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Breast Cancer

The Role of Level III Dissection in Locally Advanced Breast Cancer following Neoadjuvant Chemotherapy—A Prospective Study

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Abstract


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Breast cancer is the most common female cancer in India, with a significant number presenting as locally advanced breast cancer (LABC). Level III clearance is routinely performed in our institute in LABC following neoadjuvant chemotherapy (NACT). In our previous retrospective study, level III positivity rate was 15.5%. We aim to prospectively assess level III positivity rate in LABC patients post-NACT. This is a prospective study of female patients with LABC (defined as cT3N1–3M0 or cT4N0–3M0 or $cT_{any}N2,3M0$) who received NACT and underwent surgery including level III dissection from November 2019 to October 2021. Data collected included age, menopausal status, TNM stage at presentation, grade, hormone receptor and HER2 status, treatment response, ycT and ycN stage, and final histopathology. Univariate and multivariate analysis was undertaken. *p*-Value less than or equal to 0.05 was considered significant. Study recruited 598 patients. Level III node positivity rate was 8.4%. The clinical complete response rate (cCR) was 36% (215/598). On univariate analysis, significant association was present between level III node and cCR ($p < 0.01$), ycT0 stage ($p = 0.001$), ycN0 stage ($p = 0.028$), level II node positivity ($p = 0.001$), ypT stage ($p = 0.001$), and ypN stage ($p = 0.001$). On multivariate analysis, significant association was present between level III node and ycT stage ($p < 0.001$), ypT stage ($p = 0.001$), and ypN stage ($p = 0.001$). Level III positivity rate in LABC post-NACT is high. In patients with advanced ycT stage, it would be advisable to offer complete axillary dissection including level III. Level III dissection may be avoided in patients with ycT0 or ycN0 or with cCR.

Keywords

- level III dissection
- locally advanced breast cancer
- neoadjuvant chemotherapy
- axillary dissection
- level III positivity rate

Introduction

Breast cancer is the most common female cancer in India.[1] As per a recent Indian study, locally advanced breast cancer (LABC) accounts for 46% of all the newly diagnosed breast cancers.[2] The current concept of breast surgery is of conservation both in the breast and the axilla. The standard of care in breast surgery is currently breast conservation surgery in the primary and in the post-neoadjuvant chemotherapy (NACT) setting.[3,4] The extent of axillary dissection has decreased

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drastically in the primary surgery in early, node-negative breast cancer with the advent of sentinel lymph node biopsy (SLNB).[5] In patients with cN0 status pre NACT with non-progression on chemotherapy, SLNB using dual tracer is adequate.[6] In node-positive patients who receive NACT, the role of de-escalation is still not proven with level 1 evidence. Multiple trials like Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA), American College of Surgeons Oncology Group Z1071 (ACOSOGZ1071), and Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer (SNFNAC) have a high false-negative rate and low identification rate.[7–9] Newer techniques like targeted axillary dissection using various targeting agents have a low false-negative rate but the evidence is in the form of small trials.[10–12] Even with these techniques, if the targeted node or SLNB is positive, complete axillary dissection is advised.

As per the European Breast Cancer Research association of Surgical Trialist (EUBREAST) survey, there is no consensus on axillary management after NACT in patients with clinically node-positive breast cancer.[13] During the axillary dissection, the level I and II are routinely cleared with or without level III dissection. As per the NCCN guidelines for clinical practice in breast cancer, in the absence of gross disease in level II or III, level I and II dissection should be done.[14]

In the primary surgery setting, the level III positivity was 27.3% as per a recent Indian study.[15] The current pathological complete response (pCR) rate is 12% in hormone receptor (HR)-positive, HER2-negative, 36% in HR-positive, HER2-positive, 38% in triple-negative, and 55% in HR-negative, HER2-positive cancer.[16] Thus, there is possibility of residual disease in level III in a significant proportion of patients. In our institute, we routinely perform complete axillary dissection of all III levels in the post-NACT setting.

We analyzed our retrospective data of level III positivity in post-NACT patients.[17] The level III node was positive in 15.5% as per our study. In a retrospective study by Fan et al, the level III positivity rate was 9%.[18] With this high rate, level III dissection is unavoidable as these are the nodes that have not responded to the primary chemotherapy and represent residual tumor cells that can later cause relapse and distant metastasis. As per studies, presence of residual nodes post-NACT is a predictor of poorer survival and increased relapse in ER negative and HER2-positive patients.[19,20]

There are no prospective studies that have analyzed the level III positivity rate in post-NACT breast cancer patients. We aim to prospectively assess the rate of level III positivity in LABC patients post-NACT and identify any subgroup in which level III dissection can be avoided.

