ROLE OF ROUTINE LEVEL III AXILLARY LYMPH NODE DISSECTION IN BREAST CANCER FOLLOWING NEOADJUVANT CHEMOTHERAPY

Thesis

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Surgical Oncology

DECEMBER, 2022 **Dr. ALKESH GULHANE**

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CERTIFICATE

This is to certify that the thesis titled "**Role of Routine Level III Axillary Lymph Node Dissection in Breast Cancer following Neoadjuvant Chemotherapy"** is a bonafide work of **Dr. Alkesh Gulhane**, carried out under our guidance and supervision, in the Department of Surgical Oncology, All India Institute of Medical Sciences, Jodhpur.

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This is to certify that **Dr. Alkesh Gulhane** has satisfactorily completed his thesis titled "**Role of Routine Level III Axillary Lymph Node Dissection in Breast Cancer following Neoadjuvant Chemotherapy"** in partial fulfilment of the requirement for the degree of Magister Chirurgiae (M.Ch.) in Surgical Oncology. He has done the research work under my supervision and guidance. He has fulfilled all the requisites under the regulations laid by the All India Institute of Medical Sciences, Jodhpur and no part of the thesis has been submitted to any other university.

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I hereby declare that this thesis titled '**Role of Routine Level III Axillary Lymph Node Dissection in Breast Cancer following Neoadjuvant Chemotherapy"** is a bonafide and original research work carried out in partial fulfilment of the requirement for the degree of Magister Chirurgiae (M.Ch.) in Surgical Oncology, under the supervision and guidance, in the Department of Surgical Oncology, All India Institute of Medical Sciences, Jodhpur.

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Dr. Alkesh Gulhane

Dedicated to

My late Grandparents

Shriram Gulhane

&

Shantabai Gulhane

Contents

Abbreviation	Expansion
ALND	Axillary Lymph Node Dissection
SLN	Sentinel Lymph Node
ALN	Axillary Lymph Node
SLNB	Sentinel Lymph Node Biopsy
NACT	Neoadjuvant Chemotherapy
AUS	Axillary Ultrasonography
FNR	False Negative Rate
BCS	Breast Conservation Surgery
MRM	Modified Radical Mastectomy
ER	Estrogen Receptor
PR	Progesterone Receptor
cN	Clinical Node Status (Pre NACT)
cT	Clinical Tumour Size (Pre NACT)
BMI	Body Mass Index
DCIS	Ductal Carcinoma In Situ
LVI	Lympho-Vascular Invasion
PNI	Perineural Invasion
NCCN	National Comprehensive Cancer Network
IHC	Immuno - Histochemistry
CPR	Complete Pathological Response
LN	Lymph Node
QOL	Quality of Life

RT	Radiotherapy
RCT	Randomized Controlled Trial
NR	Not Reported
ACOSOG	American College of Surgeons Oncology Group
ASCO	American Society of Clinical Oncology
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall Survival
DFS	Disease Free Survival


INTRODUCTION

1. INTRODUCTION

Breast cancer is the most common cancer among females, both worldwide as well as in India. It has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases.[1,2] In India, the majority of females (54%) present in advanced stages of the disease. This is mainly true for females presenting from a rural background and has been attributed to poor socioeconomic status, low level of breast cancer awareness and poor access to healthcare facilities.[3]

There has been a significant decline in the breast cancer mortality over time. The increase in survival was greater for regional cancers (23%) than for localised (10%) or for distant cancers (3%). This decline is believed to be attributable to improved neoadjuvant and adjuvant systemic therapies, including cytotoxic drugs, adjuvant hormonal therapies and biologicals such as anti-human epidermal growth factor receptor 2 (HER2) therapy and radiotherapy.[4]

Surgery is the mainstay of treatment of nonmetastatic breast cancer aimed at achieving a cure for the disease. Failure to attain initial local control will allow some tumours to disseminate later to distant sites, reducing the patient's chance of long-term survival.[4,5,6] Breast cancer surgery encompasses two components- one is resection of the primary tumour with negative margins, which may be breast conservation surgery or mastectomy depending upon various factors and with or without reconstruction. The second one is axillary clearance, which may be sentinel lymph node biopsy in clinically node-negative patients or axillary lymph node dissection in most of the node-positive cases. Surgery can be performed upfront or following neoadjuvant chemotherapy (NACT).

NACT is indicated in women with locally advanced breast cancer, whereas in early breast cancer, it is given to downstage the primary tumour to achieve breast conservation. Nowadays, triple-negative breast cancer and Her2/neu enriched variants of even early breast cancer are also considered for NACT owing to higher pathological complete rates and improved prognosis. There is a lack of consensus regarding the extent of axillary lymph node dissection following neoadjuvant chemotherapy.[7]

Neoadjuvant chemotherapy that is designed to be used prior to surgical removal of a tumor has received significant attention. Response to neoadjuvant chemotherapy is evaluated by the change in tumor size from pretreatment clinical and/or radiologic measurement to post-

treatment status. The spectrum of response to neoadjuvant chemotherapy varies from complete response, partial response, stable disease to non-response. This concept is the same in breast tumors as well as axillary lymph nodes.

Axillary lymph node metastasis is a significant prognostic factor in breast cancer. The prime objectives of axillary surgery in the management of breast cancer are 1) accurate staging, 2) treatment to cure, and 3) quantitative information of metastatic lymph nodes for prognostic purposes and allocation to adjuvant protocols.[9] A complete axillary dissection is usually carried out in most node-positive cases. There is no international consensus on the anatomic levels of the axilla to be addressed as a part of routine axillary dissection .[7] The axillary nodal burden is high in patients with breast cancer in developing countries like India.[6] The extent to which the axilla should be dissected to provide accurate pathologic information remains unclear.

Under-staging the axilla is detrimental to the outcome; furthermore, locoregional tumour control is vital for survival.[9] There is mounting evidence from the randomised controlled trials (RCTs) supporting the link between local control and overall survival.[10,11]

To date, there are very few studies that have addressed the role and characters of level III axillary lymph nodes (ALN) in a subset of patients undergoing surgery following neoadjuvant chemotherapy.

Therefore, the present study was planned to assess the role of routine level III ALND in breast cancer following neoadjuvant chemotherapy.

AIMS & OBJECTIVES

2. AIMS AND OBJECTIVES

A) **RESEARCH HYPOTHESIS**

We can identify preoperatively the patient population who will or will not be benefitted from the level III lymph node dissection in breast cancer following neoadjuvant chemotherapy.

B**) RESEARCH QUESTION, AIMS, AND OBJECTIVES**

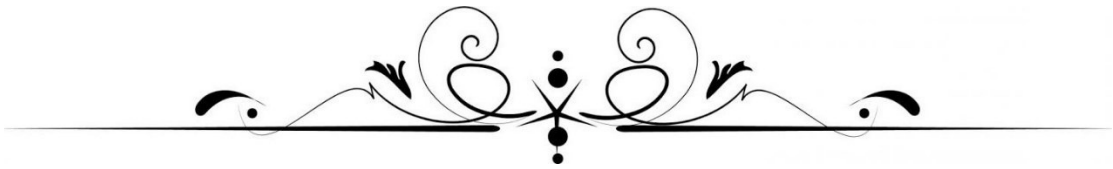
The research question of the study is "Can a necessity of level III lymph node dissection in breast cancer following neoadjuvant chemotherapy be predicted before surgery to utilize this optimally?"

Primary objective:

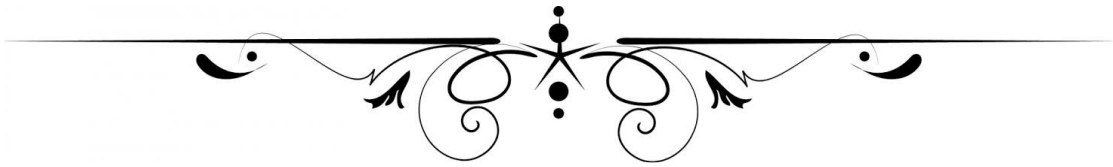
1. To study the correlation between the rate of level III ALN metastases and level I and II lymph node metastasis.
2. To study correlation between the rate of level III lymph node metastasis and clinicopathological characteristics, e.g., primary tumour stage (cT) prior to NACT, clinical nodal stage (cN) prior to NACT, lymphovascular space invasion, Perineural space invasion, Nipple-areola complex invasion, hormone receptor and Herceptin status, grade, focality and extracapsular extension in level I and II.

Secondary objective:

1. Frequency of Skip Metastasis in Level III.
2. Frequency of level III LN metastases in patients receiving partial and full course of neoadjuvant chemotherapy



REVIEW OF LITERATURE



3. REVIEW OF LITERATURE

EPIDEMIOLOGY

Breast cancer (BC) is the commonest malignancy among women globally. It has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases.[12] As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. There are more lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life.[12]

Epidemiological studies have shown that the global burden of BC is expected to cross almost 2 million by the year 2030.[13] In India, the incidence has increased significantly, almost by 50%, between 1965 and 1985. [14] As per the GLOBOCAN data 2020, in India, BC accounted for 13.5% (178361) of all cancer cases and 10.6% (90408) of all deaths with a cumulative risk of 2.81.[15] Current trends point out that a higher proportion of the disease is occurring at a younger age in Indian women, as compared to the West.[15]

RISK FACTORS

The primary risk factor for developing breast cancer is excess exposure to estrogens. Therefore, it is essential to interrogate lifetime estrogen exposure in all patients presenting a new breast mass. Early age of menarche, late age of first pregnancy, nulliparity, oral contraceptive or hormone replacement therapy, and late menopause increase estrogen exposure, while breastfeeding is a protective factor.[16] Male patients should be asked about previous hormonal treatments for prostate cancer, the use of finasteride or testosterone, episodes of orchitis/epididymitis, or previously diagnosed Klinefelter syndrome.[17] Other risk factors, such as excess alcohol intake and obesity, are thought to increase endogenous estrogens.[18]

PATHOPHYSIOLOGY

Breast cancer, the most common cancer-related causality of mortality, is a complex, heterogeneous disease classified into three main categories of hormone-receptor-positive, human epidermal growth factor receptor-2 overexpressing (HER2+), and triple-negative breast cancer (TNBC). The mentioned classification is based on histopathological findings.

The discrete identification of the breast mass is specifically helpful for further target therapy. Accordingly, estrogen-receptor-positive and HER-2 positive breast cancers would benefit from tamoxifen and trastuzumab, respectively.[19]

BREAST CANCER DIAGNOSIS

Screening

Breast cancer is generally diagnosed through either screening or a symptom (e.g., pain or a palpable mass) that prompts a diagnostic exam. Screening of healthy women is associated with the detection of tumors that are smaller, have lower odds of metastasis, are more amenable to breast-conserving and limited axillary surgery, and are less likely to require chemotherapy.[20] This scenario translates to reduced treatment-related morbidity and improved survival.

The only screening modality proven to reduce breast cancer– specific mortality is mammography.[21] Screening mammography leads to a 19% overall reduction in breast cancer mortality,[22] with less benefit for women in their 40s (15%) and more benefit for women in their 60s (32%). As a result, screening mammography is recommended by the American Cancer Society beginning at age 45, or sooner depending on individual preference. The potential negative aspects of screening mammography are false positive examinations, radiation exposure, pain, anxiety, and other negative psychological effects. Mammography has a 61% chance of a false-positive result over a 10-y period for women commencing screening between the ages of 40 y and 50 y. The risk of a false positive examination decreases with older age. [22]

The US Preventative Task Force cited a 15% breast cancer–related mortality reduction for women who were 39–49 y old and a mortality-related benefit from screening between ages 39 and 69. However, the task force released a controversial report recommending only biennial screening mammography for women who were 50–74 y old, excluding younger women to a large extent because of the high rate of false-positive results.[22, 23] Mammography for women in the 39- to 49-y-old age group was recommended if indicated after the use of a risk-based model of breast cancer screening, such as the models developed by the Population-Based Research Optimizing Screening Through Personalized Regimens network, or if requested by a patient.[24]

The addition of digital breast tomosynthesis to a conventional full field digital mammography examination reduces false-positive results and increases cancer detection.[25] One concern

about adding digital breast tomosynthesis to screening is the approximate doubling of the radiation dose over that of conventional full-field digital mammography alone. To address this issue, some institutions reconstruct synthetic 2-dimensional images from 3-dimensional tomosynthesis images; this process reduces the radiation dose by approximately 45%.[26] Initial clinical experience with synthetic 2-dimensional images has demonstrated no increase in recall examinations, so that the most significant tomosynthesis benefit is maintained.[27] Still, the reduction of false-positive examinations after tomosynthesis implementation has been modest (16/1,000),[25] and practice changes such as a lower maximum acceptable recall rate of 9%–10% (currently it is 12%) and an increase in the biopsy threshold from a 2% chance of malignancy to a 4% chance of malignancy could have a greater impact on reducing harm from screening.[28]

Supplementing mammography with other imaging modalities for higher-risk patients leads to the additional detection of mammographically occult cancers. A meta-analysis of 14 studies of high-risk women found that MRI had a higher sensitivity for malignancy (84.6%) than mammography (38.6%) or ultrasound (39.6%).[29] Further, the use of MRI as an adjunct to mammography had a higher sensitivity for malignancy (92.7%) than the use of ultrasound as an adjunct to mammography (52%).[30] As a result, for women who have a lifetime risk of breast cancer of greater than 20%, breast MRI as an adjunct to mammography is recommended by the American Cancer Society. This group includes women with genetic mutations that connote an increased risk of breast cancer and those with a history of radiation therapy for Hodgkin lymphoma that included the breast tissue. Ultrasound is a viable option for the screening of high-risk women who cannot have breast MRI or women with intermediate risk, such as those with dense breasts. The main limitations of screening ultrasound are a high rate of false-positive results and dependence on operator expertise. [31] The high rate of false-positive results (and the low positive predictive value) of ultrasound has not yet met the minimum standard recommended by the Ultrasound Agency for Health Care Policy and Research.[32] Concerning other screening modalities, some of which are discussed elsewhere in this supplement, the current American College of Radiology appropriateness criteria state, “There is insufficient evidence to support the use of [additional screening] imaging modalities such as thermography, breast-specific gamma imaging, positron emission mammography, and optical imaging.”[33]

PATHOLOGIC EVALUATION

Specimen Processing and Evaluation

In clinical practice, diseased tissue is usually obtained by fine-needle aspiration, core biopsy, or surgical excision. A diagnostic challenge for pathologists is the distinction of closely related diseases, such as atypical ductal hyperplasia and in situ disease, in situ disease and microinvasion, or ductal cancer and lobular cancer. Ancillary immunohistochemical and molecular tests can be used to assist the characterization of ambiguous morphology in many, but not all, cases. Features such as tissue handling, ischemic time, cautery, use of frozen sections, fixation, decalcification, and processing all are critical for the quality of the histologic sections used for microscopic evaluation and ancillary tests, such as immunohistochemistry (IHC), in situ hybridization, and molecular tests based on reverse transcription–polymerase chain reaction.[34]

The size of the tumor is determined by careful clinical and pathologic correlation. When a breast cancer forms a distinct mass outward from a point of origin, the size can be easily assessed by imaging and gross pathologic examination. When a tumor arises in a poorly defined field of genetic instability and there is intratumoral normal tissue, accurate sizing can be challenging. In addition, finding and accurately measuring small cancers detected by advanced imaging can be difficult when they are not visible on gross inspection of the specimen, especially because the surgical specimen presented to the pathology laboratory might greatly deviate from the in vivo shape observed by the surgeon and radiologist due to breast tissue elasticity. Surgical specimens are typically marked with ink in 6 dimensions according to the orientation given by a surgeon. However, margin assessment after surgical resection is complicated by lack of marking standardization and potential artifacts from cautery or specimen handling.[34]

Predictive Tumor Markers

Critical treatment decisions are made on the basis of protein expression assays that are independent of tumor morphologic characteristics. IHC analysis of paraffin sections is routinely performed for the evaluation of estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu (HER2) status. Although widely used to predict responses to targeted agents, histologic tumor markers are limited by significant intratumoral variation, even within a single biopsy specimen. RNA and DNA can also be tested in routine paraffin-embedded tissue samples, and in situ hybridization can detect HER2 amplification as a confirmatory test

for IHC or as a stand-alone assay. There is great interest in other actionable targets in cancer genomes for precision therapy using next-generation gene sequencing.[34]

DNA microarrays and high-throughput reverse transcription– polymerase chain reaction assays for multiple genes (e.g., 21 in Oncotype [Genomic Health, Inc.] and 70 in MammaPrint [Agendia]) can be used to categorize breast cancers into several prognostic groups.[35] Gene assays are used to predict the risk of distant recurrence in early-stage breast cancer and to influence decisions about systemic therapy. These tests rely heavily on the assessment of ER and proliferation-related genes, such as Ki-67, and have largely replaced the use of other, single markers of risk in clinical practice. Still, as mentioned earlier, ER and PR expression can be heterogeneous and cellular proliferative status can also be variable within a single tumor. Because any biopsy sample is subject to sampling error, and sectioning of the entire tumor for the analysis of predictive and prognostic biomarkers is not practical, imaging for breast cancer biomarkers can play a pivotal role in providing a global overview of gene expression. In addition to the markers already mentioned, other cancer biomarkers and oncogenic molecular genetic abnormalities have been reported; [36] however, these are not yet widely accepted as the standard of care because of continued standardization of analyses, assay protocols, and analytic methodologies.[37]

IMAGING AND STAGING

Physical examination, mammography, or ultrasound for the diagnostic work-up of a patient with newly diagnosed breast cancer is usually sufficient for local–regional staging. MRI is sometimes recommended, especially when a patient is younger, a genetic mutation or multifocal disease is suspected, or a mammogram or ultrasound yields indeterminate findings. Although breast MRI does detect additional disease in the contralateral breast approximately 3% of the time, [38] meta-analyses of preoperative breast MRI have shown an increase in rates of mastectomy[39] and no increase in local control after breast-conserving surgery (BCS) and radiation treatment.[40] Studies of breast MRI have also shown a risk for overestimation of tumor size.[41]

Further, it is possible that small additional cancers detected by MRI would never be clinically significant or responsible for a local recurrence because of adjuvant systemic or whole-breast radiation treatments. MRI may play an important role in evaluating disease extent when more limited radiation to the tumor bed or only regional node irradiation is

considered.[42] In addition, breast MRI can be obtained in patients receiving neoadjuvant chemotherapy to assess responses and aid in surgical planning.[42]

A chest radiograph and routine laboratory blood tests are sufficient for staging in a patient with clinical stage I or II breast cancer and no specific symptoms of metastatic disease. For suspected advanced (stage IIIB/C or IV) disease, National Comprehensive Cancer Network guidelines recommend either chest, abdomen, and pelvis CT or chest CT with abdomen and pelvis MRI as well as bone scan or sodium fluoride PET/CT. 18F-FDG PET/CT is listed as optional for assessing stage IIIB/C or IV disease but is not indicated for the staging of stage I or II disease. Supporting the use of PET to evaluate advanced breast cancer, a metaanalysis of 5 studies (547 patients) demonstrated a sensitivity for breast cancer of 0.97 (95% confidence interval, 0.93–0.99) and a specificity of 0.95 (95% confidence interval, 0.90–0.97).[43]

BREAST CANCER TREATMENT

SURGERY

The primary means of local and regional breast cancer treatment remains surgical intervention. During the first half of the 20th century, women diagnosed with breast cancer were commonly treated by radical mastectomy, as first described by William Stewart Halsted in 1894. Breast conservation surgery (BCS) was pioneered by Fischer et al.[44] and Veronesi et al.[45] who reported that survival with lumpectomy and radiation was equivalent to that with mastectomy in the treatment of early breast cancer. Improved breast cancer screening resulted in diagnoses of nonpalpable cancers, necessitating the development of a localization approach for surgical treatment.

Breast-Conserving Approaches

Wire localization of a breast tumor is a mainstay of BCS. This procedure is routinely performed by a breast imaging radiologist on the day of surgery. Placement of the surgical incision on the breast is guided by cosmetic considerations and tumor location. A circumareolar location is ideal for a tumor 1–2 cm from the areolar margin, but when a tumor is more than 2 cm from the areola, an incision directly over the area of concern may be advantageous so that the lumpectomy site can be easily identified if a margin re-excision is necessary. After the initial incision is made, the length of the localization needle is noted, and dissection can take place directly along the needle track.[46]

Radioactive seed localization reduces the time the patient spends in the hospital on the day of surgery and allows the surgeon to place the incision over the site with the highest counts without having to account for the site of entry of the needle, which may be in a quadrant different than the tumor. Studies comparing radioactive seed localization and wire localization demonstrated no significant difference in operative times and a possible lower re-excision rate with the seed localization technique.[46]

In women with larger breasts, wide excision can be performed with an oncoplastic procedure, which usually involves breast reduction. This procedure was pioneered by Silverstein et al. for the surgical treatment of in situ breast cancer with the goals of obtaining surgical margins of more than 1 cm and avoiding whole breast radiation.[47] One caveat for this technique is that if there are positive margins, then reexcision may be difficult because of the rearrangement of tissue planes at the time of surgery. Therefore, patients should be counseled before choosing this option that complete mastectomy may be necessary if clean pathologic margins (no invasive breast cancer on ink or DCIS farther than 2 mm from ink) are not obtained.[47]

Non–Breast-Conserving Approaches

For most women with screening-detected and early-stage breast cancer, mastectomy is a choice. However, mastectomy may be necessary for women who have had radiation to the affected side (for prior breast cancer or Hodgkin lymphoma) or for women with a relatively small breast in the setting of a large primary breast cancer, extensive calcifications, or multicentric disease. For women with a large primary breast cancer without extensive associated malignant calcifications, neoadjuvant chemotherapy may downstage the primary cancer and makes breast conservation possible.[48]

Most women electing mastectomy are candidates for immediate reconstruction.[48] The surgical approach differs for women who do not elect reconstruction; a larger skin ellipse is removed. For women undergoing immediate reconstruction, skin-sparing mastectomy with or without preservation of the nipple may be performed. Nipple-sparing mastectomy is generally oncologically safe for in situ or stage I and II invasive cancers.[49,50] Some factors predicting nipple involvement are a tumor size of greater than 5 cm, a distance from the tumor to the nipple of less than 2.5 cm, negative ER and PR status, and positive HER2 status.[51] Patients with malignant calcifications extending to within 2 cm of the nipple or inflammatory breast cancer are generally counseled against this procedure.[51]

Axilla Staging Procedure

One of the major technical advances in breast surgery was the introduction of sentinel lymph node biopsy (SLNB) to replace the conventional axillary node dissection described by Giuliano et al. in 1994.[52] SLNB is associated with a significantly lower lymphedema risk (2%–3%) than complete axillary node dissection (15%–20%).[53] The procedure is more than 98% accurate when results are negative, and further dissection is not needed. When SLNB results are positive, complete axillary dissection is not useful for improved local–regional control or survival in women who have no palpable adenopathy, 1 or 2 positive sentinel nodes, and no gross extranodal extension, as shown by a large randomized controlled clinical trial (American College of Surgeons Oncology Group Z0011 trial).[54]

Breast radiologists often perform fine-needle aspiration of non-palpable axillary nodes with suspect imaging morphology. Given the results of the Z0011 trial, this approach poses a surgical dilemma in the management of the axilla because most of the involved patients would have been eligible for SLNB. Should these patients have full axillary dissection if the fine-needle aspiration results are positive, or should they still have SLNB if the results for the axilla are clinically negative? These questions warrant further investigation.[54]

SLNB may be used in the clinically node-positive patient after a good response to neoadjuvant chemotherapy, with a few caveats. The ACOSOG Z1071 trial demonstrated that SLNB is feasible after neoadjuvant chemotherapy, with an overall rate of false-negative results of 12.6%.[55] The rates of false-negative results decreased to 10.8% when both radiotracer and blue dye were used and to 9.1% when there were at least 3 sentinel nodes.[55] In the SENTINA trial, [56] one arm contained patients who converted from clinically positive to negative results for the axilla after neoadjuvant chemotherapy (arm C) and underwent SLNB and then complete axillary node dissection. The overall rate of false-negative results of SLNB was 14.2% when lymphatic mapping was performed by either radio colloid or blue dye injection. However, subset analyses revealed that the rate of false-negative results was significantly lower when both radio colloid and blue dye were used (8.6%) and when at least 3 sentinel nodes were removed (7.3%).[56]

SYSTEMIC THERAPY

After surgical treatment, adjuvant systemic therapy should be considered to reduce risk of cancer recurrence. Various factors for individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/PR and HER2 status) are considered. Patients are stratified based on theirHR- status and HER2 expression and various factors predicting risk of disease recurrence based on anatomic and pathologic characteristics such as tumor grade, tumor size, ALN status, angiolymphatic invasion.

