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Original Research Article

Study of targeted four node sampling of axilla in management of carcinoma of breast

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ABSTRACT

Background: Axillary lymph node sampling is considered as one of the most pivotal investigations in determining the lymph node status in management of carcinoma breast. The present study attempts to assess sensitivity, specificity and positive predictive value of axillary four node sampling (FNS) in management of carcinoma of breast, and its efficacy in downstaged patients.
Methods: A total of 35 patients, node negative operable cases of carcinoma breast and locally advanced breast cancer (LABC) patients downstaged after 3 cycles of neoadjuvant chemotherapy, were enrolled. Lymph node mapping was done by injecting 3 - 5 ml of methylene blue dye, just before surgery. Level 1 lymph nodes stained by methylene blue were sampled and axillary dissection was carried out, level 3 lymph nodes were identified and sampled, rest of the axillary dissection specimen was sent as a separate sample for histopathological examination , node positivity was compared in level 1 and level 3 , and conclusions were drawn.
Results: The sensitivity, specificity for FNS in node negative operable cases were found to be 83.33% and 91.3% respectively. The negative and positive predictive value were found to be 95.40% and 71.42% respectively. Specificity of FNS in LABC downstaged patients was found to be 40%.
Conclusions: Targeted four node sampling using methylene blue dye can be considered as an alternative method for sentinel lymph node. Further study should be conducted to establish it as a reliable method for axillary lymph node staging.

Keywords: Carcinoma of breast, Four node sampling of axilla, Methylene blue

INTRODUCTION

Breast cancer is a malignant tumour arising from epithelial cells of glandular milk ducts or lobules of the breast. Breast carcinoma is classified as either non-invasive (carcinoma in situ) or invasive, depending on whether or not the tumour has started to grow outside the basal membrane. Majority of breast carcinomas arise from epithelial cells of the ducts, called ductal carcinoma, and less frequently from the lobules, called lobular carcinoma.

Breast cancer is the most common cancer in women both in developed and less developed world. Although breast cancer is thought to be a disease of developed world, almost 50 % of breast cancer cases and 58 % of deaths occur in less developed world.[1,2]

The incidence rate of breast cancer is steadily increasing worldwide, and vary almost four-fold across world regions, where the rate ranges from 27 per 100,000 in Middle Africa and Eastern Asia. Its incidence is constantly rising in urban India. This can be due to

differences in age distribution, diet, lifestyle, ethnicity, genetic background and other breast cancer risk factors between populations. The pattern of Indian disease is different from its Western counterpart; the incidence has two distinct peaks. The first peak occurs in young patients in their 30s and 40s.

Clinical examination and the use of imaging techniques to assess the node status are not reliable enough procedures because of the high rates of false positive and false negative results. Histopathological assessment has rather been considered the gold standard for the evaluation of lymph nodes. However, there are numerous ways to assess the axillary lymph nodes, depending on the surgical procedure performed and the histopathological tools used. Complete axillary dissection and the routine histopathological work up of a minimum of 10 to 11 nodes was once the standard staging and therapeutic procedure, but several alternative ways have been studied to reduce possible complications of the dissection and to spare the increasing proportion of patients without axillary metastases.[3]

Since axillary lymph node involvement is the most important prognostic marker of outcome, and important prognostic factor for breast cancer till now, axillary lymph node addressal/dissection has been considered an essential component of breast cancer management. So, standard surgical care is the resection of the primary tumor (mastectomy or breast-conserving surgery) with axillary lymph node dissection (ALND). There is potentially significant morbidity, although no mortality following conventional or modified ALND. The important and common complications associated with ALND are seroma, wound infection resulting in delayed wound healing, restriction of shoulder movement, intercostobrachial nerve syndrome (paraesthesia of the axilla, shoulder and upper arm), lymph edema predisposing to cellulitis, rarely lymphangio-sarcoma.

The alternative available for ALND are sentinel lymph node biopsy and axillary sampling (AS). Sentinel lymph node biopsy requires gamma camera and radioactive agent, hence being a costly method is not affordable at most centres. AS entails the removal of a sufficient number of suspicious lymph nodes with the aim of detecting the presence of lymph nodal metastasis.