Materials and Methods

This is a prospective observational study of female patients with LABC who received NACT and underwent surgery including level III nodal clearance from November 2019 to October 2021 at a tertiary cancer center in Kerala, India. This study was conducted after institutional review board clearance. Inclusion criteria were women aged 18 years to 80 years with LABC (defined as cT3N1–3M0 or cT4N0–3M0 or $cT_{any}N2,3M0$) and who received NACT with anthracyclines and/or taxanes. Women with history of previous malignancy, who progressed on NACT, who were HER2 positive and did not receive neoadjuvant trastuzumab, who had inflammatory breast cancer, and who did not complete their planned NACT were excluded. Data collected included age, menopausal status, T and N stage at presentation, grade, estrogen, progesterone and HER2 receptor status, response to treatment (response evaluation criteria in solid tumors (RECIST), criteria version 1.1), post-chemotherapy clinical stage, and final histopathology report.[21] Age was subdivided into less than or equal to 40 years, 41 to 60 years and over 60 years. Menopausal status was divided into premenopausal or postmenopausal. Patients with either estrogen or progesterone receptor Allred score greater than 2 were considered HR positive. RECIST 1.1 criteria weas used to assess the response to NACT. No imaging of the axilla was done post-NACT. The cT and cN stage include both clinical and radiological examination (mammogram and computed tomography, CT, scan [for internal mammary nodes staging]). In patients planned for mastectomy, we do not routinely perform mammogram of the ipsilateral breast. In such cases, cT and cN are based on clinical findings and CT scan for the internal mammary node staging. Level III nodes were defined as nodes identified in the space bounded laterally by the medial margin of pectoralis minor muscle, superiorly by the axillary vein and medially by the thoracic inlet (costoclavicular ligament).[22] Levels I, II, and III nodes were dissected and sent for histology separately. A subgroup analysis based on age, menopausal status, prechemotherapy T and N stage, grade, HR status, HER2 status, response to NACT, and post-NACT clinical stage was done. Categorical variables were analyzed using Pearson's chi-squared test. Univariate and multivariate analyses were done using Fisher's exact test and logistic regression model, respectively. A *p*-value of less than or equal to 0.05 was considered significant.

Results

There were 1532 women with breast cancer who underwent breast surgery during the study period, of whom 669 were post-neoadjuvant therapy. The inclusion criteria were met by 598 patients as shown in the consort diagram (►Fig. 1).

►Table 1 summarizes the patient and pre-surgery tumor characteristics.

The most common age group was 41 to 60 years (72.7%) and 63.2% were postmenopausal. The most common stage at presentation was cT2N2 (31.9%). cN3 disease was seen in 10.5% of the cases. Grade 3 was most common, seen in 76.1% of patients. HR positivity was present in 68.2% and HER2 was positive in 35.5%. HR positive, HER2 negative was the most common biology (42.8%) followed by triple positive (25.4%), triple negative (20.9%), and HR negative and HER2 positive (10.9%). No patient received pertuzumab. ►Table 2 summarizes the surgery and post-surgery histopathology.

Most of the patients underwent modified radical mastectomy (70.7%). Using the RECIST 1.1 criteria, the clinical complete response rate was 36%. The overall pathological complete