Treatment for hormone receptor-positive, HER2-negative tumours

Adjuvant endocrine therapy is administered to reduce the risk of recurrence. Adjuvant chemotherapy is given in patients deemed at high risk for distant recurrence despite adjuvant endocrine therapy. Choosing whether or not to provide patients with HR-positive and HER2-negative tumours with adjuvant chemotherapy, is based on a variety of variables, such as lymph node status, tumour size, grade, lymphovascular invasion, age, coexisting diseases, and/or the findings of a gene expression profile test employing multigene assays. A number of commercially accessible gene-based assays are helpful in evaluating prognosis by forecasting survival or local or distant recurrence. Only one of these, the Oncotype Dx 21-gene assay, has been clinically proven to be accurate at predicting the benefit of incorporating adjuvant chemotherapy to further lower the chance of recurrence. It calculates the Recurrence score (RS). For Subset of Patients with Node Negative disease Adjuvant chemotherapy added to endocrine therapy for tumours with RS of 0 to 10 has no additional benefit for these patients because the risk of distant recurrence is low in these cases. A clear advantage of adjuvant treatment is shown by secondary analyses of prospective studies in patients with high RS (>=31), who have a higher risk of distant recurrence.[57]

In intermediate RSA (11-25), TAILORX trail showed similar DFS in both groups. However, a subset study found that when adjuvant chemotherapy was added to endocrine therapy for patients with RS 16–25 who were 50 years of age or younger, the rates of distant recurrence were dramatically reduced.[58]

Similarly in subset of patients with node positive disease RS<=11 has 5 year DFS of 94.4 with endocrine therapy alone. The results of this and other studies suggest that patient with limited nodal disease(1 to 3 positive),low RS, the absolute benefit from chemotherapy is likely to be very small.[59]

If the RS is high (> 31), adjuvant chemotherapy clearly benefits patients with node positive, HR-positive, HER2-negative malignancies. In SWOG 8814 trail Patients with a high RS (31) who received CAF therapy saw improvements in their 10-year DFS (55% vs. 43%; HR 0.59, 95% CI 0.35-1.01) and OS (73% vs. 54%; HR 0.56, 95% CI 0.31-1.02). [60]

ENDOCRINE THERAPY

Tamoxifen and Ovarian Ablation/Suppression

For both premenopausal and postmenopausal individuals, tamoxifen is the most well-established adjuvant endocrine treatment. Regardless of the use of chemotherapy, patient age, menopausal status, or ALN status, adjuvant tamoxifen reduces the yearly odds of recurrence by 39% and the annual odds of death by 31% in patients with ER-positive breast cancer.[61]

The NCCN Panel advises tamoxifen treatment with or without ovarian suppression/ablation for patients who are premenopausal at diagnosis. Both surgical oophorectomy and ovarian radiotherapy are options for ovarian ablation while ovarian suppression is done by luteinizing hormone-releasing hormone (LHRH) agonists.

Exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a five-year period was given to HR Positive premenopausal individuals with early-stage breast cancer in two randomised trials (TEXT and SOFT). . Exemestane plus ovarian suppression had a DFS of 92.8%, whereas tamoxifen plus ovarian suppression had a DFS of 88.8% (HR for recurrence, 0.66; 95% CI, 0.55-0.80; P .001). Between the two groups, there was no discernible difference in OS (HR for death in the exemestane + ovarian suppression group, 1.14; 95% CI, 0.86-1.51; P =.37).[62]

Based on these results ovarian suppression combined with an aromatase inhibitor for five years has been approved by the NCCN Panel as an adjuvant endocrine therapy option for premenopausal patients with hormone-receptor-positive breast cancer who are at a higher risk of recurrence (eg, young age, high-grade tumour, lymph-node involvement).[63]

Aromatase Inhibitors

Anastrozole, letrozole, and exemestane are used for HR positive Postmenopausal patients. Anastrozole is superior to tamoxifen or tamoxifen and anastrozole when used as adjuvant endocrine therapy for postmenopausal individuals with HR-positive breast cancer, according

to the ATAC study. Results from the ATAC study, which included 5216 postmenopausal patients with HR-positive, early-stage breast cancer, showed that anastrozole was superior to tamoxifen in preventing recurrences (HR for DFS, 0.85; 95% CI, 0.76-0.94; P =.003). 329 There was no discernible difference in survival (HR, 0.90; 95% CI, 0.75-1.07; P =.2).[64]

Duration of adjuvant endocrine therapy

Adjuvant endocrine therapy is recommended for a minimum of 5 years. But Evidence from ATLAS and aTTom trails demonstrate greater reduction in recurrence and death from breast

CHEMOTHERAPY

Chemotherapy is used for tumours that are hormone receptor negative, alongside trastuzumab in HER2- positive tumours, and in addition to endocrine therapy in ER-positive patients, based largely on features such as anatomic stage (tumour size and nodal status), the biologic features of the cancer, and the patient's other health considerations. It is an established fact that numerous cycles of polychemotherapy are a crucial approach to increase survival and reduce the probability of breast cancer recurrence. Irrespective of age, tumour ER status, adjuvant endocrine therapy, there is long term benefit from chemotherapy according to the EBCTCG. The summary also reveals that numerous chemotherapy cycles (four to eight) have advantages over single-cycle chemotherapy.it also illustrates the superiority of anthracycline- and taxane-based chemotherapy regimens over Non-anthracycline regimens based on cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).[67] Therefore for the majority of patients with node-positive and higher risk node-negative tumours, many cycles of adjuvant chemotherapy, often involving taxanes and anthracyclines as part of the regimen, are advised.[68]

When compared to women undergoing four cycles of cyclophosphamide + doxorubicin (AC) chemotherapy, CALGB 9344 showed that the addition of sequential paclitaxel therapy increased both DFS and OS among women with node-positive breast cancer.[69]

The CALGB 9741 trial compared AC followed by paclitaxel given either every 3 weeks or every 2 weeks at the same doses and schedules. Accelerated, every-2-week treatment (so called dose-dense treatment) led to lower risk of recurrence and improved survival.[70]

Contrary to concurrent taxane, anthracycline, and alkylator combinations, sequential therapy with anthracyclines or alkylators followed by taxanes was found to be more effective.[71]

For women who warrant chemotherapy, sequential anthracycline- and taxane-based treatment remains the "gold standard." AC for four cycles followed by paclitaxel chemotherapy, with paclitaxel given as either four cycles every 2 weeks or as 12 weeks of weekly therapy is the standard therapy for the most. There has been a growing interest in sparing patients with Anthracycline therapy. In a trial of 1,016 women with node-negative disease or one to three positive lymph nodes, the two-drug combination regimen of docetaxel plus cyclophosphamide was superior to AC (each regimen given for a total of four cycles). This made docetaxel plus cyclophosphamide an option for these intermediate-risk patients.[72]

In the Anthracyclines in Early Breast Cancer (ABC) research, 337 women with HER2-negative breast cancer received eitherdocetaxel plus cyclophosphamide therapy or an anthracycline-based regimen, such as AC followed by taxane. Overall, the anthracycline-based regimens produced superior outcomes, notably in triple-negative breast cancers and higher risk node-positive, ER-positive tumours. It is therefore unclear if anthracyclines can be safely skipped among people at increased risk.[73]

NCCN has listed these Regimens as preferred: dose-dense doxorubicin and cyclophosphamide (AC) with dose-dense sequential paclitaxel; dose-dense AC followed by sequential weekly paclitaxel; and docetaxelplus cyclophosphamide (TC).[63]
Despite the fact that chemotherapy frequently results in a statistically significant risk reduction, differences in the absolute risk of recurrence for patients, particularly those with small cancers or cancers that are also receiving adjuvant endocrine therapy (ER-positive cancers), typically tend to be very small (single percentage points).[74]

Hormone receptor negativity, Her2 positivity and triple negative tumors derive substantial benefit from chemotherapy. HER2 overexpression is associated with a relative benefit from anthracycline-based chemotherapy. Other retrospective research based on defining the ER and HER2 status of tumours suggests that chemotherapy with taxanes may be particularly important in cancers that either express HER2 or lack ER expression.[75]

HER2-Directed Therapy

For HER2-positive breast cancer, trastuzumab, a HER2-specific monoclonal antibody, improves the survival of patients with early-stage breast cancer and should be given in addition to chemotherapy.

Adjuvant Trials of Trastuzumab:

Trial	Hazard Ratio— DFS	Hazard Ratio— OS
NSABP B31/ NCCTG N9831	0.48	0.67
HERA	0.64	0.63
FinHER	0.42	0.41
BCIRG 006	0.61	0.59

Because of the increased risk of heart failure with anthracycline- and trastuzumab-containing regimens, nonanthracycline, taxane-containing regimens can be used. No trials have compared the various HER2 regimens; therefore, for patients with the highest risk, a standard regimen contains an anthracycline followed by a taxane with trastuzumab. No matter which chemotherapy is used, trastuzumab should be continued for 1year, with cardiac monitoring every 3 mo. Clinicians can also consider adding pertuzumab, a monoclonal antibody that is directed against a different area on the HER2 receptor than trastuzumab. The results of NCT01358877, a phase III, double-blind, placebo-controlled trial in which patients with positive HER2 and lymph nodes were randomized to receive adjuvant pertuzumab or placebo along with standard adjuvant chemotherapy and trastuzumab, are pending.[76, 77]

RADIOTHERAPY

Prospective randomized trials have confirmed that long-term mortality from breast cancer and overall patient survival are comparable for BCS plus radiation treatment and for mastectomy. BCS plus radiation treatment is also associated with very high local control rates (90%–95%) in the preserved breast within 10 years from treatment; these rates are comparable to those obtained with mastectomy, with most women having a good or excellent cosmetic result. The low rates of local recurrence in the modern era are due to progress in the multidisciplinary care of breast cancer: treatment of disease at an earlier stage because of detection by screening; improved imaging enabling appropriate patient selection for breast conservation; improved surgical techniques and margin pathology assessment; and improved radiation techniques, which may reduce marginal miss and radiation dose escalation, with a tumor bed boost, when indicated. Additionally, chemotherapy or endocrine systemic therapies, when indicated, are in widespread use, as discussed above. Radiation also has a

proven role in the treatment of stage 0 breast cancer (ductal carcinoma in situ); 90%–95% long-term local control has been achieved with improved patient selection and surgical and radiation techniques.[78, 79]

The past decade has seen considerable advances in the delivery of postoperative radiation that aim to optimize the treatment for each person's anatomy and reduce acute or long-term toxicity. Three-dimensional planning with a CT simulator and either field-in-field 3-dimensional conformal radiation therapy (forward planning) or intensity-modulated radiation therapy (inverse planning) has replaced the simple 2-dimensional planned breast tangents. By reducing dose nonhomogeneity, these advances in techniques are associated with lower rates of complications, such as acute skin desquamation, edema, late fibrosis, or negative cosmetic effects on the breast. In addition, techniques involving the prone position and deep-inspiration breath holding are now used for left-side breast cancer or larger breast size to reduce toxicity (particularly cardiac dose sparing).[79, 80]

Radiation after BCS

Randomized trials have confirmed that recurrence rates with BCS alone are higher than those with BCS plus radiation treatment, even in patients selected for favorable clinical and pathologic features.[81-83] In addition, there is a survival advantage of radiation in patients with invasive breast cancer. However, BCS without radiation may be an option for carefully selected women. In early-stage invasive breast cancer, the combination of older age, small tumor size, negative results for lymph nodes, and hormone sensitivity has been associated with a low risk for local recurrence after BCS without radiation.[84] In ductal carcinoma in situ, BCS alone may be an option for tumors with a small size, wide margins, and a low to intermediate grade.[85] With careful patient selection, subgroups of patients with these characteristics may have acceptably low local recurrence rates even without radiation (not likely to significantly affect the odds for survival) and a high probability for salvage therapy of local recurrences. Trials have not consistently required MRI staging, which could improve the detection of additional foci that are located away from the primary tumor bed and that could lead to early recurrences in patients not receiving radiation.[85]

Regional Node Radiation

Radiation therapy has a role in the regional control of nodal disease in many patients with high-risk or node-positive stage II, and most patients with stage III, breast cancer. The

primary area at risk for regional recurrences in patients with positive lymph nodes is the supraclavicular and high axillary region. Radiation is currently directed to these areas on the basis of pathology indications, such as the number of axillary nodes with positive results, the ratio of axillary nodes with positive results to those with negative results, the extent of axillary dissection, and extensive lymphovascular invasion. Even though PET/CT has a relatively low sensitivity for axillary disease (60%), the specificity is very high (97%).[86]

The role of elective radiation of the internal mammary chain remains controversial after 50 y of study. Studies of elective nodal radiation have either yielded negative findings or resulted in only a marginal disease-free survival benefit.[86-88] Selection of patients for internal mammary node radiation is often recommended for subgroups at higher risk because of inner-quadrant tumor location with positive axillary nodes, extensive lymphovascular invasion, or hormone receptor–negative tumors. The negative findings in these trials of elective radiation may have been partly due to the randomization of large numbers of patients without actual disease involvement. Imaging could be used to select patients with nodal involvement before intervention, but this approach has not been used in prospective trials. PET/CT identifies occult lymph node metastases in the internal mammary chain in approximately 10%–15% of patients, leading to altered radiation field selection in 10%–16% of patients.[89, 90]

Postmastectomy Radiation

In women treated by mastectomy, radiation is recommended for adjuvant treatment when there are clinical or pathologic factors predicting an intermediate to high risk ($10%) of local–regional recurrence.[91] Randomized prospective trials have confirmed a reduction in local–regional recurrence and an improvement in survival with postmastectomy radiation in this subgroup of women.[92] In contrast, women with a low risk for local–regional recurrence after mastectomy do not require radiation. Patients generally treated with postmastectomy radiation include those who have 4 or more positive axillary nodes, T3 tumor size, positive resection margins, and locally advanced or inflammatory breast cancer. Radiation is also recommended for patients who have 1–3 positive nodes and other risk factors for local–regional recurrence, such as lymphovascular invasion, young age, high-grade tumors, or hormone receptor–negative breast cancer.[93]

Shortening Duration of Radiation

The past decade has seen advances in techniques for the delivery of postoperative radiation that aim to preserve high rates of local control but shorten overall treatment time, reduce cost, and improve convenience of care. Hypofractionation is the use of radiation treatments with fewer, larger doses than the conventional radiation fraction sizes of 1.8–2 Gy/d.[93]

Hypofractionated whole-breast irradiation (WBI) has been firmly established as a standard of care for post-lumpectomy radiation for early-stage breast cancer, in large part because of the favorable 10-y results of 4 prospective randomized trials from Canada and the United Kingdom.[93,94] These trials showed equal 10-y local control as well as comparable or better cosmetic outcomes and late toxicities with hypofractionation. One of the issues regarding more widespread acceptance of WBI has been the relatively low accrual into the 4 major trials of certain subgroups of patients, such as those younger than 50 y and requiring a boost or systemic chemotherapy. Currently, approximately 20% of women are treated with WBI. [95] The Radiation Therapy Oncology Group completed a phase III randomized trial (RTOG 1005) of hypofractionated WBI with a concurrent boost that had the goals of expanding the use of hypofractionation by enrolling a patient population broader than that enrolled in the existing hypofractionated WBI studies and further reducing the treatment time to only 3 wk.[95]

Accelerated partial breast irradiation (APBI) represents a departure from whole-breast irradiation because only the area around the primary tumor, including a small margin, is targeted with radiation. The major techniques used for APBI can be divided into external-beam radiation therapy and delivery of radiation through sources placed inside temporary internal catheters (brachytherapy).[96,97] Because of the much smaller treatment volume, the radiation dose is increased and the treatment time is reduced, commonly twice a day for 10 fractions over 1 wk. Not all patients with early-stage breast cancer are suitable for APBI; in past trials with promising 5-y results, enrollment was generally limited to patients with small tumor sizes and favorable histologic characteristics. The degree to which young age or adverse pathologic features will influence local control with APBI is unknown. In the NSABP B-39 trial, 10-year cumulative incidence of IBTR with APBI was 4.6% compared with 3.9% with WBRT, yielding an absolute difference of 0.7% with an HR of 1.22 (90% CI, 0.94–1.58) that did not meet the prespecified criteria for equivalence. However, given the small magnitude in IBTR differences between WBRT and APBI, it is not likely to be of clinical significance in appropriately selected patients.[97]

Axillary Lymph Node Dissection

Axillary lymph node dissection is an indispensable step in modified radical mastectomy for breast cancer. It is the most reliable method and the golden standard to determine the status of axillary lymph nodes. It also is of great importance to evaluate the prognosis and develop treatment plans for breast cancer patients.[98]

Anatomically, axillary lymph nodes are divided into three levels, with the pectoralis minor muscle as the boundary. The lymph nodes located laterally to the pectoralis minor muscle are level I axillary nodes, which include the lateral breast group, the central group, and the subscapular group. The lymph nodes located posteriorly to the pectoralis minor muscle's deep surface are level II axillary lymph nodes. The lymph nodes located medially to the pectoralis minor muscle are level III axillary lymph nodes. Level III lymph nodes are the relay station of mammary gland lymphatic drainage to the supraclavicular lymph nodes or the thoracic duct.[98]

Indications of Level III Axillary Lymph Node Dissection

The NCCN Guidelines for clinical practice in breast cancer indicate that in the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I/II). Only in cases with gross diseases in level I/II, level III dissection to the thoracic inlet should be performed.[99]

Dissection of level III may lead to postoperative paresthesia, axillary deformity, lymphedema, and so on. It is an irregular clinical procedure that has been controversial. Sentinel lymph node biopsy has a profound effect on the reduction of axillary trauma. The Z0011 trial clearly defined the lymph nodes positive breast cancer patients in whom it is safe to avoid axillary lymph node dissection: (1) with clinical T1 or T2 stage tumors; (2) with ≤ 2 positive sentinel lymph nodes; (3) receiving breast conserving surgery; (4) receiving postoperative whole breast radiotherapy; and (5) receiving systemic adjuvant therapy after surgery.[100] Liu et al applied the criteria of the Z0011 trial to Chinese patients with sentinel lymph nodes positive breast cancer and screened outpatients with better prognosis and lower risk than those in the Z0011 study.[101] These patients could safely only receive sentinel lymph node biopsy without axillary lymph node dissection. Systemic treatment, including chemotherapy, endocrine therapy, and immunotherapy, may remove residual tumor cells in the axilla and thus reduce the recurrence rate in the axilla. [102]

Studies have shown that 20–42% of patients with positive axillary lymph nodes can achieve complete pathological remission after receiving neoadjuvant therapy (chemotherapy or immunotherapy).[103] The risk of local recurrence is also reduced. Adjuvant chemotherapy and endocrine therapy can also reduce the risk of regional recurrence.[104] Despite this, 20–30% of patients with sentinel lymph node biopsy need to consider axillary lymph node dissection due to positive lymph nodes.[105] The NSABP B04 test found that the recurrence rate of patients with insufficient axillary lymph node dissection was 18.6%.13 For elderly patients, ignoring axillary lymph node dissection will not affect DFS and OS.[106] Axillary lymphadenectomy was associated with improved survival in patients presenting with clinical N2–3 invasive breast cancer.[107] Most surgeons perform axillary lymph node dissection in patients with positive axillary lymph nodes. There are many reasons for this, such as difficulties in treating axillary recurrence, the psychological impact of recurrence in patients, and problems in a rigorous followup.[107]

The effect of axillary therapy on survival is also controversial. For most patients with breast cancer, level III axillary lymph node dissection means an excessive treatment.[108,109] Kodama et al compared the effects of T1/ 2/3 and N0/1a/1b (International Union of Cancer Staging 1987) breast cancer patients with level ш or level I axillary lymph node cleaning.[108] The results show that the 10-year OS rates were 87.8% and 89.6% (P = 0.552), and the 10- year disease-free survival rates were 74.1% and 76.6%, respectively (P = 0.7). Because level III axillary lymph node cleaning did not improve the survival rate in T1/2/3 and N0/1a/1b patients, it is not recommended. Tominaga et al compared the effects on overall survival of level III with level II axillary lymph node cleaning in patients with stage II breast cancer.[109] They found that the 10-year overall survival rates were 86.6% and 85.7% (P = 0.931), and the 10-year DFS rates were 73.3% and 77.8%, respectively, in patients with level II or level III axillary lymph node dissection (P = 0.666). Therefore, they thought that extra level III axillary lymph node cleaning might be of no benefit. However, these two studies did not focus on patients with positive lymph nodes. The lymph node metastasis rates in Kodama and Tominaga's study were 32.1% and 32.7%, respectively. In the study of Kodama, level III axillary lymph nodes invasion rate was only 7.4%.[108] Level III axillary lymph node dissection could remove a higher proportion of positive lymph nodes in lymph nodes positive breast cancer patients.[108]

Although level III cleaning does not improve survival,[110] metastasis of level III axillary lymph nodes is an essential factor that causes distant recurrence.[111] It is an important index to

judge patients' prognosis with breast cancer. Once tumor cells invade axillary lymph nodes, they will spread along with the lymphatic system. Consequently, tumor cells invading level III axillary lymph nodes are mostly to spread to the neck and the chest cavity. Level III axillary lymph node cleaning can increase the completeness of axillary lymph node cleaning in patients with preoperative positive axillary lymph nodes. It also has important guiding significance to postoperative treatment and prognosis improvement. Level III axillary lymph node invasion, however, is not an independent prognostic factor. Although level III axillary lymph node cleaning can provide more accurate classification according to the American Joint Committee on Cancer Staging, cleaning the axillary lymph node does not bring a significant survival benefit.[111] Level I+II axillary lymph node dissection is standard, but level III cleaning is unusual. Only in selected patients with a wide range of axillary lymph node invasion and/or obvious level II/III axillary lymph node invasion, level III axillary lymph node dissection is performed.[111] This situation mainly occurs in locally advanced breast cancer with clinical stages T3-4 and N1-2.[112] Although level III axillary lymph node invasion is not an independent prognostic factor for regional recurrence, it may be a predictor for distant metastasis-free survival. Level III axillary lymph node dissection in modified radical mastectomy can reduce the risk of distant metastasis.[112]

Early clinical studies of the extent of lymph node metastasis in positive lymph node breast cancer patients found that 20–58% of patients with axillary lymph node metastasis were restricted to level I; 20–29% and 16–32% of patients with lymph node metastasis were confined to levels I+II and levels I+III, respectively. About 20% of patients were diagnosed with pathological level III metastasis.[113,114] The level ш metastasis rate was highest in Khafagy's study.[115] Of 59 positive axillary lymph node patients, 31 (52.5%) had level III axillary lymph node metastasis. In a study by Tao et al, of 87 positive axillary lymph nodes patients, 18 (20.7%) had level III axillary lymph node metastasis.[116] Yildirim reported a level III axillary lymph node metastasis rate of 15–31%.[111] In a study of T0-2 axillary lymph node-positive breast cancer patients who received neoadjuvant chemotherapy, 0.9% of patients had level III axillary lymph node invasion.[117]

Several studies have discussed the correlation between axillary lymph node metastasis and clinical-pathological factors. Toma et al reported that nuclear grade 3 was associated with level III axillary lymph node invasion.[118] Ung et al found that it was related to axillary lymph node palpability, pathological tumor size, and lymph vessel invasion.[119] Veronesi et al studied 539 patients with breast cancer and found that level III axillary lymph nodes were

invaded in 16.9% of T1 breast cancer patients.[114] This study also revealed the possibility that level II or III axillary lymph node invasion is connected with the number of metastatic nodes. In patients with only one level I axillary lymph node metastasis, 8% also had higher levels of axillary lymph node metastasis; in patients with two -level I axillary lymph node metastases, 25.3% also had higher levels of axillary lymph nodes metastasis; and in patients with four or more level I axillary lymph node metastases, the rate was as high as 65.8%. Yildirim found that level III axillary lymph node involvement, tumor size, lymph node, and vascular invasion, and the number of positive axillary lymph nodes were important pathological factors that predicted distant metastasis.[111]

In an original single-factor analysis, he found that tumor size, lymph node and vascular invasion, extracapsular involvement, and premenopausal status were associated with level III axillary lymph node metastasis; multiple-factor analysis showed that only the number of positive lymph nodes was related to level III axillary lymph node positivity, but this cannot be confirmed before surgery. In his study, the cut-off point of the number of positive nodes for level III involvement was 7. Dillon thought level III clearance could play a selective but definite role in patients with lymph node-positive breast carcinoma.[105]

