ROLE OF PREOPERATIVE HEMATOLOGICAL MARKERS IN CARCINOMA BREAST AND ITS EFFICACY IN CORRELATION WITH CLINICOPATHOLOGICAL STAGING – A NOVEL TECHNIQUE

By

Dr. M. Hemanth Reddy

Dissertation submitted to BLDE University, Vijayapura

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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UNDER THE GUIDANCE OF DR. VIJAYA L. PATIL MS

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CONTENTS

LIST OF ABBREVIATIONS

1. ER- ESTROGEN RECEPTOR
2. PR- PROGESTERONE RECEPTOR
3. HER2NEU- HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2
4. CRP- C REACTIVE PROTIEN
5. LMR- LYMPHOCYTE MONOCYTE RATIO
6. PLR- PLATELET LYMPHOCYTE RATIO
7. NLR- NEUTROPHIL LYMPHOCYTE RATIO
8. MPV- MEAN PLATELET VOLUME
9. RDW- RED CELL DISTRIBUTION WIDTH
10. NF-KB- NUCLEAR FACTOR KAPPA B
11. IL-6- INTERLEUKIN-6
12. mGPS- MODIFIED GLASS PROGNOSTIC SCORE
13. HRT- HORMONE REPLACEMENT THERAPHY
14. TNBC- TRIPLE NEGATIVE BREAST CANCER
15. OS- OVERALL SURVIVAL
16. DFS- DISEASE FREE SURVIVAL
17. NACT- NEOADJUVANT CHEMOTHERAPHY
18. NSABP- NATIONAL SURGICAL ADJUVANT BRAEST AND BOWEL PROJECT
19. EBCTCG- EARLY BREAST CANCER TRIALISTS COLLABORATIVE GROUP
20. CMF- CYCLOPHOSPHAMIDE, METHOTREXARTE, FLUOROURACIL

21. FNA- FINE NEEDLE ASPIRATION

22. MLO- MEDIO-LATERAL-OBLIQUE

23. CC- CRANIO CAUDAL

24. SLN- SENTINEL LYMPH NODE

25. TGF- TRANSFORMING GROWTH FACTOR

26. EGFR- EPIDERMAL GROWTH FACTOR RECEPTOR

27. MRM- MODIFIED RADICAL MASTECTOMY

28. ECOG- EASTERN COOPERATIVE ONCOLOGY GROUP

29. TNM- TUMOUR, NODE, METASTASIS

30. cGY- CENTIGRAY

31. SEER- SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS

INTRODUCTION

Carcinoma breast ranks second globally in terms of cancer-related deaths among women and is the most common disease diagnosed in women[1]. The breasts are superficially situated glandular structures that fluctuate in size and density over the pectoralis major muscle. They consist of milk-producing cells arranged into lobules, which are grouped into lobes interspersed with fatty tissue. Milk is produced in the acini and transferred by lactiferous ducts that connect to the nipple. The breasts are supported by Cooper's ligaments, which anchor them to the underlying muscle fascia[2]. The ductal epithelium(ductal carcinoma) is where the majority of carcinoma breast begin, though some arise from the lobules (lobular carcinoma). Carcinoma breast risk factors are many and well-established. In Western countries, widespread screening programs have led to early detection, often before symptoms appear. Conversely, in many developing countries, symptoms such as a palpable breast lump or abnormal nipple discharge are common presenting complaints[3]. Diagnosis typically involves a physical exam, tissue biopsy. Treatment may include surgery, chemotherapy, radiation, hormone more recently, immunotherapy. Decisions regarding treatment are tailored to the individual, based on factors such as tumour histology, stage, molecular markers, and genetic mutations.

Even with breakthroughs in early detection and dozens of novel therapeutic choices, carcinoma breast remains the most common tumour in females. It is a multifaceted illness with a range of biomolecular subgroups and clinical presentations. It has taken significant work to categorize this carcinoma according to its molecular makeup, and treatment regimens are currently defined by subtype[4]. These are typically chosen after surgery, though. Chronic inflammation and cancer have a complicated and reciprocal interaction. In this investigation, we concentrate on how inflammation contributes to the growth of breast cancer. It is now commonly known that the characteristics of the tumour do not determine the fate for cancer patients alone, but that inflammation linked to cancer plays a crucial role in the development and prognosis of most cancers[5, 6]. Systemic changes associated with the inflammatory response include an elevated neutrophil count and a modest increase in platelet count[7]. Systemic inflammatory markers have just recently been made available as trustworthy and simple prognostic indicators. Tumour characteristics such as size, histological grade, lymph node involvement, ER, PR status and HER2NEU status are important prognostic indicators. Recently, gene expression profiling has emerged as a valuable tool to further stratify risk, inform therapy choices, especially for breast cancer that has hormone receptors, where it can help determine the need for chemotherapy[8,9]. Liquid biopsy assays that detect circulating tumour cells have also entered the field of prognosis for early-stage and locally advanced breast cancer[10]. But these tests are frequently expensive, experimental, and not commonly accessible in standard healthcare settings.

The systemic inflammatory reaction of the host has also been shown to influence tumour progression.[11,12] Various serum inflammatory markers and derived scores have been proposed as prognostic tools in multiple cancers. These comprise acute-phase proteins like C-reactive protein (CRP) and albumin, as well as elements of the differential white blood cell count, PLR, LMR, and the modified Glass prognostic score(mGPS), which awards a score between 0 and 2 based on increased CRP levels and decreased albumin are often utilized scores. These indicators have demonstrated predictive significance, especially in cases of advanced gastrointestinal and lung cancers[13].

However, in primary operable breast cancer, the prognostic significance and clinical applicability of these inflammatory markers remain unclear, with no established threshold values for risk stratification. To assess the predictive value of circulating systemic inflammatory response markers in primary operable breast cancer, a systematic review and meta-analysis was conducted.

Alongside demographic and basic clinical data, a growing range of novel prognostic markers—such as haematological parameters and perioperative anaesthetic factors—have been investigated and identified[14,15]. More recently, efforts have been made to incorporate genetic and molecular biomarkers into new prognostic models for breast cancer[16]. Nevertheless, a few of these markers are still not frequently employed in standard clinical practice because to their high expense, restricted availability, and the requirement for specialized equipment and expertise. Rapid diagnosis of breast cancer can benefit from the identification of low-cost biomarkers[17]. There is growing evidence that the development and spread of many cancers, including breast cancer, are significantly influenced by systemic inflammation linked to cancer[18]. This underscores the need for simple, cost-effective prognostic tools based on routinely available haematological markers obtained from a standard complete blood count.

AIMS AND OBJECTIVES OF THE STUDY:

AIM OF THE STUDY:

To determine which preoperative haematological markers—the NLR, MPV, LMR, and RDW—are the most effective at predicting carcinoma and to correlate these markers with clinicopathological staging of breast cancer.

OBJECTIVES:

- To evaluate its relationship with clinicopathological staging and biological subtypes which in turn predict the prognosis.

- To evaluate the efficacy of hematological markers as a novel indicator of breast cancer activity in various biological subtypes.

REVIEW OF LITERATURE

1. A study titled “Is red cell distribution width a novel indicator of breast cancer activity?” was carried out by Seretis et al in 2013 demonstrated that elevated RDW could be helpful in the differential diagnosis of the nature of a breast tumour benign or malignant-, being significantly higher in the group of patients with breast cancer. RDW shows a positive correlation with tumour size and the number of infiltrated axillary lymph nodes, but an inverse correlation with tumour grade. This inverse relationship challenges the expected inflammatory response in higher-grade tumours and may be explained by immune evasion in more aggressive cancers. Elevated RDW is strongly associated with HER2 overexpression, potentially reflecting IL-6-driven inflammatory processes. This suggests RDW could be a valuable biomarker for monitoring responses to anti-HER2 therapies by comparing baseline and sequential measurements. Given its availability in routine blood tests and cost- effectiveness, RDW holds promise as a practical biomarker for assessing breast cancer activity and progression.

2. Yao D., Wang Z., Cai H., Li Y., Li B. et al has done retrospective study and identified elevated preoperative RDW as a marker associated with poor prognosis in breast cancer patients and an independent predictor of reduced survival. This finding highlights the importance of closer monitoring for patients with higher preoperative RDW, given its accessibility and low cost as part of routine blood tests. RDW could serve as a reliable, reproducible index to identify carcinoma breast patients more likely to poor outcomes. Compared to previous studies, our study includes several advancements. Unlike prior research limited to younger carcinoma breast patients under 40, our study encompasses a broader age range (≥18 years) and involves a significantly larger sample size (825 patients versus 203). Furthermore, our study incorporates clinical haematology parameters, such as high-sensitivity CRP, providing more comprehensive insights into RDW’s role in prognosis. The potential mechanisms linking elevated RDW to poor prognosis include chronic inflammation, poor nutritional status, oxidative stress, and age-related changes in erythropoiesis. Tumour-associated inflammation disrupts red cell maturation and increases RDW, while oxidative stress damages cellular DNA and modulates gene expression, further driving tumour progression. Elevated RDW may thus reflect a combination of these factors and serve as a marker of tumour growth and metastasis. In conclusion, elevated preoperative RDW levels are associated with poor OS and DFS in breast cancer patients, highlighting its potential as a predictive marker for poor prognosis.

3. Elevated neutrophil to lymphocyte ratio at initial clinical presentation was an independent predictor of poor survival in patients with breast cancer, according to the findings of a 2013 study by Noh H et al. on the utility of pre-treatment NLR in predicting disease-specific survival in breast cancer. This result is consistent with earlier findings for breast cancer and other malignancies. Co-culture studies have shown that neutrophils suppress the immune system by preventing the cytolytic activity of natural killer cells, activated T-cells, and lymphocytes. Tumour-associated neutrophils also contribute to extracellular matrix remodelling through enzymatic activity, promoting the release of growth factors, endothelial cell migration, and tumour cell dissociation. Furthermore, neutrophil-derived reactive oxygen species reduce extracellular matrix adhesion, activate nuclear factor (NF)-κB, and inhibit tumour cell apoptosis. Collectively, these processes enhance angiogenesis, tumour growth, and metastasis. Particularly in breast cancer, oncostatin M produced by neutrophils instructs tumour cells to release VEGF, which increases invasiveness and detachment. Our study also examined NLR's prognostic implications on intrinsic subtypes of breast cancer. Luminal A subtype patients had a considerably worse outcome when their NLR was elevated. HER2-enriched and triple-negative breast cancers (TNBC), which are biologically more aggressive, may be less influenced by their microenvironment than luminal A tumours. This theory is supported by research that demonstrates the critical role the microenvironment plays in the development of estrogen receptor-positive (ER+) breast tumours. Large prospective studies on hormonal therapy and breast cancer incidence also suggest that luminal A subtypes are more microenvironment-sensitive compared to other subtypes. In conclusion, patients with elevated pre-treatment NLR had poorer disease-specific survival, particularly in the luminal A subtype. NLR is a readily available, cost-effective parameter included in routine preoperative workups, offering potential as a prognostic marker.

4. Young women with breast cancer are more likely to present with more aggressive disease and have worse prognoses than older patients, according to a study by Huang, Du-Ping MD; Ma, Rui-Min MD; Xiang, You-Qun MD et al. on the Utility of Red Cell Distribution Width as a Prognostic Factor in 203 young breast cancer patients. Angiogenesis, invasion, tumour growth, and ultimately metastasis are all aided by inflammation in the tumour microenvironment. Reduced survival rates in individuals with breast cancer have been linked to elevated inflammatory markers, including interleukin-6, neutrophil-to-lymphocyte (N/L) ratio, and C-reactive protein (CRP). Additionally, by altering the red cell membrane, inflammation can interfere with the development of red blood cells, resulting in an increase in the RDW. RDW is a commonly used indicator of systemic inflammation that has recently been connected to worse clinical outcomes in a number of cancer types. In line with earlier research findings, our study showed that high pre-treatment RDW is an independent predictor of poor survival in young women with breast cancer. As far as we are aware, this is the first study to examine the predictive importance of RDW in

young women with breast cancer, and it raises the possibility that worse outcomes could be linked to higher pre- treatment RDW. RDW has potential as a trustworthy laboratory measure for identifying individuals with a worse prognosis because it is inexpensive and readily available through standard blood testing. Nevertheless, further prospective research is required to examine its function in directing treatment choices.

Furthermore, our results coincide with the research conducted by Seretis et al., which found that RDW is a valuable biomarker for differentiating between benign and malignant breast tumours. has also been strongly linked to advanced disease stages, a larger tumour size, and more invaded axillary lymph nodes. An explanation for this could be that more aggressive tumours cause a greater inflammatory response, which raises the levels of circulating cytokines such interleukin-6, CRP, and the N/L ratio. According to these results, RDW may be a useful biomarker for breast cancer tumour growth and metastasis. There are several restrictions on our study. It is a retrospective investigation based on a limited sample size and was carried out at a single centre. Larger multicentre prospective trials are therefore needed to confirm these results. Our research concludes that in young women with breast cancer, pre-treatment RDW may be related to both overall survival (OS) and disease-free survival (DFS). Since RDW is a biomarker that is easily accessible in clinical practice, more investigation is required to confirm its usefulness and ascertain its possible significance in predicting the prognosis of breast cancer in young patients.

5. The goal of Yang SH et al. (2024)[19] was to look into the relationship between NLR and AGR and breast cancer patients' prognosis and survival. There were 1,188 patients in all, 323 of whom had neoadjuvant chemotherapy (NACT), and 865 of whom had surgery up front. Higher AGR was significantly linked to better DFS (cut off > 1.55; hazard ratio [HR], 0.37; 95% CI, 0.16–0.85; p = 0.019), better CSS (cut off > 1.46; HR, 0.39; 95% CI, 0.17–0.92; p = 0.031), and a higher pCR rate (cut-off > 1.28; odds ratio [OR], 2.03; 95% confidence interval [CI], 1.13–3.74; p = 0.020). Poorer DFS (cut off > 4.09; HR, 1.77; 95% CI, 1.07–2.91; p = 0.026) and worse CSS (cut off > 4.09; HR, 1.98; 95% CI, 1.11–3.53; p = 0.021) were significantly correlated with higher NLR. Higher AGR was associated with significantly better OS (cut off > 1.17; HR, 0.54; 95% CI, 0.36–0.82; p = 0.004) in patients who had surgery up front, but higher NLR was associated with worse OS (cut off > 2.38; HR, 1.63; 95% CI, 1.09–2.44; p = 0.018). They came to the conclusion that NLR and AGR are helpful in forecasting both the prognosis of patients with breast cancer and their responsiveness to NACT.

6. In patients with cN0 HR(+) breast cancer, Wang, MF et al. (2024)[20] assessed the relationship between NLR and lymph node metastases. Significant differences were seen between various clinical stages, histological grades, tumour diameters, Ki-67 levels, and NLR levels in cN0 HR(+) breast cancer with axillary lymph node metastases, according to a univariate analysis ($P < 0.05$). Multifactorial analysis revealed that NLR, tumour size, and clinical stage were independent risk factors for lymph node metastases. NLR is a separate risk factor for lymph node metastases in cN0 HR(+) breast cancer. An increased likelihood of lymph node metastases is indicated by an NLR ≥ 2.4. The likelihood of axillary lymph node metastases is highly predicted by an elevated preoperative NLR.

7. Qi X and associates (2023)[21] The purpose of this meta-analysis was to assess the predictive significance of PLR in BC patients receiving neoadjuvant chemotherapy (NACT). The low pCR rate, poor OS, and disease-free survival (DFS) of BC patients treated with NACT were found to be substantially correlated with high PLR. As a result, PLR may serve as a prediction biomarker for NACT's effectiveness in BC.

8. In order to develop and validate a nomogram for predicting pCR, Ma, R. et al. (2023)[22] examined the function of platelet-to-lymphocyte ratio (PLR) in the complete pathological response (pCR) of patients with breast cancer (BC) following neoadjuvant chemotherapy (NAC). They came to the conclusion that, in BC patients following NAC, PLR, PLT, WBC, and tumour grade were independent predictors of pCR. A good predicting ability was demonstrated by the nomogram based on the aforementioned favourable characteristics.

9. Y. Ma et al. (2021)[23]Assessing the prognostic usefulness of inflammatory markers for pathological response and prognosis in patients with breast cancer undergoing neoadjuvant chemotherapy (NAC) was the aim of this investigation. Of the 203 patients, they discovered that 27 (13.3%) developed metastases, either local or distant. The areas under the curve (AUC) for the peripheral blood NLR, PLR, and LMR were 0.773 (0.673-0.874), 0.630 (0.508-0.753), and 0.674 (0.555-0.793), in that order. The ideal cut-off points were 6.2, 135, and 3.0, in that order. LMR was associated with breast cancer DFS and pathological complete response (pCR) rates, according to univariate and multivariate analyses ($P < 0.05$). Patients with low LMR, HER-2 positivity, and lymph node status (N2-3) had the worst DFS out of all of the patients. They came to the conclusion that LMR might serve as a marker for estimating the prognosis and effectiveness of breast cancer patients.

10. The efficacy of NLR to predict overall survival (OS) and disease-free survival (DFS) in patients with luminal A- or luminal B-HER2-negative breast cancer who had neoadjuvant chemotherapy (NACT) was examined by Grassadonia A et al. (2021)[24]. To measure NLR, 168 consecutive patients with luminal breast cancer had their pre-treatment complete blood cell counts examined. Receiving operator curve (ROC) analysis was used to determine a cut-off value, which was then used to stratify the study population into NLR low or NLR high. In comparison to patients with NLR high, those with pre-treatment NLR low had a substantially shorter OS (HR: 7.79, 95% CI: 1.25–15.07, p = 0.021) and DFS (HR: 6.97, 95% CI: 1.65–10.55, p = 0.002). Additionally linked to worse DFS were non-ductal histology, luminal B subtype, and post-treatment Ki67 > 14% (p = 0.016, p = 0.002, and p = 0.001, respectively). In a multivariate analysis, only post-treatment Ki67 ≥ 14% and NLR low had an impact on OS, although luminal B subtype, post-treatment Ki67 ≥ 14%, and NLR low continued to be independent predictive variables for DFS. The current study shows that among patients with luminal breast cancer treated with NACT, pre-treatment NLR low assists in identifying women who are more likely to die or recur.

11. In their study, Yao D et al. (2019)[25] found that 413 patients had low RDW (RDW ≤ 13.82) and 412 patients had high RDW (RDW > 13.82). The high w group develops larger tumours than the low RDW group (the rate of tumour size >2 cm: 60.7 vs 44.8%, P=0.013). The high RDW group saw a greater rate of lymph node metastases than the low RDW group (62.1 vs. 45.8%, P=0.000). Tumour stage was positively correlated with RDW. An advanced stage was indicated by the elevated RDW (P=0.000). The high RDW group tended to have greater levels of high-sensitivity C-reactive protein (P=0.000), fibrinogen (P=0.043), and lymphocytes (P=0.004) than the low RDW group. According to the current study, patients with breast cancer who had high pre-treatment RDW levels had worse OS and DFS. RDW may be a predictive factor in the differential diagnosis of all patients with a bad prognosis.

12. Seven studies totalling 3,741 patients were eventually included in the meta-analysis conducted by Zhu Y et al. (2017)[26]. In patients with breast cancer, high PLR was linked to poor disease-free survival (DFS) (HR = 1.73, 95% CI = 1.3-2.3, $p < 0.001$) and overall survival (OS) (HR = 1.55, 95% CI = 1.07–2.25, $p = 0.022$). Furthermore, PLR is still a significant predictive factor for OS in patients undergoing chemotherapy (HR = 2.82, 95% CI = 1.09–7.26, $p = 0.032$) and systemic treatment (HR = 1.78, 95% CI = 1.06–2.99, $p = 0.03$). Patients receiving chemotherapy (HR = 2.6, 95% CI = 1.47–4.61, $p = 0.001$), surgery (HR = 1.8, 95% CI = 1.12–2.89, $p = 0.016$), and systemic treatment (HR = 2.03, 95% CI = 1.03–4.01, $p = 0.042$) also have poor DFS when their PLR is high. Additionally, HER-2 positive was similarly associated with PLR (OR = 1.48, 95% CI = 1.2–1.83, $p < 0.001$). According to the findings of this meta-analysis, PLR may be a sign of a bad prognosis for breast cancer patients.

13. Dezayee ZMI et al. (2016)[27] evaluated the haematological indices in breast cancer survivorship and shown whether premenopausal and postmenopausal women's indices differed significantly. Patients in group II had significantly lower haemoglobin levels and red cell counts than those in group I. RDW and mean platelet volume (MPV) were significantly higher in group II women (16.68 ± 2.51 and 9.980 ± 1.271) than in group I women (15.12 ± 2.27 and 9.535 ± 1.082). The PWD, plateletcrit (PCT), NLR, and platelet to lymphocyte ratio (PLR) ratios did not significantly change between groups I and II. They came to the conclusion that there are certain haematological indices linked to the postmenopausal survival of breast cancer, as evidenced by the low haemoglobin levels and the high RDW and PDW that are considerably present in postmenopausal compared to premenopausal survival individuals.

14. The impact of NLR on breast cancer patients' survival was measured by Ethier, JL et al. (2017)[28], who also looked into how clinicopathologic variables affected the predictive value of NLR. They came to the conclusion that patients with breast cancer who have high NLR had a worse OS and DFS, and that this effect is more pronounced in ER and HER2-negative patients. Since NLR is a readily available prognostic marker, further research should be done on how to include it into well-established risk prediction models.

Surgical Anatomy

EMBRYOLOGY:

Around the sixth week of pregnancy, breast growth begins. Mammary ridges, also known as milk lines, are two ventral bands of thickened ectoderm that run from the axilla to the inguinal area. They first emerge around the seventh week of pregnancy. The thicker white line at the end of the eighth week gives rise to the developing primitive breast, which will eventually develop into the mature breast. The number of basal cells increases during embryogenesis. The nipple-areolar complex forms at roughly 30 weeks of gestation when the papillary bag becomes occluded. About 38 to 40 weeks will pass before the last nipple appears.

ANATOMY OF BREAST:

Planning for breast surgery and comprehending the diseases that affect the breast require a deep understanding of its anatomy. The base of the breast is formed by the pectoralis major muscle. The pectoralis major fascia and the breast are joined by the Cooper ligaments.
However, because these ligaments are flexible, the breast can shift. The axillary tail of Spence is formed by the super-lateral quadrant extending towards the axilla along the inferolateral border of the pectorals major. It might also go via the deep fascia to the axilla's apex. Above the inframammary crease, the nipple is level with the fourth rib and the midclavicular line.

SOFT TISSUE:

Normally, the breast is made up of up to 20 distinct lobes that contain connective tissue stroma-containing ductal-glandular tissue, which is made up of terminal secretory lobules and branching ducts. One primary lactiferous duct in the nipple serves as the source from which each lobe branches out. The breast's functional milk secretory organ is the terminal duct lobular unit. The interlobular connective tissue stroma is dense, fibro-collagenous, and contains variable quantities of adipose tissue, whereas the interlobular connective tissue has a lax texture that allows for the rapid formation of secretory tissue during pregnancy.

LYMPHATIC DRAINAGE:

The majority of the lymphatic outflow in the breast originates from the dermal network. The breast's lymphatics branch widely; the tiniest superficial lymph capillaries (20–70 μm in diameter) drain into bigger, smooth muscle-and valve-equipped lymph pre-collecting vessels (about 300 μm in diameter). Together, these create a subcutaneous network that connects the skin to the breast tissue. Almost invariably, this network empties into a sentinel node, which is usually found along the lateral border of the pectoralis minor. A tumour may obstruct lymphatic pathways, which could further lead to reverse flow and oedema. A vast periductal and peri-lobular network of lymphatic channels allows lymphatic channels to penetrate the regional lymph nodes, running parallel to the major venous tributaries.

Most of these lymphatics empty into the axillary group either directly or through the subareolar lymphatic plexus, and the lymphatics from the left breast ultimately terminate at the thoracic duct. Near the point where it joins the internal jugular vein, the lymphatics empty into the right subclavian vein. The parasternal nodes of the internal thoracic veins get drainage from the breasts' medial surfaces. They anastomose over the sternum as a route for contralateral nodal dissemination in medially located breast cancer.

More than 75% of the lymph that drains from the breast is received by axillary lymph nodes. There are between 20 and 40 axillary nodes, which are separated into the subsequent groups: lateral (humeral), anterior (pectoral), posterior (subscapular), central, and apical. Surgically, the nodes related to the pectoralis minor are as follows: (level 1) the low nodes are those that lie lateral or inferior to the pectoralis minor; (level 2) the middle group is made up of nodes that lie posterior to the pectoralis minor, and (level 3) the upper or apical axillary nodes are those that lie between the superomedial (upper) border of the pectoralis minor and the inferior (lower) border of the clavicle. The nodes that lie in between the pectoralis minor and major are known as interpectoral, or Rotter's nodes.

While certain efferent arteries may travel directly to the posterior axillary (subscapular) nodes, others may travel via the breast to the anterior axillary (pectoral) lymph nodes via the anterior axillary border and axillary fascia. Sometimes, a few vessels that run from the breast's upper region to the apical nodes will be blocked by the infraclavicular or interpectoral nodes. A large portion of the remaining tissue is connected to the perforating branches of the internal thoracic artery and drains from the lateral and medial parts of the breast to the parasternal nodes. Sometimes lymphatic veins follow the lateral cutaneous branches of the posterior intercostal arteries to the intercostal nodes.(Fig1)

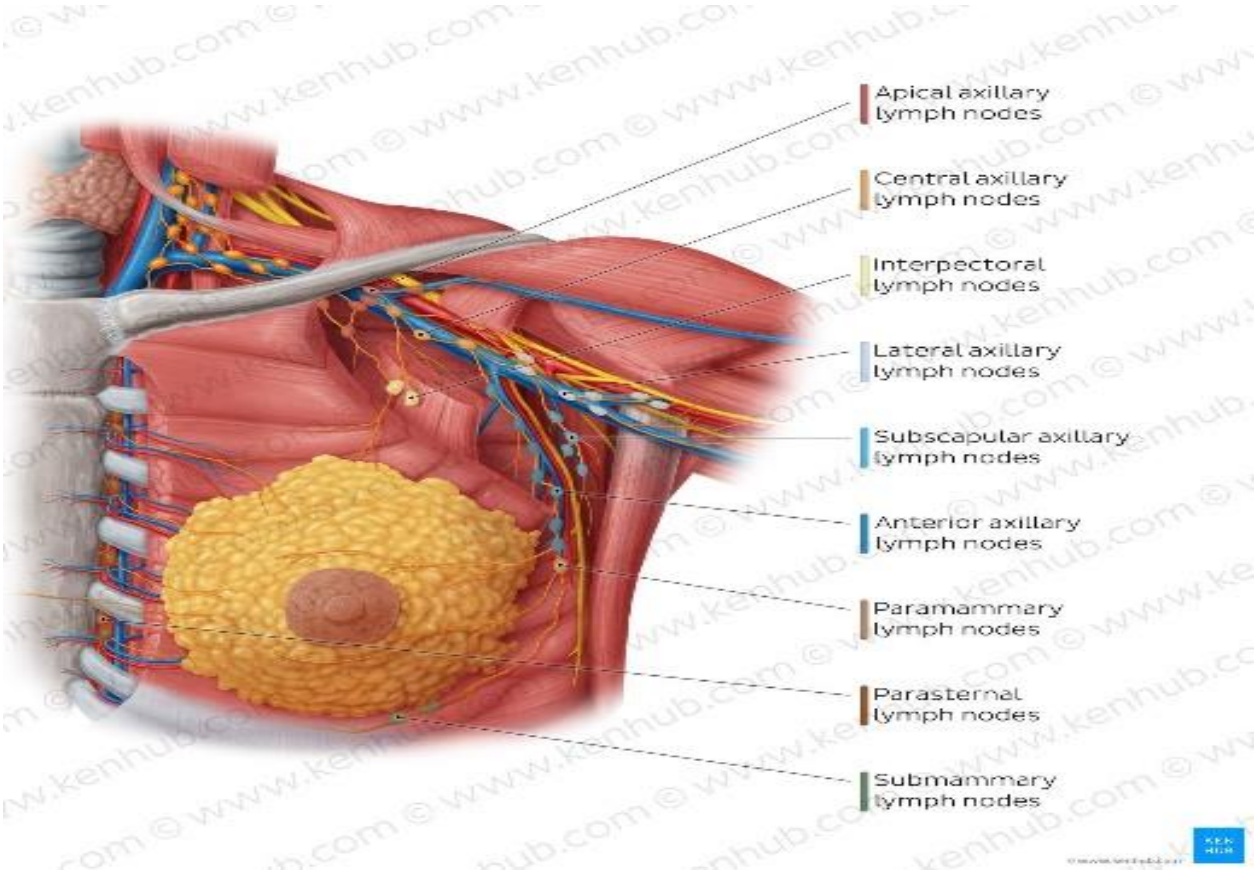


Fig1- Lymphatic drainage of breast

BLOOD SUPPLY:

The blood supply to the breast skin comes from the subdermal plexus; these microscopic blood vessels connect to the deep underlying arterioles that supply the breast parenchyma. The following is the blood supply to the breast:

- The thoraco-acromial artery
- Internal mammary perforators (second to fifth)
- Lateral thoracic artery
- Thoracodorsal artery
- Terminal branches of the intercostal perforators (third to eighth)

The internal mammary artery's superomedial perforators provide at least 60% of the blood supply overall. Vascular drainage is also abundant in the breast and is separated into superficial and deep veins. Often referred to as the venous plexus of Haller, superficial veins follow the areola route beneath the nipple-areolar complex along the front aspect of the fascia. **(**Fig2**)**

NERVES:

The lateral and anterior cutaneous branches of the fourth to sixth Intercoastal nerves innervate the breast with sensory and sympathetic motor fibres. The anterior branch of the lateral cutaneous branch of the fourth intercostal nerve supplies the nipple. This branch forms an extensive plexus within the nipple, with its fibres terminating as free endings, Merkel disc endings, and Meissner corpuscles near the epithelium. Secretory activities of the gland are controlled by neuro-hypophysial & ovarian hormones rather than by efferent motor fibres. There are fewer sensory endings in the areola.

MICROSTRUCTURE:

Age, menstrual cycle stage, pregnancy, and nursing all affect the microstructure of breast tissue. Columnar epithelium lines the ducts of adult, non-lactating (resting) breasts for the majority of their length. Near the bases of these cells are numerous myoepithelial cells that originate from the ectoderm. The assumed alveoli and ducts are surrounded by a large number of myoepithelial cells, which create a distinct layer and give the epithelium a bilayer appearance. Each breast lobe has lactiferous channels that eventually drain into up to 20 orifices after passing through the nipple. Keratinized stratified squamous epithelium that is continuous with the epidermis replaces the stratified cuboidal epithelial lining of the lactiferous ducts surrounding their nipple apertures.

The duct's diameter varies across the breast, and it is slightly enlarged at the base of the nipple. A complicated network of ducts and lobules, encircled by a stroma of connective tissue, is connected to each lactiferous duct to produce a breast lobe. Lobes vary in size, shape, and depth. A single lobe may comprise from 1% to as much as 25% of the entire breast. Vestigial lobes have been identified and are composed of long ducts running deep into the breast with very few or no branches or glandular tissue. The presence of these lobes suggests a competitive process of ductal expansion and in part explains the observation of fewer functional lobes during lactation. Whilst ducts can be intertwined, there is no evidence of anastomotic connections between lobes. The morphology of lobules, which are glandular components with the ability to secrete, vary depending on the hormonal state.

In the adult non-lactating resting breast, each lobule is composed of a collection of ductules with branches and blind ends. The nipple contains many elastic fibres that generate wrinkles in the skin and is primarily composed of collagenous dense connective tissue on the inside. It is thought that the remnants of the panniculus carnosus, a thin striated muscle layer that is connected to the deep surface of the skin and seen in other animals, are represented by bundles of smooth muscle cells that are dispersed radially and circumferentially inside connective tissue deep to the nipple and areola.

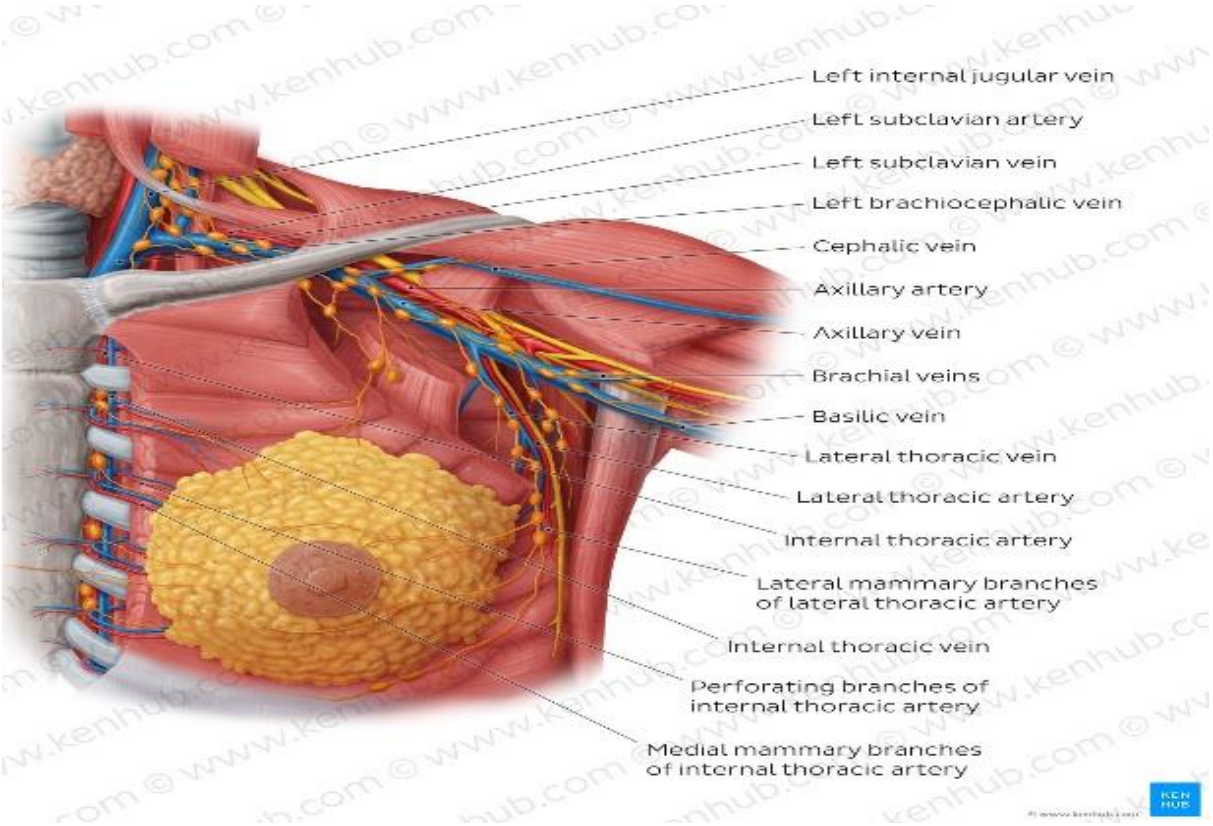


Fig2- Blood supply of breast

AGE-RELATED CHANGES:

PREPUBERTY

The new-born breast lacks alveoli but has primitive lactiferous ducts. The ducts branch to some extent until adolescence, and any breast expansion is symmetric and reflects the formation of fat and fibrous stroma.

PUBERTY

The stimulation of ovarian oestrogens causes the ducts to elongate and branch in post pubertal females. Oestrogens also encourage the development of mesenchymal cells in the interlobular stroma into adipocytes, and the adipocytes' storage of fat throughout puberty is primarily responsible for the expansion of the breast volume. From puberty onwards, externally recognizable breast development (thelarche) is divided into five separate phases:

phase I: elevation of the breast bud

phase II: glandular subareolar tissue is present & both the nipple & breast project from the chest wall as a single mass

phase III: the areola increases in diameter and becomes pigmented, & there is proliferation of palpable breast tissue

phase IV: further pigmentation & enlargement occur in the areola so that the nipple & areola form a secondary mass anterior to the main part of the breast

phase V: smooth contour to the breast develops

POSTMENOPAUSAL

Following menopause, a decrease in ovarian function causes lobules and ducts to gradually atrophy. Additionally, fatty replacement of glandular breast tissue is seen. Collagenous fibres shrink, the stroma loses some of its cellularity, and there may still be fewer ducts and atrophic lobules. Both the volume of glandular tissue and the amount of adipose tissue vary greatly amongst individuals, however HRT usually increases the volume of glandular tissue.

PHYSIOLOGY:

Mammary gland development, maturation, and differentiation are regulated by hormones and growth factors acting on stroll and epithelial cells. In short, progesterone promotes ductal branching and lobuloalveolar development, prolactin controls the generation of milk protein, and estrogen promotes the growth of ductal tissue.

As puberty sets in, levels of progesterone and oestradiol rise to stimulate breast growth. A complicated tree-like structure is created by the five to ten major milk ducts that start at the nipple, the twenty to forty segmental ducts, and the ten to one hundred sub-segmental ducts that lead to the terminal duct lobular units.

During the luteal phase of the menstrual cycle, cell division is encouraged by increases in progesterone and estrogen. Proliferation is balanced by apoptosis, depending on the cycle. The breast can grow up to 15% larger during the luteal phase because of its increased growth.

AGE-RELATED CHANGES IN MORPHOLOGY

Between early adolescence and menopause, the breast experiences significant modifications. The typical appearance varies from more fibrous alterations and cyst formation to the predominance of ducts, lobules, and intra- and inter-lobular stroma. The term "fibrocystic disease" was abandoned in favour of "fibrocystic changes" because this pattern is present in between 50 and 60 percent of women. Crucially, clinically identified fibrocystic alterations do not raise the risk of breast cancer.

The stromal, ductal, and glandular tissue of the breast also exhibit certain distinct alterations with advancing age. Stromal hyperplasia during the early reproductive years may result in juvenile breast hypertrophy or, in rare cases, more severe issues such as unilateral or bilateral macromastia (enlarged breast tissue). At this time, glandular and ductal tissue alterations are uncommon.

Hormone levels affect glandular tissue, which may experience significant adenosis throughout the middle reproductive years. Although stromal hyperplasia can cause areas to feel full or hard upon examination and may require a biopsy, ductal alterations are also uncommon in this case.

CARCINOMA BREAST

BRIEF HISTORY OF CARCINOMA BREAST:

Breast cancer has drawn the attention of surgeons for centuries. The earliest known reference to breast cancer appears in the Smith Surgical Papyrus (3000–2500 B.C.), which described a case in a man and highlighted many common clinical features. The conclusion was stark: "There is no treatment."[29] Historical references to breast cancer remained sparse until the first century. In *De Medicina*, Celsus discussed the potential value of surgery for early-stage breast cancer, noting, "None of these may be removed but the cacoethes (early cancer); the rest are irritated by every method of cure. The more violent the operations are, the more angry they grow."[30]

By the second century, Galen provided a detailed clinical observation, describing the disease's resemblance to a crab: "We have often seen in the breast a tumour exactly resembling the animal the crab. Just as the crab has legs on both sides of his body, so in this disease the veins extending out from the unnatural growth take the shape of a crab's legs." Galen emphasized the importance of early intervention, stating, "We have often cured this disease in its early stages, but after it has reached a large size, no one has cured it. In all operations, we attempt to excise the tumour in a circle where it borders on the healthy tissue."[31] The Galenic system of medicine attributed cancers to an excess of black bile, asserting that removing a localized tumour could not address the underlying systemic imbalance. These theories, rooted in Galen's teachings, dominated medical thought until the Renaissance. In 1652, Nicolaes Tulp proposed the idea that cancer might be contagious.

Halsted and Meyer pioneered the complete dissection of axillary lymph node levels I to III, routinely removing the long thoracic nerve and the thoracodorsal neurovascular bundle along with the axillary contents[32]. In 1943, Haagensen and Stout identified the "grave signs" of breast cancer, which included: (a) oedema of the breast skin, (b) skin ulceration, (c) chest wall fixation, (d) axillary lymph nodes larger than 2.5 cm, and (e) fixed axillary lymph nodes. Women exhibiting two or more of these signs faced a 42% local recurrence rate and a mere 2% five-year disease-free survival rate[33]. Based on these findings, they concluded that radical surgery could not cure patients with grave signs.

In 1948, Patey and Dyson of Middlesex Hospital in London introduced the modified radical mastectomy for managing advanced operable breast cancer. Acknowledging the limitations of surgery, they stated, "Until an effective general agent for treatment of carcinoma of the breast is developed, a high proportion of these cases are doomed to die." Their technique involved removing the breast and axillary lymph nodes while preserving the pectoralis major muscle. To access and clear axillary lymph node levels I to III, they included the removal of the pectoralis minor muscle[34].

In the 1970s, American surgeons transitioned from the Halsted radical mastectomy to the modified radical mastectomy as the preferred surgical treatment for breast cancer. This shift was driven by several factors: (a) fewer patients presented with advanced local disease or the grave signs described by Haagensen, (b) removal of the pectoralis major muscle was deemed unnecessary for achieving local-regional control in stage I and II breast cancer, and (c) neither the modified radical mastectomy nor the Halsted radical mastectomy consistently ensured local-regional control in stage III breast cancer.

Radiation therapy emerged as part of the management strategy for advanced breast cancer, showing improvements in local-regional control. In the early 1970s, the National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted the B-04 trial to evaluate the impact of local and regional treatments on survival in operable breast cancer. The trial enrolled 1,665 women between 1971 and 1974, prior to the widespread availability of effective systemic therapies, making the findings reflective of survival outcomes linked solely to local-regional treatments.

Clinically node-negative patients were randomized into three groups: (a) Halsted radical mastectomy, (b) total mastectomy with radiation therapy, and (c) total mastectomy alone. Clinically node-positive patients were randomized to either Halsted radical mastectomy or total mastectomy with radiation therapy. Results revealed no survival differences among the three node-negative groups or between the two node-positive groups. These survival equivalence patterns have persisted even after 25 years of follow-up.

A significant advancement in the surgical management of breast cancer was the introduction of breast-conserving surgery. This approach was first reported by Geoffrey Keynes of St. Bartholomew's Hospital, London, in the *British Medical Journal* in 1937, where he combined breast-conserving surgery with radium treatment[35]. Decades later, the NSABP initiated the B-06 trial, a phase III study that randomized 1,851 patients to three groups: total mastectomy, lumpectomy alone, or lumpectomy with breast irradiation. The results showed no significant differences in disease-free survival, distant disease-free survival, or overall survival among the groups. However, omitting radiation therapy led to significantly higher rates of ipsilateral breast tumour recurrence in the lumpectomy-alone group.[36]

The B-06 trial excluded patients with palpable axillary lymph nodes. For those randomized to breast-conserving surgery, frozen sections were analysed during surgery; if margins were involved, a mastectomy was performed, though these patients were still analysed as if they had undergone lumpectomy. Furthermore, in B-06, in-breast recurrences were classified as "non-events" in terms of disease-free survival. Both the B-04 and B-06 trials challenged the Halstedian concept that cancer spread regionally through the breast to lymphatics and then to distant sites. Bernard Fisher proposed the "alternative hypothesis," suggesting that breast cancer is often systemic at diagnosis, with tumour cells having access to both blood and lymphatic systems. According to this view, regional lymph nodes serve as markers of systemic disease rather than

barriers to cancer dissemination. Fisher argued that host factors play a crucial role in metastasis development and that variations in local-regional treatment approaches are unlikely to significantly affect survival outcomes.

Although Fisher's hypothesis dominated for many years, it was later challenged by the Early Breast Cancer Trialists' Collaborative Group overview analysis. This analysis revealed that avoiding recurrence in a conserved breast prevents approximately one breast cancer death over 15 years for every four recurrences avoided.[37] This finding suggests that not all breast cancer cases are systemic diseases at the time of presentation. In the 1970s, clinical trials began exploring the value of systemic therapy as an adjuvant to surgery in the postoperative management of breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was established in 1985 to coordinate meta-analyses of randomized clinical trials and evaluate the impact of adjuvant treatments on recurrence and mortality.

The EBCTCG's analyses have revealed several key findings. First, anthracycline-containing regimens were shown to be superior to CMF (cyclophosphamide, methotrexate, and fluorouracil), and the addition of a taxane to an anthracycline-based regimen was found to reduce breast cancer mortality by one-third. Second, tamoxifen was demonstrated to benefit only patients with estrogen receptor (ER)-positive breast cancer, potentially reducing breast cancer mortality by up to 50%.[38]

Importantly, EBCTCG data have shown that proportional reductions in risk were not significantly influenced by standard clinical and pathological factors such as tumour size, ER status, and nodal involvement.[39] These findings highlight the critical role of risk stratification in determining adjuvant therapy decisions. Proper stratification helps to minimize the toxicities of treatments in patients unlikely to benefit while maximizing the survival and local-regional control advantages for those at higher risk. In early randomized clinical trials, breast cancer was largely treated as a homogeneous disease, with all patients receiving similar treatments. Historically, breast cancer classification relied on pathologic determinants observed through conventional light microscopy and basic histologic techniques. However, the 1980s marked a significant advancement with the introduction of immunohistochemistry, which enabled the evaluation of individual tumour markers, most commonly proteins.

