"EVALUATION OF CLINICAL AND PATHOLOGICAL RESPONSE FOLLOWING NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER"

Dissertation Submitted to

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY

In partial fulfilment of the regulations for the award of the degree of

M.S. GENERAL SURGERY

BRANCH - I

GOVERNMENT VELLORE MEDICAL COLLEGE

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY

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APRIL 2020

CERTIFICATE BY THE HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"EVALUATION OF CLINICAL AND PATHOLOGICAL RESPONSE FOLLOWING NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER"** at GOVT VELLORE MEDICAL COLLEGE AND HOSPITAL is a bonafide research work carried out by **DR.JEYADURGA.C**, Post graduate student in Department of General Surgery, Government Vellore Medical College and Hospital,Vellore.

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Title of the Study – EVALUATION OF CLINICAL AND PATHOLOGICAL RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

Principal Investigator – Dr. Jeya Durga, I Year PG, MS General Surgery

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Professor of General Surgery

The request for an approval from the Institutional Ethical and Scientific Committee (IEC) was considered on the IEC meeting held on 03.10.2018 at the Conference Hall, Govt. Vellore Medical College, Vellore-11.

The Convenor, Chairperson, Member Secretary and committee members decided to approve the proposed work mentioned above submitted by the Principal Investigator.

The Principal Investigator is instructed to submit the status of this project periodically to this College Office.

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PROF.DR.D.LOGANATHAN,M.S.,
Professor and HOD of General Surgery
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CERTIFICATE

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CERTIFICATE II

This is to certify that this dissertation entitled, "**Evaluation of clinical and pathological response following neoadjuvant chemotherapy in locally advanced breast cancer** in **Government Vellore Medical College and Hospital"** is done by the candidate**Dr.JEYADURGA .C**with registration number **221711653** for the award of **M.S.** degree in the branch of general surgery. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from the introduction to conclusion pages and shows the result of 14 percent of plagiarism in the dissertation.

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DECLARATION

I, certainly declare that this dissertation titled "**EVALUATION OF CLINICAL AND PATHOLOGICAL RESPONSE FOLLOWING NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER"** represents a genuine work of me. The contributions of any supervisors to the research are consistent with normal supervisory practice and are acknowledged.

I also affirm that this bonafide work or part of this work was not submitted by me or any others for any award, degree or diploma to any other university board, either in India or abroad. This is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery Degree Branch-I (General Surgery).

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Last but not the least, I thank all my patients for their kind cooperation in this study.

CONTENTS

AIM OF THE STUDY

1. To analyse the clinical and pathological response rates following neoadjuvant chemotherapy in locally advanced breast cancer.
2. To determine the clinicopathological factors associated with pathological response and survival outcomes.
3. To study the outcomes in terms of disease-free survival and overall survival.

INCLUSION CRITERIA:

1. Patients with locally advanced breast cancer
2. Age more than 25 years

EXCLUSION CRITERIA:

1. Prior breast surgery
2. Metastatic disease

STUDY	**:**	Observational Study
SAMPLE SIZE	**:**	60
PERIOD OF STUDY	**:**	2 years
ETHICAL CLEARANCE	**:**	Yes

METHODOLOGY:

- Patients more than 25 years of age presenting with malignant breast lump were evaluated.
- Diagnosis confirmed by core needle biopsy, grade and metastatic workup were done.
- 60 patients who fulfilled the inclusion criteria were chosen and sent for neoadjuvant chemotherapy (FAC/PACLITAXEL REGIMEN).
- Clinical response was assessed after 3 cycles of chemotherapy and modified radical mastectomy was done.
- Specimen was analysed for pathological response and observations were made.

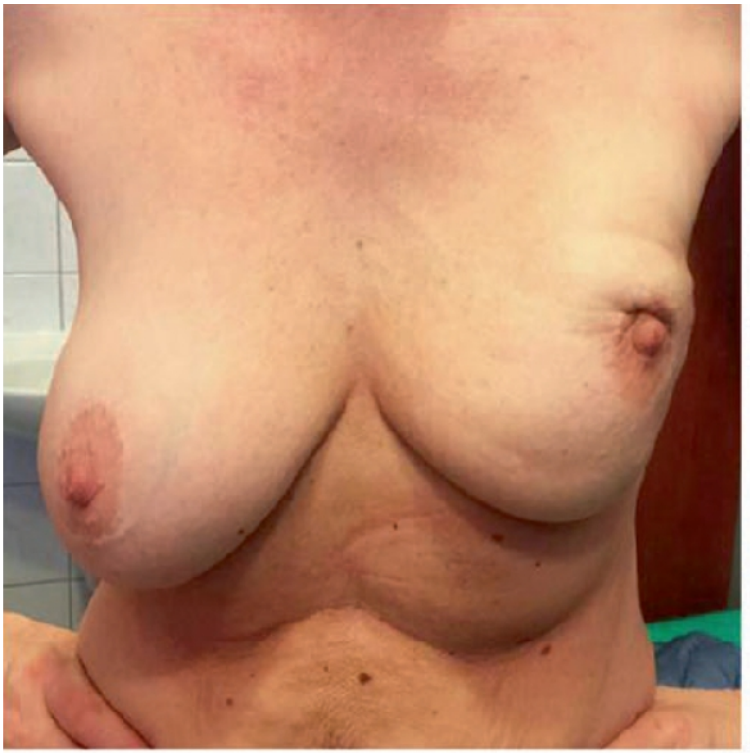
REVIEW OF LITERATURE

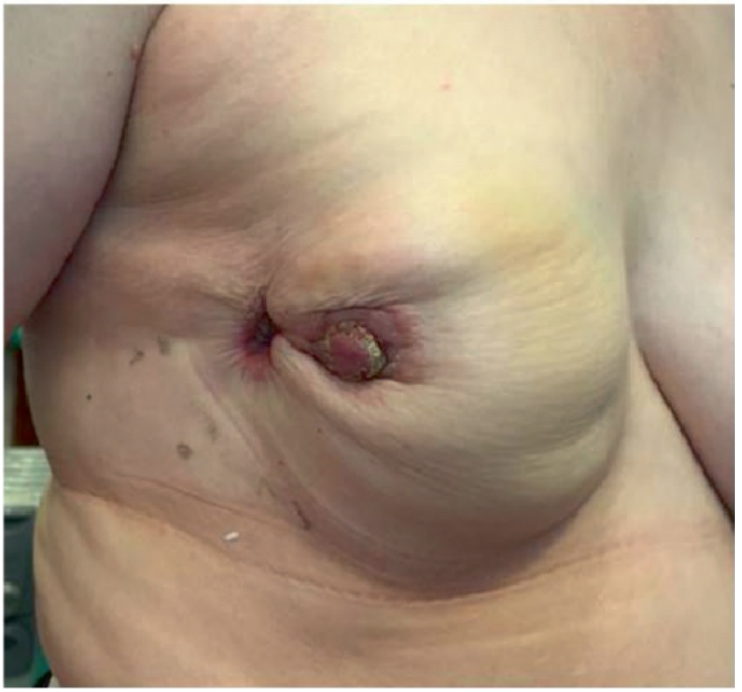
The definition of locally advanced breast cancer (LABC) usually includes stage III disease defined as any primary tumours with clinically detectable axillary (fixed or matted), ipsilateral infraclavicular, supraclavicular or internal mammary lymph nodes (N2 or N3 disease) or tumour extension to the chest wall or skin (T4).

Some LABC definitions also include patients with primary tumour ≥5 cm and no or mobile axillary nodal involvement (T3 N0–1). However, mostly categorised as large operable breast cancers, in contrast to truly inoperable cases with inflammatory features or skin or chest wall involvement, fixed or bulky axillary nodal metastases and/or supraclavicular or internal mammary nodal disease.

Locally advanced breast carcinoma is considered as inoperable either because they are technically unresectable or they have an extremely high chance of metastasis, local recurrence or death despite of aggressive surgical resection. Although multidisciplinary therapy with combination of systemic and locoregional therapy became the treatment of choice, the optimal sequencing of the individual component was not well defined.

Based on the concept of breast cancer as a systemic disease chemotherapy was introduced for the treatment of LABC, and drastic clinical and pathological response to neoadjuvant chemotherapy was noted in majority of patients, and long-term outcome was associated with significant higher disease-free survival and overall survival.





Patient with LABC,showing skin and chest wall involvement

ANATOMY OF BREAST

The location of the female breast is between the 2nd and 6th/7th ribs,medial to the anterior axillary line and lateral to the sternum. The female breast is posteriorly associated with pectoralis major fascia, also associated with external oblique aponeurosis, serratus anterior and rectus abdominis muscle.

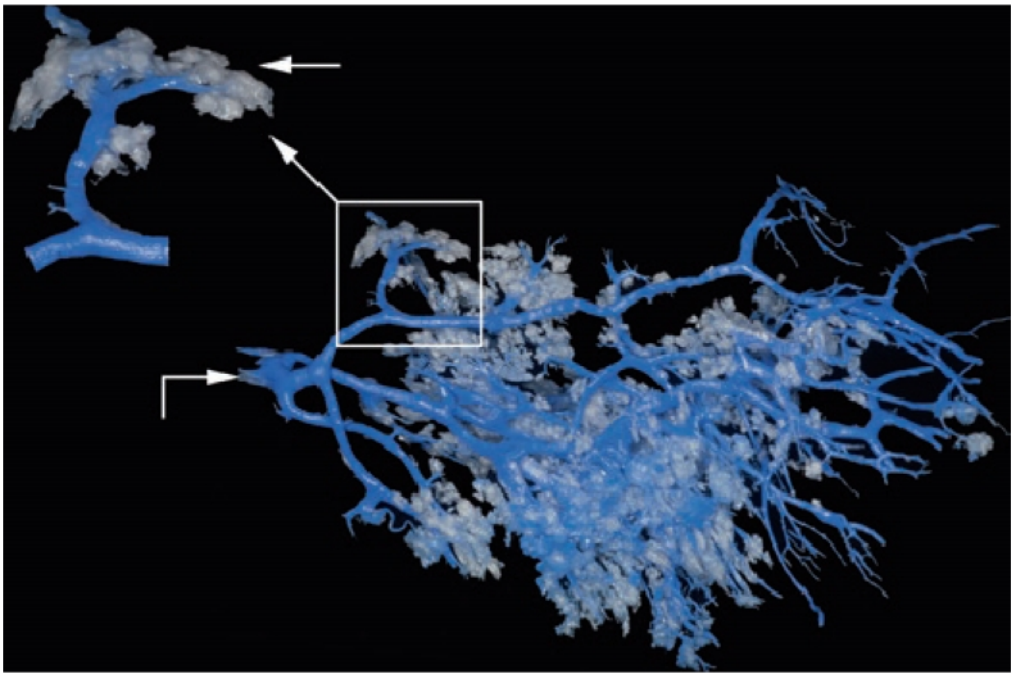
The breast's volumeis determined by the amount of fatty and glandular tissue. The glandular tissue is less dominant until the secondhalf of pregnancy. The gland becomes fullydeveloped duringlactation. The fatty andglandular tissue is suspended by thefascial-ligamentous system.

Around 15–20 radially locatedlobes are present in the glandular tissue. Thefibrous and interlobular bundles separate each of the lobes. Dense fibrous tissue surrounds the lobules.During lactation around 15–20 main ducts branch that finally terminate inthe terminal duct lobular unit (TDLU) secretes milk.(1)

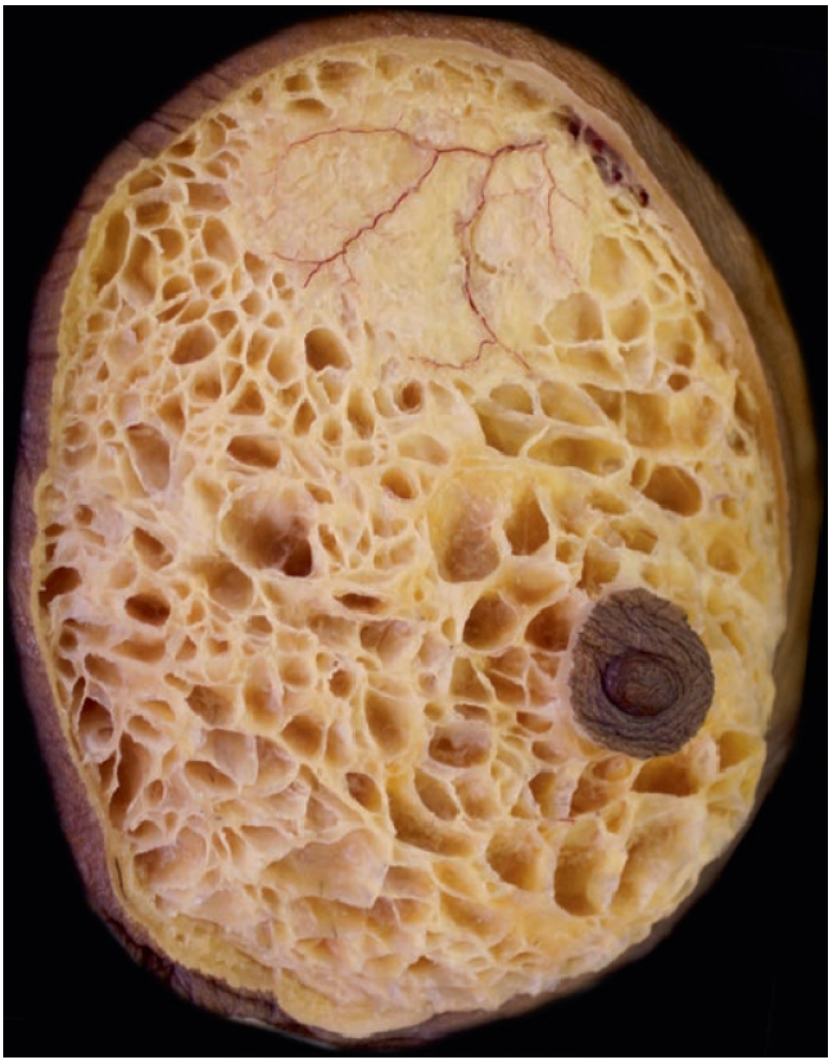
The mostprominent part of the breast consists of the nipple-areola complex (NAC). On top of the nipple there are 15–20 main ducts with 15–20 ductal orifices are present. With respect to classical anatomical descriptions,every lobe has its own main duct and orifice.

Directly underneaththe nipple, the ducts have a zone(lactiferous sinus) which expands. During lactation they serve as a milk reservoir. There are several distinctions present in the pigmented areola. They aremodified accessory glands, so-called glands of Montgomery.

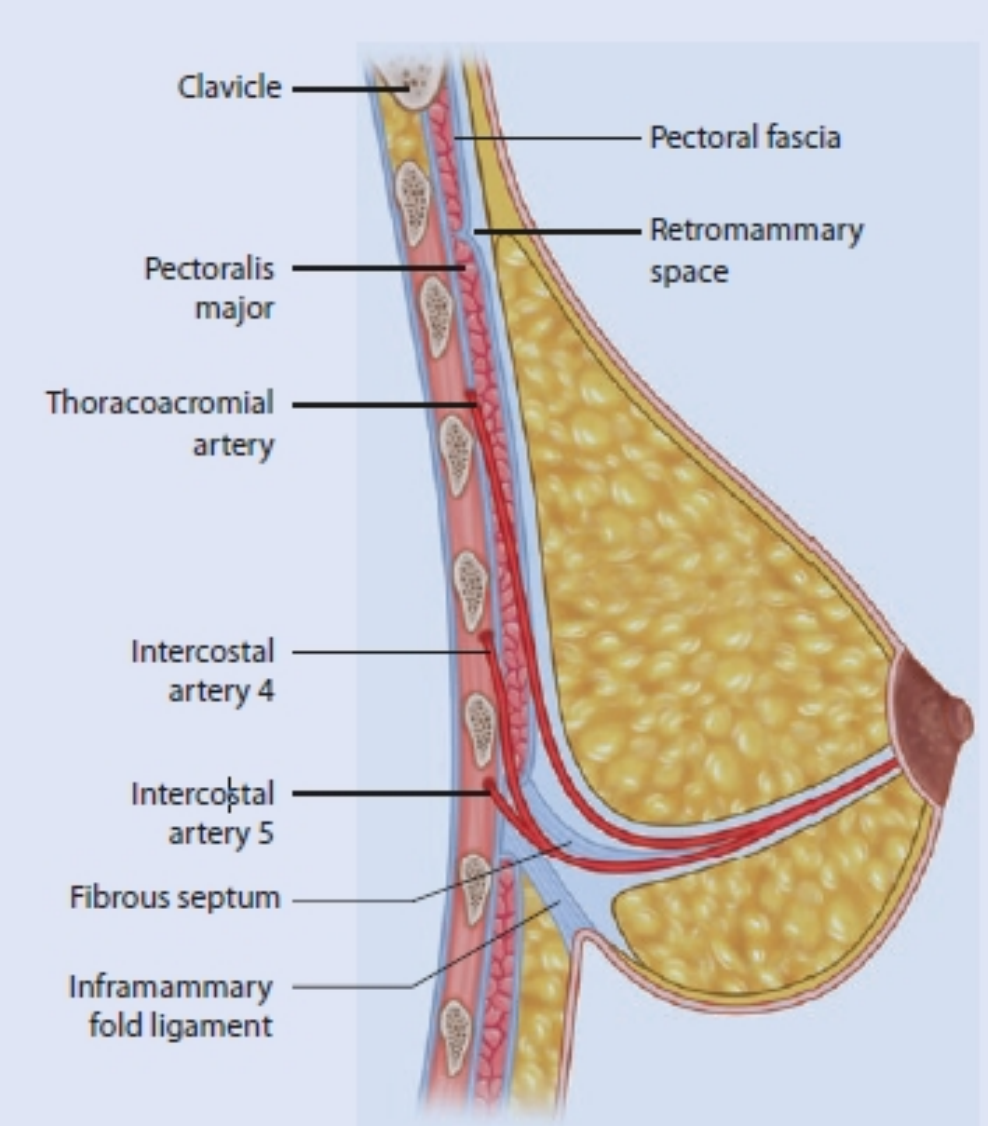
There are numerous sweat and sebaceous glands can be found amongthese, which keep the NAC protected and lubricated.The female breast can be divided into six portions.The four quadrants canbe differentiated according to the vertical and horizontal axis. Behind theareola the central substance is located, while an extension of the breast extends into the axillawhich is called the Spence’s tail.



“The picture shows the Lactiferous ducts of a pre-menopausal breast lobe”



“The picture shows the ligaments in between the skin and anterior lamella of the superficial fascia of the breast. A superficial branch of the second internal mammary artery perforator can also be seen.”



“The picture shows the schematic depiction of a lateral cross-sectional view of the fibrous septum of the female breast”

BLOOD SUPPLY:

The female breast's arterial systemis divided into superficialand deepgroups.

- The deep vessels penetrate the female breastalong the septum fibrosum in the posterior to anterior direction.
- Superficial ones travel in the subcutaneouslayer in the direction of the NAC. The superficial and deep vessels make an anastomosing subdermal network beneaththe areola that supplies to the NAC. One of the most vitalaspects of the vascular anatomy is the blood supply to theNAC.

