A STUDY OF LOCALLY ADVANCED BREAST CANCER

DISSERTATION SUBMITTED FOR M.S.GENERAL SURGERY DEGREE EXAMINATION

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CERTIFICATE

This is to certify that this dissertation titled **"STUDY OF LOCALLY ADVANCED BREAST CANCER"** is a bonafide work of Dr.G.M.Niban, and has been prepared by him under our guidance, in partial fulfillment of regulations of The Tamilnadu Dr. M.G.R. Medical University, for the award of M.S. degree in General Surgery during the year 2007.

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CONTENTS

INTRODUCTION

Carcinoma breast is one of the most common cancers afflicting the females. The presentation of carcinoma breast gives as varied a panorama as the surgical field itself. Locally advanced carcinoma breast is one of the most common modes of presentation of carcinoma breast in the surgical wards. The lack of awareness in the general populace regarding breast lumps in general and the explicit mode of presentation of LABC contribute to the plethora of forms of appearance of this disease.

The various modalities of therapy offered to patients with LABC and the synchronized mode of treatment protocol are needed to ensure adequate control of morbidity and mortality of this disease. The fine line between wide-spread metastasis signifying a death sentence and an eminently controllable situation epitomized by LABC is of primal importance in the study and therapy of breast cancer. The slowly increasing incidence of LABC in the general female populace also stresses the need to gain more insight into the behavioral pattern of this dreaded disease. The importance of adjuvant therapy in the form of chemo/radio/endocrine and the modality of administration of the

same and the type of surgical remedies offered are also in need of critical evaluation

This study is an attempt to understand the profile of the disease as is epitomized in the presentation of the LABC in Tirunelveli Medical College Hospital and an effort has been made to analyze the disease in its entirety. It also entails a comparison to the picture of LABC in clinical situations in other institutions.

AIMS AND OBJECTIVES

The aims of this study are epitomized as follows:

a) To study and understand the factors in the patho physiology of the LABC and evaluate the factors responsible.

b) To analyze the variables involved in the causation and etio pathogenesis of locally advanced breast cancer.

c) To understand the importance of the various risk factors involved in the interplay of manifestations of this disease

d) To evaluate the efficacy of multimodality treatment as provided in this institution

e) To compare the efficiency of treatment protocols by way of incidence of loco regional recurrences.

MATERIALS AND METHODS

This study is based on the follow up of patients with locally advanced breast cancer who were studied during the period between July 2004 and July 2006.

A total of one hundred and fourteen patients under went surgery for symptoms and diagnosis of carcinoma breast, of which thirty-nine patients who had locally advanced breast cancer were studied in detail as they presented for regular follow-up at Tirunelveli Medical College Hospital.

The selection criteria of patients were based on the TNM classification of breast cancers from stage II B, stage III A and stage III B were selected.

The modalities of diagnosis and treatment of breast cancer as is being done in Tirunelveli Medical College Hospital forms the crux of this study.

Meticulous history followed by thorough clinical examination and routine biochemical and radiological examinations, invasive procedures for diagnosis like FNAC formed the basis of stratification of patients.

The investigative protocols of hormonal receptor assay and sentinel nodal biopsy were not applied due to their non-availability in this institution.

Patients were followed up as they underwent various modalities of treatment in the form of surgery, neoadjuvant and adjuvant chemotherapy and radiotherapy supplemented by hormonal therapy.

No attempt was made to modify the treatment protocols of the various units under whose care these patients were treated. An effort has been made to study the profile of locally advanced breast cancer as managed in Tirunelveli Medical College Hospital

REVIEW OF LITERATURE

LOCALLY ADVANCED CARCINOMA BREAST

HISTORICAL ASPECTS

The breast has always been a symbol of womanhood and fertility. Cosmetic considerations and fear of infertility have always hindered early diagnosis and prompt treatment of disorders of the breast.

Breast diseases have been in vogue since the times of Herodotus and Democedes(525 B.C.) The Edwin Smith surgical papyrus (3000-2500B.C.) makes special mention of breast disorders. Aulus Celsus in the first century A.D. and Galen provide detailed accounts of treatment of carcinoma breast. Leonides of Alexandria was the first to stress the importance of retraction of the nipple in breast cancer

Caustics were the treatment modalities in the times of the Egyptians, Romans and Greeks. Paul of Aegina(625),Vasalius(1514) give detailed descriptions of amputation of breast. Ambroise Pare(1510-1590) the great French surgeon treated breast lumps with wide excision.

With the description of François Le Dran regarding spread of tumor to lymphatics surgeons like Petit skillfully and successfully

attempted block dissection Sir James Paget's treatise in 1836 provided rare insights into the realm of breast diseases. Charles Moore in 1867 with the advantage of microscopic pathology underlined the importance of tumor free margins.

Though Volkmann (1875), Gross (1880), Banks, Sprengel (1882) and Kuster (1883) gave broad outlines regarding radical mastectomy it remained for Halstead and Meyer to propound the nuances of radical mastectomy as a form of definitive cure for breast cancer in 1894

Subsequently more conservative procedures were adopted by McWhirter(1948),Patey(1948) and Madden(1965)witnessing a paradigm shift in breast cancer treatment. [01]

With the acclamation of the Fisherian theory (1985) the focus has now shifted to less mutilating surgeries supplemented with multi modality therapy.

The advent of sentinel nodal biopsy for breast cancer in the mid-90's has revolutionized treatment procedures.

Improvements in administration of radiotherapy, chemotherapy and endocrine therapy from Sir Astley Cooper's time in 1836 to use of fulvestrant as a estrogen receptor down-regulator have made breast

cancer a less frightening disease for patients and a more manageable disease for surgeons. The advent of modern diagnostics and the role of reconstructive surgery have also played an important role in reduction of morbidity and mortality from breast cancer.

BREAST EMBRYOLOGY

It is essential that the surgeon dealing with breast abnormalities must be familiar with their embryologic antecedents, for only through this knowledge can variations in glandular location, shape or number and rationale for surgical maneuvers be appreciated. The breast is considered as a modified sudoriferous gland which develops as ingrowths from the ectoderm supported by vascularized mesenchyme .In the fifth to sixth weeks mammary ridges develop extending from axilla to inguinal region, the human mammary glands develop from the pectoral aspect of these ridges. Supernumerary rudiments develop along the path of the mammary ridges.[02]

As each mammary primordium develops, its ectodermal ingrowths develop into 15-20 solid buds of ectoderm to form the eventual lactiferous ducts and their associated lobes of alveoli in the fully formed gland. These are surrounded by mesenchyme which forms

the connective tissue, fat, vasculature and is invaded by nerves. By proliferation, elongation and further branching, the alveoli are formed and the duct system defined. During the last two months of gestation the ducts become canalized and the epidermis at the point of original development of the gland forms a small mammary pit into which the lactiferous ducts open. Perinatally the nipple forms by mesenchymal proliferation. At birth the mammary glands are similar in both sexes but in females at puberty, pregnancy and lactation they undergo further hormone dependent developmental changes[03]

DEVELOPMENTAL ANATOMY

The normal breast is composed of ducts and lobules lined by two cell types ,a low flattened discontinuous layer of contractile cells containing myofilament cells on the basement membrane assisting milk ejection and a second layer of epithelial cells lining the luminal surfaces. the luminal cells of the terminal duct and the lobule produce milk but those lining the large duct system do not. A committed stem cell in the terminal duct is postulated to give rise to both luminal and myoepithelial cells.

Six to ten major ducts originate at the nipple. Successive branching of large ducts leads to the terminal duct lobular unit (TDLU). In the adult female the terminal duct branches into grape-like cluster of small acini to form a lobule[04]

The uniqueness of the breast lies in the cyclic changes that occur during the reproductive life

The prepubertal breast in males and females has minimal lobule formation. at the beginning of menarche lobular formation and interlobular stromal development occurs, there is a paucity of adipose tissue and the breast appears radio-dense. There is a proliferative and apoptotic activity in consonance with the menstrual cycle.

With pregnancy there is a reversal of the lobular stromal ratio due to proliferation of lobules. After cessation of lactation the lobules regress and atrophy, however there is a permanent increase in the size and number of lobules.[05]

Involution starts after the third decade, the lobules almost totally disappear creating a morphologic pattern resembling the

male breast the increase in adipose tissue contributing to the radiolucent pattern in mammograms

OVERVIEW OF ANATOMY

The mature female breast extends from the level of second rib to the inframammary fold at the level of the sixth or seventh rib laterally extending from the sternum to the anterior or mid-axillary line. The deep surface lies on the investing fasciae of the pectoralis major, serratus anterior and external oblique muscle and upper extent of the rectus sheath.the axillary tail of Spence extends into the anterior axillary fold.the upper outer quadrant contains more glandular tissue than the rest of the breast.

The glandular portion of the breast forms a protuberant cone about 10 to12 cm in diameter and 5 to 7 cm in thickness. A typical non-lactating breast weighs between 150 and 225 grams.[03]

The breast of the nulliparous female has a typical hemispheric configuration with a flattening above the nipple. With pregnancy and lactation the breast increases in size and becomes

more pendulous. As age increases the breast becomes flattened and less firm with a decrease in volume.

The breast is located in the hypodermis, the layer deep to the dermis. In approaching the breast the dissection is done in this plane which is bloodless, raising a flap of thickness of about 2 – 3 mm. The blood vessels and lymphatics passing in the deeper layer of the superficial fascia are left undisturbed.[06]

Anterior fibrous processes, the suspensory ligaments of cooper pass from the septa that divide these lobules to insert into the skin. Posteriorly the separation from the pectoral fascia is by the retro mammary space or bursa. The two structures allow the breast to move freely against the thoracic wall. Connective tissue thickenings, the posterior suspensory ligaments attach the deep surface of the breast to the pectoralis fascia, hence the common practice to remove the adjacent portion of the pectoralis major with the breast tissue. As the breast extends into the axilla ,it has contact with the deep fascia of that region.

The working knowledge of the anatomy of the axilla is of paramount importance in breast surgery. The axilla is a pyramidal compartment having four walls, an apex and a base. The base is formed by the axillary fascia and skin, the apex leads to the cervico-axillary canal, the anterior wall is formed by the pectoralis major, posterior wall by the subscapularis, the lateral wall by the bicipital groove of the humerus and the medial wall by the serratus anterior and the thoracic wall.

The contents of the axilla are the great vessels of the upper extremity closely associated with each other and enclosed within the axillary sheath. Apart from the axillary artery and its branches, the axillary vein and its tributaries, the brachial plexus is very vulnerable during axillary dissection especially the ansa pectoralis [07] (communicating branch between lateral and medial pectoral nerves),[08]the long thoracic nerve causing paralysis of the serratus anterior and the intercostobrachial, a nerve commonly injured in axillary dissection causing numbness over the medial aspect of the arm.

BLOOD SUPPLY

The breast receives its blood supply from the perforating branches of the internal mammary artery ;lateral branches of the posterior intercostals arteries; and several branches of the axillary artery including highest thoracic, lateral thoracic and pectoral branches of the thoracoacromial artery

Branches from the second, third ,and fourth anterior perforating arteries pass to the breast as medial mammary arteries,these vessels enlarge during lactationthe lateral thoracic artery gives rise to the lateral mammary branches; in the second ,third and fourth intercostals spaces the posterior intercostals arteries give off the mammary branches, all these vessels also enlarge during lactation.

The thoracodorsal branch of the subscapular artery though not of importance in the supply to the breast is intimately associated with the central and scapular group of lymph nodes and may cause major bleeding that is difficult to control during lymph node dissection.[09]

The venous tributaries follow the pattern of arterial supply and drain chiefly to the axilla the superficial veins around the nipple form

the circulus venosus from which blood passes through the substance of the breast and reaches the periphery into the principal group of veins. Metastatic emboli reach the lungs through this direct venous route.the posterior intercosyal vessels are in direct continuity with the posterior vertebral plexuses of veins and these open a second portal of channel for direct metastasis to the vertebral bodies, ribs , and central nervous system[10].

Sensory innervation of the breast is supplied primarily by the lateral and anterior cutaneous branches of the second through sixth intercostal nerves;a small segment superiorly is supplied by the supraclavicular nerves.the intercostobrachial,lateral and medial mammary nerves also complete the nervous innervation.[11]

LYMPHATIC DRAINAGE OF BREAST

The lymphatic drainage is of utmost importance in the study of carcinoma breast. Anatomically defined lymphatic groups are

(1) **Lateral /axillary vein group**-four to six lymph nodes lying medial or posterior to the axillary vein draining the upper extremity except those that

drain into the deltopectoral lymph nodes the infraclavicular group

(2) **Anterior/Pectoral/External mammary group**-four to five nodes that are situated along the lower border of pectoralis minor receiving the major lymphatic drainage from the breast. Lymph from these nodes flow to the central group of nodes ; some may pass to the subclavicular nodes

(3) **Subscapular/Posterior/Scapular group**-six to seven nodes along the posterior border of the axilla at the lateral border of scapula receiving flow from the posterior aspects of the neck, trunk and scapula passing to the central and subclavicular nodes

(4) **Central group**- three to four large nodes embedded in the fat of the axilla posterior to the pectoralis minor muscle. Commonly palpable as they are superficially placed hence allowing estimation of

metastatic disease. Lymph from these nodes passes to the subclavicular nodes.

(5) **Subclavicular/Apical nodes**- six to twelve nodes located partly posterior and partly superior to the pectoralis minor extending to the apex of the axilla along the medial side of the axillary vein receiving lymph from all other nodes either directly or indirectly. The efferents pass to the subclavian trunk hence passing to the thoracic duct on the left and right lymphatic trunk

(6) **Rotter's/Interpectoral nodes**- one to four lymph nodes located between the pectoralis major and minor passing to the central and subclavicular nodes

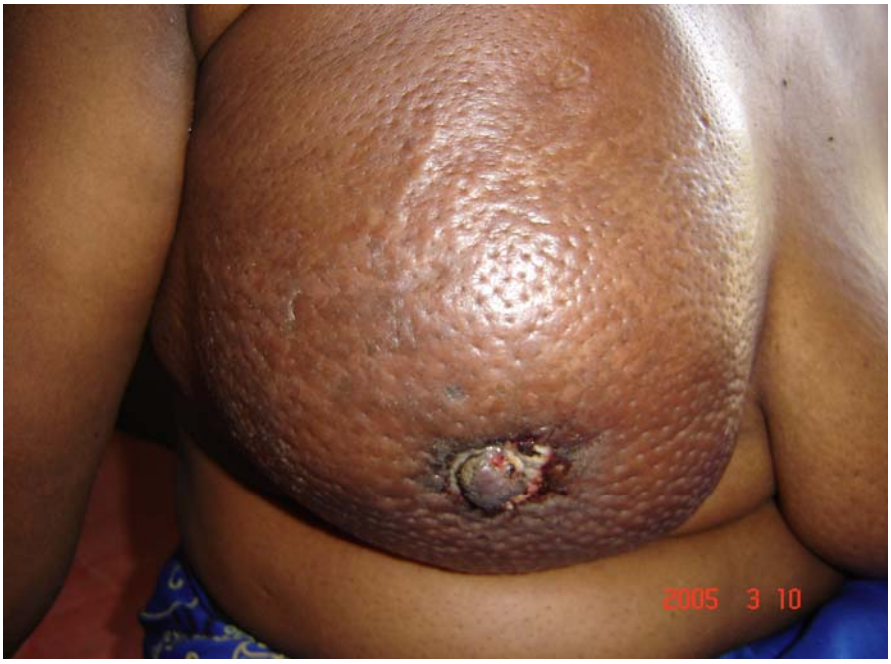
The surgical definition of the axillary lymph nodes is defined by their relationship to the pectoralis minor muscle. Lymph nodes located lateral or below the lower border of the muscle are labeled **level I** and include the external mammary, axillary vein, scapular lymph node groups. The central and some of the subclavicular nodes located deep or posterior to

the pectoralis minor are labeled **level II**. Those lymph nodes located medial or superior to the muscle are called **level III** and include the subclavicular lymph node group.[12]

