PROSPECTIVE ANALYSIS OF FAVORABLE PROGNOSTIC FACTORS IN CARCINOMA BREAST

DISSERTATON SUBMITTED FOR M.S DEGREE EXAMINATON

BRANCH I

(GENERAL SURGERY)

K.A.P.V GOVERNMENT MEDICAL COLLEGE AND MAHATMA GANDHI MEMORIAL HOSPITAL, TIRUCHIRAPALLI

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

CHENNAI

APRIL 2015

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I hereby declare that this dissertation entitled **"PROSPECTIVE ANALYSIS OF FAVORABLE PROGNOSTC FACTORS IN CARCINOMA BREAST"** is the bonafide and genuine research work carried out by me under the guidance of Dr. P. Rajagopal, M.S., Associate Professor, Department of General Surgery, KAPV Government Medical College and Mahatma Gandhi Memorial Hospital, Tiruchirapalli.

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This to certify that this dissertation entitled "**PROSPECTIVE ANALYSIS OF FAVORABLE PROGNOSTIC FACTORS IN CARCINOMA BREAST"** is a bonafide work of research done by Dr.A.S.Karthikeyan in partial fulfillment of requirement for the degree of MS in GENERAL SURGERY.

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LIST OF ABBREVIATIONS

BCT Breast conservating therapy

BRCA1 Breast cancer tumor supressor gene 1

BRCA2 Breast cancer tumor supressor gene 2

CC Craniocaudal

DCISDuctal carcinoma in situ

ER Estrogen receptor

ERBB2 EGF receptor gene

FNAC Fine needle aspiration cytology

FSH Follicle-stimulating hormone

GnRH Gonadotropin-releasing hormone

Gy Gray

HRT Hormone replacement therapy

IHC Immunohistochemical

LCIS Lobular carcinoma in situ

LH Luteinizing hormone

LHRH Luteinizing hormone releasing hormone

M Metastasis

MLO Medio lateral oblique

MRI Magnetic resonance imaging

N Node

NACT Neo-adjuvant chemotherapy

NST No special type

OCP Oral contraceptive pill

PR Progesteron receptor

PST Primary Systemic Therapy

RR Relative risk

RT-PCR Reverse-transcriptase polymerase chain reaction

T Tumor .

TC Technetium

TRAM Transverse rectus abdominis myocutaneous

US Ultrasound

INTRODUCTION

ABSTRACT

BACKGROUND AND OBJECTIVES

The cancer of breast with its uncertain cause has captured the attention of physicians throughout the ages. It is one of the most common carcinoma occurring in females and it is a devastating illness both physically and mentally. In India, Breast cancer is second most common, malignancy among women next to Ca cervix.According to the National Cancer Registry, Bangalore has the highest age adjusted incidence rate in India (36.6). Chennai ranks third (32.6).

GLOBOCAN (WHO) reports that India has the highest number of breast cancer deaths in the world (70218) followed by China (47984) and USA(43909)

AIM OF THE STUDY

The purpose of the study is to identify the prognostic factors in primary carcinoma breast and emphasize the need of awareness and public education regarding carcinoma breast and its early detection

The utility of prognostic factors lies not only in their ability to prognosticate the outcome of the disease but also in detecting early disease, monitoring of disease course, screening for recurrent diseas

METHODOLOGY

STUDY DESIGN AND SAMPLING:

This is a prospective analytical study of 95 Cases of Cancer Breast diagnosed and treated at KAPV Government Medical College and Mahatma Gandhi Memorial Government Hospital, Tiruchirapalli over a period of 2 years from May 2012 to August 2014.

At presentation a detailed history was taken and clinical examination done. Diagnosis was confirmed histologically and investigations like Blood Biochemistry, chest X-ray, ultrasound abdomen were also done to stage the disease. In patients presenting with locally advanced breast disease or metastatic disease investigations like CT abdomen, CT chest, mammogram of opposite breast, pleural fluid and ascitic fluid cytology were done.

The modality of treatment was decided based on stage of disease at presentation and operability. Most of the patients with early breast cancer I II A, II B, III A underwent modified radical mastectomy.

Inoperable stage IIIA,IIIB,IIIC were treated with neoadjuvant chemotherapy followed by Modified radical mastectomy. Patients with Metastatic disease received palliative chemotherapy and radiotherapy.

All cases were followed up at monthly interval with clinical examination, blood count and biochemistry, ultrasound abdomen, chest X ray, Mammography was done at 3 monthly interval during the follow up period. Data obtained were recorded in a specific proforma and analysed in systematic way.

INCLUSION CRITERIA

All histologically proven cases of cancer breast were included in the study. Immunohistochemical studies of ER, PR receptors were done in 20 patients

EXCLUSION CRITERIA

patients who where operated and referred for further management from outside hospital were excluded from the study.

RESULTS

1. The commonest age of presentation was 40 – 50 years of age.
2. About 47.36 were premenopausal and 46.31 were postmenopausal 5.26% were Nullipara
3. Commonest mode of presentation was painless lump in 46.31%.

4. Most of the patients presented with stage III disease 62.09%.
5. Lymphnode positivity during presentation was about 69.46%.
6. Invasive ductal carcinoma was the commonest pathological variety in our stage. Histological grade I was found in 56.84%.
7. Most of our patients presented with tumor size more than 5 cm (67.36%).
8. Modified Radical mastectomy was done in 90 patients. Toilet mastectomy was done in 5 patients presenting with ulceration/fungating lesions
9. Resected margins were found to be positive in 5 patients all of them were given radiotherapy. Three of them developed locoregional recurrence 2 developed metastasis. One in lung, one in brain.
10. Lymphnode examination for metastatic deposits in pathological specimen showed positivity in 49 patients. More than 6 nodes were positive for metastatic deposits in 13 patients. Of which 4 developed locoregional recurrence and one developed liver, lung metastasis. One patient with supraclavicular node developed spine metastasis. All patients were treated with chemotherapy and radiotherapy.

11. Histologic grade 1 found in 44.21 of patients, grade 3 found in 10.52% of our patients (10 Pts) of which 3 had locoregional recurrence. 2 developed lung secondaries during the follow up period.
12. Patients who developed lung metastasis had Tumor size more than 8cm during presentation and 1 of them had histological grade III invasive ductal carcinoma. Supraclavicular node was involved in one patient.
13. One patient with brain metastasis had Tumor size of 6 cm during presentation, she had more than 6 nodes positive for deposits in pathological resection specimen.
14. .One patient who developed both spine and liver metastasis presented with tumor involving all quadrants.
15. In the hormone receptor study done in 20 cases .(10 cases in premenopausal age group and 10 cases in postmenopausal age group), estrogenreceptor positivity was seen in 65% (13cases), negativity for both receptors in 35% (7 cases) with increase in positivity in older age group(50-59 years).
    1. ER+, PR- tumours (5/10 cases) are more prevalent in postmenopausal age group constituting 50%.

2. Special histological variants like papillary carcinoma, lobular carcinoma are positive for ER and PR.Medullary and Metaplastic variants are negative for both receptors. In our study, ER /PR negative found in 7 patients. Among them one patient with ER/PR –ve medullary carcinoma developed local recurrence, and one patient with ER/PR –ve metaplasic carcinoma developed lung metstasis.

16. Nottingham Prognostic index was found to have direct correlation with prognosis in our study. In 32 of our patients with NPI more than 5.4, 5 had local recurrence, 3 had lung metastasis, 2 developed spine metastasis and one developed brain metastasis during follow up.

CONCLUSION

The prognostic markers in carcinoma breast which needs to be routinely assessed are axillary lymphnode status, tumour size, histologic grade, estrogen and progesterone receptor status, post operative findings like positive margins as they are needed in planning of adjuvant treatment.

KEY WORDS

MODIFIED RADICAL MASTECTOMY,ER/PR STATUS,AXILLARY NODE STATUS, LOCALRECURRENCE,METASTASIS, NOTTINGHAM PROGNOSTIC INDEX,MAMMOGRAPHY.

INTRODUCTION

Carcinoma breast is the world's most common cancer among females.

It is one of the most common carcinoma occurring in females and it is a devastating illness both physically and mentally.

In India, it is the leading cancer among women in cities and second most common cancer in rural women. According to the National Cancer Registry, Bangalore has the highest age adjusted incidence rate in India (36.6). Chennai ranks third (32.6).

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AIM AND OBJECTIVE

AIM OF THE STUDY

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The utility of prognostic factors lies not only in their ability to prognosticate the outcome of the disease but also in detecting early disease, monitoring of disease course, screening for recurrent disease

OBJECTIVES OF THE STUDY

1. To study the incidence of carcinoma breast in relation with age and socioeconomic status of patients**.**
2. To study the relationship of carcinoma breast with menstrual status and menstrual history.
3. To study the relationship of carcinoma breast and use of hormonal pills.
4. To study the TNM stage at which the patients report to hospital and its relation to prognosis.
5. Relationship of Tumor size to prognosis

6. To study the relationship between the number of lymph nodes in the axilla in relation to prognosis.

7. Significance of histologic tumour type in relation to prognosis.

8. Relationship of histologic grade of tumour and prognosis.

9. Relationship of positive resection margins and prognosis.

10. Evaluation of hormone receptor status namely estrogen and progesterone receptor (ER, PR) in carcinoma breast, distribution of ER,PR receptors in different age groups,pre and post menopausal women and to identify the hormone receptor status in different histological types of breast carcinoma.

11. .To suggest the prognostic factors that can be assessed and routinely followed up in carcinoma breast

REVIEW OF LITERATURE

REVIEW OF LITERATURE

AGE

A few decades ago, 65 to 70 percent of breast cancer patients were women above 50 years. Women under 50, constituted only 30 to 35 percent.

However, in recent studies, by NCRP, breast cancer in women under 50 years of age has risen to 49 percent.

SEX

Male breast cancer constitute less than 1% of the total incidence with female to male ratio 1 : 0.01.

SOCIO ECONOMIC STATUS

According to world statistics, cancer breast was more common in women with higher socio economic status.

DIETARY FACTORS

Weight correlate with risk for carcinoma breast. However, studies have not demonstrated a causal relationship between high fat or cholestoral rich diet and carcinoma breast. Other dietary factors include Vitamins A, C, E and selenium which are thought to prevent cancer through antioxidant properties. Vitamin D decreases cell proliferation and

facilitates cell differentiation and its deficiency has been postulated to cause breast cancer.

There is increasing evidence that alcohol intake increases a person's chance of developing breast cancer. Relative risk for one unit of alcohol per day is 1.1 and increases to 1.3 to 1.5 if intake increases to two glasses a day.

SMOKING

Cigarette smoke produces mutations which have been demonstrated in breast fluid indicative of a direct carcinogenic effect. However, women smokers have a lower BMI, low levels of urine estrogen and early menopause, indirectly making them less susceptible to postmenopausal breast cancer**.**

IONIZING RADIATION

Women treated with radiotherapy for Hodgkins lymphoma and post partum mastitis are more prone to develop carcinoma breast. Women treated with irradiation under the age of 35 show an obvious increase in risk of developing carcinoma breast,and latent time of 10 to 15 years. Chest wall exposed to high amount of ionizing radiation increase risk of to develop carcinoma breast.

EXERCISE

Physical activity and exercise decrease the risk of cancer. This slight protective effect is more effective in premenopausal women, women with normal BMI and those who have had full term pregnancies.

ENVIRONMENTAL TOXINS

Environmental toxins like organochlorine pesticides are thought to have estrogenic effects on the human body. However, there are insufficient studies to come to a conclusion.

HORMONAL INFLUENCES:

Early menarchy, high frequency of ovulation, and high levels of urinary estrogens are associated with higher risk of carcinoma breast. Cancer cells secrete growth promoters (EGF, TGF, PDGF, FGF) and growth inhibitors (TGF – B). Studies show that estrogen induced secretion of autocrine factors and their interaction with hormone receptors expressed by tumour cells play a role in tumor progression.

Breast feeding, early age of first full term pregnancy, late menarche and early menopause are protective because of less estrogen exposure.

MENSTRUAL STATUS

For every year of delay in menarche, there is an apparent reduced risk of carcinoma breast by 20%. Women experiencing menopause after 55 years have twice risk of developing breast carcinoma compared to women attaining natural menopause before 45 years

PARITY

The relative risk of developing breast carcinoma breast in nulliparous women is 1.4.In anovulatory cycles there is more chance of developing carcinoma breast due to increased exposure to endogenous estrogen in the absence of progesterone.

AGE AT FIRST PREGNANCY

Women having first full term pregnancy before 25 years have 36% lesser incidence of carcinoma breast compared to nulligravida. This advantage is not afforded by women having late age of first parity. The terminal differentiaton of breast cells occurring in the first full term pregnancy reduce the likelihood of malignant transformation.

LACTATION

A reduction in risk of cancer have been documented but no such effect was detected in postmenopausal females.

OOPHERECTOMY

Oopherectomy below 40 years is protective.

ORAL CONTRACEPTIVES AND CANCER RISK Birth control pills recent users has slightly higher chance of to develop breast cancer.After stoppage of oc's 10 years OR more return to normal risk level those with oc's never used before.

HORMONE REPLACEMENT THERAPY AND CANCER RISK

The impact of HRT use on breast cancer risk varies depending upon BMI, breast density,race and ethinicity. Low or normal BMI with HRT use has high chance of developing breast cancer. However, HRT use among women with high BMI does not increase the risk.

DES USE AND CARCINOMA BREAST

DES use increased the possibility of developing carcinoma breast by 30%. However, this probability of chance return to normal over a period of time.

ABORTION AND BREAST CANCER

Spontaneous and induced abortions have no impact on risk of developing carcinoma breast.

PAST HISTORY OF CARCINOMA BREAST

For patients younger than 45, the risk for contralateral breast is five to six times that of general population. In absolute terms the actual risk varies between 1% per year in young patients to 0.2% in older patients.

HISTORY OF BENIGN BREAST DISORDER

Patients with history of proliferative disease or atypical ductal or lobular hyperplasia have increased risk of developing cancer breast. Relative risk of invasive cancer breast based on American college of pathologists consensus statement is as follows.

NO INCREASED RISK:

Fibroadenoma, fibroadenosis, hyperplasia, squamous, apocrinemetaplasia, micro, macrocysts, ductal ectasia, periductal mastitis has no increased risk of breast cancer

SLIGHTLY INCREASED RISK (1.5 – 2 TIMES)

Moderate or florid solid or papillary hyperplasia, papilloma with fibro vascular core has 1.5 to 2 times increased risk of carcinoma breast

MODERATELY INCREASED RISK

Atypical hyperplasia with positive family history has 20% risk to develop carcinoma breast at 15 years.Atypical hyperplasia of breast cumulative risk of breast cancer is 10% at 55 months

FAMILIAL BREAST CANCER:

Women with BRCA1and BRCA2 mutations have a 40 to 55% risk of developing carcinoma breast during life time. Carriers with previous history of breast cancer have a 5% per year increasing risk of developing carcinoma in the opposite breast.

BRCA1 situated in chromosome 17q and BRCA2 is situated in chromosome 13q Most of cases of cancer breast in families are due to expression of random mutations rather than due to genetic defect So prophylactic mastectomy is limited to cases of

1. Young patients whose first degree relative had bilateral premenopausal breast cancer.
2. Families with an established genetic defect.
3. Families with many members affected with a consistent pedigree.

Syndromes associated with multiple cancers which can run in families include

Lynch type II	–	cancer breast and ovary
Lifraumeni Syndrome	–	soft tissue sarcomas, brain tumor, leukaemia, melanoma and cancer breast.

RISK FACTOR FOR BREAST CANCER

MAJOR: Gender, Age, Family History, Personal History of contra lateral cancer breast, Benign proliferastive changes with atypia, Non invasive carcinoma

MINOR: Early menarche, obesity , Late menopause, Low dose radiation

CONTROVERSIAL RISK FACTORS

- Alcohol intake, Smoking, OCP / HRT, Abortion, Diet

CLINICAL PRESENTATION

Most women with carcinoma breast will present with one of the following.

1) Painless hard lump with retraction of nipple.
2) A lump, which may be recurrent after biopsies for benign disease

3) Lump in the contra lateral breast after breast cancer of opposite side
4) An axillary/supraclavicular node mass.
5) Symptoms due to metastatic disease.
6) Discharge from nipple-mostly are benign but may be the first sign. As disease advances locally there may be skin involvement with following features.
7) Peaud' orange:-

    Blockage of cutaneous lymphatics cause lymphatic oedema and leads to deepening of mouth of sweat gland and giving an orange skin appearance.
8) Frank ulceration of the overlying skin
9) Fixation to the chest wall. (cancer-en-cuirasse)

    The chest wall skin infiltrated with cancer has been likened to a coat described as cancer 'en-cuirasse' generally occurs in cases with local recurrences after mastectomy or occasionally following irradiation to the chest wall

PATHOLOGY

Pathological classification of carcinoma Breast (WHO)

(I) EPITHELIAL TUMOURS

1. Non-invasive
    - Intraductal ca <DCIS>
    - Lobular carcinoma in situ <LCIS>

II Invasive type

a) ductal carcinoma invasive type(not otherwise specified)

b) ductal carcinoma invasive type(predominant DCIS)

c) Mucinous

d) Medullary

e) Papillary

f) Lobular

g) Adenoid cystic

h) Secretory

i) Apocrine

j) Carcinoma with metaplasia

(i) Squamous

(ii) Spindle cell

(iii) Cartilaginous and osseous

(iv) Mixed

k) Others

LOBULAR

a) Invasive Lobular carcinoma

b) Combined Ductal and Lobular.

c) Paget's disease of Nipple.

(II) MIXED CONNECTIVE TISSUE AND EPITHELIAL TUMOURS

Fibroadenoma, carcinosarcoma,cystosarcomaphylloides

(III) MISCELLANEOUS TUMOURS

Soft tissue tumours, Skin Tumours, Tumours of Hemato poietic, lymphoid tissues

(IV) UNCLASSIFIED

(V) MAMMARY DYSPLASIAS

(VI) TUMOUR LIKE LESIONS

- Duct ectasia, Inflammatory pseudotumours, Hamartomas Gynaecomastia, Others

Table 1:- DISTRIBUTION OF HISTOLOGICAL TYPES OF BREAST CANCER

Invasive carcinoma	Percentage(%)
Invasive carcinoma NOS type	79
Lobular carcinoma	10
Tubular/cribriform carcinoma	6
Mucinous carcinoma	2
Medullary carcinoma	2
Papillary carcinoma	1
Metaplastic carcinoma	<1

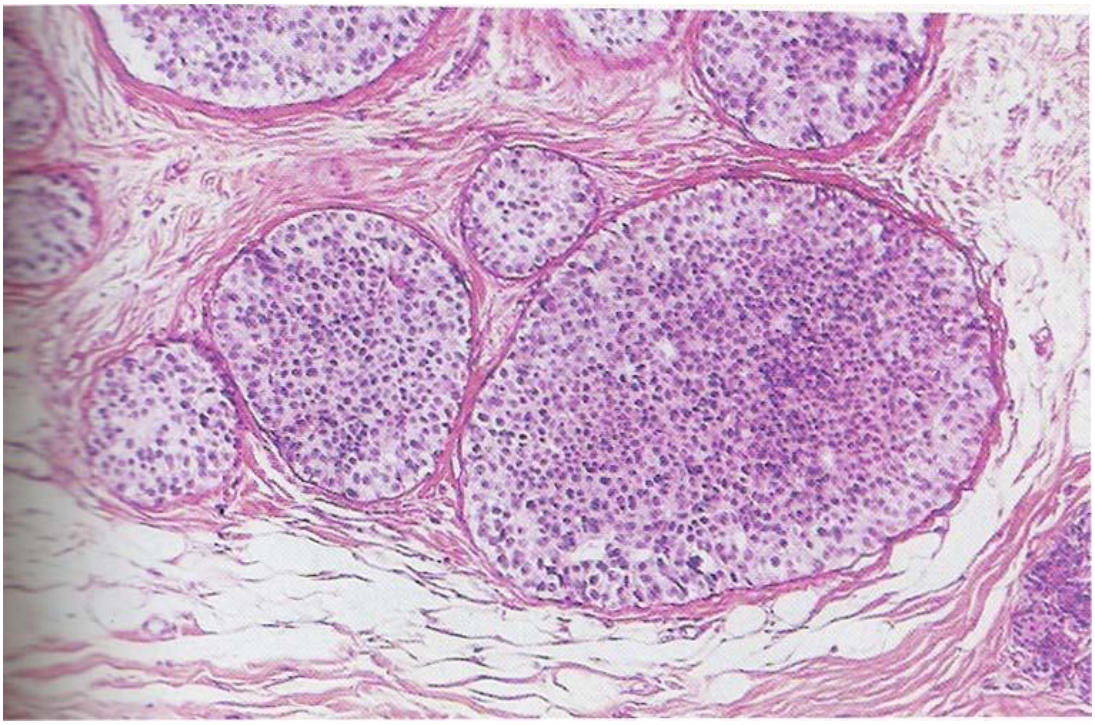


Figure 1: Ductal carcinoma in situ (DCIS)

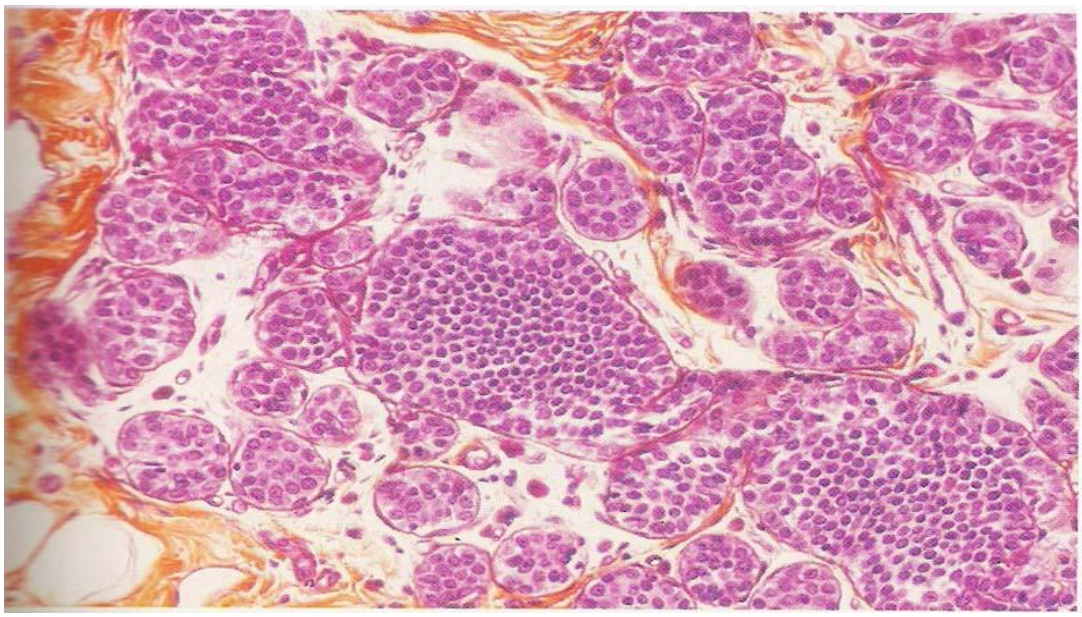


Figure 2: Lobular carcinoma in situ (LCIS)

