A STUDY ON THE EFFECT OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of the degree of

M.S (GENERAL SURGERY)
BRANCH I

MADURAI MEDICAL COLLEGE AND GOVT. RAJAJI HOSPITAL
THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI.
INDIA

SEPTEMBER - 2006

CERTIFICATE

This is certify that this dissertation entitled **"A STUDY ON THE EFFECT OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER"** submitted by **Dr.A. GOWRI SANKAR** to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.S. degree Branch I (General Surgery) and is a bonafide research work carried out by him under direct supervision and guidance.

Dr. N.Sivaprahasam, M.S.,
Additional Professor,
Department of Surgery,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

Dr. M.Kalyana Sundaram M.S., FICS, FACS
Professor and Head,
Department of Surgery,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I solemnly declare that this dissertation ***"A study on the Effect of Neoadjuvant chemotherapy in Locally advanced breast Cancer"*** was prepared by me from the Department of General Surgery in association with the Department of Medical Oncology, Madurai Medical College and Govt Rajaji Hospital, Madurai, under the guidance and supervision of

Prof. Dr. N. Sivaprakasam, M.S., MMC, Madurai .

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the university regulations for the award of the degree of M.S., Branch I General Surgery examinations to be held in September 2006.

Place:

Date:

Dr. A. Gowri Sankar

ACKNOWLEDGEMENT

My sincere thanks to the honorable ***DEAN***, Madurai Medical college for permitting me to carry out this study at Madurai Medical College and Government Rajaji Hospital.

I express my deep sense of gratitude to our revered Professor of Surgery ***Dr. N. Shivaprakasam, M.S.,*** for allotting me this topic to work on. I also thank him for the invaluable guidance, unfailing enthusiasm and constant encouragement, which helped me carry out my study successfully.

I express my heart felt thanks to the esteemed ***Prof.Dr.M. Kalyana Sundaram, M.S.,F.I.C.S.,*** professor and Head of the Department of General Surgery, Government Rajaji Hospital and Madurai Medical College, Madurai, for the keen interest, encouragement and motivation towards the progress of my study.

My special thanks to ***Dr. Muthukumaraswamy, M.D., D.M.,*** Professor and head of the Department of Medical Oncology, Government Rajaji Hospital, Madurai, for the constant encouragement and the valuable suggestion to carry out my study successfully.

My sincere thanks to ***Dr. M. Jebamani, M.S., Dr. P. Saravana Boopathy, M.S., Dr. S. Kalirathinam, M.S., Dr. R. Prabhakaran, M.S.,*** for their constant support and valuable guidance through out my study.

I also thank all the postgraduates who have rendered their valuable help and time whenever necessary.

I also extend my thanks to all the patients who participated in my study.

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INTRODUCTION

"GROWTH FOR THE SAKE OF GROWTH IS THE IDEOLOGY OF CANCER CELLS"

- Edward abbey

Breast cancer is a devastating illness both physically and emotionally for tens of thousands of women around the world. The morbidity and mortality of breast cancer make it a leading cause of death in women aged 35 to 55 years[1]. It accounts for 33% of all female cancers and is responsible for 20% of cancer related death in women[2, 3].

In India breast cancer ranks second to cancer cervix[4]. But it is proportionally on the increase. In the metropolitan areas of India they appear to be relatively on the increase due to late marriage, birth of the first child at a later age, and short period of breast feeding which are common practices among educated urban women[4]. As facility of screening in India is mostly limited, 2/3rd of cancers detected are locally advanced disease[5].

Locally advanced breast cancer encompass a heterogenous group of patient that includes those with a neglected slow growing tumour as well as those with aggressive disease. LABC is relatively uncommon presentation in developed world accounting for only 5 to 20%. But in the developing world like India it constitutes about 50% of the cases.

Aggressive local treatment such as surgery or radiotherapy did little to improve the survival rates, but resulted in increased complications[6, 7, 8, 9]. Predominant pattern of failure in LABC is development of distant metastasis . With the development of systemic therapy to address micrometastasis, chemotherapy is routinely incorporated in the treatment of LABC[6, 7, 8, 9]. It can be given preoperatively/post operatively

Neoadjuvant chemotherapy is the primary chemotherapy given to patient prior to surgery or radiotherapy. This has been used for treatment of Locally advanced breast cancer. With development and testing of increasingly effective agents particularly anthracyclines, dramatic responses had been seen in significant proportion of patients[10, 11]. Thus leading to interest in breast conservation[12, 13] treatment in larger tumours and to the use of neoadjuvant chemotherapy in less advanced operable breast cancer.

Neoadjuvant chemotherapy is said to have a number of theoretical and practical advantages in treatment of LABC probably including[10, 11, 12, 13]

- Early treatment of Micrometastasis
- Limiting the rapid growth of metastatic foci after removal of primary tumour.
- Decreased emergence of chemoresistant clones.
- Extension of BCT to more patients with larger tumours.

Perhaps greatest potential advantage of the approach is opportunity to observe clinical responses to treatment and to assess the effect by pathological examination of surgical specimen. Further more if clinical/pathological response of primary tumour to neoadjuvant chemotherapy correlates with or predicts the response of metastasis and the prognosis of the patient such as overall survival[14], it could greatly accelerate progress in designing newer treatment.

Though neoadjuvant CT in the treatment of LABC had been used in clinical trials for the past 2 decades in the developing world, not many studies have been conducted in developing countries like ours, where LABC constitutes about 50% of cases. Hence this study was planned to evaluate the clinico/pathological response to Neoadjuvant CT in the treatment of LABC.

AIM OF STUDY

The role of adjuvant chemotherapy in the management of LABC showed significant improvement in progression free and overall survival rates. Conventionally adjuvant systemic CT is administered after local treatment in LABC. However since introduction of conservative treatment modalities, there has been considerable interest in the efficacy of preoperative chemotherapy. Neoadjuvant CT is said to decrease tumor size there by helping in breast conservation treatment modalities.

Therefore logical next step was to plan a study with the following objectives.

1. To evaluate the clinical/pathological response of primary tumour and lymph node to preoperative chemotherapy (CAF regimen)
2. To assess the relationship between patient outcome and tumor response to chemotherapy.
3. To study whether preoperative chemotherapy permits breast conservation by reducing tumour size
4. To assess the tumour involvement of resected margin.

REVIEW OF LITERATURE

Embryology of the breast:[32 33]

At the fifth of the sixth week of the fetal development, two ventral bands of thickened ectoderm (mammary ridge) 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. These ridges are not prominent in human embryos and disappear after a short time, except for small portions that persist in the pectoral region.Each breast develops when an ingrowth of ectoderm forms a primary tissue bud in the mesenchyme. The primary bud inturn initiates the development of 15 to 20 secondary buds. Epithelial cords develop from the secondary buds and extend into the surrounding mesenchyme. Major ducts open into shallow mammary pits, the proliferation of mesenchyme transforms the mammary pit into nipple.(Ref 9).

Functional anatomy[32 33]

Breast is composed of 15 to 20 lobes which are each composed of several lobules. Fibrous bands of connective tissue, travel through the breast

and insert perpendicularly into the dermis. It is called the suspensory ligaments of Cooper. It provides structural support. The mature female breast extends from the level of infra mammary fold at the sixth or seventh rib. It extends transversally from the lateral border of the sternum to the anterior axillary line. The deep surface of the rest on the fascia of the pectoralis major, serratus anterior, external oblique abdominis, and the upper part of the rectus sheath. Axillary tail of Spence extends laterally across the anterior axillary fold. The upper outer quadrant of the breast contains greater volume of the tissue than the other quadrant.

Nipple areola complex.

The epidermis of the nipple areola complex of the breast is pigmented and variably corrugated, during puberty the pigment become darker and the nipple assumes an elevated configuration. During pregnancy the areola enlarges and the pigment becomes further enhanced. The areola contains sebaceous glands, sweat glands, accessory glands. Dermal papillae at the tip of the nipple contains sensory nerve endings and meissner's corpuscles. Smooth muscle bundle fibres which lie circumferentially and longitudinally along the major ducts, are responsible for the nipple erection.

Blood supply of the breast.[37 40]

Breast receives its blood supply from

1) perforating branch of the internal mammary artery
2) Lateral branch of posterior intercostals arteries
3) Branches from the axillary artery including the lateral thoracic and pectoral branches of the thoraco acromial artery.

The second , third and the 4th anterior intercostals perforators and the branches of the internal mammary artery arborize as medial mammary artery. The lateral thoracic artery give rise to lateral mammary branches. The veins of the breast and the chest wall follow the course of the artery with the venous drainage being towards the axilla. The 3 principal groups of veins are perforating branches of

1) internal thoracic vein
2) posterior intercostals veins
3) axillary veins

The vertebral plexus of veins (Batson's plexus)[34 35 36]: It provides second route for spread of breast carcinoma via veins. This venous plexus surrounds the vertebra and extends from the base of the skull to the sacrum. Venous channels exist between this plexus and the veins

associated with thoracic, abdominal and pelvic organ. These veins do not have valves, making it possible for blood to flow through them in either direction. This venous communication is of particular importance in the breast as the posterior intercostals arteries are in direct continuity with the vertebral plexus. This potential pathway explains the metastasis of breast cancer to the vertebrae, skull, pelvic bone, and the CNS when there is no pulmonary metastasis.

Innervation of the breast[41]

Lateral cutaneous branches of third through the 6th intercostals nerve provides sensory inervation of the breast and of the anterolateral chest wall. Anterior branch of the supraclavicular nerve supplies a limited area of the skin over the upper portion of the breast.

Lymphatic drainage of the breast.[38 39]

The boundaries for the lymphatic drainage of the axilla are not well demarcated, and there is considerable variation in the position of the axillary lymph node. Six axillary lymph node groups recognized by surgeons

1) Axillary vein group (lateral group)- consist of 4 to 6 lymph nodes , lies medial to the vein and receives most of the lymph drainage from the upper extremity.
2) External Mammary group: (Anterior or pectoral group) : consist of 5 to 6 lymph nodes , lies along the lower border of pectoralis minor muscle contiguous with the lateral thoracic vessels. It receives most of the lymph drainage from the lateral aspect of the breast.
3) Scapular group: (Posterior or subscapular) It consists of 5 to 7 lymph nodes lie along the posterior wall of the axilla at the lateral border of the scapula, contiguous with the subscapular vessels. It receives lymph drainage from the lower posterior neck, posterior trunk and posterior shoulder.
4) Central Group: It consists of 3 to 4 lymph nodes embedded in the fat of axilla lying immediately posterior to the pectoralis minor muscle. It receives lymph drainage from the axillary vein, external mammary, and scapula and directly from the breast.
5) Sub clavicular group(Apical): It consists of 6 to 12 lymph nodes lying posterior and superior to the upper part of the pectoralis minor muscle. It receives lymph drainage from all other group of axillary lymph node.

6) The interpectoral group: (Rotter's) It consists of 1 to 4 lymph nodes, interposed between the pectoralis major and minor muscle. It receives lymphatic drainage directly from the breasts. From interpectoral group of lymphnodes lymph fluid passes directly to the central and subclavicular group of lymphnodes.

Surgeons also define the axillary lymphnodes with the respect to their relationship with the pectoralis minor muscle.Lymph nodes that are located lateral to and below the lower border of the pectoralis minor are called the level 1. It consists of external mammary, axillary vein and scapular group of lymph nodes. Those lymph nodes located deep or posterior to the pectoralis minor muscle are called level 2. It includes central and interpectoral group of lymph nodes. Lymph nodes located medial or above to the upper border of the pectoralis minor is called level 3 nodes. It includes subclavicular growth.

Lymph flow: The plexus of lymph vessels in the breast arises in the inter lobular connective tissue and in the walls of lactiferous ducts, and communicates with the sub areolar plexus of lymph vessels. Efferent lymph vessels from the breast pass around the lateral edges of pectoralis major muscle, and pierce the clavipectoral fascia ending in the external mammary group of lymph nodes. Some vessels may travel directly to the scapular

group of lymph nodes . From the upper part of the breast few lymph vessels pass directly to the sub clavicular group of lymph nodes. Axillary lymph nodes usually receives more than 75% of the drainage from the breast. The rest is derived primarily from the medial aspect of the breast, flows through the lymph vessels that accompany the perforating branches of the internal mammary artery and enters the internal mammary group of lymph nodes.

Epidemiology and Natural history of breast Cancer :

The Breast Cancer is the most site specific cancer in women, and is the leading cause of death from cancer for women aged 40 to 45 years, It accounts for 33% of all female cancers and is responsible for 20% of the cancer related deaths in women.

Natural History: Natural history of breast cancer is extremely complex and not fully understood. There is wide spectrum of behaviour some cancers may disseminate very early and cause death even before primary is clinically apparent, where as the other patient may live for decades, and treated with indolent disease. It is not uncommon to have recurrent disease 20 – 30 years after initial treatment, very young men tend to develop aggressive disease with less than 50% 5 year survival. Bloom and colleagues described the natural history of breast cancers based on records of 250 women with

untreated breast cancers between 1805, and 1933. The Median survival of population is 2.7 years after initial diagnosis.

Etiology: Breast cancer is a heterogeneous disease with no single characterized

cause.