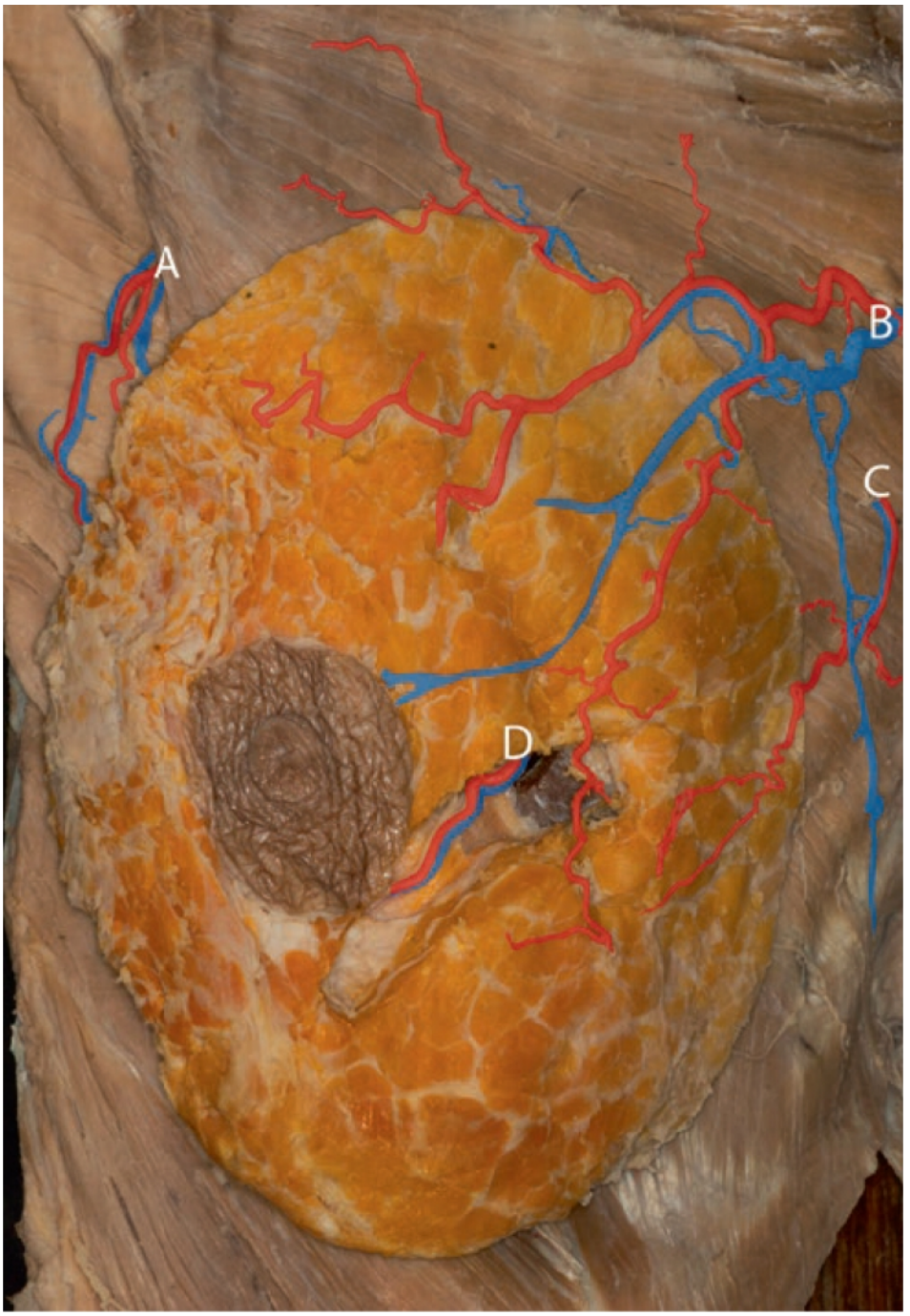
After penetrating the chestwall, the second to the fourth internal mammary artery perforators which belongs to the superficial group get into the subcutaneous tissue, where they travelfurther towards the nipple. They are the main blood supplyof the NAC anatomic variation in the number and direction of NACfeeding vessels which may account for some cases ofnipple necrosis following surgery.(2)

Blood supply for the breast is received laterally from the lateral thoracic artery. It travels under the lateral margin of the pectoralis major muscle, and then it passes round the margin and gets into the substance of the breast. It has two main branches.One of them stays deep, the "deep group" and the other becomessuperficial, the "superficial group". Both travel towards thenipple.

Thoracoacromial arterywhich belongs to the deep group arises directlyfrom the axillary artery and then branches underneath thepectoralis minor muscle. Its pectoral branchessupply theupper pole of the breast.The second to sixth intercostal artery perforators belongto the deep group of arteries.

They are smaller in general and randomvessels are supplying the base of the breast. Someof these arteries from time to time can be more prominent, particularly thefourth intercostal artery perforator. It travels in the axis of thecentral parenchyma and supplies it. From time to time this arterytravels underneath the parenchyma and passes around theinferior pole of the breast. The fifth to sixth intercostalartery perforators are located in the area of the inframammaryfold in particular.

The breast also has superficial and deepgroups of veins. Deep veins accompany the deep arteries. Superficial veins accompany the superficial arteries and aresuperficial to them. Superficial venous system is created by them.The venous blood flows towards the axillary, the internal mammaryand the intercostal veins. The venous plexus underthe areola is called the areolar venous plexus.



“The picture depicts the blood supply of the breast.”

a) Deep and superficial branches of the lateral thoracic vessels

b) The second internal mammary vessel perforator

c) Third internal mammary vessel perforator.

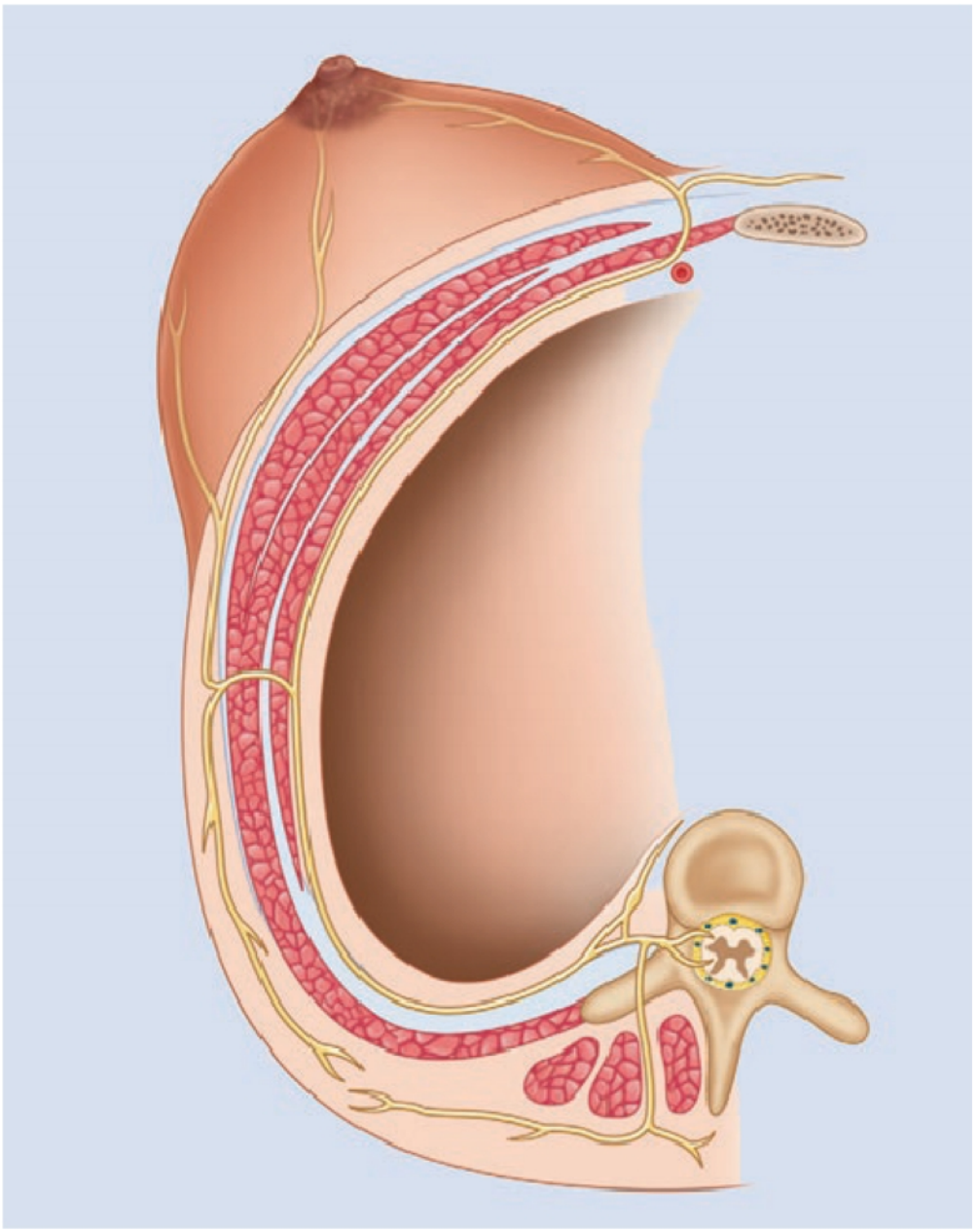
d) Intercostal vessel perforator

INNERVATION OF THE BREAST :

The anteriorand lateral cutaneous branches of the second to sixthintercostal nerves and the supraclavicular branches of thecervical plexus innervate the breast.

- Anterior cutaneousbranches of theintercostal nerves pierce the chest wall parasternally, andthen they travel superficially to laterally and innervate themedial part of the breast.
- Lateral cutaneous branches pierce the chest wall inthe mid-axillary line and then travel towards the NAC toinnervate the outer part of the breast. Upper polereceives its sensory innervation from the supraclavicularnerves.From a surgical point of view, the most important pointis to preserve the sensory innervation of the NAC, whichis ensured most commonly by the deep division of thelateral cutaneousbranches of the fourth intercostal nervelaterally and by the third and fourthanterior cutaneous branches medially in a superficial course.

The deep division of the lateral cutaneousbranches travels in the pectoral fascia and then centrallypierces the gland and innervates the NAC fromposteriorly.Since secretion is hormonally regulated, the exclusively vasomotor sympathetic fibres reach thebreast along the aforementioned nerves and vessels, whileparasympathetic fibres do not run to the breast.(3)



“Schematic representation of the nerve supply to the breast.”

LYMPHATIC DRAINAGE OF THE BREAST:

Fourcommunicating lymphatic plexuses provides the lymphatic drainage of the breast.

- The superficial networkis located in the layers of the skin, the cutaneous plexusdrains the lymph of the dermis and the subcutaneous plexusdrains the lymph of the subcutaneous tissue.
- The deep networkconsists of the fascial plexus which is located in the pectoralfasciaand the glandular plexus which drains the gland. The densityof the lymphatic vessels is the highest directly under theareola in the subcutaneous layer which is also called as “Sappey’s subareolarplexus”. The cutaneous plexus with perforating branches, theglandular plexus along the ducts and the fascial plexus along the connective tissue fibres connect directly to Sappey’s subareolar plexus.

Lymph drainage of the breast is provided on one handby the lymph vessels from the Sappey’s subareolar plexus andon the other hand by the direct efferents from the glandulartissue. The primary drainage is towards the axilla by the lateralefferents, which is responsible for 75 percentage of the breastdrainage.(4)

Axillary lymph nodes are anatomically divided into 5 groups as anterior,posterior, lateral, apical and central.

- The anterior lymph nodes are underneath thelateral margin of the pectoralis major muscle, along the lateralthoracic vein. Their afferents drain directly the glandulartissue.

- The posterior lymph nodes lay on the posterior wall of theaxilla, along the thoracodorsal bundle.
- The lateral lymphnodes are located laterally in tight topographic relationshipwith the distal axillary vein. They receive the lymph of theupper limb (except the lymph vessels, which accompany thecephalic vein).
- The central lymph nodes are located centrally,close to the axillary base, behind the pectoralis minor muscle,and receive afferents from the aforementioned lymph nodes(anterior, posterior, lateral).
- The apical lymph nodes arelocated in the apex of the axilla, on the medial side of theproximal axillary vein.

All these lymph nodes receive their afferentfrom all of the above lymph nodes and thecephalic vein associated lymph nodes. The efferent vessels of the apical lymph nodes combine to make the subclavian lymphtrunk. This trunk opens into the lymphatic duct on theright and into the thoracic duct and sometimes directly into thevenous angleon the left.

Berg defined three groups of axillary lymphnodes according to their position relative to the pectoralisminor muscle.

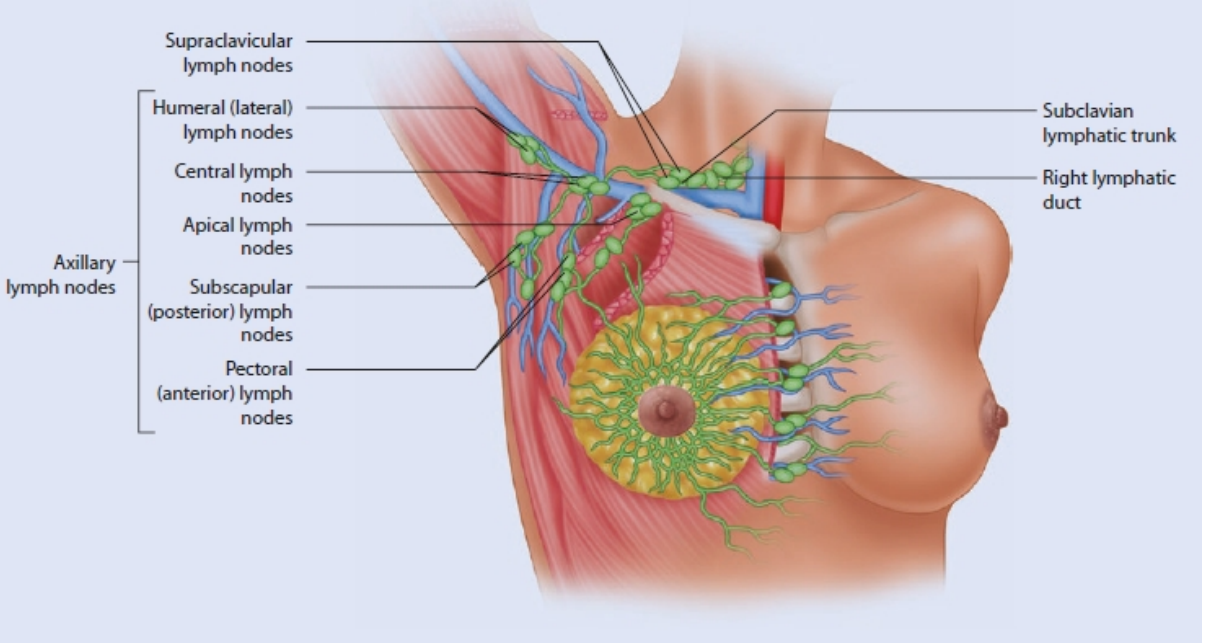
- Level I lymph nodes are located laterally tothe lateral margin of the muscle.Level I lymph nodes corresponds to the anatomical anterior, posterior and lateral lymph nodes.
- Level II lymph nodes arelocated behind the muscle. Level II lymph nodes corresponds to the central lymph nodes and some of the apical lymph nodes.

- Level III lymph nodes arelocated medially to the medial-superior margin of the muscle and corresponds to the apical lymphnodes.

It is important to note that Berg's classification usesjust the pectoralis minor muscle as a reference point, asopposed to the anatomical classification, which uses fixedanatomical landmarks. That is why the positioning of thearms has enormous consequences during surgeries of thebreast and axilla, marking of the sentinel lymph node andradiation therapy. Changing the arm position changes thelymph node levels, which are relative to the pectoralisminor muscle.

Other 25 percent of the lymph drainage splits amongthe extra-axillary efferent which serve as secondaryefferent pathways. They play a substantial clinical role, when the primary lymph efferent vessels close up or becomeblocked by previous surgery or tumour emboli, and this secondary efferent form the main direction of lymphdrainage.

From time to time the lymph drainage of the breast coursestowards the sub-diaphragmatic plexus through the abdominalwall called as "Gerota'spath". These pathwaysmay explain some of the cases of liver metastases.



"Schematic representation of lymphatic drainage of the breast"

ANATOMY OF AXILLA:

Axilla consists of four walls between thechest andthe arm with a pyramid like structure.

- Axilla's anterior wall consists of the pectoralisminor and major and subclavius muscles.
- The posteriorwall has the subscapularis, teres major and latissimusdorsi muscles.
- The medial wall is created by the lateral thoracicwall.
- The lateral wall is created by the structures ofthe arm.

Axillary opens with incision of the axillaryfascia. Thelymph nodes, vessels and nervesmake a complex network in the axillary fat.(5)

The intercostobrachial nerve is the lateral cutaneousbranch of the second intercostal nerve, which travels fromthe second intercostal space obliquely through the axillabetween the anterior and central lymph nodes,and then itanastomoses with the medial brachial cutaneous nerve. Itparticipates in sensory innervation of the medial part of theupper arm. The long thoracic nerve travels downwards, coveredby the fascia of the serratus anterior muscle. It innervatesthe serratus anterior muscle with motor nerves. Totalinjury to the nerve leads to a so-called winged scapula. Thethoracodorsal nerve runs along with the subscapular, thoracodorsalvessels along the posterior wall of the axilla andinnervates with motor nerves the latissimus dorsi muscle.

Axillary vessels are important during axillarysurgery. Approaching the axilla, the main landmark isthe axillary vein, which is themost anterior and most medialpart of the neurovascular bundle supplying the arm. Axillaryvein travels along the lateral wall, close to the posteriorwall, towards the apex of the axilla. The lateral thoracic arteryand vein and the direct branches of the axillary artery andvein travel along the inferior edge of the pectoral minor muscle.

They run among the anterior lymph nodes and supply theserratus anterior, pectoralis major, subscapular muscles andthe mammary gland inpart. They also supply the anterior, central and posterior lymph nodes withsmall branches.

Thethoracodorsal artery and vein, the subscapular artery and thedirect branches of the axillary vein run deeply, in tight topographicalrelationship with the posterior lymph nodes alongthe posterior wall of theaxilla. They supply the

latissimusdorsi muscle and, with small branches, the posterior and laterallymph nodes.

EPIDEMIOLOGY OF BREAST CANCER

Cancer of the breast accounts for 25 percentage of all female cancers diagnosed worldwide. Although, there is a large global inequality between continents and countries in its occurrence as well as mortality.

Cancer of the breast is the most common cause of cancer death in women globally. Although worldwide more women are surviving breast cancer with improved awareness, implementation of screening programmes and superior treatments, there are still vast changes in both incidence and mortality globally as well as within nations. Minority of breast cancers are due to known genetic mutations.(6)

Most breast cancers are called sporadic and are related with a number of factors, some possibly modifiable. As more evidence-based works is available on the relevance of these risk factors to breast cancer, it will be possible to understand the modifications between causation and association of these factors. Keeping this is mind, targets for preventative healthcare are highlighted, and possible interventions can be made with the overall aim to progress survival in breast cancer consequences.