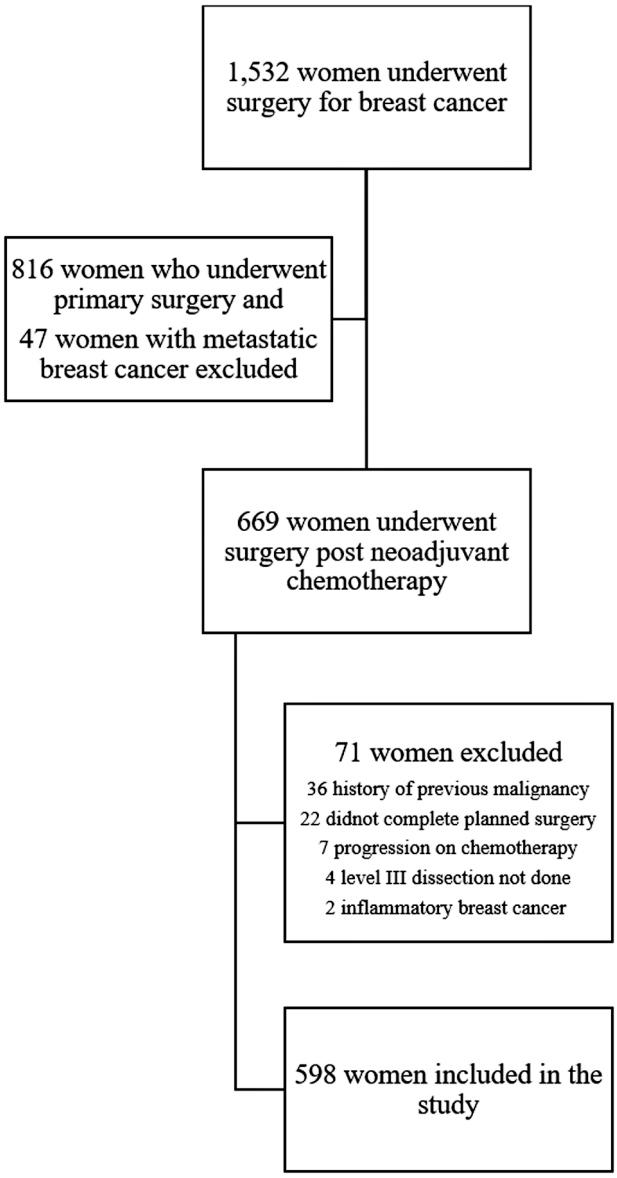

Fig. 1 Consort diagram of the study population.

Table 1 Patient and tumor characteristics

Characteristic	Patient number	Percentage
Age		
≤ 40years	69	11.5
41–60 years	435	72.7
>60 years	94	15.8
Menopausal status		
Premenopausal	220	36.8
Postmenopausal	378	63.2
Clinical stage (cTNM) prechemotherapy		
cT0N2M0	4	0.6
cT1N2M0	23	3.9
cT1N3M0	4	0.7
cT2N2M0	191	31.9
cT2N3M0	13	2.2
cT3N1M0	95	15.9
cT3N2M0	8	1.3
cT3N3M0	11	1.8
cT4N0M0	24	4.1
cT4N1M0	135	22.6
cT4N2M0	54	9
cT4N3M0	36	6
Grade		
2	143	23.9
3	455	76.1
Hormone receptor status		
Positive	408	68.2
Negative	190	31.8
HER2 status		
Positive	212	35.5
Negative	386	64.5
Biology		
Hormone receptor positive, HER2 negative	256	42.8
Triple positive	152	25.4
Hormone receptor negative, HER2 positive	65	10.9
Triple negative	125	20.9
Clinical response assessment		
Complete response	215	36
Partial response	350	58.5
Stable disease	33	5.5
Post-chemotherapy clinical stage (ycTNM)		
ycT0N0M0	215	36
ycT0N1M0	67	11.2
ycT0N2M0	4	0.6
ycT1N0M0	74	12.4
ycT1N1M0	36	6
ycT2N0M0	35	5.9
ycT2N1M0	26	4.5
ycT2N2M0	3	0.5
ycT2N3M0	1	0.2
ycT3N0M0	3	0.5

Table 1 (*Continued*)

Characteristic	Patient number	Percentage
ycT3N1M0	11	1.7
ycT3N2M0	2	0.3
ycT4N0M0	71	11.8
ycT4N1M0	38	6.4
ycT4N2M0	10	1.7
ycT4N3M0	2	0.3

Table 2 Surgery and histopathology characteristics

Characteristic	Patient number	Percentage
Type of surgery		
Breast conservation surgery	175	29.3
Modified radical mastectomy	423	70.7
T stage on final histopathology (ypT)		
ypT0	233	39.0
ypT1	215	36.0
ypT2	120	20.0
ypT3	28	4.7
ypT4	2	0.3
N stage on final histopathology (ypN)		
ypN0	346	57.9
ypN1	133	22.2
ypN2	67	11.2
ypN3	52	8.7
ypTN stage on final histopathology		
ypT0N0	188	31.4
ypT0N1	25	4.2
ypT0N2	15	2.5
ypT0N3	5	0.8
ypT1N0	103	17.2
ypT1N1	70	11.7
ypT1N2	24	4
ypT1N3	21	3.5
ypT2N0	44	7.4
ypT2N1	31	5.2
ypT2N2	25	4.2
ypT2N3	16	2.6
ypT3N0	7	1.2

