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ASSESSMENT OF LEVEL III LYMPH NODES IN PATIENTS OF LEVEL I/II LYMPH NODE INVOLVEMENT IN BREAST CANCER

General Surgery

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ABSTRACT

Introduction: Breast cancer is the most prevalent cancer among women globally, ranking as the second most commonly diagnosed cancer overall, with over 2 million new cases annually. In 2020, breast cancer impacted 2.3 million women worldwide, leading to 685,000 deaths by the end of the year. By that time, 7.8 million women had received a breast cancer diagnosis within the previous five years, confirming its position as the most prevalent cancer among women globally. **Aim and Objective:** The objective of this study is to assess the involvement of level III lymph nodes in patients with level I/II lymph node involvement in breast cancer. **Methods:** This institution-based prospective observational study involves patients who, after confirming the diagnosis and conducting a metastatic workup along with ensuring anesthetic fitness, undergo Modified Radical Mastectomy or Breast Conservative Surgery, with or without oncoplastic breast surgery. These procedures are performed by the same group of surgeons under general anesthesia. During axillary dissection, levels I and II lymph nodes are dissected, and level III lymph nodes are also dissected and sent for histopathological examination (HPE) separately. **Conclusion:**Patients with positive pathological markers indicating aggressiveness have a potential involvement of level III lymph nodes perioperatively, especially if grossly involved nodes are identifiable. This perioperative assessment is crucial for tailoring the surgical strategy according to individual patient requirements and optimizing treatment outcomes. By carefully balancing the benefits and potential drawbacks, healthcare providers can ensure that patients receive personalized and efficient care. This approach aims to enhance the effectiveness of treatment while minimizing unnecessary interventions, thereby improving overall patient prognosis and quality of life.

KEYWORDS

Breast cancer, Lymph Nodes, Axillary Dissection,Lymph Node Involvement Oncoplastic Breast Surgery, Pathological Markers

INTRODUCTION

Cancer is one of the most ancient and notable diseases in human history, with attempts to treat it traceable back to ancient Egyptian times. Our evolving understanding of breast cancer biology, along with progress in surgical and medical treatments, has been shaped by the work of many skilled and dedicated physicians and researchers over the years. These medical advancements have shifted the perception of breast cancer from being an incurable ailment to a condition that can be effectively managed through surgery[4]

In India, breast cancer is the most frequently diagnosed cancer in women, accounting for 27.7% of all new cancer cases identified in 2018. Alarming statistics reveal that every 4 minutes, a woman in India is diagnosed with breast cancer, and every 8 minutes, a woman dies from the disease [3]

Advancements in cancer biology have resulted in the creation of systemic therapies, hormonal treatments, and targeted medications. Identifying molecular subtypes within breast cancer has shown that it is a diverse group of diseases, each with unique prognoses and treatment approaches .[5]

This study was aimed to evaluate different lymph node stations in the axilla independently among breast cancer patients, including those who were clinically and radiologically negative for nodes, as well as those who were node-positive. Our objective was to accurately assess the extent of metastasis in various groups of axillary lymph nodes. This research aims to contribute valuable insights for potentially implementing selective nodal dissection strategies in future clinical practice.

Methodology

Study Design

A prospective observational study was conducted in the Department of General Surgery, Sarojini Naidu Medical College, Agra, from October 2022 to April 2024. After obtaining institutional ethical committee approval, informed consent was taken from the patients.

Participants

The study included 80 female patients diagnosed with breast cancer via core biopsy, covering all age groups with level I/II lymph node involvement attending the General Surgery OPD and Super Specialty OPD, SNMC Agra. Patients with metastatic breast disease, ipsilateral supraclavicular lymph nodes, no axilla involvement, or post-NACT breast cancer were excluded from this study.

Data Collection

Demographic data such as age, sex, address, and occupation were noted. Relevant history, important clinical findings, TNM staging, radiological evaluation, and metastatic workup were conducted as per standardized protocols.

Procedure

Patients underwent either modified radical mastectomy or breast-conserving surgery with axillary lymph node dissection. Level III axillary lymph nodes were dissected separately and submitted for histopathological evaluation, along with the primary specimen. The histopathological examination, including immunohistochemical markers, was analyzed statistically. Patients were operated on by the same group of surgeons under general anesthesia, with Level I/II lymph nodes dissected and Level III dissected separately for HPE.

Statistical Analysis

Data were analyzed using appropriate statistical tests to determine the significance of findings. Statistical significance was set at $p < 0.05$. All analyses were performed using [software, e.g., SPSS version 25].

Ethical Considerations

This study complies with the Declaration of Helsinki and has been approved by the Institutional Ethics Committee S.N.M.C Agra, SNMC/IEC/2024/235. Written informed consent was obtained from all participants or their guardians.

