J Surg Res 2021; 4 (3): 484-490 *DOI: 10.26502/jsr.10020160*

Research Article

Clinico-Immuno-Histo-Chemical Interpretation- Approach to Level III Axilla in Operable Breast cancers

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Received: 12 August 2021; **Accepted:** 18 August 2021; **Published:** 27 September 2021

Citation: Ajay Boralkar, Harshad Chavan, Abhishek Potnis, Anagha Varudkar. Clinico-Immuno-Histochemical Interpretation of Level Iii Nodes in Operable Breast Tumors. Journal of Surgery and Research 4 (2021): 484-490.

Abstract

Background

Management involves upfront surgery or neoadjuvant chemotherapy followed by surgery. Surgery involves Modified radical mastectomy (MRM) or Breast Conservation surgery followed by axillary dissection with level I, II with or without III node clearance or sentinel lymph node biopsy. It is possible to forgo level III clearance in a clinically node negative axilla, which can reduce morbidity of ipsilateral arm oedema. The risk of partial axillary clearance is residual positive axilla. This study aims to correlate various primary tumour characteristics with level III lymph nodal positivity in a clinically positive axilla, to provide a pre-operative insight in the level of dissection to be performed.

Methods

A total of 75 patients who satisfied the inclusion criteria were evaluated pre-, intra- and post-operatively to obtain a correlation with level III nodal metastasis. This data was then analysed and significance of each parameter in influencing level III nodal positivity was determined.

Results

It is seen that size, site of tumour, pre- and post-operative pathological grade do not significantly affect the level III nodal metastasis (p= 0.352, 0.351, 0.475, 0.072 respectively) while intra-operative palpability, number of nodes, lymphovascular invasion (LVI), extranodal extension and oestrogen receptor (ER) and progesterone receptor (PR) negativity significantly

affect level III nodal positivity.

Conclusions

Preoperative ER, PR, LVI assessment of primary tumour with intraoperative assessment of different levels of axillary lymph nodes gives an idea about the need for further axillary dissection. Axillary involvement and thus the need for additional loco-regional treatment can be predicted from the patients clinicohistochemical characteristics.

Keywords: Operable breast cancer; Modified radical mastectomy; Level III nodal metastasis; Clinicopathologic correlation

1. Introduction

Most of the breast cancers receive mastectomy or lumpectomy with some form of axillary dissection, or with sentinel lymphnode biopsy upfront or after neoadjuvant chemotherapy. In a clinically positive axilla, axillary dissections are indicated in almost all breast cancers. Lymph node involvement was treated as most important prognostic factor until recently. Hyosun Kim et al have argued that biological subtype of the tumour is more important but lymph nodes remain important factor even in early breast cancers [1]. The involvement of levels of axilla is unpredictable. About 9% of node positive T0-T2breast cancer will have residual positive nodes in level III even after neoadjuvant chemotherapy [2]. This emphasizes the need to address level III lymph nodes. The recurrence after partial axillary dissection is significantly high as noted by Yiangou et al [3]. The literature is divided over the need to excise level III lymph nodes as lymphadenectomy in axilla is largely ascribed a prognostic rather than therapeutic significance [4]. It is a well known fact that though, the overall survival is not affected by level III lymphadenectomy, the disease free survival is better. To gather information and staging of axilla, examination of a minimum of 10 axillary lymph nodes needs to be done (American Joint Cancer Committee 8th edition). While most of literature agrees upon level I and II lymphadenectomy as optimum, certain parameters could be evaluated to independently predict risk of failure in level III axilla after partial lymph node dissection in a clinically positive axilla; so that a balance can be struck between morbidity of arm oedema, arm dysfunction and axillary recurrence.

2. Materials and Methods

Seventy-five patients of operable breast cancer with clinically positive axilla were enrolled for modified radical mastectomy or lumectomy with complete axillary clearance between 2016 and 2019. Patients were clinically evaluated, subjected to mammography and core needle biopsy. The biopsy reports were analysed for tumour type, grade, lymphovascular invasion and receptor status of oestrogen, progesterone and Herceptin (Her-2-neu). Tumour metastatic workup was done with computed tomography of chest, bone scan and ultrasound abdomen as per merits of each case. Positron emitted tomography (PET scan) was not done in any of the case. Patients were subjected to modified radical mastectomy or breast conservation surgery. Level III lymph nodes were sent separately for pathologic assessment. All pathological parameters were noted against level III lymph nodes and analysed using Chi-square test (x^2) and p- values obtained. Daily drain output was monitored and drain was removed when the per day output was less than 25 ml, usually between 5^{th} and 10^{th} day.