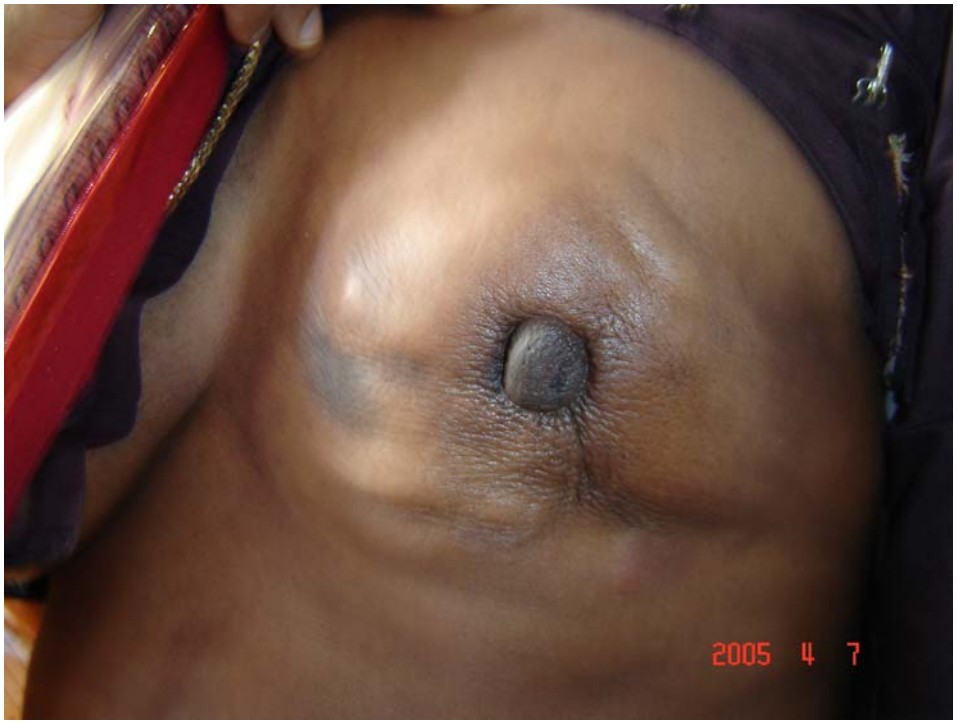
Lymph nodes of the thoracic wall and those draining the thoracic cavity namely the parasternal, intercostals,diaphragmatic, anterior mediastinal, posterior mediastinal, and tracheobronchial also are eminently involved in the spread of cancer cells in cancer breast.

The **internal mammary nodal group** anatomically situated in the retrosternal interspaces between the costal cartilages near the sternal margin and the **supraclavicular lymph nodes** representing the termination of the major lymphatic trunks situated beneath the lateral margin of the inferior aspect of the sternocleidomastoid beneath the clavicle represent common sites of distant metastasis in mammary carcinoma.

PEAU D'ORANGE



SKIN INFILTRATION



CLINICO-PATHOLOGIC CONSIDERATIONS

Clinico-pathologic considerations play an important role in prediction of long term outcome in patients with breast cancer. Generally accepted prognostic factors include

Clinical factors

Clinical staging is based on a thorough physical examination of the breast tissue, skin overlying the breasts, regional lymph nodes and various imaging modalities. Important characteristics in physical examination are tumor size, extension into chest wall, overlying skin (erythema, edema, ulceration) and the regional lymph nodes; mobility of which is an important prognostic indicator with fixed nodes having a worse prognosis. Imaging modalities such as mammograms, CT scans, serve as adjuncts to physical examination, newer imaging options include digital mammography, MRI scans and PET[13].

PRIMARY TUMOR CHARACTERISTICS

(a) AGE

The influence of age and menopausal status at diagnosis on the prognosis of patients with primary breast cancer remains controversial. Some studies have found that younger patients have

worse clinical outcomes than older patients. Others have reported that younger patients have a more favorable outcome. Still others have found no relation between outcome and age. Explanations for these conflicting results have included small numbers of patients in the studies, differences in patient selection, and differences in the age groupings used in the analyses.

(b) TUMOR SIZE

Defined as the maximal size of the invasive component of the primary tumor on pathologic specimen. Clinical examination of size has been included as an independent predictor for survival. Metastasis does not occur until a size of 3.6 cm diameter is reached. Axillary nodal metastasis occurs more consistently when tumor size is 3.1- 4.0 cm in diameter. Disease free survival and overall prognosis is also dependent on tumor size.[14]

(c) TUMOR LOCATION

In patients with negative nodes location plays an important role in defining prognosis. The risk of axillary metastasis increases in lateral versus medial cancers. Studies also indicate that medial and

central locations are associated with two-fold increase in developing systemic relapse and breast cancer related death due to risk of occult spread to the internal mammary nodes.[15]

(d) TUMOR HISTOLOGY

The histologic classification of malignant breast tumors include

EPITHELIAL TUMORS

carcinoma, NOS (not otherwise specified)

ductal

intraductal (in situ)

invasive with predominant intraductal component

invasive, NOS

comedo

inflammatory

medullary with lymphocytic infiltrate

mucinous (colloid)

papillary

scirrhous

tubular

other

lobular

in situ

invasive with predominant in situ component

invasive

nipple

Paget's disease, NOS

Paget's disease with intraductal carcinoma

Paget's disease with invasive ductal carcinoma

other

undifferentiated carcinoma

MIXED CONNECTIVE TISSUE AND EPITHELIAL TUMORS
MISCELLANEOUS TUMORS
UNCLASSIFIED TUMORS[16]

Of the malignant tumors, the medullary, papillary, and colloid subtypes have a better prognosis than do ductal invasive tumors Hoge and colleagues classify tumors based on histologic characteristics as

]

CLASS A all in-situ lesions 91% 5-yr survival

CLASS B medullary, mucinous, tubular,adenoid cystic 75% 5-yr survival

CLASS C infiltrating ductal and lobular carcinomas 66% survival

CLASS D inflammatory and undifferentiated carcinomas 33% survival rate[17]

(e)TUMOR GRADE

Histologic grading is based on Bloom and Richardson's criteria such as size, shape and hyperchromatism along with percentage and number of mitotic figures and tubules. Survival was estimated to be 41% for grade 1, 29% for grade 2 and 21% for grade 3. The SBR grading system consists of three components (degree of differentiation, extent of pleomorphism, and mitotic index), each scored on a scale from 1 to 3. The degree of differentiation is evaluated according to the ability of the tumor to form tubular, glandular, or papillary formations. Pleomorphism describes the shape of the nuclei, with particular attention to irregular cells distorted in size. The mitotic index evaluates the number of mitoses found in the tumor

specimen. The scores for the three components are summed and categorized as grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated). A modified SBR (MSBR) system considers only the extent of pleomorphism and the mitotic index, and rearranges the scoring system to yield five classifications of nuclear grade.[18]

Fisher's grading system includes a combined assessment of nuclear grade and the presence of tubule or gland formation. Nuclear grade considers nuclear size, shape, nucleolar content, chromatin pattern, and mitotic rate. Although histologic grading is only applicable to the invasive component of ductal carcinomas, the nuclear grade can be determined on all components of all histologic types of breast cancer.[19]

(f) RECEPTOR STATUS

Receptor status forms an important aspect of determining the prognostic evaluation in breast cancer. ER and PR positivity correlates with better prognosis and response to chemotherapy with nor without use of tamoxifen. Another study

indicates longer survivorship for patients with PR positive tumors compared to PR negative cohorts[20]

(g) LYMPH NODE STATUS

The presence of lymph nodes obviously indicates a worse prognosis but the location of positive nodes is also of primal importance. Involvement of apical axillary and infraclavicular nodes indicate grim prognosis. Internal mammary nodal involvement markedly decreases overall survival. Supraclavicular nodes are considered to indicate systemic spread but recent studies indicate survival rates that parallel those with locally advanced disease. Data indicate that metastasis to nodal groups other than regional suggest the presence of systemic disease.[21]

(h) LOCALLY ADVANCED /INFLAMMATORY CANCER BREAST

Tumors invading into skin or skeletal muscle are associated with concurrent or subsequent systemic disease. Women presenting with clinical appearance of breast swelling and skin induration (inflammatory breast cancer) have a particularly poor prognosis with 3 year survival rates of only 3% to10%

(i) LYMPHOVASCULAR INVASION

Tumor cells may be seen within vascular spaces surrounding tumors. This finding is strongly predictive of lymph node metastasis and associated with a poor prognosis.Presence of tumor cells in dermal lymphatics is strongly associated with inflammatory breast cancer and a poor prognosis.

(j) BIOLOGIC FACTORS

Biologic prognostic factors include

(1) Angiogenesis -VEGF

(2) Proliferation –(MIBI/Ki67/TLI)

(3) Growth factor receptors- EGFR/cerbB2/cneu

(4) Cellcycle regulators-p53/c-*myc*/cyclins

(5) Proteases- urokinase/plasminogen activator/cathepsin D

(6) Metastasis proteins –laminin 67kDa receptor/nm23

(7) Heat shock proteins-

(k) OTHER CHARACTERISTICS

(1) Age at menarche-

Women reaching menarche before 11 years of age have a 20% increased risk compared to those attaining menarche at 14.

(2) First live birth

Women with a first full term pregnancy at less than 20 years of age have half the risk compared to nulliparous women or those over the age of 33.

(3) Heredity/familial breast cancer

First degree relatives, presence of BRCA-1, BRCA-2 in families pose increased incidence risk and likelihood of breast cancer.

(4) Race

Risk of developing breast cancer is high in Caucasians compared to Asian descendants.

(5) Breast biopsies

Increased risk seen in prior breast biopsies showing atypical hyperplasia.

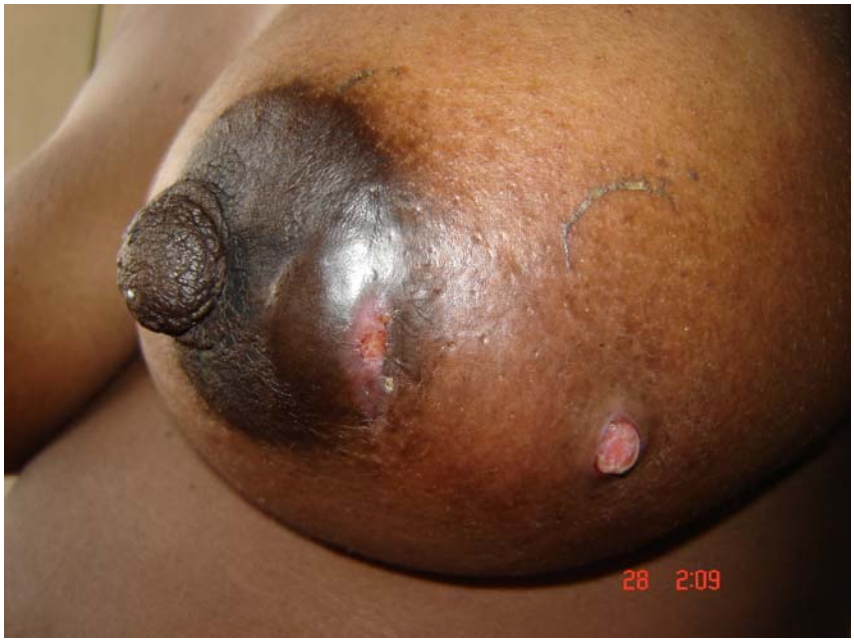
(6) Miscellaneous risk factors.

Estrogen exposure/ radiation exposure/carcinoma of contra lateral breast or endometrium/breast feeding increase risk of breast cancer. Geographical influence,diet,obesity,

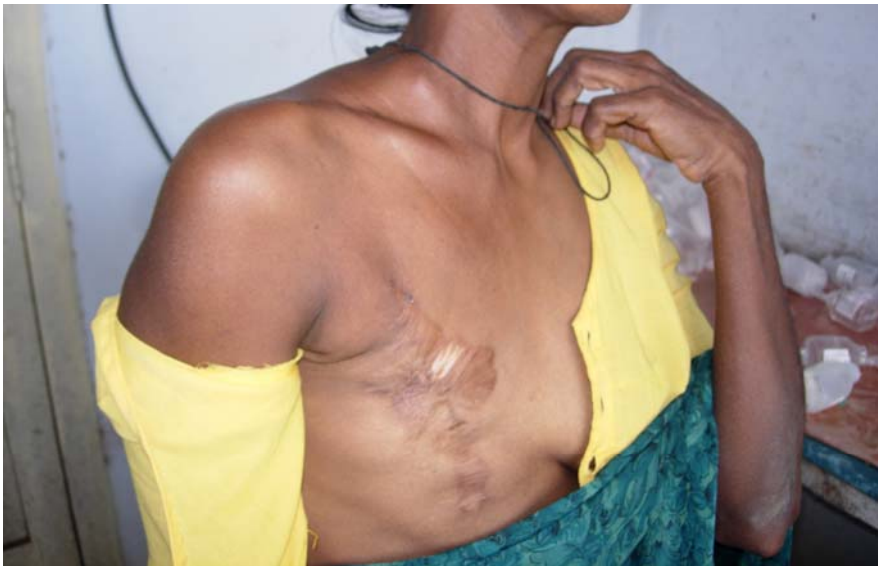
exercise,environmentalcontaminants/pesticides,tobacco(periductal mastitis) also pose increased risk.

Accurate diagnosis of breast cancer is critical before treatment and management decisions can be made. The diagnosis should clearly differentiate between invasive and noninvasive breast tumors, and it should include a description of the histologic subtype. The prognosis of the patient can then be estimated based on axillary lymph node status, pathologic tumor size, nuclear or histologic grade, and rate of proliferation. ER and PR status can be used to determine the likelihood of response to endocrine therapy. Even if a decision is made not to administer adjuvant endocrine therapy, determination of ER and PR status at the time of diagnosis provides valuable information in the event that the patient subsequently has a recurrence of breast cancer. If trastuzumab (Herceptin) or another anti–HER-2/neu antibody therapy is among the potential treatment options, determination of HER-2/neu status is also recommended.

ULCER BREAST



POST MASTECTOMY



OVERVIEW OF BREAST CANCER

The most common clinical presentation of breast cancer is usually a lump in the breast identified mostly by the patient and occasionally by the physician. More than 66% of cases of breast cancer present as a lump in the breast 11% as a painful breast mass, 9% as nipple discharge, 5% as nipple retraction, and 4% as local edema. Other less common modes of presentation are ulceration of the breast, local erythema, arm edema, breast abscess, skin puckering..

Breast cancer is most commonly located in the upper outer quadrant of the breast (47-50%). The upper inner quadrant is the site in 12 to 15% of cases, the lower inner in 2-5%, and the lower outer in 6-12% of presentations. Centrally located lesions, beneath the nipple and areola presenting as Paget's account for 15-22% of cases. An overall left preponderance has been repeatedly noted in various studies.

The accuracy of diagnosis of breast cancer diagnosis by physical examination is 70% in most experienced hands. Tumors need to reach a size of about 1 cm to become palpable. Estimates of calculations

indicate that it takes approximately 5 years to reach this size from a single cell stage.

Examination of both breasts and the axillae in meticulous fashion helps immensely in accurately to stage the tumor to help plan the modalities of further treatment. A search should be made for secondary deposits in the liver, lungs and bones. Rectal and vaginal examinations are also necessary to detect distant metastasis.

