Involvement of Level III axillary lymph nodes in node-positive breast cancer: a retrospective single-institution study

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Abstract

Purpose: Axillary dissection provides prognostic information and regional control and possibly improves overall survival. The usefulness of level III lymph node dissection is less well studied. The study aims to identify the rate of level III nodal positivity and factors that can predict its involvement.

Methods: A retrospective analysis of 190 breast cancer patients (cT1-3, N0-1, M0) who underwent surgery(Modified radical mastectomy or Breast conservation surgery) between May 2017 and December 2020 at a tertiary care centre was done. Clinical and pathological details were obtained from the electronic medical record.

Results: The rate of level III nodal positivity in patients with pathologically positive level I/II lymph nodes was 23.15% (n=22). Skip metastasis in level III without involvement in levels I and II was 0.52%(n=1). There was a significant correlation between involvement of level I/II lymph nodes(p=<0.001), lymphovascular invasion(p=0.001), pathological tumour size(p=0.015), extranodal extension in level 1/2 lymph nodes (p<0.00001) and level III lymph node metastases.

Conclusion: Level III lymph node dissection should be performed in all patients with metastases in level I/II axillary lymph nodes.

Introduction

Surgical management of breast cancer comprises complete removal of the primary tumour in the breast and address of lymph nodes in the axilla. Axillary lymph node dissection(ALND) allows staging of the axilla, provides prognostic information, guides adjuvant therapy and provides regional control. Whether axillary lymph node dissection improves the overall survival of the patient is still controversial. Anatomically axilla is divided into three levels based on their relationship to the pectoralis minor muscle. Level I lymph nodes are lateral to the lateral border of pectoralis minor. Level II lymph nodes are located posterior to the pectoralis minor muscle between its medial and lateral borders. Level III lymph nodes are situated medial to the medial border of pectoralis minor. Surgical clearance of lymph nodes in Levels I and II of the axilla is the standard practice in clinically node-positive breast cancer[1]. At present, there is no consensus regarding the dissection of level III lymph nodes in node-positive breast cancer. This study aims to calculate the rate of level III lymph node positivity in patients with positive level I/II lymph nodes and to identify the factors that can predict level III nodal involvement.

Material and Methods

A retrospective analysis of all the patients with invasive breast cancer, cT1-3, N1, M0 breast cancer [American Cancer Committee on Cancer Tumor Node Metastases (AJCC TNM) staging, 8th edition], who underwent surgery (Modified Radical Mastectomy or Breast Conservation Surgery) at a tertiary cancer centre from 1/6/2017 to 1/3/2021 was conducted after obtaining clearance from Institutional Ethics Committee. Patients who had received Neoadjuvant Chemotherapy(NACT) were excluded. Patients were

subjected to NACT if they had cT4, cN2/N3 disease or for downstaging of the tumour in those who desired breast conservation surgery but were ineligible for the same due to unfavourable tumour-breast ratio.

All the patients underwent bilateral sonomammogram and corecut biopsy of the breast lump preoperatively. Staging work-up included Chest X-ray alone for Stage I and II whereas Stage III patients were subjected to either Positron Emission Tomography and Computed Tomography(PETCT) or Contrast Enhanced Computed Tomography(CECT) thorax, abdomen, pelvis and a bone scan. Lymph nodes were considered clinically significant if lymph nodes were palpable on clinical examination. Axillary lymph nodes were considered metastatic on ultrasound examination if there was any of the following features: 1)loss of fatty hilum 2)irregular border 3)hypoechogenecity 4)rounded morphology 5)increased peripheral vascularity 6)increased cortical thickness. A rounded or irregular lymph node or a node with eccentric cortical thickening on CECT scan was considered clinically significant. On PETCT scan, any lymph node that showed increased uptake of fluorine 18-fluorodeoxyglucose was considered metastatic. Intraoperatively, the lymph nodes were considered metastatic if they had one of the following features: 1)round shape 2)irregular surface/border 3)hard consistency 4)size > 1 cm. Axilla was staged as cN0 if no significant nodes were present on clinical examination and/or on imaging (CECT/ PETCT/ Ultrasonography) of the axilla. Fixed or matted lymph nodes in the axilla were staged as cN2 and ipsilateral supraclavicular/infraclavicular lymph node involvement was staged as cN3.

Patients were classified into different molecular subtypes based on Estrogen Receptor(ER)/ Progesterone Receptor(PR)/ Human Epidermal Growth factor Receptor2(HER2) receptor status. ER/PR + ve and HER2 - ve patients were labelled as Luminal A subtype, ER/PR + ve and HER2 + ve as Luminal B, ER/PR/HER2 -ve as Triple-negative and ER/PR -ve and HER2 + ve patients as HER2 + ve subtype.