Pathological features of primary tumors can help judge the risk of level III axillary lymph node invasion. In axillary lymph node positive breast cancer patients, level III infiltration predicting factors include: tumor size (OR = 1.36, 95% CI: 1.2–1.5, P < 0.001), invasive lobular carcinoma (OR = 3.6, 95% CI: 1.9–6.95, P < 0.001), extracapsular involvement (OR = 0.27, 95% CI: 0.18–0.4, P < 0.001), and lymph node vascular infiltration (OR = 0.58, 95% CI: 0.35–1, P = 0.04). In patients with tumors larger than 3 cm in diameter, the risk of level III metastasis was as high as 34%. In invasive lobular carcinoma patients with positive lymph nodes, the level III axillary lymph node positive rate was 41%. Prediction factors of level III invasion in sentinel lymph node-positive patients included invasive lobular carcinoma (OR = 4.1, 95% CI: 1–16.8, P = 0.049), lymph node extracapsular involvement (OR = 0.18, 95% CI: 0.06–0.57, P = 0.003), and at least one positive sentinel lymph node (OR = 4.9, 95% CI: 1.5–16.1, P = 0.009). Fan's research showed that factors such as tumor size, lymph node biopsy methods, and primary tumor response to neoadjuvant chemotherapy by ultrasound could predict the risk of level III axillary lymph node involvement.[117]

The pathological complete response rate of axillary lymph nodes in the primary tumor effective group after neoadjuvant chemotherapy was significantly higher than that in the ineffective group (36.5% [73/200] vs 19.1% [17/89], P = 0.003). Effective neoadjuvant

chemotherapy might reduce the incidence rate of level III positivity. Node positivity as proved by ultrasound guided needle biopsy, large tumor size, and primary tumor nonresponse to neoadjuvant chemotherapy are independent predictors of axillary lymph node positivity. The level III axillary lymph node-positive rate was only 4.9% in patients with no risk factors, and in patients with three risk factors (T > 2 cm, axillary lymph node positivity as proved by fine needle biopsy and noneffective neoadjuvant chemotherapy), the rate of level III invasion was as high as 23.7%. Patients who have two or more risk factors should be considered to have level III clearance because in these patients the rate of level ш involvement was at least 20%. Wang et al considered level III axillary lymph node dissection should be taken into account (i) for tumors at stage T3 or above whose estrogen receptor (ER) expression is negative as confirmed by preoperative breast tumor needle biopsy and (ii) for the intraoperative detection of axillary lymph node metastasis that is suspected to be of level I–II or to be accompanied by extra lymph node tissue infiltration.[120]

The number of axillary lymph node metastases at levels I–II, the involvement of external nodes, and the negative expression of ER are risk factors for axillary lymph node metastasis. Further stratified analysis showed that level III axillary lymph node metastasis was more likely to occur if the tumor above T3 was located laterally (P = 0.035). If ER expression is negative, with the increase of tumor stage, level III lymph nodes are more likely to metastasize.[120]

Complications of Level III Axillary Lymph Node Dissection

It has been reported that the dissection of level I–III axillary lymph nodes cannot improve the long-term efficacy of breast cancer surgery,[121] but can increase the complications such as lymphedema of the affected limb, paresthesia, pain, limitation of shoulder joint activity, effusion, and so on, [122] which may be caused by overtreatment. However, no significant axillary lymph node dissection complication has been found, and serious complications such as axillary vein/artery thrombosis or injury and axillary motor nerve injury have rarely been reported in the literature. Although level III axillary lymph node dissection takes longer and can result in more blood loss than the level I dissection, it does not affect its clinical effect. There were no statistically significant differences between the two groups in terms of follow-up symptoms such as upper limb pain, pectoralis major atrophy, upper limb motor function, and social function.[109] The incidence of malformation associated with additional lymph node dissection did not increase in patients with breast cancer at similar stages who underwent

standard axillary lymph node dissection. The incidence of postoperative upper extremity lymphedema ranges from 6% to 30%,[115] depending on the methods used to define lymphedema and follow-up adequacy. At present, it is generally believed that the incidence of lymphedema is very low if the adventitia of the axillary vein is not damaged. Therefore, surgeons should be cautious to avoid damaging the outer membrane around the axillary vein if they want to separate the brachial plexus fat above the axillary vein for lymph node dissection.[123]

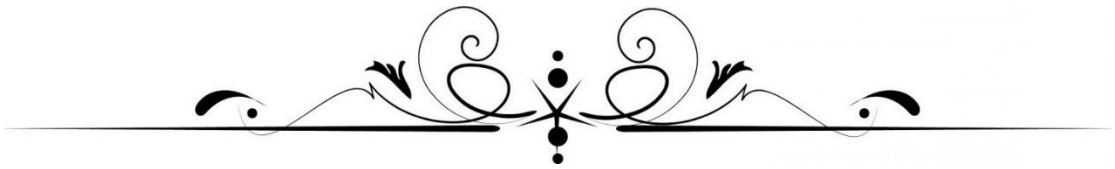
Surgical Options for Level III Axillary Lymph Node Dissection

There are two commonly used ways to expose the subclavian area for level III dissection. One is to retract the pectoralis major and minor muscles. The other one is to split the pectoralis major muscle (Kodama method). On this basis, a series of studies put forward several improved ways. Muscolino et al proposed a practical method to reach level III axillary lymph nodes: splitting the pectoralis major muscle and immobilizing the pectoralis minor muscle.[124] Although the exposed space is limited, this approach has been recommended by other clinicians.[125] This method can expose the axillary apex and facilitate the dissection of the upper axillary vein lymph nodes (supraclavicular lymph nodes) that may be penetrated in locally advanced breast cancer. Also, prepectoral lymph node dissection is recommended because of muscle preservation. Alfredo et al found that subpectoral dissection usually results in retention of lymph nodes at the axillary apex.[112] If we need to preserve the pectoralis major and minor muscles during dissection of level I–III lymph nodes in breast cancer patients, it is suggested to clean level III lymph nodes subpectoral through the posterior space of the pectoralis major muscle. Hadjiminas et al introduced a method conducive to safe cleaning of level III axillary lymph nodes.[126] Access to level III is achieved through a muscle splitting transverse incision on the pectoralis major, centered on the point where the axillary vein crosses the first rib. This is located 5 cm lateral and 1 cm superior to the suprasternal notch. The pectoralis minor can be retracted laterally, and the neurovascular bundle to the pectoralis major can be dissected out of the surrounding fat and retracted in a silicone sling. It is recommended for patients undergoing mastectomy since the muscle splitting incision can be performed without the need for a separate skin incision. This method is especially ideal for patients with level III recurrence. It allows the surgeon to access level III without going through previously operated levels I and II, thereby minimizing the risk of nerve or vessel injury during dissection.[125]

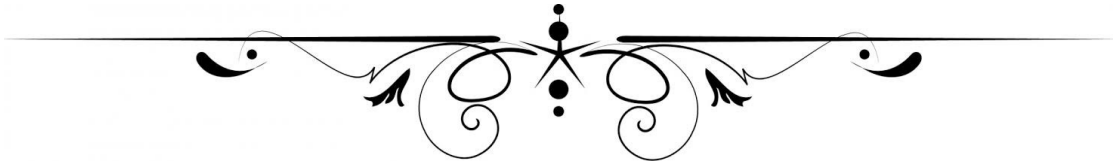
Level III Axillary Lymph Node Dissection Following Neoadjuvant Chemotherapy

Only a few studies have tried to demonstrate the relation of clinicopathological factors with level III ALN. In the largest series from India level III, involvement was found to be 27.3% of all node-positive patients.[7]

In other series level III LN positivity ranges from 15% to 59%.[127] A study conducted at one of largest cancer centre in India demonstrated that four or more ALNs in level I and II, inner/central quadrant tumor location, poor histologic grade, and presence of PNE and LVI were associated with higher-level III ALN positivity.[7] In a similar study by Chua et al.[128] 320 patients were evaluated. Involvement of lymph nodes in level III was observed in 22 patients (7%), and 51 patients (16%) had four or more positive nodes. Palpability of ALNs, pathologic tumour size, and LVI was significantly associated with level III involvement and four or more positive nodes by univariate and multivariate analyses. Up to 42% of patients had involved level III ALNs when four or more ALNs were positive, similar to the 53.2% seen in a study from India. [7] Khafagy et al.[115] reported that 53.5% of patients had level III ALN involvement when a lower level had nodal metastases. Veronesi et al. [114] also reported an incremental risk of level III involvement with an increasing number of positive lower-level nodes. The level III involvement was 8%, 25.3%, and 65.8%, respectively, when 1, 2, and 4 or more ALNs were positive in level I. Skip metastasis, although rare, is found in up to 15 %.[127, 129] In another study from China by Fan et al.[130] the incidence of residual positive nodal disease in level III was 9% (47 of 521), even after preoperative neoadjuvant chemotherapy in stage I and II breast cancer. They showed a significantly worse distant DFS when level III ALNs were involved (84.9% and 91.6%in level III positive and negative groups, respectively; P =0.011). Also, Involvement of level III ALNs is a poor prognostic factor.[7,131] It stated that Node positivity proved by ultrasound-guided needle biopsy, large tumour size and primary tumour non-response to neoadjuvant chemotherapy were independent predictors of level III lymph nodes positivity. The incidence of level III region involvement in this study was lower than the previous report. Neoadjuvant chemotherapy might contribute to decreasing level III lymph nodes involvement rate. The previous study reported 22% to 23% of patients had a pathological complete response of axillary lymph node after neoadjuvant chemotherapy.[132]



MATERIALS & METHODS



4. MATERIALS AND METHODS

STUDY DESIGN

This is a prospective observational study

STUDY PARTICIPANTS INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

1. Patients aged 18 years to 80 years.
2. Patients with stage I-III breast cancer (as per AJCC 8th edition)
3. Patients who have received neoadjuvant chemotherapy and planned for curative surgery with axillary lymph node dissection.

Exclusion criteria

1. Metastatic breast cancer
2. Inflammatory breast cancer

SAMPLE SIZE

All the breast cancer patients admitted during study period and who fits the inclusion criterion were included in the study.

STUDY DURATION

The study was conducted from 1st January 2021 to 31st December 2022.

STUDY METHODOLOGY

The study includes all the patients with stage I-III carcinoma breast who have received neoadjuvant chemotherapy and underwent curative surgery in the Department of Surgical Oncology at AIIMS, Jodhpur during the study period.

Patients were evaluated by a multidisciplinary team and subsequently underwent mastectomy or breast conservation surgery based on patient choice and disease characteristics. Axillary levels I, II, and III were dissected up to the costoclavicular ligament of Halsted. The apical or level III ALNs were addressed via subpectoral/ interpectoral space approach and sent for pathologic evaluation separately (level I, II together and level III separately). Patient characteristics and Histopathological details were subsequently recorded. Results of each patient are recorded in a specified proforma. Data collection proforma is attached. The subsequent analysis was carried out.

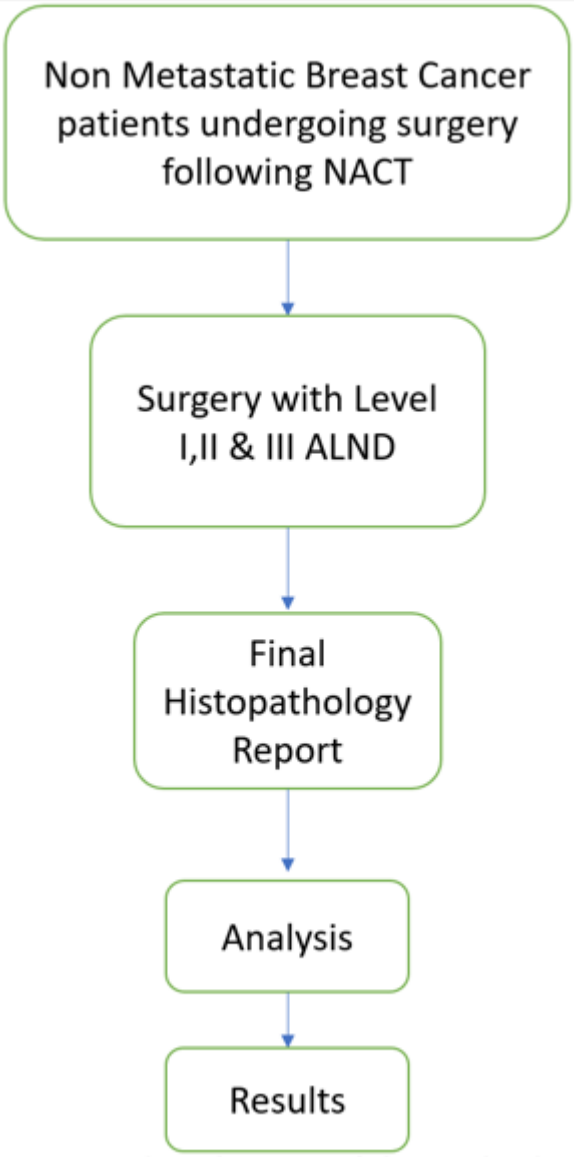
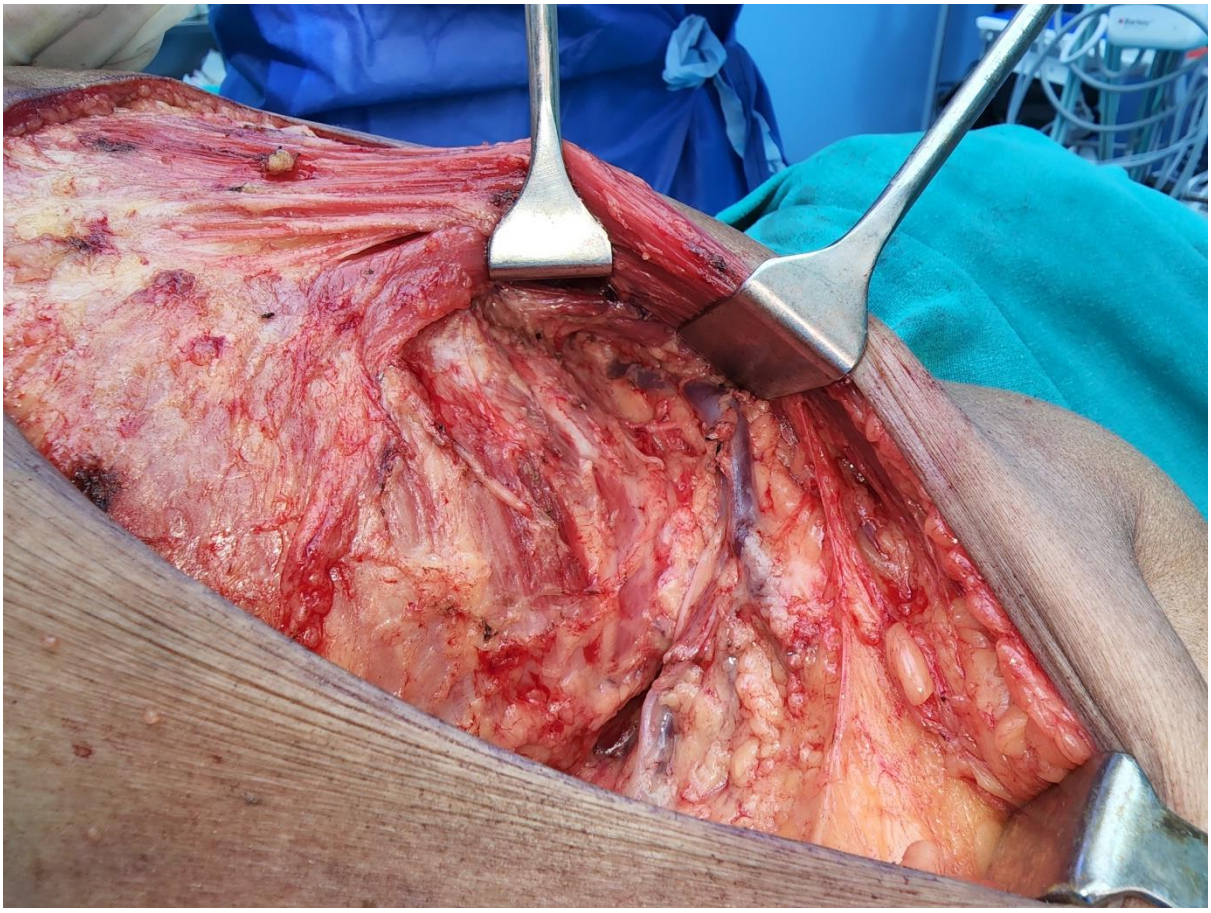


Figure: Flow diagram of the study plan



Clinical Intraoperative Photograph

STATISTICAL ANALYSIS

Baseline clinicopathologic factors are reported as numbers and percentage. Association between Level III ALN metastasis and other Categorical Variables are done by Univariate analysis using Fisher's exact test. Multivariate analysis was performed by logistic regression to identify independent predictors of level III ALN involvement. Data was analysed using SPSS version 20.0 (IBM, Armonk, NY) for Windows.

ETHICAL JUSTIFICATION

- Informed written consent was taken from all the study subjects. No pressure or coercion was exerted on subjects for participation in the study.
- Confidentiality and privacy will be maintained at all stages.
- Enrolment in the study did not pose any additional risk to the patient and neither did it increase the cost of the treatment. Informed written consent was taken from the patient/guardian of all the patients as per the attached proforma.
- Details were sent to an institutional ethical committee for necessary ethical approval

RESULTS

5. RESULTS

We evaluated the cases of breast cancer who underwent axillary level III lymph node dissection post Neoadjuvant Chemotherapy. We got a total of 89 cases satisfying our study inclusion criteria during our study period. After neoadjuvant chemotherapy, it was found that 7 out of these 89 cases didn't show any residual carcinoma on histopathologic examination.

The results and observations are as explained in following tables:

Table 1: Distribution of the study participants according to age group

Age group (yr.)	Frequency	Percent
<= 30	4	4.50%
31 - 40	15	16.90%
41 - 50	27	30.30%
51 - 60	23	25.80%
61 - 70	16	18.00%
71 - 80	4	4.50%
Total	89	100.00%

Table 1 explains the age distribution of the study participants. The most common age group decade was 41 to 50 years with 27 cases (30.30%) followed by 51 to 60 years with 23 cases (25.80%), 61 to 70 years with 16 cases (18%) and 31 to 40 years with 15 cases (16.90%). The mean age of the study participants was 50.38 ± 11.54 years with a range of 26 – 74 years.

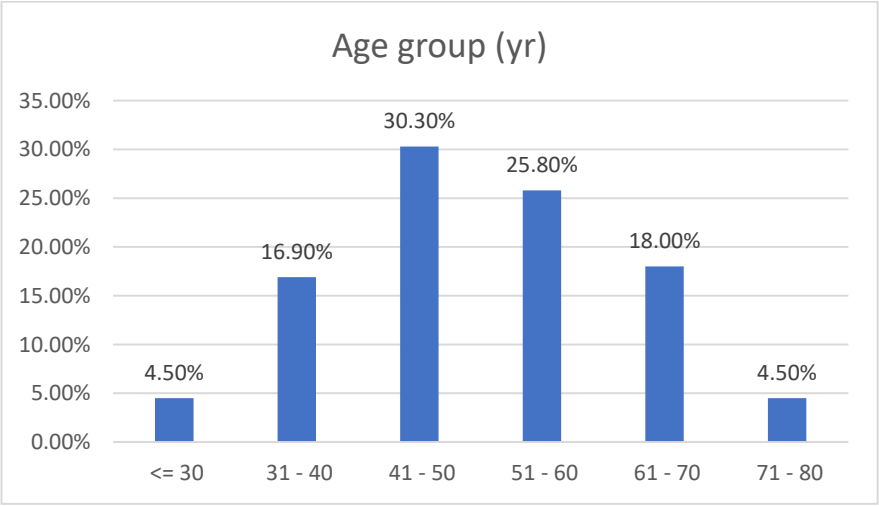


Fig 1: Age group wise distribution of the study participants

Table 2: Procedures done in the study participants

Procedure Done	Frequency	Percent
MRM	72	80.90%
BCS	15	16.85%
Radical mastectomy	1	1.12%
Skin sparing mastectomy	1	1.12%
Total	89	100.00%

Table 2 explains the Operative Procedures done in the study participants. The most common procedure done in our breast cancer patients after they received Neoadjuvant chemotherapy was Modified Radical Mastectomy (MRM) done in 72 cases (80.90%) followed by Breast Conservative Surgery in 15 cases (16.85%), radical mastectomy and skin sparing mastectomy in 1 case each (1.12%).

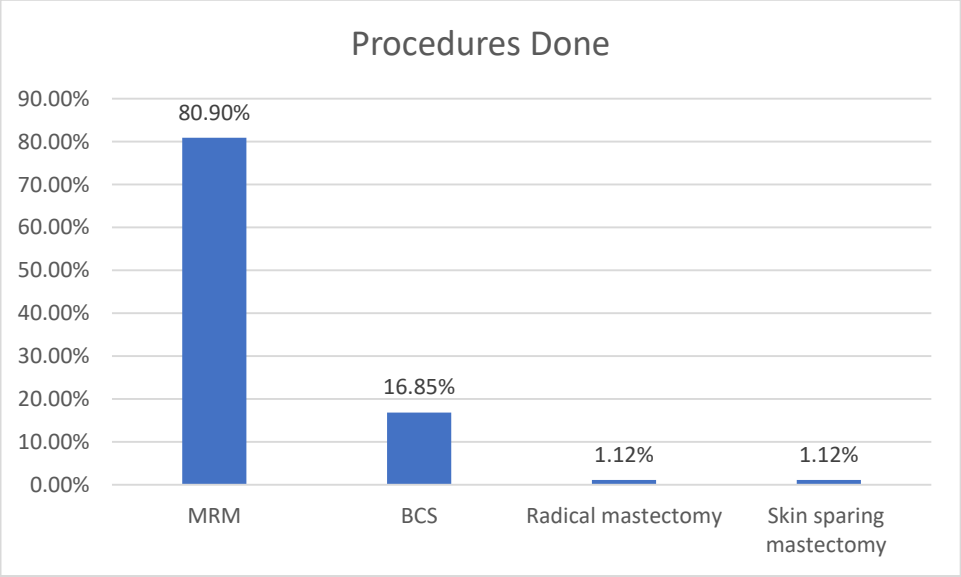


Fig 2: Procedures done in the study participants

Table 3: Distribution of the study participants according to the duration of Neoadjuvant chemotherapy

NACT Given	Frequency	Percent
Full Course	62	69.70%
Partial Course	27	30.30%
Total	89	100.00%

Table 3 explains the Distribution of the study participants according to the duration of Neoadjuvant chemotherapy. We observed that 62 out of total 89 cases (69.70%) received full course of Neoadjuvant chemotherapy, while rest 27 cases (30.30%) received partial course of Neoadjuvant chemotherapy before they underwent surgery for breast cancer.

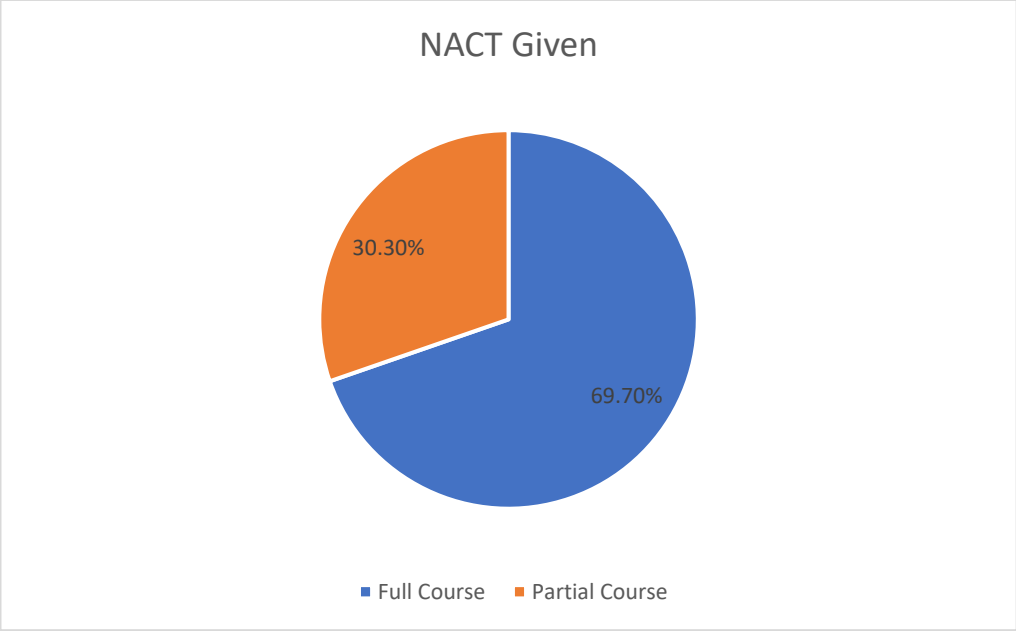


Fig 3: Distribution of the study participants according to the duration of Neoadjuvant Chemotherapy

Table 4: Distribution of the study participants according to clinical T stage (cT)

cT	Frequency	Percent
T1	1	1.10%
T2	45	50.60%
T3	19	21.30%
T4	24	27.00%
Total	89	100.00%

Table 4 explains the cT stage wise distribution of the study participants. We observed that majority of the participants, 45 cases were T2 (50.60%), 24 cases were T4 (27.0%) and 19 cases were T3 (21.30%).