Epidemiological studies have identified many risk factors that increase the chance for a woman to develop breast cancer:

- Factors with relative risk greater than 4
    - Advanced age
    - Being born in North America or northern Europe
    - High premenopausal blood insulinlike growth factor (IGF)–1 level
    - High postmenopausal blood estrogen level
    - History of mother and a sister with breast cancer

- Factors associated with a relative risk of 2-4
    - High socioeconomic status
    - Age at first full-term pregnancy older than 30 years

- History of cancer in one breast
- Any first-degree relative with a history of breast cancer
- History of a benign proliferative lesion, dysplastic mammographic changes, and a high dose of ionizing radiation to the chest

- Factors associated with a relative risk of 1.1-1.9
  - Nulliparity
  - Early menarche (age <11 y)
  - Late menopause (age >55 y)
  - Postmenopausal obesity
  - High-fat diet/saturated fat–rich diet
  - Residence in urban areas and northern United States
  - White race - Older than 45 years
  - Black race - Younger than 45 years
  - History of endometrial or ovarian cancer

- Identified factors with a protective role against breast cancer
    - Age at first period older than 15 years
    - Breastfeeding for longer than 1 year
    - Monounsaturated fat–rich diet
    - Physical activity
    - Premenopausal obesity

Genetic factors

As with other cancers, breast cancer is the result of multiple genetic changes or mutations. Early mutations may be inherited (eg, mutations of breast stem cells) or acquired (eg, somatic mutations due to ionizing radiation, chemical carcinogens, or oxidative damage).

Estrogens, by their proliferation-promoting effect on the breast epithelium later, increase the chance of DNA replication errors leading to carcinogenic mutations. Indeed, the common denominator to many of these risk factors is their effect on the level and duration of exposure to endogenous estrogenic stimulation.

Early menarche, regular ovulation, and late menopause increase lifetime exposure to estrogens in premenopausal women, while obesity and hormone

replacement therapy increase estrogen levels in postmenopausal women. Conversely, late menarche, anovulation, and early menopause (spontaneous or induced) are protective, owing to their effect on lowering the level or shortening the duration of estrogenic exposure.

Lactation and premenopausal obesity are associated with lower estrogen levels as a result of anovulation. For unknown reasons, pregnancy decreases breast tissue susceptibility to somatic mutations; thus, the earlier the first pregnancy, the shorter the susceptibility period.

Hereditary breast cancers have been thought to represent a small proportion (5-10%) of all breast cancers. However, based on new data derived from the comparison of identical and nonidentical twins, up to 27% of breast cancers may be attributed to inherited factors. The mutated genes *BRCA1* and *BRCA2* are responsible for approximately 30-40% of inherited breast cancers.

The prevalence of *BRCA1* in the general population is 0.1%, compared with 20% in the Ashkenazi Jewish population. The gene is encountered in 3% of the unselected breast cancer population and in 70% of women with inherited early-onset breast cancer. Up to 50-87% of women carrying a mutated *BRCA1* gene develop breast cancer during their lifetime.

Risks for ovarian and prostate cancers are also increased in carriers of this mutation. *BRCA2* mutations are identified in 10-20% of families at high risk for breast and ovarian cancers and in only 2.7% of women with early-onset breast cancer. The lifetime risk of developing breast cancer in female carriers is 25-30%. *BRCA2* is also a risk factor for male breast cancer; carriers have a lifetime risk of 6% for developing the cancer. *BRCA2* mutations are associated with other types of cancers, such as prostate, pancreatic, fallopian tube, bladder, non-Hodgkin lymphoma, and basal cell carcinoma.

Li-Fraumeni syndrome, characterized by a mutation of *TP53,* is associated with multiple cancers, including the SBLLA syndrome (sarcoma, breast and brain tumors, leukemia, laryngeal and lung cancer). Cancer susceptibility is transmitted by an autosomal dominant pattern, with penetrance approximating 90% by age 70 years. Li-Fraumeni syndrome is identified in 1% of women with early-onset breast cancer. Bilateral breast cancer is noted in up to 25% of patients.

Cowden disease is a rare genetic syndrome associated with papillomatosis of the lips and oral mucosa, multiple facial trichilemmomas, and acral keratosis. The prevalence rate of breast cancer in women with this disease is

29%. Benign mammary abnormalities (eg, fibroadenomas, fibrocystic lesions, ductal epithelial hyperplasia, nipple malformations) are also more common. Other rare genetic disorders, such as Peutz-Jeghers and Muir-Torre syndromes, are associated with an increased risk of breast cancer.

Lab Studies:

- CBC count with differential and platelet count
- Chemistry and renal function studies
- Liver function tests
- Calcium and phosphorus evaluations

Imaging Studies:

- Mammography: Bilateral study is necessary for screening, diagnosis, and follow-up care. Malignant and benign breast lesions have the following mammographic characteristics:

    - Malignant breast lesions
        - Irregular speculated mass
        - Clustered calcifications
        - Calcifications - Smaller than 0.5 mm in diameter
        - Architectural distortion
        - Focal asymmetric density

- Benign breast lesions
    - Solid- or lucent-centered spheres
    - Smooth and round calcifications
    - Calcifications - Larger than 1 mm in diameter
    - Architectural distortion - Usually not present

- Chest radiograph

- CT scan of the brain, chest, abdomen, and pelvis: if the patient has neurologic symptoms, abnormal chest radiograph results, supraclavicular lymphadenopathy and hepatosplenomegaly, or abnormal liver function test results. CT scan of respective part done
- Bone scan: a bone scan is done if any of the following conditions are present:
    - Advanced local disease
    - Lymph node metastases
    - Distant metastases
    - Bony symptoms

Other Tests:

- Pathologic study of tumor specimens: Three features are evaluated and given scores from 1-3, ie, tubule formation, nuclear pleomorphism, and mitotic activity.
    - Tubular grade is defined based on the degree of development of tubular formations.
        - Well differentiated if tubular structures occupy more than 75% of the tumor - 1 point
        - Moderately differentiated if tubular structures represent 10-75% of the tumor - 2 points
        - Poorly differentiated if the tubular structures represent less than 10% of the tumor - 3 points
    - The nuclear grade is defined based on the nucleus size, stain density, and shape variations.
        - Small and uniformly staining nucleus, good prognosis - 1 point
        - Moderate variation in nuclear size and shape, intermediate prognosis - 2 points

        - Marked nuclear polymorphism with dark staining, poor prognosis - 3 points

    - Determine the cycling fraction (mitotic index and S-phase). While the determination of the S-phase requires the use of flow cytometry, the mitotic index is the easiest and fastest way of assessing proliferation. Score the mitotic index as follows:
        - Low (0-3.3/mm^2) - 1 point
        - Medium (3.3-7/mm^2) - 2 points
        - High (>7/mm^2) - 3 points

    - The histologic grade is a composite index obtained by totaling the tubular, nuclear, and mitotic scores. Invasive breast cancer is graded as follows:
        - Well differentiated - 3-5 total points
        - Moderately differentiated - 6-7 total points
        - Poorly differentiated - 8-9 total points

- ER and PR evaluation: Two types of assays are used to quantitate ERs and PRs.

- For ligand-binding methods (eg, dextran-coated charcoal assay), results are expressed in femtomoles of receptor protein per milligram of cytosol protein (fmol/mg). Cutoffs vary from 3-20 fmol/mg, depending on the laboratory. To ensure accuracy and reproducibility, specimens should be large and must be immediately fixed in liquid nitrogen. Results of this method may be affected by the presence of estrogens or tamoxifen in the specimen.

- With regard to monoclonal antibody–based methods (eg, immunohistochemistry [IHC], enzyme immunoassay), IHC has 2 advantages. First, it can be performed on any type or size of specimen, including cell blocks from body fluids or those fixed or imbedded in paraffin. Second, it measures total protein; therefore, it is not affected by the presence of estrogens or tamoxifen. IHC is a semiquantitative technique that depends on the observer and the type of antibodies used. Enzyme immunoassay results are more objective because of the use of a spectrophotometer to quantitate the receptor protein; however the technique is limited by the need for a sufficiently large fresh, frozen specimen.

- HER2/neu status: Several methods have been used to detect and quantitate HER2/neu.
    - IHC methods have been extensively used. This method is a semiquantitative assay using a monoclonal antibody.
    - Scoring of HER2/neu overexpression using the DAKO HercepTest (DAKO Cytomation; Carpinteria, Calif) follows. The cell membrane staining pattern, the interpretation, and the score are listed.
        - Strong complete membrane staining in more than 10% of tumor cells - Interpreted as strongly positive; score of 3+
        - Weak-to-moderate complete membrane staining in more than 10% of cells - Interpreted as weakly positive; score of 2+
        - Faintly perceptible membrane staining in more than 10% of tumor cells - Interpreted as negative; score of 1+
        - No staining or staining in 10% of tumor cells - Interpreted as negative; score of 0
        - Cytoplasmic staining of any intensity - Interpreted as negative; score of any

- Detection of gene amplification with fluorescence in situ hybridization (FISH) is highly specific and has an 82% overall concordance rate with IHC. However, when FISH results are expressed in the function of the IHC scores, they are positive in 92% of 3+ and 39% of 2+ IHC specimens. Only 7% of 1+ IHC specimen results are FISH-positive.

- Certain authorities consider FISH to be the criterion standard for HER2/neu evaluation; however, because this test is not readily available in many laboratories, they recommend use of IHC as a first-line test; 3+ and 1+ IHC results correspond to positive and negative expression of HER2/neu, respectively, and a 2+ IHC result is considered borderline. In these cases, only FISH is performed because a significant number of true HER2/neu–positive patients may be identified in the 2+ IHC group.

Diagnostic Procedures:

- Surgical procedures for nonpalpable lesions
    - Image-guided core-needle biopsy
        - This is the preferred method for needle biopsy of a nonpalpable lesion. Because of sampling error, it carries a higher risk of false-negative findings than open biopsy. Negative or equivocal results in the face of suggestive mammogram findings or residual calcifications should be followed by an open biopsy. False-negative results are encountered in 1-10% of biopsies, with the highest rates occurring with the least-experienced operators.
        - For the technique, ultrasound is the method of choice to guide the core-needle biopsy. Stereotactic mammographic guidance is used in lesions not visualized on ultrasound images. Stereotactic core-needle techniques have the advantages of lower complication rates and lower costs, although they cannot be used when the lesion is very close to the chest wall or areola, where open biopsy is the best approach. The radiograph should

be compared with the mammogram to ensure that all calcifications are included within the core biopsy specimen.

- Open biopsy with needle localization
  - Invasive localization techniques with small radiopaque needles to guide a surgical biopsy are used more commonly than noninvasive techniques.
  - For the technique, local anesthesia with or without intravenous sedation is sufficient in most cases. A thin needle and a fine wire with a thickened distal segment are used for immediate preoperative localization of the lesion. The incision may include the wire entry site if the lesion is superficial. A core of tissue along and around the wire is excised (including the lesion easily identified by the previous placement of the thickened segment inside it) and sent en bloc for radiographic evaluation. However, when the wire entry site is located far from the lesion, the incision should be placed directly over the lesion; dissection is then performed to find the wire.

        - Once identified, the free end of the wire is pulled up through the incision. A core of tissue around the wire is excised (including the lesion) and sent for radiographic evaluation. Closure should not proceed until radiographic confirmation that the entire lesion was excised.

- Surgical procedures for palpable lesions

    - Fine-needle aspiration biopsy

        - In experienced hands, FNA biopsy may provide a high accuracy rate when combined with physical examination and mammography (sensitivity ~80-98%, specificity ~100%). However, negative results from a palpable lesion cannot exclude carcinoma. Lesions most suited for this procedure are T3 and T4 tumors and axillary or chest wall relapses.
        - Owing to the high false-negative rate with FNA in lesions smaller than 1 cm in diameter, another diagnostic procedure should be used. Because false-positive rates are extremely low (<2%), positive results are sufficient to plan surgery, without the need for further investigation.

However, perioperative frozen sections are necessary to distinguish between invasive and in situ carcinoma and to determine the need for axillary dissection because FNA results cannot be used to make this distinction.

- Cutting-needle (core-needle) biopsy
  - Although the cutting-needle biopsy technique is associated with a higher true-positive rate than the FNA technique, a negative result may reflect sampling error. This biopsy provides a cylinder of tissue for pathological rather than cytological analysis. Determination of ERs and PRs is possible. Its best indications are large tumors and chest wall relapses. Small lesions or those surrounded by fibrocystic tissue are better studied using FNA. .

- Excision (open) biopsy
  - The entire lesion is removed with excisional biopsy, along with a margin of normal breast tissue.
  - Local anesthesia, occasionally with intravenous sedation, is sufficient to perform most of these procedures. A

curvilinear incision should be placed directly on the tumor mass and oriented in such a way that it could be included within a future mastectomy incision. In extremely lateral or medial lesions, a radial incision placed over the lesion is preferable.

- Once the tumor is removed, the margins should be inked. After hemostasis is achieved, deep breast tissue approximation is performed only if this does not result in deformity of the breast contour. Lastly, the skin is closed with a subcuticular closure.

- Incisional biopsy: This is indicated for lesions 4 cm or larger and whenever neoadjuvant chemotherapy or RT is contemplated.