3. Results

The mean age at presentation is 53 years (range 32-75yrs). The most common site of tumour was upper outer quadrant (33 cases/75) while multicentric tumour was seen in 18 cases. 11(33.3%) of 33 cases in upper and outer quadrant had positive level III nodes and in cases with multicentricity 9 (50 %) cases showed level III positive nodes. Though 50% of tumours presened as T2, increase in level III positivity is noted with an increase in size of the tumour at presentation. These results didn't reach level of statistical significance (p> 0.05). Nodes when palpable in level I and II nodes intra-operatively, the histologically positive level III nodes rises to 61.5% cases while when palpable in all the three levels there was 100% positivity of level III nodes. The relation between study parameters and the level 3 nodes is indicated in Table 1 and 2. It is seen that with higher grades of tumor pathology, the incidence of positive level III nodes increases. It was seen in 30.7% cases of well differentiated tumor while poorly differentiated had positivity in 42% of cases. Number of histologically positive nodes less than 4 at level I and II shows decrease in the level III positivity Either of these result didn't not find statistical significance. Presence of LVI in primary was seen in 30% cases (24). A significant observation made was 50% (12/13) cases with LVI in primary and palpable axilla showed involvement of level III axilla while only 32% of LVI negative cases were found to have positive level II nodes (p=0.036). Extranodal extension as suggested by nodes clung to other nodes or fat at level 1 or 2 appears to be associated with positive nodes at level III.23 of 25 patients with ENE at level 1 or II had positive lymphnodes at level III. While 16 of 50 patients with no ENE had levelII lymphnodes (p<0.0001). The oestrogen receptor (ER) and progesterone receptor (PR) negativity correlates significantly with level III node positivity. Of 25 patients of level three positive axilla, 23 (92%) were ER negative, and 22 (88%) were PR negative (p <0.0001 and 0.001 respectively). While the Herceptin receptor status and positive level III axilla shows non significant relation (p=0.260). Chart 1 indicates relation between receptor status and level III node positivity.

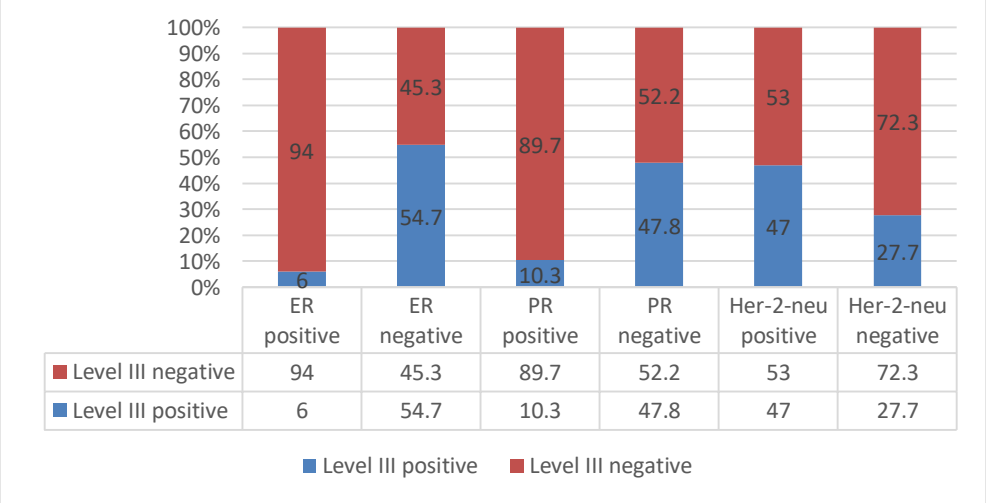

Chart 1: Relation between receptor status and level III node positivity.

Parameter	Positive level III nodes	Negative level III nodes
Quadrant location of primary:		
Upper outer	11	22
Upper inner	2	8
Lower outer	3	9
Lower inner	0	2
Multicentric	9	9
x^2= 4.43	p= 0.352	not significant
Stage of tumour:		
T1	1	2
T2	14	36
T3	10	12
x^2= 2.09	p= 0.351	not significant
Grade of tumour:		
Well differentiated	4	9
Mod. differentiated	8	21
Poor differentiated	13	18
x^2= 2.5	p= 0.475	not significant
Number of positive nodes:		
Level I (more than 4/less than 4)	17/06	Aug-15
Level II (more than 4/less than 4)	09/12	10-Oct
x^2= 1.81/2.98	p= 0.179/0.043	not significant for more than 4/ significant for less than 4
Lymphovascular invasion:		
Yes	12	12
No	13	38
x^2= 4.41	p= 0.036	**significant**
Extra-nodal extension:		
Yes	23	16
No	2	34
x^2= 24	p< 0.0001	**significant**
Oestrogen receptor status (ER):		
Positive	2	31
Negative	23	19
x^2= 19.7	p< 0.0001	**significant**
Progesterone receptor status (PR):		
Positive	3	26
Negative	22	24
x^2= 11.2	p< 0.001	**significant**
Herceptin receptor status (Her-2-neu):		
Positive	8	9
Negative	15	39
x^2= 2.6	p= 0.260	not significant