RESULT AND ANALYSIS

In the present study, the analysis revealed the following findings: The

most prevalent age group among patients was 36-55 years, with an average age of 48.65 years. The majority of patients identified as Hindu (68.75%), and a significant portion were married (61.25%). Among the 80 patients, 41 (51.25%) had their first childbirth between the ages of 24 and 29 years, and the vast majority had no family history of breast cancer. Of these patients, 48 (60%) were diagnosed with Invasive Ductal Carcinoma, while 32 (40%) were diagnosed with Invasive Lobular Carcinoma.

Patients underwent Breast-Conserving Surgery (BCS) and Modified Radical Mastectomy (MRM). In the BCS group, 83.72% had axillary surgery, compared to 72.97% in the MRM group. Overall, 78.75% of patients underwent axillary surgery, reflecting its common use. The slightly higher rate in BCS suggests potential differences in clinical decision-making, though a significant minority in both groups did not have the procedure, possibly due to individual factors or assessments.

Relation Between Er & Pr With Her2 Neu

Immunohistochemical evaluation was performed on all tissue samples to assess ER/PR and Her-2-neu expression, and the data were analyzed accordingly. Tumors were further classified into molecular subtypes including Luminal-A, Luminal-B, Basal-like (Triple-negative), and Her2/neu-positive based on these markers.Among the study population of 80 patients, Luminal A variety was the most common variant found in 39 patients. Luminal B variant was found in 6 patients, Triple Negative or Basal like in 28 patients and Her2 enriched variant in 13 patients.

I. Table 1: Distribution of ER,PR with Her2neu

ER & PR	Her2 Neu		
	Positive	Negative	Total
Positive	6 (7.50)	33(41.25)	39 (48.75)
Negative	13(16.25)	**28 (35.00)**	41(51.25)
Total	19 (23.75)	61(76.25)	80 (100.00)

The chi-square analysis shows no significant association between ER & PR status and Her2 Neu status, with a chi-square value of 2.95, which is below the critical value of 3.84. This suggests that Her2 Neu positivity does not significantly differ between ER & PR positive and negative cases.

Relation Between Level1/2/3

Ii. Table 2 : Distribution Of Lymph Node Level I/ii/iii

Level	Positive	Negative
Level- 1 (N=80)	74 (92.50)	6 (7.50)
Level-2 (N=80)	76 (95.00)	4 (5.00)
Level -3 (N=80)	16 (20.00)	64 (80.00)

*The Chi-square statistic of 136.14 with a very low p-value (2.74×10^{-30}) indicates a highly significant difference in the distribution of positive and negative lymph nodes across the three levels. Positive involvement is much higher in Levels 1 (92.5%) and 2 (95.0%) compared to Level 3 (20.0%). This indicates that as lymph node levels increase, the likelihood of positivity decreases. Thus, Levels 1 and 2 are crucial for initial staging and treatment, while Level 3 should still be monitored for thorough disease assessment.

Relation Between Level1 & Level2 With Level 3

III. Table 3 : Distribution of Level I/II with Level III

Level 1+Level 2	Level 3	
	Positive	Negative
Positive (N=76)	16 (20.05)	60 (78.95)
Negative(N=4)	0	4 (100.00)

Among patients with positive Level 1 + Level 2 nodes, 21.05% had positive Level 3 nodes, while 78.95% had negative Level 3 nodes. None of the patients with negative Level 1 + Level 2 nodes had positive Level 3 involvement. *The chi-square test yielded a p-value of 0.700, indicating no significant association between Level 1 + Level 2 lymph node status and Level 3 lymph node involvement.

Relation Between Er, Pr And Her2neu With Level Iii Lymph Node

IV. Table 4 : Shows the distribution of level 3 lymph nodes positive with ER & PR

ER & PR	Level 3 lymph nodes positive		
	Positive	Negative	Total
Positive	6(15.38)	33(84.62)	39(100.00)
Negative	10(24.39)	31((75.61)	41(100.00)
Total	16(20.00)	64(80.00)	80(100.00)

*The Chi-square statistic of 0.53 with a p-value of 0.47 indicates that there is no statistically significant association between ER & PR status and the presence of positive Level 3 lymph nodes.

V. Table 5: Shows the distribution of level 3 lymph nodes positive with Her 2 Neu

Her2 Neu	Level 3 lymph nodes positive		
	Positive	Negative	Total
Positive	5(26.32)	14(73.68)	19(100.00)
Negative	11(18.03)	50(81.97)	61(100.00)
Total	16(20.00)	64(80.00)	80(100.00)

*The Chi-square statistic of 0.21 with a p-value of 0.65 indicates that there is no statistically significant association between Her2 Neu status and the presence of positive Level 3 lymph nodes.