Histologic Findings: The various histopathologic types are as follows:

- I - Ductal
  - Intraductal (in situ)
  - Invasive with predominant intraductal component: Infiltrating or invasive ductal cancer is the most common breast cancer histologic type, comprising 70-80% of all cases.

    - Invasive, not otherwise specified
    - Scirrhous
    - Tubular
    - Medullary with lymphocytic infiltrate
    - Mucinous (colloid)
    - Papillary
    - Inflammatory
    - Comedo
    - Other
- II - Lobular
    - In situ
    - Invasive with predominant in situ component
    - Invasive
- III - Nipple
    - Paget disease, not otherwise specified
    - Paget disease with intraductal carcinoma
    - Paget disease with invasive ductal carcinoma
- IV - Undifferentiated carcinoma
- V - Rare tumor subtypes: The following are not considered typical breast cancers.

- Cystosarcoma phyllodes
- Angiosarcoma
- Primary lymphoma

In situ carcinoma

In situ carcinoma is characteristically contained within the epithelium, with the basement membrane intact, and no signs of invasion. Many features distinguish lobular carcinoma in situ (LCIS) from DCIS.

LCIS arises from the terminal duct lobular apparatus and shows a rather diffuse distribution throughout the breast, without evidence of a palpable mass. DCIS originates from the major lactiferous ducts and tends to be a localized disease frequently associated with a palpable mass.

This explains the high incidence of synchronous involvement in the contralateral breast (bilaterality) or in other quadrants of the same breast (multicentricity) in LCIS (90-100%) compared with DCIS (10-15%), suggesting that complete surgical resection of DCIS is not only possible but also desirable, particularly if the index lesion manifests as a palpable mass. Conversely, locoregional modalities, such as surgery or RT, have no role in the treatment of LCIS except for prophylactic bilateral mastectomy.

DCIS originates by proliferation of the ductal luminal cells, which form protrusions into the lumen (papillary DCIS). These become more coalescent, leaving a few empty, rounded spaces (cribriform DCIS). When the lumen is filled with proliferating cells, it becomes completely obliterated (solid DCIS). Central areas of these ducts undergo necrosis because of the ischemic microenvironment (comedo DCIS), with secondary deposition of calcium responsible for the appearance of microcalcifications, a typical radiographic feature of this disease.

DCIS is probably a continuum of successive steps of the same process, with increasing malignant potential as the disease progresses from papillary to comedo forms. Indeed, cells in the earliest stages are well differentiated with no atypia or mitoses, while cells in advanced stages become more anaplastic with frequent mitotic figures.

From a practical standpoint, dividing DCIS into 2 categories, comedo-type and non–comedo-type, is helpful. Both DCIS and LCIS occasionally may be difficult to differentiate from atypical hyperplasia (eg, atypical ductal hyperplasia, atypical lobular hyperplasia), which is a benign change of the mammary gland preceding the in situ disease.

- Local recurrence
    - Comedo - High
    - Noncomedo - Low
- Prognosis
    - Comedo - Poor
    - Noncomedo - Good

Invasive ductal carcinoma develops in 30-50% of patients with DCIS over a 10-year period, usually in the same quadrant where the DCIS was found. In contrast, only 10-37% of patients with LCIS develop invasive carcinoma, mostly of the ductal variety and with equal frequency in both breasts. Therefore, DCIS may be considered a true precancerous process, while LCIS is only a marker of increased risk for cancer.

Infiltrating ductal carcinoma with productive fibrosis (scirrhous, simplex, not otherwise specified) represents approximately 80% of ductal carcinoma of the breast cases, with the highest prevalence associated with perimenopause or early postmenopause. Typically, the mass is solitary, firm, and nontender with poorly defined borders. Heterogeneity is a characteristic feature of the malignant cells, which are arranged in single rows, producing

the so-called Indian filing. Typical sites of metastases are bone, lung, and liver.

Medullary carcinoma is relatively uncommon (5-7%) and occurs in younger persons. It manifests as a bulky palpable mass, with axillary lymphadenopathy in 40% of patients. Microscopically, the tumor has a syncytial growth pattern, without tubuloglandular differentiation in 75% of the tumor, mixed with intense lymphoplasmacytic infiltrate and, in most cases, associated with reactive lymphadenopathy. Nuclei are large and pleomorphic (grade 2 or 3). DCIS may be observed in the neighboring normal tissues, although there is no increased risk of bilaterality or multicentricity. ER, PR, and HER2/neu are usually negative and *TP53* is commonly mutated. The prognosis of patients with this type is usually very good.

Mucinous carcinoma is another uncommon histologic type of invasive breast cancer (<5%). It is more common in the seventh decade of life and manifests clinically as a palpable mass or mammographically (with increasing frequency) as a poorly defined tumor with rare calcification. Its histologic hallmark is the presence of mucin production occupying more than 90% of the tumor in pure mucinous forms and variable percentages in the mixed

forms. The cells are clustered in small islets dispersed in a pool of mucin. DCIS is often present in the vicinity of the tumor. ERs and PRs are positive in 90% and 68% of cases, respectively. HER2/neu overexpression is extremely rare. Patients with pure mucinous carcinoma have a better prognosis than those with mixed forms or other breast cancers of no special type.

Inflammatory breast cancer is diagnosed clinically based on the association of edema, erythema, and skin ridging (peau d'orange). Although subdermal lymphatic and vascular invasion is nearly constant, it is not a mandatory criterion for diagnosis. The mass is not palpable in most cases. Molecularly, ERs and PRs are negative, HER2/neu is overexpressed, *TP53* is commonly mutated, and the thymidine-labeling index is frequently high. Inflammatory carcinoma is an aggressive but fortunately rare disease, with a sudden onset and a rapidly progressive course. It is uniformly fatal if not treated with multimodality therapy. It should be differentiated from benign cellulitis by the characteristic absence of polymorphonuclear leukocytes in the involved area and from locally advanced breast cancer with a secondary inflammatory component, which has a more indolent course and is often responsive to HT.

Lobular carcinoma

Invasive lobular carcinoma is the second most common histologic type after ductal carcinoma, accounting for 5-10% of all breast cancers. It is associated with a high rate of multifocality and bilaterality. LCIS is identified in 70-80% of cases. It may manifest as a palpable mass clinically and mammographically indistinguishable from ductal carcinoma, except that the extent of the tumor is often underestimated in lobular carcinoma. Typical lobular carcinoma is composed of small, homogenous cells that invade the stroma in a single-file pattern. Signet-ring cells may be observed. Their stromal desmoplastic reaction is mild or absent. While ERs and PRs are expressed in the majority of tumors, HER2/neu overexpression and *TP53* mutation are rare.

Tumor behavior is characterized by more common bone metastases and less frequent lung, liver, and brain metastases than ductal carcinoma. Metastases to the leptomeninges, peritoneum, retroperitoneum, GI tract, and reproductive system seem to be more common in lobular carcinoma compared with ductal carcinoma. Patients with the classic form of lobular carcinoma share the same prognosis as those who have ductal carcinoma,

patients with the tubulolobular variant fare slightly better, and those with the signet-cell variant fare significantly worse than average

Nipple

Paget disease of the breast is a relatively rare entity comprising approximately 1% of all breast cancer cases, with the highest incidence in the seventh decade of life. However, pathologic evidence of the disease can be observed in 2-5% of mastectomy specimens. Approximately half the patients present with an underlying mass, which is an invasive cancer in 93% and a DCIS in 7%. In patients with no mass upon presentation, invasive cancer is present in approximately 40% and DCIS in approximately 60%. Histologically, the disease is localized to the epithelium of the nipple-areola complex and the characteristic cells, or Paget cells, are contained within the basement membrane. Paget cells are large, pale cells with prominent nuclei and large nucleoli, dispersed between the keratinocytes as single or clusters of cells.

Other

Tubular carcinoma is an uncommon type with limited metastatic potential and a very good prognosis. The average size of pure tubular carcinomas is

smaller than 1 cm, and they are associated with axillary metastases in approximately 15% of cases. Mammographically detected tumors (60-70%) tend to be smaller and less frequently associated with nodal metastases than clinically detected tumors. Characteristic features of this type include a single layer of epithelial cells with low-grade nuclei and apical cytoplasmic "snoutings" arranged in well-formed tubules and glands. Tubular elements comprise more than 90% of pure tubular carcinomas and different proportions of mixed tubular tumors. DCIS is associated with most of these tumors. ERs and PRs are positive in 70-100% and 60-83%, respectively. HER2/neu overexpression and *TP53* mutation are very uncommon in this type.

Papillary carcinoma is rare (<1% of breast cancers), occurring mainly in postmenopausal women. Histologically, the tumor is circumscribed with cells arranged in delicate or blunt papillae. Nuclei are of intermediate grade. Occasionally, extracellular mucin production can be observed. ERs and PRs are positive in approximately 100% and 80% of cases, respectively. Lymphatic vessel invasion occurs in a third of the cases; however, axillary lymph node enlargement can be related to benign reactive changes in a significant number of cases. This type has a good prognosis. The papillae in the micropapillary type lack the lymphvascular core. This type is associated

with lower ER and PR positivity and a higher percentage of HER2/neu overexpression, which explain its worse prognosis.

Staging: The American Joint Committee on Cancer staging system groups patients based on the tumor size (T), lymph node status (N), and distant metastases (M) into 4 stages, thus allowing clinicians to derive prognostic information necessary for therapeutic decisions. ER and PR status in the tumor tissue, menopausal status, and the general health of the patient are the other factors required for the final therapeutic plan.

TNM definitions

- Primary tumor
    - TX - Cannot be assessed
    - T0 - No evidence of primary tumor
    - Tis - Carcinoma in situ, intraductal carcinoma, LCIS, or Paget disease of the nipple with no associated tumor (Note: Paget disease associated with a tumor is classified according to the size of the tumor.)

- T1 - Tumor 2 cm or smaller in greatest dimension
    - T1mic - Microinvasion 0.1 cm or less in greatest dimension
    - T1a - Tumor larger than 0.1 cm but not larger than 0.5 cm in greatest dimension
    - T1b - Tumor larger than 0.5 cm but not larger than 1 cm in greatest dimension
    - T1c - Tumor larger than 1 cm but not larger than 2 cm in greatest dimension
- T2 - Tumor larger than 2 cm but not larger than 5 cm in greatest dimension
- T3 - Tumor larger than 5 cm in greatest dimension
- T4 - Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below (Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not pectoral muscle.)
    - T4a - Extension to chest wall
    - T4b - Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast

        - T4c - Both of the above (T4a and T4b)
        - T4d - Inflammatory carcinoma (Note: Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiologically, a detectable mass and characteristic thickening of the skin may be present over the breast. This clinical presentation is due to tumor embolization of dermal lymphatics with engorgement of superficial capillaries.)

- Regional lymph nodes
    - NX - Cannot be assessed (eg, previously removed)
    - N0 - No regional lymph node metastasis
    - N1 - Metastasis to movable ipsilateral axillary lymph node(s)
    - N2 - Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures
    - N3 - Metastasis to ipsilateral internal mammary lymph node(s)

- Pathologic classification
    - pNX - Regional lymph nodes cannot be assessed (eg, not removed for pathologic study or removed previously)
    - pN0 - No regional lymph node metastasis
    - pN1 - Metastasis to movable ipsilateral axillary lymph node(s)
        - pN1a - Only micrometastasis (none >0.2 cm)
        - pN1b - Metastasis to lymph node(s), any larger than 0.2 cm
            - pN1bi - Metastasis in 1-3 lymph nodes, any larger than 0.2 cm and all smaller than 2 cm in greatest dimension
            - pN1bii - Metastasis to 4 or more lymph nodes, any larger than 0.2 cm and all smaller than 2 cm in greatest dimension
            - pN1biii - Extension of tumor beyond the capsule of a lymph node metastasis, smaller than 2 cm in greatest dimension
            - pN1biv - Metastasis to a lymph node 2 cm or larger in greatest dimension

- pN2 - Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures
- pN3 - Metastasis to ipsilateral internal mammary lymph node(s)

- Distant metastasis
  - MX - Cannot be assessed
  - M0 - No distant metastasis
  - M1 - Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)

- **American Joint Committee on Cancer stage groupings**
  - Stage 0 - Tis, N0, M0
  - Stage I - T1 (includes T1mic), N0, M0
  - Stage IIA
    - T0, N1, M0
    - T1 (includes T1mic), N1 (The prognosis of patients with pN1a disease is similar to that of patients with pN0 disease.), M0
    - T2, N0, M0

- Stage IIB
  - T2, N1, M0
  - T3, N0, M0
- Stage IIIA
  - T0, N2, M0
  - T1 (includes T1mic), N2, M0
  - T2, N2, M0
  - T3, N1, M0
  - T3, N2, M0
- Stage IIIB
  - T4, Any N, M0

Stage IIIC

Any T,N3, M 0

Stage IV- Any T, Any N, M1

LOCALLY ADVANCED BREAST CANCER

It includes heterogenous group of patients with a varying biology and a range of prognosis. This group includes

1) Tumor size of more than 5 cm with a mobile axillary node
2) Tumour of any size with a fixed axillary node
3) Ttumour of any size with the skin/chest wall fixity.

4) Tumour of any size with supraclavicular node.