RISK FACTORS OF BREAST CARCINOMA

Relative risk factors more than four	Relative risk factors less than four
Female sex	Family history
Increase in age	Individual's history of benign breast disease
Proliferative breast disease.	Substantial family history
Breast cancer in the past	Earlier age at menarche
The past history of otherhigh-risk pathology	First pregnancy at a older age
Radiation therapy in the past.	Older age at first pregnancy.
	Use of hormone replacement Therapy.
	Use of oral contraceptives.
	Lack of physical activity.
	Increased alcohol intake.
	Smoking.

TNM STAGING SYSTEM FOR BREAST CARCINOMA

Primary tumour size (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease (Paget disease) of the nipple *not* associated with invasive carcinoma and/or carcinoma in situ (DCIS and/ or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease.
T1	Tumour ≤20 mm in greatest dimension.
T1mi	Tumour ≤1 mm in greatest dimension.
T1a	Tumour >1 mm but ≤5 mm in greatest dimension.
T1b	Tumour >5 mm but ≤10 mm in greatest dimension.
T1c	Tumour >10 mm but ≤20 mm in greatest dimension.
T2	Tumour >2 cm but ≤5 cm in greatest dimension.
T3	Tumour >5 cm in greatest dimension.
T4d	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion.

T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including peaud'orange) of the skin.
T4c	Both T4a and T4b.
T4d	Inflammatory carcinoma.

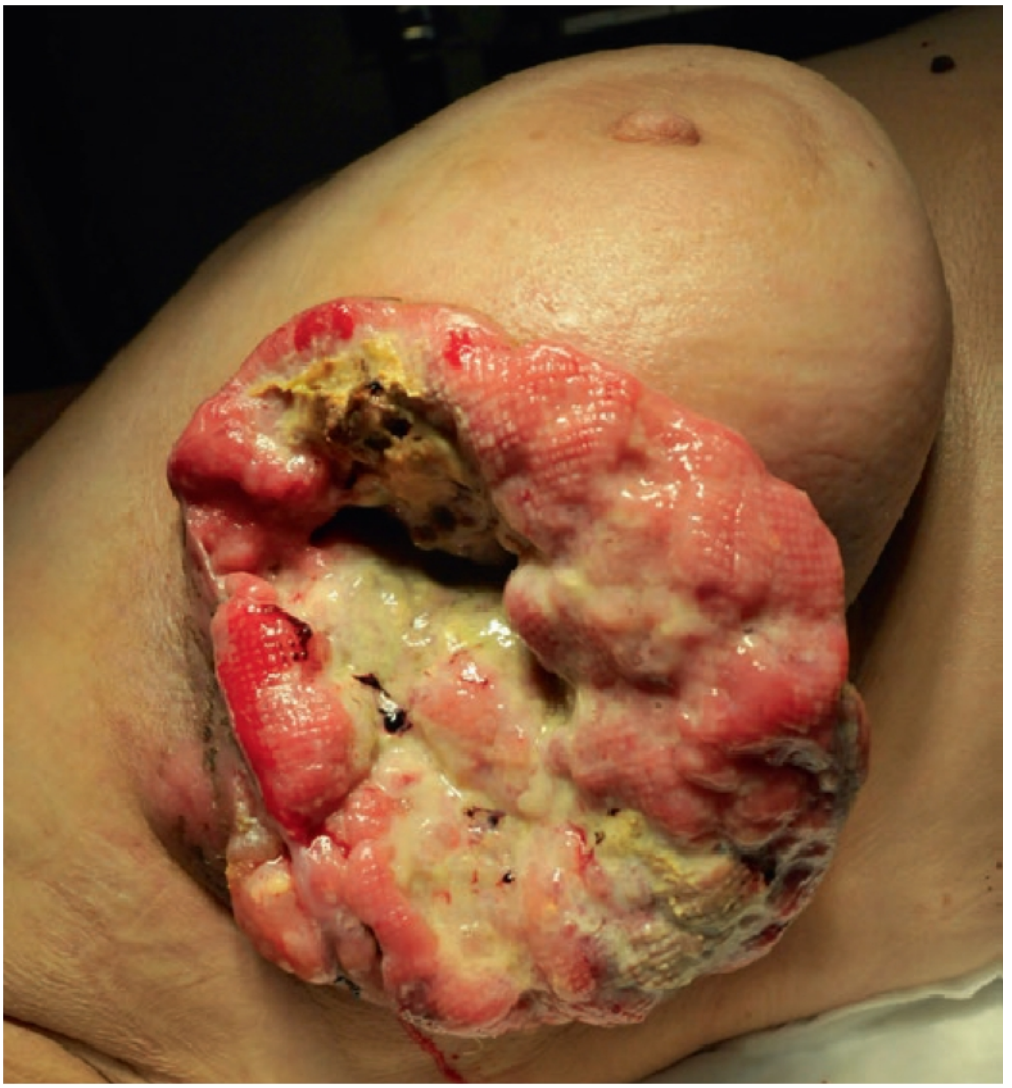
Regional lymph node	
NX	Regional lymph nodes cannot be assessed (e.g. previously removed)
N0	No regional lymph node metastases.
N1	Metastases to movable ipsilateral level I, II axillary lymph node.
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detectedeg.Ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases.
N2a	Metastases in Ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures.
N2b	Metastases only in clinically detectedeg. Ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in Ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detectedeg. ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular

	lymph node(s) with or without axillary or internalmammary lymph node involvement.
N3a	Metastases in ipsilateral infraclavicular lymph node.
N3b	Metastases in ipsilateral internal mammary lymph node and axillary lymph node.
N3c	Metastases in ipsilateral supraclavicular lymph node.

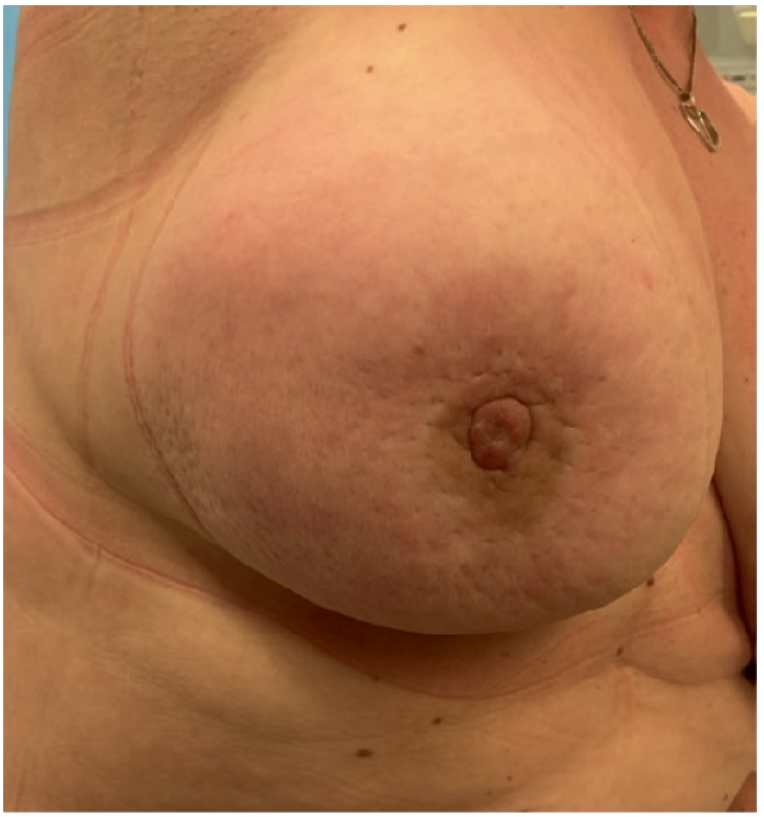
Pathological Staging	
pNX	Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathologic study).
pN0	No regional lymph node metastasis identified histologically.
pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC).
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including isolated tumour cellclusters (ITC)).
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR).
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC.
pN1	Micrometastases: or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected.

pN1mi	pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm).
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2 mm.
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the *absence* of axillarylymph node metastases.
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumour deposit greater than 2.0 mm).
pN2b	Metastases in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph node metastases.
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected. ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or inmore than three axillary lymph nodes and in internal mammary lymph nodes withmicrometastases or macrometastasesdetected by sentinel lymph

	node biopsy but not clinically detected or in ipsilateral supraclavicular lymph nodes.
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumour deposit greater than 2.0 mm) or metastases to theinfraclavicular (level III axillary lymph) nodes.
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillarylymph nodes or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases ormacrometastases detected by sentinel lymph node biopsy but not clinically detected.
pN3c	Metastases in ipsilateral supraclavicular lymph nodes.(7)



“Locally advanced Breast cancer with necrosis, Bleeding and secondary bacterial infection”



“Inflammatory breast cancer”

- “Redness and edema of the skin (paeu d’orange) and nipple retraction is noted.”

Inflammatory breast cancer is a distinct subtype ofLABC. It tends to appear ata younger age.

- The clinical signs develop relatively rapidly overa few weeks ormonths. It typically presents symptomaticallyas a rapidly growing mass or with a swollen,red or tender breast.
- In most cases, the axillarylymph nodes are involved, and approximately 30% ofpatients have distant metastasis at diagnosis. Thebreast skin is thickened and warm and shows varyingdegrees of redness.
- If the nipple is involved, it is usuallyflattened, showing varying degrees of redness, nippleinversion and crusts are also common. The typicalskin appearance resembles the skin of an orange (peaud’orange).

- Due to the clinical presentation, it is ofteninitially misdiagnosed as mastitis, and many womenare initially treated with antibiotics.(8)

PATHOLOGY OF BREAST CANCER:

Histopathological analysis of breast cancer tissue samples is the primary modality for establishing the breast cancer diagnosis. According to WHO classification breast cancer is divided into

i) Insitu carcinoma

ii) invasive carcinoma

WHO CLASSIFICATION OF BREAST TUMORS:

Invasive breast carcinoma

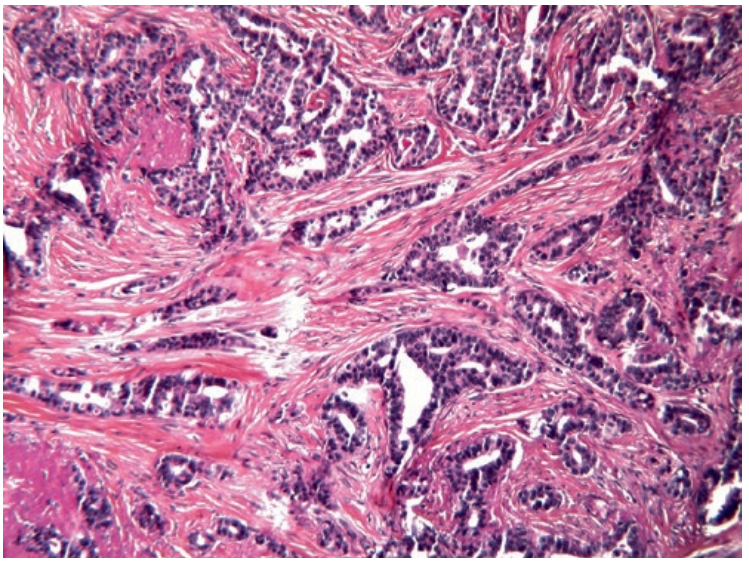
Invasive carcinoma of no special type (NST) (formal ductal carcinoma and rare variants, pleomorphic carcinoma, carcinoma with osteoclast-like stromal giant cells, carcinoma with choriocarcinomatous features, carcinoma with melanotic features).(9)

Special types

- Invasive lobular carcinoma
    a) Classic lobular carcinoma.
    b) Solid lobular carcinoma.
    c) Alveolar lobular carcinoma.
    d) Pleomorphic lobular carcinoma.
    e) Tubulo-lobular carcinoma.
    f) Mixed lobular carcinoma.

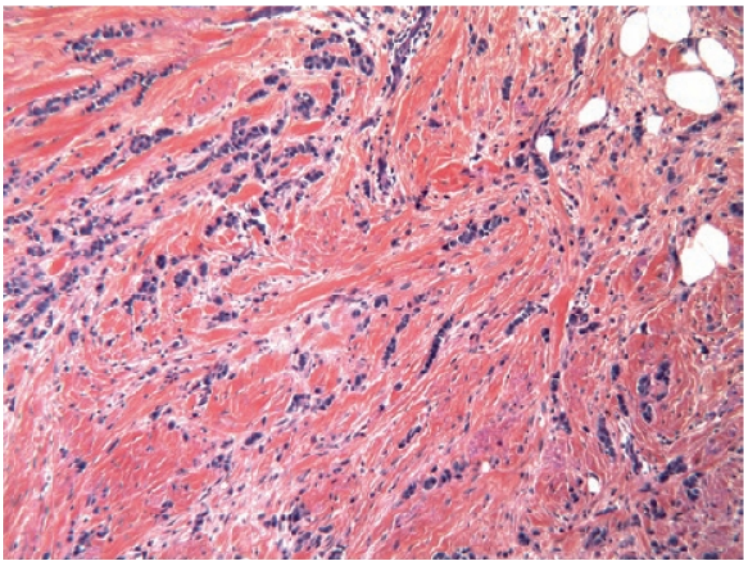
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Carcinoma with medullary features
    a) Medullary carcinoma.
    b) Atypical medullary carcinoma.
    c) Invasive carcinoma NST with medullary features.
- Carcinoma with apocrine differentiation
- Carcinoma with signet-ring differentiation
- Invasive micropapillary carcinoma
- Metaplastic carcinoma of no special type
    a) Low-grade adenosquamous carcinoma.
    b) Fibromatosis-like metaplastic carcinoma.
    c) Squamous cell carcinoma.
    d) Spindle cell carcinoma.
    e) Metaplastic carcinoma with mesenchymal differentiation
        i. Chondroid differentiation.
        ii. Osseous differentiation.
        iii. Other types of mesenchymal differentiation.
- Mixed metaplastic carcinoma
- Myoepithelial carcinoma
- Rare types
- Carcinoma with neuroendocrine features

a) Neuroendocrine tumour, well differentiated.
b) Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma).
c) Carcinoma with neuroendocrine differentiation.
d) Secretory carcinoma.
e) Invasive papillary carcinoma.
f) Acinic cell carcinoma.
g) Mucoepidermoid carcinoma.
h) Polymorphous carcinoma.
i) Oncocytic carcinoma.
j) Lipid-rich carcinoma.
k) Glycogen-rich clear cell carcinoma.
l) Sebaceous carcinoma.
m) Salivary gland/skin adnexal type tumours
    i. Cylindroma.
    ii. Clear cell hidradenoma.

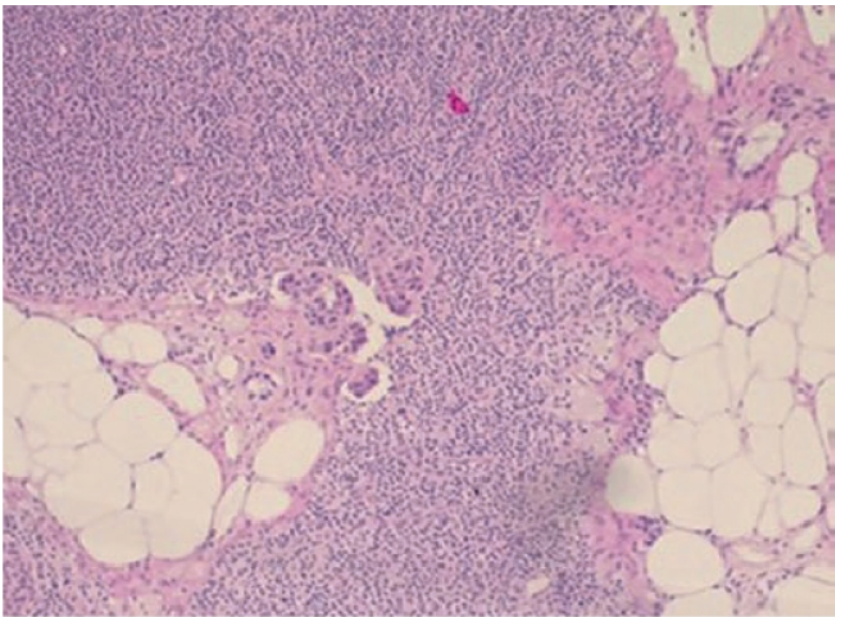


"Invasive breast cancer –

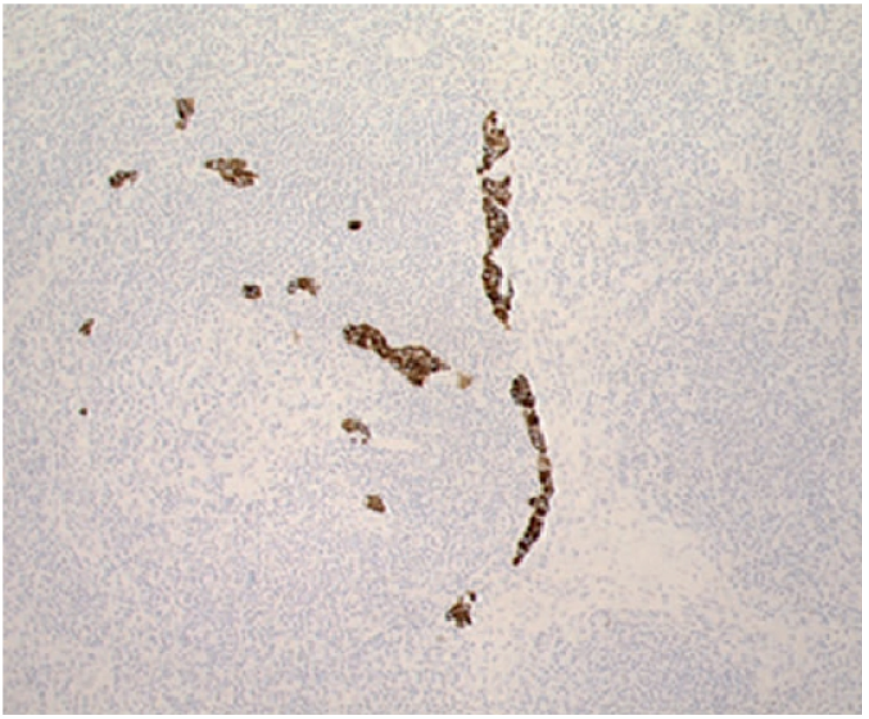
NOS Type"



"Invasive lobular carcinoma"



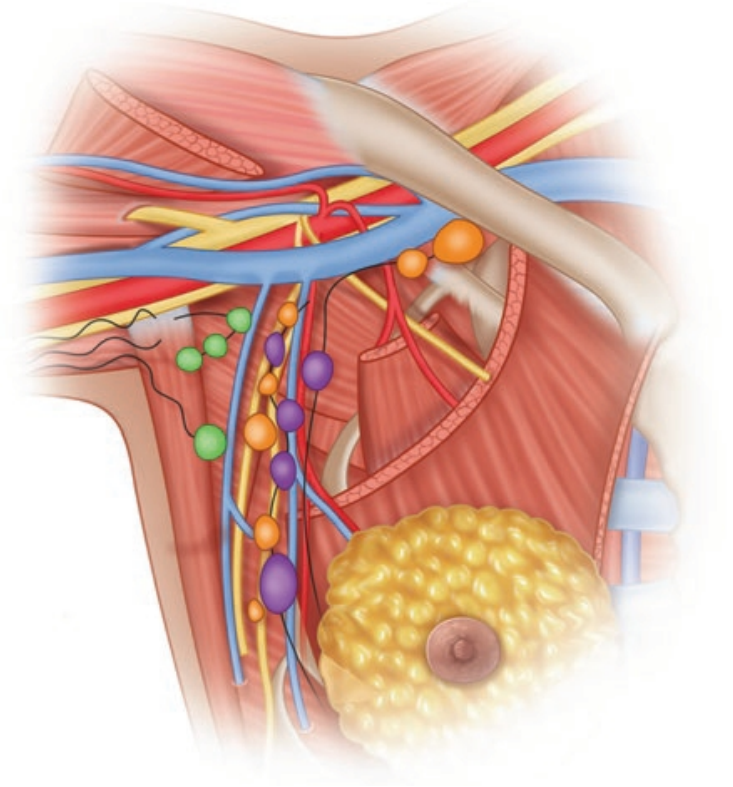
“Histological section of the lymph node containing micrometastatic deposits.”



