interested to participate must send me the documents urgently. A passport size coloured photo should also be mailed; the photograph can be scanned and sent by e-mail.
2. Intimation of expected date of arrival in Pakistan.
3. Tentative date for department.
4. Names of cities to be visited.

Further I am to inform you that International Medical Sciences Academy has established **Dr. Pinamaneani Narasimha International Award** in memory of Late President of IMSA, Dr. P. Narsimha Rao. This is a very prestigious Award which will be given every year during IMSACON. The awardee for a very prominent medical scientist, will be given a citation, gold plated medal and cash award. I request all fellows/members to contribute generously to raise funds this Award to all since the award fund is open. Depending upon the funds collected, the awardees from difference specialistes will be selected.

I feel pleasure in informing that IMSACON 2008 will be held in Dubai. Dr. J. Shanmugam - our esteem fellow, will be the Organizing Secretary and will organize the conference with the help of Dr. Nishi Singh.

Any other information desired can be obtained from Dr. Shaheena Asif, Organizing Secretary, IMSACON 2006. Her mailing address is given below :

Conference Secretariat

Prof. Shaheena Asif

Organising Secretary IMSACON 2006

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I look forward to see you and your spouse at Lahore.

Dr. R.R. Thukral

Vice President , IMSA



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FROM EDITOR'S DESK

Dear Colleagues

Breast carcinoma is one of the commonest malignances in women with a very high mortality and morbidity if detected in late stages of the disease. In early stages, breast carcinoma is less aggressive with low incidence of metastasis and is potentially curable; hence early detection is crucial. An effective screening method has not yet been developed; self examination of breast and mamography have their own limitations. Estrogen is a crucial hormone; anti-estrogens are affective in reducing recurrence; chemotherapy has its own hazardous effects and should be replaced by hormone manipulation in future. The ideal goal should be prevention of breast cancer; dietary manipulation is an attractive idea as high fat in take is known to increase the chances; development of vaccine remains a remote possibility; gene therapy is another exciting field which needs to be explored. The enormous increase in our knowledge about breast cancer has unfortunately brought about only a relatively modest reduction in mortality. It is time that we review this common subject in detail so as to get acquainted with approaches to its early detection, newer diagnostic and therapeutic modalities.

Friends, I take pride in presenting to you this special issue 'Advances in Breast Cancer Management'. I am indeed grateful to **Dr. Chintamani**, a senior consultant surgeon at Safdarjung Hospital and Vardhman Mahavir Medical College, New Delhi, India, for pains taking efforts put in by him and his team members and several experts for their contribution to the special issue. The issue is well planned; scientific material is of high standard with good representative photographs/illustrations; latest developments in early diagnosis and treatment of carcinoma breast have been amply highlighted. I am indeed indebted to Dr. Chintamani for bringing out this excellent monogram.

I would like to take this opportunity to express my gratitude to all members of editorial/advisory boards, for their fruitful suggestions, cooperation and help rendered in the compilation of this issue. I am thankful to all the advertisers without whose help this publication would not have been possible.

P.D. Gulati

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Our Guest Editor

Dr. Chintamani is a senior surgeon at the Vardhman Mahavir Medical College & Safdarjang Hospital, New Delhi, one of the busiest tertiary care center in the treatment of cancer patients. His fields of interest include Breast and Head and neck Cancers, besides other cancers of surgical importance. He has to his credit more than 15 projects on breast cancer, either published in the International journals or under consideration for the same. He has been involved in many randomized controlled trials in breast and other cancers some of which have been included in the journal under *Literature Review* of this issue. He had earlier done a special issue of JIMSA on "Oral cancers" which was widely appreciated.

He is a postgraduate and an undergraduate teacher with a keen desire to learn and practice the science and art of surgery. He has many distinctions and honors to his credit. He has been awarded the Honorary Fellowship (FRCS) of the Royal College of Surgeons of Edinburgh for his outstanding contributions in the field of surgery-a rare honour for an Asian surgeon. He is also a recognized faculty of the Royal College of Surgeons of Edinburgh for the BSS course (as a pre-requisite for MRCS examination). He has also been awarded the Fellowship of the International College of Surgeons (FICS) and is a senior Fellow of the International Medical Sciences Academy (FIMSA).

Dr. Chintamani is the Chief Editor of the Surgical Clinics of India, an international publication from India and is also the Chief editor of the Delhi Journal of Surgery (an official publication of the Association of Surgeons of India-Delhi Chapter). He is a peer reviewer for the BMC (cancer) and World Journal of Surgical Oncology (both international journals on cancer. He is also a peer reviewer for the Indian Journal of Surgery.

He has more than 130 scientific papers published in the National and International Journals and has authored many chapters in various books on surgery. His latest book was released in the december 2005 titled "Step by step neck dissections" which has become very popular amongst the postgraduate and undergraduate students of surgery and Head and neck surgeons.

Dr. Chintamani is an examiner for both undergraduate and postgraduate courses of various universities and is also on the panel of the Union Public Service Commission (UPSC) as an advisor and examiner.

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Breast Cancer - Past, Present and the Future:

CHINTAMANI

Department of Surgery, Vardhman Mahavir Medical College, Safdarjang Hospital, New Delhi, India

If anyone thinks he knows all about breast cancer, he probably knows nothing about it. The treatment of no other cancer has been so extensively studied, researched and debated over the last century. The Halsteadian view of a predictable pattern of spread and therefore the most radical loco-regional control (surgery) formed the basis of most of the treatment protocols for the management of this dreaded cancer until late twentieth century. The approach showed gratifying results in the form of reduction in mortality with an expected result, an increase in the morbidity. The living problem being better than a dead solution, it was fairly acceptable at that time as the reduction in mortality was the aim. The treatment of breast cancer continued to be radical and more radical surgery but the survival rates did not show significant improvement after reaching a plateau in the mid twentieth century.

Halstead vs. Fishers view and the middle path:

In the seventies and eighties, the Fishers view changed to a great extent our perception about cancer and it was proposed that breast cancer is a systemic disease at the very inception, therefore a local extra-radical approach recommended by Halstead was not justified, a treatment for the systemic micro-metastases that did not show at the time of first presentation became mandatory. This also explained to an extent the reasons for distant failures inspite of an extra radical treatment locally. Thus came the role of effective adjunctive therapies like chemotherapy and /or radiotherapy along with hormonal therapies.

Fishers view presented a rather depressing scenario as if it was a fight against the inevitable (systemic disease at inception!!). The thought although noble could take away the initiative from the cancer treating clinician. There had to be some truth outside this concept also i.e. probably both local and distant or systemic treatment would be necessary. The role of neoadjuvant chemotherapy for the micrometastases present at the time of initial presentation in most of the breast cancers therefore became important^{1,2}.

The middle path:

While Halstead's view is adapted and based on the predictable pattern of spread of malignancy has become the basis for *sentinel node mapping and biopsy*, systemic neoadjuvant and adjuvant therapies have become an integral part of therapy for breast cancer based on the Fishers view. Thus the middle path [or shall we say the middle path of Buddha!] now forms the basis of treatment for breast cancer.

“The opposite of a correct statement is a false statement, the opposite of a profound truth will be another profound truth”—Niels Bohr

The research in to the molecular biology of breast cancer has enabled us to learn more about the different behavior patterns observed in cancers in two different patients staged and graded

similarly. To a great extent this has also made it possible, to assess the response patterns to various therapeutic regimes^{2,3,4}. In future it should surely be possible to assess and predict the response of breast cancers to a particular therapeutic regime with targeted therapies further helping in getting the optimum response. The tailoring of the treatment protocols for a particular patient would not only improve survival but will also be helpful in avoiding the toxic chemo/radio therapeutic regimes in patients that are likely to be non-responders.

Surgery alone therefore is no longer the only treatment modality for breast cancer. With organ preservation becoming the theme of cancer management, effective adjuvant and adjunctive therapies are also going to play a significant role in the management of breast cancer. In order to, therefore preserve an organ or to perform a less radical and mutilating surgery it is mandatory to have an effective adjunctive therapy available. Further research in to finding out effective markers of response to chemotherapy is therefore required in order to find out the responders and non-responders. In a prospective study the *author* had observed the role of toxicity as a predictor of response to neoadjuvant chemotherapy^{1,2}. This ongoing study has been able to highlight the role of toxicity as a predictor of response to neoadjuvant chemotherapy successfully. When titrated against the apoptotic markers and other biological markers it was found to be a sensitive, effective and cheap solution to predicting response to chemotherapy in a poor country like ours.

Role of surgeon:

The message to be carried home is “it is worthwhile thinking about organ preservation, in this case, breast preservation if the results of the surgery are R0 resection (microscopic freedom from disease)”. However, no amount of chemo and/or radiotherapy is a replacement for a bad i.e. an inadequate surgery. The surgery has to be optimum and surgeon's role continues to be pivotal. The initial diagnosis and initial management are his domain but it is a group of professionals rather than, the surgeon alone, that needs to be involved in the management of breast cancer.

Other therapies

While there has been a tendency to move more and more towards organ preservation with therapies becoming more and more conservative, the adjunctive modalities have assumed greater significance and have developed in to becoming less and less morbid and more focused.

HER-2neu receptor status and chemotherapy:

The newer drugs like Herceptin based on the HER-2 neu receptor status are showing remarkable results in terms of response and survival. Her-2 neu over-expressing tumors show an extremely positive response to trastuzumab (Herceptin), which is a monoclonal IgG, humanised murine antibody directed against extracellular portion of Her-2/neu being used in the treatment of advanced metastatic breast carcinoma. In Her-2 neu positive

tumors trastuzumab therapy is associated with longer time to disease progression, higher rate of objective response, longer, duration of response and longer survival^{5,6}.

Hormone therapy and the aromatase inhibitors:

Breast cancers have traditionally been managed using Tamoxifen, an antiestrogenic drug with endometrial carcinoma and osteoporosis as the most dreaded side effects. First and second line of aromatase inhibitors have also been used and found to improve survival rates. They have been used after Tamoxifen therapy and also as the sole modality with improved survival rates demonstrated in many studies⁵.

Future:

The hope lies in the early diagnosis with effective, widespread National screening programmes and better understanding of the genetics and biological behavior of the disease. Unlike in the western countries our cancers continue to be locally advanced at presentation with very little hope of organ preservation. A dedicated awareness programme is mandatory along with screening facilities if mortality and morbidity from this cancer have to reduce. We in any case must find "Indian solutions to Indian problems". The future therapies are likely to become more and more tailored and targeted with an aim to preserve the form and function without a compromise on the disease survival.

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New Pot-pourri of Markers related to invasive Breast Cancer

BHARAT REKHI, SUNITA SAXENA

Institute of Pathology, I C M R, Safdarjang Hospital, New Delhi, India

Breast cancer is one of the most frequent malignancies amongst Indian women¹. About 60-80% of these cases present at a locally advanced stage². This aspect is of constant anxiety to the clinicians, engaged in its treatment. One-way has been, identifying premalignant lesions, followed by conservative treatment and follow-ups. Premalignant lesions are well documented in breast and prostate^{3,4}. The other is identification of biological markers helpful in predicting clinical outcome, once the cancer has set in. Several molecular components related to development of breast carcinomas and associated with therapeutic and prognostic value viz. p53, RB, ER, Cerb B-2; have been studied in great detail⁵⁻⁷. Identification of newer markers has always been of great interest to the pathologists and clinical onco surgeons, for developing newer therapeutic modalities to combat this disease. While the 1950's saw identification and role of steroid hormones in breast cancer, the researchers in 1980 developed a focus on studying implications of growth factors, including oncogenes and tumor suppressor genes. The 1990's were met with discovery of genes causing familial forms of breast cancer. Final decade ushered advances in cell cycle, DNA repair, cell death (apoptosis) and regulation, with the recent emphasis on identifying markers related to tumor metastasis, which is the major cause of morbidity and mortality in these patients⁸.

A cell, with an intrinsic malignant potential, passes through various stages before assuming a tumor collection. This ranges from early hyperplastic to premalignant to malignant stage, under the influence of wide range of genetic factors and events. The malignant cells further become invasive. Invasive growth of malignant cells is eased by the production of proteolytic activity at the advancing edge of the tumor. Factors relating to these processes, along with those related to uncontrolled cell proliferation and cell dissemination have a major impact on the invasive and metastatic propensity of the tumor. A number of proteins form the underlying basis for tumor invasion.

Cathepsin D is a lysosomal protein that is over expressed and secreted by tumor cells. Its role in invasiveness of breast cancer has been substantiated by a study showing over expression of this protein in node negative, aneuploid tumors, with 60% chance of recurrence in 5 years, thereby poorer survival rates⁹.

Invasion and metastasis of solid tumors like breast requires tumour-biologic factors that promote the dissolution of the surrounding matrix and basement membranes. In this context, a set of serine protease plasminogen activators and inhibitors is of major interest. Increased levels of urokinase type plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1) form independent predictors of overall survival rates in breast cancers. uPA, produced by tumor cells and macrophages, has a significant role in angiogenesis. Its levels in cancer cells correlate with microvessel density, vascular invasion, macrophages number and proliferation rate¹⁰. It has been shown that uPA negative tumors have a better response to tamoxifen treatment than those with uPA positive tumors. Patients with higher levels of plasminogen-

activator inhibitor rates also respond better than those with a similar negative status¹¹.

Cell cycle plays a very significant role in development of tumors with the aid of various checkpoints. A set of proteins known as cyclins, regulated by cyclin dependent kinases (CDK's) is responsible for transitions of cells entering into various phases of cell cycle¹². One such protein molecule is cyclin D, which transfers cells from G1 to S phase of cell cycle. Over-expression of this gene, as seen in many breast carcinomas, even though, its amplification being seen only in a few cases; leads to uncontrolled entry of cells in the S phase, leading to further proliferation¹³.

Certain specific cell-to-cell adhesion molecules have been found to be responsible for embryonic development. One such molecule is a family of "Cadherins". It is a group of genetically related transmembrane glycoproteins, involved in calcium-dependent cell-to-cell adhesion mechanism and are sub classified, based on their binding characteristics and tissue distribution like E-, P- and N-cadherins^{14,15}. Significant among these is E-cadherin, also known as uvomorulin, an invasion-suppressor gene. Damsky and colleagues¹⁶ first identified human E-cadherin as cell-CAM 120/80 using polyclonal antibody. In epithelial cells, this transmembrane molecule is considered as one of the key molecules for the formation of the intercellular junctional complex and for establishment of cell polarization¹⁷. At the structural level, E-cadherin (E-CD) has extracellular portion responsible for homophilic cellular interaction and an intracellular part that provides link to actin cytoskeleton through an association with various catenins, of which α -catenin has significant role in cell adhesion and signal transduction^{18,19}. A positive association between abnormal E-CD expression and occurrence of invasion and metastasis has been reported in cancers of stomach, breast, and other organs²⁰⁻²². Berx et al²³ have reported that protein-truncating mutations in extracellular part of E-CD are responsible for lack of E-CD expression, thereby resulting in characteristic scattered tumor cell growth in infiltrative lobular breast cancer, which further has a propensity for dissemination. Lack of E-CD expression has been known to be linked with invasive tumor types, higher grades and a similar lack of ER expression²⁴. Forced expression of E-CD in tumor cell lines has been shown to result in reversion from an invasive to benign tumor cell phenotype²⁵. Besides, the reversibility of E-CD down regulation has been demonstrated by the observation that treating the tumor cells with antiestrogen tamoxifen can restore the invasion suppressor activity of E-CD²⁶. KA1-1 is another gene responsible for suppressing metastasis and its down regulation is an added factor to loss of E-CD expression, thereby increasing the invasive potential and poor survival in carcinomas, as of breast²⁷.

nm-23-H1 and nm-23 H2 (non metastatic proteins) are another set of genes with possible implications in progressive breast carcinomas. They are located on 17q22 and separated from each other by no more than 18 kb. The two have arisen by tandem duplication²⁸. Differential colony hybridization between low and

highly metastatic murine K-1735 melanoma cell lines led to identifying function of nm 23, with a ten fold lower expression in the more aggressive cell lines²⁹. Its lower expression is associated with higher metastatic potential of breast carcinomas. According to Royds et al³⁰, reduced nm 23-H1 expression correlated with increasing grade of invasive duct carcinoma. However, its role in predicting lymph node metastasis is unclear. It has been shown that restoration of nm23 in breast carcinoma cell lines leads to a 50-90% reduction of nm 23 in breast carcinoma cell lines leads to a 50-90% reduction in the invasive potential of the same in human breast carcinoma cell lines²⁹. In a study by Hartsough et al³¹, it was concluded that DNA methylation inhibitors like 5-Aza-2'-deoxycyclidine (5-Aza-CdR) can directly or indirectly cause both elevation of nm-23-H1 expression, thereby leading to decreased function in one aspect of metastasis, motility.

Thus, a wide range of newer markers are on their way to help oncologists predict outcome of breast cancer in individual cases. At times, a clinician is faced with the management of node-negative breast cancers due to lack of reliable prognostic parameters that distinguish patients who benefit from adjuvant chemotherapy. Since surgery alone forms a curative mode of management in approximately 70% of such cases, there is an impasse of possible over treatment or under treatment. Traditional CMF regime is added as a compromise, rather than newer effective regimes containing anthracyclins or taxanes. There are relatively recent reports on usage of uPA and PAI-1 for identifying high-risk patients in node negative cancer groups, for intensive effective treatment, in order to reduce groups, for intensive effective treatment, in order to reduce mortality³². Reduction of tumour cell mobility could be achieved by restoration of certain adhesion molecules like E-cadherin and proteins like nm-23-H1^{25,28}. In this way, a research into development of newer markers, relating to predicting the propensity of tumor cells to metastasise, could form a useful basis to contrive specific drug targets for reducing mortality and morbidity, as a result of breast cancer.

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Staging and Pathology of Breast Cancer - Recent Advances

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Abstract: Significant developments in the field of early detection, diagnosis, management and standardization of multimodality therapies have necessitated the need for updating the staging system for breast cancer. These revisions essentially represent a 'fine tuning' of the initial judgment that tumour size, lymph node status, presence of distant metastases are significant prognostic factors and likely in the future histological grading will join this group of independent markers

Keywords: Breast cancer, staging, lymph nodes, metastases.

Introduction

Breast carcinoma is a devastating illness both physically and emotionally, affecting thousands of women, with special preponderance in the urban population. Comprehensive breast cancer management involving multimodality therapies which include surgery, neo adjuvant chemotherapy, radiation, immunotherapy, hormonal therapy is a must, to achieve optimum cure and survival rates. The foundation to decide the optimum therapy or combination therapy depends on staging the disease. Proper staging of breast cancer assists the treating clinician in making appropriate treatment decisions and in evaluating the results of different treatment strategies. The staging system for carcinoma of the breast applies to infiltrating breast carcinoma, including micro invasive and in situ carcinomas. Microscopic confirmation is mandatory and the histological type and grade of the carcinoma should be recorded.

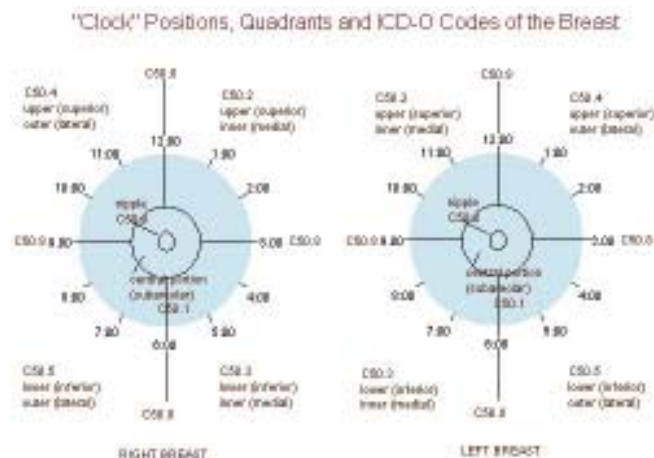
The American Joint Committee on Cancer (AJCC) staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions are formulated in part according to staging categories but primarily according to tumor size, lymph node status, estrogen-receptor and progesterone-receptor levels in the tumor tissue, menopausal status, and the general health of the patient

Anatomy

Primary Site

Breast tissue extends from below the collarbone to the level of the sixth or seventh rib, and from the breastbone to the underarm (axilla). In the center of the breast is the nipple, or mammilla, and areola (circular area around the nipple). Montgomery's glands, located around the edge of the areola, release a fatty substance that protects the nipples during nursing. The breasts of an adult woman are milk-producing, tear-shaped glands. They are supported by and attached to the front of the chest wall on either side of the breast bone or sternum by ligaments. They rest on the major chest muscle, the pectoralis major. The breast has no muscle tissue. A layer of fat surrounds the glands and extends throughout the breast. The breast is responsive to a complex interplay of hormones that cause the tissue to develop, enlarge and produce milk. The three major hormones affecting the breast are estrogen, progesterone and prolactin, which cause glandular tissue in the

breast and the uterus to change during the menstrual cycle. Each breast contains 15 to 20 lobes arranged in a circular fashion. The fat (subcutaneous adipose tissue) that covers the lobes gives the breast its size and shape. Each lobe is comprised of many lobules, at the end of which are tiny bulb like glands, or sacs, where milk is produced in response to hormonal signals. Ducts connect the lobes, lobules, and glands in nursing mothers. These ducts deliver milk to openings in the nipple. The areola is the darker-pigmented area around the nipple.



Chest wall

The chest wall includes the ribs, intercostals muscles, and serratus anterior muscle; the pectoral muscles are not included.

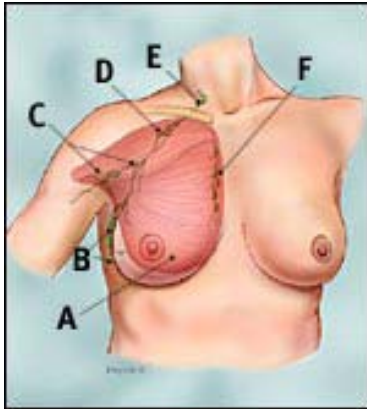
Regional Lymph nodes

The breast lymphatics drain by way of three major routes – axillary, transpectoral and internal mammary. For staging purposes intramammary nodes are classified as axillary and supraclavicular nodes as regional group.

The regional nodes are classified as

1. Axillary – Ipsilateral – Rotter's nodes and lymph nodes along the axillary vein and its tributaries and are divided into the following levels –
 - a) Level I - Lymph nodes lateral to the lateral border of pectoralis minor muscle.
 - b) Level II – Lymph nodes between the lateral and medial borders of the pectoralis muscle and the Rotter's nodes.

- c) Level III – Lymph nodes medial to medial border of pectoralis minor muscle and originally classified as apical group.
2. Internal Mammary - Ipsilateral – lymph nodes along the edge of the sternum in the endothoracic fascia.
3. Supraclavicular - lymph nodes in the supraclavicular fossa. Adjacent lymph nodes outside of this triangle are considered to be lower cervical nodes (M1).



Lymph node areas adjacent to breast area

- A Pectoralis major muscle
- B Axillary lymph nodes: levels I
- C Axillary lymph nodes: levels II
- D Axillary lymph nodes: levels III
- E Supraclavicular lymph nodes
- F Internal mammary lymph nodes

Metastatic Sites

The four major sites of involvement are bone, lung, brain and liver, but tumor cells are capable of metastasizing to many other sites.

Rules of classification.

Clinical staging

This includes physical examination, with careful inspection and palpation of the skin, breast and lymph nodes, imaging and pathologic examination of the breast and other relevant tissues to establish the diagnosis. Imaging findings are considered as part of staging, only if they are collected within 4 months of diagnosis in the absence of disease progression or through completion of surgery. Imaging and surgical findings obtained after a patient has been treated with neo adjuvant chemotherapy, hormonal therapy, immunotherapy or radiation therapy are not considered elements of initial staging

Pathologic Staging

Pathologic staging includes all data used for clinical staging plus data from surgical exploration and resection as well as pathologic examination of the primary carcinoma, regional lymph nodes and metastatic sites. If there is only microscopic but no macroscopic involvement at the margin, it is classified as pT: whereas if there is tumor in the margin of resection it would be pTX (total extent cannot be assessed). If the primary tumor is invasive, resection of at least the level I axillary lymph nodes should be done and should include at least six nodes. Alternatively Sentinel Lymph node biopsy can be done. Histological types which do not require a lymph node biopsy are : pure tubular carcinoma < 1 cm, pure mucinous carcinoma < 1 cm and micro invasive carcinoma. Cancerous nodules in the axillary fat adjacent to the breast, without histological evidence in lymph nodes are classified as regional lymph nodes (N). if surgery occurs after the patient has

received neo adjuvant chemotherapy, hormonal therapy, immunotherapy or radiation therapy, the prefix “y” should be used.

TNM Classification

T – Primary Tumor

Determining tumor size – the clinical measurement is based on physical examination or imaging such as mammography or ultrasound. The pathologic tumor size is a measurement of only the invasive component and the size is assessed before any tissue is removed for special studies, such as estrogen receptors.

Tis classification - carcinoma *in situ* with no evidence of an invasive component is classified as Tis, cases of ductal carcinoma-*in-situ* and cases with both ductal and lobular component are classified as Tis (DCIS). Lobular carcinoma *in situ* is designated as Tis (LCIS), Paget’s disease of the nipple without an associated tumor is classified as Tis (Paget’s) and Paget’s disease with a demonstrable mass or invasive component is classified as according to the tumor or invasive component.

Microinvasion of breast carcinoma – microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. The size of only the largest focus is used for classification.

Multiple Simultaneous Ipsilateral Primary cancers – in infiltrating, macroscopically measurable multiple simultaneous ipsilateral primary carcinomas, the following guidelines are used

- a) Use the largest primary carcinoma to classify T.
- b) Record that this is a case of multiple simultaneous primary carcinomas.

Simultaneous Bilateral Breast Carcinoma – each carcinoma is staged as a separate primary carcinoma in a separate organ.

Inflammatory Carcinoma – a clinicopathologic entity characterized by diffuse erythema and edema (peau d’orange) of the breast, often without an underlying palpable mass and the clinical presentation is due to tumor emboli within the dermal lymphatics. It is classified as T4d

Skin changes – dimpling of skin, nipple retraction, or any other skin change except those under T4b or T4d may occur, without changing the classification.

N - Regional Lymph Nodes

Macrometastasis – clinically apparent is defined as detected by imaging studies, excluding lymphoscintigraphy or by clinical examination or grossly visible pathologically. A case in which classification is designated purely by sentinel lymph node biopsy is suffixed as “(sn)” e.g. – pN1 (sn).

Isolated Tumor Cells and Micrometastases – Isolated Tumor Cells (ITCs) are defined as single cells or small clusters of cells, not greater than 0.2 mm in largest dimension, usually with no histological evidence of malignant activity. If an additional immunohistochemical examination was made, it should be designated as pN0 (i-) or pN0 (i+). Macrometastases are defined as tumor deposits greater than 0.2 mm and greater than 2 mm in the largest dimension. If histologically and immunohistochemically

negative lymph nodes are examined using molecular methods (reverse transcriptase-polymerase RT-PCR), lymph nodes are classified as pN0 (mol-) or pN0 (mol+), as appropriate.

M - Distant Metastasis

A negative clinical history and examination are sufficient to designate a case as M0, extensive imaging and other testing is not required. Positive supraclavicular lymph nodes are now classified as N3 and not as M1.

Defintion of TNM

T – Primary Tumor – definitions for classifying primary tumor are same for clinical and pathological classification.

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis (DCIS)	Ductal Carcinoma <i>is situ</i>
Tis (LCIS)	Lobular Carcinoma <i>is situ</i>
Tis (Paget's)	Paget's disease of the nipple with no tumor.
T1	Tumor 2 cm or less in greatest dimension,
T1mic	Microinvasion 0.1 cm or less in greatest dimension.
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension.
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension.
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension.
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension.
T3	Tumor more than 5 cm in greatest dimension.
T4a	Extension to the chest wall, not including pectoralis muscle.
T4b	Edema, including peau d'orange, ulceration of skin, or satellite nodules to the same breast.
T4c	Both T4a and T4b.
T4d	Inflammatory carcinoma.

N – Regional Lymph Nodes

Clinical

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph nodes metastasis.
N1	Metastasis to movable Ipsilateral axillary lymph nodes.
N2a	Metastasis to Ipsilateral axillary lymph nodes fixed to one another or to other structures.
N2b	Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph nodes.
N3a	Metastasis in Ipsilateral infraclavicular lymph nodes.
N3b	Metastasis in Ipsilateral internal mammary and axillary lymph nodes.
N3c	Metastasis in Ipsilateral supraclavicular lymph nodes.

Pathologic

pNX	Regional lymph nodes cannot be assessed.
pN0	No regional lymph node metastasis histologically.
pN0 (i-)	No regional lymph node metastasis histologically, negative IHC.
pN0 (i+)	No regional lymph node metastasis histologically, positive IHC.
pN0 (mol-)	No regional lymph node metastasis histologically,

pN0 (mol+)	negative molecular findings. No regional lymph node metastasis histologically, positive molecular findings.
pN1mi	Micrometastasis greater than 0.2mm but none greater than 2.0mm.
pN1a	Metastasis in 1 – 3 axillary lymph nodes.
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by SLNB but not clinically apparent.
pN1c	Metastasis in both 1 – 3 axillary and internal mammary lymph nodes.
pN2a	Metastasis in 4 – 9 axillary lymph nodes.
pN2b	Metastasis in clinically apparent internal mammary nodes in the absence of axillary node involvement.
pN3a	Metastasis to 10 or more axillary lymph nodes or to infraclavicular lymph nodes.
pN3b	Metastasis in clinically apparent Ipsilateral internal mammary nodes in the presence of 1 or more axillary nodes or, in more than 3 axillary lymph nodes and in internal mammary nodes detected by SLNB but not clinically apparent.
pN3c	Metastasis in supraclavicular lymph nodes.

M – Distant Metastases

MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant Metastasis – bone (OSS), lung (PUL), brain (BRA), liver (HEP)

Staging

Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neo adjuvant therapy

Simplified Staging of Breast Cancer

Stage	Tumor Size	Lymph node involvement	Metastasis
I	Less than 2 cm	No	No
II	2-5 cm	No or in same side breast	No
III	Greater than 5 cm	Yes or in same side breast	No
IV	Not applicable	Not applicable	Yes

Detailed Staging

Stage	Tumor Size	Lymph node involvement	Metastasis
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M0

Histopathology

Histological Grading

All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is currently recommended. The grade of a tumor is determined by assessing morphologic features – tubular formation, nuclear pleomorphism, mitotic count, assigning a value of 1 (favorable) to 3 (unfavorable) for each feature and adding together the scores for all three categories.

- GX Grade cannot be assessed.
 G1 Score 3 – 5, low combined histological grade – favorable.
 G2 Score 6 – 7, intermediate combined histological grade – moderately favorable.
 G3 Score 8 – 9, high combined histological grade – unfavorable.

Histological Typing

Invasive Carcinomas

NOS (not otherwise specified)

Ductal

Inflammatory

Medullary, NOS

Medullary with lymphoid stroma

Mucinous

Papillary (predominantly micropapillary pattern)

Tubular

Lobular

In situ Carcinomas

NOS

Intraductal

Paget's disease and

Intraductal

Paget's disease and Infiltrating

Undifferentiated

Squamous Cell

Adenoid Cystic

Secretory

Cribiform

Summary of Recent Changes.

- Micrometastasis are distinguished from isolated tumor cells on the basis of size and histological evidence of malignant activity.
- Specifications added to the classification to indicate the use of Sentinel Lymph Node Biopsy (SNLB) and immunohistochemical or molecular techniques.
- Involvement of regional lymph nodes is designated according to number of involved axillary nodes as determined by routine H & E staining or by immunohistochemical staining.
- The classification of metastasis to the infraclavicular lymph nodes has been added as N3.
- Metastasis to the supraclavicular lymph nodes has been reclassified as N3, rather than as M1.
- Metastasis to the internal mammary lymph nodes, based on the method of detection and the presence or absence of axillary lymph nodal involvement has been reclassified.

