EFFICACY OF SINGLE CYCLE NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST

By

Dr. CHANDAN.K.R

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

GENERAL SURGERY

Under the Guidance of

Dr. SHASHIREKHA.C.A

Associate Professor

DEPARTMENT OF GENERAL SURGERY,
SRI DEVARAJ URS MEDICAL COLLEGE,
TAMAKA, KOLAR-563101

2016

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by me under the guidance of

Dr. SHASHIREKHA.C.A,

Associate Professor,

Department of General Surgery,

Sri Devaraj Urs Medical College & Research center,

Tamaka, Kolar.

DATE: SIGNATURE OF THE CANDIDATE

PLACE: KOLAR **DR. CHANDAN K.R.**

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION,

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Dr. CHANDAN.K.R

Under my guidance and supervision,

in partial fulfillment of the requirement for the Degree of

M.S. in ***GENERAL SURGERY***

Signature of the Guide

Dr.SHASHIREKHA.C.A,

Associate Professor,

Department of general surgery,

Sri Devaraj Urs Medical College,

& Research Center, Tamaka, Kolar.

Date:

Place : Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA

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Dr. MOHAN KUMAR. K
Professor & HOD
Department of General Surgery,
Sri Devaraj Urs Medical College,
& Research Center, Tamaka, Kolar

Date:
Place: Kolar

Dr. B. G. RANGANATH
Principal,
Sri Devaraj Urs Medical College
& Research Center, Tamaka, Kolar

Date:
Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College & Research Center, Tamaka, Kolar has unanimously approved

Dr. CHANDAN.K.R

Post-Graduate student in the subject of

GENERAL SURGERY *at Sri Devaraj Urs Medical College, Kolar*

to take up the Dissertation work entitled

"EFFICACY OF SINGLE CYCLE NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST"

to be submitted to the

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA,

Date:

Place: Kolar

Member Secretary

Sri Devaraj Urs Medical College,

& Research Center,

Tamaka, Kolar–563101

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LIST OF ABBREVIATIONS USED

ALND	Axillary lympn node dissection
BCT	Breast conserving therapy
CBC	Complete Blood count
CC	Craniocaudal view
CEA	Carcino embryonic antigen
DCIS	Ductal carcinoma in situ
ER/PR	Estrogen receptor/progesterone receptor
FNAC	Fine needle aspiration cytology
LABC	Locally advanced breast cancer
LFT	Liver Function test
MLO	Mediolateral oblique view
MRI	Magnetic resonance imaging
MRM	Modified radical mastectomy
NACT	Neo adjuvant chemotherapy
NOS	Nothing otherwise specified
NSABP	National Surgical Adjuvant Breast and Bowel Project
PCR	Polymerase chain reaction
QUART	Quadrantectomy, Axillary dissection, radiotherapy
SD	Stable disease
SLN	Sentinel lymph node
USG	Ultrasonography

ABSTRACT

TITLE OF THE TOPIC: EFFICACY OF SINGLE CYCLE NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST

NEED FOR THE STUDY: Carcinoma of the breast from the very beginning has been a feared disease. Medical research and efforts by various groups and individuals has given number of modalities of treatment of breast cancer, each of which are incomplete in themselves, and have to be supplemented by another.

Our hospital is a tertiary care center in rural side, since most of the patients with carcinoma breast are from poor socioeconomic status they are not affordable for full course of neo adjuvant chemotherapy and it difficult to follow up the patients due to their ignorance about the disease so our intention is to see the efficacy of single cycle neo adjuvant chemotherapy in carcinoma breast.

OBJECTIVES OF THE STUDY:

- To evaluate and quantify the response to single cycle neo-adjuvant chemotherapy in terms of
  a) Reduction in size of primary tumor
  b) Change in the clinical stage of the tumor , in stage IIB and IIIA breast cancer.

MATERIAL AND METHODS:

Source of Data: A total number of 25 cases of breast carcinoma were selected for the study. All the patients diagnosed as breast carcinoma with stage IIB and IIIA and admitted in surgical wards were selected for this prospective study at R.L.JALAPPA. HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR attached to SRI

DEVARAJ URS MEDICAL COLLEGE between December 2013 and June 2015 Clinical tumor size was estimated before the start of chemotherapy (FAC regimen) and after an interval of 10 days by sonomammographically.

RESULTS:

In our study we found that there is decrease in tumor size in 16% of patients (i.e 4 patients among 25) in those who received single cycle neo adjuvant chemotherapy in patients with stage IIB and IIIA patients. With 95% confidence interval ranging from 6.40-34.65.

This decrease in tumor size has resulted in down staging among three cases (down staged from stage IIB to stage IIA).

INTERPRETATION AND CONCLUSION:

In our study we found that single cycle NAC does not decrease the tumor size in significant number. The decrease in tumor size was noticed in patients who had no nodal involvement and in multiparous women.

Single cycle Neoadjuvant chemotherapy is preferred in patients who cannot take up 3 cycles of NAC. These patients can be tried with single cycle NAC which helps to halt the disease in tumor progression.

Keywords: Single cycle, Neo adjuvant chemotherapy, Breast Cancer.

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INTRODUCTION

Carcinoma of the breast from the very beginning has been a feared disease. Till today, there is an aura of fear that surrounds the mention of this name 'breast cancer'. Medical research and efforts by various groups and individuals has given number of modalities of treatment of breast cancer, each of which are incomplete in themselves, and have to be supplemented by another.

Among all modalities of treatment, surgery has come to be accepted as the 'golden standard', to which all other modalities of treatment have to be compared. Halsted's radical mastectomy has been accepted as the main factor for comparison of results of any form of treatment, that is, the results of treatment of breast cancer by any modality or a combination of modalities have to be compared to results obtained by Halsted with his radical mastectomy. Other modalities of treatment such as chemotherapy and radiotherapy are considered as adjuvant to surgery and are incomplete by themselves.

Chemotherapy in the treatment of breast cancer has assumed a greater significance ever since researchers have given breast cancer the status of a systemic disease. Surgery as such can eradicate only the local disease, and eradication of the systemic component involves the use of chemotherapeutic agents. Chemotherapy may be given as an adjuvant post operatively , or as Neo-adjuvant chemotherapy where two to three doses are given prior to surgery, followed by the remaining cycles post-operatively. Occasionally in very advanced cases, chemotherapy alone

may be given as a palliative measure, when any form of surgery is likely to result in extensive deformity that will compromise on quality of life without a significant increase in life span.

Our hospital is a tertiary care center in rural side, since most of the patients with carcinoma breast are from poor socioeconomic status they are not affordable for full course of neo adjuvant chemotherapy and it difficult to follow up the patients due to their ignorance about the disease so our intention is to see the efficacy of single cycle neo adjuvant chemotherapy on carcinoma breast. This dissertation deals with the administration of Neo-adjuvant chemotherapy in patients who have been worked up for surgery. All patients were given one cycle of a chemotherapeutic regimen as per recommended doses, and the effect was studied ten days after the cycle, just prior to surgery. However, the long term follow up of patients and a formal comparison of the 5 – year survival rates and recurrence/metastasis between Neo-adjuvant and routine post operative chemotherapy was out of the scope of this dissertation.

AIMS AND OBJECTIVES

- To evaluate and quantify the response to single cycle neo-adjuvant chemotherapy in terms of :

  a) Reduction in size of primary tumor

  b) Change in the clinical stage of the tumor , in stage IIB and IIIA breast cancer

REVIEW OF LITERATURE

HISTORY [1] Cancer of the breast, with its uncertain cause has captured the attention of physicians throughout the ages. Despite centuries of theoretical meanderings and scientific enquiry, breast cancer remains one of the most dreaded of human diseases. However progress has been made in lessening the horrors that formerly devastated the body and psyche by the contribution of many doctors and scientists over many hundred years, although the milestones listed here are important ones, the list is by no means comprehensive.

A well documented case history of Hippocrates (b.460 BC) describes a woman with breast cancer associated with bloody discharge from nipple. He also associated breast cancer with cessation of menstruation. Aurelius Celsus (b.25BC) - wrote "De Medicina" which contains an early clinical description of cancer .In it he mentions the breast of women as one of the sites of cancer and describes a fixed irregular swelling with dilated torturous veins and ulcerations. The great physician Leonides is credited with the first operative treatment of breast cancer in first century AD. Galen (b.131AD) described breast cancer as swelling with dilated veins resembling the shape of a crab's leg. Rhazes (b.860) one of the great Arabic physician condoned excision of breast cancer only if it could be completely removed and the underlying tissue cauterized.

Anrdeas Vesalius (b.1514) recommended mastectomy for breast cancer and the use of sutures rather than cautery. Ambrose Pare (b.1510) condoned the excision of superficial breast cancer but attempted to treat other breast cancer through application of lead plates which were intended to arrest blood supply and tumor growth.He made the important observation that breast

cancer often caused the swelling of the axillary glands. Wilhelm Fabry (b.1560) who is held in esteem as the "Father of German surgery", he devised an instrument that compressed and fixed the base of the breast so that a knife could amputate it more swiftly and less painfully. Pieter Camper (b.1722) described and illustrated the internal mammary lymph nodes. Henri Le Dran (b.1685) concluded that cancer was a local disease in its early stages and that it's spread to the lymphatic system signalled a worsened prognosis.

In the later years of 20th century, Donold Morton at the John Wayne cancer centre in Santa monica, CA developed the sentinel lymph node biopsy technique. Two months after the invention of x-ray, Emil Grubbe (b.1875) irradiated a patient with breast cancer. In 1889 Albert Schinzinger (b.1827) proposed oophorectomy before mastectomy to produce early aging in menstruating woman. In 1953 Charles Huggins advocated oophorectomy and adrenalectomy to remove the major source of oestrogen in the body.

Cooper advised combination chemotherapy for advanced carcinoma of breast. Fisher used tholepin during and immediately after surgery. He used chemotherapy for premenopausal women if four or more lymph nodes positive for metastases with improved survival rates. McMahon and co-workers (1973) raised the hypothesis that women who developed breast cancer were more exposed to estradiol and estrone.

The NSABP (National Surgical Adjuvant Breast and Bowel Project) in USA used a two year course of Melphalan (L-pam) in patients with histopathologically positive nodes and showed recurrence free survival rate as 22% in the placebo group compared with 9.7% percent for the patients receiving Melphalan. But subsequently Fisher (1981) in long term trails failed to show any advantage in survival and concluded that any effect of the Melphalan is to delay the

appearance of clinically detectable metastasis without having any effect on subsequent survival. This was confirmed by a British study of the same design (Rubbens-1983 combined results from south Manchester and Guy's Hospital). Jones advised combination of cytoxan and adriamycin in adjuvant chemotherapy. Bonadonna from the Milan trial started CMF(Cyclophosphamide, Methotrexate, 5-Flurouracil) regimen in both pre and post menopausal node positive woman and showed significantly improved relapse free survival compared to controls. Rossi in 1981 showed that the Milan CMF trial does continued to give some encouragement after longer follow up. At five years the predicted survival rate and for treated patients is 78% compared with 68% for controls and this is significantly better. Exactly similar results from England for CMF therapy were found by the Manchester – Guy's group.

In 1977 a British Multicenter trial was set up to evaluate Tamoxifen as an adjuvant to local treatment for patients with operable breast cancer and showed statistically significant survival. Samalley et al and Blumenschien et al started FAC regime (5- Fluorouracil, Adriamycin, Cyclophosphamide) with improved survival rates. Nisen Meyer from Scandinavia showed 6 day course of intravenous Cyclophosphamide, immediately after operation having survival advantage of more than 10% which is still apparent at 15 years of follow up with reduced toxicity problem.

French Epirubicin study group (1988) and Italian Multicentre Breast Study (1988) started using FEC regime (5- Fluorouracil, Epirubicin, Cyclophosphamide) in clinical trials with less cardio-toxicity and comparable survival rates. Millward et al introduced Ifosfamide and Doxorubicin regime in clinical trials. Jodreu et al introduced Mitoxantrone, Methotrexate, Folinicacid and Mitomycin regime. Becher et al introduced Ifosfamide , Epirubicin, Ifosfamide,

Methotrexate and 5-FU trials. Recently, a number of prognostic variables are described for breast cancers that determine recurrence and overall survival.

The first preliminary clinical evaluation of tamoxifen to treat advanced breast cancer was conducted by Cole 26 at the Christie Hospital in Manchester. The efficacy of tamoxifen proved to be equivalent to that of androgens or high dose estrogens in post menopausal women, but the side effects of tamoxifen were mild in comparison. Similarly Ward 27 conducted a small dose response study of tamoxifen and found side effects to be insignificant. Tamoxifen is now the most successful and widely used endocrine therapy for the treatment for breast cancer. Tamoxifen's antitumour effect is believed to be mediated primarily through the ER, although other potential mechanisms of action may contribute. In most of the early clinical trials of tamoxifen in patients with advanced disease, the daily oral dose of 20-40mg was administered. No significant increase in tumor response was observed with higher daily dose.

EMBRYOLOGY

At the fifth or sixth week of fetal development, two ventral bands of thickened ectoderm (mammary ridges or milk lines) are evident in the embryo. In most mammals, paired breasts develop along these ridges, which extend from the base of the forelimb to the region of the hind limb (inguinal area). Each breast develops when an ingrowth of ectoderm forms a primary tissue bud in the mesenchyme. The primary bud, in turn initiates the development of 15 to 20 secondary buds and extend into the surrounding mesenchyme.[2] At birth the breasts are identical in males and females. Enlargement of breast may be evident and a secretion, referred to as witch's milk may be produced. The breast remains undeveloped in the female until puberty,

when it enlarges in response to ovarian estrogen and progesterone, which initiates proliferation of the epithelial and connective tissue elements.

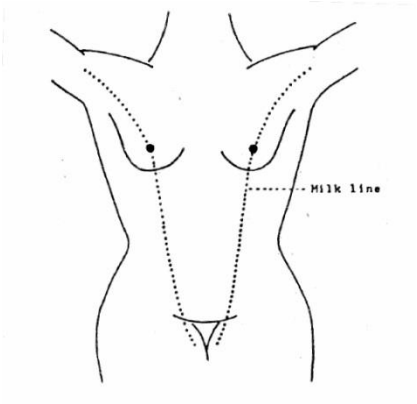


Fig 1:- Mammary Ridge

FUNCTIONAL ANATOMY EXTENT:

The breasts are modified sweat glands, which extend from the level of second to seventh rib. It extends transversely from the lateral border of the sternum to the anterior axillary line.[3] The deep surface of the breast rests on the fascia of the pectoralis major, serratus anterior and external oblique abdominal muscles. The axillary tail of Spence extends laterally across the anterior axillary fold.

SHAPE: The breast has a protuberant conical form. The base of the cone is roughly circular, measuring 10 to 12 cm in diameter. The nulliparous breast has a hemispheric configuration with distinct flattening above the nipple. With pregnancy and lactation the breast becomes larger and increases in volume and density, while with senescence, it assumes a flattened, flaccid, and more pendulous configuration with decreased volume.

NIPPLE-AREOLA COMPLEX: The epidermis of nipple-areola complex is pigmented and corrugated. During puberty, the pigment becomes darker and nipple assumes an elevated configuration. During pregnancy, the areola enlarges and pigmentation is further enhanced. The

areola contains sebaceous glands, sweat glands and accessory glands, which produce small elevations on the surface of areola (Montgomery tubercles). Smooth muscle fibers lie circumferentially in the dense connective tissue and longitudinally along major ducts; extend upward into nipples, which are responsible for nipple erection.

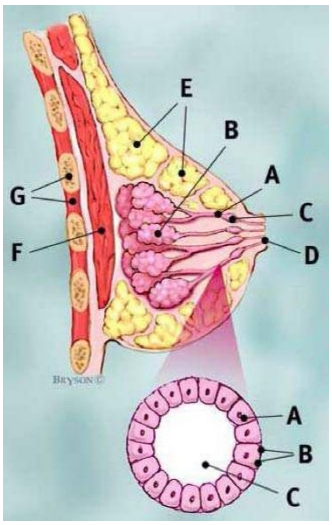


Fig 2: Breast anatomy A. Ducts B. Lobules C. Dilated section of duct to hold milk D. Nipple E. Fat F. Pectoralis major muscle G. Chest wall/rib cage Enlargement A. Normal duct cells B. Basement membrane C. Lumen (Center of duct)[4]

MICROSCOPIC ANATOMY

The mature breast is composed of three principal tissue types[5] : i) Glandular epithelium ii) Fibrous stroma with supporting structures and iii) Fat. Infiltrating cells, including lymphocytes and macrophages are also found within the breast. In youth, the predominant tissues are epithelium and stroma, which is replaced by fat in the breasts of older women.[5] Throughout the fat of breast, coursing from the overlying skin to the underlying deep fascia, strands of dense connective tissue called Cooper's ligament provide shape and hold the breast upward. Because

they are anchored into the skin, tethering of these ligaments by scirrhous carcinoma commonly produces dimple or subtle deformity on the otherwise smooth surface of the breast.

BLOOD SUPPLY:

The breast receives its principal blood supply from:

1. Perforating branches of the internal mammary, which penetrate through the 1st, 2nd, 3rd and 4th intercostal spaces just lateral to the sternum through the pectoralis major and enter the medial part of the breast. The main branch is via 2nd intercostal space. This supplies more than 50% of the blood to the breast.

2. The lateral thoracic artery is a branch of axillary artery and courses along the lateral border of pectoralis minor muscle. It supplies the lateral part of the breast through lateral mammary branches.[6]

3. The pectoral branch of the acromiothoracic artery, also a branch of axillary artery, this supplies the posterior part of the breast.

4. The other sources of blood supply come from highest thoracic, lateral perforating branches of the posterior intercostals arteries and branches from subscapular artery.[3,4,7]

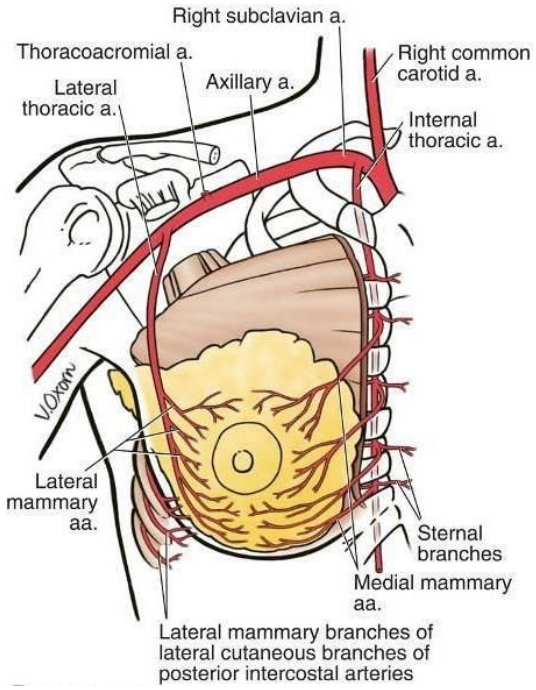


Fig 3:- Arterial supply of breast

VENOUS DRAINAGE:

Can broadly be classified into deep veins and superficial veins.