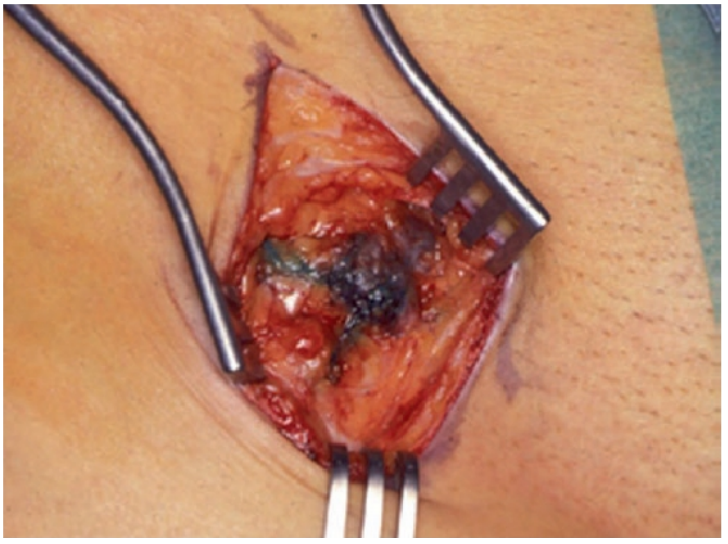
“Immunohistochemical staining of a lymph node containing isolated tumor cells.”

Indications of a Sentinel Lymph Node Biopsy:

Condition	**Remark**
T0–T2 tumour	SLNB recommended
T3 tumour	SLNB useful, but fewer patients can be spared ALND
T4 tumour and inflammatory cancer	ALND still standard procedure
DCIS – mastectomy and GIII	SLNB recommended
DCIS GI–II or breast-conserving surgery	Refrain from SLNB
Multicentric/multifocal tumour	SLNB recommended but slightly higher FNR reported
Previous breast operation	SLNB recommended with lymphoscintigraphy
Previous SLNB	New SLNB recommended
Previous ALND	SLNB can be tried, but lower detection rate expected
Neoadjuvant treatment	SLNB recommended before start of treatment in cN0 patients
Neoadjuvant treatment	SLNB after treatment controversial, low detection rate, high FNR
Old age	SLNB recommended
Obesity	SLNB recommended
Pregnancy	SLNB can be used, low dose to foetus, avoid blue dye



“Distribution of sentinal lymph nodes in Axila”



“Sentinal lymph node stained with patent blue, afferent and efferent lymph vessels are also stained.”

HORMONAL RECEPTORS:

Luminal breast cancers, which represent the most frequent subtypes of breast cancer, include tumours expressing ER. They are defined as a group of tumours with a great heterogeneity in histology, natural history, molecular signatures and response to treatments. According to their different gene expression profiles, two main ER-positive breast cancer subtypes are recognized, specifically luminal A and luminal B. As compared to the luminal A subtype, the luminal B subtype is characterized by lower expression of ER levels, lower or no expression of PR and a higher proliferation index.(10)

LUMINAL A:

The majority of luminal A tumours have an outstandingprognosis with endocrine therapy alone. In this subset theuse of chemotherapy is much discussed, particularly in node-negativedisease. The International Breast Cancer StudyGroup (IBCSG) trial IX for postmenopausal women and theIBCSG trial VIII for premenopausal patients comparedthree or six courses of adjuvant cyclophosphamide,methotrexate and fluorouracil (CMF) with or without endocrinetherapy versus endocrine therapy alone. In these studies,chemotherapy showed no benefit in ER-positive/HER2- negative breast cancer patients (hazard ratio [HR]0.90; 95% CI, 0.74–1.11) in the subset of ER-positive, HER2-negativeand low-Ki67 tumours, which corresponds to theproxy definition of luminal A disease.

LUMINAL B:

Luminal B tumours are characterized by higher proliferationrates and an increased risk of relapse when compared topatients with luminal A tumours. Hence, the addition of chemotherapyto endocrine treatment is indicated for the majorityof these patients. The benefit of chemoendocrine therapiescompared to endocrine therapies alone was clear in severaltrials. Particularly, data from a large meta-analysis ofpatients with ER-positive tumours from the Early BreastCancer Trialists' Collaborative Group (EBCTCG) reportedthat proportional risk reductions from chemotherapy wereslightly affected by age, nodal status, tumour size or differentiation,estrogen receptor status or tamoxifen use. Forpatients with luminal B subtype cancers, the majority of theSt.Gallen panellists considered the use of chemotherapy.

Normally, chemotherapy regimens should comprise anthracyclinesand taxanes. The optimal adjuvant chemotherapyduration is not established yet, but a duration of 4–6 monthsis considered to be reasonable.

HER2 POSITIVE:

About 15% of breast cancer presents with HER2 overexpression/amplification. This feature is associated with a poorprognosis and remains the main predictive biomarkerfor the use of the humanized monoclonal antibody trastuzumaband other anti-HER2 drugs. Since 2005, theadjuvant treatment of this breast cancer subtype has drasticallychanged with the publications of the

findings from thefirst-generation adjuvant trials combining trastuzumab withchemotherapy, either concomitantly orsequentially.

Additionally, HER2 amplification is associated with greatersensitivity to chemotherapy, including anthracyclines and taxanes . Actually the most relevant issue iswhether or not to include an anthracycline in the adjuvanttreatment of HER2+ breast cancers, particularly in view ofthe risk of cardiotoxicity which is increased with sequentialtrastuzumab therapy . An interesting discovery is thatHER2 and topoisomerase IIa (TOPO2A) gene coamplificationis associated with high sensitivity to anthracycline-based chemotherapy . According to these data, the BCIRG(Breast Cancer International Research Group) retrospectivelylooked at the predictive value of TOPO2A geneamplification in patients with HER2-overexpressing breastcancer in a randomized trial, which compared anthracycline-taxane- based chemotherapy with taxane only-based chemotherapy.(11)

The investigation confirmed a greater benefit foranthracyclines in patients with HER2+/TOPO2A-amplifieddisease. Nonetheless, the predictive value of TOPO2A geneamplification has not been independently validated andchromosome 17 polysomy may be the more influential predictor. To date, there are insufficient proofs for modifyingchemotherapy regimens on the basis of TOPO2Aexpression, HER2 status or chromosome 17 copy number. So far, for patients with HER2-positive disease, the standardadjuvant treatment is trastuzumab plus chemotherapy, whichshould include a taxane and an anthracycline according tothe St. Gallen guidelines.

TRIPLE NEGETIVE:

Triple-negative breast cancers (TNBCs), defined by their lackof immunohistochemical staining for ER and PgR and lack ofoverexpression or amplification of HER2/neu, are characterizedby their aggressive clinical course and poor prognosis. Lacking specific targeted therapy, chemotherapywith standard cytotoxic agents is the only systemic treatmentoption approved for these patients. There is no robust evidenceto advice use, or avoidance, of specific chemotherapyagents in the TNBC subset. Several studies have demonstrateda broadchemosensitivity for these tumours, mainlyin the neoadjuvant setting. In these trials, TNBCsrevealed higher response rates (RR) than other BC subtypesbut showed a poor overall survival rate. The TNBC subtype isassociated with a paradox, despite a subgroup of patientswho are very chemosensitive, the whole subgroup showspoor disease-free and overall survival.

LOCALLY ADVANCED BREAST CANCER

DIAGNOSIS:

An accurate determination of the diagnosis, the biologic features of the tumour and the stage of disease is necessary to plan treatment. Mammography and ultrasound are the standard of care and should be performed in all patients, if feasible. Breast magnetic resonance imaging (MRI) is helpful to evaluate disease extent in the breast, in particular the presence of multicentric disease and invasion of the chest wall. As MRI demonstrates the best concordance with pathologic tumour size, it is increasingly

used in patients with LABC, in particular those who are deemed to be potential candidates for conservation surgery.

As in any other case, the diagnosis of BC should be confirmed by histopathology. Biomarker status (oestrogen receptor [ER], progesterone receptor [PgR], human epidermal growth factor receptor 2 [HER2] and proliferation markers such as Ki-67) of the tumour must be assessed. Core needle biopsy under image guidance is the preferred technique. In patients with suspected IBC or skin involvement, a full thickness skinbiopsy is indicated. If BCT is planned, a radiopaque markershould be placed in the tumour before primary systemic therapy(PST) to facilitate surgery (not applicable to IBC) andpathologic assessment in case of complete response. In patientswith palpable or suspicious axillary lymph nodes, an ultrasound-guidedfine needle aspiration biopsy should be performed.

A complete history, physical examinations and laboratorytests, including full blood count, liver and renal function testsand serum alkaline phosphatase and calcium, are essentialparts of the staging workup. Computed tomography (CT) of the chest, abdomen and pelvis and a bone scan should beperformed to rule out metastases. An 18F-fluorodeoxyglucosepositron emission tomography scan (FDG-PET) may beused as an alternative and in case of inconclusive results ofotherimaging studies. Brain imaging is not necessary inasymptomatic patients.

Clinical presentation of most of the locally advanced breast cancer are

- Tumour size more than 5 cm.
- Regional lymph node involvement.
- Involvement of skin/underlying chest wall.
- Tumors that are inoperable but without distant metastasis.
- Inflammatory breast carcinoma.

Inflammatory breast cancer typically presents with pain and rapidly progressing, warm, tender, firm enlarged breast. Diffuse brawny induration of the skin of the breast with a peau-d orange appearance usually without an underlying palpable mass. Malignant cells form tumor emboli invading the dermal lymphatics that results in blockage of lymphatics which are responsible for local signs and symptoms and distance spread.(12)

Once LABC diagnosis is established following studies are done.

- Complete history with physical examination.
- Bilateral mammography.
- Complete basic blood investigations.
- Chest radiography/CT or USG abdomen and breast.
- Determination of ER, PR and HER-2 status.

PROGNOSTIC FACTORS:

Prognostic factors of LABC include

- Age
- Menopausal status
- Tumor stage
- Histological grade
- ER/PR status and response to therapy

Lymph node status and tumor size have the strongest effect of survival. The prognosis for patient without a lymph node metastasis is better than for those with lymph node involvement and greater the number or higher nodal stage predict poor survival. Role of ER and PR negativity is associated with shorter overall survival outcomes.

With above indicated prognostic factors,patients with axillary lymph node negative are classified into three groups.

LOW RISK	MODERATE RISK	HIGH RISK
• Tumor<1cm	Tumor 1-2 cm	Tumor>2 cm
• Histology-tubular,colloid ,comedo form		
• ER/PR positive	ER/PR positive	ER/PR negative
• Nuclear grade 1	Nuclear grade II	Nuclear grade II
• Age >35 yrs		Age <35 yrs
• DNA diploidy,Cathesin D		Over expression
• Low ‘S’ Phase fraction		High ‘S’ phase Fraction.

- Other variables evaluated as possible prognostic markers in LABC includes HER 2, P53 and nuclear grade.
- P53 positivity is associated with shorter overall survival rate'
- HER 2 and nuclear grade have not consistently emerged as independent predictors of survival.
- Thymidine labelling index is a prognostic factor with a high TL1 predicting poorer survival.
- BRCA 1 and BRCA 2 status.(13)

Less common prognostic factors:

- Proliferative indices like ki-67.PCNA/Cyclin ,MIB-1.
- Topoisomerase II.
- Histone H3.
- Transforming growth factors (a,b).
- Epidermal growth factors.
- Oncogene products (c-erb2 ,c-myc,ras,rb,Bcl2)
- Invasion related proteins like cathepsin-D,Laminin,Stromelysin,UPA/PA-1.
- Angiogenesis factors.
- PS 2
- NM 2
- Heat shock proteins
- MDR-1 Protein (multi drug resistant protein).

MULTIMODALITY TREATMENT OF LOCALLY ADVANCED BREAST CANCERS

Treatment for locally advanced breast carcinoma consists of

- Systemic chemotherapy
- Surgery
- Radiotherapy.

Patients with chest wall fixation, skinedema, ulceration, presence of satellite skin nodules, inflammatory breast carcinoma, matted or fixed lymph nodes, supraclavicular lymph nodes or ipsilateral armedema are all found to develop recurrences and are considered markers of inoperable disease.Neoadjuvant chemotherapy introduced in management of LABC found to have drastic clinical responses and some patients was found to have no invasive tumor remaining in the breast or regional lymph nodes during surgery.

Neoadjuvant chemotherapy helps in downstaging the tumor in breast carcinoma,and allows breast conservation surgery to become possible in patients who would otherwise have been eligible for mastectomy.(14)

The advantages of Neoadjuvant chemotherapy in LABC include:

- It reduces the size of primary tumor rendering inoperable tumorsresectable and allowing breast conserving surgery possible.
- It permits a direct in vivo measure of the the sensitivity of the tumor cells to the chemotherapeutic drug in the regimen.

- It allows early identification of any resistance that allows to change to an alternative effective regimen.
- It enables drug delivery through an intact tumor vasculature.

CHEMOTHERAPY REGIMENS

- Anthracyclin based regimens (FAC)
- Doxorubicin followed by CMF and intensive multidrug regimen

The recommended dose and schedule are the same as those used in adjuvant chemotherapy.Taxanes add substantial efficacy to adjuvant chemotherapy and are increasingly used for node positive breast cancer.

Anthracycline based chemotherapy followed by taxanes are associated with 2 fold higher pathological complete response with better disease free survival and overall survival rate. Four cycles of Anthracycline based regimen or as a component of an established Anthracycline based regimen substituting for an existing older drug (eg. Docetaxel instead of flurouracil).(15)

CHEMOTHERAPY REGIMENS:

REGIMEN	DRUGS	DOSE	ROUTE	DAYS
CMF3 weekly	Cyclophosphomide	600 mg/m2	IV	Day 1
	Methotrexate	50 mg/m2	IV	Day 1
	5-Fluro-Uracil	600 mg/m2	IV	Day 1
FAC3 weekly	5-Fluro-Uracil	600 mg/m2	IV	Day 1
	Adriamycin	40 mg/m2	IV	Day 1
	Cyclophosphamide	600 mg/m2	IV	Day 1
FEC-603 weekly	5-Fluro-Uracil	600 mg/m2	IV	Day 1
	Epirubicin	60 mg/m2	IV	Day 1
	Cyclophosphamide	600 mg/m2	IV	Day 1
TE3 weekly	Epirubicin	60 mg/m2	IV	Day 1
	Paclitaxel	175 mg/m2	IV	Day 1

TRASTUZUMAB:

Trastuzumab is a monoclonal antibody that binds to a specific epitope of the HER 2/NEU Protein.Approximately 20% of the breast cancers have amplified or over expressed HER-2/NEU (c-erB-2) gene which encodes a cell surface growth factor receptor.multiple doses can be given safely both alone or in combination with other chemotherapeutic agents.(16)

DURATION OF NEOADJUVANT CHEMOTHERAPY

- Three to four cycles of an Anthracycline based regimen or a taxanes followed by reassessment of response.
- If there is been a complete or nearly complete clinical response to induction therapy definite local treatment is appropriate.
- Patients with a lesser response could be considered for additional cycles of non- cross resistant drugs.
- Eight total cycles of adjuvant therapy are recommended.They may all be administered preoperatively or split between induction and post operative treatment.
- In the absence of progressive disease,atleast 2 or preferably 4 cycles should be given before concluding patients as non responders.

RESPONSE TO NEOADJUVANT CHEMOTHERAPY :

Clinical measurements of breast masses are often used to assess the response to neoadjuvant chemotherapy.Universally accepted criteria for assessment to response of neoadjuvant chemotherapy is classified by World health organisation / International union against cancer (WHO/UICC) that have been used for many years.

- Clinical complete response (CCR) is defined as the complete disappearance of all clinically detectable diseasein the breast or regional lymph node.
- Clinical Partial response (CPR) requires a > 50% reduction in the sum of the product of the 2 largest dimensions of measurable tumor.

- Non responders or Stable disease (SD) defined as there is no change in the clinical status.
- Progressive disease (PD) defined as >25% increase in the sum of the product of 2 largest perpendicular dimension of the tumor.
- Pathological response is analysed after performing surgery.(17)
- Complete pathological response-pCRis defined when there is no evidence of residual tumor on histopathological examination of surgical specimen.
- Partial pathologic response- pPR The presence of scatteredindividual or small clusters of tumor cells in desmoplastic or hyaline stroma.
- Pathological nonresponders-pNRincludes all other than complete pathological responders.

MILLER-PAYNE SYSTEM

- Grade 1 – No change or some alteration to individual malignant cells,but no reduction in overall cellularity.
- Grade 2 -A minor loss of tumor cells ,but overall cellularity is still high,upto30% loss.
- Grade 3 – Between an estimated 30% and 90% reduction in tumor cells.
- Grade 4 – A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; 90% loss of tumor cells.
- Grade 5N0 – Malignant cells identifiable in sections from the site of tumor, only vascular fibroelastic stroma remains,often containing macrophages, however ductal carcinoma insitu may be present.

SATALOFF METHOD

TUMOR

- T-A Total or near total therapeutic effect
- T-B 50% therapeutic effect,but less than total or near total
- T-C 50% therapeutic effect ,but effect evident
- T-D No therapeutic effect.

NODES

- N-A Evidence of therapeutic effect,no metastatic disease.
- N-B No nodal metastasis or therapeutic effect.
- N-C Evidence of therapeutic effect,but nodal metastasis present.
- N-D Viable metastatic disease ,no therapeutic effect.

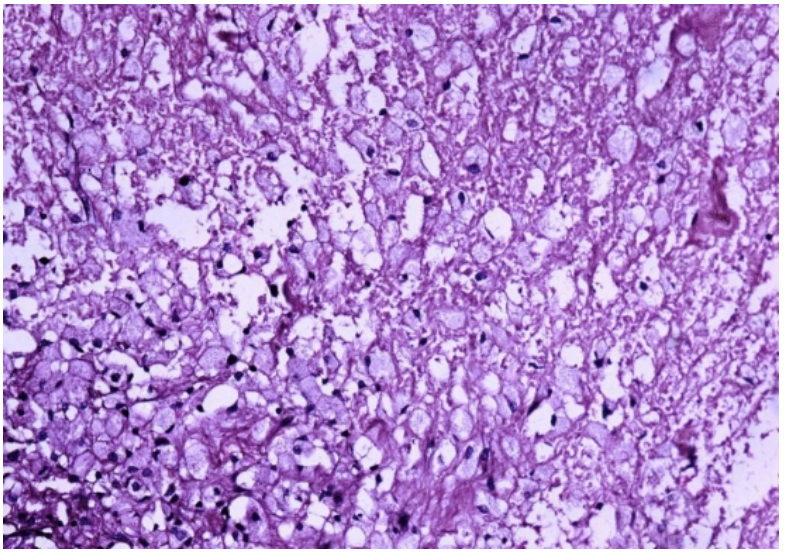
CHEVALLIER METHOD

- Class I Disappearence of all tumor.
- Class II Presence of DCIS in the breast,no invasive carcinoma and negative lymph node.
- Class III Presence of invasive carcinoma with stromal alteration.
- Class IV Few modifications of the tumor appearance.