DNA analysis initially focused on ploidy status. Over time, more sophisticated techniques were developed to analysed breast cancer at the DNA level. Genes of interest were labelled with fluorescent dyes, allowing for the quantification of specific genes and the simultaneous comparison of numerous genes within a single specimen. Gene expression arrays revealed that breast cancers cluster into at least five intrinsic subtypes based on their gene expression patterns, and these subtypes are strongly correlated with clinical outcomes.[40] Today, breast cancers are classified by molecular subtypes, which play a crucial role in risk stratification and inform decisions regarding local-regional and systemic therapies.

INTRODUCTION

For people aged 20 to 59, breast cancer is the most common primary cause of cancer-related death. It is responsible for 14% of cancer-related fatalities and 29% of all newly diagnosed cancers in females. It was anticipated that there would be about 40,030 deaths from breast cancer in 2013 and 234,580 new cases identified in the US[41]. Before lung cancer overtook carcinoma breast in 1987, lung cancer was the primary cause of cancer-related death for women.

From 1 in 13 in the 1970s to 1 in 8 in 2004, the lifetime risk of breast cancer for American women has risen over time. The incidence of breast cancer has been steadily rising since the mid-1940s, according to data from cancer registries in Connecticut and upper New York State. Between 1973 and 1980, the incidence rose by approximately 1% per year, with an additional 4% increase between 1980 and 1987, primarily due to the detection of small primary tumours. These trends coincided with increased mammography use among women aged 55 and older. Breast cancer death rates started to drop during this time, and the incidence of regional metastatic disease decreased as well. From 1960–1963 to 2002–2008, the five-year survival rates for breast cancer increased dramatically, rising from 63% for white women and 46% for African American women to 92% and 78%, respectively.

The incidence of breast cancer varies by tenfold globally. Age-adjusted death rates are lowest in Haiti (2.0 per 100,000), while they are highest in countries like Malta and Cyprus (29.6 per 100,000). It is 19.0 per 100,000 in the United States. With the notable exception of Japan, women in less developed countries often have a lower incidence of breast cancer than those in industrialised ones.

The 1990s saw a rise in the prevalence of breast cancer worldwide, with an estimated 1.4 million new cases in 2010. Similar to patterns in eastern Asia, nations such as China record yearly incidence rises of 3% to 4%. However, recent SEER statistics show drops in the incidence of breast cancer in the United States, which are mostly attributable to fewer people using hormone replacement treatment after the Women's Health Initiative reports[42].

Variations in breast cancer incidence and mortality are mostly influenced by factors such as geography, lifestyle, and race/ethnicity. Early childbearing, numerous pregnancies, and prolonged lactation—characteristics prevalent in these populations—may be associated with reduced rates of breast cancer among women in Asia, Africa, and other less developed regions. In contrast, industrialized countries in Europe and North America have higher incidence and mortality rates, influenced by Western reproductive and dietary patterns. Within the U.S., these international trends are reflected across racially, ethnically, and culturally diverse populations[43].

Although incidence and mortality rates are often related, they are influenced by different factors. Lower incidence rates are common in populations with early childbearing and high fertility rates, such as in underdeveloped or eastern nations. However, the absence of efficient mammography screening programs and restricted access to multimodal cancer treatments may result in increased mortality rates for these populations. The disproportionate mortality risks seen in developing countries and among specific racial and ethnic groups in the United States are probably caused in part by these inequities. It's interesting to note that when second- and third-generation Asian Americans embrace Western lifestyles, the prevalence and mortality of breast cancer increases. Research on genetics and breast cancer subtypes has led to conjecture regarding racial and ethnic ancestry-related hereditary influences on breast cancer risk[44]. When analysing the differences in the incidence of breast cancer between African American and Caucasian women, these factors are especially pertinent.

Despite having a decreased lifetime risk of breast cancer, African American women paradoxically have higher death rates from the disease. Compared to women of other races, African American women also exhibit breast cancer at an earlier age. The prevalence of breast cancer is higher among African American women under 45. Furthermore, estrogen receptor-negative tumours, which are frequently linked to more aggressive disease and worse outcomes, are substantially more common in African American women of all ages.

Similar patterns are seen in the contemporary female population in western and sub-Saharan Africa, which is linked to African American ancestry through the slave trade during the colonial era. Notably, male breast cancer is more common among African American and African cultures.

DIAGNOSIS OF BREAST CANCER:

Approximately 30% of women find that the first sign of breast cancer is a lump in their breast. Breast growth or asymmetry, nipple alterations including retraction or discharge, breast skin ulceration or erythema, an axillary mass, and musculoskeletal pain are less frequent presenting signs and symptoms. Up to 50% of women who present with breast issues, however, do not exhibit any outward symptoms of breast disease. More often than not, benign illnesses are linked to breast pain.

The most malpractice claims involving diagnostic errors and the most paid claims are both connected to misdiagnosed breast cancer. Younger women are frequently involved in these cases, and their mammography and physical examinations may yield conflicting results. In order to prevent delays in diagnosis, ultrasonography and biopsy are crucial for women 45 years of age or younger who present with a palpable breast lump and unclear mammogram results. The majority of paid claims are for misdiagnosed breast cancer, which is also the main source of malpractice lawsuits involving diagnostic errors. Mammograms and physical exams can yield false results in these circumstances, which usually involve younger women.

A. EXAMINATION:

I. **INSPECTION:** The patient's arms at her sides, straight over her head, and hands on her hips, both with and without pectoral muscular contraction, are some of the postures the surgeon uses to assess the patient's breast[45, 46]. The surgeon evaluates the breast's size, shape, and symmetry while observing any indications of erythema, nipple or skin retraction, or oedema (peau d'orange). The patient sits with her arms outstretched and leans forward to assess skin retraction further(Fig3).

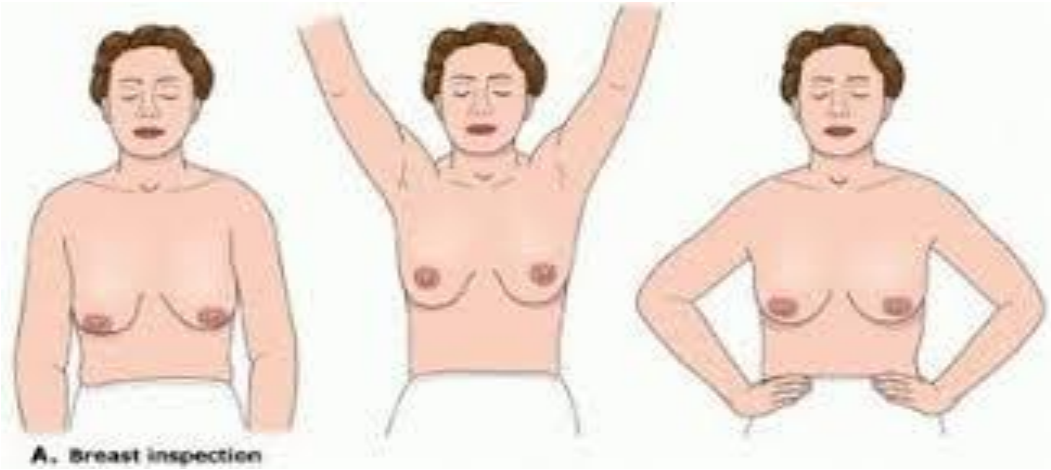


FIG 3- Inspection of breast

II. **PALPATION:** The goal of ongoing randomized controlled trials is to assess tomosynthesis and its function in breast cancer screening in greater detail. The palmar aspects of the fingers are used for the palpation; no pinching or clutching actions are used. To check for retraction, the surgeon may also cup or mold the breasts with his hands. A systematic evaluation for lymphadenopathy follows. For axillary examination, the surgeon stabilizes the shoulder girdle by supporting the patient's upper arm and elbow. Gentle palpation is used to examine all three levels of axillary lymph nodes. Furthermore, the parasternal and supraclavicular lymph node areas are carefully palpated. To record the position, size, consistency, form, movement, fixation, and other features of any palpable breast mass or lymphadenopathy, a thorough diagram of the chest and the surrounding lymph node sites is helpful(Fig4).

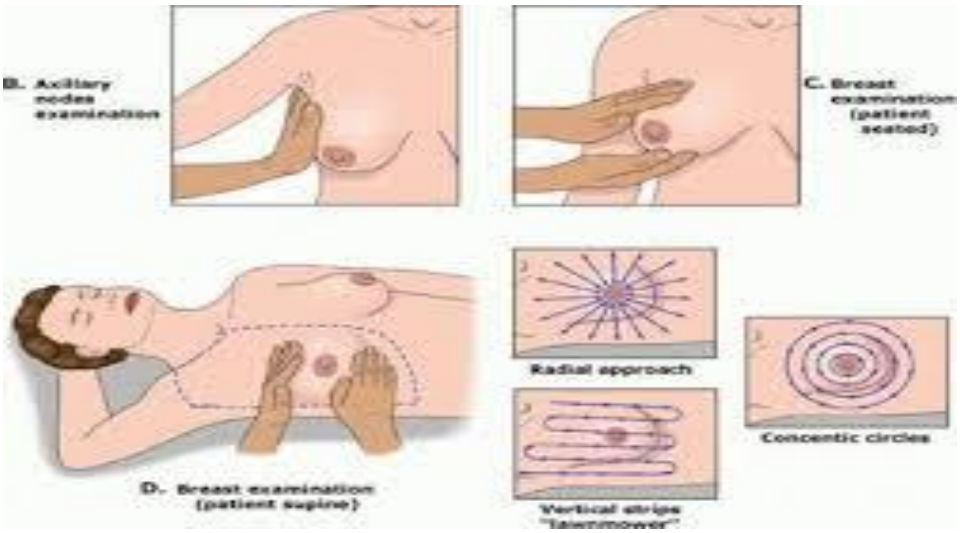


FIG 4 – Palpation of breast

A. IMAGING TECHNIQUES:

I. **MAMMOGRAPHY:** Mammography has been used in North America since the 1960s, with continuous advancements improving image quality.[47-50] Conventional mammography delivers a radiation dose of approximately 0.1 cGy per study, which is four times higher than that of chest radiography but is not associated with an increased risk of breast cancer. Screening mammography is designed to detect asymptomatic breast cancer and complements history-taking and physical examination. Two standard views are obtained: the craniocaudal (CC) view and the mediolateral oblique (MLO) view (Fig.5). The MLO view captures the largest volume of breast tissue, including the upper outer quadrant and the axillary tail of Spence, while the CC view provides better visualization of the medial breast and allows for greater compression.

Diagnostic mammography is performed for abnormal findings such as breast masses or nipple discharge. In addition to CC and MLO views, diagnostic exams may include specialized views like 90-degree lateral and spot compression views. The 90-degree lateral view helps triangulate the exact location of abnormalities, while spot compression improves detail by separating overlying tissues, minimizing motion artifacts, and reducing the radiation dose. Magnification (×1.5) is often combined with spot compression to enhance visualization of calcifications and tumour margins. Mammography also guides interventional procedures, including needle localization and biopsy.

Specific mammographic features suggestive of breast cancer include solid masses (with or without stellate features), asymmetric breast tissue thickening, and clustered microcalcifications. Fine, stippled calcium deposits are particularly important, as they can indicate cancer in up to 50% of nonpalpable cases, often serving as the sole abnormality in younger women. The clinical impetus for screening mammography originated from the Health Insurance Plan study and the Breast Cancer Detection Demonstration Project, which demonstrated a 33% reduction in mortality among women undergoing screening. Mammography is more accurate than clinical examinations for early cancer detection, with a true-positive rate of 90%.

Women with nonpalpable cancers had significantly fewer cases of axillary lymph node metastasis (20%) compared to those with palpable cancers (50%).[51] The National Comprehensive Cancer Network (NCCN) recommends breast examinations at least every three years for women aged ≥20 and annually from age 40 onward, along with yearly mammograms. For women aged ≥50, screening mammography reduces breast cancer mortality by 20–25%.[52-54] The United Kingdom recently convened an expert panel to evaluate the benefits and harms of its national breast screening program.

The panel estimated that 11% of breast cancer diagnoses in screened women represent overdiagnosis but concluded that screening provides significant benefits and should continue. For women under 50, screening is more controversial due to reduced sensitivity, lower specificity, and lower cancer incidence. Targeting higher-risk women under 50 for screening improves the balance of risks and benefits, supported by risk assessment models for estimating individual risk. Screen-film mammography has replaced xeromammography due to its lower radiation dose and comparable image quality.

Digital mammography further advances breast imaging by allowing manipulation of image contrast, particularly helpful in women with dense breasts or those under 50. The DMIST

trial, which included over 42,000 women, showed similar accuracy between digital and screen-film mammography, with digital performing better for women under 50, those with dense breasts, and premenopausal or perimenopausal women.

Digital breast tomosynthesis, which generates 3D images, offers an alternative to standard 2D mammography. It reduces limitations caused by breast parenchyma superimposition and density. The STORM trial demonstrated higher cancer detection rates and fewer false-positive recalls with 3D mammography compared to 2D imaging. Ongoing randomized controlled trials aim to further evaluate tomosynthesis and its role in breast cancer screening.

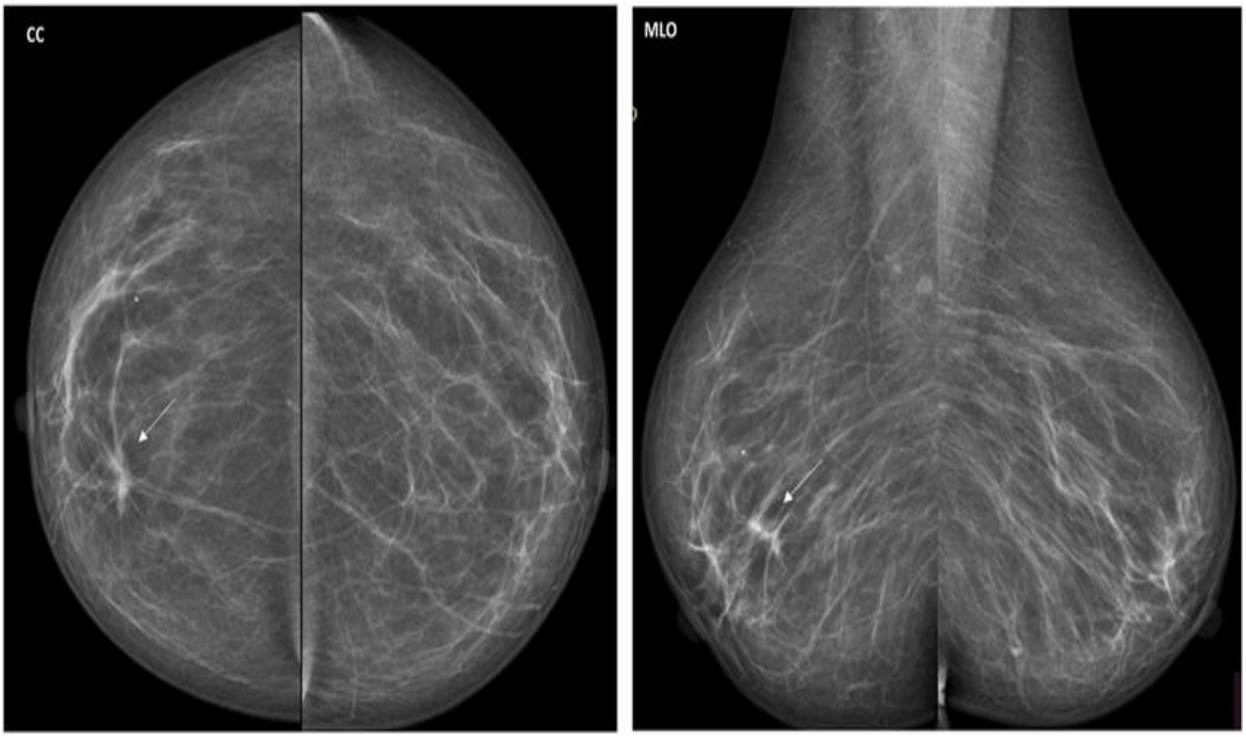


FIG.5 – Craniocaudal and mediolateral oblique views of mammography

II. **DUCTOGRAPHY:** The primary indication for ductography is nipple discharge, particularly when the discharge contains blood. This procedure involves the injection of radiopaque contrast media into one or more major ducts, followed by mammographic imaging. Under sterile conditions, the duct is gently dilated with a dilator, and a small, blunt cannula is inserted into the nipple ampulla. With the patient in a supine position, 0.1 to 0.2 mL of dilute contrast media is injected, and craniocaudal (CC) and mediolateral oblique (MLO) mammographic views are obtained without compression. Ductography can identify intraductal lesions. Intraductal papilloma's typically appear as small filling defects

surrounded by contrast media (Fig.6). Cancers, on the other hand, may present as irregular masses or multiple intraluminal filling defects.

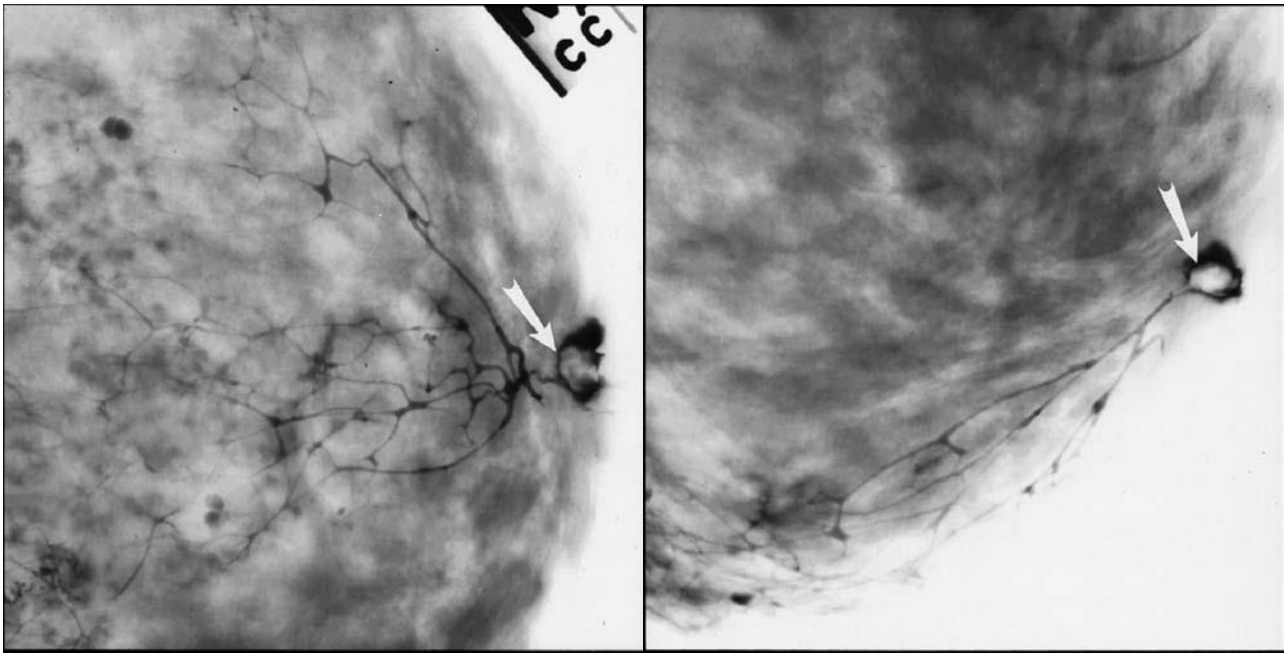


FIG.6 – Craniocaudal and mediolateral oblique views in ductogram demonstrating a mass posterior to nipple and outlined by contrast

III. **ULTRASONOGRAPHY:** After mammography, ultrasound is the second most commonly utilized imaging modality for breast examination. It is particularly helpful in diagnosing cystic masses, establishing the echogenic properties of solid abnormalities, and clarifying ambiguous mammography data. Breast cysts usually show up on ultrasound as well-defined, with smooth edges and a centre free of echo. Benign breast tumours include round or oval shapes, smooth contours, well-defined anterior and posterior margins and weak interior echoes. On the other hand, although it can occasionally have smooth borders with acoustic enhancement, breast cancer typically appears with uneven walls. Ultrasound is frequently used to assist fine needle aspiration biopsies, core-needle biopsies, and needle localisation of breast lesions. Although the method is quite repeatable and well-liked by patients, it is less accurate in identifying lesions that are less than 1 cm in diameter. Patients with breast cancer can also have their regional lymph nodes imaged by ultrasonography**.** Additionally, ultrasound can image regional lymph nodes in breast cancer patients. The sensitivity of ultrasound for assessing axillary lymph node status ranges from 35% to 82%, with specificity between 73% and 97%. Features indicative of cancer involvement in lymph nodes include cortical thickening, a change to a more circular shape, a size exceeding 10 mm, absence of a fatty hilum, and hypoechoic internal echoes.[55]

IV. MAGNETIC RESONANCE IMAGING: Magnetic resonance imaging (MRI) has been evaluated as a tool for characterizing mammographic abnormalities, with the additional benefit of detecting other breast lesions(Fig.7). However, in cases where both mammography and physical examination are negative, the likelihood of diagnosing breast cancer through MRI is extremely low. MRI is currently of interest for screening high-risk women and for evaluating women with newly diagnosed breast cancer. In high-risk women, such as those with a strong family history of breast cancer or known genetic mutations, MRI is advantageous due to its ability to overcome limitations posed by increased breast density in younger women, which reduces mammographic sensitivity. Additionally, MRI can identify contralateral breast cancer in 5.7% of women with a known breast cancer.

It also detects additional tumours in the index breast, such as multifocal or multicentric disease, which are sometimes missed by routine imaging, potentially influencing surgical planning. While MRI has been suggested for routine use in surgical planning due to its ability to detect additional disease and more accurately assess disease extent, its clinical utility remains debated. The COMICE trial, conducted in the United Kingdom with 1,623 participants, found no reduction in reoperation rates between women who underwent MRI in addition to mammography and ultrasonography (19%) and those who received standard imaging without MRI (19%).[56]

Similarly, a meta-analysis by Houssami and colleagues, which included two randomized trials and seven comparative cohort studies, reported that preoperative MRI was associated with increased mastectomy rates.[57] This raises concerns, as the additional disease detected by MRI may not be of clinical or biological significance, particularly given the low local-regional failure rates in patients undergoing breast-conserving surgery with whole breast irradiation and systemic therapies. MRI breast imaging requires the use of dedicated breast coils. Each examination is assigned a BI-RADS lexicon, and any abnormalities detected on MRI but not seen on mammography warrant a focused ultrasound for further evaluation. If the abnormality is not visible on either mammography or ultrasound, an MRI-guided biopsy is necessary.

MRI may be particularly useful in several clinical scenarios, including:

- Identifying the primary tumour in cases of nodal metastasis with no detectable breast tumour,
- Assessing response to neoadjuvant systemic therapy,
- Selecting candidates for partial breast irradiation techniques, and
- Evaluating the treated breast for tumour recurrence.

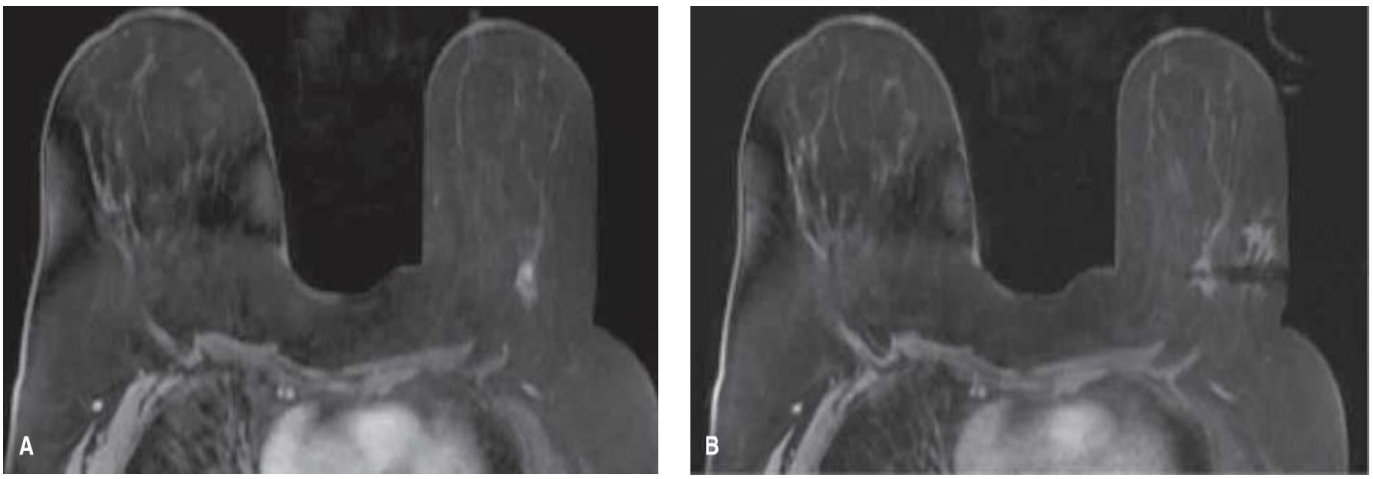


FIG.7 – MRI showing invasive lobular carcinoma

B. BREAST BIOPSY:

I. NONPALPABLE LESIONS: Image-guided breast biopsy is often necessary to diagnose nonpalpable lesions(Fig.8).[58] Ultrasound localization techniques are utilized when a mass is present, while stereotactic techniques are employed for lesions without a mass, such as those with microcalcifications or architectural distortion. Combining diagnostic mammography, ultrasound or stereotactic localization, and fine-needle aspiration (FNA) biopsy achieves nearly 100% accuracy in the preoperative diagnosis of breast cancer. While FNA biopsy allows for cytologic evaluation, core-needle biopsy offers the added advantage of assessing breast tissue architecture. This enables pathologists to determine whether invasive cancer is present, allowing the surgeon and patient to discuss specific treatment plans before initiating therapy. Core-needle biopsy is preferred over open biopsy for nonpalpable breast lesions because it enables a single, well-planned surgical procedure based on the biopsy results. The

advantages of core-needle biopsy include a low complication rate, minimal scarring, and reduced costs compared to excisional breast biopsy.

II. **PALPABLE LESIONS:** A palpable breast mass's FNAC is usually carried done in an outpatient environment[59]. A 14-gauge core biopsy needle or a 1.5 inch, 22-gauze needle with a 10-mL syringe are frequently utilized. A syringe holder for FNA enables the surgeons to stabilize the breast mass with one hand while controlling the syringe and needle with the other. After inserting the needle into the mass, it is pushed back and forth inside the lesion while suction is administered.

Suction is released and the needle is withdrawn when cellular material is visible at the needle hub. Both air dried and ethanol fixed microscope slides are prepared for analysis after the collected material is expressed onto them. The sensitivity and specificity of FNA biopsy are almost 100% in situations where a breast mass is clinically and mammographically worrisome. A 14-gauge needle, like the Tru-Cut needle, is used for core- needle of palpable masses, and automated tools are available for this purpose.

Vacuum assisted core biopsy instruments with 8–10 gauge needles are commonly used for lesions that need imaging guidance because they enable the collection of 4–12 samples from various locations inside a mass, region of architectural distortion, or microcalcifications. The specimen's radiography guarantees appropriate sampling while aiming for microcalcifications. To make future interventions easier, a radiopaque marker is positioned at the biopsy site. The marker guarantees precise targeting for surgical excision if required, and in certain situations, the entire lesion may be eliminated during the biopsy. Formalin is used to preserve tissue samples before they are turned into paraffin blocks.

A negative result from a core-needle biopsy does not completely rule out breast cancer because of the risk of sampling mistake, even if the false-negative rate is extremely low. The pathological, radiographic, and clinical results must line up. If there are differences, the multidisciplinary team—which consists of the pathologist, radiologist, and clinician—should examine the case to decide whether more open or image-guided biopsies are necessary to guarantee sufficient sampling of the target lesion.

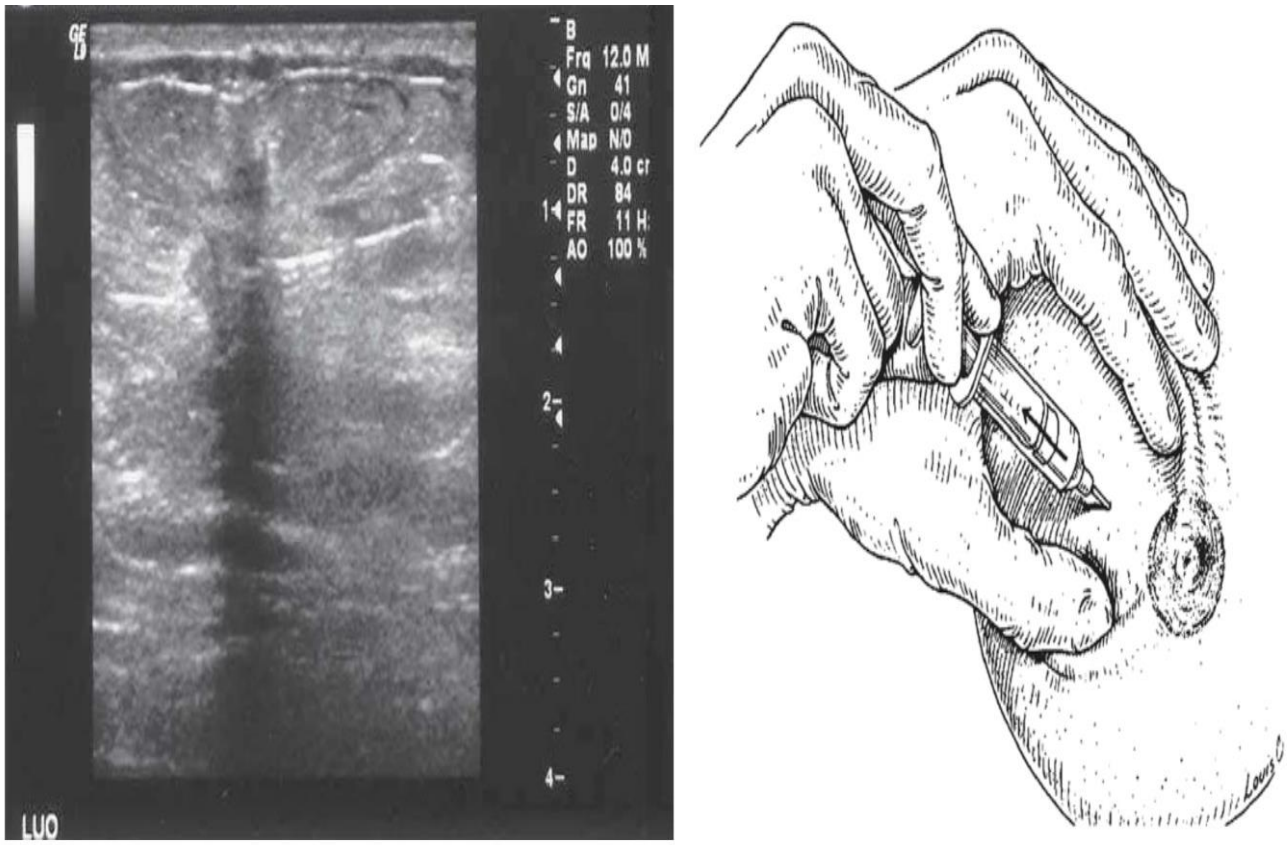


FIG.8 – USG guided FNAC and technique of FNAC of breast mass

RISK FACTORS OF BREAST CANCER:

Breast cancer risk factors can be divided into seven main groups: age and sex, personal history of breast cancer, histologic risk factors, family history and genetic predispositions, reproductive factors, and the use of exogenous hormones. Determining the factors linked to an increased risk of breast cancer is essential for effective health screening in women.

I. **AGE AND SEX:** With the age-adjusted incidence of breast cancer rising as the female population ages, age is likely the most important risk factor for the disease's development. In women under 20, breast cancer is uncommon, occurring in less than 2% of cases. As women age, the incidence increases:1 in 233 between the ages of 30 and 39, 1 in 69 between the ages of 40 and 49, 1 in 42 between the ages of 50 and 59, 1 in 29 between the ages of 60 and 69, and 1 in 8 by the age of 80. The lifetime probability of receiving a breast cancer diagnosis is 12.2% overall. Given that women account for the majority of occurrences of breast cancer, sex is another significant risk factor. While breast cancer does occur in men, it is much rarer,

comprising less than 1% of cases in women. Of the 235,030 invasive breast cancer cases projected in 2014, only 2,360 were expected to occur in men. Lumps in men are more likely to be benign, often caused by gynecomastia or other noncancerous conditions, rather than breast cancer.

II. **PERSONAL HISTORY:** The chance of getting a second primary cancer in the opposite breast is greatly increased if one breast has previously experienced breast cancer. The age at which the first cancer was diagnosed, the initial tumour's estrogen receptor (ER) status, and the use of adjuvant systemic chemotherapy and endocrine therapy are some of the variables that affect the risk level. For younger patients, the risk is between 0.5% and 1% year, while for older patients, it drops to about 0.2% annually.[60, 61]

Final Assessment Categories			
Category		Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval-follow-up (6 month) or continued	>0 % but ≤ 2%
4	Suspicious	Tissue diagnosis	4a. low suspicion for malignancy (>2% to ≤ 10%) 4b. moderate suspicion for malignancy (>10% to ≤ 50%) 4c. high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	n/a

Risk Factors That Cannot be Modified

Increasing age
Female sex
Menstrual factors
Early age at menarche (onset of menses before age 12 yr)
Older age at menopause (onset beyond age 55 yr)
Nulliparity
Family history of breast cancer
Genetic predisposition (*BRCA1* and *BRCA2* mutation carriers)
Personal history of breast cancer
Race, ethnicity (white women have increased risk compared with women of other races)
History of radiation exposure

Risk Factors That Can Be Modified

Reproductive factors
Age at first live birth (full-term pregnancy after age 30 yr)
Parity
Lack of breastfeeding
Obesity
Alcohol consumption
Tobacco smoking
Use of hormone replacement therapy
Decreased physical activity
Shift work (night shifts)

Histologic Risk Factors

Proliferative breast disease
Atypical ductal hyperplasia
Atypical lobular hyperplasia
Lobular carcinoma in situ

III. **HISTOLOGIC RISK FACTORS:** Histologic abnormalities identified through breast biopsy are significant risk factors for breast cancer, including lobular carcinoma in situ (LCIS) and proliferative changes with atypia.

Lobular Carcinoma In Situ (LCIS) is a rare condition, primarily observed in younger premenopausal women. It is usually an incidental finding during biopsies for other conditions and does not present as a palpable mass or suspicious microcalcifications on mammography. A study of over 5,000 biopsies for benign disease found LCIS in 3.6% of cases. In a review of 297 LCIS patients managed with biopsy and observation, the actuarial probability of developing carcinoma within 35 years was 21.4%. Data from the Connecticut Tumour Registry revealed a 7:1 risk ratio for invasive breast cancer in LCIS patients compared to the general population. Notably:

- 40% of subsequent carcinomas were in situ lesions.
- The invasive carcinomas were predominantly ductal rather than lobular in histology.

- 50% of the carcinomas occurred in the contralateral breast.

LCIS is not classified as breast cancer but is instead considered a histologic marker for increased breast cancer risk. This risk is estimated at slightly less than 1% per year over a patient's lifetime. For most patients diagnosed with LCIS, a conservative approach is recommended. Three management options can be discussed: close observation, chemoprevention with tamoxifen or raloxifene, and bilateral mastectomy. LCIS confers a lifelong risk of developing carcinoma, which is equal for both breasts. A five-year course of tamoxifen reduces the risk of breast cancer by 56%.[62] For patients who choose surgery over observation, bilateral total mastectomy is the preferred procedure.

Benign breast disease encompasses a range of histologic lesions that can be broadly categorized into non-proliferative and proliferative epithelial changes.

- **Non-proliferative changes** include mild to moderate hyperplasia of luminal cells within breast ducts. These changes do not significantly increase a woman's lifetime risk of developing breast cancer.
- **Proliferative changes**, on the other hand, involve the breast ductal system and are associated with an increased risk of breast cancer development.

Dupont and Page further classified proliferative lesions into two subtypes: lesions with atypia and lesions without atypia, with the latter sometimes referred to as severe hyperplasia. Subsequent studies have refined the classification of benign breast lesions into three categories: non-proliferative lesions**,** proliferative changes without atypia (severe hyperplasia), and proliferative changes with atypia**.**

Proliferative changes with atypia include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH)**.** Women with ADH or ALH have a breast cancer risk approximately four to five times higher than the general population. This risk increases nearly ninefold when a family history of breast cancer is combined with atypical hyperplasia.
The annual risk of developing breast cancer in women with ADH or ALH ranges from 0.5% to 1% per year**.** Risk estimates based on histologic findings are further influenced by factors such as age at diagnosis**,** menopausal status, and family history**.**

IV. **REPRODUCTIVE RISK FACTORS:** Reproductive milestones that prolong a woman's lifetime exposure to estrogen are associated with an increased risk of breast cancer. These factors include menarche before age 12, first live childbirth after age 30, nulliparity, and menopause after age 55. Each 2-year delay in menarche is associated with a 10% reduction

in breast cancer risk, while menopause after age 55 doubles the risk. Women who have their first full-term pregnancy before age 18 have half the risk of developing breast cancer compared to those who experience their first full-term pregnancy after age 30. Importantly, induced abortion is not associated with an increased risk of breast cancer. Breastfeeding has been shown to reduce breast cancer risk, likely due to a decrease in the number of lifetime menstrual cycles. While reproductive risk factors are relatively mild contributors to breast cancer risk compared to sex, age, histologic factors, and genetics (relative risk, 0.5 to 2.0), they significantly influence breast cancer prevalence at the population level.

V. **EXOGENOUS HORMONE USE:** Therapeutic or supplemental estrogen and progesterone are commonly used for conditions such as contraception in premenopausal women and hormone replacement therapy (HRT) in postmenopausal women. Other indications for exogenous hormone use include menstrual irregularities, polycystic ovary syndrome, fertility treatments, and hormone insufficiency. Studies suggest that breast cancer risk is increased in current or past users of oral contraceptives, but the risk diminishes over time after cessation.[63,64] The Women's Health Initiative (WHI)**,** a large, prospective, randomized controlled trial, studied the effects of HRT on cancer, cardiovascular disease, and osteoporosis-related fractures in healthy postmenopausal women aged 50 to 79 years.

From 1993 to 1998, 16,608 women were randomly assigned to receive combined conjugated equine estrogens (e.g., Premarin, 0.625 mg/day) with medroxyprogesterone acetate (2.5 mg/day) or a placebo. Screening mammography and clinical breast exams were conducted at baseline and annually. At a mean follow-up of 5.2 years, the study reported 245 breast cancer cases (invasive and noninvasive) in the combined HRT group compared to 185 cases in the placebo group.

Combined estrogen and progesterone therapy, specifically Prempro, was associated with a 20% increased risk of developing breast cancer in postmenopausal women with an intact uterus. Moreover, breast cancers in the HRT group were more likely to be diagnosed at a more advanced stage, and women in this group had a significantly higher likelihood of abnormal mammograms. In another WHI study, 10,739 women who had undergone hysterectomy were randomly assigned to either conjugated equine estrogens (Premarin, 0.625 mg/day) or a placebo. After 7 years, no significant difference in breast cancer rates was observed between the two groups (RR 0.80; 95% CI, 0.62–1.04). However, the need for short-interval follow-up mammograms was higher in the Premarin group (36.2% vs. 28.1%). These

findings indicate that combination HRT with estrogen and progesterone increases breast cancer risk by approximately 20% after 5 years of use. However, women receiving estrogen-only formulations**,** typically due to prior hysterectomy, do not appear to have an elevated breast cancer risk.

VI. BRCA MUTATIONS:

i. BRCA1: Up to 5% of breast cancers are caused by inherited germline mutations, such as BRCA1 and BRCA2, which are transmitted in an autosomal dominant manner with variable penetrance (Table).[65-71]

Incidence of sporadic, familial, and hereditary breast cancer	
Sporadic breast cancer	65%–75%
Familial breast cancer	20%–30%
Hereditary breast cancer	5%–10%
BRCA1^{a}	45%
BRCA2	35%
p53^{a} (Li-Fraumeni syndrome)	1%
STK11/LKB1^{a} (Peutz-Jeghers syndrome)	<1%
PTEN^{a} (Cowden disease)	<1%
MSH2/MLH1^{a} (Muir-Torre syndrome)	<1%
ATM^{a} (Ataxia-telangiectasia)	<1%
Unknown	20%

BRCA1 is located on chromosome 17q, spanning approximately 100 kilobases (kb) of DNA and containing 22 coding exons that encode 1863 amino acids. Both BRCA1 and BRCA2 act as tumour suppressor genes, requiring the loss of both alleles for cancer initiation. Studies since the isolation of BRCA1 suggest its role in transcription regulation, cell-cycle control, and DNA damage repair pathways. More than 500 sequence variations in BRCA1 have been identified. Germline mutations in BRCA1 are associated with 45% of hereditary breast cancers and at least 80% of hereditary ovarian cancers. Female mutation carriers may have up to an 85% lifetime risk of developing breast cancer (reported in some families) and up to a 40% lifetime risk of ovarian cancer. While earlier studies indicated high penetrance, the average lifetime risk for breast cancer is now estimated at 60%–70%. Breast cancer in BRCA1 mutation carriers often presents as invasive ductal carcinoma, is poorly differentiated,

and typically has a triple-negative phenotype (ER-negative, PR-negative, HER-2-negative). These cancers have distinctive clinical features, including:

- Earlier age of onset compared to sporadic cases.
- Higher prevalence of bilateral breast cancer.
- An association with other cancers, particularly ovarian cancer, and possibly colon and prostate cancers.

BRCA1-associated breast cancer follows an autosomal dominant inheritance pattern with high penetrance, meaning that approximately 50% of the children of carriers inherit the mutation. Several founder mutations have been identified in BRCA1, with the two most common being 185delAG and 5382insC, accounting for 10% of all BRCA1 mutations. These mutations occur at a 10-fold higher frequency in the Ashkenazi Jewish population compared to non-Jewish Caucasians. In the Ashkenazi Jewish population:

- The carrier frequency of the 185delAG mutation is 1%.
- Together, 185delAG and 5382insC account for nearly all BRCA1 mutations in this group.
- Approximately 20% of Jewish women who develop breast cancer before age 40 carry the 185delAG mutation.

Founder mutations have also been identified in other populations, including Dutch, Polish, Finnish, and Russian populations.[72-76]

ii. **BRCA2:** BRCA2 is located on chromosome 13q and spans approximately 70 kilobases (kb) of DNA. Its 11.2-kb coding region includes 26 exons that encode a protein consisting of 3,418 amino acids. Unlike BRCA1, BRCA2 shows no homology to previously described genes and lacks defined functional domains. Although the exact biological function of BRCA2 is not well understood, it is believed to play a role in DNA damage response pathways, similar to BRCA1. BRCA2 messenger RNA is highly expressed during the late G1 and S phases of the cell cycle, with protein regulation kinetics similar to BRCA1, suggesting these genes are coregulated.

More than 250 mutations in BRCA2 have been identified, though its mutational spectrum is less well-characterized compared to BRCA1. Female BRCA2 mutation carriers have a lifetime breast cancer risk of up to 85%, while their lifetime ovarian cancer risk is lower than that associated with

BRCA1, estimated at approximately 20%. Breast cancer susceptibility in BRCA2 families is inherited in an autosomal dominant manner with high penetrance, and 50% of children of carriers are at risk of inheriting the mutation.

Unlike male BRCA1 carriers, men with BRCA2 mutations have an estimated 6% lifetime risk of developing breast cancer, a 100-fold increase compared to the general male population. BRCA2-associated breast cancers are typically invasive ductal carcinomas, which are more likely to be well-differentiated and hormone receptor-positive compared to BRCA1-associated tumours. Clinical features of BRCA2-associated breast cancer include:

- Early age of onset compared to sporadic cases.
- Higher prevalence of bilateral breast cancer.
- Associated cancers in some individuals, including ovarian, colon, prostate, pancreatic, gallbladder, bile duct, stomach cancers, and melanoma.