Suggested Further Reading

- Ismail Jatoti, Singletary E A – Guest Editors – Breast Cancer : New Concepts in Management, The Surgical Clinics of North America, Vol 83, No 4, Aug 2003.
- AJCC Cancer Staging Handbook, Sixth Ed, TNM Staging of Malignant Tumors, Publisher – Springer (India) Pvt Ltd, N Delhi, India.

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A Radiologist's Perspective in Breast Cancer

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Abstract: Breast cancer is the most common malignancy in females with a steadily increasing incidence and the second leading cause of cancer death. One out of seven women either has or will develop breast cancer in her lifetimes. A gamut of investigations is available for its detection. The advantage and disadvantage of each of them is discussed below. Screening mammography is very useful in the early detection of non-palpable breast masses. It is recommended every 1 to 2 years in women of 40-49 years and every year in 50 years age group. Diagnostic mammography is done in clinically palpable lesions. BIRADS system of reporting provides a useful framework for categorizing the recommendation for management of a breast mass. Sonography is used not as a screening modality but primarily to differentiate between solid and cystic masses and to provide ultrasound guided biopsies and aspiration. Other methods of biopsy include fenestrated grid (X-ray Mammography) guided and Stereotactic guided biopsy. Ductogram is procedure of choice for evaluating the cause of nipple discharge. Role of MRI in the present scenario is restricted to specific conditions where a mammography is less sensitive (as in dense breast) with the high risk of malignancy.

Keywords: Breast carcinoma, mammography, ultrasound.

Introduction

Hope for altering the course of breast cancer and improving the mortality rates and five-year survival rates entirely depends on its early detection. Detection and evaluation of breast masses can be one of the most challenging and rewarding areas of Radiology. The following article attempts to give a Radiologist's perspective of imaging of the breast for cancer, with primary emphasis on Mammography and ultrasound.

Initial Imaging protocol for a patient presenting with a clinically palpable mass should vary with patient's age and family history of breast cancer, as shown in Table 1.¹

Table 1 : Imaging Protocol vis-a-vis patients age

Patients age (years)	Imaging protocol
Younger than 20	Sonography only
20-30 years	Sonography first. Mammography (usually unilateral single view) if U/S does not show a simple cyst.
30-35years	If no close family history of breast cancer, same as for age 20-30.If mother or sister with breast cancer, same as for age 35 and older.
35 and older	Bilateral two view per breast mammogram first. Sonography if mammography negative or nonspecific.

Mammography is the preferred examination for breast especially in females more than 40years.It detects 75% of cancer at least a year before they can be felt. It has a false negativity rate of 8-10%. Also 1-3% of women with a clinically suspicious abnormality are known to have a normal mammography as well as sonography².

There are two types of mammography - screening and diagnostic mammography. Screening mammography is done in asymptomatic patients. It is recommended every 1-2 year in women of 40-49 years age group and once every year after 50 years age group. It can be done in <40years age group in case of very strong family history of breast cancer. [2] Diagnostic mammography is performed in symptomatic patients, for e.g.: palpable breast lump or nipple discharge. Several additional views are done when required in diagnostic mammography.

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For screening mammography each breast is imaged separately in both cranio-caudal (CC) and medio-lateral oblique (MLO) views. Supplemental views include lateromedial (LM), Mediolateral (ML), exaggerated CC views, Magnification views, spot compression views and others. Special skin markers can be used.

Breast compression is necessary to flatten the breast so that:

- Maximum amount of tissue can be imaged and examined.
- It allows lower dose of radiation.
- Immobilization of breast allows reduction of motion blur .
- Reduces X-ray scatter and improves quality.

Breast Imaging Reporting & Data System (BIRADS)

The American College of Radiology (ACR) has developed a Breast Imaging Reporting and Data System (BI-RADS), intended to standardize terminologies used in the mammography report as well as to outline the organization of the report³. It contains a lexicon of standard terminology and a coding system with a specific course of action.

It consists of an overall description of breast parenchymal pattern as : (1) extremely dense; (2) heterogeneously dense; (3) scattered fibroglandular density; (4) entire fat.

Lexicon/Terminology

- Mass :** This term is a space occupying lesion seen in two different projections.
- Density:** This term is used if a potential mass is seen in only one single projection.
 - Circumscribed (well-defined or sharply-defined) margins:** The margins are sharply demarcated with an abrupt transition between the lesion and the surrounding tissue.
 - Indistinct (ill defined) margins:** The poor definition of the margins may be due to infiltration by the lesion and this is not likely due to superimposed normal breast tissue.
 - Spiculated Margins:** The lesion is characterized by lines radiating from the margins of a mass.
- Architectural Distortion:** The normal architecture is distorted with no definite mass visible. This includes spiculations radiating from a point, and focal retraction or distortion of the edge of the parenchyma. Architectural distortion can also be an associated finding.

D. **Asymmetric Density:** It is visible as asymmetry of tissue density with similar shape on two views, but completely lacking borders and the conspicuity of a true mass. It could represent an island of normal breast, but its lack of specific benign characteristics may warrant further evaluation. Additional imaging may reveal a true mass or significant architectural distortion.

E. **Calcification:**

Amorphous or Indistinct Calcifications: These are often round or "flake" shaped calcifications that are sufficiently small or hazy in appearance that a more specific morphologic classification cannot be determined.

Pleomorphic or Heterogeneous Calcifications: These are usually more conspicuous than the amorphous forms and are neither typically benign nor typically malignant irregular calcifications with varying sizes and shapes that are usually less than 0.5 mm in diameter.

Fine, Linear or Fine, Linear, Branching (Casting) Calcifications: These are thin, irregular calcifications that appear linear, but are discontinuous and under 0.5 mm in width. Their appearance suggests filling of the lumen of a duct involved irregularly by breast cancer.

Benign Calcifications: Benign calcifications are usually larger than calcifications associated with malignancy. They are usually coarser, often round with smooth margins and are much more easily seen.

Table 2 : Assessment Categories in Breast Cancer

Assessment Categories

Category 0 / Need Additional Imaging Evaluation	Finding for which additional imaging evaluation is needed. Almost always used in a screening situation and should rarely be used after a full imaging work up.
Category 1 / Negative	The breasts are symmetrical and no masses, architectural disturbances or suspicious calcifications are present
Category 2 / Benign Finding.	This is also a negative mammogram with no mammographic evidence of malignancy Involuting, calcified fibro- adenomas, multiple secretory calcifications, fat containing lesions such as oil cysts, lipomas, galactoceles, and mixed density hamartomas all have characteristic appearances, and may be labeled with confidence.
Category 3 / Probably Benign Finding - Short Interval Follow-Up Suggested.	Findings having very high probability of being benign. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability.
Category 4 / Suspicious Abnormality - Biopsy Should Be Considered	These are lesions that do not have the characteristic morphologies of breast cancer but have a definite probability of being malignant. The radiologist has sufficient concern to urge a biopsy.
Category 5 / Highly Suggestive of Malignancy - Appropriate Action Should Be Taken	These lesions have a high probability of being cancerous. Referring clinician should be alerted immediately.

Table 3 : Management of Breast mass based on BIRADS classification

Category	Description	Risk of Malignancy	Care Plan and Comments
1.	Negative	5 in 10,000	Continue annual screening mammography for women 40 years or older.
2	Benign finding, non-cancerous	5 in 10,000	Same as above. This category is for cases with a characteristically benign finding (e.g., cyst,

3	Probably benign finding	<2%	fibroadenoma). Usually, 6-month follow-up mammography is performed. Most category 3 abnormalities are not evaluated with biopsy.
4.	Suspicious abnormality	25-50%	Most category 4 abnormalities are benign but may require biopsy.
5.	Highly suggestive of malignancy	75-99%.	Classic signs of cancer are seen on the mammogram. All category 5 abnormalities are typically evaluated with biopsy; if the results are benign, repeat biopsy is done to ensure correct sampling.

Interpretation of abnormal mammogram :

Mass lesion: Whenever one comes across a mass lesion, one has to describe them under the following headings-

A. Shape of the lesion :

1. Round-commonly seen in benign masses exceptionally sarcoma, lymphoma and mucinous carcinoma)
2. Oval-typically fibro-adenomas fall under this category
3. Lobular mass with undulations is seen in both benign and malignant condition.
4. Irregular shape - by and large seen in malignant cases.

However benign conditions like inflammatory masses can also have irregular shape. Hence, U/S correlation is required.

B. Margins:

It constitutes an important criteria in evaluation of any mammographic lesion. They can be sub-classified under the following headings:

1. Circumscribed: largely seen in benign masses. However, medullary/mucinous malignancies can also appear circumscribed.
2. Lobulated margin: seen in both benign and malignant lesions.
3. Obscure: due to overlying fibro-glandular tissue.
4. Ill defined/poorly marginated: both benign and malignant lesion.
5. Spiculated margin: largely seen in malignant condition. (>95% probability) with the exception of radial scar/changes due to previous surgery.
6. Irregular margin or micro lobulate margins are also strong suspect of malignancy.

C. Density:

Malignant lesions especially schirrous cancers have greater density than normal breast tissue. Fatty lesions such as oil cyst, lipomas, galactocoele, and hamartomas have very low density.

D. Calcification:

As described under BIRADS.

Associated findings like skin/trabacular thickening, nipple retraction, architectural distortion, asymmetric density, axillary adenopathy should be noted.

Malignant lesion: Mammographic criteria for a malignant lesion are broadly considered under the following heads.

- | | |
|-----------------------|--------------------------|
| ➤ Direct signs | ➤ Indirect signs |
| Mass lesion | Asymmetric density |
| Microcalcification | Architectural distortion |
| | Breast edema |

Direct signs - Malignant mass lesions typically appear as central dense lesions with spiculated border. The most diagnostic appearance of an invasive breast cancer either ductal or lobular is an irregularly shaped mass with spiculated margins and high density with or without calcification. The spiculation results from

a desmoplastic response as the tumor extends into the surrounding tissue. Other causes for spiculation include radial scar, fat necrosis, and previous surgery. In malignant lesion, density is more than the adjacent glandular tissue as compared to benign masses. In the absence of previous surgery, a lesion with dense center with spiculated margin is virtually diagnostic of breast cancer. As compared to ductal carcinoma, invasive lobular carcinoma has a tendency to diffusely infiltrate the breast tissue and may masquerade as an asymmetric density and be visible only in one view⁴.

Micro-calcification: It is another direct sign of presence of malignancy. It may or may not be associated with mass lesion. It is found in clusters and is pleomorphic /granular type having different shape, size, density, with > 5 calcific foci in 1 cm diameter and must always be investigated further with FNAC/excision biopsy. The indeterminate calcification also labeled as indistinct or amorphous type are also associated with malignancy. Fine branching /casting type are highly suspicious of malignancy and usually seen in ductal carcinoma in situ.

Indirect signs of malignancy:

Asymmetric density-Many times, we do not find the presence of direct signs i.e. spiculated mass or micro-calcification but we may only pickup early malignancy as focal asymmetrical density or architectural distortion-especially lobular invasive variety. Summation artifact is also seen as asymmetrical density but is seen only in one view. Hormone replacement therapy HRT is another cause leading to asymmetric density

Architectural distortion: It is commonly seen in infiltrating duct carcinoma, lobular invasive and also in post operative scarring and radial scar.

Other associated findings seen in mammography in carcinoma of breast:

Edema of breast due to angio-lymphatic spread, seen as diffuse increase in density involving a large part of breast. Other causes for edema include post irradiation changes, inflammatory pathologies, post axillary surgery, enlarged axillary lymph nodes causing lymphatic obstruction and consequent to general body edema. Skin thickening, nipple retraction, are other features associated with malignancy, can be clinically correlated.

Some carcinoma may have relatively well circumscribed margin which include medullary, mucinous (colloid) and papillary carcinoma. Primary breast lymphoma, tumors of mesenchymal origin (osteosarcoma, fibrosarcoma, liposarcoma) present with minimal marginal irregularity and no calcification. Metastases to breast from extra mammary neoplasms are most common from melanoma with other possibility like lymphoma, leukemia, ovarian and soft tissue sarcoma. These lesions generally tend to be well circumscribed, single or multiple, U/L or B/L and have similar appearance to multiple cysts or fibroadenoma.

Phyllodes tumor is an uncommon mass, mostly benign but 5% have malignant potential. It grows rapidly 5-10cm size, appearing round, oval or slightly lobulated lesion with high density with relative well defined margins, with no calcification.

Current role of ultra sound in breast imaging:

Although U/S has not proved useful in breast cancer screening, it has become a valuable problem solving tool, particularly in differentiation of cysts from solid masses.

Indications for breast U/S:

1. *Differentiation of cysts from solid masses:* Ultrasound is 96 to 100% accurate in diagnosis of cysts⁵. in circumscribed or obscured non calcified masses seen on mammography or found on palpation. It also avoids unwanted biopsies

performed for benign cysts.

2. *Evaluation of a palpable mass that is not visible in a radio-graphically dense breast in mammography.* U/S is of great value here, to localize and characterize such masses into solid or cystic types, and further helps in U/S⁶ guided biopsies. If a palpable mass is not visible by either mammography or U/S, the lesion should be assumed to be solid and biopsy should be considered if clinical findings are suspicious for malignancy.
3. *Assessment of a mass that cannot be completely evaluated by mammography because of location.* In rare cases, a palpable mass cannot be placed on the mammographic plate due to extreme peripheral location in a very thin patient.
4. *Evaluation of a young patient <30 years with a palpable mass.* The breast of such patients tends to be radio-graphically denser and also more sensitive to radiation and also with a lesser incidence of cancer. For this reason, we usually perform a U/S as the initial study. If it is cystic, no further evaluation is required. If solid or not visible on U/S, one can go in for a single view mammogram, primarily to look for micro-calcification.
5. *Evaluation for an abscess:* Mammography is very difficult because of pain and edema and often does not demonstrate discrete abscess, just showing an area of increased density due to inflammation. U/S is an excellent method for detecting abscess cavity and for guidance for surgical or percutaneous drainage.
6. Guidance for Interventional procedure.

Inappropriate use of U/S:

1. As a screening modality.
2. As a routine evaluation of post operative breast cancer.
3. Evaluation of asymmetric breast density:
4. It does not detect micro-calcification and many small solid masses are sonographically invisible.

It has an unacceptably high false negative rate (20-47%). It also fails to detect a number of non palpable mammographically occult carcinomas. It also has a substantial false positive rate. Use of U/S as an adjuvant to mammography may add up to 7.4% of its accuracy⁷.

Sonographic appearance of solid masses: The benign ones like fibroadenoma are oval, smooth, isoechoic or hypoechoic. Also, most benign lesions are broader than taller. The sonographically visible malignant lesions, such as infiltrating carcinomas are irregular, hypoechoic with speculated margins with posterior acoustic shadowing and are generally taller than broader (AP dm>Transverse dm)⁹. Malignant lesions on colour Doppler show an increased resistivity index (RI > .07) and shows increased peripheral vascularity. However, these are not very reliable criteria.

Needle biopsy techniques:

The ability to obtain a definitive diagnosis of a breast lesion without surgery has changed the face of breast radiology. Based upon the lesion's location and surgeon's choice, the following guided procedures are available which provide satisfactory results.

- I. U/S guided: (a) FNAC, (b) Hookwire localization, (c) Core biopsy,
- II. Fenestrated grid (x-ray mammography) guided : (a) FNAC, (b) hook wire,
- III. Steriotactic guided : (a) core biopsy, (b) hook wire, (c) FNAC,
- IV. MR directed biopsy with MR compatible wires and needles. (not widely available).

V. CT guided I/V bolus pre-operative needle localization

U/S guided technique: It is extremely useful in both palpable and non palpable masses; should be the first investigation of choice, being simple, quick, safe, cheap, accurate, non-ionizing. It has a sensitivity of 77-97% with a specificity of 91-100%.

U/S guided hookwire localization is performed in non-palpable lesion where in FNAC has been non conclusive or in highly suspicious lesions (both BIRADS III & IV). U/S guided core biopsies and or in evaluation of suspicious clusters of micro-calcification, mammographically detected non-palpable lesion not appreciated on high-resolution sonography and for deeper lesions in large fatty replaced breast.

Fenestrated grid guidance: Perforator grid compression plate is a standard attachment with most of International manufacturers of dedicated mammographic equipment. It is much cheaper and more easily available as compared to steriotactic guided biopsy which is much more costly (equipment cost is more than the cost of mammography unit). Hence it is not so widely available. But it is the most accurate of all procedures, ideally suited for core biopsies and or in evaluation of suspicious clusters of micro-calcification, mammographically detected non-palpable lesion not appreciated on high-resolution sonography and for deeper lesions in large fatty replaced breast.

Ductogram

A ductogram, or galactogram, is the diagnostic procedure of choice for determining the cause of U/L single pore spontaneous nipple discharge and helps in guiding accurate surgical intervention⁸. In this x-ray procedure, a fine plastic tube is placed into the opening of the duct in the nipple. A small amount of contrast medium is injected, which outlines the shape of the duct on an x-ray image and shows whether a mass is present inside the duct. Features of ductal carcinoma include irregular filling defects, wall irregularity with ductal distortion all seen in the dilated ductal system.

Magnetic Resonance Imaging (MRI)

Role of MRI in breast cancer detection is limited to specific clinical situations and currently only used as a diagnostic adjunct, for further characterizing the extent of invasive breast cancer in select population of younger women in the high risk group (strong family history) with dense breast, where mammography is less sensitive and in other situations like presence of implants and surgical scarring and multiple areas of distortion secondary to surgery¹⁰.

Main Advantages include tomographical capability, chemical information, function of tissue vascularity, high sensitivity for invasive carcinoma in breast, with dense parenchyma and chest wall visualization and of course non ionizing nature.

Disadvantages of MRI: High cost of scan and contrast, availability, time consuming, expertise required in interpretation, volumes of data, enhancement varies with menstrual cycle, unable to image micro-calcification, low specificity (many benign lesions and normal tissue enhance).

Normal breast: MR appearance:

Pre contrast T1WI-fat is seen as high signal intensity (bright), glandular and ductal structures are intermediate signal intensity, fibrous tissue and ligament of Cooper having low signal intensity (dark). Pectoralis muscles have intermediate signal intensity and lung has low signal intensity on all sequences.

Women with glandular breast should be imaged in the mid cycle to minimize enhancement of background breast parenchyma that might limit lesion detectability¹¹. Simple cysts do not enhance on post contrast T1WI and show high signal on T2WI. Fibroadenomas often produce a high and rapid signal intensity change that mimics the enhancement pattern of invasive carcinoma. Invasive breast carcinoma are low signal intensity on T1 precontrast MR

sequence, that increase to 90% or greater in signal intensity within the first 60-90sec on 2-D dynamic scan with a cut off point of 70% enhancement at 1 minute¹². On a 3-D volumetric scan, cancers show >300 units of enhancement at 5-10 minute post infusion¹³. Axillary, internal mammary adenopathy, muscle, bony involvement, cross metastasis can also be identified.

Future potential of MRI includes MR directed biopsy especially in MR detected lesions that are not seen even on retrospect on mammography or U/S. MR compatible needles and wires are available.

Digital mammography, computer aided diagnosis and tele-mammography: A mammographic system that acquires images directly in digital form and thus overcoming the limitations of conventional mammography such as contrast, noise, resolution. It has post processing, storage, retrieval, reproduction and transport of images.

Computer aided detection and diagnosis are two potential revolutionary technology in which the radiologist can attain a second opinion from the image analysis, from a computer by using artificial intelligence to estimate the likelihood of malignancy.

Tele-mammography is the transmission of mammographic image from one location to another, anywhere on earth, in a digital format. It allows online interpretation, discussion, second opinion, interactive teaching conferences, all from a distant location.

Summary: With the ability to perform a good diagnostic mammography, breast U/S, ductography, MRI, Scintimammography, cyst aspiration, abscess drainage, steriotactic or U/S guided percutaneous biopsy, the modern breast radiologist should play the central role in breast cancer diagnosis. The future holds even more exciting challenges for the radiologist, as percutaneous lumpectomy is becoming a reality. Thus the breast radiologist, armed with the techniques and the technologies of the twenty-first century, truly stands on the threshold of a new era.

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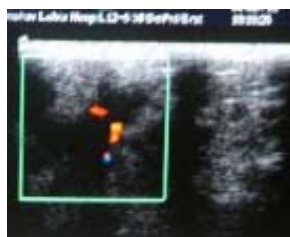


Case 1. (a)



Case 1. (b)

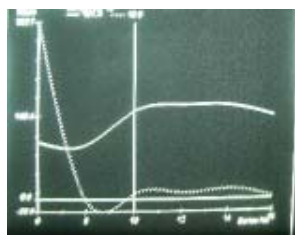
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Case 1. (c)



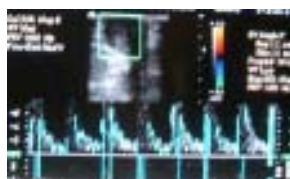
Case 1. (d)



Case 1. (e)



Case 2. (a)



Case 2. (b)



Case 2. (c)

Case1 Infiltrating duct Carcinoma :

- Mammography right breast showing irregular mass lesion with increase density with ill-defined spiculated margin.
- Ultrasound showing irregular hypo echoic mass lesion whose depth is > AP diameter. There is posterior acoustic shadowing.
- Doppler shows increase peripheral vascularity.
- MRI Post Contrast T1 weighted images showing hyperintense mass lesion right breast with intense

enhancement within 60 seconds,

- with complete washout of contrast.

Case 2. Infiltrating ductal Carcinoma:

- Mammography shows ill-defined mass lesion with asymmetric density.
- Ultrasound showing hypo-echoic solid mass with high RI.
- MRI showing intensely enhancing infiltrating lesion.

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What's New in Breast Cancer Imaging?

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Imaging technology has changed rapidly over the last four decades. This is especially true in the area of breast cancer. In the late 20th century, aim of the imaging was anatomic delineation of the breast, while recently the major focus has been shifted toward physiologic and molecular tumor detection.

The goals of imaging are three folds: 1) the earliest possible detection of the tumor, 2) correlation of imaging results with other clinical parameters to assess disease biology and 3) accurate staging and follow up after treatment.

Some of the **newer imaging technologies** are:

1. Digital Mammography
2. Digital Subtraction Mammography
3. Computer Aided Detection and Diagnosis (CADD)
4. Power Doppler ultrasound
5. Magnetic Resonance Imaging
6. Scintimammography
7. Positron Emission Tomography
8. Electro potential Measurements
9. Electrical Impedance Imaging
10. Ductoscopy

Digital Mammography:

It is a type of mammography that records the radiographic images electronically in a digital format and is stored in computer. These can be displayed on a fluorescent monitor or transferred to hard copy. X rays passing through the breast are converted in to an electric signal that can then be processed by a computer. These mammography systems count the numbers of X ray photons passing through the breast at every point and provide a number (digit) for each point that indicate the count.

Basic difference between conventional and digital mammography is that in conventional mammography the film acts both as detector (that acquires the image) and as display media. While in digital mammography, image acquisition occurs in three steps: 1) detection of photons 2) computer display of image 3) storage of image.

In conventional mammography, film mammogram is the only film. It is fixed for ever once it is acquired. It can be under/over exposed so information can be lost requiring repeat exposure to the patient. With film mammography, bad images can't be readjusted or corrected. We see what we get. Similarly, a film mammogram is the only copy of the study. It is difficult to copy as information is lost on the copy. In digital mammography, an image can be optimized and adjusted to allow visualization of subtle details. It can also be duplicated as many times as needed and can be transmitted anywhere in the world. Identical copies can be saved electronically.

Under lying technologies in Digital mammography may be 1) conversion of x-ray photon into visible light by a fluorescent screen and then conduction of these light photons through fibro optic coupling devices that covert light into electric signals.2)

direct conversion of photons in to electric signals 3) conversion of photon to light and the measurement of this light by at each pixel by solid state detectors in a matrix over a large area.

Digital mammography will solve many of the problems inherent to film mammography, such as limited contrast, lost films, limited film storage. Added **advantage** includes, ability to do image manipulation on display monitor, to use computer added diagnosis (to be discussed later), and to transmit the images over long distances (tele-radiography). **Disadvantages** of digital mammography include: high cost, limited resolution of current monitors and limited image storage capacity.

Digital mammography- practical utility: To date, there has been only one large screening trial² to evaluate digital mammography. This trial enrolled 4,521 asymptomatic women who underwent both digital and screen film mammography. All 6,768 examinations were interpreted independently, with patients recalled for additional testing if either test was positive. This study showed a statistically significant reduction in recall rates for digital mammography (11%) vs. screen – film mammography (15%). In addition there were significant fewer biopsies caused by the digital studies than by the screen film mammography. As for breast cancer detection, there was no significant difference in the number of cases detected using digital or screen film mammography. Further studies will be needed to determine exact role of digital mammography in the evaluation of breast cancer.

Digital Subtraction Mammography:

Digital mammography is done using intravenous contrast. Precontrast images are subtracted from post contrast images electronically. It is believed that this may be of value in visualizing the breast cancer better; particularly gauging extent of disease in patient with high risk for multicentricity. This may be especially useful in women with dense breast, and those with invasive lobular carcinoma, as this lesion is especially difficult to fully characterize using traditional technology

Computer Aided Detection and Diagnosis (CADD) :

It is possible because of digital mammography. Detection algorithms for specific mammographic features associated with malignancy are used. CADD uses software to assist radiologists in interpreting mammograms. Diagnostic accuracy can be improved these programs. Large numbers of normal and abnormal digital mammograms are needed to train the computer in how to distinguish abnormal areas. CADD enhance the mammographer's ability to detect breast cancer. With the increasing numbers of women screened, it is evident that there are pitfalls, with radiologists missing a small but significant numbers of cancers. There are different options to diminish the numbers of missed cancers. One option is the reading of mammogram by two radiologists. The other alternative is CADD. CADD can detect cancers that are otherwise missed even after double reading³.

Power Doppler Ultrasound³: Doppler technologies have been now used to differentiate benign from malignant lesions. The fact of angiogenesis occurring in malignant lesion has been used.

Doppler ultrasound has the capability not only to document the presence of this microvasculature, but also to characterize vessels further in terms of benign and malignant characteristics. Presently the question of usefulness of Doppler is still unanswered. McNicholas et al⁴ found that detection of angiogenesis by Doppler did not aid in diagnosis. However when the spatial pattern and maximal velocity were evaluated, an overall sensitivity of 94%, specificity of 93% was found. Raza and Baum⁵ correlated patterns of vascular distribution and morphology of blood vessels with histology. They found that using the presence of penetrating vessels, sensitivity of Doppler was 68% and specificity was 95%. Additional role of Doppler ultrasound requires further studies.

Magnetic Resonance Imaging⁶

Earlier there was reluctance towards use of MRI mainly because of lack of standardized protocols and a greater difficulty in accessing MRI units. But new protocols, image interpretation criteria and terminology have been standardized. In MR imaging of breast, Gadolinium chelate is given as a rapid intravenous bolus injection. During the first pass phase of the contrast, the difference between intravenous and extra venous compartment is maximum, and in this phase, transportation of contrast from vessel into the tissue occur rapidly. Contrast medium present in capillaries and extra vascular extra cellular compartment provide enhancement. Regions of hypervascularity, increased capillary permeability, and increased interstitial space develop predominantly at the margins of tumor because of angiogenesis. This creates beds of pooling of contrast. Most important determinant of image quality in MR imaging of the breast is the choice of pulse sequence. Mainly two types of pulse sequence are used in MR imaging of breast: 1) gradient echo technique with/ without routine subs traction 2) techniques using fat suppression.

MR Rodeo: Rotating Delivery of Excitation off resonance sequence is a specialized high resolution fat suppressed technique first described by Harms et al⁷. It has a sensitivity of 95% in the diagnosis of breast cancer. Most important role of MR imaging is in identification of tumors not detected with conventional imaging methods. The **sensitivity** of MR imaging in the diagnosis of breast cancer is **80% - 100%**⁶ and **specificity** exceeds **80%**⁸. MR imaging is especially useful in dense breast that significantly impair mammography. While mammography and ultrasonography depend on architectural distortion to detect tumors, MRI uses morphological and physiological properties, allowing it to assess tumors that cause no architectural distortion. In addition MRI depicts soft tissue with more gradations of contrast than mammography and ultrasound, and provide thin- section and multiplanar imaging, thus allowing better characterization of lesion.

MR imaging & breast cancer staging: Assessment of disease extent is important for planning, prognosis and considering treatment modalities. Optimal surgical results rely on the surgeon's ability to obtain clear histological margins. Ideally complete loco regional staging requires the assessment of tumor size, and multicentricity, and of the involvement of the nipple, skin, chest wall, and Axillary lymph nodes. To attain this goal with the highest diagnostic confidence, high spatial resolution is needed. The improved sensitivity of MR imaging in breast cancer detection has made it possible to do loco regional staging of the breast cancer with higher accuracy.

I. Assessment of tumor size: Lesion identification depends on contrast enhancement within the breast after intravenous

injection of contrast. As both normal and abnormal breast tissue will enhance after contrast administration, characterization of a malignant lesion with in normal breast tissue is based on kinetic and architectural features of malignant lesion. **Mammography and ultrasonography significantly underestimate tumor size by 14% and 18 % respectively**, while a MR imaging show no significant difference compared with that determined by pathological examination⁹. Mumtaz et al¹⁰ also demonstrated that MRI was more accurate than mammography in determining tumor size in 85 invasive tumors. **MRI gives the most accurate measurement of tumor size of invasive tumor**¹¹. Because of this fact, MR imaging has the potential for supplanting clinical and mammographical tumor size assessment in the preoperative TNM/UICC staging system. The sensitivity of MRI in detecting DCIS is known to be lower than for invasive disease. The reported sensitivity of MRI for DCIS is about 77%¹². MRI studies with lesion size assessment of DCIS and correlation to maximal DCIS diameter have not yet been published. Also, because MRI is relatively insensitive to microcalcification, its exact role in DCIS is debatable. An extensive intraductal component (EIC) was assessed in a study of 92 patients reporting a sensitivity of 81% for MRI vs. 62% for mammography, and a specificity of 93% for MRI and 81% for mammography¹⁰. More adequate tumor size measurement by MRI may reduce the percentage of positive margins after the breast conserving surgery and therefore decrease the numbers of subsequent surgical reexcision to obtain clear surgical margins.

II. Assessment of multifocality and multicentricity: At MRI **multifocality is diagnosed if two or more clearly separated suspicious enhancing lesions are identified**. Cancers are considered **multicentric if suspicious, focally enhancing lesions are present in more than one breast quadrants**. For the diagnosis of **mutifocal** disease MR imaging is found to be **60-100% sensitive**¹¹. For the diagnosis of **multicentric** lesion, MRI is **89% -100%** sensitive in **bilateral** imaging and **95% -100%** sensitive in **unilateral** imaging. It is **82%- 97% specific**¹¹. Multicentricity in the breast cancer has been reported at MR imaging in a substantial number of the patients whose mammogram otherwise showed unifocal disease. In one study¹⁵ MR imaging detected additional unsuspected disease confined to one quadrant in 6 patients, and in two or more quadrants in four patients. In this study, as a consequence, treatment was changed from breast conservation to mastectomy in four patients. Lower sensitivity of mammography in detecting multicentricity depends on breast density. Greatest value of MRI is in patients with homogenous or heterogenous breast parenchyma. Patients with dense parenchyma are considered ideal candidate for preoperative staging with MRI.