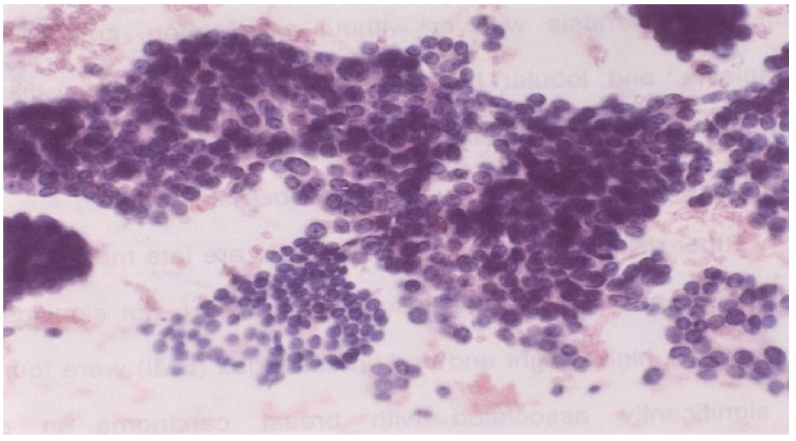
RCB SYSTEM

- RCB-0 No carcinoma in breast or lymph node
- RCB- I Partial response
- RCB-II Partial response
- RCB-III Chemoresistant.

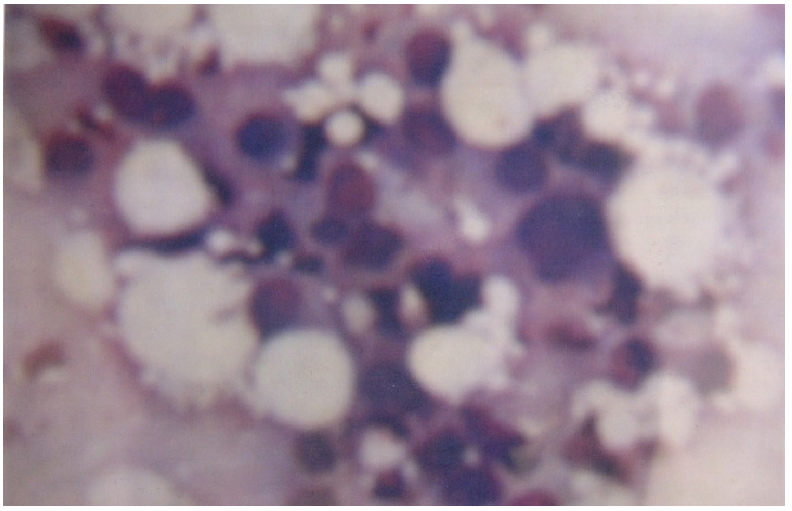
Mastectomy specimen showing grossly visible fibrotic tumor bed without residual tumor.



Histopathological slide showing complete pathological response that demonstrates histiocytes within the tumor bed.



Fnac of Primary Tumor Before Neoadjuvant Chemotherapy



Hpe of Primary Tumor after Neoadjuvant Chemotherapy showing Cytoplasmic Vacuoles.

Breast Conservation Surgery

The role of breast-conserving surgery was established during the 1980s, thanks to the pioneering (and at the time controversial) work of Umberto Veronesi in Italy and Bernard Fisher in the USA. They published randomized trials showing that overall survival after breast conservation plus adequate radiotherapy was similar to that following mastectomy.

Quality of life is better after breast conservation when compared with mastectomy. Therefore, breast conservation should be performed if technically possible if this is the patient's preference, and there are no contraindications. Likewise a woman's request for mastectomy must be respected, but careful counselling should always be provided as some women have misconceptions about the oncological and treatment-related benefits of mastectomy.

There are only two absolute contraindications to breastconserving surgery: a failure to achieve negative margins without causing breast deformity and inflammatory breast cancer. All other contraindications are more or less relative and often relate to an increased risk of local recurrence.

However, distant metastasis is the most common first recurrence event, even among patients with small primary tumours. Therefore, all the relative contraindications should be weighed against the prognosis of the patient, their life expectancy due to age and comorbidities and, last but not least, the patient's preference for breast conservation.

The most important independent risk factors for local recurrences after breast conservation include positive margins and young patient age. However, local recurrence rates are currently much lower than in the past, at approximately 0.5% per year. The decrease in local recurrence rates has been most significant in premenopausal patients.

The reason for the decreased risk of local recurrence is multifactorial. Improved patient selection, better quality surgery, better histopathological evaluation of resection margins, and use of tumour bed radiotherapy boost have all contributed, especially in younger patients. However, perhaps the most important reason is the more extensive use of systemic adjuvant treatment and also the use of more effective regimens, like aromatase inhibitors instead of tamoxifen, use of

trastuzumab in patients with HER2- positive tumours and better chemotherapy regimens such as anthracycline- and taxane-based protocols.

The Role of Neoadjuvant Systemic Treatment in Breast Conservation Surgery

The size of the tumour may be just too large to allow breast conservation even with an oncoplastic approach. In these cases, the tumour can often be downsized by using primary systemic therapy, either chemotherapy or endocrine therapy. Careful patient selection is crucial: patients with multifocal or multicentric disease and those with extensive microcalcifications are not optimal candidates for this treatment

option.

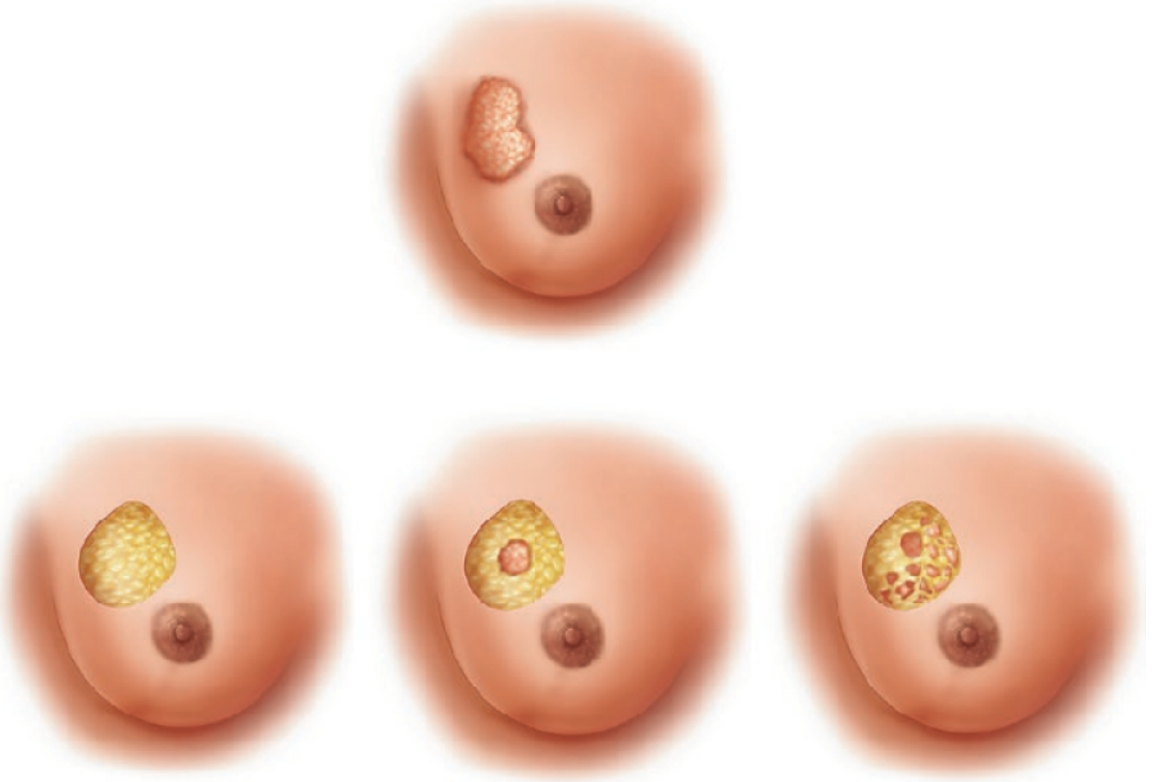
Although the response rate in general is good or even excellent (depending on the biological subtype of the disease), not all responders will achieve breast conservation. The response can be total or partial. If partial, the response may be concentric, but not sufficient. The response may also be honeycomb-like, so that the extent of the tumour is the same as before the treatment.

As regards neoadjuvant chemotherapy to facilitate breast conservation, there should be a good oncological indication for chemotherapy in terms of disease prognosis and subtype. Patient should also be a good candidate for chemotherapyas regards to their age and comorbidities. It is also advisable to discuss the expected

response and the probability that breast conservation will be possible after chemotherapy.

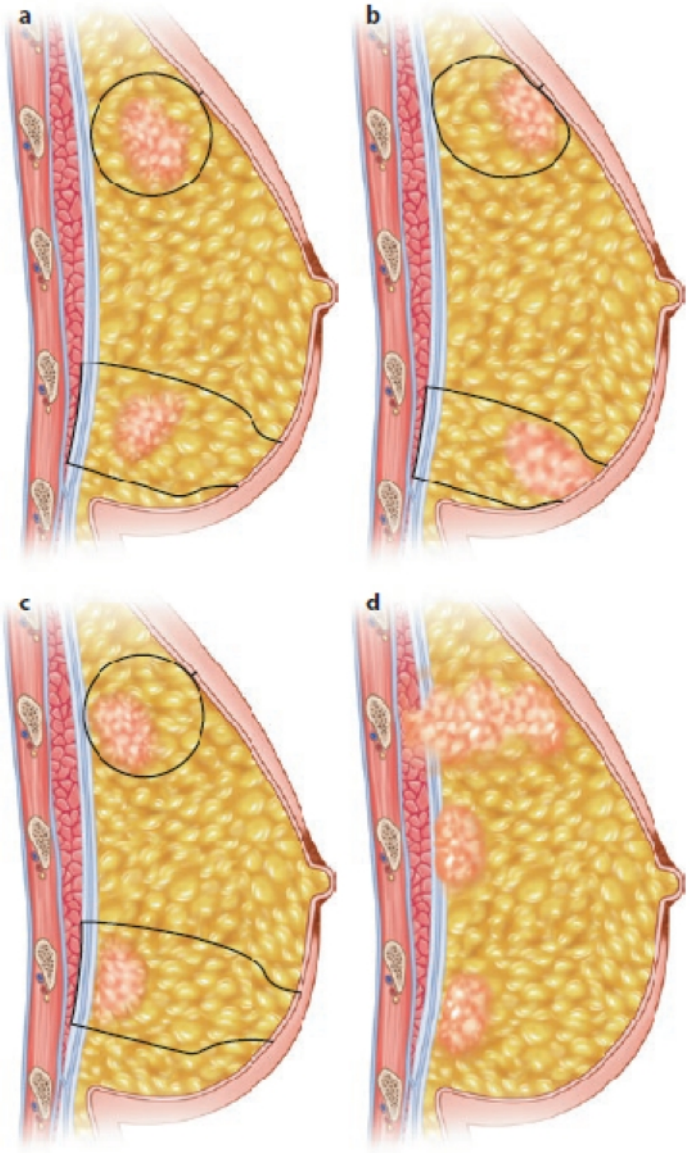
Tumour biology influences the response rate. The response is best in triple negative and HER2-positive tumours, when compared with luminal-type tumours.

Patients with invasive lobular cancer often have multicentric or multifocal disease and tend to respond poorly to neoadjuvant chemotherapy, although for some of these patients the response may be sufficient to achieve breast conservation. In patients with ER-positive tumours, breast conservation can also be attempted with neoadjuvant endocrine therapy.



The response to neoadjuvant chemotherapy may be complete, partial but concentric or partial and honeycomb-like. The latter case which is breast conservation is not feasible

The clinical response to neoadjuvant treatment can be complete tumour regression. Therefore, the tumour should be marked with a clip before starting neoadjuvant treatment. A radioactive seed may be used for this purpose or a simple metal clip. The radioisotope in the seed is I125, which has a half-life of 60 days. This has the advantage that the radioactivity remains for long enough that it can be used to permit gamma probe localization at surgery without an extra localization method, even after neoadjuvant chemotherapy. When the aim of neoadjuvant treatment is breast conservation, the response should be monitored by breast imaging. MRI is the most accurate method to evaluate the size and the pattern of residual disease. Breast ultrasound may also be used. Ideally the same imaging method should be used throughout when evaluating the response as switching modalities may misinterpret response.



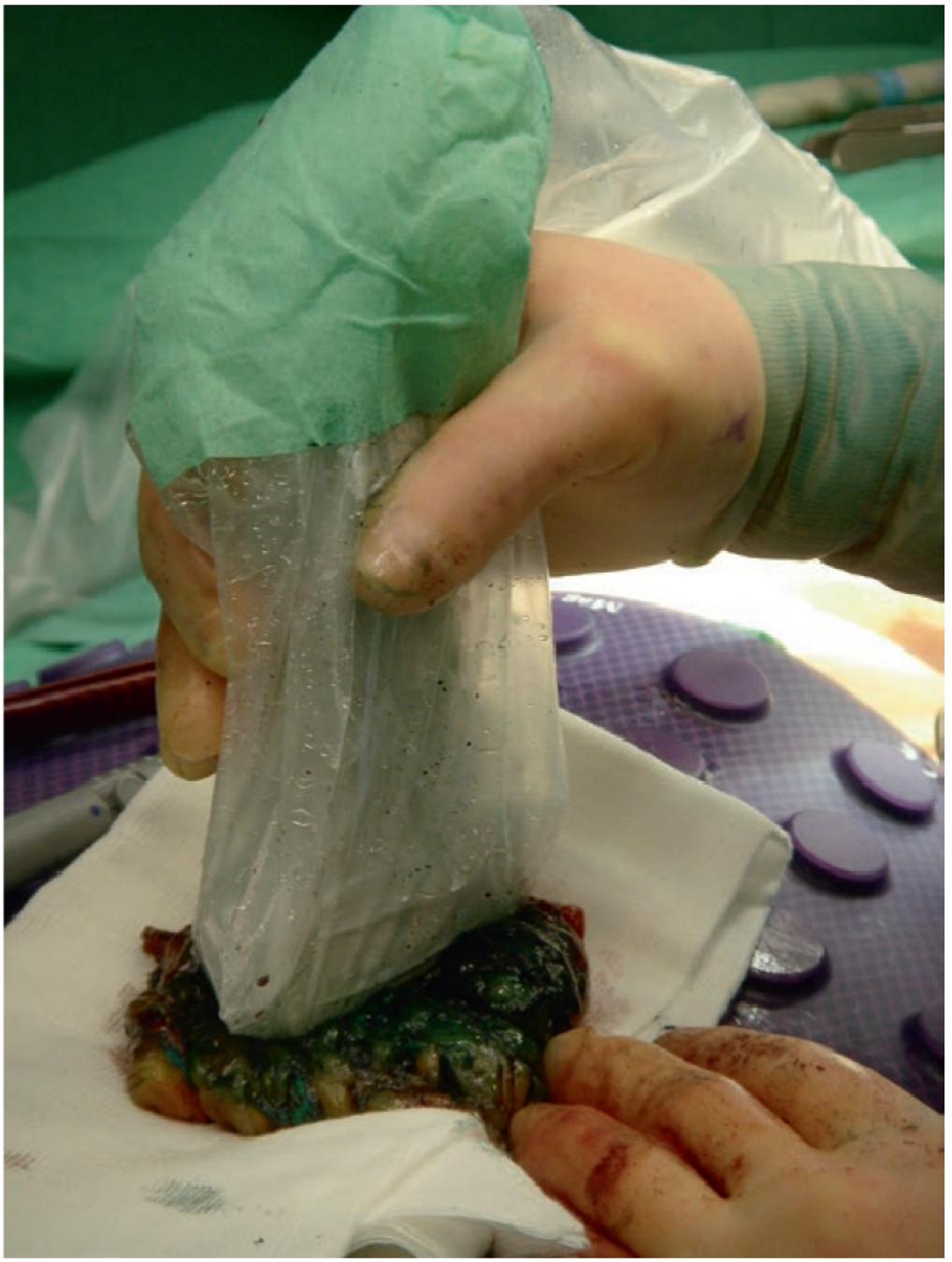
a) wide local excision can be either full-thickness type including both the overlying skin and underlying fascia. When the tumour is not located close to the skin or fascia, a full-thickness resection is not necessary, but in these case also anterior and posterior margins matter.

b) When the tumour is located adjacent to the skin, excising a slice of the overlying skin ensures anterior margin.

c) When the tumour is located adjacent to the pectoral fascia, excising the underlying fascia and overlying skin ensures posterior margin.

d) The tumour may infiltrate the underlying pectoral fascia or even the muscle. In this case, local excision of the underlying pectoral fascia and underlying muscle ensures posterior margin

e) The resection margins can be assessed using an intraoperative ultrasound



The resection margins can be assessed using an intraoperative ultrasound

NEOADJUVANT HORMONAL THERAPY

In patients withestrogen receptor positive breast cancer,hormonal therapy can be implemented although the likelihood of complete pathological response appears to be lower than with systemic therapy.

TAMOXIFEN:

Neoadjuvant tamoxifene decreases overall tumor volume in approximately one half of the LABC and pathological complete response appears to be low about approximately 5 %.Since response tends to occur gradually,treatment for 3-6 months is necessary in the absence of progression before concluding thatdisease is unresponsive.

SERM like raloxifene and ormeloxifene can also be used.