Sentinel lymph node biopsy has been incorporated into standard guidelines as an appropriate initial alternative to routine staging ALND for patient with early stage breast cancer with clinically negative axillary lymph nodes. The early validation of sentinel node biopsy (SNB) procedure has been based on multiple small studies with variable identification rates, accuracy and false negative rates. However high cost of gamma probe and need for radio-colloid have limited its widespread acceptance in developing countries. Many centres in UK, and Japan have tested and adapted, as an alternative to targeted SNB, 4 node axillary sampling as standard procedure for axillary prediction in clinically node negative operable breast cancer. The anatomically defined, low axillary sampling ensures the procedure is less subjective more standardized and uniform with low inter-observer variability. Low axillary sampling will be performed in this thesis work for predicting axillary nodal metastasis in operable breast cancer by completing ALND in all cases.[3,4]

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The aim of this study was to assess the role of targeted four node sampling (FNS) in axillary mapping in operable breast cancer to find an inexpensive solution for the developing countries.

METHODS

Patients admitted in tertiary health care centre were included in the study. It is a prospective hospital based analytical study. The present study was carried out in department of general surgery of our institution from July 2016 to November 2018. The sample size was calculated using the reference values from the study conducted by ICMR, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi India, wherein they have achieved a sensitivity of 89.5% of the test and considering the prevalence of the 41%, the sample size was estimated as 28 with the help of Epi info version 7 software.[6]

The study was performed after approval from Institutional Ethics Committee, Maharashtra. The procedure was performed in accordance with ethical standards and patients consent.

Inclusion criteria

All consenting patients of cytologically/histologically proved cases of ca breast with operable breast cancer (EOBC/LOBC) with clinically node negative axilla undergoing total mastectomy with axillary lymph node dissection and patients with locally advanced breast cancer (LABC) undergoing total mastectomy with axillary lymph node dissection after neoadjuvant chemotherapy.

Exclusion criteria

Nonconsenting patients, patients not undergoing surgery, patients lost to follow up, patients undergoing simple mastectomy, operable breast cancer with clinically positive axilla.

Histopathologically and cytologically confirmed cases of operable breast cancer admitted in department of surgery were enrolled in the present study. The essential work up included clinical examination, ultrasonography or

mammography imaging, a complete metastatic work up for accurate staging of the disease. Patients were also be evaluated for fitness by carrying out blood investigations (complete blood counts, kidney function tests), cardiac imaging (electrocardiogram and 2-D echocardiography).

Operative technique of targeted four node sampling which was followed was, after draping the patient, 3-5 mL of methylene blue dye was injected intradermally in the peri areolar region followed by breast massage for 5 min. After raising the superior flap, axilla was dissected and blue nodes at level-I was picked up from within the anatomical boundaries of the defined quadrangle bounded by upper intercostobrachial nerve superiorly, chest wall medially, thoracodorsal pedicle laterally, lateral border of pectoralis major anteriorly, and lateral border of latissimus dorsi laterally. Blue nodes from the above-mentioned quadrangle were sampled and sent for histopathological examination. Meanwhile, MRM and conventional ALND (up to Level III) was completed and this specimen was sent in a separate container for final histopathological examination. The final histopathology reports of rest of the axilla were compared with the sampled blue nodes to assess the sensitivity/specificity and positive predictive and negative predictive value of the technique.