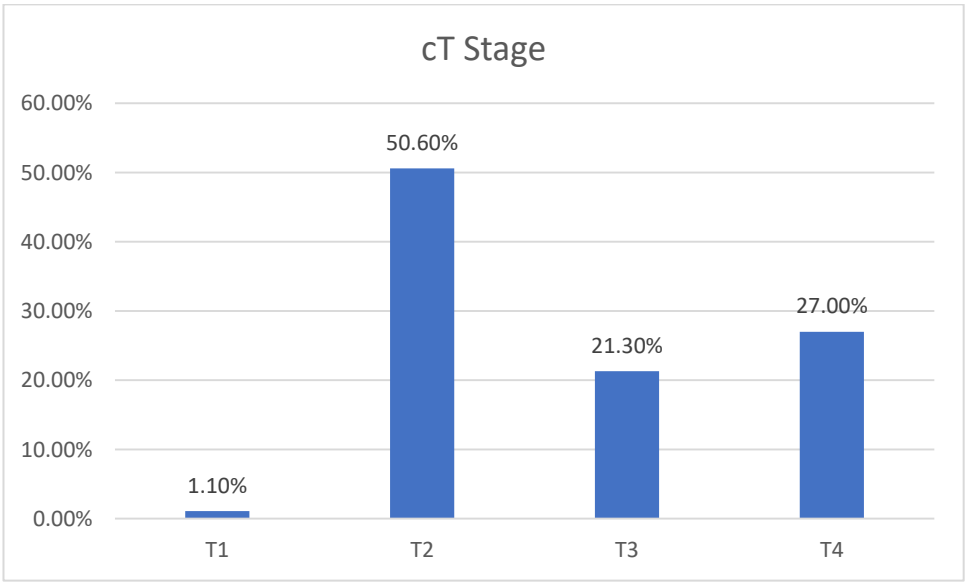


Fig 4: cT stage wise distribution of the study participants

Table 5: Distribution of the study participants according to cN stage

cN	Frequency	Percent
N0	18	20.20%
N1	43	48.30%
N2	18	20.20%
N3	10	11.20%
Total	89	100.00%

Table 5 explains the cN stage wise distribution of the study participants. We observed that majority of the participants, 43 cases were N1 (48.31%), 18 cases each were N2 and N0 (20.20%) and 10 cases were N3 (11.20%).

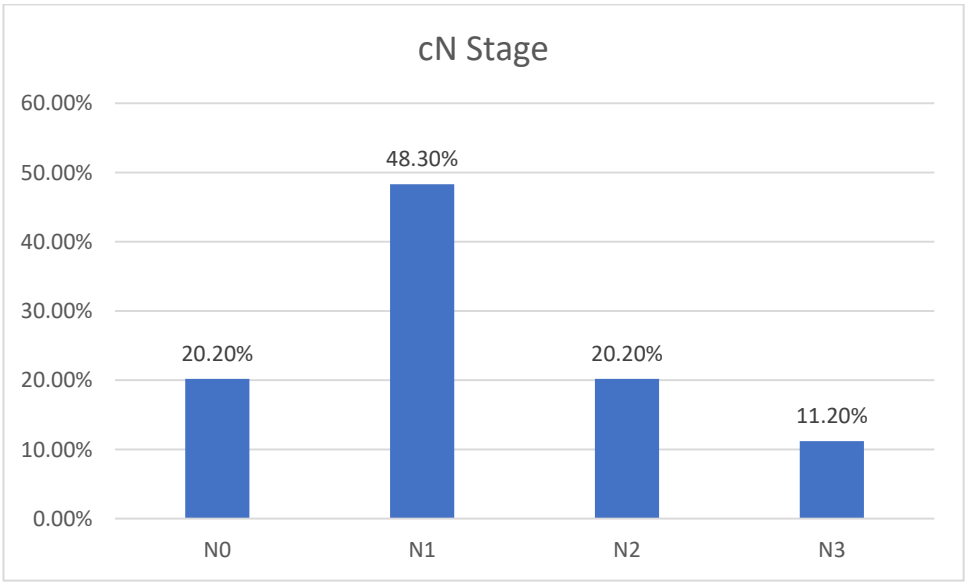


Fig 5: cN stage wise distribution of the study participants

Table 6: Histological types of carcinoma breast in Final Histopathology examination

Histological Type	**Frequency**	**Percent**
Invasive Breast carcinoma NST	67	75.28%
IBC with Apocrine Differentiation	2	2.20%
Microinvasive carcinoma	2	2.20%
Mixed Mucinous carcinoma and IBC	2	2.20%
IBC with Mucinous Differentiation	1	1.10%
Invasive carcinoma with medullary features	1	1.10%
Invasive Cribriform carcinoma Breast	1	1.10%
Invasive Micropapillary	1	1.10%
Malignant adenomyoepithelioma	1	1.10%
Metaplastic carcinoma	1	1.10%
Metaplastic Spindle cell carcinoma	1	1.10%
Metastatic Papillary Epithelial Malignancy	1	1.10%
Mucinous Carcinoma	1	1.10%
No residual carcinoma	7	7.90%
Total	89	100.00%

Table 6 explains the Histological types of Carcinoma breast in our study participants. The most common type diagnosed was Invasive Breast carcinoma No Special Type seen in 67 cases (75.28%), there were 2 cases each (2.20%) of IBC with Apocrine Differentiation, Microinvasive carcinoma Breast, Mixed Mucinous carcinoma and IBC.

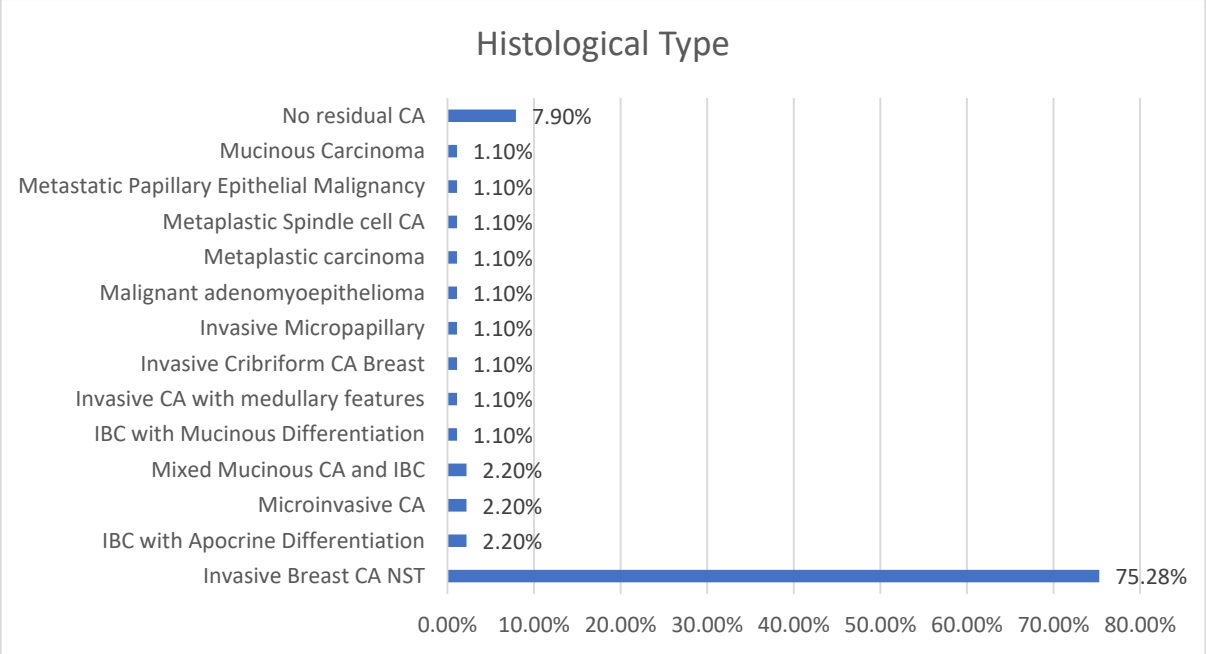


Fig 6: Histological types of Carcinoma breast in Final Histopathology examination

Table 7: Histological grade of Carcinoma breast in our study participants

Histological Grade	Frequency	Percent
Grade 1	6	6.74%
Grade 2	55	61.80%
Grade 3	21	23.60%
*NA	7	7.87%
Total	89	100.00%

*NA – 7 cases were no residual carcinoma post NACT

Table 7 explains the Histological grade of Carcinoma breast in our study participants post NACT. We observed that 7 cases didn't show any carcinoma post NACT (7.87%). While majority of the cases showed Grade 2 carcinoma, as seen in 55 cases (61.80%) followed by Grade 3 in 21 cases (23.60%) and Grade 1 in 6 cases (6.74%).

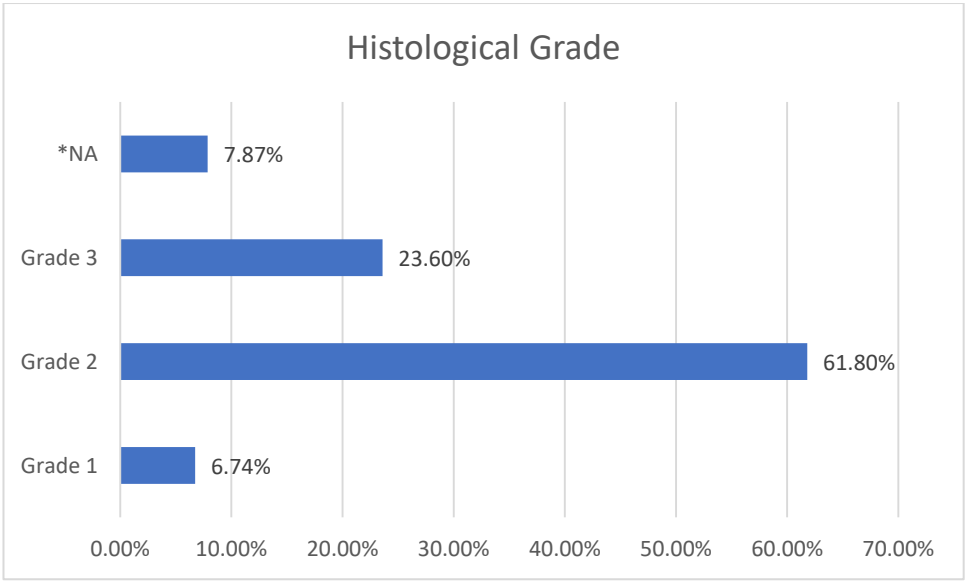


Fig 7: Histological grade of Carcinoma breast in our study participants

Table 8: Tumor focality wise distribution of the study participants

Tumor Focality	**Frequency**	**Percent**
Multifocal	17	19.10%
Unifocal	72	80.90%
Total	89	100.00%

Table 8 explains the Tumor focality wise distribution of CA breast in our study participants. We observed that there were 72 unifocal cases (80.90%) and 17 multifocal cases (19.10%) in our study.

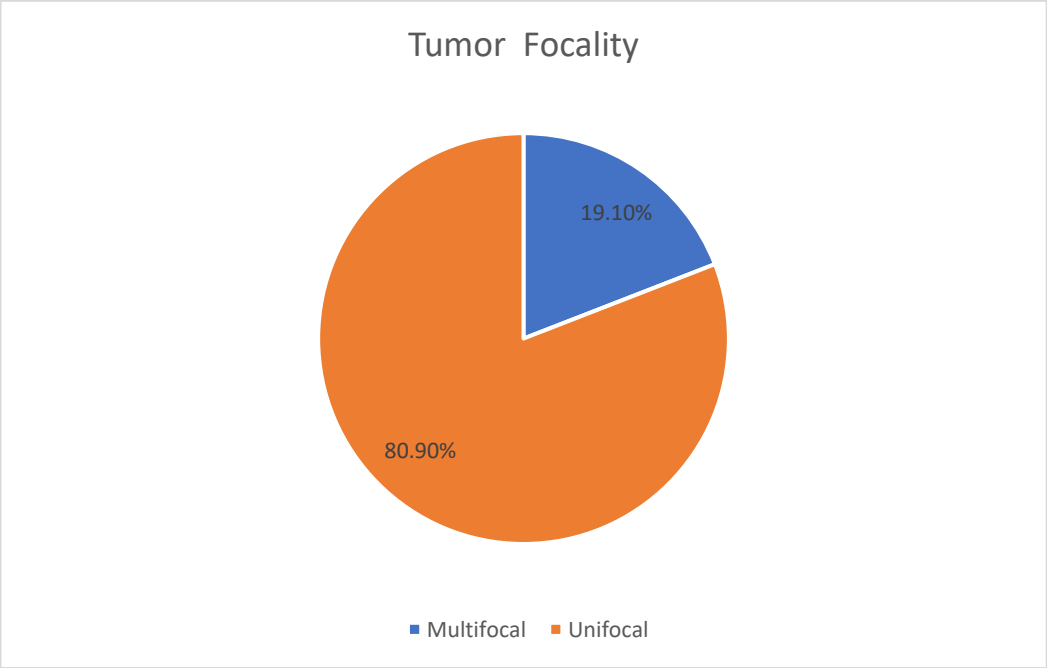


Fig 8: Tumor focality wise distribution of the study participants

Table 9: Tumor quadrant wise distribution of the study participants

Tum Quadrant	Frequency	Percent
Central	19	21.35%
Lower Inner	7	7.87%
Lower Outer	12	13.48%
Upper Inner	20	22.47%
Upper Outer	31	34.83%
Total	89	100.00%

Table 9 explains the Tumor quadrant wise distribution of the study participants. We observed that the majority of the cases were seen in Upper Outer quadrant with 31 cases (34.83%), followed by Upper Inner quadrant with 20 cases (22.47%), central quadrant with 19 cases (21.35%), lower outer quadrant with 12 cases (13.48%), followed by lower inner quadrant with 7 cases (7.87%).

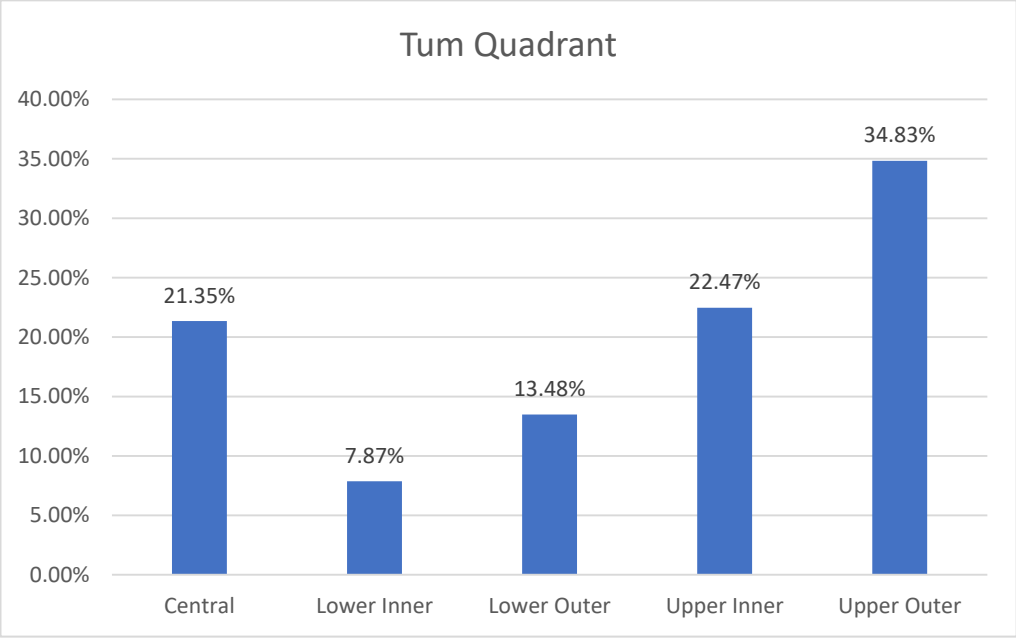


Fig 9: Tumor quadrant wise distribution of the study participants

Table 10: Peripheral invasion of the tumor in the study participants

Invasion	Present	%	Absent	%
Nipple areola complex invasion	8	8.99%	81	91.01%
Lympho-vascular invasion	32	35.96%	57	64.04%
Perineural Invasion	13	14.61%	76	85.39%
Extracapsular Invasion	12	13.48%	77	86.52%

Table 10 explains the Peripheral invasion of the tumor seen in our study. We observed that majority of the cases had Lymphovascular invasion as seen in 32 cases (35.96%), followed by Perineural Invasion in 13 cases (14.61%), Extracapsular Invasion in 12 cases (13.48%), and involvement of Nipple – Areolar complex in 8 cases (8.99%).

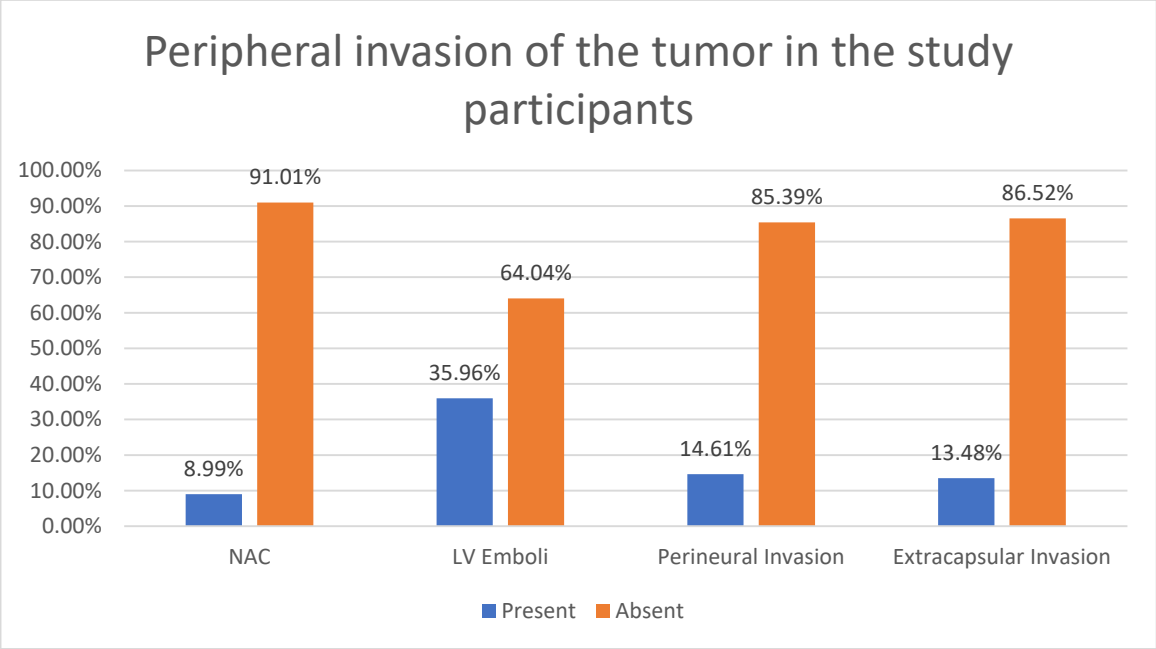


Fig 10: Peripheral invasion of the tumor in the study participants

Table 11: Distribution of the study participants according to hormonal receptor and Her2 status

Hormonal Receptor	**Positive**	**%**	**Negative**	**%**
ER / PR positive	33	37.08%	56	62.92%
Her2 positive	21	23.60%	68	76.40%
Triple Negative	45	50.56%	44	49.44%

Table 11 explains the Hormonal Receptor positivity in our study participants. We observed that majority of the participants were triple negative seen in 45 cases (50.56%), followed by ER / PR positive as seen in 33 cases (37.08%) and Her2 positive in 21 cases (23.60%).

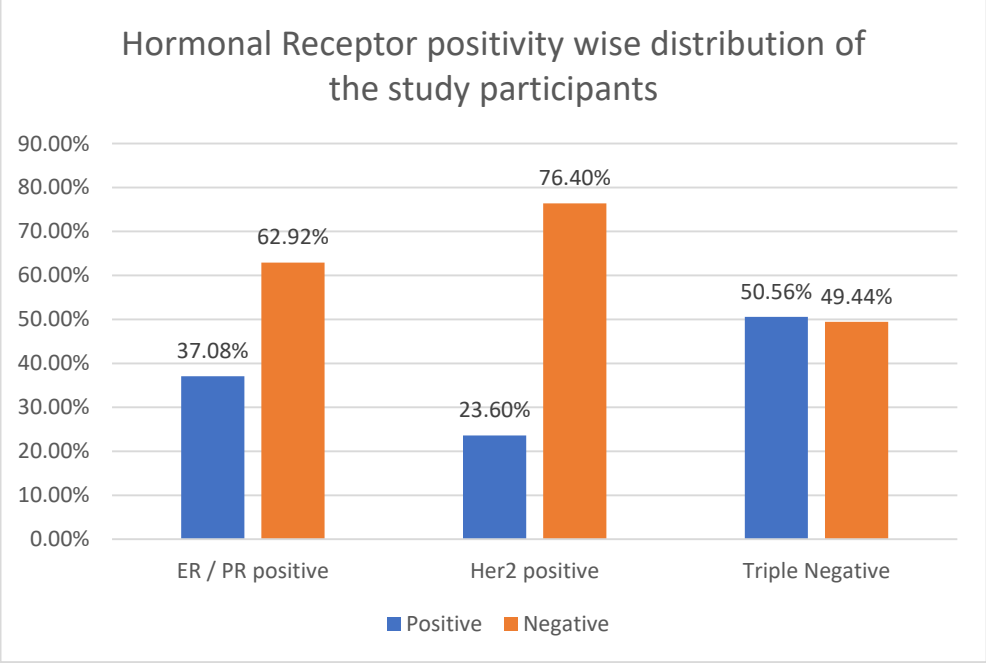


Fig 11: Hormonal Receptor positivity wise distribution of the study participants

Table 12: Descriptive statistics of quantitative data in the study

Descriptive Statistics	Median	Minimum	Maximum	Mean	SD
Age	50	26	74	50.38	11.55
NACT	8	1	12	6.76	2.06
Level I & II LN - No. Dissected	15	1	36	15.61	5.82
Level I & II LN - Involved	0	0	25	1.75	4.08
Level III LN – No. Dissected	2	1	9	2.54	1.94
Level III LN - Involved	0	0	6	0.20	0.76

Table 12 explains the Descriptive statistics of quantitative data in the study.

The mean age of the participants was 50.38 ± 11.55 years (range 26 – 74 yr.). The mean cycles of NACT received were 6.76 ± 2.06 cycles, with a median of 8 cycles and range of 1 – 12 chemotherapy cycles. The median Level I & II LN - Number Dissected was 15, with median cancerous growth seen in 0 nodes. The mean of Level I & II LN - Number Dissected was 15.61 with mean cancer involvement in 1.75. The median Level III LN - Number Dissected was 2, with median cancerous growth seen in no any node (0). The mean of Level I & II LN - Number Dissected was 2.54 with mean cancer involvement in 0.20.

Table 13: Distribution of the study participants according to level I & II LN positivity

Level I & II LN Involvement	**Frequency**	**Percent**
Level I & II LN positive	35	39.33%
Level I & II LN negative	54	60.67%
Total	89	100.0%

Table 13 explains the Distribution of the study participants according to level I & II LN positivity. We observed 35 cases were Level I & II LN positive (39.33%).