III. Assessment of disease extent to the Nipple, Skin and Chest wall: Morris et al evaluated¹³ MRI in patients with posterior breast tumors and clinical or mammographical suspicion of chest wall invasion. Abnormal enhancement of the pectoralis muscle was found to represent the best diagnostic criteria to confirm muscle involvement at surgery. Five out of 19 patients had masses that abutted the muscles, with the obliteration of the fat planes and muscle enhancement. All 5 had muscle involvement at surgery. In

the remaining 14 patients, no enhancement was seen; none of them had muscle invasion. MRI can assess involvement of pectoralis muscle as well as chest wall. Assessment of nipple involvement is necessary in surgical planning of patients undergoing conservative surgery. In case of nipple involvement, MRI shows disruption of the normal "two layered" linear contrast enhancement, thickening of dermis and confluent, nodular enhancement extending directly from abnormally enhancing retro-areolar mass.

- IV. Axillary Lymph nodes involvement:** Few MRI studies have focused on the assessment of axilla. These studies indicate that MRI may have a role in the diagnosis of axillary nodal metastases. A major technical limitation is current breast coil design, which covers only the lower portion of breast. Mumtaz et al¹⁰ found that lymph nodes measuring > 5 mm in short axis and appearing as high signal spot were likely to be malignant. Sensitivity to predict axillary involvement was 90% and specificity was 82% in that study. However there was poor correlation between total numbers of malignant lymph nodes identified on MRI and the pathological analysis. MR imaging may be useful in evaluating patients with metastatic axillary lymph nodes with unknown primary i.e. normal mammography, sonographic and no evidence of primary lesion on clinical examination in breast or elsewhere. Previously these patients were offered mastectomy as treatment, despite the fact that only two third of these patients had a primary cancer found on histopathological examination of mastectomy specimens. In one study¹⁴ MR imaging showed disease with in the breast of 3 patients with normal mammogram and Axillary adenopathy, MR findings of single unifocal lesion in the breast altered treatment from mastectomy to breast conservation in two of these patients. The reported sensitivities of available MRI methods are close to the reported sensitivities of **sentinel node assessment**. Therefore, further use of breast MRI including the axilla may avoid surgical staging procedure.
- V. MR imaging and Distant Metastases:** Total body echoplanar MRI has been proposed as an alternative to conventional imaging, such as bone scintigraphy, abdominal ultrasound, and computed tomography, to detect distant metastases. The main advantage of total body MRI is a decreased time of staging workup (6 minutes) and the fact that it is completely noninvasive. However, it depends on the availability of this fast imaging technique that is not routinely available in all MRI units.
- VI. MRI extent of Disease Classification:** Recommended by the Breast Cancer Staging working Group¹⁵, the maximum diameter of the index lesion (T); the maximum diameter of area that includes all foci of suspicious enhancement and the index lesion (F); and the numbers of the quadrants involved, one quadrant occupying 25% of the breast (Q), have been taken in to account for the staging. This staging pattern is still under evaluation.
- VII. MRI and local recurrence:** MR imaging is useful in evaluating the irradiated conserved breast. Heywang et al¹⁶ observed that reliable distinction between scar tissue and recurrent tumor was not possible in the first 9 months after surgery. By this time inflammatory changes that resulted in overlap in the pattern of the speed of enhancement between

benign and malignant lesions had resolved in the majority of patients. In other study¹⁷, MRI showed a sensitivity of 93% in the diagnosis of local recurrence compared with mammography (50% sensitive) and fine needle aspiration (75% sensitive). MR imaging with RODEO sequences may be able to depict residual tumor in the immediate post operative period with greater accuracy than conventional MRI¹⁸.

VIII. MRI and assessment of Neoadjuvant treatment:

Currently, increasing numbers of breast cancer patient are treated with neoadjuvant chemotherapy. MRI has shown definitive role in several studies. Knopp et al¹⁹ showed that a decrease in the rate of contrast enhancement correlated with response to chemotherapy. In another study²⁰, MR RODEO imaging was done to evaluate response to neoadjuvant chemotherapy in 40 breasts of 39 patients. The clinical assessment of response by the surgeon and the medical oncologist agreed with MR imaging in 52% and 55% cases, respectively and mammography correlated with MRI in 52 % cases. MRI accurately predicted the pathological determination of residual disease in 97 % of the ceases.

MRI is the most accurate of current imaging modalities at predicting response to primary chemotherapy.

- IX. MRI and Silicon implant^{10,21}:** The attenuation of x-rays by silicon limits the mammographic demonstration of breast cancer. This problem is more in breasts with silicon injections. Silicon does not impair MRI imaging for cancer detection. Further, specialized silicon sequence have been developed that can be used to provide specific information on the composition of the mass. When these sequences are used in conjunction with contrast enhancement, masses in patients with silicon implants can readily be characterized. MRI has also been useful in assessing silicon implant integrity. Loss of integrity can be classified in to silicon gel bleed (producing inverted drop sign); intracapsular rupture (producing linguine sign) and extra capsular rupture in which free silicon is seen in the soft tissue surrounding the implant. MRI can distinguish silicon granuloma from small tumors and is considered the "gold standard" for assessing intracapsular rupture. MRI is likely to have a promising role in percutaneous ablation of breast cancer using thermal ablative techniques, such as interstitial laser photocoagulation, focused ultrasound and bipolar radiofrequency ablation.

Recommended indications of MRI of breast²² (1. Investigation of the source of Axillary adenopathy when mammography and ultrasound are unhelpful. (2. Follow up for recurrence of the breast cancer after surgery or radiotherapy. (3. Evaluation of augmented breast. (4. Staging of DCIS, lobular carcinoma, and suspected multifocal breast cancer. (5. Assessment of high risk patient who carry the BRCA gene and have dense breast.

To summarize, MRI of the breast is more accurate than mammography and ultrasonography in the local staging of the primary breast cancer, diagnosis of local recurrence, assessment of response to neoadjuvant chemotherapy and evaluation of silicon implant.

Scintimammography

Nuclear medicine breast imaging provides functional or metabolic

information of breast tumors as these techniques are based on physiologic and biochemical characteristics of tumor. ^{99m}Tc -Technetium sestamibi and ^{99m}Tc -tetrafosmin are most commonly used radiotracers in scintimammography. ^{99m}Tc -Technetium sestamibi was initially developed as a cardiac imaging agent to document myocardial blood flow. As it is avidly taken by the tumor cells, its role in cancer imaging has been studied. Mammoscintigraphy has excellent sensitivity in the diagnosis of breast cancer for tumors larger than 1 cm; sensitivity is poor for smaller, nonpalpable or medially located tumors. In another study²³, sensitivity of ^{99m}Tc -Technetium sestamibi was 26% for T1a, 56% for T1b, 95% for T1c, and 97% for T2 tumors. Overall sensitivity for palpable lesion is upto 100%, while for nonpalpable lesions, as low as 25%. Specificity ranges from 74% to 90%³

Mechanism: The mechanism by which ^{99m}Tc -Technetium sestamibi enters and exits tumor cells is not fully understood. A number of **hypothesis** have been investigated: degree of neovascularity, increased cell membrane permeability, intracellular mitochondrial density, cellular proliferation and desmoplastic activity, modification of cellular metabolism such as calcium transport, pH changes²⁴.

There has been a great deal of interest in the detection of multidrug resistant (MDR 1) phenotype in the breast cancer. MDR1 gene produces P-glycoprotein, a transmembrane protein which is believed to be responsible for active removal of chemotherapy drugs from cancer cells. ^{99m}Tc -Technetium sestamibi is a transport substrate of the P glycoprotein (Pgp) which appears to actively transport ^{99m}Tc -Technetium sestamibi out of the tumor cells. High levels of Pgp results in rapid efflux of ^{99m}Tc -Technetium sestamibi and can be used in the in vivo identification of the MDR 1 phenotype²⁵. This has been used to predict response to neoadjuvant chemotherapy for locally advanced breast cancer. **The rapid clearance of ^{99m}Tc -Technetium sestamibi may predict lack of response to chemotherapy**²⁶. Standard scintimammography has been also used to monitor response to chemotherapy and also been used to assess patients with suspected recurrent disease and found to be 85% accurate²⁷. It can be used as an alternative to MRI in indeterminate lesions as assessment of recurrence may be difficult with mammography, ultrasonography and by FNAC.

^{99m}Tc -Tetrafosmin (^{99m}Tc -TF): It is a lipophilic agent, routinely used for cardiac imaging. It has also been used in tumor imaging. Mechanisms are similar to ^{99m}Tc -Technetium sestamibi scan and poorly understood. It is also a substrate for P glycoprotein. There are few controlled trials of the two agents, so it is difficult to assess at present which might be more useful. ^{99m}Tc -Tetrafosmin SPET (Single Photon Emission Tomography) acquisition improves the accuracy of the ^{99m}Tc -Tetrafosmin planar scintimammography. It has particularly important role in the detection of non palpable primary breast cancer and Axillary involvement. In one study²⁸, overall sensitivity of SPET and planar imaging was 95.8% and 75.9% respectively. For palpable lesion SPET was more sensitive (96.5%) than planar (79.5%). For nonpalpable lesion also, SPET was more sensitive (90%) than planar imaging (45%). For palpable axillary adenopathy, SPET was 100% sensitive and was 90.5% sensitive for nonpalpable adenopathy. The specificity was 91% (for SPET) and 100% (for planar).

Although it is not easy to localize lesions seen only on scintimammography, successful **nuclear medicine – guided Stereotactic prebiopsy localization** of the occult breast lesion has been reported²⁹. With a specially designed device, infiltrating ductal carcinomas were found in two patients with normal clinical

and mammographic evaluation.

Lymphoscintigraphy, with use of ^{99m}Tc colloids, has also been used for preoperative and intraoperative localization of nonpalpable breast lesions.

To summarize,

1. Scintimammography can not be recommended as screening test due to poor sensitivity for small lesions,
2. Value in assessment of dense breast,
3. Value in cases of Axillary lymphadenopathy with unknown primary,
4. Value in assessing response to chemotherapy

Positron Emission Tomography Scan

It is a functional imaging technique. It can be used to measure tumor metabolism, assess blood flow, and quantitate estrogen and progesterone density. Compounds labeled with positron emitting radionuclide without losing their chemical properties are injected intravenously. After reaching in to the tissue, these compounds emit positron (positively charged electrons). These positrons travel only a short distance (0.2-2.5 mm). With in surrounding tissue before they collide with a local electron. This collision produces two gamma rays at 180° to each other. Patient is placed in the center of a ring of gamma ray detector and simultaneous emission of these gamma rays is detected. Tomographic images are produced with the help of computer. The most commonly used positron emitting tracer is the glucose analogue **2-(18F)-fluoro-2-deoxy-D-glucose (FDG)**. This compound is thought to accumulate in malignant cells because 1) malignant cells have high level of hexokinase. This enzyme catalyze rate limiting step in glycolysis i.e. conversion of glucose to glucose-6- phosphate. If the positron emitting substance is provided for substrate for the hexokinase catalyzed reaction, 2-(18F)-fluoro-2-deoxy-D-glucose-6-phosphate is produced. This compound can not be metabolized further. Therefore the rate limiting hexokinase catalyzed reaction has effectively been isolated from main glycolytic pathway and thus the rate at which FDG accumulate in the cells is proportional to the rate of cellular glycolysis. 2) Malignant cells have increased membrane Glut-1 and Glut-3 transport proteins which allow malignant cells to accumulate glucose at higher rate than normal cells.

PET scan is **80-100% sensitive** and up to **100% specific** (30). As lesions smaller than 1 cm may be missed, PET will not be able to replace conventional imaging in the diagnosis of breast cancer. PET has also been used to monitor response to neoadjuvant chemotherapy: PET is able to show any change in metabolism before any morphological change. In one study³¹, FDG uptake declined rapidly just 8 days after chemotherapy. Further decline in FDG uptake was apparent at a later time intervals in patients with complete or partial response, while no significant decline in FDG uptake was seen in the non-responders.

Digital Absorption Ratio (DAR) using PET scan may be useful prognostic indicator for patients with breast cancer. In one study³², DAR was found to be one of the most important factors predicting relapse free survival. FDG scan has also been evaluated for its ability to diagnose Axillary lymphadenopathy. In his study, Adler et al³³ found that it had a sensitivity of 95%. They concluded that patients with negative scan in the axilla did not require Axillary dissection.

FDG PET scan is **more sensitive than 99mTc bone scan for the detection of bone metastases from breast cancer**³⁴. It is also superior to other modalities in the detection of soft tissue metastases.

Estrogen and progesterone density has been measured with 16- (¹⁸F) fluoroestradiol (FES)³⁰. It allows 1) assessment of tissue estrogen receptor density 2) assessment of tumor response to tamoxifen therapy after as little as 7 days of therapy. However, only 30% of tumors show estrogen receptor positive imaging. Progesterone receptor ligands have not been as successful due to high uptake in liver.

To summarize,

- PET scan is not superior to conventional imaging methods of mammography, sonography and MRI.
- FDG scan has a high sensitivity but is unlikely to replace conventional imaging.
- It is expensive and not available at most of the centers.
- The radioisotopes have short half life and to be produced by a cyclotron.
- It predicts response to chemotherapy earlier than any other method.
- May be used as an independent prognostic indicator.

Electropotential Measurements³⁰

Rapidly proliferating benign and malignant cells have electrically depolarized cell membranes as compared to normal cells. This effect is thought to extend from the cancerous area to the adjacent areas and is measurable at the skin surface above the lesion. It is 90% sensitive and 55% specific. Further assessment is required of this method of detection of breast cancer, particularly in relation to impalpable tumors.

Electrical Impedance Imaging³⁰

It maps local distribution of tissue impedance on the breast by applying a tiny electrical signal over a range of measured frequencies. It is 74-85% sensitive and 64-71% specific. This novel approach requires further investigation.

Ductoscopy and Ductal Lavage³⁵

Breast ductoscopy has evolved over last decade. The fibro-optic ductoscopy can be used to visualize intraductal lesions, lavage the duct, and administer laser treatments to superficial papillomas. Although size of the scope has decreased from 1.7mm to 0.65mm, limitation of ductoscopy is inability to perform biopsy and to visualize peripheral ducts. It can inspect at a depth of 4-5 cm on average and at a maximum of 9.5 cm. ductoscopy in future will allow for direct intraductal ablation of the lesion by mechanical or chemical means, which would spare surgery in selected cases. Presently ductoscopy is primarily used in the management of patients with spontaneous nipple discharge. In one study³⁶, it demonstrated intraductal lesions in 36% patients with nipple discharge and found to be 77% sensitive and 88% specific. A microcatheter has been developed and has been used for the lavage of ducts. In his study, Dooley et al³⁷ reported ductal lavage in 422 high risk women and a total of 543 breasts; 16.3% and 4.7% of lavaged breasts yielded a cytological diagnosis of mild to moderate changes. One patient yielded frank diagnosis of malignancy. Ductal lavage seems to be a safe, well tolerated and minimally invasive procedure for the determination of the presence

of premalignant cells. It may be adjunct to mammography and other modalities for the early detection of intraductal breast pathology.

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Literature Review

Compiled by Dr. Chintamani

Half versus full vacuum suction drainage after modified radical mastectomy for breast cancer - a prospective randomized clinical trial [ISRCTN24484328]. *Chintamani*, Singhal V, Singh J, Bansal A, Saxena S. *BMC Cancer*. 2005;5(1):11

85 FNAC (fine needle aspiration cytology) proven cases of locally advanced breast cancer were randomized. (using randomly ordered sealed envelopes, which were opened immediately before the closure of the wound) in to 50 patients with full vacuum suction (pressure=700g/m²) and 35 cases in to half vacuum suction drainage (pressure=350g/m²) groups. The two groups were comparable in respect of age, weight, and technique of operation and extent of axillary dissection. Surgery was performed by the same surgical team comprising of five surgeons (two senior and three resident surgeons) using a standardized technique with electrocautery. External compression dressing was provided over the axilla for first 48hrs and following that patients were encouraged to do active and passive shoulder exercises. The outcomes measured were postoperative morbidity and the length of hospital stay. Statistical methods used were descriptive studies performed with SPSS version 10 and group characteristics were compared using student t-test.

Half vacuum suction drains were removed earlier than the full suction vacuum suction drains. There was no significant difference in the incidence of seroma formation in the two groups and there was a significant reduction in the total hospital stay in patients with half vacuum suction drainage systems as compared to the full suction drainage group (p<0.001) without any added morbidity. **CONCLUSIONS:** Half negative suction drains provide an effective compromise between no suction and full or high suction drainage after modified radical mastectomy by reducing the hospital stay and the post operative morbidity including post operative seromas.

Clinico-morphological patterns of breast cancer including family history in a New Delhi hospital, India—a cross-sectional study. Saxena S, Rekhi B, Bansal A, Bagga A, *Chintamani*, Murthy NS. *World J Surg Oncol*. 2005;13;3:67. sunita_saxena@yahoo.com

In an attempt to evaluate the clinico-morphological patterns of breast cancer patients, including their family history of breast and/or other cancers, a detailed analysis of 569 breast cancer cases diagnosed during the years 1989-2003 was carried out. Mean and standard deviation and Odds ratios along with 95% confidence intervals were estimated. Chi2/Fisher's exact test were employed to test for proportions. Mean age of the patient at presentation was 47.8 years, ranging from 13-82 years. Among the various histo-morphological types, Infiltrating duct carcinoma (IDC) was found to be commonest type i.e. in 502

cases (88.2%), followed by infiltrating lobular carcinoma (ILC) in 21 cases (3.7%) and other types forming 9(1%). Out of 369 cases where TNM staging was available, stage IIIB (35.2%) was the commonest. Lymph node positivity was observed in 296 cases (80.2%). Out of 226 cases evaluated for presence of family history, 47 cases (20.7%) revealed positive family history of cancer, among which breast or ovarian cancer were the commonest type (72.0%). Patients below 45 years of age had more frequent occurrence of family history as compared to above 45 years. Amongst familial cases, Infiltrating duct carcinoma was the commonest form accounting for 68.8% cases while ILC was found to be in a higher proportion (12.5%) as compared to non-familial cases (5.4%).

PMID: 16236180 [Pub Med]

Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer (T4b N0-2 M0). Deo SV, Bhutani M, Shukla NK, Raina V, Rath GK, Purkayasth J. *J Surg Oncol*. 2003;84(4):192-7. svsdeo@yahoo.co.in

Locally advanced breast cancer (LABC) remains a major problem in developing countries. While trials utilizing neo-adjuvant chemotherapy demonstrate superior survival rates compared to historic controls, randomized studies evaluating the precise role of neo-adjuvant chemotherapy in LABC are lacking. In the present trial, neo-adjuvant chemotherapy was compared against adjuvant chemotherapy to assess survival advantage in operable T4b N0-2 M0 breast cancer.

A total of 101 women with operable LABC (T4b N0-2 M0) were randomized. In arm A, 50 patients received 3 cycles of CEF chemotherapy before and 3 cycles following surgery. In arm B, 51 patients had primary surgery followed by 6 cycles of CEF chemotherapy. In both arms, loco-regional radiotherapy was given after completion of CEF.

The response of primary tumor to neo-adjuvant chemotherapy was 66%, complete response (CR) 14% and partial response (PR) 52%. Clinical nodal response occurred in 95% of node positive patients. Only two (4%) patients had pathologic CR both in tumor and axilla. There was a significant (P = 0.02) increase in incidence of pathologically negative nodes in arm A. At a median follow up of 25 months, there was no significant difference in overall and disease free survival (DFS) in both arms (P = 0.42 and 0.18). Patients showing a response to neo-adjuvant chemotherapy had better DFS (P = 0.04) compared to those who had no response.

PMID: 14756429

Early Breast Cancer

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Abstract: The management strategies for breast cancer have undergone revolutionary changes with increased frequency of early detection, thanks to advanced imaging modalities. The effort is more and more towards the preservation of form and function without a compromise in oncologic principles. Breast conservation surgery has evolved with the advent of newer adjuvant modalities. The concept of early breast cancer and its recommended management protocol is discussed in this overview on early breast cancer.

Keywords: *Early breast cancer, breast conservation therapy (BCT), axillary lymph node dissection, sentinel lymph node biopsy.*

Definition

According to AJCC staging system the term early breast cancer includes patients with breast cancer of

Stage I	T1N0M0	Stage II	T1N1M0 T2N0M0 T2N1M0
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Why is this terminology needed?

As per the National Institute of Health consensus development conference on treatment of early breast cancer¹; breast conservation (BCT) is an appropriate method of primary therapy for a majority of patients with early breast cancer. The recommended technique for BCT includes wide local excision of primary tumor with clear margins, at least level I and II axillary clearance and total breast irradiation. The scientific basis for BCT is based on the results of prospective randomized trials comparing BCT and total mastectomy with axillary clearance. These studies have demonstrated equivalent overall survival rates in both groups with maximum cosmetic results and maintenance of normal function in patients with BCT.

Surgical options

- Breast conserving surgery i.e. wide local excision with axillary clearance
- Modified radical mastectomy
- Mastectomy with breast reconstruction
- Partial mastectomy with reconstruction

Requirements for BCT

- Patient's psychological acceptance with emphasis on cosmesis.
- Breast tumor ratio should be such that in spite of wide excision of tumor, adequate breast tissue be present to give good cosmetic appearance. In general, tumor should be <5 cm in size for BCT.
- Patient willing to take radiotherapy and come for regular follow-up. This is a very important factor in our setup, as follow-up rates at most centers (even with special breast

cancer clinics) are unsatisfactory.

Contraindication of BCT

Absolute Contra indications:

- First or second trimester of pregnancy
- Two or more tumors in separate quadrants of breast
- Diffuse malignant micro calcification
- History of prior therapeutic radiation to the breast region.

Relative contraindications:

- Large tumor / breast ratio
- History of connective tissue disorder
- Large breast size
- Tumor location beneath the breast nipple.

Controversies regarding contraindications

There is a controversy regarding whether certain clinical and pathological factors which indicate high recurrence rates should be considered as contraindications for BCT.

- Younger the patient (<35 years), more aggressive the tumor.
- Presence of extensive intraductal component (>25% within tumor) and focal positive margins after resection.
- Breast that is difficult to evaluate by physical examination and mammography (large pendulous breast) should be considered a contraindication for BCT.

However, clinical and/or pathological positive axillary lymph nodes are not a contraindication for BCT.

Treatment of early breast cancer:

Evaluation of the patient

- Clinical staging and
- Evaluating for contra indications to Breast Conservative Surgery (BCS) or immediate breast reconstruction

Clinical staging should include:

- Clinical evaluation and
- Investigations

Most important components of clinical evaluation are:

- Breast mass
- Skin changes
- Nipple changes and
- Nodes

In the breast mass it is important to exactly measure the size of the lesion, its location and distance from the nipple, consistency and fixation to skin, chest wall and pectoral muscles.

In the skin changes special examination is made about edema and erythema of skin, dimpling satellite nodules and ulceration.

In the nipple note should be made of its retraction, discoloration, erosion or any discharge (color, location of discharge).

In the nodes, the axillary, supraclavicular and infraclavicular nodes should be examined and mention be made of their size, number and fixation.

Investigations

1. Bilateral 2 view diagnostic mammograms of both breasts.
Medio lateral oblique (MLO)
Cranio caudal(CC)
2. Metastatic workup includes LFT and CXR.
3. DCIS patients do not require metastatic workup
4. Bone scan—In stage I and Stage II – only 5% of patients have occult bony metastasis; hence the value of a bone scan is questionable^{2,3}. In stage III – 20% of patients have occult bony metastatic, hence a bone scan is recommended in stage III^{4,5}.
5. Liver scan yield is even lower than bone scan in early breast cancer. Liver scan is advised if LFT's are abnormal^{6,7}.
6. Pre-operative serum markers are of no value⁸.

Halsteadian era (1900-1950) believed that breast cancer spreads in a systematic manner and that lymph nodes were primary filters before blood borne metastasis occurred.⁽¹⁹⁾ Hence more and more radical surgeries including extended radical and supraradical mastectomies were later carried out. These showed no change in 10 yrs overall survival but added to the morbidity. In these operations the breast and the underlying pectoralis muscles are sacrificed and regional lymph nodes along with axillary vein to the Halstead's ligament (costoclavicular ligament) are removed.

Fisher^{9,10} (from 1950 and onwards) in laboratory animals showed that there were venous lymphatic communications in breast cancer and that microscopic systemic disease is present at the time of presentation, and hence variations in local and regional treatment was unlikely to influence long term cure. The mortality of breast cancer was mainly due to distant spread and that to control distant metastatic disease there was need for adjuvant chemotherapy.

As it became widely known that treatment failure after breast cancer surgery was usually due to systemic dissemination of cancer cells before surgery and was not due to inadequate local operation. Modified Radical Mastectomy came into existence in 1960 & 1970. From 1970 onwards retrospective and prospective studies showed no difference in the overall survival with Radical Mastectomy or Modified Radical Mastectomy. Two forms of MRM are in use by the surgeons the Patey procedure and modifications described by Scanlon & the procedure described by Auchincloss. Patey developed a procedure that preserves the underlying pectoralis major muscle and sacrifices the pectoralis

minor muscle to remove axillary lymph nodes. Scanlon modified the Patey's procedure by dividing and not removing the pectoralis minor muscle allowing removal of lateral pectoral nerves to the major muscle. Auchincloss procedure allows ALND by retracting the pectoralis minor muscle.

NSABP (National Surgical Adjuvant Breast Project) trial of Fisher, of patients with mastectomy with or without axillary node dissection, showed that overall survival in both groups was the same even though a large number of patients without axillary nodal treatment presented with axillary metastasis. This presented the first evidence that systemic disease is likely to be present before surgery is performed and doesn't arise from incompletely dissected axillary nodes.

This formed the basis for breast conservative surgery (BCS).

Occult breast cancer

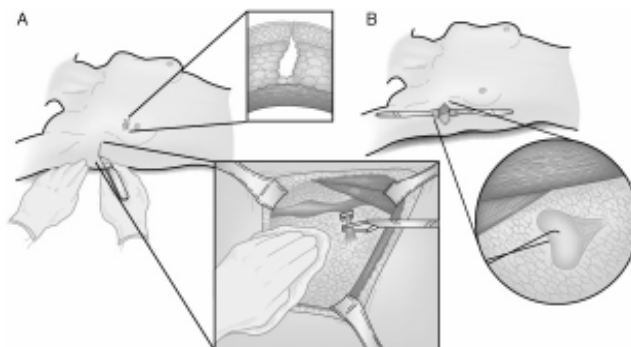
On rare occasions, a breast cancer may present with large axillary glands but without any evidence of primary in the breast. Lloyd and Nash¹¹ made a retrospective review of TONIMO cases at their clinic. They found that in six cases there was evidence of occult breast cancer. Neither mammogram nor ultrasound scans had shown any evidence of suspicious lesion in either breast. Neither patient had undergone MRI of breast. In 1997, at Rotterdam¹², it was concluded that true occult breast cancer is rare in incidence and MRI is investigation of choice in such cases.

NSABP Guidelines for Breast Conservative Surgery (BCS)

Major goal of BCS is to have cosmetically acceptable breast with resection of tumor and reasonable amount of normal breast tissue around it so as to get negative microscopic margins.

Incision and Flaps

- | Incision should generally be placed directly over the tumor even for a mammographically detected lesion.
- | Circumareolar incisions shouldn't be used.
- | Incisions should be curvilinear or transverse both in the upper and lower quadrants. There is no need to remove the skin except for superficial tumors.
- | Subcutaneous fat should be preserved.
- | Haemostasis should be adequate to avoid distortion and follow up evaluation.
- | Best cosmetic results are obtained by not putting in a drain.
- | Incision should preferably be closed by a subcuticular stitch.



Breast - conserving surgery. A, Incisions to remove malignant tumors are placed directly over the tumor, without tunneling. A transverse incision in the low axilla is used for either the sentinel node biopsy or the axillary dissection. The axillary dissection is identical to the procedure in a modified radical mastectomy. The boundaries of the operation are the axillary vein superiorly, the latissimus dorsi muscle laterally, and the chest wall medially. The inferior dissection should enter the tail of Spence (the axillary tail) of the breast. The *inset* shows the excision cavity of the lumpectomy; no attempt is made to approximate the sides of the cavity, which fills with serous fluid and shrinks gradually. **B,** In the sentinel node biopsy, a similar transverse incision is made (it may be located by percutaneous mapping with the gamma probe if radiolabeled colloid is used) and extended through the clavipectoral fascia and the true axilla entered. The sentinel node is located by virtue of its staining with dye or radioactivity, or both, and dissected free as a single specimen.

Preoperative Needle Biopsies and Localization

Subclinical architectural deformities are removed with the aid of preoperative radiograph localization. If a preoperative needle core biopsy is not possible it is better to manage these abnormalities as if they were carcinomas.

1. If after wide local excision, the margins are negative there will be no need for a second procedure. After excision the specimen is sent for radiography to see the adequacy of excision.
2. If margins are positive, the proper markings and handling of the specimen by the pathologist will enable the surgeon to revise the excised area with little sacrifice of further tissue.

Radiation therapy

As stated earlier, BCS involves wide lumpectomy followed by ERT. Radiotherapy with linear accelerator is considered ideal with limited radiation to lung volume. Whole breast dose is in the range of 45-50 Gy given at 1.8- 2 Gy / day.

To boost or not to boost?

Delivery of boost dose to primary site increases the probability of local tumor control. Recht and Harris¹³ discussed the rationale for administration of a boost dose to a limited volume of the breast that could reduce the incidence of local recurrence. Tumor bed boost can be administered to all patients undergoing BCT except those with tumor <1 cm with tumor free margins of 2 cm or following Quadrantectomy. Doses range between 10-20 Gy depending the tumor size and status of excision margins. Tumor bed boost can be administered by electron beam therapy or interstitial brachytherapy.

Preoperative Chemotherapy

NSABP trial of B-18¹³ where preoperatively Adriamycin and Cyclophosphamide was given to one arm confirmed that the preoperative chemotherapy would shrink the tumor to make BCS possible more frequently and that lymph node involvement was

down staged no difference was demonstrated in disease free survival or overall survival.

Summary of Breast Conservative Surgery (BCS)

The 1992 NIH Consensus Development Conference reported that "Breast Conservation Treatment is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast"¹⁵.

Surgeons should balance the cosmetic factors with techniques required for good local control. The primary concern should be adequate removal of the primary tumor with histologically negative margins.

Adjuvant Systemic Therapy

Most data indicate that adjuvant CT and or hormonal therapy in stages I and II diminish local recurrence rates compared to those not receiving adjuvant treatment. But that long term survivals and distant metastasis is not affected whether women had BCS or mastectomy.

Indications for Post op Radiation therapy

Postoperative Radiation refers to the irradiation of chest wall and / or draining lymph nodes regions used as an adjuvant treatment following definitive mastectomy.

Aim of radiation therapy is to prevent loco regional recurrence, which can be hazardous to the patient in two ways

1. psychologically; 2. recurrence besides being the persistent site for cancer can also be the source of distant metastasis.

Note:- (1) Though RT is routinely not indicated in patients with uninvolved axillary nodes except when there is a clear evidence of positive margins especially at the depth. A recent trial (16) concludes that omission of radiotherapy was associated with a increase in risk of ipsilateral breast tumor recurrence and with a small increase in patient mortality. (2) In patients with involved axillary nodes especially when more than 4 nodes are involved, ERT will greatly reduce the incidence of local recurrence and may improve overall survival in premenopausal patients. (3) Patients with 10 or more positive nodes treated with high dose chemotherapy routinely receive post operative ERT following completion of chemotherapy. This is to reduce a high early local failure rate when patients were not irradiated.

Management of Axilla in early breast cancer

Axillary dissection of lymph nodes has following benefits:

- a) To stage the disease accurately
- b) Local control of tumor in the axilla
- c) Prognostic significance
- d) To provide a rational basis for subsequent systemic therapy.
- e) To increase the likelihood of cure → ? Survival benefit.

Axillary dissection is principally a prognostic rather than therapeutic procedure. A number of studies were undertaken to determine the extent of axillary surgery needed to determine

whether nodes were positive. Many of the studies examined likelihood of skip metastasis i.e. involvement of level III nodes in the absence of involvement of level I or II and involvement of level II nodes in the absence of involvement of level I. The conclusion from these studies is that removal of both level I and II is required as it is effective in providing local control in the axilla and provides enough nodes for prognosis¹⁷.