5) Inflammatory breast cancer.

Incidence:[2] Percentage of patients in stage IIIB is 8.1% in 1991. 10% of low income patients presented with stage III disease compared to 7% of the high income patients. Stage III is diagnosed in approximately 13,000 women annually making it still a major health problem.

Historical Perspective: Haagensen and stout analysed 1135 cases of breast cancer treated with radical mastectomy during the period of 1915 to 1942. They identified 5 features of locally advanced breast cancer and called it as Grave sign. It includes edema of less than 1/3 rd of the skin of the breast, Ulceration of the skin, fixation to the chest wall, fixed axillary node, and axillary node more than 2.5 cm. They have noted a 5 year clinical cure, 5 to 38% of the LABC patients treated by radical mastectomy. Local recurrence ranged from 13 to 40%. Baclesse observed 5 year survival rate for LABC was 30% , among the patient with LABC treated with primary radiation alone. This observation suggested that LABC was systemic disease with micrometastasis present at the time of diagnosis. Hence local therapy alone was insufficient to cure most patients with this disease.

Prognostic factor :

1) ***Size of the primary tumour:*** fisher and coworkers[42] concluded that patients with tumours greater than 6 cms had a 63% of axillary nodal metastasis compared to 30% in patients with 1 to 2 cm tumours. There was direct relation ship of primary tumour size to the extent of axillary metastasis and tumour recurrence rate.
2) ***Oestrogen receptor status:*** Steward and colleagues[44] reported significant increase in the overall survival for operable LABC with positive estrogen receptor status. However in patients with inoperable breast carcinoma, estrogen receptor status had no effect on prognosis.
3) ***Thymidine labeling index:*** Silvestrini and coworkers[45] observed that high labeling index was associated with high recurrence rate. A short time to disease progression and low survival rate.

Management of Locally advanced breast cancer.

Surgery: Donegan[49] reported a 50% local recurrence rate in patients with inoperable disease treated with surgery alone. Fracchia observed survival rate of 21% in stage IIIA patients. It was clear that surgery alone was inadequate treatment.

Radiotherapy : Zucaly and colleagues[51] reported 5 year survival rate of 30% in patients with LABC treated only with primary radiotherapy. It could be concluded from the studies , large tumour burden was not treated adequately by radiation alone.

Surgery and Radiotherapy: Surgery followed by radiation resulted in local control rate of 70 to 86% and 5 year survival rate of 30 to 45 %

Combined Modality Therapy: The Unimodality experiences demonstrated that good local control rates by surgery or radiotherapy alone did not correlate with good prognosis and ultimate survival. Hematogenous metastasis were not being controlled with either radical surgery or radical radiotherapy alone. In early 1970's systemic chemotherapy was incorporated as integral part of primary management of LABC. Grohn and coworkers[53] reported that 5 year disease free survival was 22% for those given radiotherapy and 30% for those given chemotherapy and 67% for those given multimodality treatment. (surgery followed bychemotherapy and radiotherapy)

Derman and coworkers [54]observed patients who had received systemic treatment after surgery had significant increase in disease free survival, without increase in overall survival.

Olson and colleagues,[55] suggested combined modality of treatment resulted in fewer loco regional failure in LABC. These randomized trials revealed that a modest increase in survival when chemotherapy was used in conjunction with local therapy. Local treatment alone did not affect overall survival. So combined modality of treatment was the standard for the treatment of LABC.

PRIMARY CHEMOTHERAPY or NEOADJUVANT CHEMOTHERAPY:

NSABP B- 18 study[56] evaluating the role of primary chemotherapy, in women with operable breast cancer, showed that there was no significant difference in disease free or overall survival of those patients treated with primary chemotherapy followed by surgery and radiotherapy compared to patients treated with surgery, followed by chemotherapy and radiation. Eventhough there was no advantage of survival benefit in Neoadjuvant chemotherapy over adjuvant chemotherapy it had following benefits:

1) Ability to convert the inoperable tumours to operable ones.
2) Assessment of tumour response to chemotherapy in vivo.
3) Chemotherapeutic ablation of primary tumour may alter the growth characteristics of residual metastasis.

4) Initial response to primary chemotherapy predicted the disease free and overall survival rate.

Assessment of disease response to Neoadjuvant Chemotherapy

Mammography: Maskowic and coworkers [46]reported that clinical and mammographic findings were in concurrence in 79% of the patients. Digital mammography had the capacity of achieving the spatial resolution of images as small as 1/20th of millimeter. It has the potential to detect areas of breast tissue that harbour the occult cancer.

Ultrasonography: Powles and coworkers[47] noted that there was better correlation of tumour shrinkage to clinical response on ultrasonography than on mammography. Fornage and colleagues reported that sonographic measurement of established breast cancer correlated with pathological examination more closely than the mammographic measurement.

Magnetic resonance imaging: A recently developed MRI technique for evaluating breast cancer had shown better pathological correlation than conventional imaging techniquies. This new MRI technique utilized a new pulse sequence called RODEO (ROTATING DELIVERY OF EXCITATION OFF-RESONANCE) that produced high-resolution images emphasizing the gadolinium contrast – enhancement qualities of cancers over the background tissues, including fat and normal breast parenchyma.

In a study of 39 patients with locally advanced breast cancer receiving primary chemotherapy RODEO MRI was able to accurately predict the extent of residual disease in 30 of 31 cases reviewed (97%).[48]

Clinical and histological response: Feldman and coworkers reported that histological response more than the clinical response to primary chemotherapy was the single most important prognostic factor for both and disease free and overall survival rate in patients with LABC. Although complete clinical response ranged from 5 to 66%, histological negative disease occurred only in 2 to 29%. The following table summarizes various studies with complete clinical and histological responses.

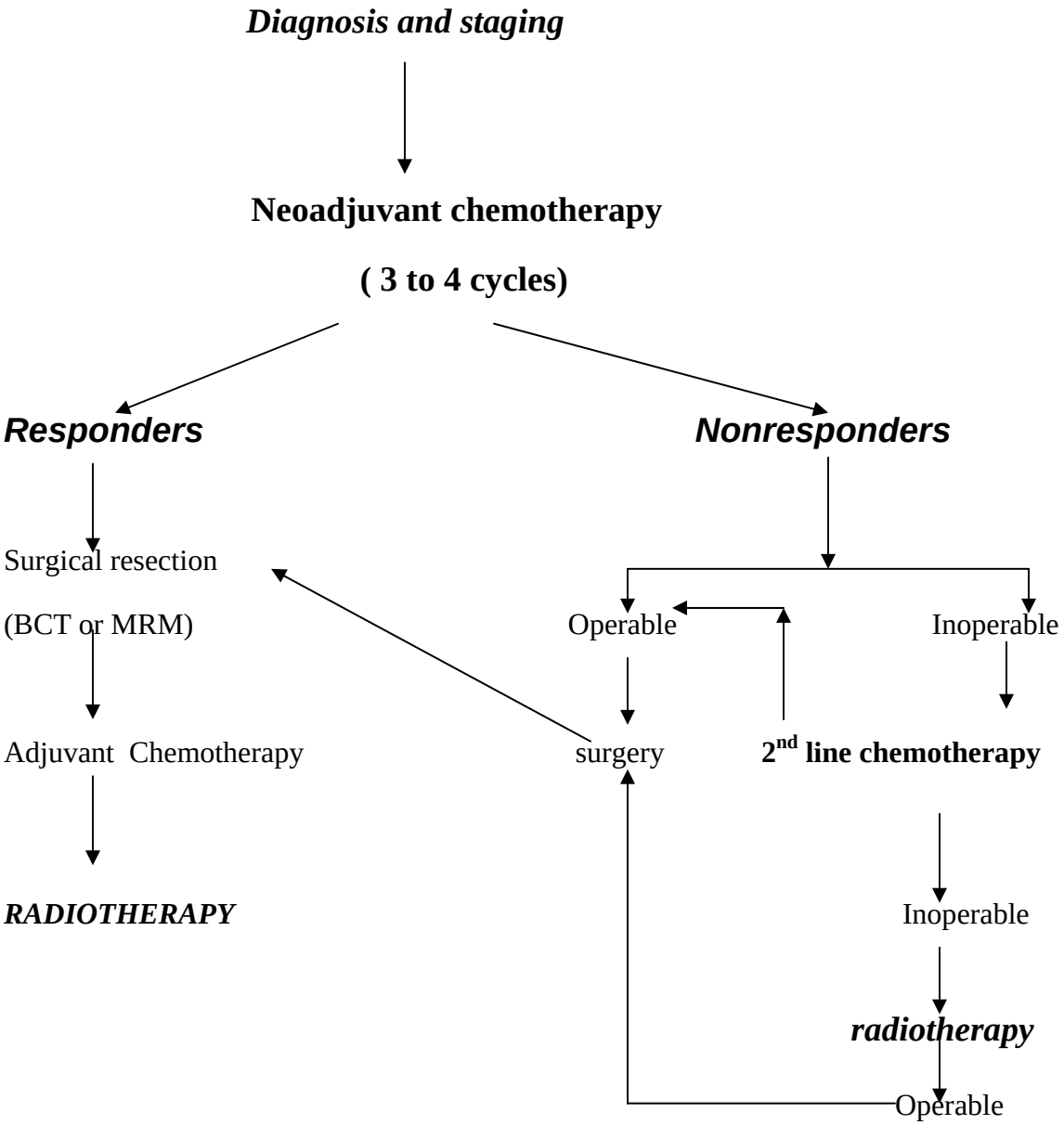
thor and year	***Treatment design***	***No. of patients***	***Complete clinical response***	***Complete histologic response***
Conte (1987)[61]	***CT+S+RT***	***39***	***15***	***8***
Hortbagyi(1988)[59]	***CT±S+RT+CT***	***174***	***17***	***8***
Hobar(1988)[57]	***CT+S+RT+CT***	***36***	***8***	***11***
Cocconi(1990)	***CT+S+CT+RT***	***49***	***8***	***14***
Schwartz(1994)[60]	***CT+S+RT+CT***	***189***	***8***	***10***
Bonadona(1995)	***CT+S+RT+CT***	***227***	***21***	***4***
Sataloff(1995)[62]	***CT+S+CT+RT***	***36***	***33***	***39***

Breast conservation in LABC

There has been growing interest in breast conservation for patients with LABC, after the advent of Neoadjuvant Chemotherapy Jacquelet and coworkers[63] reported that five years of overall survival rate and disease free survival rate of those patients who had undergone a breast conservation surgery was similar to those patients who had undergone Modified Radical Mastectomy. Singletary and Coworkers observed none of the patients who underwent breast conservation surgery after neoadjuvant therapy had evidence of local reference. Therefore it can be concluded that there was a subset of patients with a LABC who would be candidates for BCS following primary chemotherapy.

TREATMENT RECOMMENDATION FOR LABC

The following is the treatment alogorithm for stage III Breast carcinoma



MATERIALS AND METHODS

This study was carried out in the Department of Surgery, Government Rajaji Hospital Madurai, during the period December 2004 to February 2006 in collaboration with Department of Medical Oncology, Government Rajaji Hospital, Madurai.

The women of any age group who attended the surgical OP and presented with a lump in the breast were screened for Carcinoma of the breast by subjecting them to FNAC or Tru cut biopsy, of the lump. After confirming the diagnosis the patients with locally advanced breast cancer were included in the study group.

CRITERIA FOR PATIENT SELECTION:

INCLUSION CRITERIA:

1. Patients with ipsilateral breast tumor in size excess of 5cm with mobile axillary node.
2. Patients with ipsilateral breast tumor of any size with skin fixity.

were included in the study

EXCLUSION CRITERIA: Patients with following criteria were excluded from the study

1. Bilateral breast cancer
2. Performance status – KPS <60 (unlikely to attend the chemotherapy regularly)
3. inflammatory breast cancer.
4. tumor of any size with chest wall fixity or fixed axillary node.

By above mentioned inclusion and exclusion criteria **33 [thirty three]** patients had been enrolled for the study. All the women enrolled in the study were subjected to the following protocol. They had been explained about the chemotherapy regimen and insisted to attend chemotherapy regime regularly. They had been told about surgical and radiation therapy following the neoadjuvant chemotherapy.

Before giving Chemotherapy the size of the tumor and the lymph node were measured manually and using ultrasonogram. In both the methods the greatest perpendicular diameters of the lump were measured and the product obtained as the baseline value for the further follow up[15, 18].

The patients were subjected to investigations like:

Routine:

1. Blood Hemoglobin, Total count, Differential count
2. Blood sugar, Blood Urea, serum creatinine
3. Liver function tests.
4. X-ray chest PA view
5. Echocardiogram
6. ultrasonogram

Some special investigations like ER/PR status and bone scan could not be done due to unavailability of facilities in our institution.

After the investigations the patients were given the NEO ADJUVANT CHEMOTHERAPY.

NEO ADJUVANT CHEMOTHERAPY REGIMEN:

The following chemotherapy regimen was given to the patients: **CAF**

INJ CYCLOPHOSPHAMIDE[17, 19]: an alkylating agent given as 800mg/m^2 of body surface area. It was diluted with 500ml of dextrose solution and infused over 3 hours.

