

Original Research Article

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Evaluation of axillary lymph node metastasis in relation to size and metastatic status of sentinel lymph node in carcinoma breast

Vineet Kumar Pandey¹*, Deepak Ghuliani¹, Sushanto Neogi¹, Nita Khurana², R. K. Jindal¹

¹Department of Surgery, ²Department of Pathology, Maulana Azad Medical College, New Delhi, India

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***Correspondence:**

Dr. Vineet Kumar Pandey,
E-mail: drvineetkp@gmail.com

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ABSTRACT

Background: Sentinel lymph node (SLN) is the first node in the nodal basin of a tumor and the most likely site for earliest lymph node metastasis. Modified radical mastectomy with axillary lymph node dissection (ALND) has been the standard of care for carcinoma breast. The SLN is the only involved node in majority (40-70%) of the patients undergoing ALND for a positive SLN biopsy. ALND is associated with significant morbidities like seroma, infection, lymphedema and nerve injury. The purpose of this study was to evaluate the axillary node metastasis with respect to the size and tumoral load of positive SLN.

Methods: Thirty patients of biopsy proven early breast carcinoma underwent SLN biopsy with methylene blue dye followed by modified radical mastectomy (MRM). After measuring the size of the SLN with Vernier caliper, SLN and MRM specimen were sent for histopathological examination. Status of non-sentinel ALNs was compared with the size and tumoral load of SLN.

Results: Among 30 patients, 5 patients had positive SLN. Patients with positive SLNs were younger (mean 36 vs. 52 years), had larger diameter (10.8 vs. 7.4 mm, $p<0.03$) with higher number of non-sentinel ALN metastasis (35% vs. 4.86%). Macrometastasis in positive SLN was associated with higher risk of metastasis to non-sentinel ALNs.

Conclusions: A SLN size of more than 7.5mm has higher risk of harboring metastasis. A SLN size higher than 10mm and macrometastasis is associated higher risk of metastasis to non-sentinel ALNs.

Keywords: Carcinoma breast, Sentinel lymph node biopsy, Axillary lymph node dissection, Macrometastasis

INTRODUCTION

The surgical management of breast cancer has undergone substantial transformation over the years from radical mastectomy to lumpectomy, lymph node dissection and irradiation in appropriately selected patients. The approach towards a more conservative surgical management without compromising cure is also being applied to the management of ALNs.

The SLN is the first node in the nodal basin of a primary tumor and a likely site for the earliest lymph node metastasis.¹ ALN dissection was previously the routine

procedure for axillary node staging but it is associated with significant morbidities like lymphedema, nerve injury, infection and seroma formation which hamper the quality of life.

The very high negative predictive value of SLN biopsy in staging patients with clinically node-negative breast carcinoma allows almost 40% to 70% of patients to be spared of ALN dissection and its associated morbidities.² Conversely, in case of a positive SLN biopsy, the standard of care remains completion ALN dissection for a more accurate staging.

The status of axillary lymph nodes is one of the most important prognostic factors in patients with breast carcinoma. Sentinel lymph node is the axillary node most likely to harbor metastasis as it is the first node in the nodal basin of a tumor. It not only provides important staging information but also helps in planning with subsequent management. More is the number of SLNs removed more is the likelihood of having removed lymph nodes which otherwise would have been part of axillary lymph node dissection. After surgery, the requirement of adjuvant chemo/radiotherapy is also guided by the status of the axilla.

Several clinicopathological factors like tumor size, tumoral burden, lymphovascular invasion have been studied to predict the involvement of axillary lymph nodes in patients with a positive SLN.^{3,4} However, the size of tumoral burden in SLN has been found to be one of the strongest predictor of axillary metastasis. In particular, patients with macrometastatic SLN (metastasis size >2 mm) are at significantly higher risk of axillary metastasis than patients with micrometastatic SLN (45-79% vs. 13-24%).⁵⁻⁷ In light of this background, the purpose of this study was to determine the relationship between ALN metastasis with the size and tumoral load of sentinel lymph node.

METHODS

Thirty patients of biopsy proven and clinically node negative early breast carcinoma were included in this study conducted from November 2016 to November 2018 at Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi.

Inclusion criteria

Inclusion criteria were all female patients of early carcinoma breast who underwent modified radical mastectomy.

Exclusion criteria

Exclusion criteria were any N2, N3 disease; Stage IV carcinoma breast; patients with prior history of axillary surgery; patients who have received prior radiotherapy; patients who have received prior neo-adjuvant chemotherapy.