AROMATASE INHIBITORS:

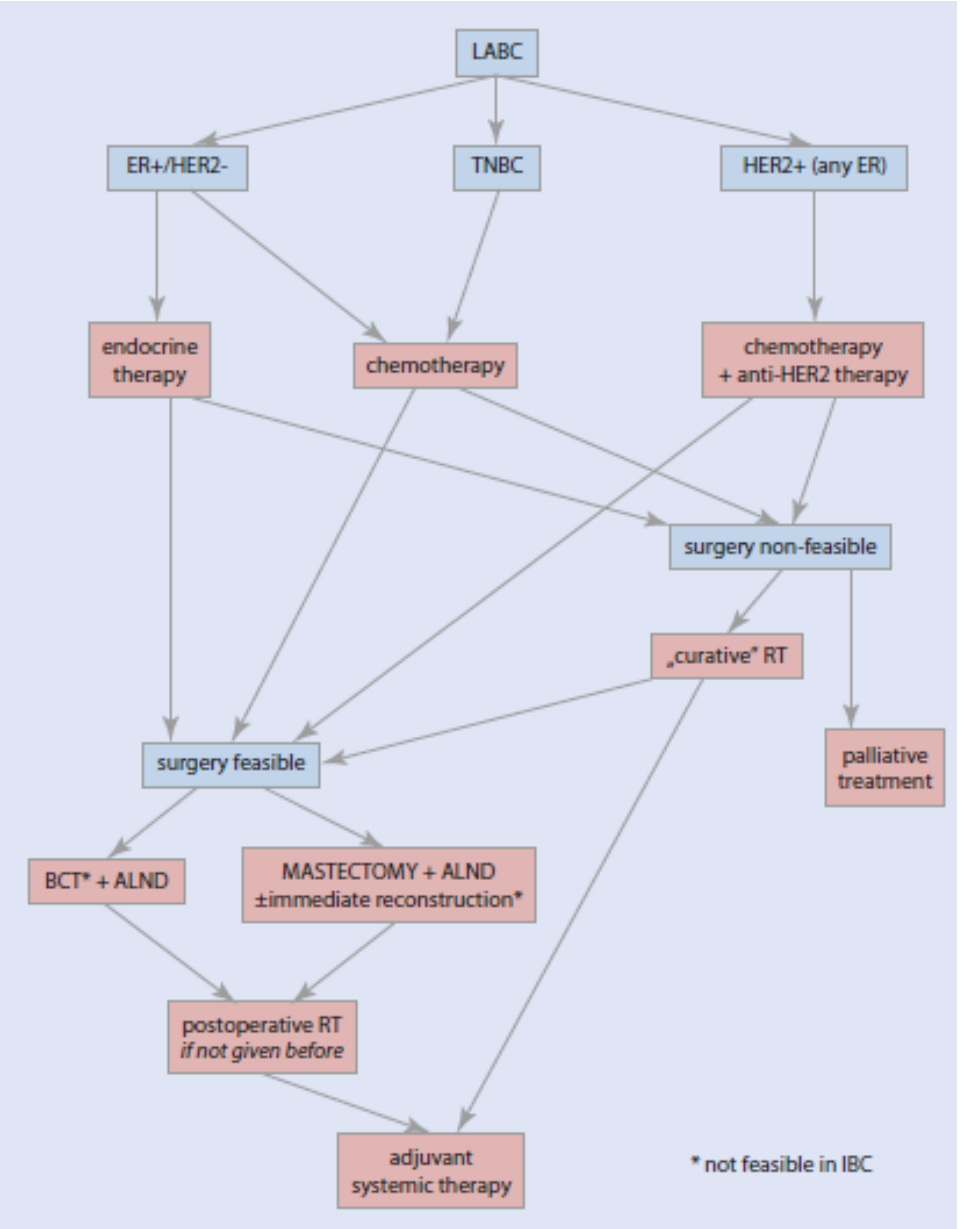
Aromatase inhibitors reduce the median tumor volume over 12 weeks upto 70to 80 % in ER positive Locally advanced breast cancers patients and in women whose tumor expresses HER 2/neu and erbB-1 may preferentially benefit from NAHT with aromatase inhibitors.

NAHT is effective treatment for patients with LABC but may be reserved for elderly woman with impaired organ function .patient who are not willing to accept chemotherapy related toxicity and those with poor performancestatus.(18)

The concurrent neoadjuvant chemoradiation has shown better local regional control and survival outcomes.

The demerits of concurrent chemoradiation given in neoadjuvant settings are

- Acute radiation effects.
- Slight increase in hematological toxicity.
- Impairs cosmetic results of Breast conservation surgery.
- Cardiac toxicity.(19)



Algorithm of locally advanced breast cancer management

ALND - axillary lymph node dissection,

BCT - breast-conserving therapy,

ER - oestrogen receptor,

HER2 - human epidermal growth factor receptor 2,

LABC – locally advanced breast cancer,

RT - radiotherapy,

TNBC - triple-negative breast cancer

STUDY METHODOLOGY

Out of all the breast cancer patients who attended the surgical outpatient department 60 patients with locally advanced breast cancer where enrolled in the study and evaluated. Every patient was examined to confirm the diagnosis of LABC, clinical staging of the disease were evaluated and the response to chemotherapy was noted.

Workup done include

i. Complete history and physical examination
ii. Complete blood counts
iii. Renal function and Liver function test
iv. EGC/Echocardiogram
v. Chest radiograph, abdominal ultrasonogram
vi. Trucut biopsy from the tumor
vii. Ultrasound bilateral test

Three cycles of Neoadjuvant chemotherapy was administered at a 21 days interval. The regimen used includes

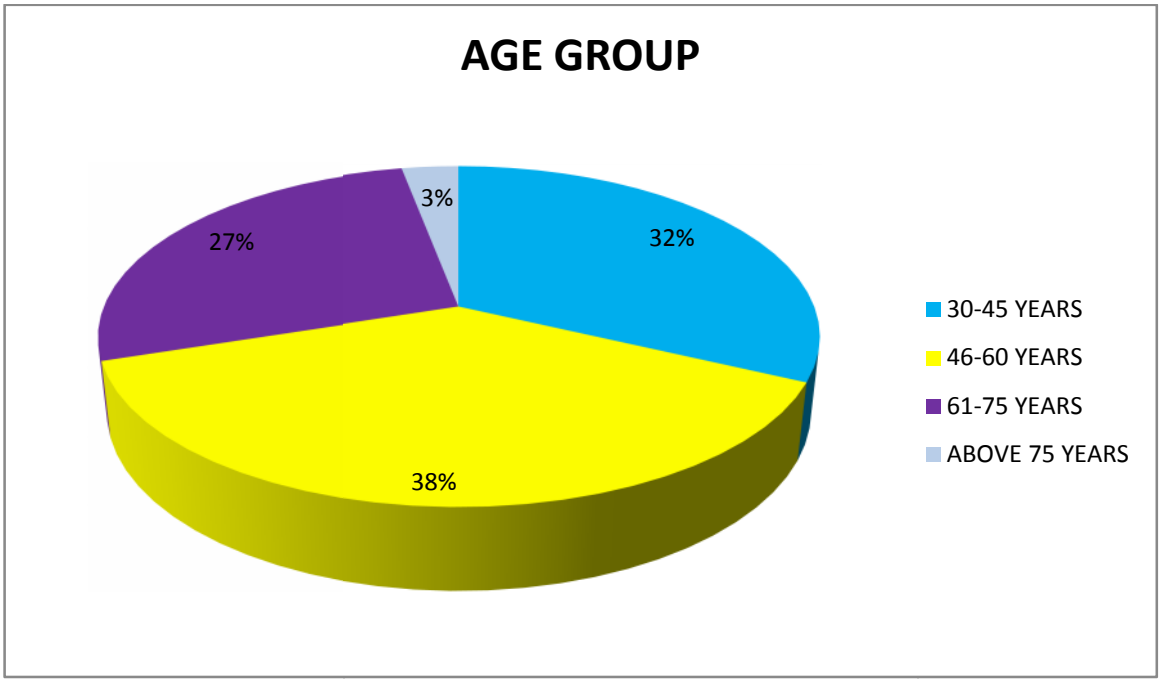
i. 5-Fluro-Uracil - 600 mg/m2
ii. Adriamycin - 40 mg/m2
iii. Cyclophosphamide – 600 mg/m2

Clinical responses and physical examination were done on every visit. All patients underwent modified radical mastectomy after completing 3 cycles of neoadjuvant chemotherapy. Post operatively patients received 5 cycles of AC and during each follow-up, complete physical examination and blood investigation was done. Two patients defaulted due to intolerance to chemotherapy and one patient withdrawn due to metastatic disease.

Data were analysed using SSPS.

RESULTS AND DISCUSSION

CHART 1:

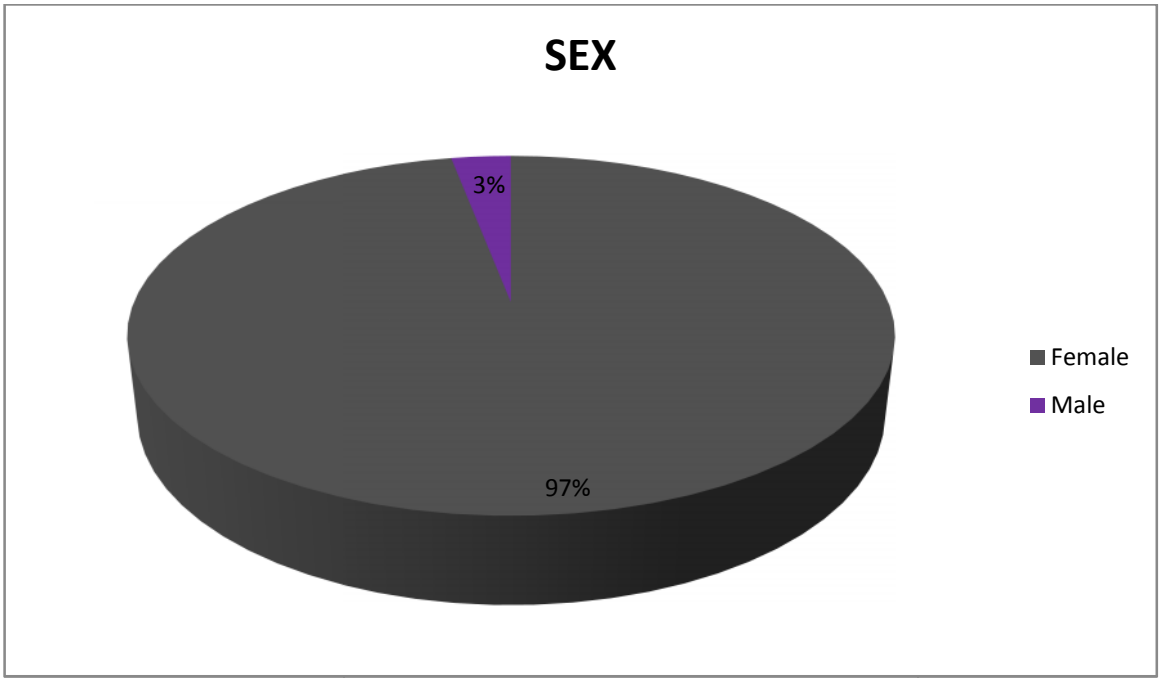


In the study maximum number of patients were in the range of 45 to 60 years.

FREQUENCY TABLE:

AGE GROUP	Frequency	Percent
30-45 YEARS	19	31.7
46-60 YEARS	23	38.3
61-75 YEARS	16	26.7
ABOVE 75 YEARS	2	3.3
Total	60	100.0

CHART 2:

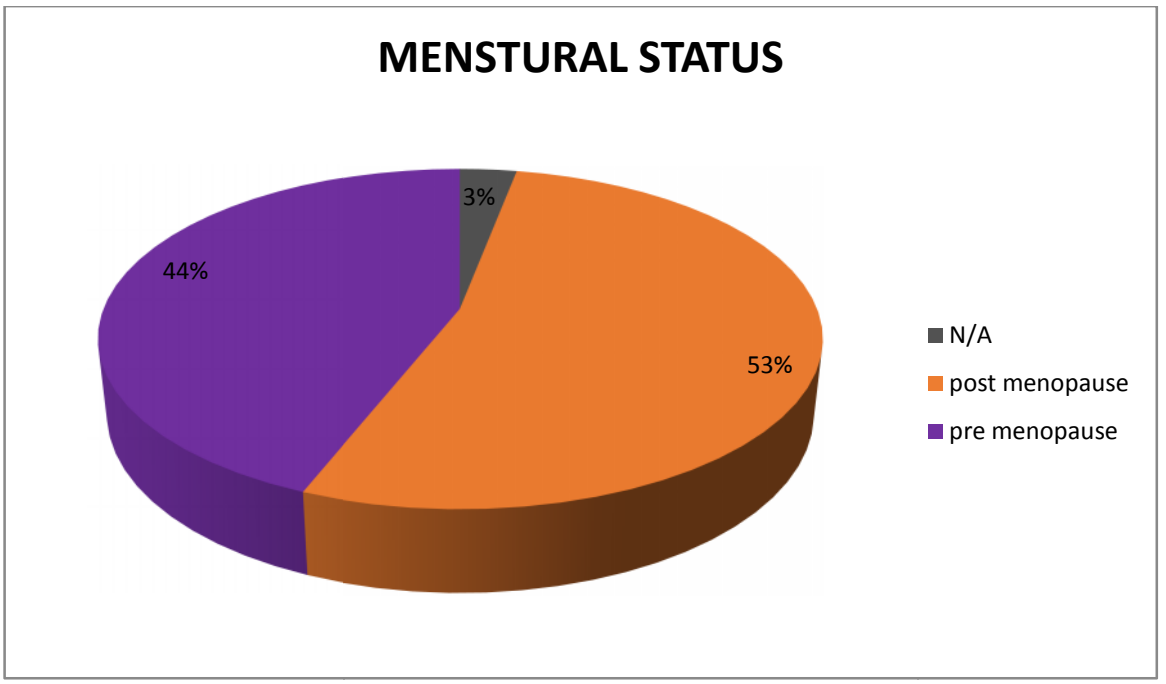


FREQUENCY TABLE:

SEX	Frequency	Percent
Female	58	96.7
Male	2	3.3
Total	60	100.0

In our study, 58 patients were female, 2 patients were male.

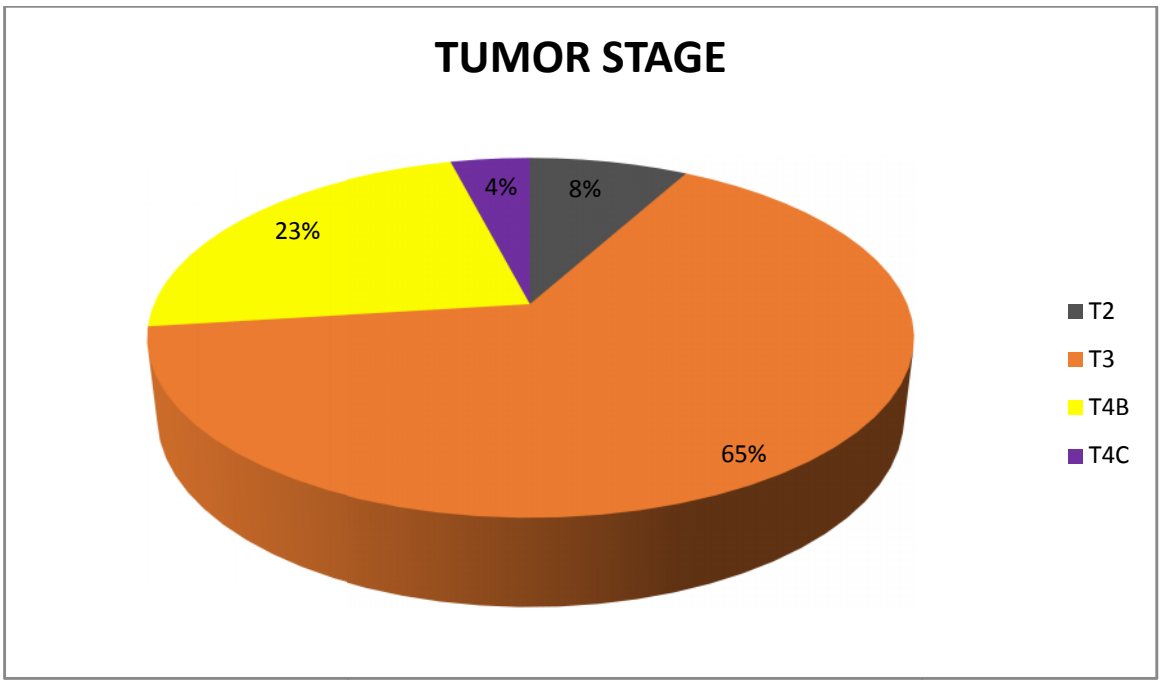
CHART 3:



MENSTURAL STATUS	Frequency	Percent
N/A	2	3.3
post menopause	32	53.3
pre menopause	26	43.3
Total	60	100.0

In our study,53% of patients were post menopausal women,43% of patients were premenopausal females.

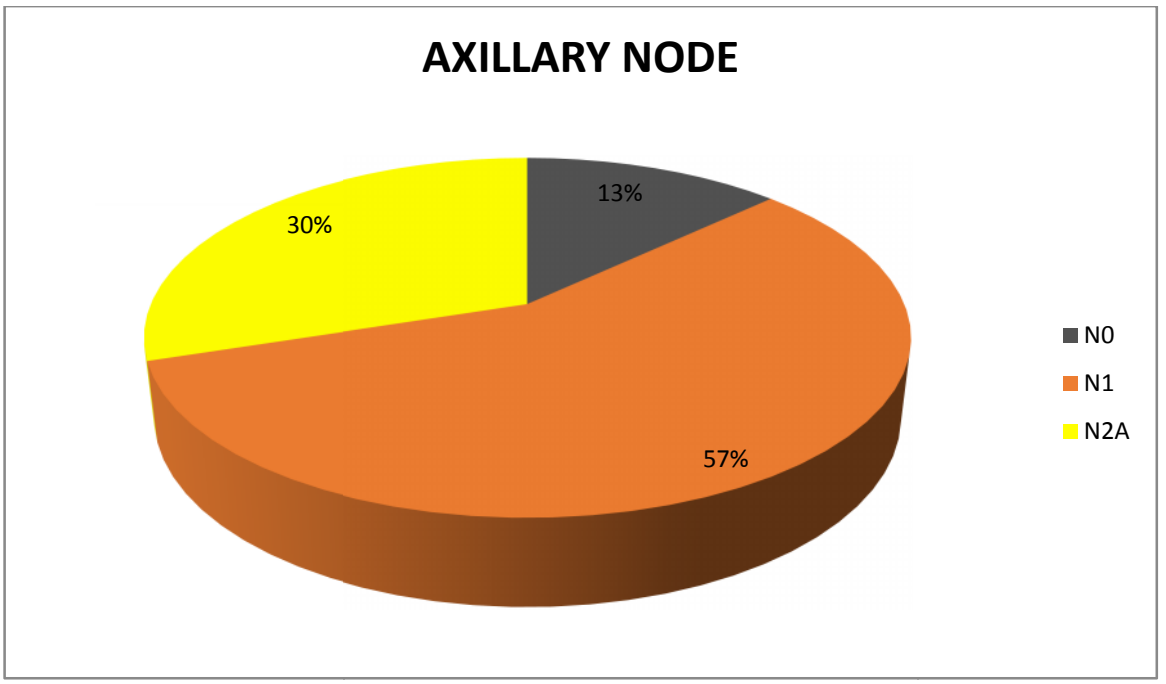
CHART 4:



TUMOR STAGE	Frequency	Percent
T2	5	8.3
T3	39	65.0
T4B	14	23.3
T4C	2	3.5
Total	60	100.0

In our study, after following the inclusion and exclusion criteria,60 patients were enrolled. All these patients were having locally advanced breast cancer.Based on the TNM staging, patients were categorised into the following groups.65 % patients come in T3 stage,23 % of patients come under T4B stage,only 8% and 3% patients come under T2 and T4C stage respectively.