INJ DOXORUBICIN[17, 19]: an anthracyclin antibiotic administered in the dose of 50mg/ m^2 of the surface area. Each 10mg was diluted with 5ml of

distilled water (70 mg in 35ml) and given as direct i.v over the period of 20 mins.

INJ 5 – FLUOROURACIL[17, 19]: a pyrimidine analogue administered as 400mg/m^2 it was given as direct i.v. over a period of 5 mins.

8mg of inj Ondansetron ($5HT_3$ Antagonist) and 8mg of inj dexamethasone was given intravenously half an hour before chemotherapy to prevent vomiting. The patient was given another dose of Ondansetron 4 hours later to prevent breakthrough vomiting.

Patients were subjected to the above mentioned chemotherapy regimen once in 21 days till maximum response was achieved or till response became plateau [16, 31]or if patients were detected to have intolerable toxicity to the drugs given during chemotherapy.

Every time before the next cycle of chemotherapy was given, the patient was assessed for response to chemotherapy and toxicity to chemotherapy

TOXICITY OF CHEMOTHERAPY[17, 19]:

Chemotherapy is toxic to normal tissue and causes numerous significant side effects and complications. Severe toxicity requires withdrawal of chemotherapy. The drugs used in our chemotherapy were CAF. They were known to produce the following toxicities.

INJ 5-FLUOROURACIL: when administered as bolus injection it is known to cause

1. Myelosuppression
2. Stomatitis
3. Diarrhoea
4. Cerebellar ataxia
5. Coronary vasospasm
6. Plantar and Palmar erythema also called as hand foot syndrome.

INJ CYCLOPHOSPHAMIDE: when given may cause

1. Hemorrhagic cystitis
2. Hemorrhagic myocarditis
3. Bonemarrow suppression.

INJ DOXORUBICIN: is associated with

1. Cardiomyopathy consisting of intractable congestive cardiac failure,
2. Dysrrhythmia

To rule out the toxic side effects, complete hemogram and liver function tests were done, the patients with intractable toxicity like uncontrolled vomiting, myelosuppression, cerebellar ataxia, cardiomyopathy, were withdrawn from the chemotherapy regimen and were subjected to surgical intervention. Modified radical mastectomy (MRM) was done for these patients.

ASSESSMENT OF CLINICAL RESPONSE[15, 18, 22,23]

Response to chemotherapy was assessed clinically by measuring the size of the tumour and lymph node manually and using ultrasonogram. The product of two greatest diameters were measured before each chemotherapy. Chemotherapy was terminated when patient achieved maximum response or response showed a plateau. Based on the response the patients were categorized into 4 groups.

GROUP I - ***COMPLETE CLINICAL RESPONSE***:

Here there was no evidence of measurable tumour or new disease for a specified interval usually 4 weeks. .

GROUP II – ***PARTIAL CLINICAL RESPONSE***:

Tumour size decreased 50% or more than 50% determined by two observations not less than 4 weeks apart.

GROUP III – *NO RESPONSE* or ***STABLE DISEASE***

Tumour size decreased less than 50%

GROUP IV – ***PROGRESSIVE DISEASE***:

If 25% or greater increase was seen in the product of one or more measurable lesion or appearance of new lesion, was termed progressive disease.

For each patient the clinical response was assessed and recorded. Depending on the response the patients were subjected to surgery (Breast conservation surgery or Modified Radical Mastectomy) followed by chemotherapy and Radiotherapy.

SURGICAL TREATMENT OPTION:

1) If the clinical and radiological responses were complete breast conservation surgery was considered.
2) If the response was partial and if feasible breast conservation surgery was done or MRM was done.
3) In Stable or progressive disease, modified radical mastectomy with or without reconstruction was considered.

4) If the disease progressed locally with inoperability, preoperative radiotherapy was given followed by reassessment for surgery later.

MODIFIED RADICAL MASTECTOMY (MRM)

For many years radical mastectomy was believed to be only appropriate surgical procedure for treatment of breast cancer. Halstedian view of tumour biology according to which breast cancer was thought to spread in an orderly fashion from the site of primary tumour to axillary lymphnode then via lymphatics to distal sites, required radical surgery. As time passed by it became apparent that distant metastasis developed in many women who underwent radical surgery for breast cancer, this in turn promoted the need to re-examine breast cancer biology. Demonstration of the fact that moderate dose of radiation and chemotherapy successfully eradicated microscopic deposits of breast cancer opened the door for use of Modified radical mastectomy (MRM) or Breast conservation surgeries (BCS)

TYPES OF MRM:

PATEY'S: It included enbloc removal of breast with axillary lymphatics level 1, 2, 3, and overlying skin near the tumour with 3 to 5 cm margin. Pectoralis major muscle was preserved, pectoralis minor muscle was resected.

AUCHINCLASS AND MADDAN'S: This was similar to Patey's MRM but differed from it by preservation of the pectoralis minor muscle and the medial pectoral nerve and removal of Level 1 2 axilary node

Procedure:

1) Patient was positioned on the operative table in the supine position with rolled sheet under the ipsilateral hemithorax so as to allow the motion of arm without limitation.
2) Incision was ideally made transversely from lateral border of sternum to just below anterior axillary fold. This incision included the nipple areola complex 5 cms skin around the lesion and the scar of the previous biopsy if any.
3) Skin flap was elevated in the plane between the subcutaneous fat and the mammary fat. Initially cephalic flap was raised upto subclavius muscle. Pectoralis fascia was dissected from pectoralis muscle in the plane parallel to the course of the muscle bundle. Perforators of the lateral thoracic and anterior intercostal arteries were ligated.

4) Lateral flap was elevated upto anterior border of lattismus dorsi.
5) Inferior flap was raised to upto 3 cms below inframammary fold. After elevating the breast from the chest wall, the breast was attached only to the axilla.
6) Axillary vein was identified at lateral axillary space while anterior border of lattismus dorsi was dissected from inferior to superior direction.
7) Shoulder was abducted and arm was extended to facilitate the dissection of inferior and lateral margin of pectoralis major. Pectoralis major was retracted to identify the pectoralis minor.Inter pectoral nodes were removed preserving the medial pectoral nerve.
8) Loose areolar tissue at the junction of the axillary vein with the anterior margin of lattismus dorsi was swept inferiorly to include the lateral group of axillary nodes, thoraco dorsal vessels and nerve were preserved. Subscapular group of nodes between the thoraco dorsal nerve and chest wall, were dissected enbloc.

9) Central group of nodes were dissected enbloc along with pectoral group, and the Long thoracic nerve of Bell was preserved.

10) After removal of specimen hemostasis was obtained. Two vacuum drains, one for the flap and the another for the axilla were inserted.

11) Skin was sutured with subcuticular sutures.

BREAST CONSERVATION SURGERY:

It included terms such as wide local excision, Lumpectomy, Segmental mastectomy, Tylectomy. In BCS, tumour along with one cm of normal tissue was removed. The extent of surgical resection was determined by clinical and mammographic extent of cancer.

ASSESSMENT OF PATHOLOGIC RESPONSE[21]:

Mastectomy specimens from the patients who underwent MRM were sent for histopathological assessment. In histo pathological examination the following factors were studied.

1. The presence of tumour cells.
2. Whether resected margins were free of tumour
3. Status of lymph node metastasis.

Depending on the pathologic response the patient was categorized into two groups

PATHOLOGICAL COMPLETE RESPONSE (PCR) : No tumour cells were detected in the resected specimen.

PATHOLOGICAL NON RESPONDERS (PINV) : Presence of tumour cells in the resected specimen.

POST OPERATIVE RADIOTHERAPY:

All patients with LABC received radiotherapy of the breast or chest wall to a dose equivalent of 50Gy/25#/5weeks.

ADJUVANT CHEMOTHERAPY (Total 6 cycles) : remaining cycles of CT completed postoperatively.

FOLLOW UP[24, 25]

In the first two years after surgery , the patients were seen atleast once in every 6 months. In the following 3 years they were followed up for every 6 to 12 months.

The minimum requirement for follow up were, physical examination, locoregional evaluation, performance scale assessment, mammography (done once in every 18 months)

No other investigations in asymptomatic patients were performed to detect the metastasis, since it was not cost effective and it did not prolong the survival.

During the follow up period they were examined for the following factors,

1. Local Recurrence
2. Development of metastasis

Local recurrence[24, 25] : Recurrence in the post mastectomy chest wall was most common in the first two years, so the patient was examined for any nodule in the post mastectomy chestwall.

Metastasis[24,25]: Patient after mastectomy go on to develop metastasis. About 80% develop metastasis in about 5 to 10 years. So patients during the follow up period need to be checked for metastasis. Patients were enquired for symptoms of metastasis like bone pain, headache, dyspnea, hemoptysis, jaundice and seizures.

They were subjected to investigations like X-ray chest, Ultrasonogram of the liver, X- ray of the Lumbar spine, alkaline phosphatase levels, CT brain to rule out metastasis.

RESULTS AND DISCUSSION

Table1

Stage	***No. of patients***	***Percentage***
Stage IIIA	***15***	***45***
Stage IIIB	***18***	***55***
Stage IIIC	***--***	***--***

In the current study, after following the inclusion and exclusion criteria, 33 patients were enrolled, all these patients were having locally advanced breast cancer. Based on the TNM stage grouping, the patients were categorized into 3 groups under stage III. Out of 33 patients 15 patients (45%) were categorized under stage IIIA. 18 patients (55%) were categorized under stage IIIB, There were no patients under stage IIIC.

Table 2 :

Patient characteristics	*Number of patients*	*percentage*
Age		
< 50 years	*27*	*81%*
> 50 years	*6*	*19%*
Stage IIIA		
Total	*15*	*45%*
Tumour size		
< 10cm	*12*	*80%*
>10cm	*3*	*20%*
Stage IIIB		
T4a	*--*	*--*
T4b	*18*	*100%*
Total	*18*	*55%*
Axillary node status		
No node palpable	*--*	*--*
1 node palpable	*27*	*81%*
2 to 4 nodes palpable	*6*	*19%*

Table 2

The above table summarizes the patient characteristics and the clinical features. Out of the 33 subjects enrolled, 27 (81%) patients were less than 50 year age group. 6 patients (19%) were aged above 50 years. Among 15 patients grouped under stage IIIA , 12 patients (80%) had tumour size less than 10 cms. 3 patients (20%) had tumour size more than 10 cms. Among the 18 patients categorized under stage IIIB, all of them had involvement of skin.

In the study group of 33 patients, all of them had palpable axillary node. Single node was palpable in 27 patients (81%). Remaining 6 patients had axillary node status of more than one node palpable.

Table3

Clinical response	**Number of patients**	**percentage**
Clinical complete response	**3**	**9**
Clinical partial response	***15***	***46***
No response or stable disease	***9***	***27***
Progressive disease	***6***	***18***

TABLE 3:

Evaluation of the clinical response of primary tumour and lymph node was one of the primary objective of study. The product of two greatest perpendicular diameter was measured both manually and using ultrasonogram before and after every cycle of Neoadjuvant chemotherapy as defined by criteria.

The clinical response of 33 patients was observed and recorded. Out of the 33 patients the overall objective clinical response of 55% was observed. Complete clinical response of 9% (3 Patients) was noted. Partial clinical response was noted in 15 among 33 patients (46%). No response (<50% response)was observed in 9 patient (27%). However 6 patients (18%) showed progressive disease.Out of the 6 patients, two of them had developed supraclavicular node, and 4 patients developed vertebral metastasis.

In similar studies conducted by maraz B, Boross G, Cyanti [26]et al an over all objective response of 60%, complete clinical response of 4%, partial clinical response of 56% had been reported. In their study there were no progressive disease observed after Neoadjuvant chemotherapy.

Allassas, choq, Burton[27] et al conducted a study at Lousiana state university health science, the complete clinical response, partial response. Minimal residual disease and no change was reported to be 22% , 33%, 29% and 15% respectively.

Table 4:

Stage	***No. of patients with clinical response***				***Percentage of clinical response***			
	CCR	***CPR***	***NR***	***PD***	***CCR***	***CPR***	***NR***	***PD***
Stage IIIA	***3***	***6***	***6***		***20***	***40***	***40***	
Stage IIIB		***9***	***3***	***6***		***50***	***16***	***33***

Table 4

Compares clinical response of patients categorized under different groups of stage III. Total of 15 patients were categorized under stage IIIA. Among the 15 patients, 6 (40%) showed partial clinical response. 6 patients (40%) showed no response. Complete clinical response was observed in 3 patients (20%). However progressive disease was not reported in stage IIIA patients.

Among the 18 patients grouped under stage IIIB, 9 patients showed partial clinical response 50%, no response was detected in 3 patients (16%), progressive disease was observed in 6 patients (33%). There was no complete clinical response reported in stage IIIB patient.

In our study, percentage of complete response was higher for patient. in stage IIIA than for the patient in stage IIIB. In a similar study conducted by Hortobogyi, Ames and Ruzdar [28]et al, in the department of Medical Oncology, in Anderson Hospital, Houston, it was reported that complete clinical response after Neoadjuvant chemotherapy was better for patient in stage IIIA than for patient in stage IIIB. This correlated with the present study.

Table 5.

The second objective in our study was to evaluate the pathological response of the primary tumour and lymph node to preoperative chemotherapy. The pathological response was classified into 2 categories, namely pathological complete response and PINV(invasive cells seen). PCR constituted a group of patients who showed no invasive cells detected.