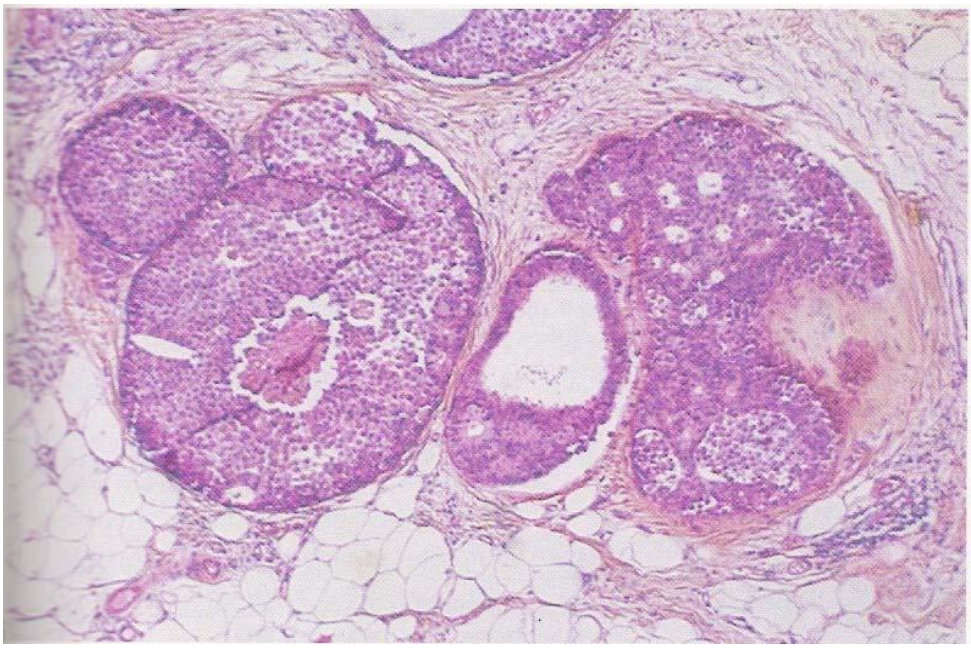


Figure 3: IDC/ Lobular carcinoma

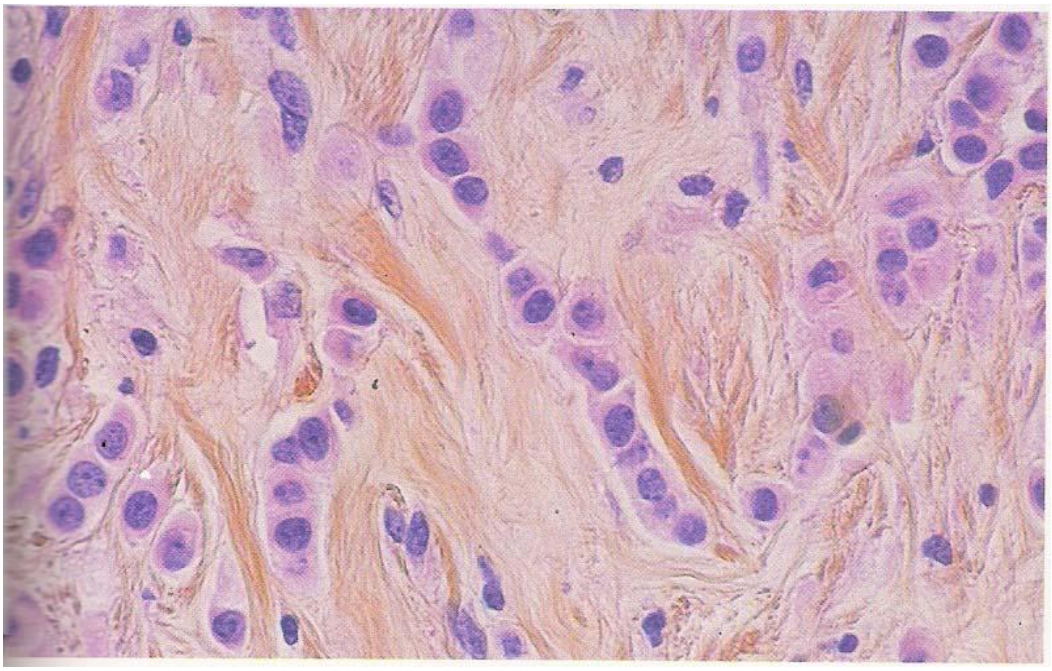


Figure 4: Invasive lobular carcinoma

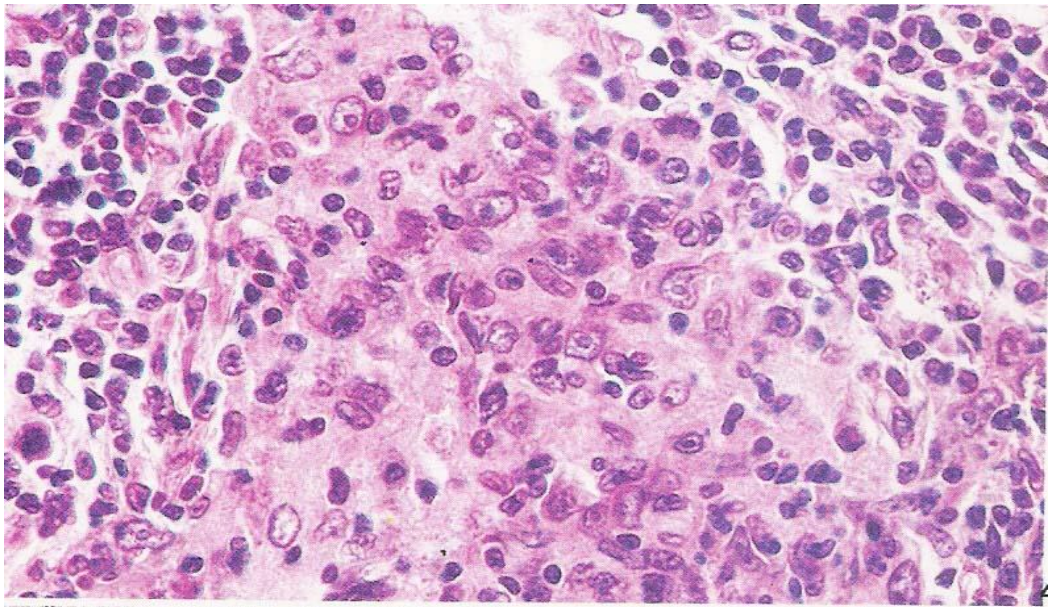


Figure 5: Medullary carcinoma of the breast

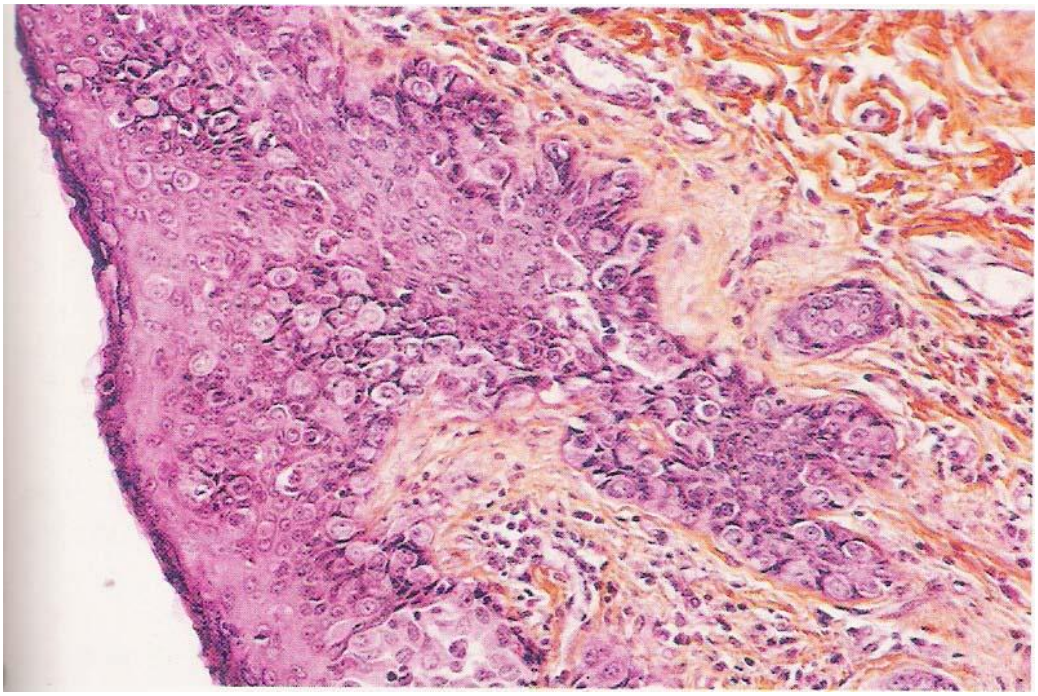


Figure 6: Paget's disease of the nipple

STAGING OF CANCER BREAST

The American Joint Committee on Cancer (AJCC) provides a strategy for grouping patients with respect to prognosis. This system of staging is called TNM classification of breast cancer.

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Intraductal carcinoma, lobular carcinoma in situ, or Paget disease of the nipple with no associated invasion of normal breast tissue

Tis (DCIS): Ductal carcinoma in situ

Tis (LCIS): Lobular carcinoma in situ

Tis (Paget): Paget disease of the nipple with no tumor. [Note: Paget disease associated with a tumor is classified according to the size ofthe tumor.]

T1: Tumor not larger than 2.0 cm in greatest dimension

T1mic: Microinvasion not larger than 0.1 cm 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 1.0 cm in greatest dimension

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

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

T3: Tumor larger than 5.0 cm in greatest dimension

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

T4a: Extension to chest wall, not including pectoralis muscle

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 T4a and T4b

T4d: Inflammatory carcinoma Regional lymph nodes (N)

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

N0: No regional lymph node metastasis

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

N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis

N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

N2b: Metastasis only in clinically apparent iipsilateral internal mammary nodes and in the absenceof clinically evident axillary lymph node metastasis

N3: Metastasis in ipsilateral infraclavicular lymphnode(s) with or without axillary lymph node involvement, or in clinically apparent ipsilateralinternal mammary lymph node(s) and in the presenceof clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a: Metastasis in ipsilateral infraclavicular lymph node(s)

N3b: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c: Metastasis in ipsilateral supraclavicular lymph node(s)

PATHOLOGIC CLASSIFICATION (PN)

Pnx - regional nodes cannot be assessed

Pno - no regional lymph node metastasis

Pn1 - metastasis to mobile ipsilateral axillary nodes

Pn1a - only micro metastasis (none > 0.2 cm)

Pn1b - metastasis to node > .2 cm

Pn1bi - metastasis to 1 – 3 lymph nodes (0.2 – 2 cm)

Pn1bii- metastasis to 4 or more nodes (0.2 – 2 cm)

Pn1biii- extension of tumour beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension

Pn1biv- metastasis to node > 2cm

Pn2 - metastasis to ipsilateral axillary nodes fixed to each other

Pn3 - metastasis to ipsilateral internal mammary nodes.

Distant metastasis (M)

MX: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

Table 2:- AJCC staging of breast cancer

Stage	Grouping		
0	T1s	No	Mo
1	T1	No	Mo
IIA	T0	N1	Mo
	T1	N1	Mo
	T2	N0	Mo
IIB	T2	N1	Mo
	T3	N0	Mo
IIIA	To	N2	Mo
	T1	N2	Mo
	T2	N2	Mo
	T3	N1	Mo
	T3	N2	Mo
IIIB	T4	N0	Mo
	T4	N1	Mo
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

MANCHESTER CLASSIFICATION

Stage I - Tumour confined to breast, skin involvement less than size of tumour

Stage II - Tumour confined to breast, with mobile palpable axillary nodes

Stage III - Tumour extends beyond breast tissue, skin involvement more than size of tumour, fixed to underlying fascia, pectoral muscle

Stage IV - Growth fixed to chest wall, satellite nodules, fixed axillary nodes, supraclavicular nodes, distant metastasis

SPREAD OF BREAST CANCER

Carcinoma breast spread by following means

1. Local spread within the breast

   By - direct infiltration along ducts
   - direct infiltration into breast parenchyma
   - Breast lymphatics

   Invades skin, pectoral muscles, chest wall

2. Regional spread

   Occurs to axillary and internal mammary nodes.
   Involvement of lymphnodes is an independent prognostic indicator

   No histological positive nodes - 80% 5 year survival
   1-3 histological positive nodes - 50% 5 year survival
   >4 histological positive nodes - 21% 5 year survival

LEVEL OF INVOLVEMENT

Level I - Lymphnodes lateral to border of pectoralis minor 65% 5 year survival rate

Level II - Lymphnodes deep to insertion of pectoralis minor 31% 5 year survival

Level III - Lymphnodes medial to pectoralis minor muscle.

Lymph passing through either axillary or internal mammary nodes reaches the jugulosubclavian venuous confluence. If this is obstructed, lymph passes in retrograde way to supraclavicular nodes.

Lymph channels also cross the diaphragm where they communicate with lymphatics of the liver.

3.Spread by blood stream

Metastasis occurs to bones, liver, lung, brain, adrenals, ovaries. The intercostal veins in addition to draining into azygos, communicate with vertebral veins, thus explaining predeliction to axial skeleton. The skeletal metastasis are usually osteolytic. Their order of frequency is to lumbar vertebra, femur, thoracic vertebra, rib, skull.

INVESTIGATIONS

OBJECTIVE

1. To confirm diagnosis
2. To know extent of disease
3. To use the information in predicting response to certain type of treatment.

A. **TO CONFIRM THE DIAGNOSIS** : FNAC / BIOPSY

FNAC - To be done in all palpable, suspicious masses

- Therapeutic in cysts.

FNAC PROCEDURE

The lump is immobilized and if possible the skin over the lesion is stretched and cleaned with spirit, so that the needle reaches the target easily.

The instrument is introduced into the lesion, then vacuum is created by about 2-3 ml, and the needle is moved back and forth 5-6 times.By this time in the hub of the needle will shows tissue, if not seen then needle is withdrawn from the target till the subcutaneous tissue and redirected in other direction to repeat the same procedure.

Then the syringe is withdrawn filled with air and needle is brought in contact with the slide and one drop of tissue is deposited on one, tissue is spread with cover slip or a haematological smear is prepared if blood or aspirate is more.

Following the air dried preparation slide is stained with wrights/wrights Giemsa/May Grunnwald Giemsa. If not air-dried it is immediately fixed with 95% alcohol and staining is done with H&E stain/with pap stain.

Combination of physical examination, mammography and FNAC will produce a diagnostic accuracy approaching 100%. FNAC is done in palpable mass, mass on mammogram. Sensitivity of test is approximately 80%, false negative varies b/w 2-10%. Axillary US – FNAC reliably detect the node metastasis arising from both primary invasive ductal and lobular tumours.

Advantages:

Less expensive

Less invasive

Complications of FNAC:

Growing out of tumor along needle tract, which is less in case of calibre < 20 gauze.

Acute mastitis

Pneumothorax

Haematomas

Interval of weeks required b/w FNAC and mammography as they form hematomas and result in false positive mammographic studies.

Sensitivity of breast FNAC performed on palpable masses is reported to be 90 percent. The specificity and predictive value of breast FNAC approaches 100 percent because false positive results are rare.

BIOPSY

- Core needle biopsy
- Open biopsy
    - Excisional biopsy
    - Incisional biopsy

Can be used for histological grading and ER / PR assay

CORE NEEDLE DIRECTED BIOPSY

Large bore needles are often used
More invasive
Better accuracy
Can perform receptor determinations
Can be done stereotatically
USG-guided core biopsy used for preoperative axillary lymph node staging

OPEN BIOPSY

EXCISION

Removal of all evidence of disease with rim of normal breast tissue.

INCISIONAL

For larger not amenable to excisional biopsy, incisional biopsy can be done. Usually one ml of tumor is required for receptor status study.

NONPALPABLE MAMMOGRAM ABNORMALITY

1. Needle localized core biopsy under mammographic guidance.
2. Needle core biopsy directed into lesion under stereo tactic control
3. USG guided percutaneous biopsy can be done.

Image directed needle localization done under local anesthesia. Wire and hook passed and positioned in area of calcification density or suspicious area. Specimen excised with the wire and radiograph taken to confirm calcifications present in biopsy specimen.

IMAGING TECHNIQUES

MAMMOGRAPHY

Bilateral mammography is useful as a screening and diagnostic tool. In screening mammography, imaging is done in two views.

Medio lateral oblique (MLO)

Craniocaudal (CC)

MLO is the most effective single view because it includes the greatest among breast tissue and is the only whole breast view to include view to include all of the upper-outer quadrant and axillary tail.

The medial aspect of the breast is better visualised through CC view. It also offers greater detail. But because of lower specificity of single view screening most radiologists believe that screening examination should include both MLO and CC views.

Breast compression is a must in mammography because

- Holds breast still.
- Brings objects closer to film.
- Separates overlapping tissue that might obscure underlying lesions.
- Decreases radiation dose of mammography.

Disadvantages of mammography

- Pain
- Uncomfortable due to compression of breast

Mammography is done in the following individuals for diagnosis and as a part of screening.

- Women between 40-49 years-studies should be screened every 12 to 24 months.

- For those>50 years annual mammogram.
- For women younger than 50 years of age who are in high-risk group, (i, e. those with previous/family h/o breast ca).

DIAGNOSTIC MAMMOGRAPHY

Also called consultative or problem solving. It is indicated when there are clinical findings such as palpable lump or abnormal results on a screening examination.

Capabilities

- Can define the nature of many breast abnormalities.
- Can identify unexpected malignancy.
- Can identify multi focal disease.

Indication of Diagnostic mammography;

- Over 30 years
- With/without lump before performing biopsy.
- Detect unexpected lesions of ipsilateral/contralateral breast.
- Identifying and extensive intraductal component of a palpable invasive
- carcinoma.
- To detect carcinoma in contra lateral breast after mastectomy.

- After surgery before radiotherapy to document all the calcification were removed
- At 6 months interval for 2 years after lumpectomy in later years.

Normal findings

Four categories

1. Breast entirely fat.
2. Scattered fibro glandular densities.
3. Breast tissue is heterogenetically dense.
4. Extremely dense.

Characteristics of malignant breast lesions

Microcalcification

Irregular speculation

Branching calcification

Clustered calcification

Architectural distortion

Loss of symmetry

BENIGN BREAST LESIONS

CHARACTERISTCS

Macrocalcification

Smooth, round lesion

Radioopaque or radiolucent lesions

MAMMOGRAM

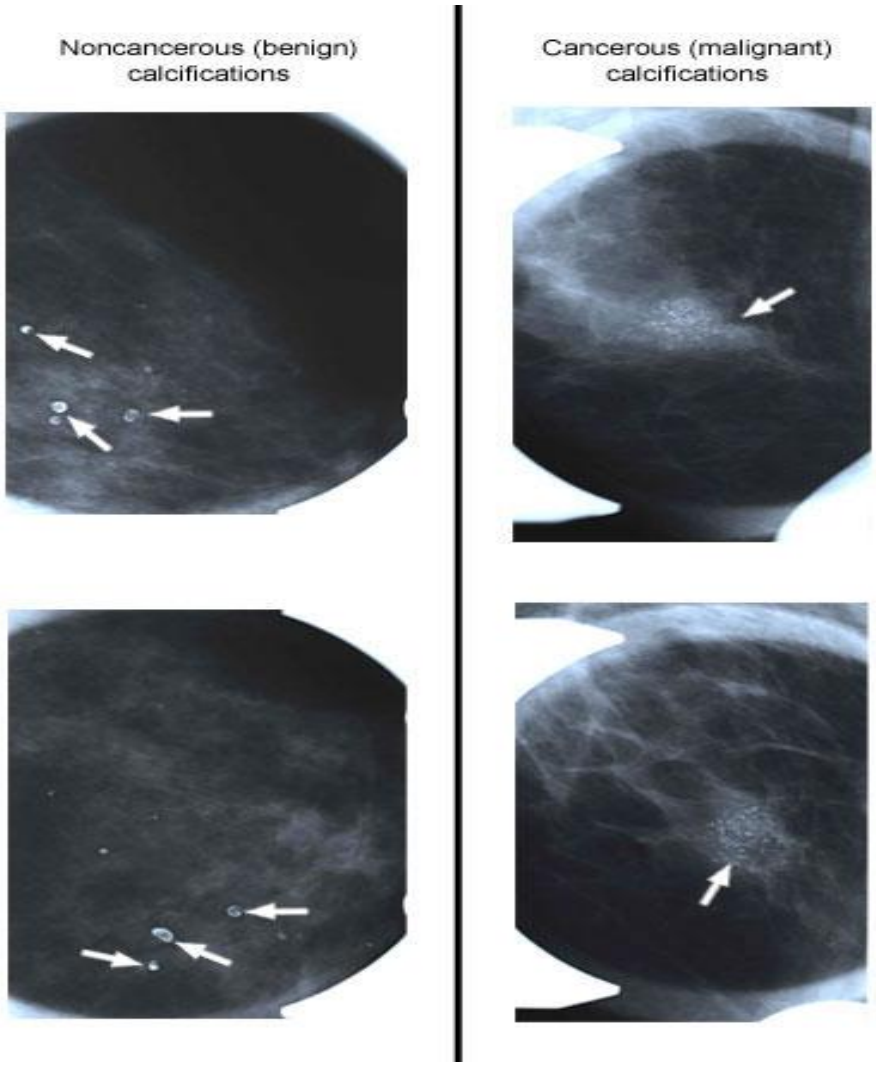


Figure 7: Mammogram showing calcification in benign and malignant breast cancer

DIGITAL MAMMOGRAPHY

This type records the radiography image electronically in a digital format rather than a film.

It is left in computer and is displayed on fluorescent monitor

B TO KNOW ANATOMICAL EXTENT OF THE DISEASE

1 X RAY CHEST

To rule out pulmonary metastasis

2. USG ABDOMEN

Used to investigate masses of the breast in young women with dense breasts in whom mammogram interpretation is difficult.

Distinguish cysts from solid lesion.

Used to localise impalpable areas of breast pathology.

Although USG is not efficacious as a screening modality, combined mammography and USG pick up more cancers than mammography alone.

To rule out liver metastasis, free fluid retroperitoneal lymphadenopathy

3. BONE SCAN

In stage I and II incidence of skeletal metastasis is 2-6%

In stage III it is 14%

Bone scan has a lead of 6-18 months over radiograph in demonstrating metastasis.

Most bony metastasis appear 20 months to 4 years after mastectomy.

Bone scan is indicated in higher stage of disease, in patients who have bone pains, raised level of serum alkaline phosphatase, positive skeletal radiogram, palpable regional or metastatic disease.

This investigation can identify occult osseous metastases before they become radiologically detectable. Bone seeking isotopes such as strontium 85 and technetium 99m are generally used.

(ii) Skeletal survey:

Usually done in bone scan is positive. All cases of skeletal pain must be evaluated.

4. Liver studies

Abnormalities in levels of serum enzymes such as alkaline phosphatase, lactic dehydrogenase and SGOT are suggestive of liver metastasis. An isotope scan of liver using sulphur colloid labelled 99mTechnitium will give valuable information in doubtful cases, supporting clinical and radiological studies. The ultrasound may help in detecting the secondary involvement in liver.