Table 1: Relation between clinicohistochemical parameters and level III node positivity.

Size	Level -III positive LNs [n=25]		Level -III Negative LNs [n=50]		Total [n=75]	Chi-square Value	P-value
	No	%	No	%			
Level 1	8	19.5	33	80.5	41	24	P<0.0001 S
Level 2	0	0	1	100	1		
Level3 (Skip metastasis)	1	100	0	0	1		
Level 1,2	8	61.5	5	38.5	13		
Level 1,2,3	8	100	0	0	8		
Level 2,3	0	0	0	0	0		
Level 1,3	0	0	0	0	0		

Table 2: Relation between intraoperative palpability and level III node positivity.

(S: Significant at $p<0.05$, NS: Not Significant $p\geq 0.05$)

4. Discussion

The mean age of present study was comparable with similar studies like Chua et al and others [5-8]. The most common site of tumour was upper outer quadrant. However, the location of the primary tumour or multicentricity was not found to be a risk factor for level III node involvement. Dillon et al suggested size of primary tumour to be most commonly 2 to 5cm [9]. It was seen that only 24 cases (32%) had no postoperative nodal involvement (N_0 cases); thus, the efficacy of a clinicopathological examination in determining a positive axilla is 68%. The present study showed high percentage of level III nodal involvement comparable to similar studies indicating a delay in presentation of cases. The involvement of axilla in the level III was observed to be varied by different authors. While Yildrim et al. found level III involvement as low as 2%, other authors like Sabahattin et al and Joshi et al had 32% and 27% respectively, we concur withlatr at 33%. Involvement of less than 4 nodes at levels I and II have shown a non-significant involvement of level III nodes [5]. Post-operative histopathological poor differentiation was seen in majority cases as per Joshi et al and Chua et al; in concordance with present study while others showed larger percentage of moderate differentiation [5-9]. Except Fan et al. all studies including the present indicated an inverse relation between pathological grade of tumour and level III involvement. Studies show that LVI and ENE are present in more than 50% (except Yildrim et al. which showed ENE in less than 50% cases) of the tumours indicating the severity of tumour. All the similar studies (except Chua et al) showed positive correlation between size of tumour, LVI and level III nodal involvement [5-9]. Joshi et al in coherence with present study indicated a significant correlation between ENE and level III positivity. ER/PR status was seen to be positive and Her-2-neu was negative in majority cases as per Chua et al. Yildrim et al and Sabahattin et al. which was in gross contradiction to present study.A direct relation was seen between ER/PR positivity and Her-2-neu negativity with level III positivity in multiple studies including the present study. The uniqueness of the

study lies in the inclusion of intraoperative assessment of the axillary nodes at various levels. The presence of palpability at any level of axilla showed a significant involvement of level III nodes (61.5% at level I/II and 100% at level III) thereby, marking a poorer prognosis.

5. Conclusion

We conclude that about 55% patients withlevel I and level II nodal burden run the risk of having residual disease in the axilla after surgery if level III is not addressed. We conclude that routine axillary clearance up to level III in node positive axilla and especially when lower level axillary nodesare involved. The grades of primary tumour are not significantly associated with level III metastases. It can be inferred that size of primary tumour (T) is a risk factor for level III metastases.T1 lesions need further evaluation with respect to level III lymph node metastases. Lympho-vascular invasion and extra-nodal extension are significantly associated with level III lymph nodes metastases. The negative receptor status of ER-PR and Her-2-neu corelates with probability of level III axillary metastasis, particularly when combined with other risk factors of it. Significance of Her-2-neu receptor status could not be confirmed as risk factor for level III lymph nodes metastases. Careful intraoperative assessment of different levels of axillary lymph nodes gives an idea about the need to further axillary dissection.Axillary involvement and thus the need for additional loco-regional treatment can be predicted from the patients' clinicopathological characteristics.

Declarations

Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

Authors possess written informed consent of the patients and an ethics committee approval letter which may be produced if required.

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