Note:- (i) 5 years probability of an axillary recurrence is about 20% in patients with no nodes examined and about 10% when one or two negative nodes are removed. It is thus recommended that more than ten nodes be removed to avoid misclassification and to void local recurrence. This normally would involve level I and II axillary nodal clearance. (ii) Axillary nodal clearance at level I and II, also called 'partial axillary lymph node dissection' (ALND), involves removal of axillary nodes superior to the level of the axillary vein, lateral to the latissimus dorsi muscle and medially to the medial border of the pectoralis minor muscle. Long thoracic nerve, which supplies serratus anterior, should be saved. Thoracodorsal nerve with its vein and artery should also be preserved if possible.

Complications of ALND

Major complications of injury or thrombosis of axillary vein for ALND are few. Minor complications of seroma formation, shoulder dysfunction, loss of sensation in the underarm and upper arm, and edema of the arm and breast are common.

Recent developments have led to the change in philosophy of axillary dissection under some special circumstances. Breast cancer with low risk of axillary involvement could be spared the axillary dissection. Tumors with microinvasive cancers, tubular cancers and DCIS have axillary metastasis in less than 5%. At present DCIS, DCIS with microinvasive element and pure tubular cancers less than 1 cm can be spared the axillary dissection.

Sentinel lymphnode biopsy (SLNB) (18)

Sentinel node technique has the potential to allow the axillary dissection to be carried out in those with positive nodes and leave out the ones with negative nodes. Morton described the 'Sentinel node' as the first lymph node to receive lymphatic drainage from a tumor. Sentinel lymph node is the first lymph node in the ipsilateral axilla or internal mammary chain to drain the tumor in the breast. The sentinel lymph node is usually located by the injection of technetium radio labeled sulfur colloid, isosulfan blue dye, or both. If radio labeled colloid is used, the node in the axilla is located using a handheld gamma detector. If only blue dye is used then the node is detected by meticulous dissection into the axillary space until a blue stained node or afferent lymphatic is located. Several studies have shown that SLNB reliably predicts the status of axillary nodes. If histopathological examination is negative then axillary dissection can be spared. But in the presence of positive sentinel lymph node current medical practice dictates additional treatment to axilla. This is most commonly performed with a completion level I & Level II axillary dissection. In a recent randomized control trial (19) the

efficacy and safety of sentinel lymph node biopsy was tested. A total of 516 patients with primary breast cancer in whom T < 2 cm in diameter were randomized either to sentinel lymph node biopsy and total axillary dissection or to sentinel lymph node biopsy followed by axillary lymph node dissection only if it is positive for metastasis. The authors concluded that sentinel lymph node biopsy is a safe and accurate method of screening the axillary nodes for metastasis in women with small breast cancer.

Contraindications for SLNB

1. Palpable axillary lymphadenopathy
2. Prior axillary surgery
3. Locally advanced disease
4. Pregnant & lactating woman

Aim of SLNB is to minimize the complications & side effects of ALND.

False negative rates: - A review of the published data by Cox and colleagues found a world wide false negative rate of 3.1%.

Interpretations Nodal metastasis is termed macro metastasis if the tumor deposit is larger than 0.2cm and micro metastasis if the deposit is 0.2 cm or smaller. If each node is sliced every 0.2 to 0.3 cm, and then stained with Hematoxylin & Eosin (H&E), all macro metastasis are detected though micro metastasis may be missed. This is the method currently recommended by the college of American Pathology.

In the future axillary dissection might be avoided in patients who have no metastatic involvement of the sentinel node.

Radiotherapy to the axilla

A total dose 30 to 70 Gy is generally used. The mean dose is usually 50 Gy. Most fractionation schemes employ daily doses of 1.8 – 2 Gy over six weeks. Axillary RT is generally considered a treatment option only for the patient with clinically impalpable nodes. NSABP B-04²¹ and Institute Curie²⁰ trials have compared Radical Mastectomy, Mastectomy with RT to axilla/chest, and Mastectomy alone. At 10 years there was no significant difference between the groups that did and did not receive RT with respect to overall survival or local recurrence in the axilla. This study suggested that ALND and RT are equally effective treatment options in clinically node negative patients. The trial also suggested that delayed treatment of the axilla does not adversely affect breast cancer survival. These trials assert that "Axillary lymph node metastasis are an expression of bad prognosis rather than a determinant of overall survival". The biggest disadvantage of treating the axilla with ERT is that the prognostic significance of axillary nodes is lost forever.

35 to 40% of patients with clinically detected invasive breast cancer proved to be node positive following ALND. Although the extent of ALND seems to have no effect on breast cancer mortality, it does influence the risk of axillary relapse. Greater the extent of ALND, lesser the risk of axillary relapse. Following a level I and II dissection the risk of recurrence is reduced to 1-2 % while for level I ALND the risk of recurrence is more than

10%.

Summary of axillary treatment

Treatment of axilla with either ALND or radiotherapy remains an integral part of the management of patients with invasive breast cancer. The issue of survival benefit of axillary treatment remains controversial. Axillary node dissection is an effective staging procedure and is essential for local control of disease in the axilla.

With breast cancer awareness, routine mammography and early detection of cases, less and less number of patients is node positive and hence many undergo unnecessary nodal dissection and the associated morbidity. Hence SLNB may eventually prove to be a preferred alternative to routine ALND. It must first be demonstrated that SLNB (without completion ALND) doesn't adversely affect outcome.

Patients with DCIS, DCIS with micro invasion and pure tubular carcinomas less than 1 cm in size need not have axillary dissection. All other patients require level I and II axillary dissection to prognosticate, to design adjuvant chemotherapy and to change the type of chemotherapy and to enter into high dose and newer chemotherapy trials.

Sequencing of systemic and radiation therapy in patients with mastectomy

The integration of adjuvant chemotherapy and RT is also controversial. Initial RT may inhibit the ability to administer full doses of chemotherapy hence modification of drug doses is required as RT reduces lymphocytic counts significantly and also causes cardiac toxicity. RT given after chemotherapy reduced the risk of local recurrence to a level comparable with that seen with immediate post-operative RT. Hence there is support for the use of RT after completion of adjuvant chemotherapy. **Hence post operative RT is not indicated in patients with uninvolved axillary lymph nodes except when there is evidence of disease extending beyond the deep margins of resection.**

Follow - up

It is extremely important to closely monitor patients treated with BCT, because early detection of a local recurrence may allow for another wide excision or a total mastectomy, without significantly comprising the overall survival of the patient. The follow-up protocol followed at most centers is 3 monthly visits to the hospital for the first two years, six monthly till 5 years and yearly thereafter. During the visit clinical evaluation is performed to detect any loco regional or systemic disease. Periodic self examination during the intervening period should also be emphasized. The optimal interval for follow-up mammography is not clear. But most centers recommend a baseline mammogram within 6 months after completion of treatment and bilateral mammograms every 6 months or yearly for the first 2-3 years and yearly thereafter. If there is strong evidence of suspicious micro calcification or masses, or architectural distortions of the breast after BCT, a biopsy should be performed to rule out recurrence. At times, these patients are difficult to evaluate. Post

treatment hematomas, fat necrosis, seromas, cysts, and scar tissue pose difficult diagnostic dilemmas. Close coordination between surgeon, radiologist and pathologist is essential for optimal management.

In conclusion, careful clinical examination and mammography are critical in the post treatment evaluation of patients of early breast cancer who have undergone BCT. At least yearly evaluation is mandatory even 10 years after therapy because of possibility of late breast recurrences and occasional distant metastasis.

Prevention of Breast cancer

Efforts in the primary prevention of breast cancer will increase as promising information becomes available from prospective studies.

Various drugs available are

- a) *Tamoxifen* the real value and its role in the prevention of breast cancer remains unclear because of variations in the outcome of different trials carried out on healthy women. One Italian trial has demonstrated a small risk reduction in favour of Tamoxifen but IBIS²² study did not demonstrate a difference for invasive breast cancer. It is unfortunate that selection criteria for entry into these studies varied thus explaining the differences in outcome. A meta-analysis²³ of these studies concluded that Tamoxifen if taken for five years is followed by a significant reduced risk of developing breast cancer. Tamoxifen has been authorized by FDA for this purpose.
- b) *Raloxifene* Like tamoxifen, raloxifene is a selective oestrogen receptor modulator (SERM). If taken for eight years²⁴ it reduces the risk of breast cancer in women with osteoporosis, the group in which it was studied. In one trial 1% of the women on raloxifene developed breast cancer during that time compared with 1.6% of women on placebo group showing a risk reduction by 59%.

Genetic Predisposition and prophylactic surgery

Although it seems certain that prophylactic mastectomy and/or oophorectomy will not be the ultimate answer in preventing cancer in these organs for people carrying gene mutations, it is likely that these surgeries will be carried out in the foreseeable future where the indications for such interventions becomes better defined. At present criteria for gene testing include a family history in which (1) Three cases of breast or ovarian cancer have been identified in the first degree relatives, one of whom has been diagnosed when under 50 years of age (2) Where two cases of breast or ovarian cancer have been identified in the first-degree relatives, one of whom was under 40 years of age at diagnosis. (3) Where breast or ovarian cancer occurs in a woman under 30 years of age.

Various probability models have been described for BRCA 1 or BRCA 2 mutations^{25,26} the risk of cancer developing by the age of 70 years in mutation carriers with BRCA 1 is 65% for breast cancer and 39% for ovarian cancer. For carriers of BRCA 2 the risk of developing breast cancer is 45% and is 11% for ovarian

cancer by the age of 70 years. The risk is larger if the index cancer patient is younger than 35 years. In a prospective study of BRCA 1 carriers with and without prophylactic mastectomy followed for five years, 187 patients underwent a surveillance policy and 23 of them developed breast cancer and two of them died²⁷.

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Check-List

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- (i) Copyright statement/declaration (not submitted or published elsewhere) signed by all the authors.
- (ii) Three hard copies of manuscript with illustrations attached to each; **floppy** in addition will be desirable.
- (iii) **Title page** : Title of manuscript, Name(s) and affiliation of author(s); institution(s) and city(ies) address of corresponding author (Tel; Fax; e-mail).
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- (vi) **References** maximum number of references for update-20, original-10, Case reports-6.
- (vii) Each table on separate sheet; maximum number=4 in original article.
- (viii) Photographs/Figures in envelope, each marked figure number on reverse with legends on separate sheet. Number not to exceed 3, preferably.
- (ix) Statement regarding adherence to **standard ethical guidelines** prescribed by ICMR 2000. (see page 35)

Management of axillary lymph nodes in breast cancer patients in India: Axillary Lymph Node Dissection (ALND) vs. Sentinel Lymph Node Biopsy (SLNB).

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Abstract: Increased use of screening mammography, early detection of small tumours in breast cancer and the associated significant morbidity of ALND has led to the emergence of SLNB as a powerful tool in identifying a subset of node negative patients in whom the axilla is minimally disturbed. The same however, may not be feasible in an Indian scenario and therefore it may be recommended that Indian surgeons treating breast cancer should offer ALND for all invasive breast cancer patients routinely. Academic surgical divisions and dedicated high volume breast centers should initiate SLNB program for training and validation only, till the long term results of large western randomized trials are available.

Keywords: Breast cancer, Axillary lymph node dissection, Sentinel lymph node biopsy.

Introduction:

Surgery is the most effective and proven therapeutic intervention available for the treatment of breast cancer. Surgery was responsible for obtaining local control and long term disease free survival in more patients over the past century than any other treatment modality. Axillary lymph node dissection (ALND) became part of the accepted management of breast cancer in the mid 1800s, and continued to be the accepted standard of care well into the 1990s. Axillary lymph nodal involvement is still considered to be the single most important prognostic indicator in breast cancer patients^{1,2} and decisions about adjunct chemotherapy were weighted heavily by nodal status. This treated paradigm is shifting gradually, as the increasing use of screening mammography has resulted in the detection of very small tumors in the west with low probabilities of nodal involvement. In addition, significant morbidity is associated with ALND; 5 to 60% of patients experience some degree of side effects, including lymphedema of the arm, sensory numbness, and limitation of arm motion and strength³. Because of these developments, the acceptance of ALND as standard therapy for all breast cancer patients is diminishing in the west. Before abandoning ALND, however, several issues remain to be resolved, and are the subject of current intensive study. For clinically node-positive patients, recommendations are straightforward. Most practitioners agree that ALND remains important for loco-regional disease control, even if not necessary for adjuvant treatment decisions. In the case of clinically node-negative patients, however, there are additional issues. Is it appropriate to provide no treatment of the axilla? Is there a good alternative to ALND for the detection of occult nodal metastases? Sentinel lymph node biopsy (SLNB) is emerging as a powerful staging tool to identify the subset of node negative patients in whom an ALND and the attendant morbidity can be avoided⁴. The challenge today as we move closer to a selective approach to the axilla is to ensure that patients with positive nodes have those nodes identified and removed and patients with negative nodes experience minimal disturbance of axilla. However, there are other factors which can affect the breast cancer care adversely, especially in a country like India. The patient profile is different in India in comparison to the west and the general standards of surgical care of breast cancer are suboptimal. If the concept of SLNB is not well understood among the vast majority of Indian surgeons dealing with breast cancer, the potential for mismanagement are enormously high.

Need for ALND in Breast Cancer :

1. Staging
2. Prognostication
3. Therapeutic

Currently ALND is considered a gold standard as far as staging and prognostication of breast cancer patients is concerned^{1,2}. Whereas, the issue of therapeutic role of ALND is still a subject of debate.

The risk of providing 'No Axillary treatment':

The NSABP –B04⁵ study addressed the issue of therapeutic role of ALND and concluded that routine ALND does not contribute to survival. However, in a large review by Bland et al⁶ it has been shown that omission of ALND significantly decreases the survival in patients with invasive breast cancer. Recently, Kingsmore et al⁷ have shown that suboptimal axillary lymph nodal management significantly affects breast cancer survival. There are three groups of patients for whom the risk of nodal involvement is so low that ALND can be routinely avoided:

- patients with ductal carcinoma *in situ* (DCIS),
- patients with pure tubular carcinoma, and
- patients with microinvasive carcinoma.

Nodal metastasis is seen in less than 1% of cases with mammographically detected DCIS or pure tubular carcinoma <1 cm in diameter, and in about 3% of patients with microinvasive carcinoma. In a review by Singletary et al⁸, the incidence of nodal positivity ranged from 5 to 10% in patients with tumors 0–0.5 cm in size and from 10 to 20% in patients with tumors 0.6–1.0 cm in size. In patients with more 1 cm size the incidence of nodal involvement varies from 20 – 40% and in Locally advanced breast cancer patients 70 to 80 % have nodal involvement.

Relapse in Untreated and Treated Axilla:

The risk of axillary recurrence in untreated axilla varies from 10 to 40%^{6,7,9,10}. The risk is high in patients with T2 tumors, clinically palpable nodes and in patients showing LN invasion. There is a significant morbidity and increased mortality associated with axillary relapse. Whereas, axillary recurrence after axillary dissection is seen in less than 0-3% of patients^{6,8,11,12}.

Morbidity of ALND:

A significant number of patients experience post ALND morbidity; 5 to 60% experience some degree lymphedema of the arm, sensory numbness, and limitation of arm motion and strength^{3,8,13}. Incidence of lymphoedema varies from 5 to 50% in different

series depending on the criteria and method used for assessment of lymphedema. Combination of radiotherapy and surgery is a significant risk factor for development of lymphedema. However with the shift from radical to modified radical era and judicious use of radiotherapy, over all lymphedema rates have shown a decline in the 80s and 90s. Recent reported rates of post ALND lymphedema with out axillary irradiation ranges between 5- 10 %⁷.

Anatomical basis of ALND & Patterns of lymphatic Spread:

Three levels of lymph nodes (LN) are described in the axilla based on the relationship with pectoralis minor muscle. Anatomical studies have shown that Level –I harbors 75% of normal LNs and level II 20 % and level III 5%. Studies analyzing the pattern of spread of breast cancer reported a incidence of skip metastases to level III in the absence of level I or II LN metastases in less than 1% of patients¹¹. Chua et al¹⁴ reported an overall LN involvement of 45% in 308 operable breast cancers of which 78 % had involvement of level I only. Skip metastases to level I or II were noted in less than 1%.

Types/Variations of ALND:

1. Complete ALND- Dissection of Level I, II, and III nodes.
2. Level I & II ALND
3. Low Axillary Sampling – Removal of few level I nodes
4. Nerve sparing ALND
5. Sentinel Lymph Node Biopsy (SLNB)
6. Axilloscopic ALND

Based on the current evidence a complete ALND or Level I & II ALND is required to achieve optimum staging information and regional control in patients with invasive breast cancer (15). Axillary sampling and SLNB are good staging procedures. Axilloscopic ALND is still investigational. As per NSABP guidelines dissection of a minimum of 10 nodes is mandatory to avoid misclassification⁴.

Sentinel Lymph Node Biopsy (SLNB):

Sentinel lymph-node biopsy (SLNB) has been proposed as an alternative to routine ALND for the detection of occult lymph-node metastases in patients with clinically node-negative breast cancer. SLNB is based on the observation that specific areas of the breast drain by efferent lymphatics to a specific lymph node (‘sentinel’ lymph node – SLN), and then to other lymph nodes in the axilla. If the SLN is negative, the remaining lymph nodes are assumed also to be negative and no ALND is necessary. If the SLN is identified as positive by intra operative frozen section or imprint cytology, an ALND is carried out during the same surgery. If the SLN is identified as positive by more detailed histological or immunohistochemical techniques, an ALND can be carried out during a subsequent surgery.

The SLN is identified by injecting a vital dye (1% isosulfan blue) or a radioactive suspension (technetium sulfur colloid), into the breast parenchyma around the tumor^{16,17}. Some groups have also successfully used intradermal injections into the skin over the tumor and injections into the subareolar lymphatic plexus. The tracer can then be detected visually during surgery (when the dye is used) or by using hand held gamma probe while using radio active isotope.

To date, the results of SLNB have been impressive. The SLN can be identified in more than 90% of cases; of these, the SLN accurately predicts the status of the remaining lymph nodes in

more than 97% of cases. When the SLN is positive for metastatic disease, it is often the only affected node, especially in women with small primary tumors¹⁸. A trial from the American College of Surgeons is currently recruiting women who are SLN-positive by routine H&E staining to determine if completion ALND after SLNB will affect clinical outcome in this population. Can axillary lymph node treatment be safely eliminated in patients who are cytologically and histologically SLN-negative? Because of a significant frequency of false-negative results in SLNB, caution is urged in answering this question. False-negative rates reflect those cases in which the SLN was negative for metastasis even though there was histologically verified metastatic disease in the remaining axillary basin. In various studies the false negative-rate ranged from 1 to 11%¹⁸. Recent reports have associated high false-negative rates with increasing patient age, presence of medial tumors and the surgeon’s limited experience with SLNB. To gain further information about this issue, the NSABP B-32 is currently recruiting women who are pathologically SLN-negative to compare long-term locoregional recurrence rates in women who receive SLNB alone with those in women who receive SLNB followed by standard ALND. Recently Veronesi et al¹⁹ have published the results of SLNB alone in 953 SLN negative early breast cancer patients and showed a very low rate of axillary relapse.

IRCH – AIIMS Experience:

The feasibility of SLNB using Blue dye method along with intra operative imprint cytology was initiated as a validation study in the surgical oncology department of AIIMS and between 2000 and 2004, 250 node negative early breast cancers were included in the study. Over all accuracy of SLNB identification was 93 %, false negative rate was 8 % and accuracy of imprint cytology was 98 %. The preliminary work was published by Deo et al²⁰ in Asian Journal of Surgery. Currently we are not offering SLNB as therapeutic modality in breast cancer patients.

Pros and Cons of ALND & SLNB:

Advantages of ALND:

1. Time tested technique with proven efficacy.
2. Most accurate staging and prognostication tool
3. Evidence for therapeutic role available in node positive patients
4. Surgeon familiarity.
5. Very low risk of axillary relapse after ALND
6. Less patient apprehension as far as regional relapse is concerned

Disadvantages of ALND

1. High morbidity
2. Doubtful therapeutic role in node negative patients
3. Morbidity more than benefit in early node negative patients

Advantages of SLNB:

1. Accurate staging tool in node negative breast cancer patients
2. Proven technical feasibility & reproducibility
3. Minimal tissue dissection
4. Avoid ALND in SLN negative patients
5. Low incidence of lymphedema and arm morbidity
6. Limited tissue for detailed pathological evaluation

Disadvantages of SLNB:

1. SLNB role is mainly limited to node negative early breast cancers
2. Combination of techniques (dye and radio isotope) are required for accurate staging
3. Additional cost for the dye and gamma probe.

4. Need for Surgical training and validation.
5. Dedicated oncopathology divisions with frozen & cytology facilities are mandatory for SLNB program
6. High false negative SLN rate can lead to under treatment of patients
7. Long term oncologic out come in large randomized trials is yet to be proven

Indian Scenario:

Basically SLNB has evolved as an alternative staging tool for ALND in patients with node negative early breast cancer in the west. Seventy percent of breast cancer population in the west consist of screen detected node negative early breast cancer. This was possible because of the wide spread use of screening programs and public awareness campaigns held during the last three decades. Whereas, in India majority of breast cancer patients present with advanced stage disease and 60 to 70 % are node positive at presentation. We don't have a comprehensive screening program for early detection of breast cancer in India. Most of the breast cancer patients have no access to quality diagnostic and treatment facilities and currently primary level surgical mismanagement (under treatment) is prevalent in most parts of the country. Very few centers are following standard surgical guidelines. The media and physicians treating breast cancer should understand these issues and exercise caution before publicizing SLNB as a new surgical technique for managing breast cancer. If these relevant issues are not propagated by the Indian scientific community the potential for mismanagement of Indian breast cancer patients will be enormous.

In view of the issues discussed earlier, we would like to recommend that Indian surgeons treating breast cancer should offer ALND for all invasive breast cancer patients routinely. Academic surgical divisions and dedicated high volume breast centers should initiate SLNB program for training and validation only, till the long term results of large western randomized trials are available.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trials* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy** and **confidentially**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest** and **distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

Conventional Surgical Techniques for Breast Cancer with special reference to important anatomical landmarks

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Abstract: In spite of various developments in the diagnostic and therapeutic modalities in breast cancer, patients in developing countries continue to present at a locally advanced stage and therefore are subjected to the routine protocol of neoadjuvant chemotherapy followed by modified radical mastectomy and subsequent adjuvant therapies. Various surgically relevant technical and anatomical aspects need to be emphasized in the overall management of breast cancer.

Keywords: *Modified radical mastectomy,*

Surgical technique for modified radical mastectomy (MRM):

MRM includes removal of breast along with nipple areola complex, pectoral fascia and axillary tail of Spence along with all the three levels of axillary lymph nodes (i.e. level-I lateral to pectoralis minor, Level-II behind the Pectoralis minor and level-III medial to Pectoralis minor muscle)



Fig.1: The position of the patient => sand bag under the right shoulder with right arm draped separately.



Fig.2: A patient with a lesion in the right breast (T3N1M0) being subjected to MRM after having received neoadjuvant chemotherapy with CAF regime.



Fig.3: The incision should preferably be transverse in order to avoid the contracture across the shoulder. The optimum margin should be 2.5cm from the tumour



Fig.4: The upper and lower flaps are raised and should not have any breast tissue on them. The weight of the breast provides the required traction for medial dissection, if performed first. More than thickness of the flap, it is vital to proceed between the breast fat globules and the subcutaneous fat (subcutaneous fat has smaller globules of fat)

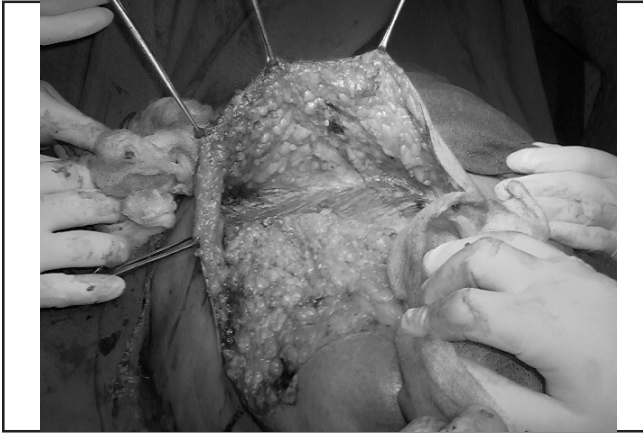


Fig.5: The pectoralis major muscle fibers should be laid bare as the deeper limit of resection is the pectoralis fascia

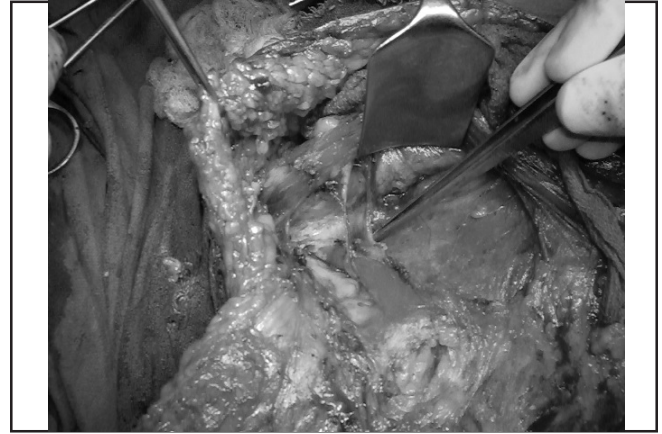


Fig.6: Axillary dissection may require the transection of Pectoralis minor to facilitate the clearance of the level-III group of lymph nodes. The medial and lateral pectoral nerves are identified and preserved (medial being lateral and the lateral being medial in real life situation).



Fig.6 (a): Level-III may be cleared by retracting the pectoralis minor muscle also (Auchinclauss)



Fig 6 (b): Level III may also be cleared by transecting the pectoralis minor muscle (Sinclair)



Fig.7: The medial limit of axillary dissection is the Hallstead's ligament or the costoclavicular ligament; the superior limit being the axillary vein, the lateral limit is taken as subscapular vein including the thoracodorsal pedicle. The lower limit of axillary dissection is taken as "Angular vein" which has been found to be a relatively fixed landmark and drains in to the thoracodorsal vein. The aim in a classical axillary dissection therefore is to have the triangle of axillary vein, subscapular vein and Hallstead's ligament completely cleared off all the lymphatic and fatty tissue preserving the axillary vein, pectoralis major muscle, nerve to serratus anterior and thoracodorsal nerve.



Fig 7 (a): The flaps being demonstrated before closure of the incision.



Fig.8: The wound closed with suction drains in situ

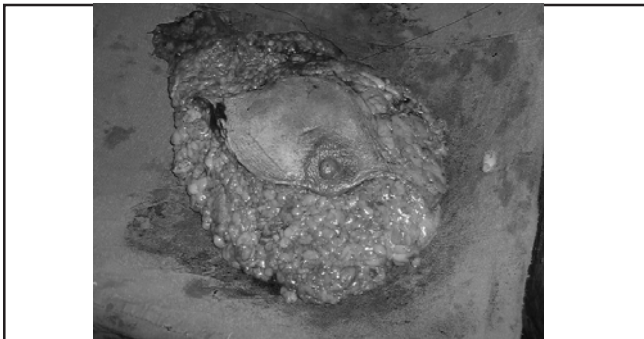


Fig 9: The resected specimen of breast with nipple areola complex and axillary tail of Spence, pectoralis fascia, axillary lymph nodes

The classical MRM therefore requires a thorough understanding of the surgical anatomy of this region and the important landmarks in order to achieve a good oncological clearance. Angular vein has been observed to be a constant and reliable landmark as the lower limit of axillary dissection¹. The author has also used this landmark in over 100 MRMs and found it as a reliable anatomical landmark besides the Hallstead's ligament and the subscapular pedicle. Optimum axillary dissection is mandatory in accurate staging and prognostication of the disease and adhering to a standardized protocol of surgical technique is mandatory.

The wound is closed in two layers and two suction drains in situ, one under the chest wall and the other one in the axilla. The arm strapping with axillary padding may be done for initial 24 hours, however active shoulder exercises should be encouraged thereafter. The author has recommended and published as a randomized controlled trial, the advantages of using half suction drains over full suction vacuum drains in minimizing seroma formation and reducing flap failure rates².

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Surgical Options for covering soft tissue defects in locally advanced and recurrent Breast Cancer

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Abstract : Radical surgical extirpation in locally advanced and recurrent breast cancer produces extensive loss of skin and soft tissues of the chest wall with resultant large defects and the primary aim in these groups of patients is to replace skin rather than to replace breast tissues. Skin grafts were one of the initial methods used but poor cosmesis, infection and post radiation problems prompted development of newer surgical options. Latisimus dorsi myocutaneous flap was one of the first flaps to be described, using the latisimus dorsi muscle based on thoracodorsal artery; but was not the ideal option in large defects. Thereafter, the techniques of Transverse Rectus Abdominis myocutaneous flaps, based on the Rectus abdominis muscles were developed. Multiple techniques of Transverse Rectus Abdominis myocutaneous flaps were developed and used depending on the given operative situation.

Keywords : *Locally advanced treatment breast cancer, myocutaneous flaps, omental transposition.*

Introduction :

Globally Breast cancer is one of the commonest malignancies encountered in woman and is a leading cause of death from cancer in females¹. In the developing world, it may account for 300,000 cases and 150,000 deaths annually². Locally advanced and Recurrent Breast cancer comprise 10%-25% of all breast cancer in developed countries and 40% -50% in developing countries¹. Radical surgical extirpation in these patients produces extensive loss of skin and soft tissues of the chest wall with resultant large defects that may not be suitable for primary closure. In addition, resections for recurrent breast cancer and post radiation ulcers also result in extensive skin loss with or without chest wall defects. Several methods have been tried during the last four decades including skin grafts, local flaps, omental flaps, abdominal flaps and myocutaneous flaps to cover soft tissue defects following surgery for LABC and recurrent breast cancer. Recently deo et al^{3,4} have published their experience of Thoraco abdominal flap for managing such defects efficiently. The aim of reconstruction in this group of patients should be an expeditious and simple closure with good quality skin cover so that they can receive early post operative radiation with minimal morbidity. There is no clear consensus on the method of repair to be adopted in such cases.

Review of Literature :

In the developing world almost half of all patients of breast cancer presents with locally advanced disease¹ where lack of resources and expertise often determine the kind of therapy to be offered and logistic considerations override aesthetic options. The primary aim following mastectomy in such patients is to replace lost breast skin rather than to replace breast tissue. Until skin grafting became available radical mastectomies were all allowed to heal by secondary epithelialisation⁵. Skin grafts were developed in 1920s but was available in only few centres and it was utilised for post mastectomy cover in the 50's, when radical mastectomy was the treatment of choice⁶. But it is unattractive and less durable, needs extended period of time for recipient and donor site healing. Also, poor cosmesis, infection and an increased late loss following radiation led to the development of other surgical options. Further developments in the field of myocutaneous flaps as well as free tissue transfer have led to a paradigm shift in the reconstructive options available to the surgeon and split thickness skin grafts have almost totally been replaced by other alternatives⁷.

The primary objective of reconstruction of the post –mastectomy defect after removal of locally advanced disease is to provide durable full-thickness skin cover with quick wound healing and minimal perioperative morbidity to enable rapid administration of regional radiotherapy and systemic chemotherapy⁸.