Prominent veins in the region of tumor are indicative of blockade of venous return. Edema of the arm, edema of skin, peau d'orange appearance, satellite nodules are suggestive of tumor infiltration into sub-dermal and dermal lymphatics. Cervical sympathetic chain involvement is diagnosed by appearance of Horner's syndrome

INVESTIGATIVE MODALITIES

Apart from meticulous clinical examination various investigations are utilized to ascertain the exact stage of tumor to plan treatment.

(a) MAMMOGRAPHY

The primary role of mammography is to screen asymptomatic women with the goal of detecting breast cancer at a smaller size and earlier stage than the woman's own surveillance or her doctor's

routine examination might ordinarily achieve. Mammography is also used to evaluate women with palpable abnormalities; however, its use in this setting is limited. The mammogram may reinforce the diagnosis of cancer and help avoid overlooking a malignancy.

(b) ULTRASOUND

The routine use of ultrasound in the evaluation of palpable masses is controversial. From a purely scientific perspective, the use of ultrasound to evaluate palpable masses should be limited to those that have resisted aspiration but are still believed to be cysts. On occasion, a cyst may have a thick wall or be sufficiently mobile to defy clinically guided aspiration. The demonstration by ultrasound that these lesions are indeed cysts can avoid an excisional biopsy. Unfortunately, because a number of medicolegal cases have been decided or settled against radiologists who did not use ultrasound for palpable masses, many now practice defensively and examine all palpable masses with ultrasound.

(c)BIOPSY

Fine-needle aspiration (FNA) guided by physical examination has been used effectively for years to evaluate patients

with palpable breast lumps. A review of 3,000 cases of nonpalpable lesions evaluated by FNA with histologic follow-up concluded that the results were comparable to FNA of palpable breast lumps. The sensitivity of FNA for palpable lesions ranged between 72% and 99% and for nonpalpable lesions between 82% and 100%. Multiple other studies have compared the accuracy of FNA for evaluating nonpalpable breast lesions with results from surgical biopsy. These studies have yielded mixed and conflicting results. The reported sensitivity has varied from 68% to 93% and the specificity from 88% to 100%. The false-negative rate for FNA of nonpalpable lesions ranges from 0 to 32% and may be due to inaccurate lesion localization, small lesion size, deflection of the fine needle by firm masses, or a combination of these. Reported false-positive rates in nonpalpable lesions vary from 0 to 6%.This is usually due to misinterpretation of atypical abnormalities found in areas of proliferative breast changes. The type of needle used for lesion sampling is different for FNA and for core biopsy and results in significantly different specimen material. Core biopsy is performed with a large cutting needle, usually 14 gauge, deployed into the breast by a rapid-fire, spring-loaded, automated biopsy

instrument, commonly called a biopsy gun. The sampled material consists of a core of tissue suitable for standard histologic analysis, familiar to most pathologists. Insufficient sampling is infrequent with core biopsy, because more tissue is removed and the tissue cores are easily seen during the procedure so that more tissue can be obtained if the sample is visibly inadequate. In contrast, FNA is performed with a 20- to 22-gauge needle manually inserted into the breast. The fine needle yields cellular material suitable for cytologic evaluation. Accurate cytologic interpretation requires an experienced cytopathologist, which may not be available in all sites. The material extracted with FNA is smaller and prone to be insufficient for diagnosis.

Breast needle biopsies of nonpalpable lesions, be they FNA or core biopsy, require imaging to guide needle placement. Imaging guidance can be performed with stereotactic mammography or ultrasound. Both imaging modalities are widely available. The choice of imaging technique used for guidance depends on the visibility of the lesion and does not affect the accuracy of the procedure. Generally, ultrasound guidance is preferred for masses visualized with ultrasound,

as it is faster and does not require breast compression, making it better tolerated by most patients. Stereotactic biopsy is used for mammographically detected lesions not identified with ultrasound.

(d). SENTINEL LYMPH NODE BIOPSY

Sentinel lymph node biopsy offers the possibility of reliably identifying patients with axillary node involvement with a low-morbidity operation, allowing axillary dissection to be limited to patients with nodal metastases who can benefit from the procedure.

The concept of lymphatic mapping and sentinel lymph node biopsy was popularized by Morton et al. in patients with melanoma. The sentinel node is defined as the first lymph node that drains a cancer. Morton et al. demonstrated that the intradermal injection of a vital blue dye around the primary melanoma resulted in the identification of a sentinel node in the majority of patients, and the status of this node would predict the status of the remaining nodes in the nodal basin. This technique was subsequently adapted to breast tumors by Giuliano et al. A sentinel node was identified in 65.5% of cases and accurately predicted the status of the remaining axillary nodes in 95.6% of cases. The ability to identify the sentinel node improved as the technique was

refined, with a sentinel node found in 58.6% of the first 87 cases and 78% of the last 50 cases. After these initial reports, lymphatic mapping with radiolabeled colloids alone, or a combination of a radiolabeled colloid and blue dye, was undertaken by a variety of groups.. Patient selection criteria and the technique of sentinel node identification varied widely in these studies. The injection of the radiolabeled colloid in the majority of studies was around the tumor sitebut in the report of Veronesi et al., subdermal injection was used. The dose of radioactivity, the interval from injection to operation, and the use of lymphoscintigraphy also varied. However, in spite of these variations in patient selection and technique of mapping, it is evident that with experience, a sentinel node can be identified in more than 90% of cases and can predict the status of the remaining axillary nodes with 95% accuracy.[25]

(e).ESTIMATION OF HORMONAL RECEPTORS

The laboratory discovery and subsequent measurement of ER and PR in tumors has given the clinician useful and powerful tools to aid in the management of women with breast cancer. Overall, 30% to 40% of patients with metastatic breast cancer objectively respond to hormone

therapyA substantial fraction of patients also exists whose disease becomes stable, neither progressing nor regressing, for a clinically significant period of time. With first-line cytotoxic chemotherapy,the response rate is 50% to 60%. Although the response rate is higher than the objective response rate to hormone therapy, with chemotherapy, the toxicity is much greater, and the likelihood of a sustained response is low. Hormone therapy, on the other hand, is relatively nontoxic, and responses can sometimes last for years. Thus, hormone treatment offers several significant advantages to particular subsets of patients. It is now well established that measurement of ER levels, as well as PR levels, can distinguish those patients most likely to benefit from hormone therapy from those unlikely to respond, so the latter group may receive other more effective and appropriate management strategies, such as cytotoxic chemotherapy.

Although a multitude of assay methods are available that differ in detail, at present all clinically practical methods for quantitating ER and PR are based on two distinct and mechanically different strategies. The first strategy involves the competitive binding of radiolabeled

steroid ligand to detect the receptor, whereas the second relies on the recognition of the receptor protein by specific antibodies.

Ligand-Binding Methods[26]

The prototype for ligand-binding methods, and the one that remains most in use, is the dextran-coated charcoal (DCC) assay. With this assay, radiolabeled steroid (ligand) is first added to homogenized breast tumor cytosol and is incubated, allowing the labeled steroid to bind all available receptor protein. For simultaneous determination of ER and PR, estradiol labeled with iodine[125] and progestin labeled with tritium (3H) are used. DCC, which has the property of adsorbing unbound steroid, is added to the homogenate; the charcoal with adherent unbound steroid is then separated by centrifugation. Because the receptor-bound portion remains in the supernatant and the free fraction is found in the charcoal precipitate, the bound and unbound fractions can then be quantified and the results used to create a Scatchard plot. When the DCC assay is used to measure receptor levels, a range of 3H-tagged steroid is used to generate this multipoint plot. From the Scatchard plot, total concentration of receptor protein in the cytosol is obtained and is usually expressed as femtomoles of

receptor protein per milligram of total cytosol protein. Various cutoff values for separating ER+ from ER– samples are used in different laboratories; usually, the cutoff is between 3 and 20 fmol/mg.

Variability in assay results can occur for a number of reasons. The tumor is usually divided into several portions, each to be used for different purposes. Tumor cellularity may be variable, with some regions being more necrotic or having a high proportion of connective or inflammatory tissue. Variation is also seen in the receptor content of the malignant epithelial component; areas of clonal proliferation may be found that are relatively richer or poorer in receptor protein. As mentioned above, treatment with ligands that bind ER or PR could influence the assay.

Assays Using Monoclonal Antibodies[27]

The second general strategy for detection of ER and PR uses antibodies specifically directed against epitopes unique to each receptor protein. These antibodies may be monoclonal or polyclonal. At least two methodologic variations on this general strategy are commonly performed: immunohistochemical (IHC) analysis and enzyme immunoassay (EIA). IHC analysis can be performed on thin sections of

tumor cut from formalin-fixed, paraffin-embedded or frozen biopsy specimens. Initially, 4- to 5-μm sections are cut and mounted on protein-coated glass slides. To increase detection sensitivity, the sections are sometimes first heated to uncover protein epitopes lost in the fixation process or from the passage of time. The sections are exposed to a primary antibody directed against ER or PR, and then a secondary antibody that recognizes the first is added to amplify the subsequent signal Attached to these secondary antibodies are enzymes, such as horseradish peroxidase that convert substrates like diaminobenzidine into colorized molecules on exposure to a developer. The sections are counterstained and can then be viewed to semiquantitate the amount of protein present For ER and PR, the staining produces distinct nuclear signals, and heterogeneity of staining of malignant epithelium is frequently seen.

IHC analysis offers several advantages. It can be performed on fine-needle aspirates, core biopsies, small tumors, and cell blocks from body fluids, such as pleural effusions. It can be done on either frozen or fixed, paraffin-embedded archival tissue. It measures the total receptor protein resent, not just the unbound fraction, and is not

affected by very high levels of endogenous or exogenous steroids or tamoxifen treatment. It allows the direct quantification of receptor protein in the malignant cell fraction. Due to the reasons outlined above and its relative simplicity and lack of requirements for specialized equipment, it is rapidly becoming the predominant method for measuring ER and PR in clinical practice.

(g).OTHER MODALITIES

1. **XERORADIOGRAPHY/THERMOGRAPHY**.

Non specific,high incidence of false positives.

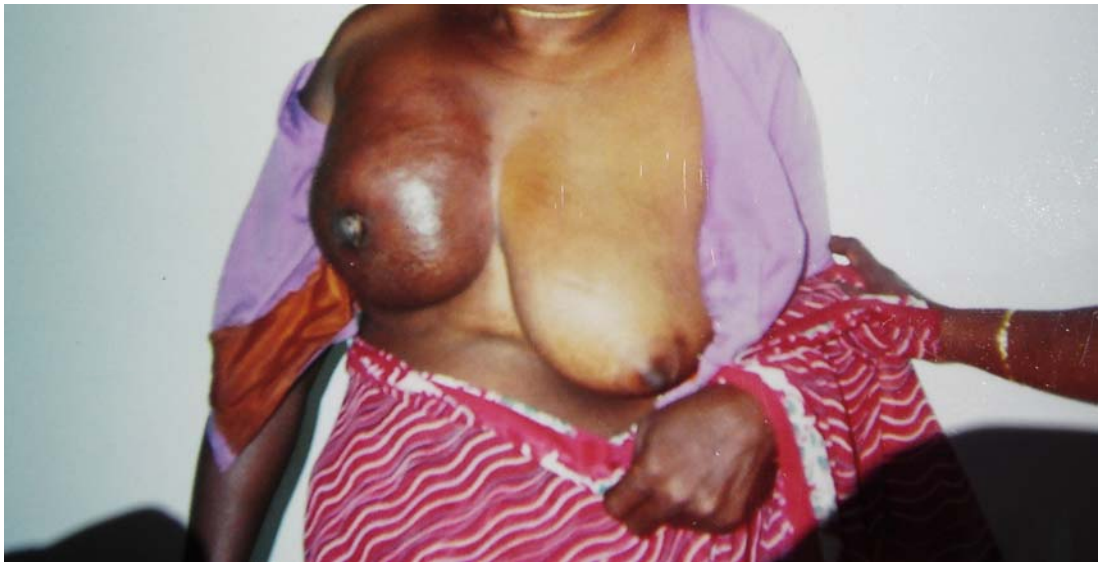
2. **CHEST X-RAY/BONE SCAN/ SKELETAL SURVEY/ BONE MARROW ASPIRATION/LIVER STUDIES**

To detect distant metastasis.serve as adjunct to follow-up and palliation.

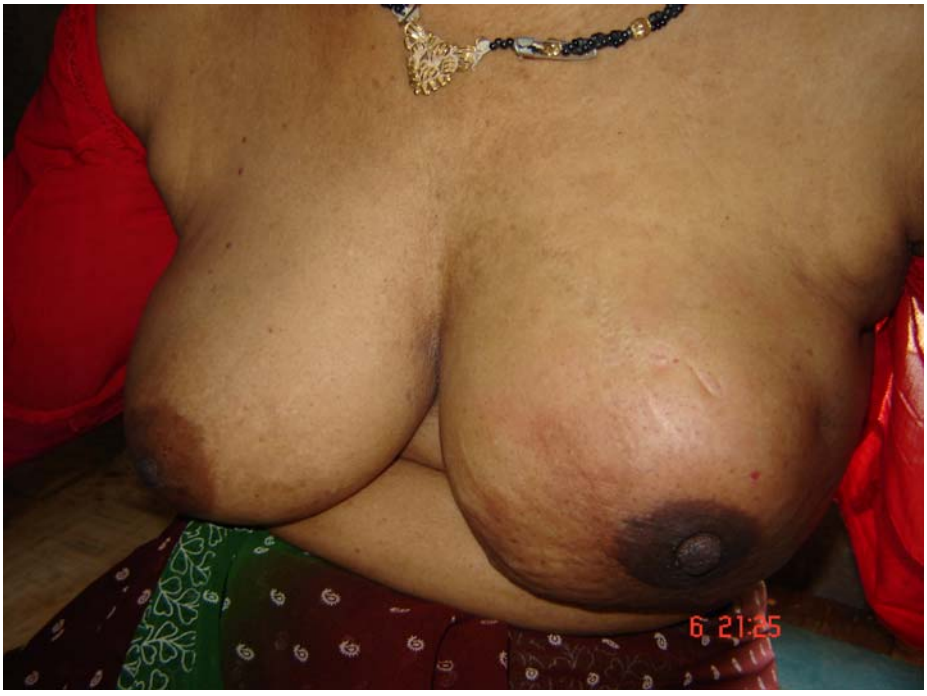
3.**MRI/ PET SCAN**

Newer modalities of investigations. Costly but very effective in analysis of tumor characterisitics

LABC EXTENSIVE SKIN INVOLVEMENT



LABC



LOCALLY ADVANCED BREAST CANCER

Breast cancer is the commonest malignant disease among women in the Western world accounting for 1/5 th (18%) of all cancers in women. Every year about one million women and several thousand men are diagnosed with breast cancer worldwide and approximately 60,000 die from it. It is also rapidly emerging as a very common cancer in the developing countries as well. In India, it is the second most common cancer in females with 75,000 new cases occurring every year as per the cancer registries in the country[28]

Breast cancer is categorized into operable and advanced breast cancer for the management purpose. Advanced breast cancer is either locally advanced or metastatic disease. Locally advanced breast cancer (LABC) is characterized by varying clinical presentations such as presence of a large primary tumour (>5 cm), associated with or without skin or chest-wall involvement or with fixed (matted) axillary lymph nodes or with disease spread to the ipsilateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastases. These cancers are classified as stage IIB, IIIA, IIIB or IV breast cancer according to the American Joint

Committee for Cancer Staging and End Results Reporting. Locally advanced breast cancer is a very common clinical scenario especially in developing countries (30-60%) possibly due to various factors like lack of education and poor socio-economic status. With this wide spectrum of presentation, management of LABC is a challenge for the oncologist. Treatment of LABC has evolved from single modality treatment, consisting of radical mutilating surgery or higher doses of radiotherapy in inoperable disease to multimodality management consisting of surgery, radiation therapy (RT), chemotherapy with or without hormonal therapy,

MODALITIES OF TREATMENT

SURGERY

Historically, surgery has been the oldest treatment for breast cancer, yet its enthusiasm has waxed and waned over a period of time. Different surgeries have been devised, discarded, rediscovered, changed and abandoned again in seemingly endless fashion as physicians sought to employ the science and technology of their own times. William Halsted at the end of nineteenth century described a surgical technique for removal of the entire breast and en bloc removal of all

axillary lymphatics, the chest wall muscles and at times a part of chest wall with the majority of cases being locally advanced in that era. With the success of Halstedian mastectomy, this surgery became a standard in the management of breast cancer. However the long-term results were poor with survival ranging from 13-20% at 5 years. The pioneering work by McWhirter et al.[29] in the mid 20th century showed that less mutilating surgery produced results equal to that of radical mastectomy (RM). The switch from RM to less mutilating surgery came when it was largely recognized that treatment failure from breast cancer was largely due to systemic dissemination prior to surgery. A number of prospective randomized trials comparing RM with modified radical mastectomy (MRM) confirmed the evidence. The failure of Halstedian principle of en bloc extirpation of breast and draining lymph nodes to cure many patients of breast cancer, frequent identification of small breast cancer by mammography and success of moderate doses of RT in eliminating sub clinical foci of breast cancer led to the development of MRM. MRM is the term used to describe a variety of surgical procedures, but all involve complete removal of the breast and some of the axillary lymph nodes. Although it may not seem to differ

significantly, it seemed to represent a major departure from Halstedian mastectomy. Considering the above evidence, MRM became the standard of care as compared to RM (NIH consensus conference).