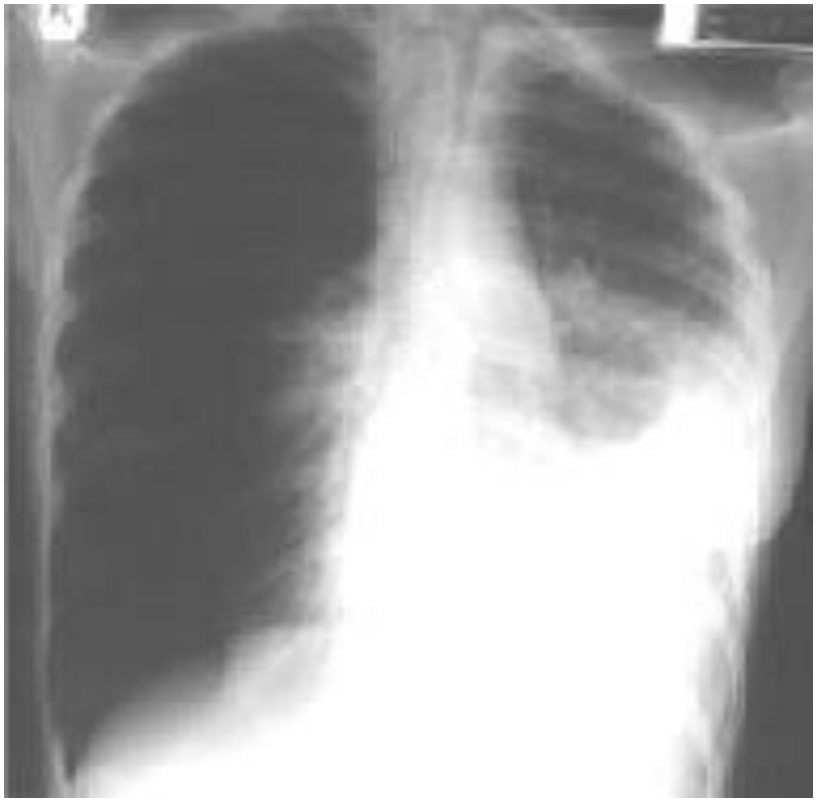


Figure 8: X-ray lung metastases

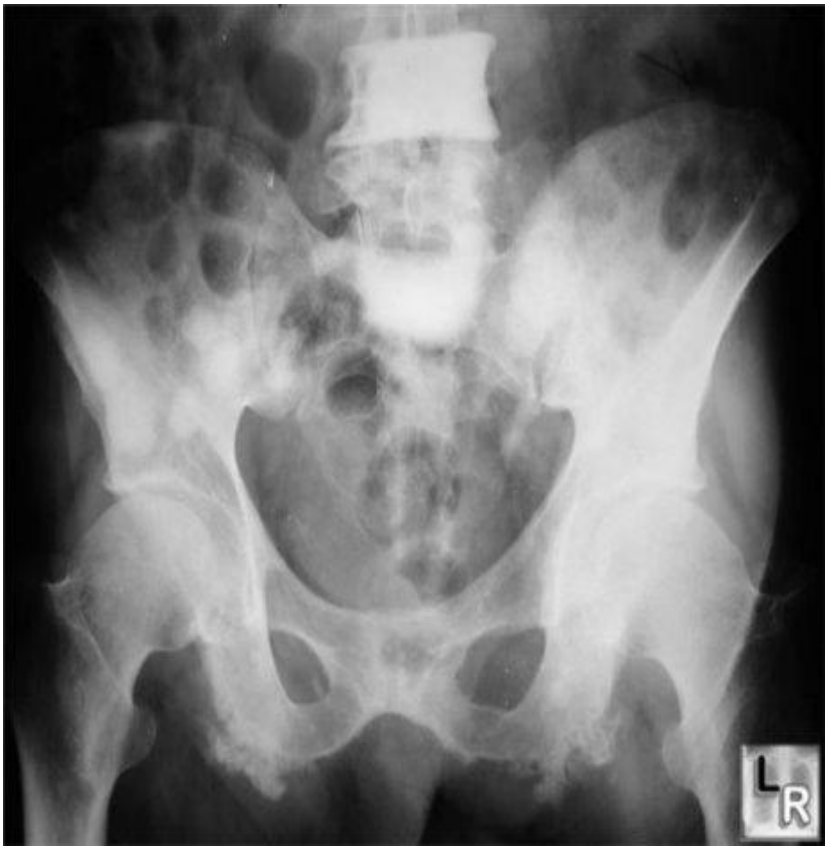


Figure 9: X-ray bone metastases

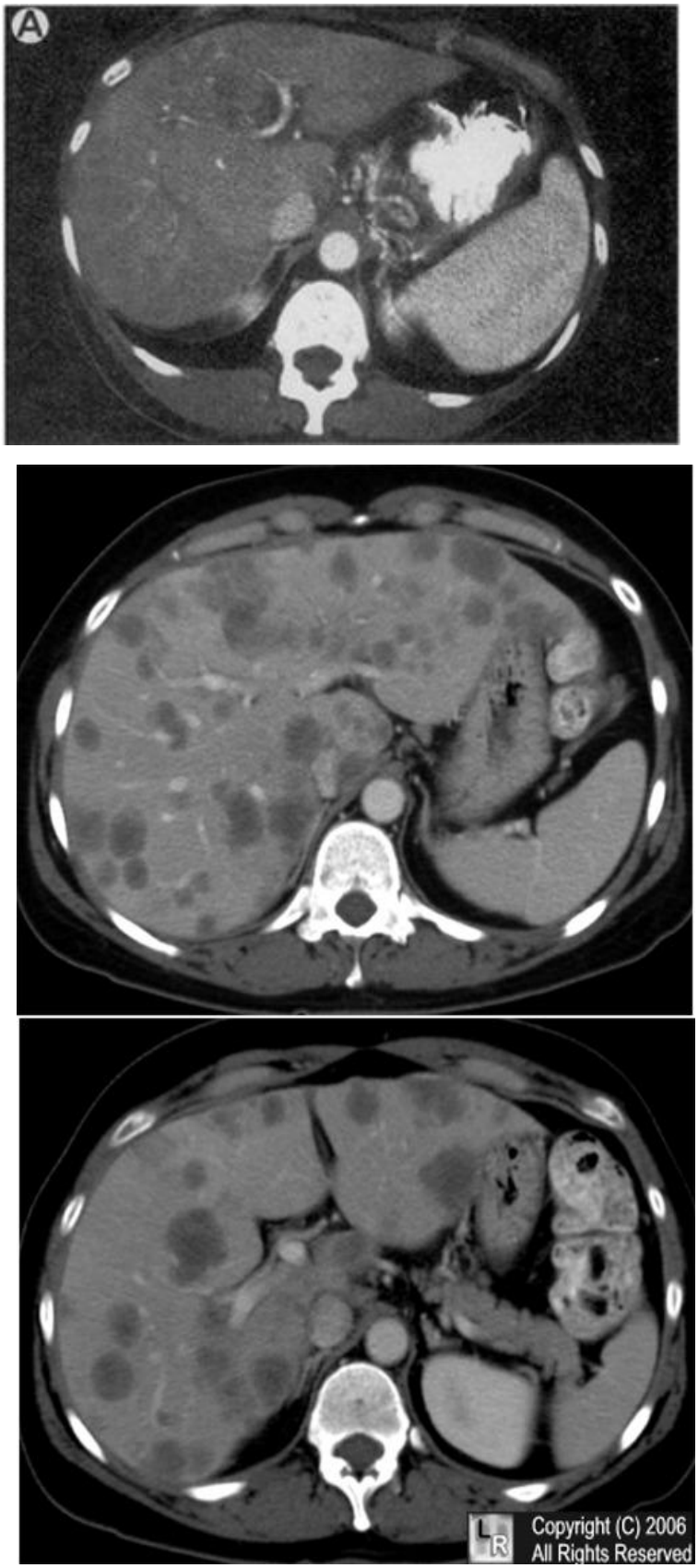


Figure 10: CT scan showing liver metastasis

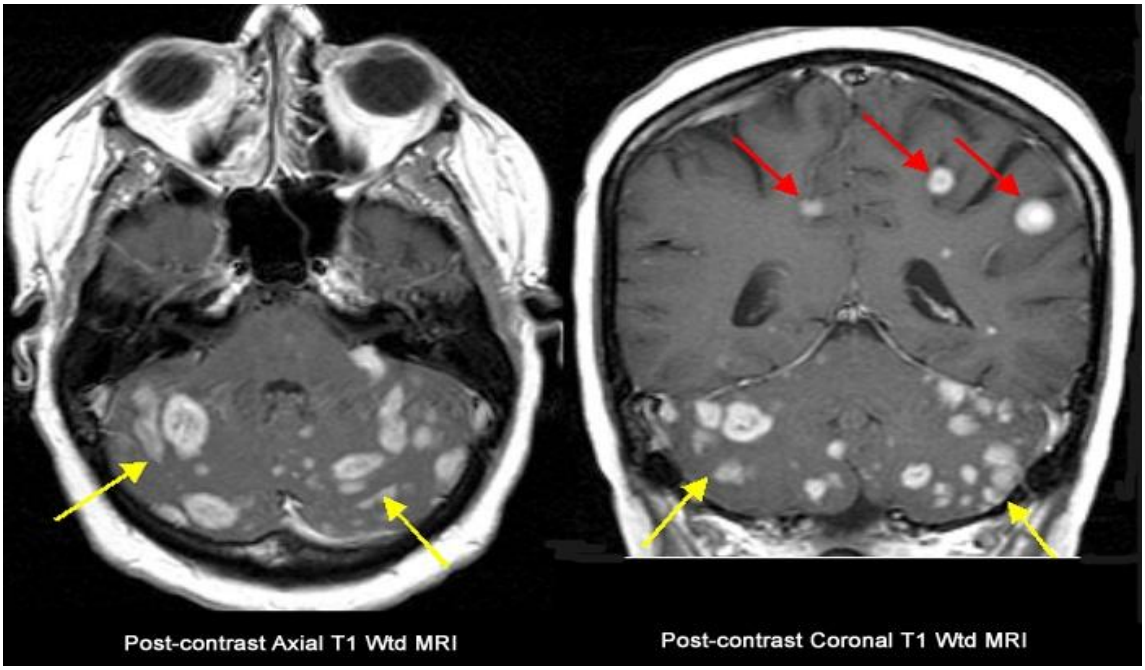


Figure 11: MRI scan showing multiple metastases to the brain

5. CAT and MRI

They aid in evaluating axilla, mediastinum, supraclavicular area for adenopathy.

MRI helps to evaluate patients after prosthetic implants. To diagnose recurrence after surgery. It is often difficult to predict whether it is local recurrence or fibrosis or scarring. In MRI the scar tissue will not be enhanced with contrast media whereas the tumour (recurrence) is seen as enhanced area. It is a highly effective screening tool in women with high risk of breast cancers having positive family history.It is less useful than ultrasound in the management axilla both in primary breast disease and recurrent disease

C.ER, PR – AS BASIS FOR RESPONSE TO HORMONAL THERAPY:

As a prognostic factor, ER and/or PR positivity can be correlated withdecreased death rate and an improved survival when compared with ER, PR negative tumours[52]. It has been documented that 5-year overall survival is 83% in ER+/PR+ patients but it is reduced to 69% in the receptor negative individuals**.**

When patients were treated with tamoxifen for five years, it reduced the probability of developing tumour in the opposite breast by 47%. It was not beneficial to the women with the receptor-negative tumours more selective breast cancer treatments.

Breast cancer-related deaths havemarkedly decreased with the discovery of endocrine agents (e.g. tamoxifen and aromatase inhibitors) that selectively target ER- expressing breast tumours. This serves as a motivation to continue to define potential druggable targets for hormone receptor- and HER2-negative(triple-negative) breast cancers that do not respond to endocrine therapies or totrastuzumab and for which cytotoxic chemotherapy is the only systemic treatmentoption. In-depth characterization of breast tumours is imperative for the development of targeted therapies.

Hormone receptor status as determined by immunohistochemistry correlated with therapy regimens like chemotherapy, hormone therapy.

All tissues should be analyzed for receptors whenever adequate volumes are available more than 60 percent of ER positive tumours will respond to adjunctive endocrine therapy

Two types of assays are used to quantitate ERS and PRS

Quantitative analysis of ERS and PRS can be done through two different types of assays.

I. Radiolabelled ligand binding assays are more accurate than immunohistochemical assays because of rigorous validation and standardization procedures used for the former. An example is the Dextran coated charcoal assay. These assays were done on tumor cytosols extracted from tumor specimen and hence the unit of such assays is femtomoles per receptor protein per milligram of total cytosol protein (fmol/mg). The results may range from 3 to 20 Fmol/mg. These assays require large specimens which should be immediately frozen in liquid nitrogen for accurate results. The presence of estrogen/tamoxifen in the sampled specimen alters the results of this assay.

Immunohistochemical assays and enzyme immunoassays assess ER, PR status by monoclonal antibody methods. They have some advantages

over radiolabelled ligand assays in not requiring a large specimen sample. They can be performed even on archived tissue (formalin fixed and paraffin embedded), frozen sections,etc. The presence of estrogen and tamoxifen will not alter the results because these tests quantitate the total proteins.

The Immunohistochemistry assay has substituted the older methods like ligand binding assay and is nowadays preferred as the mode of choice for analysing the hormone receptors. It estimates the proportion of cancer cells expressing the positivity. To a greater extent, there is a notification that variations in the procedures and techniques of the assay used could make alterations in the results and interpretations. The changes can also be due to the study group of patients with distinct and modified clinical stages and aggressive phenotypes of carcinomas.

The outcome will also be influenced by inadequate fixation. So the specimens should be obtained immediately after the surgical procedures. The commonly used fixatives are formal-saline and neutral buffered formalin. The fixation should be quick and the fixative should be evenly distributed throughout the specimen

A hybrid block which encompasses distinct tissues containing areas abundant with receptors admixed with receptor deplete and negative tissues should be used. It is likely that the tumour tissues that should be evaluated possess normal appreciable breast parenchyma to serve the

purpose of positive internal control. The process should be repeated when difficulties are encountered in the staining of normal parenchymal tissue. The type and grade of the tumour should also be considered so that they both have been proved to have impact on the interpretation of inferences. This is supported by the fact that the tumours that are well differentiated are highly improbable to yield negative results

Scoring system:

Various respective scoring methods have been imparted in the literature. The positivity should be depicted by taking in to account the staining in the nuclei of the tumour cell. It is important to estimate the entire invasive element of the tumour. The importance of establishing a definite scoring system is to make certain that homogeneity should exist between various laboratories. On considering this issue retrospectively, it is essential to bring emphasis to Allred score assigned by Craig Allred few years ago. In 2010, Asim et al added an adjunct for widespread use of this method nowadays and supplemented by the study report that the sensitivity as well as the specificity of the Allred score was very high in contrast to other methods.The score is allocated by the estimation of two scores, first is the proportion score from 0 to 1, given by analysing the percentage of nuclei in the cells, having taken the stain and secondly, the intensity score from 0 to 1 given by exploring the strength and magnitude

of staining as negative, weak, average and intense. Both the scores are added to give the total score.

Various rational motives for identifying both the hormone receptor positivity and analysing the intensity of the reaction of breast carcinomas are as follows:

1. Several reviewed facts and materials about the evaluation of both receptors are accounted to the management of carcinomas with metastasis in the view of, greater the percentage and intensity of positivity of tumour cells, then higher the possibility of better outcome and effects to endocrine therapy.
2. Virtually, there would not be any anticipation of response in individuals with breast carcinomas which do not exhibit the staining pattern.
3. The consideration of progesterone receptor along with estrogen receptor is ideal and worth. The tumours that have very low ER positivity but high PR positivity could still respond to hormonal treatment is the contributory evidence provided by the progesterone receptor.
4. Even though the degree of staining is low in the tumours scoring 2 or less than 2, the adjuvant endocrine therapy has been proved beneficial in those patients too. This highlights and foregrounds that it is necessary to develop sensitive and standardised

procedures which have the ability to trace out these low receptor levels.

HER2 / NEU. STATUS

IHC methods are used to semiquantitively assess HER2/neu status through the use of monoclonal antibodies.

Scoring of HER2 / neu over expression by DAKO Hercep test.

- Score 3+ -positive - Complete intense staining in more than 30% of tumour cells
- Score 2+ -equivocal non uniform or weak complete membrane staining showing circumferential distribution in atleast 10% of cells or intense complete staining in less than 30% cells
- Score 1- negative- Faintly perceptible membrane staining in any proportion of tumour cells or complete membrane staining of <10%
- Score 0- no staining observed

  Gene amplification detected through fluorescence in site hybridization (FISH) shows high specificity and is 82% concordant with immunohistochemical assays.

HER2 / neu over expression is associated with poor prognosis Studies show that taxanes are highly efficacious in tumors with

overexpression of HER2 in relation to HER2 negative tumors. The relative risks of recurrence in the two groups are 65% and 35% respectively.

MANAGEMENT

In the management of carcinoma breast, cure should take precedence over cosmesis without disregarding it. Management falls into 2 main categories.

- Loco regional control
- Systemic

I. SURGICAL MANAGEMENT

A century ago William Hallstead published his first report on radical mastectomy for control of breast cancer. At that time this was considered as appropriate solution to the problem. Later review showed that long term rates were not changed despite dramatic reduction in local recurrence rate.

Fisher stated that venous lymphatic communication exist and that particles injected into lymphatic drainage of breast rapidly appeared in venous circulation. Hence the disease was considered to be systemic long before clinical diagnosis was made. Fisher hypothesis indicated that variation in local and regional treatment were unlikely to influence long

term cure. A systemic therapy would be necessary from the beginning which led to clinical trials of adjuvant systemic therapy

Different surgical procedures available are

1) RADICAL MASTECTOMY

Here the breast, pectoralis major, regional lymphnodes along axilla upto costoclavicular ligament are resected.

2) EXTENDED RADICAL MASTECTOMY

Here the breast, pectoralis major, regional lymphnodes along axilla upto costoclavicular ligament are resected with internal mammary nodes are also removed.

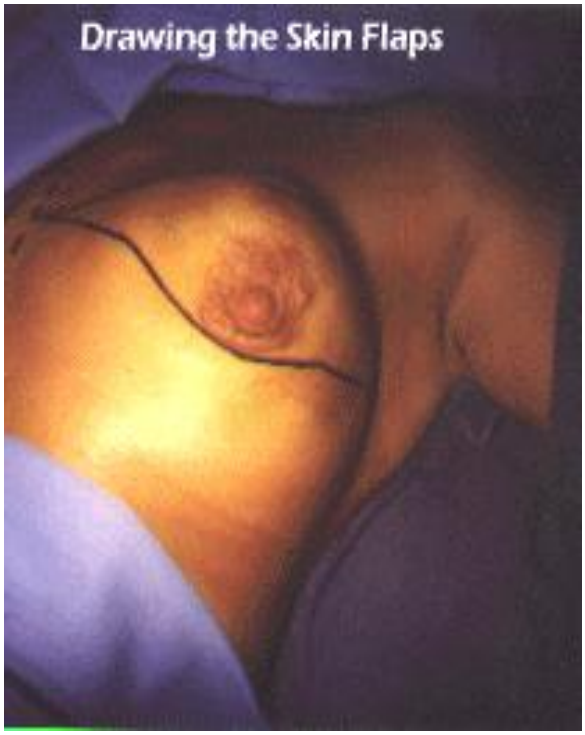
3) MODIFIED RADICAL MASTECTOMY

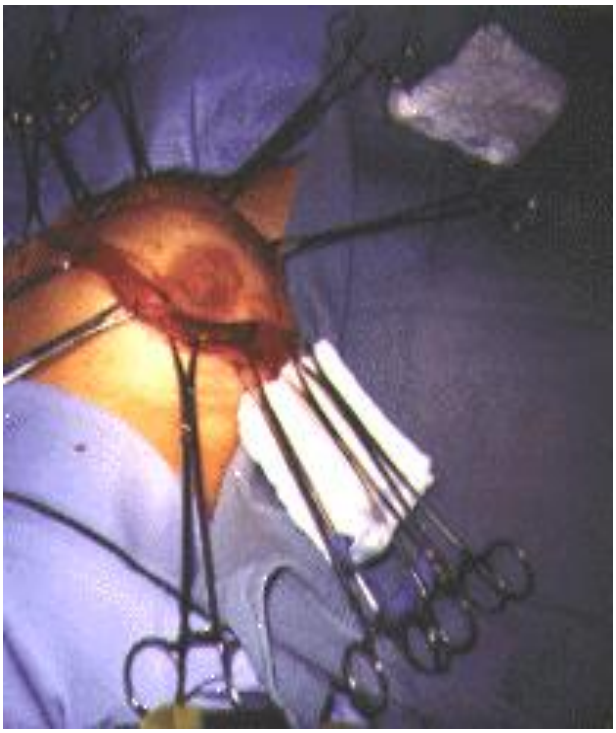
In modified radical mastectomy, the pectoralis major muscle is left intact .

(i) Patey's Modification Pectoralis minor is removed and level I, II, III Lymph nodes are removed.

(ii) Scalon's Modification Pectoralis minor divided level I, I, III Lymph nodes are removed.

(iii) Auchincloss Modification Pectoralis Minor is left intact level I / II nodes are only removed.





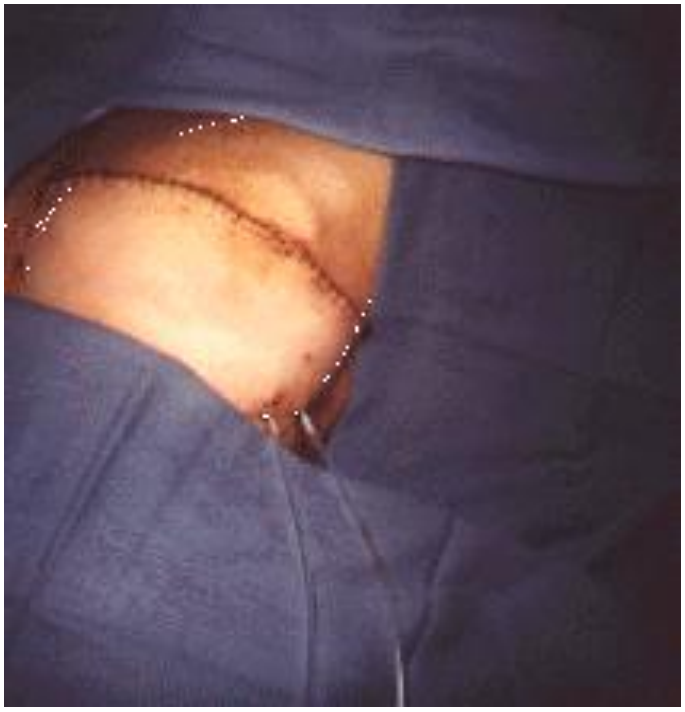


Figure 12: Modified radical mastectomy

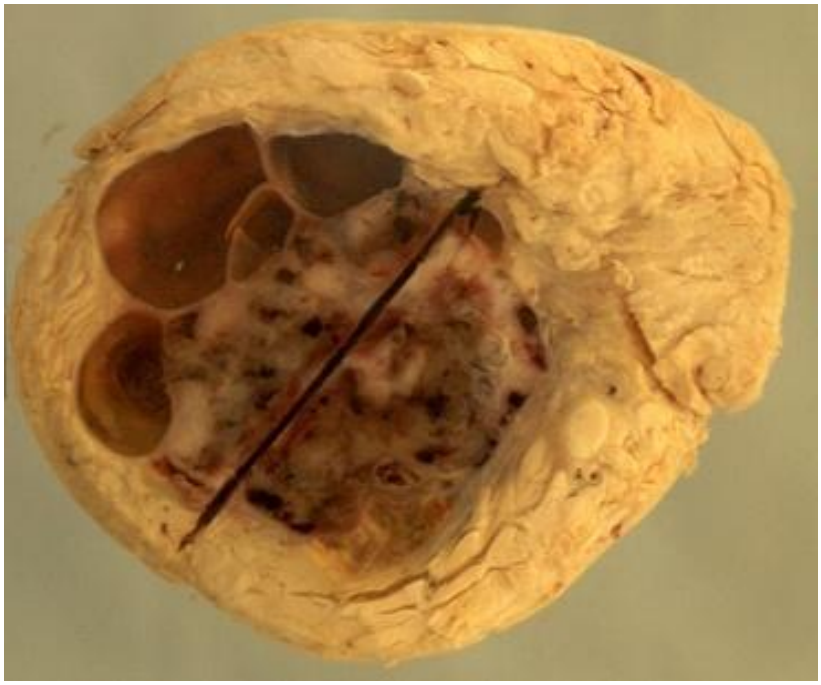


Figure 13: Pathological specimen of carcinoma breast

4) BREAST CONSERVING SURGERIES

i. Wide local excision (lympectomy, tylectomy, segmental or partial mastectomy)

ii. Lump with 1 cm margin of grossly normal breast tissue is removed

iii. Quadrantectomy

The quadrant of breast containing the lesion is removed.

5) SKIN SPARING MASTECTOMY

Skin envelope is preserved while removing nipple areola complex, all underlying breast & axillary contents followed by immediate reconstruction with TRAM Flap or Expandable implants with small graft at areola site.

6) SIMPLE OR TOTAL MASTECTOMY

Breast, Axillary tail of Spence and lymphnodes along it (low anterior group) are removed. This involves the complete removal of all mammary gland including the nipple and areola. Elliptical/transverse incision is put and surrounding skin is excised depending upon the site and size of the tumor or ulceration. Skin flaps are raised to separate from the underlying gland and mammary gland is swept off laterally from underlying pectoralis major muscle fibers.

AXILLARY DISSECTION

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

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

It is recommended for all patients with invasive cancer, as pathological staging is most importmant prognostic factor with survival rate being related to

axillary node status.