(*Continued*)

Table 2 (*Continued*)

Characteristic	Patient number	Percentage
ypT3N1	6	1
ypT3N2	3	0.5
ypT3N3	10	1.7
ypT4N0	1	0.2
ypT4N1	1	0.2
ypT4N2	3	0.5
Level I on final histopathology		
Positive	242	40.5
Negative	356	59.5
Level II on final histopathology		
Positive	72	12
Negative	526	88
Level III on final histopathology		
Positive	50	8.4
Negative	548	91.6

Table 3 Univariate analysis of factors and level III nodal status

Characteristic	Level III positive patients	*p*-Value
Age		0.133
≤ 40 years	10/69 (14.5%)	
41–60 years	34/435 (7.8%)	
>60 years	6/94 (6.4%)	
Menopausal status		
Premenopausal	20/220 (9.1%)	0.677
Postmenopausal	30/378 (7.9%)	
Clinical T stage (cT)		
cT0	0/4 (0%)	0.096
cT1	2/28 (7.1%)	
cT2	11/213 (5.2%)	
cT3	7/105 (6.7%)	
cT4	30/248 (12.1%)	
Clinical N stage (cN)		
cN0	1/42 (2.4%)	0.056
cN1	17/281 (6.1%)	
cN2	24/212 (11.3%)	
cN3	8/63 (12.7%)	
Grade		
2	19/143 (13.3%)	0.064
3	31/455 (6.8%)	

(*Continued*)

Table 3 (*Continued*)

Characteristic	Level III positive patients	*p*-Value
Hormone receptor status		
Positive	50/485 (10.3%)	0.176
Negative	10/113 (8.9%)	
HER2 status		
Positive	12/215 (5.6%)	0.181
Negative	38/383 (9.9%)	
Biology		
Hormone receptor positive, HER2 negative	28/228 (12.3%)	0.254
Triple positive	10/152 (6.6%)	
Hormone receptor negative, HER2 positive	5/65 (7.7%)	
Triple negative	7/125 (5.6%)	
Clinical response assessment		
Complete response	11/215 (5.1%)	<0.01
Partial response	35/350 (10%)	
Stable disease	4/33 (12.1%)	
Post-chemotherapy clinical T stage (ycT)		
ycT0	15/286 (5.3%)	0.001
ycT1	6/110 (5.5%)	
ycT2	6/65 (9.2%)	
ycT3	1/16 (6.3%)	
ycT4	22/121 (18.2%)	
Post-chemotherapy clinical N stage (ycN)		
ycN0	31/397 (7.8%)	0.028
ycN1	13/178 (7.3%)	
ycN2	5/20 (25%)	
ycN3	1/3 (33.3%)	
Type of surgery		
Modified radical mastectomy	35/423 (8.3%)	0.056
Breast conservation surgery	15/175 (8.6%)	
T stage on final histopathology (ypT)		
ypT0	5/233 (2.2%)	0.001
ypT1	21/217 (9.7%)	
ypT2	15/117 (12.8%)	
ypT3	9/26 (34.6%)	
ypT4	0/2 (0%)	
N stage on final histopathology (ypN)		
ypN0	0/346 (0%)	0.001
ypN1	3/133 (2.3%)%)	
ypN2	3/67 (4.5%)	
ypN3	44/52 (84.6%)	

response rate was 31.4% (188/598). The overall nodal pathological complete response rate was 57.9%. The level III positivity rate was 8.4%. The association between level III positivity and the various subsets is depicted in ►Table 3.

In patients with ycN0, the level III positivity was 7.8%. In patients with complete clinical response, the level III positivity was only 5.1%. Level III node positivity was 10.9% in HR + HER2-, 6.6% in triple positive, 7.7% in HR- HER2 +, and 5.6% in triple-negative subset. Level III was the only positive node in six patients (1%). On univariate analysis, a significant association was present between level III node positivity and complete clinical response ($p < 0.01$), ycT0 stage ($p = 0.001$), ycN0 stage ($p = 0.028$), ypT stage ($p = 0.001$), ypN stage ($p = 0.001$), and level II node positivity ($p = 0.001$). On multivariate analysis, significant association was present between level III node positivity ycT stage ($p < 0.001$), ypT stage ($p = 0.001$), and ypN stage ($p = 0.001$). No significant association was seen between level III positivity and age, menopausal status, clinical T stage, HR status, HER2 receptor status, biology, or type of surgery.