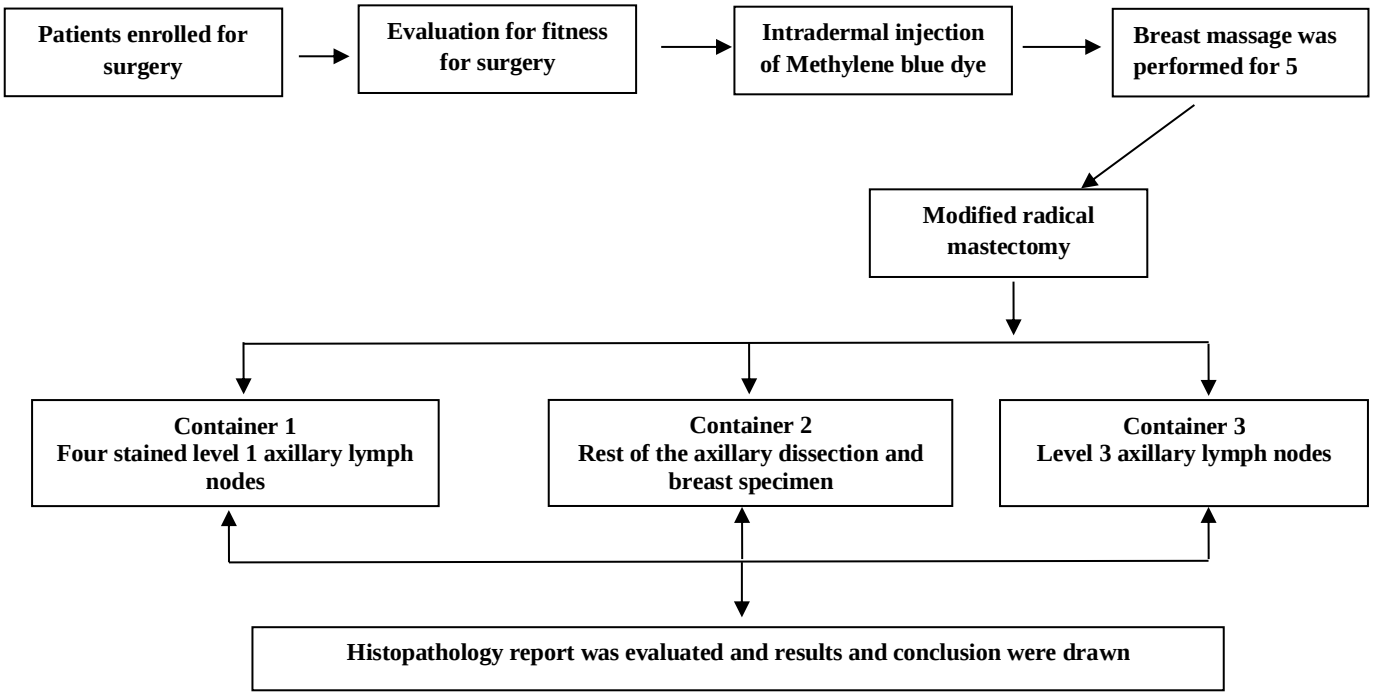

Figure 1: The protocol followed for the work.

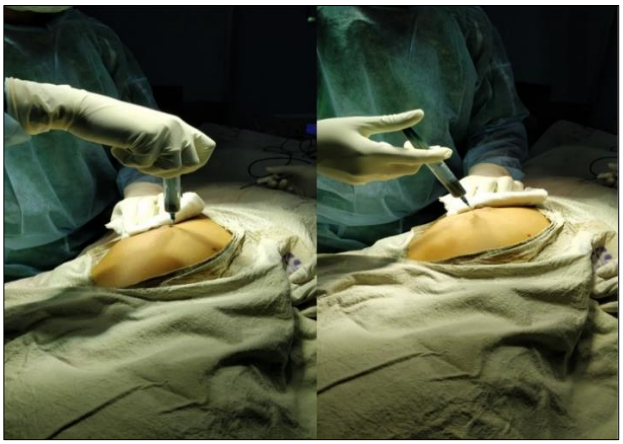

Figure 2: Pre-operative instillation of methylene blue dye in sub areolar plexus.

Figure 3: Intra operative stained blue level I axillary lymph node and dissected level I axillary lymph node (FNS).

RESULTS

The present study was conducted under department of general surgery, the 34 cases who fulfilled the inclusion criteria of carcinoma breast admitted in the department indoor wards, were included in the study.

FNS in comparison with rest level III lymph nodes

In the present study, it was observed that, 10 patients had four node sampling positive for malignancy, out of these level III lymph nodes were positive in 5 patients i.e. 50 % of patients. At the same time, four node sampling was negative in 24 patients, out of these in, level 3 lymph nodes were found to be negative in 23 patients i.e. 95.83%. FNS was negative, but level 3 lymph node was positive was observed only in 1 patient.

Table 1: FNS validation as compared with rest of the axilla (n=34).

FNS	Level III lymph nodes		Total
	Positive	Negative	
Positive	5	5	10
Negative	1	23	24
Total	6	28	34

It was observed that, level III lymph nodes were positive for malignancy in 6 patients out of these, 5 patients four node sampling was also positive for malignancy, hence the sensitivity of four node sampling method to diagnose the metastasis is found to be 83.33%. while level III lymph node were negative for malignancy in 28 patients out of these, 23 patients four node sampling was also negative for malignancy, hence the specificity was observed to be 82.14%, It was observed that, positive predictive value of 50% and negative predictive value of 95.83%. Hence overall diagnostic accuracy of FNS in the present study was observed to be 82.35% (Table 1).