After induction of general anesthesia, cleaning and draping was done. Before raising the flaps for mastectomy 5 ml of methylene blue dye (1%) was injected peritumorally and breast massage was given for 5 minutes in order to stain the node. After this, skin incision was given over axilla and axilla opened by meticulous dissection. Thereafter, the blue lymphatics were identified and traced to the node(s) which had taken up the blue dye. Excision biopsy of the sentinel lymph node was done. This was followed by standard procedure of modified radical mastectomy.

The dimensions (length, breadth and height) of isolated SLN(s) were measured with Vernier caliper and then dipped in a formalin container. The isolated SLN and MRM specimen were marked separately and sent for histopathological examination (HPE). During histopathological examination, immunohistochemistry (IHC) of positive sentinel node was done to look for tumoral load (micrometastasis/macrometastasis/isolated tumor cells). The size of metastatic focus in sentinel lymph node was classified as:⁸

- Macrometastasis- size of metastasis >2 mm.
- Micrometastasis- size of metastasis >0.2 mm but not more than 2 mm and/or >200 cell (pN1mic in AJCC).
- Isolated tumor cells- size of metastasis <0.2 mm and or ≤200 tumor cells.

The non-sentinel axillary nodes included in the MRM specimen were examined for metastatic focus. The total number of axillary lymph nodes and number of metastatic nodes in the axilla were recorded. The recorded data was analyzed using SPSS version 17.

RESULTS

There were 34 patients of early breast carcinoma who underwent MRM but SLN could be isolated in 30 patients, only those were then included in the study. The mean age of the patient was 49.5 years with a range of 39 to 87 years. Sixteen patients (53%) had left breast cancer and 14 patients (47%) had right breast cancer. The tumor was located in upper outer quadrant in 18 patients, in upper inner quadrant in 6 patients, in lower outer quadrant in 4 patients and in lower inner quadrant in 2 patients. 12 patients were hormone (ER/PR) positive while 18 patients were hormone negative. Similarly, 8 patients were Her-2 positive and 22 patients were Her-2 negative. The mean number of SLNs isolated was 1.4 with a range of 1-4. The mean diameter of positive SLN was 10.8 mm with a range of 7-14 mm while that of negative SLN was 7.4 mm with a range of 5-9 mm (Table 1).

The mean number of ALNs isolated was 12.4 with a range of 9-18. In patients with positive SLN, 35% of the non-sentinel ALN were found to be metastatic while in patients with negative SLN only 4.86% of the ALNs were positive for metastatic focus.

The mean number of SLN isolated was 1.8 with a range of 1-4. SLNs were isolated in 30 patients but only 5 patients had positive SLN (16.6%). Among these 5 patients, 4 had macrometastasis and 1 had micro-metastasis in the positive SLNs. The mean size of the positive SLN was 10.8 mm with a range of 7-14 mm while the mean size of negative SLN was 7.4 mm with a range of 5-9 mm (Table 2).

Table 1: Clinicopathological data of the cases.

Clinicopathological data of the patients	
Age (years)	
Mean	49.5
Range	35-87
Side	
Left breast	16 (53%)
Right breast	14 (47%)
Location	
Upper outer	18 (60%)
Upper inner	6 (20%)
Lower outer	4 (13%)
Lower inner	2 (7%)
ER/PR status	
Positive	12
Negative	18
Her 2-neu status	
Positive	8
Negative	22
SLN variables	
No. of SLN isolated	
Mean	1.8
Range	1-4
Size of SLN (mean diameter in mm)	
Positive SLN	10.8 (7-14)
Negative SLN	7.4 (5-9)

Table 2: Comparison of SLN size with its metastatic status.

	Status of SLN			P value			
	Negative (n=13)		Positive (n=2)				
Size of SLN (mm)	Mean±SD	Min-Max	Median	Mean±SD	Min-Max	Median	
7.40 ±1.50		5.0-9.0	8.0	10.8±4.95	7.0-14.0	10.50	0.03

Table 3: Comparison of ALN status with the status of SLN.

SLN status	Size of SLN (mean size)	ALN status		P value
		Positive	Negative	
Positive	10.8mm	35%	65%	
Negative	7.4mm	4.86%	95.14%	

In patients with positive SLN, the mean size of SLN was 10.8 mm and 35% dissected non-sentinel ALNs were harbouring metastasis. In patients with negative SLN, the mean size of SLN was 7.4 mm and only 4.86% dissected non-sentinel ALNs were harbouring metastasis (Table 3).

The percentage of metastatic non-sentinel ALNs was 40%, 10% and 4.86% in patients with macrometastasis, micrometastasis and negative SLN respectively.