Several founder mutations have been identified in BRCA2. Among Ashkenazi Jews, the 6174delT mutation is prevalent (1.2%) and accounts for 60% of ovarian cancer and 30% of early-onset breast cancer cases in this population. Other notable mutations include 999del5, found in Icelandic and Finnish populations, and 3036delACAA, identified in several Spanish families.[77-80]

iii. IDENTIFICATION OF BRCA MUTATION CARRIERS:

Identifying hereditary breast cancer risk involves a four-step process:

- Obtaining a complete, multigenerational family history.
- Assessing the appropriateness of genetic testing for the patient.
- Providing counselling to the patient.
- Interpreting the genetic testing results.[81]

Genetic testing should not be performed in isolation but must include patient education and counselling, often with the involvement of a genetic counsellor. The initial step is to determine whether the patient is a suitable candidate for testing and whether the results will inform personal or clinical decision-making.

A thorough family history, including both maternal and paternal sides, is critical since approximately 50% of women with a BRCA mutation inherit it from their fathers. Statistically based models, such as the Manchester Scoring System and BOADICEA, can calculate the probability of carrying a BRCA mutation, offering clinicians tools to determine whether a patient should be referred to a specialist genetic clinic. These models have been shown to provide reliable calibration and discrimination.

Hereditary breast cancer risk is considered when a family history includes any of the following:

- Ashkenazi Jewish heritage.
- A first-degree relative with breast cancer before age 50.
- A history of ovarian cancer at any age in the patient or a first- or second-degree relative.
- Breast and ovarian cancer in the same individual.
- Two or more first- or second-degree relatives with breast cancer at any age.
- Bilateral breast cancer in the patient or a relative.
- Male breast cancer in a relative at any age.[82]

The threshold for genetic testing is lower in ethnic groups with a higher prevalence of BRCA mutations, such as the Ashkenazi Jewish population.

iv. **BRCA MUTATION TESTING:** Appropriate counseling is strongly recommended for individuals undergoing testing for BRCA mutations, and documentation of informed consent is required.[83] The clinically available method for analyzing BRCA mutations is gene sequence analysis**.** In families with a history suggestive of hereditary breast cancer, the most informative approach is to first test an affected family member. This individual undergoes complete sequence analysis of both the BRCA1 and BRCA2 genes. If a mutation is identified, other relatives are typically tested only for that specific mutation. For individuals of Ashkenazi Jewish ancestry, testing begins with the three specific mutations most commonly associated with hereditary breast and ovarian cancer in this population. If these results are negative, full sequence analysis of BRCA1 and BRCA2 may be appropriate.

Interpreting Test Results

- A positive test result indicates the presence of a BRCA mutation that disrupts translation or the function of the BRCA protein. Women with a deleterious mutation may have up to an 85% lifetime risk of breast cancer (in some families) and a significantly increased risk of ovarian cancer.
- A negative test result is interpreted based on the individual's personal and family history. If a familial mutation has been previously identified and is not present in the tested individual, their breast and ovarian cancer risk may be no greater than the general population, and they cannot pass the mutation to their children. However, if no mutation has been previously identified in the family, a negative result generally indicates that a BRCA mutation is not responsible for the familial cancer.

There are exceptions:

- An unusual or undetectable mutation may still be present in BRCA1 or BRCA2 but not identified through clinical testing.
- The tested individual may have sporadic cancer rather than hereditary cancer, a scenario known as phenocopy**.** This is more likely if the cancer occurred at an age typical for sporadic cases (≥60 years) rather than the earlier onset characteristic of BRCA mutation carriers.

The false-negative rate for BRCA testing is less than 5%**.**

Indeterminate Results

Some test results, such as those involving single base-pair changes (missense mutations), are challenging to interpret. These mutations do not always result in a non-functional protein. Mutations outside critical functional domains or causing minimal structural changes may not be disease-associated and are reported as indeterminate results**.** Indeterminate genetic variants account for approximately 12% of test results**.** When communicating these results, it is essential to explain the uncertain cancer risk and emphasize that ongoing research may clarify their significance. Testing other affected family members

can help determine whether the genetic variant correlates with breast cancer in the family.

Concerns About Genetic Discrimination

Concerns about potential discrimination based on genetic information have been raised, particularly regarding access to affordable health insurance. Discrimination refers to unfair treatment of individuals or families based solely on genetic variations. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 prohibits group health plans from using genetic information to deny or limit coverage or to classify it as a pre-existing condition. Additionally, most U.S. states have laws protecting against genetic discrimination in health insurance.

Importantly:

- Individuals applying for health insurance are not required to disclose whether relatives have undergone genetic testing but only whether those relatives have been diagnosed with cancer.
- Documented evidence of genetic discrimination resulting from available genetic tests remains limited at this time.

v. CANCER PREVENTION FOR BRCA MUTATION CARRIERS:

Risk management options for individuals with BRCA1 and BRCA2 mutations include:

- Risk-reducing mastectomy and reconstruction
- Risk-reducing salpingo-oophorectomy
- Intensive surveillance for breast and ovarian cancer
- Chemoprevention

Risk-Reducing Mastectomy:

While mastectomy significantly reduces the likelihood of developing breast cancer, it does not eliminate all breast tissue, meaning that residual tissue still carries risk due to the germline mutation. Postmenopausal BRCA mutation carriers who have not undergone mastectomy are advised to avoid hormone replacement therapy, as its effects on BRCA-related breast cancer risk are unknown.

Screening recommendations for BRCA mutation carriers who do not undergo mastectomy include:

- Clinical breast examination every 6 months.
- Mammography every 12 months starting at age 25.
  These guidelines address the increasing risk of breast cancer in BRCA mutation carriers after age 30.

MRI for Breast Cancer Screening:

MRI is more sensitive than mammography in detecting breast cancer in younger women with dense breasts and is particularly useful for BRCA mutation carriers. However, MRI often detects benign lesions that may lead to unnecessary interventions, such as biopsies. The American Cancer Society recommends annual MRI screening for women with a 20–25% or greater lifetime breast cancer risk, including BRCA mutation carriers, women with a strong family history, and those treated for Hodgkin's disease in their teens or early twenties.

Chemoprevention with Tamoxifen:

The NSABP P1 trial reported a 49% reduction in overall breast cancer incidence and a 69% reduction in estrogen receptor-positive tumours in high-risk women taking tamoxifen. However, tamoxifen is not uniformly recommended for BRCA1 mutation carriers because their breast cancers are often high-grade and hormone receptor-negative. Approximately 66% of BRCA1-associated DCIS lesions are estrogen receptor-negative, indicating an early transition to hormone independence. In contrast, BRCA2 mutation carriers, who often have estrogen receptor-positive tumours, experience a 62% reduction in breast cancer incidence with tamoxifen, similar to the overall trial results.

Ovarian Cancer Risk and Prevention:

BRCA mutation carriers have a 20–40% lifetime risk of ovarian cancer, which is 10 times higher than the general population. Risk-reducing salpingo-oophorectomy is a recommended prevention option for BRCA mutation carriers. It is typically performed between ages 35–40, after the completion of childbearing. Removal of the ovaries reduces the risks of both ovarian and breast cancer in premenopausal mutation carriers. Hormone replacement therapy is discussed at the time of oophorectomy.

For carriers deferring surgery, the Cancer Genetics Studies Consortium recommends:

- Annual transvaginal ultrasound (timed to avoid ovulation).
- Annual serum CA-125 level measurement, starting at age 25.

Other Hereditary Syndromes Associated with Breast Cancer
In addition to BRCA mutations, other hereditary syndromes linked to increased breast cancer risk include:

- Cowden Syndrome: Associated with PTEN mutations, thyroid cancers, gastrointestinal cancers, and benign skin/subcutaneous nodules.
- Li-Fraumeni Syndrome: Caused by p53 mutations and linked to sarcomas, lymphomas, and adrenocortical tumours.
- Syndromes involving breast and melanoma.

HISTOPATHOLOGY OF BREAST CANCER:

Cancer cells are classified as in situ or invasive based on whether they have penetrated the basement membrane.[84,85] Broder's original definition of in situ breast cancer emphasized the absence of invasion into surrounding stroma, with cancer cells confined to natural ductal and alveolar boundaries. Because areas of invasion can be minute, diagnosing in situ cancer accurately requires examining multiple microscopic sections to rule out invasion.

In 1941, Foote and Stewart published a landmark study distinguishing lobular carcinoma in situ (LCIS) from ductal carcinoma in situ (DCIS). Later, in the late 1960s, Gallagher and Martin described a stepwise progression from benign breast tissue to in situ cancer and eventually to invasive cancer, using whole-breast section studies.

Before the widespread adoption of mammography, breast cancer diagnosis relied on physical examination. At that time:

- In situ cancers accounted for less than 6% of all breast cancers.
- LCIS was more frequently diagnosed than DCIS, with a ratio of over 2:1.

However, with the advent of screening mammography**,** there was a 14-fold increase in the incidence of in situ cancers, which constituted 45% of all breast cancers. DCIS became more commonly diagnosed than LCIS, with the ratio reversing to greater than 2:1**.**

Multicentricity vs. Multifocality

- Multicentricity refers to the presence of a second cancer outside the quadrant of the primary cancer (or at least 4 cm away).
- Multifocality describes a second cancer within the same breast quadrant as the primary cancer (or within 4 cm).

Incidence in LCIS and DCIS

- Multicentricity occurs in 60% to 90% of women with LCIS, compared to 40% to 80% in DCIS.
- LCIS is bilateral in 50% to 70% of cases, whereas DCIS is bilateral in 10% to 20%**.**

I. **LOBULAR CARCINOMA INSITU:** Lobular Carcinoma In Situ (LCIS) originates in the terminal duct lobular units and occurs exclusively in the female breast. It is characterized by the distention and distortion of terminal duct lobular units by cells that are large but maintain a normal nuclear-to-cytoplasmic ratio. A distinguishing cellular feature of LCIS is the presence of cytoplasmic mucoid globules(Fig.9). While LCIS may be observed in breast tissues with microcalcifications, these calcifications typically occur in adjacent tissues rather than within the LCIS itself—a unique diagnostic feature of LCIS. The exact frequency of LCIS in the general population is difficult to determine because it is often an incidental finding. The average age at diagnosis is 45 years, approximately 15 to 25 years younger than the average age for invasive breast cancer. LCIS shows a racial predilection, occurring 12 times more frequently in white women than in African American women. Approximately 25% to 35% of women with LCIS develop invasive breast cancer, which can occur in either breast, regardless of the side initially affected by LCIS. Invasive cancer is detected synchronously with LCIS in 5% of cases. Of the invasive cancers that develop in women with a history of LCIS, up to 65% are ductal rather than lobular in origin. For this reason, LCIS is considered a marker of increased risk for invasive breast cancer rather than an anatomic precursor.

   Women diagnosed with LCIS should be counselled about their elevated risk of developing breast cancer and the available risk reduction strategies, which include:

   - Observation with regular screening (e.g., mammography or MRI).
   - Chemoprevention, such as with tamoxifen or raloxifene.
   - Risk-reducing bilateral mastectomy.

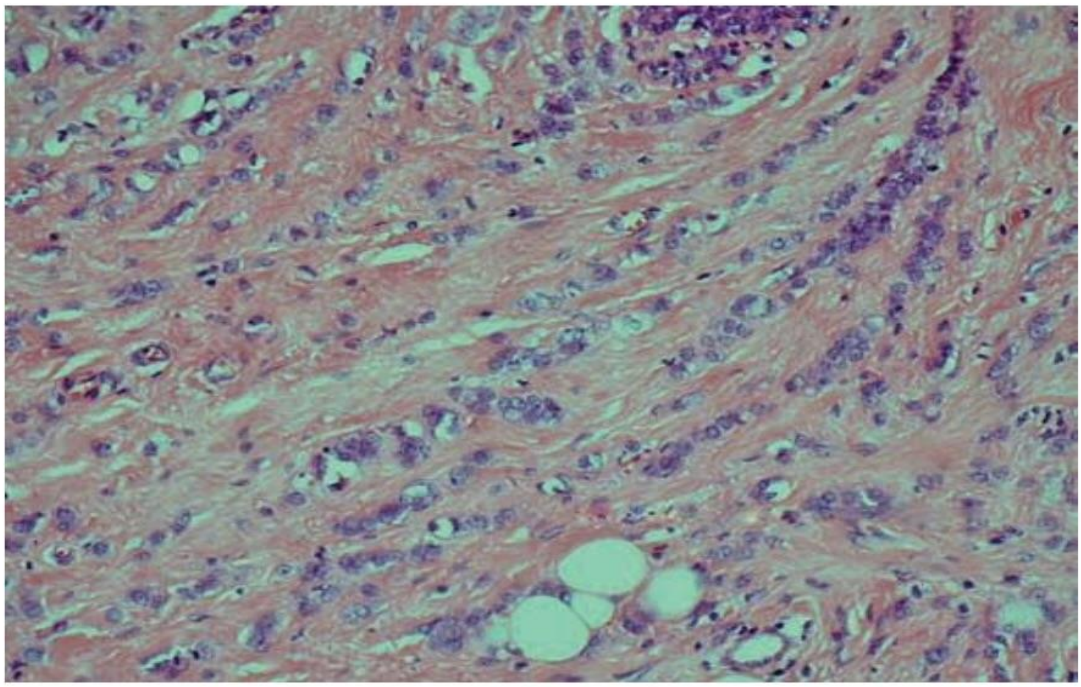


FIG.9 – Histological view of Lobular carcinoma

Salient characteristics of in situ ductal (DCIS) and lobular (LCIS) carcinoma of the breast		
	LCIS	DCIS
Age (years)	44–47	54–58
Incidence[a]	2%–5%	5%–10%
Clinical signs	None	Mass, pain, nipple discharge
Mammographic signs	None	Microcalcifications
Premenopausal	2/3	1/3
Incidence of synchronous invasive carcinoma	5%	2%–46%
Multicentricity	60%–90%	40%–80%
Bilaterality	50%–70%	10%–20%
Axillary metastasis	1%	1%–2%
Subsequent carcinomas:		
Incidence	25%–35%	25%–70%
Laterality	Bilateral	Ipsilateral
Interval to diagnosis	15–20 y	5–10 y
Histologic type	Ductal	Ductal

II. **DUCTAL CARCINOMA INSITU:** Although ductal carcinoma in situ (DCIS) is primarily seen in the female breast, it accounts for 5% of male breast cancers**.** Studies have reported a detection frequency of 7% in all biopsy tissue specimens. The term intraductal carcinoma is often used to describe DCIS, reflecting its high risk for progression to invasive cancer. Histologically, DCIS is marked by the proliferation of epithelial cells lining the minor ducts, leading to papillary growths within the duct lumina. In the early stages, the cancer cells may lack pleomorphism, mitotic activity,

and atypia, making early DCIS difficult to distinguish from benign hyperplasia. As the disease progresses, the papillary growths coalesce, filling the duct lumina, leaving only scattered, rounded spaces between clusters of atypical cells. This results in a cribriform growth pattern**,** characterized by hyperchromasia and loss of cellular polarity(Fig.10). Further progression leads to the emergence of pleomorphic cancer cells with frequent mitotic figures, filling and distending the ducts, known as the solid growth pattern**.** As growth continues, the cells can outstrip their blood supply, resulting in necrosis, which is identified as the comedo growth pattern**.** Calcium deposition often occurs in areas of necrosis, a common feature visible on mammography. DCIS is frequently classified based on nuclear grade and the presence of necrosis. Although there is no universally agreed-upon classification, most systems use cytologic grade and the presence or absence of necrosis, as recommended by multiple consensus meetings.[86] Women with DCIS have an approximately fivefold increased risk of developing invasive breast cancer.[87] The invasive cancers typically occur in the ipsilateral breast**,** often in the same quadrant as the initial DCIS, suggesting that DCIS is an anatomic precursor to invasive ductal carcinoma

Classification of breast ductal carcinoma in situ (DCIS)			
Histologic Subtype	DETERMINING CHARACTERISTICS		DCIS GRADE
	NUCLEAR GRADE	Necrosis	
Comedo	High	Extensive	High
Intermediate	Intermediate	Focal or absent	Intermediate
Noncomedo	Low	Absent	Low

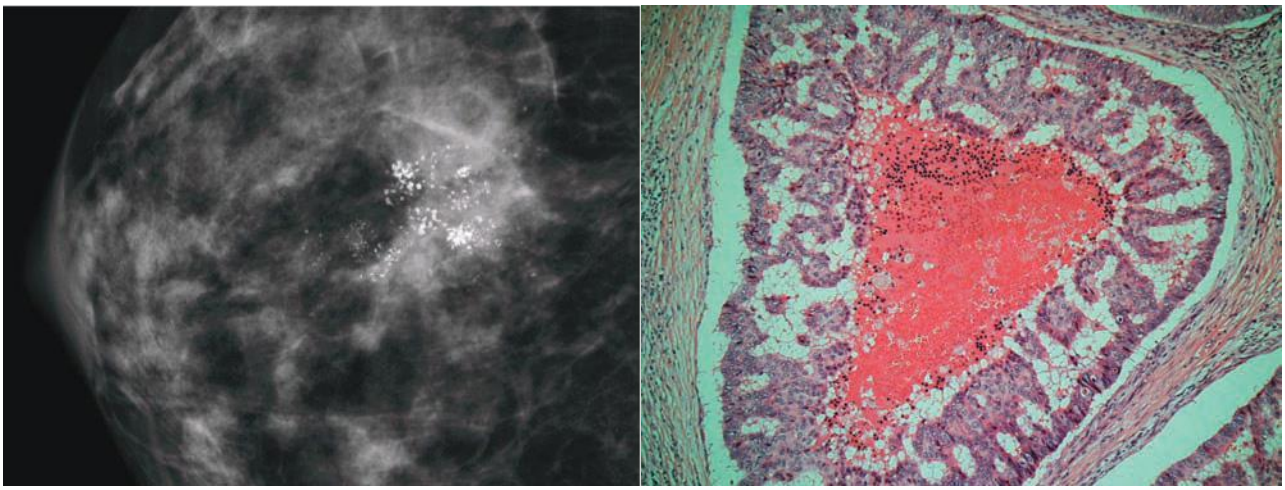


FIG.10 – Mammographic view and histologic view of Ductal carcinoma in situ(DCIS)

III. INVASIVE BREAST CARCINOMA: Invasive breast cancers are classified as lobular or ductal based on origin(Fig.11). While older classifications linked lobular carcinoma to LCIS and labeled others as ductal, modern histologic classifications recognize special-type breast cancers (10% of cases) with specific histologic features. For a cancer to be classified as a special type, 90% of its histology must meet defining criteria. Invasive ductal carcinoma of no special type (NST) makes up 80% of invasive cancers and typically has a worse prognosis than special types. Foote and Stewart proposed a detailed classification, identifying major subtypes, including Paget's disease**,** invasive ductal carcinoma (80%)**,** invasive lobular carcinoma (10%)**,** and rare forms like mucinous, medullary, and tubular carcinomas**.**

Paget's disease of the nipple**,** first described in 1874, often presents as a chronic, eczematous eruption that may progress to an ulcerated, weeping lesion**.** It is commonly associated with extensive DCIS and may accompany invasive cancer**,** with or without a palpable mass**.** Paget cells—large, pale, vacuolated cells—are pathognomonic and found in the rete pegs of the epithelium. It can mimic superficial spreading melanoma**,** but differentiation relies on immunostaining**:** S-100 antigen for melanoma and carcinoembryonic antigen for Paget's disease. Surgical treatment ranges from lumpectomy to mastectomy**,** depending on the extent and underlying cancer.

Invasive ductal carcinoma (IDC) of no special type (NST**)** represents 80% of breast cancers**,** frequently affecting perimenopausal and postmenopausal women in their fifth to sixth decades**.** It often presents as a solitary, firm mass with poorly defined margins**.** The cut surface has a stellate configuration with chalky white or yellow streaks**.** Axillary lymph node metastases are found in 25% of screen-detected cases and up to 60% of symptomatic cases**.** Histologically, cancer cells form small clusters with variable cellular and nuclear grades**.** Estrogen receptor expression is seen in 75% of IDC cases**,** according to SEER data.

Medullary carcinoma**,** a special-type breast cancer**,** accounts for 4% of invasive breast cancers and is frequently linked to BRCA1 mutations**.** Grossly, it appears soft and hemorrhagic**,** with rapid growth due to necrosis and hemorrhage. It often presents as a bulky mass deep in the breast, with bilaterality in 20% of cases**.** Microscopically, it features a dense lymphoreticular infiltrate**,** poorly differentiated large pleomorphic nuclei, and a sheet-like growth pattern**.** DCIS is found at the cancer periphery in 50% of cases, but <10% are hormone receptor positive. Despite its aggressive appearance, 5-year survival is better compared to NST or invasive lobular carcinoma, partly due to the intense lymphocyte response**.**

Mucinous carcinoma (colloid carcinoma) is a special-type breast cancer comprising 2% of invasive breast cancers, typically affecting the elderly. It presents as a bulky tumor with a glistening, gelatinous cut surface due to extracellular mucin pools surrounding low-grade cancer cells. Fibrosis can vary, giving the tumor a firm consistency in some cases. Over 90% of mucinous carcinomas express hormone receptors. Lymph node metastases occur in 33% of cases, with 5-year survival at 73% and 10-year survival at 59%. Diagnosis requires multiple microscopic sections due to the uneven distribution of mucinous components.

Papillary carcinoma, a special-type breast cancer, represents 2% of invasive breast cancers, typically affecting women in their seventh decade, with a higher prevalence in non-white women. These cancers are generally small (≤3 cm) and characterized by papillae with fibrovascular stalks and multi-layered epithelium. 87% express estrogen receptor positivity, as per SEER data. Axillary lymph node metastases are uncommon, and 5- and 10-year survival rates are similar to those of mucinous and tubular carcinoma, indicating a favourable prognosis.

Tubular carcinoma, a special-type breast cancer, accounts for 2% of invasive breast cancers and is frequently detected through mammographic screening in perimenopausal or early menopausal women. Microscopically, it shows a haphazard array of small, randomly arranged tubular structures. According to the SEER database, 94% express estrogen receptor positivity. Axillary lymph node metastases occur in 10% of cases, but survival is unaffected when limited to one or two lymph nodes. Distant metastases are rare, and long-term survival approaches 100%, indicating an excellent prognosis.

Invasive lobular carcinoma (ILC) accounts for 10% of breast cancers. Histologically, it is composed of small cells with rounded nuclei, inconspicuous nucleoli, and scant cytoplasm, sometimes showing signet-ring cell morphology due to intracytoplasmic mucin. Clinically, it ranges from inapparent forms to diffuse breast involvement with a poorly defined mass. Multifocality, multicentricity, and bilaterality are common. Its insidious growth and subtle mammographic findings make it challenging to detect. Over 90% of invasive lobular carcinomas are estrogen receptor-positive, contributing to its treatment approach and prognosis.

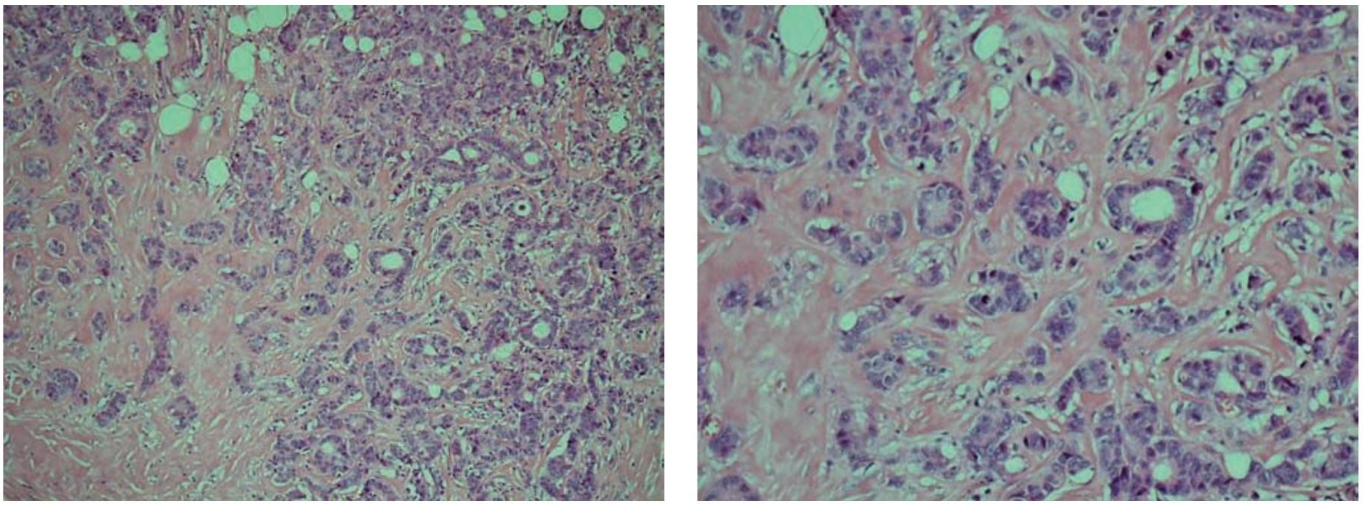


FIG11 – Invasive ductal carcinoma with productive fibrosis

BREAST CANCER STAGING: This passage outlines the staging process for breast cancer, emphasizing the importance of both clinical and pathologic evaluation in determining disease progression.

1. **Clinical Staging**
    - Primarily based on physical examination of the breast, skin, and regional lymph nodes (axillary, supraclavicular, and internal mammary).
    - However, axillary lymph node metastases detection by physical exam has a low accuracy (33%).
    - Ultrasound (US) is more sensitive in evaluating lymph node involvement.
    - Fine-needle aspiration (FNA) or core biopsy improves diagnostic certainty when lymph nodes appear suspicious on ultrasound.
2. **Pathologic Staging**
    - Conducted after surgical resection of the tumour and lymph nodes.
    - Examination of 10+ level I and II axillary nodes provides more accurate prognostic data regarding distant metastases.
    - The TNM (Tumour, Nodes, Metastasis) system, modified by the AJCC, is widely used for staging.
    -
3. **Prognostic Factors**
    - Tumour size correlates with axillary lymph node involvement, which in turn affects disease-free survival.
    - Number of metastatic axillary lymph nodes is a key predictor of 10- and 20-year survival rates.

4. **Lymph Node Evaluation and Biopsy**
    - Routine biopsy of internal mammary lymph nodes is generally not performed.
    - However, the "triple node biopsy" approach (internal mammary, low axillary, apical nodes) helps refine prognosis.
    - Sentinel lymph node dissection and preoperative lymphoscintigraphy allow for targeted biopsy of internal mammary nodes.
    - The 7th edition of the AJCC staging system permits staging based on internal mammary sentinel node findings.
5. **Changes in Staging Criteria**
    - Supraclavicular lymph node metastases are no longer classified as stage IV disease.
    - Routine biopsy of scalene or supraclavicular lymph nodes is not recommended.

BIOMARKERS:

1. Growth Factors and Receptors
    - HER-2/neu (ErbB2): Overexpressed in aggressive breast cancer; targeted by trastuzumab (Herceptin) and pertuzumab.
    - EGFR (ErbB1): Linked to tumor progression; potential target for EGFR inhibitors.
    - Transforming Growth Factor (TGF): Regulates proliferation and invasion; involved in cancer progression.
    - Platelet-Derived Growth Factor (PDGF): Promotes tumor angiogenesis and metastasis.
    - Insulin-Like Growth Factor (IGF) Family: Stimulates cell growth and survival; implicated in endocrine therapy resistance.
2. Proliferation Markers
    - Proliferating Cell Nuclear Antigen (PCNA): Essential for DNA replication; indicates high cell turnover.
    - Ki-67: A widely used marker for tumor proliferation; high levels correlate with poor prognosis.
3. Angiogenesis Markers
    - Vascular Endothelial Growth Factor (VEGF): Drives new blood vessel formation; targeted by bevacizumab (Avastin).
    - Angiogenesis Index: Measures micro vessel density, reflecting tumour vascularization.

4. mTOR Signalling Pathway
    - Mammalian Target of Rapamycin (mTOR): Regulates cell growth and metabolism; targeted by everolimus in hormone receptor-positive breast cancer.
5. Tumour Suppressor Genes
    - p53: Key regulator of apoptosis and DNA repair; mutations lead to uncontrolled growth and poor prognosis.
6. Cell Cycle Regulators
    - Cyclins and Cyclin-Dependent Kinases (CDKs): Control cell division; CDK4/6 inhibitors (e.g., Palbociclib, ribociclib) are used in HR+/HER2- breast cancer.
7. Proteasome Pathway
    - Involved in degrading misfolded proteins; inhibition can induce apoptosis in cancer cells.
8. Inflammation and Metabolic Regulators
    - COX-2 Enzyme: Promotes inflammation-driven cancer progression; COX-2 inhibitors may have therapeutic potential.
    - Peroxisome Proliferator-Activated Receptors (PPARs): Regulate lipid metabolism and cell differentiation; potential therapeutic targets.
9. Apoptosis Modulators
    - bcl-2: Anti-apoptotic protein, often overexpressed in breast cancer.
    - bax:bcl-2 Ratio: A higher ratio promotes apoptosis, while a lower ratio enhances tumor survival.

These biomarkers are critical in breast cancer classification, prognosis, and targeted therapy selection, helping to personalize treatment strategies.

TNM STAGING OF BREAST CANCER:

TNM staging system for breast cancer

Primary tumor (T)

The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's 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 categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤5 cm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)*
T4a	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peaud'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma** *Note: Invasion of the dermis alone does not qualify as T4 **Note: Inflammatory carcinoma is restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.

Regional lymph nodes—Clinical (N)

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(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* 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 detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastasis in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* 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 internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph nodes(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s) *Notes: "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, e.g., cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g., cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Regional lymph nodes—Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0[b]	No regional lymph node metastasis identified histologically Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
pN0(i–)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings [reverse-transcriptase polymerase chain reaction (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	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 2.0 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 apparent*** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor 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 10 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 in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes * Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(sn). ** RT-PCR: reverse transcriptase/polymerase chain reaction. *** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination. **** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

STAGING OF BREAST CANCER:

TNM stage groupings			
STAGE 0	TIS	N0	M0
Stage IA	T1[a]	N0	M0
Stage IB	T0	N1mi	M0
	T1[a]	N1mi	M0
Stage IIA	T0	N1[b]	M0
	T1[a]	N1[b]	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

OVERVIEW OF BREAST CANCER THERAPHY:

Before performing a biopsy, surgeons must assess the likelihood of breast cancer based on clinical and imaging findings. The treatment approach is guided by disease stage, biological subtype, and patient health. Initial staging determines the need for laboratory tests and imaging. Clear communication between the patient and surgeon is essential before therapy, ensuring an informed treatment plan.

A. INSITU BREAST CANCER (STAGE 0):

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from cancers with early invasion.[88-93] Expert pathologic review is required in all cases. Bilateral mammography is performed to determine the extent of the in situ cancer and to exclude a second cancer. Because LCIS is considered a marker for increased risk rather than an inevitable precursor of invasive disease, the current treatment options for LCIS include observation, chemoprevention, and bilateral total mastectomy. The goal of treatment is to prevent or detect at an early stage the invasive cancer that subsequently develops in 25% to 35% of these women. There is no benefit to excising LCIS, because the disease diffusely involves both breasts in many cases and the risk of developing invasive cancer

is equal for both breasts. The use of tamoxifen as a risk reduction strategy should be considered in women with a diagnosis of LCIS. Women with DCIS and evidence of extensive disease (>4 cm of disease or disease in more than one quadrant) usually require mastectomy. For women with limited disease, lumpectomy and radiation therapy are generally recommended. For nonpalpable DCIS, needle localization or other image-guided techniques are used to guide the surgical resection. Specimen mammography is performed to ensure that all visible evidence of cancer is excised. Adjuvant tamoxifen therapy is considered for DCIS patients with ER-positive disease. Mastectomy is considered the benchmark for evaluating breast conservation therapy for DCIS, as it results in local recurrence and mortality rates below 2%.

No randomized trials directly compare mastectomy to breast-conserving surgery, and existing trials on the latter lack sufficient power to detect mortality differences. Lumpectomy with radiation lowers local recurrence rates compared to lumpectomy alone, with nearly 45% of recurrences being invasive if radiation is omitted. The NSABP B-17 trial confirmed the benefit of radiation, though margin status was not prospectively assessed. Several other randomized trials with margin assessments, including those by EORTC and the UK/Australia/New Zealand, support the role of radiation in reducing recurrence. Although randomized trials have shown a benefit of radiation in all DCIS patient subgroups, efforts have been made to identify cases where radiation may be avoided to reduce costs and inconvenience. Some studies have shown that patients treated with excision alone did not develop invasive cancer even after 25 years. Silverstein et al. advocated for omitting radiation in patients with widely negative margins, reporting no additional benefit when margins exceeded 10 mm. Their findings indicated a higher recurrence risk with smaller margins, suggesting that carefully selected patients may safely forgo radiation therapy.

The ECOG 5194 trial aimed to determine which DCIS patients could safely undergo breast-conserving surgery without radiation. Patients with low or intermediate-grade DCIS (≤2.5 cm) and negative margins (≥3 mm) had a 6.1% recurrence rate, while those with high-grade DCIS (≤1 cm) and similar margins had a significantly higher recurrence rate of 15.3% at a median follow-up of 6.2 years. Approximately 4% of patients in both groups developed contralateral breast cancer. The study concluded that excision alone is a viable option for selected low/intermediate-grade DCIS cases but not for high-grade DCIS due to its high recurrence risk.

The RTOG 9804 trial investigated the role of whole breast irradiation in “good risk” DCIS patients, defined as unicentric, low or intermediate grade tumors (≤2.5 cm) with margins of ≥3 mm. The trial closed early due to slow accrual, but results from 585 patients with a median follow-up of 6.46 years showed a 5-year local recurrence rate of 0.4% with radiation and 3.2% without it. While the findings suggest radiation significantly reduces recurrence, the study has only been reported in abstract form,

and further follow-up is ongoing. Solin et al. used samples from the ECOG 5194 trial to develop a multigene RT-PCR assay, the DCIS Score, to predict recurrence risk in DCIS patients treated with surgery alone. The score categorizes patients into low, intermediate, and high-risk groups for both DCIS and invasive recurrences. While promising, further validation studies are needed. Treatment decisions for DCIS should consider clinical and pathological factors, including tumor characteristics and patient preference, as there is no single optimal surgical approach.

Axillary staging is generally limited to mastectomy cases due to a 20% likelihood of invasive cancer being found after needle core biopsy diagnosis. Sentinel node dissection is recommended at the time of mastectomy for DCIS since it cannot be performed afterward. The NSABP B-24 trial demonstrated that adjuvant tamoxifen significantly reduces local recurrence in women with ER-positive DCIS. Based on this, guidelines suggest offering 5 years of tamoxifen post-surgery and radiation for ER-positive patients without contraindications. The trial initially randomized 1,804 women to lumpectomy and radiation with or without tamoxifen, showing a recurrence reduction (8.2% vs. 13.4%, $P = 0.0009$). Further analysis by Allred et al. found that 76% had ER-positive DCIS**,** which benefited more from tamoxifen (5.2% recurrence vs. 11% in ER-negative cases, $P < 0.001$). However, 15% of patients had tumor at the resection margins, meaning tamoxifen may have compensated for inadequate excision. The use of tamoxifen is not universally adopted post-breast conservation therapy worldwide.

B. EARLY INVASIVE BREAST CANCER (STAGE1, STAGE 2A OR STAGE 2B):

Six randomized trials have compared breast-conserving surgery (BCS) and mastectomy in early-stage breast cancer, consistently showing equivalent survival rates. However, most trials restricted tumour size (≤2.5 cm), except NSABP B-06 (4 cm) and NCI (5 cm). NSABP B-06, the largest study, demonstrated similar disease-free and overall survival rates between mastectomy and lumpectomy (with or without radiation), though lumpectomy alone had a higher recurrence rate**.** A 20-year follow-up reaffirmed no difference in survival but confirmed that radiation significantly reduces recurrence (39.2% vs. 14.3%).

However, the study had limitations**,** including lymphadenopathy exclusion**,** mandatory frozen section for lumpectomy patients (leading to some mastectomies counted as BCS due to intention-to-treat analysis), and recurrences in the lumpectomy group being classified as "non-events"**.** These findings solidified lumpectomy with radiation as the standard for early-stage, unifocal, BRCA-negative breast cancer. The EBCTCG meta-analysis of randomized trials found that radiation therapy after lumpectomy reduces mortality by 5.1% in node-negative and 7.1% in node-positive patients at 15 years, highlighting its impact beyond local control. However, studies have explored

omitting radiation in selected older patients with small, low-grade tumours. The CALGB C9343 trial randomized women ≥70 years with T1N0 breast cancer to lumpectomy with or without radiation, with all receiving adjuvant tamoxifen. While radiation reduced local recurrence **(**1% vs. 4%, P<0.001**),** disease-free and overall survival were unaffected. A similar Canadian trial of women ≥50 years (mean age 68, 80% ER-positive) found radiation lowered local recurrence (0.6% vs. 7.7%, P<0.001)**,** but DFS and OS remained unchanged**.** These findings suggest radiation may be omitted in T1N0, ER-positive breast cancer patients over 70 with limited life expectancy.

Accelerated partial breast irradiation (APBI) is an alternative radiation approach for carefully selected DCIS and early-stage breast cancer patients. Since most recurrences occur near the tumour bed, APBI focuses radiation on that area with a margin of normal tissue, delivered over 5 days (twice daily) at a lower total dose than the 5–6 week whole breast irradiation (WBI) regimen (50 Gray ± boost). APBI proponents argue that its shorter duration may enhance feasibility and compliance with breast conservation. The RTOG 04-13/NSABP B-39 trial is comparing WBI and APBI, but results are not yet available. The TARGIT study randomized 3,451 patients across 10 countries to intraoperative radiation therapy (IORT) or external beam radiation therapy (EBRT). Preliminary 2012 results (median follow-up: 2.4 years) showed higher recurrence with IORT (3.3% vs. 1.3% for EBRT), indicating a 2% increased recurrence risk with IORT. Further long-term data are needed to assess the effectiveness of APBI and IORT compared to standard radiation therapy.

The American Society for Radiation Oncology (ASTRO) established guidelines for APBI eligibility outside clinical trials:

- "Suitable": Women ≥60 years, unifocal T1, ER-positive tumours, no lympho vascular invasion (LVI), and ≥2 mm margins.
- "Cautionary": Patients with invasive lobular histology, tumour size 2.1–3 cm, ER-negative disease, focal LVI, or margins <2 mm.
- "Unsuitable": T3 or T4 tumours, ER-negative disease, multifocal/multicentric tumours, extensive LVI, or positive margins.

For stage I and II breast cancer, mastectomy with axillary staging and breast-conserving surgery with axillary staging and radiation therapy are considered equivalent treatments. Breast conservation is preferred for its cosmetic benefits and survival equivalence but is not recommended for BRCA mutation carriers due to their higher lifetime breast cancer risk.

Relative contraindications to breast conservation therapy include:
(a) Prior chest/breast radiation,

(b) Persistently positive surgical margins after re excision,
(c) Multicentric disease, and
(d) Autoimmune conditions (scleroderma, lupus erythematosus).

For early-stage breast cancer, immediate reconstruction at the time of mastectomy is often preferred, as it allows for skin-sparing techniques, enhancing cosmetic outcomes. Over the past decade, skin-sparing mastectomy with immediate reconstruction has gained popularity due to low local-regional failure rates and advances in reconstructive surgery.

There is growing interest in nipple-areolar sparing mastectomy, but long-term safety data are limited. This technique is not ideal for patients requiring postmastectomy radiation therapy (PMRT), as radiation can negatively impact the preserved nipple.

Benefits of immediate reconstruction include:
Better cosmesis (preservation of skin and nipple-areolar complex)
Psychological benefits (patients wake up with a breast mound)
Economic advantage (combined extirpative and reconstructive procedures)

Reconstruction options:
Implants or autologous tissue flaps (e.g., TRAM, DIEP, or latissimus dorsi flap)
If PMRT is needed, a tissue expander can be placed to maintain breast shape. The expander is deflated during radiation to allow chest wall irradiation and is replaced with autologous tissue reconstruction 6–12 months post-radiation.

Axillary lymph node status has long been a key factor in staging and prognosis for early-stage breast cancer. Traditionally, axillary lymph node dissection (ALND) was used for staging and regional control, but trials comparing immediate vs. delayed ALND found no survival disadvantage with delayed dissection. With increased mammographic screening, smaller node-negative breast cancers were more frequently detected, making routine ALND unnecessary for up to 75% of women with clinically negative axillae at diagnosis.

This led to the adoption of sentinel lymph node (SLN) dissection as a less invasive alternative. SLN dissection is typically unnecessary in patients with metastatic axillary lymphadenopathy confirmed by biopsy, allowing direct progression to ALND or preoperative systemic therapy. While SLN dissection is recognized for axillary staging in larger tumors and post-neoadjuvant cases, its role remains debated due to a lack of randomized studies on outcomes for locally advanced cancer with negative SLN findings. Adjuvant chemotherapy is recommended for early-stage invasive breast cancer based on tumor size, nodal status, and adverse prognostic factors, while endocrine therapy is

considered for hormone receptor-positive cases. HER-2/neu–positive patients benefit from trastuzumab, with evidence supporting its efficacy both concurrently with taxane-based regimens and following anthracycline therapy.

C. Advanced Local-Regional Breast Cancer (Stage IIIA or IIIB):

Women diagnosed with stage IIIA and IIIB breast cancer have advanced local-regional disease without any clinically detected distant metastases(Fig.12)[94]. To optimize both local-regional and distant disease-free survival, their treatment typically involves a combination of surgery, radiation therapy, and chemotherapy. However, it is important to recognize that most of these patients may already have undetected distant metastases, which often become evident through imaging techniques such as bone scans, PET scans, or CT scans. Even if these imaging results are negative, elevated serum tumour markers may suggest that the cancer has already spread.

The approach used for treating small, screen-detected breast cancers—where more than 90% of patients can achieve a cure with local treatment alone—does not apply to locally advanced cases. In fact, a prior randomized study comparing neoadjuvant therapy followed by modified radical mastectomy, postoperative radiotherapy, and endocrine therapy with an alternative strategy of primary endocrine therapy followed by sequential treatment upon disease progression found no significant difference in overall survival or the rate of uncontrolled local disease at the time of death[95].

Preoperative, or neoadjuvant chemotherapy, plays a crucial role in the initial management of locally advanced stage III breast cancer, particularly in patients with oestrogen receptor (ER)-negative tumours. However, for select cases of clinically indolent, ER-positive locally advanced tumours, primary endocrine therapy may be considered, especially when the patient has significant co-morbid conditions.

A study involving 195 patients with ER-positive locally advanced breast cancer (median age 69 years, median tumour size 6 cm, median follow-up 61 months) reported the following outcomes:

- Five-year overall survival: 76%
- Breast cancer-specific survival: 86%
- Metastasis-free survival: 77%
- Median time to alternative treatment: 48 months.

Although this study spanned 20 years, the number of such cases was relatively small, and clinicians should consider these findings when discussing treatment options.

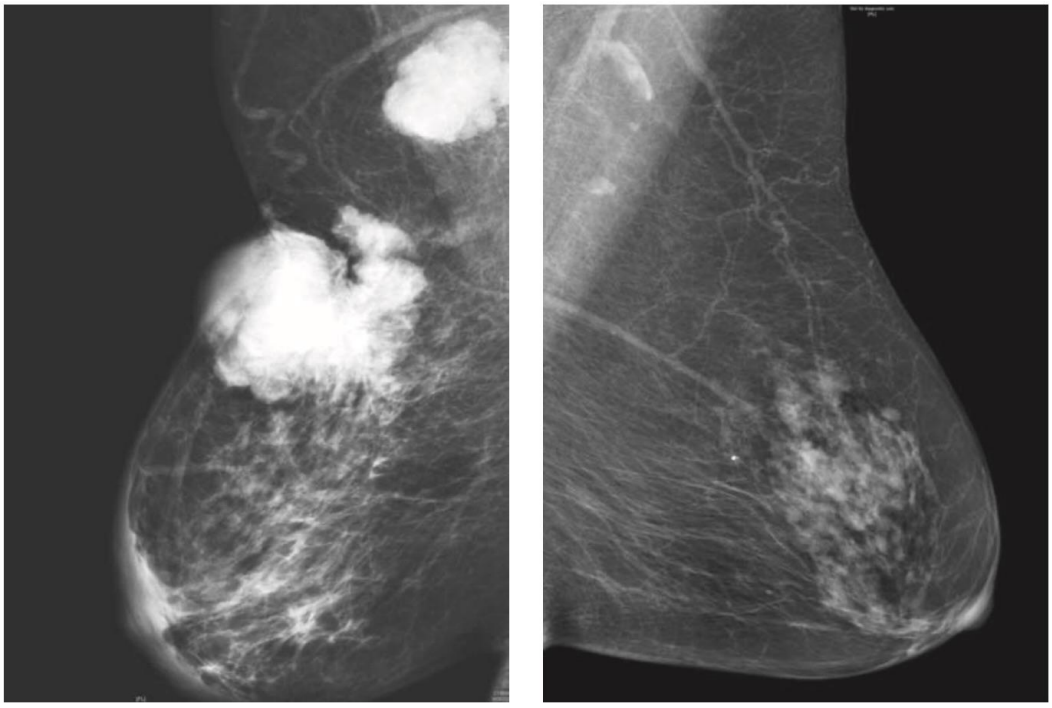


FIG.12 – Mammography showing image of locally advanced breast cancer(left) and normal breast(right)

Surgical and Radiation Therapy in Stage III Breast Cancer:

For women with stage III disease, the standard surgical approach is a modified radical mastectomy, followed by adjuvant radiation therapy. While chemotherapy aims to improve distant disease-free survival, radiation therapy focuses on enhancing local-regional control and disease-free survival.