RADIOTHERAPY

After the criteria of inoperability by Haagensen and Stout it was suggested that RT could be used alone in radical treatment of breast cancer. Radiation therapists in the early 20th century inherited and applied the concept of radical en bloc ablation. In the initial studies doses administered to the breast were limited by acute skin reactions from the available orthovoltage treatment units. Protracted fractionation with higher doses of upto 60 Gy showed improvement in survival in women with T3, T4 disease Higher doses of 80-90 Gy were also attempted which led to higher complications such as cardiac and pulmonary complications, breast edema, arm edema, brachial plexus injury, shoulder stiffness, fibrosis and necrosis of chest wall. The survival of these patients who received radical radiotherapy alone was dismal.

RADIATION AND SURGERY

Irradiation, which was initially focused on inoperable cases, was then considered as an adjunct to radical surgery. Extensive experience using RT alone or in combination with surgery (pre or post Surgery) has been reported from large institutional series. In a large randomized trial, Kaae and Johnson demonstrated the effectiveness of RT in control of sub clinical disease. Initial experiences with radical surgery and postoperative radiotherapy showed that significant improvement in local control does occur when surgery is followed by RT but at the same time these trials consistently showed higher cardiac morbidity, the reason for which was the larger volume of heart and lung that was irradiated in order to encompass the internal mammary lymph nodes., An overview analysis by Cuzick (patients treated in four randomized trials) demonstrated equivalent survival for patients treated with RM Vs simple mastectomy (SM) + RT. But all these trials consistently showed that in the post RT arm the survival advantage due to RT was lost due to high treatment related cardiac mortality. The two biggest trials which showed unequivocal survival advantage with RT in stage II and III breast cancer were by Danish breast cancer group (DBCG) in

both premenopausal and post menopausal women. In DBCG 82b 1,708 premenopausal women after MRM were randomly assigned to nine cycles of chemotherapy alone or 8 cycles of CMF chemotherapy and local RT. At a median follow up 114 months, the 10 year loco regional recurrence rate was 32% vs 9% and the overall survival 45% vs. 54% in the chemotherapy alone and combined chemotherapy and radiation therapy arm respectively. In the DBCG 82c study 1,375 postmenopausal women with stage II and III breast cancer were randomly assigned to tamoxifen for 1 year + loco regional RT. At a median follow up of 123 months, the 10 year loco regional failure improved from 35% vs. 8% with the overall survival was 36% vs. 45% in the tamoxifen and tamoxifen + RT arms respectively. Another trial that showed the value of postmastectomy is the British Columbia trial, which clearly showed an improvement in overall survival and disease free survival in favor of RT in high risk women. The cardiac and pulmonary toxicity in these trials decreased to <2% as they included patients who were treated with improved radio therapeutic techniques and with the use of megavoltage units and more importantly cardiac safe techniques employing computerized planning and use of electron

beam for internal mammary chair portals. Therefore with the availability of level I evidence from these well conducted large studies, postoperative RT has now become the standard of care for stage III breast cancer. Although these above trials did include some patients with LABC, no specific randomized trial has addressed this category of disease. The practice of post mastectomy radiotherapy in LABC is based on the data from various large single institutional series. One such series from M.D. Anderson cancer centre addressing women with non-inflammatory LABC who were treated with mastectomy followed by external beam RT, showed loco regional control rate of 88% for stage IIIA disease and 74% for stage IIIB disease at a median follow up of 17.7 years with doses of 50Gy of external beam RT. As the role of RT was established, trials were done to compare RT alone with surgery followed by post op RT. Perez et al treated 281 patients with LABC reported a loco regional control of 81% at 5 years and 70% at 10 years respectively in the patients treated with mastectomy and RT compared to 42% and 35% at 5 and 10 years respectively for RT alone. It was observed that with higher doses of RT there was significant improvement in the loco regional control. Thus RT has become an

integral component in the loco regional management of LABC with improvement in the loco regional control and survival. Radiation therapy to the chest wall and supraclavicular fossa (SCF) to a dose equivalent of 50 Gy has now become the standard even after a good and adequate surgery.[30]

CHEMOTHERAPY

After achieving reasonable local control with a combination of surgery and radiation therapy, the overall survival of LABC still remained dismal with distant metastasis the most common type of treatment failure, appearing in majority of patients within 24 months.[31] Therefore addressing the systemic component of the disease was considered important with an aim to achieve good survival in these women. Adjuvant chemotherapy has over the last 3-4 decades established a firm place in the management of operable and advanced breast cancer. Specifically for LABC management, both adjuvant systemic therapy and neoadjuvant chemotherapy (NACT) were developed simultaneously. In the last three decades, NACT especially has gained a major foothold in the management of LABC. The use of NACT in LABC dates back to 1973, when a regimen containing

doxorubicin caused prompt tumor shrinkage and thereby facilitated subsequent radiation therapy or mastectomy. The use of NACT in LABC was based on the rationale that these patients present with a relatively high burden of micro metastasis and therefore makes sense to initiate systemic therapy upfront at the earliest Further studies also showed that response to NACT could be considered as a short-term surrogate marker for long-term outcome and therefore act as an in-vivo marker for tumor response to chemotherapy, especially in the primary tumor. There is however a debate in the application of this strategy. While the use of NACT certainly allows an early initiation of systemic treatment, inhibition of post surgical growth spurt, delivery of chemotherapy through intact tumor vasculature, in vivo assessment of response, and down staging of primary tumor and lymph node metastases to even facilitate less radical loco regional therapy, the local treatment for non responders could become delayed with risk of drug resistance, chemotherapy having to act on a larger tumor burden, inaccurate pathological staging and a possible increase in the risk of surgery and radiotherapy related complications. With the increasing usage of NACT, an interesting spin off was noted. Since a number of

patients achieved significant reduction in their tumor and nodal masses, it became apparent that breast conservation therapy (BCT) could be explored even in these patients, a possibility almost unimaginable in the conventional management paradigm.

NEOADJUVANT CHEMOTHERAPY AND POST-OP CHEMOTHERAPY

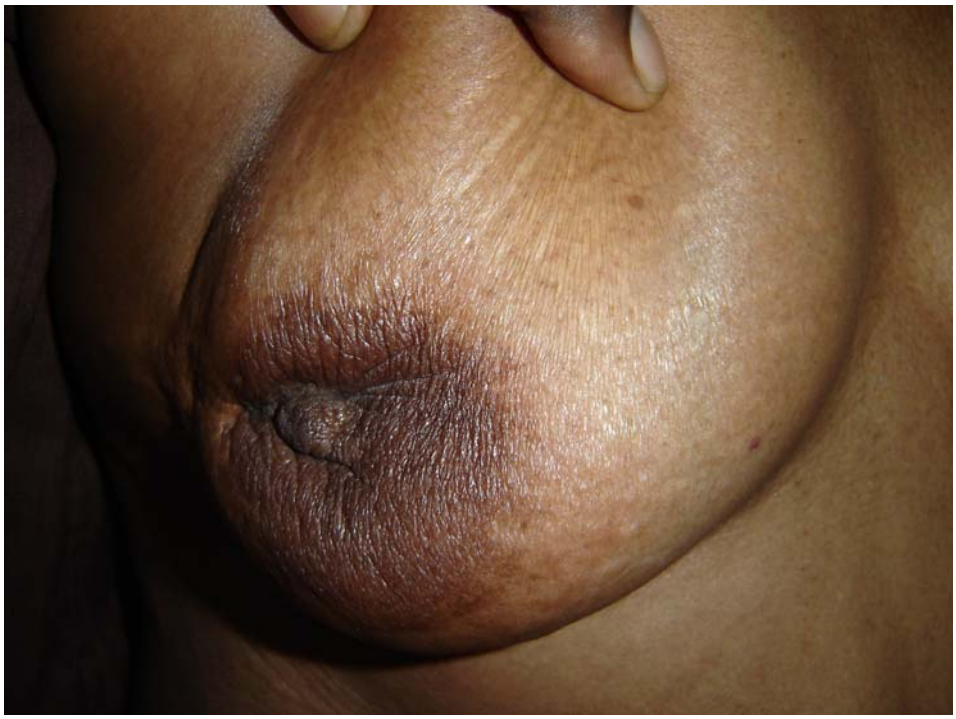
Multiple large randomized trials have proven the safety of NACT in LABC Most of these trials have shown a good objective response rate of about 60-80% without a detriment in survival as opposed to post-operative chemotherapy. The biggest randomized trial comparing pre-op versus post operative chemotherapy is NSABP B-18 in which 1523 patients with primary operable breast cancer were randomized to preoperative doxorubicin and cyclophosphamide (AC) therapy vs. postoperative AC therapy.[32] Tumors with a clinical complete response (cCR) were further categorized as either pathologic complete response (pCR) or invasive cells (pINV). There was no significant difference in the disease free and overall survival in either group. However the frequency of BCT was greater in the NACT arm (67% for NACT Vs 60% post operative chemotherapy, Outcome was better in women whose tumors showed a pCR than in

those with a pINV, clinically partial response (cPR), or clinically no response (cNR) (relapse-free survival [RFS] rates, 85.7%, 76.9%, 68.1%, and 63.9%, respectively), even when baseline prognostic variables were controlled. NACT is therefore considered as effective as postoperative chemotherapy and permits more breast conserving surgeries. In the light of the current evidence it may be concluded that although there is no survival benefit, there is no disadvantage. NACT leads to complete clinical response in 10-30% of patients and a partial response in 50-60%. Only a third of patients with a clinical CR have been found to have pathological CR. The best data in this regard comes from the NSABP B18, which showed that out of the 608 patients that received NACT, breast tumor size was reduced in 80% of patients after NACT of which 36% had a cCR. Tumor size and clinical nodal status were independent predictors of cCR. Twenty-six percent of women with a cCR had a pCR. Clinical nodal response occurred in 89% of node-positive patients: 73% had a cCR and 44% of those had a pCR. There was a 37% increase in the incidence of pathologically negative nodes. Overall, 12% more lumpectomies were performed in the NACT group; in women with tumors 5.1 cm, there was a 17% increase in

lumpectomies. Thus approximately 13% of primary breast carcinoma cases exhibited both cCR and pCR. In addition 7% of patients exhibited a pCR in the absence of a cCR. A pCR occurred in 38% of those patients determined to have achieved a cCR. The assessment of clinical response in the axilla has yet not been standardized and is measured by different techniques. Kuerer et al. found that of 55 patients with LABC who appeared to have had complete resolution of axillary disease by both physical examination and ultrasonography, 29 patients (53%) had pathologic evidence of axillary metastasis after NACT.

Despite the difficulty in accurately assessing the tumor response it has been shown that patients who achieve a complete clinical or pathological response have better outcome. Kuerer et al in their series of 372 patients with LABC observed pathological CR in 43 (12%) patients and showed better survival outcome in these patients as compared to those who did not have pCR When pathology specimens in the NSABP-B18 trial were reviewed, patients with the pCR exhibited a better OS and DFS compared with those with a pathologic partial response (presence of sparse invasive tumor [pPR]) or[33] no pathologic response(pNR).

NIPPLE RETRACTION



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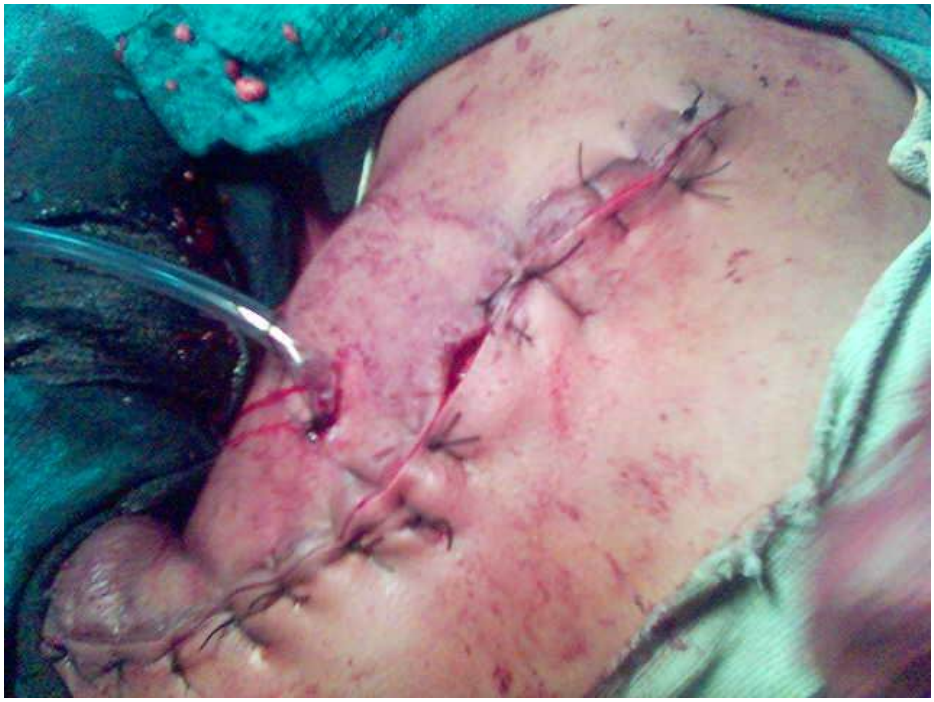


TYPE OF CHEMOTHERAPY

Over the years it has been proven in large randomized trials that anthracycline based chemotherapy are the most effective agents in the management of invasive breast cancers. The EBCTG meta- analysis involving 11 randomized trials comparing anthracycline based poly chemotherapy and non anthracycline based chemotherapy clearly showed a modest benefit in terms of recurrence rates and overall survival. The results can be further improved if anthracyclines can be combined with other non-cross resistant chemotherapy i.e. taxanes. Taxanes namely docetaxel and paclitaxel given as either single agents or as a combination are emerging to be quite effective in the management of breast cancer.[34] Given the encouraging response rates to taxanes in metastatic breast cancer and the significant disease-free and overall survival benefit shown by the addition of paclitaxel in stage II disease, taxanes are used extensively as non-cross-resistant agents with doxorubicin in stage III breast cancer. When docetaxel has been compared head -on with anthracycline based chemotherapy it seems to show a better response rate in selected patients as reported in a small series. The NSABP B-27 trial has shown that use of taxanes

with doxorubicin sequentially did show a better response rates in terms of superior partial and complete response both in estrogen receptor positive and negative patients. The final word regarding the routine use of taxanes and the choice of drug has not been conclusively resolved as yet and awaits confirmation from ongoing studies.