1. The deep veins of the breast drain along routes of corresponding arterial supply, so major drainage is via perforating veins into the internal mammary veins. The next way is through multiple tributaries following path of lateral thoracic artery into axillary vein. The third major way of venous drainage is along lateral perforating branches into the intercostal veins. This last route has got surgical importance, which explains why breast cancer metastasizes so easily to vertebral bodies, sacrum and pelvis.

2. The superficial veins are quite rich and sometimes dilated during pregnancy and neoplasm. The majority of these veins drain into the internal mammary vein and axillary vein. Some of these veins also drain into superficial veins of the neck.[3,7]

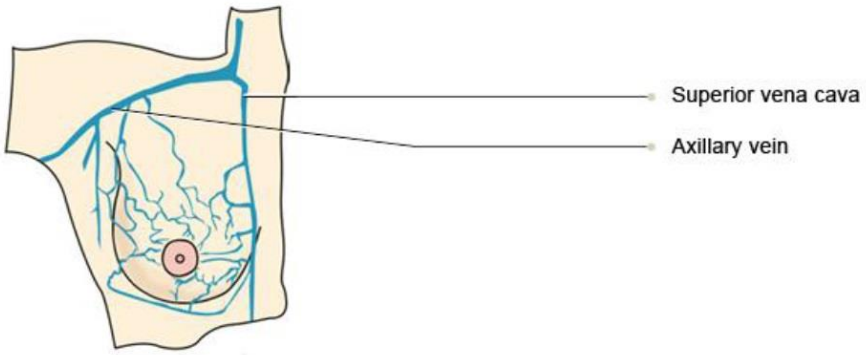


Fig 4:- venous drainage of breast

NERVE SUPPLY:

Lateral cutaneous branches of third through sixth intercostals nerves provide sensory innervations of the breast (lateral mammary branches) and of the anterolateral chest wall. These branches exit the intercostals spaces between slips of the serratus anterior muscle. Cutaneous branches that arise from cervical plexus, specifically[8] the anterior branches of the supraclavicular nerve, supply a limited area of skin over the upper portion of the breast.

LYMPHATIC DRAINAGE:

Without doubt an adequate knowledge of the lymphatic drainage of the breast is very essential since this is the route through which carcinoma metastasizes early.[4] Like venous drainage, the lymphatics of breast are classified into:

- Lymphatics of the overlying skin: These drain the integuments over the breast, but not the skin of areola and nipple. They pass in a radial direction and end in the surrounding nodes. Those from outer side go to the axillary nodes. The skin from upper part drain into supraclavicular lymph nodes. Certain vessels may end in the cephalic node. The vessels from the skin over the inner part of the breast go to the internal mammary nodes. The lymphatics of the skin over

breast communicate across the middle line, and a unilateral disease may become bilateral by this route. Mammary cancer may spread along this route to produce nodules in the skin.

- Lymphatics of the parenchyma of breast: Specialized lymphatic channels collect under the nipple and areola, forming Sappey's plexus named after the anatomist who described them in 1885.[4,9] 75% of breast lymph is drained into the axillary lymph nodes, 20% into internal mammary nodes and 5% into posterior intercostals lymph nodes. The six axillary lymph nodes recognized by surgeons are : [10]
- The axillary vein group (lateral) that consists of 4 to 6 nodes which lie medial or posterior to vein receive most lymph drainage from upper extremity.
- The external mammary group (anterior or pectoral) that consists of 5 to 6 lymph nodes, which lie along lower border of pectoralis major, receive most of the drainage from lateral aspect of the breast.
- The scapular group (posterior) consists 5 to 6 nodes which lie along posterior wall of axilla at lateral border of scapula receives lymph drainage from lower posterior neck, posterior trunk and posterior shoulder.
- The central group that consists 3 to 4 nodes which are embedded in the fat of axilla lying posterior of pectoralis minor muscle and receive lymph drainage both from axillary vein, external mammary and scapular groups and directly from the breast.
- The subclavicular (apical) group that consists of 6 to 12 nodes, which lie posterior and superior to the upper border of pectoralis, minor muscle and receive drainage from all the other axillary groups.
- The interpectoral group or the Rotter's nodes which are interposed between the pectoralis major and minor and receive lymph drainage directly from the breast. Lymphatics arising in

the lobules pass directly outwards in the substance of the breast receive tributaries on the way, and pass through the axillary tail to the axilla.[11] Most go to the anterior group, a few pass to the posterior group, and from there they run to central and apical groups. The internal mammary nodes receive lymph from medial portions of the breast. Lymph enters the thorax along anterior perforating branch of internal mammary artery. Most of this lymph goes to the internal mammary chain, but a small amount pass to posterior intercostals nodes lying near the heads of the ribs. At the level of the first interspace, fine lymphatics connect the right and left internal mammary chains behind the manubrium sterni. Tumors of the outer half of the breast may metastasize to internal mammary nodes without involvement of axillary nodes. The lymph nodes are assigned levels according to their relationship to pectoralis minor muscle:

- LEVEL I: Lymph nodes located lateral to or below lower border of pectoralis minor, which include the lateral, anterior and scapular groups.
- LEVEL II: Lymph nodes located superficial or deep to pectoralis minor, which include central and interpectoral groups.
- LEVEL III: Lymph nodes located medial to or above upper border of pectoralis minor, which consists of subclavicular (apical) group.[12, 13.]

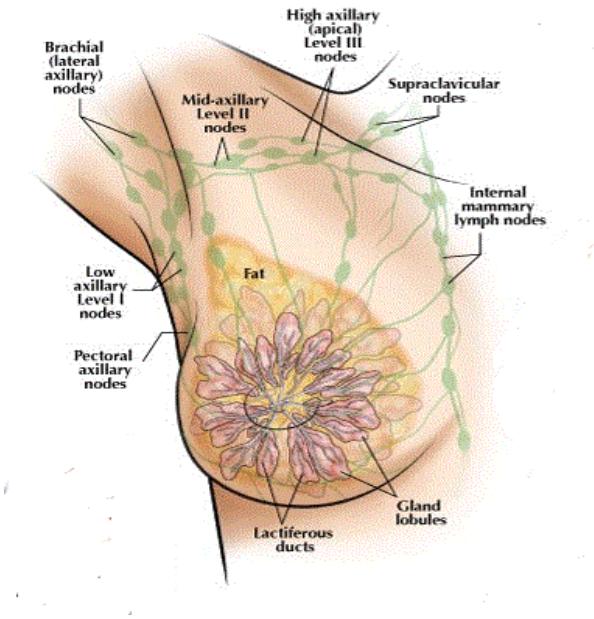


Fig 5: Lymphatic drainage of breast

PHYSIOLOGY OF THE BREAST.[8]

Breast development and function are initiated by a variety of hormonal stimuli, including estrogen, progesterone, prolactin, oxytocin, thyroid hormone, cortisol and growth hormone. Estrogen initiates ductal development, while progesterone is responsible for differentiation of epithelium and for lobular development. Prolactin is the primary hormonal stimulus for lactogenesis in late pregnancy and postpartum period.

The gonadotropins leutenizing hormone (LH) and follicle-stimulating hormone (FSH) regulate the release of estrogen and progesterone. In turn, the release of LH and FSH from anterior pituitary is regulated by gonadotropin-releasing hormone GnRH from hypothalamus. Positive and negative feedback effects of circulating estrogen and progesterone regulate the secretion of LH, FSH and GnRH. At birth the breast contains entirely of lactiferous ducts, no alveoli being present, this persists till puberty because of low circulating hormone levels.

With onset of puberty there is increase in GnRH, LH and FSH levels and ultimately an increase in estrogen and progesterone from ovaries leading to establishment of menstrual cycle. The breast tissue growth is stimulated with ductal differentiation and formation of alveoli. Estrogen stimulates the growth of stroma and ductal system whereas progesterone causes the development of terminal ductal complex[15].

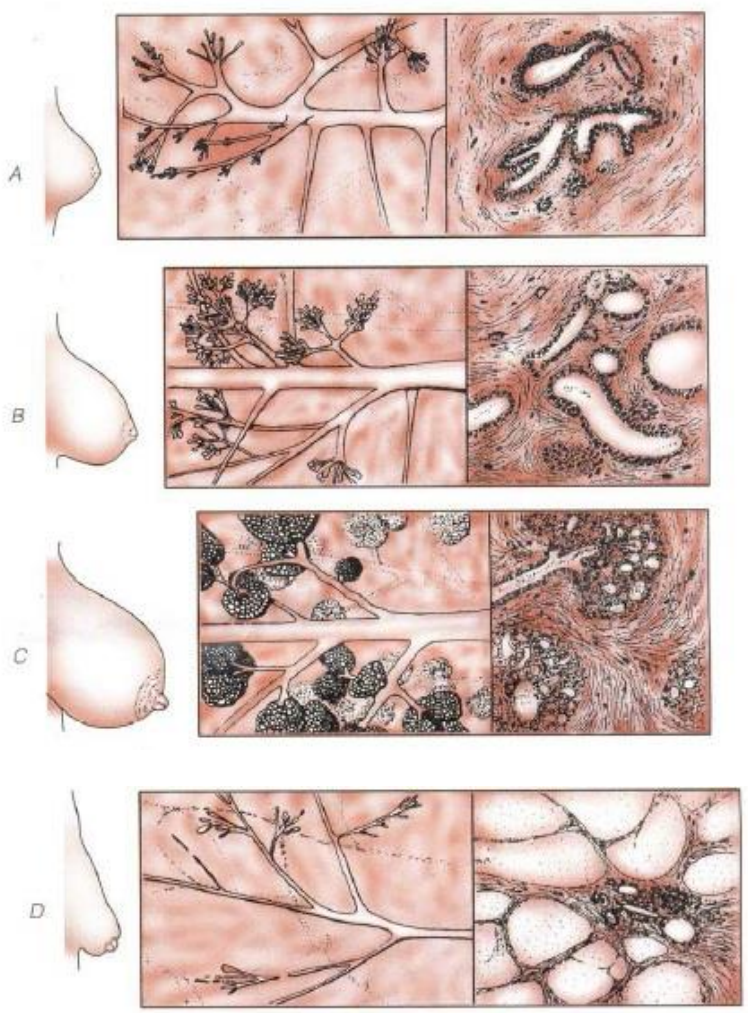


Fig 6 :- The breast at different physiological status, the central column contains three dimensional depictions of microscopic pictures

At the beginning of menstrual cycle there is an increase in size and density of breast, which is followed by engorgement of breast tissues and epithelial proliferation. With the onset of menstruation, the breast engorgement subsides and epithelial proliferation decreases. Pregnancy causes further growth in size of the gland. During second trimester of pregnancy, there is florid epithelial proliferation, with development of true functional acini from the terminal ductules. The areolar skin darkens, the montgomery glands become prominent. During third trimester fat droplets accumulate and colostrum fills the alveolar and ductal spaces. In late pregnancy prolactin stimulates the synthesis of milk. Following delivery estrogen and progesterone levels decrease with full expression of lactogenic action of prolactin.

Neural reflexes stimulate milk production by the action of prolactin and expulsion by the action of oxytocin, which acts on the myoepithelial cells of milk ducts. [12] Breast starts undergoing involution in preclimacteric phase. There is moderate loss of glandular tissues, replacement by fibrous tissue and round cell infiltration. Thus there is fibrosis, cyst formation and apocrine metaplasia. Changes at menopause have two clinical implications; firstly fat infiltration of breast produces the low-density appearance of the parenchyma seen on mammography, and thus makes this technique more successful in older women. Secondly, aberrations of this involutional change may explain some of the benign disorders that occur in this group. At the end after menopause, there is marked loss of glandular tissue, increase in adipose tissue with relative preponderance of connective tissue.[16]

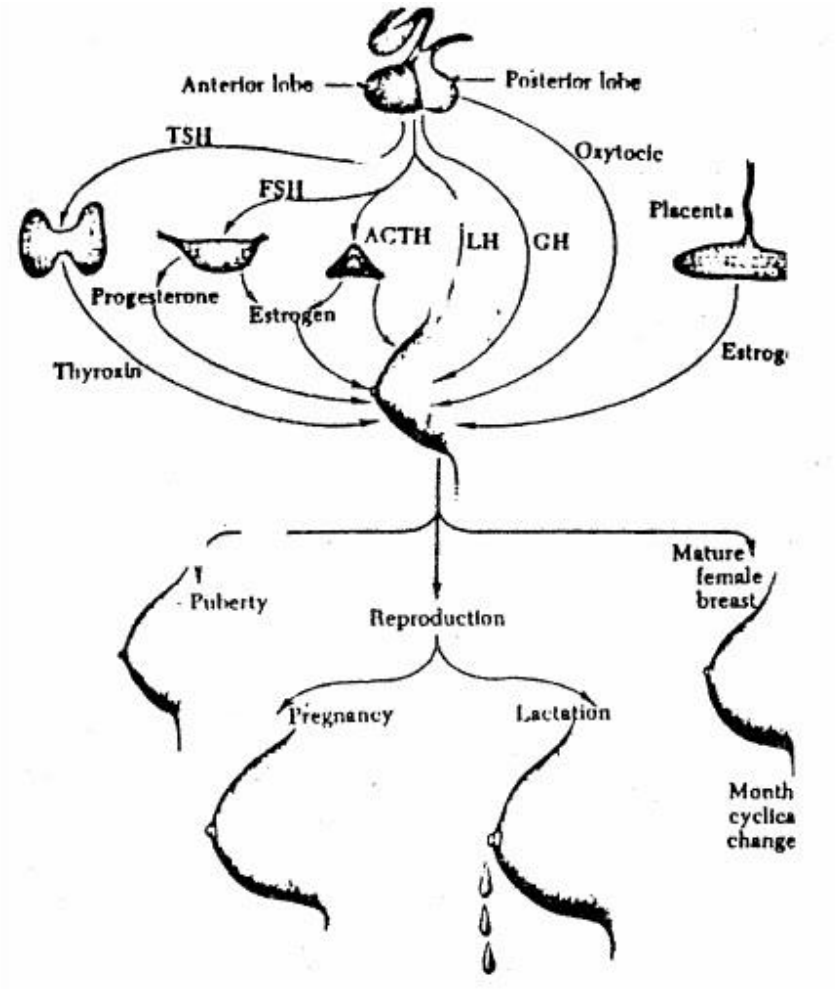


Fig 7 :-Neural reflexes and milk production

RISK FACTORS.[17]

The cause of breast cancer is unknown. However, epidemiological data indicate well-defined factors that show an increased likelihood of developing the disease. Such risk factors for breast cancer fall into three main groups: genetic, endocrine and environmental; each may be of major, intermediate or minor importance.

Major risk factors.[17]

Gender: Breast cancer is 100 times more common in women than in men. In strict epidemiological terms, therefore female sex is a major risk factor for breast cancer.

Age: As for other epithelial cancers the incidence of breast cancer increases with age. Breast cancer is only occasionally seen in the late teens but thereafter there is a rapid rise in age-specific rates. Upto the age of 40 years, the increase rate is very steep; the rate of increase then slows dramatically, although the overall cancer rate continues to rise until old age. The cumulative risk of developing breast cancer between ages of 20 to 40 is 0.5% whereas between 50 to 70 it is 5%.[10, 11]

Previous breast cancer: The development of breast cancer may be a clinical manifestation of multifocal origin of the first cancer or may be an entirely new cancer. Thus, the relative risk of developing a second, non-synchronous primary 20 years after initial diagnosis of breast cancer is 1.2 to 1.5. The risk appears greatest in young women if their initial breast cancer is diagnosed before the age of 40.[18]

Family history and genetic predisposition: A family history of breast cancer is associated with an increased risk of the disease. The risk is greatest in patients with first degree relatives (mother or sister) affected, especially if under the age of 50 when the disease developed. The relative risk of developing breast cancer is 1.7 to 2.5 in women with a history of breast cancer in a first-

degree relative, and 1.5 among those with an affected second-degree relative. Multiple family members with breast cancer, the existence of bilateral disease, or the identification of an affected male all indicate excessive risk especially if in association with ovarian cancer among other relatives.[12]

5 to 10% of breast cancers are caused by inheritance of germline mutations such as BRCA-1 and BRCA-2, which are inherited in an autosomal dominant fashion. BRCA- 1 is located on chromosome 17q, contains 22 coding exons. BRCA-2 is located on chromosome 13q and contains 26 coding exons. Both function as tumor suppressor genes, and for each gene, loss of both alleles is required for initiation of cancer. It is now known that germline mutations in BRCA-1 represent a predisposing genetic factor in as many as 45% of hereditary breast cancers and in at least 80% of hereditary ovarian cancers. BRCA-1 associated cancers are mostly invasive ductal, poorly differentiated, hormone receptor negative and have higher prevalence of being bilateral.[13]

The breast cancer risk for BRCA-2 mutation carriers is close to 85%. BRCA-2 associated breast cancers are invasive ductal, well-differentiated and express hormone receptors. Breast cancer is also associated with certain genetic disorders like

Li-Fraumeni syndrome (p53 gene affected),

Peutz-Jeghers syndrome (STK11/LKB1 gene affected),

Cowden disease (PTEN),

Muir-Torre syndrome (MSH2/MLH1) and

Ataxia telangiectasia.[19]

Benign breast disease: It is not usually recognized as major risk factor, although multiple papillomatosis may be regarded as such. Intermediate risk factors Diet and alcohol intake:

Weight does correlate with breast cancer risk, high fat intake is said to increase serum estrogen levels. Evidence for an association between alcohol consumption and an increased likelihood of developing breast cancer is becoming stronger. The relative risk of one unit of alcohol per day is 1.1 and increases to 1.3 to 1.5 if intake increases to two glasses a day.[14]

Endocrine factors: Breast cancer is related to hormones and reproductive factors. Estrogen is the principal hormone and prolonged exposure of breast issue to unopposed action of estrogen increases the incidence of breast cancer. Early Menarche increases duration of exposure of breast tissue to estrogen. There is 20% decrease in risk for each year delayed. Similarly increase number of menstrual cycles, nulliparity and late menopause are associated with increased risk. Longer lactational period, factors that decrease the number of menstrual cycles are protective.