DISCUSSION

The incidence of breast carcinoma continues to rise worldwide and in India as well which is evident by the

fact that it has become the most common cancer in Indian females.⁹ Traditionally surgical management in the form of modified radical mastectomy has been the standard treatment of breast carcinoma to ensure complete removal of the disease. Other surgical procedures like wide local excision or breast conservation surgery can be done in early breast cancer patients.

The status of axillary lymph nodes is one of the most important prognostic factors in patients with breast carcinoma. Sentinel lymph node is the axillary lymph node most likely to harbor metastasis as it is the first node in the nodal basin of a tumor. It not only provides important staging information but also helps in planning with subsequent management. After surgery, the requirement of adjuvant chemo/radiotherapy is also guided by the status of the axilla. In modified radical mastectomy, a complete axillary dissection up to level II axillary lymph nodes is usually performed. However, axillary dissection is associated with considerable morbidities like lymphedema, seroma formation, infection etc. This can be avoided by doing sentinel lymph node biopsy and then tailoring the management

according to the status of sentinel lymph node i.e. modified radical mastectomy with or without axillary lymph node dissection or breast conservation surgery.

In our study SLN biopsy was done in 34 patients using methylene blue dye but SLN could be isolated in 30 patients only with an identification rate of 88%. SLN could not be isolated in 4 patients. This might be due to higher regional immunological activity as lymph node size is also influenced by immunological activity and inflammation. Only these 30 patients were included in the study. We reviewed the published data comparing SLN localization using different techniques. The identification rate with methylene blue dye alone was 77-88%, with isosulfan blue alone 85-93%, with radio-isotope alone 92% and when combination of dye method and radio-isotope method was employed the localization rate increased to 93-98%.¹⁰⁻¹² The combined method has higher identification rate due to detection of 'hidden' sentinel lymph nodes through probe directed mapping, in addition to those detected by the dye alone. In the present study we have achieved comparable identification rate using methylene blue dye alone (88%).

The risk of metastasis to non-sentinel axillary lymph nodes increases with the involvement of SLNs by tumor cells. This holds true for our study as the percentage (35%) of positive axillary nodes is substantially higher in patients with positive SLN. This is because there exists an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin. In patients with negative SLN only 4.86% non-sentinel axillary lymph nodes were positive.

Another important factor predicting the risk of metastasis in non-sentinel axillary lymph node is the tumoral load of positive SLN. Viale et al demonstrated that as the tumoral load in positive SLN increases the risk of non-sentinel axillary node metastasis also increases.¹³ In our study, positive sentinel lymph nodes were isolated in five patients, four of which had macrometastasis and one had micrometastasis on IHC examination. These patients also had metastasis in the non-sentinel axillary lymph nodes. Correlation between axillary status and ITC could not be established in this study as no ITC was isolated in any of the positive sentinel lymph nodes.

In general, it is thought that lymph node size is associated with increased immune activity and immune system plays a critical role in fighting cancer. In cancer patients, lymphadenopathy is often associated with an increased likelihood of lymph node metastasis.¹⁴ In this study we have also tried to correlate the size of isolated positive SLN with the risk of metastasis to non-sentinel axillary nodes so that we may be able to determine the "cut-off" size of a positive SLN below which ALND can be safely omitted obviating the need of its histopathological examination. The mean size of negative SLN was 7.4 mm with a range of 5-9 mm while the mean size of positive SLN was 10.8 mm with a range of 7-14 mm with a p

value of 0.03. It was noted that bigger is of SLN, greater is the chance of it harboring metastasis. Patients with mean size of positive SLN >10 mm are more likely to have metastasis in non-sentinel axillary lymph node (35%) as demonstrated in our study. It was also observed that patients with SLN size of 7-10 mm and with macrometastasis on IHC had metastasis in non-sentinel lymph nodes as well. We reviewed literature for correlation between the size of SLN and risk of metastasis in non-sentinel axillary lymph nodes but no such study has been done till date for breast carcinoma

CONCLUSION

In this study, we found that the size of SLN correlates with the risk of axillary metastasis. SLN size of more than 7.5 mm has high risk of harboring metastasis. Metastasis to non-sentinel ALN is higher when SLN size is more than 10mm. SLN size between 7-10 mm with macrometastasis has higher chance of metastasis to non-sentinel ALN. In patients with positive SLN, there is higher percentage of non-sentinel ALNs being positive (35%) compared to patients with negative SLN (4.86%).

A more conservative surgical approach to the axilla limited only to SLND with or without biopsy or limited dissection of ALNs in the vicinity of SLN may be adopted in patients with low risk of non-sentinel ALN metastasis. Since the sample size of our study was relatively small, a larger study with higher number of patients would be required to validate the association between size of SLN and its tumoral load with the risk of axillary metastasis.

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