Number of neo adjuvant chemotherapy cycles

There is a lot of variation in the number of cycles of chemotherapy that are given in neo adjuvant setting in the literature. Investigators have administered either 3-4 cycles of chemotherapy were administered or chemotherapy was continued up to maximal response. This is an important issue, and may have several pitfalls. Current techniques of evaluating response to NACT (physical examination, mammography, and ultrasound) remain imprecise. The significance of small reduction in tumor mass may be difficult to evaluate because of peri tumoral edema and fibrosis. There is fear amongst the clinicians that tumor might actually grow during a protracted treatment of NACT. The biological significance of an early clinical response may be entirely different from that of a late response, a possibility suggested by complete lack of correlation

between response and outcome as shown by Pierce et al. As maximal response is always determined retrospectively this may result in delay in surgical planning and thus consequent reduction of chemotherapy Dose intensity

The advantages of giving chemotherapy upto maximal response are that if the patient has achieved good clinical response in less than planned cycles, continuation of further chemotherapy consolidates the complete response by maintaining the dose intensity. However it is well known that the complete clinical response does not equate to complete abolition of all disease pathologically. Another advantage of continuing NACT upto maximal response is that it may be possible that a fixed number of cycles may not be enough to achieve the amount of response necessary to do BCT and if chemotherapy is continued there may be still further regression. Most of the retrospective studies have shown that post NACT tumor burden has a direct effect on loco regional control and survival. Even in control of the systemic micro metastasis giving more no. of cycles is beneficial and has an effect on the loco regional disease. This can be based on the Skipper's theory that the primary tumor and its micro metastasis may respond differently to

chemotherapy. Further data can be extrapolated from the studies in metastatic breast cancer. In patients with metastatic breast cancer the median number of cycles to achieve an objective response (mostly partial response) were three, whereas that required to achieve a complete response is five.[35]

NEOADJUVANT HORMONAL THERAPY

Efforts to improve response to chemotherapy include attempts to synchronize tumor cells with hormonal agents. Conte and associates used estrogenic recruitment in conjunction with cytotoxic chemotherapy and achieved a 15% clinical complete response rate. The 3-year rate of progression-free survival was 54%. A subsequent randomized trial done by Chua et al. with FAC chemotherapy, with or without diethylstilbestrol, showed higher response and disease-free survival but no overall survival benefit for patients receiving estrogenic recruitment. Others also found higher objective response rates with hormonal manipulation, without improvements in overall survival rates. Pierce and associates and Lippman and colleagues[36] at the NCI also used a strategy for hormonal synchronization with both estrogens and antiestrogens in their approach to locally advanced

disease. Despite complete clinical response rates of 50% with stage IIIA disease and 57% with inflammatory disease, the 5-year survival rates did not significantly differ from survival results in other series that did not use hormonal synchronization

Adjuvant hormonal therapy

Bartelink et al.[37] did the largest randomized trial completed in patients with LABC with adjuvant hormonal therapy. A reanalysis of the same was done after 8 years. Specifically, 410 patients with LABC, including 48 women with inflammatory disease, were randomized to receive radiation therapy alone, radiation therapy with chemotherapy, radiation therapy with hormonal therapy, or radiation therapy with both chemotherapy and hormonal therapy. Patients who were randomized to receive chemotherapy received 12 cycles of CMF. Premenopausal women who were randomized to receive hormonal therapy received ovarian irradiation, whereas postmenopausal women who were randomized to receive hormonal therapy received tamoxifen. With a median follow-up of 8 years, both hormonal therapy and chemotherapy reduced the risk of loco regional failure from approximately 60% to 47%. Hormonal therapy significantly improved

survival, with a 25% reduction in the death hazards ratio. Unlike an interim analysis that showed a significant improvement in survival in the chemotherapy arm, this benefit did not remain statistically significant with further follow-up. In the most recent analysis, however, the greatest survival benefit was observed in women who received both hormonal therapy and chemotherapy with radiation, with a 35% reduction in the death hazards risk.

LOCO-REGIONAL THERAPY FOLLOWING NACT

Currently the sequencing of different modalities and their choice is a topic of major controversy. Oncologists across the globe have combined these modalities in various sequences and combinations. With more and more number of patients of LABC being treated with NACT a difference in the local therapy offered has been observed amongst various institutions. After NACT, surgery alone, radiotherapy alone or a combination of both has been attempted in the context of multidisciplinary management. Surgery has mainly been in the form of MRM, even though wide excision lumpectomy has been attempted. Multiple randomized trials and non-randomized studies have been conducted to address the issue of choosing the best local therapy

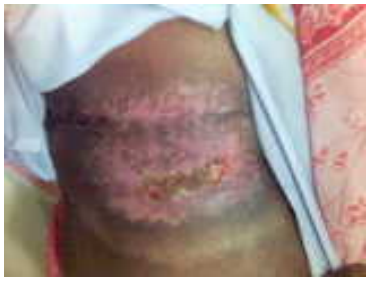
either alone or in combination. The Cancer and Leukemia Group B attempted to define the choice of local treatment following NACT in patients with inoperable disease. One hundred and thirteen patients (67% with stage IIIB disease) received 3 months of NACT with CAFVP. Eighty one percent of patients were deemed operable and randomized to either surgery or radiotherapy, followed by an additional 2 cycles of CAFVP. At a median follow up of 37 months, there was no significant difference in either DFS (29.2 vs. 24.4 months) or OAS (39.3 vs. 39 months) between the two groups. However, the local recurrence rates were much higher in radiotherapy arm (55%) than surgery (42%). De Lena et al from Milan treated 132 patients with three cycles of NACT (doxorubicin and vincristine) followed by surgery or radiation therapy, than an additional seven cycles of same chemotherapy. Although the group randomized to surgery following initial chemotherapy had better initial local control than those treated with radiation therapy alone (100% vs 60%). The short and the long term outcome in both the groups were essentially same (75%) after completion of the additional cycles of chemotherapy. The results of the study failed to indicate that surgery improved the

overall results including local control, over radiotherapy in a combined modality setting. Thus both these trials clearly showed that although initial local control is higher when NACT is followed by surgery there was no difference in ultimate local control and survival. Although no randomized data exists, indirect comparisons between trials that included only one form of regional therapy versus two types of regional treatment, have suggested that when both surgery and radiotherapy are employed, ultimate local control rates are higher than when only surgery or radiotherapy is utilized. However, only one randomized trial that addresses this question has been reported, and no significant differences between the two arms were detected. This trial included 184 patients with LABC that received 2 cycles of NACT with CAFVM, which was followed by mastectomy and after which they were randomized to receive RT vs. no RT. This was then followed by 10 additional cycles of chemotherapy. They found that those patients who received radiotherapy had a higher incidence of distant metastasis as compared to those not receiving RT. This was attributed to delayed institution of chemotherapy due to the use of radiotherapy and immunosuppresion caused by mediastinal irradiation. [38]

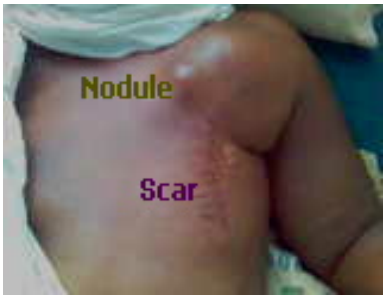
BREAST CONSERVATION AND LABC

While MRM still perhaps remains the standard of care for the surgical management of women with LABC, less extensive surgeries (without compromising local control and/or survival) are being increasingly explored with the use of NACT. The down-staging of tumors seen in 60-70% of women not only makes them operable but also, on many occasions can be considered for BCT. Attention has therefore been directed towards the identification of patients with an excellent response to NACT who could possibly be the candidates for BCT. The goals of this approach are to achieve optimal loco regional control with acceptable cosmesis. A lot of interest has been generated in the last 15 yrs, to make BCT feasible in the patients suffering from large operable breast cancer (LOBC) and LABC. Several centres have reported their experience with combined modality therapy of LABC and BCT. However there is a great variability in the methods utilized, as well as the selection criteria for patients to undergo BCT. As in early breast cancer, presence of multicentric disease, extensive micro-calcification, extensive skin changes, and lymphatic permeation are generally considered as contraindications for BCT in these scenarios as well.[39]

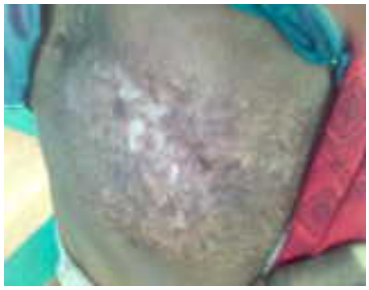
POST RADIO THERAPY



RECURRENCE



FOLLOW UP



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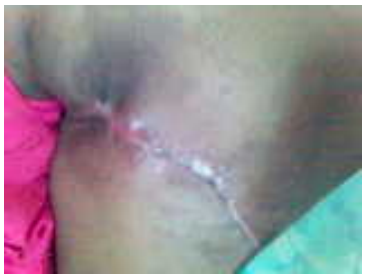
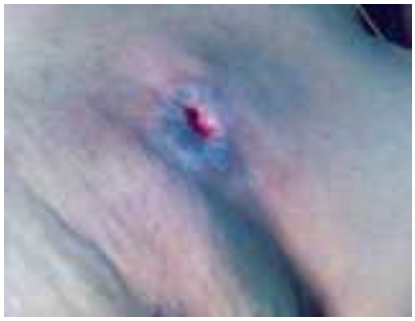


PAGET'S - DISEASE



SUMMARY OF TREATMENT OPTIONS

Stage III (locally advanced) breast cancer is further classified into stage IIIA and stage IIIB disease. Stage IIIA disease is often operable when axillary lymph nodes are mobile. However, if the lymph nodes are fixed or if the tumor is very large, neoadjuvant chemotherapy is indicated to shrink the tumor before surgery.

TREATMENT OPTIONS (STAGE IIIA):

Standard:

1. In operable cases, 1 of the following surgical procedures for initial treatment:

Modified radical mastectomy.

Radical mastectomy.

2. Because of the high risk of local recurrence for this stage, radiation therapy should be considered as part of the overall treatment plan:

Postoperative external-beam irradiation to the chest wall- A boost can be given if clinically indicated for positive or close margins.

3. Chemotherapy regimens with or without hormones are given in conjunction with the above surgical and radio therapeutic procedures. Chemotherapy can be given prior to surgery in cases where primary resection is not feasible or is technically difficult. Some equally effective combination chemotherapy regimens commonly used are:

CMF: cyclophosphamide + methotrexate + fluorouracil

CAF: cyclophosphamide + doxorubicin + fluorouracil

CA: cyclophosphamide + doxorubicin

Under clinical evaluation:

1. Clinical trials evaluating the role of combination chemotherapy with or without hormonal manipulation are ongoing. Preliminary data indicate that neoadjuvant preoperative chemotherapy may allow breast conservation therapy in patients whose lesion and breast size would not have allowed this option

2. High-dose chemotherapy with hematopoietic stem cell support.

STAGE IIIB

(LOCALLY ADVANCED, INCLUDING INFLAMMATORY)

The treatment of inflammatory breast cancer is similar to options for stage IIIB or IV breast cancer

In stage IIIB breast cancer, initial surgery is generally limited to biopsy. Removal of residual tumor may be performed if a good response is achieved with chemotherapy with or without radiation therapy.

Treatment options

Standard:

1. Core needle biopsy, fine-needle aspiration or incisional biopsy for diagnosis and receptor protein assay followed by preoperative chemotherapy. If the patient has a good response, local therapy with surgery and/or irradiation is recommended. If the response is poor, palliative radiation therapy may be recommended.

2. Chemotherapy regimens with or without hormones are given in conjunction with the above surgical and radio therapeutic procedures. Chemotherapy can be given prior to surgery in cases where primary

resection is not feasible or is technically difficult. Commonly used chemotherapy regimens include:

CMF: cyclophosphamide + methotrexate + fluorouracil.

CAF: cyclophosphamide + doxorubicin + fluorouracil.

CA: cyclophosphamide + doxorubicin.

3. If combination chemotherapy is contraindicated, pretreatment with tamoxifen may be recommended for patients whose tumors are positive for estrogen- and progesterone-receptor proteins.

Under clinical evaluation:

1. Phase II studies evaluating newly developed chemotherapeutic or biologic agents may be considered for patients whose local disease is not controllable by standard measures.