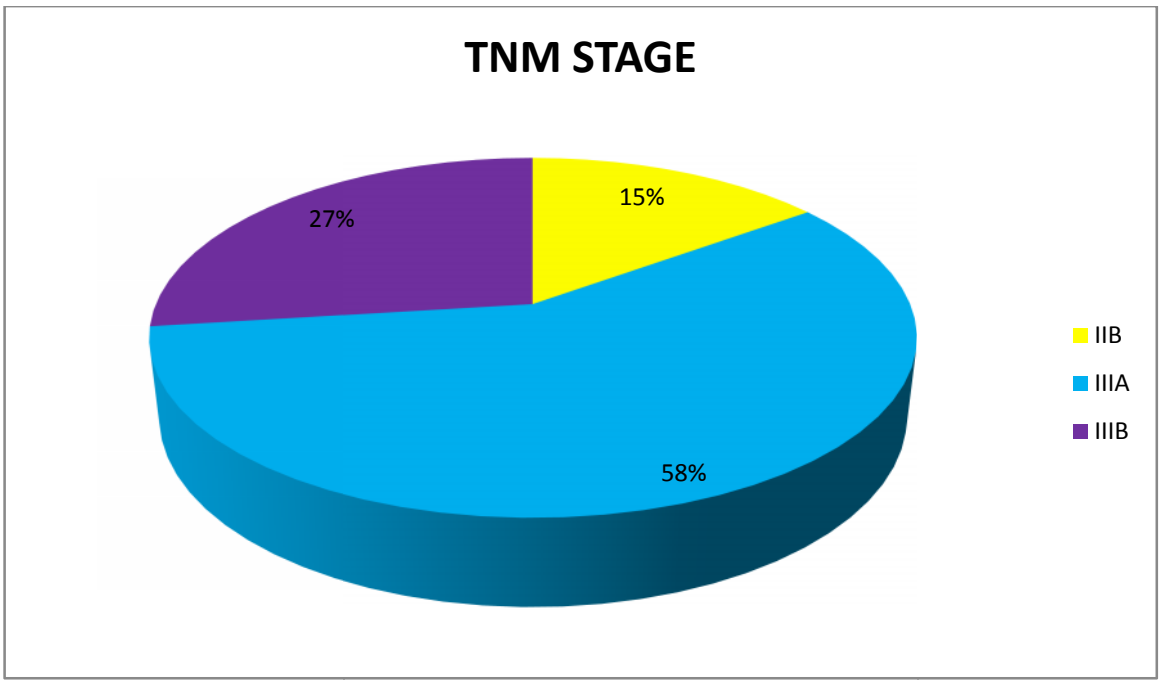
CHART 5:



AXILLARY NODE	Frequency	Percent
N0	8	13.3
N1	34	56.7
N2A	18	30.0
Total	60	100.0

In our study, 34 patients have single ipsilateral axillary node,18 patients have ipsilateral matted,fixed axillary lymph nodes.8 patients had no palpable lymph nodes.

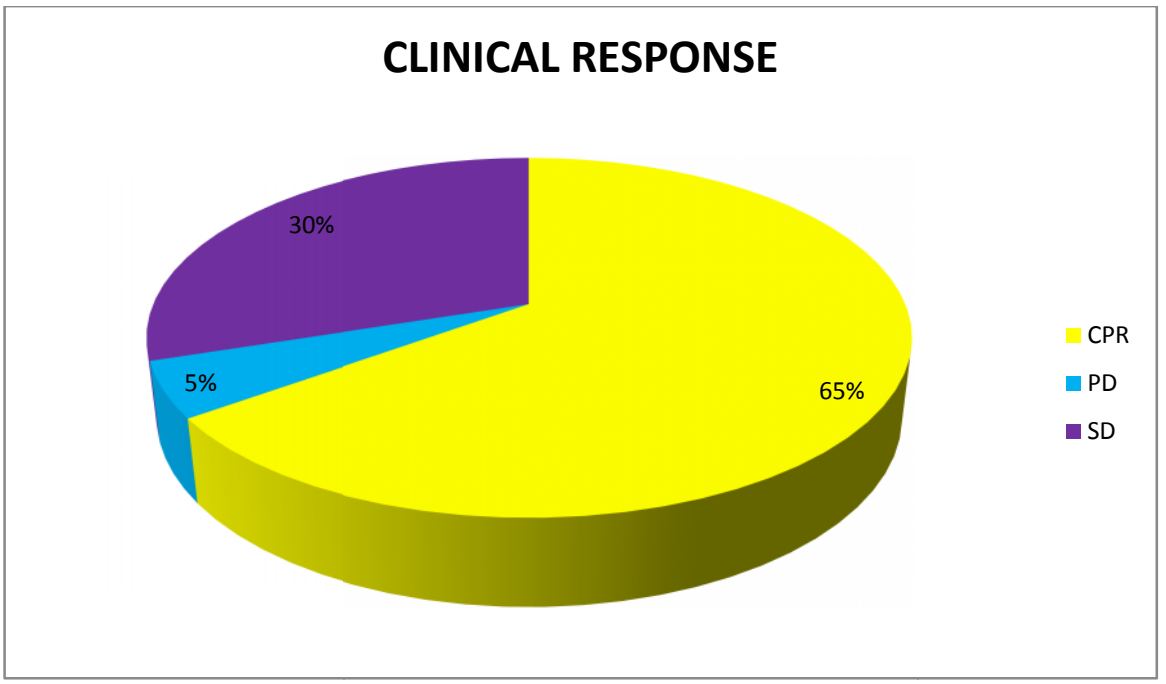
CHART 6:



TNM STAGE	Frequency	Percent
IIB	9	15.0
IIIA	35	58.3
IIIB	16	26.7
Total	60	100.0

In the study,according to TNM Staging,patients were categorised into three groups,58% of patients come under III A Stage,26 % of patients come under III B and 15 % of patients are in IIB Stage.There were no patients with supraclavicular or infraclavicular lymph nodes (III C).

CHART 7:



CLINICAL RESPONSE	Frequency	Percent
CPR	39	65.0
PD	3	5.0
SD	18	30.0
Total	60	100.0

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

The clinical response of 60 patients were observed and recorded,Out of the 60 patients,Overall objective response of 65% was observed.complete clinical response was not noted in any patient.Partial clinical response was observed in 39 patients.No response (<50 %) was observed in 18 patients.However 3 patients showed progressive disease.

Frequency Table :

PATHOLOGICAL RESPONSE		**Frequency**	**Percent**
Valid	pCR	3	9
Valid	PNR	57	90.9

The second objective of this study is to evaluate the Pathological response of the primary tumor and lymph node to neo adjuvant chemotherapy .The pathological response is divided into two categories , namely Pathological complete response and Pathological non responders. pCR constituted of the patients who showed no invasive cells in the Histopathological report.Pathological non responders ,in whom invasive cells are seen.

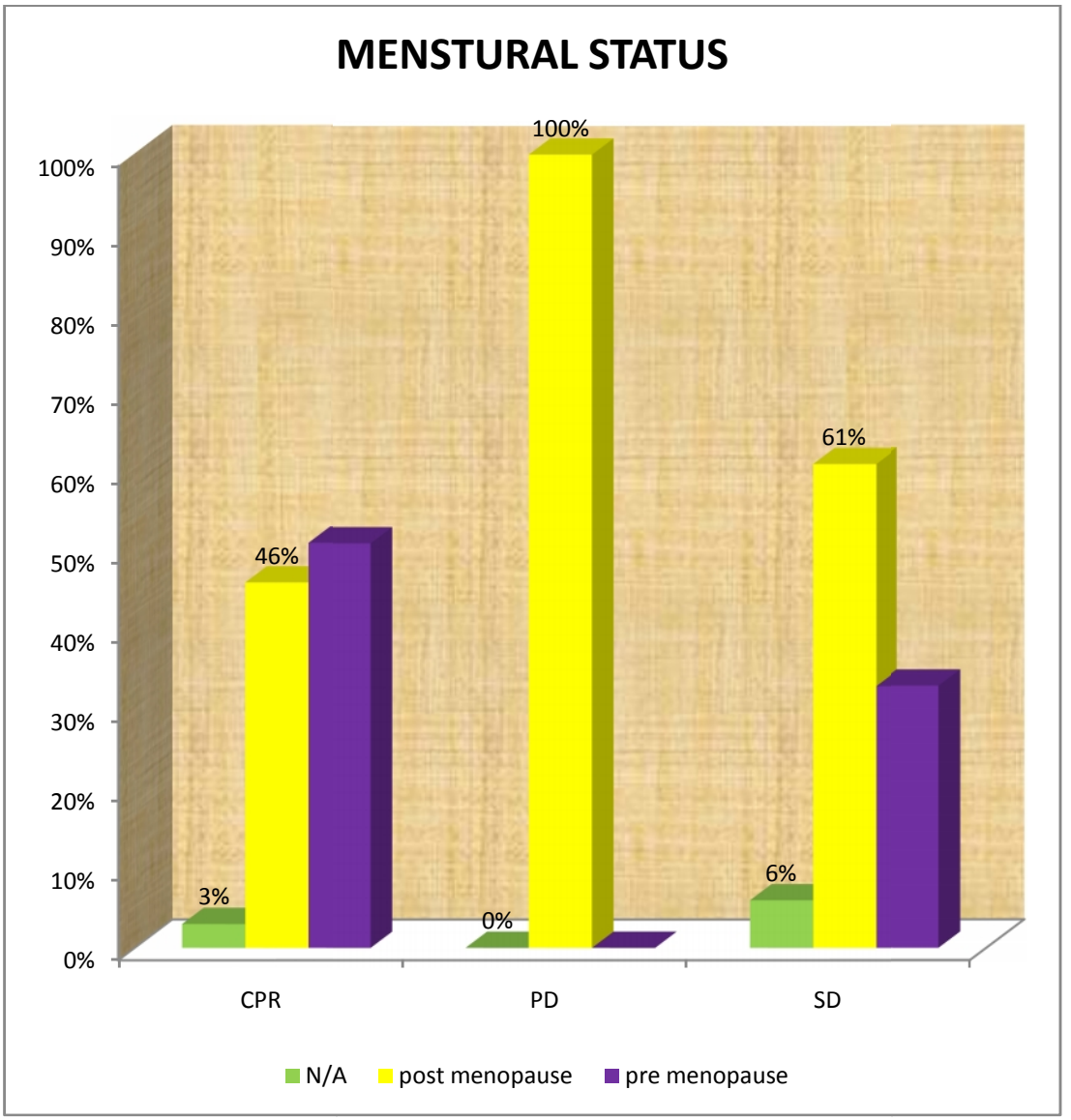
In our study, 3 patients(9%) showed complete pathological response following neo adjuvant chemotherapy.Invasive cells were detected in the mastectomy specimens of 57 patients in Histopathology (90%).

Paired Samples Statistics							
		Mean	N	Std. Deviation	Std. Error Mean	T value	P value
Pair 1	Before_Max_Size	6.2500	60	1.20205	.15518	11.559**	
	After_Chemo	4.0333	60	1.31441	.16969		p<0.001

			Clinical__Response			Total
			CPR	PD	SD	
Menstural_Status	N/A	Count	1	0	1	2
		% within Clinical__Response	2.6%	0.0%	5.6%	3.3%
	post menopause	Count	18	3	11	32
		% within Clinical__Response	46.2%	100.0%	61.1%	53.3%
	pre menopause	Count	20	0	6	26
		% within Clinical__Response	51.3%	0.0%	33.3%	43.3%
		Count	39	3	18	60
		% within Clinical__Response	100.0%	100.0%	100.0%	100.0%

Pearson chi square =4.526

P = 0.339


MENSTURAL STATUS
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
3%
46%
0%
100%
6%
61%
CPR
PD
SD
N/A
post menopause
pre menopause

			CLINICAL__RESPONSE			Total
			CPR	PD	SD	
TUMOR STAGE	T2	Count	3	0	2	5
		% within Clinical__Response	7.7%	0.0%	11.1%	8.3%
	T3	Count	27	2	10	39
		% within Clinical__Response	69.2%	66.7%	55.6%	65.0%
	T4B	Count	7	1	6	14
		% within Clinical__Response	17.9%	33.3%	33.3%	23.3%
	T4C	Count	2	0	0	2
		% within Clinical__Response	5.1%	0.0%	0.0%	3.3%
Total		Count	39	3	18	60
		% within Clinical__Response	100.0%	100.0%	100.0%	100.0%

Pearson chi square = 3.253 p = 0.776

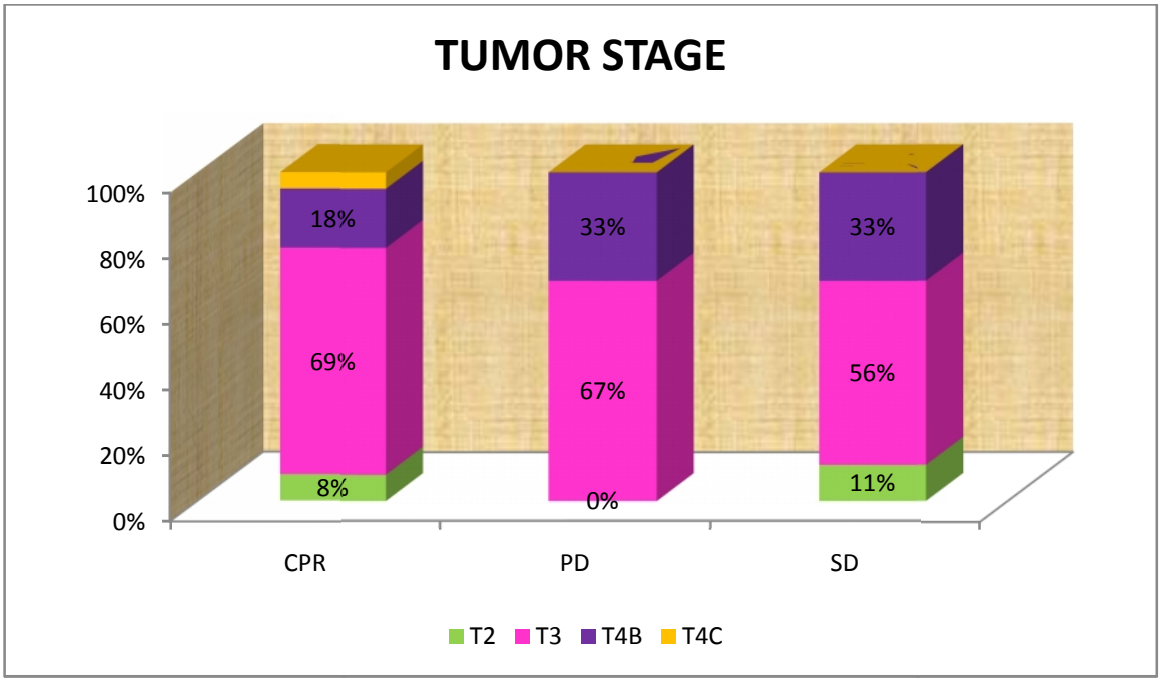
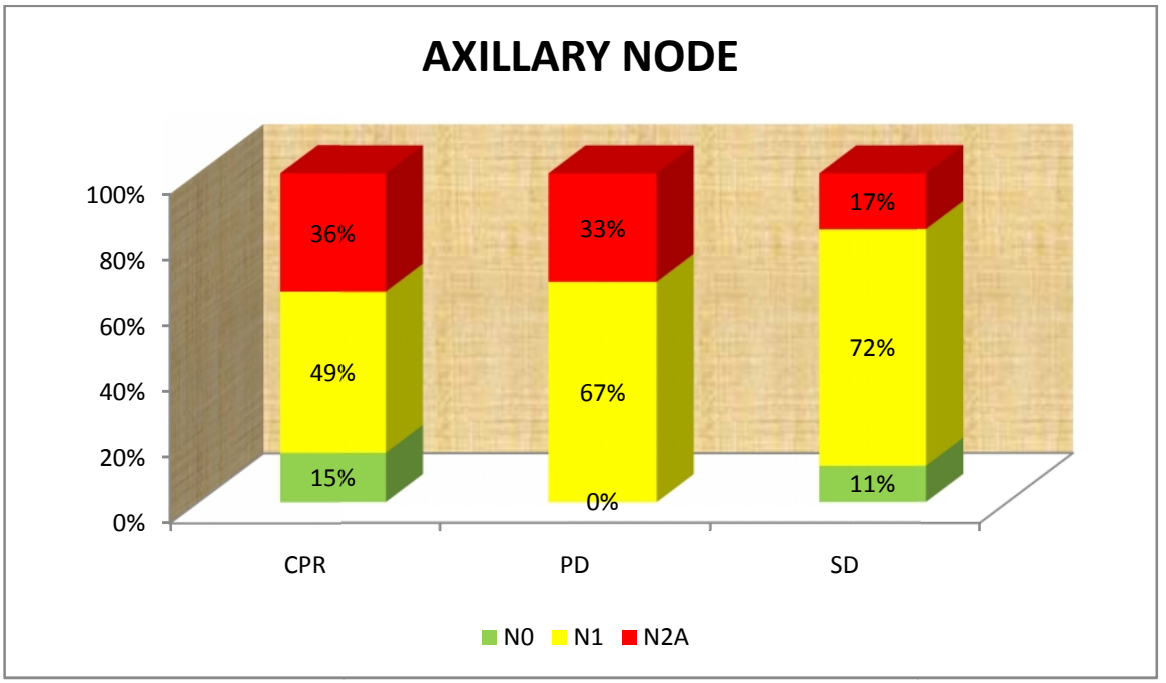


TABLE :

			CLINICAL__RESPONSE			Total
			CPR	PD	SD	
Axillary_Node	N0	Count	6	0	2	8
		% within Clinical__Response	15.4%	0.0%	11.1%	13.3%
	N1	Count	19	2	13	34
		% within Clinical__Response	48.7%	66.7%	72.2%	56.7%
	N2A	Count	14	1	3	18
		% within Clinical__Response	35.9%	33.3%	16.7%	30.0%
Total		Count	39	3	18	60
		% within Clinical__Response	100.0%	100.0%	100.0%	100.0%

Pearson chi square = 3.376 p = 0.497

This table demonstrates the clinical response in patients with respect to the nodal stage .In patients with N1 Disease ,clinical partial response is about 48 % and in N2A disease,the CPR is 35%.



