

Level 3 Axillary Nodal Status in the Absence of Metastatic Disease in Level 1 and 2 Axillary Node in Carcinoma Breast – A Retrospective Analysis

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Abstract

Introduction: The intention of axillary lymph node dissection (ALND) is to stage the axilla precisely for prognostic information. This study is to assess the possibility of skip lesion in Level 3 in the absence of disease in Level 1 and 2 which may help in undertaking randomized controlled study to avoid Level 3 nodal dissection in our patients.

Materials and Methods: Retrospective analysis of 60 patients who underwent surgery for invasive breast cancer from October 2013 to October 2019 in the Department of Surgical Oncology, Government Thoothukudi Medical College Hospital, Thoothukudi, was performed.

Results: About 33.3% of patients (20) were disease free in the axilla and the remaining 66.7% (40) had nodal involvement. Of those 39 patients who had nodal involvement in Level 1 and 2, 15 were found to have the disease in 4 or more nodes, 24 had the disease in <4 nodes. Totally 16 patients had metastases in Level 3 nodes. There is a 60% chance of involvement of Level 3 when there is 4 or more nodal positivity in Level 1 and 2 and it drops to 25% if the involved nodal count becomes <4. One patient had skip lesion in Level 3 (4.8%) without disease in Level 1 and 2.

Conclusion: Since there has been a dearth of randomized studies about levels of nodes to be addressed in ALND and studies about skip lesion in Level 3 from our country, we urge the need for more studies probably multicentric, regarding the extent of ALND. Until then, it may be fruitful to do complete ALND up to Level 3 for the better staging of the axilla.

Key words: Axillary lymph node dissection, Carcinoma of breast, Level 3 nodes

INTRODUCTION

Breast cancer tops the list of cancers affecting women in many parts of India.^[1] It tends to affect the younger age group also.^[2] Surgery is a critical part in the management of breast cancer. Even though breast surgery has undergone a paradigm shift from the Halstedian era of radicalism to Fisher's concept of breast cancer being a systemic disease from the beginning, the foundation of locoregional therapy still relies on the complete eradication of the disease from breast and axilla.

Axillary nodal involvement is the most important prognostic factor in cancer breast. Axillary lymph node dissection (ALND) has long been considered as the gold standard treatment in node-positive patients. The principle behind complete ALND is to stage the axilla for accurate prognostic information, to maintain adequate local control, to provide a rational basis for decisions regarding adjuvant therapy, and possibly to maximize survival. Even in clinicoradiological node-negative axilla, there lies the possibility of occult metastasis in 30–40% of patients.^[3] Hence, axilla has to be addressed in all cases. Anatomically axillary space is divided into three levels by the pectoralis minor muscle. The assumption was that metastases from primary usually would first involve Level 1, then Level 2, and only later Level 3.^[4]

The dissection of Level 3 nodes located between the costoclavicular ligament and medial border of pectoralis minor muscle needs experience and may require slightly

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longer surgical time. Since there is no international consensus regarding the levels of nodes to be removed and paucity of specific studies to find out skip lesions in apical nodes (Level 3), our policy is to do complete ALND up to Level 3 as followed in many dedicated cancer centers in India.^[5,6]

Aim

The aim of the study was to assess the status of Level 3 node in the absence of disease in Level 1 and 2. This may lay the foundation for further studies to assess the feasibility of skipping Level 3 dissection without compromising oncological safety in our population.

MATERIALS AND METHODS

A retrospective analysis of data of patients who underwent modified radical mastectomy (MRM) for invasive breast cancer between the periods, October 2013–October 2019 in the Department of Surgical Oncology, Government Thoothukudi Medical College Hospital was carried out. All patients were treated with curative intent after getting informed consent and are being followed up regularly. The Institutional Ethical Committee of our hospital has given approval for this study. Until date, sentinel lymph node biopsy (SLNB) was not performed in our department due to a lack of technical expertise.

Only the data of those 60 patients whose Level 3 nodal status was known is taken for analysis. All surgeries were done by a single qualified surgical oncologist. The grossing of the specimen and histopathological reporting was done by multiple pathologists over the above period. In all patients, ALND was done up to Level 3. Level 1 and 2 axillary nodes were removed *en bloc* with mastectomy, and Level 3 nodes were removed separately by interpectoral approach.

We follow the stepwise approach identifying all structures carefully while doing mastectomy and ALND.^[6-8] In almost all cases, pectoralis minor muscle was preserved. We use diathermy for raising the flaps. A suction drain was used in all cases. Level 3 area was reached by the interpectoral approach retracting the pectoralis minor muscle laterally, retracting pectoralis major muscle above and medially. Complete clearance was done up to costoclavicular ligament. Specimens (breast with Level 1 and 2 nodes, Level 3 nodal tissue) were sent in separate containers.