In selected stage IIIA cases, preoperative chemotherapy may significantly shrink the primary tumour, enabling breast-conserving surgery instead of mastectomy. A study from MD Anderson Cancer Centre demonstrated that low local-regional failure rates could be achieved in carefully chosen stage III patients who underwent preoperative chemotherapy, breast-conserving surgery, and radiation therapy[96].

- The 5-year actuarial ipsilateral breast tumor recurrence-free survival rate in this study was 95%.
- However, recurrence rates increased in patients with:

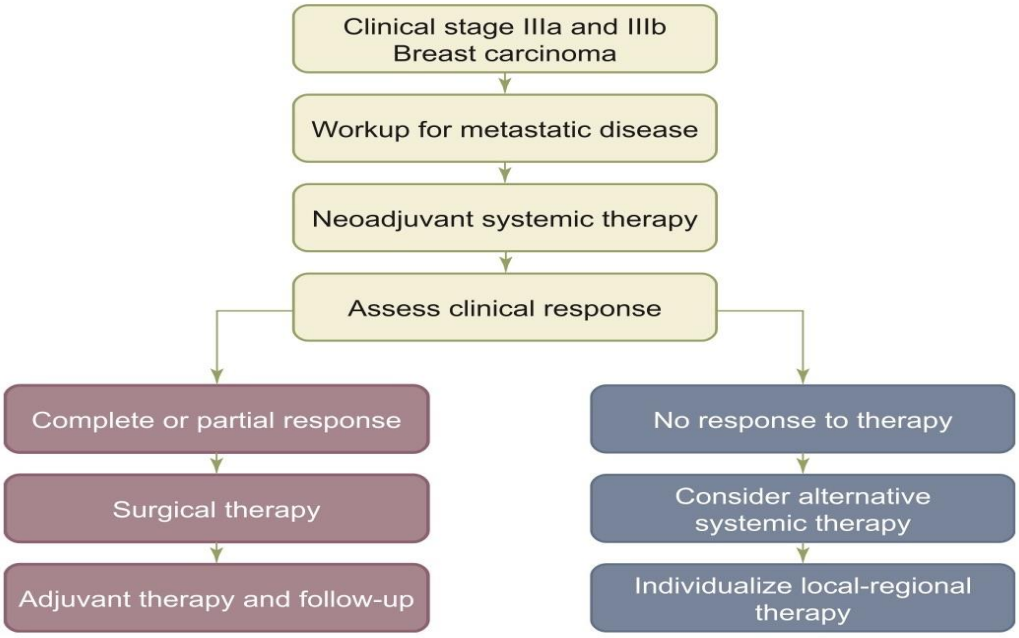
- Clinical N2 or N3 disease
- More than 2 cm of residual disease in the breast at surgery
- Multifocal residual disease in the breast
- Lympho-vascular space invasion in the primary tumour.

Risk of Local Recurrence with Neoadjuvant Therapy:

Despite these promising results, data from the Oxford overview of randomized trials comparing neoadjuvant vs. adjuvant therapy reported a hazard ratio (HR) of 1.5, indicating a 50% increase in local recurrence rates for patients who received neoadjuvant therapy. A separate meta-analysis found a slightly lower but still concerning HR of 1.3[97]. These findings are particularly important because preventing local recurrence in a preserved breast can reduce breast cancer mortality over the next 15 years—with one breast cancer death prevented for every four local recurrences avoided. Additionally, the German Breast Cancer Group analysed 5,535 patients across seven studies, reporting local recurrence rates ranging from 7.6% to 19.5% for T1-T4 tumours and 6.4% to 17.9% for N0-N3 tumours treated with neoadjuvant therapy[98]. These results highlight the need for further research into neoadjuvant therapy for locally advanced breast cancer.

Surgical Planning for Stage IIIA and IIIB Disease:

For patients with stage IIIA disease who exhibit minimal response to chemotherapy, as well as those with stage IIIB breast cancer, preoperative chemotherapy can still reduce the tumour burden enough to allow for a subsequent modified radical mastectomy to establish local-regional control. In both stage IIIA and IIIB disease, surgery is followed by adjuvant radiation therapy. However, a small percentage of patients may experience disease progression during neoadjuvant therapy. For this reason, surgeons and oncologists should regularly assess patient progress throughout the neoadjuvant treatment regimen to adjust management strategies accordingly.



D. DISTANT METASTASES:

The treatment of stage IV breast cancer is not curative; however, it can extend survival and improve quality of life[99]. For patients with estrogen receptor (ER)-positive disease, endocrine therapy is preferred over cytotoxic chemotherapy due to its lower toxicity.

Endocrine Therapy for Hormone Receptor-Positive Disease:

Women with hormone receptor-positive metastatic breast cancer who do not have immediately life-threatening disease (also known as a "visceral crisis") are considered suitable candidates for initial endocrine therapy. This includes:

- Women with bone or soft tissue metastases
- Women with limited visceral metastases

Symptoms alone, such as breathlessness, do not automatically necessitate chemotherapy. For instance:

- If breathlessness is due to a pleural effusion, it can often be relieved through percutaneous drainage, after which the patient may begin endocrine therapy.
- If breathlessness is caused by lymphangitic spread of cancer, chemotherapy would be the preferred treatment.

A similar symptom-based approach applies to pain management and other metastatic symptoms.

Systemic Chemotherapy for Advanced Disease:

Chemotherapy is typically reserved for:

- Women with hormone receptor-negative cancers
- Patients experiencing a visceral crisis.
- Those with hormone-refractory metastases (progression despite endocrine therapy)

Localized Treatment in Stage IV Breast Cancer:

Women with stage IV disease may develop anatomically localized complications that can benefit from individualized surgical or radiation therapy. These include:

- Brain metastases
- Pleural or pericardial effusion
- Biliary or ureteral obstruction
- Impending or existing pathological fractures of long bones
- Spinal cord compression
- Painful bone or soft tissue metastases

In patients with bone metastases, bisphosphonates may be administered alongside chemotherapy or endocrine therapy to strengthen bones and reduce skeletal-related complications

The Role of Surgery in Stage IV Breast Cancer:

There has been ongoing debate regarding whether surgical resection of the primary tumour benefits women with metastatic breast cancer. Some studies suggest that removing the primary tumour improves survival, while others attribute this finding to selection bias, arguing that surgery should be reserved for symptom palliation.

Multidisciplinary Approach to Surgical Management:

Until further data is available, surgical intervention for stage IV breast cancer should be carefully considered with input from a multidisciplinary team. The decision should take into account:

- The patient's treatment goals.
- The recommendations of the treating physicians
- The individual's overall prognosis and symptom burden

In summary, while systemic therapy remains the cornerstone of stage IV breast cancer treatment, local therapies such as surgery and radiation may be beneficial in select cases, particularly for symptom relief and anatomical complications.

E. LOCO-REGIONAL RECURRENCE:

Women who experience local-regional recurrence of breast cancer can be categorized into two groups: those who previously underwent mastectomy and those who had a lumpectomy.

- For women who had a prior mastectomy, treatment involves surgical resection of the recurrent tumour, followed by appropriate reconstruction if necessary. Additional chemotherapy and antiestrogen therapy may be considered. Adjuvant radiation therapy is given if the chest wall was not previously irradiated, or if the radiation oncologist determines that further radiation is feasible, particularly for palliative purposes.
- For women who previously had breast-conserving surgery (lumpectomy), the standard approach is mastectomy with reconstruction. Chemotherapy and antiestrogen therapy are also considered as part of systemic treatment.

SURGICAL TECHNIQUES IN BREAST CANCER THERAPHY:

A. EXCISIONAL BIOPSY WITH NEEDLE LOCALIZATION:

An excisional biopsy involves the complete removal of a breast lesion along with a margin of normal-appearing breast tissue. Historically, surgeons would obtain prior consent from patients to proceed with a mastectomy if the initial biopsy confirmed cancer. However, modern practice emphasizes the importance of discussing local therapy options—such as lumpectomy or mastectomy (with or without reconstruction)—as well as the need for nodal assessment via sentinel lymph node (SLN) dissection. Needle core biopsy is now the preferred diagnostic method, while excisional biopsy is typically reserved for cases where needle biopsy results do not align with imaging findings or clinical examination (Fig.13).

Surgical Incision Considerations:

- For subareolar lesions or those near the nipple-areolar complex, circumareolar incisions are commonly used.
- For other breast areas, incisions should follow natural skin tension lines, which are generally concentric with the nipple-areola complex.
- In the lower half of the breast, radial incisions usually provide the best cosmetic and functional outcomes.
- For tumors distant from the central breast, the biopsy incision can be separate from the primary mastectomy incision in case a mastectomy is later required.
- Radial incisions in the upper breast should be avoided due to the risk of scar contracture, which can displace the nipple-areolar complex.
- Curvilinear incisions in the lower breast should also be avoided, as they may lead to downward displacement of the nipple-areolar complex.

After excising a suspicious breast lesion**,** the specimen should be X-rayed to ensure that the lesion has been completely removed with adequate margins**.** The biopsy specimen is then oriented for the pathologist using sutures, clips, or dyes**.** If the specimen X-ray reveals that the lesion is too close to one or more margins**,** additional margin samples(superior, inferior, medial, lateral, superficial, and deep) may be taken from the surgical bed**.** Some surgeons also perform additional shavings from the margins to further confirm complete excision of the lesion. To achieve haemostasis**,** electrocautery or absorbable ligatures are

used. For cosmetic outcomes, the surgical defect is approximated using 3-0 absorbable sutures**,** followed by a running subcuticular skin closure with 4-0 or 5-0 absorbable monofilament sutures. In most cases, wound drainage is not required.

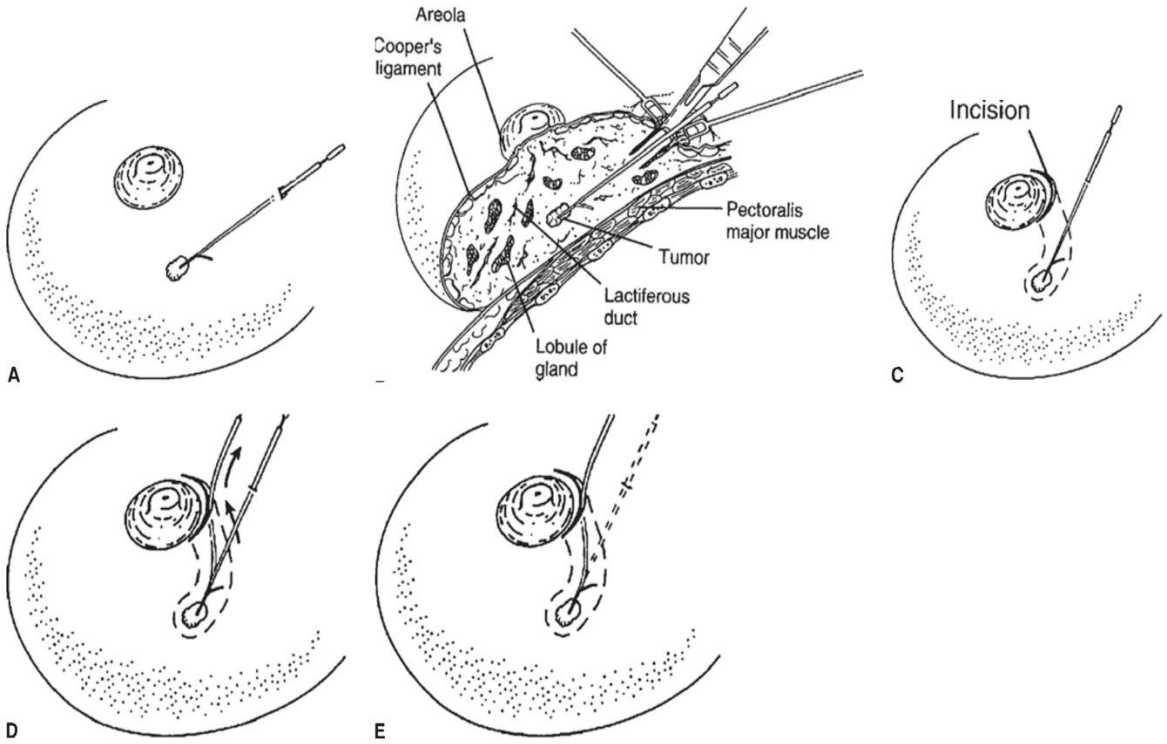


FIG.13 – Operative technique for needle localization biopsy of a deep subareolar lesion

Excisional Biopsy with Needle Localization:

For non-palpable breast lesions, excisional biopsy requires needle localization before surgery. This involves a preoperative visit to the mammography suite, where a localization wire or radiolabelled seed is placed to mark the lesion. The radiolabelled seed can be detected intraoperatively using a handheld probe**.** Alternatively, the lesion may be targeted with ultrasound in either the imaging suite or the operating room**.**

Once the lesion has been accurately localized by mammography, the tip of a thin wire hook is positioned close to the lesion(Fig.14)**.** Using this wire as a guide, the surgeon excises the lesion**,** along with a margin of normal-appearing breast tissue. Before the patient leaves the operating room, a specimen X-ray is performed to confirm that the lesion has been completely excised**.**

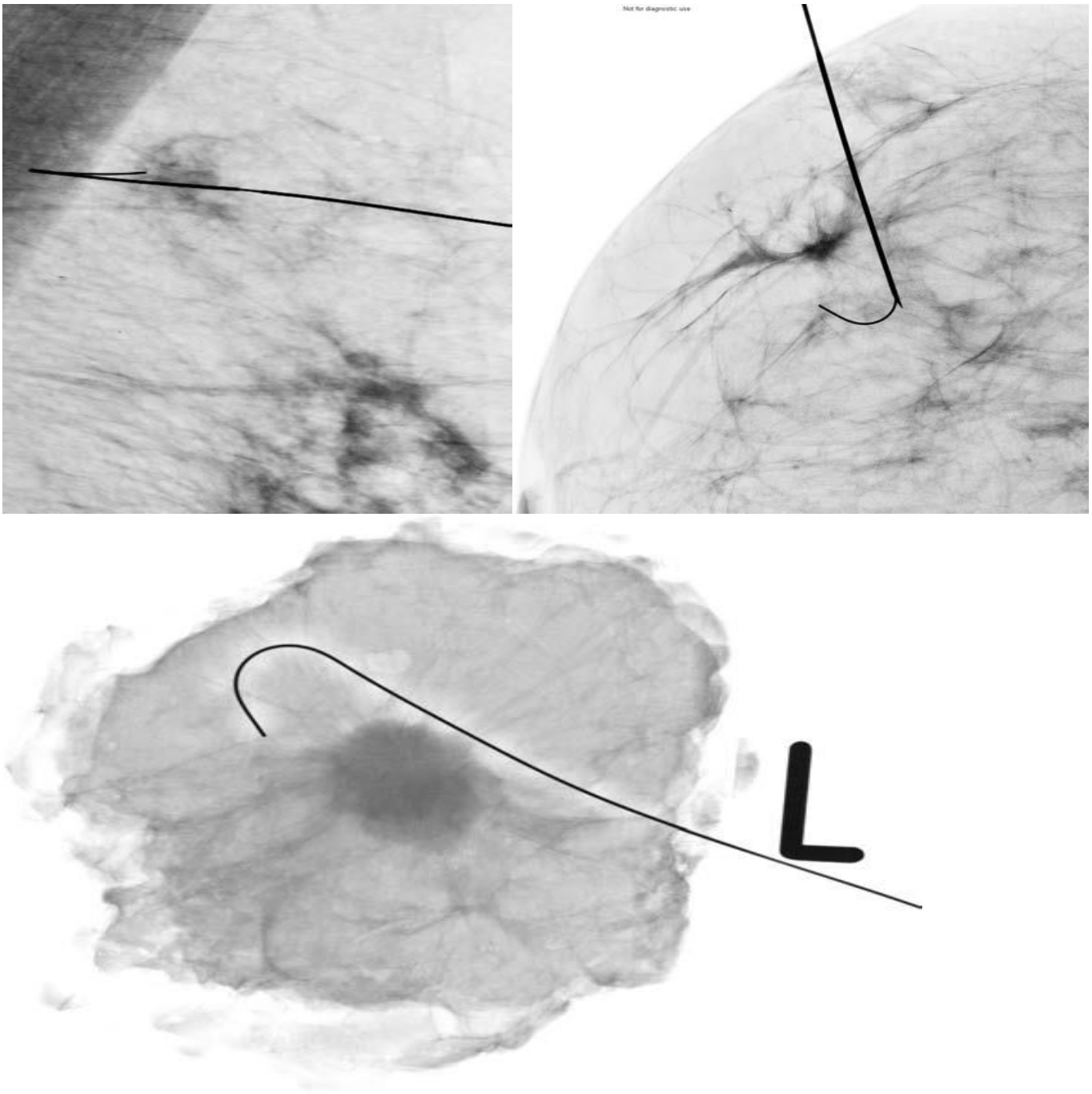


FIG.14- Sentinel lymph node biopsy

B. SENTINEL LYMPH NODE BIOPSY:

Sentinel lymph node (SLN) dissection is primarily used to evaluate regional lymph nodes in women with early-stage breast cancer who are clinically node-negative based on physical examination and imaging studies[100-108.] This technique is also effective in assessing larger tumours (T3 N0); however, nearly 75% of these patients will have axillary lymph node metastases upon histologic examination. Identifying nodal involvement preoperatively, when possible, allows for a more definitive surgical approach to treat known axillary disease.

SLN dissection has also demonstrated accuracy in staging the axilla after chemotherapy in women who were clinically node-negative at diagnosis[109,110]. A meta-analysis by Tan et al. reviewed 449 cases of SLN biopsy in clinically node-negative breast cancer, reporting:

- Sensitivity: 93%
- False-negative rate: 7%
- Negative predictive value: 94%
- Overall accuracy: 95%[111].

SLN dissection is not advised in the following cases:

- Inflammatory breast cancer
- Palpable axillary lymphadenopathy with biopsy-confirmed metastasis
- Ductal carcinoma in situ (DCIS) without mastectomy
- Patients with a history of prior axillary surgery

  Although data is limited, SLN dissection appears to be safe during pregnancy when performed using radioisotope alone.

Large prospective studies suggest that using a combination of intraoperative gamma probe detection (with radioactive colloid) and visualization with blue dye (isosulfan blue or methylene blue) is more accurate for identifying sentinel lymph nodes (SLNs) than either method alone. Some surgeons also incorporate preoperative lymphoscintigraphy, although it is not required for SLN identification.

Radioactive Colloid Injection for SLN Detection:

On the day before surgery or the day of surgery, the radioactive colloid is injected in one of the following locations(Fig.15):

- Breast parenchyma around the primary tumor or prior biopsy site
- Subareolar region
- Subdermal layer near the primary tumour site

Injection protocol:

- For same-day surgery → 0.5 mCi of 0.2-μm technetium-99m–labelled sulphur colloid is injected using a 25-gauge needle.
- For next-day surgery → A higher dose of 2.5 mCi of technetium-labelled sulphur colloid is used

Subdermal injections are placed either near the tumour site or in the subareolar region.

Blue Dye Injection for SLN Visualization:

In the operating room, 3 to 5 mL of blue dye is injected into either(Fig.16):

- The breast parenchyma
- The subareolar location

However, subdermal injections of blue dye are not recommended, as they may cause:

- Skin tattooing (with isosulfan blue dye)
- Skin necrosis (with methylene blue)

For nonpalpable breast cancers, the technetium-labelled sulphur colloid injection can be guided by either:

- Ultrasound
- Mammography

Radiologists may mark the skin overlying the tumour site with an indelible marker during needle localization to assist the surgeon.

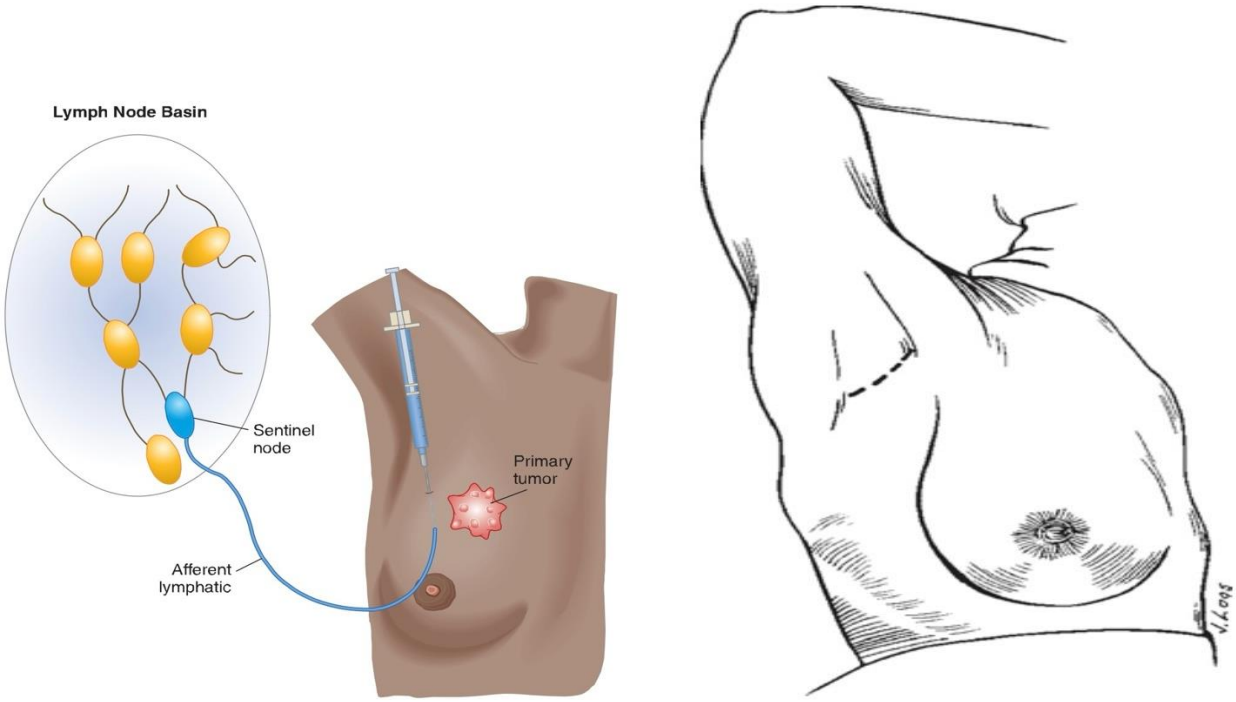


FIG.15 – Injection on the axillary side of the tumor and the placement of incision

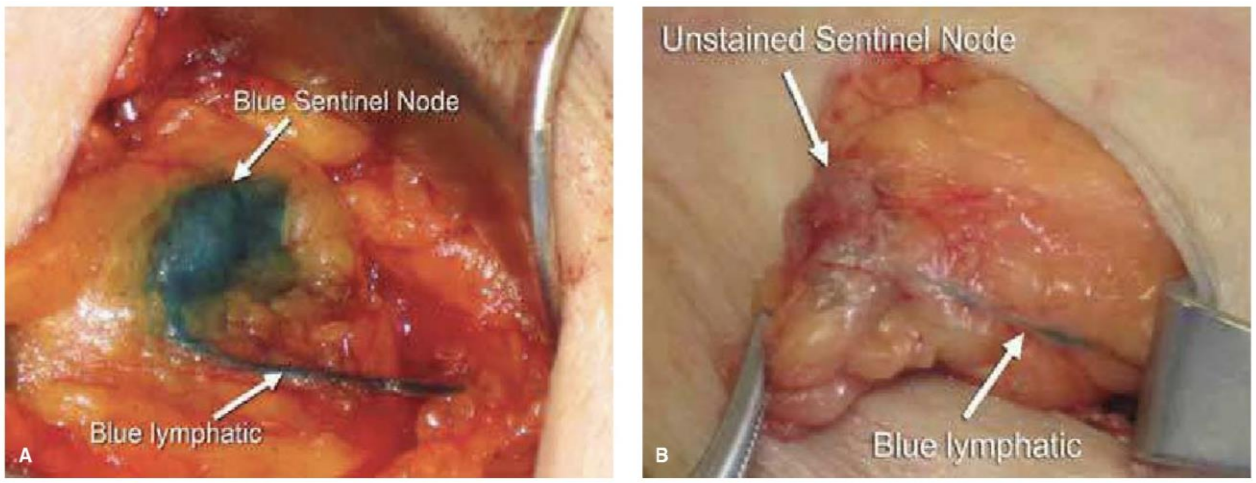


FIG.16 – Visualisation of blue stained sentinel node and unstained sentinel node

SLN Biopsy in Patients with Previous Excisional Biopsy:

For women who have previously undergone excisional biopsy, injections should be made around the biopsy cavity but not inside the cavity itself.

Patient Information and Safety Considerations:

- Patients should be informed preoperatively that isosulfan blue dye may cause a temporary discoloration of urine.
- The risk of an allergic reaction to isosulfan blue dye is extremely low (1 in 10,000), but anaphylactic reactions have been reported.
- Some centers use a prophylactic regimen of antihistamines, steroids, and histamine H2-receptor antagonists to reduce the risk of allergic reactions.
- The use of radioactive colloid is considered safe, with minimal radiation exposure.
- In pregnant women, sentinel node dissection can be performed using radioactive colloid, but blue dye should be avoided.

A handheld gamma counter is used transcutaneous to locate the sentinel lymph node (SLN), helping to guide the incision placement. A 3- to 4-cm curved transverse incision is made in the lower axilla, just below the hairline, following the typical approach for axillary dissection.

After dissecting through the subcutaneous tissue, the surgeon carefully opens the axillary fascia, paying attention to blue lymphatic channels. Following these dye-stained channels can lead directly to the SLN, minimizing unnecessary dissection through axillary tissues. The gamma probe is then used throughout the procedure to pinpoint the SLN's exact location. As dissection progresses, the radioactive signal intensifies, indicating proximity to the SLN. The SLN can also be identified visually by the blue dye staining in the afferent lymphatic vessel and the lymph node itself.

SLN Removal and False-Negative Prevention:

- Before excising the SLN, a 10-second in vivo (within the body) radioactive count is recorded.
- After removal, an ex vivo (outside the body) count is measured for 10 seconds, and the node is sent for pathologic analysis (either permanent or frozen-section evaluation).
- To achieve the lowest false-negative rates, surgeons adhere to the “10% rule”, meaning:
    - All blue-stained lymph nodes and
    - All nodes with counts >10% of the 10-second ex vivo SLN count must be harvested.

Before closing the axillary wound, the gamma probe is used to measure residual radioactivity in the surgical bed. If counts remain high, the surgeon searches for additional SLNs, repeating the process until the remaining radioactivity is <10% of the most radioactive SLN and all blue nodes have been removed.

Studies show that removing four SLNs is sufficient for 98% recovery of all positive SLNs, meaning that removing more than four SLNs is generally unnecessary for accurate axillary staging.

The false-negative rate of SLN dissection is influenced by:

1. Tumour location
    - Lateral breast tumors have higher false-negative rates, likely due to difficulty distinguishing the "hot spot" in the axilla when the radioisotope is injected near the lateral breast tumor site.
2. Type of diagnostic biopsy
    - Patients who had an excisional biopsy prior to SLN biopsy were significantly more likely to have a false-negative SLN result.
    - This finding underscores the importance of using needle biopsy whenever possible, reserving excisional biopsy only for cases where needle biopsy results are inconclusive or discordant.
3. Number of SLNs removed
    - Removing more SLNs at surgery reduces the false-negative rate:
        - 2 SLNs removed → False-negative rate: 10% (*reduced from 17.7%*)
        - 3 SLNs removed → False-negative rate: 6.9%

Yi and colleagues further emphasized that the optimal number of SLNs required for accurate staging varies depending on individual patient characteristics and primary tumour factors[112].

In the B-32 trial, sentinel lymph nodes (SLNs) were found outside the level I and II axillary nodes in 1.4% of cases. The site of radioisotope injection significantly influenced this occurrence.

- When a subareolar or peri areolar injection was used, no SLNs were detected outside the level I or II axillary nodes.
- When a peritumoral injection was used, 20% of cases had SLNs located outside the level I or II axilla.

These findings reinforce the concept of the SLN as the first site of lymphatic drainage from the primary tumour. While many patients exhibit similar drainage patterns regardless of whether the radioisotope is injected at the primary tumour site or in the subareolar plexus, some patients show extra-axillary drainage, either alone or in combination with axillary node drainage. This pattern is best assessed when the radioisotope is injected peritoumorally.

Additionally, Kong et al. reported that internal mammary node drainage detected on preoperative lymphoscintigraphy was associated with worse distant disease-free survival in early-stage breast cancer patients[113].

C. BREAST CONSERVATION:

Breast conservation therapy (BCT) involves the surgical removal of the primary breast cancer with a margin of normal-appearing tissue, followed by adjuvant radiation therapy and assessment of regional lymph node status[114,115]. The surgical procedure is also referred to as segmental mastectomy, lumpectomy, partial mastectomy, wide local excision, or tylectomy.

For many women with stage I or II breast cancer, BCT is preferred over total mastectomy because it offers equivalent survival rates while preserving the breast[116]. Findings from six prospective randomized trials have confirmed that overall survival and disease-free survival are comparable between BCT and mastectomy. However, three studies reported higher local-regional recurrence rates in patients who underwent BCT, with two studies lacking clear criteria for histologically negative margins.

Benefits of Breast Conservation Therapy:

Beyond oncologic equivalence, BCT offers advantages over mastectomy in terms of:

- Quality of life and aesthetic outcomes
- Preservation of breast shape, skin, and sensation
- Psychological benefits associated with breast preservation.

Current Standard of Care in Breast Conservation:

BCT is now the standard treatment for women with stage 0, I, or II invasive breast cancer.

- For patients with ductal carcinoma in situ (DCIS) → Treatment requires only tumor resection and adjuvant radiation therapy, without the need for regional lymph node assessment.

Surgical Approach to Lumpectomy:

- For tumors in the upper breast, a curvilinear incision is made concentric to the nipple-areola complex.
- For tumors in the lower breast, radial incisions are preferred.
- Skin excision is unnecessary unless the tumor directly invades the overlying skin.

The tumour is removed with a margin of normal-appearing tissue sufficient to ensure cancer-free surgical margins. However, the optimal margin width for BCT remains controversial(Fig.17,18)[117].

Margin Assessment and Pathologic Evaluation:

- A specimen X-ray should be performed to confirm that the lesion has been fully excised with adequate margins.
- The surgeon orients the specimen for the pathologist.
- Additional margins may be removed from the surgical bed if needed to obtain a histologically negative margin.
- Requests for determination of ER, PR, and HER-2 status are communicated to the pathologist for further analysis.

The surgeon is responsible for ensuring complete removal of breast cancer, as achieving clear surgical margins minimizes the risk of local recurrence and improves cure rates. Among the factors influencing local recurrence after breast conservation surgery, the adequacy of surgical margins is the most critical. In contrast, tumour size and the extent of skin excision have less impact on recurrence rates.

Margin Assessment and Re-Excision:

Many North American and European surgeons follow the practice of re-excising when residual cancer is detected within 2 mm of a surgical margin on histopathologic examination. If negative margins cannot be achieved with re-excision, a mastectomy is required.

Sentinel Lymph Node (SLN) Biopsy Timing:

SLN biopsy is performed before the primary breast tumour is removed. When necessary, intraoperative assessment of the sentinel node can be conducted simultaneously with segmental mastectomy.

Oncoplastic Surgery for Breast Conservation:

Oncoplastic surgery may be considered at the time of segmental mastectomy or as a secondary procedure to enhance cosmetic outcomes. These techniques range from:

- Simple reshaping of breast tissue
- Local tissue rearrangement
- Use of pedicled flaps

- Breast reduction techniques

The primary goal of oncoplastic surgery is to achieve the best possible aesthetic result while ensuring complete tumour excision.

Key Factors in Oncoplastic Surgery Candidacy:

When determining whether a patient is suitable for oncoplastic breast surgery, factors to consider include:

- Extent of breast tissue resection needed for negative margins.
- Tumor location within the breast
- Breast size and overall body habitus

Indications for Oncoplastic Techniques:

Oncoplastic approaches are particularly useful when:

1. A significant area of breast skin requires resection to achieve negative margins.
2. A large volume of breast parenchyma is removed, leading to a substantial defect.
3. The tumor is located between the nipple and the inframammary fold, a region often linked to poor cosmetic outcomes.
4. Excision and closure of the breast could result in nipple mispositioning.

By incorporating oncoplastic techniques, surgeons can optimize both oncologic and cosmetic outcomes, ensuring breast preservation with minimal deformity.

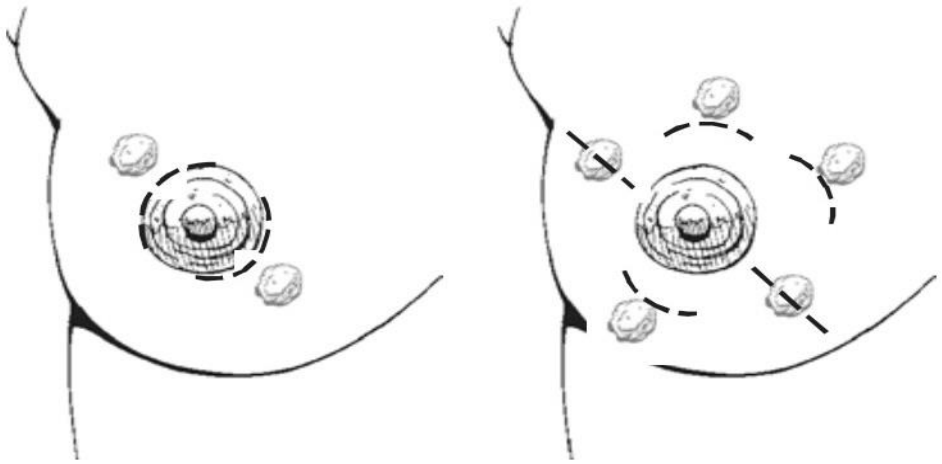


FIG.17 – Placement of incisions for breast-conserving surgery

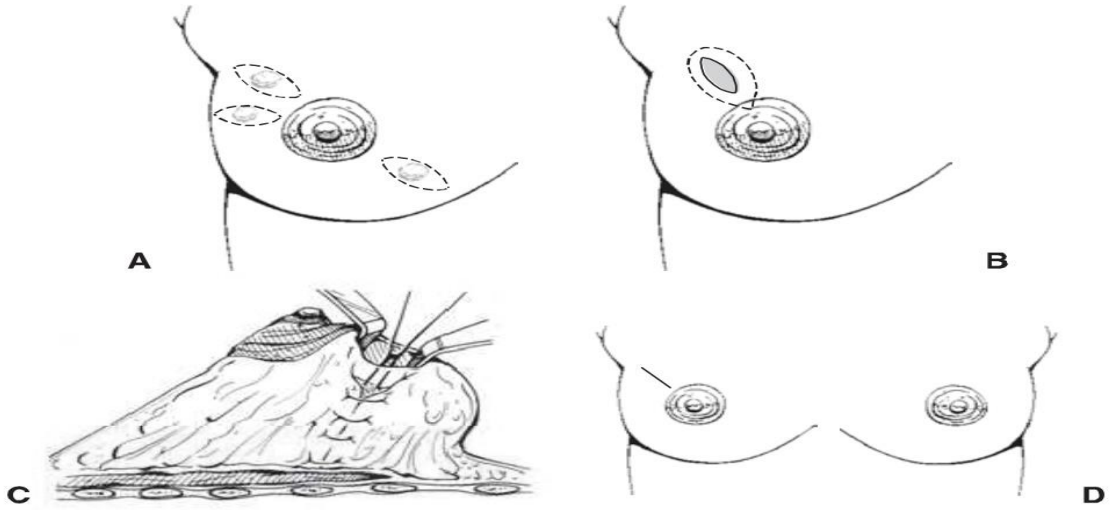


FIG.18 – Details of segmental resection and oncoplastic wound closure

D. MASTECTOMY AND AXILLARY DISSCETION:

A skin-sparing mastectomy involves the removal of all breast tissue, the nipple-areola complex, and any scars from prior biopsy procedures[118,119]. When performed in patients with Tis to T3 breast cancers, it has a recurrence rate of 6% to 8%, which is comparable to standard mastectomy outcomes over the long term.

Types of Mastectomy Procedures:

- Total (Simple) Mastectomy: Removes all breast tissue, the nipple-areola complex, and skin.
- Extended Simple Mastectomy: Removes all breast tissue, the nipple-areola complex, skin, and level I axillary lymph nodes.
- Modified Radical (Patey) Mastectomy: Removes all breast tissue, the nipple-areola complex, skin, and level I, II, and III axillary lymph nodes. The pectoralis minor muscle, which was traditionally divided and removed by Patey, may now be divided and left in situ or, in some cases, completely preserved while still allowing axillary clearance.
- Radical (Halsted) Mastectomy: Removes all breast tissue and skin, the nipple-areola complex, pectoralis major and minor muscles, and the level I, II, and III axillary lymph nodes.

With advancements in systemic chemotherapy, hormonal therapy, and adjuvant radiation therapy, the radical mastectomy is now rarely needed for breast cancer treatment.

Nipple-Areolar Sparing Mastectomy:

Over the past decade, nipple-areolar sparing mastectomy has gained popularity, particularly for risk-reducing mastectomy in high-risk women. For patients with a breast cancer diagnosis, eligibility for this procedure is often based on the following factors:

- Tumor location more than 2–3 cm from the areolar border
- Smaller breast size
- Minimal breast ptosis
- No prior breast surgeries with peri areolar incisions
- Body mass index (BMI) below 40 kg/m^2
- No active tobacco use
- No prior breast irradiation
- No evidence of collagen vascular disease

Considerations for Mastectomy Over Breast Conservation:

Some women opt for mastectomy instead of breast conservation due to biological, economic, or psychosocial reasons. Women less concerned about cosmetic outcomes may prefer mastectomy as it eliminates the need for radiation therapy, reducing costs and treatment duration.

Mastectomy is also the preferred approach in cases where:

- Achieving a reasonable cosmetic outcome with breast conservation is not feasible.
- Extensive microcalcifications are present.
- Large tumors involving the subareolar, and central breast require removal.
- Multicentric breast cancer (multiple tumors in different quadrants of the breast) is diagnosed.

By considering oncologic, aesthetic, and patient-specific factors, surgeons and patients can make informed decisions about the most appropriate surgical approach.

E. MODIFIED RADICAL MASTECTOMY:

A modified radical mastectomy (MRM)(Fig.19) involves the removal of level I, II, and III (apical) axillary lymph nodes while preserving the pectoralis major muscle.

This procedure was first described by David Patey, a surgeon at St Bartholomew's Hospital in London, who performed pectoralis minor muscle removal to facilitate complete dissection of level III axillary lymph nodes while preserving the pectoralis major and the lateral pectoral nerve.

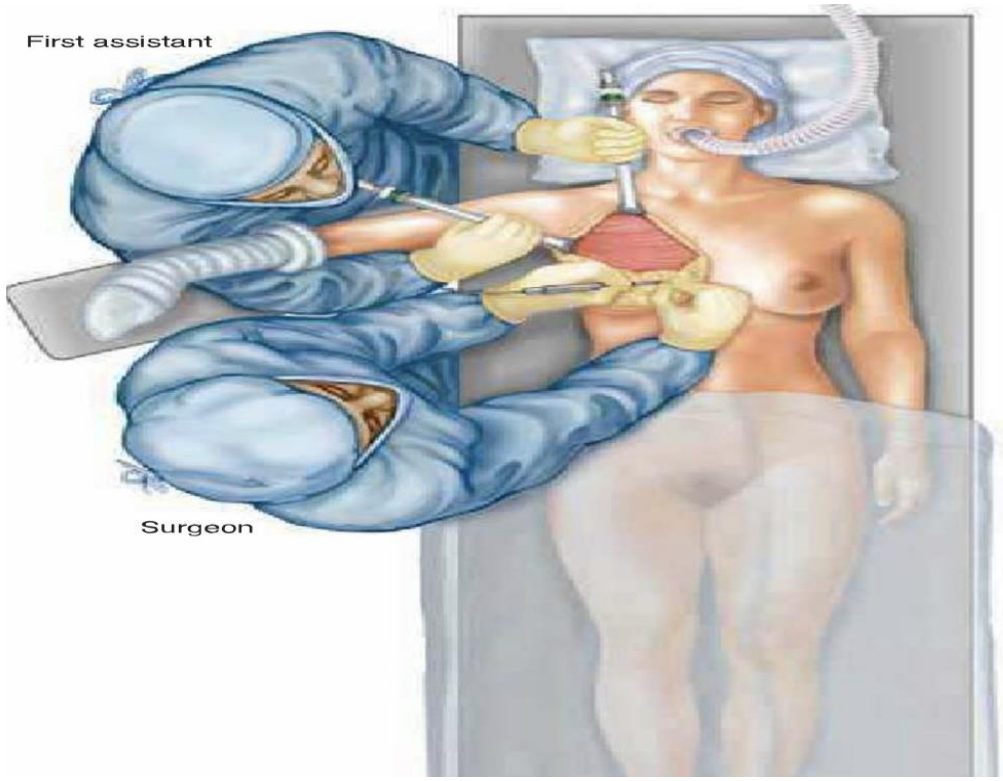


FIG.19 – Position of patient for left modified radical mastectomy

Nerve Preservation in Modified Radical Mastectomy:

MRM allows for the preservation of the medial (anterior thoracic) pectoral nerve, which runs within the lateral neurovascular bundle of the axilla and typically penetrates the pectoralis minor muscle to supply the lateral border of the pectoralis major muscle.

The anatomical landmarks of MRM include:

- `Lateral boundary: Anterior margin of the latissimus dorsi muscle
- Medial boundary: Midline of the sternum
- Superior boundary: Subclavius muscle
- Inferior boundary: 2 to 3 cm below the inframammary fold

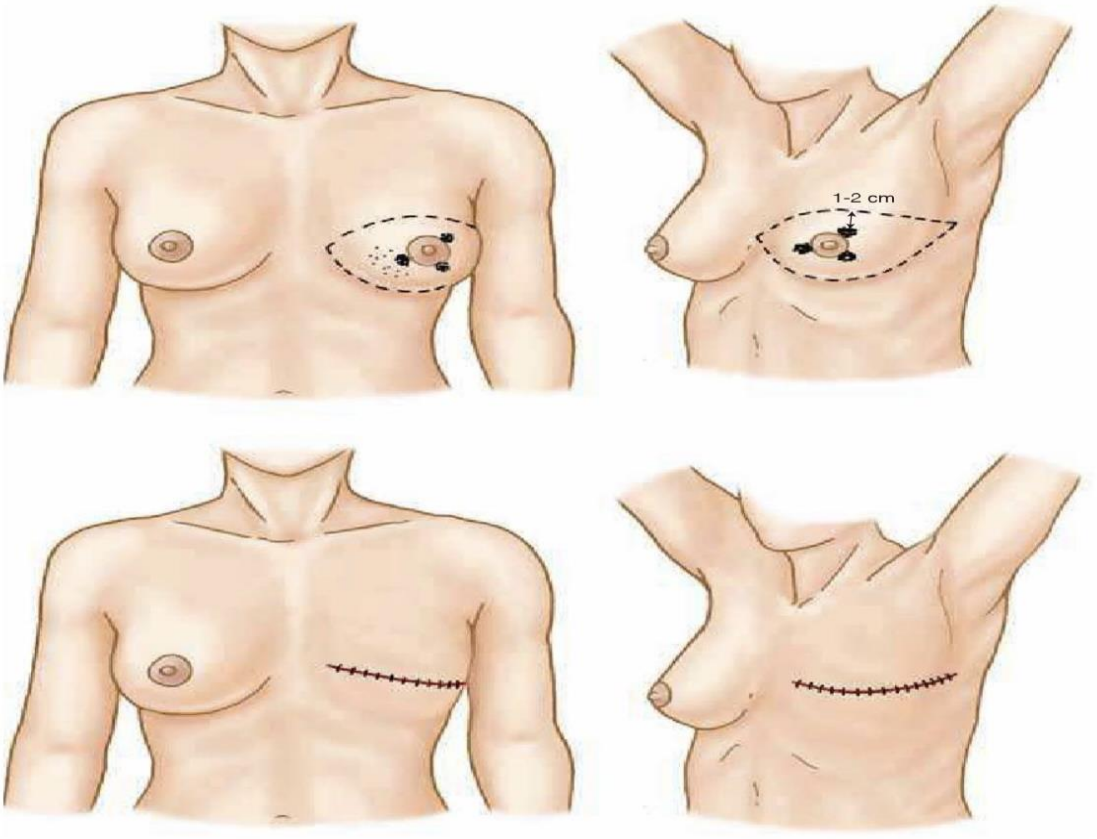


FIG.20 – Classic Stewart elliptical incision for modified radical mastectomy

Skin-Flap Thickness and Breast Tissue Removal:

The thickness of the skin flaps varies depending on body habitus but is ideally 7 to 8 mm, including skin and subcutaneous (Fig.20). Once the skin flaps are fully developed, the fascia of the pectoralis major and the overlying breast tissue are elevated off the underlying musculature, allowing for the complete removal of the breast.

