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Original Research Article

Skip Metastasis in Axillary Lymph Nodes in Carcinoma of the Breast: A Single-Center Study

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Abstract

Introduction: This study is a single-centred prospective descriptive study investigating skip metastasis in axillary lymph nodes in breast carcinoma, conducted. The study aimed to determine the proportion of patients with skip metastasis, ascertain the extent of lymph node involvement through detailed dissection, and identify predisposing factors for skip metastasis to Level 2. The cohort comprised 35 breast cancer patients who underwent complete axillary lymph node dissection and had no prior neoadjuvant therapy.

Results: We observed a proportion of 5.71% for skip metastasis to axillary Level 2, with no cases observed for Level 3. Overall, Level 1 axillary lymph node involvement was observed in 51.42% of participants. Comparative analysis with existing literature indicates that the observed incidence of skip metastasis aligns broadly with reported ranges, which vary significantly (e.g., 1.5% to 14.6%).

Discussion: The clinical significance of skip metastasis lies in its potential for understaging and under treatment, although aggressive management of certain higher-level nodal involvement, such as supraclavicular metastasis, has shown improved patient outcomes. This suggests a nuanced prognostic role, where detected and treated skip lesions may still represent regional rather than immediately systemic disease.

Conclusion: The reviewed study contributes descriptive data on skip metastasis within its specific cohort highlighting the need to identify predisposing factors and further elucidate the full clinical and prognostic implications of this phenomenon.

Keywords: breast carcinoma, skip metastasis, axillary lymph node, radical dissection.

Introduction

Breast malignancy remains a significant health challenge worldwide, leading the most common cancer and a major cause of cancer-related mortality among women. [1] A cornerstone of breast cancer management and prognosis is the accurate assessment of axillary lymph node (ALN) status as they are one of the most significant predictors of patient outcome and guide critical treatment decisions, including the need for adjuvant therapy and radiotherapy. [2]

The traditional understanding of lymphatic spread in breast cancer suggests a sequential progression, where cancer cells typically disseminate from lower axillary levels (Level I) to progressively higher levels (Level II and Level III). This sequential pattern forms the basis for current surgical staging practices, including sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND). [3] During radical mastectomy or breast conservations surgery, axillary clearance involves the removal of lymph nodes from Levels I, II, and III, with specific anatomical boundaries defined for each level. Level I encompassed contents from the lateral border of latissimus dorsi to the lateral border of pectoralis minor up to the axillary vein; Level I-II included Level I plus contents posterior to pectoralis minor; and Level I-III extended to contents medial to the medial border of pectoralis minor up to the subclavius muscle. This detailed anatomical dissection is fundamental for accurate staging and identification of skip metastasis. [4]

However, the phenomenon of "skip metastasis" challenges this conservative chronological model. Skip metastasis is defined as “the involvement of higher-level lymph nodes in the axilla or other regional basins without concomitant metastatic disease in the lower, anatomically contiguous lymph nodes. It represents a discontinuous spread across anatomic sites". Skip metastasis, if

undetected, it can lead to erroneous disease staging, possibly resulting in insufficient or under treatment, which may compromise patient's prognosis. Therefore, a comprehensive understanding of skip metastasis, its incidence, associated factors, and prognostic implications is crucial for enhancing management of the breast carcinoma. [5]

In other definition, Skip metastases to the axillary lymph nodes in breast cancer refer to the uncommon phenomenon in which metastases do not follow the conventional stepwise pattern from level I to level II, to level III (infraclavicular), to the supraclavicular fossa, and or internal jugular chain. [6]

One more definition, specific to the surgical findings of a clear Level I lymph node basin mentions that "A skip metastasis was defined as level I absence but level II and/or level III involvement." [7]

The present study, conducted in a multispecialty hospital, aimed to contribute to this understanding by addressing three specific objectives:

1. To determine the proportion of patients having skip metastasis.
2. To ascertain the extent of lymph node metastasis by dissecting and labeling them separately for pathological examination and proper staging.
3. To determine whether there are any factors predisposing to skip metastasis level 2.

Materials and Methods

The study under review was designed as a prospective descriptive study, on breast cancer patients admitted to the Surgical Oncology department of Indraprastha Apollo Hospital, who underwent complete axillary lymph node dissection and had not received any prior treatment such as chemotherapy or radiotherapy as they known to alter nodal status and could confound the assessment of primary lymphatic spread patterns.