Second group consisted of patients who were termed pathological non responders. (PINV), since their mastectomy specimen showed invasive cells on Histopathological examination.

In the present study, 3 patients (9%), showed complete pathological response after neoadjuvant chemotherapy. Invasive cells were detected in the mastectomy specimen of 30 patients on HPE (90.9%).

TABLE 5

Pathological response	***No,. of patients***	***% of pathological response***
Pathological complete response (PCR)	***3***	***9***
PINV (pathological non responders)	***30***	***90.9***

Table 6:

This table compares the pathological response of patient in our study group categorized under stage IIIA and Stage IIIB.

Out of the 15 patient grouped under stage IIIA, 3 patients (20%) showed complete pathological response and 12 patients were pathological non responders (80%). However all 18 patients included under stage IIIB were pathologically non responders. So in our study complete pathological response was not reported in stage IIIB patients.

TABLE 6:

Stage	*Pathological response*		*Percentage*	
	PCR	***PINV***	***PCR***	***PINV***
Stage IIIA	***3***	**12**	***20%***	***80%***
Stage IIIB	***--***	***18***	***--***	***100%***

Table 7 :

Shows number of patients with resected margin free of tumour in stage IIIA and Stage IIIB. There were 14 (93%) patients with resected margin free of tumour in stage IIIA. Among 14patients in stage IIIB, 13(92%) were found to have resected margin free of tumour. Hence over all tumour free resected margin of 92% was detected in our study.The remaining 4 patients in the stage IIIB had received radiation therapy to the vertebrae as they had vertebral metastasis. They did not undergo surgery

Table 7

Stage	*No of patients with resected margin free of tumour*	*percentage*
Stage IIIA	***14/15***	***93%***
Stage IIIB	***13/14***	***92%***
Total	***27***	***92%***

A similar study conducted by Allassus, chuq, Burton[27] et al, had reported tumour free resected margin of 92% in patients of LABC in stage III after neoadjuvant chemotherapy.

TABLE 8

To detect whether Neoadjuvant chemotherapy could decrease the tumour size there by permitting breast conservation treatment modalities was one of the objective of the present study. In the study population, out of 15 patients categorized under stage IIIA 3 patients showed clinical complete response. Hence breast conservation treatment (BCT) was planned. Since patients opted for mastectomy MRM was done.

Table 8:

Stage	***Total no. of patients***	***No. of patients planned for BCT***
Stage IIIA	***15***	***3***
Stage IIIB	***18***	--

Table 9 summarise clinical and pathological response of each patient in the study group. In the present study, one of the patient in stage IIIA had clinically complete response, where as the pathological response showed invasive cells.

On the other hand one of the patient in stage IIIA in our study group showed clinincally detectable disease where as HPE revealed no invasive cells, indicating complete pathological response.

Zambetti , Oriana,[16] et al had conducted a trial to study the clinical outcome of breast cancer patients with complete pathological primary tumour/lymph node response to adriamycin based chemotherapy. In this trial, it was stated that 1/3rd of the patients with pathologically complete response had clinically measurable residual disease. Conversely 1/3rd of patients with complete clinical response had invasive cells in their mastectomy specimen on HPE.

Table 9

Stage	S.No	Clinical response	Pathological response	Number of cycles
Stage IIIA	*1*	*CCR*	*PCR*	*4*
	2	*CCR*	*PCR*	*4*
	3	*CCR*	*PINV*	*4*
	4	*CPR*	*PCR*	*4*
	5	*CPR*	*PINV*	*3*
	6	*CPR*	*PINV*	*3*
	7	*CPR*	*PINV*	*3*
	8	*CPR*	*PINV*	*3*
	9	*CPR*	*PINV*	*3*
	10	*CNR*	*PINV*	*3*
	11	*CNR*	*PINV*	*3*
	12	*CNR*	*PINV*	*3*
	13	*CNR*	*PINV*	*3*
	14	*CNR*	*PINV*	*3*
Stage IIIB	*15*	*CNR*	*PINV*	*3*
	16	*CPR*	*PINV*	*3*
	17	*CPR*	*PINV*	*3*
	18	*CPR*	*PINV*	*3*
	19	*CPR*	*PINV*	*3*
	20	*CPR*	*PINV*	*3*
	21	*CPR*	*PINV*	*3*
	22	*CPR*	*PINV*	*3*
	23	*CPR*	*PINV*	*3*
	24	*CPR*	*PINV*	*3*
	25	*CNR*	*PINV*	*3*
	26	*CNR*	*PINV*	*3*
	27	*CNR*	*PINV*	*3*
	28	*PD*	*PINV*	*3*
	29	*PD*	*PINV*	*3*
	30	*PD*	*--*	*3*
	31	*PD*	*--*	*3*
	32	*PD*	*--*	*3*
	33	*PD*	*--*	*3*

TABLE 9

To detect whether Neoadjuvant chemotherapy could decrease the tumour size there by permitting breast conservation treatment modalities was one of the objective of the present study. In the study population, out of 15 patients categorized under stage IIIA 3 patients showed clinical complete response. Hence breast conservation treatment (BCT) was planned. Since patients opted for mastectomy MRM was done.

Table 10:

Stage	***No of patients***	***No of patients with metastasis***	***Follow up period***	***Response of the patient with metastasis to NACT***	
				Clinical	***Pathological***
Stage IIIA	***15***	***1***	***15 months***	***CPR***	***PINV***
Stage IIIB	***18***	***1***	***4 months***	***PD***	***PINV***

TABLE 10 :

During the follow up period, 1 patient in stage IIIA who was assessed to have clinical partial response/histopathologically invasive cell was detected to have pulmonary metastasis after a period of 15 months.

Another patient categorized under stage IIIB was detected to have cerebral metastasis after a period of 4 months, this patient had progressive disease during preoperative chemotherapy and was a pathological non responder.

It was evident from the above mentioned facts in our study that patients who had a complete clinical response, had a comparably good prognosis than those patients who showed a partial or no response to neoadjuvant chemotherapy.

Y.W. Moon Rha [30]et al in their study showed that those patients with a good response to neoadjuvant chemotherapy had a good prognosis. Gajdas and Tarttar[29]et al had concluded in their study, that patients with a complete pathological and clinical response were observed to have good prognosis than those patients with partial or no clinical response and than those who had invasive cells on HPE of their resected specimen.

CONCLUSION

From this study it was evident that neoadjuvant chemotherapy could

1) Downstage the disease so as to make the inoperable tumour to operable one and to plan breast conservation for operable disease.
2) Patients who did not respond to NACT or who showed disease progression during NACT were predicted to have poor prognosis compared to those who had shown objective response to neoadjuvant chemotherapy.
3) NACT also made it possible to resect locally advanced disease with tumour free margin in most cases (92%)

Thus NACT plays an important role in clinical trials as it allows more rapid comparison of treatment regimes than can be accomplished in the adjuvant settings. It also provides an opportunity to analyze biological markers as predictors of response to CT.

BIBLIOGRAPHY

1) Clive peedell concise clinical oncology-Ist edition, page No. 144
2) Guinee VF: epidemiology of breast cancer in Blind KI, Copeland EM, (III edition) the breast: Comprehensive management of Benign and Malignant disease. Philadelphia WB Saunder 1998 P 339
3) Jemal A, Murray et al Cancer statistics 2003, CA Cancer Journal Clin. 53:5, 2003
4) WHO Health Situation in South East Asia region. NewDelhi 1994-1996.
5) WHO Health situation in south East Asian region, NewDelhi 1998-2000.
6) Hortobagyi, strom EA et al: Treatment of LABC: disease of Breast IInd Edition.
7) Delana M, Zucali Bonadonna combined chemotherapy approach in LABC, Cancer Chemotherapy Pharmacol.
8) Valgussa P Zametti et al : Factors affecting results in Combined Modality of treatment, Clinical exp metastasis 1983-1. 191
9) Swain SM. Sorace Neoadjuvant chemotherapy in Combined Modality approach in LABC, Cancer Research 1987: 47; 3889

10) Calais G, Berger C, Descamps et al: Conservative treatment feasibility with induction Chemotherapy, surgery and Radiotherapy for patient with Breast Carcinoma larger than 3 cm 1994: 74, 1785-1788.

11) Delana Varini et al Multimodal treatment for LABC, cancer Clinical Trial, 1981:4: 229-236.

12) Singletary SE MC Neese MD, Hortobagyi Feasibility of BCS after induction chemotherapy, for LABC cancer 1992, 69- 2849-2852.

13) Schwartz GF Birchansky et al : Induction Chemotherapy followed by breast conservation for LABC cancer 1994:73:362-369.

14) FisherB, Bryant J, Wolmark N et al : effect of Preoperative chemotherapy on the outcome of woman with LABC. J.Clin. Oncology 1998:16, 2672:85.

15) Herrada, Iyer Atkinson et al, Relative value of physical examination/ Mammography, Breast sonography in evaluating response of tumour/lymphnode, clin. Cancer research 1997: 3: 1565

16) Zambetti m, Oriana et al, combined sequential approach to LABC, Annals of Oncology 1999.10,305.

17) Joane E Mortimer: Morry and Blind, Medical Management of Malignant disease, the Washington Manual, 27th edition Page no:357-374

18) Schott AF Hayes DF et al, Clinical and radiological assessment to predict breast cancer pathologic complete response to NACT. Breast cancer Res Treat. 2005 Aug 92(3): 231-235.

19) Puge R, Principle of chemotherapy in Pazd, Coia et al cancer management: Multidisciplinary approach.

20) Loeburg CR, Lux MP, etal, Department of OG, University of Erlangan Germany, Neoadjuvant chemotherapy in Breast, what diagnostic procedure can be used.

21) Feldman LD: Hortobagyi et al, pathological assessment of response to induction chemotherapy in breast cancer, Cancer Res 46: 2578-2587,1986

22) S.J. Cleator and Mafris et al, Good clinical response of breast cancer to NACT in association with improved overall survival, Annals of Oncology, Feb 2005: 16(2) 267-272.

23) Hayward JC: Carbone PD et al, Assessment of response to therapy in LABC, Br. Cancer 35: 292-298 1997

24) Clinical Recommendation for diagnosis, adjuvant treatment and follow up of primary breast cancer, Annals of Oncology 12: 1047-1048, 2001.

25) Intensive diagnostic follow up after treatment of LABC, randomized trial, Rosseti, pall et al, JAMA 1994: 271, 1593-1597.

26) Maraz Boros Gyanti et al, response rate following Neoadjuvant chemotherapy in patients with LABC, Annal on Oncology, 205, 16(11), 1750-1754.

27) Allassas, Chu D, Borton et al, Lousiana State university health sciences, Am Surgery 2005, January71(6) 487-492.

28) Hortobagyi: Amos FC, Ruzdar et al: MD Anderson hospital management of stage III primary breast cancer with primary CT/Surgery/ Radiation.

29) Gajdas Tarttar,et al Jour. surgical oncology 2002;80 4-11 Relationship of clinical and pathological response to neoadjuvant chemotherapy and outcome of LABC

30) Y.W.Moon Rhe et al Neoadjuvant chemotherapy in LABC-Early response predict good prognosis – Am oncology November 2005 16 (11) 1778-1785

31) Tamara shankier, Mark Levine et al. For steering committee on clinical practical guidelines for cancer treatment of Breast cancer : 15, treatment for women with stage III , CMAJ 2004, 170(6), 983-994.

32) Anson Bj, Mc Vay CB: Thoracic walls: Breast or mammary region. In Anson BJ, Mc Vay Cb (eds): Surgical Anatomy. Vol I, Philadelphia, WB Saunders, 1971, pp 330-369.

33) Morehead JR: Anatomy and embryology of the breast. Clin Obstet Gyneccol 25: 353-357,1982.

34) Batson OV: The function of the vertebral veins and their role in the spread of metastases. Ann Surg 112: 138-149,1940.

35) Batson Ov: The role of the vertebral veins and metastatic processes. Ann Intern Med 16: 38-45,1942.

36) Henricques C: The veins of the vertebral column and their role in the spread of cancer. Ann R Coll Surg Engl 31: 1-2. 1962.

37) Cunningham L: The anatomy of the arteries and veins of the breast, J Surg Oncol 9: 71-85,1977.

38) Halsell JT, et al: Lymphatic drainage of the breast demonstrated by vital dye staining and radiography. Ann Surg 162: 221-226,1965.

39) Turner- Warwick RT: The lymphatics of the breast. Br J Surg 46: 574-582, 1959.

40) Massopust LC Gardner WD: Infrared photographic studies of the superficial thoracic veins in the female. Surg Gyneco Obstet 91:717-727,1950.

41) Miller M, R Kasahara M: Cutaneous innervation of the human breast, Anat Rec 135: 153-167,1959,

42) Fisher B, Slack NH, Bross IDJ: Cancer of the breast: Size of the neoplasm and prognosis. Cancer 24:1071-1081,1969.

43) Valagussa P, Bonadonna G, VeronesiV, et al: Patterns of relap;se and survival following radical mastectomy. Cancer 41: 1170-1178,1978.