Functional and aesthetic reconstruction has also been used for locally advanced breast cancer in selected centers⁹. However, the guarded prognosis of patients with locally advanced breast cancer and lack of resources and expertise limits the use of complex reconstructive options in many of these cases. Myocutaneous flaps such as the latisimus dorsi flap and the rectus abdominis flap (RAMF) provide excellent results^{7,10}. The latisimus dorsi myocutaneous flap (LD) was first described by Ignio Tansini, Professor of Surgery at University of Pavia in Italy in 1896. He utilised it to cover post mastectomy defects in the early part of the 20th century¹¹. The purpose of the flap was to replace the pectoralis major muscle and skin following radical mastectomy utilising tissue from the back to cover the defect. However between 1920-1974 this procedure was completely abandoned as Halstead thought this to be unnecessary and hazardous¹². This was reintroduced in 1975 for cover as well as for reconstruction¹³. From 1977 to 1982 LD myocutaneous flap was the standard against which all other method of reconstruction was measured¹⁴. This flap utilises skin paddle based on latisimus dorsi muscle supplied by thoracodorsal artery and branches of posterior intercostal arteries. Its advantages are reliable blood supply and lack of donor site morbidity. Because of excellent blood supply it is rarely lost and can be used in conditions where rectus abdominis myocutaneous flap is not suitable such as obesity, diabetes mellitus and smoking. Its main disadvantage are limited size of donor skin that does not stretch well. Muscle utilised can be wide but if more than 8 to 10 cms skin is mobilised then primary closure of donor site can't be achieved. Hence, it may not always be adequate for large wounds following mastectomy for LABC.

Beginning in 1982 was the era of Hartramp's TRAM flap (15). By 1985 LD flap was replaced by the TRAM flap. Rectus abdominis (RA) muscle can be utilised to raise large flaps (10). *Four different versions* can be used (a) Vertical rectus abdominis flap (VRAM); (b) Single pedicle TRAM; (c) Double pedicle TRAM; (d) Free TRAM³.

VRAM is the earliest to be described and easiest technically. Skin paddle is positioned vertically over contralateral RA muscle. It has got abundant blood supply and because of lax abdominal skin in woman large amount of skin can be mobilised and donor site closed primarily and hence suitable for large defects. Single

pedicle TRAM utilises transeversely oriented skin paddle, but has got less blood supply and depends on small number of perforating vessels. Moreover, circulation may be inadequate in smokers, diabetes mellitus and presence of abdominal scar. Double pedicle TRAM is a variation based on both RA muscle that avoids the blood supply problem and flaps can be made large. It helps in cover and forms a mound as well. Free tissue transfer has also been described for cover. In 1990s microvascular TRAM expanded the indication for cover and reconstruction^{16,17}. Free TRAM is based on deep inferior epigastric artery and is associated with fewer complications and revisions. It can be used in high risk patients. However, it requires highly specialised equipments and well trained personnel.

Omental transposition flap and *split skin graft* has also been utilised for large fungating and discharging lesions encountered in LABC¹⁸. It helps in local control and relief of symptoms¹⁹. Many reports of Omental transposition and skin grafting for coverage of post mastectomy defects are available in literature. Lee et al¹⁸ have reported a success rate of 76% and abdominal herniation of 8% in 50 patients undergoing omental transposition for advanced breast cancer. Williams et al¹⁹ in a series of 43 recurrent and advanced breast cancer patients undergoing omental transposition reported 23% partial omental necrosis, and 14% incisional hernia rate. Basically omentum provides a healthy bed for skin grafting¹⁸. The major drawbacks are a laparotomy procedure and a split skin graft.

Another interesting and grossly underutilized option is a *thoracoepigastric or thoracoabdominal fasciocutaneous flap*. The thoraco-abdominal (TA) flap was described by Brown et al in 1975²⁰. It has been used for breast reconstruction along with a prosthesis and as a soft tissue cover following surgery for locally advanced breast cancer in some studies during late 70s and early 80s^{20,21,22}. However with the advent of Myocutaneous flaps in 80s TA flap usage has declined significantly. This flap utilises the skin and subcutaneous tissue of the anterior abdominal wall and is a rotation advancement random pattern fasciocutaneous flap based on direct circumferential branches arising from the aorta forming the subcoastal and lumbar arteries. They give off two main perforating branches- the *lateral* at the level of the anterior border of the latissimus dorsi and the *medial* at the level of the lateral border of the rectus abdominis. There is presence of subfascial anastomosis between the anterior and lateral perforators that may also receive a contribution from the perforating branches of the deep superior and inferior epigastric arteries. For post mastectomy defects on the lateral side of the chest wall (and axilla), a medially based flap based on the anterior perforating branches of the intercostal arteries can be used where as for medial soft tissue defects (upto the clavicle), a laterally based flap based on the lateral perforators of the intercostal arteries offers a better reconstructive option. The limits of the flap extend from the midline medially to the anterior axillary line laterally, Inframammary crease superiorly to a horizontal plane at the level of anterior superior iliac spine inferiorly. The operative technique of TS flap is described in detail by deo et al³. In a recent study by deo et al⁴ from a tertiary care center in north india the superiority of TA flap over myocutaneous flaps for covering soft tissue defects in LABC was clearly demonstrated in terms of simplicity of procedure, operative time, blood loss and wound morbidity.

Conclusions :

Locally advanced breast cancer is a problem of developing countries like India. Radical surgical resection in such patients results in major soft tissue defects not amenable for primary closure, hence surgery - the most effective locoregional modality for controlling breast cancer is denied in majority of patients.

Various techniques are available for managing such defects. Skin grafting and omental flaps have major limitations and expertise for complex reconstructive procedures using myocutaneous flaps is not widely available in developing countries. The basic aim in such patients is to achieve a healthy and simple skin cover expeditiously so that patients can receive adjuvant chemo and radiotherapy in time. Thoraco abdominal flap seems to be a very attractive option in such patients because of its simplicity and reliability.

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Breast Conservation Surgery

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Abstract : Breast conservation therapy for early-stage invasive breast cancer provides survival equivalence to mastectomy. Careful patient selection and surgical technique are necessary to minimize local recurrence. Studies over the past fifteen years have identified the risk factors for local recurrence. Patients previously thought to be ineligible for breast conservation earlier like locally advanced breast cancer, macromastia, cancer in pregnant women can be managed by modified BCT approaches. Local recurrences should be managed aggressively as long term survival can be frequently achieved.

Keywords: *Breast conservation therapy, Neoadjuvant chemotherapy, breast irradiation, local recurrence.*

Surgical management of breast cancer has undergone extensive transition from over the past century. From Halstedian radical mastectomy to extended radical mastectomy and modified radical mastectomy: surgery for breast cancer has evolved to more conservative approaches over the past century. The National Surgical Adjuvant Breast Cancer Project (NSAB) B-4 study demonstrated that less extensive chest wall surgery was not associated with inferior disease control.

Although breast conservation was proposed as far back as the 1930s¹, insight regarding breast cancer biology and the concept that lumpectomy and breast irradiation could adequately control local extent of disease did not receive widespread acceptance until several decades later, when several Phase III clinical trials were initiated in USA & Europe. Long term result from these trials have been reported, with the consistent demonstration that breast cancer survival in early stage breast cancer regardless of whether they are treated with breast sparing procedure or mastectomy is equal.

Trends in use of breast conservation therapy

Despite the abundance of data on the safety of breast conservation in stage II & I breast cancer it has not gained wide spread acceptance even in the USA. Reported patterns of BCT vary between 10-45%^{2,3}. Indian data for BCT is not easily available and its use is confined to few centers only.

Eligibility and Exclusion criteria for breast conservation therapy

Established criteria for BCT eligibility are predicted on three issues 1) Capability to deliver breast irradiation 2) Achieving a cosmetically acceptable breast 3) Obtaining margin negative lumpectomy. The accepted **guidelines** as per the American College of Radiology and the American College of Surgeon (4) include the following:

- | Multicentric disease (tumors in the separate quadrants of the breast)
- | Diffuse, malignant appearing micro-calcifications on pre-operative mammogram – this usually suggest Extensive Intraductal Carcinoma in Situ (EICS)
- | Prior therapeutic chest irradiation with fields that overlap the proposed breast field.
- | Radiotherapy is contraindicated in pregnancy, because of scatter effect on fetus.
- | Positive margin on lumpectomy and re-excision specimen.
- | History of collagen vascular disease such as scleroderma or lupus erythematosus – these patients may experience excessive radiation toxicity.

- | Tumor size preferably less than 5cm. Preoperative downsizing with chemotherapy may increase breast conservation rates and better cosmesis.

Special considerations in breast conservation surgery

Following additional issues deserve particular attention

- | Impact of family history of breast cancer
- | Impact of tumor histology (Lobular carcinoma & Lobular carcinoma in situ)
- | Definition of what exactly constitutes a pathologically negative margin.
- | Extensive intraductal component.

Family history

There was a concern that genetic predisposition to breast cancer might increase the likelihood of subsequent neoplastic events in the treated breast. Numerous studies have investigated the issue and found no increased risk of local recurrence following BCT in this subgroup of patients⁵.

Approximately 10% of breast cancer patients have mutations in BRACA 1 & BRACA 2 genes. There was a similar belief that these mutations may lead to higher local recurrences and radiation to breast would lead to greater toxicity and increased risk of new primary tumor. Available data though limited, suggest that breast conservation can be done in selected group of patients. But patients should be counseled about the risk of higher ipsilateral new primaries. Also patients with these mutations have a higher incidence of contralateral breast cancer averaging four to five folds than sporadic cancers⁶⁻⁸.

Primary tumor histology

Invasive lobular carcinoma is notorious for its insidious presentation, vague area of thickened breast tissue and lacking any specific finding on mammogram and ultrasound. A substantial amount of microscopic disease may underlie this nonspecific and misleading clinical picture. Not surprisingly, margin control may become a challenging problem under such circumstances. Moreover, lobular carcinoma is associated with higher incidence of caontralateral breast cancer. There is also a higher possibility of breast field effect of diffuse microscopic tumor foci in ipsilateral side.

Margin evaluation

The margin is characterized as the closet microscopic distance between the inked lumpectomy tissue edge and any cancerous

tissue invasive or ductal carcinoma in situ (DCIS). Obtaining a negative margin in the lumpectomy specimen of a breast cancer patient is the basic pre-requisite for standard of care in BCT. The conceptual goal is to resect the area of grossly apparent cancer and control the microscopic occult disease elsewhere in the breast with radiation. Positive margin may be difficult to control in post surgical hypoxic field and it may also represent excessive tumor burden. Numerous studies have shown an increased risk of local recurrence in patients with positive margins. Despite this there is no consistent universally accepted definition for tumor free distance that constitutes a negative margin.

NSAB has defined margin negativity as absence of any cancerous cells at the inked rim of lumpectomy specimen. Variations in the extent of margin negativity probably accounts for variability in BCT related recurrence rates. Several studies have tried to critically evaluate the minimal margin clearance required for adequate tumor control without unnecessary sacrifice of normal tissue. In general, a minimum of 2mm tumor free margin clearance results in reliably low recurrence rates. The number of margin positive foci, presence of EIC positive lesion all influence recurrence rates. *In practice one should aim for a 1cm margin during excision and 2mm margin on microscopic examination.*

Conservative Surgery without Radiation Therapy

An unresolved question is whether RT is necessary in all patients with invasive breast cancer after CS. Six randomized clinical trials with published results have compared CS alone with CS and RT in patients with early-stage breast cancer^{9,10}. These trials vary with regard to patient selection, the details of the surgery and RT, the use of adjuvant systemic therapy, and the length of follow-up. These trials all show a large reduction in the rate of local recurrence after RT, with an average crude rate of reduction of approximately 75% (range, 63% to 89%). None of the six trials shows a significant survival benefit for RT; however, in the trials with published data, the survival rate is slightly better for irradiated patients than for non-irradiated patients. A large trial (or perhaps a metaanalysis of multiple smaller trials) is necessary to detect a small, but clinically significant difference in survival, if it in fact exists.

Attempts have been made to identify a subgroup of patients (based on various clinical and histologic features) that has a low risk of local recurrence after CS alone. It was not possible to identify such a subgroup^{10,11}. *Local recurrence rates are generally lower in trials using more extensive surgery than in those using lumpectomy and in older patients than in younger patients.*

The use of adjuvant systemic therapy substantially reduces the rate of local recurrence in patients treated with CS and RT,¹² but does not seem to reduce greatly the rate of local recurrence after CS alone. There are no published trials directly comparing CS with and without either chemotherapy or tamoxifen. Information on this is available from indirect comparisons within randomized clinical trials for both adjuvant chemotherapy and tamoxifen.

There is particular interest in avoiding RT in older patients. It is often less convenient for such patients to receive RT, and their local recurrence rate appears lower after CS alone compared with younger patients. Results so far indicate that no such category could be identified and breast radiation reduces the risks in all categories of patients¹⁰.

In conclusion, the use of breast irradiation after CS is associated with a large reduction in the rate of local recurrence. The available

data from the randomized trials do not show a survival benefit; however, none of the available trials has the statistical power to eliminate a small survival difference. A subset at low risk of local recurrence following CS has not been clearly identified, and RT is currently considered standard. The addition of adjuvant systemic therapy to CS alone has not been demonstrated to decrease local recurrence. In elderly patients, particularly those with significant comorbidity, RT is commonly omitted because of the practical difficulties of delivering such therapy in this group of patients.

BCT & Neoadjuvant chemotherapy

Preoperative chemotherapy has become a standard of care for locally advanced breast cancer patients. It results in primary response rates of approximately 80% and disease progression in 2-3 %¹³⁻¹⁵. The sequence allows improved operability and in vivo assessment of chemosensitivity. Concerns that downsized tumors might leave a field of satellite nodules rather than shrink concentrically, however, lead to resistance regarding BCT in these patients.

The benefits of induction chemotherapy have led to its application in early stage disease. Several randomized control trials have proved its efficacy and shown its efficacy in improving eligibility for BCT without increasing local recurrence rates. Clinical assessment of response tends to overestimate the pathological response by approximately threefold. *Resecting the site of the original tumor is therefore mandatory in obtaining accurate chemo sensitivity information and optimal marginal control. Local recurrence rates are higher when radiotherapy replaces surgery in patients with complete response¹³.*

The NSAB 18 randomized 1500 women with stage I-III breast cancer to receive preoperative vs. postoperative chemotherapy. The trial showed statistically significant higher breast conservation rates in patients receiving preoperative chemotherapy with equal local recurrence rates. However subset analysis showed that local recurrence rates were higher in patients who were down staged to become eligible for BCT than those who were eligible for BCT at presentation. This could be explained by various factors such as predominantly T3 tumors, inconsistent use of radiation boost, use of tamoxifen only in patients over 50 years & the criteria of absence of tumor cells for margin negativity. A more aggressive approach for margin control might be necessary for lumpectomies down staged by chemotherapy. Newman et al¹⁵ from MD Anderson also showed higher conversion to BCT by the use of preoperative chemotherapy. However on histopathological examination of the mastectomy specimen revealed clinical assessments of BCT eligibility following induction chemotherapy was inaccurate in patients with invasive lobular carcinoma, multicentric disease and diffuse micro calcifications.

Patients should be monitored very closely to assess the response to treatment. Base line USG and Mammography along with clinical monitoring should be done to assess the tumor size after completion of all preoperative chemotherapy cycles. Those showing dramatic response should have an image guided clip placement to guide the location of tumor in case of complete response. Mammograms may uncover diffuse calcifications masked by tumor size.

Induction chemotherapy is therefore a reasonable and safe treatment provided the clinician is certain that patient will require postoperative chemotherapy. Maximizing the benefits of neoadjuvant chemotherapy requires a truly multidisciplinary

approach between the surgeon, radiotherapist, medical oncologist, pathologist & radiologist.

Macromastia

Patients with heavy breast present particular challenge to radiation oncologist. The larger breast requires larger dose, dose inhomogeneity causes skin toxicity and very ptotic is difficult for proper fixation & positioning. Bilateral reduction mammoplasty and tumor directed segmental resection overcomes many of these problems.

Bilateral breast cancer

Heaton et al [16] have demonstrated the safety of BCT in synchronous or metachronous bilateral breast cancer patients. They emphasized the importance of avoiding overlapping radiation fields.

Inadequate breast- to-tumor size ratio

Traditionally breast reconstruction has been recommended for patients with small breast. Few studies have shown the feasibility of plastic procedures using local rotational flaps or mammoplasties to remodel the lumpectomy defect.

Central subareolar tumors and Paget's disease

Previously these were considered a relative contraindication for BCT. If the disease is unifocal and there is no diffuse micro calcification on mammography a central segmental resection can be done with delayed nipple areola reconstruction after completion of radiation [16].

Local recurrence

Local recurrence deserves special mention. Many patients will experience prolonged survival and should be detected early and treated appropriately.

Biological significance

Local recurrence is an independent marker of underlying tumor biology. Those patients whose tumor outgrows margin negative lumpectomy and breast irradiation do tend to have more aggressive disease. Fischer et al showed this in Cox regression outcome analysis of NSAB – 06 study. Patients were 3.41 times more likely to develop subsequent distant metastases than those without local recurrence. Because overall survival is equivalent between BCT and mastectomy patients, it can be reasonably inferred that local recurrence is a risk factor for distant metastases but it does not cause them.

Risk Factors

The concept of local recurrence as a marker of tumor biology does not justify inadequate surgery or poor patient selection. Untreated residual disease left in the breast places the patient at risk for uncontrolled systemic spread. Every attempt should be made to avoid local recurrence due to inadequate surgery. A clear understanding of the risk factors associated with higher recurrences is warranted.

As discussed young age, margin involvement, EIC and omission of postoperative have all been documented to be associated with higher incidence of local recurrence in multiple studies. This may warrant additional surgeries in future. In deciding between BCT and lumpectomy all these factors must be considered and the final decision left to the patient.

Adjuvant systemic therapy both in the form of chemotherapy or hormonal therapy can suppress local recurrences in BCT patients¹⁷. Less well documented risk factors for local recurrence include estrogen receptor negativity, lymphovascular invasion, micro calcification on preoperative mammogram. But none of these weaker risks should be considered a contraindication to BCT as long margin negativity can be insured. Delay of more than 7 weeks in starting breast radiation increased local recurrence rates. Similarly, it was found that when radiation was delivered first the local recurrence rates though were lower the distant metastases rates were higher. As distant failure has a greater impact on long-term survival the conventionally accepted practice is to give chemotherapy first. Concomitant chemo radiation increases the chances of treatment related toxicity.

Management and outcome

Because of the association between local and distant recurrence, it is reasonable to conduct a metastatic work up in patients presenting with local recurrences. Majority will be isolated recurrences. Almost half of recurrences occur at or near the primary tumor site at a median time interval of 3 – 5 years from the time of surgery. Remote site of recurrences develop after a more prolonged time and represent new primaries^{18,19}. A minority present as diffuse inflammatory patterns of recurrence.

Standard management for patients with a local recurrence will be a salvage mastectomy and an immediate reconstruction may be offered. Risk factors for distant metastases following a local recurrence include a short interval to detection of local recurrence, nodal status and extent of recurrence. Overall five-year survival following treatment for local recurrence ranges from 50% to 80% and disease free survival averages 50 – 60%²⁰⁻²⁵.

Technique and Complications of Breast-Conserving Surgery

The goal of breast-conserving surgery is to minimize the risk of local recurrence while leaving the patient with a cosmetically acceptable breast. The surgical technique of *lumpectomy* differs from that used for mastectomy in that lumpectomy is not an en bloc cancer operation. *Quadrantectomy* is another type of breast-conserving surgery that is designed to remove an anatomic segment of breast tissue and frequently includes removal of the overlying skin and underlying pectoral fascia. Because excision of a large amount of breast tissue is the major factor responsible for a poor cosmetic outcome after BCT, lumpectomy is considered the appropriate initial surgical approach in many centers.

Other surgical factors that influence the cosmetic appearance are the size and placement of the incision, the management of the lumpectomy cavity, and the extent of axillary dissection. A number of technical aspects of lumpectomy are worth emphasizing. In general, the incision should be placed directly over the area of the tumor. This is true even when a biopsy is performed for a mammographically detected lesion. In the upper part of the breast, incisions should be curvilinear or transverse and follow the natural skin creases (Langer's lines) of the breast. In the lower part of the breast, the choice of a curvilinear or radial incision depends on the contour of the patient's breast, the distance from the skin to the tumor, and the amount of breast tissue to be resected. It is not necessary to remove skin (except for superficial tumors) or to remove needle tracks from core-needle biopsies or FNAC. Preservation of the subcutaneous fat and the avoidance

of thin skin flaps are also important in maintaining normal breast contour. Raising flaps is necessary only to allow access to the tumor. Meticulous hemostasis is important because a large hematoma distorts the appearance of the breast and makes reexcision and follow-up evaluation more difficult. The presence of a post biopsy hematoma, however, is not a contraindication to BCT. It is best to avoid reapproximation of the breast tissue since this can result in distortion of the breast contour, which may not be apparent with the patient supine on the operating table. The best cosmetic results usually are obtained by allowing the lumpectomy cavity to fill in with serum and fibrin. Drainage of the lumpectomy cavity should be avoided. Finally, the incision should be closed with a subcuticular suture to avoid cross-hatching of the skin.

A critical step in lumpectomy is the evaluation of the completeness of excision of the tumor. To allow adequate histologic evaluation, the specimen should be removed as a single piece of tissue and should not be transected unless the pathologist is present. The use of marking sutures to orient the specimen for the pathologist allows reporting of the status of individual margins. Gross inspection of the specimen in the operating room allows identification of positive or close margins, facilitating immediate reexcision. Frozen-section histologic study is sometimes useful to evaluate grossly suspicious areas, but the routine use of frozen sections to evaluate grossly normal margins is of doubtful value. The ideal amount of grossly normal breast tissue around the tumor that should be resected has already been discussed earlier. A resection of 0.5 to 1.0 cm of grossly normal breast tissue results in histologically negative margins in a large percentage of patients. Larger resections may be necessary for invasive ductal carcinomas with an extensive intraductal component and for infiltrating lobular carcinomas. Thin pieces of tissue can be shaved off each wall of the biopsy cavity and sent as separate specimens, with the new margin surface marked for the pathologist. Metal clips can be left at the edge of the cavity for subsequent radiotherapy planning. When axillary dissection is performed as part of breast-conserving surgery, a separate incision should be used, except in patients with tumors high in the tail of the breast. A curvilinear incision at the edge of the hair-bearing axillary skin provides the best cosmetic result. The incision should not extend anterior to the fold of the pectoralis major or posterior to the latissimus dorsi.

The primary indications for a reexcision are positive or unknown histologic margins of resection on the initial excision. Several studies have demonstrated residual carcinoma in approximately one-half of cases when reexcision is performed for positive or unknown margins^{25,26}.

No consensus exists on the best technique for reexcision. When reexcision is done within 1 to 2 weeks of the biopsy, it is not usually possible to re-excise an entire biopsy cavity as a single specimen without sacrificing large amounts of breast tissue. One technique of reexcision in most cases is to re-excise each of the walls of the biopsy cavity separately. If the initial specimen is marked with orienting sutures, reexcision can be limited to the involved margins. When longer intervals have elapsed between the biopsy and the time of reexcision, contraction of the biopsy cavity may allow excision of the entire cavity as a single specimen without sacrificing excessive amounts of breast tissue. The status of the final margin should be used to determine the patient's suitability for BCT.

There are relatively few complications of breast-conserving surgery. Wound infection is infrequent, although rates of infection may be increased when reexcision is performed. The late occurrence of breast abscess after BCT has been reported. The median time to abscess development was 5 months (range, 1.5 to 8.0 months). The only factor found to correlate with abscess formation was larger size of the lumpectomy specimen. Cellulitis of the breast occurring at a median of 4 months after BCT also has been reported in approximately 3% of cases²⁷.

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Fig.1: The lump marked along with the margins of resection [T1N0M0]

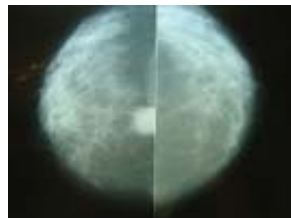


Fig.1a: Mammographic findings of the lump



Fig.4: The specimen with axillary lymph nodes



Fig.5: The specimen



Fig.2: After Lumpectomy

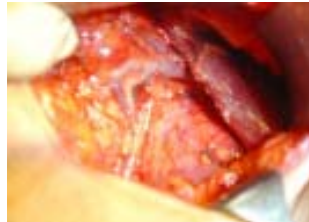


Fig.3: Axillary dissection in progress, axillary vein may be seen



Fig.6: The incisions closed



Fig.7: After two years

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Breast Oncoplasty - A New dimension in the Surgical Management of Breast Cancer

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Abstract : The availability of effective multiple systemic therapy options and early detection of breast cancer; leading to improved quality of life has led to amalgamation of inter professional cross speciality – Breast Oncoplasty. Post mastectomy total breast reconstruction is generally offered to stage I/II breast cancer patients and is often done at the time of mastectomy or after a delay as a second option. Post mastectomy total breast reconstruction can be done using implants or flaps or as a combination of flaps and implants. Oncoplastic procedures following Breast conservation surgery can be equally challenging trying to achieve breast conservation along with adequate tumor clearance and maintaining breast's shape and contour.

Keywords: *Breast reconstruction, Breast implants, myocutaneous flaps, Breast conservative surgery.*

Introduction

Breast cancer poses a dual threat to women - attacking their lives as well as their femininity. Most of the current surgical procedures^{1,2} for breast cancer cause permanent loss or disfigurement of breast leading to physical and psychological morbidity³. As the long term survival of breast cancer patients is increasing with early detection and availability of effective multiple systemic therapy options the focus of therapy is gradually shifting towards improving the quality of life. The modern breast surgeon can play a crucial role in minimizing the physical disfigurement and improve quality of life of breast cancer patients. Breast Oncoplasty is an emerging subspeciality of surgical oncology which deals with post mastectomy breast reconstruction and minimizing disfigurement following breast conservative surgery using various oncoplastic surgical techniques. Plastic and oncological breast surgeries are becoming more and closer as one surgical treatment. The term "Breast Oncoplastic surgery" refers to the use of plastic surgery techniques in breast cancer surgery in order to avoid and to correct the adverse aesthetics effects. The principals of oncoplastic surgery of the breast are based on minimal scarring and producing optimal size and shape. The concept of dedicated breast surgeon well versed with resection and reconstruction techniques is catching up in the west and inter professional, cross specialty (Breast and Plastic surgery) training fellowships are being offered in most of the high volume breast centers.

There are three clinical settings for Breast Oncoplasty –

1. Post Mastectomy Total Breast Reconstruction (PMTBR),
2. Oncoplastic Procedures following Breast Conservation Surgery and
3. Correction of asymmetry relative to the contra lateral breast⁴.

Post Mastectomy Total Breast Reconstruction (PMTBR) :

In the last two decades, breast reconstruction has progressed from a rarely requested procedure to one that is an integral part of a woman's breast cancer management when local treatment for her disease is considered. The development of new techniques and their application by well-trained breast surgeons have resulted

in more natural and aesthetically acceptable reconstructions. Experience over the past twenty years has demonstrated that breast reconstruction is a safe and reliable operation; it does not hide local recurrences and does not accelerate the rate or risk of breast cancer spread. In addition, breast reconstruction yields positive psychological benefits for many women, offering them a sense of normality, a "return to wholeness," and an opportunity to put the cancer experience behind them⁵.

Selection and Timing of Breast Reconstruction

A woman's motivation and desire for a breast reconstruction are the most important factors before an assessment for reconstruction is made. Patients with stage I and II breast cancer not suitable or not desirous of breast conservation therapy are generally offered PMTBR. This operation can be performed immediately at the time of the mastectomy (Primary Breast Reconstruction) or after a delay as a second operation (Secondary Breast Reconstruction). Primary breast reconstruction has become an appealing option for women undergoing mastectomy, and they are choosing it with greater frequency because it combines a proven treatment for breast cancer with immediate breast restoration. This approach ameliorates the woman's experience of breast loss and the psychological and physical problems. It usually does not interfere with or delay adjuvant chemotherapy. Primary breast reconstruction often permits shorter incisions with less skin removal. By preserving certain breast landmarks such as the inframammary fold, the result may also be better balanced than secondary breast reconstruction. Only one hospitalization, one anesthesia, and one rehabilitation are necessary with this approach. Immediate breast reconstruction does not imply, however, that the entire reconstruction is completed in one procedure; additional operations are usually needed to rebuild the nipple-areola and to achieve the best aesthetic results. For some women secondary breast reconstruction is the only option - women who have had their mastectomies earlier before they knew that breast reconstruction was possible. And some breast cancer patients may choose a delayed procedure because they do not have access to a surgical expertise or because they prefer to approach their treatment one step at a time, first completing the cancer therapy and then after an appropriate interval having their breast reconstructed.

Types of Post Mastectomy Total Breast Reconstruction (PMTBR):

There are basically three types of PMTBR

1. Implant based PMTBR
2. PMTBR using flaps
3. PMTBR using a combination of implants and flaps.

Implant Based PMTBR:

The silicone gel-filled breast implant was first developed in 1963 for women with small breasts who desired breast augmentation. The same technology was later applied to breast reconstruction to restore the breast shape and contour in women who had mastectomies.

Implants can be used alone or in combination with tissue expanders. For women following mastectomy, these devices have represented the simplest, most economical, least time-consuming approach to breast restoration. Despite the long experience with breast implants, they have become the source of widespread controversy, publicity, and misunderstanding during the past few years due to investigations by FDA regarding the role of silicone in inducing connective tissue disorders. Saline-filled implants are now most frequently used for breast reconstruction. The major drawback of implant based reconstruction procedures is a high morbidity. The reported rates of morbidity range from 30 to 50%⁵. The most frequently encountered morbidities include capsular contracture, implant rupture, displacement, extrusion and infection. In addition implant based reconstruction results in suboptimal outcome in patients with medium to large breasts. Due to these factors implant based reconstructions are ideally suited for breast augmentation and PMTBR in elderly patients with small breasts who are keen for PMTBR but not suitable for complex flap surgeries.

PMTBR using Flaps:

Advances in breast reconstruction during the past decade now offer women the option of having breast reconstruction with their own tissues (autologous) without the need for breast implants or expanders. Musculocutaneous flaps permit the transposition of substantial amounts of skin, underlying fat, and muscle from the back, lower abdomen, or buttocks to the chest area for breast reconstruction. Flap reconstructions are particularly helpful in situations in which skin is needed to rebuild a woman's missing breast. With immediate breast reconstruction, the use of a flap can often permit the creation of a breast that is symmetrical with the opposite breast without modifying it. The most commonly used flaps for PMTBR are Rectus abdominis based flaps – TRAM flap (Transverse rectus abdominis myocutaneous flap) VRAM flap (Vertical rectus abdominis myocutaneous flap). Rectus based flaps can be used as pedicle flap, free flap (micro vascular tissue transfer) or as a supercharged flap (pedicle with micro vascular augmentation). Rectus based flaps are ideal for reconstruction of medium to large breasts in parous women with lax lower abdominal tissues. Since these flaps are harvested in supine position most surgeons prefer rectus based flaps for PMTBR. Abdominoplasty is an added benefit to these patients. The Rectus based flap operations are complex and requires the skill of an experienced surgeon as well as a properly selected patient who understands the magnitude of the operation. The second most common flap used for PMTBR is Latissimus dorsi (LD) based flap. However the volume of tissue available with

LD flap is relatively less in comparison to rectus based flaps. Recent advances in surgical techniques using extended LD flap⁶ has allowed to increase the volume of tissue harvested and facilitated PMTBR even in patients with medium to large breasts. Another popular option is the usage of a combination of implant and LD flap. By combining both the volume of the reconstructed breast can be increased and the incidence of implant related morbidity can be decreased. Gluteus Maximus Musculocutaneous Flap with microsurgical transfer is the most technically demanding of all breast reconstruction techniques. It is also prone to more serious complications, because it takes longer to perform and usually requires an extended hospital stay. Inset of the flap in the breast requires additional breast scars, and the donor scar is in the buttocks area. Liposuction may also be needed to contour the opposite buttock for symmetry.