All patients were given proper adjuvant therapy depending on our institutional protocol. Patients were being followed up monthly in the 1st year, 2 monthly in the 2nd year, 3 monthly in the 3rd year, 6 monthly for 4th, and 5th years and yearly thereafter as per our department protocol.

Follow-up included clinical examination at each visit, yearly chest X-ray and ultrasonography abdomen with the pelvis and other investigations as indicated. We routinely teach shoulder mobilization exercises for the patients and encourage them to follow it regularly.

RESULTS

In this study, 60 patients who underwent MRM, whose Level 3 nodal status in their post-operative histopathology report is known, were included in the study. The median age of the study patients was 52.5 years in range 30–90 years [Table 1]. Twenty-one patients were below 50 years of age. The average node count retrieved in Level 1 and 2 is 10.7 which meets the optimum requirement suggested by international guidelines. The average node count retrieved in Level 3 is 2.6. The average node count retrieved in complete ALND is 12.8.

Of those 60 patients, 28 received pre-operative chemotherapy and 32 underwent upfront surgery. Thirty-seven patients had a tumor on the right breast and 23 were left sided. A total of 33.3% of the patients were disease-free in the axilla and the remaining 66.7% had nodal involvement. Of those 39 patients who had the disease in Level 1 and 2, 24 were found to have the disease in <4 nodes and 15 were found to have the disease in 4 or more nodes. A total of 26.7% of the patients had the disease in Level 3 (16 patients) [Figure 1]. One patient had skip lesion in Level 3 in the absence of nodal positivity in Level 1 and 2 (4.8%). This patient underwent surgery after neoadjuvant chemotherapy.

Table 1: Clinicopathological details

Clinicopathological characteristics		Measure
Age	Median (range)	52.5 (30–90)
Side of lesion	Right	37
	Left	23
Status of ALND	Uninvolved patients	20
	Involved patients	40
Status of involved nodal level	Level 1 and 2	15
	(more than 4 nodes)	
	Level 1 and 2 (<4 nodes)	24

ALND: Axillary lymph node dissection

Table 2: Percentage of skip lesion in Level 3 in various studies

Studies	Year of study	Sample size	% of skip lesion in Level 3 axillary node
Aslan ^[20]	2007	87	1.14
Khafagy <i>et al.</i> ^[21]	2011	59	1.70
Joshi <i>et al.</i> ^[5]	2019	1591	0.70
Our study	2020	60	4.80

Of those 15 patients who had 4 or more nodal positivity in Level 1 and 2, 9 had the disease in Level 3 (60%). Of those 24 patients who had <4 nodal involvements in Level 1 and 2, 6 had the disease in Level 3 (25%) [Figure 2]. The nodal burden in Level 3 increases with the number of nodes involved in Level 1 and 2.

DISCUSSION

In this era of organ conservation, the radicalism of surgery is gradually losing its shine. For breast cancer, surgery for the primary as well as axilla is moving from radicalism toward conservation.^[9,10] SLNB is the current strategy in clinically node-negative axilla in many centers.^[11] In some centers, low axillary sampling is considered as an alternative to SLNB.^[12]

SLND for clinically node-negative axilla gained popularity following the advent of the landmark NSABP-32 trial.^[11] If the sentinel node is negative, ALND is avoided which may help to avoid the potential complications of ALND. When the sentinel node is positive, the patient will be subjected to complete ALND. Further advancement in SLNB was obtained with the advent of the landmark trial ACOSOGZ0011.^[13] On the other hand, ALND is still the gold standard procedure for the management of axilla in many parts of the world where these technological advances are not available. There is no international consensus regarding the levels to be removed in ALND. NCCN guidelines recommend dissection of Level 1 and 2 with the advice that, Level 3 to be removed when there is gross disease in Level 1 and 2.^[14] In fact, there are questions whether the evidence from early screen-detected cancers in the western population can be blindly followed in our population with a possibly different tumor biology and presentation as locally advanced disease.

In general, Level 1 nodes are commonly involved in breast cancer.^[15] Involvement of Level 2 or Level 3 lymph nodes without the involvement of the Level 1 is uncommon. The involvement of Level 3 lymph nodes with negative Levels 1 and 2 lymph nodes is rare, occurring in <3% of all patients with positive nodes.^[16,17] The risk of involvement of the higher lymph-node levels increases substantially with increasing numbers of involved nodes or when lower levels are involved.