2. High-dose chemotherapy with hematopoietic cell support.

OBSERVATION AND RESULTS

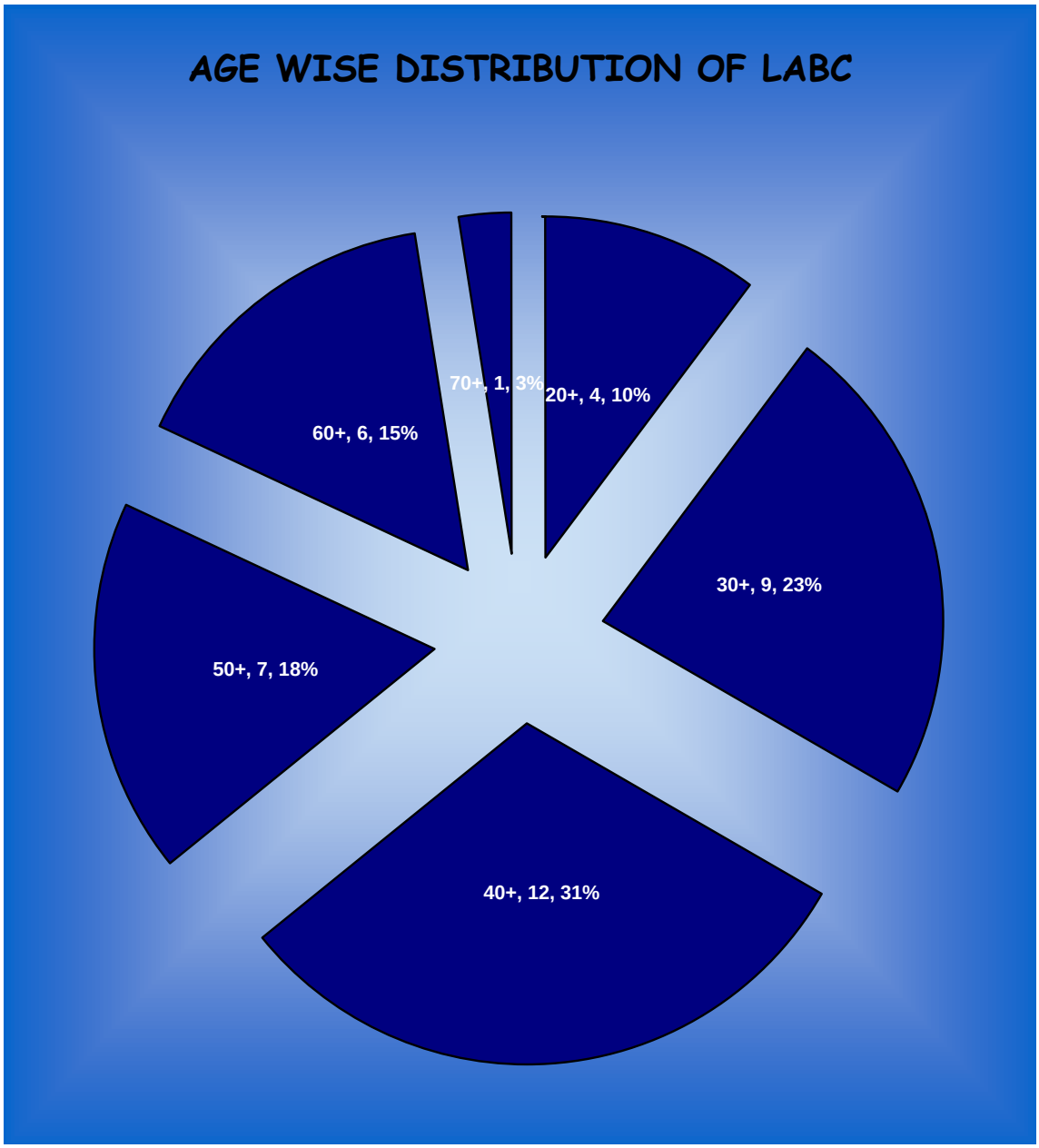


FIGURE-1 AGE-WISE INCIDENCE OF LABC

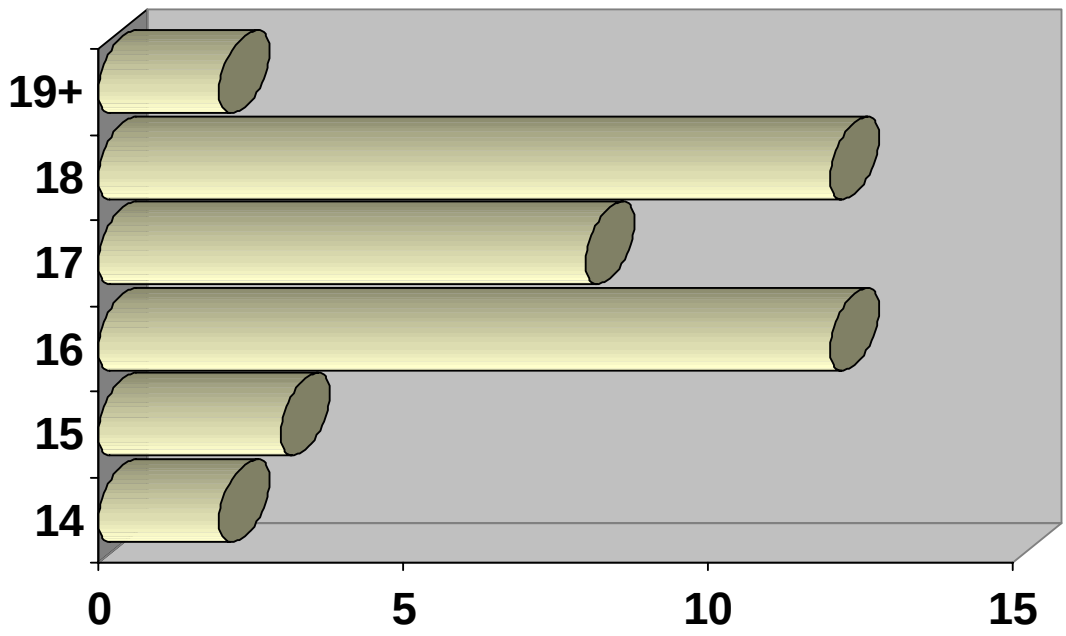


FIGURE-2 AGE OF MENARCHE IN PATIENTS WITH LABC

AGE WISE INCIDENCE OF LABC

AGE	NO. OF PATIENTS	
	TOTAL	PERCENTAGE
20+	04	10
30+	09	23
40+	12	31
50+	07	18
60+	06	15
70+	01	03

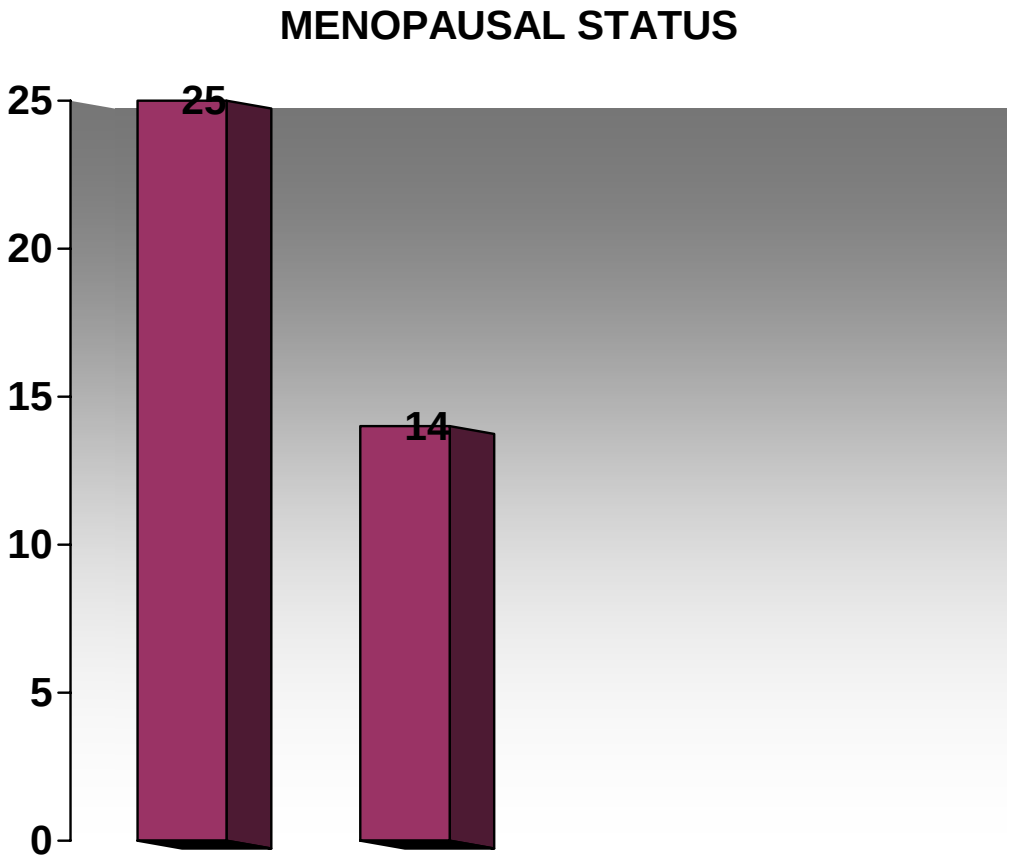
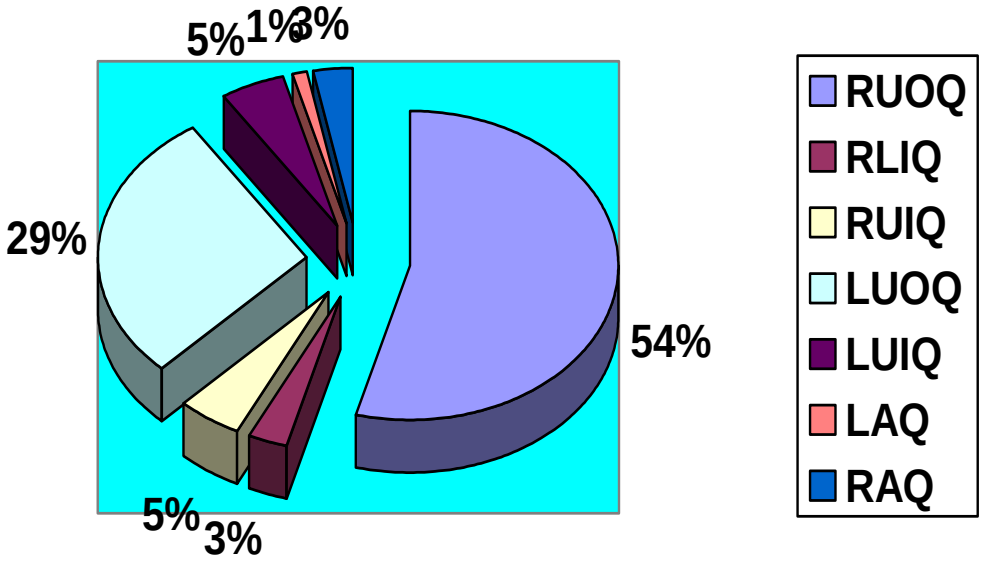


FIGURE-3 MENOPAUSAL STATUS IN LABC

MENSTRUAL STATUS

MENSTRUAL STATUS	NO. OF PATIENTS	PERCENTAGE
PRE-MENOPAUSAL	25	64
POST-MENOPAUSAL	14	36

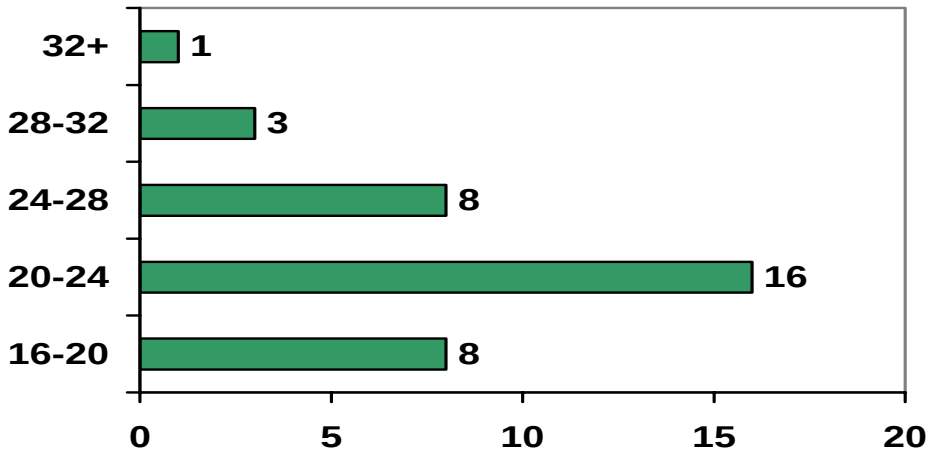
FIGURE-4 SITE OF OCCURENCE



SITE OF OCCURRENCE

SITE OF OCCURRENCE		TOTAL NO.	PERCENTAGE
RIGHT	UOQ	53	65
	LOQ	00	
	UIQ	05	
	LIQ	03	
LEFT	UOQ	28	35
	LOQ	00	
	UIQ	05	
	LIQ	00	

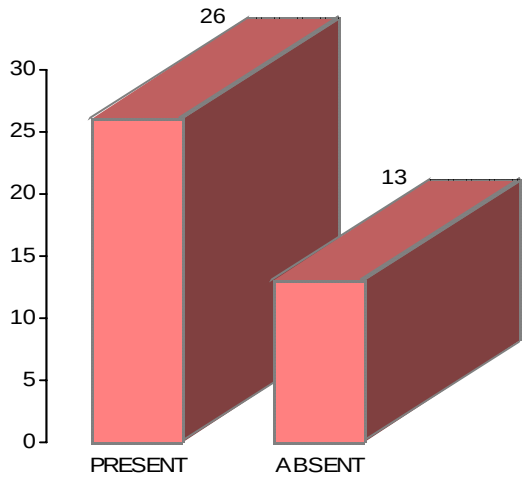
FIGURE-5 AGE AT FCB



AGE AT FCB

AGE AT FCB	TOTAL NO.	PERCENTAGE
16-20	08	22
20-24	16	45
24-28	08	22
28-32	03	08
32+	01	03

FIGURE-6 NODAL INVOLVEMENT



NODAL STATUS

NODAL STATUS	PRESENT	ABSENT
	67	33

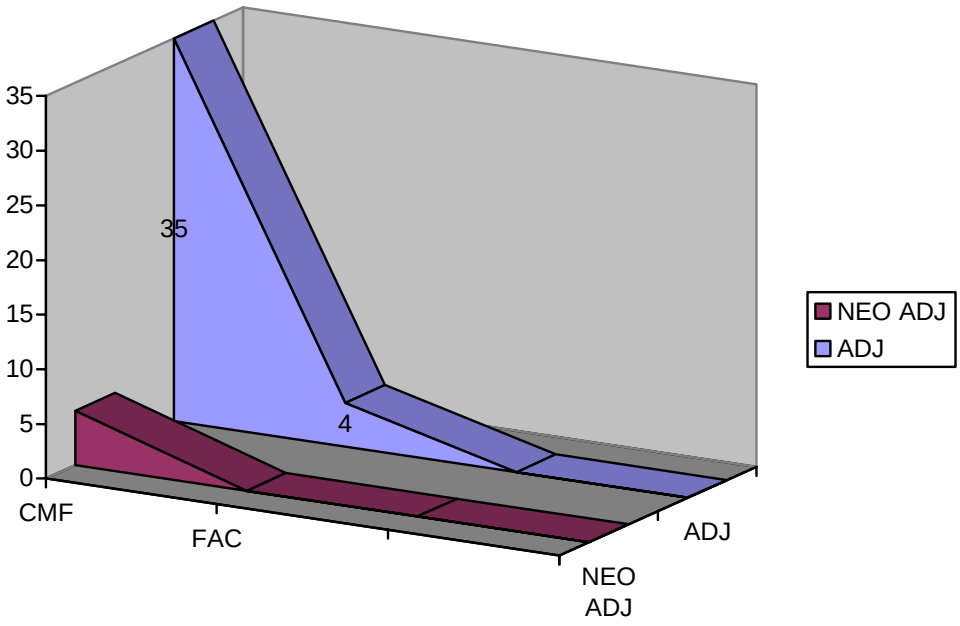


FIGURE-7 CHEMOTHERAPY

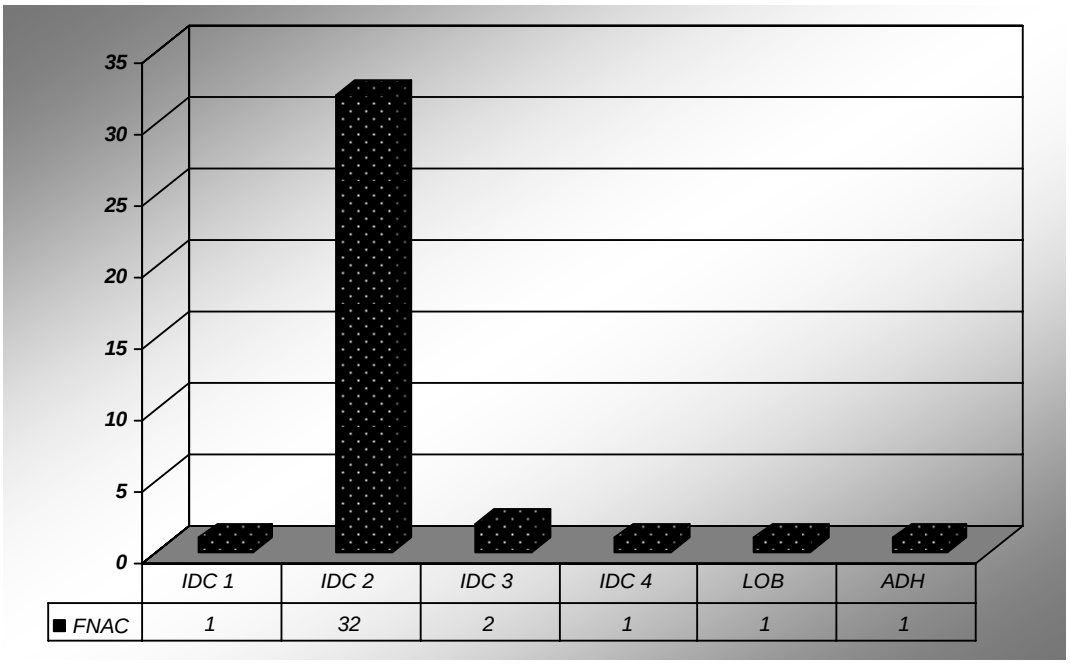
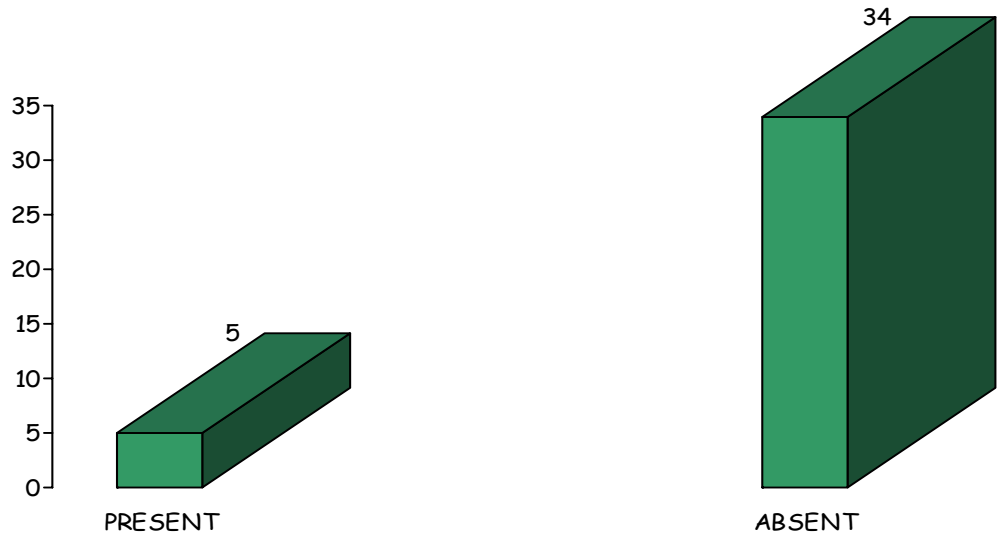


FIGURE-8 HISTOPATHOLOGICAL CORRELATION

FIGURE-9 RECURRENCE



RECURRENCE

RECURRENCE	PRESENT	ABSENT
	05(12.8%)	34(80.2%)

OBSERVATION AND RESULTS

A total of thirty-nine patients with the disease profile of labc were analyzed for the study. Patients belonged to various socioeconomic and geographical backgrounds.