Following the modified radical mastectomy, an axillary lymph node dissection is performed. The lateral boundary of the axillary vein is first identified, and the areolar tissue of the lateral axillary space is elevated as the vein is cleared along its anterior and inferior surfaces.

Dissection of Axillary Lymph Node Levels:

1. Level I (Lateral and Subscapular Lymph Nodes):
    - The areolar tissue at the junction of the axillary vein and the anterior edge of the latissimus dorsi muscle is carefully dissected to remove level I lymph nodes.
    - Thoracodorsal neurovascular bundle preservation is a key consideration during this step.
2. Level II (Central Axillary Lymph Nodes):
    - The dissection continues medially to clear the central axillary lymph nodes.
    - The long thoracic nerve (Bell's nerve), which travels along the investing fascia of the serratus anterior muscle, is identified, and meticulously preserved to prevent injury.
    - Damage to this nerve can result in permanent disability, winged scapula, and shoulder weakness, emphasizing the importance of careful dissection.
3. Level III (Apical Axillary Lymph Nodes):
    - Originally, Patey's modified radical mastectomy involved dividing and removing the pectoralis minor muscle to access the apex of the axilla.
    - Currently, many surgeons opt to divide only the tendinous portion of the pectoralis minor muscle near its insertion onto the coracoid process (Fig.21,22), leaving the rest of the muscle intact, while still allowing adequate access to the apex of the axilla.
    - The axillary vein is dissected medially up to the costoclavicular (Halsted's) ligament.

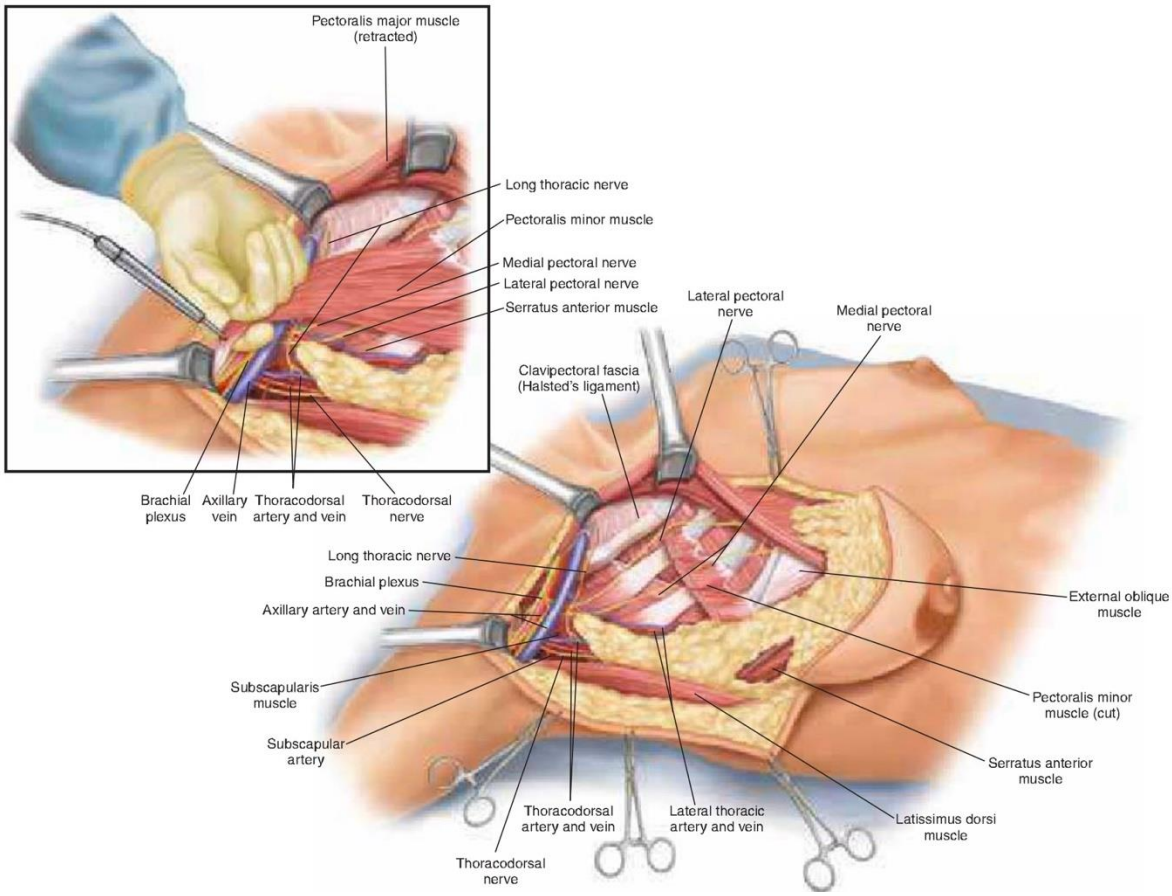


FIG.21 – Modified radical mastectomy with axillary node dissection

Once the breast tissue and axillary lymph nodes have been completely removed, they are sent for pathologic assessment**.** This ensures a comprehensive evaluation of tumor involvement, nodal status, and margin clearance.

Seromas, which form beneath the skin flaps or in the axilla, are the most common complication following mastectomy and axillary lymph node dissection, occurring in up to 30% of cases. The use of closed-system suction drainage helps reduce the risk of seroma formation. Drainage catheters are typically left in place until the daily drainage volume decreases to less than 30 mL.

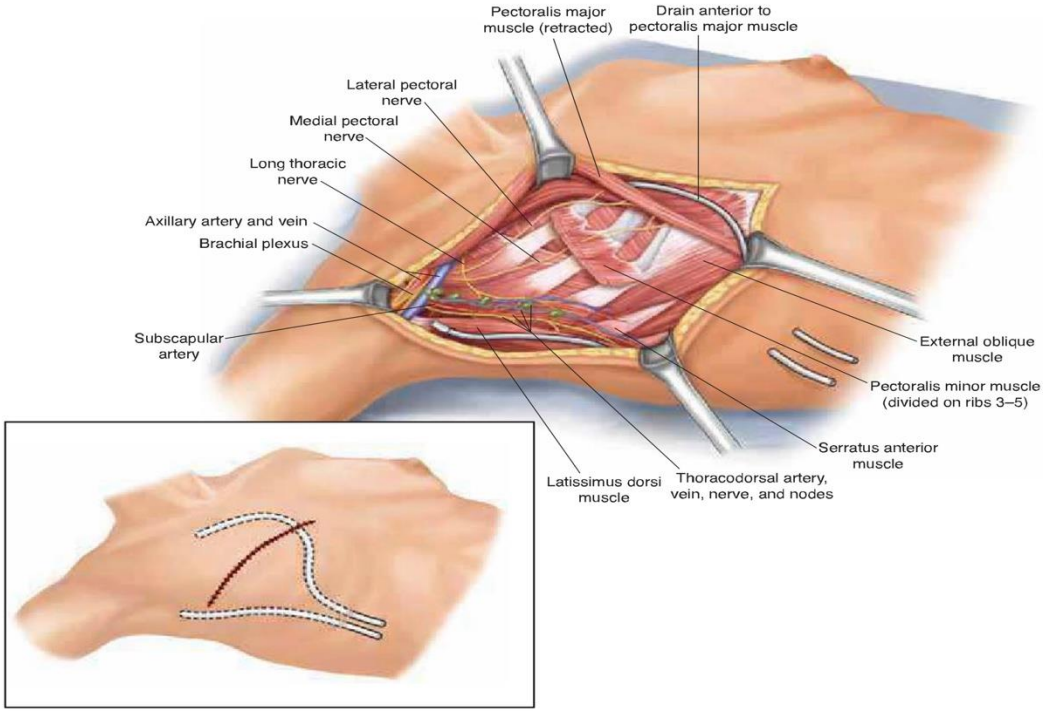


FIG.22 - Patey axillary dissection variant of modified radical mastectomy

Postoperative Complications and Management:

- Wound Infections:
  - Uncommon after mastectomy but usually result from skin-flap necrosis.
  - Management includes:
    - Wound cultures for aerobic and anaerobic bacteria.
    - Debridement of necrotic tissue.
    - Antibiotic therapy based on culture results.
- Postoperative Haemorrhage:
  - Moderate to severe hemorrhage is rare but requires early wound exploration to:
    - Identify and control the bleeding source.
    - Re-establish closed-system suction drainage.
- Lymphedema:
  - The risk of functionally significant lymphedema after a modified radical mastectomy is approximately 20%, but it increases to 50%-60% when postoperative radiation therapy is given.
  - Predisposing factors include:
    - Extensive axillary lymph node dissection
    - Postoperative radiation therapy

- Pathologic lymph node involvement
- Obesity

Lymphedema Prevention and Management:

- Early referral to physical therapy is recommended at the first signs of lymphedema to prevent progression.
- Management strategies include:
  - Individually fitted compressive sleeves
  - Complex decongestive therapy to improve lymphatic drainage and reduce swelling.

By implementing proactive measures and early interventions, the risk and severity of complications following mastectomy and axillary lymph node dissection can be minimized.

F. RECONSTRUCTION OF BREAST AND CHEST WALL:

Goals of Reconstructive Surgery After Mastectomy:

The primary objectives of reconstructive surgery following mastectomy for breast cancer are:

1. Wound closure
2. Breast reconstruction, which can be performed either immediately or delayed[120].

In most cases, simple approximation of the wound edges is sufficient for wound closure. However, if extensive skin and subcutaneous tissue removal is necessary, a pedicled myocutaneous flap from the latissimus dorsi muscle is the preferred method for wound coverage.

While skin grafts can provide functional coverage and tolerate adjuvant radiation therapy, they are not ideal because poor graft adherence may delay radiation therapy delivery.

Breast Reconstruction Timing and Techniques:

- Immediate Reconstruction
  - Can be performed after risk-reducing mastectomy or mastectomy for early-stage breast cancer.
  - Allows for skin-sparing mastectomy, which provides the best cosmetic outcomes.
  - Reconstruction methods include:
    - Expander/implant reconstruction
    - Autologous tissue reconstruction using:

- Pedicled myocutaneous flaps
- Free flaps with microvascular techniques

- Delayed Reconstruction
  - Typically performed for patients with locally advanced breast cancer after completion of adjuvant radiation therapy to ensure local-regional disease control.
  - Radiation therapy after reconstruction is associated with inferior cosmetic outcomes, making delayed reconstruction preferable in these cases.
  - If a skin-sparing approach is desired, a tissue expander may be placed, but this should be discussed with the radiation oncologist and the multidisciplinary treatment team.

Myocutaneous Flaps for Chest Wall Coverage:

When chest wall reconstruction is needed due to a large skin or soft tissue defect, various myocutaneous flaps can be used, with the most common being:

- Latissimus Dorsi Myocutaneous Flap(Fig.23)
  - Composed of a skin paddle based on the latissimus dorsi muscle.
  - Blood supply: Thoracodorsal artery with contributions from the posterior intercostal arteries.

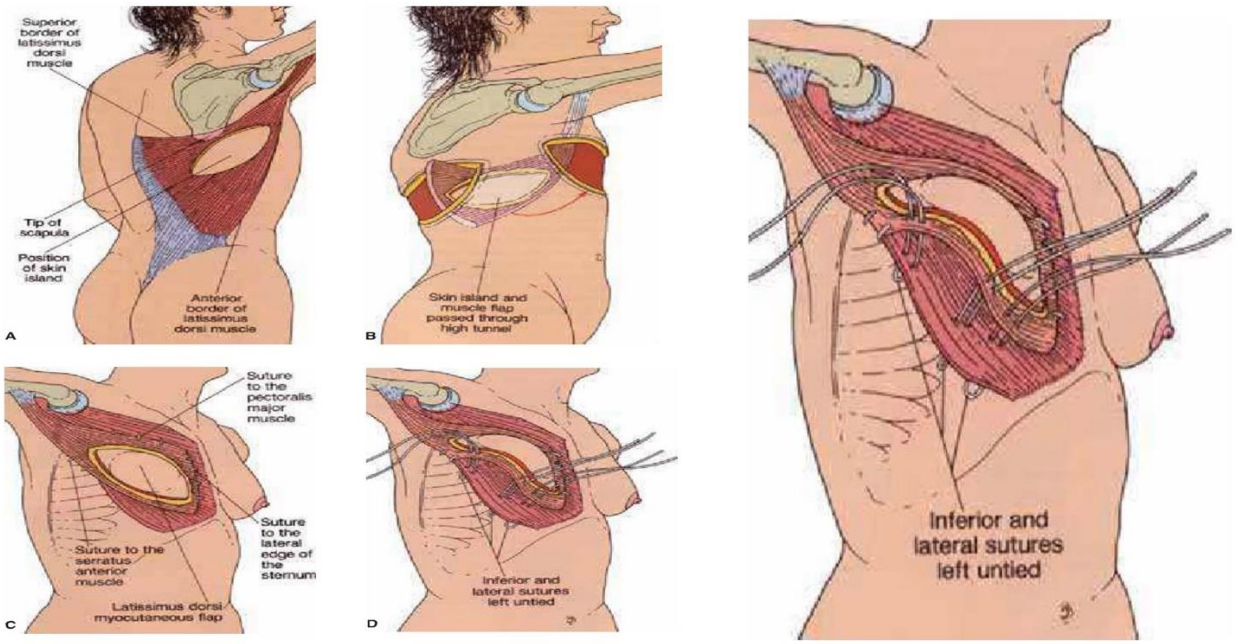


FIG.23 - Latissimus dorsi myocutaneous flap procedure and its anatomical relations

- Transverse Rectus Abdominis Myocutaneous (TRAM) Flap(Fig.24)
    - Consists of a skin paddle based on the rectus abdominis muscle.
    - Blood supply: Deep inferior epigastric artery.
    - A free TRAM flap utilizes microvascular anastomoses to establish blood flow to the flap.

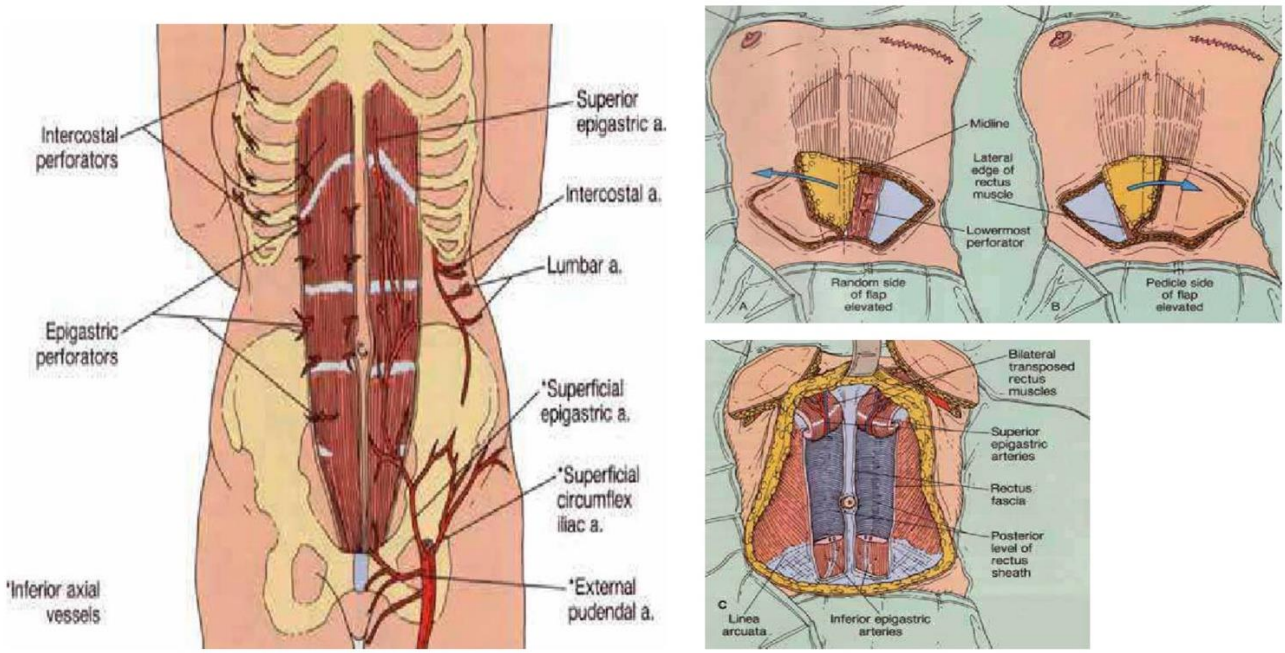


FIG.24 – TRAM flap procedure and the blood vessels involving the procedure

Chest Wall Resection and Reconstruction:

- If the bony chest wall is involved with cancer, resection of affected ribs may be required.
- If only one or two ribs are removed, reconstruction is not usually necessary, as scar tissue provides stabilization.
- If more than two ribs are resected, prosthetic materials are recommended to stabilize the chest wall, followed by soft tissue coverage using either a latissimus dorsi or TRAM flap.

By tailoring the reconstructive approach based on the extent of resection, oncologic needs, and patient factors, optimal functional and cosmetic outcomes can be achieved.

NON-SURGICAL BREAST CANCER THERAPHIES:

1. RADIATION THERAPHY:

Radiation therapy is utilized across all stages of breast cancer, depending on whether the patient has undergone breast-conserving therapy (BCT) or mastectomy[121-126].

- For patients with ductal carcinoma in situ (DCIS) and early-stage breast cancer, adjuvant radiation therapy has already been discussed.
- For mastectomy patients, those with cancer at the surgical margins face a high risk of local recurrence, making postoperative adjuvant radiation to the chest wall necessary.
- Women with metastatic disease involving:
    - Four or more axillary lymph nodes, or
    - One to three lymph nodes (if premenopausal)
    - Are at an increased risk of recurrence and should receive radiation therapy to the chest wall and supraclavicular lymph nodes.

Radiation Therapy for Advanced Local-Regional Breast Cancer (Stage IIIA & IIIB):

Women with stage IIIA or IIIB breast cancer have a high recurrence risk after surgery. Adjuvant radiation therapy is recommended to reduce recurrence. The standard recommendations include:

1. After neoadjuvant chemotherapy and segmental mastectomy (with or without axillary lymph node dissection) →
    - Adjuvant radiation therapy to the breast and supraclavicular lymph nodes.
2. After neoadjuvant chemotherapy and mastectomy (with or without axillary lymph node dissection) →
    - Adjuvant radiation therapy to the chest wall and supraclavicular lymph nodes.
3. After segmental mastectomy or mastectomy with axillary lymph node dissection and adjuvant chemotherapy→
    - Adjuvant radiation therapy to the chest wall and supraclavicular lymph nodes.

Partial Breast Irradiation (APBI) for Breast-Conserving Surgery:

Accelerated Partial Breast Irradiation (APBI) is an alternative approach for select patients undergoing breast-conserving surgery. APBI can be delivered using:

- Brachytherapy
- External beam radiation therapy (three-dimensional conformal radiation therapy)
- Intensity-modulated radiation therapy (IMRT)

While initial results are promising in highly selected low-risk populations, APBI should currently be used only in clinical trials as part of a prospective study to further evaluate its long-term effectiveness.

2. CHEMOTHERAPHY:

Adjuvant Chemotherapy in Early-Stage Breast Cancer:

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis has shown that adjuvant chemotherapy significantly reduces recurrence and mortality in women ≤70 years with stage I, IIA, or IIB breast cancer[127-131]. However, for women ≥70 years, the lack of robust clinical trial data has made it difficult to establish definitive chemotherapy recommendations.

- Adjuvant chemotherapy is not recommended for women with node-negative tumors ≤0.5 cm, as the benefit is minimal.
- For node-negative tumors between 0.6–1.0 cm, patients are categorized into:
    - Low-risk group (chemotherapy generally not needed).
    - High-risk group (with unfavorable prognostic factors requiring chemotherapy).

Unfavorable Prognostic Factors for Chemotherapy Consideration

- Blood vessel or lymphatic invasion
- High nuclear grade
- High histologic grade
- HER-2/neu overexpression
- Negative hormone receptor status

According to NCCN guidelines, chemotherapy is recommended for women with these unfavourable features.

Chemotherapy in Hormone Receptor-Negative and Special-Type Breast Cancers:

- For hormone receptor-negative tumours >1 cm, adjuvant chemotherapy is appropriate.
- For node-negative, hormone receptor-positive T1 tumours, treatment options include:
    - Antiestrogen therapy (with or without chemotherapy).

    - Risk assessment using prognostic factors or the 21-gene recurrence score assay to guide chemotherapy decisions.
- Special-type breast cancers (e.g., tubular, mucinous, medullary) are usually strongly estrogen receptor-positive:
    - For tumors >1 cm, adjuvant antiestrogen therapy is recommended.
    - For node-positive tumors or special-type cancers >3 cm, chemotherapy is appropriate, with hormone receptor-positive cases receiving antiestrogen therapy as well.

Preoperative Chemotherapy for Stage IIIA Breast Cancer:

- For stage IIIA breast cancer, preoperative (neoadjuvant) chemotherapy is recommended, particularly for estrogen receptor-negative disease.
- Preferred regimens include:
    - Anthracycline-based chemotherapy
    - Taxane-containing chemotherapy.
- Surgical options following chemotherapy:
    - Modified radical mastectomy.
    - Segmental mastectomy with axillary dissection, followed by adjuvant radiation therapy.

Neoadjuvant Treatment Considerations for ER-Positive Disease:

- Estrogen receptor-positive tumors generally respond less well to chemotherapy:
    - <10% pathological complete response (pCR) rate overall.
    - <3% pCR rate for lobular cancers.
- Alternative treatment strategies include:
    - Neoadjuvant endocrine therapy followed by local-regional treatment.
    - Primary endocrine therapy (in select cases based on tumor characteristics, comorbidities, and patient preference).

By tailoring adjuvant and neoadjuvant therapies based on tumour biology, nodal status, and patient-specific factors, treatment can be optimized for better outcomes.

3. NEOADJUVANT CHEMOTHERAPHY:

Neoadjuvant Chemotherapy in Breast Cancer: Historical and Clinical Trials:

In the early 1970s, the National Cancer Institute in Milan, Italy, conducted two prospective randomized multimodality clinical trials for women with T3 or T4 breast cancer[132]. The best results were seen when surgery was performed between chemotherapy courses, achieving:

- 82% local-regional control
- 25% 5-year disease-free survival

The NSABP B-18 trial examined the role of neoadjuvant chemotherapy in operable stage II and III breast cancer.188 Women were randomly assigned to one of two treatment strategies:

1. Surgery followed by chemotherapy.
2. Neoadjuvant chemotherapy followed by surgery.

While 5-year disease-free survival rates were similar in both groups, neoadjuvant chemotherapy resulted in:

- Increased lumpectomy rates (by shrinking tumors)
- Decreased incidence of node positivity

These findings suggest that neoadjuvant chemotherapy should be considered for breast cancers initially too large for lumpectomy.

Neoadjuvant vs. Adjuvant Chemotherapy: Meta-Analyses and Local-Regional Recurrence (LRR):

Several prospective clinical trials and two meta-analyses have found that neoadjuvant chemotherapy is equivalent to adjuvant chemotherapy in terms of overall survival (OS)[133].

However, studies also found that patients receiving neoadjuvant chemotherapy followed only by radiation (without surgery) had higher local-regional recurrence (LRR) rates.

A study by Mittendorf et al., analysing nearly 3,000 breast cancer patients treated with breast-conserving surgery and radiation, found that:

- The risk of LRR was determined by tumor biology and disease stage,

- The timing of chemotherapy (neoadjuvant vs. adjuvant) did not significantly impact LRR rates[134].

These findings highlight the importance of multidisciplinary breast cancer management in achieving the best outcomes.

Benefits of Neoadjuvant Chemotherapy:

Neoadjuvant chemotherapy provides a unique opportunity to assess the tumour's response to treatment in real-time[135.]

- If the tumor remains stable or progresses, switching to a different chemotherapy regimen may be considered.
- However, there is no randomized data proving that changing regimens improves overall outcomes.

Pathologic Complete Response (pCR) and Survival Outcomes:

After neoadjuvant chemotherapy, patients are evaluated for clinical and pathologic response.

- Patients achieving a pathologic complete response (pCR) tend to have significantly improved survival outcomes.
- Patients with only a partial response, stable disease, or tumor progression have poorer survival.[136,137]
- Patients with disease progression during neoadjuvant chemotherapy have the worst prognosis.

Current NCCN Recommendations for Advanced Local-Regional Breast Cancer:

For operable advanced local-regional breast cancer, NCCN guidelines recommend:

1. Neoadjuvant chemotherapy with an anthracycline- or taxane-based regimen (or both)
2. Surgical management with lumpectomy or mastectomy (with axillary lymph node dissection if necessary)
3. Adjuvant radiation therapy

- For HER-2-positive breast cancer, trastuzumab is added to neoadjuvant chemotherapy to improve pCR rates.

- For inoperable stage IIIA and IIIB breast cancer, neoadjuvant chemotherapy is used to reduce tumor burden, allowing for a subsequent modified radical or radical mastectomy, followed by adjuvant radiation therapy.

By individualizing treatment strategies and utilizing neoadjuvant chemotherapy when appropriate, clinicians can maximize tumour response, improve surgical options, and optimize long-term outcomes for breast cancer patients.

Management of the Axilla After Neoadjuvant Chemotherapy:

The optimal approach to axillary management following neoadjuvant chemotherapy has not been definitively established in randomized trials. Standard practice has been to:

1. Perform an axillary lymph node dissection (ALND) after chemotherapy.
2. Perform a sentinel lymph node (SLN) biopsy before chemotherapy to assess nodal status prior to treatment initiation.

Several small single-institution studies, a multicentre study, and a recent meta-analysis have evaluated the use of SLN dissection after neoadjuvant chemotherapy. These studies have demonstrated that SLN biopsy is feasible in this setting.

Contraindications for SLN Dissection After Neoadjuvant Chemotherapy:

Although randomized trials have not directly addressed this issue, most experts consider suspected or confirmed axillary metastases at initial diagnosis a contraindication to SLN dissection after neoadjuvant chemotherapy.

Patients with documented axillary metastases at presentation typically undergo axillary lymph node dissection (ALND) after chemotherapy, rather than relying on SLN biopsy alone.

4. NEOADJUVANT ENDOCRINE THERAPHY:

There is limited randomized data on the use of neoadjuvant endocrine therapy, and local recurrence rates following this approach have not been well-documented. Unlike neoadjuvant chemotherapy, neoadjuvant endocrine therapy has not been established through randomized controlled trials. Historically, it has been most commonly used in elderly women who are considered poor candidates for surgery or cytotoxic chemotherapy.

As clinical experience with neoadjuvant therapies has grown, it has become evident that estrogen receptor (ER)-positive tumours respond less effectively to chemotherapy than ER-negative tumors[138]. In fact, the pathologic complete response (pCR) rate for ER-negative tumours is approximately three times higher than for ER-positive tumours.

Potential Benefits of Neoadjuvant Endocrine Therapy:

Neoadjuvant endocrine therapy has demonstrated the ability to shrink tumours, enabling some women with hormone receptor-positive breast cancer—who would otherwise require mastectomy—to undergo breast-conserving surgery. However, long-term recurrence rates following this approach remain unknown[139].

Defining Adjuvant Therapy Based on Neoadjuvant Response:

By utilizing neoadjuvant chemotherapy or endocrine therapy, clinicians have the opportunity to observe tumour and nodal response in real-time. This could help determine which patients would derive the most benefit from specific adjuvant therapies.

- Adjuvant clinical trials typically use survival as the primary endpoint.
- Neoadjuvant trials, however, often focus on clinical or pathologic response rates.

Given the reported increase in local recurrence rates and the established link between local recurrence and survival(as highlighted by the Early Breast Cancer Trialists' Collaborative Group), surgeons should place greater emphasis on local recurrence as a key endpoint when evaluating neoadjuvant therapies.

Ongoing Clinical Trials and Future Directions:

Several clinical trials are currently comparing neoadjuvant chemotherapy and endocrine therapy regimens. These studies involve pre-treatment and posttreatment biopsy samples, which are being analysed using:

- Genomic profiling
- Proteomic analysis

These approaches aim to establish a more personalized and individualized treatment strategy for breast cancer management in the future.

5. ABLATIVE ENDOCRINE THERAPHY:

Historical Endocrine Therapies for Metastatic Breast Cancer:

In the past, oophorectomy, adrenalectomy, and hypophysectomy were the primary endocrine treatment options for metastatic breast cancer, but these procedures are now rarely performed.

- Oophorectomy was commonly used for premenopausal women.
- Postmenopausal women were treated with high-dose exogenous estrogen therapy for similar cancer recurrences.
- Both approaches resulted in a response rate of approximately 30%.

For patients who initially responded to oophorectomy or estrogen therapy, additional procedures such as adrenalectomy or hypophysectomy were sometimes performed, yielding a 30% response rate in these individuals as well.

Aminoglutethimide as a Medical Alternative to Adrenalectomy:

Aminoglutethimide is a non-surgical alternative that inhibits steroidogenesis by blocking:

1. The enzymatic conversion of cholesterol to γ-5-pregnenolone
2. The conversion of androstenedione to estrogen in peripheral tissues

Side Effects and Adrenal Suppression:

- Transient, dose-dependent side effects include:
    - Ataxia
    - Dizziness
    - Lethargy
- Adrenal suppression occurs with prolonged aminoglutethimide use, necessitating glucocorticoid therapy.
- However, permanent adrenal insufficiency or acute adrenal crises have not been observed.

Comparison with Surgical Approaches:

Since the adrenal glands are the primary source of estrogen production after menopause, aminoglutethimide has been prospectively compared with surgical adrenalectomy and hypophysectomy in postmenopausal women. Studies have shown that it is equally effective as these surgical procedures, making it a preferred medical alternative in modern breast cancer management.

6. ANTI-HER2NEU THERAPHY:

HER-2/neu Testing and Its Role in Breast Cancer Treatment:

Determining HER-2/neu expression or gene amplification is now recommended for all newly diagnosed breast cancer patients[140-143]. This assessment helps guide the selection of adjuvant chemotherapy for both node-negative and node-positive patients.

- HER-2-positive patients tend to have better outcomes when treated with anthracycline-based adjuvant chemotherapy regimens.
- Adding trastuzumab to paclitaxel significantly benefits HER-2-positive tumors.
- However, concurrent use of trastuzumab and anthracycline-based chemotherapy may lead to cardiotoxicity and should be avoided.

New HER-2-Targeted Therapies for Metastatic Breast Cancer:

Several new agents have been approved for treating HER-2-positive metastatic breast cancer.

- Lapatinib: A dual tyrosine kinase inhibitor that targets both HER-2 and EGFR, offering another treatment option for HER-2-positive patients.

BREAST CANCER AND CHRONIC INFLAMMTION:[144]

Chronic Inflammatory Changes Associated with Normal Breast Tissue

Normal breast tissue is a complex structure composed of multiple cell types, each with the potential to promote or inhibit chronic inflammation. These cell types include innate and adaptive immune cells (NK cells, CD4+ and CD8+ T cells, γδ T cells, macrophages, dendritic cells), adipocytes, fibroblasts, epithelial cells and the microbiome. Each of these cells may play a role in the inflammatory process. In addition, these cells are also in close proximity to regional draining lymph nodes (axillary, internal mammary) where dendritic cells from normal breast tissue may activate, for example, CD4+ cells to generate Th1, Th2, and Th17 cells, which can further influence inflammatory events. Normal breast tissue thus appears to provide the environment for chronic inflammatory changes to influence the development of breast cancer.

Evidence of Inflammation Associated with Breast Cancer Risk

There is evidence, both indirect and direct, that chronic inflammatory changes are associated with an increased risk for breast cancer in women. (A) Indirect studies include those demonstrating inflammatory changes which are reflected in plasma biomarkers such as C-reactive protein (CRP), and studies examining the effect of anti-inflammatory agents such as aspirin on risk for breast cancer. CRP is an acute phase protein considered to be a classic marker for inflammation. A meta-analysis demonstrated that elevated plasma CRP levels were associated with an increased risk for breast cancer (OR, 1.22), with the association strongest in Asian women (OR, 1.57). Among premenopausal women, high TNF-α was associated with significantly increased risk, and high leptin with reduced risk. Additional systemic evidence of chronic inflammatory changes associated with breast cancer is provided by studies of the anti-inflammatory agent aspirin (ASA). When taken regularly, ASA has been shown to reduce the risk for breast cancer in women. The proinflammatory gene COX-2, a key driver of chronic inflammation, is induced by a variety of inflammatory stimuli, and its expression results in synthesis of prostaglandins with subsequent induction of the inflammatory response. Collagen deposition in the microenvironment of breast cancer is also significantly associated with high stromal expression of COX-2 and CD163 macrophages. The COX-2 gene and immunoreactive proteins have also been shown to be highly expressed and elevated in adipose tissue (AT) under morbid obesity conditions, another important risk factor for breast cancer. Together, these findings provide evidence for the association of chronic inflammation in women and the risk for breast cancer.

Immune Cells and Inflammatory Cell Infiltrates in Normal Breast Tissue

Normal breast tissue contains multiple cell types including innate (dendritic cells, macrophages, NK cells) and adaptive (CD4+, CD8+, B cells) immune cells, adipocytes and fibroblasts.

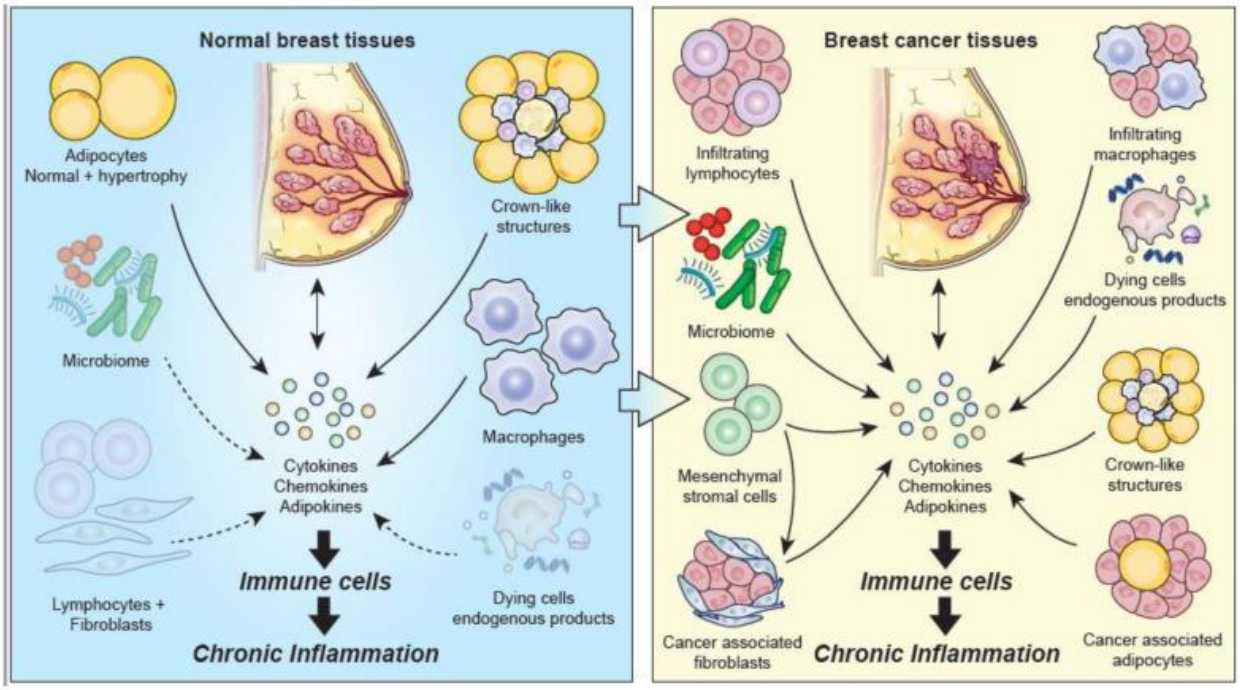


Fig 25: Chronic inflammatory processes in normal breast tissue and breast cancer tissue.

Immune cells are present in breast tissue but do not appear to be infiltrative on the order of inflammatory lymphocyte or macrophage infiltrates such as are seen in breast cancer. Inflammatory Changes of Adipose Tissue Associated with Maintaining Homeostasis and with Breast Cancer Risk. Adipose tissue is a complex structure composed of preadipocytes, adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes. White adipose tissue (WAT) is the predominant form in adults and, under normal conditions, serves to maintain homeostasis through secretion of multiple cytokines, adipokines and growth factors, which regulate a wide range of processes including immunity, angiogenesis, glucose and lipid metabolism, fibrinolysis, and body weight homeostasis.

These events may include proinflammatory changes involved in proper extracellular matrix remodelling and angiogenesis, two processes known to facilitate adipogenesis in vivo. Adipose tissue inflammation under these conditions is considered an adaptive response that enables safe storage of excess nutrients and contributes to a visceral depot barrier that effectively filters gut derived endotoxins. Adipose tissue in the healthy individual also contains several anti-inflammatory mechanisms and adipokines, including adiponectin, C1q/TNF-related proteins

(CTRPs), omentin, and secreted frizzled-related protein 5 (SFRP5). Adiponectin, for example, abrogates LPS-stimulated TNF production by macrophages, inhibits Toll-like receptor (TLR)-mediated NF-κB activation in macrophages, and stimulates the production of the anti-inflammatory cytokine IL-10 by human macrophages. Macrophages in lean adipose tissue are primarily M2 macrophages involved in downregulating inflammation and initiating wound repair through the release of anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and TGFβ. Adipose tissue can also represent an important source of chronic inflammatory changes associated with increased risk for breast cancer, and these changes may occur in lean as well as overweight or obese tissue.

Chronic Inflammatory Changes Associated with Breast Cancer

Chronic Inflammatory Cell Infiltrates in Breast Cancer Tissues

Breast cancer contains a prominent chronic inflammatory component consisting of cells of the immune system (lymphocytes, macrophages, dendritic cells, monocytes, neutrophils) as well as cancer-associated adipocytes, crown-like structures of adipocytes, and cancer-associated fibroblasts. Inflammatory cell infiltrates consisting of lymphocytes (CD4+ and CD8+ T cells and B+ cells) and macrophages are a common feature of breast cancer.

Macrophages play an important role in chronic inflammation in breast cancer. Tumor-associated macrophages (TAMs) are among the most common cells in the leucocyte infiltrate and may constitute over 50% of the number of cells within the tumor. Macrophages may be present as the classically activated M1 phenotype or the alternatively activated M2 phenotype; however, there is evidence that macrophages exhibit different phenotypes during different stages of tumor initiation and progression. During early stages of transformation, recently recruited macrophages are exposed to a wide variety of proinflammatory signals derived from the epithelial cells and the surrounding stroma, and often express M1-related factors that have protumorigenic properties, such as IL-1β and IL-6. M1 macrophages exhibit potent microbicidal and tumoricidal activity by releasing proinflammatory cytokines (such as TNF, IL-1, IL-6, IL-12, IL-23), promoting strong proinflammatory Th1 immune responses and exerting antiproliferative and cytotoxic activities, which result from the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS). TNFα has been shown to be increased in breast cancer compared with healthy normal breast tissue. In established, progressive breast cancers, IL-4 and IL-13 derived from Th2 cells elicit alternative M2 activation of TAMs, with production of immunosuppressive factors such as IL-10 and TGF-β that are capable of actively suppressing the antitumor immune response. Most TAMs in the tumor microenvironment are closely related to the M2-like

phenotype. Chemokines, including CC chemokines, are major determinants of macrophage and lymphocyte infiltration in carcinoma of the breast.

Interestingly, several studies have demonstrated an increase in inflammatory infiltrates in the subtype hormone receptor-negative breast cancer, including high lymphocytic infiltrate, plasma cell infiltrate, other inflammatory cell infiltrate and macrophage infiltrate associated with ER neg/PR neg tumors, higher numbers of peri- and paratumoral tumor infiltrating B lymphocytes associated significantly with hormone receptor (ER/PR) negative ($p = 0.008$) and HER2+ status, and high granulin expressing bone marrow cells recruited to breast cancer expression and correlated with the most aggressive triple-negative, basal-like tumor subtype. On the other hand, serum CRP, a marker of chronic inflammation, appears to be independent of tumor subtype, with elevations in receptor-positive as well as receptor-negative tumors.

Potential Contributors to Chronic Inflammation in Breast Cancer

Breast cancer contains a prominent microbiome which is considered dysbiotic and with the potential to influence breast carcinogenesis. Microbiota may trigger inflammation through release of a variety of substances (MAMPS or PAMPS, such as dsRNA, LPS and lipopeptides) which react with pattern recognition receptors (PRRs) on innate immune cells. Engagement of the PRRs on macrophages, for example, activates the macrophage to the M1 subtype, triggering signalling pathways that lead to the release of the inflammatory cytokines TNFα, IL-1, IL-12, IL-23, chemokines and the recruitment and activation of lymphocytes, with the propagation of chronic inflammation. Bacterial antigen activation of CD4+ lymphocytes to Th1, Th2, and Th17 cells was described above. It has recently been shown, for example, that microbially driven TLR5-dependent IL-6 signalling promotes breast cancer malignant progression through tumour-promoting inflammation.

Chronic Inflammation and the Promotion of Metastatic Disease

Breast cancer is clearly a systemic disease, and an important consequence of chronic inflammation in breast cancer is the potential for promotion of metastatic disease. This has been emphasized in several publications discussed above and may be associated with proinflammatory activities of multiple cell types including adipocytes, MSC, and CAFs, or from associated immune cells. A very interesting recent study demonstrated a possible mechanism for the promotion of micro metastases by inflammation. It was shown that the systemic inflammatory and immunosuppressive response to surgery triggers the outgrowth of distant immune-controlled tumours in mouse models of dormancy.