Advantages of complete axillary LN dissection are as follows

- No risk of under staging the disease, when level 1 and 2 are done risk of under staging the disease is at least 2.6%.
- No additional surgical treatment required if the axilla is pathologically positive
- Complete dissection minimizes the risk of local recurrence.
- It is widely accepted that involvement of axillary nodes occurs in a progressive manner from lower to higher level. But when level 1 node are positive chances of higher level being positive varies from 22-42.9% and node positivity increases with tumor size. .

Axillary lymph node status is the most important prognostic factor of breast cancer. The number of lymph nodes retrieved in ALND during surgery varies considerably. A minimum of 10 nodes is required for reliable lymph node staging.

Complications of axillary lymph node dissection

Lymphedema, seroma, frozen shoulder, chronic pain syndrome/ neuropathies and thrombophlebitis of the axillary vein.

The axillary lymphnodes should be staged to aid in determining prognosis and therapy.

Removal of Lymphnode level I and II for assessment while reducing morbidity from the procedure can be adopted.

Factors identified as predictors of axillary lymph node metastasis were tumour size, grade and tumor palpability.

Steele et al reported sampling 3 or 4 ALNS provides accurate assessment of axilla with false negative rate of 10%

3 methods used are:

1) Axillary lymph node dissection
2) Axillary node sampling.
3) Sentinel lymph node biopsy

Sentinel node is the first node involved in tumour metastasis. Identification of SLN done by injecting sulfur colloid labeled with technetium, vital blue dye or both in 92-98% of patients. Biopsy of sentinel lymph node and complete dissection of axillary lymph node have been reported to have a 97.5 to 100% concordance.

BREAST RECONSTRUCTION

It is an integral part of management of breast cancer.

It may either be done immediately following surgery or after 6 months. Various techniques available are

1) Implants or expanders.
2) Autologous tissue
    (i) pedicled flap
    (ii) free flap.
3) Combination of both.

SUB PECTORAL IMPLANTS

Involves placement of a tissue expander subpectorally and creating the breast mound by repeated expansion introducting saline and later placement by a permanent implant. Modern breast implants are manufactured with an outer shell of polydimethyl siloxane (silicone) and contains a filler material such as silicone gel to give its volume. The disadvantages of implants are

1) Leakage of silicone gel into surrounding tissue and 2) Capsule Contracture.

AUTOLOGOUS FLAPS

They are more complex, expensive procedures requiring comprehensive training and experience.

TRAM FLAP(Transverse rectus abdominis myocutaneous)

TRAM flap is the most commonly performed autogenous reconstructive procedure. Although first suggested in 1979 by Robbins, Hatrampf and coworkers popularized the TRAM flap in 1983. This flap can be harvested as a single or double pedicle flap, utilizing the deep superior epigastric blood supply.

COMPLICATIONS

Partial/complete flap necrosis

Donor site complications can include

abdominal wall laxity; diastases,

abdominal skin necrosis, umbilical malposition, seroma, severe pain.

LD Myocutaneous flap

Latissimus dorsi is a flat, triangular muscle that originates from the spines of the lumbar and sacral vertebrae and inserts into the intertubular groove of the humerus. Its blood supply comes from the thoracodorsal artery and from multiple segmental perforators of the lumbar inter-costal arteries.

This flap is ideally suited for single stage reconstruction for women with small breasts and a moderate degree of breast ptosis. If the breast

volume requirements exceed the available tissue from this region, a breast implant can be used to augment the reconstruction.

The LD myocutaneous flap not only increases the amount of tissue between the breast flaps and the prosthesisbut also provides well-vascuralised muscle that can reduce the amount of caspsular contracture.

II. RADIOTHERAPY

It is now proved that radiation therapy not only improves local control of breast cancer but along with surgery and chemotherapy improves the probability of survival.

A number of studies have examined the value of adding postoperative RT to adjuvant chemotherapy and important ones are.

1) British Columbia trial

2) Denmark trial.

In both trials, RT resulted in large reduction in local recurrence. The 7 years survival rate for premenopausal patients was 62% with radiotherapy compared to 55% without radiotherapy.

Two main types of techniques

a) Whole breast irradiation

Done following breast conservation surgery.

b) Loco regional technique

Breast or chest wall, ipsilateral axilla, supra and infra clavicular lymph nodes region, internal mammary chain of nodes are irradiated.

POST OPERATIVE RADIOTHERAPY

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

Breast conserving treatment included removal of bulk of the tumor surgically and to use moderate dose of radiation to eradicate any residual cancer.

Careful observation of treated patient determined that best results are achieved by delivering relatively small doses of radiation daily over extended period.

The use of breast irradiation after breast conservation surgery is associated with a large reduction in the rate of local recurrence.

For operable stage II, the post op administration of chemotherapy and radiotherapy resulted in better local control and higher survival rate than the use of either adjuvant treatment alone

INDICATIONS FOR CHEST WALL IRRADIATION

1) Positive margin or gross residual disease.
2) T3 tumour, especially with positive node.

3) T4 tumour

4) Four or more positive axillary lymph nodes.

5) Close surgical margin (< 2cm)

6) Following breast conservation therapy.

INDICATIONS FOR AXILLARY IRRADIATION

1) 4 or more axillary lymph nodes positive.

2) Extra nodal disease.

3) Inadequate axillary sampling.

4) More that 50% of lymph nodes positive.

PALLIATIVE RADIOTHERAPY

Radiation therapy is effective in relief or avoidance of symptoms of metastasis to many different anatomic sites. The most common problem is metastases to bone causing pain or threatening structural integrity. Using a schedule of 9 Gy in a single increment to 30 Gy in 10 increments reported a total response rate of 82%. For patients suffering pain from wide spread metastases, a single hemi body irradiation of 6Gy to upper body and 8 to 10 Gy to lower body results in 80% to 100% response in terms of reduction in pain. In case of locally advanced carcinoma moderate total doses of 45 to 50 Gy in 25 fractions in 5 weeks plus a

boost of 10 to 15 Gy to high risk sites used pre and post operatively with total mastectomy gives good results and least sequel.

OPTIMAL RADIATION THERAPY TECHNIQUE AND DOSES.

Following excision of primary tumour and lymph node dissection, radiation is delivered to entire breast for a total of 4500 to 5000 CGY over 4.5 to 5.5 weeks 100 – 200 CGY / day followed by supplemental boost of 1000 to 1600 CGY.

SIDE EFFECTS

- Fatigue, Skin erythema, Dry and moist desquamation, Arm Edema
- Shoulder discomfort
- Progressive Parasthesia / weakness of arm, hands
- Radiation pneumonitis
- Radiation induced soft tissue sarcoma, osteosarcoma angiosarcoma.
- Bronchogenic carcinoma in ipsilateral lung in smokers.

III. CHEMOTHERAPY

In 1960s first modern trails of combination chemotherapy were initiated for breast cancer management. First adjuvant chemotherapy was

administered to women with positive nodes; later in 1980s the use was extended to node negative women as well.

Combination chemotherapy has been more effective than single agent therapy, single agents generally achieve partial remission of 10% - 30%, and combination of three or more agents repeated in cycles could achieve 50% - 80% response without additive toxicity. The therapeutic intervals in combination therapy that allow normal rapidly dividing stem cell to recover can explain the lack of toxicity of these regimen.

Aims of Primary Systemic Therapy (PST)

1. Reduce the risk of disease recurrence by treating potential areas of distant microscopic metastatic disease.
2. To reduce breast and lymph node tumor burden.
3. To improve surgical respectability.
4. Provide early information or surrogate, markers for long term outcome.

Chemotherapy is given to all premenopausal women with positive nodes.

Chemotherapy is highly effective in keeping patients disease free for a longer period after treatment and increase the survival rates in premenopausal patients having stageII carcinoma breast. It is started once surgical wound is healed.

INDICATIONS

1) Premenopausal patients with positive nodes.
2) Patients who test negative for estrogen and progesterone receptors
3) Patients presenting with visceral metastasis

Commonly used Chemotherapeutic agents in breast cancer

Table 3:- Chemotherapeutic agents in breast cancer

Regimen	**Dose / schedule**	**Interval days**	**Cycles**
CMF (standard) Cyclophosphomide Methotrexate 5-flurouracil	100mg / m^2 /d po for 14 day 40mg / m^2 / d IV days 1 and 8 600mg / m^2 /d IV days 1 an 8	28	6
CMF (IV, node negative patients) Cyclophosphomide methotrexate 5-flurouracil	 600mg / m^2 IV 40mg / m^2 IV 600mg / m^2 IV	21	12
CAF Cyclophosphomide Adriamycin 5- flurouracil	 100mg / m^2 /d Po for 14 days 30mg / m^2 /d IV 1 and 8 500mg / m^2 /d IV 1 and 8	28	6
CAF Cyclophosphomide Doxorubucin 5- flurouracil	 600mg / m^2 IV day 60mg / m^2 IV day 600mg / m^2 / d IV day	21-28	4-6

SIDE EFFECTS

Alopecia, Bone Marrow suppression, Immuno suppression, Nausea / vomiting, Cardio toxicity

ADJUVANT HORMONE THERAPY

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

TAMOXIFEN

Tamoxifen is the most preferred drug for adjuvant hormone therapy and prevention of recurrence over the last two decades. It acts by selective modulation of estrogen receptors thus inhibiting estrogen from acting on its receptor. Studies have shown that Tamoxifen reduces relapse in patients by as much as 47% after treatment for 5 years and 36% decrease in proportional risk of death by 10 years.

Tamoxifen is given to post menopausal women with positive hormone receptor assay. It is given in the dose of 20mg daily for 5 years.

SIDE EFFECTS

Flushing, Vaginal dryness, Weight gain, Endometrial cancer, Thromboembolism

Table 4:- Guidelines for Chemo / Hormonal Therapy

Node Positive	**Premenopausal**	**Postmenopausal**
ER / PR + ve	Combination chemo therapy + Tamoxifen	Tamoxifen ± CCT
ER / PR – ve	CCT	CCT ± Tamoxifen
Node Negative		
Favorable tumour character	Tamoxifen	Tamoxifen
unfavorable	CCT	Tamoxifen

Favorable : Size < 2cm. ER / PR + ve, histological grade I,II.

Unfavorable : Size > 2cm. ER / PR – ve, histological grade III.

AROMATASE INHIBITORS

The third generation aromatase inhibitors exemestane, anastrezole , letrozole have been proven to show more efficacy than tamoxifen in treatment of metastatic carcinoma breast with ER positive status in postmenopausal patients. MA17 trial demonstrated reduced risk of recurrence of carcinoma breast and , decreased risk of development of contra lateral breast cancer improvement in overall survival in women with positive nodes and have received aromatase inhibitors.

Table 5:- Aromatase inhibitors-dosage and adverse effects

DRUG / DOSAGE	**ADVERSE EFFECT**
Anastrozole 1 mg / d	Hot flushes, fatigue, vaginal dryness nausea, diarrhoea headache, osteoporosis, rarely DVT, MI Stroke.
Exemestane 2.5 mg / day	Hot flushes, nausea, fatigue Sweating, decreased Bone mineral density, lymphocytopenia
Letrozole 2.5 mg / day	Hot flushes, arthalagia, myalgia, faligue dizziness osteoporosis decreased bone mineral density rarely M.I, stoke.

TRASTUZUMAB

Overexpression of her2 / neu receptors is known to occur in roughly 25% of cases of breast cancer. A 3 year study showed that its addition to chemotherapy decreased recurrence risk by 50% and increased survival rates of patients by 20%. It belongs to the monoclonal antibody group of drugs and acts by binding to her2/neu receptors.

OOPHORECTOMY

Oophorectomy described by Beaston was the only ablative procedure for years. This bilateral oophorectomy is presumed to work by elimination of ovarian hormones including oestrogen, progesterone and androgen. This produces objective regression of the disease process. The amount of regression was increased with exclusion of ER-velesions. Little can be gained with opphorectomy in postmenopausal women, as there is nosecretion of hormones from the ovaries of postmenopausal women. Surgical castration is preferred because it acts rapidly and results in complete reduction in hormone levels. The patients who are unfit or refuse surgery can undergo radiation ablation but it takes a minimum of two months to completely suppress the hormones by radiation

ADRENALECTOMY

Adrenalectomy was popular in earlier days as it showed regression of metastatic disease. Because of less risk, less side effects and as it is more familiar to the surgeons operating carcinoma breast, it was very commonly used. This was known to increase disease free interval in metastatic disease

PROGNOSTIC FACTORS IN BREAST CANCER

A. COMMONLY ASSESSED

1. Number of involved lymph nodes in axilla
2. Tumour size
3. Tumour TNM Stage
4. Lymph vascular invasion
5. Histologic Tumour type
6. Histologic Grade
7. Nuclear grade
8. Sex steroid receptor
9. Ploidy
10. Proliferative indices (S Phase fraction, Thymidine labeling index, mitotic index)

B. INVESTIGATIONAL

1. Proliferative indices

   (Ki67, PCNA / Cycline, M1B1)
2. His tone H3
3. Transforming growth factor (a,b).
4. Epidermal growth factor
5. Insulin like growth factor
6. Once gene products (HER2 / neu or cerb B2, C-myc, ras)

7. P53 Protein
8. Invasion related markers

   (Cathepein D, Stamelysin 3, Laminin receptor)
9. Angiogenesis factors(PS2, heat stock protein, MDRI)

I. TUMOUR SIZE

< 2 cm – favorable

> 2 cm – Bad prognosis

II. LYMPH NODE STATUS

Positive axillary nodes are the major risk factor for systemic disease and most oncologists believe that all women with involved lymph nodes should have adjuvant therapy because the clinical staging of axillary nodes is so inaccurate.

Axillary LN dissection is necessary to stage patient accurately and to determine the benefit of adjuvant therapy

No histological involvement - 80% 5 year Survival

1-3 positive Lymph nodes - 50% 5 year Survival

> 4 positive Lymph nodes - 21% 5 year Survival

III. Tumour Type

Mucinous Papillary, Tubular, medullary - favourable prognosis

IV. TUMOUR GRADE

Based on Bloom and Richardson grading includes

- Tendency to form tubules
- Pleomorphism
- Hyper chromatic nuclei and mitotic figures

Grade I, II - good prognosis

Grade III - poor prognosis

Table 6:- Bloom and Richardson histological grading of tumor in carcinoma breast

POINTS	TUBULAR GRADE	NUCLEAR GRADE	MITOTIC INDEX
1.	Well differentiated if tubular structures constitute greater than 75% of tumour	Small, uniform staining nucleus	Low (.0-3.3 / mm^2)
2.	Tubular structures represent 10 –75% of tumour	Moderate variation in nuclear size and shape	Medium(3.3-7/mm^2)
3.	Tubular structures represent less than 10% of tumour	Marked nuclear pleomorphism with dark staining	High > 7/mm^2

Well differentiated cancer - 3-5 Pts - GRADE I

Moderately differentiated - 6-7 Pts - GRADE II

Poorly differentiated - 8-9 Pts - GRADE III

V. HORMONAL STATUS

ER / PR Positive - Good prognosis

VI. HER-2 NEU

Over expression of HER-2 neu is a poor prognostic factor in breast carcinoma.

A) RISK FACTOR BIOMARKERS

These constitute factors such as familial clustering, hereditary germ line mutations, proliferative breast disease showing atypia, densities in mammogram.

B) EXPOSURE BIOMARKERS

Include measurement of carcinogen exposure such as DNA adducts.

C) DRUG EFFECT BIOMARKERS

The biochemical effect of drugs can be assessed by serum levels of enzymes like glutathione reductase and ornithine decarboxylase.

D) PROGNOSTIC BIOMARKERS

A) INDICES OF PROLIFERATION

PCNA is DNA polymerase associated nuclear protein showing increased expression in G1 phase. Its correlates with high S phase fraction, aneuploidy, high mitotic index, high tumour grade.

B) INDICES OF ANGIOGENESIS

Tumor invasion in breast cancer occurs through angiogenesis. Over expression of VEGF (Vascular Endothelial Growth Factor) correlates with recurrence of carcinoma breast with lymph nodes testing negative for cancer cells.

a) p53:

P53 is a tumor suppressor gene. It plays a key action in DNA repair, arresting the cell cycle, and apoptosis . Cells with overexpression of p53 show high nuclear grade, high preliferative fraction, aneuploidy, hormone receptor negative status.

A study of molecular biomarkers as prognostic factors in carcinoma breast was conducted in the University of Alabama at Birmingham. It was found that the combination of Her/2 neu and p53 overexpression was superior to clinicopathologic factors in predicting disease free period and survival rate among patients with carcinoma breast.

OVERVIEW OF BREAST CANCER THERAPY

I. CARCINOMA – IN SITU (STAGE 0)

1) DCIS involving two or more quadrants require mastectomy.
2) Limited disease – lumpectomy + radiation therapy

3) Low grade DCIS, < 0.5cm – Lumpectomy alone

4) Nonpalpable DCIS – Needle localization and surgical resection

Adjuvant tamoxifen in patients who underwent mastectomy has brought the recurrence rates and mortality below 2%

Patients who underwent lumpectomy and radiotherapy had local recurrence rate of 9% mortality 2%.

Recurrence occurred when tumor size is more than 2.5 cm, DCIS was of comedo type.

LCIS

Invasive cancer occurs in 25 to 30% of patients presenting with LCIS. LCIS is a marker of increased risk of invasive cancer. It is advised to observe these patients with or without tamoxifen and to identify as early as possible the occurrence of invasive carcinoma through regular screening. Excision of LCIS does not confer any benefit because it diffusely pervades both breasts with equal risk for invasive disease.

Table 7:- Van Nuys Prognostic index for DCIS

Score	**Size**	**Margin of excision**	**Grade**
1.	< 1.5 cm	> 0.9 cm	Non high grade, no necrosis
2.	1.5 – 4 cm	0.1 – 0.9 cm	Non high grade with necrosis
3.	> 4 cm	< 0.1 cm	High grade with or with out necrosis

3 – 4 -> small low grade lesions treated by excision alone.

5 – 7 -> Excision + Radiation
8 – 9 -> Mastectomy

III. EARLY BREAST CANCER

Includes stage I, II A, II B

SURGICAL TREATMENT

1) Breast conserving surgery including

   Lumpectomy, irradiation of breast tissue , staging of axillary nodes

2) Modified Radical mastectomy

ADJUVANT RADIATION THERAPY

4 or more nodes positive

ADJUVANT CHEMOTHERAPY

All nodes positive cancers

All node negative cancers with adverse prognostic factors like high nuclear histologic grade, negative hormone receptor status.

CONTRAINDICATION TO BREAST CONSERVATION SURGERY

1) Multicentric disease
2) Prior radiation therapy
3) Positive surgical margins
4) Contraindication for radiotherapy
5) Connective tissue disorder

III. LOCALLY ADVANCED BREAST CANCER

(STAGE III A / III B)

A) Operable disease (Stage III a)

Modified radical mastectomy, with subsequent adjuvant chemotherapy and radiotherapy.

Chemotherapy - maximize distant disease free survival

Radiotherapy - maximize loco regional disease free survival

B) In selected stage III a patients

Neo adjuvant chemotherapy is used to decrease tumor size and facilitate breast conservation surgery

C) Inoperable stage III A / III B / IIIC

Neo adjuvant chemotherapy is used to decrease loco regional tumor burden permitting subsequent surgery followed by adjuvant chemo and radiotherapy.

IV. METASTASIC DISEASE (STAGE IV)

Treatment for stage IV disease is mainly to enhance a woman's quality of life.

HORMONE THERAPY

Given in patients testing positive for hormone recptors, women with limited metastastic to visceral tissue who are asymptomatic, and presenting metastasis to bone and soft tissues only.

SYSTEMIC CHEMOTHERAPY

INDICATIONS

1) Women with ER/PR negative cancer
2) Symptomatic patients with visceral involvement
3) Metastasis not responding to hormone therapy

SURGERY

Mastectomy for fungating breast cancer, Pleural effusion, Pericardial effusion, Pathologic fracture, Spinal cord compression

RADIATION THERAPY

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

FOLLOW UP

American society of clinical oncology recommendations for breast cancer follow up care.

1. All patients should learn correct method of breast self examination and should practice it every month.
2. Follow up for first 2 years: visit at 3 months interval

- ❖ At 3 monthly interval : history, physical examination
- ❖ At 6 monthly interval : blood count and biochemistry, USG abdomen mammography
- ❖ At yearly interval : chest X ray, pelvic examination and pap smear, mammography

Follow up for Next 3 years: visit at 6 months interval

- ❖ At 6 monthly interval: history, physical examination
- ❖ At yearly interval : blood count and biochemistry, USG abdomen mammography chest X ray, pelvic examination and pap smear.

Follow up for Next 5 years: visit at 1 year interval

- ❖ At yearly interval : history, physical examination
- ❖ At 2 yearly interval: blood count and biochemistry, USG Abdomen mammography chest X ray, pelvic examination and pap smear.

BREAST CANCER PROGNOSIS

5 years survival rate for

Stage I	94%	III A	52%
Stage II a	85%	III B	48%
Stage II b	70%	IV	18%

TREATMENT

Modified radical mastectomy / Radical mastectomy when muscle is involved is the treatment of choice with postoperative radiotherapy and adjuvant CMF in node positive males.

METHODOLOGY

METHODOLOGY

1) SOURCE OF DATA:

Cases admitted in KAPV Medical College and Mahatma Gandhi Memorial Government Hospital with carcinoma breast

2) STUDY DESIGN AND SAMPLING:

This is a prospective analytical study of 95 Cases of Cancer Breast diagnosed and treated at KAPV Government Medical College and Mahatma Gandhi Memorial Government Hospital, Tiruchirapalli over a period of 2 years from May 2012 to August 2014.

At presentation a detailed history was taken and clinical examination done. Diagnosis was confirmed histologically and investigations like Blood Biochemistry, chest X-ray, ultrasound abdomen were also done to stage the disease. In patients presenting with locally advanced breast disease or metastatic disease investigations like CT abdomen, CT chest, mammogram of opposite breast, pleural fluid and ascitic fluid cytology were done.

The modality of treatment was decided based on stage of disease at presentation and operability. Most of the patients with early breast cancer I, II A, II B, III A underwent modified radical mastectomy.

Inoperable stage IIIA, IIIB, IIIC were treated with neoadjuvant chemotherapy followed by modified Radical mastectomy. Metastatic disease received palliative chemotherapy and radiotherapy.

All cases were followed up at monthly interval with clinical examination, blood count and biochemistry, ultrasound abdomen, chest X ray, Mammography was done at 3 monthly interval during the follow up period. Data obtained were recorded in a specific proforma and analysed in systematic way.

INCLUSION CRITERIA

All histologically proven cases of cancer breast were included in the study. Immunohistochemical studies of ER, PR receptors were done in 20 patients

EXCLUSION CRITERIA

patients who where operated and referred for further management from outside hospital were excluded from the study.

OBSERVATION AND DISCUSSION

OBSERVATION AND DISCUSSION

SEX

Only < 1% of cases of cancer breast occurred in men. In our study only two patients were male. One had invasive intraductal carcinoma and was treated with modified Radical mastectomy and other had malignant fibrous histiocytoma with lung metastasis during presentation treated with chemotherapy. They account for 2.10%.

AGE

Incidence of breast cancer increases with age. In U.S lifetime risk of developing breast cancer is 12.2% or 1in 8 women. The incidence of carcinoma breast adjusted for age shows increase in incidence to 4% between 1980 and increase occurred primarily in women aged 55 yrs or older.