The terminal differentiation of breast tissue associated with full-term pregnancy is also protective, so older age at first live birth is associated with increased risk. Abortions offer no protection and may be responsible for increased risk.[20] Oophorectomy before 50 years decreases the risk for breast cancer. Finally in postmenopausal women the major source of estrogen is conversion of androstenedione to estrone by adipose tissue; hence obesity is associated with a long-term increase in estrogen exposure.[11,13]

Meta analysis has demonstrated the relative risk of developing breast cancer while taking Oral contraceptive pills is 1.24 and on stopping the risk diminishes to 1.1. Thus there is no lifetime risk from oral contraceptive use as had previously been feared? Hormone replacement therapy for more than 10 years is associated with relative risk of 1.3.

Irradiation: Young women who receive mantle radiation therapy for lymphoma, survivors of atomic bomb blasts and patients having multiple chest radiographs have increased risk.[15] Benign

breast disease: Severe atypia with hyperplasia is associated with moderately increased risk of developing breast cancer. Minor and controversial risk factors.

Body size: There is minor relationship between body size and breast cancer but this is dependent on age and whether height or body mass is considered.

Stress: There is no evidence that stress may lead to the development of breast cancer. [21]

Benign breast disease: The patients with recurrent apocrine cysts, lesser degree of atypia have slightly increased risk but convincing evidence is lacking.

EPIDEMIOLOGY. [9]

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women age 40 to 44 years. It accounts for 33% of all female cancers and is responsible for 20% of the cancer related deaths in women. Breast cancer was the leading cause of death until 1985, when it was surpassed by lung cancer. There is a tenfold variation in breast cancer incidence among different countries worldwide. England and Whales have highest age adjusted mortality for breast cancer while South Korea has the lowest. Women living in less industrialized countries have a lower incidence of breast cancer than women living in industrialized countries.

HISTOPATHOLOGY OF BREAST CANCER. [19,20] Breast cancer may arise from the epithelium of the duct system anywhere from the nipple end of major lactiferous ducts to the terminal duct unit, which is in the breast lobule. Previously, descriptive terms were used to classify breast cancer (scirrhous means woody, medullary-means brain like). More recently, histological descriptions have been used.

CLASSIFICATION OF PRIMARY BREAST CANCER

Non-invasive Epithelial Cancers

• Lobular carcinoma in situ (LCIS)

• Ductal carcinoma in situ (DCIS) or intraductal carcinoma

Invasive Epithelial Cancers (percentage of total)

• Invasive lobular carcinoma (10-15)

• Invasive ductal carcinoma

• Invasive ductal carcinoma, NOS (50-70)

• Tubular carcinoma (2-3)

• Mucinous or colloid carcinoma (2-3)

• Medullary carcinoma (5)

• Invasive cribriform (1-3)

• Invasive papillary (1-2)

• Adenoid cystic and metaplastic carcinoma (1 each).[22]

Mixed Connective and Epithelial Tumors

Phyllodes tumors, benign and malignant carcinosarcoma and angiosarcoma.

DIAGNOSING BREAST CANCER[12].

CLINICAL PRESENTATION: Although any portion of breast, including axillary tail, may be involved, breast cancer is found most frequently up to 60%, in the outer, upper quadrant (due to increased amount of breast tissue). 12% each are found in upper inner quadrant and beneath the nipple. Lower half of the breast accounts for the rest.

Symptoms caused locally by tumor Lump: In 33% of breast cancer cases, the woman discovers a lump in her breast often when washing or looking into a mirror.

Pain: Pain is an uncommon symptom, except for vague pricking sensation in the breast. Pain is often suggestive of a benign condition. If present in malignancyit suggests aggressive type, like mastitis carcinomata.

Nipple retraction: Usually present in later part of the disease process. Recent onset of nipple retraction in an elderly female patient is highly suggestive of malignancy.

Nipple discharge: Present in 3-11% of cases, blood stained discharge usually indicates a intraductal carcinoma, Paget's disease or the tumor has grown into a major duct.[23]

Nipple erosion: It is the commonest mode of presentation in Paget's disease, also seen in advanced intraductal carcinomas. As the disease advances locally there may be skin involvement with peau d orange or frank ulceration and fixation to the chest wall. This is described as cancer-encuirasse. About 20% of breast cancers in developing countries present in locally advanced stage.

Symptoms caused due to metastases

Lymphatic spread: Patients may present with swelling in the axilla or supraclavicular region, which may be mobile or fixed. Swelling of arm due to lymphatic (or even venous obstruction) in the axilla, is an uncommon but significant presentation.

Hematogenous spread: Respiratory symptoms like cough, breathlessness due to pulmonary metastases. Backache, caused by secondary infiltration and collapse of lumbar vertebrae, with nerve root pains radiating to both the legs, is a common symptom.[24] A pathological fracture may be the first indication of the presence of the disease due bone metastases. Cerebral metastases may cause a fit or behavioral abnormality. Mass in the right upper abdomen, jaundice may be caused due to liver metastases. Curiously, the general symptoms commonly associated with

cancer, such as malaise, weight loss and cachexia, are rare in patients with breast cancer. Even those with disseminated fatal disease usually feel well in themselves until the final stages.

CLINICAL EXAMINATION. [22,25]

The patient must be fully undressed to the waist, resting comfortably on an examination couch with her upper body raised at 45 degree to the legs. This position is the best compromise between lying flat sideways, and sitting upright, which makes the breast pendulous. Patients sometimes say that their lump can only be felt when they adopt a certain posture and they should therefore be examined in this position as well.

Inspection:

The surgeon inspects the women's breast in following positions:

1. Arms by the side.

2. Arms straight up in the air and

3. Hands on her hips.

The following observations are made:

Breast: -Position: whether displaced in any direction.

Symmetry: Marked size difference of recent onset is likely to be caused by significant pathology.

Skin: The skin may be pulled in or puckered by an underlying cancer. There may be edema caused by obstruction of skin lymphatics by cancer cells, which is commonly referred to as peau d' orange. Other skin changes include nodules of tumor or a malignant ulcer due to direct invasion of skin by cancer.

Nipple and areola: The levels of nipples on both the sides are compared. In case of carcinoma the affected side is drawn towards the lump. Look for flattening, retraction, cracks, fissures or

eczema. Any discharge from nipple and nature of discharge is noted. Diminution in size of areola around a retracted nipple is a feature of malignancy. Skin changes may become prominent by making patient to raise her hands above her head. By asking to press the hands against the hips previously invisible swelling may become prominent. Inspect the axillae, arms and supraclavicular fossa to look for enlarged glands, distended veins or arm lymphoedema.

Palpation: The breast should be palpated with the flat of the fingers and not with the palm of the hand. Surgical mythology says that the breast should be felt with 'the flat of the hand'-this is wrong, use the fingers, which is more sensitive. With the patient sitting up at 45 degree, begin with the normal side first and then palpate the other.

The commonest palpatory finding is a hard lump. It is felt most commonly in the outer upper quadrant, which may be irregular in shape and size. There is difference between skin fixation and tethering, when a lesion is fixed to the skin it has spread into the skin and cannot be moved or separated from it. Tethered lesions is one more deeply situated and by distorting the fibrous septa which separate the lobules of breast tissue (the ligaments of Cooper), puckers and pulls the skin inwards, but remain separate from the skin and can be moved independently. Ascertain the mobility of the lump within the breast tissue and with relationship to pectoralis major muscle, this may be done by asking the patient to press against her hips. Also look for fixity to chest wall. If there is nipple inversion it may be possible to evert it by gently squeezing, if the nipple will not evert, there is likely to be underlying disease. Unilateral inversion is more significant than bilateral inversion. Discharge may be gently expressed out and the character of the fluid noted.

Lymph nodes palpation: The axillary lymph glands form a three-sided pyramid whose apex is in the narrow gap between the first rib and axillary vessels. The examination is carried out in sitting position with muscles and fascia around the axilla well relaxed. If the patient's left axilla is to be examined, the left arm is taken and supported by the left hand of the examiner. Then the examiner's right hand palpates the anterior fold of axilla for pectoral lymph nodes. The hand is gently introduced gently into the apex of the axilla to palpate the apical lymph nodes, and passed down to palpate the central group over the medial wall of axilla. The posterior and lateral groups can more easily be felt from behind. The posterior wall of axilla the scapular groups of nodes are felt around the serratus anterior and latissimus dorsi and lastly feel for the lateral group around the neck and shaft of humerus. The size, number, consistency and mobility must be fully documented. Obstruction of lymphatics may give rise to edema of the arm. Other groups of nodes that must be examined are the supraclavicular and infraclavicular nodes. Note particularly the presence of scalene node behind the insertion of sternocleidomastoid.

Systemic examination: This is important for the clinical assessment of distant metastasis. Abdominal examination for liver metastasis (hepatomegaly), ovarian secondaries or presence of free fluid. Respiratory system examination for pulmonary metastasis should be done. Skeletal system examination particularly lumbar spine, pelvis, ribs, sternum, upper ends of femur and humerus should be done to look for tenderness or restricted mobility. Rectal and vaginal examinations are necessary to detect deposits and Kruckenberg's tumor respectively.

Triple assessment: suspected cases receive triple assessment which consists of

1) History and examination;

2) Diagnostic imaging by mammography or ultrasonography and

3) Cytology or histology.

Sensitivity ranges from 85% to 95%.[26]

BREAST CANCER STAGING: [27] Staging of breast cancer is essential to plan the treatment and assess the prognosis of the disease. Staging relates to the classification of breast cancer according to the anatomical extent of disease, each stage serving to aggregate cases having an approximately similar prognosis. Many staging systems have been proposed, none has been shown to be significantly better than others. The clinical stage of breast cancer is determined primarily through physical examination of skin, breast and lymph nodes. Clinical determination of axillary lymph nodes is only 33%. Mammography, chest x-ray and intraoperative findings provide necessary information. Common staging systems are:

TNM STAGING: This system is based on the description of the primary tumor (T), status of regional lymph nodes (N) and distant metastases (M). The breast cancer staging is complex, reflecting the introduction of sentinel node biopsy, the scrutiny of axillary lymph nodes by immunohistochemistry and polymerase chain reaction.[28]

American Joint committee on Cancer (AJCC) staging system-2006 Primary tumor (T)

• Tx- Primary tumor cannot be assessed.

• T0- No evidence of primary tumor.

• Tis- DCIS, LCIS, Paget's disease with no tumor.

• T1- Tumor 2 cm or less in greatest dimension.

• T1-mic Micro-invasion 0.1 cm or less in greatest dimension.

• T1a- Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension.

• T1b- Tumor more than 0.5 cm but not more than 1 cm in greatest dimension.

• T1c- Tumor more than 1 cm but not more than 2 cm in greatest dimension.

• T2- Tumor more than 2 cm but not more than 5 cm in greatest dimension.

• T3- Tumor more than 5 cm in greatest dimension.

• T4- Tumor of any size with direction extension to (a) chest wall or (b) skin

• T4a- Extension to chest wall.

• T4b- Edema or ulceration of the skin of breast, or satellite nodules on same breast.

• T4c- Both 4a and 4b.

• T4d- Inflammatory carcinoma.

Regional lymph nodes-clinical (N)

• Nx -Regional lymph nodes cannot be assessed (eg; previously removed).

• N0 -No regional lymph nodes.

• N1- Metastases to movable ipsilateral axillary lymph node(s).

• N2 -Metastases in ipsilateral fixed axillary lymph nodes or ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph nodes.

• N2a- Metastases in ipsilateral axillary lymph nodes fixed to one another.

• N2b -Metastases to clinically apparent internal mammary nodes with no axillary nodes.

• N3- Metastasis in ipsilateral infraclavicular, internal mammary with axillary nodes or Metastasis to ipsilateral supraclavicular lymph nodes.

• N3a- Metastasis in ipsilateral infraclavicular lymph nodes.

• N3b- Metastasis in ipsilateral internal mammary nodes with axillary nodes.

• N3c- Metastasis in ipsilateral supraclavicular lymph nodes.

Distant metastasis (M)

• Mx- Distant metastasis cannot be assessed.

• M0- No distant metastasis.

• M1- Distant metastasis.

TNM STAGE GROUPINGS: American Joint Committee on Cancer: AJCC.

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Table 1 : TNM staging

INVESTIGATIONS

Breast biopsy

1. Fine needle aspiration cytology: FNAC of a palpable breast mass is performed in an out patient setting. A 1.5 inch, 22-guage needle attached to a 10 ml syringe is commonly used. A syringe holder enables the surgeon performing the procedure to control the syringe with one hand while positioning the breast mass with the opposite hand. After the needle is placed inside the mass, suction is applied while the needle is moved back and forth with the mass. The cellular

material expressed is put onto microscope slide. Both air-dried and ethanol fixed microscopy sections are prepared for analysis. The sensitivity and specificity approaches 100% when breast mass is clinically and mammographically suspicious. The false negative rate is 5% and false positive rate is 2%.[29]

2. Core biopsy: Core biopsy can be performed on palpable breast masses with a 14 gauge needle, such as Tru cut needle. A variety of instruments can be used to provide a core or tissue such as automated biopsy guns which has replaced aspiration cytology in many departments. This technique has to be performed under local anesthetic. Tissue specimens are placed in formalin and then processed to paraffin blocks. The only disadvantage is because of sampling errors.

3. Open surgical biopsy: Biopsy is required when FNAC or core biopsies have failed to demonstrate malignant disease. It has the disadvantage of requiring hospital admission, although majority of patients can be treated and discharged the same day. Its advantage is that it provides a definitive method of proving or excluding malignant disease. Open biopsy can occasionally be performed under local anesthesia but more easily under general anesthesia.

4. Open surgical biopsy and frozen section: This procedure of excising the specimen at the time of definitive surgery has become less common with more wide spread use of FNAC. Modern surgical practice should avoid the outmoded approach of performing mastectomy on the basis of frozen section.[12]

5. Incisional biopsy: For cases presenting with an ulcer this method was used. Not used routinely and has been replaced by FNAC. Breast imaging and image guided diagnostic

techniques Image guided breast biopsies are frequently required to diagnose non-palpable lesions. Ultrasonography and mammography assisted techniques have been used to a variable extent in different hospitals.

Ultrasonography of breast[30]

The use of breast ultrasound was first described by Wild and Neal, who investigated the usefulness of ultrasound for defining the normal breast as well as breast masses. Most procedures are done using hand held 7.5 MHz to 10 MHz probes with a penetration depth of 4 to 6 cm.

Benign lesions are characterized by smooth, well-defined margins, homogenous internal echo pattern, symmetric posterior enhancement and compressibility. Suspicious lesions show irregular, fuzzy or jagged margins, irregular internal echoes, irregular posterior shadowing and show no compressibility.[31]

Indications

• Breast ultrasound can be primarily used to distinguish between solid and cystic lesions with an accuracy of 96% to 100%.

• Ultrasound is the first choice for evaluating mammographically benign appearing lesions.

• Pregnant women having suspicious lesions.

• Ultrasound is part of evaluation and work up of patients with abnormal nipple discharge.

Ultrasound guided biopsy techniques

• Ultrasound guided needle biopsy.

• Ultrasound guided cyst aspiration- if contents are clear no need for cytological examination.

• Ultrasound guided FNAC and Core biopsy.

• Ultrasound guided, Vacuum assisted breast biopsy (VAB): Uses the handheld VAB device. Less patient discomfort caused by multiple needle repositioning.

• Ultrasound guided, vacuum assisted excisional biopsy: Ensures both biopsy specimen as well as complete removal of lesions under ultrasound guidance.[32]

MAMMOGRAPHY. [33,34] Mammography has been used in North America since 1960's. Conventional mammography delivers a radiation dose of 0.1 centigray (cGy) per study. By comparison a chest x-ray delivers 25% of this dose. However there is no increased breast cancer risk associated with the radiation dose.

Screening Mammography: It is used to detect unexpected breast cancer in asymptomatic women. Two views of the breast are obtained, the craniocaudal (CC) and mediolateral oblique (MLO) view. The MLO view images the greatest volume of the breast, including the upper outer quadrant and the axillary tail. The CC view provides better visualization of the medial aspect of the breast and permits greater breast compression.

At present screening mammography should be offered:

1. Annually to women aged 50 and older.

2. At least biennially in women aged 40 to 49.

3. Annually in younger women with significant family history, histological risk or a history of prior breast cancer.[35]

Diagnostic Mammography It is used to evaluate women with abnormal findings such as a breast mass, nipple discharge, or an abnormality on screening mammography. It includes magnification and compression imaging in addition to MLO and CC views. The additional views are 90 degree lateral and spot compression views.

Compression device minimizes motion artifact, improves definition, separates overlying tissues and decreases radiation dose. Magnification (x1.5) improves better visualization of margins.

Diagnostic mammography may be offered to:

1. Evaluate opposite breast.

2. To evaluate questionable or ill defined mass or other suspicious changes in breast.

3. To search for occult cancer in patients with axillary nodes.

4. When women is undergoing conservative breast surgery to detect concomitant lesion in the same breast.

Mammographic abnormalities suggestive of malignancy can be divided into:

• Density abnormalities-masses, architectural distortion and asymmetries.

• Micro calcifications-The presence of fine, stippled, clustered calcium in and around a suspicious lesion is highly suggestive of malignancy, especially in younger women.[36]

Mammography assisted biopsy techniques.[9]

1. Needle Localization Breast Biopsy: Until 1990, this was the only method to evaluate non-palpable Mammographic abnormality, which included surgical excision of breast masses marked with preoperative wire localization.

2. Large core needle biopsy (LCNB): Can be either performed under ultrasound or mammographic guidance. Mammographic calcifications are sampled using stereotactic capabilities. Histological detail can be obtained. Stereotactic LCNB involves the patient lying prone on core biopsy table with breast in compression. A robotic arm and biopsy gun is positioned by computed analysis of triangulated mammographic images. Xeroradiography techniques are identical to those of mammography with the exception that it provides a positive

image rather than a negative one, which allows easy interpretation, good visualization. It requires less irradiation and is carried out in lighted rooms.

Ductography: The primary indication is nipple discharge, particularly when the fluid contains blood. Contrast media is injected into one or more major ducts and CC and MLO mammography views are obtained. Intraductal papillomas appear as small filling defects, whereas cancers appear as irregular masses or as multiple filling defects. Ductal lavage and cytology using microcatheters is used in women with increased breast cancer risk[37].