BIOMARKERS FOR BREAST CANCER

Biomarkers that aid in the diagnosis, prognosis, and prediction of breast cancer are essential for timely identification and appropriate control of the disease throughout treatment. Moreover, an increasing percentage of patients are demanding personalized or unique treatments, demanding the development of novel biomarkers for diagnostic and prognostic procedures as well as intact cells, are utilized as biomarkers in the diagnosis of cancer. Biomarkers may be used to assess the biological condition of a disorder, which can then be used to identify the type of the tumor, its progression, or therapy responses, assisting in the control of breast cancer. Because tumor cells are so heterogeneous, a singular biomarker is insufficiently sensitive or precise to effectively diagnose cancer growth and metastasis, hence a combination of biomarkers is preferred.[145]

HAEMATOLOGICAL BIOMARKERS IN BREAST CANCER

Blood parameters, including numbers of white blood cells (WBCs), neutrophils, platelets, lymphocytes, and neutrophil: lymphocyte ratio (NLR), platelet: lymphocyte ratio (PLR), lymphocyte: monocyte ratio (LMR), and hypersensitive CRP, are regarded as reliable indicators of systemic inflammation. The NLR, PLR, and LMR have been proposed as simple and inexpensive independent predictors in many diseases. The NLR has been proven as a prognostic predictor in many types of malignant tumours, including pancreatic cancer, oesophageal cancer, metastatic melanoma, colorectal cancer, diffuse large B-cell lymphoma, and non–small cell lung cancer. In other diseases, elevated NLR has been found to be a marker of poorer outcomes, such as chronic kidney disease, coronary artery disease, appendicitis, systemic lupus erythematosus, and cystic fibrosis PLR and LMR are other indices of systemic inflammation. Studies have demonstrated the prognostic role of PLR and LMR in many diseases, such as breast cancer, laryngeal squamous-cell carcinoma, non–small cell lung cancer, and thoracolumbar kyphotic deformity.[146]

Determinations of haematological indices are used in the assessment of the clinical entities related to the oncology. There are four determinants of the blood platelet used in the clinical practice and they are helpful in the assessment of the pathological conditions. They are platelets count, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT). The neutrophil to lymphocyte ratio (NLR) is a useful marker for the prediction and the prognosis of breast cancer. Red cell distribution width (RDW) is also used in parallel with the PDW in the assessment of breast cancer. In invasive breast cancer, the pre-treatment value of the MPV is significantly higher than post-treatment value and its value is significantly correlated with the primary tumour size and local or distant metastasis, suggesting that MPV is a good prognostic

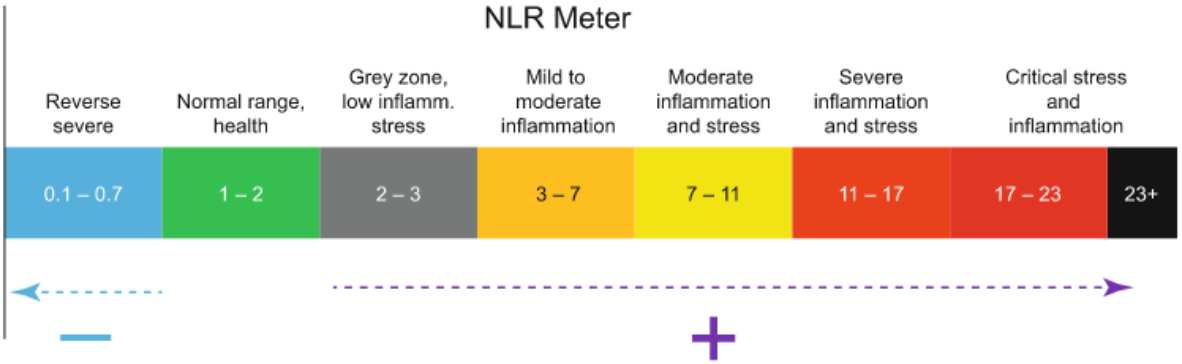
marker. In postmenopausal breast cancer women treated with tamoxifen, an endocrine therapy, the value of MPV was significantly higher than the corresponding value at pre-treatment level (8.97 FL versus 8.2 FL). A lower survival rate of breast cancer is significantly associated with high NLR (> 2.57) and RDW (> 13.45%) and the latter is significantly associated with a high RDW measurement. A high NLR is a negative prognostic marker in breast cancer women and considered as a predictor for overall survival, disease-free survival and recurrence-free survival in those patients. Breast cancer women who had a high NLR and platelet to lymphocyte ratio (PLR) at the pre-treatment state carried a risk of a high mortality rate.[147]

Normal range of physiological values of NLR in adults[148]

In our original paper, we assumed that pathological values of NLR are higher than 5. The priority of the article was clear, namely to postulate that the increase in NLR measures the severity of immune-inflammatory response and in general reflects the tensity of supraphysiological insults, severity of ongoing disease, and pathological state in general (Zahorec, 2001). Simply, high NLR values are associated with severe inflammation, stress, injury, trauma or major surgery, or cancer, and marks the worsening of the prognosis regarding morbidity or mortality. But what are the normal physiological values of NLR? Several studies explored the "normal" values of NLR in an adult healthy population. The most robust is the study by Azab et al (2014) conducted on a population of 9,427 citizens of the New York state. The average value of neutrophil and lymphocyte counts were 4,300/μl and 2,100/μl, respectively, while the mean value of NLR was 2.15 (reference range 1.71–2.28). The lowest average value of NLR was assessed among Afro-American individuals (NLR = 1.76), the mean value of NLR among Hispanic individuals was 2.08, while NLR among Caucasian individuals was 2.24. The risk factors like smoking, obesity and diabetes mellitus were associated with mild elevation in NLR (2.21, 2.34, 2.44).

The concept of NLR has brought about a new and deep insight of the dynamic course of immune-inflammatory response as a reaction between innate and adaptive cell immune systems during various pathological states and illnesses.

Figure 9: NLR Meter



NLR is a novel parameter that is opening a new dimension in clinical medicine, while improving the understanding of the biology of inflammation, pathophysiology of cellular immune response, coupling and antagonism between innate and adaptive immunity and its clinical consequences for health and disease. NLR is a novel marker of cellular immune activation, a valid index of stress and systemic inflammatory response syndrome of various origins. It can be used for stratification and evaluation of the severity of disease in many clinical disciplines. NLR is a cheap, simple and easily available parameter with high sensitivity and lower specificity. It is a dynamic parameter with a quick response to insults; it reflects improvement or deterioration of the clinical status. It can be used as part of a panel with valid biomarkers of infection inflammation. NLR alone or along with other markers may be helpful in the process of decision making and management of various acute and/or chronic diseases.

PLATELET LYMPHOCYTE RATIO and LYMPHOCYTE MONOCYTE RATIO IN BREAST CANCER[149, 150]

The platelet-lymphocyte ratio (PLR) is a novel inflammatory marker, which may be used in many diseases for predicting inflammation and mortality. Recently, inflammatory responses in tumour microenvironment have been shown to be associated with tumour progression and metastases. Cancer-related inflammatory responses and assist cancer cells in the processes of proliferation, infiltration, neovascularization, and dissemination. Some haematological biomarkers are easy available and costless because they are derived from laboratory tests. There parameters include C-reactive protein (CRP), Glasgow Prognostic Score (GPS), platelet- lymphocyte ratio (PLR), Lymphocyte Monocyte Ratio (LMR) and neutrophil-lymphocyte ratio (NLR). PLR is calculated as platelet counts divided by lymphocyte counts. PLR is reported to be correlated with worse outcomes in different malignant tumours such as colorectal cancer, lung cancer, and gastric cancer.

Growing evidence also showed that PLR could provide implications for therapeutic modalities selection and prognosis prediction for breast cancer patients. PLR is an independent predictor of

breast cancer. The clinical prognostic effect of elevated PLR is better than that of NLR and LMR. Considering the ease of measurement and reproducibility of NLR, LMR, and PLR, they have been increasingly studied as an independent factor in the survival of breast cancer patients. However, the importance of these indicators to determine the effect of breast cancer treatment and the associated prognostic value remains controversial.

RED CELL DISTRIBUTION WIDTH

Red cell distribution width (RDW) is a standard parameter of the complete blood count (CBC) and indicates variability in red blood cell (RBC) size; RDW is calculated as the proportional variation in mean corpuscular volume (MCV) (normal range: 11.5% to 14.5%).[151] In the last years, a number of studies have demonstrated that this simple parameter, automatically reported by laboratory blood analysers, may have multiple clinical applications: an increased RDW has a high negative predictive value (NPV) for diagnosing a variety of disorders and may be useful to evaluate short- and long-term prognosis in cardiovascular and thrombotic disorders. Considerable attention has been paid for the observation that RDW is a strong predictor of all-cause, cardiovascular- and cancer-related mortality in the general population.

Despite the fact that cancer is widely accepted to stand as both a cause and a result of chronic inflammation, RDW elevation has scarcely been investigated as a potential biomarker of solid cancer activity, with no studies assessing RDW in breast cancer, with the exception of a single study which demonstrated that RDW was significantly correlated with bone marrow metastatic spread in a sample of breast cancer patients.[152, 153]

MEAN PLATELET VOLUME AND BREAST CANCER

Platelets are the smallest but highly active morphological components of blood. They are produced by the megakaryocytes of the bone marrow and under normal conditions are 157.000–351.000 in women and 135.000–317.000 in men per microliter of blood. The average lifespan of platelets is 5–9 days. They play a major role in the coagulation process and also participate in fibrosis, normal haemostasis, and other pathophysiological processes. Platelets accumulate at the site of damage, and changes in their morphology are observed upon their activation with inflammatory markers and several agonists such as Platelet-Activating Factor (PAF) and Adenosine Diphosphate (ADP) in vitro and ex vivo.

The number of platelets is determined by the balance between the rate of production and consumption and genetic factors. Platelets differ in functional activity and size, and the function of platelets is related to their size. New and more active platelets are larger than old ones. In other words, larger platelets may be younger and more metabolically and enzymatically active than smaller ones, they aggregate more easily and could be more easily stimulated to release chemical mediators. This suggests that platelet volume reflects platelet activation. Activated platelets play an important role during the formation and development of clots. They are active in systemic inflammation and have a higher prothrombotic potential in health and disease. Tumour cells secrete cytokines that contribute to a prothrombotic microenvironment, which includes platelet activation. By secreting proinflammatory and growth factors, platelets play an important role in cancer progression and metastasis, since inflammation is a critical component of tumour progression.

Complicated interactions between platelets and cancer cells lead to tumour growth, neoangiogenesis, tumour cell dissemination, the release of adhesion molecules, and growth factors, all of which provide basic ingredients for tumour growth and metastasis. Mean Platelet Volume (MPV) is one of the key platelet parameters, along with platelet count (PLT) and Platelet Distribution Width (PDW). MPV is a non-invasive, low-cost parameter, easily assessed and readily available in clinical practice, which shows the average size of platelets in the bloodstream and reflects their production rate and their degree of stimulation. As a marker of platelet activation, MPV has attracted attention in recent decades, and many studies have evaluated its association with various malignancies. The in-depth investigation of MPV alterations in cancer can reveal the potential usefulness of this index for cancer diagnosis, treatment response, and prognosis. This new perspective of a routine test may give additional information on the diagnosis and course of the disease, which is important given that several cancers may be asymptomatic until advanced stages.[154]

The role of MPV in inflammatory diseases has been previously reviewed. To our knowledge, there are few reviews on the relationship between MPV and cancer; including studies up to 2015,[155] is a recent review that has evaluated platelet indices with oesophageal squamous cell carcinoma,[156] and it includes a meta-analysis of 2421 patients, which has focused on the relation of MPV to survival in lung cancer patients.

MATERIAL AND METHODS:

- **Study design:** Retrospective and Prospective Observational Study
- **Study area:** Department of General Surgery at B.L.D.E. (Deemed to be University) Shri B.M. Patil Medical College, Hospital, and Research Centre, Vijayapura, Karnataka.
- **Study period:** Research study was conducted from April 2023 to March 2025. Below is the work plan.

Table 1: Work plan of the study with percentage of allocation of study time and duration in months

Work plan	**% of allocation of study time**	**Duration in months**
Understanding the problem, preparation of questionnaire.	5-10%	April 2023 to June 2023
Pilot study, Validation of questionnaire, data collection and manipulation	Upto 80%	July 2023 to August 2024
Analysis and interpretation	5-10%	September 2024 to December 2024
Dissertation write-up and submission	5-10%	January 2025 2025 to March 2025

- **Sample size**: A total of 65 patients with clinically and histopathologically confirmed diagnosis of breast carcinoma were included in the study. The sample size was calculated using the formula

  $n = [z^2 p*q]/d^2$,

  where

  z is the z score (1.96 for 95% confidence level)

  d is the margin of error (0.05), and

  p is the population proportion (0.044, based on previous studies).

  This calculation yielded a minimum required sample size of 65 patients, which was achieved during the study period.

INCLUSION CRITERIA:

- All patients with proven diagnosis of carcinoma breast of all stages through biopsy and HPR reports were included in the study.
- Data is collected through computerized hospital data.

EXCLUSION CRITERIA:

- All patients diagnosed with any chronic inflammatory conditions.
- All patients undergoing neoadjuvant chemotherapy.
- All patients with anaemia.
- All patients with bleeding and platelet disorder.
- All patients on medications which alter coagulation profile and platelet count.

METHODOLOGY:

This study was designed as a mixed retrospective and prospective observational study conducted in the Department of General Surgery at B.L.D.E. (Deemed to be University) Shri B.M. Patil Medical College, Hospital, and Research Centre, Vijayapura, Karnataka. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants in accordance with the ethical principles for medical research involving human subjects.

A comprehensive approach to data collection was employed, incorporating detailed clinical examination, laboratory investigations, and radiological assessments. A pretested structured proforma was used to systematically collect relevant information for each individual patient, ensuring consistency and completeness of data. For each patient, demographic data including age, gender, and relevant medical history were recorded. Clinical parameters such as tumour characteristics, lymph node status, and evidence of metastasis were assessed through thorough physical examination and imaging studies.

Preoperative blood samples were collected from all patients as part of the routine preoperative workup. Complete blood count analysis was performed using an automated haematology analyser, yielding measurements of various haematological parameters including red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), and lymphocyte-to-monocyte ratio (LMR). The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count, while the LMR was derived by dividing the absolute lymphocyte count by the absolute monocyte count. All blood samples were processed according to standardized laboratory protocols to ensure accuracy and reliability of results.

In addition to the haematological parameters, other routine preoperative investigations were conducted, including bleeding and clotting time, urine analysis (sugar, albumin, microscopy), random blood sugar, blood urea, serum creatinine, electrocardiogram, and chest X-ray. Screening for Human Immunodeficiency Virus and Hepatitis B virus was also performed as part of the standard preoperative assessment.

Diagnostic imaging, including ultrasonography and/or computed tomography of the breast, was performed to evaluate tumour characteristics and the extent of disease. Histopathological examination of biopsy specimens was conducted to confirm the diagnosis, determine the histological subtype, and assess hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2) expression. Immunohistochemistry was used for the determination of hormone receptor status and HER2 expression, with results categorized as positive, negative, or equivocal (for HER2).

Tumour staging was performed according to the TNM classification system, which considers the size and extent of the primary tumour (T), involvement of regional lymph nodes (N), and presence of distant metastasis (M). Clinical outcomes, including mortality, recurrence, and metastasis, were documented during the follow-up period, providing a comprehensive assessment of disease progression and patient prognosis.

Statistical Analysis

The data obtained were entered into a Microsoft Excel spreadsheet and analysed using the Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics were presented as mean values and standard deviations for continuous variables, and as counts and percentages for categorical variables. Graphical representations were utilized to enhance the visualization and interpretation of results.

The associations between haematological parameters and various clinicopathological features were evaluated using appropriate statistical tests. Comparisons between two groups (such as ER-positive versus ER-negative) were performed using independent samples t-tests for continuous variables, while comparisons across more than two groups (such as different histopathological subtypes) employed analysis of variance (ANOVA) or the Kruskal-Wallis test, depending on the distribution of data.

The diagnostic and prognostic value of the laboratory parameters in relation to clinicopathological staging and molecular subtypes of breast cancer was assessed using receiver operating characteristic (ROC) curve analysis. This approach allowed for the determination of optimal cut-off values for each haematological parameter, along with their corresponding sensitivity, specificity, and area under the curve (AUC).
Statistical significance was set at a p-value less than 0.05, indicating a confidence level of 95%. All statistical analyses were conducted with attention to methodological rigor to ensure the validity and reliability of the findings.

RESULTS

The present observational study was conducted in the department of General surgery at B.L.D.E Shri B.M. Patil Medical College, Hospital, and Research Centre from April 2021 to March 2025 to corelate the relationship between preoperative haematological markers with clinic pathological staging of breast cancer and to investigate which marker is most useful as predictor of carcinoma. Total of 65 patients were considered for the study.

Following are the results of the study:

Table 1: Distribution of patients according to age

Age (in years)	Frequency	Percentage
20-40	11	16.9%
41-60	35	53.8%
61-80	19	29.2%
Total	**65**	**100%**

Table 1 and graph 1 shows the age distribution of breast cancer patients in the study. The majority of patients (53.8%) were in the middle age group of 41-60 years, comprising 35 patients. The elderly group (61-80 years) represented 29.2% with 19 patients, while the youngest group (20-40 years) made up 16.9% with 11 patients. This suggests that breast cancer was most commonly diagnosed in middle-aged patients in this study population.

Graph 1: Distribution of patients according to age

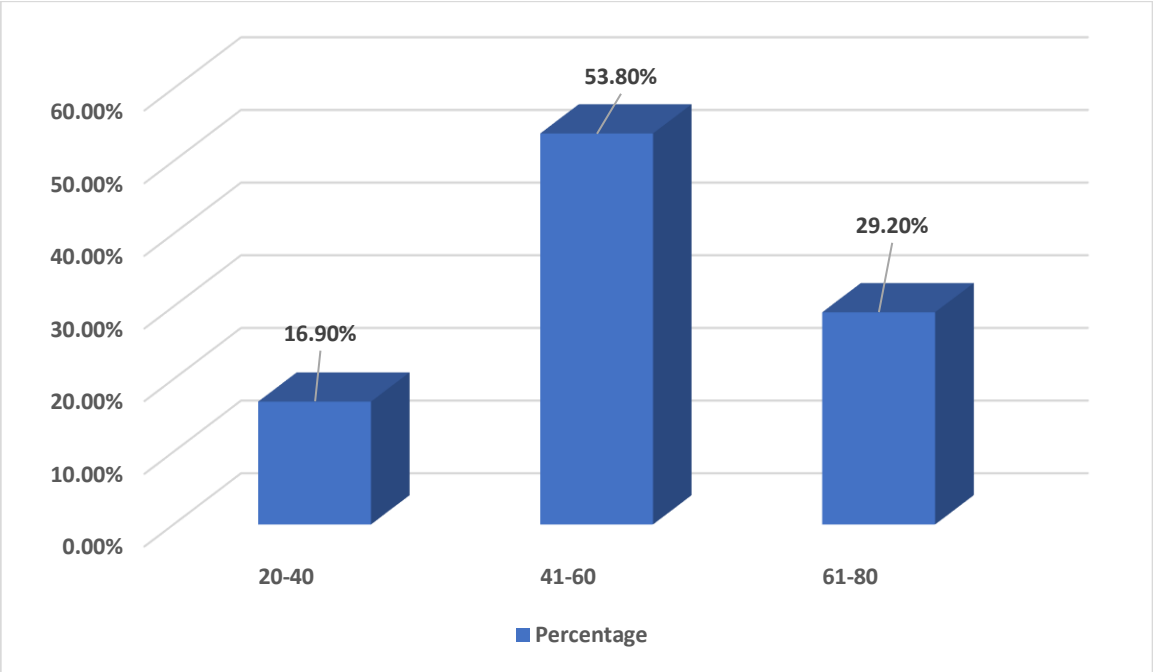


Table 2: Distribution of patients according to gender

Gender	Frequency	Percentage
Female	64	98.5%
Male	1	1.5%
Total	**65**	**100%**

Table 2 and graph 2 presents the gender distribution. The gender distribution shows a stark predominance of female patients, with 64 patients (98.5%) being female and only 1 patient (1.5%) being male. This aligns with the known epidemiology of breast cancer, which predominantly affects women, though men can also develop the disease.

Graph 2: Distribution of patients according to gender

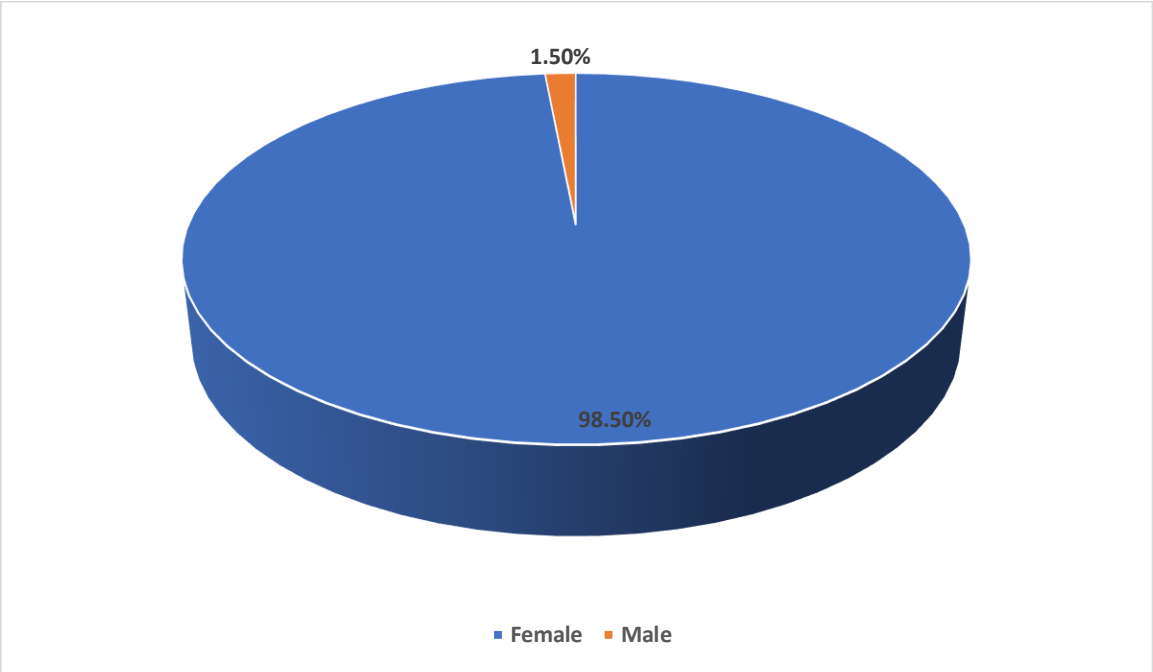


Table 3: Distribution of patients according to laterality

Laterality	Frequency	Percentage
Left	28	43.1%
Right	37	56.9%
Total	**65**	**100%**

Table 3 and graph 3 presents the distribution of breast cancer cases between left and right breasts. There was a slightly higher occurrence in the right breast (56.9%, 37 patients) compared to the left breast (43.1%, 28 patients). While this shows some right-sided predominance, the difference is not dramatically skewed.

Graph 3: Distribution of patients according to laterality

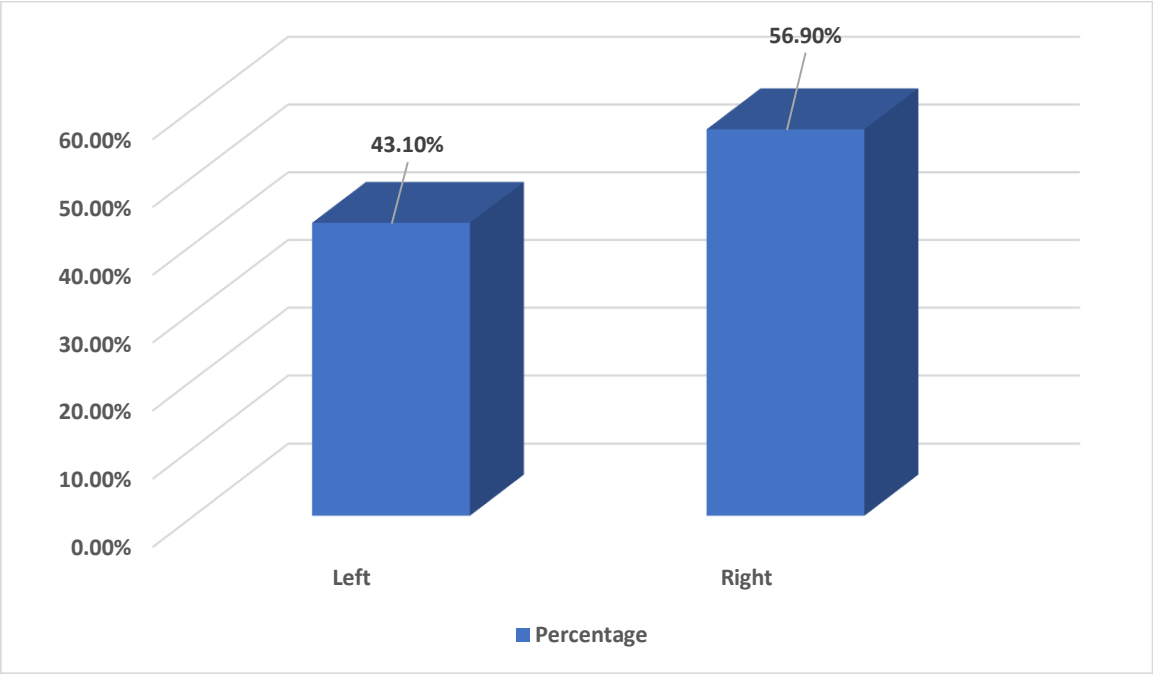


Table 4: Distribution of patients according to haematological parameters

Haematological parameters	RDW	NLR	MPV	LMR
Mean	13.47	3.79	9.91	5.27
SD	1.86	1.79	1.41	2.61
Minimum	9.4	1.46	6.9	1.3
Maximum	18.6	11.7	13.4	13.2

Table 4 and graph 4 displays four key haematological markers: RDW (Red Cell Distribution Width), NLR (Neutrophil-to-Lymphocyte Ratio), MPV (Mean Platelet Volume), and LMR (Lymphocyte-to-Monocyte Ratio). The mean values were: RDW of 13.47 (±1.86), NLR of 3.79 (±1.79), MPV of 9.91 (±1.41), and LMR of 5.27 (±2.61). These parameters show considerable variation as evidenced by their ranges from minimum to maximum values.

Graph 4: Distribution of patients according to haematological parameters

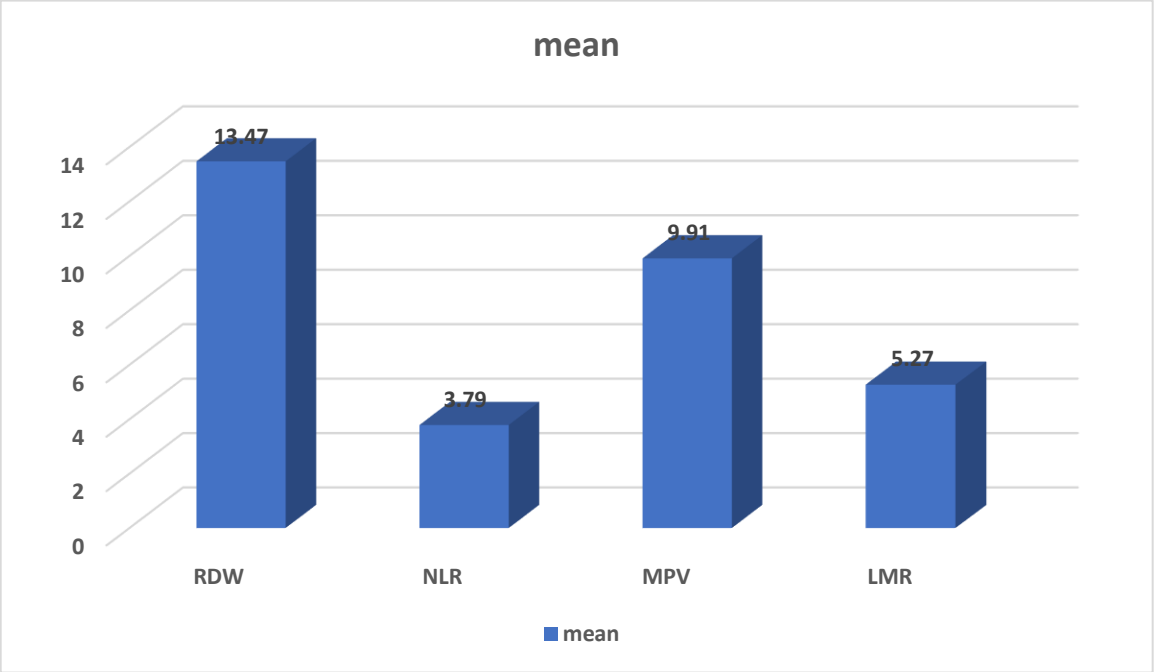


Table 5: Distribution of patients according to tumour markers

Tumour markers		Frequency	Percentage
ER	Negative	30	46.2%
	Positive	35	53.8%
PR	Negative	36	55.4%
	Positive	29	44.6%
HER2NEU	Negative	41	63.1%
	Positive	21	32.3%
	Equivocal	3	4.6%

Table 5 and graph 5 presents the distribution of important breast cancer markers. ER (Estrogen Receptor) was positive in 53.8% of cases, PR (Progesterone Receptor) was positive in 44.6% of cases, and HER2NEU was positive in 32.3% of cases. Notably, 4.6% of cases showed equivocal HER2NEU results.

Graph 5: Distribution of patients according to tumour markers

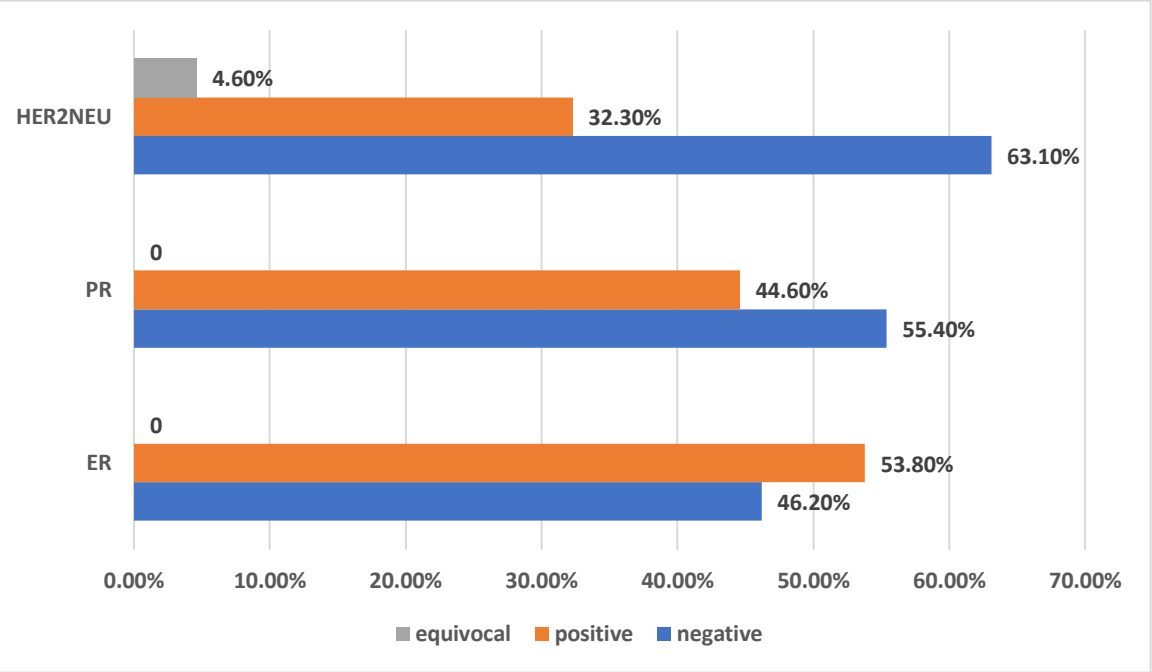


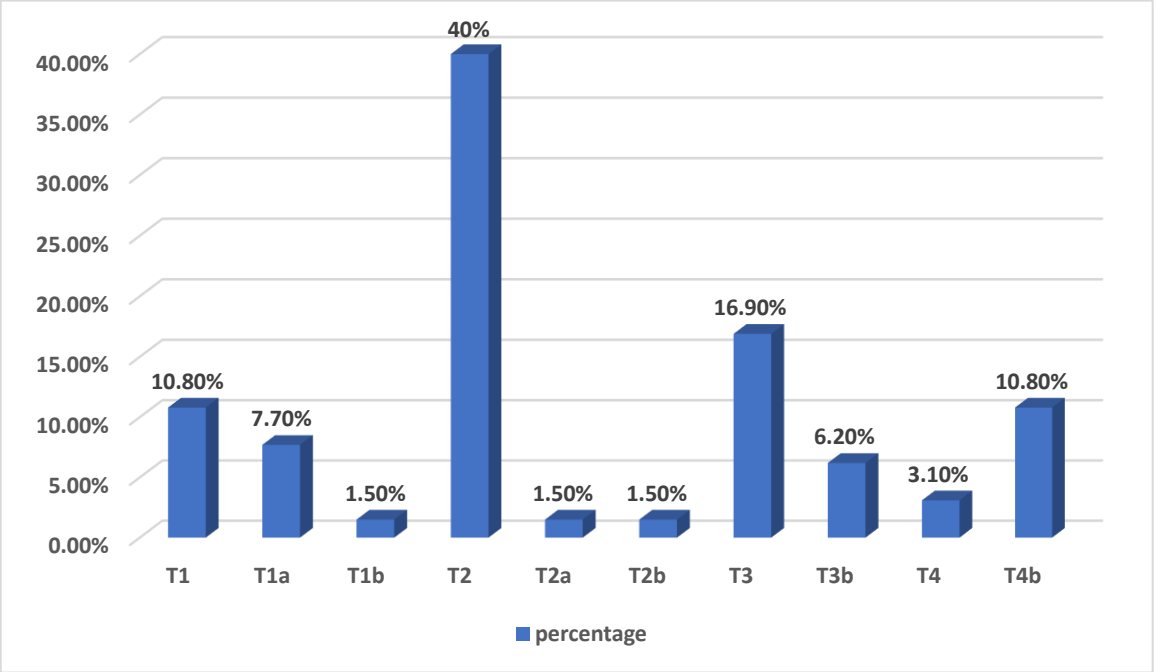
Table 6: Distribution of patients according to TNM staging

TNM staging	Frequency	Percentage
Tumour		
T1	7	10.8%
T1a	5	7.7%
T1b	1	1.5%
T2	26	40%
T2a	1	1.5%
T2b	1	1.5%
T3	11	16.9%
T3b	4	6.2%
T4	2	3.1%
T4b	7	10.8%
Lymph node		

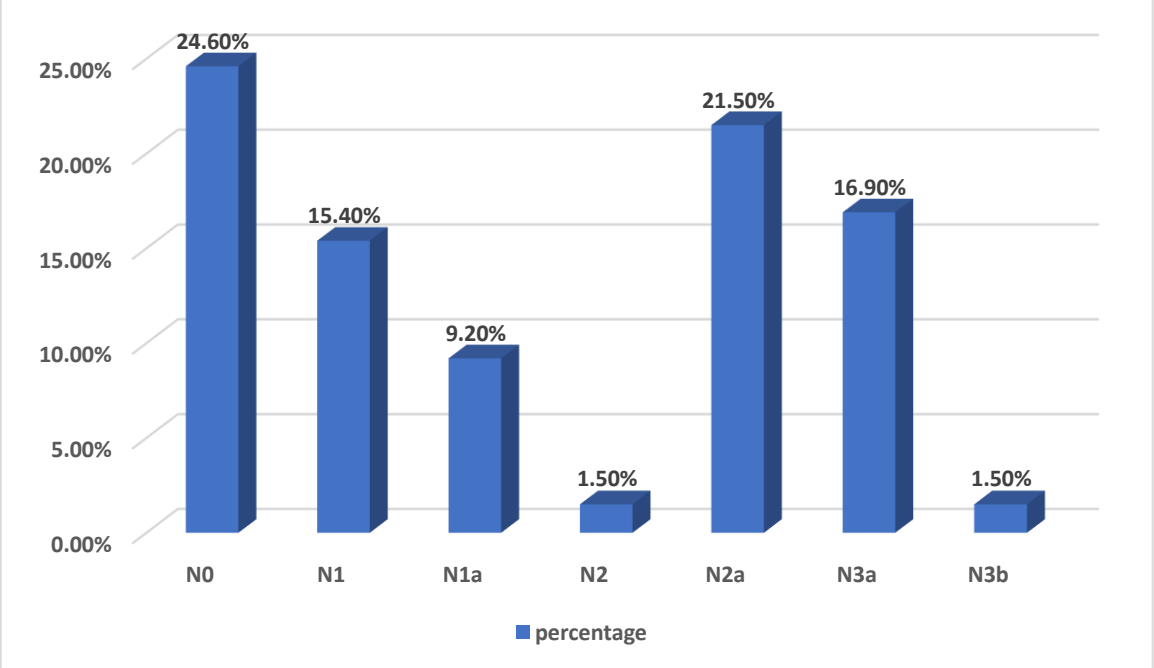
N0	16	24.6%
N1	10	15.4%
N1a	6	9.2%
N2	1	1.5%
N2a	14	21.5%
N3a	11	16.9%
N3b	1	1.5%
Distant metastasis		
M0	59	90.8%
Pathologic (pN)		
pN	1	1.5%
pN0	4	6.2%
pN3a	1	1.5%

This comprehensive table breaks down the tumour staging. For tumour size (T), T2 was most common (40%), followed by T3 (16.9%). In lymph node staging (N), N0 (24.6%) and N2a (21.5%) were most frequent. Regarding distant metastasis (M), the vast majority (90.8%) were M0, indicating no distant metastasis. Pathologic staging (pN) was reported in a small number of cases.

Graph 6 A: Distribution of patients according to Tumour staging



Graph 6 B: Distribution of patients according to lymph node staging



Graph 6 C: Distribution of patients according to pathologic staging

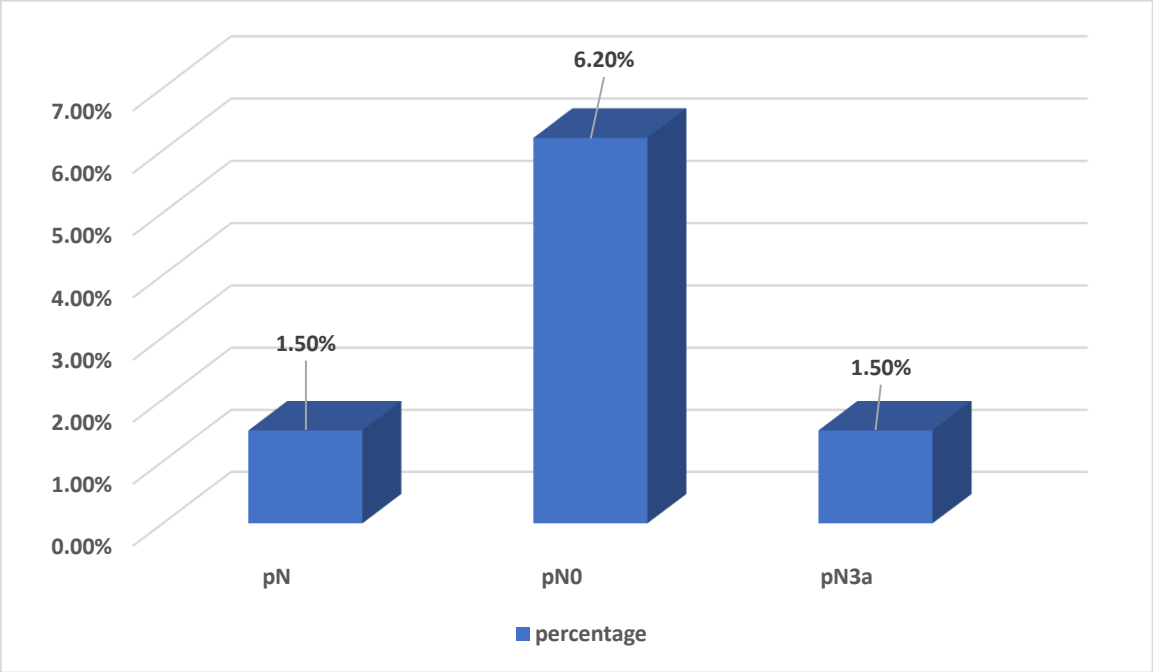


Table 7: Distribution of patients according to histopathological diagnosis

Histopathological diagnosis	Frequency	Percentage
Invasive carcinoma	28	43.1%
Invasive ductal carcinoma	35	53.8%
Invasive lobular carcinoma	1	1.5%
Papillary carcinoma	1	1.5%
Total	**65**	**100%**

Table 7 and graph 7 presents a comprehensive breakdown of the histopathological diagnoses in the study population. Invasive ductal carcinoma predominates, accounting for 53.8% (35 patients) of the total cases, making it the most common histological subtype. Invasive carcinoma follows as the second most frequent diagnosis, representing 43.1% (28 patients) of the cases. The remaining diagnoses are rare in this cohort, with invasive lobular carcinoma and papillary carcinoma each representing a minimal 1.5% (1 patient) of the total sample.

Graph 7: Distribution of patients according to histopathological diagnosis

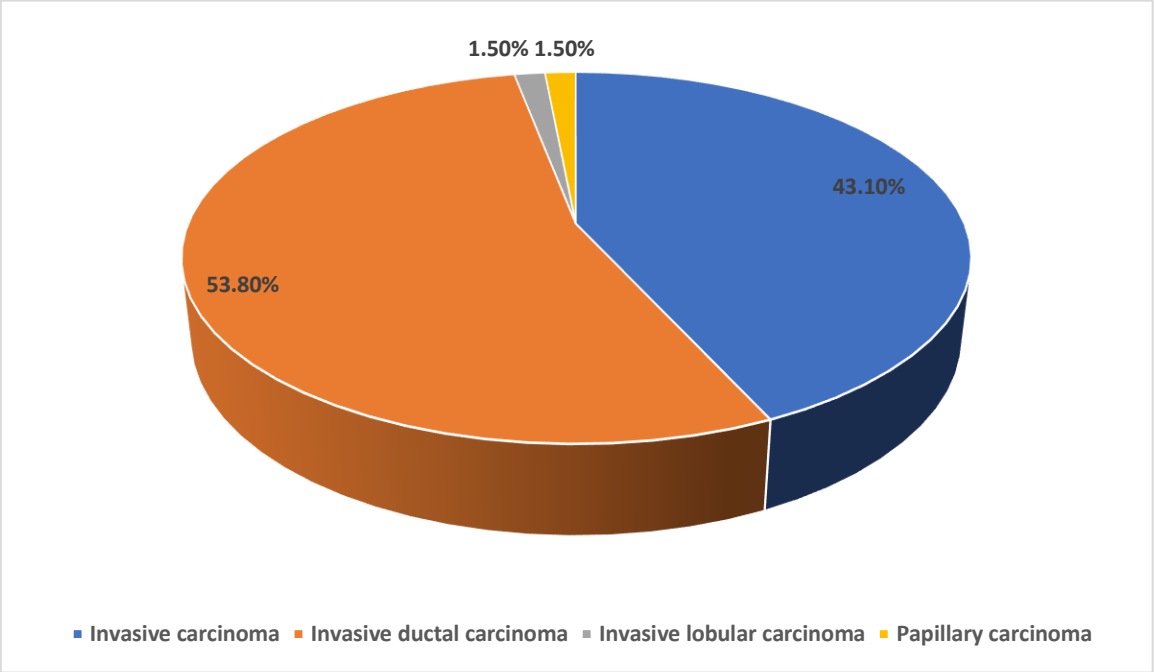


Table 8: Distribution of patients according to different variables

Variables	Frequency	Percentage
Mortality	20	30.8%
Recurrence	6	9.2%
Metastases	7	10.8%

Table 8 and graph 8 provides a critical overview of key clinical outcomes in the study population. Mortality emerges as the most significant outcome, with 20 patients (30.8%) experiencing fatal progression. Metastases were observed in 7 patients (10.8%), indicating the spread of cancer to other body parts. Recurrence was noted in 6 patients (9.2%), suggesting a subset of patients experienced cancer return after initial treatment.

Graph 8: Distribution of patients according to different variables

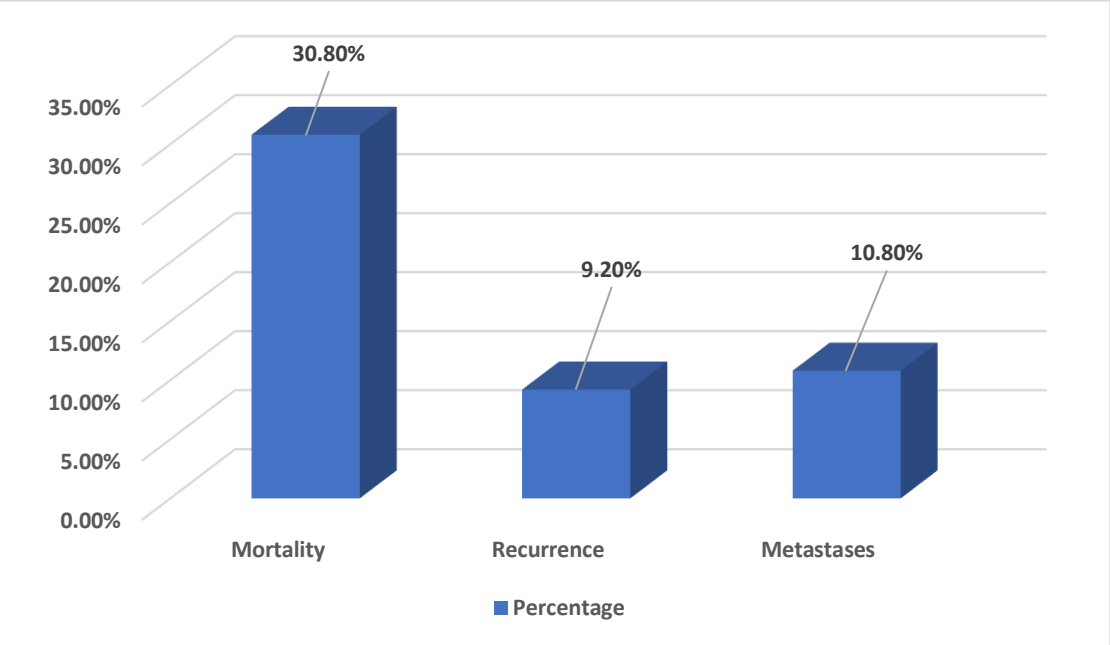


Table 9: Association of histopathological diagnosis with tumour staging

Tumour staging	Histopathological diagnosis				p-value
	Invasive carcinoma	Invasive ductal carcinoma	Invasive lobular carcinoma	Papillary carcinoma	
T1	5 (17.9%)	2 (5.7%)	0	0	0.98
T1a	2 (7.1%)	3 (8.6%)	0	0	
T1b	1 (3.6%)	0	0	0	
T2	9 (32.1%)	16 (45.7%)	0	1 (100%)	
T2a	1 (3.6%)	0	0	0	
T2b	0	1 (2.9%)	0	0	
T3	5 (17.9%)	5 (14.3%)	1 (100%)	0	
T3b	1 (3.6%)	3 (8.6%)	0	0	
T4	1 (3.6%)	1 (2.9%)	0	0	
T4b	3 (10.7%)	4 (11.4%)	0	0	
Total	**28 (100%)**	**35 (100%)**	**1 (100%)**	**1 (100%)**	

Table 9 and graph 9 correlates histopathological diagnosis with tumour staging. Invasive ductal carcinoma and invasive carcinoma were the predominant types, with T2 being the most common stage in both types. The p-value of 0.98 suggests no significant association between histological type and tumour stage.