Discussion

The current trend in breast cancer surgery is of de-escalation. The breast conservation surgery has been accepted for the breast primary with evidences with 20 years follow-up data proving its equivalence to mastectomy.[21,22] SLNB has revolutionalized the management of N0 axilla in the primary surgery setting.[5] In the post-NACT setting, the role of SLNB is not proven in node-positive axilla.[7–9] Newer techniques like targeted axillary dissection, radioisotope tagging of the positive node, Magseed, Radio Frequency Identification (RFID) tags, and activated carbon injection into the positive node have been tried in small series.[10–12,23–26] These techniques have their pros and cons and there is no level 1 evidence to support their use in current practice.

A recent study has shown the level III positivity rate in case of primary surgery is 27.3% in clinically node-positive axilla.[15] Even if we consider the best pCR rate of 60% as in a recent meta-analysis, there is the possibility of residual disease in approximately 11% of the patients in the level III nodes.[27] In the post-NACT setting, these are the tumor cells that are resistant to the chemotherapy. There is risk of local and systemic that may be resistant to standard chemotherapy if these nodes are not removed surgically. There is role of adjuvant chemotherapy based on the presence or absence of residual disease.[28,29] These level III nodes may contain the only residual tumor cells as was present in six patients in our study. Thus, if these nodes are not removed, the patient may be wrongly diagnosed as to have achieved pCR and may not receive adjuvant therapy that has shown survival advantage.[28,29] The presence of level III node positivity upstages the cancer to N3a that has prognostic implications. The current NCCN guidelines do not specify any difference in the axillary dissection in the primary and post-NACT setting. The dissection of level III nodes is at the discretion of the surgeon depending on the presence of clinically suspicious

level II and III nodes during surgery that is subjective. In the post-NACT setting, the axillary tissues undergo fibrosis due to chemotherapy and it is difficult to differentiate the tumor from fibrosis. The clinicopathological correlation in the post-NACT setting of the axilla is low.[17] As per previous studies, there is no survival benefit with level III dissection, but presence of tumor in the level III nodes is an essential factor that causes distant recurrence and has prognostic implications.[30,31] A recent propensity matched study has advised discretion in de-escalation of axilla in patients who have a heavy nodal burden.[31]

Complete axillary dissection including all three levels is routinely practiced our institute in the post-NACT setting. A retrospective study of the level III dissection in post-NACT from our institute revealed at level III positivity rate of 15.5%.[17] The retrospective study by Fan et al had a level III positivity of 9%.[18] As both these studies have the inherent drawbacks due to their retrospective nature, a prospective study was conducted to identify the level III positivity rate and to identify any subset in which level III dissection can be avoided. Literature review did not reveal any prospective studies of role of level III dissection in the post-NACT setting.

In this study, all the three levels were sent separately for histopathological analysis. The level III positivity was 8.4% that is less than that of our previous study. Level III node positivity was low in patients with ycT0 stage, ycN0 stage, and clinical complete response on univariate analysis. On multivariate analysis, advanced ycT stage was associated with significantly with level III positivity. Thus, level III dissection may be avoided in patients with complete clinical response, ycT0 and ycN0 stage, and must be done in patients with advanced ycT stage post-NACT. It is understandable that in patients with complete clinical response to NACT in the breast and axilla would have a good response in the level III nodes as well. However, a patient with poor response with persistence T4 disease in the breast would be more likely to have residual nodal disease including at level III. There was a significant association with the higher final pathological T and N stage and level III positivity, but this has no clinical benefit in planning the level III dissection.

With the advent of pertuzumab and newer agents like immunotherapy and cell cycle inhibitors, the pCR rate may increase and the level III positivity may further decrease. None of our study patients received pertuzumab. In our resource restricted setting, the use of these agents is limited due to economic constraints. The response to such agents may further reduce the indications for level III dissection in the future.

Conclusion

Level III positivity rate in LABC post-NACT is high. In patients with advanced ycT stage, it would be advisable to offer complete axillary dissection including level III. Level III dissection may be avoided in patients with ycT0 or ycN0 or with complete clinical response.

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Conflict of Interest
None declared.

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