At our institution, Level III lymph node dissection was carried out if level I/II or III lymph nodes are found to be involved clinically, radiographically, or found significant intra-operatively. Sentinel lymph node biopsy and frozen section were not used for assessment of axillary lymph nodes as these facilities were unavailable at our institute. Adjuvant chemotherapy, hormonal therapy, targeted therapy and radiotherapy were given as per institution guidelines. All the clinical details were maintained in the electronic medical record.

Results

A total of 250 breast cancer patients underwent upfront surgery between May 2017 and December 2020. Forty-six of these patients did not undergo level III lymph node dissection. Four patients had DCIS and ten patients had T4b disease, hence were excluded from the study. The final analysis included 190 patients. The age of the patient ranged from 31–82 years (median = 55). The commonest histology was infiltrating ductal carcinoma, not otherwise specified (n = 174, 91.5%) followed by mucinous carcinoma (n = 7, 3.6%). Metaplastic carcinoma was found in four patients (2.1%), papillary carcinoma and lobular carcinoma in two patients each(1.05%). Only one patient had medullary carcinoma(0.52%). The majority of the

patients were women (n = 188, 98.9%) and two patients were men (1.05%). Tumour was located in the upper outer quadrant in the majority of the patients (n = 91, 47.8%). Most of the patients had clinical stage II breast cancer at presentation(n = 135, 71.05%). Thirty-two patients presented in stage I(16.84%) and fifteen (7.89%) patients in stage III breast cancer. The clinical stage couldn't be ascertained in 8 patients(4.21%). The most common molecular subtype found was Luminal A(n = 91,47.89%) followed by triple negative(n = 41, 21.57%). Luminal B subtype was found in 35 patients (18.42%) and 18 patients were HER2 + ve (9.47%). Demographic details are shown in Table 1.

Table 1: Patient characteristics	
	n = 190 (%)
Surgery	**142 (74.73)**
Modified Radical Mastectomy	**48 (25.26)**
Breast Conservation Surgery	
Side	93 (48.94)
Right	97 (51.05)
Left	
Clinical Tumor size	33 (17.36)
< 2 cm	131(68.94)
2–5 cm	17 (8.94)
> 5 cm	9 (4.73)
Couldn't be ascertained (Tx)	
Tumor location (Quadrant)	91 (47.89)
Upper outer	33 (17.36)
Upper inner	37 (19.47)
Lower outer	15 (7.89)
Lower inner	14 (7.36)
Central	
Sex	2 (1.05)
Male	188 (98.94)
Female	

Table 1: Patient characteristics	
	n = 190 (%)
Surgery	**142 (74.73)**
Modified Radical Mastectomy	**48 (25.26)**
Breast Conservation Surgery	
Histology	174 (91.57)
Infiltrating ductal carcinoma, not otherwise specified	2 (1.05)
Infiltrating lobular carcinoma	7 (3.68)
Mucinous carcinoma	2 (1.05)
Papillary carcinoma	4 (2.10)
Metaplastic carcinoma	1 (0.52)
Medullary carcinoma	
Receptor Status	132 (69.47)
Estrogen Receptor + ve	58 (30.52)
Estrogen Receptor -ve	110 (57.89)
Progesterone Receptor + ve	80 (42.10)
Progesterone Receptor -ve	54 (28.42)
Human epidermal growth factor receptor + ve	134 (70.52)
Human epidermal growth factor receptor -ve	2 (1.05)
Human epidermal growth factor receptor equivocal	
Molecular Subtype	94 (49.47)
Luminal A	35 (18.42)
Luminal B	18 (9.47)
HER2-Enriched	41 (21.57)
Triple negative	2 (1.05)
Couldn’t be ascertained	

Table 1: Patient characteristics	
	n = 190 (%)
Surgery	**142 (74.73)**
Modified Radical Mastectomy	**48 (25.26)**
Breast Conservation Surgery	
Clinical stage	32 (16.84)
Ia	0 (0)
Ib	74 (38.94)
IIa	61 (32.10)
IIb	15 (7.89)
IIIa	0 (0)
IIIb	0 (0)
IIIc	8 (4.21)
x (Couldn't be ascertained)	
Pathological stage	28 (14.73)
Ia	0 (0)
Ib	66 (34.73)
IIa	44 (23.15)
IIb	30 (15.78)
IIIa	0 (0)
IIIb	21 (11.05)
IIIc	1 (0.52)
x (Couldn't be ascertained)	
Grade	10 (5.26)
1	41 (21.57)
2	139 (73.15)
3	