In a study by Gaglia *et al.*, 9% of patients with 1–3 positive lymph nodes and 47% of those with 4 and more positive lymph nodes had involvement of Level 3 lymph nodes.^[18] In the study by Boova *et al.*, Level 1 lymph nodes were found to be positive, the Level 2 lymph nodes were involved in 41% of patients, and Level 3 lymph nodes were involved in 21%. When Level 2 lymph nodes were involved, 31% of patients also had metastases to Level 3.^[15] Similar trend had been reported by Chevinsky *et al.*^[16] Moreover, a higher

incidence of Level 3 involvement has been noted when lymph nodes in lower levels were grossly involved by tumor (41%) compared with when they were only involved microscopically (15%).^[17]

In a study by Fan *et al.*, there is a 9% chance of residual positive nodes in Level 3 after neoadjuvant chemotherapy. They found that tumor size, non-responsiveness of the primary tumor to neoadjuvant chemotherapy were independent predictors for Level 3 nodal positivity. Disease-free survival (DFS) was found to be lower for Level 3 positive group.^[19]

Joshi *et al.* in a prospective single-institution study from a reputed cancer center in India have found that 9.4% had the disease in Level 3 when 1–3 positive nodes were present

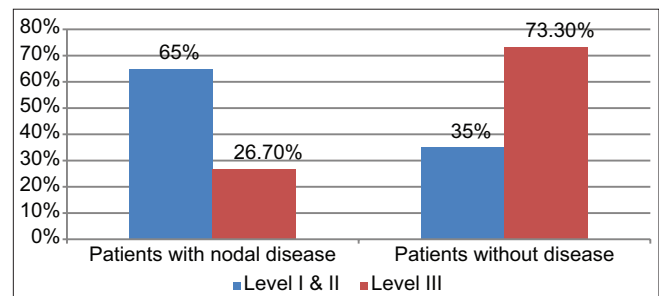


Figure 1: Status of axillary lymph node dissection

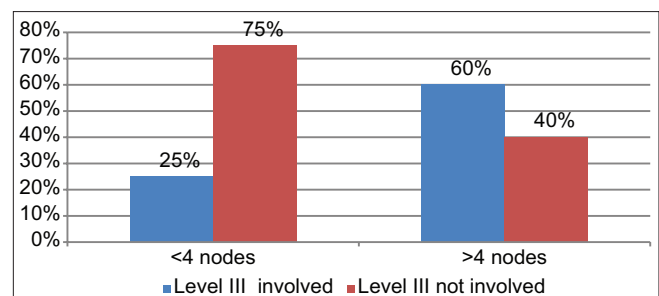


Figure 2: Status of Level 3 nodes in the presence of disease in Level 1 and 2

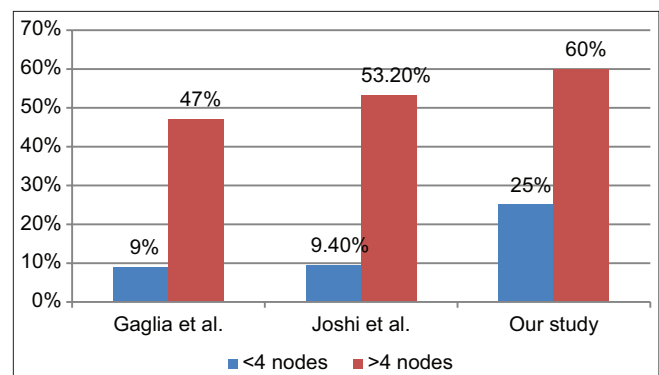


Figure 3: Involvement of Level 3 depending on diseased nodal count in Level 1 and 2

in Level 1 and 2 and it increased to 53.2% if 4 or more nodes are positive in Level 1 and 2 [Figure 3]. In their study, 0.7% had skip lesion in Level 3 in the absence of nodes in Level 1 and 2. DFS was significantly worse for Level 3 ALN metastases on univariate analysis.^[5]

In our study, 25% had the disease in Level 3 when 1–3 positive nodes were present in Level 1 and 2 and it increased to 60% if 4 or more nodes are positive in Level 1 and 2 [Figure 2]. In our study, 4.8% had skip lesion in Level 3 in the absence of nodes in Level 1 and 2 [Table 2]. In a study by Boova *et al.*, 3.5% manifested skip lesions in Level 2 and 3 without the involvement of Level 1.^[15]

With the available data, as the positive nodal count in Level 1 and 2 is 4 or more, there is a high chance of involvement of Level 3 (60%) which is statistically significant ($P = 0.029$). If a partial (Levels 1 and 2) ALND is done as per current recommendation, one of two patients with 4 or more positive nodes in Level 1 and 2 may have residual disease in Level 3. Since the axillary nodal burden is higher in developing countries like India, many surgeons feel that leaving behind Level 3 nodes may amount to inadequacy of dissection defeating the therapeutic intention of ALND. The morbidity of doing Level 3 dissection is very minimal in the hands of experienced surgeons who know the finer aspects of oncological clearance. Hence, complete ALND may be the highly rewarding procedure in the accurate staging of axilla in our population.

CONCLUSION

In carcinoma breast, individualized treatment based on disease burden and availability of technical expertise along with multidisciplinary cooperation is considered as the best option. Since there has been a dearth of randomized studies about levels of nodes to be addressed in ALND and studies about skip lesion in Level 3 in our country, we urge the need for more studies probably multicentric, regarding the extent of ALND. Until then, it may be fruitful to do complete ALND up to Level 3 for the better staging of axilla.

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