A minimum of 35 patients were enrolled, a number justified by a previous PASS Software formula that suggested a sample size of 25.6. Comprehensive pre-operative assessments were conducted, including detailed patient history, clinical examination, routine laboratory investigations and staging investigations (e.g., Mammogram/USG Breast, Chest X-Ray, USG Abdomen, and targeted imaging like Bone scan, PET CT, or MRI if indicated). Written informed consent was obtained from all participants.

Surgical procedures performed included Modified Radical Mastectomy (MRM), Breast Conservation Surgery (BCS) with axillary clearance, and Completion Axillary Clearance. The statistical analysis section of the document states that results were expressed descriptively as range, mean, and median. SPSS version 23 was used for data analysis

Results

In this study among the investigated 35 breast cancer patients who underwent complete axillary lymph node dissection. The findings, after careful review and necessary statistical modifications and error corrections, are presented below.

Demographic and Clinical Characteristics: The demographic profile of the study participants is summarized in Table 1. The mean age of the cohort was 49.65 ± 4.78 years, with an age range of 42-65 years. The largest proportion of patients (40.00%) fell within the 46-50 years age group, followed by 51-55 years (25.71%) and 40-45 years (22.85%).

Regarding tumor location, the lower outer quadrant was the most frequent site of breast carcinoma, observed in 31.42% of patients. This was followed by the upper outer quadrant and retroareolar region, each accounting for 25.71% of cases. The lower inner and upper inner quadrants each represented 8.57% of cases. In terms of laterality, right-sided carcinoma was predominant, affecting 62.85% of patients, while left-sided carcinoma was observed in 34.28%. Bilateral involvement was noted in 5.71% of patients.

Comorbidities were present in a subset of the cohort, with 14.28% of patients having both diabetes mellitus (DM) and hypertension (HTN). Isolated HTN was present in 5.71% of patients, DM in 2.85%, and hypothyroidism in 5.71%.

Pathological and Surgical Characteristics: Table 2 provides a summary of the pathological findings and surgical procedures. The most common IDC (Invasive Ductal Carcinoma) grade observed was Grade 2, found in 54.28% of patients, followed by Grade 3 (40.00%) and Grade 1 (5.71%). Tumor receptor status revealed that ER/PR (Estrogen Receptor/Progesterone Receptor) positivity was present in 28.57% of patients, while Her2neu positivity was observed in 40.00%.

Regarding tumor size, the majority of patients (71.42%) presented with T2 tumors, followed by T1 (17.14%), T3 (8.57%), and T4 (2.85%). Lympho-vascular invasion (LVI) was identified in the histopathology reports of 34.28% of patients. Multi-centricity of the tumor was present in 8.57% of cases.

Modified Radical Mastectomy (MRM) was the most frequently performed operation, accounting for 51.42% of procedures. Other surgical interventions included Breast Conservation Surgery (BCS) with Latissimus Dorsi (LD) flap and Lymph Node Dissection (LND) in 20.00% of cases, BCS

with LND in 17.14%, and Completion LND and MRM with LD flap each performed in 5.71% of patients.

Prevalence of Axillary Lymph Node Involvement and Skip Metastasis: The primary findings concerning axillary lymph node involvement and the occurrence of skip metastasis are presented in Table 3. Axillary lymph node involvement at Level 1 was observed in 51.42% of the study participants. Involvement at Level 2 and Level 3 was less frequent, each seen in 5.71% of patients.

Skip metastasis to Level 2 axillary lymph nodes was identified in 2 patients, representing 5.71% of the total cohort.

No cases of skip metastasis to Level 3 were observed (0%).