Thermography: Malignant lesions are hotter than normal and benign lesions due to increased vascularity and increased metabolism. It has 85% diagnostic accuracy.

Magnetic Resonance Imaging: There is current interest in using MRI to screen the breasts of high-risk women and of women with a newly diagnosed cancer.[38]

1. It can be useful to distinguish scar from recurrence in women who have had previous breast conservation therapy.

2. It is the gold standard for imaging breasts of women with implants.

Investigations to assess the metastases

- **Liver function tests:** Enzyme levels may be elevated in hepatic metastases.
- **Serum calcium:** elevated in patients with bony metastases.
- **Chest X-ray:** Features suggestive of secondaries include coin lesions, interstitial infiltration, mediastinal widening, pleural effusion and rib secondaries.
- **Bone X-rays:** Usually present osteolytic lesions and rarely osteogenic.
- **Bone Scan:** Technetium Tc99 labeled bone scans are more sensitive than X-rays. They are most helpful when strong suspicion of skeletal metastases is present.

- **Ultrasound scan of abdomen** is used to assess liver metastases, lymph nodes, free fluid in abdomen, ovarian secondaries or any pelvic deposits.

HORMONE RECEPTORS [9]. The laboratory discovery and subsequent measurement of estrogen receptors (ERs) and progestin receptors (PRs) in breast tumors have given the physician useful tools to aid in the treatment of women with breast cancer. The ER and PR belong to a large class of nuclear receptor proteins, are present in normal breast, and other tissues and are expressed in up to 60% to 70% of breast cancers. In both normal and tumor cells, estrogen binds to the ER, which is a large protein molecule located in the cytoplasmic and nuclear fractions of the cell.

BIOMARKERS[39] Breast cancer biomarkers are of several types. Risk factor biomarkers are those associated with increased cancer risk. These include BRCA-1, BRCA-2 and other germline mutations. Exposure biomarkers include measurement of carcinogen exposure. Surrogate endpoint biomarkers are biologic alterations in tissue that occur between initiation and cancer development. These biomarkers are used as endpoints in short term chemoprevention trials, include histologic changes and indices of proliferation. Drug effect biomarkers (serum glutathione reductase activity, ornithine decarboxylase activity) are used to monitor biochemical effect of drugs. Candidate prognostic and predictive biomarkers for breast cancer include:

1. **Indices of proliferation:** Proliferating cell nuclear antigen (PCNA), a nuclear protein, which is overexpressed in tumor with high mitotic index, high histologic grade.
2. **Indices of apoptosis:** Bcl-2 family proteins appear to inhibit apoptosis. The death signal protein bax is induced by growth factor deprivation. The bax:bcl-2 ratio represent intracellular regulatory mechanism with prognostic implications.

3. Indices of angiogenesis: Such as vascular endothelial growth factor (VEGF) and angiogenesis index.

4. Growth factor receptors and growth factors: Such as Human epidermal growth factor (HER)-2/neu and epidermal growth factor receptor (EGFr). Over expression is associated with receptor negative, p53 positive tumors. Anti HER2/neu therapy is now an important breast cancer therapy.

5. p53 overexpression correlates with high histologic grade, high proliferative fraction, aneuploidy, HER2/neu overexpression and ER/PR negative tumors.

TREATMENT OPTIONS IN CARCINOMA BREAST: Surgery In 1894, Halsted presented his first 50 patients treated by the complete operation, which became the radical mastectomy. Later in 1970s realization that 90% of treatment failures will be systemic/visceral recurrences had led surgeons to explore alternatives to radical mastectomy, which lead to the abrupt shift from mastectomy to modified radical mastectomy.[40]

Radical Mastectomy: Described by Halsted, is a procedure that is rarely preformed in modern management of carcinoma breast. In radical mastectomy, the breast and underlying pectoralis muscle is sacrificed and regional lymph nodes along the axillary veins to the costclavicular ligament are removed[51].

Modified radical mastectomy: Two forms of modified radical mastectomy are in use.

i) One described by Patey

ii) Modifications described by Scanlon & Auchincloss.

Patey described a procedure that preserves the pectoralis major muscles and sacrificed the underlying pectoris minor muscle to remove level I, II& III lymph nodes in axilla. The

survivals of the patients were comparable to radical mastectomy and thus preservation of pectoralis major did not give inferior results. Scanlon described a procedure by dividing but not removing the pectoralis minor muscle allowing the removal of apical (level III) nodes and preservation of lateral pectoral nerves to the pectoralis major muscle. Auchincloss differed from the Patey procedure by not removing or dividing of the pectoralis minor muscle. **Simple / total mastectomy:** This involves the complete removal of all mammary gland including the nipple and areola. Elliptical / transverse incision is put and surrounding skin is excised depending upon the site and size of the tumor or ulceration. Skin flaps are raised to separate from the underlying gland and mammary gland is swept off laterally from underlying pectoralis major muscle fibers.

Wide local excision: Excision of the primary tumor with preservation of the breast has been referred to many names-

Partial mastectomy

Segmentectomy

Lumpectomy

Wide local excision.

Wide local excision seems to be the most descriptive which involves the removal of the tumor with a rim of surrounding grossly normal tissue. Breast conservative treatment refers to wide excision of the cancer, leaving the breast largely intact, and with or without surgery on the axillary nodes, with or without post surgical radiation.[41]

Axillary lymph node dissection.[42] Axillary lymph node dissection has been part of surgical treatment of breast cancer for following reasons.

- To allow proper staging
- To provide useful prognostic information
- To guide for subsequent treatment.
- To increase potential therapeutic gains

It is recommended for all patients with invasive cancer, as pathological staging is most important prognostic factor with survival rate being related to axillary node status. Axillary lymph nodes are divided depending upon the anatomy.

Level 1 – Nodes below / lateral to the lower border of pectoralis minor and medial to the latissmus dorsi muscle (including axillary, External mammary, scapular). It contains most numerous nodes.

Level 2 – Nodes behind the pectoralis minor (central). These form 20% of total axillary nodes.

Level 3 – Nodes above / medial to the upper border of prectoralis minor and below (cost clavicular ligament, including apical). These form 20% of total axillary nodes.

Extent of dissection:[43] Advantages of complete axillary LN dissection are as follows

(1) No risk of under staging the disease, when level 1 & 2 are done risk of under staging the disease is at least 2.6 %.

(2) No additional surgical treatment required if the axilla is pathologically positive

(3) Complete dissection minimizes the risk of local recurrence.

(4) It is widely accepted that involvement of axillary nodes occurs in a progressive manner from lower to higher level. But when level 1 node are positive chances of higher level being positive varies from 22-42.9% and node positivity increases with tumor size.

Complications:[44]

• Lymphadema

• Seroma

• Frozen shoulder

• Chronic pain syndrome/ Neuropathies

• Thrombophlebitis of axillary vein.

Radiotherapy

Emil Grubbe, a Chicago medical student, developed severe dermatitis of the skin of his hand while testing the Crioles tube with that hand. A physician who had seen Grubbe's lesion referred a patient with breast cancer to him for irradiation, because of apparent biological damaging effect of X-rays. This formed the basis of modern radiotherapy for carcinoma breast.

Post Operative Radiation[**45**].

Postoperative Radiotherapy refers to the use of irradiation to the chest wall & draining lymph node regions as an adjuvant after mastectomy

Possible reasons are:

1. To decrease the rate of loco regional tumor recurrence
2. To improve survival by eradicating residual local disease which is the only site of persistent cancer after mastectomy along with effective use of systemic therapy

Breast conserving treatment (BCT) included removal of bulk of the tumor surgically & to use moderate dose of radiation to eradicate any residual cancer. Careful observation of treated patient determined that best results are achieved by delivering relatively small doses of radiation daily over extended period.

Use of 45 to 50 Gy in 4.5 to 5.0 weeks eradicates sub clinical deposits of breast cancer in a high percentage of cases. Thus, the use of breast irradiation after breast conservation surgery is associated with a large reduction in the rate of local recurrence. For operable stage II, the post op administration of chemotherapy and radiotherapy resulted in better local control & higher survival rate than the use of either adjuvant treatment alone.

Palliative radiotherapy:[46] Radiation therapy is effective in relief or avoidance of symptoms of metastasis to many different anatomic sites. The most common problem is metastases to bone causing pain or threatening structural integrity. Using a schedule of 9 Gy in a single increment to 30 Gy in 10 increments reported a total response rate of 82%.

For patients suffering pain from wide spread metastases, a single hemi body irradiation of 6 Gy to upper body & 8 to 10 Gy to lower body results in 80% to 100% response in terms of reduction in pain.

In case of locally advanced carcinoma moderate total doses of 45 to 50 Gy in 25 fractions in 5 weeks plus a boost of 10 to 15 Gy to high risk sites used pre & post operatively with total mastectomy gives good results and least sequel.

Chemotherapy

In 1960s first modern trails of combination chemotherapy were initiated for breast cancer management. First adjuvant chemotherapy was administered to women with positive nodes; later in 1980s the use was extended to node negative women as well.

Indications for chemotherapy

Depending on the node status; the proportional reduction in recurrences & mortality are similar in node positive & negative patients hence it is used in both cases, but given the better prognosis of node negative patients especially those node negative patients with small tumors (<1cm), the absolute benefit of therapy is very small so may not be used in such condition.

Younger females have proportionally greater reduction in both recurrence & mortality than older women with carcinoma breast. Combination chemotherapy has been more effective than single agent therapy, single agents generally achieve partial remission of 10% - 30%, and combination of three or more agents repeated in cycles could achieve 50% - 80% response without additive toxicity. The therapeutic intervals in combination therapy that allow normal rapidly dividing stem cell to recover can explain the lack of toxicity of these regimen.[47]

The following are the acceptable regimens: -

1. FAC - 4-6 Cycles,
2. AC - 4Cycles, A—ADRIAMYCIN, C-CYCLOPHOSPHAMIDE
3. AC – 4Cycles, PACLITAXEL 4 Cycles, E—EPIRUBICIN
4. CEF - 6Cycles. C-CYCLOPHOSPHAMIDE , E—EPIRUBICIN,

   F- 5-FLOUROURACIL
5. CMF - 6 Monthly cycles,
6. A - 4Cycles CMF 8Cycles.

DOSAGE AND SCHEDULE [48]:

Choosing the regimen:

There is no single regimen that has emerged as the treatment of choice. Several trials have demonstrated that a 10% - 20% higher response rate has been observed with Doxorubicin / Epirubicin containing regimen with an increase in median survival from 14 – 18 months & an increase in median time of treatment failure from 5 to 7 months. The shorter duration of regimen and relative ease of administration has led to the popularity of AC regime and favor this regimen as the first choice of therapy.[48]

CMF x 8 : C – 100 mg/m2 PO day 1 to 4

M-40 mg//m2 IV 1 & 8

F 600 mg IV on day 1 & 8 Repeat every 28 days for 6 cycles

CMF : C-600 mg/m2 IV on day 1

M – 40 mg/m2 IV on day 1

FU – 600 mg/m2 IV on day 1

AC A 60 mg/m2 IV on day 1

C – 600 mg/m2 IV on day

AC – T AC (as above) + Taxol – 175 mg/m2 IV on day 1

Repeat every 21 days for 4 cycles

CAF C – 600 mg/m2 IV on day 1

A – 60 mg/m2 IV on day 1

F – 600 mg/m2 IV on 1 & 8

FAC F – 500 mg/m2 IV on 1 & 8 day

A – 50 mg/m2 IV on 1 day

C – 500 mg/m2 IV on day 1

TIMING OF TREATMENT:

As an adjuvant therapy[48]:

It is thought that carcinoma breast is a systemic disease since its appearance and by the time tumor has grown to 1 cm size it would have metastasized and it is thought that occult metastasis is already present with operable carcinoma. It is observed in clinical trials that improvement in long term outlook for newly diagnosed breast cancer even the early stage can only be accomplished with systemic therapy. Since the introduction of the chemotherapy as adjuvant treatment, it has been decreasing the death rate.

Neoadjuvant therapy[49]: Recently, neoadjuvant chemotherapy, also termed preoperative, induction, or primary chemotherapy, has assumed an increasingly important role in the management of several solid-organ malignancies, including cancers of the breast, bone, head and neck, bladder, esophagus, and lung.

Neoadjuvant chemotherapy has become the standard of care for patients with locally advanced breast cancer and has rapidly come to the forefront among potential treatments for patients with earlier – stage operable disease.

Tumor down staging with neoadjuvant chemotherapy can convert inoperable disease to operable disease and can even allow breast conservation surgery in patients for whom mastectomy is initially the only option for control of local or regional disease.

Locally advanced breast cancer can be further divided into operable and inoperable disease. Patients who have breast cancer with diffuse breast edema or erythema, direct skin involvement,

fixation to the chest wall, or a tumor that is so large that the mastectomy effect would require autogenous tissue coverage for closure are generally considered to be initially inoperable. Several studies have confirmed that operation or irradiation alone is inadequate treatment for unselected patients with locally advanced breast cancer.

But the risk of occult axillary and distant micrometastass is greater then 50% when a breast tumor reaches 2 to 3 cm in size. The rationale for the use of chemotherapy in the adjuvant or neoadjuvant setting is to decrease the mortality risk associated with occult cancer micrometastasis.

The clinical response to neoadjuvant therapy is determined by the reduction in size of the primary tumor and axillary metastasis as measured by both physical examination and radiographic evaluation Whether breast surgery after neoadjuvant chemotherapy is necessary in

all patients is controversial. Some authors advocate no surgery at all if there is a complete clinical response, other advocate lumpectomy with or without axillary dissection, and still others advocate modified radical mastectomy regardless of the clinical response, particularly in patients who initially present with locally advanced disease.

As a palliative therapy [48].

Chemotherapy is of more use in-patients with metastatic breast cancer and is of more use in younger individuals than older individuals.

Depending on the receptor status, although chemotherapy was effective both in ER +ve & ER-ve tumors it was of greater benefit in women with ER -ve tumor. Distant sites and those experiencing distant relapse after adjuvant treatment are treated by palliative intent either by

endocrine manipulation or chemotherapy. Patients who are candidates for chemotherapy are those who fail hormonal therapy or presence of visceral metastasis. Patients who do not respond to a first line combination chemotherapy regimen or respond and subsequently relapse are candidate for second line regimen or one of single agents. A future trend in chemotherapy is inclusion of Taxanes. The Taxanes both Paclitaxel & Docetaxel have been incorporate into chemotherapy. Some trials with 4 cycles of paclitaxels have shown to improve disease free interval and overall survival in node positive cases.

REGIMEN USED:

Pathologic tumor response and subsequent disease-free survival are improved in patients receiving four cycles of preoperative 'Docetaxel' after four cycles of doxorubicin as opposed to four cycles of preoperative doxorubicin alone.

Several important recent trials have now demonstrated that neoadjuvant chemotherapy can increase the resectablity rate of primary breast cancer, can allow more patients to successfully undergo breast conservation surgery, and does not confer a survival disadvantage compared with standard adjuvant chemotherapy. These findings indicate that neoadjuvant chemotherapy is preferred initial treatment for patients with locally advanced or inflammatory breast carcinoma[48].

ENDOCRINE MANIPULATION:

TAMOXIFEN[50].

It functions as a competitive partial agonist inhibitor of estrogen and binds to the Estrogen receptor of estrogen sensitive tissues and tumors. But it has 10 fold less affinity than the

oestradiol, indicating the importance of ablation of endogenous estrogen for optimal antiestrogen effect.

The objective benefit is seen largely in those patients who

(1) Lack the endogenous oestrogen

(2) Have breast caner who are ER\PR positive.

Adverse effects

– Hot flushes

- Nausea

- Fluid retention

- Endometrial cancer after long term use.

In advanced breast carcinoma, clinical improvement is observed in 40 – 50% of ER +ve tumors and 10% in ER-ve tumors. Oophorectomy, hypophysectomy and adrenalectomy with or without oophorectomy are various procedures utilized for hormonal manipulation.[51]

Oophorectomy described by Beaston was the only ablative procedure for years. This bilateral oophorectomy is presumed to work by elimination of ovarian hormones including oestrogen, progesterone & androgen. This produced objective regression of the disease process, the amount of regression was increased with exclusion of ER-ve lesions. Little can be gained with oophorectomy in postmenopausal women, as there is no secretion of hormones from the ovaries of postmenopausal women. Surgical castration is preferred because it acts rapidly and results in complete reduction in hormone levels. This has no effect of bone marrow depression, patients who are unfit or refuse surgery can undergo radiation ablation but it takes a minimum of two months to completely suppress the hormones by radiation.[51] Adrenalectomy was popular in earlier days as it showed regression of metastatic disease. Because of less risk, less side effects

and as it is more familiar to the surgeons operating carcinoma breast, it was very commonly used. This was known to increase disease free interval in metastatic disease.[51]

TREATMENT BY STAGE OF DISEASE:

DCIS (Ductal Carcinoma in Situ)

Mastectomy is a curative treatment for approximately 98% to 99% of patients with DCIS, whether gross or mammographic.[48]

STAGE I AND II

Primary operable breast cancer may be treated surgically by total mastectomy or a less radical procedure (wide local excision or segmental mastectomy with total gross removal) followed by radiation therapy. If a total mastectomy is used, we usually recommend immediate reconstruction as well. An axillary lymph node dissection (at least levels 1 and 2) is performed whether the patient is treated with a total mastectomy or a partial mastectomy.

The patient is encouraged to take an active part in deciding between these alternatives. Patients with infiltrating ductal carcinoma are usually treated with radiation therapy and no further surgical resection, whereas those with extensive intraductal carcinoma or infiltrating lobular carcinoma are considered for re-excision or mastectomy, depending on the extent of disease.[52]

Patients treated with BCT are treated with 50 Gy of external beam radiation followed by an electron boost to the tumor bed. After a total mastectomy with lymph node dissection, radiation therapy is also recommended for women with T3 lesions, extranodal extension of tumor, extensive lymphatic invasion within the tumor, or four or more positive lymph nodes.

Node negative women with low risk of micrometastasis: Patients with DCIS of any size, node-negative patients with invasive tumors of special types (tubular, papillary, mucinous, colloid, and typical medullary types) and a T less than 2 cm, and patients with the more usual forms of invasive breast cancer with favorable prognostic factors and a T less than 0.5 cm are not candidates for adjuvant therapy. Tamoxifen may be given if the ER is positive or the patient is concerned with decreasing the risk of contralateral breast disease.[52]

Node-Negative Women with a High Risk of Micrometastasis: This group includes all node-negative women with the usual invasive tumors measuring between 2 and 5 cm as well as those with smaller tumors (Tis or T > 1 to < 2 cm) and unfavorable tumor characteristics.