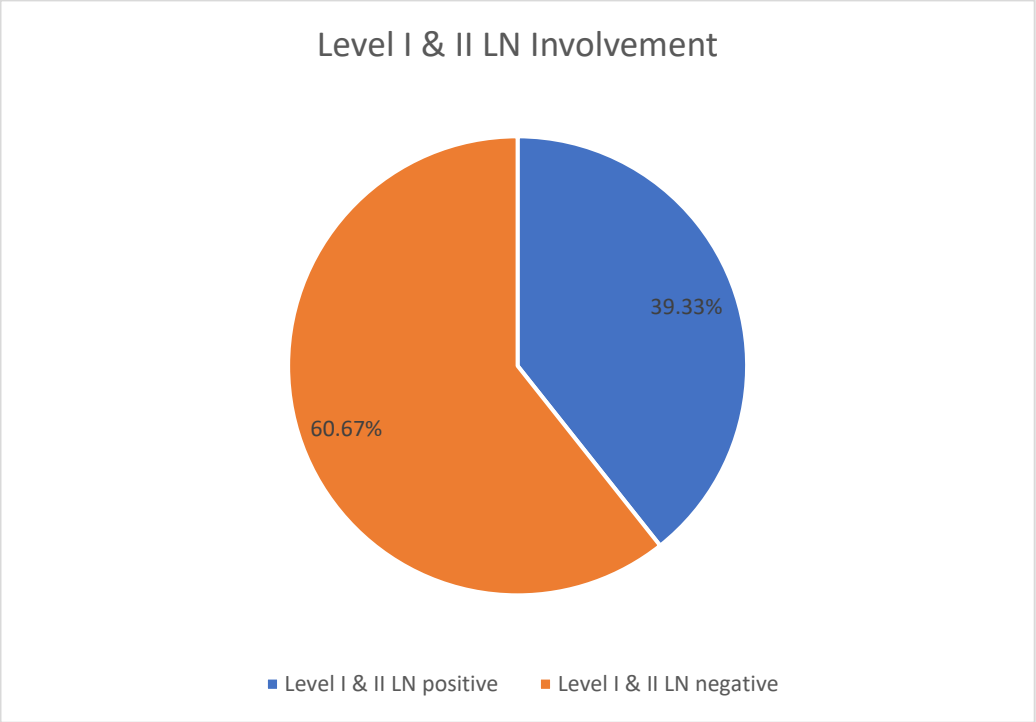


Fig 13: Distribution of the study participants according to level I & II LN positivity

Table 14: Distribution of the study participants according to level III LN positivity

Level III LN Involvement	**Frequency**	**Percent**
Level III LN positive	11	12.36%
Level III LN negative	78	87.64%
Total	89	100.0%

Table 14 explains the Distribution of the study participants according to level III LN positivity. We observed that the level III Lymph node positivity was seen in 11 cases (12.36%) in our study. We observed Skip metastasis in one case – where Level I & II LN were negative and Level III LN was positive was seen in 1 case (1.12%).

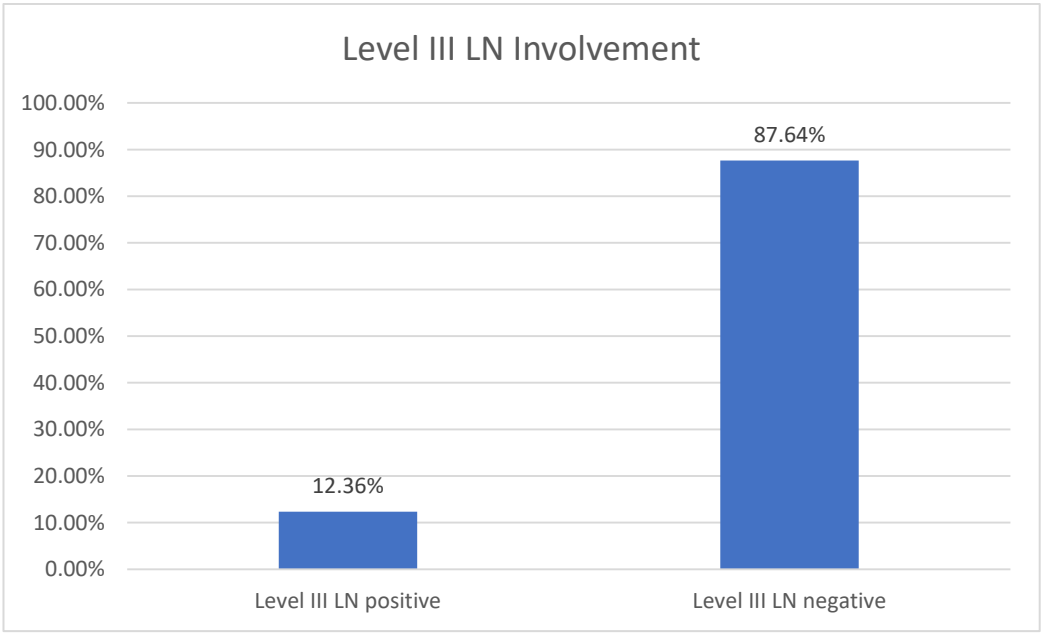


Fig 14: Distribution of the study participants according to level III LN positivity

Table 15: Association between Level III LN positivity and Age group in the study participants

Age group (yr.)	Level III LN positive	Percent	Level III LN Negative	Percent
≤ 30	0	0.00%	4	5.13%
31 - 40	1	9.09%	14	17.95%
41 - 50	2	18.18%	25	32.05%
51 - 60	5	45.45%	18	23.08%
61 - 70	2	18.18%	14	17.95%
71 - 80	1	9.09%	3	3.85%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.538, Not Significant

Table 15 explains the association between Level III LN positivity and Age group in the study participants. There was no significant association between the age group and level III LN positivity (p = 0.538). Out of 11 cases with Level III LN positivity, 5 were in the age group of 51 to 60 years (45.45%), 2 each were from age group of 41 to 50 and 61 to 70 years (18.18%).

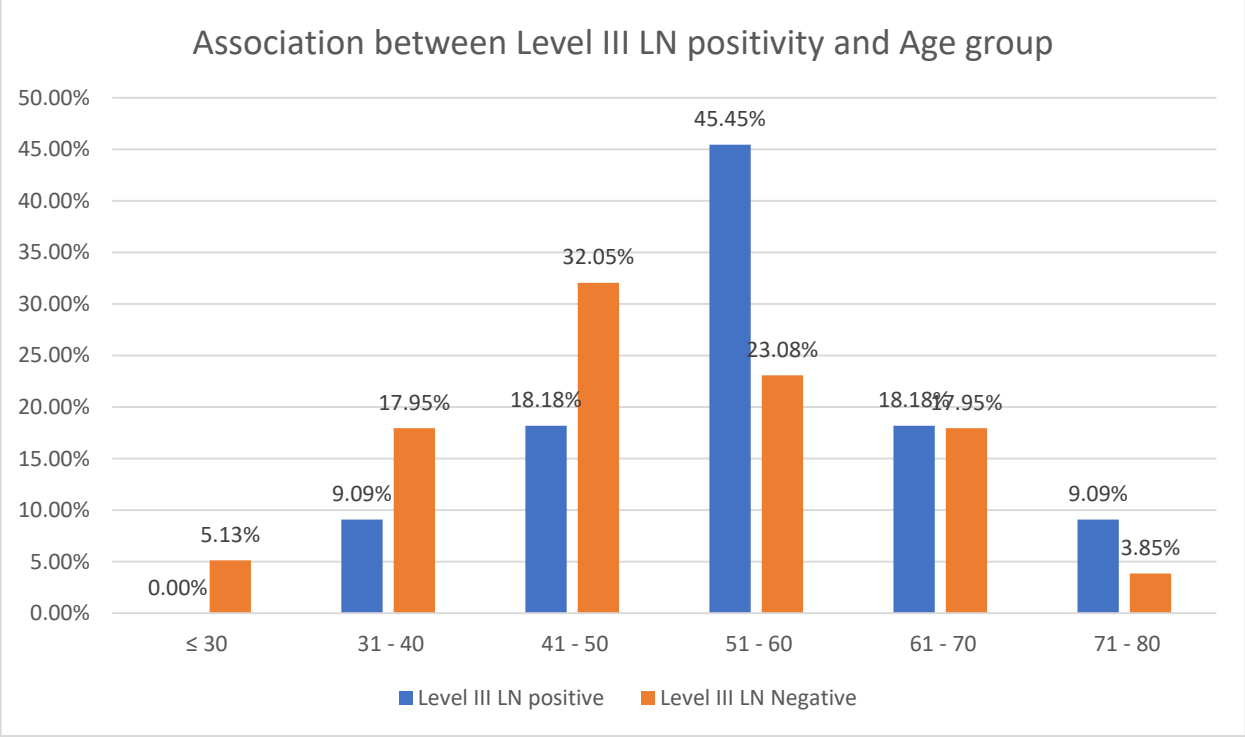


Fig 15: Association between Level III LN positivity and Age group in the study participants

Table 16: Association between Level III LN positivity and the duration of Neoadjuvant chemotherapy in the study participants

NACT Given	Level III LN positive	Percent	Level III LN Negative	Percent
Full course	4	36.36%	58	74.36%
Partial course	7	63.64%	20	25.64%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.013, Significant

Table 16 explains the association between Level III LN positivity and the duration of Neoadjuvant chemotherapy in the study participants. We observed a significant association between Level III LN positivity and the duration of Neoadjuvant chemotherapy in the study participants (p = 0.013). We observed that out of Level III LN positive cases, 7 had received partial course NACT (63.64%) as compared to the 4 cases who had received full course NACT (36.36%). Out of 78 Level III LN negative cases 58 received full course NACT (74.36%) and 20 got partial course NACT (25.64%).

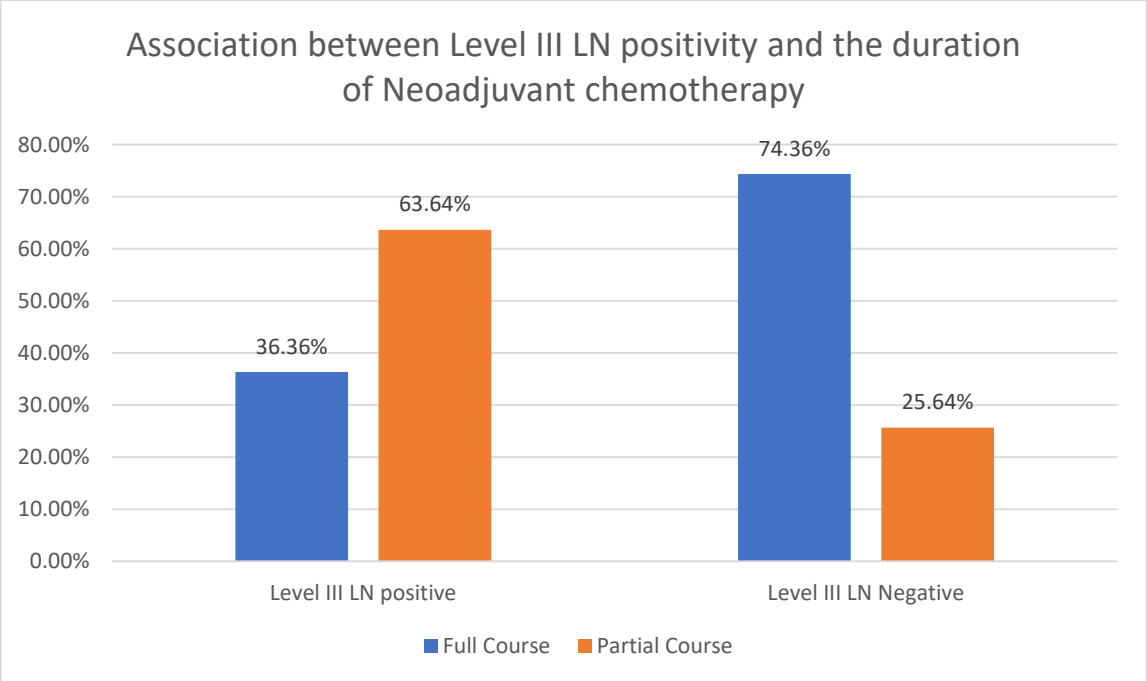


Fig 16: Association between Level III LN positivity and the duration of Neoadjuvant chemotherapy in the study participants

Table 17: Association between Level III LN positivity and cT stage wise distribution of the study participants

cT	Level III LN positive	Percent	Level III LN Negative	Percent
T1	0	0.00%	1	1.28%
T2	5	45.45%	40	51.28%
T3	2	18.18%	17	21.79%
T4	4	36.36%	20	25.64%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.129, not significant

Table 17 explains the association between Level III LN positivity and cT stage wise distribution of the study participants. We observed no significant association between the Level III LN positivity and cT (p = 0.129). Out of the 11 cases with Level III LN positivity, 5 were T2 (45.45%), 4 were T4 (36.36%) and 2 were T3 (18.18%).

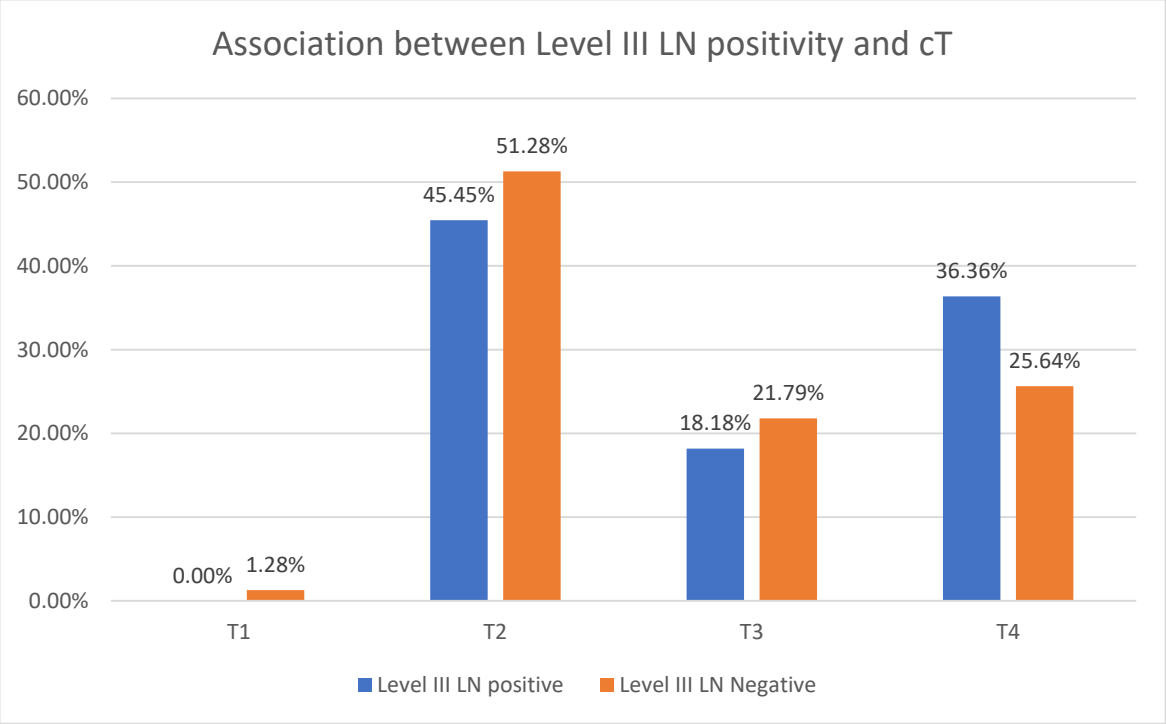


Fig 17: Association between Level III LN positivity and cT stage wise distribution of the study participants

Table 18: Association between Level III LN positivity and cN stage wise distribution of the study participants

cN	Level III LN positive	Percent	Level III LN Negative	Percent
N0	0	0.00%	18	23.08%
N1	2	18.18%	41	52.56%
N2	3	27.27%	15	19.23%
N3	6	54.55%	4	5.13%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value < 0.001, Significant

Table 18 explains the association between Level III LN positivity and cN stage wise distribution of the study participants. We observed significant association between the Level III LN positivity and cN stage ($p < 0.001$). Out of the 11 cases with Level III LN positivity, 6 were N3 (54.55%), 3 were N2 (27.27%) and 2 were N1 (18.18%). This shows greater association between the cN3 and level III Lymph Node positivity.

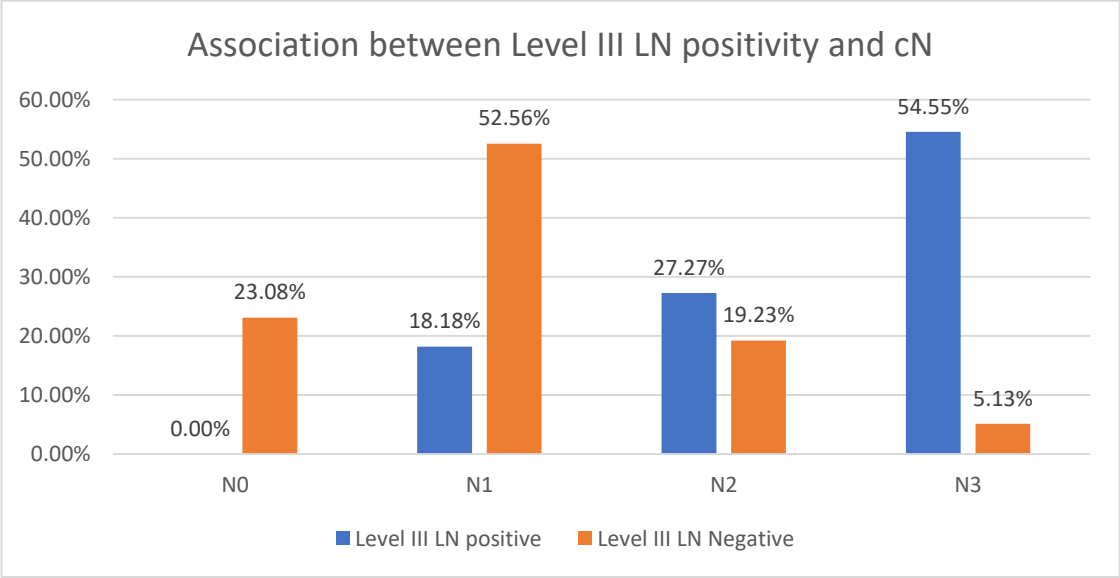


Fig 18: Association between Level III LN positivity and cN stage wise distribution of the study participants

Table 19: Association between Level III LN positivity and Histological grade of Carcinoma breast in our study participants

Histological Grade	Level III LN positive	Percent	Level III LN Negative	Percent
Grade 1	1	9.09%	5	6.41%
Grade 2	4	36.36%	51	65.38%
Grade 3	6	54.55%	15	19.23%
NA	0	0.00%	7	8.97%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.044, Significant

Table 19 explains the association between Level III LN positivity and Histological grade of carcinoma breast in our study participants. We observed significant association between Level III LN positivity and Histological grade of carcinoma breast. (p = 0.044) Majority of the Level III LN positive cases were Grade 3 seen in 6 cases (54.55%) as compared to majority of Level III LN Negative cases being Grade 2 with 51 cases (65.38%).

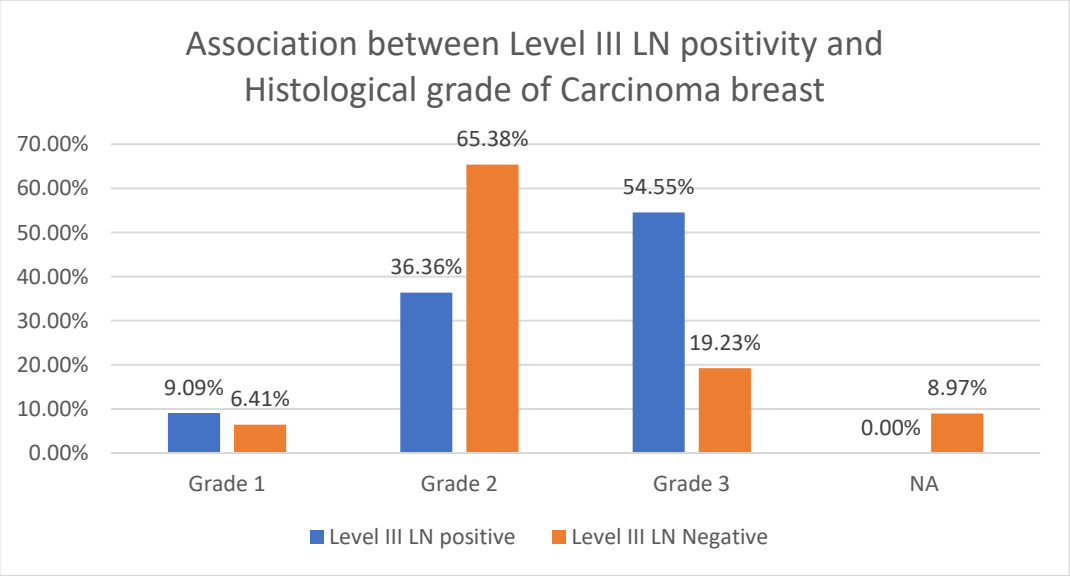


Fig 19: Association between Level III LN positivity and Histological grade of carcinoma breast in our study participants

Table 20: Association between Level III LN positivity and Tumor focality wise distribution of the study participants

Tumor Focality	Level III LN positive	Percent	Level III LN Negative	Percent
Multifocal	7	63.64%	10	12.82%
Unifocal	4	36.36%	62	79.49%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.001, Significant

Table 20 explains the association between Level III LN positivity and Tumor focality wise distribution of the study participants. We observed significant association between Level III LN positivity and Tumor focality wise distribution of the study participants (P = 0.001). Majority of the Level III LN positive cases were multifocal (63.64%) as compared to Level III LN Negative cases being unifocal (79.49%).

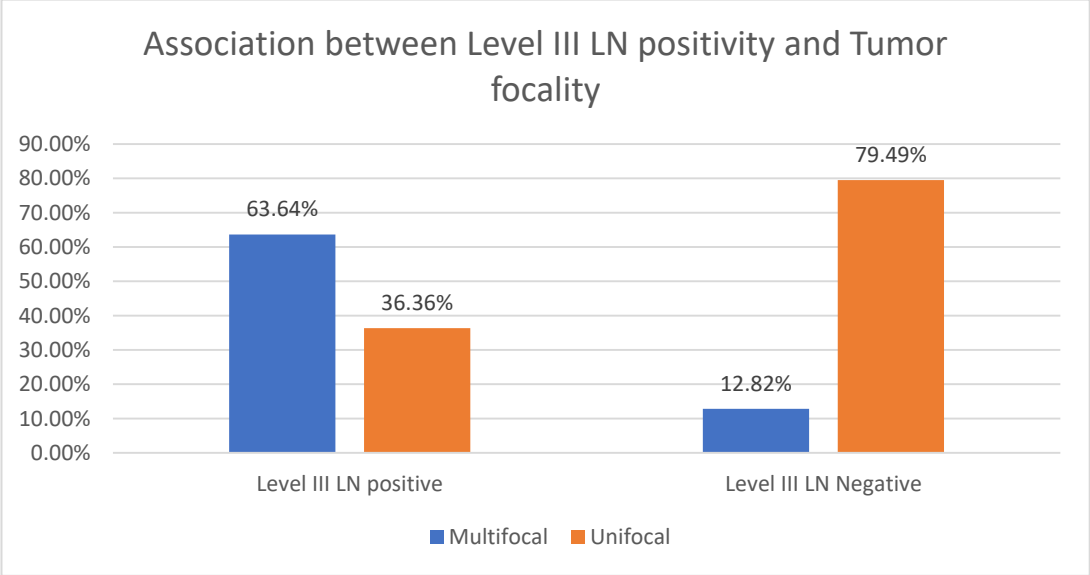


Fig 20: Association between Level III LN positivity and Tumor focality wise distribution of the study participants

Table 21: Association between Level III LN positivity and NAC involvement in the study participants

NAC	Level III LN positive	Percent	Level III LN Negative	Percent
Involved	5	45.45%	3	3.85%
Not Involved	6	54.55%	75	96.15%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value < 0.001, Significant

Table 21 explains the Association between Level III LN positivity and NAC involvement in the study participants. We observed significant association between Level III LN positivity and NAC involvement in the study participants (p< 0.001). NAC was involved in 45.45% cases with Level III LN positivity and in 3.85% cases with Level III LN Negativity.

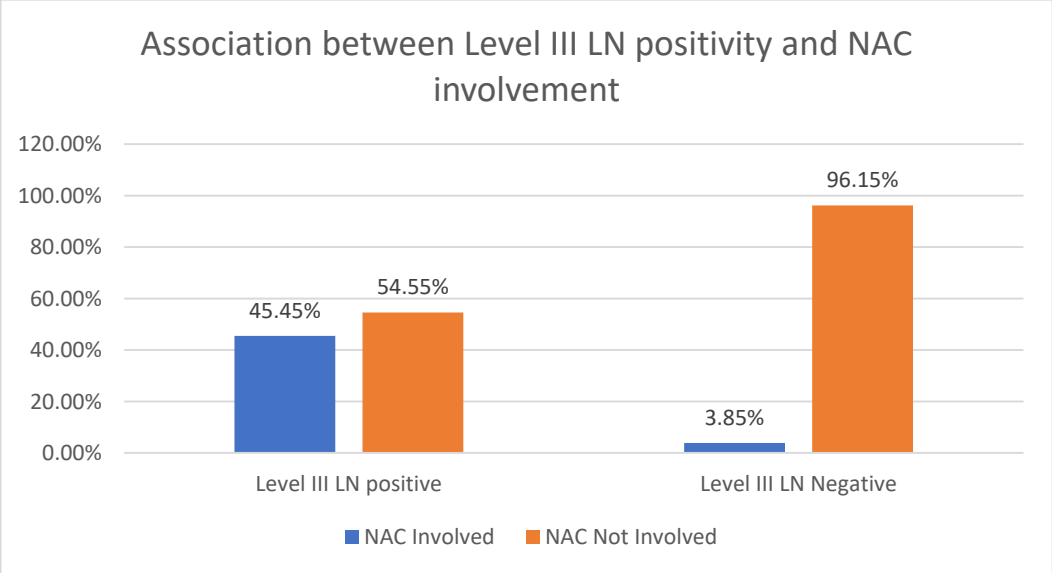


Fig 21: Association between Level III LN positivity and NAC involvement in the study participants

Table 22: Association between Level III LN positivity and lymphovascular invasion in the study participants

Lymphovascular Invasion	Level III LN positive	Percent	Level III LN Negative	Percent
Present	10	90.91%	22	28.21%
Absent	1	9.09%	56	71.79%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value < 0.001, Significant

Table 22 explains the Association between Level III LN positivity and presence of Lymphovascular Invasion. We observed significant association between Level III LN positivity and Lymphovascular Invasion in the study participants ($p < 0.001$). LVI was seen in 90.91% cases with Level III LN positivity and in 28.21% cases with Level III LN Negativity.