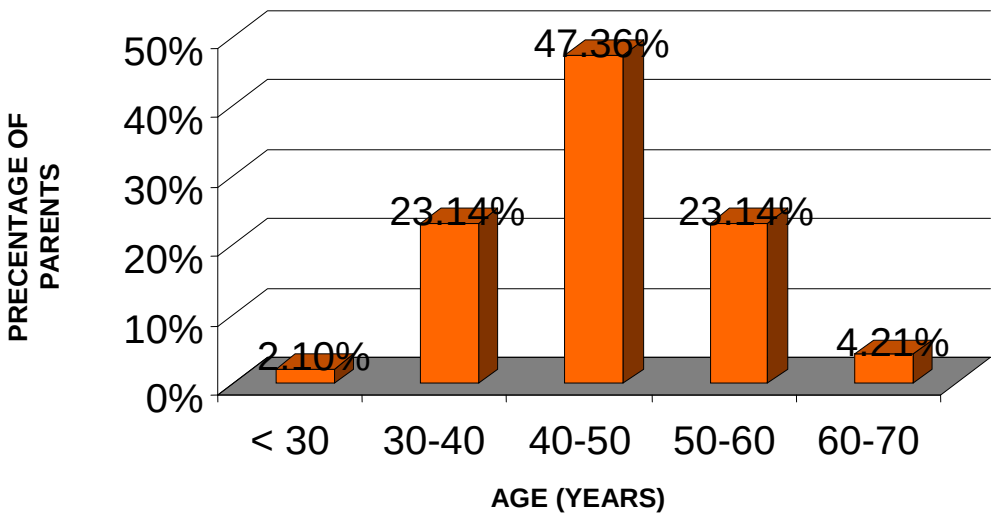
In our study.

Table 8:- Age wise distribution of breast cancer cases in KAPV

Age Group (years)	No. of Patients	Percentage
< 30	2	2.10%
30-40	22	23.14%
40-50	45	47.36%
50-60	22	23.14%
60-70	4	4.21%

Youngest age was 24 years.

Oldest age was 65 years.



Graph 1: Age wise distribution of breast cancer cases in KAPV

Most of our patients were between 40 – 50 years.

FAMILY HISTORY

Women with first degree relatives affected by carcinoma breast have a 1.7 to 2.5 relative risk of breast cancer development. 1.5 with an affected second degree relative. About 5% of breast cancers appear to have inherited gene mutations that are dominant and highly penetrant.

In our study there was no significant family history.

SOCIOECONOMIC STATUS

Cancer breast is more common in women of higher socioeconomic status, but in our study most of the patients belonged to lower socioeconomic status.

This can be explained by the fact that most of the people utilizing the health services of this institution are from lower socioeconomic group.

DIETARY FACTORS

Epidemiological studies of fat consumption and cancer risk have produced inconclusive results. But however weight does correlate with breast cancer risk. Multiple studies demonstrate a relative risk of 1.4 for each 24 Grams of alcohol (about two drinks) consumed

In our study all were taking mixed diet. None of them consumed alcohol.

(IONISING RADIATION) ENVIRONMENTAL FACTORS

Radiation exposure after age 40 produces minimal increase in risk. Women with Hodgkins disease younger than 15 years of age treated with mantle radiation demonstrate a higher risk for carcinoma breast than the general population. High electromagnetic fields and environmental exposure to organochlorine pesticides are known risk factors in the development of carcinoma breast.

In our study none gave history of previous radiation

MENSTRUAL STATUS

Increased exposure to endogenous estrogen peaks during menstrual cycle and predisposes to carcinoma breast. For every year of delay in menarche, there is an apparent decreased risk of breast carcinoma by 20%. Women with menopause after 55 years have twice the risk of developing carcinoma breast compared to women attaining natural menopause before 45 years.

In our study 3 patients attained menarche before age of 12 and 6 attained menopause after 55 years 4 underwent total abdominal hystrectomy with bilateral salphingo opherectomy for co.existing gynaecological problems like dysfunctional uterine bleeding, fibroid

45 patients were premenopausal 47.36%

44 Patents were postmenopausal 46.31%

PARITY

- Nulliparous women have a relative risk of about 1.4.
- In our study 5 patients were nullipous which was about 5.26%.

AGE AT FIRST PREGNANCY

First full term pregnancy after age 30 have a twofold to fivefold increase in breast cancer risk compared with women having a first full term pregnancy before age 18 or 19. In our study 9 patients had their first child above the age of 28 years.

LACTATION

It is difficult to determine the beneficials effects of breast feeding independent of pregnancy with regards to breast cancer. Some studies indicate that breast feeding for longer duration of time has a protective effect.

In our study 3 patients had not breast fed their children.

ORAL CONTRACEPTIVE PILLS

Women who are on oral contraceptive pills have a 1.24 relative risk of developing carcinoma breast. On stopping therapy risk diminishes to 1.01 over ensuring 10 years.

HORMONE REPLACEMENT THERAPY

Estrogen replacement therapy increases relative risk by 1.8 for use of 5 years or less and 2.65 for longer than 5 years.

In our study none of the patients had used either OCP/HRT.

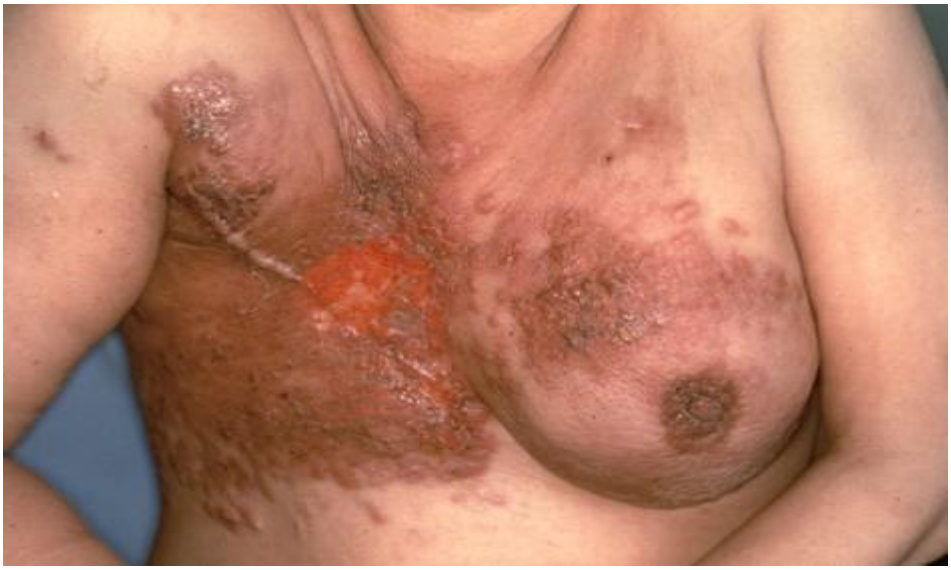


Figure 14: Cancer en cuirasse

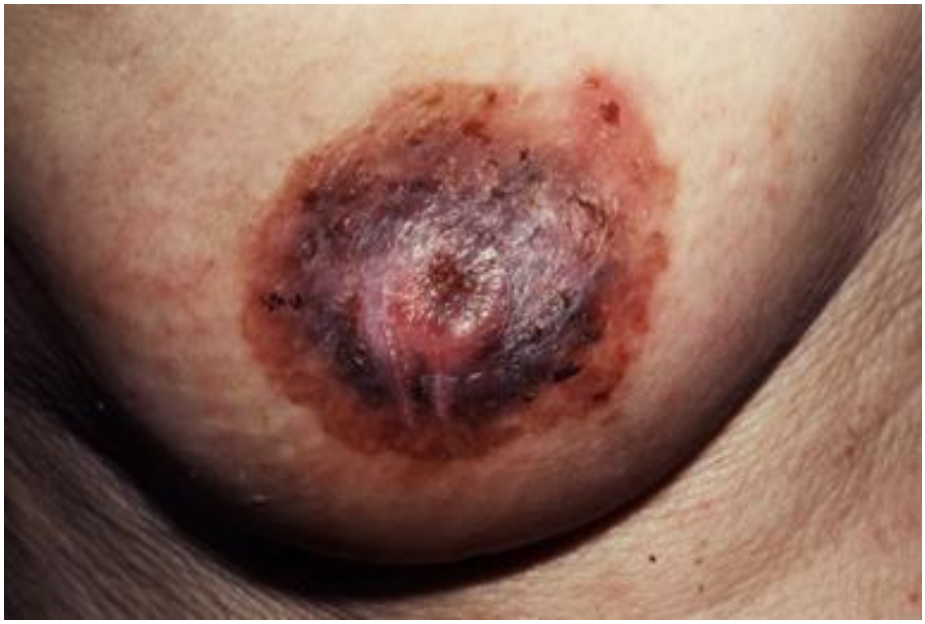


Figure 15: Paget's disease of the nipple

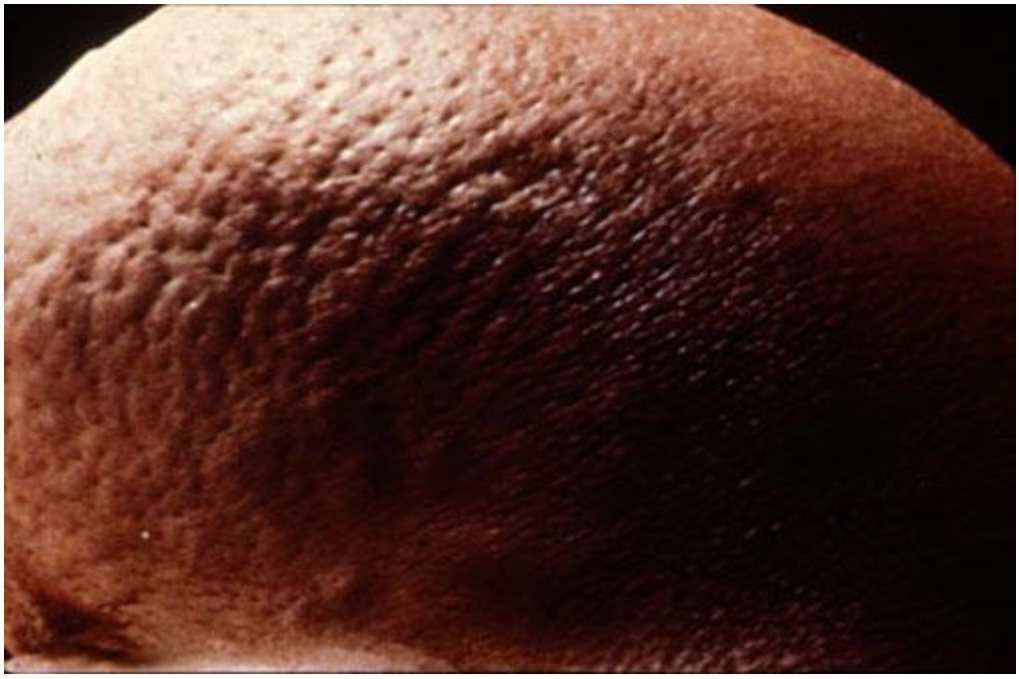


Figure 16: Peau d'orange appearance

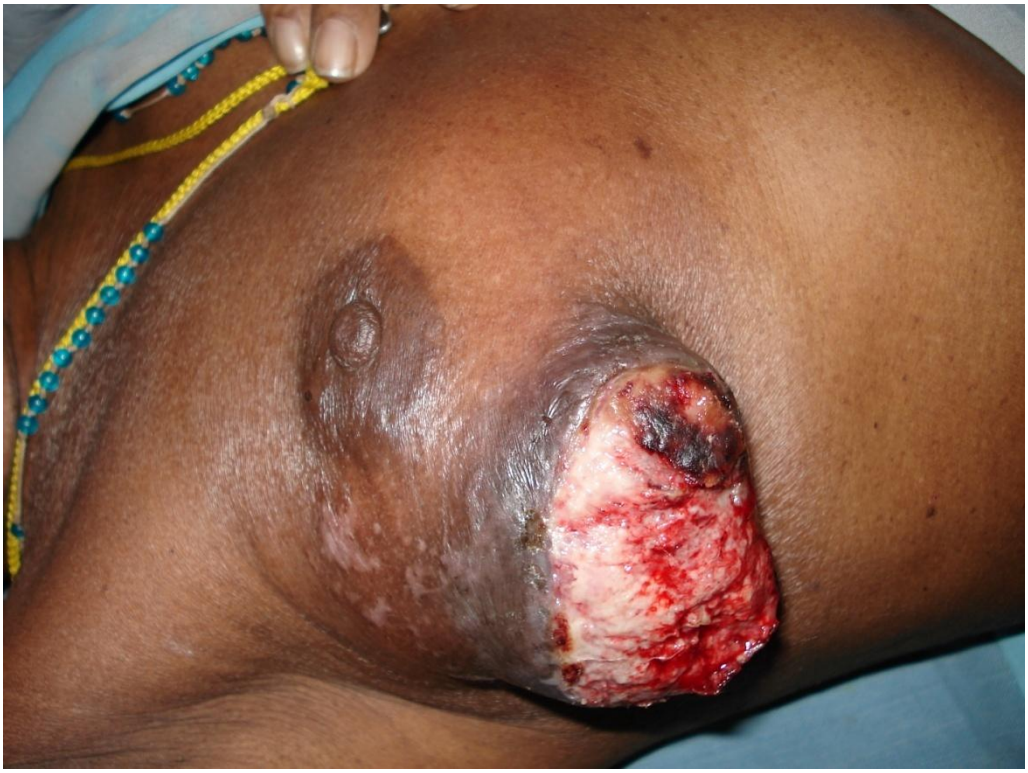


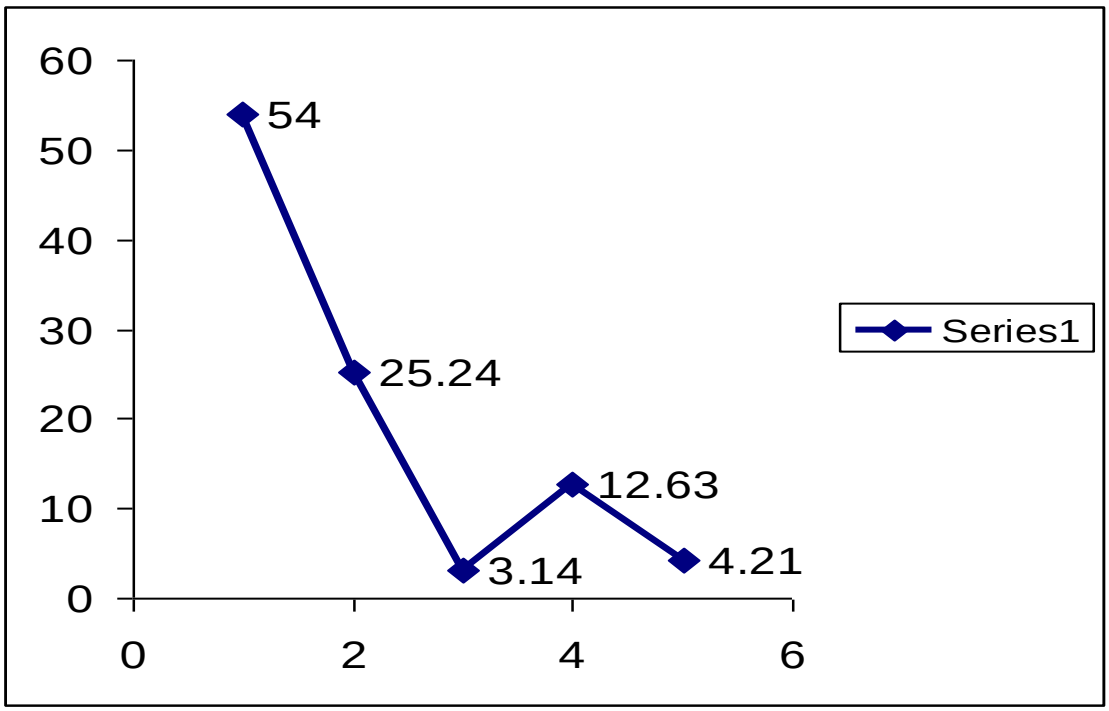
Figure 17: Ulcerative growth

CLINICAL PRESENTATION

- In our study clinical presentation were as follows

Table 9:- Clinical presentation of breast cancer in KAPV

	NO. OF PATIENTS	PERCENTAGE
Painless lump	52	54
Lump with pain	24	25.24
Lump with ulcer	3	3.14
Nipple discharge	12	12.63
Metastatic symptoms	4	4.21



Graph 2: Clinical presentation of breast cancer in KAPV

Most of the patients present with painless lump

1 – Presented with weakness of lower limb

1 – Presented with Seizures

2- dyspnea

SITE OF INVOLVEMENT

- Commonest site involved in ca breast is upper outer Quadrant.

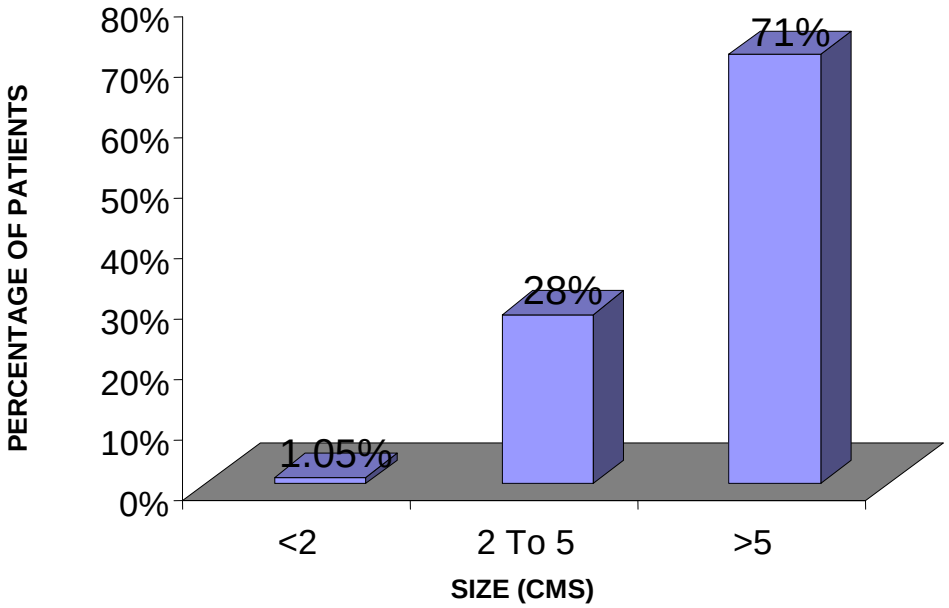
In our study it was as follows.

Table 10:- Distribution of site of tumor

SITE	NUMBER	PERCENTAGE
Upper outer	54	56.84%
Upper inner	12	12.63%
Lower outer	4	4.21%
Lower inner	4	4.21%
Central	12	12.63%
All	9	9.46%

Table 11:- Tumor size at the time of presentation

SIZE IN (CMS)	NUMBER	PERCENTAGE
<2	1	1.05%
2-5	25	28%
>5	64	71%



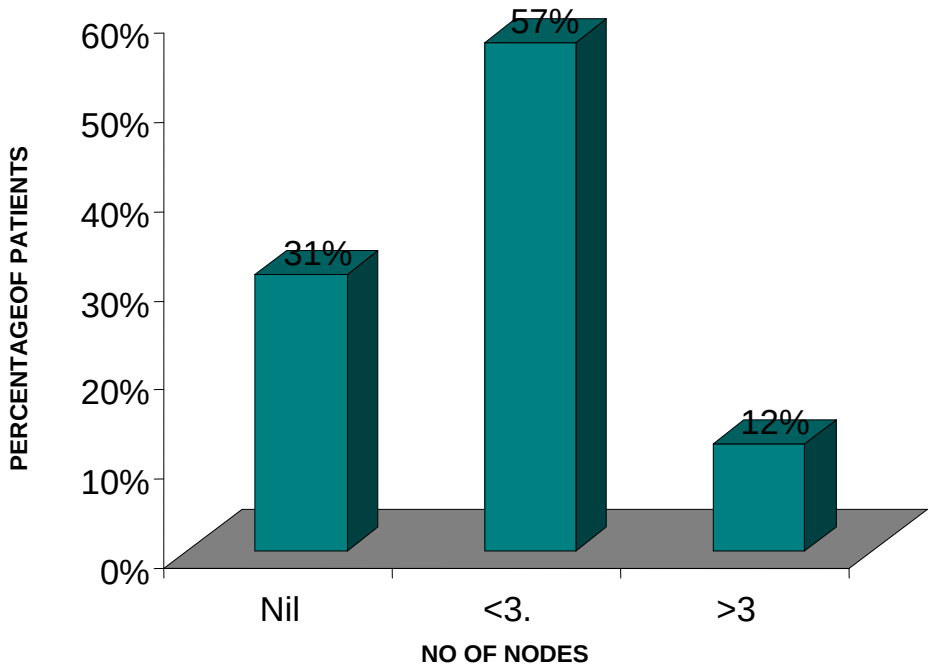
Graph 3: Tumor size during presentation

Increased tumor size is associated with early local recurrence, 5 cases who had local recurrence in our study had tumor size greater than 8 cm during presentation.

Four patients with lung metastasis had tumor size than larger than 8 cm

Table 12:- Lymphnode Involvement in Relation to Survival Rates

No. of nodes	No. of patients	%	5 years survival
Nil	29	31%	80%
<3.	54	57%	50%
>3	12	12%	21%



Graph 4: Lymph node involvement in relation to survival rates

69 patients show clinically positive lymphnodes

21are node negative

3 – had bilateral axillary nodes

More than 3 nodes were positive in 12 of our patients

Of which one patient presented with lung metastasis 4 patients developed local recurrence during follow up

3 had opposite axillary node involvement during follow up

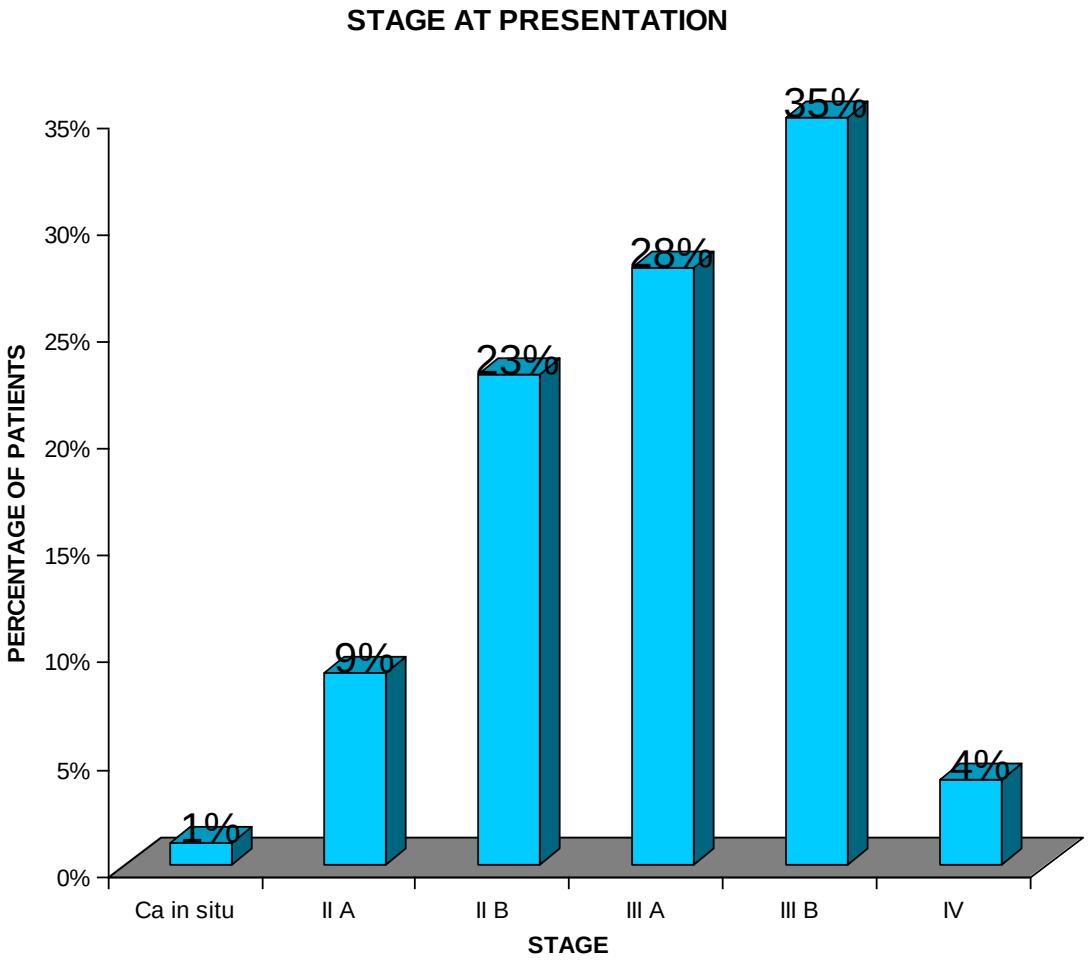
3 had supraclavicular node involvement

One patient with supraclavicular node involvement developed liver metastasis

Table 13:- Stage at Presentation of Breast Cancer

STAGE	**NUMBER**	**PERCENTAGE**
Carcinoma in situ	1	1.05
II A	9	9.47
II B	22	23.15
III A	26	27.36
III B	33	34.73
IV	4	4.21

Most of the patients presented in stage III that is 62.09% for which 5 year survival rate is only about 41%.