Most of the contemporary clinical trails for patients in this group use one of several doxorubicin-containing regimens (AC or CAF). Alternatively, in the non trial setting, classic CMF is reasonable choice.

The duration of tamoxifen therapy should extend for 5 years. It is unclear whether tamoxifen should be given concurrently with chemotherapy or following chemotherapy, if adjuvant chemotherapy is employed.[52]

Node positive patients: Adjuvant chemotherapy is clearly indicated for node-positive patients. The intensity of the adjuvant regimen is dependent on tumor risk factors, usually determined by the size of the primary tumor and number of involved axillary lymph nodes. Classic CMF or a doxorubicin-based regimen is employed to treat patients with one to three positive nodes. An anthracycline in patients with other adverse prognostic factors (e.g., poly differentiated histology, lymphovascular invasion, or hormone receptor negativity). Patients are generally treated with four cycles of AC or six cycles of CAF. For patients with 4 to 9 nodes involved, options include six cycle of CAF or sequential therapy with four cycles of AC followed by four

cycles of a taxane or the Milan A-CMF regimen. All node-positive patients with positive hormone receptors should receive 5 years of tamoxifen therapy as well.[52]

Contraindications for Breast-Conservation Treatment with Radiation Therapy.[48]

Absolute Contraindications Women with two or more primary tumors in separate quadrants of the breast or with diffuse malignant-appearing microclacifications are not considered candidates for breast-conservation treatment.

A history of previous therapeutic irradiation to the breast region that combined with the proposed treatment, would result in an excessively high total radiation dose, to a significant volume is another absolute contraindication.

Pregnancy is an absolute contraindication to the use of breast irradiation. However, in many cases, it may be possible to perform breast-conserving surgery in the third trimester and to treat the patient with irradiation after delivery.

Finally, persistent positive margins after reasonable surgical attempts absolutely contraindicate BCT with radiation. The importance of a single focally positive microscopic margin needs further study and may not be an absolute contraindication.[53]

Relative Contraindications

A history of collagen vascular disease is a relative contraindication to BCT because published reports indicate that such patients tolerate irradiation poorly. Most radiation oncologists will not treat patients with sclerodema or active lupus erythematosus considering it as an absolute contraindication. In contrast, rheumatoid arthritis is not a contraindication Patients with multiple gross tumors in the same quadrant and indeterminate calcifications must be carefully assessed for

suitability, because studies in this area are not definitive. Tumor size is not an absolute contraindication to BCT, although few reports have been published about treating patients with tumors larger than 4 to 5 cm. however, a relative contraindication is the presence of a large tumor in a small breast in which an adequate resection would result in significant cosmetic alteration.

STAGES IIIA AND IIIB

Stage IIIA disease is technically operable but carries a high risk of early relapse. Stage IIIB disease is considered technically inoperable, but preoperative chemotherapy can reduce the size of the tumor in some patients so that surgical resection is possible.

Patients who have locally advanced breast cancer are treated with four cycles of doxorubicin based chemotherapy, regardless of the distinction between IIIA and IIIB. This therapy is followed by surgical resection, if possible (either a segmental resection or total mastectomy, depending on lesion size, plus a lymph node dissection) and postoperative radiation therapy. Postoperatively, patients are treated with two or three additional cycles of anthracycline-based therapy or four cycles of a taxane.[54]

Patients with positive hormone receptors are treated with tamoxifen at the conclusion of chemotherapy. In our view, surgical resection of the tumor is important for these patients, even if the tumor responds completely to chemotherapy. This resection is sometimes referred to as Ghostectomy, but these lesions may contain viable tumor, and local control is improved by the surgical procedure.[52]

INFLAMMATORY CARCINOMA OF BREAST: The initial management of localized inflammatory breast cancer is combination chemotherapy. Anthracycline – based regimens are commonly used, and some now employ anthracyclines plus taxanes as first-line treatment in inflammatory breast carcinoma. Radiation therapy and additional course of chemotherapy follow this treatment.[55]

Tamoxifen is used for at least 5 years after completion of local-regional therapy and adjuvant chemotherapy in-patients who are hormone receptor positive.

STAGE IV: (METASTATIC DISEASE) Patients with Metastatic Breast cancer to distant sites and those who experience distant relapse after adjuvant treatment are treated with palliative intent by endocrine manipulation or chemotherapy. Patients with positive hormone receptors and nonvisceral involvement are treated initially with endocrine manipulation. For premenopusal patients, this treatment starts with tamoxifen or medical oophorectomy with a LHRH-GnRH agonist. Traditionally, megestrol acetate has been a good second-line choice for endocrine therapy for premenopausal and postmenopausal patients. Surgical oophorectomy is rarely performed for postmenopousal patients. For patients who are candidates for chemotherapy because of failure of hormonal management or the presence of life threatening visceral disease and lymphangitic pulmonary metastases, be initiated with classic CMF or a doxorubicin-containing regimen or a single-agent taxane or a oral chemotherapy with 5FU-related drugs.[56]

RADIATION

Radiation therapy is effective in alleviating the bone pain from tumor progression. Radiation is used as first line for solitary metastasis. The effective dose for palliation has not been evolved & various trials have shown 8 Gy at 4 weeks as a single fraction schedule is optimal.

OPERATIVE TREATMENT

Patient presenting with either a complete or impending pathologic fracture of lower extremity should undergo operative stabilization or reconstruction in majority of cases. In cases of spinal involvement treatment depends on factors like neurological involvement.[55]

BREAST RECONSTRUCTION:

Timing: The timing of breast reconstruction after mastectomy has been advanced from delayed to immediate because of advance and refinements in breast reconstructive techniques. Because studies have shown that, with immediate breast reconstruction a psychological benefit, cost effectiveness, cosmetic advantage and no increased risk of complications or oncologic risk has been noted, so immediate breast reconstruction has become the preferred time for reconstruction. Virtually all patients are potential candidates for immediate reconstruction; the most commonly cited reason for delaying reconstruction is the known need for postoperative radiation, which is a relative contra indication[77].

Types of reconstruction:

1) Tissue expansion followed by implant.

2) TRAM flap (free/pedicle).

3) Latissimus dorsi with implant.

PROGNOSTIC FACTORS

(1) **Axillary lymphnodes.** Positive axillary nodes are the major risk factor for systemic disease & most oncologists believe that all women with involved lymph nodes should have adjuvant therapy because the clinical staging of axillary nodes is so inaccurate. Axillary LN dissection is necessary to stage patient accurately & to determine the benefit of adjuvant therapy.[57]

(2)Tumor size Tumor size is the most important single, secondary prognostic factor for risk of recurrence & benefit from therapy in axillary node-Negative breast cancer. Tumor size 1cm or smaller was associated with a very favorable prognosis in studies by Rosen & colleagues. Patients with <1cm Tumor were given adjuvant therapy only an investigative protocol, >2 cm benefit significantly from adjuvant therapy and those whose tumors measure 1 to 2 cm should be evaluated for risks and benefits from careful examination of other factors.[57]

(3) Histological grading system Prognosis varies according to the Histological grade & type of the Tumor. The most favorable prognosis is found in-patients with mucinous, tubular or medullary cancers.

(4) Steroid receptors Reproductive and certain other sensitive tissues possess high affinity protein receptors for estrogen and progesterone. Specific receptors for both hormones may be present in tumor tissue of mammary origin. Activation of these receptor leads to activation of numerous cellular genes, including those that may encode critical enzymes & secrete peptide growth factors.

The presence of ERs provides a molecular basis for the distinction between human breast carcinomas that are responsive to hormone therapy / organ ablative surgery and those that are not. Analysis of ER in primary lesion indicate that, patient with breast cancer containing these regulatory proteins exhibit increased disease free survival as compared with patients whose tumors did not contain ERs.

Not all women with breast tumors containing ER respond to hormone therapy. Simultaneous determination of PR with ER increases the accuracy for selecting breast carcinoma patients most likely to respond to hormonal therapy.[58]

Methods of assay

1) Radionuclide – Binding Procedures.

2) Enzyme linked immunoassay – most commonly used.

3) Sucrose density gradient centrifugation.

4) High performance liquid chromatography methods.

5) Immunohistochemistry.

Reference range

The cut off point for the presence of receptors is generally accepted to be 10 fmol/mg and 15fmol/mg of receptor cytosol proteins by the binding methods & Enzyme linked immunoassay method respectively. The sensitivity of assay and the biological data suggest that < 3 fmol/ mg of protein is a clinically insignificant quantity of receptors in human breast tumors.[59]

(2) **DNA & S-phase fraction**

Proliferative rate can be determined by studying the percentage of cells in the DNA synthesis phase of cell (s-phase). Recent reports demonstrate that increased percentage of s-phase predicts early recurrence or poor survival. DNA ploidy is also an important factor.

(3) **epidermal growth factors**

EGF receptor expression is associated with poor prognosis and hormone resistance.[60]

(4) **Patient Characteristics**

Young age has been hypothesized to be an adverse prognostic factor for women with carcinoma Breast.[61]

MATERIALS AND METHODS

TITLE OF THE STUDY:
Efficacy of single cycle Neoadjuvant chemotherapy in carcinoma breast.

SOURCE OF DATA:

All the patients diagnosed as breast carcinoma with stage IIb and IIIa and admitted in surgical wards were selected for this prospective study at R.L.JALAPPA. HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR attached to SRI DEVARAJ URS MEDICAL COLLEGE between December 2013 and June 2015

SAMPLE SIZE: A total number of 25 cases of breast carcinoma were selected for the study.

INCLUSION CRITERIA:

1. Patients with IIb and IIIa breast cancer (TNM classification).

EXCLUSION CRITERIA:

1. Patients with systemic metastasis.
2. Pregnant/lactating patients.
3. Patients who are allergic to above mentioned drugs
4. Impaired renal and hepatic function.
5. Patients with cardiac diseases.

Female patients fulfilling the inclusion criteria were included in this study based on:

- Detailed history
- Clinical examination
- FNAC/Trucut biopsy,
- Ultrasonography(USG) breast and axilla
- USG abdomen, mammography and chest x-ray.

The breast carcinoma was staged according to TNM staging (AJCC) and stage IIb and IIIa received a single cycle of chemotherapy consisting of

- 5- Fluorouracil 500 mg/m2
- Adriamycin 50 mg/m2
- Cyclophosphamide 80 mg/m2 (FAC regimen) which was administered intravenously.

Clinical tumor size was estimated before the start of chemotherapy and after an interval of 10 days by sonomammographically.

SONOMAMMOGRAPHICAL ASSESSMENT

The product of the two greatest perpendicular diameters and volume of tumor was used to compare tumor size before and after chemotherapy, as defined by the International Union Against Cancer criteria.

STATISTICAL METHODS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made,

Assumptions: 1.Dependent variables should be normally distributed,

2.Samples drawn from the population should be random, Cases of the samples should be independent

95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% is associated with statistical significance.

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

OBSERVATIONS AND RESULTS

1. AGE DISTRIBUTION

The age of the patients ranged from 41 to 80 years .The highest number

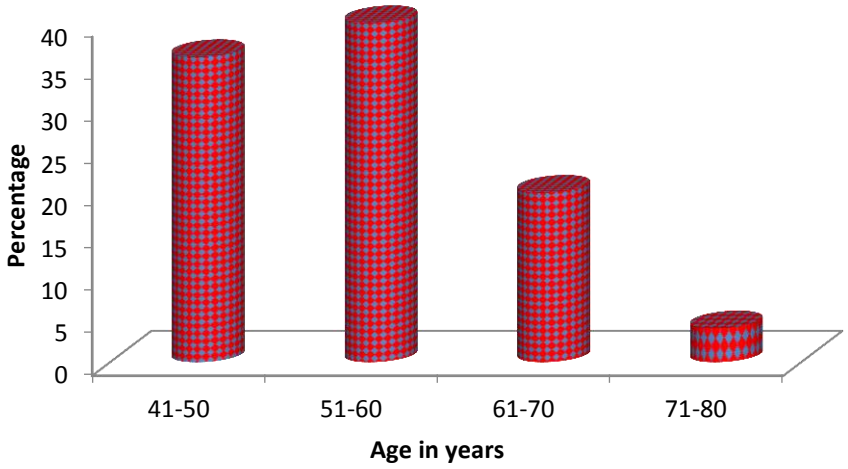
of patients were in the age group of 51-60 years age group with 40% (10 patients), followed by 41-50 years age group with 36% (9 patients). The mean age of patients was 54.2 years.

TABLE 2: AGE DISTRIBUTION OF PATIENTS STUDIED

Age in years	No. of patients	%
41-50	9	36.0
51-60	10	40.0
61-70	5	20.0
71-80	1	4.0
Total	25	100.0

Mean ± SD: 54.24±8.21

GRAPH 1: AGE DISTRIBUTION



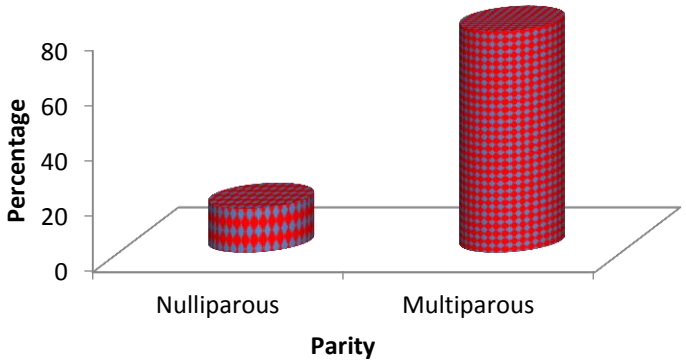
2. PARITY STATUS

16% (4 patients) of the patients were nulliparous and 84% (21 patients) were multiparous.

TABLE 3: PARITY DISTRIBUTION

Parity	No. of patients (n=25)	%
Nulliparous	4	16.0
Multiparous	21	84.0

GRAPH 2: PARITY DISTRIBUTION



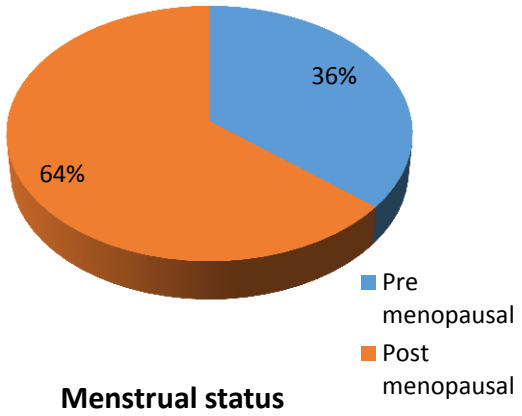
3. MENSTRUAL STATUS

36% (9 patients) of the patients were pre menopausal and 64% (16 patients) were post menopausal.

TABLE 4: MENSTRUAL STATUS

Menstrual status	No. of patients (n=25)	%
Pre menopausal	9	36.0
Post menopausal	16	64.0

GRAPH 3: MENSTRUAL STATUS



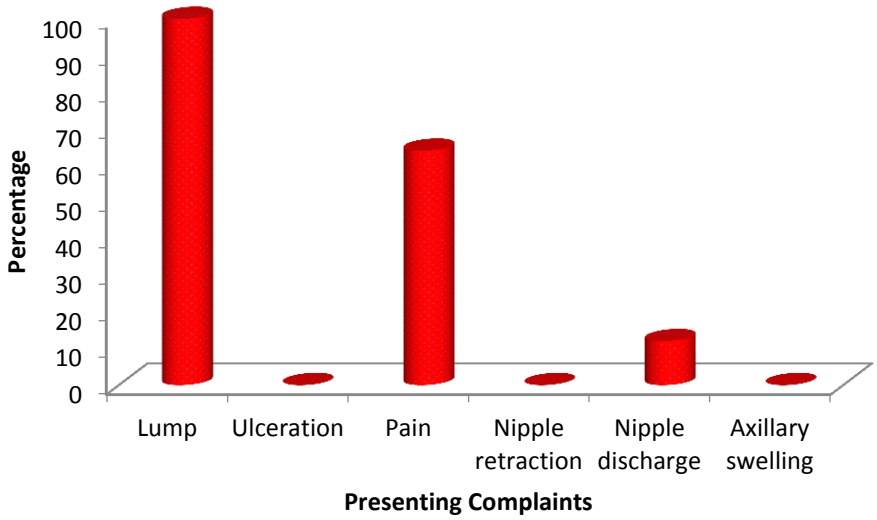
4. SYMPTOMS AT PRESENTATION.

Lump was the most consistent symptom which was present in all patients 100% (25 cases) who were included in stage IIB IIIA. Pain was the second most common presentation noticed in 64% (16 cases) and nipple discharge was observed in 12% (3 cases). None of them had an ulcer over the lump or nipple discharge.

TABLE 5: PRESENTING COMPLAINTS

Presenting Complaints	No. of patients (n=25)	%
Lump	25	100.0
Ulceration	0	0.0
Pain	16	64.0
Nipple retraction	0	0.0
Nipple discharge	3	12.0
Axillary swelling	0	0.0

GRAPH 4: PRESENTING COMPLAINTS



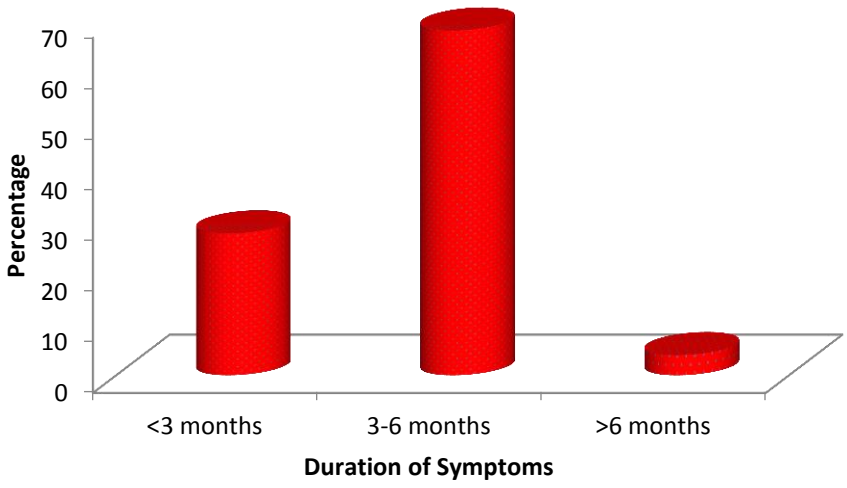
5. DURATION OF SYMPTOMS

Most of the patients presented in a span of 3 months to 6 months i.e 68% (17 patients). The duration of symptoms ranged from 1- 7 months.