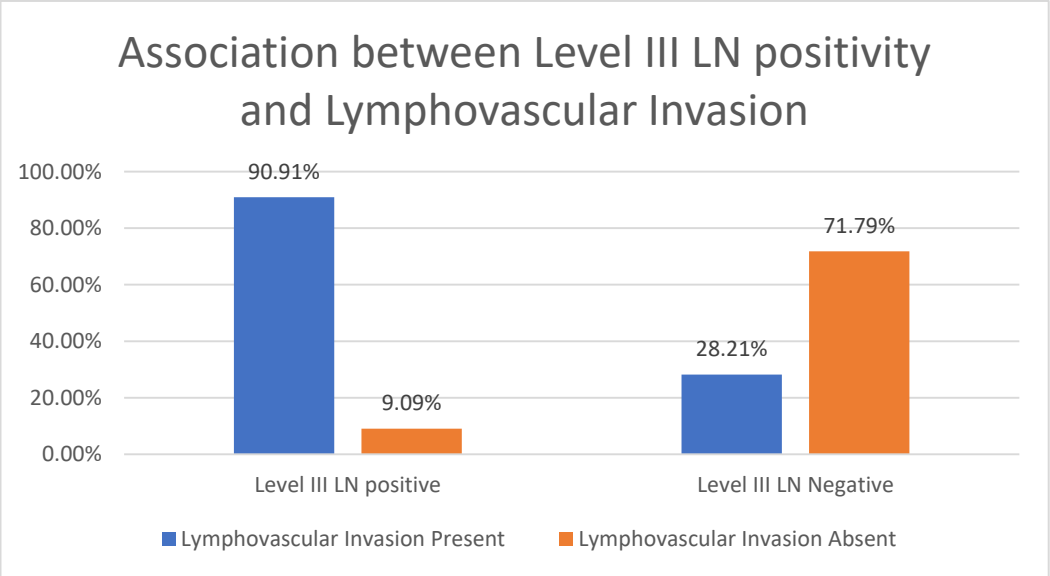


Fig 22: Association between Level III LN positivity and Lymphovascular Invasion in the study participants

Table 23: Association between Level III LN positivity and Perineural Invasion in the study participants

Perineural Invasion	**Level III LN positive**	**Percent**	**Level III LN Negative**	**Percent**
Present	4	36.36%	9	11.54%
Absent	7	63.64%	69	88.46%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.029, Significant

Table 23 explains the Association between Level III LN positivity and Perineural Invasion. We observed significant association between Level III LN positivity and Perineural Invasion in the study participants (p = 0.029). Perineural Invasion was seen in 36.36% cases with Level III LN positivity and in 11.54% cases with Level III LN Negativity.

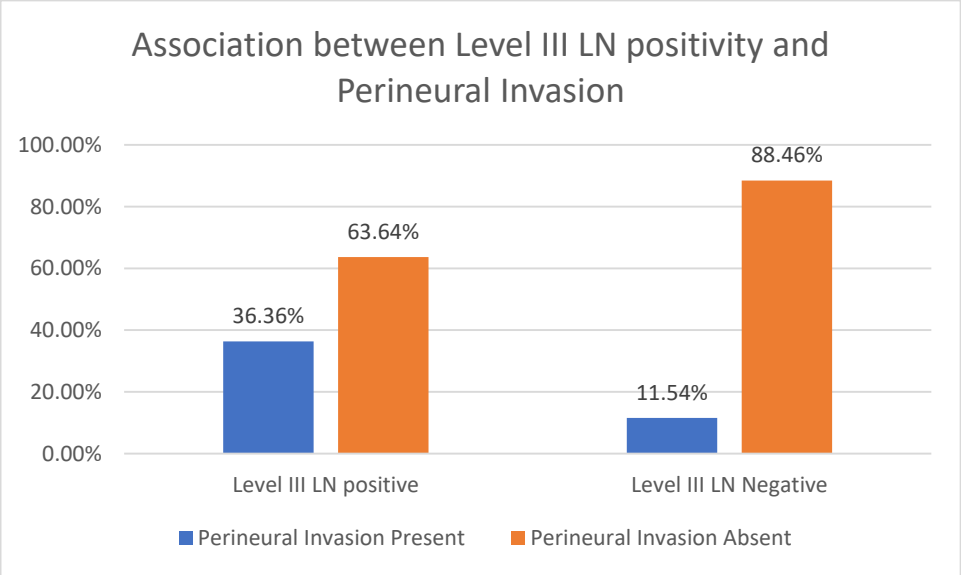


Fig 23: Association between Level III LN positivity and Perineural Invasion in the study participants

Table 24: Association between Level III LN positivity and Extracapsular Extension in the study participants

Extracapsular Extension	Level III LN positive	Percent	Level III LN Negative	Percent
Present	5	45.45%	7	8.97%
Absent	6	54.55%	71	91.03%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value < 0.001, Significant

Table 24 explains the association between Level III LN positivity and Extracapsular Extension. We observed significant association between Level III LN positivity and Extracapsular Extension in the study participants ($p < 0.001$). Extracapsular Extension was seen in 45.45% cases with Level III LN positivity and in 8.97% cases with Level III LN Negativity.

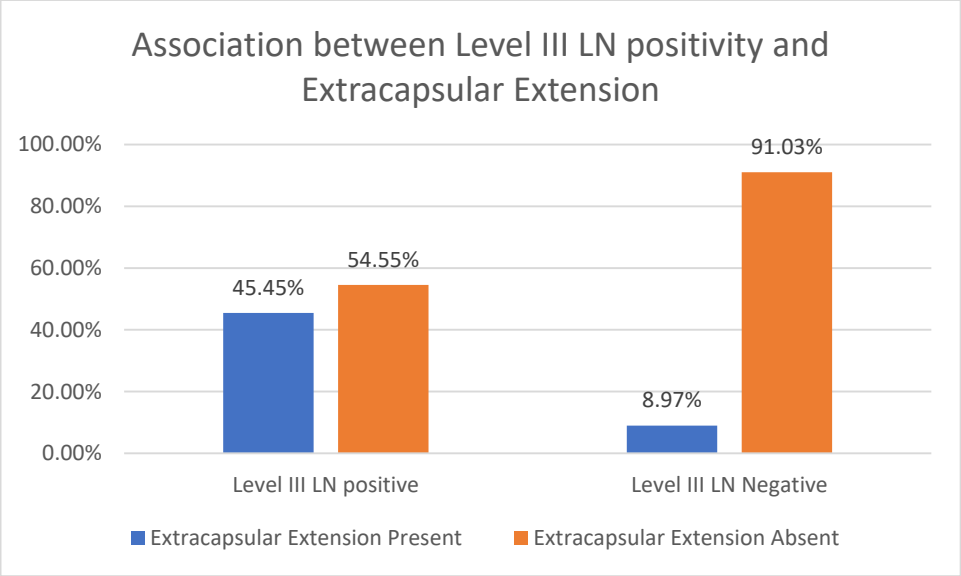


Fig 24: Association between Level III LN positivity and Extracapsular Extension in the study participants

Table 25: Association between Level III LN positivity and ER/PR positivity in the study participants

ER/PR	Level III LN positive	Percent	Level III LN Negative	Percent
Positive	3	27.27%	30	38.46%
Negative	8	72.73%	48	61.54%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.47, Not Significant

Table 25 explains the association between Level III LN positivity and ER/PR positivity. We observed no significant association between Level III LN positivity and ER/PR positivity in the study participants (p = 0.47).

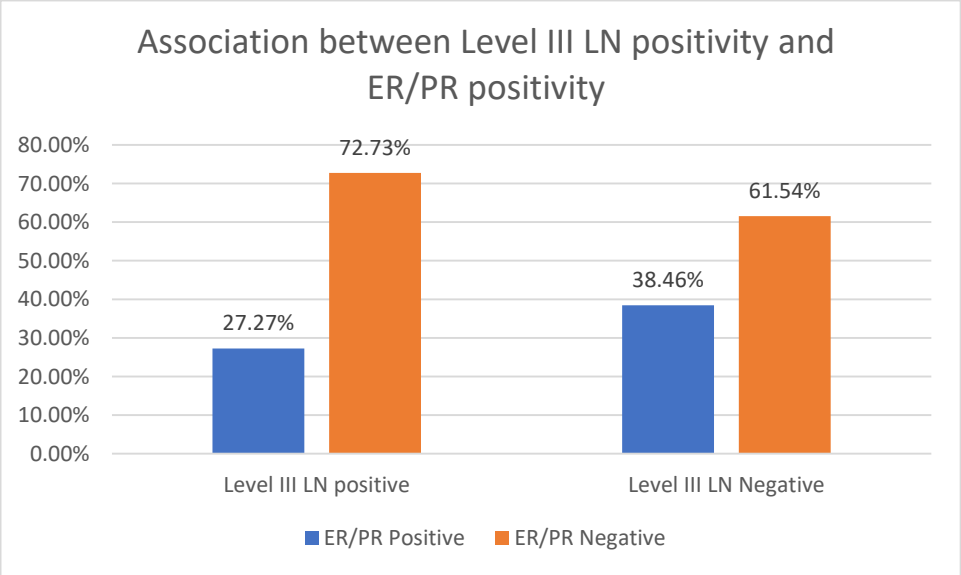


Fig 25: Association between Level III LN positivity and ER/PR positivity in the study participants

Table 26: Association between Level III LN positivity and HER2 positivity in the study participants

HER2	Level III LN positive	Percent	Level III LN Negative	Percent
Positive	6	54.55%	15	19.23%
Negative	5	45.45%	63	80.77%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.01, Significant

Table 26 explains the association between Level III LN positivity and HER2 positivity in the study participants. We observed significant association between Level III LN positivity and HER2 positivity in the study participants (p = 0.01). HER2 positivity was seen in 54.55% cases with Level III LN positivity and in 19.23% cases with Level III LN Negativity.

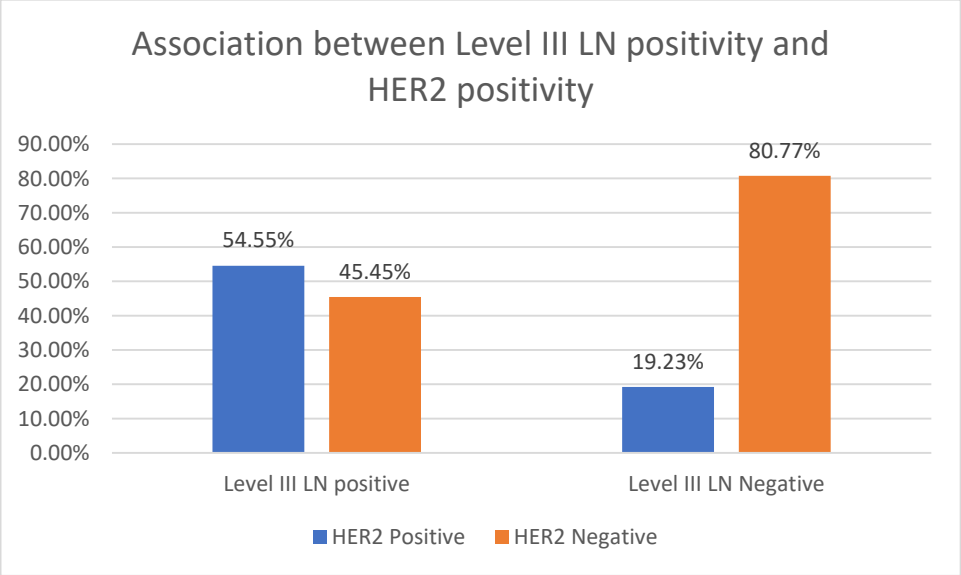


Fig 26: Association between Level III LN positivity and HER2 positivity in the study participants

Table 27: Association between Level III LN positivity and Triple negative hormonal status in the study participants

Triple negative	Level III LN positive	Percent	Level III LN Negative	Percent
Present	4	36.36%	41	52.56%
Absent	7	63.64%	37	47.44%
Total	11	100.00%	78	100.00%

Fisher's Exact Test, P value = 0.314, Not Significant

Table 27 explains the association between Level III LN positivity and Triple negative hormonal status of the study participants. We observed no significant association between Level III LN positivity and Triple negative status in the study participants (p = 0.314).

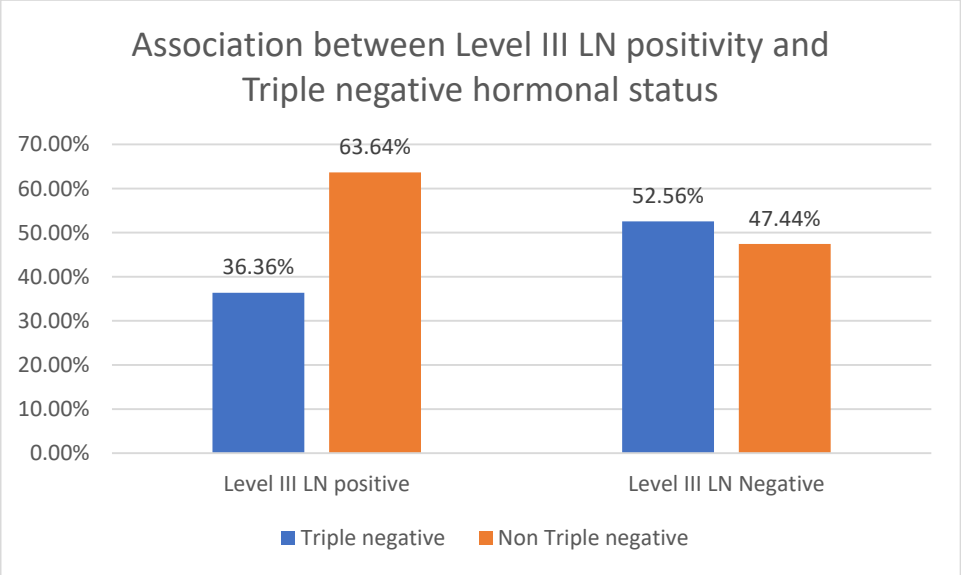


Fig 27: Association between Level III LN positivity and Triple negative hormonal status in the study participants

Table 28: Correlation between the Level III LN positivity and Level I & II LN positivity in the study participants

Level III LN Involvement	**Level I & II LN positive**	**Level I & II LN negative**	**Total**
Level III LN positive	10	1	11
Level III LN negative	25	53	78
Total	35	54	89

Fisher's Exact Test, P value < 0.001, Significant

Table 28 explains the Correlation between the Level III LN positivity and Level I & II LN positivity. We observed significant association between Level III LN positivity and Level I & II LN positivity in the study participants ($p < 0.001$).

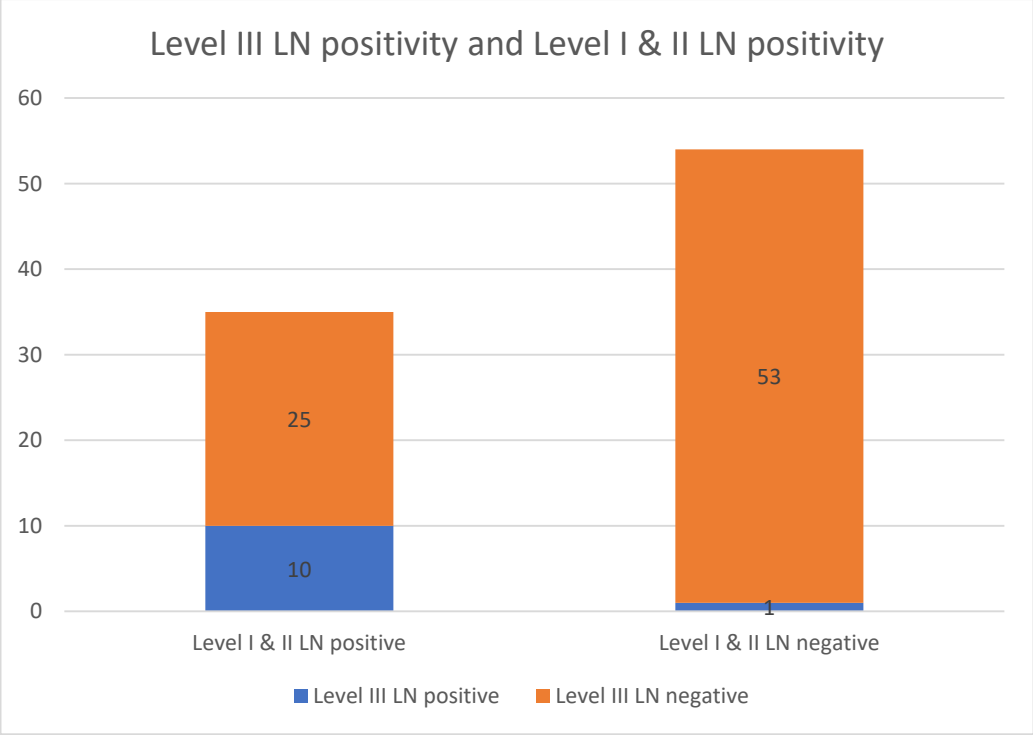


Fig 28: Correlation between the Level III LN positivity and Level I & II LN positivity in the study participants

Table 29: Level I & II LN 1 / 2 / 4 positive and percentage of Level III involvement in the study participants

	Level III Positivity			Percentage of Level III LN involvement	Level III LN Involvement
Level I & II LN - Inv	**Level III Not positive**	**Level III positive**	**Total cases**		
0	54	0	54	0%	< 4 nodes in Level II – 3.89% (3 out of 77)
1	10	1	11	9.09%	
2	6	1	7	14.29%	
3	4	1	5	20%	
4	2	1	3	33.33%	≥ 4 nodes in Level II – 66.67% (9 out of 12)
5	0	1	1	100%	
6	1	1	2	50%	
7	1	0	1	0%	
9	0	1	1	100%	
10	0	1	1	100%	
16	0	1	1	100%	
20	0	1	1	100%	
25	0	1	1	100%	
Total	78	11	89		P < 0.001

Significant difference was seen when we compared the level III lymph node involvement in terms of less than 4 level I & II lymph nodes involved or ≥ 4 level I & II lymph nodes involved ($p<0.001$).

We observed that in 77 cases with less than 4 level I & II lymph nodes involvement, only 3 cases showed Level III lymph node positivity (3.89%) while out of 12 cases of level I & II lymph nodes involvement, 9 cases showed Level III lymph node positivity (66.67%).

Table 30: Multivariate analysis between the Level III LN positivity and various study parameters

Study parameters	Mean Square	F	p Value
Age > 50	0.75	3.03	0.085
Incomplete NACT	1.39	6.95	0.01*
cT (T3 T4)	0.05	0.19	0.663
cN (N3)	2.35	31.40	< 0.001*
Histological Grade	2.47	4.09	0.046*
Tum Focality - Multifocal	2.49	19.23	< 0.001*
NAC involved	1.67	25.87	< 0.001*
Lymphovascular invasion	3.79	19.74	< 0.001*
Perineural Involvement	0.59	4.92	0.029*
ECE	1.28	12.27	0.001*
ER/PR	0.12	0.51	0.478
HER2	1.20	7.05	0.009*
Triple Negative	0.25	1.00	0.32
Level I & II LN - Involvement	646.82	68.74	< 0.001*

Multivariate analysis of level III lymph node positivity with the study parameters showed a significant association with incomplete NACT received by patients, cN grade N3 tumors, Histological grade, multifocal tumors, peripheral involvement in the form of NAC involvement, Lymphovascular invasion, Perineural involvement, Extracapsular extension, Her2 positive status and level I and Level II lymph node involvement. All these factors were found to be significantly associated with Level III lymph node involvement in our study ($p<0.05$).

DISCUSSION

6. DISCUSSION

Breast cancer patients may benefit from axillary lymph node dissection both therapeutically and prognostically. It provides axillary recurrence prevention by local control, and the information acquired from the number of positive lymph nodes enables precise staging and adjuvant therapy options.[130] Patients with four or more positive lymph nodes should be offered post-mastectomy radiation therapy because this signals a more aggressive form of the illness. A minimum of 10 lymph nodes must be submitted for pathological assessment in order to perform an acceptable axillary lymph node dissection and stage the axilla.[133]

We evaluated the cases of breast cancer who underwent axillary level III lymph node dissection post Neoadjuvant Chemotherapy. We got a total of 89 cases satisfying our study inclusion criteria during our study period. After neoadjuvant chemotherapy, it was found that 7 out of these 89 cases didn't show any residual carcinoma on histopathologic examination.

J Hu et al [134] in 2021 studied in detail the importance of axillary lymph node dissection in breast cancer patients. They found that the dissection of the axillary lymph nodes is a crucial component of a surgical treatment for breast cancer. It is the best way to assess the health of the axillary lymph nodes. Developing treatment regimens and assessing the prognosis for breast cancer patients are also very important. Anatomically, there are three levels of axillary lymph node dissection: I, II, and III. The clinical standard of care for axillary lymph node positive breast cancer is level I and level II axillary lymph dissection, however level III axillary lymph node dissection has generated a debate since generations. One of the crucial elements that might quickly lead to distant metastasis and recurrence is level III axillary lymph node metastases, which should be strictly controlled. Level III axillary lymph nodes are also a prognostic indicator in breast cancer patients.

J Alhgren et al [135] studied prediction of axillary lymph node metastasis in breast cancer patients. They analysed the frequency of pathologically confirmed lymph node metastases depending on tumour size, hormonal receptors, DNA ploidy, S-phase fraction (SPF), and clinical nodal status among 1145 patients with stage 1-2 breast cancer. They found that the clinical nodal status and tumour size were strongly correlated to pathological nodal status in their participants. Also SPF > 10% was strongly correlated to node positivity in univariate analysis. In multivariate analysis they found a significant correlation among cases with tumour size < 20mm. They concluded that the patients with clinically negative nodal status, and tumour size < 20 mm and < 10 mm had pathologically positive nodes in 25% and 15% of

cases respectively. The addition of SPF did not lower these figures significantly since small tumours with high SPF were rare. Their study results show the importance of axillary lymph node dissection to ensure complete tumor removal and involved axillary lymph node removal in the planned surgery for breast cancer patients.

6.1 Distribution of the study participants according to age group

The most common age group decade was 41 to 50 years with 27 cases (30.30%) followed by 51 to 60 years with 23 cases (25.80%), 61 to 70 years with 16 cases (18%) and 31 to 40 years with 15 cases (16.90%). The mean age of the study participants was 50.38 ± 11.54 years with a range of 26 – 74 years.

There was no significant association between the age group and level III LN positivity (p = 0.538). Out of 11 cases with Level III LN positivity, 5 were in the age group of 51 to 60 years (45.45%), 2 each were from age group of 41 to 50 and 61 to 70 years (18.18%).

Kodama H et al [108] observed that the mean age of the participants in their study was 50.6 ± 10.1 years. They did not find any significant association between the level III LN positivity and the age of the patients, these findings were similar to our study.

S Joshi et al [7] observed that there was no association between the age and level III LN positivity status. (p>0.05) which are similar to our observations.

DG Nderitu [136] found that the mean age of their participants was 48 years (range 30 – 80).

6.2 Procedures done in the study participants

The most common procedure done in our breast cancer patients after they received Neoadjuvant chemotherapy was Modified Radical Mastectomy (MRM) done in 72 cases (80.90%) followed by Breast Conservative Surgery in 15 cases (16.85%), radical mastectomy and skin sparing mastectomy in 1 case each (1.12%).

Kodama H et al [108] observed that out of total 258 cases, 96 cases had undergone mastectomy (37.21%) while rest 162 cases (62.79%) had breast conservative surgery, these findings are different from our study.

S Joshi et al [7] observed that 55.9% cases underwent Modified Radical Mastectomy (MRM) followed by Breast Conservative Surgery in 44.1% cases.

6.3 Distribution of the study participants according to duration of NACT

We observed that 62 out of total 89 cases (69.70%) received full course of Neoadjuvant chemotherapy, while rest 27 cases (30.30%) received partial course of Neoadjuvant chemotherapy before they underwent surgery for breast cancer.

We observed a significant association between Level III LN positivity and the duration of Neoadjuvant chemotherapy in the study participants ($p = 0.013$).