Table 1: Patient characteristics	
	n = 190 (%)
Surgery	**142 (74.73)**
Modified Radical Mastectomy	**48 (25.26)**
Breast Conservation Surgery	
Lymphovascular invasion	85 (44.73)
+ve	105 (55.26
-ve	
Perineural invasion	35 (18.42)
+ve	155 (82.10)
-ve	

Patient Characteristics

The median number of Level I and II lymph nodes harvested was 20(range = 2–46). The median number of level III lymph nodes harvested was 4(range = 0–20). Only 22(11.4%) patients had metastases in level III lymph nodes. Level I/II and level III nodal positivity rate in all patients who underwent axillary clearance was 50% and 11.4%(n = 22) respectively. In patients with pathologically involved level I/II lymph nodes, level III nodal positivity was 23.15%(n = 21). Skip metastases in level III without involvement in levels I and II were found in only one patient(0.52%).

Correlation of level III lymph node metastases with level/II lymph node metastases, size of the tumour, location of the tumour, lymphovascular invasion, grade of the tumour and subtype of the tumour was done using the Chi-square test(Table 2). There was a significant correlation between pathological involvement of level I/II lymph nodes(p = < 0.001), lymphovascular invasion(p = 0.001), pathological tumour size(p = 0.015), extranodal extension in level I/II lymph nodes (p < 0.00001) and level III lymph node metastases. Clinical tumour size (p = 0.18), clinical nodal status(p = 0.005) tumour location(p = 0.78), grade of the tumour (p = 0.5), ER/PR(p = 0.22), HER2 status(p = 0.989), histology(p = 0.942), molecular subtype(p = 0.899) and perineural invasion(p = 0.56) did not show any significant association with level III lymph node metastases.

Table 2: Correlation of Clinical and Pathological features with Level III Lymph node Metastases

Variable	Level III Lymph Nodes		P value
	Negative	Positive	
	n (%)	n (%)	
Histology	19 (86.3)	155 (92.2)	0.942
Infiltrating ductal carcinoma, not otherwise specified	1 (4.5)	1 (0.5)	
Infiltrating Lobular carcinoma	1 (4.5)	3 (1.7)	
Metaplastic carcinoma	1 (4.5)	6 (3.5)	
Mucinous carcinoma	0 (0.0)	2 (1.1)	
Papillary	0 (0.0)	1 (0.5)	
Medullary			
Quadrant	79 (47.0)	12 (54.5)	0.78
Upper outer	29 (17.3)	4 (18.2)	
Upper inner	35 (20.8)	2 (9.1)	
Lower outer	13 (7.7)	2 (9.1)	
Lower inner	12 (7.1)	2 (9.1)	
Central			
Clinical Tumor Size	31 (19.3)	1 (5)	0.18
<=2 cm	114 (70.8)	18(90)	
2–5 cm	16 (9.9)	1 (5)	
> 5 cm			
Pathological Tumor Size	0 (0.0)	30 (17.8)	0.015
< 2 cm	16 (72.7)	126 (75.0)	
2–5 cm	6 (27.2)	12 (7.1)	
> 5 cm			
Clinical Nodal Status	102 (60.7)	6 (27.3)	0.005
Negative	66 (39.3)	16 (72.7)	
Positive			

Table 2: Correlation of Clinical and Pathological features with Level III Lymph node Metastases			
Pathological Nodal Status	95 (56.5)	0 (0.0)	< 0.001
Negative	73 (43.5)	22 (100)	
Positive			
Extranodal Extension	15 (68.1)	37 (22.0)	< 0.00001
Present	7 (31.8)	131 (77.9)	
Absent			
Grade	10 (6.0)	0 (0.0)	0.50
1	36 (21.4)	5 (22.7)	
2	122 (72.6)	17 (77.3)	
3			
Estrogen/Progesterone Receptor	114 (67.9)	18 (81.8)	0.22
Positive	54 (32.1)	4 (18.2)	
Negative			
Human epidermal growth factor receptor	6 (27.2)	48 (29.2)	0.846
Negative	16 (72.7)	116 (70.7)	
Positive			
Molecular Subtype	13 (59.0)	81 (48.7)	0.899
Luminal A	5 (22.7)	29 (17.4)	
Luminal B	1 (4.5)	17 (10.2)	
HER2-Enriched	3 (13.6)	39 (23.4)	
Triple negative			
Lymphovascular Invasion	68 (40.5)	17 (77.3)	0.001
Positive	100 (59.5)	5 (22.7)	
Negative			
Perineural Invasion	30 (17.9)	5 (22.7)	0.56
Positive	138 (82.1)	17 (77.3)	
Negative			
Correlation of Clinical and Pathological features with Level III Lymph node Metastases			