Operable breast cancer with clinically node negative axilla

Among the operable breast cancer with node negative axilla, in whom four node axillary sampling was performed, It was observed that, level III lymph nodes were positive for malignancy in 6 patients out of these, 5 patients four node sampling was also positive for malignancy, hence the sensitivity of four node sampling method to diagnose the metastasis is found to be 83.33%. while level III lymph node were negative for malignancy in 23 patients out of these, 21 patients four node sampling was also negative for malignancy, hence the specificity was observed to be 91.30%, It was observed that, positive predictive value of 71.42% and negative predictive value of 95.45%. Hence overall diagnostic accuracy of FNS in the present study was observed to be 89.65% (Table 2 and 3).

Table 2: FNS as compared to level III axillary lymph nodes in operable breast cancer with clinically node negative status (n=29).

Four node sampling	Level III lymph nodes		Total
	Positive	Negative	
Positive	5	2	7
Negative	1	21	22
Total	6	23	29

Table 3: Diagnostic accuracy of FNS compared in total number of study patients and operable breast cancer with clinically node negative status.

Diagnostic accuracy parameter	Values (%) (n=34)	Values (%) (n=29)
Sensitivity	83.33	83.33
Specificity	82.14	91.30
Positive predictive value	50	71.42
Negative predictive value	95.83	95.40
Diagnostic accuracy	82.35	89.65

Table 4: FNS as compared to level III axillary lymph nodes in LABC patients after downstaging (n=5).

FNS	Level III lymph nodes		Total
	Positive	Negative	
Positive	-	3	3
Negative	-	2	2
Total	-	5	5

Downstaged patients after chemotherapy

In the present study, four node sampling was also performed in locally advanced breast cancer patients, after been downstaged by chemotherapy and radiotherapy we observed that total patients were 5 downstaged. Among the down staged patients only specificity could be calculated. Specificity recorded in the study is 40% (Table 4).

DISCUSSION

Breast cancer incidence rates are increasing worldwide. In India, it is the most common cancer among women in many regions and has overtaken cervix cancer, which was the commonest cancer a decade ago. Axillary lymph node dissection is an important factor which determines the prognosis and help in staging of the disease. In our study we evaluated the efficacy of four node sampling of axilla as a reliable alternative to SLNB, as resources required for SLNB are seldom available in rural setup.

In the present study, we assessed the histopathological findings of level I lymph nodes. We observed that 29.41% cases found positive for level I lymph nodes and 24 cases (70.58%) were negative. And in histopathological findings of level III lymph nodes

(axillary specimen) we observed that 17.64% cases found positive for level III lymph nodes and 28 cases (82.35%) were negative. Our study had the following findings (Table 5).

Table 5: FNS validation as compared with rest of the axilla in present study.

FNS	Rest of axilla		Total
	Positive	Negative	
Positive	4	5	9
Negative	1	24	25
Total	5	29	34

In comparison with other studies, Study conducted by Tanaka et al they had observed true positive, false positive, false negative, true negative to be 58, 0, 4, 175 respectively.[5] Chintamani et al, Parmar et al, Parmar et al observed the lymph node status as follows.[6-8]

Table 6: FNS validation or axillary sampling as compared with rest of the axilla.

Four-node sampling validation as compared with rest of the axilla Chintamani et al[6]			
FNS	**Rest of axilla**		Total
	Positive	**Negative**	
Positive	28	0	28
Negative	3	19	22
Total	31	19	50
Axillary sampling validation as compared with rest of the axilla Parmar et al[7]			
Axillary sampling	Positive	Negative	Total
Positive	42	62	104
Negative	10	241	251
Total	52	303	355
Axillary sampling validation as compared with rest of the axilla Parmar et al[8]			
Axillary sampling	Positive	Negative	Total
Positive	41	104	145
Negative	17	311	328
Total	58	415	473

Four node sampling

In the present study, the cases were subjected for FNS, in which 26% cases were found positive for level 1 lymph nodes. However, when we sampled level 3 lymph nodes and subjected them for histopathological examination, we observed that 5 cases out of them were found positive.