TABLE 6: DURATION OF SYMPTOMS

Duration of Symptoms	No. of patients (n=25)	%
<3 months	7	28.0
3-6 months	17	68.0
>6 months	1	4.0

GRAPH 5: DURATION OF SYMPTOMS



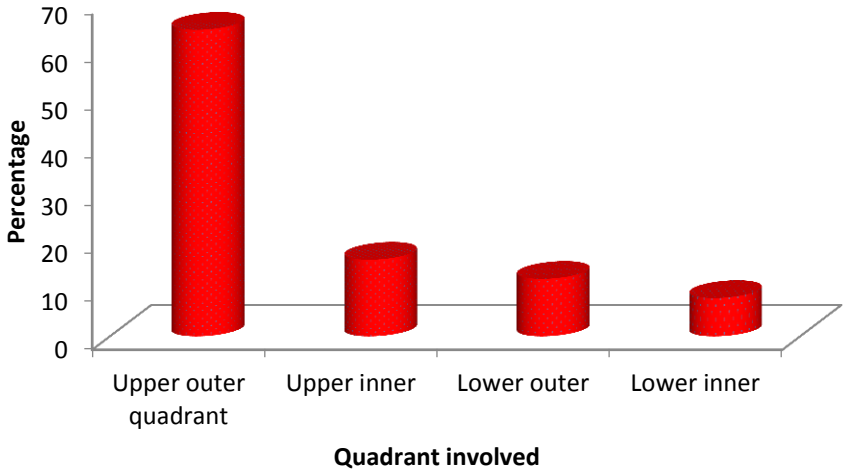
6. QUADRANTS INVOLVED

The upper outer quadrant was the most commonly involved quadrant with a total of 64% (16 cases). Most of them fall under less than 5 cm in the study.

TABLE 7: QUADRANTS INVOLVED

Quadrant involved	No. of patients	%
Upper outer quadrant	16	64.0
Upper inner	4	16.0
Lower outer	3	12.0
Lower inner	2	8.0
Total	25	100.0

GRAPH 6: QUADRANT INVOLVED

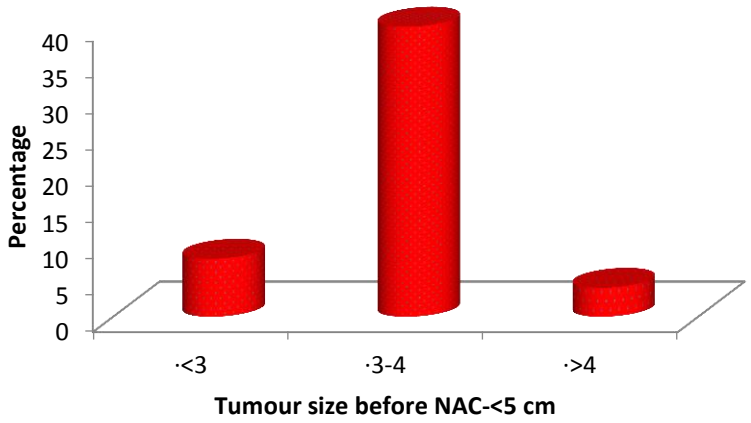


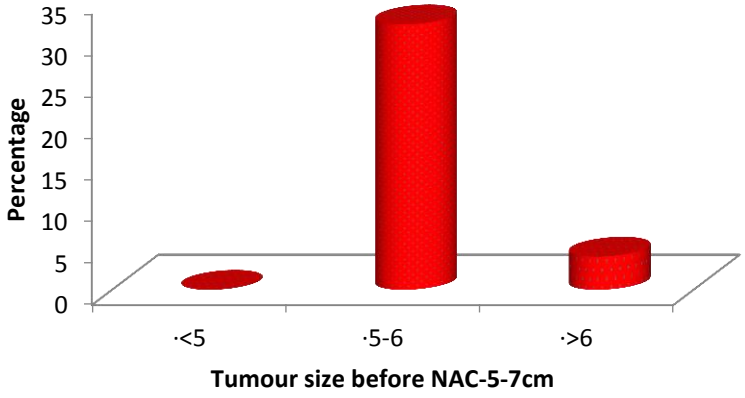
7. TUMOUR SIZE

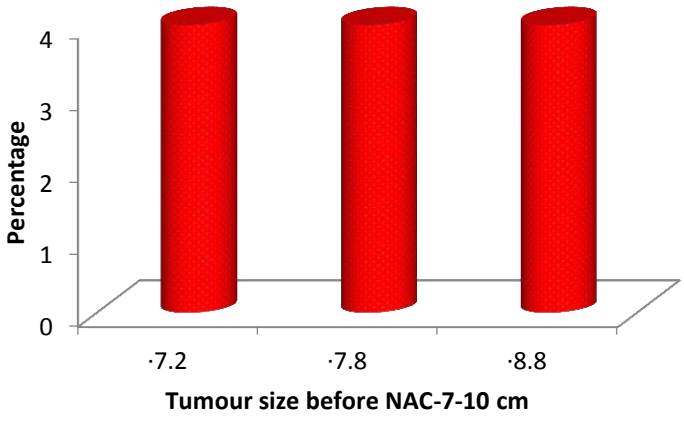
The tumour size ranged from 1.9 cm to 8.8 cm in the dimension. The smallest tumor measured 1.9cms in the greatest dimension while the largest 8.8 cms. Majority of the tumours were of the size less than 5 cms. The mean size of the tumours was 3.4 cms.

TABLE 8: TUMOUR SIZE BEFORE NAC

Tumour size before NAC	No. of patients (n=25)	%	Mean ± SD
<5 cm	13	52.0	
• <3	2	8.0	3.35±0.94
• 3-4	10	40.0	
• >4	1	4.0	
5-7 cm	9	36.0	
• <5	0	0.0	5.82±0.57
• 5-6	8	32.0	
• >6	1	4.0	
7-10 cm	3	12.0	
• 7.2	1	4.0	7.93±0.81
• 7.8	1	4.0	
• 8.8	1	4.0	


40
35
30
25
20
15
10
5
0
Percentage
·<3
·3-4
·>4
Tumour size before NAC-<5 cm


35
30
25
20
15
10
5
0
Percentage
·<5
·5-6
·>6
Tumour size before NAC-5-7cm


4
3
2
1
0
Percentage
·7.2
·7.8
·8.8
Tumour size before NAC-7-10 cm

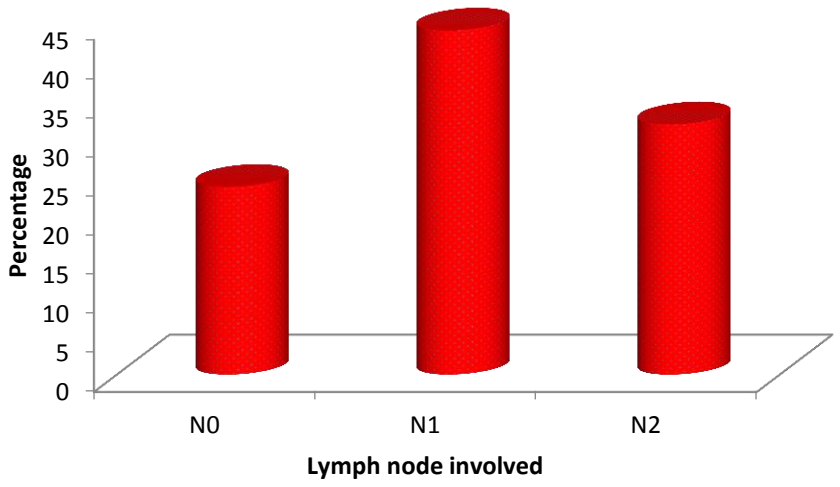
8. **LYMPH NODE STATUS**.

The axillary node status seen in the study is depicted in the following table and graph. Majority of patients had N1 involvement.

TABLE 9: LYMPH NODE INVOLVED

Lymph node involved	No. of patients (n=25)	%
N0	6	24.0
N1	11	44.0
N2	8	32.0

GRAPH 8: LYMPH NODE INVOLVED



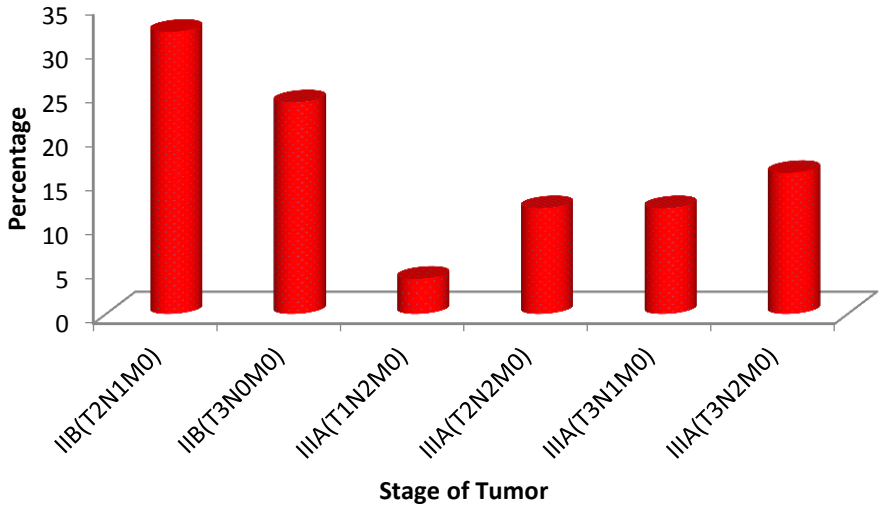
9. STAGE OF THE DISEASE

Among 25 cases studied 14 cases are in stage IIB and 11 cases are in stage IIIA

TABLE 10: STAGE OF TUMOR

Stage of Tumor	No. of patients	%
IIB(T2N1M0)	8	32.0
IIB(T3N0M0)	6	24.0
IIIA(T1N2M0)	1	4.0
IIIA(T2N2M0)	3	12.0
IIIA(T3N1M0)	3	12.0
IIIA(T3N2M0)	4	16.0
Total	25	100.0

GRAPH 9: STAGE OF TUMOR



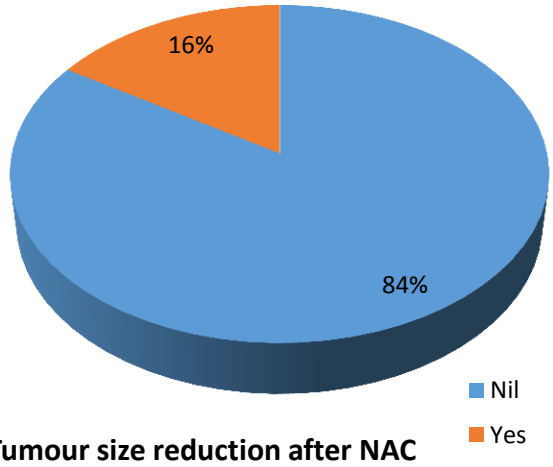
10. SIZE REDUCTION AFTER NEOADJUVANT CHEMOTHERAPY

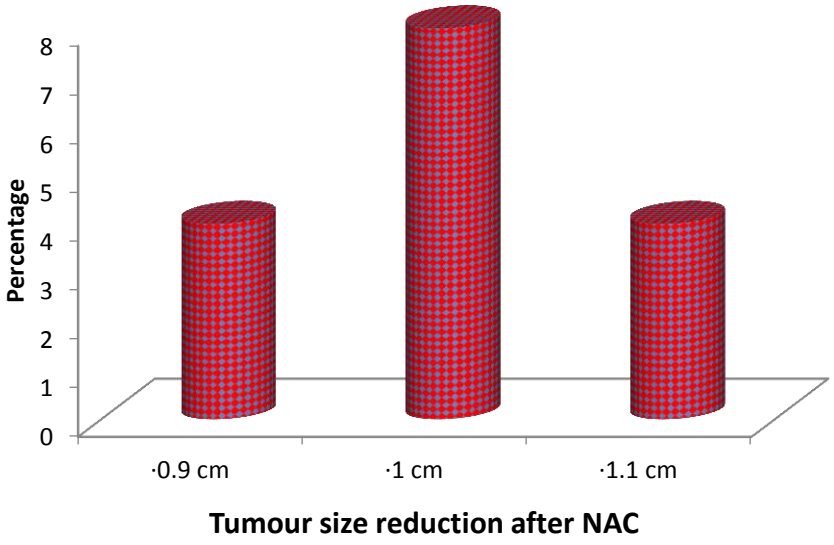
Among 25 cases 4 cases have shown decrease in tumor size following single cycle neo adjuvant chemotherapy

TABLE 11: TUMOUR SIZE REDUCTION AFTER NAC

Tumor size reduction after NAC	No. of patients	%
Nil	21	84.0
Yes	4	16.0
• 0.9 cm	1	4.0
• 1 cm	2	8.0
• 1.1 cm	1	4.0

GRAPH 10: TUMOUR SIZE REDUCTION AFTER NAC





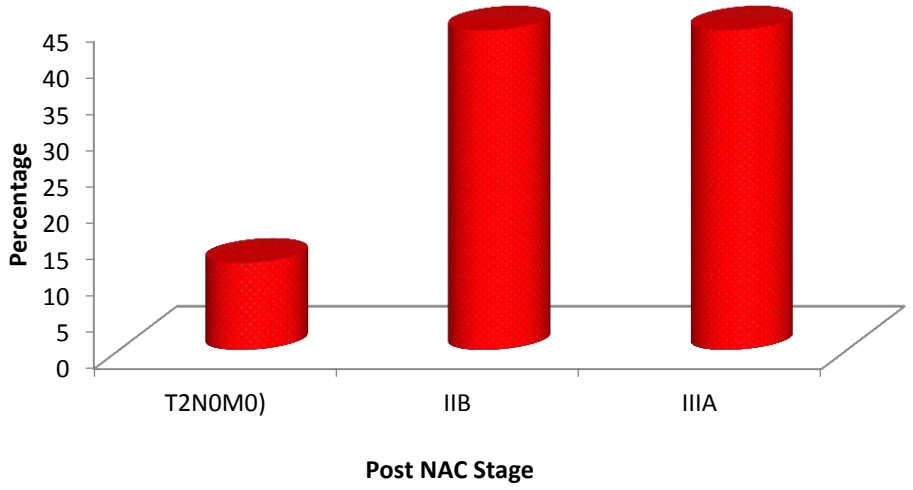
11. STAGING AFTER NEO ADJUVANT CHEMOTHERAPY

There was down staging of three cases. 3 cases were down staged from stage IIB to stage IIA following single cycle of neo adjuvant chemotherapy

TABLE 12: POST NAC STAGE

Post NAC Stage	No. of patients	%
IIA(T2N0M0)	3	12.0
IIB	11	44.0
IIIA	11	44.0
Total	25	100.0

GRAPH 11: POST NAC STAGE



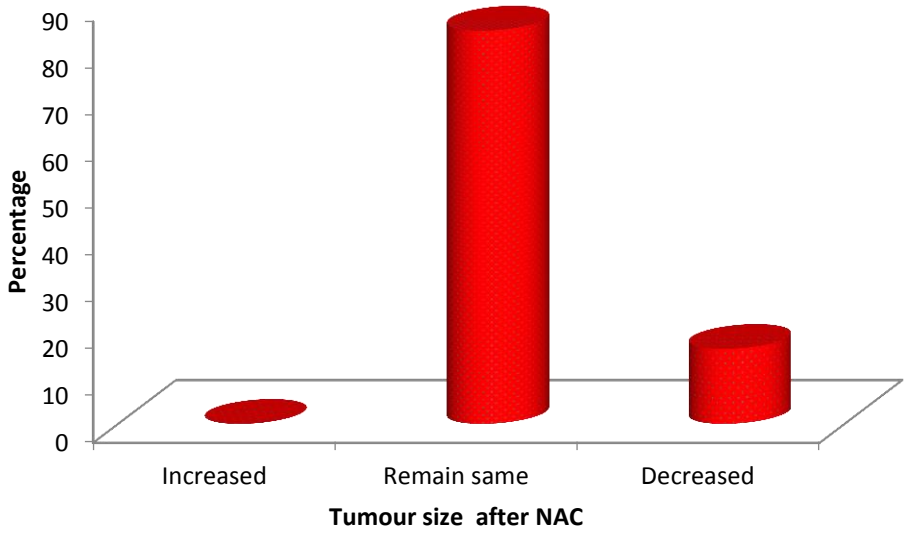
13. EFFECT ON TUMOR SIZE FOLLOWING NAC

There was decrease in tumor size noted in 16% of cases (4 patients) while 84% of cases (21 patients) remained unchanged.

TABLE 13: TUMOUR SIZE CHANGES AFTER NAC

Tumour size after NAC	After NAC	%	95%CI
Increased	0	0.0	0.0
Remain same	21	84.0	65.35-93.60
Decreased	4	16.0	6.40-34.65
Total	25	100.0	-

GRAPH 12: TUMOUR SIZE CHANGES AFTER NAC



DISCUSSION

1. PROPORTION OF CASES

In our study 44% of the patients admitted for the treatment of breast cancer were locally advanced. Chopra R states the proportion of LABC to the total number of reported breast cases to be 28.9%, 40.5% and 52% in Mumbai, Trivandrum and Chennai respectively. The proportion of LABC is very high in developing countries compared to the western countries. 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.[62]

Late diagnosis is a major factor for increased mortality as the majority of the patients present in advanced or metastatic stage. This is primarily attributed to lack of access to medical facilities, virtually non-existent breast cancer screening programs, lack of awareness and social-cultural attitudes.[63]

2. AGE DISTRIBUTION.

The age incidences are compared in the table below. The highest number of cases are seen in the age group of 51-60 years, other studies showing highest incidence in age group in 41-50 years except in Amit Goel et[64] al the peak is seen in 31-40 years age group.

Age groups	Current Study	Sen and Dasgupta[67] series	Chopra R[68]	Amit Goel [64]et al
31-40yrs	--	23.8%	18.0%	40%
41-50 yrs	36%	36.9%	32.5%	20%
51-60yrs	40%	25.2%	25.8%	15%
> 60yrs	24%	11.4%	20.0%	15%

TABLE 14 : COMPARISON OF AGE DISTRIBUTION

The mean age in our study was 54.2 years which is different from Amit aggarwal et al[65] and DS Sandhu et al[66] which was 46.5years and 47.39 years. In general, breast cancer has been reported to occur a decade earlier in Indian patients compared to their western counterparts. While the majority of breast cancer patients in western countries are postmenopausal and in their 60s and 70s, the picture is quite different in India with premenopausal patients constituting about 50% of all patients.[69]

3. SYMPTOMS AT PRESENTATION

The presenting features are compared with the percentages of presenting features in some of the similar series from India. The most consistent symptom is that of a lump and is seen in all cases in our study and 87.9%, 74%, 96.5% in Sandhu DS et al[66], Gang et al[70] and Raina et al[71] series respectively.