VI. Table 6 : Shows the distribution of level 3 lymph nodes positive with ER PR/ Her2 Neu

ER PR/ Her2 Neu	level 3 lymph nodes positive		
	Positive	Negative	Total
Positive	1(16.67)	5(83.33)	6(100.00)
Negative	6(21.43)	22(78.57)	28(100.00)
Total	7(19.05)	27(80.95)	34 (100.00)

The analysis shows that ER & PR negative patients (24.39%) and HER2/neu positive patients (26.32%) have higher rates of Level 3 lymph node involvement compared to their positive counterparts. Patients with negative biomarkers also exhibit a higher rate of Level 3 involvement (21.43%) than those with positive biomarkers (16.67%).
*Chi-square tests show p-values greater than 0.05 for all comparisons, indicating no significant association between these biomarkers and Level 3 lymph node involvement.

DISCUSSION

Breast cancer-related lymphedema is well-documented to be linked with various challenges, such as increased anxiety, depression, fatigue, chronic pain, heightened susceptibility to infections, and functional impairment . Trials like AMAROS and ACOSOG Z0011 have shown that adopting a minimalistic approach to axillary surgery can reduce the incidence of lymphedema, focusing on patients in the early stages of breast cancer with low axillary disease burden .

In mid to low socioeconomic countries, about 30-40% of breast cancer patients present with locally advanced disease and considerable axillary involvement. Unfortunately, facilities for sentinel lymph node biopsy (SLNB) are not universally available in these regions. Consequently, patients undergoing axillary clearance experience significant morbidities, including disabilities affecting the arm, shoulder, and hand, as indicated by impairments measured on scales like the Disability of Arm, Shoulder, and Hand (DASH).

There is still no definitive consensus on the optimal extent of lymph node dissection to reduce breast cancer-related lymphedema, especially in regions where there is a higher burden of axillary disease or in mid to low socioeconomic countries. For our study, patients were recruited from the outpatient departments of General Surgery and Superspecialty. The study objectives were clearly explained to the patients, and those who agreed to participate provided informed written consent.

All patients included in the study underwent comprehensive evaluations, which included detailed history-taking, thorough physical examinations, and a series of investigations such as ultrasound or mammography, core biopsy, and metastatic workup, including liver function tests, CT scans of the abdomen and thorax. Additionally, some patients with symptoms like low back pain underwent a bone scan. Only patients with negative findings in the metastatic workup were eligible for inclusion in the study.

Among all 80 patients enrolled in the study, standard investigations were conducted, including complete blood counts, fasting/random blood sugar assessments, serum urea and creatinine measurements, serum electrolyte analyses, ECG, and chest radiographs. Additionally, all patients underwent anesthesia clearance prior to their participation. Subsequently, after obtaining informed consent, surgical procedures were performed based on each patient's clinical presentation. Different groups of axillary lymph nodes, as previously outlined, were excised

and sent for histopathological examination (HPE). Finally, the collected data were analyzed.

Age Distribution
In our study, patients diagnosed with breast cancer had an average age of 48.65 years, and a median age at presentation of 49.5 years. These results are comparable to those reported by El Sisi AA et al., who noted that 46% of their patients were younger than 45 years, 20% were aged 45-50 years, and 34% were older than 50 years, with a mean age of 47.78 years. This is consistent with findings from Barranger E et al., where the average age of 119 female patients was 49.6 years, and similar to Mashoori N et al., who reported a mean age of 43.52 years .

Menstruation
In our study, the average age of menarche was 13.09 years, with a median age of 13 years. This suggests an earlier onset of menarche compared to the global median age of 14 years, which typically ranges from 11 to 18 years. This early menarche pattern is observed among breast cancer patients in our cohort. Studies on Indian women have shown that both premenopausal and postmenopausal breast cancer risks decrease with delayed menarche onset .

Regarding menopause, the mean age was 44.786 years, with a median age of 45 years in our study. Late menopause is associated with an increased breast cancer risk, with risk increasing by nearly 3% for each year older at menopause, whether natural or surgery-induced. Women experiencing menopause at 55 years rather than 45 years face approximately a 30% higher risk . It's notable that in our study, most women reached menopause at around 45 years of age.

Site of the Tumor
Our study found that 46% of patients had lesions in the left breast, while 34% presented with lesions in the right breast. This observation aligns with the findings reported by Magid H. Amer, who noted a higher incidence of left-sided breast cancer among women. Specifically, Magid's study reported 50.9% of cases on the left side, 46.1% on the right side, and 3% bilateral breast cancer cases. These results are similar to the distribution observed in our study .