Table 1: Corrected Demographic and Clinical Characteristics of the Study Cohort (N=35)

Characteristic	Category	Frequency (N)	Percentage (%)
Age Group (Yrs)	40 to 45	08	22.85
	46 to 50	14	40.00
Mean±SD: 49.65±4.78 yrs, Range: 42-65 yrs	51 to 55	09	25.71
	56 to 60	03	8.57*
	> 60	01	2.85
Gender	Female	35	100.00
	Male	00	0.00
Site of Breast Lump	Lower Inner Quadrant	03	8.57
	Upper Outer Quadrant	09	25.71
	Lower Outer Quadrant	11	31.42
	Retro areolar Region	09	25.71
	Upper Inner Quadrant	03	8.57
Side of Breast	Right	21	60.00
	Left	12	34.29
	Both	02	5.71
Co-morbidities	HTN	02	5.71
	DM	01	2.85
	Both (DM with HTN)	05	14.28
	Hypothyroidism	02	5.71

Table 2: Pathological Findings and Surgical Procedures of the Study Cohort (N=35)

Characteristic	Category	Frequency (N)	Percentage (%)
IDC Grade	Grade 1	02	5.71
	Grade 2	19	54.28
	Grade 3	14	40.00
Tumour Receptor	ER/PR Positive	10	28.57
	ER/PR Negative	25	71.42
	Her2neu Positive	14	40.00
	Her2neu Negative	21	60.00
Tumour Size	T1	06	17.14
	T2	25	71.42
	T3	03	8.57
	T4	01	2.85
Lympho-vascular Invasion	Present	12	34.28
	Absent	23	65.71
Multi-centricity	Present	03	8.57
	Absent	32	91.42
Operation	Modified Radical Mastectomy (MRM)	18	51.42
	Completion LND	02	5.71
	BCS with LND	06	17.14
	MRM with LD flap	02	5.71
	BCS+LD flap+ LND	07	20.00

Table 3: Axillary Lymph Node Involvement and Skip Metastasis in the Study Cohort (N=35)

Axillary Lymph Node Level	Frequency (N)	Percentage (%)
Level 1 Involvement	18	51.42
Level 2 Involvement	02	5.71
Level 3 Involvement	02	5.71
Skip Metastases to Level 2	02	5.71
Skip Metastases to Level 3	00	0.00

Discussion

The skip metastasis (SM) of axillary lymph nodes (ALN) in breast cancer represents a critical phenomenon challenging conventional lymphatic progression patterns and influencing surgical decision-making. Our study identified skip metastasis in 5.71% of all cases (8.33% of node-positive cases), aligning with contemporary literature reporting rates between 1.6% and 7.2%. Wang et al. [8] found skip metastasis in 3.2% of all patients and 7.5% of node-positive cases, while Rosen et al. [9] reported 1.6% overall incidence in their landmark study of 1,228 patients. The mechanism remains unclear, though Gli1 protein, a core EMT regulatory factor, has emerged as a potential predictor of skip metastasis through alternative lymphatic pathways. [10]

Patient Demographics and Tumor Characteristics: Our cohort's mean age of 49.65±4.78 years was younger than comparative studies: Medhat Khafagy et al. (52.9±13 years) [11], Daniel F. Roses et al. (median 59 years) [12], and Woo Gyeong Kim et al. (52.3±10.2 years) [13]. Both skip metastasis cases occurred in younger patients (40-45 years), supporting emerging evidence of age-related skip metastasis patterns. [14]

Tumor location showed lower outer quadrant predominance (31.42%), with right-sided preference (62.85%), similar to Daniel F [12], but differing from Robert S. et al [15], who reported upper outer quadrant dominance (41.5%).

Grade distribution revealed predominantly Grade 2 IDC (54.28%) versus Medhat Khafagy et al.'s 79.9% Grade 2 tumors. [11] Remarkably, both skip metastasis cases were Grade 1 tumors, contradicting expectations that higher-grade tumors demonstrate complex metastatic patterns. [8]

Molecular Markers and EMT Mechanisms

ER/PR positivity (28.57%) and HER2 positivity (40%) aligned with Woo Gyeong Kim et al.'s findings (ER 29.9%, PR 26.8%). Both skip metastasis cases were hormone receptor-positive, supporting Wang et al.'s association between luminal B1 subtype and skip metastasis risk. [3,8]

Gli1 protein's role as an EMT regulatory factor provides mechanistic insights, with Gli1 overexpression facilitating non-sequential metastatic spread through EMT-mediated pathways. Recent studies demonstrate that EMT cells increase breast cancer metastasis via paracrine Gli activation, which can be blocked by Gli1 inhibitor GANT-61. [8,10]