TABLE 15 : COMPARISON OF SYMPTOMS ON PRESENTATION

Symptoms	Current study	DS Sandhu[66]	Gang et al[70]	Raina et al[71]
Lump	100%	87.9%	74%	96.5%
Ulcer	-	9.5%	-	-
Pain	16%	13.9%	13.9%	15.8%
Nipple discharge	3%	2.78%	2.78%	4.9%
Swelling in axilla	4%	-	-	-

4. QUADRANTS INVOLVED

In all the series the percentage in the upper outer quadrant by far exceeds the percentage of location in other quadrants. The percentages of lump in the upper outer quadrants are 64%, 47%, 49% and 48% in the current, Sandhu DS et al, Sen and Dasgupta et al and Fields et al series.

TABLE 16 : COMPARISON OF QUADRANTS INVOLVED

Quadrant involved	Current study	DS Sandhu[66]	Sen and das Gupta[67]	Fields et al[72]
Upper outer	64%	47%	49%	48%
Upper inner	16%	9.5%	13%	15%
Lower outer	12%	3.6%	11%	11%
Lower inner	8%	1.6%	7%	3%

The possible explanation is that the upper outer quadrant has a relatively larger volume of breast tissue.

5. DURATION OF SYMPTOMS.

Most of the cases present with 3-6 months duration. The percentage of patients in this range was 68% and 32.9% in our study and in DS Sandhu et al[66] series respectively. The cases with less than 3 months duration were higher in DS sandhu series compared to our study.

TABLE 17 : COMPARISON OF DURATION OF SYMPTOMS

Duration	Current study	DS sandhu et al[66]
<3 months	28%	37.5%
3-6 months	68%	32.9%
>6 months	4%	29%

6. MENSTRUAL STATUS

In our study more patients were post menopausal 64% (16 patients) than pre menopausal 36% (9 patients). Similar profile can be seen in KarlssoN YA et al series.

TABLE 18 : COMPARISON OF MENSTRUAL STATUS

Menstrual status	Current study	DS sandhu Amit	Aggarwal et al	Karlsson YA et al.[73]
Pre menopausal	36%	44.24%	56%	41%
Post menopausal	64%	55.76%	4%	59%

In Sandhu DS et al study 44.27% of the patients were pre menopausal and 55.76%. Karlsson YA et al reported 41% pre menopausal and 59% post menopausal. Compared to the west the percentage of premenopausal patients are less in our study.

7. TUMOR SIZE.

The tumor sizes in our study are compared with Chintamani et al and Aggarwal Himanshu et al studies. Maximum tumors are in the range of 5-8 cms. The percentage of tumours in that range is considerably lower in our study.

TABLE 19 : COMPARISON OF TUMOR SIZE

Tumor size	Current study	Chintamani et al[74]	Aggarwal Himanshu et al[70]
<5cms	52%	16.2%	16.7%
5-7cms	36%	36.6%	56.7%
7-10cms	12%	26.7%	26.6%

The patients ignore the mass as it is commonly painless and does not interfere with the regular lifestyle of the patient. There is also considerable delay in presenting to the hospitals due to ignorance allowing the lump to attain larger proportions. But in our study as we are confined to stage IIb and IIIa patients with tumor size less than 5cms are 52%

8. LYMPH NODE STATUS

TABLE 20: COMPARISON OF LYMPH NODE STATUS

Node status	Current study	Jaiganesh Vishambaran LK et al[75]	Chintamani et Al[74]	Aggarwal Himanshu et Al[70]
N0	22%	2%	12%	10%
N1	44%	91%	48%	34.2%
N2	32%	7%	40%	55.8%

Jaiganesh Vishambaran LK et al reported N0 to be 2%, N1 stages to be 91% and N2 stages to be 7%.Compared to this study our patients showed a higher incidence of N1 disease. Same results seen in Chintamani et al.

This dissertation deals with the study of breast cancer patients who were admitted at R L JALAPPA medical college Hospital and received anterior chemotherapy. A total of 25 patients who presented in stage IIb, IIIa were included in the study during the period December 2013 to August 2015.

Most common stage in Indian population is stage III .[75] In our study we have included only the patients who have presented with stages of IIB and IIIA.

25 patients with breast cancer received single cycle of Neo-adjuvant chemotherapy with 5-Flurouracil, Cyclophosphamide and Adriamycin.

Results of NSABP B-18 (National Surgical Adjuvant Breast Project) on the effect of preoperative chemotherapy on tumor response indicate that following administration of preoperative chemotherapy, 36% of patients obtained a clinical complete response and 43% of patients obtained a clinical partial response, for an overall response rate with downstaging of 79%.[76,77] Study conducted by Veeram sunil kumar reddy with 3 cycles of neo adjuvant chemotherapy shows the down staging of 76.6%.

Study conducted by Awad Ali M. Alawad with 2 cycles of neo adjuvant chemotherapy shows the clinical response rate was 83%; 11 patients (11.2%) had a complete clinical remission (cCR); 71 had a partial remission (72.4%); 13 had stable disease (13.3%), and 3 had progressive disease (3.1%). Seven patients had complete pathological respons also it states that Neoadjuvant chemotherapy can achieve a high objective response rate in patients with locally advanced breast cancer even after two cycles.[79]

Our present study shows that following one cycle of neoadjuvant chemotherapy there is decrease in tumor size among 16% with down staging among 12% of cases, the observation made here is decrease in tumor size is seen in patients with no axillary metastasis and with multiparous women.

So our study concludes that single cycle of Neo adjuvant chemotherapy is effective in small group of patients with stage limited to IIB and IIIA, but however the advanced staged cancers needs minimum of three cycles of chemotherapy followed by adjuvant chemotherapy after surgery.

CONCLUSION

In our study we found that single cycle NAC does not decrease the tumor size in significant number. The decrease in tumor size was noticed in patients who had no nodal involvement and in multiparous women.

Single cycle Neoadjuvant chemotherapy is preferred in patients who cannot take up 3 cycles of NAC. These patients can be tried with single cycle NAC which helps to halt the disease in tumor progression.

SUMMARY

This study was done to find out the Efficacy of single cycle Neoadjuvat chemotherapy in carcinoma breast.

This dissertation involved the study of 25 patients with Stage IIB and IIIA disease who were admitted at R L JALAPPA hospital, Dept of General surgery. This is a prospective cohort study during a period of 2 years 8 months from December 2013 and August 2015.

Clinical tumor size was estimated before the start of chemotherapy (FAC regimen) and after an interval of 10 days by sonomammographically.

The objectives of this study were to evaluate and quantify the response to neo-adjuvant chemotherapy by physical examination and Imaging modalities, Reduction in size of primary tumour, Change in the clinical stage of the tumour after single cycle neoadjuvant chemotherapy.

In our study 44% of the patients admitted for the treatment of breast cancer were locally advanced. The highest number of cases are seen in the age group of 51-60 years, the most consistent symptom is that of a lump and is seen in all cases, the percentages of lump in the upper outer quadrant is 64%, most of the cases present with 3-6 months duration. Maximum tumors are in the range of 5-8 cms.

In our study we found that there is decrease in tumor size in 16% of patients (i.e 4 patients among 25) in those who received single cycle neo adjuvant chemotherapy in patients with stage IIB and IIIA patients. With 95% confidence interval ranging from 6.40-34.65.This decrease in tumor size has resulted in down staging among three cases (down staged from stage IIB to stage IIA).

We found that single cycle NAC does not decrease the tumor size in significant number. The decrease in tumor size was noticed in patients who had no nodal involvement and in multiparous women.

Single cycle Neoadjuvant chemotherapy is preferred in patients who cannot take up 3 cycles of NAC. These patients can be tried with single cycle NAC which helps to halt the disease in tumor progression.

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.

ANNEXURES

PROFORMA

Name : IP No :

Age : DOA :

Sex : DOD :

Address :

Religion :

Socio-economic status :

Complaints : 1)

2)

3)

Details of history

1) **Lump** :

Mode of onset - Insidious / Sudden

Progress - Slow / Gradual/ Rapid

Sudden increase in size - Yes / No

2) **Pain** : Present / Absent , if present :

Duration :

Site :

Type :

Radiation :

Bearable / Unbearable

3) Ulcer : Present / Not present, if present:

Duration :

Mode of onset :

Progress :

4) Discharge from the nipple: Yes / No

If yes, nature of discharge: Blood stained /serous /dark green / Purulent /Milk /Black.

Axillary, supraclavicular lymph nodes: Yes / No , If any –

Any symptoms of – Cough / Hemoptysis / Dyspnea / Chest pain - Present /Not present

Bony pain: Present / not present - Spine/Ribs/Pelvis/Femur

Loss of weight: Yes / No If yes, how much

Application of counter irritants:

Any history of taking, OCP: Yes / No . If yes - Duration

Any other complaints :

Past History

Previous breast disease : Yes / No

If yes, Fibroadenoma /Fibroadenosis /Breast abscess /Duct papilloma /Not known

Personal History

Marital status-

Age at marriage -

Age at first pregnancy -

Number of pregnancy-

Details of pregnancy -

No : Age: Termination(FTND) Present age of child:

Number of viable births: No. of abortions:

Menstrual history-

Age at menarche : years

Frequency : days

Duration of flow : days

Regular / Irregular :

Whether patient is pregnant : Yes / No

If no, last pregnancy - Year back

Menopause: Attained/Not attained, if attained age at onset:

Lactation history -

Whether children breast fed/not breast fed-

Whether fed with – One/both breasts

Duration of lactation-

Family history -

Any family history of breast cancer. If preset, the relationship to patient.

General physical examination

Build-

Emaciation : Present / Not present

Pallor : Present/Not present

Jaundice : Present/Not present

Edema, cyanosis : Present/Not present

Mental state : Anxiety/depressed

Pulse : Height:

B.P : Weight:

R.R:

Temperature :

Local examination

Examination of breast:

- Sitting posture

- Bending forward position

- Recumbent position

Inspection: Right/Left breast

Nipple: Position-Elevated/Retracted

Size and shape: Prominent/flattened retracted

Surface: Cracks/fissure/Eczema/ulceration/Normal

Discharge: Present/Not present

If present, nature of discharge:

Areola: Normal/Size diminished

Any cracks/fissure/Ulcer/Eczema/Discharge swelling

Skin over the breast: Inflammation/Veins/Dimpling/Peau-de-orange/nodular

Breast proper: Affected breast(right/left)

Inspection:

Position: Displaced in any direction: Yes/No

Size and shape: Smaller/Larger than its fellow

Any localized swelling present/not, if present;

Position (relation to quadrants): -

Size -

Shape -

Surface -

Any ulcer present

If present

Position-

Size-

Shape-

Surface -

Oedematous arm: Present /Not present

Any swelling in the supraclavical/infraclavical/axilla

If present-

Site Number

Size Shape

Surface

Other breast tissue:

Palpation:

Examination done: Sitting posture/Recumbent posture

Affected side breast : Right/Left

Local temperature : Raised/Normal

Tenderness : Present/Not present

Situation of Lump (in which quadrant):

Right breast/Left breast

Size and shape

Surface : Smooth/Uneven

Margin : Well defined and regular / III defined and

irregular

Consistency : Cystic/Firm/Hard/Variable

Fluctuation : Present/Not present

Fixity to skin : Present/Not present

Fixity to breast tissue : Yes/No

Whether mass moves with breast

Fixity to underlying : Fixed/Not fixed

Fascia and muscles

Fixity to chest wall : Fixed/Not fixed

If ulcer present-

Inspection:

Number

: Single/Multiple

Position :

Size and shape :

Discharge :

Surrounding area :

Palpation:

Tenderness : Present /Not present

Edge and surrounding : Indurated/Not

Tissue -

Base -

Mobility -

Bleeding -

Examination of regional lymphnodes – Right/left/both

Axillary group of lymphnodes: Palpable/Not Palpable

If palpable-

Group:

Number of lymphnodes

Size-

Tenderness-

Consistency-

Mobility-

Matted-

Cervical lymphnodes

If palpable-

Group -

Number -

Size -

Tenderness- Present/Not present

Consistency- Soft/Cystic/Firm/Hard

Mobility Present/Not present

Matted Yes/No

Internal mammary lymphnode involvement (by percussion method) - Yes/No

Opposite breast examination:

Nipple Normal

Areola Normal

Breast proper: Any lump felt - Yes/No

If yes,

Opposite axilla examination:

Any lymphnode enlarge: Yes/No

If yes, details:

Systemic examination

Abdominal examination :

Respiratory system examinatiSon :

Cardiovascular examination :

Per-rectal examination :

Per-vaginal examination:

Bone tenderness: Spine/Sternum/Humerous/Femur/Ribs - Present/Not present

Clinical diagnosis

If carcinoma:

TNM Stage: I II III IV

If not carcinoma:

Investigations

Blood:

Hb: gm% ESR: mm hg TC: cells/cu.mm

RBS: mg/dl

Blood group:

BU:

LFT:

Urine: Albumin Sugar

Chest X-ray :

ECG:

FNAC and Biopsy of:

i. Lump

ii. Lymphnode

MAMMOGRAPHY :

Ultrasound: Of involved breast

	PRE-NAC	POST-NAC
VOL		
LENGTH		

i. Abdominal scan

ii. Axilla

DOWNSTAGED:- YES/NO

ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿಯ ನಮೂನೆ

ಕಾರ್ಸಿನೋಮ ಸ್ತನದಲ್ಲಿ ಒಂದೇ ಸುತ್ತಿನ ನವ ಸಹಾಯಕ ಚಿಕಿತ್ಸೆಯ ಫಲದಾಯಕತೆ

ಸ್ತನ ಕ್ಯಾನ್ಸರ್ ಭಾರತದ ಮಹಿಳೆಯರಲ್ಲಿ ಎರಡನೇ ಅತ್ಯಂತ ಸಾಮಾನ್ಯ ಕ್ಯಾನ್ಸರ್ ಮತ್ತು ಸ್ತನ ಕ್ಯಾನ್ಸರ್ ಮತ್ತು ಭಾರತದಲ್ಲಿ ಮಹಿಳೆಯರಲ್ಲಿ ಎಲ್ಲಾ ಕ್ಯಾನ್ಸರ್ಗಳಲ್ಲಿ ಐದನೇ ಒಂದು ಜಾಗತಿಕ ಹೊಣೆ 7 % ನಷ್ಟಿದೆ. ಶಸ್ತ್ರಚಿಕಿತ್ಸೆಗೆ ಮುಂಚೆ ಅಥವಾ ನವ ಸಹೌಷಧದ ರಾಸಾಯನಿಕ (ಎನ್ಎಸಿ) ವ್ಯಾಪಕವಾಗಿ ನಿಷ್ಕ್ರಿಯ ಹಾಗೂ ಇಂತಹ ಸ್ತನ ಕ್ಯಾನ್ಸರ್ ರೋಗಿಗಳಲ್ಲಿ ಆರೈಕೆಯ ಪ್ರಮಾಣಿತ ಸ್ವೀಕರಿಸಲಾಗಿದೆ . ಇಂತಹ ಸ್ತನ ಕ್ಯಾನ್ಸರ್ನ ಎನ್ಎಸಿ ತಾರ್ಕಿಕ ಅತ್ಯಂತ ಆಕ್ರಮಣಶೀಲ ಸ್ತನ ಕ್ಯಾನ್ಸರ್ ವ್ಯವಸ್ಥಿತ ರೋಗಗಳ ಎಂಬುದು.

ಎನ್ಎಸಿ ಶಸ್ತ್ರಚಿಕಿತ್ಸೆಗೆ ಮುನ್ನ ಸ್ಥಾನಾಂತರ ರೋಗ ಕಡಿಮೆ ಮತ್ತು ಟ್ಯೂಮರ್ ಗಾತ್ರವನ್ನು ಕಡಿಮೆ , ಹೀಗೆ ಸ್ತನ ಸಂರಕ್ಷಣಾ ದರವನ್ನು ಹೆಚ್ಚಿಸುವ ಮತ್ತು ಸ್ತನ ಸಂರಕ್ಷಿಸುವ ಶಸ್ತ್ರಚಿಕಿತ್ಸೆ ಮತ್ತು ಮಾನಸಿಕ ರೋಗ ಹರಡುವಿಕೆಯನ್ನು ಕಡಿಮೆ ಪ್ರಮಾಣದಲ್ಲಿ ಸುಧಾರಿತ ಕಾಸ್ಮೆಟಿಕ್ ಫಲಿತಾಂಶ ಅವಕಾಶ ಮಾಡಬಹುದು .

ಈ ಅಧ್ಯಯನವು ಡೋಸು ನವ ಸಹೌಷಧದ ರಾಸಾಯನಿಕ ರೋಗಿಯ ಅನುಸರಣೆ ಮತ್ತು ಶಸ್ತ್ರಚಿಕಿತ್ಸೆಯ ಅನಾರೋಗ್ಯ ಪೋಸ್ಟ್ ಕಡಿತ ಪರಿಣಮಿಸುತ್ತದೆ ಗೆಡ್ಡೆ ನಡೆಯುತ್ತಿದ್ದ ಕೆಳಗೆ ಮಾಡುತ್ತದೆ ಎಂಬುದನ್ನು ವೀಕ್ಷಿಸಲು ನಡೆಸಲಾಗುವುದು.

ನವ ಸಹೌಷಧದ ರಾಸಾಯನಿಕ ಲಾಭಗಳು:-

ಇದು ಸಹಾಯಕ ವ್ಯವಸ್ಥೆಯಲ್ಲಿ ಕಿಮೊತೆರಪಿ ಪ್ರತಿಕ್ರಿಯೆ ಮಾಪನ ನಿರ್ದೇಶಿಸಲು ಖಂಡಿತಾ ಇವೆ ಆದರೆ ಜೀವಿಯ ವ್ಯವಸ್ಥಿತ

ಚಿಕಿತ್ಸೆ

ಪ್ರತಿಕ್ರಿಯೆಯಾಗಿ ನೇರ ಮೌಲ್ಯಮಾಪನ ಶಕ್ತಗೊಳಿಸುತ್ತದೆ.