Graph 9: Association of histopathological diagnosis with tumour staging

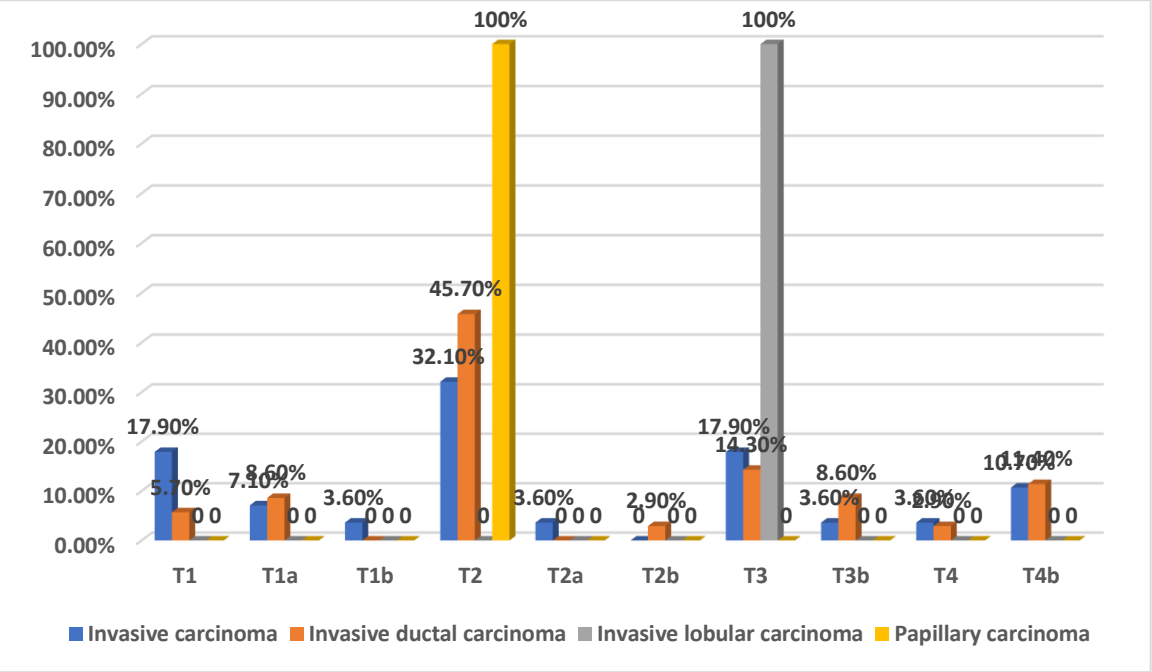


Table 10: Association of histopathological diagnosis with lymph node staging

Lymph node staging	Histopathological diagnosis				p-value
	Invasive carcinoma	**Invasive ductal carcinoma**	**Invasive lobular carcinoma**	**Papillary carcinoma**	
N0	7 (25%)	8 (22.9%)	0	1 (100%)	0.53
N1	4 (14.3%)	6 (17.1%)	0	0	
N1a	4 (14.3%)	2 (5.7%)	0	0	
N2	0	1 (2.9%)	0	0	
N2a	4 (14.3%)	9 (25.7%)	1 (100%)	0	
N3a	3 (10.7%)	8 (22.9%)	0	0	
N3b	0	1 (2.9%)	0	0	
Total	**28 (100%)**	**35 (100%)**	**1 (100%)**	**1 (100%)**	

Table 10 and graph 10 shows the relationship between histopathological diagnosis and lymph node involvement. The distribution varies across different N stages, with no statistically significant association (p=0.53) between histological type and lymph node status.

Graph 10: Association of histopathological diagnosis with lymph node staging

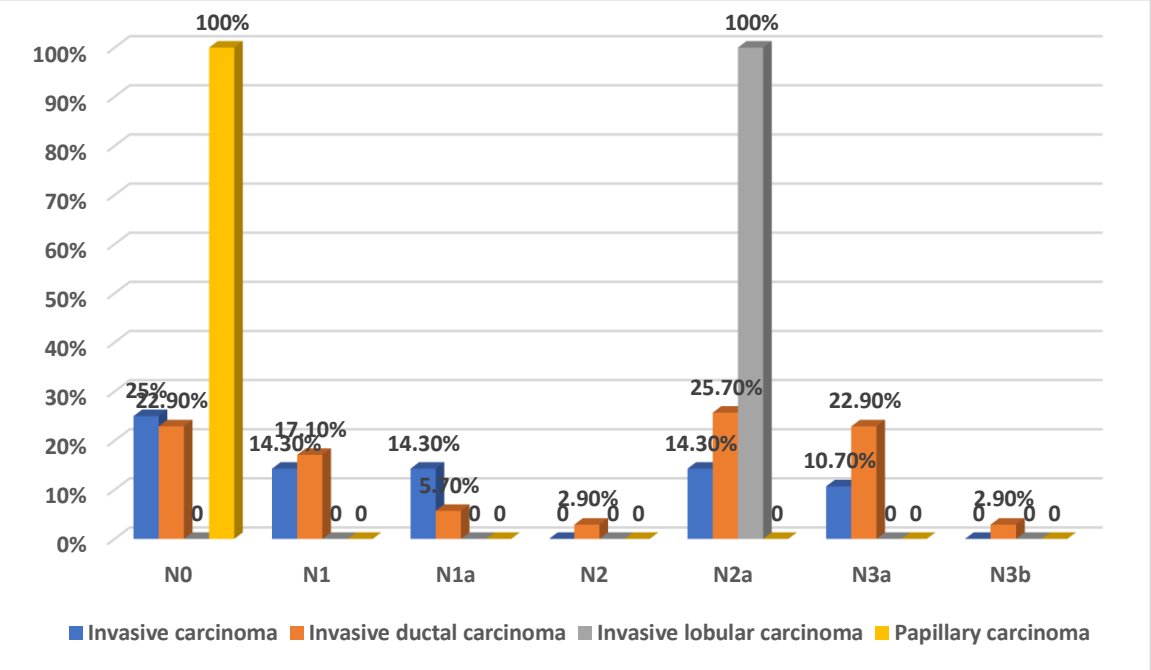


Table 11: Association of histopathological diagnosis with pathologic staging

Pathologic staging	Histopathological diagnosis				p-value
	Invasive carcinoma	Invasive ductal carcinoma	Invasive lobular carcinoma	Papillary carcinoma	
pN	1 (3.6%)	0	0	0	0.46
pN0	4 (14.3%)	0	0	0	
pN3a	1 (3.6%)	0	0	0	

Table 11 and graph 11 examines the correlation between histopathological diagnosis and pathologic staging. Only invasive carcinoma showed pathologic staging results, but with no significant association (p=0.46).

Graph 11: Association of histopathological diagnosis with pathologic staging

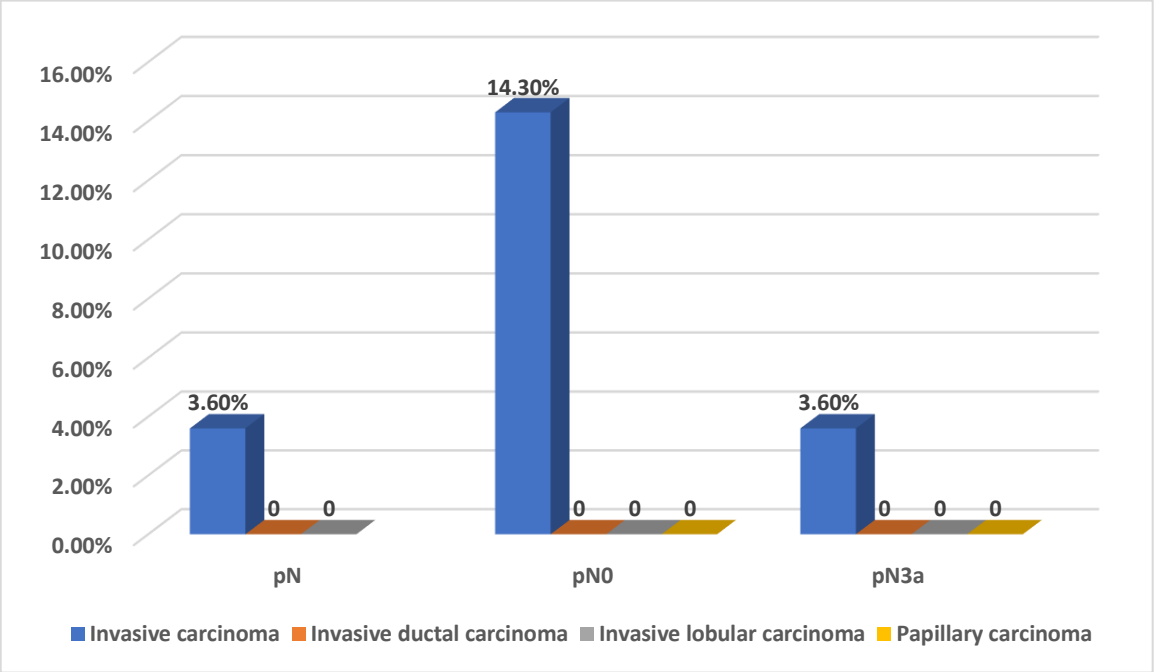


Table 12: Association of histopathological diagnosis with haematological parameters

Haematological parameters	Histopathological diagnosis				p-value
	Invasive carcinoma	Invasive ductal carcinoma	Invasive lobular carcinoma	Papillary carcinoma	
RDW	13.4±1.7	13.5±2.01	14.8±0	11.6±0	0.67
NLR	3.77±1.51	3.71±1.97	7.2±0	3.6±0	0.303
MPV	9.95±1.44	9.85±1.42	11.4±0	9.9±0	0.76
LMR	5.7±2.6	4.91±2.6	5.6±0	5.3±0	0.701

Table 12 and graph 12 correlates histopathological types with haematological markers. There were no statistically significant differences in RDW, NLR, MPV, or LMR values across different histological types (all p-values >0.05), suggesting that these haematological parameters don't vary significantly based on the histological type of breast cancer.

Graph 12: Association of histopathological diagnosis with haematological parameters

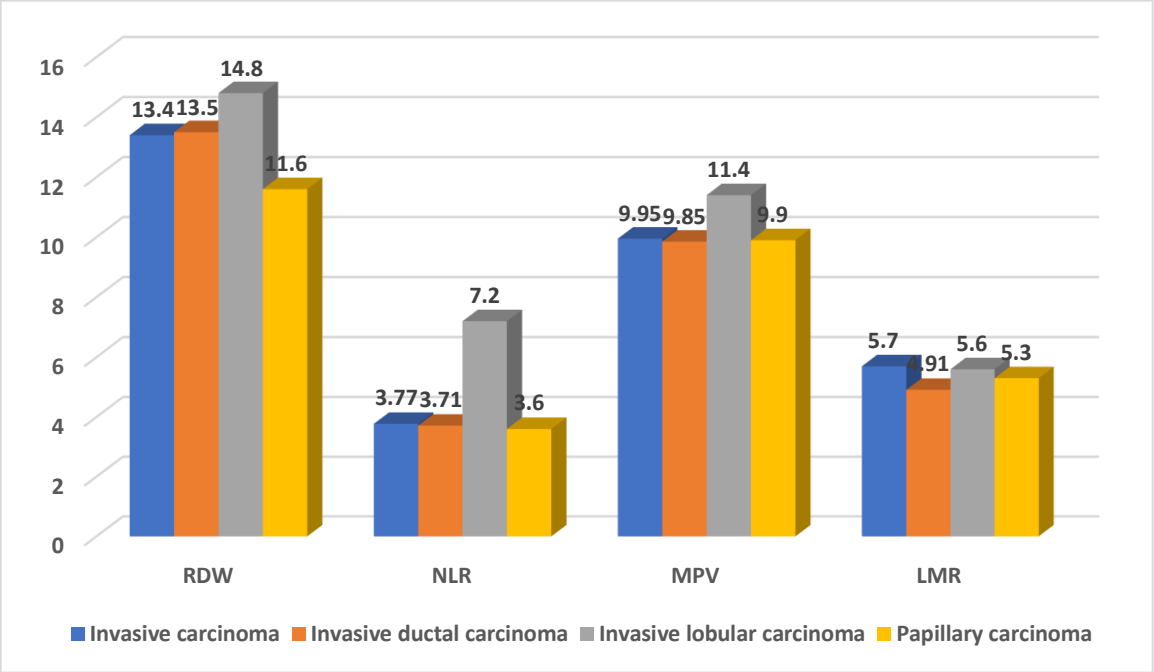


Table 13: Association of ER with haematological parameters

Haematological parameters	ER		p-value
	Negative	Positive	
RDW	14.08±1.4	12.96±2.07	**0.01**
NLR	4.3±2.02	3.35±1.46	**0.03**
MPV	10.6±1.33	9.31±1.18	**<0.001**
LMR	5.12±2.36	5.4±2.8	0.66

Table 13 and graph 13 presents a crucial analysis of the relationship between Estrogen Receptor (ER) status and various haematological parameters in breast cancer patients. The findings reveal significant associations with three out of four blood markers. ER-negative tumours demonstrated notably higher values in RDW (14.08 ± 1.4 vs 12.96 ± 2.07, p=0.01), NLR (4.3 ± 2.02 vs 3.35 ± 1.46, p=0.03), and most significantly in MPV (10.6 ± 1.33 vs 9.31 ± 1.18, p<0.001) compared to ER-positive tumours. Only LMR showed no significant difference between ER-negative and positive groups (5.12 ± 2.36 vs 5.4 ± 2.8, p=0.66).

Graph 13: Association of ER with haematological parameters

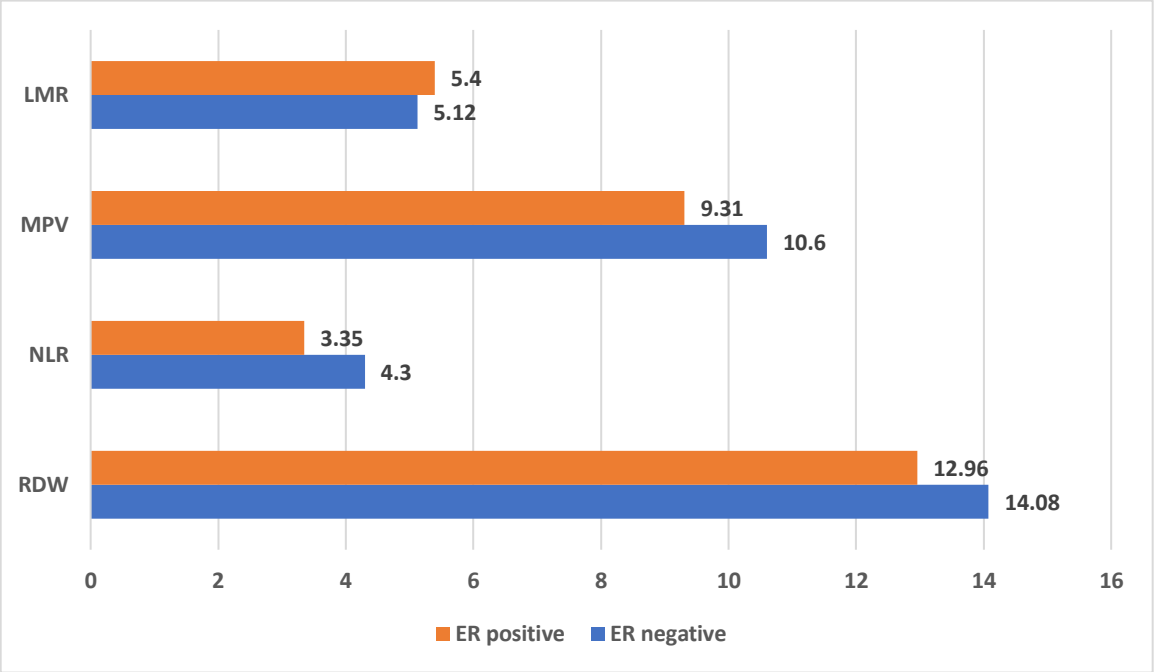


Table 14: Association of PR with haematological parameters

Haematological parameters	PR		p-value
	Negative	Positive	
RDW	14.26±1.58	12.5±1.74	**<0.001**
NLR	4.36±2.01	3.08±1.17	**0.003**
MPV	10.35±1.38	9.38±1.26	**0.005**
LMR	5.13±2.5	5.44±2.7	0.63

Table 14 and graph 14 provides important insights into the relationship between Progesterone Receptor (PR) status and haematological parameters in breast cancer patients. The analysis shows strong statistical correlations between PR status and three blood markers: RDW values were significantly higher in PR-negative tumours (14.26 ± 1.58) compared to PR-positive tumours (12.5 ± 1.74) with a highly significant p-value <0.001; NLR showed a similar pattern with higher values in PR-negative cases (4.36 ± 2.01) versus PR-positive cases (3.08 ± 1.17), p=0.003; and MPV was also elevated in PR-negative tumours (10.35 ± 1.38) compared to PR-positive ones (9.38 ± 1.26), p=0.005. Only LMR showed no significant difference between PR-negative and positive groups (5.13 ± 2.5 vs 5.44 ± 2.7, p=0.63).

Graph 14: Association of PR with haematological parameters

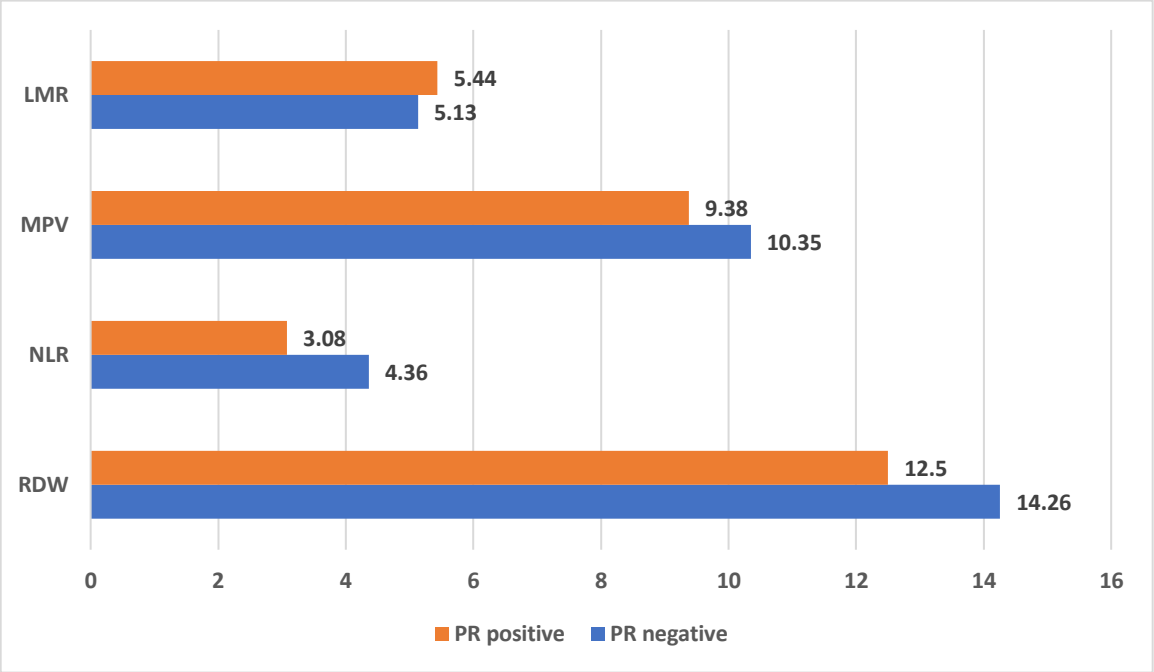


Table 15: Association of HER2NEU with haematological parameters

Haematological parameters	HER2NEU			p-value
	Negative	Positive	Equivocal	
RDW	13.9±1.74	12.8±1.95	12.6±0.64	0.03
NLR	3.89±1.45	3.7±2.4	2.84±0.98	0.61
MPV	10.1±1.36	9.6±1.51	9.4±1.18	0.39
LMR	5.05±2.58	5.52±2.77	6.57±2.14	0.54

Table 15 and graph 15 analyses the relationship between HER2NEU status and haematological parameters in breast cancer patients. The results demonstrate that only RDW showed a statistically significant correlation with HER2NEU status (p=0.03), with highest values in HER2NEU-negative tumours (13.9 ± 1.74), followed by HER2NEU-positive (12.8 ± 1.95), and lowest in equivocal cases (12.6 ± 0.64). The other parameters - NLR (p=0.61), MPV (p=0.39), and LMR (p=0.54) - showed no statistically significant differences across HER2NEU status groups. This pattern differs from what was observed with ER and PR status, where multiple parameters showed significant correlations.

Graph 15: Association of HER2NEU with haematological parameters

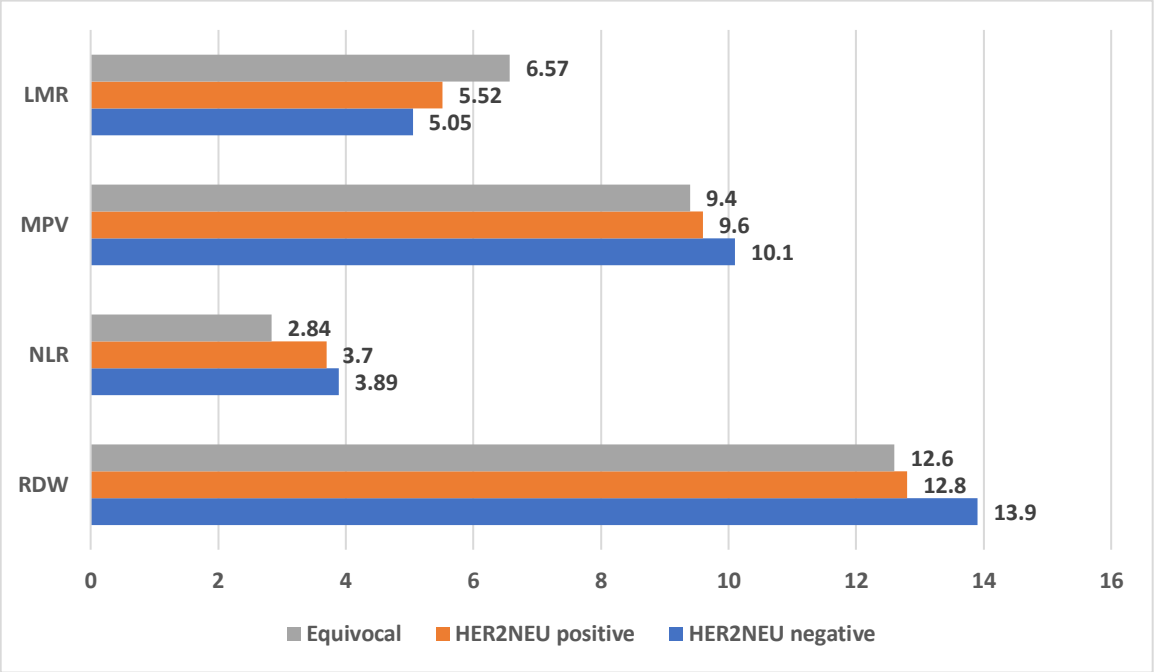


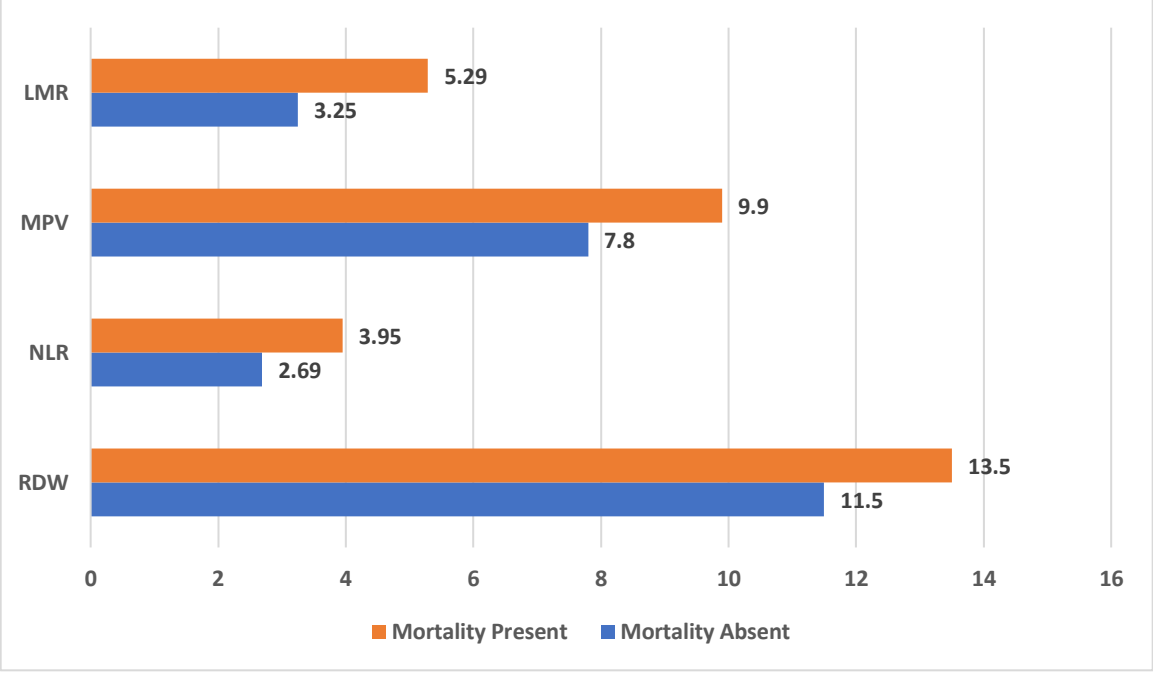
Table 16: Association of mortality with variables

Variables	Mortality		p-value
	Absent	Present	
Haematological parameters			
RDW	11.5±1.94	13.5±1.78	**<0.001**
NLR	2.69±1.8	3.95±1.670	**0.006**
MPV	7.8±1.34	9.9±1.45	**<0.001**
LMR	3.25±2.7	5.29±2.45	**0.003**
Tumour markers			
Triple negative	14 (31.1%)	3 (15%)	0.88
HER2NEU Positive	14 (31.1%)	7 (35%)	0.41
TNM staging			
Stage 3	31 (68.9%)	13 (65%)	0.78

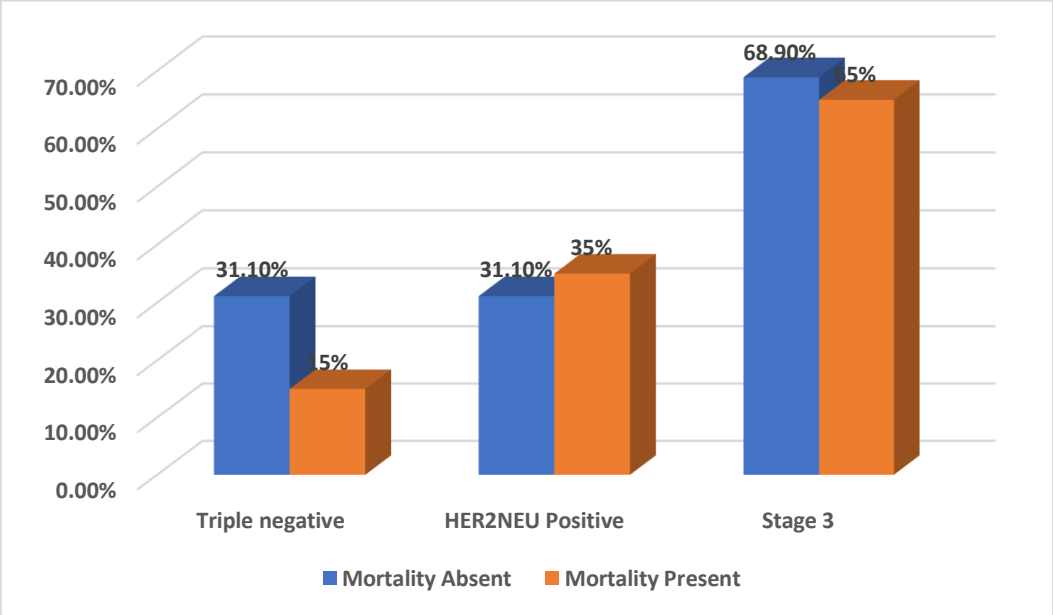
Histopathological diagnosis			
Invasive carcinoma	21 (46.7%)	7 (35%)	0.57
Invasive ductal carcinoma	22 (48.9%)	13 (65%)	
Invasive lobular carcinoma	1 (2.2%)	0	
Papillary carcinoma	1 (2.2%)	0	

Table 16 and graph 16 reveals critical insights into factors associated with patient mortality. The haematological parameters emerged as the most significant predictors, with statistically significant differences in Red Cell Distribution Width (RDW), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), and Lymphocyte-to-Monocyte Ratio (LMR). Patients who experienced mortality demonstrated notably higher values in these parameters, suggesting their potential as prognostic markers. Interestingly, tumour markers like Triple Negative and HER2NEU Positive status, TNM staging, and histopathological diagnoses did not show statistically significant associations with mortality, indicating that haematological parameters might provide more nuanced insights into patient outcomes than traditional clinical classifications.

Graph 16 A: Association of mortality with haematological parameters



Graph 16 B: Association of mortality with tumour markers and staging



Graph 16 C: Association of mortality with histopathological diagnosis

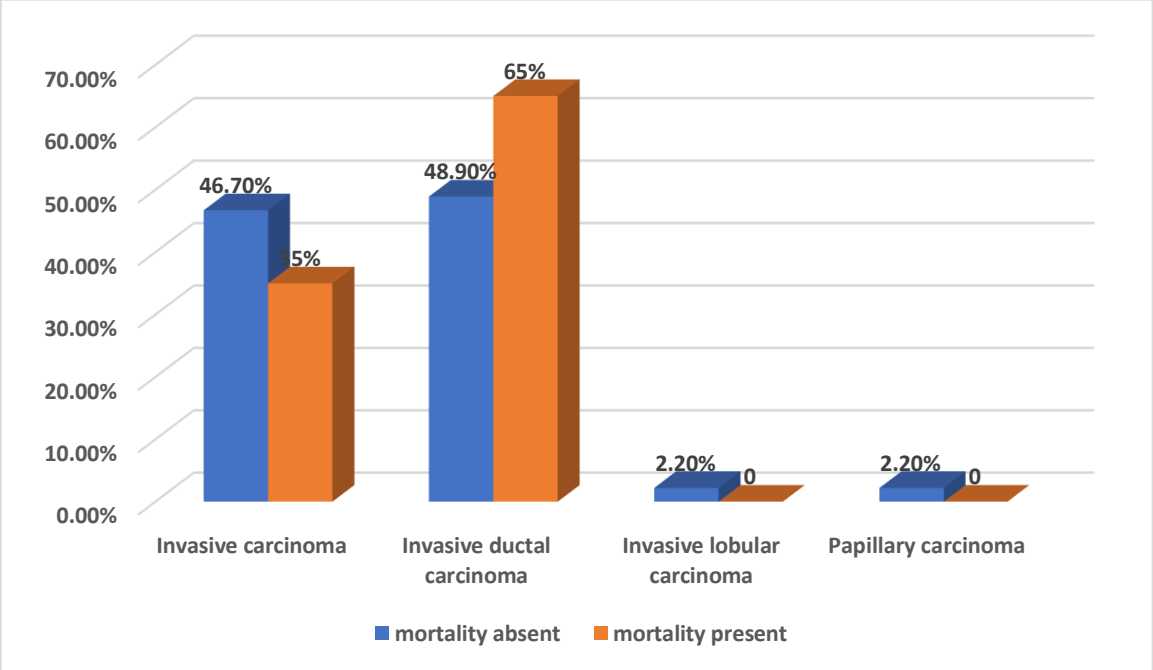


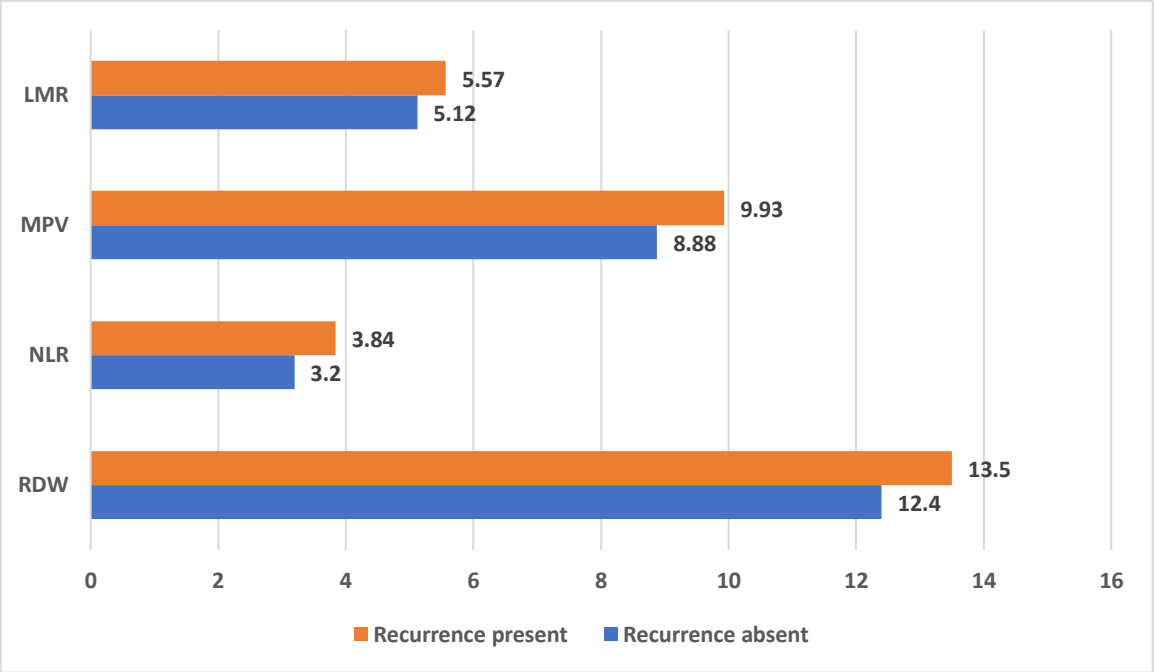
Table 17: Association of recurrence with variables

Variables	Recurrence		p-value
	Absent	Present	
Haematological parameters			
RDW	12.4±1.89	13.5±1.85	**0.03**
NLR	3.2±1.93	3.84±1.51	0.14
MPV	8.88±1.44	9.93±1.41	**0.006**
LMR	5.12±2.7	5.57±2.45	0.38
Tumour markers			
Triple negative	16 (27.1%)	1 (5%)	0.57
HER2NEU Positive	20 (33.8%)	1 (5%)	0.38
TNM staging			
Stage 3	42 (71.2%)	2 (33.3%)	0.06
Histopathological diagnosis			
Invasive carcinoma	23 (39%)	5 (83.3%)	0.23
Invasive ductal carcinoma	34 (57.6%)	1 (16.7%)	
Invasive lobular carcinoma	1 (1.7%)	0	
Papillary carcinoma	1 (1.7%)	0	

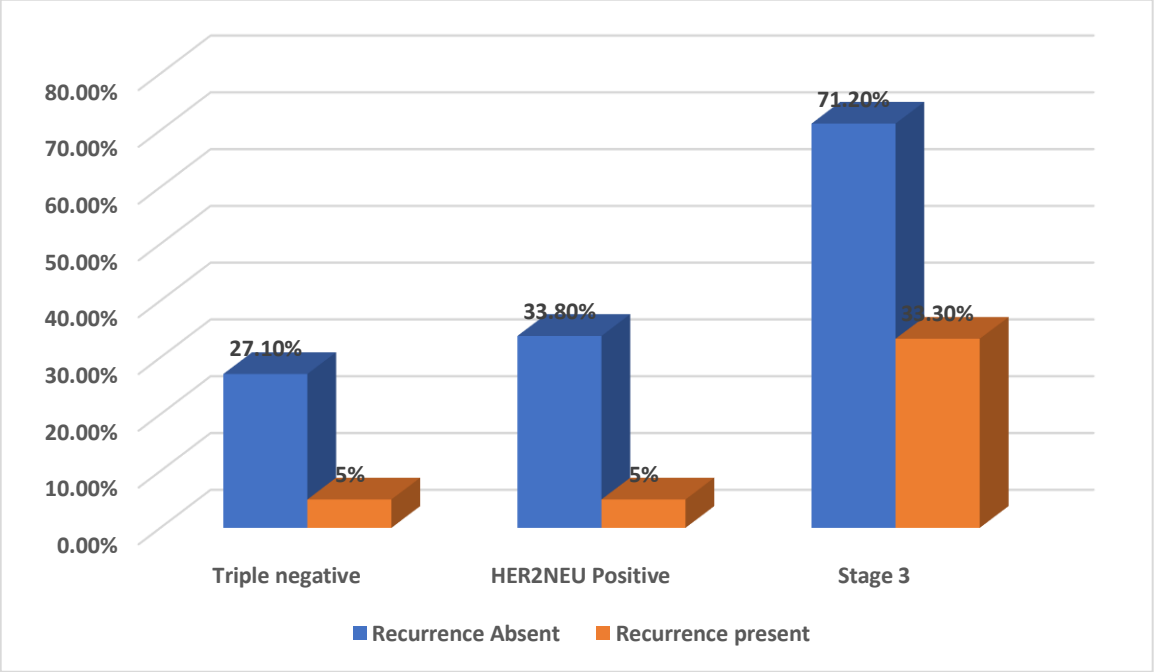
Table 17 and graph 17 highlights the importance of different variables in predicting cancer recurrence. Red Cell Distribution Width (RDW) and Mean Platelet Volume (MPV) showed statistically significant differences between patients with and without recurrence, with higher values associated with recurrent cases. While the Neutrophil-to-Lymphocyte Ratio (NLR) and Lymphocyte-to-Monocyte Ratio (LMR) did not demonstrate significant variations, TNM Stage 3 exhibited a trend towards significance in recurrence prediction. Tumour markers such as Triple Negative and HER2NEU Positive status did not show

substantial associations with recurrence. The histopathological diagnoses also failed to reveal significant correlations, suggesting that haematological parameters might offer more reliable indicators of potential cancer recurrence compared to traditional diagnostic classifications.

Graph 17 A: Association of recurrence with haematological parameters



Graph 17 B: Association of recurrence with tumour markers and staging



Graph 17 C: Association of recurrence with histopathological diagnosis

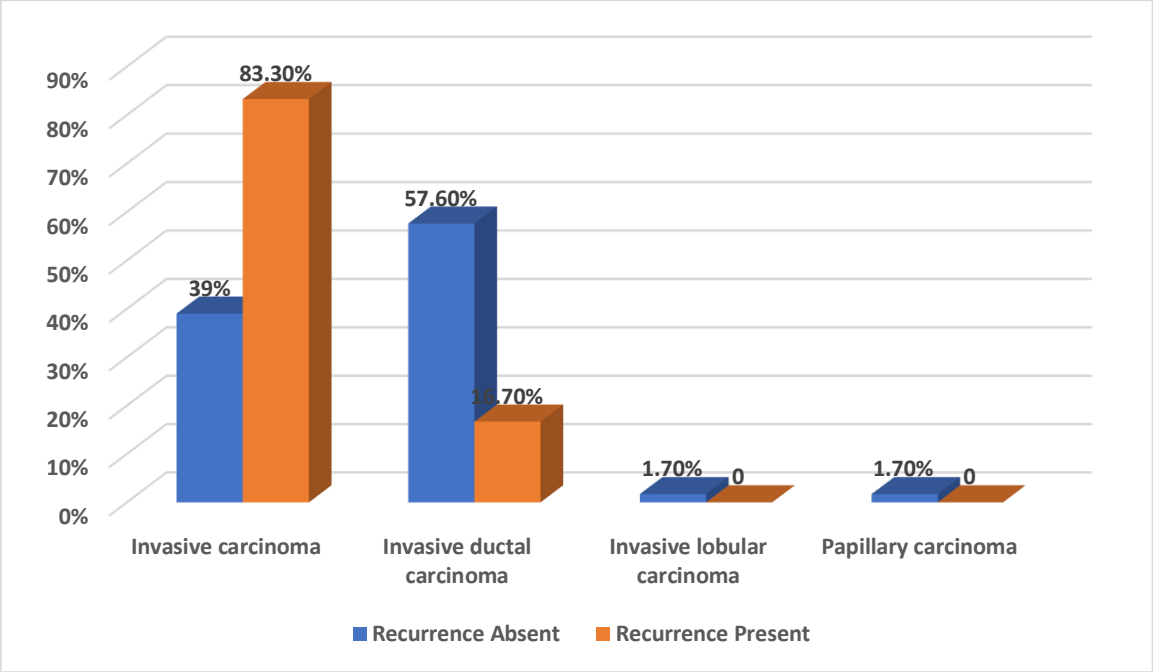


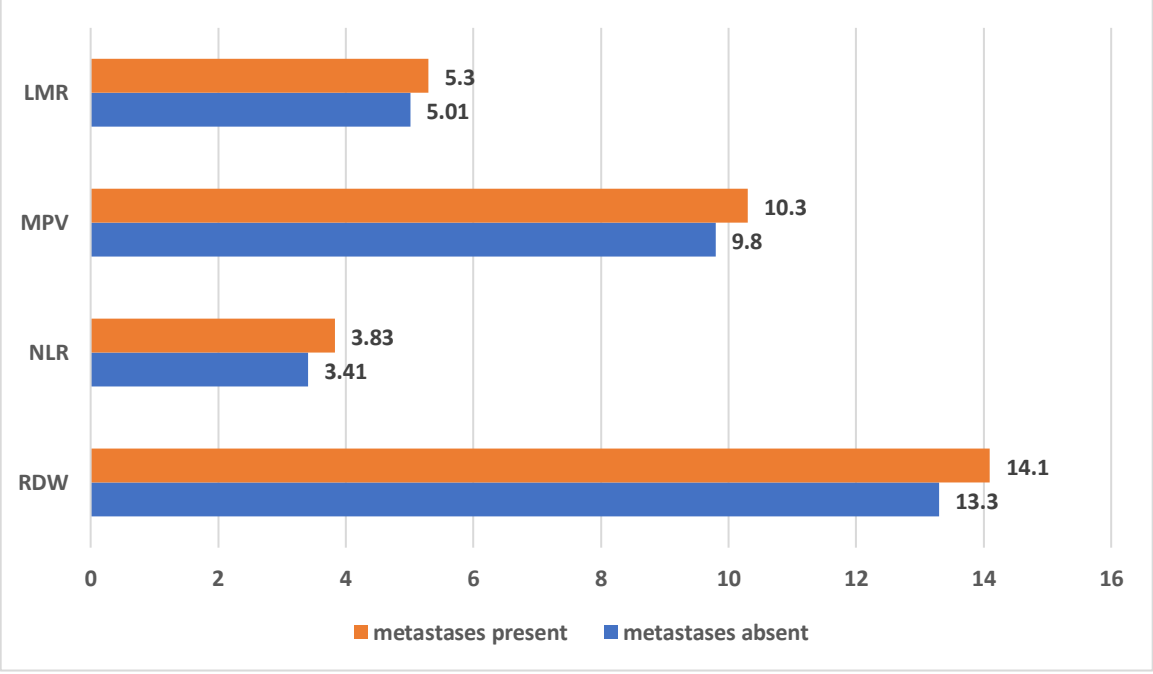
Table 18: Association of metastases with different variables

Variables	Metastases		p-value
	Absent	Present	
Haematological parameters			
RDW	13.3±1.8	14.1±1.64	0.29
NLR	3.41±0.97	3.83±1.87	0.55
MPV	9.8±1.44	10.3±1.1	0.42
LMR	5.01±2.9	5.3±2.6	0.78
Tumour markers			
Triple negative	14 (31.1%)	3 (15%)	0.17
HER2NEU Positive	17 (37.8%)	4 (20%)	0.15
TNM staging			
Stage 3	37 (63.8%)	7 (100%)	**0.05**

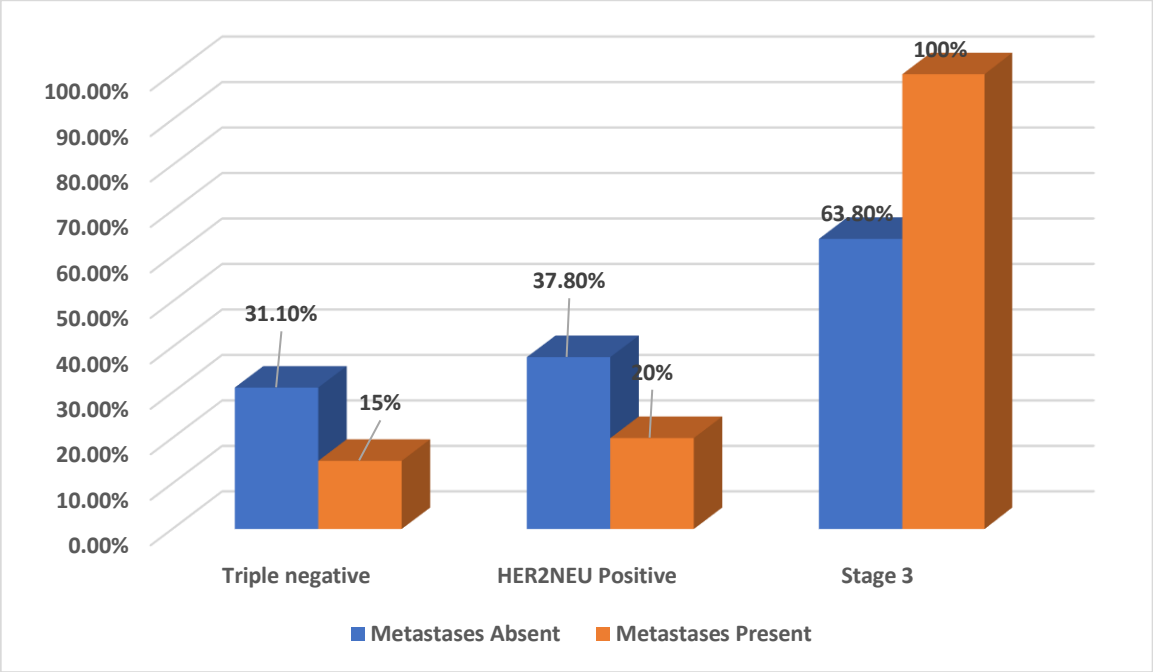
Histopathological diagnosis			
Invasive carcinoma	24 (41.4%)	4 (57.1%)	0.85
Invasive ductal carcinoma	32 (55.2%)	3 (42.9%)	
Invasive lobular carcinoma	1 (1.7%)	0	
Papillary carcinoma	1 (1.7%)	0	

Table 18 and graph 18 provides a nuanced view of potential predictive factors for cancer spread. Among the investigated parameters, TNM Stage 3 emerged as the most significant predictor, with a statistically significant association with metastases (p-value 0.05). Notably, all patients in the metastasis group were classified as Stage 3, highlighting the critical role of advanced staging in metastatic potential. Surprisingly, haematological parameters including RDW, NLR, MPV, and LMR did not show statistically significant differences between patients with and without metastases. Similarly, tumour markers like Triple Negative and HER2NEU Positive status and histopathological diagnoses failed to demonstrate significant correlations with metastatic spread. This suggests that while TNM staging remains a crucial predictor, the relationship between haematological parameters and metastases may be more complex than initially anticipated.