Here the sensitivity of FNS method to diagnose the metastasis is found to be 80%, while specificity was observed to be 82.75%, with positive predictive value of 44.44% and negative predictive value of 96%. Hence overall diagnostic accuracy of FNS in the present study was observed to be 82.35%. The present study observed false negative rate of 17.24%. Chintamani et al, in their study found sensitivity of FNS as 89.5%, specificity of 100%, diagnostic accuracy of 93.3%, FNR of 10.5% and negative predictive value of 84.6%.[6]

RD Macmillan et al, in their study observed that 30% cases were positive for FNS, with sensitivity of 96% and FNR of 17%. They found PPV of 86%.[9]

"Nottingham Breast Unit", studied 200 patients (T1-2/ N0) and directly compared SLNB using hot node technique (lympho-scintigraphy) with 4NAS (Edinburgh technique).[13] Sentinel lymph node was identified in 191 patients (96%) and when compared with SLNB, 4NAS failed to identify metastasis in one patient (2%). On the contrary, SLNB failed to identify metastasis in eight (14%) patients in whom 4NAS detected axillary lymph node metastasis and hence under-staged the axilla. They concluded that SLNB performed using radio labeled colloid has no advantage over 4NAS.

Steele et al, described the 4NAS as an accurate procedure when compared with ALND. Only in one AS (0.5%), they failed to identify positive nodes, after doing a randomized study of 417 patients.[3]

Table 7: Comparison with different studies as per sensitivity, specificity and FNR.

Studies	Sensitivity (%), Specificity (%)	FNR (%)
Present study	Sensitivity: 80 Specificity: 82.75 NPV: 96	17.24
Hoar et al[12]	Accuracy: 98 Sensitivity: 96	3.6
Chintamani et al[6]	Accuracy: 93.3 Sensitivity: 89.5	10.5
Macmillan et al[9]	Sensitivity: 96 PPV: 86	17
Tanaka et al[5]	Sensitivity: 92.9 Specificity: 100	6.5
Ahlgren et al[10]	Sensitivity: 97.3 NPV: 98.5	-
Parmar et al[7]	Sensitivity: 80.7 NPV: 96	-
Parmar et al[8]	Sensitivity: 70.68 NPV:93	16.6
Sato et al[13]	Sensitivity: 96 Specificity: 98	-

Ahlgren et al, reported a sensitivity of 97.3% and a negative predictive value of 98.5% for five-node biopsy, and thus proposed five-node dissection as an alternative to axillary clearance in early stage breast cancer, after performing the procedure in 415 patients.[10] Barthelmeset al, in a retrospective review comprising 312 patients

echoed the reliability of the concept of AS (average sample=eight nodes) in the management of axilla.[11]

Parmar et al reported a sensitivity rate of 80.7%, negative predictive value of 96% and accuracy of 79% for LAS to identify metastasis, and thus put forth that anatomical guided LAS as a low-cost alternative to SLNB in developing countries.[7] Parmar et al, observed that, LAS had sensitivity of 70.68%, FNR of 10.5% and NPV of 94.8%. In their study, they observed that LAS is as effective as SNB in predicting axillary nodal status.[8]

Tanaka et al, in a study (4NAS followed by ALND) of 237 patients (T1-2/N0-1) revealed that 4NAS may be as accurate staging procedure as ALND and reported an overall false negative rate of 6.5% with 4NAS.[5]

CONCLUSION

In the present study we have observed a sensitivity, specificity, positive predictive value, negative predictive value of 83.33%, 82.14%, 50%, 95.83% respectively for four node sampling of axilla amongst all the patients included in this study, which is comparable with other studies. We have observed a sensitivity, specificity, positive predictive value, negative predictive value of 83.33%, 91.30%, 71.42%, 95.45% respectively for four node sampling of axilla, among operable breast cancer patients having node negative axilla. Only specificity was observed for four node sampling of axilla in locally advanced breast cancer patients who were downstaged by chemotherapy and radiotherapy, which was 40%. The fallacy of the study is its low sample size, so further studies with larger sample size are necessary to establish four node sampling of axilla as procedure in routine use.

Four node axillary sampling is easy, non-time-consuming procedure. It has no increased financial burden or skill requirement, so it is a reasonable option as an axillary staging procedure. It would provide to be a good alternative for resource starved establishments, especially in developing and underdeveloped countries where expensive infrastructure is a luxury.

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