• ಇದು ನಂತರ ಸ್ತನ ಸಂರಕ್ಷಣಾ ಶಸ್ತ್ರಚಿಕಿತ್ಸೆ ಅನುಮತಿಸುವ ಪ್ರಾಥಮಿಕ ಗೆಡ್ಡೆಯ ಗಾತ್ರ , ಒಂದು ಕಡಿತ ಉಂಟುಮಾಡುತ್ತದೆ.

• ನಿಯೋ ಸಹೌಷಧದ ರಾಸಾಯನಿಕ ಸಹ ಸೂಕ್ಷ್ಮ ವರ್ಗಾವಣೆ ಪರಿಗಣಿಸುತ್ತದೆ ಹೆಚ್ಚು ಪರಿಣಾಮಕಾರಿಯಾಗಿ ಗ್ರಂಥಿಗಳು

ದುಗ್ಧರಸ .

• ಕಾರ್ಯ ರೋಗಿಯ ತಪಾಸಣೆ ಜ್ಞಾನ , ಕಿಮೋಥೆರಪಿ ಕ್ಲಿನಿಕೊ ರೋಗ ಪ್ರತಿಕ್ರಿಯೆ .

ನವ ಸಹೌಷಧದ ರಾಸಾಯನಿಕ ಅನಾನುಕೂಲಗಳು:-

ವ್ಯವಸ್ಥಿತ ಚಿಕಿತ್ಸೆಗೆ ಮೊದಲು ದುಗ್ಧರಸ ಗ್ರಂಥಿ ಸ್ಥಿತಿ ಬಗ್ಗೆ ಮಾಹಿತಿ ನಷ್ಟ

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿದಲ್ಲಿ ನಾವು ನೀವು ಪರೀಕ್ಷಿಸಲು ಮತ್ತು ನಿಮ್ಮ ಆಸ್ಪತ್ರೆಯ ದಾಖಲೆ ನಿಮ್ಮ ಬಗ್ಗೆ ಚಿಕಿತ್ಸೆ ಮತ್ತು ಸಂಬಂಧಿಸಿದ ವಿವರಗಳನ್ನು ಸಂಗ್ರಹಿಸುತ್ತದೆ. ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಮಾತ್ರ ಸಂಶೋಧನೆಗೆ ಬಳಸಲಾಗುತ್ತದೆ. ಈ ಅಧ್ಯಯನವು ಸ್ಥಳೀಯ ನೈತಿಕ ಪರಿಶೀಲನಾ ಮಂಡಳಿಯಿಂದ ಪರಿಶೀಲಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಕೇವಲ ಅವರ ಔಪಚಾರಿಕ ಅನುಮೋದನೆ ನಂತರ ಪ್ರಾರಂಭಿಸಲಾಗುವುದು. ನೀವು ಭಾಗವಹಿಸಲು ಇಚ್ಛಿಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುತ್ತಾನೆ ರಕ್ಷಣೆ ಬದಲಾಗುವುದಿಲ್ಲ. ನೀವು / ಸೈನ್ ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ಮಾತ್ರ ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ಒದಗಿಸುವ ಅಗತ್ಯವಿದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆ ನೀವು ಯಾವುದೇ ವೆಚ್ಚದಲ್ಲಿ

ಒಳಗೊಳ್ಳುವುದಿಲ್ಲ. ಯಾವುದೇ ತೊಡಕು ಮೇಲೆ ತಂತ್ರ ಸಮಯದಲ್ಲಿ ಉಂಟಾದರೆ ಇದು ಉಚಿತವಾಗಿ ಪರಿಗಣಿಸಲಾಗುತ್ತದೆ. ಇದು ನೀವು ಆಸ್ಪತ್ರೆಯಲ್ಲಿ ಸ್ವೀಕರಿಸುವ ರಕ್ಷಣೆ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ.

ನಾನು ಓದಲು ಅಥವಾ, ನನ್ನ ಅಧ್ಯಯನದಲ್ಲಿ ತೊಡಗಿರುವ ಮತ್ತು ಸಂಗ್ರಹಿಸಿ ಅಧ್ಯಯನ ಮಾಡುವ ಸಂದರ್ಭದಲ್ಲಿ ಬಹಿರಂಗಪಡಿಸಲಾಗುತ್ತದೆ ಮಾಹಿತಿಯನ್ನು ನಿಸರ್ಗದ ಜತೆ ಸಂಬಂಧ ಅಪಾಯ ಮತ್ತು ಲಾಭಗಳನ್ನು ಬಳಸಲಾಗುತ್ತದೆ ಎಂದು ವಿಧಾನ ನನಗೆ ಓದಲು ಮತ್ತು ಅಧ್ಯಯನ ಉದ್ದೇಶ ಅರ್ಥ ಮಾಡಲಾಗಿದೆ. ನಾನು ಅಧ್ಯಯನ ವಿವಿಧ ಅಂಶಗಳನ್ನು ಬಗ್ಗೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶ ಹೊಂದಿದ್ದರು ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ನನ್ನ ತೃಪ್ತಿ ಉತ್ತರಿಸುತ್ತದೆ. ನಾನು ರುಜುಮಾಡಿರುವ ನನ್ನ ಸಂಶೋಧನೆಗೆ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವಿಕೆಯ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಮತ್ತು ಪ್ರಮಾಣೀಕರಿಸಲು ಒಪ್ಪುತ್ತೇನೆ

ರೋಗಿಯ ಹೆಸರು ಮತ್ತು /ಅರ್ಜಿದಾರರ ಸಹಿ ದಿನಾಂಕ:

ಹೆಸರು ಮತ್ತು ಸಾಕ್ಷಿ ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು/ ಸಹಿ: ದಿನಾಂಕ

ಹೆಸರು ಮತ್ತು ವ್ಯಕ್ತಿ ಪಡೆಯುವ ಒಪ್ಪಿಗೆ ಸಹಿ ದಿನಾಂಕ

INFORMED CONSENT FORM

EFFICACY OF SINGLE CYCLE NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST

Breast cancer is the second most common cancer among women in India and accounts for 7% of global burden of breast cancer and one-fifth of all cancers among women in India. Preoperative or neoadjuvant chemotherapy (NAC) has been widely accepted as a standard of care in patients with inoperable as well as operable breast cancer. The rationale for NAC in operable breast cancer is that most invasive breast cancers are systemic diseases.

NAC can reduce metastatic disease before surgery and reduce the size of the primary tumor, thus increasing breast conservation rates and to allow an improved cosmetic outcome with breast conserving surgery and lower levels of psychological morbidity.

This study will be conducted to observe whether single dose neoadjuvant chemotherapy helps in downstaging the tumor which results in patient compliance and the reduction of morbidity post surgically.

ADVANTAGES OF NEOADJUVANT CHEMOTHERAPY

- It enables direct assessment of response to systemic therapy in vivo whereas there are no means to direct measurement of chemotherapy response in the adjuvant setting.
- It causes a reduction of the primary tumor size, which then allows breast conservation surgery.
- Neoadjuvant chemotherapy also treats micrometastases of the lymph nodes more effectively.

- Prior knowledge of the patient's prognosis, in function to the clinicopathologic response to chemotherapy.

DISADVANTAGES OF NEOADJUVANT CHEMOTHERAPY

- Loss of information regarding lymph node status prior to systemic treatment

If u agree to participate in the study we will examine you and we will collect the treatment and relevant details about you from your hospital record. The information collected will be used only for research. This study will be reviewed by local ethical review board and will be started only after their formal approval. The care you will get will not change if you don't wish to participate. You are required to sign/provide thumb impression only if you voluntarily agree to participate in this study. Participation in this study does not involve any cost for you. If any complication happens during above technique it will be treated free of cost. This also does not affect the care that you receive in the hospital.

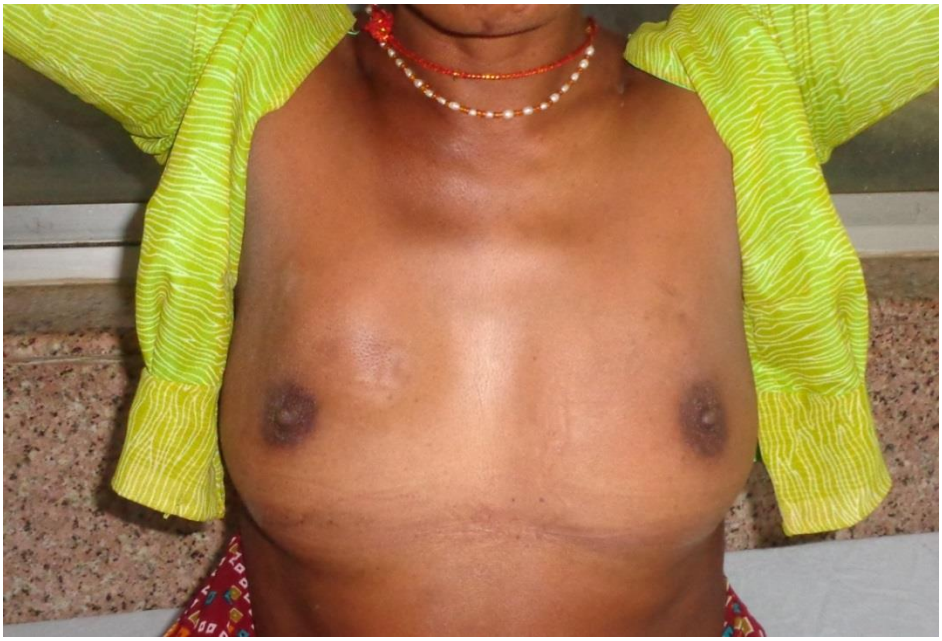
I have read or have been read to me and understand the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for my research

Subject’s name and signature /thumb impression Date:

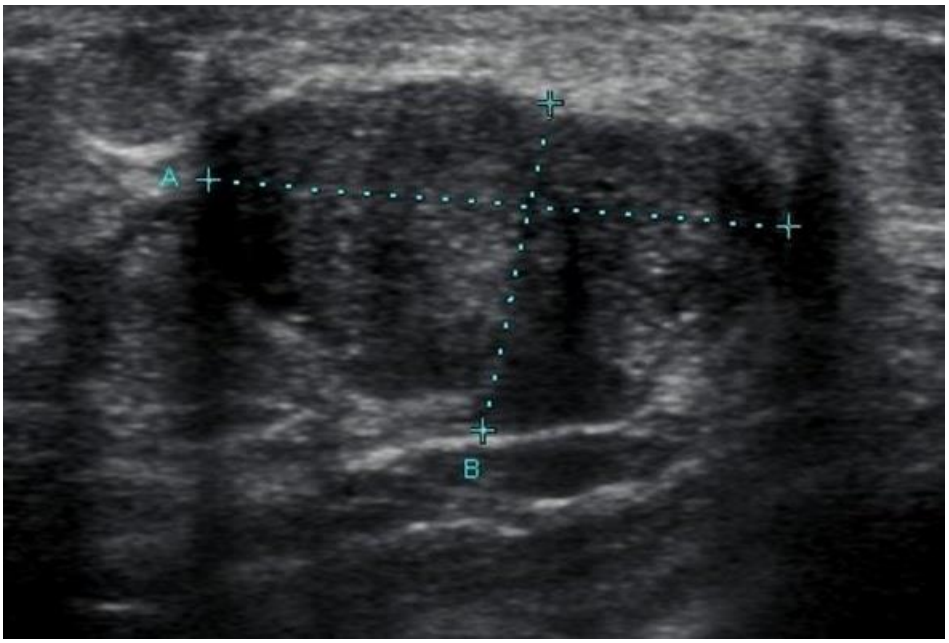
Name and signature of witness/thumb impression Date:

Name and signature of person obtaining consent Date:

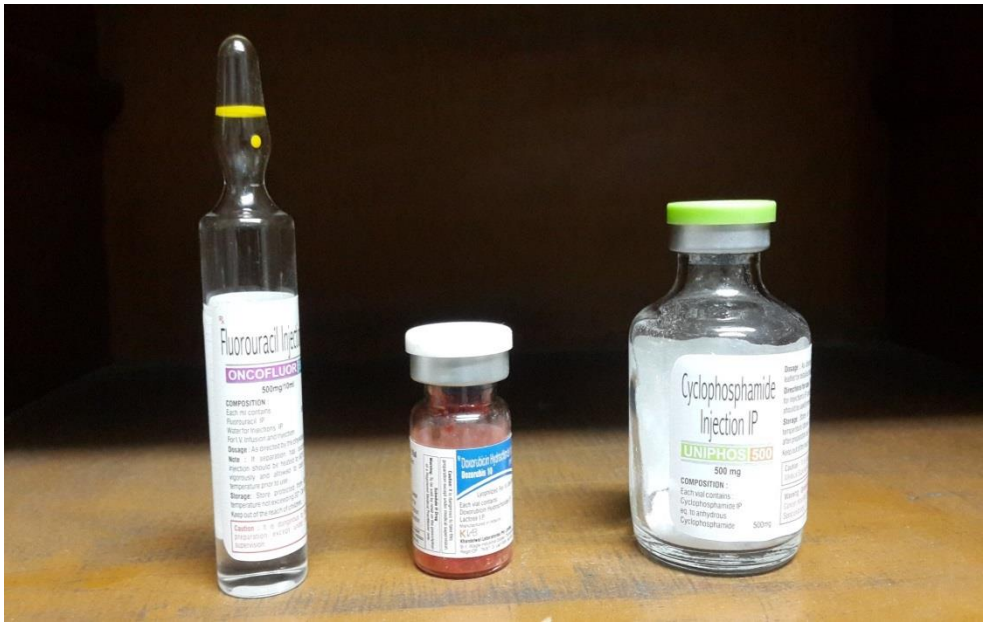
PHOTOGRAPHS



Color plate 1:- Clinical picture of a patient showing lump in upper inner quadrant of right breast



Color plate 2:- Sonological measurement of breast lump



Color plate 3:- Drug regimen used for neo adjuvant chemotherapy (5-Flurouracil, Adriamycin, Cyclophosphamide)

Color plate 4:- Patient receiving Neo adjuvant chemotherapy

KEY TO MASTER CHART

M- Multiparous

N- Nulliparous

PRE MP- Pre Menopausal

POS MP- Post Menopausal

L- Lump

U- Ulcer

P-Pain

Nr- Nipple retraction

Nd- Nipple deviation

X- Axillary swelling

NAC- Neo adjuvant chemotherapy

SL NO.	NAME	IP NO.	AGE	PARITY		MENSTRUAL STATUS		PRESENTING COMPLAINTS						DURATION OF SYMPTOMS			QUADRANT INVOLVED	TUMOUR SIZE BEFORE NAC			LYMPH NODE INVOLVED			STAGE OF TUMOUR	TUMOUR SIZE REDUCTION AFTER NAC	POST NAC STAGE
				M	N	PRE MP	POST MP	L	U	P	Nr	Nd	X	<3 MO	3-6 MO	>6 MO		<5CM	5-7CM	7-10CM	N0	N1	N2			
1	SAROJAMMA	976101	50	M		PRE MP		L						3 MON			UO			8.8			N2	IIIA(T3N2M0)		IIIA
2	NAGAMMA	62056	60	M			PO	L							4		UI		5.3		N0			IIB(T3N0M0)		IIB
3	LAKSHMI	51655	66	M			PO	L						2 MON			UO		5.4				N2	IIIA(T3N2M0)		IIIA
4	BYAMMA	64224	60	M			PO	L		P					6 MON		LI	4.3				N1		IIB(T2N1M0)		IIB
5	BHAGYAMMA	53647	50	M		PRE MP		L		P				3MON			UO		6.8				N2	IIIA(T3N2M0)		IIIA
6	RATHNAMMA	54269	65	M			PO	L		P				15 DAYS			UO		5.1				N2	IIB(T3N0M0)	1CM	IIA(T2N0M0)
7	APARNA	1007672	71	M			PO	L		P					6		UO	4.6				N1		IIB(T2N1M0)		IIB
8	MUNIRATHNAMMA	65453	46	M		PRE MP		L		P					5 MON		LO	2.7				N1		IIB(T2NIM0)		IIB
9	LAKSHMINARASAMMA	62641	56	M			PO	L		P					5 MON		UO			7.8			N2	IIIA(T3N2M0)		IIIA
10	JAYAMMA	7959	51	M		PRE MP		L		P					6 MON		UO		6.2		N0			IIB(T3N0M0)		IIB
11	ALUVELAMMA	999337	42	N		PRE MP		L		P		ND			5.6 MON		UI	3.9				N1		IIB(T2N1M0)		IIB
12	VENKATAMMA	995047	45	M		PRE MP		L		P						7 MON	LO	2.5				N1		IIB(T2N1M0)		IIB
13	SAROJAMMA	943556	63		N		PO	L				ND			4.5 MON		UO			7.2		N1		IIIA(T3N1M0)		IIIA
14	MEENAKSHAMMA	169021	56		N		PO	L		P				3 MON			UI	3				N1		IIB(T2N1M0)		IIB
15	SUMITHRA. M	175651	49	M			PO	L							4 MON		UO	2.1				N1		IIB(T2N1M0)		IIB
16	NARAYANAMMA	176606	54	M			PO	L							6 MON		UO	4.4			N0			IIB(T2NOM0)	0.9 CM	IIB
17	KALAVATHI	152455	64	M			PO	L							4 MON		UO	3.4					N2	IIIA(T2N2M0)		IIIA
18	RATHNAMMA	100213	41	M		PRE MP		L		P					5 MON		LO		5.7			N1		IIB(T3NIM0)		IIB
19	THIMAKKA	160078	51		N		PO	L		P				3 MON			UO	1.9					N2	IIIA(T1N2M0)		IIIA
20	CHOWDAMMA	163299	58	M			PO	L		P					4 MON		UO		6.4			N1		IIIA(T3N1M0)		IIIA
21	NARASAMMA	93491	46	M		PRE MP		L				ND			5 MON		UO		5.5		N0			IIB(T3N0M0)	1.1	IIA(T2N0M0)
22	JAYAMMA	163650	52	M			PO	L		P				3 MON			UI	2.6					N2	IIIA(T2N2M0)		IIIA
23	SUSHEELAMMA	102140	62		N		PO	L		P					4 MON		UO	4.4					N2	IIIA(T2N2M0)		IIIA
24	RAMADEVI	109869	55	M			PO	L		P					4 MON		UO	3.8				N1		IIB(T2N1M0)		IIB
25	SHANTHA	123371	43	M		PRE MP		L							4MON		LI		6		N0			IIB(T3N0M0)	1CM	IIA(T2N0M0)