Discussion

Axillary surgery is an integral component of the locoregional management of breast cancer. Axillary lymph node dissection is associated with complications such as lymphedema (~ 20%), paresthesia of the medial aspect of the arm(30%), limitation of shoulder joint movement, chronic pain and the possibility of injury to the long thoracic nerve and thoracodorsal nerve [2,3]. The majority of the patients with cN0 disease will have pathologically free nodes and subjecting these patients to complete ALND will expose them to the morbidity of the procedure unnecessarily. In clinically node-negative patients sentinel lymph node biopsy(SLNB) has become the standard of care and complete axillary dissection is carried out only in those patients where the sentinel lymph node is positive. Sentinel lymph node biopsy avoids unnecessary ALND and thus complications associated with it[4,5]. American College of Surgeons Oncology Group(ACOSOG) Z0011 trial showed that complete axillary dissection can be omitted in a subset of patients with positive SLNB if they fulfil the following criteria (1) tumour size < 5 cm (2) undergoing BCS (3) whole breast irradiation (4) 1–2 positive sentinel lymph nodes [6].

In patients with clinically positive nodes, level I and II clearance is the standard. Whether Level III lymph nodes should be addressed in the case of positive level I/II lymph nodes is still controversial. According to NCCN(National Comprehensive Cancer Network) guidelines Level III lymph node dissection is to be carried out when there is gross involvement of Level III lymph nodes or metastases was found in level I or II[1]. This study aimed to identify the factors that predict level III nodal involvement.

The status of lymph nodes in level III has prognostic value. If level III nodes are metastatic then patients are directly staged as pN3(stage IIIc) [7]. Many studies have shown that the rate of level III nodal positivity is around 17–31%. [8.9,10,11]. In our study, the overall level III lymph node positivity rate was 11.4%. In patients with positive nodes in level I/II the positivity rate was 19.5%.

The possibility of involvement of level III lymph nodes without the involvement of lymph nodes in levels I and II are very less and almost negligible. So, skip metastases is not a justification to perform routine level III lymph node dissection. Many studies have shown that skip metastases to level III lymph nodes are less than 6%[9,12,13]. In our study level III skip metastases rate was 0.5%.

Clinical and pathological factors that can predict the involvement of level III lymph nodes have been explored only in a few studies. In a study by Dillon et al. tumour size, invasive lobular cancer, lymphovascular invasion and extranodal extension were associated with level III lymph node positivity [8]. Chua et al. found that large tumours, LVI, > 4 positive nodes were associated with positive level III nodes [13]. A retrospective study undertaken at Tata Memorial Centre, Mumbai by Joshi et al. showed that > 4 positive nodes, extranodal extension and inner/central quadrant tumours were associated with level III nodal involvement[12]. A study by Toma et al. found that only grade was associated with level III positivity [10]. Yildirim et al. showed that > 7 involved nodes were associated with level III positivity [11]. Ung et al. found that level III lymph node positivity was related to pathological tumour size, clinically palpable lymph nodes and lymphovascular invasion[14]. Our study showed that pathological tumour size, pathological level I/II lymph node positivity, lymphovascular invasion and extranodal extension

predicted level III lymph node involvement. Location of the tumour, histology, grade, perineural invasion, ER/PR/HER2 status or molecular subtype didn't predict level III nodal involvement.

Though level III axillary lymph node dissection may give us prognostic information and accurate staging, it may not improve the overall survival of the patients. Kodama et al. conducted a randomised controlled trial that compared level I/II LND with level I/II/III LND [9]. They found that there was no difference in 10-year disease-free survival(DFS) and 10-year overall survival (OS) between the two groups. Tominaga et al. also arrived at a similar conclusion when they compared Level I/II LND with level I/II/III LND in patients with stage II breast cancer[15].

It is assumed by the surgeons that level III LND may lead to more morbidity than the level I/II LND alone. Kodama et al. showed that the complication rates (lymphedema, shoulder disturbances) were similar between Level I/II LND and Level III LND[9]. However, level III LND was associated with increased blood loss and longer operative time.

The study has certain limitations. The impact of level III lymph node dissection on regional control, disease frees survival or overall survival has not been studied. The side effects, if any, of level III lymph node dissection over and above level I/II dissection such as lymphedema, shoulder dysfunction and increased operative time have not been studied.

Conclusion

Since level III lymph node involvement by metastases shows a correlation with level I and II lymph node metastases, pathological tumour size and lymphovascular invasion, it is prudent to perform level III lymph node dissection in patients with suspicious or involved level I/II lymph nodes.

Declarations

Statements & Declarations

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Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval: The study was approved by Institute Ethical Committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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