44) Stewart JF, King RJB ,Winter PJ,et al: Oestrogen receptors Clinical features and prognosis in state III breast cancer. Eur J Cancer Clin Oncol 18: 1315-1320, 1982.

45) Silverstrini R, Daidone MG, Valagussa P, et al: Cell kinetics as a prognostic marker in locally advanced breast cancer. Cancer Treat Res 71:379, 1987.

46) Moskovic EC, Mansi JL, King DM, et al: Mammography in the assessment of response to medical treatment of large primary breast cancer. Clin Radiol 47:339-344, 1993.

47) Powles Tj, Hickish TF, Makris A, et al: Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. J Clin. Oncol 13(3):547-552, 1995.

48) Breast Cancer and magnetic resonance imaging, Presented at the 48th Annual Cancer Symposium of th Society of Surgical Oncology: Boston, Massachusetts, March 23-26, 1995.

49) Donegan WL: Cancer of the Breast, 3rd ed. Philadelphia, WB Saunders, 1979,pg 263.

50) Fracchia AA, Evans JF, Eisenberg BL: Stage III carcinoma of the breast: A detailed analysis. Ann Surg 19: 705-710, 1980.

51) Zucali R, Uslenghi C, Kenda R, Bonadonna G: Natural history of survival of inoperable breast cancer treated with radiotherapy and radiotherapy followed by radical mastectomy. Cancer 37: 1422-1431. 1976.

52) Sorace RA, Lippman Me: LABC. In Lippman ME, Lichter AS, Danforth DN Jr (eds): Diagnosis and Management of Breast Cancer: Philadelphia, WbB Saunders, 1988, pp 272-295.

53) Grohn P, Heinonen E, Klefstrom P, et al : Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. Cancer 54: 670-674,1984.

54)Derman DP, Browde S, Kessel IL, et al: Adjuvant chemotherapy for stage III breast cancer: A randomized trial. Int J Radial Oncol Biol Phys 17: 257-261,1989.

55) Olson JE, Neuberg D, Pandya K, Richter M, Falkson G: The management of resectable stage III breast cancer: The Eastern Cooperative Oncology Group trial. Proceedings of ASCO 8:23, 1989. Abstract 85.

56) Fisher B, RocketteII, Robidoux A, et al: Effect of preoperative therapy for breast cancer on local- regional disease: First report of NSABP B-18. Proc Am Soc Clin Oncol 12:64, 1994.

57) Hobar PC, Jones RC, Schouten J, Lietch AM, Hendler F: Multimodality treatment of LABC . Arch Surg 123: 951-955, 1988.

58) Feldman LD, Hortbobagyi GN, Buzdar AU, et al: Pathological assessment of response to inductuion chemotherapy in breast cancer. Cancer Res 46: 2578-2581,1986.

59) Hortobagyi GN, Ames FC, Buzdar AU, et al: Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer 62, 2507-2516, 1988.

60) Schwartz GF, Birchansky CA, Jinarbicky LT, et al: Induction chemotherapy followed by breast conservation for LABC. Cancer 73(2): 362-369.

61) Conte PF, Alama A, Bertelli G: Chemotherapy with estrogenic recruitment and surgery in LABC: Clinincal and cytokinetic results. Int J Cancer 40: 490-494,1987.

62) Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber patholoogical response to induction chemotherapy in LABC: A determinant of outcome. J Am Coll Sug 180: 297-306,1995.

63) Jacquillat C, Weil M, Baillet F, et al, Neoadjuvant chemotherapy and radiation therapy in the breast conservating treatment of 250 patients with all stages of infiltrative breast cancer. Cancer 66:119-129,1990.

ABBREVIATIONS

LABC – Locally advanced breast cancer

NACT – Neoadjuvant chemotherapy

MRM – Modified radical mastectomy

BCS – Breast conservation surgery

BCT – Breast conservation treatment

CCR – Clinical complete response

CPR – Clinical Partial response

CNR – Clinical No response

PD – Progressive disease

PCR – Pathological complete response

PINV – Pathologically invasive cells

CT – chemotherapy

RT – Radiotherapy

AJCC – American Joint committee on cancer

UICC – International union against cancer

P

PROFORMA FOR ROLE OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

NAME: ***AGE:*** ***SEX:*** ***I.P.NO***

ADDRESS: ***HEIGHT:*** ***WEIGHT:***

CLINICAL EXAMINATION:

CLINICAL STAGING:

INVESTIGATION:

a) ***FNAC/TRU CUT BIOPSY***
b) ***BLOOD Hb***
c) ***BLOOD UREA***
d) ***BLOOD SUGAR***
e) ***SERUM CREATININE***
f) ***LFT: SERUM BILIRUBIN***
g) ***SERUM ALKALINE PHOSPHATASE***
h) ***SGOT***
i) ***SGPT***
j) ***X-RAY CHEST PA VIEW***
k) ***ULTRASONOGRAM ABDOMEN***
l) ***ECHOCARDIOGRAM***

MEDICAL ONCOLOGIST OPINION:

CHEMOTHERAPY:

Number	***Date***	***Breast lump size***	***Lymph Node size***	***Response %***
Ist cycle				
2nd cycle				
3rd cycle				
4th cycle				
5th cycle				
6th cycle				

CLINICAL RESPONSE: CCR/CPR/CNR/PD

TREATMENT GIVEN:

SURGERY: WIDE LOCAL EXCISION WITH AXILLARY DISSECTION / MRM

ADJUVANT CHEMOTHERAPY:

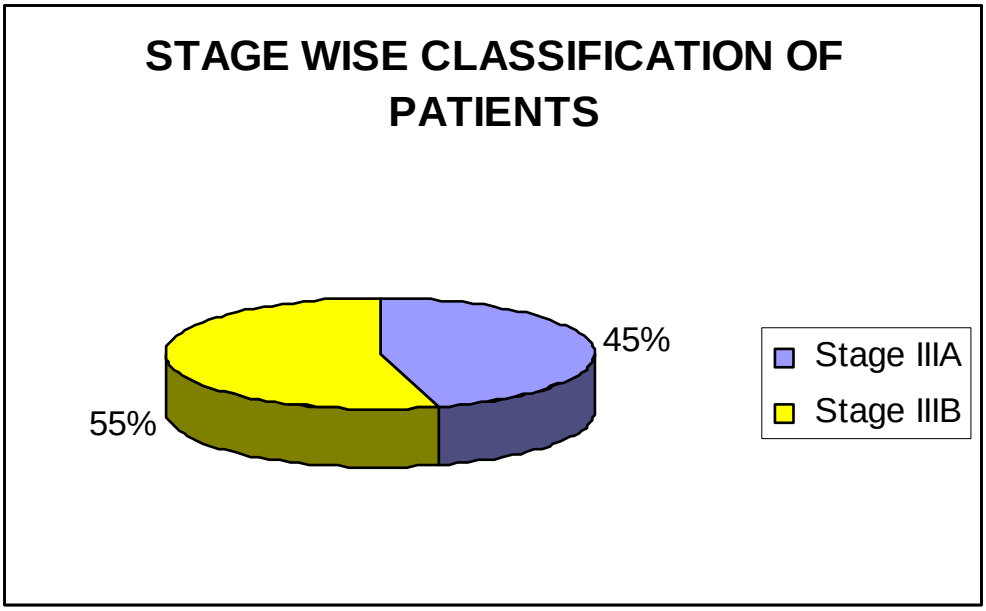
RADIOTHERAPY:

HARMONAL THERAPY:

POSTOPERATIVE BIOPSY REPORT:

PATHOLOGICAL RESPONSE: PCR/PINV

FOLLOW UP :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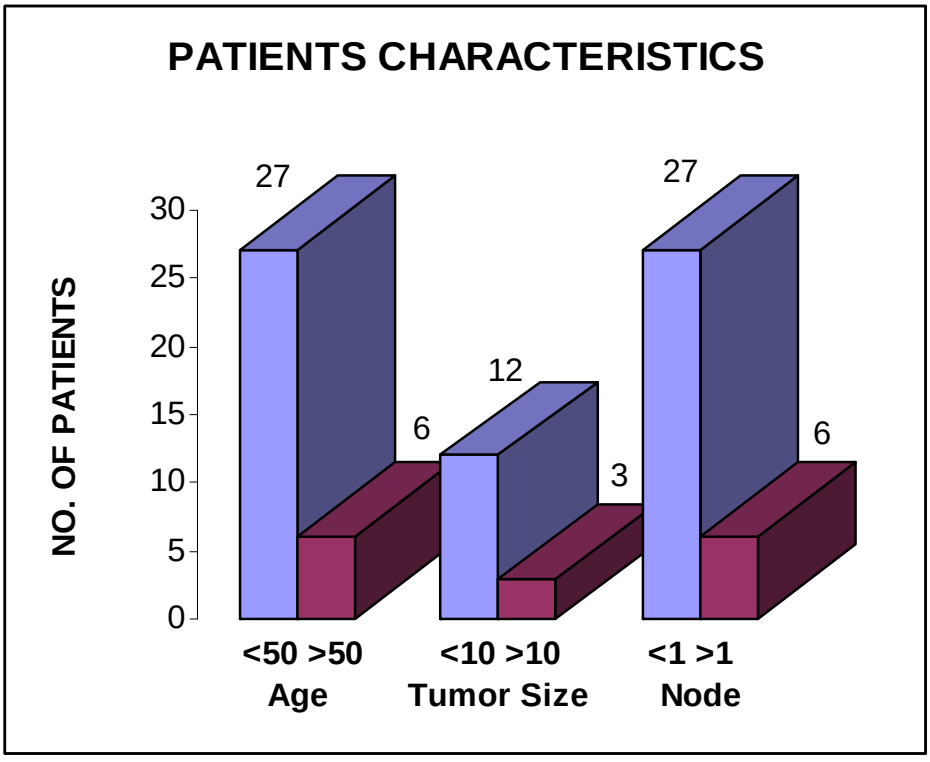
Stage IIIB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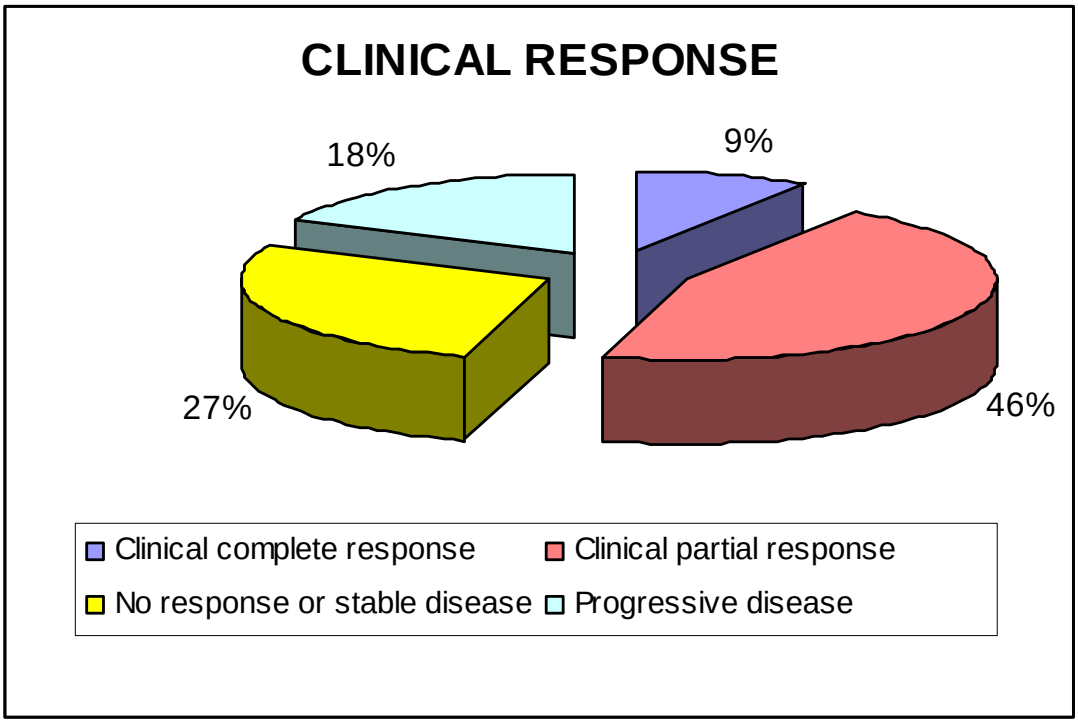
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27%
46%
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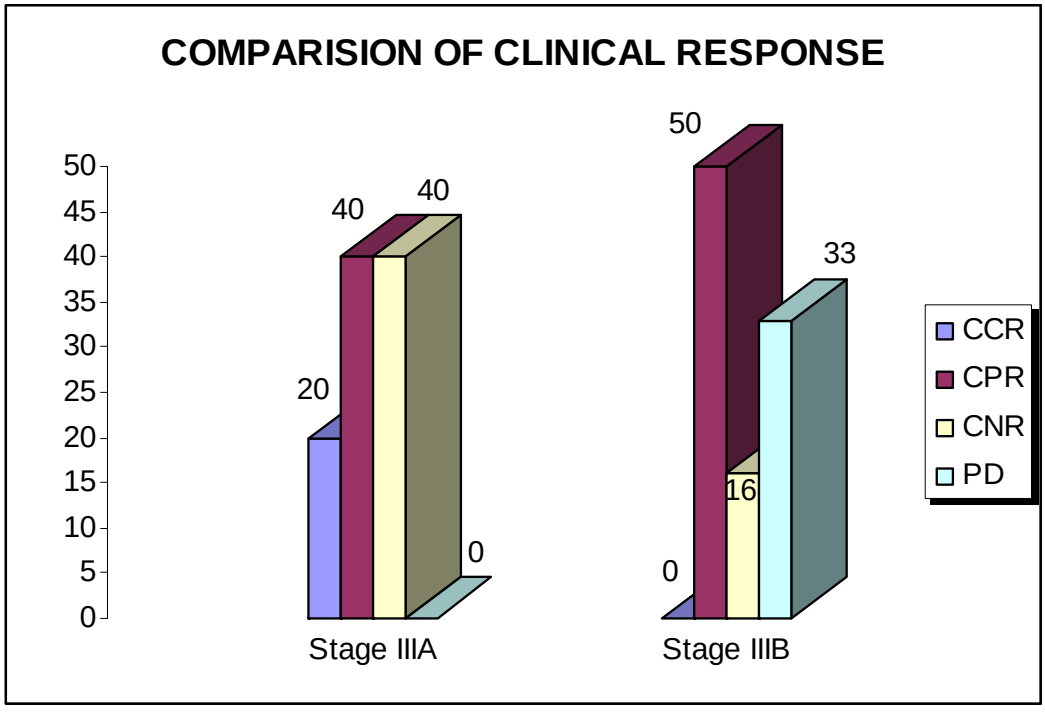
Clinical partial response
No response or stable disease
Progressive disease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20
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Stage IIIB
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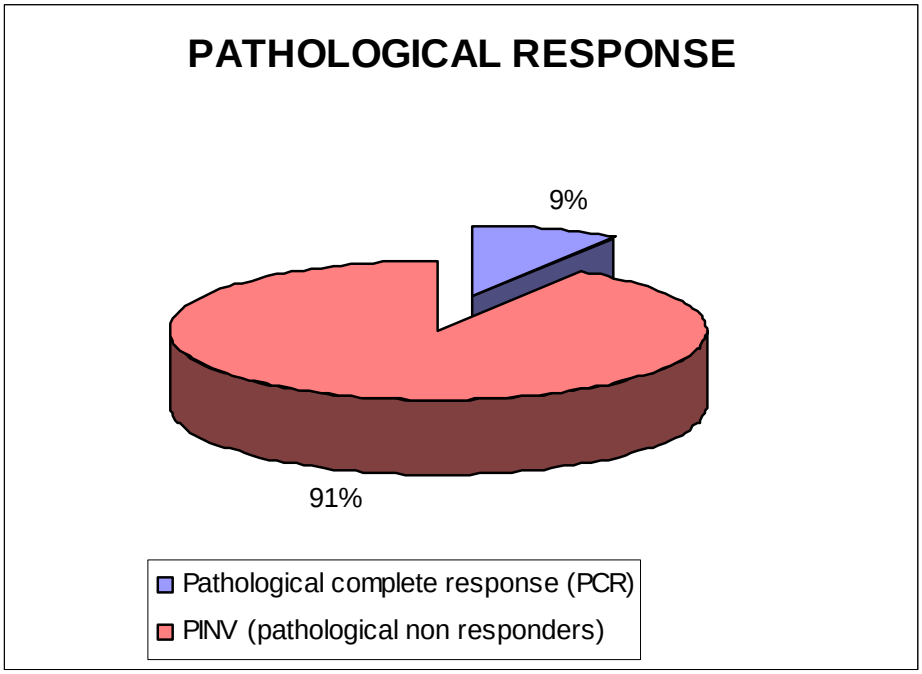
CPR
CNR
PD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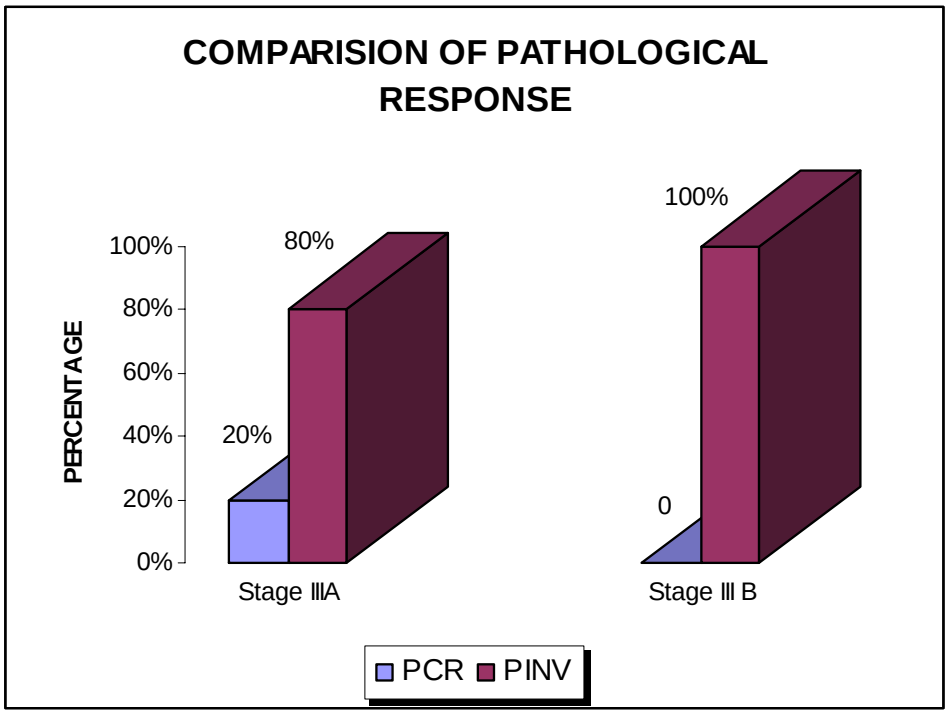
PINV (pathological non responders)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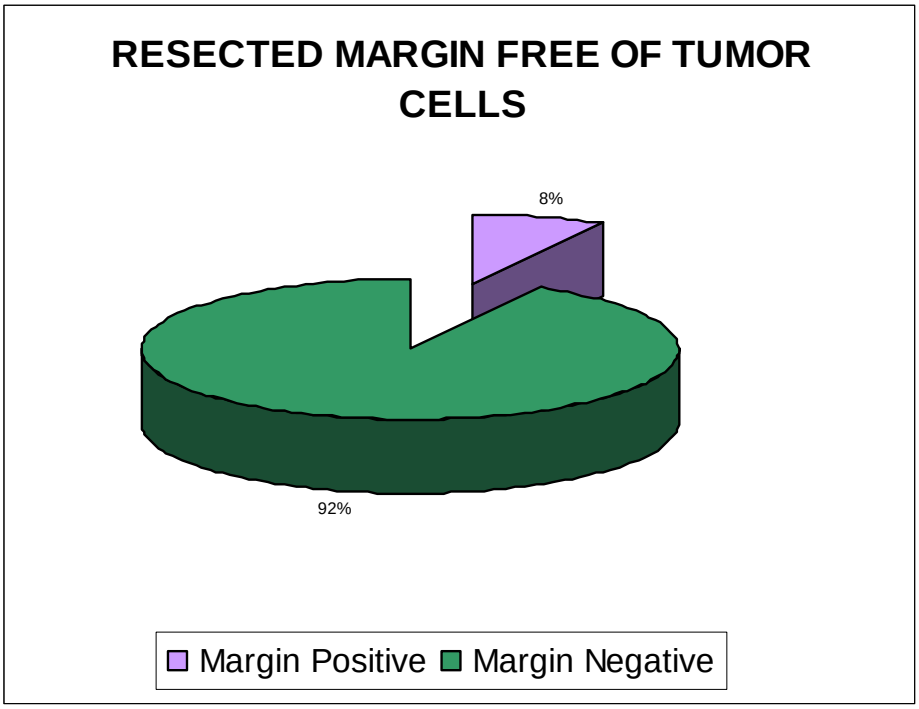
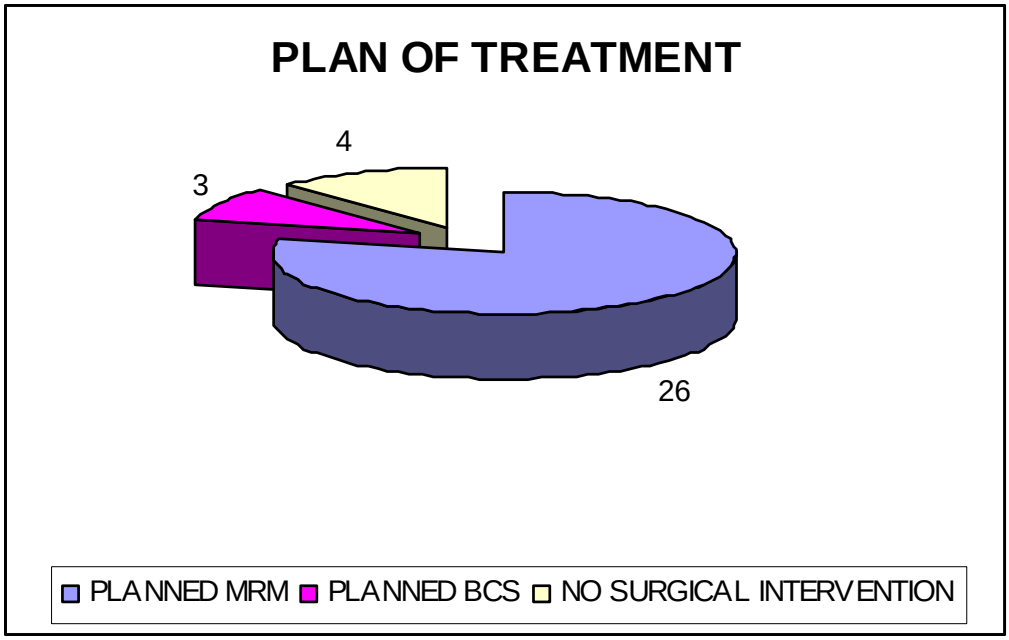
60%
40%
20%
0%
20%
80%
100%
0
Stage IIIA
Stage III B
PCR
PINV


RESECTED MARGIN FREE OF TUMOR CELLS
8%
92%
Margin Positive
Margin Negative


PLAN OF TREATMENT
4
3
26
PLANNED MRM
PLANNED BCS
NO SURGICAL INTERVENTION

MASTER CHART

S.No	NAME	AGE	I.P.No	STAGE GROUPING	NO OF CYCLES OF NACT	CLINICAL RESPONSE	PATHOLOGICAL RESPONSE	SURGERY DONE	FOLLOW UP
1	Panchavarnam	45	343866	Stage III A	4	CCR	PINV	MRM	No Locoregional recurrence or metastasis
2	Pappa	45	393663	Stage III A	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
3	Kala	32	363612	Stage III A	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
4	Pandiammal	40	356799	Stage III A	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
5	Kangalakshmi	40	294960	Stage III A	4	CPR	PCR	MRM	No Locoregional recurrence or metastasis
6	Oyyammal	45	390042	Stage III A	3	CCR	PCR	MRM	No Locoregional recurrence or metastasis
7	Amina	42	294072	Stage III A	3	CCR	PCR	MRM	No Locoregional recurrence or metastasis
8	Rabha	50	372672	Stage III A	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
9	Kanagam	49	412721	Stage III A	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
10	Ramayee	45	402242	Stage III A	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
11	Amirtham	47	384219	Stage III A	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
12	Selvi	50	414120	Stage III A	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
13	Archana	49	424162	Stage III A	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
14	Karthika	47	384271	Stage III A	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
15	Rani	46	387992	Stage III A	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
16	Chinnammal	60	344344	Stage III B	3	PD	PINV	MRM	Cerebral etastasis after 4 months
17	Palaniammal	30	297138	Stage III B	3	CPR	PINV	MRM	Pulmonary metastasis after 15 months
18	Selvi	50	377370	Stage III B	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
19	Algammal	45	360684	Stage III B	3	PD	-	Pateints received RT to vertebral metastasis	
20	Irulayee	65	243293	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
21	Meenakshi	40	345607	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
22	Karupayee	60	298071	Stage III B	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
23	Backyalaksmi	42	394216	Stage III B	3	PD	-	Pateints received RT to vertebral metastasis	Pateints received RT to vertebral metastasis
24	Jayanthi	47	421672	Stage III B	3	CNR	PINV	MRM	No Locoregional recurrence or metastasis
25	Prema	45	407216	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
26	Shanthi	50	396086	Stage III B	3	PD	PINV	MRM	No Locoregional recurrence or metastasis
27	Parameshwari	49	400423	Stage III B	3	PD	-	Pateints received RT to vertebral metastasis	
28	Pandeswari	62	400262	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
29	Murugalakshmi	46	420011	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
30	Rajeswari	47	416680	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
31	Muniammal	48	306072	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis
32	Chinnathai	61	367200	Stage III B	3	CPR	PINV	MRM	No Locoregional recurrence or metastasis

33	Jeevarathinam	62	421021	Stage III B	3	PD	-	Pateints received RT to vertebral metastasis	