We observed that out of Level III LN positive cases, 7 had received partial course of NACT (63.64%) as compared to the 4 cases who had received full course NACT (36.36%). Out of 78 Level III LN negative cases 58 received full course NACT (74.36%) and 20 got partial course NACT (25.64%).

Neoadjuvant chemotherapy might contribute to decreasing level III lymph nodes involvement rate. The previous study by Rouzier R et al reported 22% to 23% of patients had a pathological complete response of axillary lymph node after neoadjuvant chemotherapy. [132]

Fan Z et al[117] observed that the effective neoadjuvant chemotherapy might reduce the incidence rate of level III positivity. Node positivity as proved by ultrasound guided needle biopsy, large tumor size, and primary tumor nonresponse to neoadjuvant chemotherapy are independent predictors of axillary lymph node positivity.

6.4 Distribution of the study participants according to cT and cN stage

We observed that majority of the participants, 45 cases were T2 (50.60%), 24 cases were T4 (26.97%) and 19 cases were T3 (21.30%).

We observed that majority of the participants, 43 cases were N1 (48.31%), 18 cases each were N2 and N0 (20.20%) and 10 cases were N3 (11.20%).

We observed no significant association between the Level III LN positivity and cT staging ($p = 0.129$). Out of the 11 cases with Level III LN positivity, 5 were T2 (45.45%), 4 were T4 (36.36%) and 2 were T3 (18.18%).

We observed significant association between the Level III LN positivity and cN staging ($p < 0.001$). Out of the 11 cases with Level III LN positivity, 6 were N3 (54.55%), 3 were N2 (27.27%) and 2 were N1 (18.18%). This shows greater association between the N3 stage and level III Lymph Node positivity.

E Popa et al [137] observed that most patients (57,1%) from their study group were classified as cT4 using clinical examination, mammography and ultrasonography. After NACT, the number of T4 patients decreased to 3 (8,5%) and the number of patients with T1 and T2 tumors increased to 60%.

S Joshi et al [7] observed that N1 was seen in 56.4% cases, N2 in 26.7% cases and N3 in 16.9% cases.

DG Nderitu [136] found that most common tumor type was T2 seen in 52.1% cases.

6.5 Histological types of Carcinoma breast in Final Histopathology examination

The most common type diagnosed was Invasive Breast Carcinoma No Special Type seen in 67 cases (75.28%), there were 2 cases each (2.20%) of IBC with Apocrine Differentiation, Microinvasive Carcinoma Breast, Mixed Mucinous Carcinoma and IBC.

Fan Z et al [117] observed that most common histological type was IDC seen in 92.5% cases.

S Joshi et al [7] observed that IDC was seen in 98% cases.

DG Nderitu [136] found that most common histological type was ductal carcinoma in 66 (90.3%) of the patients. These findings are similar to our study

6.6 Histological grade and tumor focality of Carcinoma breast in our study participants post NACT.

We observed that 7 cases didn't show any carcinoma post NACT (7.87%). While majority of the cases showed Grade 2 carcinoma, as seen in 55 cases (61.80%) followed by Grade 3 in 21 cases (23.60%) and Grade 1 in 6 cases (6.74%).

We observed that there were 72 unifocal cases (80.90%) and 17 multifocal cases (19.10%) in our study.

We observed significant association between Level III LN positivity and Histological grade of Carcinoma breast. ($p = 0.044$).

We observed significant association between Level III LN positivity and Tumor focality wise distribution of the study participants ($P = 0.001$).

Fan Z et al [117] observed that amongst the cases of breast cancer in their study, 73.7% were grade 2, 10.6% were grade 3 and 7.7% were grade 1 tumors.

S Joshi et al [7] observed that majority of the patients were grade 3 seen in 80.4% cases while grade 1 and 2 were 18.9% cases. They found significant association between the histological grade 3 and Level III LN positivity similar to our study.

DG Nderitu[136] found that Grade 2 and grade 3 tumors comprised 90.4% of the cases.

6.7 Tumor quadrant wise distribution of the study participants

We observed that the majority of the cases were seen in Upper Outer quadrant with 31 cases (34.83%), followed by Upper Inner quadrant with 20 cases (22.47%), central quadrant with 19 cases (21.35%), lower outer quadrant with 12 cases (13.48%), followed by lower inner quadrant with 7 cases (7.87%).

S Joshi et al [7] observed that most common area involved was outer (49%) followed by central (21%) and inner (20%).

Fan Z et al [117] observed that majority of the cases had tumor location in upper quadrants (69%) followed by lower (14.6%) and central regions (11.4%).

DG Nderitu [136] found that the most common involved site was upper quadrant seen in 39.7% cases, similar to our study.

6.8 LVI, PNI and NAC involvement of the tumor in the study participants

We observed that majority of the cases had Lymphovascular invasion positive as seen in 32 cases (35.96%), followed by Perineural Invasion in 13 cases (14.61%) , Extracapsular Invasion in 12 cases (13.48%), and involvement of Nipple – Areolar complex in 8 cases (8.99%).

We observed significant association between Level III LN positivity and NAC involvement, LVI involvement, Perineural Invasion and Extracapsular Extension in the study participants ($p< 0.05$).

S Joshi et al [7] observed that perinodal extension was seen in 78.2% cases and LVI was seen in 32.7% cases.

DG Nderitu found that Lymphovascular invasion and positive resection margins were found in 53 (72.6%) and 10 (13.7%) of their study cases.

D Santini et al [138] studied the involvement of the nipple-areolar complex in 1,291 available consecutive mastectomy specimens with primary invasive breast carcinoma. They found that the Tumor involvement of the nipple-areolar complex was seen in 150 specimens (12 percent) and was not suspected on gross examination in 99 patients (8 percent). Their finding of 12% involvement of NAC are approximately similar to our finding of 8% NAC involvement.

SG Karak et al [139] studied 1,136 cases of CA breast for Perineural invasion and lymphovascular invasion. They found that 13 cases (1.14%) showed Perineural invasion and 146 cases (12.9%) showed lymphovascular invasion.

6.9 Distribution of the study participants according to Hormonal Receptor and Her2 status

We observed that majority of the participants were triple negative seen in 45 cases (50.56%), followed by ER / PR positive as seen in 33 cases (37.08%) and Her2 positive in 21 cases (23.60%).

We observed no significant association between Level III LN positivity and ER/PR positivity and Triple negative status in the study participants ($p > 0.05$).

We observed significant association between Level III LN positivity and HER2 positivity in the study participants ($p = 0.01$).

Kodama H et al [108] observed that out of total 258 cases, 161 cases were ER positive (62.40%).

Dawood S. et al [140] mentioned that the triple receptor-negative breast cancer (TNBC) subtype are seen in approximately 10–15% of breast carcinomas. They reported that Risk factors for TNBC include young age at breast cancer diagnosis, young age at menarche, high parity, lack of breast feeding, high body mass index and African American ethnicity. They observed that TNBC has a worse prognosis and tends to relapse early compared with other subtypes of breast cancer.

Fan Z et al [117] observed that out of 521 cases in their study, around 74% were ER/PR positive, and 22% were Her2 positive.

S Joshi et al [7] observed that Her2 receptor positivity in Carcinoma breast cases are significantly associated with the Level III LN positivity ($p<0.05$) They did not find significant association between the ER/PR status and level III LN positivity. These findings are similar to our study.

DG Nderitu [136] found that the hormonal and HER2 receptor status in their study was seen in 59 (80.8%) of the cases. Twelve (20.3%) of their cases had triple negative breast cancer. Their findings are different from our study.

6.10 Level I & II and Level III LN positivity wise distribution of the study participants

We observed 35 cases were Level I & II LN positive (39.33%). We found that the level III Lymph node positivity was seen in 11 cases (12.36%) in our study. We observed Skip metastasis in one case – where Level I & II LN were negative and Level III LN was positive was seen in 1 case (1.12%).

In another study from China by Fan et al. [117] the incidence of residual positive nodal disease in level III was 9% (47 of 521), even after preoperative neoadjuvant chemotherapy in stage I and II breast cancer. These findings were similar to our study.

Only a few studies have tried to demonstrate the relation of clinicopathological factors with level III ALN. In the largest series from India level III involvement was found to be 27.3% of all node-positive patients.[7] We did our study post neoadjuvant chemotherapy, that's why our Level III lymph node positivity was less than this study.

We observed significant association between Level III LN positivity and Level I & II LN positivity in the study participants ($p < 0.001$). Significant difference was seen when we compared the level III lymph node involvement in terms of less than 4 level I & II lymph nodes involved or ≥ 4 level I & II lymph nodes involved ($p<0.001$). We observed that in 77 cases with less than 4 level I & II lymph nodes involvement, only 3 cases showed Level III lymph node positivity (3.89%) while out of 12 cases of level I & II lymph nodes involvement, 9 cases showed Level III lymph node positivity (66.67%).

A study conducted at one of largest cancer center in India demonstrated that four or more ALNs in level I and II, inner/central quadrant tumor location, poor histologic grade, and presence of PNE and LVI were associated with higher-level III ALN positivity.[7]

In a similar study by Chua et al.[128] 320 patients were evaluated. Involvement of lymph nodes in level III was observed in 22 patients (7%) and 51 patients (16%) had four or more positive nodes. They observed that up to 42% of patients had involved level III ALNs when four or more ALNs were positive.

Khafagy et al.[115] reported that 53.5% of patients had level III ALN involvement when a lower level had nodal metastases. Veronesi et al. [114] also reported an incremental risk of level III involvement with an increasing number of positive lower-level nodes. The level III involvement was 8%, 25.3%, and 65.8%, respectively, when 1, 2, and 4 or more ALNs were positive in level I.

Kodama H et al [108] observed that Level I LN involvement was seen in 30-32% cases, Level II in 4.7% cases and Level III LN involvement was seen in 7.4% cases.

Skip metastasis, although rare, is found in previous studies in up to 15% of the cases.[127, 129]

Fan Z et al [117] observed that Skip metastasis was present in one patient which showed level I and II nodal negativity but level III nodal positivity. This finding is similar to our study

S Joshi et al [7] observed that there was significant association between the ≥ 4 level I & II lymph nodes involved and level III LN involvement ($p<0.001$)which are similar to our study anaylsis.

We observed that the median Level I & II LN - Number Dissected was 15, with median cancerous growth seen in 0 node. The mean of Level I & II LN - Number Dissected was 15.61 with mean cancer involvement in 1.75.

The median Level III LN - Number Dissected was 2, with median cancerous growth seen in no any node (0). The mean of Level III LN - Number Dissected was 2.54 with mean cancer involvement in 0.20.

Fan Z et al [117] observed that a median of 19 axillary nodes was harvested per case (range: 5-46, average: 19.8). Two hundred and sixty three patients had positive lymph nodes in level I or II region. Level III lymph nodes were harvested in 78.7% (410/521) of operation samples (range: 1 - 8, average: 1.9, median: 2). The incidence of positive level III lymph nodes were 9.0% (47/521). One patient of NB positive subgroup had level I and II nodal negativity but level III nodal positivity.

S Joshi et al [7] observed that A median of four (zero to 20) level III ALNs were dissected and a median of two (one to 17) nodes were positive. A total of 27.3% (434 of 1,591) patients had level III ALN metastasis. This was higher than what was observed in our study because patients in their study were not given NACT.

6.11 Multivariate analysis

Multivariate analysis of level III lymph node positivity with the study parameters showed a significant association with partial course NACT received by patients, cN stage N3 tumors, Histological grade, multifocal tumors, peripheral involvement in the form of NAC involvement, Lymphovascular invasion, Perineural invasion, Extracapsular extension, Her2 positive status and level I and Level II lymph node involvement. All these factors were found to be significantly associated with Level III lymph node involvement in our study ($p<0.05$).

Chua et al.[128] studied 320 cases of CA breast, they observed that Palpability of ALNs, pathologic tumour size, and LVI was significantly associated with level III involvement and four or more positive nodes by univariate and multivariate analyses. ($p<0.05$)

Wang R et al [120] observed that more the number of axillary lymph node metastases at levels I–II, with the involvement of external nodes, and the negative expression of ER are risk factors for level III axillary lymph node metastasis. Further stratified analysis showed that level III axillary lymph node metastasis was more likely to occur if the tumor above T3 was located laterally ($P = 0.035$). If ER expression is negative, with the increase of tumor stage, level III lymph nodes are more likely to metastasize.

Fan Z et al [117] observed that clinical tumor T stage before neoadjuvant chemotherapy, age, node biopsy method and primary tumor response to neoadjuvant chemotherapy were the factors associate with level III positivity.

S Joshi et al [7] observed that tumor size >5 cm, histological grade 3, >4 axillary LN positive, negative ER/PR status were significantly associated with more level III LN positivity.

MJ Silverstein et al [141] found that after doing Multivariate analysis of patients with invasive Breast cancer four factors as independent predictors of axillary lymph node metastases were identified, these were lymphovascular invasion, tumor size, nuclear grade, tumor palpability. Among a group of 189 patients with nonpalpable, non-high-grade invasive lesions 15 mm or smaller without lymph/vascular invasion, only 6 (3%) had metastases to lymph nodes. If any three of the favorable factors were present, lymph node positivity was 6% or less. Their

study concluded that the clinical and pathologic feature of the primary lesions can be used to estimate the risk of axillary lymph node metastases. They recommended that this risk assessment should be used for the treatment decision-making process.

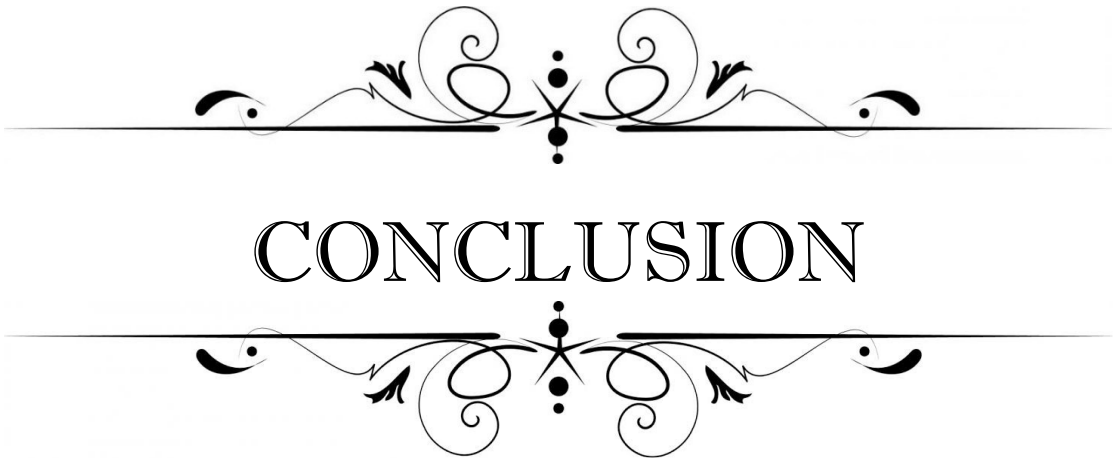
SUMMARY

7. SUMMARY

- We evaluated the 89 cases of breast cancer who underwent axillary level III lymph node dissection post Neoadjuvant Chemotherapy.
- After neoadjuvant chemotherapy, it was found that 7 out of these 89 cases didn't show any residual carcinoma on histopathologic examination.
- Age group wise distribution of the study participants
    - The most common age group decade was 41 to 50 years with 27 cases (30.30%) followed by 51 to 60 years with 23 cases (25.80%), 61 to 70 years with 16 cases (18%) and 31 to 40 years with 15 cases (16.90%).
    - The mean age of the study participants was 50.38 ± 11.54 years with a range of 26 – 74 years.
    - There was no significant association between the age group and level III LN positivity ($p = 0.538$). Out of 11 cases with Level III LN positivity, 5 were in the age group of 51 to 60 years (45.45%), 2 each were from age group of 41 to 50 and 61 to 70 years (18.18%).
- Procedures done in the study participants
    - The most common procedure done in our breast cancer patients after they received Neoadjuvant chemotherapy was Modified Radical Mastectomy (MRM) done in 72 cases (80.90%) followed by Breast Conservative Surgery in 15 cases (16.85%), radical mastectomy and skin sparing mastectomy in 1 case each (1.12%).
- cT and cN stage wise distribution of the study participants
    - We observed that majority of the participants, 45 cases were T2 (50.60%), 24 cases were T4 (26.97%) and 19 cases were T3 (21.30%).
    - We observed that majority of the participants, 43 cases were N1 (48.31%), 18 cases each were N2 and N0 (20.20%) and 10 cases were N3 (11.20%).
    - We observed no significant association between the Level III LN positivity and cT staging($p = 0.129$). Out of the 11 cases with Level III LN positivity, 5 were T2 (45.45%), 4 were T4 (36.36%) and 2 were T3 (18.18%).
    - We observed significant association between the Level III LN positivity and cN staging ($p < 0.001$).
    - Out of the 11 cases with Level III LN positivity, 6 were N3 (54.55%), 3 were N2 (27.27%) and 2 were N1 (18.18%). This shows greater association between the N3 stage and level III Lymph Node positivity.

- Histological types of Carcinoma breast in Final Histopathology examination
    - The most common type diagnosed was Invasive Breast CA Non Special Type seen in 67 cases (75.28%), there were 2 cases each (2.20%) of IBC with Apocrine Differentiation, Microinvasive CA Breast, Mixed Mucinous CA and IBC.
- Histological grade and tumour focality of Carcinoma breast in our study participants post NACT.
    - We observed that 7 cases didn't show any carcinoma post NACT (7.87%). While majority of the cases showed Grade 2 carcinoma, as seen in 55 cases (61.80%) followed by Grade 3 in 21 cases (23.60%) and Grade 1 in 6 cases (6.74%).
    - We observed that there were 72 unifocal cases (80.90%) and 17 multifocal cases (19.10%) in our study.
    - We observed significant association between Level III LN positivity and Histological grade of CA breast. ($p = 0.044$)
    - We observed significant association between Level III LN positivity and Tumour focality wise distribution of the study participants ($P = 0.001$).
- Tumour quadrant wise distribution of the study participants
    - We observed that the majority of the cases were seen in Upper Outer quadrant with 31 cases (34.83%), followed by Upper Inner quadrant with 20 cases (22.47%), central quadrant with 19 cases (21.35%), lower outer quadrant with 12 cases (13.48%), followed by lower inner quadrant with 7 cases (7.87%).
- LVI,PNI & ECE character of the tumour in the study participants
    - We observed that majority of the cases had Lymphovascular Invasion as seen in 32 cases (35.96%), followed by Perineural Invasion in 13 cases (14.61%) , Extracapsular Invasion in 12 cases (13.48%), and involvement of Nipple – Areolar complex in 8 cases (8.99%).
    - We observed significant association between Level III LN positivity and NAC involvement in the study participants ($p< 0.001$).
    - We observed significant association between Level III LN positivity and LVI in the study participants ($p< 0.001$).
    - We observed significant association between Level III LN positivity and Perineural Invasion in the study participants ($p = 0.029$).
    - We observed significant association between Level III LN positivity and Extracapsular Extension in the study participants ($p < 0.001$).

- Distribution of the study participants according to Hormonal Receptor and Her2 status
    - We observed that majority of the participants were triple negative seen in 45 cases (50.56%), followed by ER / PR positive as seen in 33 cases (37.08%) and Her2 positive in 21 cases (23.60%).
    - We observed no significant association was there between Level III LN positivity and ER/PR positivity in the study participants ($p = 0.47$).
    - We observed significant association between Level III LN positivity and HER2 positivity in the study participants ($p = 0.01$).
    - We observed no significant association between Level III LN positivity and Triple negative status in the study participants ($p = 0.314$).
- Level I & II LN positivity wise distribution of the study participants
    - We observed 35 cases were Level I & II LN positive (39.33%).
- Level III LN positivity wise distribution of the study participants
    - We observed that the level III Lymph node positivity was seen in 11 cases (12.36%) in our study.
    - We observed Skip metastasis in one case – where Level I & II LN were negative and Level III LN was positive was seen in 1 case (1.12%).
    - We observed significant association between Level III LN positivity and Level I & II LN positivity in the study participants ($p < 0.001$).
    - Significant difference was seen when we compared the level III lymph node involvement in terms of less than 4 level I & II lymph nodes involved or ≥ 4 level I & II lymph nodes involved ($p<0.001$).
    - We observed that in 77 cases with less than 4 level I & II lymph nodes involvement, only 3 cases showed Level III lymph node positivity (3.89%) while out of 12 cases of level I & II lymph nodes involvement, 9 cases showed Level III lymph node positivity (66.67%).
- Multivariate analysis
    - Multivariate analysis of level III lymph node positivity with the study parameters showed a significant association with partial course NACT received by patients, cN stage N3 tumours, Histological grade, multifocal tumours, NAC involvement, Lymphovascular Invasion, Perineural involvement, Extracapsular extension, Her2 positive status and level I and Level II lymph node involvement.



CONCLUSION

8. CONCLUSION

The stage at presentation and the frequency of axillary nodal involvement are higher in lower-middle-income nations like India.Approximately 12% of these patients will harbour a Level III axillary lymph node if they are not cleared as a part of axillary lymphnode dissection. Factors like partial course NACT received by patients, cN stage N3 tumors(prior to the NACT), Histological grade, multifocal tumors, NAC involvement, Lymphovascular Invasion, Perineural involvement, Extracapsular extension, Her2 positive status and $\geq$ 4 level I and Level II lymph node involvement have significant association with Level III Axillary Lymph nodes positivity.

These factors can be used as a guide to consider Level III axillary lymph node dissection in subset of patients of breast cancer post Neoadjuvant chemotherapy.

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ANNEXURES

10. ANNEXURES

1. Ethical Clearance Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/ 3531 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3366**

Project title: **"Role of routine level III axillary lymph node dissection in breast cancer following neoadjuvant chemotherapy"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.Ch. Dissertation**
Student Name:	**Dr. Alkesh Gulhane**
Guide:	**Dr. Jeewan Ram Vishnoi**
Co-Guide:	**Dr. Sanjeev Misra, Dr. D Jayakumar , Dr. Puneet Pareek, Dr. Rakesh Kumar Vyas & Dr. Poonam Elhence**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

2. Proforma

Name	
Age/Sex	
AIIMS ID	
Menstrual Status	

Histologic type		**Hormone Receptor Status (ER & PR)**	
Invasive ductal carcinoma		Positive	
Others		Negative	
Histologic grade (MRB)		**Her 2 status (IHC or FISH in case of equivocal IHC)**	
1		Positive	
2		Negative	
3		**Hormone Receptor status(ER & PR)**	
cT size(Pre NACT)		Positive	
T1		Negative	
T2		No. of NACT Cycles	
T3		Full course	
T4		Partial Course	

Surgery	
BCS	

MRM	
Lymph Node Status (Pre NACT)	
cN1	
cN2	
cN3	
Perinodal extension	
Present	
Absent	
The yield of axillary Lymph Nodes (Level I & II)	
Total	
Involved	
The yield of Level III lymph nodes	
Total	
Involved	
Tumour Focality	
Unifocal	
Multifocal	
NAC Involvement	
LV emboli	
PNI invasion	

3. Informed consent (English)

Title of Thesis/Dissertation: **Role of Routine Level III Axillary Lymph Node Dissection in Breast Cancer Following Neoadjuvant Chemotherapy**

Name of investigating Student : **Dr. Gulhane Alkesh Dipak** Tel. 8335009898

Patient/Volunteer Identification No. : _____

I, _____ S/o or D/o _____

R/o _____ after reading the patient information sheet dated ___/___/____ give my full, free, voluntary consent to be a part of the study "**Role of Routine Level III Axillary Lymph Node Dissection in Breast Cancer Following Neoadjuvant Chemotherapy**", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary, and I am aware of my right to opt-out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____(Company Name) or regulatory authorities. I permit for these individuals to have access to my records.