Literature Comparison and Clinical Cases (table no. 4): Our skip metastasis rate falls between conservative findings (Rosen et al. 1.6%-) and higher contemporary rates (Chung et al. 7.2%), with historical studies reporting up to 20% and recent series showing 1.5-19.2% variation. [9,16] Robert S. et al [15] reported 5.5% skip metastasis, while Sun JY et found 14.6% in positive axillae. [17] Clinical cases of skip metastasis demonstrated characteristic patterns: a 48-year-old diabetic female with bilateral T2N0M0 tumors (right-sided IDC Grade 1 with LVI and skip to level 2), and a 67-year-old female with T2N0M0 central quadrant tumor (IDC Grade 1, LVI, multicentricity, ER/PR+/HER2- with level 2 skip metastasis). Lymphovascular invasion was present in both cases (34.28% overall), supporting LVI's role in facilitating alternative lymphatic spread. [18]

Table 4: Comparative Incidence Rates of Axillary Skip Metastasis in Breast Cancer

Study	Sample Size (N)	Definition of Skip Metastasis	Reported Incidence Rate (%)
Current Study	35	Involvement of higher-level nodes "out of step with the system" (specifically Level 2 without Level 1 involvement)	5.71% (to Level 2), 0% (to Level 3)
Newell et al [16]	1300 (all invasive cancers) / 470 (metastatic cancers)	Spread across discontiguous nodal levels or distant metastases in absence of ipsilateral nodal metastases	2.6% (all invasive), 7.2% (metastatic)
Khafagy M et al [11]	59	Without involvement of Level 1	8.4%

Rosen et al [9]	Not specified	1.5% Level 1 skipped; 0.4% Level 1 & 2 skipped	1.5%, 0.4%
Sun JY et al [17]	814	Discontinuous or "skip" metastases	14.6%

Clinical Implications: Skip metastases can cause under treatment if only sentinel lymph node biopsy is performed, particularly in high-risk patients. Modern staging using nodal ultrasound improves detection of skip metastases, enhancing accuracy and minimizing under treatment. [19]

Paradoxically coupled with lower-grade, young-patient tumors, the skip metastasis has implications of different biological pathways instead of frank disease progression. Future studies should confirm Gli1 expression as a skip metastasis predictor and establish risk stratification models with EMT (Epithelial-Mesenchymal Transition) markers included. Multicenter collaboration would be needed to provide sufficient statistical power and retain clinical applicability in this relatively rare but surgically important phenomeno. [20]

Our findings support individualized axillary management approaches accounting for patient age, tumor grade, molecular subtype, and EMT marker expression to optimize oncological outcomes while minimizing surgical morbidity.

Recommendations for further Research

To advance the understanding of skip metastasis in breast cancer, future research should address the limitations observed in the reviewed study:

- Larger Sample Sizes: Studies with significantly larger sample sizes are essential to ensure adequate statistical power for accurately determining the true prevalence of skip metastasis and for identifying its risk factors with greater confidence.
- Standardized Definitions: Adoption of standardized and unambiguous definitions for skip metastasis across studies would greatly facilitate direct comparisons and enable more robust meta-analyses, leading to a clearer understanding of its epidemiology and clinical relevance.
- Longitudinal Studies: Prospective longitudinal studies with extended follow-up periods are necessary to comprehensively assess the precise prognostic impact of skip metastasis on recurrence-free survival, distant metastasis-free survival, and overall survival in breast cancer patients.

Conclusion

Although skip metastasis is a rare phenomenon, it retains its importance regarding understaging and under treatment of breast cancer in the clinic. But this has important prognostic significance: while skip lesions may represent a more aggressive tumor biology and hence worse outcomes if missed, there is emerging research to suggest that aggressive local treatment of certain high level nodal metastases such as supraclavicular lymph node involvement can give rise to dramatic improvements in survival within our patient population. The reverse is that, if this spread is detected, it can still mean a treatable regional rather than immediately an evidence of ill-breeding.

Standardized definitions and long-term follow-up studies are equally important in the establishment of a more uniformed body of evidence with identification of breast cancer patients at different risk profiles, to provide accurate staging information for higher levels of staging accuracy, personalized treatment strategies.

Ethical clearance: This study was approved by the institutional ethical committee for dissertation topic for the partial fulfilment of DNB Surgical oncology.

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