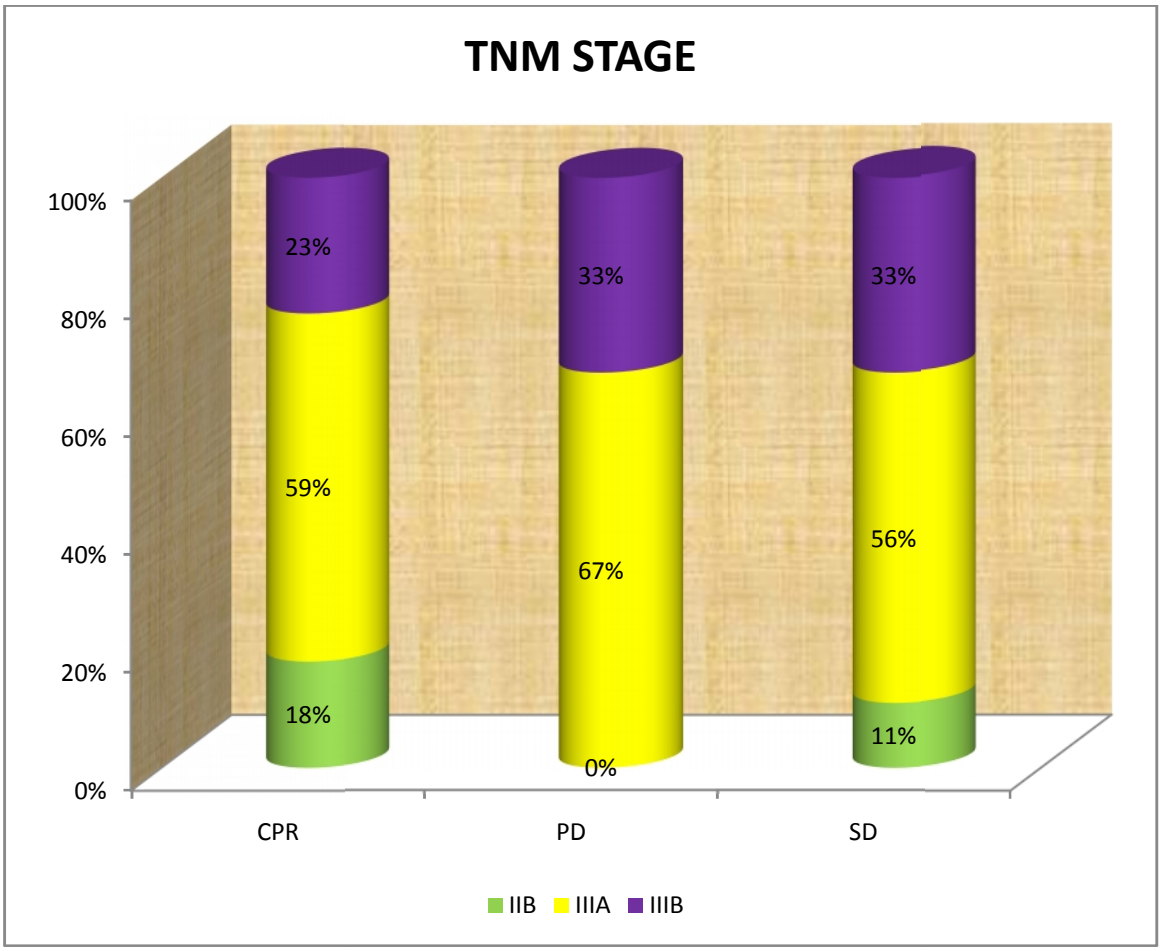
Table

			CLINICAL__RESPONSE			Total
			CPR	PD	SD	
TNM STAGE	IIB	Count	7	0	2	9
		% within Clinical__Response	17.9%	0.0%	11.1%	15.0%
	IIIA	Count	23	2	10	35
		% within Clinical__Response	59.0%	6.7%	55.6%	58.3%
	IIIB	Count	9	1	6	16
		% within Clinical__Response	23.1%	3.3%	33.3%	26.7%

According to TNM STAGING ,following neoadjuvant chemotherapy ,17 % of II B patients showed clinical partial response. 59 % of III A Patients showed partial response and 23 % OF III B patients showed CPR. 10 patients in IIIA and 6 patients in III B showed stable disease.

Finally 2 patients from IIIA and 1 patient from IIIB showed progressive disease.

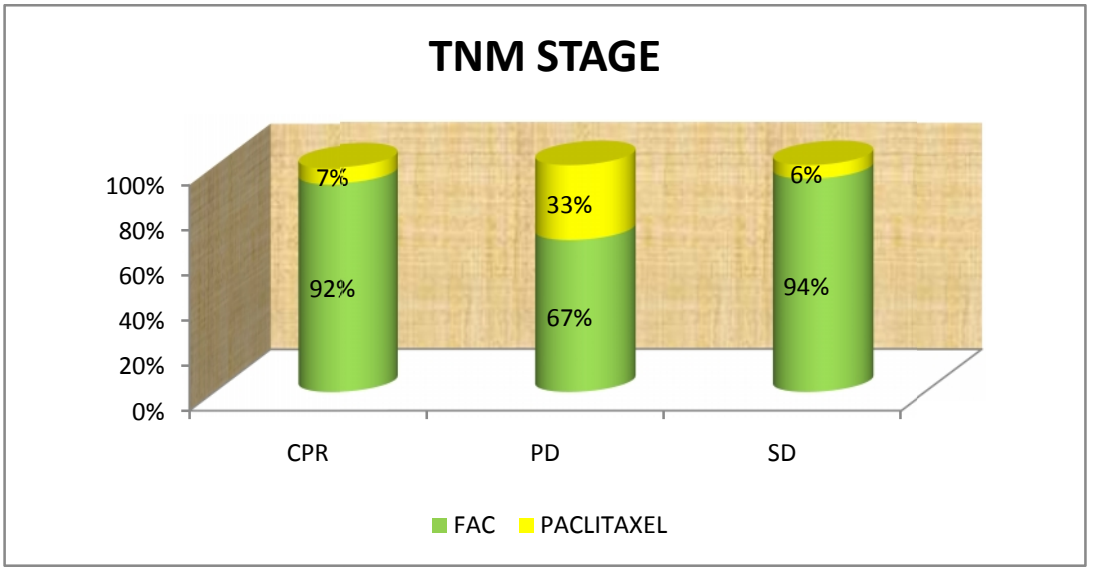
CHART :



Crosstab						
			Clinical__Response			Total
			CPR	PD	SD	
CHEMO REGIMEN	FAC	Count	36	2	17	55
		% within Clinical__Response	92.3%	6.7%	46.4%	91.7%
	PACLITAXEL	Count	3	1	1	5
		% within Clinical__Response	7.7%	3.3%	5.6%	8.3%

Pearson chi square = 2.657 p = 0.265

In our study, 55 patients underwent FAC Regimen and 5 Patients underwent PACLITAXEL Regimen.Amongthe patients who underwent FAC cycle, 36 patients showed clinical partial response,17 patients had stable disease and 2 patients had progressive disease.Among patients who underwent PACLITAXEL regimen, 3 patients showed clinical partial response,2 patients showed1 stable and 1 progressive disease respectively.



DISCUSSION

In our study**,** the results indicate that in majority of patients with LABC,neoadjuvant chemotherapy has a drastic reduction in size of the tumor as well as axillary Lymph node.In our study group , after three cycles of FAC regimen,65 % of patients showed clinical partial response, experiencing significant shrinkage of primary tumor therefore facilitating subsequent surgery.(20)

One major goal of systemic therapy in the early eradication of subclinical distant metastasis in an attempt to improve survival. The response of axillary lymph nodes to systemic therapyreflects the sensitivity of occult metastasis in the other organ compartments.

In our study the follow up period was only 2 years and median follow up period of 18 months and probably 5 years disease free survival and overall survival rates may be on par with this short study and it is too early to comment on it.

CONCLUSION

The results from this study suggests that maximal tumor shrinkage and downstaging of axillary lymph nodes after the neoadjuvant chemotherapy in locally advanced breast carcinoma rendered surgically resectable in majority of patients.It also explains that complete regression in number of metastatic lymph nodes in complete pathological response is associated with eradication of distant occult metastasis which is an important prognostic factor and shows significant improvement in disease free survival of breast carcinoma patients. The results from the study suggests that neoadjuvant chemotherapy is the standard management in patients with locally advanced breast carcinoma which is followed by surgery and adjuvant chemoradiation.The prediction of response to neoadjuvant chemotherapy remains to be determined and studies are being focussed on potential biologic markers thatinfluence the response to neoadjuvant chemotherapy.

GOVERNMENT VELLORE MEDICAL COLLEGE HOSPITAL

EVALUATION OF CLINICAL AND PATHOLOGICAL RESPONSE FOLLOWING NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCINOMA

PROFORMA

Name: Age: Sex: IP.no:

Address:

Occupation:

Socioeconomic status:

CLINICAL HISTORY

Presenting symptoms:

1. Swelling.
2. Pain.
3. Nipple retraction.
4. Nipple discharge.
5. Axillary lump.
6. Loss of appetite and weight.
7. Inflammatory symptoms.
8. Systemic:
    a. Pyrexia
    b. Sweating
    c. Malaise

9. Local:
    a. Pain
    b. Change in colour
    c. Edema
    d. Cellulitis.
10. Symptoms suggestive of metastasis.
    a. Back pain
    b. Head ache and convulsion
    c. Chest symptoms
    d. Jaundice
    e. Opposite breast Swelling

Past history:

1. H/o associated medical conditions like HT/DM/IHD/TB
2. H/o similar swelling in the breast.
3. H/o surgery for benign breast disease

Family history:

1. H/o breast cancer in 1st degree relative

Drug history:

1. H/o OCP intake/HRT.
2. H/o previous exposure to radiation

Menstrual history:

1. Age at menarche
2. Age at menopause
3. Alterations in cycles.

Marital history:

1. Age at marriage:

Obstetric history:

1. Parity:

a) Age of the patient at 1st child birth

b) Age of patient at last child birth

c) History and duration of breast feeding

Personal history:

1. H/o smoking

Dietetic history:

EXAMINATION:

PRECHEMOTHERAPY STATUS:

General examination:

Built/pallor/icterus/pedaledema/lymphadenopathy

Local examination:

Breast:

1. Side and Quadrant involved
2. Tumour size
3. Axillary nodal status
4. Opposite breast/opposite axilla
5. Other systems

Abdomen:

1. Cardiovascular system
2. Respiratory system
3. Central nervous system
4. Spine and Cranium

INVESTIGATIONS:

1. Trucut Biopsy.
2. Hematological investigations.
3. X-ray Chest.
4. X -ray LS Spine, humerus, femur ,pelvis with both hips and X - ray Skull.
5. USG breast Bilateral.
6. USG Abdomen and pelvis.
7. ECG/ECHO

STAGING

NEOADJUVANT CHEMOTHERAPY:

1. Type of regimen:
    a. Patient details on each cycle -Tumor status(size).
    b. Axillary lymphnodestatus.
    c. Any symptoms and signs of metastasis.
2. No. of cycles.

TREATMENT

Type of surgery

POST NEOADJUVANT CHEMOTHERAPY STATUS

HISTOPATHOLOGY REPORT

1. Primary Tumor
    a. Macroscopic features
    b. Histological features
2. Axillary nodal status.

POST OPERATIVE ADJUVANT CHEMOTHERAPY

- Duration after surgery
- Type of regimen:
- No. of cycles

FOLLOW UP:

Complaints:

1. Nodule/Swelling
    a. Single/multiple
    b. Chest wall
    c. Axilla
    d. Supraclavicular region
2. Ulcerations
3. Arm edema
4. Symptoms suggestive of metastasis

General examination

Local Examination

1. Swelling/ulcer
2. Operative Scar
3. Tumour bed
4. Axilla

Distant metastatic sites

1. Bone
2. Lungs and pleura
3. Brain
4. Liver
5. Peritoneal &Krukenbergtumor.

Opposite breast and Axilla

FOLLOW UP INVESTIGATIONS:

1. Basic investigations
2. Hematologicalinvestigations
3. Specific investigations
    a) FNAC/ Biopsy if any recurrence
    b) serum Calcium /serum alkalinephosphatase
    c) Liver function test
    d) X-ray Chest/spine
    e) USG Abdomen and pelvis
    f) CT Brain if indicated

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MASTERCHART

S. NO	NAME	AGE/ SEX	IP NO	MS*	TS*	TSt*	AN*	TNM St*	CHEMO REGI-MEN	TS*	AN*	CR*	PR*
1	Maragathammal	65/f	53497	post	5*3	T4B	N2A	IIIB	FAC	3*2	N1	CPR	PNR
2	Sumathi	42/f	65812	pre	6*4	T3	NI	IIIA	FAC	5*4	N1	SD	PNR
3	Thanjammal	51/F	89966	post	7*4	T3	N1	IIIA	FAC	3*3	N0	CPR	PNR
4	Jayalakshmi	70/f	80041	post	4*3	T4B	N1	IIIB	FAC	4*3	N1	SD	PNR
5	Gandhi	66/f	51713	post	6*5	T3	N2A	IIIA	PACLI-TAXEL	4*3	N1	CPR	PNR
6	Devi	45/f	9880	pre	6*4	T3	N0	IIB	FAC	3*3	N0	CPR	PNR
7	Chinnaponnu	50/f	73585	post	7*5	T4C	N2A	IIIB	FAC	3*4	N1	CPR	PNR
8	Baby	43/f	48766	pre	6*4	T3	N1	IIIA	FAC	4*4	N0	CPR	PNR
9	Amudha	35/f	51994	pre	6*5	T3	N0	IIB	FAC	4*4	N0	CPR	PNR
10	Govindammal	47/f	72400	pre	7*4	T3	N1	IIIA	FAC	6*4	N1	SD	PNR
11	Janaki	45/f	5540	pre	7*6	T3	N1	IIIA	FAC	3*3	N0	CPR	PNR

12	Indira	39/f	43490	pre	6*4	T3	N1	IIIA	FAC	4*3	N1	SD	PNR
13	Ganga	43/f	42342	post	7*5	T3	N1	IIIA	FAC	7*6	N1	SD	PNR
14	Sulochana	64/f	12823	post	6*5	T4B	N1	IIIB	PACLI-TAXEL	3*2	N0	CPR	PNR
15	Rani	55/f	60707	post	8*6	T3	N1	IIIA	FAC	4*3	N0	CPR	PNR
16	Padmavathi	61/f	12822	post	6*6	T3	N0	IIB	FAC	6*5	N0	SD	PNR
17	Neela	54/f	33668	pre	7*6	T4B	N2A	IIIB	FAC	4*5	N1	CPR	PNR
18	Kuppammal	72/f	71501	post	8*5	T3	N2A	IIIA	FAC	4*3	N1	CPR	PNR
19	Pitchaiyammal	55/f	50323	post	7*5	T3	N1	IIIA	FAC	6*4	N1	SD	PNR
20	Lalitha	40/f	4697	pre	8*6	T3	N0	IIB	FAC	4*4	N0	CPR	PNR
21	Jayamani	65/f	57089	post	6*5	T3	N1	IIIA	FAC	6*4	N1	SD	PNR
22	Sujatha	47/f	58787	pre	5*4	T3	N0	IIB	FAC	3*3	N0	SD	PNR
23	Sudhabai	40/f	28479	pre	4*2	T2	N2A	IIIA	FAC	2*2	N1	CPR	pCR
24	Sarada	57/f	41908	post	6*4	T3	N2A	IIIA	FAC	3*2	N1	CPR	PNR
25	Rameeza bee	46/f	53402	post	6*5	T4B	N1	IIIB	FAC	7*6	N2A	PD	PNR

26	Rajeshwari	35/f	14509	pre	8*6	T3	N1	IIIA	FAC	4*3	N0	CPR	PNR
27	Pushpa	40/f	56683	pre	7*5	T4B	N1	IIIB	FAC	4*3	N1	CPR	PNR
28	Kantha	50/f	65907	post	7*6	T3	N2A	IIIA	PACLI-TAXEL	8*6	N2A	PD	PNR
29	Navaneetham	57/f	29897	post	5*5	T3	N1	IIIA	FAC	4*3	N1	SD	PNR
30	Siva	55/f	64019	post	7*5	T3	N0	IIB	FAC	3*3	N0	CPR	PNR
31	Mummathi	47/f	60420	pre	6*5	T3	N1	IIIA	FAC	4*3	N1	CPR	PNR
32	Lily	60/f	90224	post	6*5	T4B	N1	IIIB	FAC	3*2	N0	CPR	PNR
33	Maheshwari	30/f	64010	pre	6*7	T3	N1	IIIA	FAC	3*3	N0	CPR	PNR
34	Latha	49/f	22912	pre	7*6	T3	N1	IIIA	FAC	4*3	N0	CPR	PNR
35	Kuppammal	72/f	71501	post	8*6	T4B	N1	IIIB	FAC	7*5	N1	SD	PNR
36	Indumathi	44/f	43562	pre	4*4	T2	N2A	IIIA	FAC	3*2	N2	SD	PNR
37	Jagadhammal	74/f	17714	post	8*5	T3	N2A	IIIA	FAC	3*2	N1	CPR	PNR
38	Kanchana	70/f	44712	post	7*5	T4B	N2A	IIIB	FAC	6*4	N2	SD	PNR
39	Kannan	80/m	33964	N/A	5*4	T4B	N1	IIIB	FAC	5*4	N1	SD	PNR

40	Mahalakshmi	42/f	68222	pre	6*5	T3	N0	IIB	FAC	3*3	N0	CPR	PNR
41	Najmun	55/f	79724	post	5*5	T3	N1	IIIA	FAC	6*5	N2A	PD	PNR
42	Marimuthu	45/f	74214	pre	4*3	T2	N2A	IIIA	FAC	4*3	N2A	SD	PNR
43	Poongavanam	57/f	23234	post	8*6	T3	N2A	IIIA	FAC	4*3	N1	CPR	PNR
44	Saroja	65/f	88347	post	5*4	T4B	N1	IIIB	FAC	4*3	N1	SD	PNR
45	Sathya	49/f	33881	pre	6*4	T3	N0	IIB	FAC	3*2	N0	CPR	PNR
46	Shenbagavalli	55/f	63977	post	6*5	T4B	N1	IIIB	PACLI-TAXEL	3*3	N0	CPR	PNR
47	Porkodi	46/f	42341	pre	6*5	T3	N1	IIIA	FAC	3*3	N0	CPR	PNR
48	Ganesan	69/m	40068	N/A	7*6	T3	N1	IIIA	FAC	4*3	N0	CPR	PNR
49	Devagi	65/f	70130	post	8*5	T3	N2A	IIIA	FAC	4*4	N1	CPR	PNR
50	Chinnapappa	38/f	15295	pre	7*5	T3	N1	IIIA	FAC	3*3	N0	CPR	PNR
51	Selvi	43/f	52467	pre	4*3	T2	N2A	IIIA	FAC	2*2	N1	CPR	pCR
52	Kanthammal	82/f	14520	post	6*5	T4B	N1	IIIB	FAC	4*4	N0	CPR	PNR
53	Valarmathi	50/f	34578	post	8*6	T3	N1	IIIA	FAC	4*3	N0	CPR	PNR

54	Kamatchi	67/f	11876	post	5*4	T4B	N1	IIIB	PACLI-TAXEL	3*3	N1	SD	PNR
55	Sankari	48/f	65224	pre	6*4	T3	N1	IIIA	FAC	3*3	N0	CPR	PNR
56	Pattu	64/f	43998	post	7*6	T4C	N2A	IIIB	FAC	3*4	N1	CPR	PNR
57	Bhuvaneshwari	45/f	22786	pre	3*3	T2	N2A	IIB	FAC	2*2	N1	CPR	pCR
58	Karpagam	53/f	11879	post	6*5	T3	N2A	IIIA	FAC	3*3	N1	CPR	PNR
59	Manjula	43/f	56621	pre	7*7	T3	N1	IIIA	FAC	4*3	N0	CPR	PNR
60	Unnamalai	67/f	27684	post	5*6	T3	N1	IIIA	FAC	4*3	N1	SD	PNR

Abbreviations:

- MS – Menstural status
- TS – Tumor size
- TSt – Tumor stage
- AN – Axillary node
- CR – Clinical response
- PR – Pathological response

- FAC – 5 Fluorouracil , Adriamycin , Cyclophosphamide
- CCR – Complete clinical response
- CPR – Clinical partial response
- SD – Stable disease
- PD – Progressive disease
- pCR- Pathological complete response
- PNR – Pathological non responders.

CONSENT FORM

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பத்திற்கு)

ஆய்வு செய்யப்படும் தலைப்பு:
பங்கு பெறுவரின் பெயர்:
பங்கு பெறுவரின் வயது:

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
1.	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
2.	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
3.	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்காள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
4.	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
5.	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	☐

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கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
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