Date : _____ _____

Place : _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date : _____ _____

Place : _____ Signature of PG Student

1. Witness 1

   _____

   Signature

   Name: _____

   Address: _____

   _____

2. Witness 2

   _____

   Signature

   Name: _____

   Address: _____

   _____

4. Informed consent (Hindi)

सूचित सहमति प्रपत्र

थीसिस / शोध प्रबंध का शीर्षक : नवसृजवंत रसायन चिकित्सा के बाद स्तन कैंसर में रूटीन स्तर **III** एक्सिलरी लिम्फ नोड डिस-सेक्शन की भूमिका

पीजी छात्र का नाम : डॉ गुलहणे अलकेश दीपक फ़ोन. 8335009898

रोगी / स्वयंसेवक पहचान संख्या : _____

मैं _____ ,S/O या D/O _____

_____के निवासी, सूचना पत्रक दिनांक ___/___/_____ पढ़ने के बाद अध्ययन का एक हिस्सा बनने के लिए मेरी पूर्ण ,स्वतंत्र ,स्वैच्छिक सहमति दें "नवसृजित रसायन चिकित्सा के बाद स्तन कैंसर में रूटीन स्तर III अक्षीय लिम्फ नोड विच्छेदन की भूमिका", जिस प्रक्रिया और प्रकृति को मुझे अपनी पूरी संतुष्टि के लिए अपनी भाषा में समझाया गया है . मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मुझे किसी भी कारण दिए बिना किसी भी समय अध्ययन से बाहर निकलने का मेरा अधिकार है।

मैं समझता हूं कि मेरे और मेरे मेडिकल रिकॉर्ड के बारे में एकत्रित की गई जानकारी को _____ (कंपनी नाम) या विनियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन लोगों के लिए मेरे रिकॉर्डों तक पहुंच की अनुमति देता हूं

तारीख : _____

_____

जगह: _____ हस्ताक्षर / बाएं अंगूठे का छाप

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है

तारीख : _____

_____

जगह: _____ पीजी छात्र के हस्ताक्षर

1. गवाह 1 2. साक्षी 2

_____ _____

हस्ताक्षर हस्ताक्षर

नाम: _____ नाम : _____

पता: _____ पता : _____

5. Patient information sheet (English)

PROTOCOL: "**Role of Routine Level III Axillary Lymph Node Dissection in Breast Cancer Following Neoadjuvant Chemotherapy**"

PATIENT INFORMATION SHEET

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study being conducted in AIIMS, Jodhpur, because you satisfy our eligibility criteria.

What is the purpose of the research?

This study is done to see the characteristics and predictors of level III axillary lymph nodes in breast cancer following neoadjuvant chemotherapy. We have obtained permission from the Institutional Ethics Committee for conducting this study.

The study design

The study will be a single-centre Prospective as well as Retrospective observational study, and patients will be recruited from the Department of Surgical Oncology.

Study Procedures

You will be given the standard of care surgical treatment for your disease based on your tumour characteristics and your wishes. Your clinical data may be taken from AIIMS Hospital information system.

Possible risks to you.

There is no added risk other than the risk involved due to surgery and disease.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/ or therapeutic as well as prognostic benefit to future patients.

The alternatives you have

If you do not wish to participate, you will still get the standard treatment for your condition.

Reimbursement

You will not be paid to participate in this research study.

What should you do in case of injury or a medical problem during this research study?

Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided with the necessary care/treatment.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law like the Drug Controller General of India to view your data, if needed. The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you, and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary, and you have the right to withdraw from this study at any time during the course of the study without giving any reasons.

Can the investigator take you off the study?

You may be taken off the study without your consent if you do not follow instructions of the investigators or the research team or if the investigator thinks that further participation may cause you harm.

Right to new information

Suppose the research team gets any new information during this research study that may affect your decision to continue participating in the study or may raise some doubts. In that case, you will be told about that information.

Contact person: Dr Gulhane Alkesh Dipak

Senior Resident, Department of Surgical Oncology, AIIMS Jodhpur

Phone: 8335009898

email: dralkeshgulhane@gmail.com

6. Patient information sheet (Hindi)

“नवसृजवंत रसायन चिकित्सा के बाद स्तन कैंसर में रूटीन स्तर **III** एक्सिलरी लिम्फ नोड डिस-सेक्शन की भूमिका”

रोगी सूचना पत्रक

आप इस शोध अध्ययन में भाग लेने के लिए आमंत्रित कर रहे हैं । इस दस्तावेज़ की जानकारी का अर्थ यह है कि आप निर्णय लें कि वह भाग ले या नहीं । कृपया अगर आप किसी भी प्रश्न या चिंताओं है पूछने के लिए स्वतंत्र महसूस हो रहा है ।

आपको एम्स, जोधपुर में किए जा रहे इस अध्ययन में भाग लेने के लिए कहा जा रहा है क्योंकि आप हमारे पात्रता मानदंड को संतुष्ट करते हैं ।

शोध का उद्देश्य क्या है?

यह अध्ययन स्तन कैंसर में स्तर 3 एक्सिलरी लिम्फ नोड्स के गुणों को देखने के लिए किया जा रहा है.

हम इस अध्ययन के संचालन के लिए संस्थागत नैतिकता समिति से अनुमति प्राप्त की है ।

अध्ययन डिजाइन ।

अध्ययन एक एकल केंद्र भावी अवलोकन अध्ययन किया जाएगा और रोगियों सर्जिकल ऑन्कोलॉजी विभाग से भर्ती किया जाएगा ।

अध्ययन प्रक्रियाओं

उपचार आपको मानक ऑन्कोलॉजिकल सिद्धांतों के अनुसार दिया जाएगा आपका नैदानिक डेटा एंस के अस्पताल सूचना प्रणाली से लिया जा सकता है ।

आप के लिए संभावित खतरों ।

वहां सर्जरी और रोग के कारण शामिल जोखिम के अलावा कोई जोखिम नहीं जोड़ा है ।

अंय लोगों को संभावित लाभ

अनुसंधान के परिणाम भविष्य में रोगियों को चिकित्सा ज्ञान और/या चिकित्सीय लाभ की उंनति की दृष्टि से समाज को लाभ प्रदान कर सकते हैं ।

आपके पास विकल्प

यदि आप भाग लेने की इच्छा नहीं है, तुम अब भी अपनी हालत के लिए मानक उपचार मिल जाएगा ।

प्रतिपूर्ति

आप इस शोध अध्ययन में भाग लेने के लिए भुगतान नहीं किया जाएगा ।

आप से प्राप्त जानकारी की गोपनीयता

आप अपने चिकित्सा जानकारी की गोपनीयता के बारे में गोपनीयता का अधिकार है) व्यक्तिगत जानकारी, शारीरिक परीक्षाओं के परिणाम, जांच, और अपने चिकित्सा के इतिहास (। इस दस्तावेज पर हस्ताक्षर करके आप अनुसंधान टीम के जांचकर्ताओं, अन्य अध्ययन कार्मिकों, प्रायोजकों, संस्थागत नैतिकता समिति और भारत के ड्रग कंट्रोलर जनरल की तरह कानून द्वारा आवश्यक किसी भी व्यक्ति या एजेंसी को अपने डेटा को देखने की अनुमति देंगे, यदि आवश्यक हो तो .नैदानिक परीक्षणों और चिकित्सा के इस शोध के भाग के रूप में प्रदर्शन के परिणाम आपके मेडिकल रिकॉर्ड में शामिल किया जा सकता है । इस अध्ययन से जानकारी, यदि वैज्ञानिक पत्रिकाओं में प्रकाशित या वैज्ञानिक बैठकों में प्रस्तुत की गई, तो आपकी पहचान उजागर नहीं होगी.

अध्ययन में भाग नहीं लेने का आपका निर्णय आपको कैसे प्रभावित करेगा?

आपके इस शोध अध्ययन में भाग लेने के निर्णय नहीं अपने चिकित्सा देखभाल या अंवेषक या संस्था के साथ अपने रिश्ते को प्रभावित करेगा । अपने डॉक्टर अभी भी आप का ख्याल रखना होगा और आप किसी भी लाभ है जो आप हकदार हैं खोना नहीं होगा ।

आप एक बार जब आप शुरू अध्ययन में भाग लेने को रोकने के लिए तय कर सकते हैं?

इस शोध में भागीदारी विशुद्ध रूप से स्वैच्छिक है और आपको बिना किसी कारण बताए पढ़ाई के दौरान किसी भी समय इस अध्ययन से निकालने का अधिकार है ।

क्या जांचकर्ता आपको अध्ययन से दूर ले जा सकते हैं?

यदि आप जांचकर्ताओं या अनुसंधान टीम के निर्देशों का पालन नहीं करते है या जांचकर्ता यह सोचता है कि आगे की भागीदारी से आपको नुकसान हो सकता है, तो आपको आपकी सहमति के बिना अध्ययन से बाहर रखा जा सकता है ।

नई सूचना का अधिकार

यदि अनुसंधान टीम इस शोध अध्ययन है कि आपके अध्ययन में भाग लेने के निर्णय को प्रभावित कर सकते है के दौरान कोई नई जानकारी मिलती है, या कुछ संदेह बढ़ा सकते हैं, तो आप उस जानकारी के बारे में बताया जाएगा ।

संपर्क व्यक्ति :डॉ अलकेश गुल्हाणे

वरिष्ठ निवासी, सर्जिकल ऑन्कोलॉजी विभाग, एंस जोधपुर

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Sr No	Age group	Age	Gender	Procedure	NACT cycles	cT	cN	Histo Type	Histo Grade	Tum Focality	Tum Quadrant	NAC involved	LV Emboli	Perineural Inv	ER/PR	HER2	Triple Neg	Level I & II LN - No.	Level I & II LN - Inv	Level III LN - No	Level III LN - Inv	Level III Positive	ECE
1	D 51 - 60	60	F	MRM	Incomplete	T3	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Pos	Neg	No	26	1	5	0	No	negative
2	E 61 - 70	66	F	MRM	Incomplete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Pos	Neg	Neg	Neg	Yes	19	7	4	0	No	positive
3	C 41 - 50	48	F	MRM	Complete	T1	N1	Invasive Breast CA NST	2	Unifocal	Lower Inner	No	Pos	Neg	Pos	Neg	No	0	0	1	0	No	negative
4	C 41 - 50	50	F	MRM	Incomplete	T4	N3	Invasive Micropapillary	2	Multifocal	Lower Outer	No	Pos	Pos	Neg	Pos	No	10	10	2	1	Yes	negative
5	B 31 - 40	40	F	MRM	Incomplete	T2	N2	Invasive Breast CA NST	2	Unifocal	Lower outer	No	Neg	Neg	Pos	Neg	No	20	0	1	0	No	negative
6	C 41 - 50	45	F	MRM	Complete	T4	N0	Invasive Breast CA NST	2	Multifocal	Upper Outer	No	Neg	Neg	Pos	Pos	No	13	0	2	0	No	negative
7	A <= 30	28	F	MRM	Complete	T2	N1	No residual CA	1	Unifocal	Upper Outer	No	Neg	Neg	Pos	Neg	No	10	0	1	0	No	negative
8	E 61 - 70	61	F	MRM	Complete	T3	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Pos	Neg	Neg	Pos	No	9	0	1	0	No	negative
9	C 41 - 50	48	F	MRM	Incomplete	T3	N1	Invasive Breast CA NST	3	Unifocal	Central	No	Pos	Neg	Neg	Pos	No	22	2	1	0	No	negative
10	F 71 - 80	73	F	MRM	Complete	T4	N2	Invasive Breast CA NST	2	Unifocal	Lower Outer	No	Neg	Neg	Neg	Neg	Yes	12	0	2	0	No	negative
11	E 61 - 70	66	F	MRM	Incomplete	T3	N2	Invasive Breast CA NST	3	Unifocal	Lower Inner	No	Pos	Neg	Neg	Neg	Yes	11	4	1	0	No	negative
12	B 31 - 40	34	F	Radical mastectomy	Incomplete	T2	N1	IBC with Apocrine Differentiation	3	Unifocal	Upper Inner	No	Pos	Neg	Neg	Neg	Yes	20	0	1	0	No	negative
13	A <= 30	30	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	9	4	2	0	No	negative
14	C 41 - 50	47	F	MRM	Complete	T2	N0	Invasive Cribriform CA Breast	2	Unifocal	Upper Inner	No	Neg	Neg	Pos	Neg	No	19	2	1	0	No	negative
15	F 71 - 80	72	F	MRM	Complete	T4	N3	Invasive Breast CA NST	3	Multifocal	Lower Outer	Yes	Pos	Pos	Neg	Neg	Yes	36	25	3	1	Yes	positive
16	C 41 - 50	50	F	MRM	Complete	T3	N1	No residual CA	NA	Unifocal	Upper outer	No	Neg	Neg	Pos	Neg	No	20	0	4	0	No	negative
17	D 51 - 60	55	F	MRM	Incomplete	T2	N2	IBC	2	Multifocal	Lower Outer	No	Pos	Neg	Pos	Neg	No	23	20	2	1	Yes	negative
18	E 61 - 70	65	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Lower Inner	No	Pos	Pos	Neg	Neg	Yes	16	0	1	0	No	negative
19	E 61 - 70	65	F	MRM	Incomplete	T4	N2	Invasive Breast CA NST	3	Multifocal	Central	Yes	Pos	Pos	Pos	Neg	No	19	2	5	0	No	negative
20	C 41 - 50	43	F	MRM	Incomplete	T2	N0	Invasive Breast CA NST	3	Unifocal	Central	No	Neg	Neg	Pos	Neg	No	19	1	1	0	No	negative
21	D 51 - 60	51	F	MRM	Complete	T2	N3	Metastatic Papillary Epithelial Malignancy	2	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	18	0	2	0	No	negative
22	C 41 - 50	42	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Pos	Pos	No	14	0	5	0	No	negative
23	B 31 - 40	36	F	BCS	Complete	T2	N0	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	25	0	5	0	No	negative
24	B 31 - 40	31	F	MRM	Complete	T4	N1	Invasive Breast CA NST	2	Multifocal	Upper Outer	No	Neg	Neg	Pos	Pos	No	7	0	3	0	No	negative
25	D 51 - 60	51	F	MRM	Complete	T2	N0	Invasive Breast CA NST	3	Unifocal	Upper Outer	No	Pos	Pos	Neg	Neg	Yes	20	0	1	0	No	negative
26	D 51 - 60	51	F	MRM	Complete	T2	N1	Invasive Breast CA NST	3	Unifocal	Lower Inner	No	Neg	Neg	Pos	Pos	No	13	3	4	0	No	negative
27	D 51 - 60	56	F	MRM	Complete	T2	N1	Invasive Breast CA NST	3	Unifocal	Lower Outer	No	Pos	Pos	Pos	Neg	No	11	1	5	0	No	negative
28	E 61 - 70	63	F	MRM	Complete	T2	N2	Invasive Breast CA NST	2	Multifocal	Central	No	Pos	Neg	Neg	Neg	Yes	19	1	6	0	No	negative
29	D 51 - 60	58	F	MRM	Incomplete	T2	N3	IBC with Apocrine Differentiation	3	Unifocal	Lower Inner	No	Pos	Pos	Neg	Neg	Yes	27	16	8	6	Yes	positive
30	D 51 - 60	58	F	MRM	Complete	T4	N0	Metaplastic carcinoma	3	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	23	3	5	0	No	negative
31	D 51 - 60	59	F	MRM	Complete	T3	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Pos	Neg	No	11	0	2	0	No	negative
32	C 41 - 50	42	F	MRM	Incomplete	T2	N2	Microinvasive CA	2	Multifocal	Central	No	Neg	Neg	Neg	Pos	No	20	0	0	0	No	negative
33	C 41 - 50	47	F	MRM	Complete	T4	N1	Malignant adwnomyoepithelioma	2	Unifocal	Central	No	Pos	Neg	Neg	Neg	Yes	14	0	2	0	No	negative
34	D 51 - 60	55	F	MRM	Complete	T3	N1	Invasive Breast CA NST	2	Unifocal	Lower Outer	No	Neg	Neg	Neg	Pos	No	18	0	2	0	No	negative
35	E 61 - 70	66	F	MRM	Complete	T4	N1	Invasive Breast CA NST	2	Multifocal	Lower Outer	Yes	Pos	Pos	Pos	Pos	No	7	0	1	1	Yes	positive
36	D 51 - 60	56	F	MRM	Incomplete	T2	N3	Invasive Breast CA NST	3	Multifocal	Lower Outer	Yes	Pos	Neg	Neg	Neg	Yes	10	9	1	1	Yes	positive
37	C 41 - 50	48	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Multifocal	Upper Inner	No	Neg	Neg	Pos	Pos	No	20	0	1	0	No	negative
38	B 31 - 40	38	F	MRM	Complete	T4	N1	Microinvasive CA	2	Multifocal	Lower Outer	No	Pos	Neg	Neg	Neg	Yes	18	0	1	0	No	negative
39	E 61 - 70	66	F	MRM	Incomplete	T3	N2	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	12	2	1	0	No	negative
40	E 61 - 70	66	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Pos	Neg	No	2	0	2	0	No	positive
41	C 41 - 50	41	F	MRM	Incomplete	T4	N1	Metaplastic Spindle cell CA	2	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	12	0	3	0	No	negative
42	E 61 - 70	66	F	MRM	Complete	T4	N0	Invasive Breast CA NST	2	Unifocal	Lower Inner	No	Pos	Neg	Neg	Pos	No	14	1	2	0	No	negative
43	C 41 - 50	46	F	MRM	Complete	T2	N0	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	18	0	2	0	No	negative
44	C 41 - 50	42	F	BCS	Complete	T2	N0	Invasive Breast CA NST	3	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	4	0	1	0	No	negative
45	C 41 - 50	43	F	MRM	Complete	T2	N1	Breast swelling	NA	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	11	0	1	0	No	negative
46	C 41 - 50	43	F	BCS	Complete	T4	N3	Invasive Breast CA NST	2	Multifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	15	0	1	0	No	negative
47	E 61 - 70	61	F	MRM	Complete	T3	N3	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Pos	Neg	Neg	Pos	No	13	4	2	1	Yes	negative
48	B 31 - 40	40	F	MRM	Incomplete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	15	0	1	0	No	negative
49	C 41 - 50	48	F	MRM	Complete	T4	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Pos	Neg	No	14	0	6	0	No	negative
50	D 51 - 60	58	F	MRM	Complete	T4	N1	No residual CA	NA	Unifocal	Central	No	Neg	Neg	Neg	Neg	Yes	14	0	1	0	No	negative
51	A <= 30	28	F	MRM	Incomplete	T2	N0	Invasive Breast CA NST	3	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	30	1	4	0	No	negative
52	D 51 - 60	56	F	BCS	Complete	T2	N0	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	19	0	3	0	No	negative
53	E 61 - 70	63	F	MRM	Complete	T2	N1	No residual CA	NA	Unifocal	Central	No	Neg	Neg	Neg	Neg	Yes	23	0	1	0	No	negative
54	D 51 - 60	55	F	BCS	Complete	T3	N0	No residual CA	NA	Unifocal	Central	No	Neg	Neg	Neg	Neg	Yes	18	0	3	0	No	negative
55	B 31 - 40	35	F	BCS	Complete	T3	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	14	0	1	0	No	negative
56	B 31 - 40	37	F	BCS	Complete	T2	N1	Invasive Breast CA NST	1	Unifocal	Upper outer	No	Neg	Neg	Neg	Neg	Yes	19	0	5	0	No	negative
57	B 31 - 40	33	F	MRM	Complete	T4	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	14	1	9	0	No	negative
58	E 61 - 70	62	F	MRM	Complete	T4	N0	Invasive Breast CA NST	1	Unifocal	Upper Inner	No	Neg	Pos	Pos	Neg	No	21	6	3	0	No	positive
59	C 41 - 50	45	F	MRM	Incomplete	T3	N2	IBC with Mucinous Differentiation	1	Unifocal	Upper Outer	No	Pos	Neg	Neg	Pos	No	20	1	1	1	Yes	negative
60	D 51 - 60	60	F	MRM	Incomplete	T4	N2	Invasive Breast CA NST	2	Unifocal	Central	No	Pos	Pos	Pos	Neg	No	19	2	8	0	No	negative
61	B 31 - 40	40	F	MRM	Complete	T4	N1	Invasive Breast CA NST	2	Multifocal	Upper Outer	Yes	Pos	Pos	Neg	Pos	No	7	3	3	0	No	positive
62	D 51 - 60	55	F	MRM	Complete	T4	N0	Invasive Breast CA NST	2	Unifocal	Upper outer	No	Pos	Neg	Neg	Pos	No	17	1	6	0	No	negative
63	B 31 - 40	39	F	BCS	Complete	T2	N0	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Neg	Neg	Pos	Neg	No	15	0	1	0	No	negative
64	C 41 - 50	50	F	MRM	Complete	T4	N1	Invasive Breast CA NST	3	Unifocal	Upper Outer	No	Pos	Neg	Neg	Neg	Yes	6	2	1	0	No	positive
65	A <= 30	26	F	Skin sparing mastectomy + LD flap reconstructio n	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	13	0	1	0	No	negative
66	D 51 - 60	53	F	MRM	Complete	T2	N3	Invasive Breast CA NST	3	Multifocal	Central	Yes	Pos	Neg	Neg	Neg	Yes	19	5	6	3	Yes	negative
67	F 71 - 80	74	F	MRM	Incomplete	T3	N0	Mucinous Carcinoma	2	Unifocal	Lower Inner	No	Neg	Neg	Pos	Neg	No	17	0	2	0	No	negative
68	D 51 - 60	52	F	MRM	Complete	T4	N1	Invasive Breast CA NST	2	Unifocal	Lower Outer	No	Neg	Neg	Pos	Pos	No	11	0	1	0	No	negative
69	E 61 - 70	62	F	BCS	Incomplete	T2	N1	Invasive Breast CA NST	2	Multifocal	Upper Outer	Yes	Pos	Pos	Pos	Neg	No	17	0	2	0	No	negative
70	D 51 - 60	53	F	MRM	Complete	T3	N2	Invasive Breast CA NST	3	Unifocal	Upper Inner	No	Neg	Neg	Neg	Neg	Yes	15	0	1	0	No	negative
71	C 41 - 50	41	F	MRM	Complete	T3	N2	Invasive CA with medullary features	3	Unifocal	Lower Outer	No	Neg	Neg	Neg	Neg	Yes	13	0	2	0	No	negative
72	C 41 - 50	44	F	MRM	Complete	T4	N2	No residual CA	NA	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	12	0	1	0	No	negative
73	E 61 - 70	63	F	MRM	Complete	T3	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	14	0	1	0	No	negative
74	E 61 - 70	66	F	MRM	Complete	T2	N2	Invasive Breast CA NST	2	Unifocal	Central	No	Neg	Neg	Neg	Neg	Yes	10	0	2	0	No	negative
75	D 51 - 60	59	F	MRM	Complete	T3	N3	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Pos	Neg	No	10	0	2	0	No	negative
76	D 51 - 60	59	F	BCS	Incomplete	T2	N1	Invasive Breast CA NST	3	Multifocal	Upper Outer	No	Neg	Neg	Pos	Pos	No	12	2	1	1	Yes	positive
77	C 41 - 50	47	F	BCS	Incomplete	T3	N1	Invasive Breast CA NST	2	Unifocal	Upper Outer	No	Neg	Neg	Pos	Neg	No	10	1	2	0	No	negative
78	C 41 - 50	48	F	BCS	Complete	T3	N1	Invasive Breast CA NST	1	Unifocal	Central	No	Neg	Neg	Pos	Neg	No	20	3	0	0	No	negative
79	F 71 - 80	71	F	MRM	Complete	T2	N2	Mixed Mucinous CA and IBC	2	Unifocal	Central	No	Neg	Neg	Neg	Neg	Yes	13	1	1	0	No	negative
80	B 31 - 40	40	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Central	No	Neg	Neg	Pos	Pos	No	12	0	3	0	No	negative
81	C 41 - 50	45	F	MRM	Incomplete	T2	N2	Mixed Mucinous CA and IBC	2	Unifocal	Central	No	Neg	Neg	Neg	Neg	Yes	13	1	1	0	No	negative
82	D 51 - 60	51	F	MRM	Incomplete	T2	N1	Invasive Breast CA NST	2	Unifocal	Central	No	Neg	Neg	Pos	Pos	No	12	0	3	0	No	positive
83	B 31 - 40	38	F	BCS	Complete	T2	N0	No residual CA	NA	0	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	20	0	4	0	No	positive
84	C 41 - 50	41	F	MRM	Complete	T2	N2	Invasive Breast CA NST	3	Unifocal	Upper Outer	No	Neg	Neg	Neg	Neg	Yes	17	0	1	0	No	negative
85	B 31 - 40	32	F	MRM	Incomplete	T4	N2	Invasive Breast CA NST	3	Unifocal	Upper Outer	Yes	Pos	Neg	Neg	Pos	No	20	6	8	1	Yes	negative
86	C 41 - 50	44	F	BCS	Complete	T2	N0	Invasive Breast CA NST	1	Unifocal	Upper Inner	No	Neg	Neg	Pos	Neg	No	18	0	4	0	No	negative
87	D 51 - 60	56	F	MRM	Complete	T2	N1	Invasive Breast CA NST	2	Unifocal	Upper Inner	No	Pos	Pos	Pos	Neg	No	19	0	4	0	No	negative
88	B 31 - 40	37	F	BCS	Incomplete	T2	N1	Invasive Breast CA NST	2	Unifocal	Central	No	Pos	Neg	Neg	Neg	Yes	19	0	2	0	No	negative
89	C 41 - 50	50	F	MRM	Complete	T2	N3	Invasive Breast CA NST	2	Unifocal	Central	No	Pos	Neg	Neg	Neg	Yes	19	0	2	0	No	negative