The predominant age group of these patients was in the age group of 40-50 years (31%). The next common age of occurrence being 30-40 years (23%) and 50-60 years (18%) respectively.

The most common complaints of these patients included a sensation of lumps of varying sizes in the breast. About 30% of patients had complaints of skin manifestations like peau d'orange, skin ulceration, and retraction of the nipple was found in 5% of patients.

The presentation of lymph nodal enlargement was clinically established in 67% of the total no. of patients.the site of occurrence of the carcinoma was found to be predominantly on the right side in 65% of the studied group of patients.

The upper outer quadrant was the favoured location of occurrence of cancer in 54% of patients on the right and 29% on the left.

There was no specific correlation to the family history in any of the studied patients. Most patients had breast-fed their children from birth till the age of one year and no specific linkage could be made out in this regard.

Early attainment of menarche could be inferred from the study with 82% of patients studied attaining menarche between ages of 16-18. 64% of women had not attained menopause at the time of affliction of the disease as borne out by the study.

FNAC study of the lesions prdominantly indicated the presence of infiltrating ductal carcinoma of grade 2 and this was well substantiated by the histopathological examination of the surgical specimens.

Chemotherapy with the three drug regimen of cyclophosphamide, methotrexate, 5-flourouracil was given in a 6 cycle regimen .alternative methods of chemotherapy included neoadjuvant

therapy and addition of adriamycin in place of methotrexate in women with good cardiovascular status.

Surgical options included mainly simple mastectomy with axillary clearance through the same incision with one instance of modified radical mastectomy and one case of completion mastectomy in a case of a patient with post excision diagnosis of IDC.

Post-operative complications included only minor complications like grade-I lymphedema and shoulder stiffness

Hormonal therapy with tamoxifen formed the standard protocol and was given in the dosage of 10mg twice daily

Radiotherapy was in the form of EBRT to the chest wall and supraclavicular fossa with standard field size and 25 fractions of therapy designed to deliver 50 Gy to the intended area.

Recurrence rate of 12.8% was observed in the end of the study with three chest wall recurrences and two nodal recurrence (one in the supraclavicular nodal basin and one in Rotter's node)

DISCUSSION

The results in this study are in correlation with published results of similar hospitals around the world.

LABC forms one of the most common modes of presentation of breast cancer in developing nations as borne out by the fact that it forms 40-60% of total cancers of the breast.

The age adjusted incidence of LABC is in correlation with accepted international data.this corresponds to amean age of 48.4 to50.6 is studies in WJSO[40] and 41-50(33%) in studies at Columbia medical centre.

The paradigm shift is that witnessed in the profile of the disease occurring more in patients in the peri-menopausal/pre-menopausal age group with 64% of patients in that group.

The site of occurrence of the LABC is predominantly on the right side 65% (donegan's series-48%) and the upper outer quadrant is the commonest location 81 %(NCI database-35.7%; Donegan's series-40%)

The nodal positivity in LABC also parallels the absolute size of the tumor with an observed percentage of 67%as compared to 50.1-64.5 in studies by Nemoto et al. [41]and 80% in wjso studies.[40]

The histological correlate of IDC was in 89.7% of cases in comparison to 88.2% in wjso [40]studies and 79% in the ACS survey.

The concepts of early menarche still continue to hold sway in patients with breast cancer with 82% of subjects studied in the age group of 16-18.

The patterned administration of multimodal therapy in the form of surgery (simple mastectomy/axillary clearance) followed by six cycles of chemotherapy with cyclophosphamide/ methotrexate/5-flurouracil.

This was supplemented by hormonal therapy with tamoxifen in the dose of 20 mg daily and adjuvant radiation therapy.

No significant post-operative infections were noted in the course of the study with most patients undergoing primary closure of the skin after completion of surgical procedure. Complications were noted in some cases and included only minor degrees of lymphedema

and shoulder stiffness. No deaths were recorded in the study group as a result of surgery.

Routine follow-up done at fortnightly intervals with clinical examination of the patient for recurrence in the contra lateral breast(synchronous/metachronous),chest wall/scar site ,bilateral lymph nodal enlargement (clinical) and monthly ultrasonographic examination and bi-monthly radiological examination for distant metastasis was done.

As the period of the study was of the order of two years only definite prognostic indicators could not be assessed and needs further critical follow-up.

The loco regional recurrence was taken as an index of failure of multimodality therapy and the standardized results are envisioned as **12.8%** compared to international data following multimodality therapy.

s.no	Name of the study/author	% of loco regional recurrence
1	Delarue et al	15
2	Baker et al	22.6
3	Leis et al	13.8
4	Perez et al	19(5yrs)
5	Grohn et al	13

CONCLUSION

The following conclusions are drawn from this study

1. LABC is one of the most common presentations of carcinoma breast in this instituition .
2. The epidemiological profile is of the age group of women in the perimenopausal age group of 40-50
3. The site of occurrence of LABC is predominantly on the right side with the upper outer quadrant being the most common area.
4. Nodal affliction is one of the important prognosticators and histopathologically IDC grade 2 is the most common type.
5. Multimodality therapy administered with meticulous follow-up provides acceptable rates of loco regional failure.
6. The difficult conundrum of LABC still needs further analysis with respect to the efficacy of neo-adjuvant chemotherapy and longer periods of study are essential to validate the same.

ANNEXURES

ANNEXURE I

PROFORMA

Case No Hospital No:

Name : Age: Sex: M/F

Address :

COMPLAINTS

- Swelling/lump in the breast
- Swelling in the axilla
- Ulcer over the breast
- Discharge from the nipple
- Changes in the nipple
- Other complaints

PAST HISTORY

- Previous treatment history
- H/o Medications
- H/o previous surgery in the breast

PERSONAL HISTORY

MENSTRUAL HISTORY

- Age of menarche
- Regularity of periods
- Character of periods
- Age at menopause
- Any other significant correlate

MARITAL HISTORY/OBSTETRIC HISTORY

- Age at marriage
- Age at first child birth /mode of delivery
- Duration of breast feed
- Last child birth
- Parity
- Any method of contraception used
- Other correlates

FAMILY HISTORY

Incidence of breast swelling / Malignancy yes / No

GENERAL EXAMINATION

- Built
- Nutrition

- Weight
- Temperature
- Anaemia
- Pulse rate / rhythm / Volume/ character

SYSTEMIC EXAMINATION

- CVS
- Respiratory system
- Abdomen – Liver palpable / Non palpable
- CNS

LOCAL EXAMINATION

- CHARACTERISATION OF SWELLING
- Size
- Location right breast / left breast / quadrant / whole gland
- Surface smooth / nodular / irregular
- Consistency soft / cystic / firm / hard
- Mobility yes / no
- Position of nipple : Normal / deviated / discharge/retracted

- Skin over and around the breast
- Peau d'orange/skin fixity/deeper fixity
- Examination of ulcer (if any)
- Clinical examination of the axilla

OTHER LYMPH NODES YES / NO

- EXAMINATION OF SKELETAL SYSTEM

Bony tenderness / swelling/ fracture YES/NO

DIGITAL EXAMINATION

CLINICAL DIAGNOSIS

INVESTIGATIONS

- FNAC
- MAMMOGRAM
- USG ABDOMEN/PELVIS
- CHEST X-RAY
- LIVER FUNCTION TESTS
- OTHER ROUTINE INVSTIGATIONS
- ECG in all leads

Date of surgery

Surgical procedure done

Post operative complications

POST OP FOLLOW-UP

- Histo pathological report

CHEMOTHERAPY ADMINISTEREED

NEOADJUVANT/ADJUVANT- REGIMEN USED

CYCLES/COMPLICATIONS/RESPONSE

HORMONAL THERAPY

RADIOTHERAPY

- Dosage
- Field size
- Fractionation
- response

FOLLOW-UP

- clinical
- post chemotherapy
- post radiotherapy

RECURRENCE

- type of recurrence
- time of recurrence
- characterization of recurrence

ANNEXURE II

EVOLUTION OF STAGING SYSTEMS

PORTMANN CLASSIFICATION[22]

Stage I Skin –not involved

Tumor- localized to breast, mobile

Metastasis –none

Stage II Skin- not involved

Tumor –localized to breast, mobile

Metastasis-few axillary nodes in microscopic evaluation, no other metastasis

Stage III Skin –edematous; extensive ulcerations, multiple secondary nodules

Tumor-diffusely infiltrating breast, fixation to chest wall, edema of breast

Metastasis-axillary nodes involved or fixed, no distant metastasis

Stage IV Skin-involved or not involved

Tumor-localized or diffuse

Metastasis-evidence of distant metastasis

MANCHESTER CLASSIFICATION 1940[23]

Stage I-

Tumor confined to breast, area of skin involvement present provided area is small in relation to size of the breast

Stage II-

Tumor confined tom breast and associated axillary lymph nodes are present

Stage III-

Tumor extends beyond the breast evidenced by;

a. skin invasion of large area in relation to breast
b. tumor fixation tom underlying muscle/ fascia : nodes mobile

Stage IV –

Fixation or matting of lymph nodes

Fixation of tumor to chest wall

Deposits in supraclavicular nodes or opposite breast

Satellite nodules or distant metastasis.

COLUMBIA CLINICAL CLASSIFICATION (Haagenssen)[12]

Stage A

No skin involvement or fixation of tumor to chest wall. Axillary nodes not palpable.

Stage B

No skin involvement or fixation of tumor to chest wall.clinically palpable nodes 2.5 cm or less no evidence of fixity to deeper structures or skin.

Stage C

Any one of five grave signs of advanced breast carcinoma

Limited edema of skin involving less than 1/3rd of skin over breast.

Skin ulceration.

Fixation of tumor to chest wall

Massive involvement of axillary nodes measuring >2.5 cm in transverse diameter.

Fixation of axillary lymph nodes to skin or underlying structures.

Stage D

Advanced breast carcinoma

Combination of two or more signs under stage C

Satellite skin nodules/ extensive edema of skin/ edema of arm

Inflammatory breast cancer

Supraclavicular node/ internal mammary node involvement

Distant metastasis.

TNM CLASSIFICATION[24]

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification.

TNM definitions --

Primary tumor (T):

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated tumor.

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1: Tumor 2.0 cm or less in greatest dimension

T1mic: Microinvasion 0.1 cm or less in greatest dimension

T1a: Tumor more than 0.1 but not more than 0.5 cm in greatest dimension

T1b: Tumor more than 0.5 cm but not more than 1.0 cm in greatest dimension

T1c: Tumor more than 1.0 cm but not more than 2.0 cm in greatest dimension

T2: Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension

T3: Tumor more than 5.0 cm in greatest dimension

T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below.

Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

T4a: Extension to chest wall

T4b: Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast

T4c: Both of the above (T4a and T4b)

T4d: Inflammatory carcinoma

Regional lymph nodes (N):

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)

N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral axillary lymph node(s)

N2: Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures

N3: Metastasis to ipsilateral internal mammary lymph node(s)

Pathologic classification (pN):

pNX: Regional lymph nodes cannot be assessed (not removed for pathologic study or previously removed)

pN0: No regional lymph node metastasis

pN1: Metastasis to movable ipsilateral axillary lymph node(s)

pN1a: Only micrometastasis (none larger than 0.2 cm)

pN1b: Metastasis to lymph node(s), any larger than 0.2 cm

pN1bi: Metastasis in 1 to 3 lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension

pN1bii: Metastasis to 4 or more lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension

pN1biii: Extension of tumor beyond the capsule of a lymph node metastasis less than 2.0 cm in greatest dimension

pN1biv: Metastasis to a lymph node 2.0 cm or more in greatest dimension

pN2: Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures

pN3: Metastasis to ipsilateral internal mammary lymph node(s)

Distant metastasis (M):

MX: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)