Skin Sparing Mastectomy (SSM):

Toth and Lappert⁷ described skin sparing mastectomy in 1991 which maximized breast skin preservation and resulted in a superior aesthetic appearance and patient satisfaction following PMTBR. The concept of SSM challenges the excess and unnecessary removal skin during mastectomy with out sound oncologic basis. By preserving the uninvolved skin the aesthetic out come of PMTBR can be improved significantly especially the creation of infra mammary crease with ptosis and preservation of skin sensation. However a good patient selection and meticulous surgical technique are crucial for an optimal oncologic and cosmetic out come. Further refinements have facilitated Nipple areola sparing SSM in select group of patients⁸.

Nipple Areola Reconstruction:

Nipple-areola reconstruction contributes to a natural and realistic breast appearance and is usually performed during a separate procedure about 3 to 6 months after the breast reconstruction, once satisfactory breast symmetry has been obtained. The nipple is usually reconstructed with tissues available at the site of the new nipple. New reconstructive techniques use the skin and subcutaneous tissue of the breast mound to create a nipple with satisfactory projection. The nipple can also be reconstructed with a graft taken from an opposite nipple. The areola is reconstructed so that it is symmetrical and similar in diameter and color to the areola of the opposite breast. The most common method now relies on the use of a tattoo to create the semblance of an areola without the need for a skin graft.

Oncoplastic Procedures following Breast Conservation Surgery:

Breast-conservation therapy with lumpectomy is a valuable component of breast cancer treatment, with an equivalent survival outcome to that of mastectomy². In addition to physical preservation, women who undergo breast conservation have a better body image, are more comfortable with nudity and breast caressing, and might have less adverse physical sequelae than mastectomy⁹. However, for breast conservation to be effective, surgeons need to remove cancers completely with an adequate surgical margin width and maintain the breast's shape and appearance. The undertaking of both goals together in the same operation can be challenging, depending on the tumor location and relative size in the breast. If a large lesion is located in a small breast (poor tumor breast ratio) or in patients with lesions located in upper and central quadrants of breast and loss of more

than 30% of breast volume the cosmetic outcome following breast conservation therapy is inferior due to significant disfigurement of treated breast. Recently special plastic surgical approaches have been described to improve the cosmetic outcome in such patients.

Three types of oncoplastic surgical techniques are described to manage post breast conservation surgical defects 1) Volume displacement techniques, 2) Volume displacement with mammoplasty and 3) Volume replacement technique using Mini latissimus dorsi flap (MLDF). In volume displacement methods the adjoining uninvolved vascularized breast parenchyma is mobilized in to the partial mastectomy defect and in volume replacement method a mini LD flap is used to obliterate the defect^{10,11}. Avoidance of poor cosmetic appearance after wide excision by oncoplastic methods will increase the number of women who can be treated with breast-conserving surgery by allowing larger breast excisions with improved cosmetic results that potentially achieve widened surgical margins around the cancer.

Conclusion :

Evolution of breast cancer surgery during the last century has witnessed many mile stones. Radical ablative surgery for control of cancer was widely practiced during the early part of the century and during the 70s and 80s Breast conservation therapy has emerged as the treatment of choice for early breast cancer. Early detection and effective locoregional and systemic therapy options have improved breast cancer survival and the current emphasis is on quality of life issues. Recent exciting developments in the field of oncoplastic breast surgery will play a major role in the surgical management of breast cancer in future¹². We at our center offer the whole range of breast oncoplasty procedures to breast cancer patients and in future more high volume breast cancer centers in India should initiate breast oncoplasty programs.

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Pregabalin

Pregabalin-a new neuromodulator, is a novel compound that has analgesic, anticonvulsant, and anxiolytic effects. Pregabalin (3 isoboutyl & aminohutyricacid) is a analog of major inhibitory neurotransmitter GABA, but is functionally unrelated to it. Pregabalin does not bind to GABA or GABAB receptors and is not converted metabolically to GABA or to GABA agonist. Pregabalin's pharmacologic properties are the result of presynaptic binding to the alpha, 2-delta subunit of voltage sensitive calcium channels.

Pharmacokinetics : After oral administration, pregabalin is quickly and extensively absorbed and displays linear pharmacokinetics. Maximal plasma concentrations were achieved in approximately one hour. The extent of absorption is independent of food intake. It is not bound to plasma proteins. More than 90% of drug is eliminated unchanged in urine; elimination half life is approximately 6 hours. Dose reduction is required in patients with GFR<60 ml/min. For haemodialysis patient, a supplemented dose of 25-100 mg is required immediately after dialysis. No dose adjustment is required in hepatic impairment.

Indications : It is effective in neuropathic pain associated with post herpetic neuralgia diabetic peripheral neuropathy, in partial epilepsy as adjunctive therapy, in generalized and social anxiety disorders.

Drug Profile

Adverse Effects : Most adverse events caused by pregabalin are mild to moderate in intensity and occur within 1st or 2 week of treatment. Somnolence and dizziness are most common side effects. Peripheral oedema, ataxia, headache, asthma, infection, mouth dryness, diarrhoea are some of the frequent side effects. It is also associated with a dose related weight gain in 14% of cases. Other adverse effects include peripheral edema, blurring vision, decreased libido, ataxia, impaired memory, paresthesias, euphoria etc.

Warning & Precautions : Dizziness and somnolence associated with pregabalin treatment may increase after injury in elderly people who should avoid driving or operating complex machinery; drug should not be used during pregnancy, in lactating mothers; the drug may potentiate the effects of ethanol and lorazepam.

Dosage : The drug is administered 2-3 times daily; starting a dose of 150 mg/day; the recommended effective dose is 300-600 mg/day. The therapeutic effect is usually observed during the first week of treatment; dose reduction is needed in elderly patients.

Compiled by Dr. P. Chatterjee

Radiation Therapy in Breast Cancer

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Abstract : Radiation therapy has an important role as an adjuvant modality in management of breast cancer with improvement in the local control and thus quality of life of the patients. It is unclear with the existing data whether this translates to a higher survival in these patients, although recent studies suggest a trend in this direction. In addition, radiation therapy is useful in producing palliation of symptoms due to local and systemic disease in patients with advanced stages of breast cancer and recurrent disease.

Keywords: Radiation, carcinoma-in-situ, invasive breast cancer.

Introduction

Breast cancer is a systemic disease with a quarter of patients in early stage disease showing micro metastasis in bone marrow^{1,2}. The treatment of breast cancer essentially should include the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these.

The need for and selection of various local or systemic therapies are based on a number of prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, level of HER2/ neu expression, presence or absence of detectable metastatic disease, patient's comorbid conditions, age, and menopausal status.

This article is intended to discuss the role of radiation therapy in management of breast cancer and discussing the controversies and current status based on the guidelines from American Society of Clinical Oncology and Royal College of Radiologists^{3,4}.

For description of treatment practices, breast cancer may be divided into

- the **pure non invasive carcinomas**, which include lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) (stage 0)
- **operable, local-regional invasive carcinoma** (clinical stage I, stage II, and some stage IIIA tumors)
- **inoperable local-regional invasive carcinoma** (clinical stage IIIB, stage IIIC, and some stage IIIA tumors)
- **metastatic or recurrent carcinoma** (stage IV).

Carcinoma-In-Situ:

Ductal carcinoma-in-situ (DCIS) describes a heterogeneous group of lesions characterized by a proliferation of presumably malignant epithelial cells within the ductal lobular system of the breast, without light microscopic evidence of invasion into the surrounding stroma. It is thought to represent a transitional stage in the development of an invasive tumor, with over 25-50% of tumors progressing to invasion, usually in the same breast⁵.

Extensive DCIS has traditionally been treated by mastectomy with survival rates approaching 100%⁶. This undoubtedly represents over treatment in a substantial number of patients and breast conservation is considered to be the desired objective for asymptomatic women with localized mammographically detected DCIS. The rate of local recurrence after limited resections in many

series has been shown to be correlated with size of lesion, adequacy of excision and histological features. Recurrences occur close to or at the site of the original tumour⁷.

Large tumour size (>2.5 cm) is associated with a higher risk of residual DCIS and a wider, less cosmetic excision may be required. Mastectomy is usually recommended for lesions over 4 cm. High nuclear grade in DCIS and the presence or absence of necrosis are thought to be the significant factors in determining local recurrence^{8,9}.

To date, no study of DCIS patients has shown a statistically significant difference in mortality when the three available treatments (mastectomy, excision alone and excision plus radiation therapy) are compared.

One randomized trial of 790 patients comparing radiotherapy versus no radiotherapy (NSABP B-07) has shown a 5 year actuarial local recurrence rate of 10% for patients given radiotherapy versus 21% for patients treated with excision alone⁷. The incidence of subsequent invasive lesions was markedly reduced in the radiotherapy arm. This led the NSABP to recommend that breast irradiation after local excision was more appropriate than lumpectomy alone. The beneficial effects were seen in the high grade lesions and in those where the margins were involved or uncertain⁹.

The fifteen year results of 268 patients from several institutions treated with excision followed by radiotherapy report an overall local recurrence rate of 19% with a 96% cause specific survival⁸. There is no apparent difference between pathological subgroups, although the median interval to local recurrence is 3 years in high grade comedo lesions as compared to 6.5 years for other lesions.

Based on these data it is recommended that the use of radiation after local excision all patients with DCIS 0.5 cm or greater in diameter will be appropriate. The use of whole breast radiation after breast conserving surgery reduces the relative risk of a local failure by approximately one half. The use of a radiation boost (by photons, brachytherapy, or electron beam) to the tumor bed is recommended to maximize local control, especially in patients 50 years of age or younger³.

For lobular carcinoma in situ (LCIS) there is no standard therapy recommended apart from careful observation and screening. Radiation therapy and mastectomy is not recommended as treatment on current evidence^{4,9}.

Operable Invasive Breast Cancer

Surgery, with or without radiotherapy, remains the mainstay in the treatment of early breast cancer. There are no long-term studies to determine whether surgery for palpable breast cancer improves

survival, but the benefits for local disease control are clear. Surgical treatment for breast cancer may consist of an excision of the tumour with surrounding normal breast tissue (breast conserving surgery) or a mastectomy.

Numerous randomized, controlled clinical trials have demonstrated no differences in overall survival or distant metastases in women with operable breast cancer treated with mastectomy compared with those receiving breast conserving surgery, both with use of adjuvant radiation therapy^{10,11}. However, breast conserving surgery with post-operative radiotherapy is associated with a higher local recurrence rate compared to mastectomy¹¹. Therefore, the potential risks must be weighed against the benefits, with a full discussion with the patient regarding her choice of treatment.

The indications for radiotherapy post-operatively will depend greatly on the surgery performed and on the pathological findings in the tissues removed. The surgery to the breast can vary from local excision, through quadrantectomy to various mastectomy options. Likewise axillary surgery can vary from full formal "level III" lymph node dissection to axillary nodal sampling or no axillary surgery at all.

Radiation therapy to the Chest Wall after Mastectomy

Radiation therapy to the chest wall after mastectomy is still a highly controversial area. The major issues centre on whether radiation therapy improves local control and survival, and which patients should be selected to receive it. Local recurrences after mastectomy remain uncontrolled in over 60% of patients despite further therapy¹². This highlights the need for more aggressive local control measures after surgery in these patients.

Many centers employ post-mastectomy chest wall radiotherapy on an individual basis, as a means of preventing local recurrence. The efficacy of radiotherapy with differences in risk of relapse has not been elucidated and the selection of patients for radiotherapy will be based largely on consensus definitions of high risk¹³. For patients with four or more positive lymph nodes it was shown in two recent randomized trials that there is reduction in breast cancer mortality of approximately one-third when adjuvant chemotherapy and radiotherapy to the chest wall and lymph nodes, when compared to adjuvant chemotherapy alone^{14,15}. In addition, there is no evidence that adjuvant chemotherapy alone given to node-positive women is effective in maintaining local control, when the risk of loco-regional recurrence is high (i.e. >4 positive axillary nodes)¹⁶. On the basis of these results and few other studies which have shown definite benefit of addition of adjuvant post operative radiation therapy, the current guidelines call for the consideration of post-mastectomy radiation therapy in patients with more than four positive lymph nodes^{3,17,18}.

In women with 1 to 3 involved axillary lymph nodes, the current guidelines recommend consideration of radiation to the chest wall and supraclavicular area after chemotherapy, with consideration also given to the inclusion of the ipsilateral internal mammary field³. In node negative patients, chest wall radiation therapy is indicated only when initial tumor size was more than 5 cm, or if there is positive or close margins (< 10 mm pathologically). In these patients consideration should be given for irradiating ipsilateral supraclavicular and internal mammary region also³.

In summary, chest wall radiation therapy after mastectomy has not been shown to improve overall survival although more recent

studies suggest a trend in this direction. But radiation therapy reduces local relapse rate and is indicated for this rationale in high risk patients.

Radiation therapy to axilla after Mastectomy:

After formal axillary clearance the local relapse rate is very low, even in the node-positive axilla. Radiation therapy is not recommended after formal axillary clearance (>10 lymph nodes harvested) as local control has been shown to be excellent with surgery alone and risk of lymphoedema is very high after radiotherapy to the dissected axilla^{4,19}.

After axillary sampling, in which four or more nodes have been harvested and found to be tumour-free, the axilla can be observed and treated definitively if recurrence is detected^{4,20}. If there are involved lymph nodes when the total number of nodes harvested is less than or equal to ten, then there is a choice between a further operation to perform formal axillary dissection or radiotherapy to the axilla. The option of a further surgical clearance is recommended; given the improved prognostic information obtained from axillary dissection, the lower relapse rates achieved after axillary dissection.

Radiation Therapy to Internal Mammary Nodal Region after Mastectomy:

No randomized trial has addressed the benefit of internal mammary chain irradiation on survival although sub-group analysis of some studies did suggest a possible minor effect. The clinical occurrence of internal mammary relapse is so rare as to make local control an unimportant objective²¹. Since the treatment of the internal mammary lymph nodes will greatly increase cardiac dose from radiotherapy, its routine use is not recommended⁴.

Adjuvant Radiation Therapy to the Breast after surgery less than MRM

So far it has not been possible, using prognostic factors, to reliably identify a subgroup of patients that do not require postoperative radiotherapy when surgical procedure is anything less than modified radical mastectomy²². There is no evidence that radiotherapy can be safely omitted in elderly patients without incurring an increased risk of local recurrence, although limited data suggest that the benefits are greater in women under 55²³. Several clinical trials have shown that adjuvant radiotherapy to the breast is required following wide local excision, to reduce local recurrence²⁴. It is clear from these studies that regardless of the degree of limited surgery, there is a significant reduction in recurrence rate with the addition of radiotherapy.

Current consensus calls for adjuvant radiotherapy to be an integral part of breast conserving protocols.^{3,4}

In breast conserving therapy with lumpectomy and radiation therapy, the data is inadequate to support the use of partial breast irradiation outside the confines of a high-quality, prospective clinical trial²⁵.

In addition, the current guidelines allow for the use of breast conserving surgery (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women age 70 or older with clinically negative lymph node, ER positive breast cancer based on results of two recently published studies^{3,4,26,27}.

Adjuvant Radiation Therapy to Drainage areas after limited surgeries:

The current guideline recommends regional lymph node RT in patients treated with breast-conserving surgery analogous to that recommended in patients treated with post-mastectomy regional lymph node irradiation³.

Boost Radiotherapy

The practice of boost treatments to the tumour bed after local resection and whole breast radiotherapy varies widely, reflecting the widespread uncertainty about the indications and doses required for tumour control¹³. The NSABP study has already shown that local control with radiotherapy can be achieved without boost treatment providing local excision is complete¹¹. Boost to tumor bed is currently advisable after breast conserving surgeries where tumor size >1cm or if margins are <2cm or unknown and in young patients.

Techniques of Adjuvant Radiotherapy Delivery

Radiotherapy to the breast and chest wall has evolved empirically and is commonly delivered using 25 fractions of 2 Gy each over 5 weeks. However, several simpler schedules are also used in different parts of the world, combining slightly lower doses with fewer, larger fractions with the aim of achieving the same clinical effects. Most of the radiation oncologists use schedules that are biologically equivalent to a dose of between 45 Gy and 50 Gy in 2 Gy fractions. From radiobiological principles, these schedules probably differ very little in terms of late normal-tissue effects and tumour control²⁸. However, there is now a need to compare these regimens in prospective randomized clinical trials. In the absence of further data it is recommended that 15-25 fractions may be used to treat the breast⁴.

X-rays of 4-6MV are preferred over ⁶⁰Co ³-rays for treatment of breast after breast conserving surgery, while beams of energy more than 6MV may be used during part of treatment for large pendulous breast with tangential field bridge separation >22 cm. For treatment of chest wall after mastectomy, both ⁶⁰Co ³-rays and X-rays can be used with similar outcome.

For boost, photon or electron beam or brachytherapy (HDR, LDR or mammosite) may be used. Brachytherapy yields a cosmetically poorer result, but maybe superior in patients with large breasts, tumors deeper than 4cm from the skin, microscopically positive or unknown margins, or extensive intraductal component. The preferred sequence is whole breast radiation therapy followed by boost. If axillary radiotherapy is being offered it has been suggested that daily fractionation of less than 2.5 Gy and avoidance of patient position change between breast and axillary field delivery will reduce the risk of brachial plexus neuropathy²⁹.

A recent retrospective study in node positive breast cancer patients receiving adjuvant chemotherapy showed a higher local relapse rate in the conserved breast when radiotherapy was delayed beyond four months³⁰. The Joint Council for Clinical Oncology has issued a Consensus Statement that 'in the case of early breast cancer treated by breast-conserving surgery and post-operative treatment the time interval between the two should not exceed 20 working days except for clinical reasons³¹.

The dose prescription methodology used should conform to ICRU 50 guidelines³² to allow comparison of doses in different centers. In the short term, if ICRU 50 is not adopted as the prescription

standard then the dose should be recorded to this standard after it has been prescribed to the local custom³.

Sequencing with chemotherapy

Till date, only one randomized trial has been published addressing this issue. This study randomly assigned 244 patients with stage I and II breast cancer to receive 12 weeks of postoperative chemotherapy given either before or after radiation therapy to the conserved breast. The results of this small study showed a statistically increased incidence of distant metastases in the radiotherapy first group, but there was also a trend in poorer local control in the chemotherapy first group³³. Based on the results of this study it can be recommended that if adjuvant chemotherapy is indicated, radiation therapy should preferably be given after chemotherapy is completed, unless there are factors which place patient in high risk for local recurrence.

In addition, radiation therapy may be given concurrent with chemotherapy. But current evidence suggests that methotrexate and doxorubicin should preferably be avoided during radiation therapy³.

Primary radiotherapy in breast cancer:

Whilst it is possible to achieve acceptable rates of local control using high doses (70-75 Gy) of radiation delivered by a combination of external beam and implant radiotherapy, the outcome in terms of cosmesis has been generally poor³⁴. For this reason, primary radiotherapy should only be considered when standard treatment methods have failed, or are not possible⁴.

Locally Advanced and Locally Recurrent Breast Cancer

Locally advanced disease:

Surgery is generally limited to the initial biopsy, followed by appropriate systemic therapy to bring about tumour shrinkage. Radiation therapy is used to treat locoregional disease, preceded by surgical removal of residual tumour in cases where a good initial response has occurred, whilst those patients responding poorly have a poor prognosis, and are best managed with radiotherapy in the first instance^{4,35}. Even if surgical clearance is possible after systemic therapy, initial inoperable stage is considered to have sufficient risk of local recurrence to warrant the use of chest wall (or whole breast if breast conserving surgery is done) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, consideration may be given to including the internal mammary lymph nodes in the RT field. Treatment of axilla follows the same guidelines as that of operable breast cancer^{3,4}.

Loco-regional Recurrence after surgery and radiation therapy:

Detection of local recurrence in the conserved breast is difficult, as radiotherapy can produce changes which are difficult to interpret³⁶. Parenchymal breast recurrence is usually treated by mastectomy. Local recurrence after mastectomy is most common in the first two years and decreases with time. Many of these patients will go on to develop metastatic disease and patients should be restaged prior to local therapy³⁷. However, adequate local control is important for quality of life, as uncontrolled local recurrence is devastating, and significantly impairs quality of life. A combined approach from the breast surgeon and specialist breast oncologist is necessary for optimum results.

Isolated axillary recurrence is rare if adequate initial treatment of axilla has been carried out. Level III axillary dissection (3 % recurrence at 10 years) or prophylactic radiotherapy (8% recurrence at 10 years) at initial management are the most effective forms of prevention³⁸. If regional recurrence occurs then treatment is with further surgery or radiotherapy. In patients with axillary or internal mammary nodal recurrence and a greater than 2 year interval prior to this event, effective local salvage produces 5 year progression free survival of 25%, and a locoregional control rate of 57% at 10 years³⁹.

Metastatic Breast Cancer

Metastatic breast cancer is incurable. Once patients develop symptomatic distant metastases, the median life expectancy is two years. Modest improvements in survival from systemic therapy are generally acknowledged to occur, but there are no randomized clinical trials using control groups which did not receive chemotherapy to show this. Treatments should be aimed primarily at symptom relief and maintaining quality of life.

Despite the lack of proof of a major survival benefit, chemotherapy can be very effective in symptom palliation, and quality of life studies have confirmed this⁴⁰. Therefore all patients with metastatic breast cancer should be considered for some form of systemic therapy in form of chemotherapy or hormonal manipulation. In general, hormone therapy is used when the progression of disease is relatively slow, and a rapid clinical response is not required. Patients with oestrogen-positive tumours and those with a long disease free interval between initial surgery and relapse are most likely to respond to this therapy.

The role of radiation therapy is primarily in palliation of symptoms produced by local or systemic disease. Palliative radiotherapy can be of use in management of hemorrhagic and painful chest wall or breast lesions.

Persistent or severe localized pain from bony metastasis can be treated by radiation therapy, which is successful in over 80 % of patients. A short course of radiotherapy (1-5 fractions) is usually effective. Longer fractionation regimens are not usually required^{41,42}. Surgery may be appropriate for destructive lesions in the spine and to relieve the pain and compressive neurological symptoms of spinal instability. This should be followed by postoperative radiotherapy⁴³.

Wide-field irradiation (or hemibody irradiation) is successful for diffuse bone pain in three-quarters of patients, but is not often used in breast cancer. Radioisotope treatment with strontium has also been shown to produce benefit in 75% of patients, and is most useful in the presence of extensive blastic lesions⁴⁴.

Skull base metastases causing cranial nerve involvement necessitates prompt radiotherapy, which leads to improvement in 50-80 % of patients and is usually maintained⁴⁵.

Radiation produces general improvement in neurological function in 40-70% of patients with breast cancer with intracranial metastasis⁴⁶. Radiotherapy is the treatment of choice in patients with choroidal metastases producing benefit in 60-70% of patients⁴⁷.

Male breast cancer:

Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant

suppression of testicular steroidogenesis⁴⁸.

Paget's disease

The management essentially depends on the presence or absence of any underlying malignancy. In patients without and advanced inoperable underlying cancer, recent data demonstrates that satisfactory local control may be achieved with breast conserving surgery including the excision with negative margins of any underlying breast cancer along with resection of the nipple areolar complex followed by whole breast radiotherapy and systemic therapy according to the extent of underlying disease^{49,50}.

Phyllodes tumors of the breast

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements. Treatment of phyllodes tumors is with local surgical excision with tumor free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy and surgical staging is unnecessary

In those patients who experience a local recurrence, resection of the recurrence with wide tumor-free surgical margins should be performed. Local radiation therapy of the remaining breast or chest wall following resection of a local recurrence maybe considered, but this recommendation is controversial^{5,51}.

Lymphoma of the Breast:

The results are similar for surgery and radiation therapy in management of local disease in lymphoma of breast when combined with systemic chemotherapy. When radiation therapy is used, 45- 50 Gy is used to treat the whole breast and the lymphatic drainage areas.

Breast Cancer during Pregnancy:

Breast cancer occurring concurrent with pregnancy is an infrequent clinical event. Histologically the tumors are poorly differentiated, more frequently estrogen and progesterone receptor negative and approximately 30% are HER-2/neu positive⁵².

The management of these patients will depend of the stage of the disease, the fetal maturity and the interaction between the treatment and the pregnancy. The abdominal fetus and pelvic fetus will receive up to 2 Gy and 0.15 Gy respectively if radiation therapy of 50 Gy is delivered to chest wall of a pregnant woman even with adequate shielding. This is beyond the recommended radiation dose for fetus and so radiation therapy is contraindicated during pregnancy.

Adjuvant Ovarian Ablation

Ovarian ablation in hormone receptor positive pre menopausal patients can be carried out low dose radiotherapy. Doses in the range of 20- 30 Gy are used over a period of 1- 2 weeks. The side effects of ovarian ablation are those of a premature menopause including vasomotor, sexual and other symptoms of estrogen depletion.

Patient Follow-up

The aims of follow-up are in general to detect recurrence at an early stage, to improve the chances that prompt treatment will influence the outcome, to screen for a new primary cancer in the same or contra lateral breast, to detect and manage treatment related toxicity especially management of treatment induced menopausal symptoms and to provide psychosocial support.

In patients who has received radiation therapy, special attention is needed to detect and manage any radiation induced late toxicities, though they are rare with modern treatment techniques and quality assurance measures. The reported late effects of radiation therapy in breast cancer includes lymphoedema of the limb, radiation pneumonitis, brachial plexopathy, rib fractures, breast/ chest wall oedema and stiffness, cardiac toxicities and very rarely, second malignancies in the irradiated tissue.

Conclusion:

To conclude, radiation therapy has an important role as an adjuvant modality in management of breast cancer with improvement in the local control and thus quality of life of the patients. It is unclear with the existing data whether this translates to a higher survival in these patients, although recent studies suggest a trend in this direction. In addition, radiation therapy is useful in producing palliation of symptoms due to local and systemic disease in patients with advanced stages of breast cancer and recurrent disease.

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Abstract : Traditionally patients undergoing BCT have been given a protracted course of radiation to the whole breast, with or without nodal irradiation, lasting from 3 to 5 weeks. This protracted therapy has been a major deterrent to Breast Conservation Therapy and decreased patient compliance. Alternative methods of delivering radiation have been advocated to increase patient compliance and acceptability to radiation. These include Accelerated whole breast irradiation and Accelerated partial breast irradiation which includes modalities like interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation and external beam radiotherapy.

Keywords: *Breast irradiation, partial breast irradiation.*

Introduction

Breast-conserving therapy is an accepted treatment option for women with stage I or II invasive breast cancer. Randomized trials and retrospective studies have shown unacceptably high local failures after breast conserving surgery without radiotherapy¹. Local failure is known to compromise the long-term survival.

To prevent local recurrence, patients undergoing BCT have traditionally been given radiation to whole breast, with or without nodal irradiation. A protracted course of radiation is given, lasting from 3 weeks to 5 weeks followed by boost to the tumour bed. This prolonged treatment course has been a major deterrent to the wider use of breast conservation therapy. It has been seen that most recurrences in patients treated either with excision alone or excision plus radiotherapy are at or near the tumour bed. The distribution of tumour cells in the breast is confined to a relatively limited area around the index lesion².

NSABP B-06 demonstrated approximately 30% recurrence rates in women not undergoing irradiation after breast conservation over a ten year period³. Local failure may be salvaged with mastectomy. However, early Breast Cancer trialists Collaborative Group meta analysis of randomized trials showed that group not receiving radiation had a higher rate of mortality due to breast cancer. The recurrences that occur as a local failure are in the vicinity of the lumpectomy site and are termed as 'true recurrence' or 'marginal miss'. Recurrences after 5 years appear at more distant sites from the first incident cancer and may include new primary breast cancers.

In the last 10 years alternative methods of delivering radiation treatment have been advocated to increase the patient compliance and acceptability to radiation. They are (a) accelerated whole breast irradiation and (b) accelerated partial breast irradiation.

Accelerated whole breast irradiation (42.5 Gy in 16 fractions) was compared to conventional irradiation (50 Gy in 25 fractions) without a boost in 1234 patients in a randomized trial by Whelan et al⁴. The authors reported no difference between two arms in survival, local control, cosmesis and complications. Accelerated partial breast irradiation delivers radiation to a smaller volume of breast in and around the tumour site in a shorter interval than 5 weeks. Accelerated partial breast irradiation (APBI) is delivered in 1-5 days and covers only the area immediately surrounding the lumpectomy site. It irradiates the surrounding breast tissue which is a highest risk of recurrence. The currently available methods for **accelerated partial breast irradiation** are:

(i) Interstitial brachytherapy implant (high dose rate or low dose rate)

- (ii) Intracavitary brachytherapy (balloon catheter)
- (iii) Intraoperative radiation (orthovoltage or electron beam)
- (iv) External beam (three-dimensional conformal beam, intensity modulated radiotherapy or proton beam).

The selection criteria for partial breast irradiation are quite strict such that the patients should be in an older age group (>45 years), tumour size <3 cm, lymph node-negative disease, invasive ductal carcinoma, wide negative margins of resection, negative post biopsy mammogram and absence of extensive intraductal component.

Interstitial brachytherapy The earliest results of interstitial brachytherapy were reported by Kuske et al⁵. 50 women underwent a wide local excision, axillary dissection and either a low dose rate or high dose rate brachytherapy in alternating blocks of 10 patients. Median age of the patients was 67 years and the women were eligible if tumours were T_{is}, T₁ or T₂ <4 cm in greatest dimension with negative inked microscopic surgical margins and zero to three metastatic axillary lymph nodes. The brachytherapy target volume include 2 cm of breast tissue surrounding the excision cavity and the prescription isodose envelopes this volume. Low dose rate prescription dose is 45 Gy over 4 days at the rate of 50-75 cGy/hour and high dose rate patients receive a dose of 32 Gy in 8 fractions over 4 days, 2 fractions per day, 6 hours apart. A CT scan based 3 dimensional dose volume analysis can be used to determine the quality of interstitial implant. In another study reported by Vicini et al brachytherapy alone was compared to external beam therapy (60 Gy over 6 weeks) and the patients were followed up for a median of 5.7 years. No local or regional failures were detected and only one patient failed distantly in the high dose rate group. No significant adverse sequelae were noted and cosmetic results were reported good to excellent in 98% patients. No statistically significant differences were noted in the 5 year actuarial rates of recurrence for ipsilateral breast (3% versus 0%, p=0.17 or locoregional failure (4% vs 0%, p=0.37) between patients treated with external radiation and those treated with brachytherapy alone. Also, the authors noted no differences in overall survival or cause-specific survival.

Intracavitary brachytherapy (Balloon Catheter or MammoSite) MammoSite ® RTS is a new minimally invasive method of delivering radiation to the lumpectomy cavity. It is a small balloon holding a central catheter to carry the radioactive substance to the centre of the cavity. The balloon is left in the lumpectomy cavity and filled with saline water and contrast to distend into the cavity space. The central catheter is connected to a remote after-loading high dose rate machine and treatment is

delivered over 10 fractionated sessions, 6 hours apart over 5 days. Patient can take treatment as an outpatient and the balloon is deflated and removed after the last session of treatment without anaesthesia.

Intraoperative Radiotherapy An intraoperative radiation therapy technique (IORT) was developed by Veronesi et al⁶. A mobile linear accelerator using a robotic arm delivers electron beam energies from 3-9 Mega electron volts. Radiation is delivered using a perspex applicator directly into the lumpectomy cavity. An aluminum lead disk is placed between the breast and the pectorals muscle to protect the thoracic wall. A single fraction of 21 Gee has been estimated to be equivalent to 60 Gee over 30 fractions. Although the treatment was well accepted by patients, a large number of patients with a longer follow up mean follow up of 8 months) is yet to be reported to determine the efficacy and/or possible late side effects of such a large dose of radiation. The Target Trial is an international randomized controlled clinical trial comparing Single-Day Targeted Intraoperative Radiotherapy to Conventional Post operative Radiotherapy. This international study is designed to enroll 2,400 women, age 40 years or older with invasive breast cancer less than 3 cm in size.