Graph 5: Stage at presentation of breast cancer

2 patients who later developed lung metastasis where of stage III B

one patient developed liver metastasis.

3 patients later developed local recurrence

TABLE 14:- Incidence of Breast Carcinoma according to Histopathological Types

In our study Pathological varieties encountered were as follows.

TYPE	NUMBER OF CASES	PERCENTAGE
Invasive ductal carcinoma	80	84.21%
Ductal carcinoma in situ	1	1.05%
Lobular carcinoma	2	2.10%
Malignant Phylloides	1	1.05%
Lobular + Ductal component	2	2.10%
Fibrous Histiocytoma	1	1.05%
Colloid carcinoma	1	1.05%
Medullary carcinoma	3	3.14%
Pagets	1	1.05%
Papillary carcinoma	1	1.05%
Mucinous carcinoma	1	1.05%
Metaplastic carcinoma	1	1.05%

Breast cancer patients affected in a single breast, have roughly 1% per year risk of developing primary carcinoma in the opposite breast. Women aged less than 55 at presentation and diagnosis and those showing lobular architecture on pathological examination, have a higher risk of 1.5%

In our study, One patient with malignant fibrous histiocytoma presented with lung metastasis.

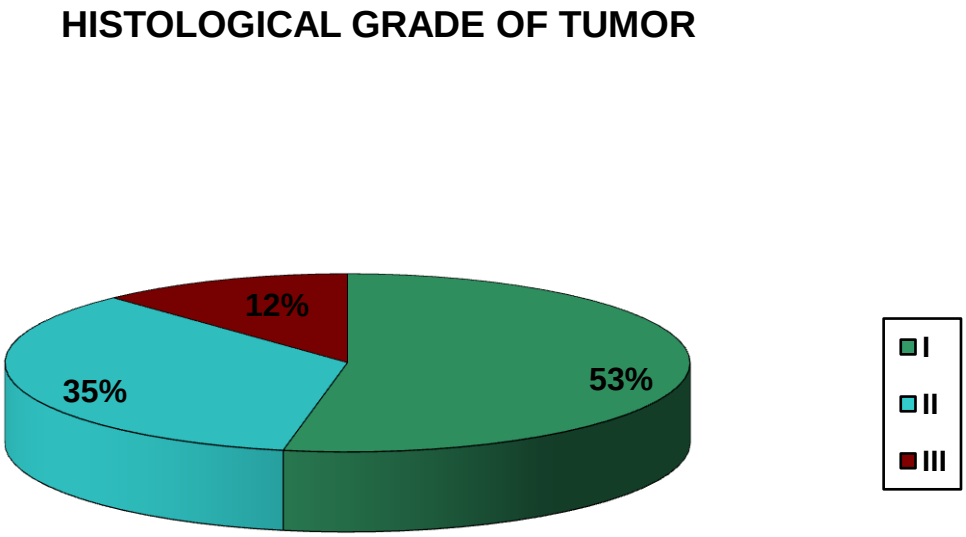
All the other patients who developed metastasis are of invasive ductal carcinoma

HISTOLOGICAL GRADE OF TUMOR

Depending on factors such as nuclear pleomorphism, formation of tubules and mitotic rate, tumor grading by Bloom and Richardson classification is as follows.

Table 15:- Incidence of breast cancer according to histological grade

GRADE	NUMBER	PERCENTAGE
I	42	53
II	32	35
III	10	12



Graph 6: Incidence of breast cancer according to histological grade

10 patients are of histological grade III of which 3 developed local recurrence

- ❖ 2 developed lung secondarius during follow up
- ❖ 1 developed spinal metastasis

CORRELATIVE STUDY OF HORMONE RECEPTOR STATUS IN BREAST CARCINOMAS:

The study of hormone receptor (ER, PR) status has been undertaken in 20 cases

Immunohisto chemical analysis was done in paraffin embedded tissue blocks, by using the Supersensitive Polymer HRP system based on

non-biotin polymeric technology that makes use of two major components, Super enhancer and poly- HRP reagent.

The retrieved antigen was bound to primary antibody and then detected by the addition of secondary antibody conjugated with horse radish peroxidase polymer and DAB substrate.

The score was calculated after adequate colour development which can be more readily visualized under a light microscope

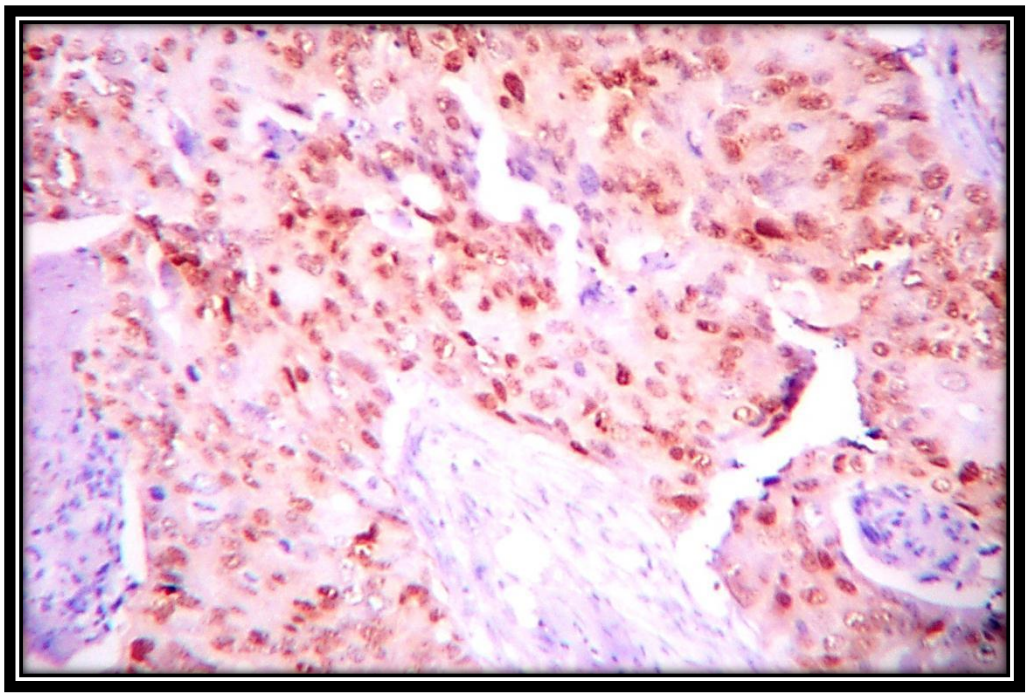


Figure 18: Immunohistochemistry for Estrogen receptors showing strong nuclear positivity in tumour cells. x100

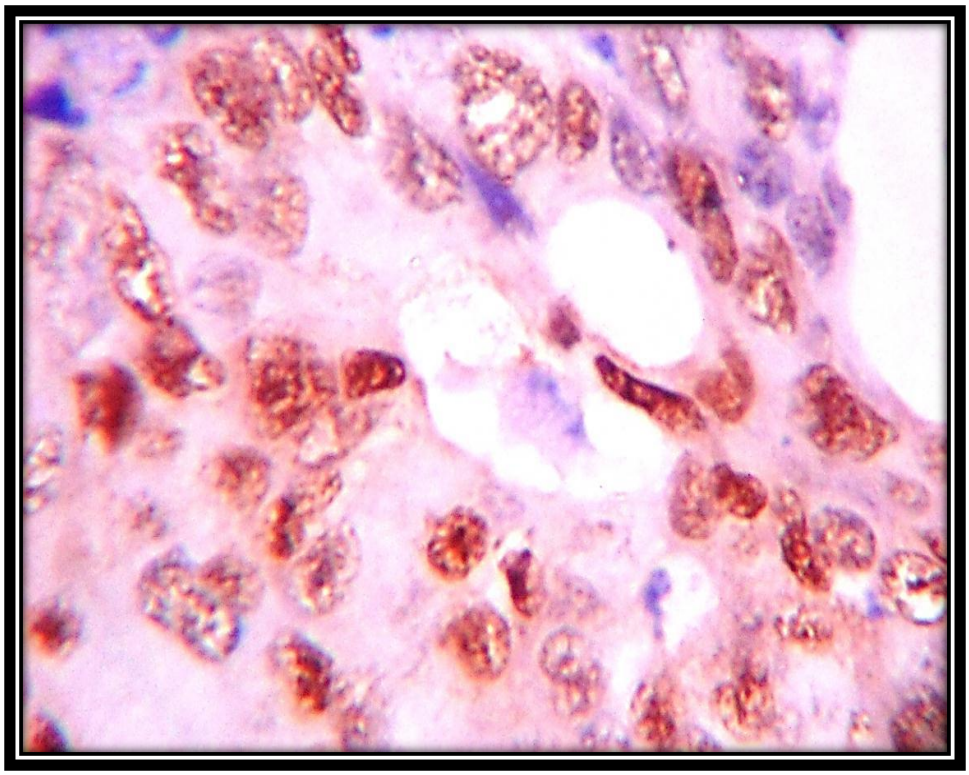


Figure 19: Immunohistochemistry for Estrogen receptor showing strong nuclear positivity intumour cells. x400

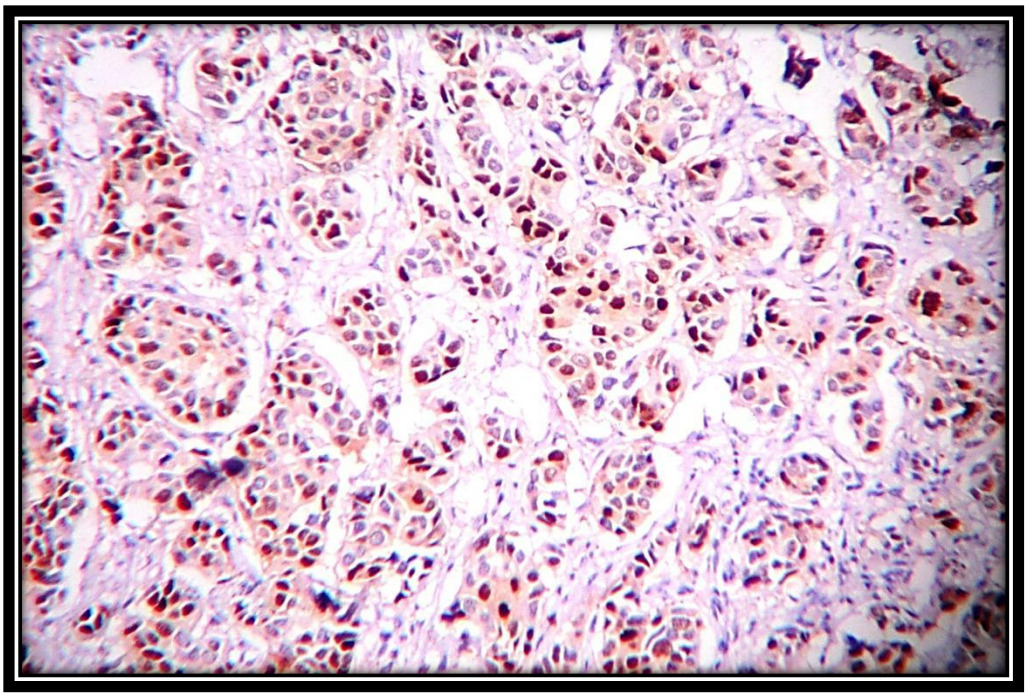


Figure 20 : Immunohistochemistry for Progestrone receptor showing strong nuclear positivity intumour cells. x100

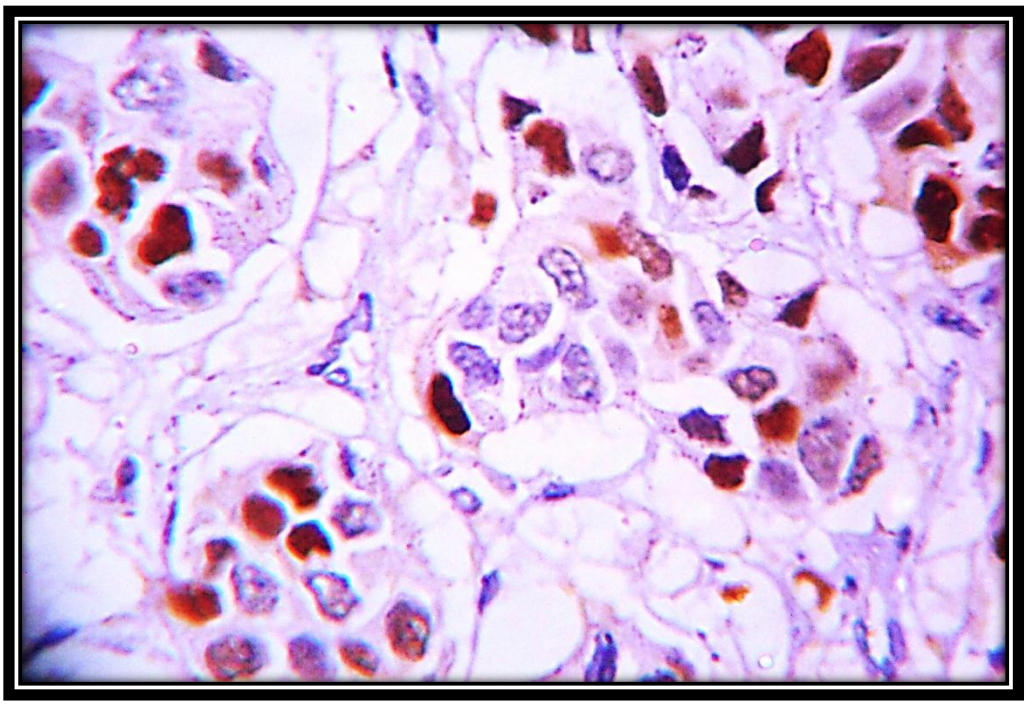


Figure 21: Immunohistochemistry for Progestrone receptor showing strong nuclear positivity in tumour cells. x400