AJCC stage groupings

STAGE 0

Tis, N0, M0

STAGE I

T1,* N0, M0

*T1 includes T1mic

STAGE IIA

T0, N1, M0

T1,* N1,** M0

T2, N0, M0

*T1 includes T1mic

**The prognosis of patients with pN1a disease is similar to that of patients with pN0 disease.

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

*T1 includes T1mic

STAGE IIIB

T4, Any N, M0

Any T, N3, M0

STAGE IV

Any T, Any N,M1

ANNEXURE III

	NAME	AGE	SYMPT.	SIZE	L.N.STAT	ASS.SIGN	ASSH/O	FAM	MARI	FCB/PARITY	MENSTRUAL PROFILE
											AOME/REG/AOMp
1	RANGAMMAL	53	LT.UOQ/LOQ	4X3	CEN./NF	RET.NIP		NIL	25	26/3	16/R/48
2	SARASWATHY	40	LT.UOQ	5X3			IHD	NIL	24	25/2	14/R/
3	SANKARAMMAL	60	LT.UOQX10/12	5X4	CEN./NF	ULCER 4X3		NIL	22	23/3	15/R/45
4	MUTHUMARI	50	RT.UOQX1/12	8X6	CEN./NF	PDO/SKI.INF		NIL	20	21/3	16/R/48
5	PACKIAJOTHI	27	RT.UOQX2/12			PECT.FIXITY	FA+	NIL	25	26/1	16/R/
6	SELVARANI	27	RT.UOQ-1/12	5X3	CEN./NF			NIL	32	36/2	16/R/
7	MANJU	41	RT.UOQ-2yrs	6X5		PECT.FIXITY		NIL	18	19/2	16/R/
8	MICHAELAMMAL	27	RT.UIQ-3yrs	5X4	ANT./NF		LAP.INF	NIL	24	NIL	16/R/
9	SUBBULAKSHMI	33	RT.UOQ-6/12	5X3				NIL	24	26/1	16/R/
10	AHMED MALLIKA	30	LT.AllQ-2/12	15X10			HT	NIL	20	23/2	14/R/
11	PAPPA	62	LT.UIQ-6/12	12X10	CEN./NF			NIL	22	23/2	16/R/45
12	STELLA	30	RT.UOQ-1.5/12	5X2	CEN./NF/2		DM	NIL	24	25/2	17/R
13	MUTHUSELVI	45	RT.UOQ-6/12	4X3	CEN./NF			NIL	18	19/3	15/R/
14	POOMANI	35	LT.UOQ-2/12	4X3	CEN./NF			NIL	16	18/4	15/R
15	SEENIAMMAL	46	LT.UOQ-2yrs	5X3	CEN./NF		BR.ASTH	NIL	22	23/4	18/R/45
16	ARUMUGHAM	53	RT.UOQ-1yr	5X3	ANT./NF			NIL	18	19/2	16/R48
17	SINGARI	38	LT.UOQ-1yr	10X8	CEN./NF	PDO/SKI.INF		NIL	20	21/2	18/R
18	LOURDUAMMAL	40	RT.UOQ	12X8	CEN./NF			NIL	22	24/2	17/R
19	FATHIMA	32	RT.UOQ	10X6	CEN./NF		ANEMIA	NIL	21	26/1	18/R
20	GANDHIMATHI	60	RT.UOQ	4X2		PDO/SKI.INF		NIL	18	31/3	18/R/49
21	GURUVAMMAL	34	RT.UOQ	10X7	CEN./NF	CYSTIC AREA+		NIL	20	21/1	17/R
22	ASHMA	45	LT.UOQ-6/12	6X5				NIL	20	22/3	17/R
23	VALLIMAYIL	50	RT.UOQ	4X2		PDO/ERY+		NIL	19	20/1	18/R
24	ARULMARI	65	RT.UOQ	5X3				NIL	19	20/6	18/R/50
25	VASANTHA	35	LT.UOQ	5X4				NIL	19	20/3	18/R
26	SELVI	25	LT.UIQ	7X6				NIL	18	23/2	17/R
27	ELISAMMAL	53	RT.UOQ	7X5		PAGET'S +		NIL	19	20/5	17/R45
28	VELLATHAI	65	RT.allquad.		MULT./NF			NIL	19	28/1	17/R48
29	MOOKAMMAL	47	LT.UOQ	10X5				NIL	17	18/3	16/R
30	SEETHALAKSHMI	40	LT.UOQ	3X3	CENT./2RT.F			NIL	17	18/4	16/R
31	MEENATCHI	50	RT.UOQ	3X4	CEN./NF	SKIN.INF	DM	NIL	20	NIL	20/IRR/45
32	MUTHAMMAL	36	LT.UOQ	5X5	CEN./NF			NIL	19	20/2	18/R
33	PATHIRAKALI	75	RT.UOQ	5X5	CEN./NF			NIL	18	19/4	17/R48
34	POOMANI	41	RT.UOQ	5X4	CEN./NF			NIL	21	30/2	18/R/
35	RAJALAKSHMI	40	RT.LIQ	6X4	CEN./NF		DM	NIL	UNM		18/R

OBST.H/O	BR.FD	CONT	FNAC	OTH.INV.	CHEMOTHERAPY		SURGERY	HPE	HOR.TPY	RT	FOLLOW UP/RECURR
FCB/PARITY					REGIME	CYCLES/PRE/POST					
26/3	Y		IDC G2		CMF	0/0/6	TM/AC	IDC	TAMX2	CHEST/SCF-25 #	
25/2	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
23/3	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
21/3	Y		IDC G2		FAC	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
26/1	Y				CMF		Compl mas	IDC	TAMX2	CHEST/SCF-25 #	
36/2	Y	PS	IDC G2		CMF	0/2/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
19/3	Y		IDC G2		CMF	0/3/3	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
NIL	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
26/1	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
23/2	Y		IDC G2		CMF	0/2/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
23/2	Y		IDC G2		CMF	0/0/6	SM/AC.PO	IDC	TAMX2	CHEST/SCF-25 #	
25/2	Y	TAT	IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
19/3	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
18/4	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
23/4	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
19/2	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
21/2	Y		IDC G2		CAF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
24/2	Y		IDC G2		CMF	0/0/6 D1-D8 REGIME	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	CHEST WALL/BONY-1 YEAR
26/1	Y		IDC G2		FAC	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	RT.SUPRACLAV.NODAL
31/3	Y		IDC G2		FAC	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
19/1	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
20/3	Y		LOBULAR	mammo-lt.ca	CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
22/3	Y		IDC G2		CMF	2/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
20/6	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
20/3	Y		IDC G2		CMF	0/0/6	SM/AC	IDC/SecN	TAMX2	CHEST/SCF-25 #	
23/2	Y		ADH		CMF	0/0/6	SM/AC	IDC/FCD	TAMX2	CHEST/SCF-25 #	
20/5	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
28/1	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
18/3	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
18/4	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
NIL			IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
	Y		IDC G2		CMF	0/0/6	MRM	IDC	TAMX2	CHEST/SCF-25 #	
	Y		IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
30/2	Y		IDC G1		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
UNMARRIED			IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
24/6	Y		IDC G4		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	I YEAR-ROTTER NODE+
21/6	Y		IDC G3	fibroadenoma.lt	CMF	2/IRREGULAR	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	
	Y	TAT	IDC G2		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	CHEST WALL-1 YEAR
	Y		IDC G3		CMF	0/0/6	SM/AC	IDC	TAMX2	CHEST/SCF-25 #	CHEST WALL-1 YEAR

BIBLIOGRAPHY

1. DAVIDSON;PAGE-BLAND&COPELAND THE BREAST THIRD EDITION;2004
2. MOREHEAD JR;ANATOMY AND EMBRYOLOGY OF THE BREAST,*CLIN OBST GYNAEC 25:353,1982*
3. SPRATT JS;ANATOMY OF THE BREAST, *MAJOR PROBL CLIN SURJ 5:1,1979*
4. SPRATT JS JR,DONEGAN WL,CANCER OF THE BREAST,ED 3,1979
5. MONTAGU A:NATURAL SELECTION IN THE FORM OF BREAST IN FEMALE,*JAMA*,180:826,1962
6. GIACOMETTI L,MONTAGNA W;THE NIPPLE AND AREOLA OF THE HUMAN FEMALE BREAST,*ANAT REC* 144;191,1962
7. GRIFE RM:*THE ANSA PECTORALIS: ANATOMY AND APPLICATIONS,*2002 AACA
8. MOOSMAN DA:ANATOMY OF THE PECTORAL NERVES AND THEIR PRESERVATION IN MODIFIED MASTECTOMY,*AM J SURG,*139:883,1980
9. CUNNINGHAM L:THE ANATOMY OF THE ARTERIES AND VEINS OF THE BREAST,*J SURG ONCOL,9:71,*1977
10. SAKKI S:ANGIOGRAPHY OF THE FEMALE BREAST:*ANN CLIN RES,*1974
11. MILLER MR:CUTANEOUS INNERVATION OF THE HUMAN BREAST,*ANAT REC* 135:153,1959
12. HAAGENSEN CD: ANATOMY OF THE MAMMARY GLANDS,*DISEASES OF THE BREAST,*ED 3,1986
13. CLARK GM: PROGNOSTIC FACTORS AND TREATMENT DECISIONS IN AXILLARY NODE NEGATIVE BREAST CANCER,*N ENGL J MED* 326:1756,1992

14. FISHER B,SLACK NH,BROSS JD: CANCER OF THE BREAST:SIZE OF NEOPLASM AND PROGNOSIS,*CANCER* 24:1071,1969
15. FISHER ER,PROGNOSTIC AND THERAPEUTIC SIGNIFICANCE OF PATHOLOGICAL FEATURES OF BREAST CANCER,*NCI MONOGR* 29,1986
16. *WHO INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS:*GENEVA,1981 ,WHO
17. HOGE AF:HISTOLOGICAL AND STAGING CLASSIFICATION OF BREAST CANCER,*SOUTH MED J* 75:1329,1982
18. BLOOM H,RICHARDSON W:HISTOLOGIC GRADING AND PROGNOSIS IN BREAST CANCER,*BR J CANCER* 11:359,1957
19. FISHER ER:DETECTION AND SIGNIFICANCE OF OCCULT AXILLARY NODE METS IN BREAST CANCER,*CANCER* 42:2025,1978
20. OSBORNE CK CURRENT USE OF STEROID HORMONE RECEPTOR ASSAYS IN BREAST CANCER,*SCNA*,58:777,1978
21. HENDERSON IC ,*NEJM,*302:17,1980
22. PORTMANN UV:*CLEVE CLIN Q* 10:41,1943
23. PATTERSON R:THE TREATMENT OF MALIGNANT DISEASE BY RADIUM AND X-RAYS,1948,EDWARD ARNOLD
24. BREAST. IN: AMERICAN JOINT COMMITTEE ON CANCER: AJCC CANCER STAGING MANUAL. PHILADELPHIA, PA: LIPPINCOTT-RAVEN PUBLISHERS, 5TH ED., 1997, PP 171-180.
25. KJ

26. McGuire WL, De La Garza M, Chamness GC. Evaluation of estrogen receptor assays in human breast cancer tissue. Cancer Res 1977;37:637.
27. King WJ, Greene GL. Monoclonal antibodies localize oestrogen receptor in the nuclei of target cells. Nature 1984;307:745.
28. Chopra R. The Indian Scene JCO 2001;19:106S-111S
29. McWhirter R, The value of simple mastectomy and radiotherapy in the treatment of cancer of the breast. Brit J Radiol 1948;21:599-610.
30. Graham MV, Perez CA, Kuske RR, et al. Locally advanced (noninflammatory) carcinoma of the breast: Results and comparison of various treatment modalities. Int J Radiat Oncol Biol Phys 1991;21:311.
31. Hortobagyi GN, Blumenschein GR, et al. Multimodal treatment of locally advanced breast cancer. Cancer 1983;51:763-8.
32. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001;30:96-102.
33. Fisher ER, Wang J, Bryant J, et al. Pathobiology of preoperative chemotherapy: Findings from the National Surgical Adjuvant

BREAST AND BOWEL (NSABP) PROTOCOL B-18. CANCER 2002;95:681-95.

34. SMITH IC, HEYS SD, HUTCHEON AW, ET AL. NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER: SIGNIFICANTLY ENHANCED RESPONSE WITH DOCETAXEL. J CLIN ONCOL 2002;20:1456-66.
35. SCHABEL FM. CONCEPTS FOR SYSTEMIC TREATMENT OF MICROMETASTASES. CANCER 1975;30:15-24.
36. LIPPMAN ME, CASSIDY J, WESLEY M, ET AL. A RANDOMIZED ATTEMPT TO INCREASE THE EFFICACY OF CYTOTOXIC CHEMOTHERAPY IN METASTATIC BREAST CANCER BY HORMONAL SYNCHRONIZATION. J CLIN ONCOL 1984;2:28.
37. BARTELINK H, RUBEN RD, ET AL. HORMONAL THERAPY PROLONGS SURVIVAL IN IRRADIATED LOCALLY ADVANCED BREAST CANCER: A EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER RANDOMIZED PHASE III TRIAL. J CLIN ONCOL 1997;15:207.
38. PAPAIOANNOU A, LISSAIOS B, VASILAROS S, ET AL. PRE- AND POSTOPERATIVE CHEMOENDOCRINE TREATMENT WITH OR WITHOUT POSTOPERATIVE RADIOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER. CANCER 1983;51:1284-90.
39. SINGLETARY S, MCNEESE M, HORTOBAGYI G. FEASIBILITY OF BREAST CONSERVATION SURGERY AFTER INDUCTION CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CARCINOMA. CANCER 1991;69:2849.
40. WJSO: CLINICAL CONSIDERATES IN BREAST CANCER

41. NEMOTO T ET AL:CANCER 45:2917,1980

42. HUTTER RVP: CANCER 46:961,1980

43. DELARUE NC ET AL:SURGICAL GYNAEC AND OBSTETRICS 129:79,1969

44. BAKER RR ET AL: ANN SURG,189:553,1979

45. PEREZ CA, GRAHAM ML, ET AL. MANAGEMENT OF LOCALLY ADVANCED BREAST CARCINOMA OF THE BREAST. I. NON-INFLAMMATORY. CANCER 1994;74:453-65

46. GROHN P ET AL:ADJUVANT POSTOPERATIVE CHEMOTHERAPY,RADIOTHERAPY,HORMONAL THERAPYIN LOCALLY ADVANCED BREAST CANCER,*CANCER,*54:670,1984

47. HORTOBAGYI GN, SINGLETARY SE. TREATMENT OF LOCALLY ADVANCED AND INFLAMMATORY BREAST CANCER. IN. DISEASE OF THE BREAST, 2ND ED. EDITOR. HARRIS JR. PHILADELPHIA: PUB. LIPPINCOTT, WILLIAMS AND WILKINS; 2000. P. 645-60.

48. BAILEY & LOVE'S SHORT PRACTICE OF SURGERY. 24TH EDITION EDITED BY R.C.G. RUSSELL, NORMAN S.WILLIAMS & CHRISTOPHER J.K.BULSTRODE

49. PRINCIPLES OF SURGERY 7TH EDITION SEYMOUR I. SCHWARTZ, G. TOM SHIRES, FRANK C SPENCER , WENDY COWLES HASSUR

50. ESSENTIAL SURGICAL PRACTICE. HIGHER SURGICAL TRAINING IN GENERAL SURGERY . FOURTH EDITION . SIR ALFRED CUSCHIERI, ROBERT J.C.STEELE , ABDOOL RAHIM MOOSA

51. OXFORD TEXT BOOK OF SURGERY 1&2ND EDITIONS, EDITED BY PETER J.MORRIS AND RONALD A.MALT

52. SABISTON TEXT BOOK OF SURGERY SEVENTEENTH EDITION COURTNEY M.TOWNSEND,JR.,

53. FROM EORTC WEB SITE www.eortc.be

54. ANONYMOUS. BREAST. IN: FLEMING ID, COOPER JS, HENSON DE, ET AL, EDS. AJCC CANCER STAGING MANUAL, 5TH ED. PHILADELPHIA: LIPPINCOTT–RAVEN1997:171.

55. HORTOBAGYI GN, BUZDAR AU. LOCALLY ADVANCED BREAST CANCER: A REVIEW INCLUDING THE M.D. ANDERSON EXPERIENCE. IN: RAGAZ J, ARIEL IM, EDS. HIGH-RISK BREAST CANCER. BERLIN: SPRINGER-VERLAG, 1991:382.

56. EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP. EFFECTS OF ADJUVANT TAMOXIFEN AND OF CYTOTOXIC THERAPY ON MORTALITY IN EARLY BREAST CANCER. AN OVERVIEW OF 61 RANDOMIZED TRIALS AMONG 28,896 WOMEN. N ENGL J MED 1988;319:1681.

57. EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP. POLYCHEMOTHERAPY FOR EARLY BREAST CANCER: AN OVERVIEW OF THE RANDOMISED TRIALS. LANCET 1998;352:930.

58. DELENA M, VARINI M, ZUCALI R, ET AL. MULTIMODAL TREATMENT FOR LOCALLY ADVANCED BREAST CANCER. RESULTS OF CHEMOTHERAPY-RADIOTHERAPY VERSUS CHEMOTHERAPY-SURGERY. CANCER CLIN TRIALS 1981;4:229

59. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997;15:2483.

60. Hortobagyi GN. Overview of new treatments for breast cancer. Breast Cancer Res Treat 1992;21:3..

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