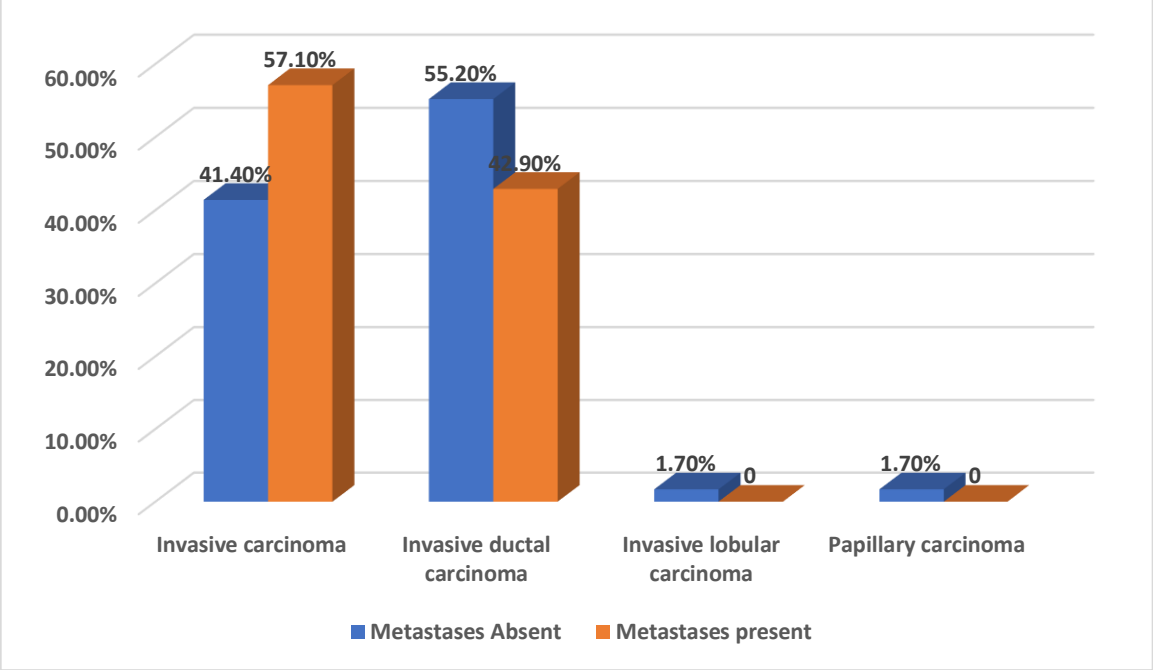
Graph 18 A: Association of metastases with Haematological parameters



Graph 18 B: Association of metastases with tumour markers



Graph 18 C: Association of metastases with histopathological diagnosis



DISCUSSION

Breast cancer remains the most commonly diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide. Despite advances in early detection and treatment modalities, the heterogeneity of breast cancer poses significant challenges for precise prognostication and individualized therapeutic approaches. The search for reliable, cost-effective, and readily available prognostic indicators has gained prominence in contemporary oncology research. Haematological parameters, which reflect systemic inflammatory responses and homeostatic disturbances in cancer patients, have emerged as promising biomarkers due to their accessibility through routine blood examinations. This study aimed to investigate the relationship between preoperative haematological markers—specifically Red Cell Distribution Width (RDW), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), and Lymphocyte-to-Monocyte Ratio (LMR)—and clinicopathological features of breast cancer, particularly focusing on their prognostic significance in predicting mortality, recurrence, and metastasis. By establishing correlations between these haematological parameters and tumour characteristics, we seek to enhance the prognostic armamentarium available to clinicians in breast cancer management, potentially informing treatment decisions and improving patient outcomes.

Age and Gender Distribution

Our study observed a predominant occurrence of breast cancer in the middle-aged population (41-60 years), accounting for 53.8% of cases, followed by elderly patients (61-80 years) at 29.2%, and younger patients (20-40 years) at 16.9%. This age distribution aligns with global epidemiological patterns of breast cancer, where the risk increases with age, with a median age at diagnosis typically in the sixth decade of life.

Fan et al. conducted a large-scale epidemiological study of 4,211 breast cancer patients and noted similar age distribution patterns, with the highest incidence in the 45-60 age group (52.7%), which corresponds closely with our findings.[157] The relatively lower proportion of younger patients in our cohort (16.9%) is consistent with data from the Surveillance, Epidemiology, and End Results (SEER) program, which reports that only about 11% of new breast cancer cases occur in women younger than 45 years.[158]

Gender-wise, our study population demonstrated the expected female predominance (98.5%), with only one male case (1.5%). This reflects the known epidemiology of breast cancer, where male breast cancer accounts for approximately 1% of all breast cancers worldwide. Gucalp et al. reported that male breast cancer represents 0.5-1% of all breast cancer diagnoses globally, which is consistent with our findings.[159] The rarity of male breast cancer often leads to its under-recognition, potentially resulting in delayed diagnosis and treatment, which underscores the importance of awareness among both patients and healthcare providers.

Histopathological Profile and Laterality

In our study cohort, invasive ductal carcinoma (IDC) was the predominant histological subtype (53.8%), followed by invasive carcinoma without further specification (43.1%), with invasive lobular carcinoma and papillary carcinoma each representing 1.5% of cases. The preponderance of IDC is consistent with established literature, where it typically accounts for 70-80% of all invasive breast cancers.

Li et al. analysed 4,970 breast cancer cases and found that IDC constituted 70.8% of all histological types, while invasive lobular carcinoma accounted for 6.3%.[160] Our lower proportion of invasive lobular carcinoma (1.5%) compared to the literature might be attributed to geographical variations in breast cancer histopathology or differences in diagnostic criteria and reporting practices.

Regarding laterality, our study found a slight right-sided predominance (56.9%) compared to left-sided involvement (43.1%). This differs somewhat from several large-scale studies that have reported a left-sided predominance in breast cancer. For instance, Roychoudhuri et al. examined over 200,000 cases and found a 5% higher incidence in the left breast compared to the right.[161] Proposed explanations for left-sided predominance include greater tissue volume in the left breast and nursing habits favouring the right breast, which may provide more frequent emptying and reduced carcinogenic exposure. Our divergent finding of right-sided predominance warrants further investigation in the context of regional variations and might suggest the influence of specific environmental or genetic factors in our study population.

Tumour Markers and TNM Staging

Our analysis of tumour markers revealed ER positivity in 53.8% of cases, PR positivity in 44.6%, and HER2 positivity in 32.3% of patients. These proportions align closely with published literature describing the molecular subtypes of breast cancer. Howlader et al., in an analysis of SEER data comprising over 50,000 cases, reported ER/PR positivity in approximately 65% of patients and HER2 overexpression in 25-30%.[162]

The TNM staging in our cohort showed T2 tumours (tumours 2-5 cm in diameter) as the most common (40%), followed by T3 tumours (16.9%). In lymph node staging, N0 (no regional lymph node metastasis) was most frequent (24.6%), followed by N2a (21.5%). The majority of patients (90.8%) had no distant metastasis (M0). This distribution is comparable to findings from Walters et al., who reported that approximately 50-60% of breast cancers are diagnosed at T1-T2 stages, with around 30% presenting with lymph node involvement.[163]

The relatively high proportion of N2a in our study (21.5%), indicating metastasis in 4-9 axillary lymph nodes, suggests that a substantial number of our patients presented with locally advanced disease. This could be

attributed to delays in seeking medical attention, limited access to screening programs, or regional differences in breast cancer biology, which has implications for both prognosis and treatment planning.

Correlation Between Haematological Parameters and Clinicopathological Features

Haematological Parameters and Histopathological Diagnosis

Our study found no statistically significant differences in RDW, NLR, MPV, or LMR values across different histological types of breast cancer (all p-values >0.05). This suggests that these haematological parameters don't vary significantly based on the histological type of breast cancer.

Contrary to our findings, some studies have reported associations between haematological parameters and histological subtypes. For example, Okuturlar et al. observed significantly higher NLR values in invasive ductal carcinoma compared to other histological types.[164] Similarly, Takeuchi et al. reported variations in RDW among different histological subtypes, with higher values in more aggressive variants.[165] The discrepancy between our results and these studies might be attributed to differences in sample size, patient demographics, or the analytical methods employed.

Haematological Parameters and Hormone Receptor Status

Our analysis revealed significant associations between haematological parameters and hormone receptor status. ER-negative tumours demonstrated notably higher values in RDW ($p=0.01$), NLR ($p=0.03$), and MPV ($p<0.001$) compared to ER-positive tumours. Similarly, PR-negative tumours showed higher values in RDW ($p<0.001$), NLR ($p=0.003$), and MPV ($p=0.005$) compared to PR-positive tumours. Only LMR showed no significant difference based on hormone receptor status.

These findings are consistent with several published studies. Yao et al. conducted a meta-analysis of 100 studies investigating the relationship between NLR and breast cancer prognosis, finding significantly higher NLR values in ER/PR-negative tumours, which were associated with poorer outcomes.[166] Similarly, Tsujikawa et al. reported elevated RDW in hormone receptor-negative breast cancers, suggesting its potential as a marker for more aggressive disease.[167]

The biological rationale for these associations may lie in the inflammatory milieu characteristic of hormone receptor-negative breast cancers. These tumours often exhibit enhanced inflammatory responses, which can influence haematological parameters. Specifically, inflammatory cytokines like IL-6 and TNF-α, which are more abundant in hormone receptor-negative tumours, can affect erythropoiesis and platelet production, potentially explaining the elevated RDW and MPV observed in these cases.[168]

Haematological Parameters and HER2 Status

In our study, only RDW showed a statistically significant correlation with HER2 status (p=0.03), with highest values in HER2-negative tumours, followed by HER2-positive, and lowest in equivocal cases. The other parameters—NLR, MPV, and LMR—showed no statistically significant differences across HER2 status groups.

This selective association of RDW with HER2 status, but not other haematological parameters, presents an intriguing finding. Yao D et al. similarly reported an association between elevated RDW and HER2-negative status, proposing that the biological aggressiveness of HER2-negative tumours might induce systemic inflammatory responses that affect erythrocyte homeostasis.[169]

The lack of association between NLR and HER2 status in our study contrasts with findings by Azab et al., who observed higher NLR in HER2-positive breast cancers and correlated this with poorer survival outcomes.[170] This discrepancy highlights the complex and potentially context-dependent relationship between HER2 signalling and systemic inflammatory responses, warranting further investigation.

Haematological Parameters as Predictors of Clinical Outcomes

Mortality

In our cohort, all four haematological parameters demonstrated statistically significant associations with mortality. Patients who experienced mortality showed higher values in RDW (p<0.001), NLR (p=0.006), MPV (p<0.001), and LMR (p=0.003) compared to survivors.

These findings align with a growing body of evidence supporting the prognostic value of haematological parameters in breast cancer. Seretis et al. conducted a prospective study of 203 breast cancer patients and found that elevated preoperative NLR independently predicted reduced overall survival (HR=2.39, 95% CI: 1.32-4.31, p=0.004).[171] Similarly, Warwick et al. reported that increased RDW was associated with higher mortality rates in breast cancer patients, even after adjusting for conventional prognostic factors.[172]

The biological mechanisms underpinning these associations are multifaceted. Elevated NLR reflects both an increased neutrophil-dependent inflammatory response and a decreased lymphocyte-mediated anti-tumour immune function.[173] Increased RDW indicates dyserythropoiesis, which may result from cancer-related inflammation and malnutrition.[174] Elevated MPV suggests enhanced platelet reactivity, which can contribute to tumour growth, angiogenesis, and metastasis through the release of pro-angiogenic and growth factors.[175] Interestingly, in our study, traditional prognostic factors like tumour markers (Triple Negative and HER2 Positive status), TNM staging, and histopathological diagnoses did not show statistically significant

associations with mortality. This unexpected finding suggests that haematological parameters might provide more nuanced insights into the complex interplay between host factors and tumour biology, potentially offering additional prognostic information beyond conventional clinical classifications.

Recurrence

In our analysis, RDW (p=0.03) and MPV (p=0.006) emerged as significant predictors of breast cancer recurrence, with higher values observed in patients who experienced recurrence. NLR and LMR, however, did not demonstrate statistically significant associations with recurrence risk.

The relationship between RDW and cancer recurrence has been explored in various malignancies. Chen et al. conducted a meta-analysis of 16 studies comprising 3,317 solid tumour patients and found that elevated RDW was significantly associated with increased recurrence risk (HR=1.85, 95% CI: 1.39-2.46, p<0.001).[176] Specific to breast cancer, Wan GX et al. reported that elevated preoperative RDW was an independent predictor of disease-free survival in early-stage breast cancer patients.[177]

Similarly, the prognostic value of MPV in cancer recurrence has been documented. Gu et al. observed that elevated MPV was associated with a higher rate of recurrence in breast cancer patients (HR=1.63, 95% CI: 1.08-2.45, p=0.019).[178] Platelets can contribute to cancer progression through various mechanisms, including the promotion of angiogenesis, protection of circulating tumour cells, and facilitation of tumour cell extravasation during metastasis.[179]

The lack of association between NLR and recurrence in our study contrasts with several published reports. For instance, Ethier et al. conducted a systematic review and meta-analysis of 15 studies involving 8,563 patients and found that elevated NLR was significantly associated with reduced disease-free survival in breast cancer patients.[180] This discrepancy might be attributed to differences in sample size, patient characteristics, or the cut-off values used to define elevated NLR.

Metastasis

Among the investigated parameters, TNM Stage 3 emerged as the most significant predictor of metastasis in our study (p=0.05), with all patients in the metastasis group classified as Stage 3. Surprisingly, none of the haematological parameters showed statistically significant differences between patients with and without metastases.

The strong association between advanced TNM stage and metastatic potential is well-established in breast cancer literature. Waks et al. analysed data from the National Cancer Database and found that patients with

Stage 3 disease had a significantly higher risk of developing distant metastases compared to those with earlier stages.[181]

The absence of significant associations between haematological parameters and metastasis in our study is somewhat unexpected, given the substantial body of evidence linking systemic inflammation to metastatic progression. Templeton et al. conducted a meta-analysis of 22 studies comprising 10,098 breast cancer patients and found that elevated NLR was significantly associated with the presence of distant metastases (OR=1.92, 95% CI: 1.50-2.45, $p<0.001$).[182]

This discrepancy might be explained by several factors. First, the relatively small number of patients with metastases in our cohort (n=7, 10.8%) might have limited the statistical power to detect significant associations. Second, the timing of haematological measurements (preoperative in our study) might not capture the inflammatory changes that accompany or precede metastatic spread. Third, the complex and multifaceted process of metastasis involves numerous factors beyond systemic inflammation, including tumour intrinsic properties, host tissue characteristics, and microenvironmental influences.[183]

Clinical Implications and Future Directions

Our findings highlight the potential utility of preoperative haematological parameters, particularly RDW, NLR, MPV, and LMR, as prognostic biomarkers in breast cancer. The significant associations observed between these parameters and clinical outcomes, especially mortality and recurrence, suggest that they could complement conventional prognostic factors in risk stratification and treatment planning.

Several aspects of our study merit consideration in clinical practice. First, the strong association between haematological parameters and hormone receptor status underscores the importance of integrating these biomarkers into the molecular classification of breast cancer. Patients with hormone receptor-negative tumours and elevated RDW, NLR, or MPV might benefit from more intensive surveillance and consideration for adjuvant therapy, given their potentially higher risk for adverse outcomes.

Second, the significant correlations between RDW, MPV, and cancer recurrence suggest that these parameters could be incorporated into post-treatment monitoring protocols. Regular assessment of these biomarkers might enable earlier detection of disease recurrence, potentially improving the efficacy of salvage therapies.

Third, the robust association between haematological parameters and mortality, independent of traditional prognostic factors, indicates that these biomarkers might capture aspects of tumour-host interactions not

reflected in conventional staging systems. This could provide additional information for personalized treatment decisions, particularly in cases where standard prognostic tools yield equivocal results.

Future research should address several limitations and unanswered questions arising from our study. Prospective studies with larger cohorts and longer follow-up periods are needed to validate the prognostic value of haematological parameters in diverse breast cancer populations. Additionally, investigation into the biological mechanisms underlying the observed associations would enhance our understanding of how systemic inflammatory responses influence breast cancer progression.

The integration of haematological parameters with other emerging biomarkers, such as circulating tumour DNA, microRNAs, or immune cell subsets, might yield more comprehensive prognostic models. Furthermore, exploring the impact of treatments on these parameters and whether changes during therapy correlate with treatment response would provide valuable insights for adaptive treatment strategies.

Lastly, determining optimal cut-off values for each haematological parameter in different breast cancer subtypes and patient populations is essential for standardizing their use in clinical practice. This would facilitate the development of risk assessment tools that incorporate these readily available biomarkers, potentially improving prognostication accuracy and treatment personalization in breast cancer.

CONCLUSION:

This study provides valuable insights into the prognostic significance of preoperative haematological markers in breast cancer patients. Our findings demonstrate that certain routinely available blood parameters, particularly Red Cell Distribution Width (RDW), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), and Lymphocyte-to-Monocyte Ratio (LMR), have significant associations with clinicopathological features and clinical outcomes in breast carcinoma.

The strong correlation between these haematological parameters and hormone receptor status (ER and PR) highlights their potential role in refining the molecular classification of breast cancer. Notably, hormone receptor-negative tumours exhibited significantly higher values of RDW, NLR, and MPV, suggesting that these parameters might serve as surrogate markers for more aggressive disease biology. Similarly, the association of RDW with HER2 status further emphasizes its potential utility in comprehensive tumour profiling.

Perhaps most importantly, our study revealed robust associations between haematological parameters and mortality risk. All four markers—RDW, NLR, MPV, and LMR—demonstrated statistically significant differences between survivors and non-survivors, outperforming traditional prognostic factors such as tumour markers, TNM staging, and histopathological diagnoses in mortality prediction. This suggests that these readily available parameters might capture aspects of tumour-host interactions not reflected in conventional staging systems, potentially offering complementary prognostic information.

In terms of recurrence prediction, RDW and MPV emerged as significant indicators, with elevated values observed in patients who experienced disease recurrence. This finding has important implications for post-treatment surveillance strategies, suggesting that regular monitoring of these parameters might enable earlier detection of recurrent disease. Conversely, metastatic potential showed a stronger association with advanced TNM staging (Stage 3) rather than haematological parameters, underscoring the complexity of the metastatic process and the continued relevance of traditional staging systems.

The accessibility, cost-effectiveness, and routine availability of these haematological markers make them particularly attractive as prognostic tools in resource-limited settings where more sophisticated molecular testing might be unavailable or prohibitively expensive. Their integration into clinical decision-making could potentially enhance risk stratification, guide treatment selection, and improve patient outcomes in breast cancer management.

However, further research, including prospective studies with larger cohorts and longer follow-up periods, is necessary to validate these findings and establish standardized cut-off values for clinical application. Additionally, investigation into the biological mechanisms underpinning these associations would enhance our understanding of how systemic inflammatory responses influence breast cancer progression and treatment response.

In conclusion, our study supports the incorporation of preoperative haematological parameters into the prognostic armamentarium for breast cancer, positioning them as valuable adjuncts to traditional clinicopathological factors in the evolving landscape of personalized cancer care.

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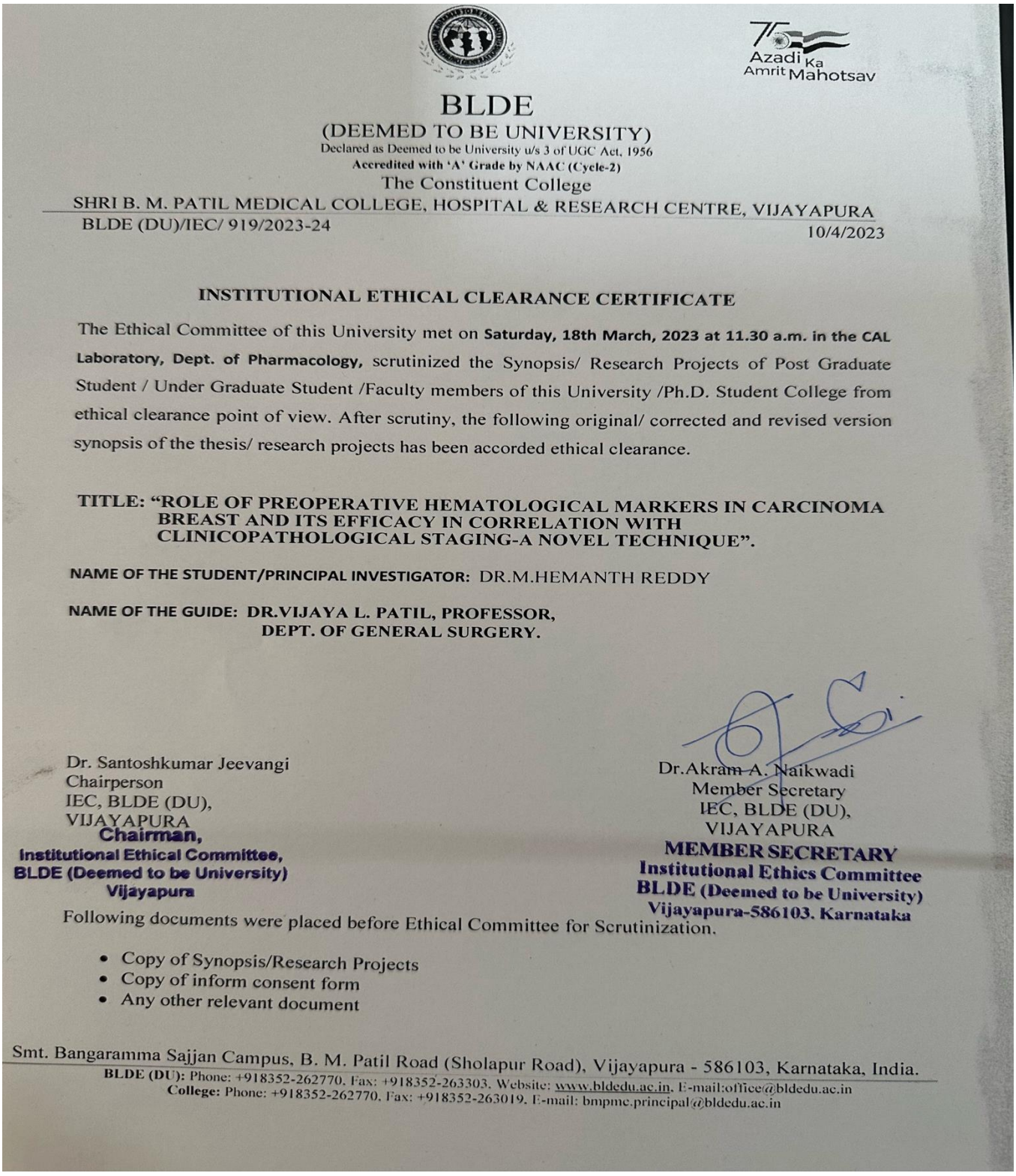
B.L.D.E.U.(DU) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCHCENTRE, VIJAYAPURA – 586103, KARNATAKA

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE



BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 919/2023-24 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinized the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "ROLE OF PREOPERATIVE HEMATOLOGICAL MARKERS IN CARCINOMA BREAST AND ITS EFFICACY IN CORRELATION WITH CLINICOPATHOLOGICAL STAGING-A NOVEL TECHNIQUE".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.M.HEMANTH REDDY

NAME OF THE GUIDE: DR.VIJAYA L. PATIL, PROFESSOR, DEPT. OF GENERAL SURGERY.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
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PROFORMA

CASE NO:

- Name: IP No:
- Age/sex: DOA:
- Occupation: DOD:
- Address:

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

PAST HISTORY:

PERSONAL HISTORY:

- Diet
- Sleep
- Appetite
- Bowel & bladder
- Habits

MENSTRUAL HISTORY:

OBSTETRIC HISTORY:

FAMILY HISTORY:

GENERAL PHYSICAL EXAMINATION

- Mental Status
- Built
- Nourishment

- Pallor
- Icterus
- Cyanosis
- Clubbing
- Edema
- Cervical Lymph Nodes
- Pulse
- Blood pressure
- Temperature
- Respiratory rate

SYSTEMIC EXAMINATION

LOCAL EXAMINATION(BREAST):

Inspection:

Palpation:

AXILLARY LYMPH NODES:

RESPIRATORY SYSTEM:

CARDIO-VASCULAR SYSTEM:

CENTRAL NERVOUS SYSTEM:

PER-ABDOMEN EXAMINATION:

DIAGNOSIS:

STAGING:

INVESTIGATIONS:

- Complete blood count- total leucocyte count, differential leucocyte count, platelet count, PDW, MPV, RDW.
- Bleeding and clotting time.
- Urine – sugar, albumin and microscopy.
- Random blood sugar, Blood urea, Serum creatinine.
- Electro-cardio-gram and Chest X-ray.
- Human Immunodeficiency Virus, Hepatitis B virus.
- Ultrasonography / computed tomography of abdomen and pelvis.

SAMPLE INFORMED CONSENT FORM

B.L.D.E.U.(DU) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCHCENTRE, VIJAYAPURA – 586103, KARNATAKA

TITLE OF THE PROJECT

ROLE OF PREOPERATIVE HEMATOLOGICAL INFLAMMATORY MARKERS AS NOVEL TECHNIQUE IN CARCINOMA BREAST AND ITS EFFICACY IN CORRELATION WITH CLINICOPATHOLOGICAL STAGING

PRINCIPAL INVESTIGATOR: **DR. M. HEMANTH REDDY**
DEPARTMENT OF GENERAL SURGERY

PG GUIDE: **Dr. VIJAYA L PATIL**

M.S. (GENERAL SURGERY)
PROFESSOR, DEPARTMENT OF GENERAL SURGERY

PURPOSE OF RESEARCH:

I have been informed that this study will analyse the usefulness of inflammatory markers (MPV, RDW,NLR,PLR) in role of breast cancer in relation to clinicopathological staging.

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that relevant history will be taken. I will do detailed clinical examination after which necessary investigations will be done whenever required, which would help the investigator for appropriate management.

RISKS AND DISCOMFORTS:

I understand that my ward may experience some pain and discomfort during the examination or during my treatment. This study is not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that I/my wards participation in this study will help in early, feasible and routinely done investigation for good prognosis of breast cancer.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. M. HEMANTH REDDY is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. M. HEMANTH REDDY will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: Dr. VIJAYA L PATIL Dr. M. HEMANTH

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. M. HEMANTH REDDY has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own understandable language.

I have been explained all the above in detail in my own language and I understand the same. Hence, I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

]]]]]

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MASTER CHART

IP NUMBER	Name of the patient	AGE	SEX	HISTO-PATHOLOGICAL DIAGNOSIS	ER	PR	HER2NEU	PDW	NLR	MPV	LMR	STAGING	
	1783 GAYATRI	38	Female	RIGHT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	13.4	3.43	11.4	6.44	ThiN- pT2N1Mx; 3/13 lymph nodes tumor deposits, All margins are free of tumor tissue	
	159450 KASTURI	60	FEMale	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	11.4	4.33	9.6	8.54	ThiN- pT2N1Mx; 3/8 lymph nodes tumor deposits, All surgical margins are free of tumor tissue	
	9826 KAUSAR BANU	63	FEMale	LEFT INFILTRATING DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	12.2	1.8	10.4	9.8	ThiN- pT1N3aM1; 4/12 lymph nodes tumor deposits, All margins are free of tumor tissue	
	48323 SARASWATI	60	Female	LEFT INFILTRATING DUCTAL CARCINOMA	POSITIVE	NEGATIVE	POSITIVE	17	1.9	8.7	8.54	ThiN- pT4bN3aMx; 23/27 lymph nodes tumor deposits, All margins are free of tumor tissue	
	23132 FARZANA MULLA	40	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	19.2	4.1	10.9	2.33	ThiN- pT3N3aMx; 37/37 lymph nodes tumor deposits, All margins are free of tumor tissue	
	147274 GANGABAI	58	Female	RIGHT INFILTRATING DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	13.9	11.7	8.4	3.1	ThiN- pT1aN2Mx; 0/15 lymph nodes tumor deposits, All margins are free of tumor tissue	
	18430 KAMALABAI HALLI	70	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	13.3	3.38	8.2	6.7	ThiN- pT4N1aj; 1/7 lymph nodes tumor deposits, All margins are free of tumor tissue	
	36920 GANGUBAI	60	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.6	3.41	10.8	2.82	ThiN- pT2N3M1; 4/ 15 lymph nodes free of tumor tissue, All margins are free of tumor tissue	
	70125 SHAKUNTALA	71	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.2	4.89	10.3	2.92	ThiN- pT2N3aj; 1 4/17 lymph nodes tumor deposits, All margins are free of tumor tissue	
	1532 DUNDAMMA	61	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	POSITIVE	10.1	1.8	7.9	3.1	ThiN- pT2N2aMx; 10/21 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	5287 MAHADEVI	42	Female	RIGHT INFILTRATING DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	12.4	3.31	9.3	6.26	ThiN- pT2N3aj; 13/14 lymph nodes tumor deposits, All margins are free of tumor tissue	
	16917 SHAMSHAD	58	Female	RIGHT INVASIVE CARCINOMA	POSITIVE	NEGATIVE	NEGATIVE	10.8	3.6	8.54	6.56	ThiN- pT2N3aj; 10/14 lymph nodes tumor deposits, All margins are free of tumor tissue	
	83671 SHANTABAI	58	Female	RIGHT INVASIVE CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	12.1	2.91	8.8	4.23	ThiN- pT1cN2aM; 8/13 lymph nodes tumor deposits, All margins are free of tumor tissue	
	69843 GOURAMMA	40	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	11.6	3.8	12.1	6.43	ThiN- pT2N1aM; 3/16 lymph nodes tumor deposits, All margins are free of tumor tissue	
	138738 SUNANDA	33	Female	INVASIVE CARCINOMA	POSITIVE	POSITIVE	EQUIVOCAL	13.1	3.9	8.8	6.4	ThiN- PTpN; 10/12 lymph nodes tumor deposits, All margins are free of tumor tissue	
	73377 JYOTI RATHOD	40	Female	INVASIVE CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	13.4	4.33	8.6	6.56	ThiN- pT1cN2aM; 8/13 lymph nodes tumor deposits, All margins are free of tumor tissue	
	17086 HUCHAVVA	52	Female	LEFT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	11.6	4.8	8.8	6.87	ThiN- pT2N2M0; 0/8 lymph nodes tumor deposits, All margins are free of tumor tissue	
	214004 LALITA	30	Female	INVASIVE CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	13.4	1.5	10.6	10	ThiN- pT2N1Mx; 2/16 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	213745 GANGABAI	55	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.8	5.2	11.6	4.4	ThiN- pT1aN3Mx; 0/15 lymph nodes tumor deposits, All margins are free of tumor tissue	
	84285 SAVANTHA	38	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.8	4.8	10.6	4.8	ThiN- pT3aN3Mx; 0/4 lymph nodes tumor deposits, All margins are free of tumor tissue	
	209497 LALBEE	50	Female	RIGHT INFILTRATING DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	12.4	3.31	10.3	6.26	ThiN- pT2N3aj; 13/14 lymph nodes tumor deposits, All margins are free of tumor tissue	
	349879 CHINAMMA	61	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	13.4	3.43	10.4	6.56	ThiN- pT1C, 6 Lymph nodes retrieved, All are free of tumor tissue	
	111068 MEHEABEEN	40	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	14	1.89	12	13.2	ThiN- pT2 N1 Mx; 3/9 lymph nodes tumor deposits, All surgical margins are free of tumor tissue	
	48383 BASAMMA	48	Female	LEFT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	15.1	5.88	10.3	3.29	ThiN- pT2N3aj; 16/18 lymph nodes tumor deposits, left axillary tail shows tumor deposits	
	71647 ERAMMA	67	Female	LEFT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	12.6	6.17	9.5	3.91	ThiN- pT4bN2bj; 9/17 lymph nodes tumor deposits, All margins are free of tumor tissue	
	GANGUBAI	80	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	10.8	4.1	8.4	3.6	ThiN- pT2N1aMx; 3/15 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	MURTUJA	55	Female	INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	15.3	4.9	12.4	6.71	ThiN- pT3N3Mx; 0/6 lymph nodes tumor deposits, All margins are free of tumor tissue	
	16830 DHANABAI	63	Female	LEFT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.7	2.76	11.6	5.15	ThiN- pT3N3aMx; 10/16 lymph nodes tumor deposits, All margins are free of tumor tissue	
	RAHANA	70	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	POSITIVE	10.6	2.2	8.8	3.6	ThiN- pT2bN2a; 9/13 lymph nodes tumor deposits, All margins are free of tumor tissue	
	PADMAVATI	50	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	13.1	3.9	7.8	6.4	ThiN- PT1aN0; 1/16 lymph nodes tumor deposits, All margins are free of tumor tissue	
	BASAVARAJESHWARI	49	Female	LEFT INVASIVE CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	11.1	3.6	8.1	4.8	ThiN- pT1aN1Mx; 4/15 lymph nodes tumor deposits, All margins are free of tumor tissue	
	NAGMA	40	Female	LEFT INVASIVE CARCINOMA	POSITIVE	POSITIVE	POSITIVE	9.4	3.5	6.9	4.4	ThiN- pT3bN3aMx; 8/9 lymph nodes tumor deposits, All margins are free of tumor tissue	
	222714 SUNITA	48	Female	INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	13.6	2.41	9.8	3.92	ThiN- pT2N3Mx; 0/13 lymph nodes tumor deposits, All margins are free of tumor tissue	
	72733 NANDA	58	Female	INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	POSITIVE	16.6	2.33	9	3.92	ThiN- pT4bN3aMx; 8/9 lymph nodes tumor deposits, All margins are free of tumor tissue	
	222916 RENUKA	41	Female	LEFT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	POSITIVE	10.7	2.2	8.7	4.8	ThiN- pT2bN2a; 3/13 lymph nodes tumor deposits, All margins are free of tumor tissue	
	136467 ANNAPURNA	77	Female	RIGHT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.4	2.39	9.9	3.19	ThiN- pT2N3; 0/15 lymph nodes tumor deposits, All margins are free of tumor tissue	
	152111 ZELIKA	40	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	NEGATIVE	NEGATIVE	14.9	3.94	8.5	2.46	ThiN- pT3N3aMx; 6/12 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	328586 SHOBHA	58	Female	RIGHT INVASIVE CARCINOMA	POSITIVE	NEGATIVE	NEGATIVE	16.9	4.88	9	2.88	ThiN- pT4bN1a; 1/11 lymph nodes show metastatic tumor deposit, All margins are free of tumor tissue	
	337697 NAZAMEEN	33	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	19.2	4.3	8.9	5.7	ThiN- pT3N3aMx; 22/27 lymph nodes shows metastatic tumor deposit, All margins are free of tumor tissue	
	302334 NAWWA	60	Female	LEFT INFILTRATING DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	18.6	3.53	11.3	5.9	ThiN- pT3N3aMx; 13/18 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	306877 RASULBI	70	Female	LEFT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	12.9	1.46	11.4	11.5	ThiN- pT2 N1; 3/18 lymph nodes are positive for tumor deposits, All margins are free of tumor tissue	
	NINGAMMA	42	Female	LEFT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	16.4	4.21	8.9	3.92	ThiN- pT1aN1; 5/15 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	1154 SHOBHA	54	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	15.6	3.2	8.9	3.2	ThiN- pT3bN2aMx; 13/18 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	59546 GEETA	60	Female	LEFT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	13.9	3.1	12.5	1.3	ThiN- T4bN2a; 4/18 lymph nodes tumor deposits, All margins are free of tumor tissue	
	79598 AMEENA	56	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	14	2.1	10.8	8.2	ThiN- pT2N2; 2/3 lymph nodes tumor deposits, All margins are free of tumor tissue	
	118023 BHAGAMMA	39	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	13.2	2.1	12.3	10.9	ThiN- pT4N1a; 1/7 lymph nodes tumor deposits, All margins are free of tumor tissue	
	343855 KAMALABAI	58	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.8	3.84	10.8	6.8	ThiN- pT2N1; 1/12 lymph nodes shows tumor deposit,	All margins are free of tumor tissue
	164568 ROOPABAI	62	Female	RIGHT BREAST PAPILLARY CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	11.6	3.6	8.9	5.3	ThiN- pT2 N0 Mx; All 14 lymph nodes are free of tumor tissue, All margins are free of tumor tissue	
	279223 GANGAVVA	74	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	EQUIVOCAL	12.9	1.84	10.8	4.92	ThiN- PTxN3bSn; 20/20 lymph nodes are free of tumor tissue, All margins are free of tumor tissue	
	GOURAMMA	70	Female	LEFT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	POSITIVE	10.1	1.8	9.2	3.4	ThiN- pT3bN2Mx; 13/15 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	MINAKSUKARNI	70	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	12.8	5.17	8.6	4.12	ThiN- pT2N1; All lymph nodes are free of tumor deposits, All margins are free of tumor tissue	
	CHANDRAMMA	41	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	13.1	6.17	8.1	3.1	ThiN- pT2N1Mx; 2/8 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	SHANKRAMMA	39	Female	LEFT INVASIVE LOBULAR CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.8	7.2	11.4	5.6	ThiN- pT2N3aMX; 13/16 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	RAJESHWARI	48	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	NEGATIVE	NEGATIVE	10.2	7.2	10.2	2.2	ThiN- pT2N3aMx; 9/12 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	SHOBHA KOHAREDDY	40	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	11.7	6.7	10.9	4.7	ThiN- pT2N1Mx; 6/13 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	247341 SHASHIKALA	51	Female	LEFT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	12.7	2.4	9.5	4.3	ThiN- pT2 pN0; All 12 lymph nodes are free of tumor tissue, All margins are free of tumor tissue	
	344884 SHRIMANT	58	MALE	RIGHT INVASIVE CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	15.1	1.5	8.2	3.1	ThiN- pT4N1mi; 3/17 lymph nodes are free of tumor tissue, All margins are free of tumor tissue	
	342123 TARABAI	50	Female	RIGHT INVASIVE CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.7	2.5	11.6	4.3	ThiN- pT1pN3; All 21 LYMPH NODES are free of tumor tissue, All margins are free of tumor tissue	
	208443 RAJESHWARI	42	Female	RIGHT INVASIVE CARCINOMA	POSITIVE	POSITIVE	POSITIVE	12.8	4.4	10	5.8	ThiN- pT2aN1a; 1 out of 20 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	209063 BASAMMA	50	Female	RIGHT INVASIVE CARCINOMA	POSITIVE	POSITIVE	NEGATIVE	13.8	3.7	9.3	2.3	ThiN- pT4bpN3a; 12 out of 17 lymph nodes show metastatic tumor deposit, all margins are free of tumor tissue	
	2351 PRIDHVA	53	Female	RIGHT INVASIVE DUCTAL CARCINOMA	POSITIVE	POSITIVE	EQUIVOCAL	11.9	2.7	8.7	6.8	ThiN- pT2N3Mx; All 16 lymph nodes are free from tumor deposits, All margins are free of tumor tissue	
	POOJA	32	Female	LEFT INVASIVE CARCINOMA	POSITIVE	NEGATIVE	NEGATIVE	16.1	7.2	8.9	4.4	ThiN- pT1N0; All 13 lymph nodes are free from tumor deposits, All margins are free of tumor tissue	
	SUSHILABAI	51	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	19.7	4.6	12.2	6.8	ThiN- pT2N3aMx; 19/20 lymph nodes shows tumor deposits, All margins are free of tumor tissue	
	64617 SHARADABAI	60	Female	RIGHT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	POSITIVE	12.6	6.2	11.3	1.8	ThiN- pT1N1; 1/9 lymph nodes show tumor deposit, All margins are free of tumor tissue	
	35456 HANABAI	60	Female	LEFT INVASIVE DUCTAL CARCINOMA	NEGATIVE	NEGATIVE	NEGATIVE	14.8	4.3	13.4	4.8	ThiN- pT2N3aMx; 7/15 lymph nodes shows tumor deposits, All margins are free of tumor tissue	

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PLAGIARISM CERTIFICATE

DR. Hemanth Reddy

ROLE OF PREOPERATIVE HEMATOLOGICAL MARKERS IN CARCINOMA BREAST AND ITS EFFICACY IN CORRELATION WITH CLINICOPATHOLOGICAL STAGING – A NOVEL TECHNIQUE.

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