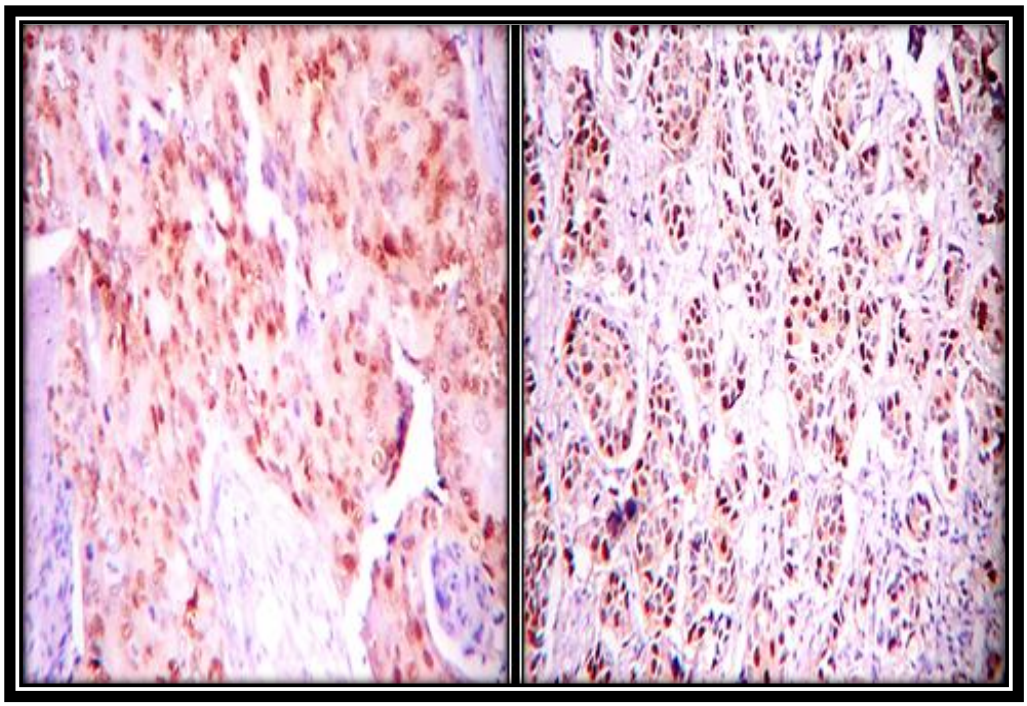


Figure 22 : Immunohistochemistry showing ER and PR positivex100

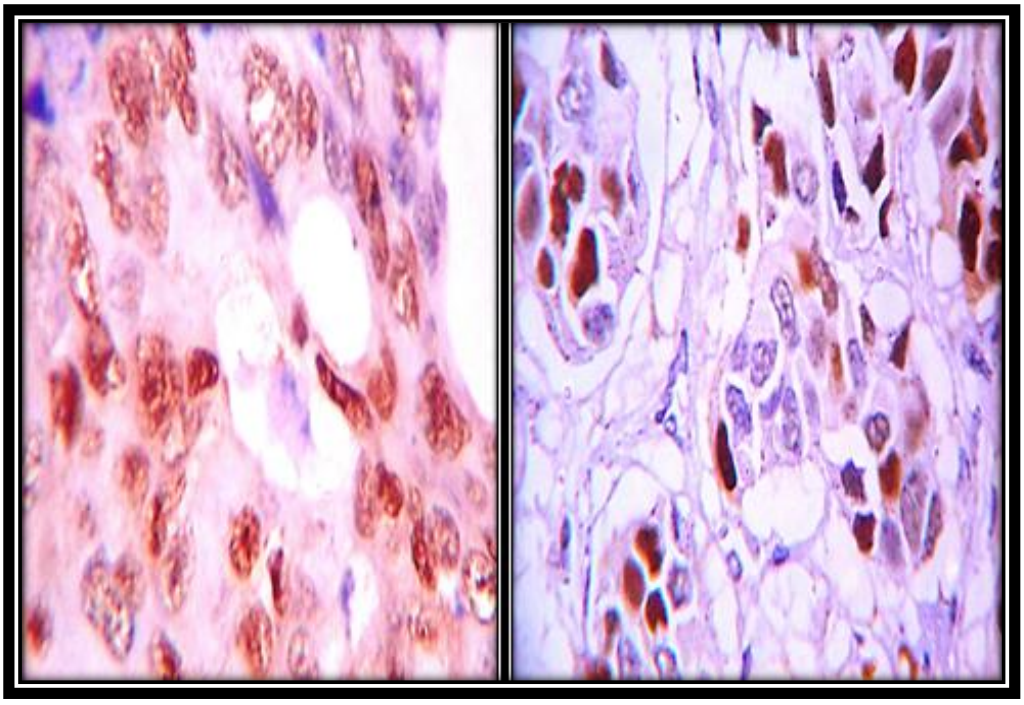


Figure 23: Immunohistochemistry showing ER and PR positivex400

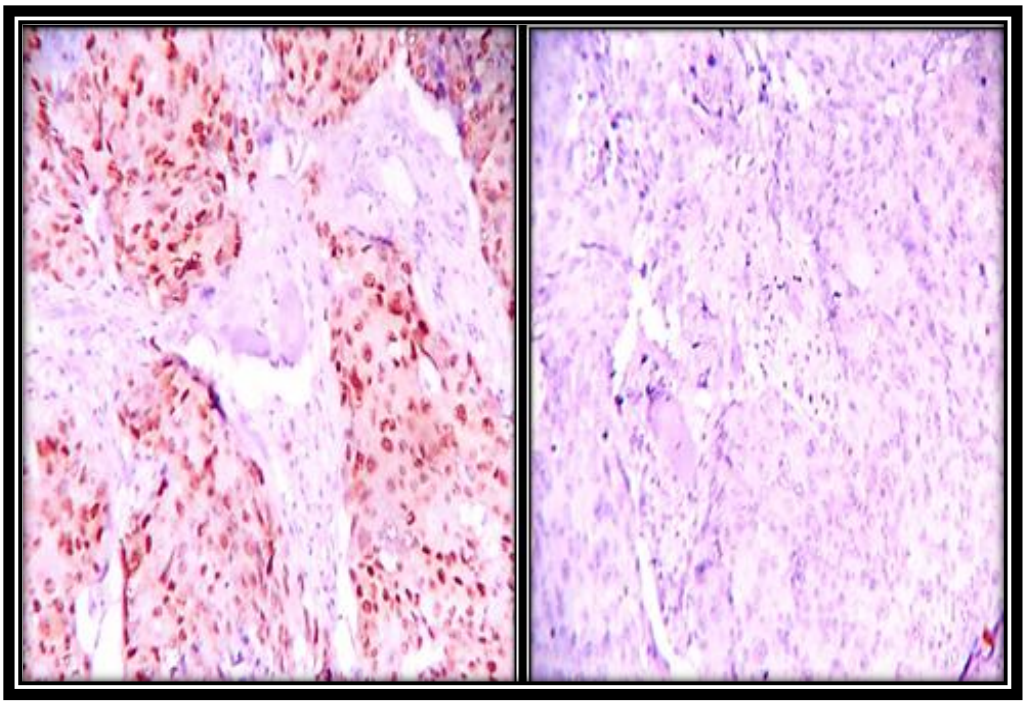


Figure 24 : Immunohistochemistry showing ER positive, PR negative.x100

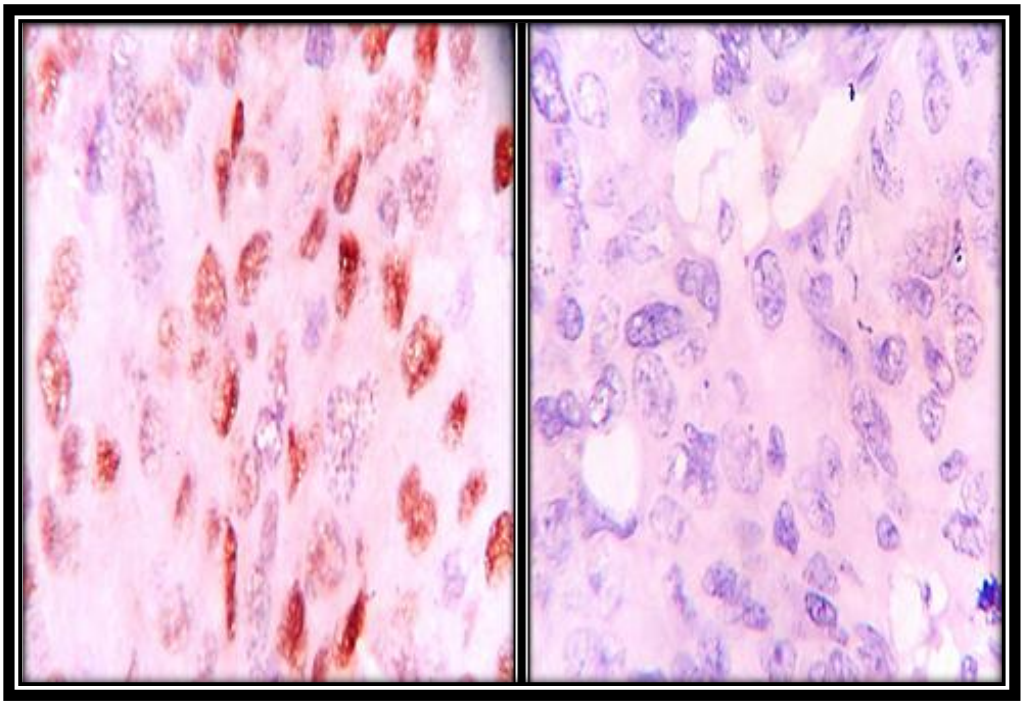


Figure 25: Immunohistochemistry showing ER positive, PR negative.x400

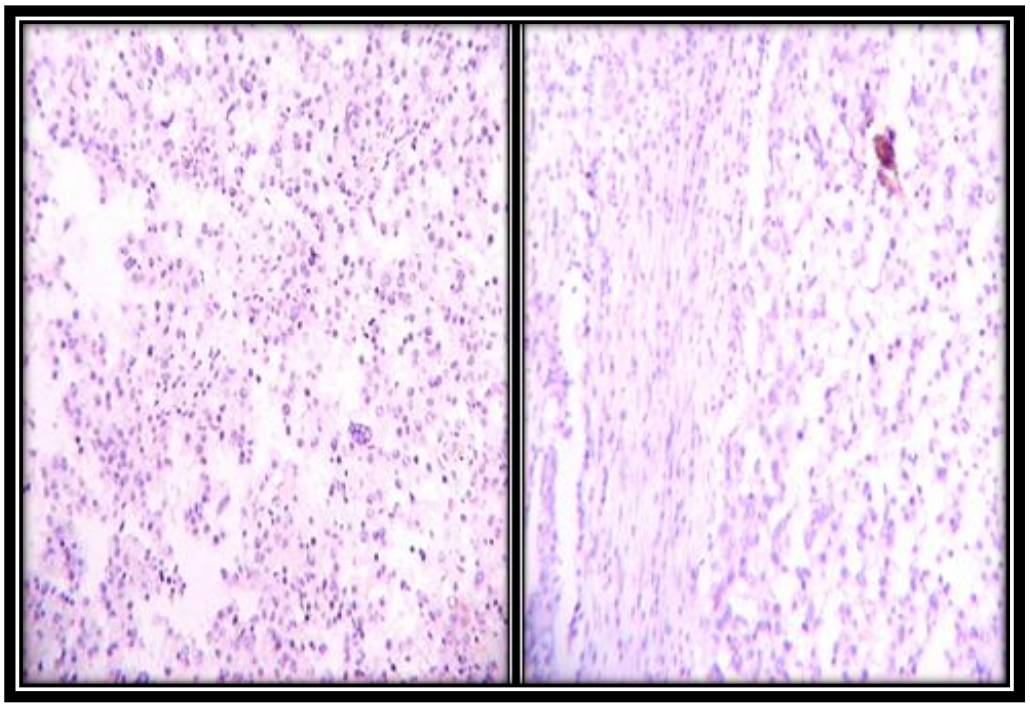


Figure 26 : Immunohistochemistry showing ER, PR negative. x100

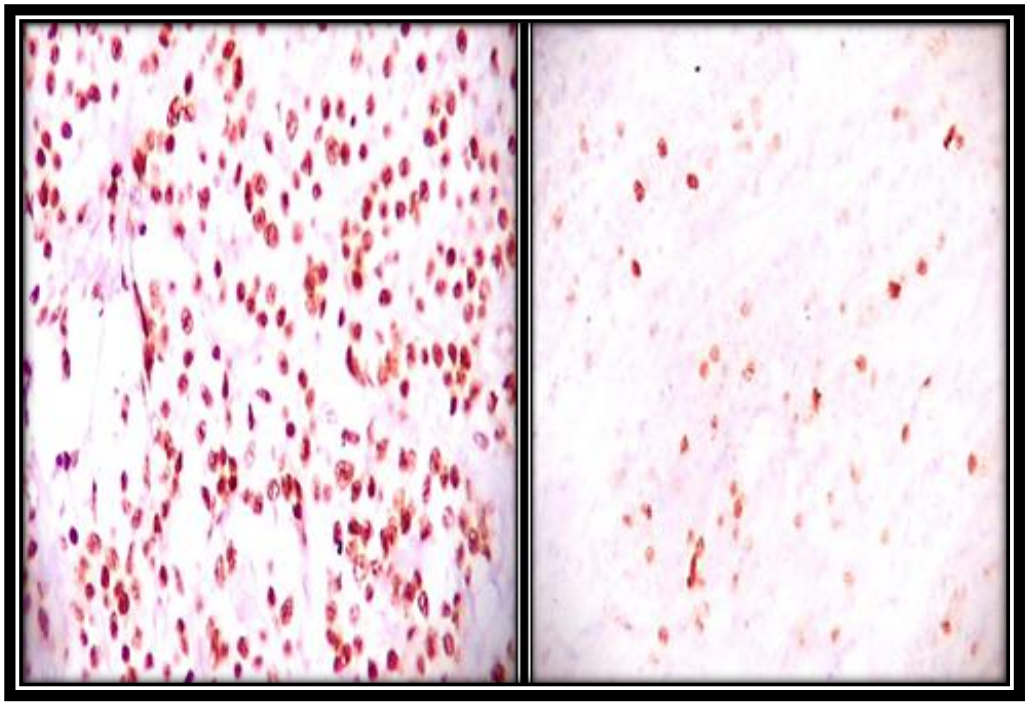


Figure 27: Lobular Carcinoma showing ER Positivity With focal PR Positivity. x100

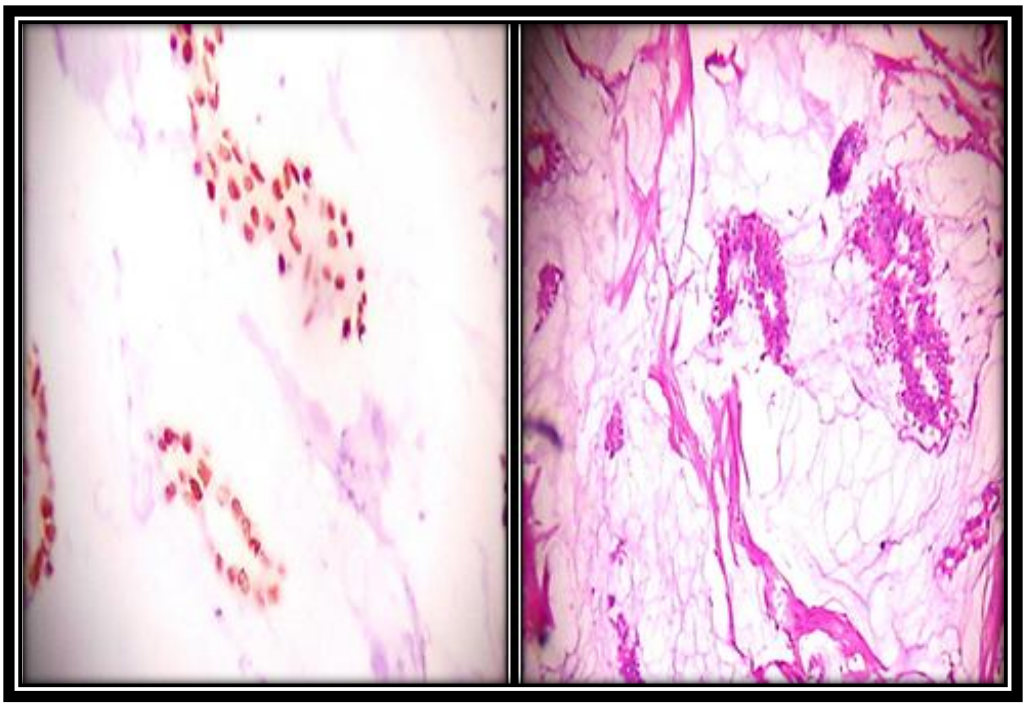


Figure 28: Mucinous carcinoma - ER Positive, PR Negative.x100

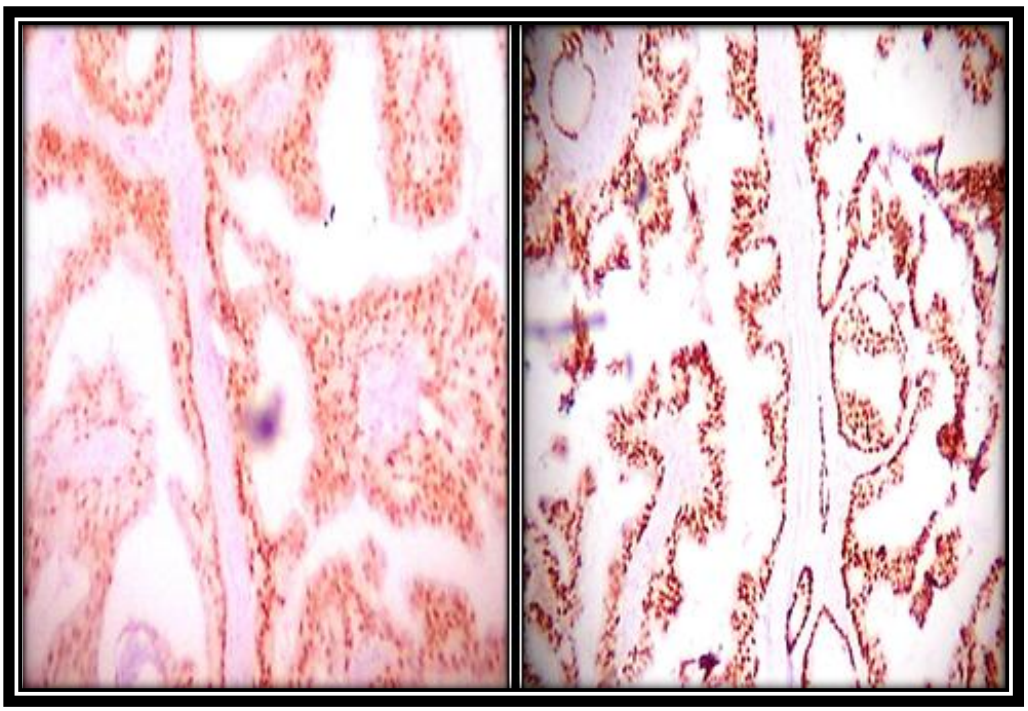


Figure 29 : Papillary carcinoma showing strong ER and PR positivity.x100

The results are shown below.

TABLE 16:- ER status in relation to age groups (n=20):

Age group	Total no of cases	No of ER+ cases	No of ER- cases
20-29	2	0	2
30-39	2	1	1
40-49	6	4	2
50-59	6	5	1
60-69	3	2	1
70-79	1	1	0
Total	20(100%)	13(65%)	7(35%)

TABLE 17:- PR status in relation to age groups (n=20):

Age group	Total no of cases	No of PR+ cases	No of PR- cases
20-29	2	0	2
30-39	2	0	2
40-49	6	2	4
50-59	6	2	4
60-69	3	1	2
70-79	1	0	1
Total	20	5(25%)	15(75%)

The above tables shows the ER/PR status in correlation with different age groups. It was observed that in the total 13 ER positive cases and total 5 PR positive cases, majority of the cases were observed in the age group of 50-59 years and 40-49 years, but the ER positivity was higher in age group 50-59 years compared with the age group of 40-49 years.

In the age group 50-59 years, 83.33% (5 of 6 cases) were positive for ER and2 of 6 cases were positive for PR. The percentage was found to be 66.66% (4 of 6) for ER positive cases and 33.33 % (2 of 6) for PR positive cases in age group 40-49 years.There were 2 cases in age group 20 – 29 years, 1 case in 30-39 age group, 1 case in 60 – 69 age group respectively were negative for ER.

HORMONE RECEPTOR STUDIES IN CORRELATION WITH MENOPAUSE:

ER, PR hormone receptor study by immunohistochemistry was done for 10 patients of the premenopausal age group and 10 patients of the postmenopausalage group with IDC NOS type and the results are shown below:

TABLE 18:- Hormone receptor study in correlation with menopause:

ER/PR STATUS	Premenopausal (n=10)	Postmenopausal(n=10)
ER+, PR+	2(20%)	3(30%)
ER+, PR-	3(30%)	5(50%)
ER-, PR-	5(50%)	2(20%)

From the above table showing the correlation of menopausal status with ER and PR status, it is evident that the hormonal positivity was greater in postmenopausal(30%) cases than that in premenopausal cases(20%). ER positivity was 80% (8 of 10 total postmenopausal cases) in postmenopausal period and 50% (5 of total 10 premenopausal cases) in premenopausal period. PR positivity was 30 % (3 of 10 total postmenopausal cases) in postmenopausal period which was higher than 20% (2 of total 10 premenopausal cases) in premenopausal patients.

In a total 13 ER positive cases, 61.53% (8 of 13 total positive cases) was observed in postmenopausal period and 38.46%(5 of 13 total positive cases) was observed in premenopausal period. In a total of 5 PR positive cases, 60% (3 of 5 total positive cases) was observed in postmenopausal period and 40%(2 of 5 total positive cases) was observed in premenopausal period. The overall percentage of the receptor status of

the patients showed that estrogen receptor positive and progesterone receptor negative tumours (ER+ and PR-) were highest in postmenopausal patients in the study group (50%). In the premenopausal group of patients, ER- PR - tumours were the highest which constitutes 50% whereas ER+ PR + tumours constitute only 20%.

ER, PR study in different histological types of breast cancers:

In correlating the ER, PR status with different histological types of breast cancers, one case of Papillary carcinoma was positive for both ER and PR. One case of Infiltrating lobular carcinoma was positive for ER and focally positive for PR. One case of Mucinous carcinoma was positive for ER but negative for PR. One case each of metaplastic carcinoma and medullary carcinoma in the present study is negative for ER and PR

Prognostic value of ER/PR receptor study

ER/PR Negative seems to have poor prognosis.

In our study, ER /PR negative found in 7 patients.Among them one patient with ER/PR –ve medullary carcinoma developed local recurrence, and one patient with ER/PR –ve metaplasic carcinoma developed lung metstasis.

NOTTINGHAM PROGNOSTIC INDEX

T Size (cms) x 0.2 +Lymphnode stage (1 – 3) + Histological grade (1-3)

1 – No Node

2 – up to 3 Node

3 - > 3 Node

NPI	Prognosis	15 years survival
<3	Good	80%
3.1 – 5.4	Moderate	42%
>5.4	Poor	13%

In our study

NPI	No. of Patients
<3	8
3.1 – 5.4	55
> 5.4	32

During follow up it was detected out of this 32 patients with NPI >5.4, 5 had local recurrence, 3 had lung metastasis, 2 spine metastasis, 1 brain metastasis, 2 had supraclavicular node involvement.

INVESTIGATION

In our study all the patients were subjected to routine investigation like urine albumin, sugar, blood urea sugar, Sr. creatinine, x ray chest, Fine needle Aspiration cytology, ultra sound abdomen.

Mammogram of opposite breast was done in all locally advanced breast cancers. 33 patients underwent mammogram and were found to be normal.

CT chest, pleural aspiration cytology was done for 2 patients who presented with lung secondaries USG abdomen, x ray of long bones and vertebrae taken to exclude other metastasis.

CT. dorsolumbar spine was done in one patient who had collapse of D6 vertebra for which local radiotherapy was given.

CT brain was done in one patient who presented with headache, Seizures which showed metastatic deposites in cerebellar hemisphere. She developed raised intracranial tension for which ventriculoperitioneal shunt was done.

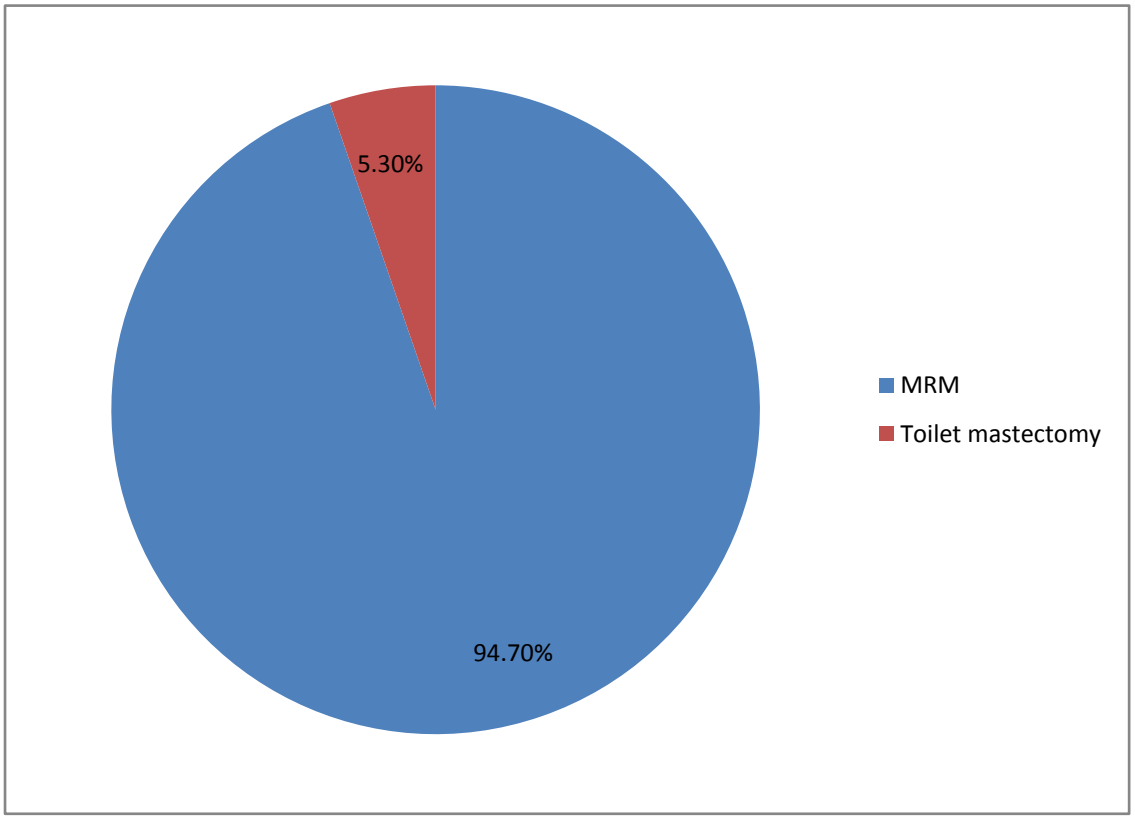
CT abdomen was done in patients with Ascites who had multiple liver secondaries. Paracentesis was done and malignant deposists detected in cytological analysis.

MANAGEMENT

After confirming the diagnosis staging was done by TNM classification most of the cases with stage I,IIA,IIB,IIIA were subjected to modified radical mastectomy. Inoperable stage IIIA and IIIB, IIIC treated with neo adjuvant chemotherapy followed by Madified radical mastectomy. Patients with ulcer/ fungating lesion treated with toilet mastectomy followed palliative chemo / radio therapy. Adjuvant chemotherapy and hormone therapy was given to most of the patients. Patients with Brain and spinal metastasis received loco regional radiation.

Table 19:- Surgical procedures performed on breast cancer patients at KAPV

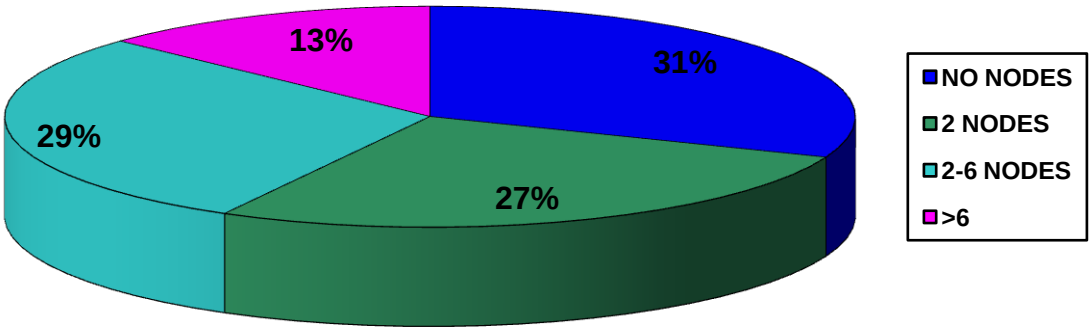
TYPE OF SURGERY	NO : OF PATIENTS	PERCENTAGE
Modified radical mastectomy	90	94.7
Toilet mastectomy	5	5.3



Graph 7: Surgical management of breast cancer cases in KAPV

Neoadjuvant chemotherapy with CMF given to 33 patients (all stage III B and inoperable stage IIIA stage).

LYMPHNODE WITH METASTATIC DEPOSITS IN RESECTED SPECIMEN



Graph 8: Percentage distribution of number of lymph nodes showing metastatic deposits

In our study minimum of three to maximum of Twentytwo lymphnodes were found in resected specimen among which.

- No metastatic deposits were found in 20 patients (31 %)
- 2 nodes positive for deposits in 17 patients. (27%)
- 2-6 nodes were positive for deposits in 19 patients. (29%)
- More than 6 nodes were positive for deposits in 13 patients. (13%)

RESECTED MARGINS

- In our study
- Positive resection margins were found in 5 patients they were given radiotherapy 3 of them developed local recurrence. 2 developed metastasis one in lung, one in brain.

ADJUVANT THERAPY:

Neo adjunt chemotherapy with CMF given to all stage III B

Patients – 33

Patients with more than 3 nodes received Chemotherapy- 12 patients

Patients presenting with metastatic disease received chemotherapy – 4 patients

Tamoxifen given to all postmenopausal patients-47

RADIOTHERAPY

- Adjuvant radiotherapy was given to patients whose Tumor size is more than 5 cm or with four or more clinically positive axillary lymphnodes or who have positive resection margins after surgery.
- Tumor size more than 5cm - 64 patients
- Positive resection margins found in 17 patients

FOLLOW UP

All the patients were followed up with clinical examination at monthly interval and with blood count and biochemistry, ultrasound abdomen, Mammography at 3 monthly interval.

Follow up period were from 6 months to 20 months.

76 out of 95 patients came for regular follow up (80%)

In our study, 7 were detected to have local recurrence. They were treated with Radiotherapy and chemotherapy.

8 developed distant metastais

Lung secondaries - 4

Brain secondaries - 1

Spine metastasis - 2

Liver metastasis -1

They were given chemotherapy .

CT chest, pleural aspiration cytology for confirmation of malignant deposits done in patients with lung secondaries and pleural effusion

CT Dorsolumbar spine done in patients with spine metastasis one had D6 vertebra compression and local radiation was given

CT brain was done in the patients with brain metastasis and one developed raisied intracranial pressure for which ventriculoperitoneal shunt was done.

CT abdomen was done in patient with liver metastasis, who had Ascites. Paracentesis of Ascitic fluid was done and malignant cells were detected in cytological analysis.

SUMMARY

SUMMARY

In our study the following observations were made.

1. The commonest age of presentation was 40 – 50 years of age.
2. About 47.36 were premenopausal and 46.31 were postmenopausal 5.26% were Nullipara.
3. Commonest mode of presentation was painless lump in 46.31%.
4. Most of the patients presented with stage III disease 62.09%.
5. Lymphnode positivity during presentation was about 69.46%.
6. Invasive ductal carcinoma was the commonest pathological variety in our stage. Histological grade I was found in 56.84%
7. Most of our patients presented with Tumor size more than 5 cm (67.36%).
8. Modified Radical mastectomy was done in 90 patients. Toilet mastectomy was done in 5 patients presenting with ulceration/fungating lesions
9. Resected margins were found to be positive in 5 patients all of them were given radiotherapy. Three of them developed locoregional recurrence 2 developed metastasis. One in lung, one in brain.
10. Lymphnode examination for metastatic deposits in pathological specimen showed positivity in 49 patients. More than 6 nodes were positive for metastatic deposits in 13 patients. Of which 4

developed locoregional recurrence and one developed liver, lung metastasis. One patient with supraclavicular node developed spine metastasis. All patients were treated with chemotherapy and radiotherapy.

11. Histologic grade 1 found in 44.21 of patients, grade 3 found in 10.52% of our patients (10 Pts) of which 3 had locoregional recurrence. 2 developed lung secondaries during the follow up period.
12. Patients who developed lung metastasis had Tumor size more than 8cm during presentation and 1 of them had histological grade III invasive ductal carcinoma. Supraclavicular node was involved in one patient.
13. One patient with brain metastasis had Tumor size of 6 cm during presentation, she had more than 6 nodes positive for deposits in pathological resection specimen.
14. .One patient who developed both spine and liver metastasis presented with tumor involving all quadrants.
15. In the hormone receptor study done in 20 cases .(10 cases in premenopausal age group and 10 cases in postmenopausal age group), estrogenreceptor positivity was seen in 65% (13cases), negativity for both receptors in 35% (7 cases) with increase in positivity in older age group(50-59 years).