External Beam Conformal radiation - Multiple CT-scan sections are obtained in the treatment position and a 3 dimensional plan is generated using advanced computer algorithms. The technique is best suited if the localization clips can be left in the lumpectomy cavity to determine the region of interest. It is possible to reduce the cardiac and lung dose while maintaining adequate tumour bed coverage with these techniques. Contralateral breast can also be spared the exit dose that is delivered by the lateral tangential field with conventional planning

Partial breast irradiation, accelerated partial breast irradiation may be an acceptable tool to augment breast preservation therapy in a resource limited country like India, however large randomized trial data in future will answer the question whether it should replace the conventional radiation.

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Compiled by Dr. Chintamani

Literature Review

Role of p-glycoprotein expression in predicting response to neoadjuvant chemotherapy in breast cancer—a prospective clinical study. Chintamani, Singh JP, Mittal MK, Saxena S, Bansal A, Bhatia A, Kulshreshtha P. *World J Surg Oncol.* 2005. 14; 3: 61.

The expression of p-glycoprotein at initial presentation has been found to be associated with refractoriness to chemotherapy and a poor outcome. Against this background a prospective study was conducted using C219 mouse monoclonal antibody specific for p-glycoprotein to ascertain whether pretreatment detection of p-glycoprotein expression could be utilized as a reliable predictor of response to neoadjuvant chemotherapy in patients with breast cancer.

Fifty (50) cases of locally advanced breast cancer were subjected to trucut biopsy and the tissue samples were evaluated immunohistochemically for p-glycoprotein expression and ER, PR status. The response to neoadjuvant chemotherapy was assessed clinically and by using ultrasound after three cycles of FAC regime (cyclophosphamide 600 mg/m², Adriamycin 50 mg/m², 5-fluorouracil 600 mg/m² at an interval of three weeks).

A significant relationship was found between the pretreatment p-glycoprotein expression and clinical response. The positive p-glycoprotein expression was associated with poor clinical response rates. When the clinical response was correlated with p-glycoprotein expression, a statistically significant negative correlation was observed between the clinical response and p-glycoprotein expression (p < 0.05). There was another significant observation in terms of development of post NACT p-glycoprotein positivity. Before initiation of NACT, 26 patients (52%) were p-glycoprotein positive and after three cycles of NACT, the positivity increased to 73.5% patients. CONCLUSION: The study concluded that pretreatment p-glycoprotein expression predicts and indicates a poor clinical response to NACT. Patients with positive p-glycoprotein expression before initiation of NACT were found to be poor responders. Thus pretreatment detection of p-glycoprotein expression may be utilized, as a reliable predictor of response to NACT in patients

with breast cancer The chemotherapy induced p-glycoprotein positivity observed in the study could possibly explain the phenomenon of acquired chemoresistance and may also serve as an intermediate end point in evaluating drug response particularly if the adjuvant therapy is planned with the same regime.

PMID: 16164742 [PubMed]

Is drug-induced toxicity a good predictor of response to neo-adjuvant chemotherapy in patients with breast cancer?—a prospective clinical study. Chintamani, Singhal V, Singh JP, Lyall A, Saxena S, Bansal A. *BMC Cancer.* 2004; 4: 48.

The change in expression of apoptotic markers (Bcl-2 and Bax proteins) brought about by various chemotherapeutic regimens is being used to identify drug resistance in the tumor cells. A prospective clinical study was conducted to assess whether chemotherapy induced toxic effects could serve as reliable predictors of apoptosis or response to neo-adjuvant chemotherapy in patients with locally advanced breast cancer.

50 cases of locally advanced breast cancer after complete routine and metastatic work up were subjected to trucut biopsy and the tissue evaluated immunohistochemically for apoptotic markers (bcl-2/bax ratio). Three cycles of Neoadjuvant Chemotherapy using FAC regime (5-fluorouracil, adriamycin, cyclophosphamide) were given at three weekly intervals and patients assessed for clinical response as well as toxicity after each cycle. Modified radical mastectomy was performed in all patients three weeks after the last cycle and the specimen were re-evaluated for any change in the bcl-2/bax ratio.

There was a statistically significant correlation observed between clinical, immunohistochemical response (bcl-2/bax ratio) and the drug-induced toxicity. Responders also had significant toxicity while non-responders did not show significant toxicity following neoadjuvant chemotherapy. The chemotherapy-induced toxicity was observed to be a cost effective and reliable predictor of response to neo-adjuvant chemotherapy.

PMID: 15310398 [Pub Med - indexed for MEDLINE]

The role of Apoptotic Markers in predicting the response to Neoadjuvant Chemotherapy in Breast Cancer - A prospective clinical study.

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Abstract: Neo-adjuvant chemotherapy is an integral part of multi-modality approach in the management of locally advanced breast cancer and it is vital to predict the response in order to tailor the regime for a patient. The common final pathway in the tumor cell death is believed to be apoptosis or programmed cell death and chemotherapeutic drugs like other DNA-damaging agents act on rapidly multiplying cells including both the tumor and the normal cells by following the same common final pathway. Absence or decreased apoptosis has been found to be associated with chemo resistance. The change in expression of apoptotic markers (Bcl-2 and Bax proteins) brought about by various chemotherapeutic regimens is being used to identify drug resistance in the tumor cells. A prospective clinical study was conducted to assess whether apoptotic markers (Bcl-2/Bax ratio) could serve as reliable predictors of response to neo-adjuvant chemotherapy in patients with locally advanced breast cancer 30 cases of locally advanced breast cancer after complete routine and metastatic work up were subjected to Trucut biopsy and the tissue evaluated immunohistochemically for apoptotic markers (Bcl-2/Bax ratio). Three cycles of Neoadjuvant Chemotherapy using FAC regime (5-fluorouracil, adriamycin, cyclophosphamide) were given at three weekly intervals and patients assessed for clinical response after each cycle. Modified radical mastectomy was performed in all patients three weeks after the last cycle and the specimen were re-evaluated for any change in the Bcl-2/Bax ratio. The immunohistochemical response (change in the Bcl-2/Bax ratio) and the clinical response were correlated and compared. Descriptive studies were performed with SPSS version 10 and the significance of response was assessed using paired t-test. Significance of correlation between various variables was assessed using chi-square test and coefficient of correlation calculated by Pearson correlation coefficient. There was a statistically significant correlation observed between clinical and immunohistochemical response (Bcl-2/Bax ratio) to neoadjuvant chemotherapy. Increase in the ratio (i.e. increase in the expression of Bcl-2) predicted a poor response to neoadjuvant chemotherapy. It was observed in this study that apoptotic markers could reliably predict the response to neoadjuvant chemotherapy in patients with breast cancer. Chemoresistance being an important aspect in tailoring the therapy for a particular patient, the changes in the Bcl/Bax ratio could be utilized in planning an alternative regime.

Key words: *Apoptosis, apoptotic markers, neoadjuvant chemotherapy*

Introduction

Carcinoma of the breast is the leading cause of cancer in women all over the world. It is the second most common malignancy in Indian women after carcinoma of the uterine cervix¹. In the past few years, considerable research has been done on the molecular aspects of breast cancer. The recognition that tumor growth rate is a product of proliferative activity and the rate of cell death has lead to a reappraisal of traditional views of tumor response and resistance to cytotoxic drugs². Apoptosis is a closely regulated form of active cell death defined by characteristic biochemical and morphological criteria. A large number of anti-cancer agents with widely differing modes of action have been demonstrated to induce apoptosis in vitro, suggesting this as a significant final common pathway through which they exert their clinical effect.

The mechanisms that suppress apoptosis may be important in the development of intrinsic and acquired resistance to cytotoxic drugs.³ It was suggested more than 20 years ago that apoptosis might account for much of the spontaneous cell loss, known from kinetic studies, to occur in many tumors. It has been clear for sometime that its extent often is enhanced in tumors by well-established modalities such as chemotherapy, irradiation and hormone ablation. However, during the past few years, advances in the understanding of the control of apoptosis at the molecular

level have extended its potential oncologic significance far beyond the mere provision of a mechanistic explanation for tumor cell deletion. In particular, the discovery that apoptosis can be regulated by the products of certain proto-oncogenes has opened up exciting avenues for future research.⁴ A variety of anti-cancer drugs have been shown to induce extensive apoptosis in rapidly proliferating normal cell population and tumors. Thus enhanced apoptosis is also responsible both for many of the adverse effects of chemotherapy and for tumor regression.⁵ The way in which anticancer drugs induce apoptosis is not known. Better understanding of the processes involved clearly might be expected to lead to improved treatment regimes. However there is an additional important consequence of the realization that anticancer drugs mediate their therapeutic effect by triggering apoptosis³.

Apoptosis is a regulated phenomenon capable of being inhibited and activated. Herein may lay a novel explanation of certain instances of drug resistance. Indeed there is evidence that stimulation of some cells by trophic cytokines or increase in their levels of expression of Bcl-2 proto-oncogeny can greatly increase their resistance to the apoptosis –inducing effect of anticancer drugs. Thus Bcl-2 proto-oncogeny expression may be implicated in the development of resistance of tumors to therapeutic agents and may contribute to tumor growth and perhaps to ontogenesis by allowing the inappropriate survival of cells with DNA abnormalities⁶ Deregulated expression of the Bcl-2 protein represents the best known example of a potent blocker of

apoptosis. Over expression of Bcl-2 has now been shown to protect a wide variety of cell types from induction of apoptosis by many different anticancer agents. Several homologues of Bcl-2 protein have also been shown to act as inhibitors of apoptosis, including Bcl-Xl and others as apoptotic proteins including bax.

In vitro data suggests that it is the relative ratios of anti-apoptotic and pro-apoptotic proteins that determine the likelihood of cells to undergo apoptosis in response to chemotherapeutic drugs^{2,7}

“The increasing use of pre-operative chemotherapy (PCT) in breast cancer offers an *in vivo* test bed to test the clinical relevance of these observations.”

It has been studied that low levels of Bax in conjunction with normal Bcl-2 levels might disrupt cellular homeostasis, leading to an accumulation of cells, which might thus become susceptible to secondary mutagenic events resulting in malignant transformation⁸. A number of studies have shown that the clinical stage of tumor at the time of presentation strongly influences the outcome of treatment. Traditional clinical staging requires accurate measurement of tumor size and assessment of axillary lymph node status. The change in the clinical stage after chemotherapy is also of prognostic significance⁹.

The **aim** of this prospective study was to assess:

- 1) The role of apoptotic markers (ratio of Bcl-2 / Bax gene expression) in predicting the response to neoadjuvant chemotherapy.
- 2) The response to neoadjuvant chemotherapy, in terms of tumor size and axillary lymph node status.
- 3) To correlate the clinical and immunohistochemical response to neoadjuvant chemotherapy in carcinoma breast

Methods:

Thirty (30) FNAC proven cases of locally advanced breast carcinoma according to AJCC (American Joint Committee On Cancer) classification were included in the study. Before contemplating the study, approval of the IRB and the Ethical committee of the hospital was taken. A thorough clinical and ultrasonographic examination (USG) of all the patients including the opposite breast was performed to stage the disease accurately. A core biopsy using a tru-cut needle was performed for immunohistochemical estimation of the apoptotic markers i.e. base-line Bcl-2/Bax ratio before initiating the chemotherapy. Routine and metastatic work up was done including complete blood examination (total blood count, platelet count), chest radiograph, ECG (Echocardiography when ECG had a positive finding), liver function tests, Bone Scan, USG abdomen, KFT (Kidney function tests).

Patients were subjected to three cycles of FAC regime (cyclophosphamide 600 mg/m², adriamycin -50 mg/m², 5-fluorouracil-600 mg/m²) at an interval of three weeks. Before each cycle the patient was clinically and sonologically examined for the breast tumor size, axillary lymph node status & appearance of systemic metastasis. All patients were given the same antitoxicity treatment according to a standardized unit protocol including adequate hydration and inject able antiemetics before initiating the chemotherapy.

All patients were subjected to Patey’s modified radical mastectomy three weeks after the last cycle and the specimen were again subjected to immuno-histochemistry to evaluate for any change in the Bcl-2/Bax ratio and for the histological tumor size, margins.

Objective clinical response was defined as >50% reduction in the tumor size after completion of three cycles of NACT, as assessed clinically, sonologically and histologically. Immunohistochemical response was taken as decrease in the Bcl-2/Bax ratio. Any increase or no change in this ratio was considered as no response.

Immuno-histochemical methods : Biopsy specimen was preserved in buffered formalin solution. Five-micron sections were prepared from paraffin embedded blocks on poly-l-lysine coated glass slides. Sections were deparaffinized in xylene for 15 min. and hydrated in alcohol for 15 minutes. Further, incubation was done in 0.3% hydrogen peroxide in methanol solution for 45 min. The slides were washed with citrate buffer and kept in a water bath at 90–95°C for 45 min. for antigen retrieval. Sections were washed with Tris buffer saline (TBS) solution and incubated with blocking antibodies (DAKO monoclonal mouse antihuman Bcl-2 oncoprotein for Bcl-2 expression and polyclonal rabbit antihuman for Bax expression) at 37°C. Sections were washed with TBS solution. Incubation with avidin-biotin complex (ABC) was done at 37°C for one hour and washed with TBS solution. 3,3 Diaminobenzidine tetra hydrochloride solution applied for 3–5 min. Counter-staining with haematoxylin solution done for 3–5 min. Sections were washed with distilled water, air dried and mounted using DPX mountant.

For Bax, positive controls were taken as germinal centers of the lymphoid follicles and normal breast tissue and negative control was taken as the test slide without primary antibody. For Bcl-2, positive controls were the mantle zone of lymphoid follicles and the negative controls were the test slides without primary antibody.

a) *The pattern of positive staining for Bcl-2 and Bax was cytoplasmic, granular. b) The primary antibodies for Bcl-2 and Bax were procured from DAKO. c) Bax-Rabbit Anti-Human code no. A 3533. d) Bcl-2 Monoclonal Mouse Anti-Human code no. M 0887. e) Dilution for both was 1: 40.*

The results were interpreted on the basis of two criteria:

- (1) Percentage of cells showing immune bodies; <5%: score = 0, 5–25%: score = 1, 25–75%: score = 2, >75%: score = 3;
- (2) Intensity of staining; mild: score = 1, moderate: score = 2, intense: score = 3.[Fig.1, Fig.2, Fig.3, Fig.4]

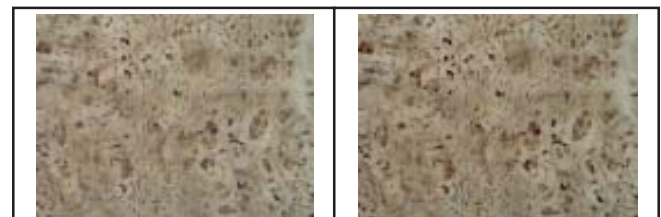


Figure.1: Immunohistochemistry showing positive (moderate) staining of tumor cells with Bax antibody

Figure.2: Immunohistochemistry showing positive (intense) staining with Bax antibody

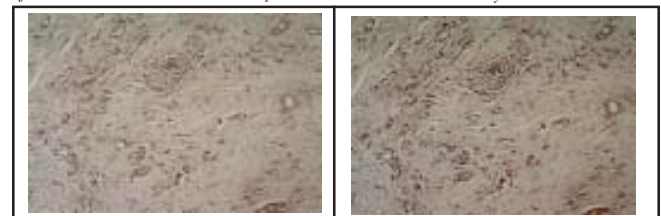


Figure.3: Immunohistochemistry showing moderate cytoplasmic staining of tumor cells with Bcl-2 antibody

Figure.4: Immunohistochemistry showing positive (intense) cytoplasmic staining of tumor cells with Bcl-2 antibody.

Table 1 Cohort Distribution (n=30)

		Clinical		Immuno-histochemical	
		Response	No response	Response	No response
Menopausal status					
Pre-menopausal	53.3%	62.5%	37.5%	56.2%	43.8%
Post-menopausal	46.7%	71.4%	28.6%	64.2%	35.8%
Tumor size					
<5cm	0%	—	—	—	—
5-8cm	56.6%	68.7%	31.3%	60%	40%
8-10cm>	26.6%	79%	29%	60%	40%
10cm	16.6%	66.6%	33.3%	60%	40%
Axillary LN status					
N0	0%	—	—	—	—
N1	57.3%	—	—	—	—
N2	42.7%	—	—	—	—
Total		70%	30%	60%	40%

"Since there was a strong correlation between the intensity of staining and percentage of cells showing immune bodies, the percentage of cells showing immune antibodies alone was considered for calculating the Bcl-2/Bax ratio".

Statistics : Descriptive studies were performed with SPSS version 10. The significance of response assessed using paired t-test. Significance of correlation between various variables assessed using chi-square test and coefficient of correlation was calculated by Pearson correlation coefficient. The clinical and immunohistochemical response were then correlated and compared.

Results:

Age of the patients ranged from 28-71 years with the mean age of 45.5 years and a standard deviation of 11.732 yrs; the median and mode were 43 years and 40 years, respectively.

Comparison of tumor size before and after neo adjuvant chemotherapy was performed using paired 't' test ,at the

Table 2. Immunohistochemical response following neoadjuvant chemotherapy

Total number of patients = 30

Immunohistochemical Response	No. of patients	% Of patients
Responders	18	60%
Nonresponders	12	40%

Table 3. Comparison between immunohistochemical and clinical response

		Immunohistochemical Response.			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Non responders	12	40.0	40.0	40.0
	Responders	18	60.0	60.0	100.0
	Total	30	100.0	100.0	

confidence limit of 95% (P <0.05) chi-square test was applied and the clinical response to NACT in terms of the change in the tumor size was found to be statistically significant.

Response observed in the axillary lymph nodes: Out of total of 17 patients that were N1 before NACT 5 (29.4%) were Down-staged to N0 whereas 12 (70.6%) remained N1. Out of a total of 13 patients who were N2 before NACT; 1 (7.7%) was down staged to N0 and 6 (46.2%) were downstaged to N1 whereas 6 (46.2%) remained N2. With confidence limit of 95% (P0.05%) chi-square test was applied and the response to NACT in terms of the down-staging of the axillary lymph node status

Clinical Response

Valid		Frequency	Percent	Valid Percent	Cumulative Percent
		Non responders	9	30.0	30.0
	Responders	21	70.0	70.0	100.0
	Total	30	100.0	100.0	

Clinical. Response. * Immunochemical Response. Cross tabulation

di.Res.		Count	Immunohist. Response.		Total
			Nn responders	Res-ponders	
Non responders	Count	9		9	
	% within cli. Res.	100.0%		100.0%	
Responders	Count	3	18	21	
	% within cli. Res.	14.3%	85.7%	100.0%	
Total	Count	12	18	30	
	% within cli. Res.	40.0%	60.0%	100.0%	
	% within imm. Res.	100.0%	100.0%	100.0%	

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	19.286(b)	1	.000		
Continuity Correction(a)	15.880	1	.000		
Likelihood Ratio	23.156	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	18.643	1	.000		
N of Valid Cases	30				

At 99% confidence limit and degree of freedom =1, n=30; c2 distribution test was applied to the above table and a statistically significant correlation was observed between the clinical and immuohistochemical response.

was found to be statistically significant

Out of the total 30 patients studied 18 (60%) showed a decrease in the Bcl-2/Bax ratio following neoadjuvant chemotherapy. In 9 (30%) of the patients the ratio increased where as in 3 (10%) of the patients the ratio remained unchanged. Paired 't' test was applied to find the statistical significance and immunohistochemical response in terms of change in ratio of bcl-2/bax gene expression was found to be statistically significant (Table 2 & 3)

Acute vomiting (taken as minimum of three vomiting in 24 hours) was observed in 63.3% patients. 81% clinical responders

Table 4 : Toxicity and Response (n=30)

	Total N=30	Clinical responders	Clinical non-responders	Immuno-histochemical responders	Immuno-histochemical non-responders
Acute vomiting	63.3%	81%(p=0.002)	22.2%	78%(p=0.04)	41.7%
Alopecia	60%	86%(p=0.000)	0%	94%(p=0.000)	8.3%
Leucopenia	10%	14%(NS)	0%	17%(NS)	0%
Alopecia+Acute vomiting	46.7%	67%(p=0.001)	0%	72%(p=0.001)	8.3%

had vomiting (p=0.002) and 78% immunohistochemical responders also had vomiting (p=0.04) which was statistically significant. Alopecia (taken as complete alopecia) was observed in 86% clinical responders (p=0.000) and 94% immuno-histochemical responders (p=0.000), which was also significant. Leucopenia (using the WHO criteria) was observed in only 14% and 17% of clinical and immuno-histochemical responders respectively and was found to be an insignificant observation factor in our study. When multiple toxicities were correlated with the clinical and immuno-histochemical response, 46.7% of patients had both acute vomiting and alopecia. 67% clinical responders (p=0.001)

had both vomiting and alopecia. 72% immunohistochemical responders ($p=0.001$) had both vomiting and alopecia. A positive significant correlation was found between the presence of vomiting ($r=+0.558$), alopecia ($r=+0.802$) and response to neoadjuvant chemotherapy. A significant negative correlation was also observed between the absence of side effects and poor response to neoadjuvant chemotherapy. The toxicity observed correlated significantly with the response to neoadjuvant chemotherapy i.e. responders showed significant toxicity also (Table 4).

Discussion:

Carcinoma of the breast is the leading cause of cancer in women all over the world and the second most common malignancy in India after carcinoma of the uterine cervix¹. No other common epithelial cancer has been so carefully studied and so extensively characterized biologically^{1,2}. In developing countries like India rate of locally advanced breast cancer at first diagnosis is estimated to be as high as 25%–30%^{2,5}. The treatment of locally advanced breast carcinoma (LABC) has also evolved from primarily local modalities to treatment regimens that combine both systemic and local therapy. The realization that patients with LABC are likely to have undetectable micro metastases at diagnosis has led to systemic treatment assuming major focus of the multi-modality approach as the studies have confirmed that surgery alone is an inadequate treatment in the management of these patients. Even aggressive surgical techniques have been observed to have a higher incidence of local recurrence in these patients^{10,11}. Most importantly surgery does not change the pattern of distant failure in patients who probably have micrometastatic disease at the time of diagnosis^{10,13}. Multi-modality therapy that included surgery, radiation therapy, chemotherapy, hormonal therapy has had the greatest impact on survival in patients with LABC^{10,13}.

Neoadjuvant chemotherapy (NACT) : A new approach in the form of neoadjuvant chemotherapy was first reported in the 1970s and was initially utilized to convert unresectable tumors to smaller tumors making them more amenable to local control with either surgery or radiotherapy. An added advantage of this approach was the ability to assess patient's response to treatment both clinically after a defined number of courses of chemotherapy and pathologically after surgical resection. Perez and colleagues reported their results of a pilot study by the South-Eastern Cancer Study Group in 1979 that the primary tumor showed partial regression (>50%) in 65% of patients after two courses of FAC¹⁶. NACT has also shown benefits in the operable breast cancers by increasing the chances of breast conservation by up to 90% in some trials^{10,13}. The other important advantage of NACT is that it represents an *in vivo* chemo sensitivity test for assessment of tumor response from which prognostic information can be obtained. It provides an early treatment of the micrometastatic disease, counteracting the increased growth rate possibly determined by the shrinkage of the tumor. The down staging converts an inoperable case amenable to curative resection^{10,13}.

Apoptosis : Introduced by Kerr et al (1972), to describe characteristic morphological changes seen during programmed cell death³. It is defined as a closely regulated form of active cell death defined by characteristic biochemical and morphological criteria^{3,14,15}. A wide range of anticancer drugs with widely differing modes of action have been demonstrated to induce

apoptosis *in vitro*, suggesting this as a significant common final pathway through which they exert their clinical effect. Further more the mechanisms that suppress apoptosis may be important in the development of acquired resistance to cytotoxic drugs. Apoptosis or programmed cell death plays an important role in the regulation of tissue development, differentiation and homeostasis. It is therefore possible that deregulation of apoptosis contributes to the pathogenesis of cancer^{3,13-15}. Apoptosis can be differentiated biochemically and morphologically from necrosis by the following criteria¹⁶:

- (1) Chromophin condensation;
- (2) Membrane blebbing;
- (3) Appearance of apoptotic bodies;
- (4) Fragmentation of genomic DNA

Certain biochemical and genetic events have been identified that are associated with multiple cell types including mammary epithelium. These include the DNA fragmentation via end nuclease activation and cleavage of intracellular proteins, expression of bcl-2 family members, tumor suppressor gene p-53 directed events, proto-oncogene activation and activation of transmembrane receptor signaling pathways such as tumour necrosis factor^{4,17-22}. Although little is known about the mechanisms, which regulate apoptosis in epithelial cells, it is conceivable that defects in apoptosis related genes are involved in the pathogenesis of human cancers. The hypothesis is supported by the fact that the tumor suppressor gene product p-53, which is frequently mutated or deleted in breast cancer, is involved in regulating apoptosis²³. The heterogeneous nature of breast cancer has resulted in overwhelming interest in search for prognostic markers to identify patients who might benefit most from the therapeutic modalities available.

Assessment of apoptosis and individual components of apoptotic pathway are therefore relevant in determining prognosis in a particular patient²⁴. DNA damaging agents such as ionizing radiations and chemotherapeutic drugs also induce apoptosis. Sakakura et al have shown an association between increased resistance to chemotherapeutic agents and decreased capacity to undergo apoptosis²⁵. Central to this response are proteins that modulate apoptosis, including Bcl-2 and Bax gene products. Bcl-2 is anti-apoptotic in function, whereas Bax is proapoptotic and it is the interaction between the two that determines the likelihood of a tumor to undergo cytotoxic drug mediated regression. Therefore any increase in Bcl-2 or decrease in Bax will push the balance towards chemo resistance and an increase in Bax or decrease in Bcl-2 will result in increased apoptosis²⁶⁻³⁰. It was observed in a study conducted by Kymionis et al¹⁵, that increase in the ratio of anti apoptotic protein Bcl-2 to pro-apoptotic protein i.e. Bax results in markedly enhanced resistance of tumor cell lines to the cytotoxic effects of essentially all currently available chemotherapeutic drugs.

In the present study the clinical response in terms of reduction in tumor size correlated significantly with the immunohistochemical response in terms of change in the Bcl-2/Bax ratio.

Conclusion:

Neoadjuvant chemotherapy is routinely used in the management of locally advanced breast cancer. The present study highlights the importance of utilizing apoptotic markers in predicting the response to neoadjuvant chemotherapy so that an alternate regime could be planned in non-responders.

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Correlation of expression of Androgen Receptors and Estrogen Receptors in female Breast Cancer cases.

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Abstract: Estrogen receptors and progesterone receptors have been extensively studied and assayed in breast cancer management as independent prognostic markers for hormonal therapy. Androgen receptors are known to induce proliferative changes in breast cancer and this has led to investigations regarding expression of androgen receptors in breast cancer. Androgen receptor expression has been found to be associated with poor breast cancer subtypes and could be an independent predictor in invasive breast cancer.

Keywords: *Breast cancer, androgen receptors.*

Introduction

Breast cancer is the second most common malignancy of the women in India, next only to cervix cancer. In the year 2001, 800,000 new cancer cases were reported, out of which about 80,000 cases were of breast cancer. The average incidence rate of breast cancer India is 16/100,000, varying from 22-28/100,000 females in urban settings to 6/100,000 in rural areas. In cities like Mumbai, Trivandrum and Delhi, it forms the most frequent female cancer. The age of presentation among Indian females is a decade later than the western population i.e. 45-54 years. About 80-90% cases of breast cancer present at a locally advanced stage. Recent advances in molecular pathology enable identification of molecular mechanisms underlying development and progression of breast cancer. Several prognostic markers have been identified for breast cancer viz. estrogen receptor (ER), PR, p53, CerbB-2 and others. Of these, estrogen receptor has long been studied and assayed for breast cancer management. Anti-estrogens (Tamoxifen) and ER blockers (SERMS) have, of late, become powerful therapeutic agents to treat breast cancers that express ER's. In addition, aromatase inhibitors are now used in postmenopausal women to block the *in-situ* conversion of adrenal androgens to estrogens.

Androgens have been found to be carcinogenic in prostate cancer. Lately, they have also been thought to play an important role in breast cancer. The risk of breast cancer is increased in postmenopausal women with high estrogen levels as also high androgen levels. Androgens are known to induce proliferative changes in breast cancer by a direct activation of ER by DHEA, 5-androstene-3bbbb ER-negative tumors. The expression of androgen receptors (AR) in breast cancer cases, particularly those that are ER negative, has long been a matter of debate, including whether AR expression has prognostic significance in ER negative tumors. Present study was undertaken with the following *aims and objectives* : 1. To study status of Androgen receptor (AR) expression in 25 cases of breast cancer. (2) To correlate Androgen receptor (AR) expression with estrogen receptor (ER) expression. (3) To correlate Androgen receptor expression with various clinical and histopathological parameters.

Review of literature

Breast cancer is the most common malignancy in females all over the world. In India it is the second most common malignancy next only to cervix cancer. In the year 2003, about 240000 cases of breast cancer were diagnosed worldwide, out of which 40000 patients died of it. In India, 80000 cases of breast cancer were reported in the year 2001. The average age of reporting in Indians is 45-54 years, which is a decade later than that in western countries. Thus the need is felt for better prognosis using better molecular markers, as every cancer, including breast carcinoma has a molecular basis for its genesis.

The genesis of breast cancers is largely hormonal and genetic. Sex hormones like estrogen and progesterone have been studied and their effects on the breast tissue used as prognostic tools in breast cancer management. Genetic factors include genetic mutations that are autosomal, defective DNA repair and some familial cases due to germ line mutations. The expression of a large number of carcinogenic genes is now detectable via assay of selected proteins using immunohistochemistry techniques (ER, PR, HER/neu, e-cadherin, p53, ki-67 etc.). This technique assays actual protein content. Immunohistochemistry uses antibodies to detect proteins on tissue sections and has the advantage of being able to identify the cell type expressing the protein and also its accurate location.

This major sex steroid hormones viz estrogens and androgens have been known to cause proliferation in tumor cells. In case of breast cancer, estrogen receptor expression is particularly thought to be of great importance, as ER + cases are known to respond better and more frequently to hormonal therapy (50-75% response rate) while ER-negative tumors has less than 10% chance of response. In addition ER positivity also is prognostic of delayed recurrence in primary breast cancer. Also, estrogen is thought to play a major role in the development and progression of breast cancer.

Estrogen receptor expression has been studied and assayed in breast cancer management as a prognostic indicator in breast cancer hormonal therapy. Antiestrogen (Tarduxitic) ER blockers (SERMs) and aromatase inhibitors (that block in situ conversion of androgens to estrogens) have gained widespread acceptance in cancer therapy. Other markers that are routinely assayed in breast carcinomas are PR, HER2/neu, e-cadherin, p53 and Ki-67). The role of adrenal androgens in carcinogenesis has also been studied. They are known to cause prostate cancer. The expression of androgen receptors, in breast cancer cases, particular house that

or ER has long been a matter of debate including whether AR expression has prognostic significance in ER-negative tumors.

The purpose of the present study was to correlate the expression of androgen receptors with their ER status in breast carcinoma, along with age tumor grade and size and lymph node status in Indian patients.

Material and Methods

The present study included 25 cases diagnosed as breast cancer at the Institute of Pathology, referred from Surgery Department, Safdarjung Hospital, New Delhi. The histopathologic diagnosis was established on conventional haematoxyline and eosin (H&E) staining. Various clinical parameters like age of the patients, tumor stage (TNM), histopathological parameter like tumor type, lymph node (LN) status, and histopathological grade, were noted. AR expression was identified in all cases and correlated with ER expression, using immunoperoxidase ABC (avidin-biotin complex) method.

Materials included : (1) blocking antibody (2) primary antibodies (AR: Monoclonal antibody Clone AR441, Neomarker), (ER: Rabbit monoclonal antibody Clone SP1, Labvision, CA USA) (3) secondary antibody (4) ABC kit (Vector labs) (5) diaminobenzidine (DAB) chromogen agent.