Histopathology
Within our study population of 80 patients, 48 patients (60%) received histopathological examination (HPE) reports indicating invasive ductal carcinoma (IDC), while 32 patients (40%) were diagnosed with invasive lobular carcinoma (ILC). In comparison, in the study conducted by El Sisi AA et al., 88% of patients were diagnosed with IDC, 2% with ILC, and 10% with mixed ductal and lobular carcinoma. Similarly, Mashoori N et al. reported that 91.2% of patients had IDC and 8.8% had ILC, which is closely aligned with the findings of Rahman MS et al., where 80.45% were classified as IDC, 13.64% as ILC, and 5.91% as mixed invasive patterns .

Immunohistochemistry
In our study, 48.75% of patients tested positive for Estrogen receptor (ER) and/or Progesterone receptor (PR), while 19% were found to be Human Epidermal Growth Factor receptor 2 (Her2)-positive. However, these results, though comparable, do not entirely coincide with those documented by Vieira RA et al., who reported 64.1% positivity for ER, 57.8% for PR, and 19% for Her2-positive cases .

Surgery Performed
In our study, 46.25% of patients underwent modified radical mastectomy (MRM), while 53.75% opted for breast-conserving surgery (BCS) with or without reconstruction. This reflects a notable shift in surgical preferences for breast cancer treatment, a trend supported by various published studies. Particularly, younger women often prioritize cosmetic and aesthetic factors in their decision-making process, which aligns with the observed trend in our

Among younger age groups (20-29 and 30-39), there was a higher preference for BCS as the chosen treatment modality. In contrast, in older age groups (50-59 and >60), the inclination towards BCS was reduced. These findings are consistent with those reported by Sauerzapf et al., who conducted a chart review of over 6000 patients in the UK, revealing that women in older age groups were significantly less likely to undergo breast-conserving therapy (BCT).

T Stage
In our study, the T stage is crucial for predicting prognosis, influencing treatment decisions, and assessing neoadjuvant chemotherapy (NACT) effectiveness. We found that 26.25% of patients were classified as T1, 18.75% as T2, 20% as T3, and 35% as T4. These findings diverge from those reported by H. Kodama et al. in 2006, suggesting that Indian patients frequently present with more advanced disease characterized by larger tumor sizes.

Lymph Node Status
In our current study, 5% of patients presented with pN0 disease, while 42% had pN1, 22.50% had pN2, and 20% had pN3 disease. A similar distribution, with a predominant number of patients in the pN1 category, was observed in the study by El Sisi AA et al., where 16% had pN0, 54% had pN1, and 30% had pN2 disease. This trend is consistent with the findings from the study conducted by El-Sayed MI et al., which reported that 20% had pN0, 55% had pN1, and 25% had pN2 disease.

Level III Lymph Node
In the current study, 20% of patients demonstrated level III lymph node positivity when level I and level II lymph nodes were positive, whereas 60% showed level III lymph node negativity despite positive findings in level I and level II nodes. These results are consistent with those reported by Shalaka Joshi et al., where 27.3% of patients (434 patients) were found to have metastasis in level III axillary lymph nodes (ALN), and 4.7% showed positive interpectoral nodes. Among the patients, 53.2% exhibited level III metastases when four or more positive level I and II ALNs were present. Additionally, 9.4% of patients showed level III involvement with one to three positive ALNs in level I and II.

Lymphedema
In the present study with the Level1, Level2 & Level3 lymph nodes, 18.75% of patients had stage 1 lymphedema, 50% had stage 2, 18.75% had stage 3, and 12.50% had stage 4 lymphedema. Similar results were found in the study by Fodor J, et al.

CONCLUSION
Based on the findings of our study, it is recommended to evaluate patients with positive pathological markers indicating aggressiveness for potential involvement of level III lymph nodes perioperatively, especially if grossly involved nodes are identifiable. Patients should undergo comprehensive counseling to facilitate informed decision-making regarding the consideration of complete axillary lymph node dissection, taking into account the associated risks of morbidity. This perioperative assessment is crucial for tailoring the surgical strategy according to individual patient requirements and optimizing treatment outcomes. By carefully balancing the benefits and potential drawbacks, healthcare providers can ensure that patients receive personalized and efficient care. Furthermore, this approach underscores the significance of shared decision-making between patients and healthcare teams, promoting a collaborative and patient-centered approach to the management of breast cancer.

Ethical Considerations
All patients provided informed consent for the use of their data in this study. The protocol of this retrospective study was approved by the local ethical committee.

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Conflicts Of Interest
The authors declare no conflicts of interest.

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