1. ER+, PR- tumours (5/10 cases) are more prevalent in postmenopausal age group constituting 50%.

2. Special histological variants like papillary carcinoma, lobular carcinoma are positive for ER and PR.Medullary and Metaplastic variants are negative for both receptors. In our study, ER /PR negative found in 7 patients. Among them one patient with ER/PR –ve medullary carcinoma developed local recurrence, and one patient with ER/PR –ve metaplasic carcinoma developed lung metstasis.

16. Nottingham Prognostic index was found to have direct correlation with prognosis in our study. In 32 of our patients with NPI more than 5.4, 5 had local recurrence, 3 had lung metastasis, 2 developed spine metastasis and one developed brain metastasis during follow up.

CONCLUSION

CONCLUSION

The aim of the study is to identify the prognostic factors in primary breast cancer. The utility of prognostic factors lies not only in their ability to prognosticate the outcome of the disease but also in detecting early disease, monitoring of disease course, screening for recurrent disease. They also help in deciding upon application of adjuvant systemic therapy and in identifying patients of poor prognosis who warrant more aggressive investigational therapies.

Commonly assessed prognostic factors are number of lymphnodes in axilla, tumour size, TNM stage, histologic tumour type, histologic tumor grade.. Immunohistochemical study of ER/PR hormone receptor in breast cancer patients will lead on to a precise and individualised management which will have better impact on the disease free survival and overall survival.

Tumor size has linear relationship with prognosis and eventual metastasis. As tumor size increased, survival decreased regardless of lymph node status and as lymph node involvement increased, survival status decreased regardless of tumor size. Medial lesions have slightly worse prognosis than lateral lesions due to involvement of mammary nodes. Histological grade of tumor also seems to correlate with

regional recurrence and metastasis. Patients with post operative positive resection margins were also at high risk of locoregioal recurrence.

Hence it is suggested that for patients with breast cancer, the prognostic markers that can be routinely assessed are axillary lymphnode status, tumour size,histologic grade, estrogen and progesterone receptor status, post operative findings like positive margins. They are helpful in planning adjuvant treatment.

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ANNEXURES

PROFORMA

Name :

Age

IP no :

DOA :

Address :

HISTORY :

Lump :

Duration :

Pain :

Discharge :

Ulcer :

Others :

Axillary node :

Metastasis :

REPRODUCTIVE HISTORY:

Age at menarche :

Age at child birth :

Parity :

Duration of breast feeding :

Menstrual status :

Hormonal therapy :

FAMILY HISTORY :

Number of relative affected :

Other coexisting malignancy :

Age at cancer detected :

Laterality :

TREATMENT HISTORY :

Previous benign diseases :

Previous malignant disaeases :

PHYSICAL EXAMINATON :

BREAST MASS :

Size :

Location :

Consistency :

Fixity :

SKIN CHANGES :

Erythema :

Dimpling :

Edema/ Peau d'orange

Satellite nodule :

NIPPLE CHANGES :

Retraction :

Eversion :

Discoloration :

Discharge :

AXILLARY NODE :

Number :

Fixity :

Location :

Supraclavicular node :

Opposite breast &axilla :

Abdomen :

Respiratory system :

Spine & Cranium :

P/R&P/V :

Stage :

Investigations :

1.FNAC :

2.X-Ray Chest :

3.Mammogram :

4.USG Abdomen :

5.CT Thorax :

6.LFT :

7.Others : X-Ray long bones

Bone scan

SURGERY :

HPE REPORT :

Type of malignancy :

Grade :

Resected margin :

Lymph node status :

Receptor status :

ER Status if done : Positive or Negative

PR Status if done : Positive or Negative:

CHEMOTHERAPY :

RADIOTHERAPY :

FOLLOW UP :

சுய ஒப்புதல் படிவம்

மார்பக புற்றுநோயின் தன்மையை தீர்மானிக்கும் காதகமான அளவுகோள்கள் பற்றி ஆராய்தல்

ஆராய்ச்சி நிலையம் : மகாத்மா காந்தி நினைவு அரசு மருத்துவமனை, திருச்சி.

பங்கு பெறும் நோயாளியின் பெயர் :

பாலினம் : ஆண் ☐ பெண் ☐ வயது:

பங்கு பெறும் நோயாளியின் எண் :

நோயாளியின் பெயர் / விலாசம் :

நோயாளி இதனை ( ) குறிக்கவும் :

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் விலக்கிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பரிசோதிக்க என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் என்னை ஈடுபடுத்த முழுமனதுடன் ஒப்புக் கொள்கிறேன். இந்த அறுவை சிகிச்சை மற்றும் அதனால் ஏற்படக்கூடிய பின் விளைவுகள் மற்றும் எதிர்பாராத விளைவுகள் பற்றி எனக்கு விளக்கமாகத் தெரிவிக்கப்பட்டது. ☐

என் நலன் கருதியே இந்த ஆய்வு மேற்கொள்ளப்பட்டது என்று தெரிந்து இந்த ஆய்விற்கு ஒப்பளிக்கின்றேன். ☐

நோயாளியின் கையொப்பம் .....இடம் .....
தேதி.....

கட்டை விரல்ரேகை(இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)
ஆய்வாளரின் கையொப்பம் ..... இடம் .....
தேதி.....
ஆய்வாளரின் பெயர் .....

K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE
TIRUCHIRAPALLI -1
INSTITUTIONAL ETHICS COMMITTEE

CERTIFICATE OF CLEARANCE

This is to certify that the project work titled **Prospective analysis of favorable prognostic factors in carcinoma breast** proposed by **Dr.Karthikeyan** part of fulfillment of M.D/M.S course in the subject of **Surgery** for the year **2012-2015** by The Tamilnadu Dr.MGR Medical University has been cleared by the ethics committee.

CHAIRMAN,
Institutional Ethics Committee
K.A.P.Viswanatham Govt. Medical
College, Tiruchirapalli -1

CONTINUING MEDICAL EDUCATION ON BIO - STATISTICS

Organized by

Department of Anaesthesiology

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Certificate of Attendance

Presented to

KARTHIKEYAN. A. S

for attending the C.M.E & Workshop on

Bio-Statistics on 7th December 2013

Conducted by the Dept. of Anaesthesiology,

Mahatma Gandhi Memorial Govt.Hospital &

K.A.P.Viswanatham Govt.Medical College, Trichy.

Credit Hours : 6 Hours.

Dean	Vice Principal	Prof & H.O.D
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PROSPECTIVE ANALYSIS OF FAVORABLE PROGNOSTIC FACTORS IN CARCINOMA BREAST

DISSERTATION SUBMITTED FOR M.S DEGREE EXAMINATION

BRANCH I

(GENERAL SURGERY)

K.A.P.V. GOVERNMENT MEDICAL COLLEGE AND MAHATMA GANDHI MEMORIAL HOSPITAL, TIRUCHIRAPALLI

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

CHENNAI

APRIL 2015

1

PROSPECTIVE ANALYSIS OF FAVORABLE PROGNOSTIC FACTORS IN CARCINOMA BREAST

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

CHENNAI

APRIL 2015

MASTER CHART

sno	NAME	AGE	IP NO	Menstrual status	parity	presentation	side	quadrant	tumor size	node	stage	surgery		HISTOLOGY						
													type	grade	lymphnode	marign	ER/PR	LR	METASTASIS	NPI
1	Neela	55	1595	Menopause	3	Lump	R	U. Outer	8x7 cm	2	IIIb	MRM	IDCNos	II	2/6+ve	free	POS/POS			6.6
2	Mariyammal	55	3261	Menopause	4	Lump, pain,discharge	R	Areola	2x1 cm	1	II a	MRM	Papillary ca	II	6/6 +ve	free	POS/POS			3.4
3	Nagammal	45	4385	Pre	Nil	Lump, pain,discharge	R	All	14x10 cm	3	IIIb	MRM	IDCNos	III	4/10+ve	Free	POS/NEG			7.8
4	Dhanabagyam	38	5854	Menstruating	2	Lump	L	U. Outer	3x2 cm	1	Iib	MRM	IDCNos	I	3/6 +ve	Free	POS/NEG			3.6
5	Sigapayee	60	26314	Hyst	3	Lump	R	U. Outer	6x5 cm	2	IIIa	MRM	IDCNos	II	7/7 +ve	Free				6.2
6	Chinammal	50	10994	Menopause	3	Lump	R	Central	6x6 cm	1	IIIa	MRM	IDCNos	I	5/7 +ve	Free	POS/NEG			5.2
7	Shanthi	50	15514	Menopause	2	Lump	R	U. Outer	4x4 cm	2	IIIa	MRM	IDCNos	I	7/12+ve	Free	POS/NEG			2.8
8	Manimeghalai	35	14950	Pre	2	Lump	R	U. Outer	7x8 cm	1	IIIb	MRM	IDC	I	4/9+ve	free	NEG/NEG			3.6
9	Balamani	48	15675	Pre	1	Lump	R	U.L. Outer	8x6 cm	2	IIIb	MRM	IDC/NOS	II	2/7+ve	Free	POS/POS			6.6
10	Alagammal	45	19212	Pre	2	Lump	L	Central	5x3 cm	1	IIIa	MRM	IDC	II	4/6 +ve	Free	POS/POS			6
11	Rajeshwari	35	56853	Pre	2	Lump	L	U. Outer	8x6 cm	2	IIIb	MRM	IDC Nos	I	Negative	Free				3.6
12	Vijaya	37	25771	Pre	2	Lump	L	U. Outer	6x5 cm	Nil	IIIb	MRM	IDC Nos	I	1/6 +ve	Free				3.2
13	Thamarai	58	27708	Post. Meno	2	Lump	R	U. Outer, L. Inner	15x10 cm	2	IIIb	MRM	IDC	I	2/6 +ve	free			Opposite axilla +ve	6
14	Saraswathi	55	28423	Menopause	3	Lump	R	U. Outer, Outer, Inner	10x8 cm	2	IIIc	Tollet M.	IDCNos	III	7/22 +ve	positive	POS/NEG			7
15	Akhilandam	52	35406	Menopause	3	Lump, pain	R	U. Outer	5x8 cm	2	IIIa	MRM	IDCNos	I	3/8 +ve	Free	NEG/NEG			4.6
16	Shakila	24	31324	Menstruating	2	Lump, discharge	R	U. Outer	6x4 cm	1	IIb	MRM	IDC Nos	I	3/7+ve	Free	NEG/NEG			4.2
17	Mariayee	40	33322	Menopause	2	Lump, pain	R	U. Outer	10x8 cm	2	IIIb	MRM	IDC	I	Negative	free				5
18	Pushpavalli	47	33060	Hyst	3	Lump, pain	R	U.Outer	7x7 cm	1	IIIa	MRM	IDC	I	4/6 +ve	free				5.4
19	Rani	60	36815	Menopause	3	Lump,pain	L	U. Outer	8x5 cm	1	IIIa	MRM	IDC	II	3/6 +ve	free				5.6
20	Kamatchi	42	43587	Pre	3	Lump, pain	R	U. Outer	3x2 cm	1	IIa	MRM	IDC/NOs	II	6/10 +ve	Free	POS/NEG			4.6
21	Indirani	45	43982	Menopause	2	Lump	L	U. Outer	3x2 cm	1	IIb	MRM	IDC	II	6/6 -ve	free				3.6
22	Kannagi	51	49575	Menopause	3	Lump	L	U.Outer	10x8 cm	2	IIb	Tollet M.	IDC/Nos	II	4/6+ve	Positive		LR	Lung	7
23	Lakshmi	45	52645	pre	3	Lump	R	U.Outer	5x2cm	Nil	IIIb	MRM	IDC/Nos	II	Negative	free				4
24	Tamilarasi	27	53029	Menstruating	2	Lump	L	U.Outer	5x4cm	Nil	IIb	MRM	IDC/Nos	II	3/10+ve	free	IEG/NEG			4
25	Valarmathi	46	55454	pre	3	Lump	R	U.Outer	5x6cm	Nil	IIb	MRM	IDC	II	6/6+ve	free				5.2
26	Ponnammal	45	54606	Menopause	2	Lump	R	U.Outer	6x3cm	1	IIIA	MRM	IDC/Nos	II	10/16+ve	free				6.2
27	Rukkumani	60	57211	menupause	6	Lump	R	U.Outer	8x5cm		IIIb	MRM	IDC	I	Negative	free				3.6
28	Ponnammal	45	57160	pre	3	Lump	R	I.Lower	6x5cm	1	IIIb	MRM	IDC/Nos	III	4/6+ve	free	NEG/NEG			7.2
29	Asharafbee	57	31460	Menopause	5	Lump	L	I.Lower	8x5cm	1	IIIA	MRM	IDC	I	3/5+ve	Free				4.6
30	Joshbinmary	60	34161	Menopause	nulli	lump,pain,ulcer,dis	R	U.Outer,CENTRAL	6x4 cm	2	IIIb	Tollet M.	IDC	III		Positive			Lung	6.2
31	Lakshmanan	65	35997	Male	3	Lump	R	Lower, Inner, Outer	10x8 cm	2	IIIb	MRM	IDC	II	3/6 +ve	free				6
32	sevathamani	45	295192	Menopause	3	Lump,node	L	U.Outer, Central	12x8 cm	1	IIIb	Tollet M.	IDC	III		Positive		LR	Spine	7.4

33	Ponnamalai	65	32338	Menopause	3	Lump, pain	R	L.Inner	8x5 cm	3	IIIa	MRM	IDC	II	Negative	free				5.6
34	Rani	45	58377	Menopause	nulli	Lump	L	U.Outer	2x5 cm	1	IIb	MRM	IDC	I	Negative	free				3
35	Malathi	50	35261	Menopause	6	Lump,pain,discharge	L	U.Outer	8x5 cm	1	IIIb	MRM	Collold		Negative	free				2.6
36	Sakunthala	43	165909	Pre	2	Lump	R	Central	6x4 cm		IIIb	MRM	Medullary	II	6/7 +ve	Free	NEG/NEG	LR		5.2
37	Kanniyammal	40	35957	Menopause	4	Lump,discharge	R	U.Inner,L.Inner	10x8 cm	4	IIIb	MRM	IDC	I	Negative	free			Opp. Axilla +	7
38	Saroja	50	173219	Menopause	2	No lump,discharge	R	No lump		1	Ca. in situ	MRM	Pagets		1/6 +ve	free				1
39	Jayamma	50	172678	Menopause	2	Lump	R	U.outer	2x1 cm		IIa	MRM	IDC,Lobular ca.	II	Negative	free				3.4
40	Arokiyamary	55	1662	Menopause	1	Lump	L	U.outer	3x3 cm		IIa	MRM	Lobular ca.		10/10 -ve	free				1.6
41	Claramarry	40	45538	Menstruating	4	Lump,pain	L	U.outer	8x7 cm	1	IIIa	MRM	IDC		Negative	free				4.6
42	Sathyanathan	31	54182		3	Lump, pain	R	U.outer	6x5cm	1	IV	MRM	MFH		Negative	free		LR	Lung	3.2
43	Chellammal	48	544457	Menopause	3	Lump,pain,dyspnea	R	All	20x14cm	1	IIIb	MRM	IDC	II	Negative	free				8
44	Gokila	43	54825	Pre	3	Lump,discharge	R	Lower inner quad	12x8cm	3	IIIb	MRM	Lobular ca.		Negative	free				3.4
45	Akilambal	55	4388	Menopause	3	Lump,pain,dyspnea	R	U.Outer	6x5cm	1	IV	MRM	IDC	I	Negative	free				3.2
46	Alamelu	53	4712	Menopause	3	Lump,pain	R	All	8x5 cm	2	IV	MRM	IDC Nos	III	6/6 +ve	free				4.6
47	Madhalaimary	35	2020	Menstruating	3	Lump	L	U.Outer	8x4 cm	1	IIIb	MRM	Alpha metallo		4/6 +ve	free				4.6
48	Nachiammal	30	1718	Menstruating	3	Lump	R	U.Outer	5x4cm		IIb	MRM	DCIS		Negative	free				3
49	Deivavirai	40	11108	Pre	3	Lump	L	U.Outer	6x5 cm	1	IIIa	MRM	Medullary ca.		3/4 +ve	free			Opp. Axilla -	3.2
50	Maragatham	40	3650	Menstruating	2	Lump,pain	R	U.Outer	8x2 cm	2	IIb	MRM	IDC	II	5/5 +ve	free				5.6
51	Chellammal	40	37289	Pre	4	Lump	R	U.Outer	5x4cm	1	IIb	MRM	IDC	I	Negative	free				3
52	Bhuvaneshwari	63	37393	Menopause	3	Lump	L	U.Outer	6x5cm	1	IIIb	MRM	Metaplastic	I	3/6+veA	free	NEG/NEG		Lung	4.2
53	Muthukali	45	37809	Hyst	3	Lump	R	U.Outer	5x4cm		IIb	MRM	IDC	I	Negative	free				3
54	Sundari	47	39077	Pre	2	Lump	L	U.Outer	4x5cm	1	IIb	MRM	IDC	I	4/6 +ve	free				5
55	Tamilmani	43	38256	Menopause	2	Lump,Ulcer,dis	R	All	8x7 cm	1	IIIb	MRM	IDC	I	Negative	free				4.6
56	Amuthavalli	50	38814	Menopause	2	Lump	R	U.Outer	6x4 cm	1	IIIa	MRM	IDC	II	2/6 +ve	free				5.2
57	Kasthuri	41	39216	Pre	nulli	Lump,pain,discharge	L	Central	10x8 cm	1	IIIa	MRM	IDC	I	3/6+Ve	free				5
58	Eswari	60	40433	Menopause	6	Lump	R	U.Outer	6x5cm	Nil	IIIb	MRM	IDCNos	I	1/6+ve	free	POS/NEG			3.2
59	Swathi	50	40431	Menopause	4	Lump	R	U.Outer	6x3cm	Nil	IIb	MRM	IDC	I	7/7+ve	free				2.2
60	Kamala	52	40432	Hyst	2	Lump	R	U.Outer	3x2 cm	Nil	IIa	MRM	IDC	I	4/6+ve	free				2.6
61	Radha	50	38812	Menopause	2	Lump	L	U.L. Outer	15x10 cm	1	IIIa	MRM	IDC	I	5/7+ve	free				7
62	Anandhi	55	40848	Menopause	3	Lump	R	All	15x10 cm	3	IIIa	MRM	IDC	I	4/6+ve	free				7
63	JamunaRani	65	43771	Menopause	3	Lump,pain	L	U.Outer	3x4cm	Nil	IIA	MRM	Infiltrating lobular	I	Negative	free	POS/POS			2.8
64	Indhumathi	45	44440	Menopause	nulli	Lump,pain	R	L.Inner	2x1 cm	3	IIa	MRM	IDC	I	6/6+ve	free				4.4
65	Chandra	50	45708	Menopause	2	Lump	L	U.Outer	10x10cm	Nil	IIIb	MRM	IDC Nos	I	6/6+ve	free				5
66	Muthammal	45	45567	Menopause	2	Lump	L	Central	10x8 cm	2	IIIb	MRM	IDC	II		free				7

67	Devi	70	45284	Menopause	3	Lump,pain	L	U.Outer	3x5cm	1	IIb	MRM	MUCINOUS	I	Negative	free	POS/NEG			3
68	Tamilselvi	32	46552	Menopause	2	Lump	L	U.outer	12x5 cm	2	IIIb	MRM	IDC Nos	II	7/7+ve	free				7.4
69	Mallika	60	46458	Menopause	3	Lump	L	U.Outer	6x4cm	1	IIIA	MRM	IDC	II	2/4+ve	free				5.2
70	Muthulakshmi	40	46762	Pre	2	Lump	R	Central	4x5cm	1	IIIb	MRM	IDC	I	Negative	free				4.8
71	Dhanalakshmi	60	53635	Menopause	3	Lump,pain	R	U.Outer	6x5cm	3	IIIa	MRM	IDC	III	2/22+ve	free				6.2
72	Jennifer	60	52638	Menopause	3	Lump,pain	L	U.Outer	3x2cm	1	IIb	MRM	IDC	II	1/6+ve	free				4.6
73	Meghala	50	52634	Menopause	3	Lump,pain,node	L	All	15x10cm	3	IIIa	MRM	IDC	III	3/10+ve	Positive		LR	Brain	8
74	Pavithra	55	52636	Menopause	2	Lump,pain	R	U.Outer	8x7cm	1	IIIb	MRM	IDC	II	3/7+ve	free				5.6
75	Sophia	35	52858	Pre	2	Lump	L	U.Outer	4x5cm	1	IIIa	MRM	IDC Nos	II	Negative	free				4.8
76	Selvi	40	34977	Pre	3	Lump	R	All	8x5cm	2	IIIa	MRM	IDC	I	Negative	free				3.6
77	Radha	52	37891	Menopause	3	Lump,Ulcer,dis	L	U.Outer	10x8cm	3	IIIb	Tollet M.	IDC	III	Negative	Positive				6
78	Gomathi	42	56044	Pre	3	Lump	L	U.Outer	6x3cm	1	IIIa	MRM	IDC	II	3/6+ve	free				5.2
79	Divyabharathi	45	56072	Pre	2	Lump	R	U.Outer	5x3cm	1	IIIb	MRM	IDC	I	4/6+ve	free				5
80	Kala	50	56213	Menopause	2	Lump	R	Central	3x4cm	Nil	IIIa	MRM	IDC	I	1/5+ve	free				2.6
81	Sulochana	35	56032	Menstruating	2	Lump	L	U.Outer	3x2cm	1	IIb	MRM	IDC	II	Negative	Negative				3.6
82	Ramya	43	56833	Pre	2	Lump	L	U.outer	4x2cm	1	IIb	MRM	IDC	I	3/3+VE	free				3.8
83	Ambika	35	5568	Menstruating	2	Lump	L	U.outer	6x5cm	1	IIIa	MRM	IDC/Nos	I	1/4+VE	free				4.2
84	Gracie Joy	45	5693	Pre	2	Lump	R	U.outer	4x2cm		IIa	MRM	IDC/Nos	II	6/12+ve	free				4.8
85	Gokila	50	6690	Pre	2	Lump	R	U.outer	5x3cm	1	IIb	MRM	IDC	I	1/6+ve	free				4
86	Chinammal	38	7411	Menstruating	2	Lump,pain,discharge	L	All	8x9cm	2	IIIb	MRM	IDC	II	6/7+ve	free				6.6
87	Shanthi	37	9567	Menstruating	2	Lump	R	U.outer	6x4cm	1	IIIb	MRM	IDC	I	1/6+ve	free				4.2
88	Annapoorani	50	11769	Menopause	2	Lump	L	U.outer	3x2cm	1	IIb	MRM	IDC	I	2/6+ve	free				3.6
89	Vedhavalli	44	13479	Pre	2	Lump	R	U.outer	7x6cm		IIb	MRM	IDC	II	Negative	free				4.4
90	Chellam	39	13454	Pre	3	Lump	L	U.outer	5x3cm	1	IIb	MRM	IDC	I	3/6+ve	free				4
91	Malarvizhi	32	95479	Menstruating	2	Headache,blurring	L	Central	8x4 cm	3	IV	MRM	IDC	II	Negative	free		LR	Brain,bone	5.6
92	Jaya	45	15554	Pre	2	Lump,pain	L	U.outer	8x4 cm	1	IIIa	MRM	IDC	III	Negative	free				6.6
93	Kavery	42	16958	Pre	4	Lump	R	U.outer	8x3cm	1	IIIb	MRM	IDC	II	Negative	free				5.6
94	Rubina	58	16941	Menopause	2	Lump,pain	R	U.outer	3x2cm	3	IIa	MRM	IDC	I	6/6+VE	free		LR		5.6
95	Ramzan Bibi	47	19215	Menopause	2	Lump,pain	L	All	10x7cm	2	IIIb	MRM	IDC	I	1/11+ve	free			[illegible]	5

KEY TO MASTER CHART

Pre	-	Pre Menstrual
Hys	-	Hysterectomy
U.O	-	Upper Outer
MRM	-	Modified Radical Mastectomy
LR	-	Local Recurrence
IDC	-	Intra carcinoma
IDC/NOS	-	Intra Ductal Carcinoma – Not Otherwise Specified
S.C Node	-	Supraclavicular noe
NPI	-	Nottingham Prognostic Index