Methods : Paraffin embedded, methanol fixed slides were preincubated 37.3°C for 30 minutes. Xylene treatment in two changes, each of 30 minutes was used to remove the wax. Methanol treatment in two changes each of 20 minutes was used for dehydration. Peroxide treatment in mixture of 47ml methanol and 3 ml H₂O₂ for 45 minutes was given. Slides were then washed in citrate buffer (pH 6.9). Heat induced epitopes retrieval was done in microwave. Slides were placed in citrate buffer (pH 6.9) and heated for 90 seconds at 800X followed by 5-minute treatment at 80X. The slides were cooled and the heating and cooling process was repeated four times. Similar process was repeated in citrate buffer (pH 6.0) another four times. After cooling blocking antibody was applied and slides were left for incubation for 1 hour at 37.3 °C. Then, anti-AR antibody was applied on to the slides (without TBS washing), and left for overnight incubation in a refrigerator. Secondary antibody was added after washing with TBS buffer pH 7.6 and left for incubation at 37 °C for 2 hours. Next, ABC antibody was added after washing with TBS buffer pH 7.6 and left for incubation at 37 °C for 2 hour. Slides were then washed again with TBS buffer. Diaminobenzidine (DAB) solution was added on to the slides with a micropipette slides were left for 3 minutes. Counterstaining was done after washing the DAB-stained slides with distilled water and applying hematoxyline with micropipette. The slides were dried and mounted with DPX mountant.

Interpretation: Tumor cells showing more than 10% expression for ER, AR were included as positive.

Results

A total of 25 cases of breast carcinoma were analyzed for present study. The age of the patients varied from 26 to 70 years, with maximum number of patients in the age group 40-49 years i.e. 10 patients (40%), followed by 9 patients in the age-group e"50 years and 6 patients with age d"39 years. Among the cases with varying tumor stage, maximum number of cases were in stage 2B (5 cases), followed by, (in descending order) 3 B (4 cases), 1

and 3a stage (3 cases each), 2 cases with stage 2A and 1 case of tumor stage 4.

Cases were categorized into different histomorphological types, with maximum number of cases of infiltrating ductal carcinoma (IDC) NOS (14 cases), followed by infiltrating lobular carcinoma (ILC) (5 cases), 2 cases each of ductal carcinoma-in-situ and mixed IDC and ILC type and 1 case each of medullary and comedocarcinoma.

Fourteen cases showed lymph node positivity while remaining 11 cases had negative lymph node status. Among 12 cases, with details of family history of breast and/ or other cancers, 7 cases revealed a positive family history of the same.

Androgen receptor (AR) expression was analyzed in all 25 cases and further correlated with the various clinical, histopathological markers. Further AR expression was correlated with ER expression. Out of 25 cases, 12 (48%) cases showed estrogen positivity and 13(52%) cases revealed negative ER expression. Expression, with various parameters is as follows:

Table No 1(Total cases=9)

AGE	AR	%
<39	2	22
40-49	3	33
>50	4	44
TOTAL	9	100

AR expression and age (Table-1):

There were nine cases that tested AR positive. Out of these four case (44%) were reported in women over 50 year of age. Least frequency of AR expression was reported in woman with age < 40 years. Thus, AR positivity has been observed directly correlating with increasing age. (Fig: 1)

STAGE	AR	%
1	1	12.5
2A	0	0
2B	2	25
3A	2	25
3B	3	37.5
4	0	0
TOTAL	8	100

AR expression and stage (Table-2): Out of eight AR positive cases for which status of tumor stage was known, most cases (3/8 or 37.5%) were reported at an advanced stage 3B. 25% cases were reported each at 2B and 3A stages. Very few (only 1/8 or 12.5%) cases were reported at primary stage-1.

Table no 3: Total cases = 9

LN Status	AR	%
LN +	4	44
LN -	5	55
TOTAL	9	100

AR expression and lymph node status (Table-3): LN status was available for all the nine AR positive cases. Of these 44% (4/9) cases showed LN metastasis while the rest 55% (5/9) cases were LN negative. Thus there was no significant correlation between AR and

Table 4 (Total cases = 5)

GRADE	AR	%
Low	1	20
Intermediate	2	40
High	2	40
TOTAL	5	100

AR expression and grade (Table-4):

Data for tumor grade was available for 5/9 cases. Of these 40% cases or 2/5 were each of intermediate and high grade. Only 20%cases (1/5) were of low grade. (Tumor grade was noted in IDC cases), ILC cases were excluded.

Table 5 (Total cases = 3)

GRADE	AR	%
Low	1	20
Intermediate	2	40
High	2	40
TOTAL	5	100

AR expression and family history (Table-5):

Family history inAR positive tumours were available only in three cases. Of these 66% or 2/3 cases showed no family history of breast cancer. Only one patient had a relative with breast cancer. Thus, family history is not significant with AR expression.

Table 6 (Total cases = 9)

TYPE	AR	%
1	3	33
2	3	33
3	2	22
4	1	11
5	0	0
6	0	0
7	0	0
8	0	0
TOTAL	9	100

AR expression and tumour type

(Table-6): Out of the nine AR positive cases, maximum cases were IDC NOS type and ILC types (33% or 3/9 cases each, respectively). Two cases (22%) were of mixed type where as only one case was of medullary carcinoma, showing positive AR expression. The maximum frequency of AR positivity in IDC and ILC tumors shows that AR positivity is marker of bad prognostic cancer types.

Table 7 (Total no. of cases = 25)

	ER+	%	ER-	%
AR+	7	58.33	2	18
AR-	5	41.66	11	82
TOTAL	12	48	13	52

AR expression and ER expression

(Table-7): Out of total 25 cases included in the study, twelve (48%) cases were ER positive and rest 13 (52%) cases were ER negative. Of the ER positive cases seven (58.33%) cases were AR positive and the rest five (41.66%) cases were AR negative. Of the ER negative cases, two (18%) cases were AR positive and the rest 11 (82%) cases were AR negative. (Fig. 2, 3, 4, 5, 6.)

Discussion

Utility of ER expression in breast cancer, as a prognostic marker, is well documented. Lately, there has been a need to identify more prognostic factors. Among these, AR expression is less documented. Earlier studies have focused on ER positive tumors and have shown some association between AR status and disease free survival, as well as response to endocrine therapy. Our study focused on AR expression in breast carcinoma cases and correlation with various established prognostic markers, including ER expression, more so in cases having negative ER expression. Positive AR expression was observed in 9 (36%) cases. Among the various prognostic parameters analyzed, AR expression showed positivity with increasing age of the patients. Agoff et al and Bryan et al in concordance with a similar study conducted this. The incidence of breast cancer is high in elderly females, when the androgenic levels are high, and the risk of breast cancer is high in women with high estrogen levels than those with high androgen levels. It has been shown in animal models that

testosterone in combination with estrogen can induce high incidence of mammary carcinoma. Increasing tumor grade and relatively poor prognostic types like IDC NOS, also showed increase in AR positivity. This was in concordance with study performed by Isola and Agoff et al. The expression was also found more in cases with higher tumor stage i.e. 37.5% cases in stage 3B. Lymph node positivity and family history, however, failed to show any significant associations.

Our study focused on identifying association of AR expression in cases of ER negative tumors. Only 18% cases with ER negativity showed positive AR expression. On the other hand 58.33% cases showed ER and AR positivity. This higher percentage was also noted by Agoff et al. However, lesser number of ER negative cases showing AR positivity was contrasting with observations by Agoff et al. This might have been due to inclusion of lesser number of ER negative cases. On the whole, however AR can be included as an independent prognostic marker for breast carcinoma. The results of Agoff et al and Bryan et al, revealing significance of survival of patients with AR expression and lacking ER expression, further substantiates the utility of studies like the present one in identifying more prognostic factors for breast carcinoma.

Conclusion:

1. Androgen receptor (AR) expression is associated with increasing age, tumor grade, stage and poor prognostic breast cancer types.
2. AR expression was seen more in ER positive cases, than ER negative cases.
3. AR expression could be an independent prognostic factor in invasive duct breast carcinomas.

Recommend Reading

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Quantitative Dermatoglyphic traits in patients with Breast Cancer - a preliminary report of an ongoing study.

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Abstract: Breast cancer is one of the most extensively studied cancers. Pattern of dermatoglyphics has been an object of interest to people for a long time for various reasons. Dermatoglyphic traits are formed under genetic control early in development and do not change thereafter, thus maintaining stability not affected by age. The study was conducted on 30 histo-pathologically confirmed breast cancer patients and their digital dermatoglyphic patterns were studied to assess their association with the type and onset of breast cancer. It was observed that "Loops" is the most common type of ridge pattern observed in all the digits ranging from 98 – 60 % including both controls and breast cancer patients. The most common pattern seen in all the digits was "Loops" (75%) in the cancer patients group. Whorl pattern frequency showed maximal changes as compared to other pattern i.e. 4 % increase in the right digits in cancer patients as compared to the controls. It was observed that the mean ridge count on the right and left hand was 10.4 and 12.4 respectively, while in the controls the ridge count in the left hand was observed to be 18.4 and 19.6 respectively. The dermatoglyphic study might contribute to various aspects of breast cancer including the genetic pattern and also may serve as a screening tool in the high risk population. In a developing country like India it might prove to be an inexpensive and effective tool for screening and studying the patterns in the high risk population.

Key words: Breast cancer, dermatoglyphics

Introduction:

The genetic component in breast cancer is well established and two genes (BRCA1 and BRCA2) have been identified as genetic links. However these account for only a small proportion of cases. Evidence is available suggesting that a family history of breast cancer might be associated with a specific fingerprint pattern. If we do find an association, fingerprints might potentially be used for screening or to guide future research in this direction¹ and one day the screening of breast cancers could be at our fingertips! The prints will thus represent a noninvasive anatomical marker of breast cancer risk². An effort in this regard has been initiated to devise a screening program for hereditary breast cancer using finger prints or dematoglyphic study.

Material and methods:

The study was conducted on 30 histo-pathologically confirmed breast cancer patients (both indoor as well as outdoor) after taking the informed consent, at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. They were asked to fill a proforma and their digital prints recorded on the sheet enclosed. The fingerprints were taken on a glossy paper, digitally photographed and were analyzed using Adobe Photoshop software for palmar ridge patterns and ridge counts. Simultaneously 20 controls were also selected who had no self or familial history of a diagnosed breast cancer and their observations were also recorded.

Observations:

The two most common patterns for a digit were recorded for keeping the numbers optimum and only for more clarity in interpretation of the data.

Table no 1. Right digital observations in Breast cancer patients:

Digit	Pattern (%age)		Ridge count (mean)
Thumb (R1)	Loop – 70	Whorl - 20	16
Index (R2)	Loop – 70	Double Loop - 20	11
Middle (R3)	Loop – 60	Tented Arch - 30	13
Ring (R4)	Loop – 77	Double Loop - 20	13
Little (R5)	Loop – 98	-	9

Ridge count S.D. 2.33

Table no 2. Left digital observations in Breast cancer patients:

Digit	Pattern (%age)		Ridge count (mean)
Thumb (L1)	Loop – 97		13
Index (L2)	Loop – 83	Whorl - 15	8
Middle (L3)	Loop – 42	Tented Arch - 42	10
Ring (L4)	Loop – 83	Tented Arch - 16	10
Little (L5)	Loop – 72	Tented Arch - 16	11

Ridge count SD 1.62

Table no 3. Right digital observations in Control group:

Digit	Pattern (%age)		Ridge count (mean)
Thumb (R1)	Loop - 75	Double Loop - 24	18
Index (R2)	Double Loop - 80	Tented Arch - 15	25
Middle (R3)	Loop - 66	Tented Arch - 30	14
Ring (R4)	Loop - 50	Tented Arch - 30	22
Little (R5)	Loop - 50	Tented Arch - 25	13

Ridge count SD 4.58

Table no 4. Left digital observations in Control group:

Digit	Pattern (%age)		Ridge count (mean)
Thumb (L1)	Loop- 30	Whorl - 30	23
Index (L2)	Tented Arch - 75	Loop- 22	25
Middle (L3)	Tented Arch - 70	Loop- 18	14
Ring (L4)	Loop- 65	Arch- 35	22
Little (L5)	Double Loop - 52	Tented Arch - 46	14

Ridge count : SD 4.67

Table no 5: Frequency of each digital pattern.

	Right digits patterns		Left digit patterns	
	Patients	Control	Patients	Control
Loops	75.0	48.2	75.4	19
Whorl	40	-	30	6
Double Loop	80	16.0	-	10.4
Tented Arch	60	20.0	14.8	29

It may be appreciated that Loops were the most common type of ridge pattern observed in all the digits ranging from 60-98%.

It was observed that overall the most common pattern seen of all the digits is Loop (75%) in the cancer patients group. (See figures 1,2,3)

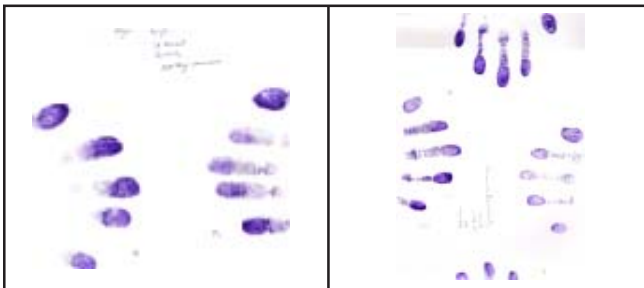


Figure 1: 40 yrs old lady with Papillary Ca breast ($T_2N_0M_0$)

Figure 2: 46 yrs old lady with Breast Ca ($T_3N_1M_0$)



Figure 3: 45yrs, Left Breast Ca ($T_4N_1M_0$)

Discussion:

More has been written about the epidemiology of breast cancer than possibly any other form of cancer affecting mankind. However, in the face of this intense interest, only a paucity of attention has been given to the role of genetics in its etiology⁴. Familial clustering of breast cancer was first recorded in the Roman medical literature at around 100AD³. We have some evidence from this preliminary study to suggest that a family history of breast cancer might be associated with a specific fingerprint pattern thus making fingerprints a potential tool to be used for screening and for guiding future research.

A pattern of six or more digital whorls is recorded more frequently in women with breast cancer than in those without the disease (Murray H Seltzer et al. 1990)⁵. No conclusions could be drawn based on this preliminary study, however certain findings that

point towards some correlation between the digital patterns and the breast cancer have been observed and the role of dermatoglyphics in future is becoming clearer.

In the present study it was observed that the loop pattern is the most frequent pattern i.e. in 75% of the patients (Table No.5) in all the digits, which is in variance from the other available data suggesting the whorl pattern to be more common in breast cancer patients (Murray). This further suggests different dermatoglyphic pattern in our population as it is reinforcing the belief that Indian breast cancer behaves differently from elsewhere⁷. This is also suggested by Gilligan et al (1985) where a significant correlation between dermatoglyphic and geographic distances was found confirming the biological validity of the social and ethnic criteria⁶. This gives us more reasons to work on these patterns extensively to come to a conclusive statement about our population for application in the field and we indeed need "an Indian solution to an Indian problem".

Presence of Whorl pattern in our study is also important but for a different reason. It is seen that the Whorl pattern frequency showed maximal changes as compared to other patterns i.e. 4% increase in the right digits in cancer patients as compared to the controls.

Moreover the ridge count was also considered for correlation as it is more objective and easier to assess. In the present study it was observed that the ridge count is significantly lower as compared to the controls. It was observed that the mean ridge count on the right hand and left hand was 10.4 and 12.4 respectively, while in the controls the ridge count in the right and left hand was observed to be 18.4 and 19.6 respectively.

Conclusion:

The study is ongoing and the pattern seems to be appearing wherein a definite approach in the form of "dermatoglyphics" might play a significant role in the near future not only for the purpose of screening but also for studying the behavior of breast cancer.

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Conference News

The Third MDRF-ADA Postgraduate Course on Diabetes will be held from 29th September to 1st October 2006 at Chennai, India. The meeting will be hosted by the Madras Diabetes Research Foundation, Chennai. For further details; contact : Dr. V. Mohan, M.D., FRCP, Ph.D., D.Sc. Madras Diabetes Research Foundation & Dr. Mohans Diabetes Specialities Centre, No.4 Conran Smith Road, Gopalapuram, Chennai-600086, India. Phone : (91 44) 28359048, 28359051, 28353351, Fax : (91 44) 28350935, E-mail : mvdsc@vsnl.com Visit website at www.mdrf-ada.com or www.drmohansdiabetes.com for details regarding registration etc.

Mismatched Repair Genes in Breast Cancer - An Overview

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Abstract: Genetic basis for differential behavioral subtypes of breast cancer is being investigated extensively; one of the focus being MisMatch Repair genes, which are found to be responsible for Early onset cancers and account for their aggressive behaviour. In breast cancer MSI has been reported in varying frequencies. But, the association between MMR and breast cancer is far from clear and more focused research in the future will definitely help in tailoring the therapy for Breast Cancer.

Keywords; *Breast Cancer, MisMatch Repair genes.*

Carcinoma Breast, being the leading malignancy in women, has attracted a lot of attention in recent years into its pathogenesis. The search for answers regarding the etiology and behavioral patterns of breast cancers is still on and although there has been movement but one is not too sure if it is in the "forward" direction. The answer to the ultimate therapy which would be targeted and tailored lies in finding out the genetic basis of response of breast cancer to various therapies. The genetic basis of Carcinoma breast is therefore being investigated extensively world wide to find out markers delineating different behavioral subtypes. Recent research is focused primarily on HER-2NEU, CHEK-2, DBC-2, EMSY and Mismatch Repair Genes. The mismatched repair genes have been found to be responsible for the early onset cancers and also account for their aggressive behaviour.

MMR genes pathway is the most important post replicative repair process involved in maintenance of genomic instability. These genes first came into light due to the implication of their dysfunction in HNPCC syndrome. In HNPCC¹ syndrome MMR genes hMLH1 and hMSH2 were implicated in 30 & 50% instances respectively. MMR genes involvement is also implicated in sporadic colon, gastric, endometrial, prostatic malignancies and lymphoma. [1, 2] These genes are called *proof readers* of the genome. They correct erroneous nitrogenous base pairing occurring at the time of replication. Novel bands of DNA in the form of expansion and contraction appear in one or both alleles of microsatellites of the genome, causing microsatellite instability (MSI), hallmark of MMR dysfunction. Cells with defects in DNA repair are said to have replication error (RER positive) phenotype.

MMR genes most commonly associated with malignancy are hMSH2, hMLH1, hMSH6, hPMS2. In breast cancer MSI has been reported in varying frequencies of 5 to 30% [3]. Overall the actual number of MSI was 64 in a total of 2499 cases studied but ranged from 0% (Lohe et al 1993) to 34% (Patel et al 1994). The relationship between MMR genes dysfunction and family history in breast cancer has also seen investigated. Glebov et al [4] (1994) noted difference in instability of genome between familial and sporadic breast cancer but Jonsson et al [5] in (1995) reported that there is no significant difference of MMR dysfunction between sporadic familial and hereditary breast cancers – all falling in the range of 5-6.6%.

The clinicopathological parameters of breast cancer whose relationship has been studied with MMR dysfunction include tumour size, lymphnode positivity, histotype in situ carcinomas and histological grade. Contegiaco et al [6] in 1995 found MSI to be significantly related to tumour size, lymphnode status and histotype. Aldaz et al [7] found lobular carcinoma to be more commonly associated with MMR dysfunction. Lee et al [8] found medullary carcinoma to be uncommon in MMR dysfunctional carcinoma breast. Walsh et al [9] found MSI to be associated

with higher nuclear grade in DCIS.

Many researchers have started reporting implications of MMR dysfunction in response to chemotherapy in breast cancer. Caligi et al [10] studied embryonic cell line with a 10 fold decrease in hMSH2 levels. These cells were RER negative and had no MSI, but they were found to be resistant to toxic effects of methylating agent MNNG. Instead these cells were highly sensitive to mutagenic effects of methylating agent. Cejka et al [11] have reported that human embryonic kidney cell lines, not expressing high levels of hMLH1 failed to arrest upon methylating agent MNNG treatment. Contellino et al [12] reported that MED1 gene, a base excision repair enzyme is associated with integrity of MMR system. It was found that MED1 negative phenotype had decreased cell cycle arrest and apoptosis induced by DNA damage. They also have resistance to MNNG (-) and 5-FU and a few other cytotoxic drugs.

The association between breast cancer and MMR genes is far from clear in the present scenario. A lot of focused research has to be done to clear all the doubts. However, if proven it could provide access to alternate therapy and prophylaxis for this deadly disease.

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Multidisciplinary approach to meeting the Information Needs of women with Breast Cancer

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Abstract: Patients with breast cancer have very high information needs especially about their disease, likelihood of cure, the treatment of their disease, investigative tests, and amongst these all; prognosis is one such area about which patients with breast cancer ask questions. Several studies have found that younger women have continued needs for information about future fertility, coping with changes to sexuality, management of premature menopause, preventive treatments, genetic counseling, diet, exercise and complimentary therapies and this persists for several years even after treatment ends. Unmet information needs can lead to depression, anxiety, psychological problems, repression of emotions and undue fears that may hamper the patient's treatment regime and have significantly effect on her coping skills, compliance patterns and health recommendations. The objectives of the study were to provide psychosocial information to patients with breast cancer and to assist their families cope with diagnosis and prognosis. It also aimed to establish a comprehensive approach to patient education within breast cancer center so as to help patients assess hospital and community services in a timely manner and it also facilitated their participation in treatment and continuity of care across multiple settings. The New Patient Information NPI and Patient Information Organizer PIO (NPI/PIO) was developed to respond to information needs and information management needs of women with Breast Cancer. All the women were asked to study it and a 20 minute telephone-survey at 1 month (T1) and 6 months (T2) post receipt NPI/PIO was undertaken namely investigator- developed survey which included 23 questions. The data was analyzed subsequently and it revealed that women were very much satisfied with the NPI and stated that it helped them to cope, they had satisfaction with their treatment decisions, it decreased their anxiety and depression patterns and brought about new degrees of hope. PIO helped them to organize and manage wide range of information they received throughout their continuum of care. Results also reveal that nurses and other health care professionals not only play a very significant role by providing information to patients and their families and hence alleviating their apprehensions, fears, anxieties and concerns but at the same time they also support cognitive strategies by which patients can cope with more effectively with treatment related strategies.

Key words: *Breast cancer, information needs.*

Introduction

Many people with cancer want detailed information about their cancer, diagnosis, prognosis and treatment options and women with breast cancer are amongst those with the strongest information needs¹. A diagnosis of breast cancer and the ensuing treatment are new experiences for most women and it is clear from a number of studies that they have high information needs irrespective of the type of treatment they receive². Infact, information seeking has been identified as a coping strategy of the breast cancer "survivor personality"³. Information allows one to discriminate the safe from the unsafe, to make the appropriate preparatory responses and to reduce the inherent aversive ness of being on a state of uncertainty. Information is the key to acceptance and help with anxiety and fears⁴. Unmet information needs are believed to increase emotional distress for patients (e.g. increased anxiety and depression), psychosocial complaints and subsequently hamper patient's adjustment to their illness⁵. depression and anxiety can interfere with cognitive functioning and adherence to health recommendations^{6,7}. Patients with cancer who receive information report benefits including increased satisfaction with treatment choices, increased satisfaction with patient-doctor interactions and decreased levels of anxiety and distress⁸. a decrease in hospital admissions, length of stay and medication usage was reported when patients in a general medical ambulatory practice received regularly scheduled telephone calls

from a member of the health care team⁹. The role of nurses in informing patients seemed to be important even before hospitalization¹⁰. The need for creative, innovative and flexible programs to provide patients with information before the procedure to allay patients fears, and to plan for discharge in this setting is a major challenge in the field of surgical oncology¹¹. The New Patient Information NPI and Patient Information Organizer PIO (NPI/PIO) were developed to respond to information needs and information management needs of women with Breast cancer.

Materials and Methods

Sixty three (63) women with Breast cancer, irrespective of their stage of cancer were selected and New Patient Information Package and Patient Information Organizer (NPI/PIO) was distributed to them at the Breast Center, Princess Margaret Hospital (PMH), Toronto, Canada. All the women were asked to study it. 20 minute telephone-survey at 1 month (T1) and 6 months (T2) post receipt of New Patient Information Package and Patient Information Organizer (NPI/PIO) was undertaken. Survey included 23 questions and was named investigator- developed survey. 6 questions collected demographic information and the rest other questions were asked about participant's satisfaction with content, readability and use of information provided and impact of NPI/PIO on their coping. The data was then statistically analyzed and patients satisfaction with NPI/PIO at 1 month and 6 months interval was made.

Results

Table 1 : Patient Satisfaction– NPI T1 : N = 63; T2 : N = 48

S No	Patient Satisfaction : NPI	T1 %	T2 %
1	Easy to understand	95	100
2	Shared with family/friends	57	69
3	Helped with coping	70	79
4	Had no effect on coping	21	19
5	Didn't help with coping	9	2
6	Should be continued	92	98

95% of patients at T1 and 100% of patients at T2 found the NPI easy to understand. 70% of women at T1 and 79% at T2 reported that NPI helped them with coping. More than half of the patients shared the NPI with family and friends. More than 90% of women agreed to the fact, that it should be continued and also stated that it was quite easy to understand.

Table 2 : Patient Satisfaction– PIO T1 : N = 63; T2 : N = 48

S No	Patient Satisfaction PIO	T1 %	T2 %
1	Helped with organizing health care information	65	40
2	Should be continued	84	79

At T1, 65% of participants reported that PIO helped them to keep track of their health care information. At T2, 40% of participants were still using the PIO to help them manage the health care information. At T1, 84% of participants desired their willingness that PIO should be continued whereas at T2, 79% participants desired their wish to continue PIO.

Table 3 : Patient Satisfaction Survey with NPI/PIO– Participant Demographics T1 : N = 63; T2 : N = 48.

		T1 %	T2 %
Age (yrs)	30 – 49	29	29
	50 – 69	54	52
	> 70	14	19
Education	High School	33	38
	College/University	59	60
First Language	English	92	100

In the age group 50 – 69 yrs, as many as 54% of participants at T1 and 52% at T2 expressed their satisfaction with NPI/PIO. As many as 59% participants at T1 and 60% participants at T2 having University education expressed their satisfaction with NPI/PIO.

Table 4 : Nurse Satisfaction Survey with Management of NPI/PIO (N = 4).

1	Storage of Materials	Yes
	NPI/PIO always available	100%
2	Distribution of NPIs	
	No difficulties encountered with distribution	100%
	Time available to review contents with patients	75%
3	Contents of NPI	
	Satisfaction with contents and format	75%
4	PIO	
	Satisfaction with information organizer	75%

All nurses reported that NPI/PIO was always available and they did encounter any difficulty with distribution of NPI/PIO to patients. Three nurses also indicated that they were always able to review the NPI contents with their patients.

The women who were surveyed in 3 months reported that New Patient Information Package (NPI) and Patient Information Organizer (PIO) helped them to organize and manage the wide range of information they received throughout their continuation of care.

Discussion

It is obvious that most patients prefer to be well informed about their situation¹²⁻¹⁵, because they use cognitive mediation to cope with stressful events¹⁷⁻¹⁹. Lack of knowledge about breast cancer may be source of considerable patient anxiety or may contribute to a “wall of silence” where energy used for repression and denial drains the patient of important energy resources needed for recovery²⁰; hence there is need to develop and establish a comprehensive approach to patient education within the Breast Cancer Center where patient and their families get enough information to allay their fears and concerns related to diagnosis, investigations, treatment, likelihood of cure and prognosis and keeping all these in view, NPI/PIO was developed.

Patients with cancer who have the opportunity to participate in treatment decision making have accrued benefits including decreased anxiety and depression, increased satisfaction with treatment decisions and care received and a high degree of hope²¹. There is increased treatment with compliance and follow up in patients²². Similar results were found in this study where 70% of women at T1 and 79% at T2 reported that NPI (New Patient Information) helped them with coping and they discussed it their family and friends also. The need for creative, innovative and flexible programs to provide patients with information before the procedure to allay patients fears and to plan for discharge in this setting is a major challenge in the field of surgical oncology¹¹. Formalized patient education programs need to be available with referrals to support groups, education programs, individual counseling and Reach to Recovery should be introduced early in the illness in both written and verbal form in order to accessible when timing is appropriate for the individual³. This correlates with our study also where at T1, 65% of participants reported that PIO (Patient Information Organizer) helped them to keep track of their health care information. At T2, 40% of participants were still using the PIO to help them manage the health care information. To ensure a satisfactory balance between recall, understanding and patient well being, supplementary information may be most beneficial when provided on an individual basis²³. In the present study more than 90% of participants at T1 and T2 were satisfied with NPI and wanted that it should be continued and similarly with PIO, majority of the patients were satisfied and wanted that supplementary information be provided to patients on an individual basis. By addressing such information needs, healthcare professionals will not only fulfill a basic responsibility to those being treated but they also support cognitive strategies by which patients can cope with more effectively with treatment related strategies²⁴. In the present study nurses and volunteers played a significant role in distributing of NPI/PIO and 75% of nurses discussed the contents of NPI/PIO with patients and were also satisfied with the contents and the format of NPI/PIO.

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IMSA News

IMSA Chapter Activities Jan-March 06

Delhi Chapter

- 05.02.2006 : Dr. S.C. Devgan : "Clinical Meeting" at Hindu Rao Hospital in collaboration with Delhi Rheumatology Association.
- 04.03.2006 : Col. V.P. Chaturvedi, "Clinical Meeting" in collaboration with Delhi Rheumatology Association at Army Hospital Research & Referral, New Delhi in collaboration.

Tamil Naidu Chapter

- 08.01.2006 : Dr. P. Chandra, "Politics of Primary Child Health Care".

12.02.2006 : Dr. A. Govindan, "Recent Trends in Imaging Sciences"

12.03.2006 : Dr. Jose M. Eason, "Blood and Marrow Transplantation".

Rural CME T.N. Chapter

- 19.02.2006 : Dr. V. Kannan, "Management of Obesity"
: Dr. V. Sethu, "Burns - Intial Management" and "Obesity - Surgical Management".
Venue : Madurantagam (Tamil Nadu)

Fellows and Members elected during Jan-March 06

Fellows

Dr. Shubha Sagar Trivedi
Dr. R. Umarani
Dr. Neeta Singh
Dr. Ravi Kashyap
Dr. H.P. Pati
Dr. Prof. Anita Chakravarti
Dr. Sanjay Mittal
Dr. Raj Kumar Lalwani
Dr. Wing. Commander V.G. Vasishta

New Delhi
Tamil Nadu
New Delhi
New Delhi
New Delhi
New Delhi
New Delhi
New Delhi
Bangalore

Dr. G.D. Goel
Dr. Amit Goel
Dr. (Mrs.) Vibhu Mendiratta
Dr. W. Selvamurthy
Dr. S.K. Verma

Members

Dr. Nikhil Agarwal
Dr. Prateek Kumar Mehrotra
Dr. Tejas Modi

New Delhi
New Delhi
New Delhi
New Delhi
Udaipur
New Delhi
Lucknow
Gujarat

Honours

H Dr.Chintamani has been awarded Honorary Fellowship of the Royal College of Surgeons of Edinburgh (FRCS) for his outstanding contribution in the field of surgery Dr. Chintamani is seen receiving the award from the President of Royal College of Surgeon of Edinburgh Mr. R. JAR Smith.



H Dr. Tarun Gupta Additional Secretary General IMSA, has been unanimously elected as President elect of Indian Medical Association, New Delhi Branch, for the year 2006-2007.

Dr. Tarun Gupta as also been elected Honorary Secretary of Rotary Club of Delhi, Chanakya Puri, New Delhi(R.I.District-3010) for the year 2006-2007.

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Special Issue : Advances in Breast Cancer Management*Guest Editor : Dr. Chintamani***Jan.-March 2006****VOL.19 No.1**

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