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A prospective audit to assess the feasibility of sentinel lymph node biopsy and/or low axillary sampling in clinicoradiologically node-negative axilla for early breast carcinoma

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ABSTRACT

Background: Sentinel lymph node (SLN) dissection was designed to minimize side effects of lymph node surgery but still offer outcomes of axillary lymph node dissection. **Aims and Objectives:** Our study is designed to determine whether SLN resection achieves the same therapeutics outcome as complete axillary dissection but with fewer side effects for node-negative axilla in clinicoradiologically operable breast cancer patients. **Materials and Methods:** Duration-based prospective observational study was carried out at the General Surgery and Surgical Oncology Department at Government Medical College and Hospital, Aurangabad with a duration of 2 ½ years from July 2019 to January 2022. A total of 36 patients of breast cancers with stages T1-T2, N0 with clinically and radiologically negative axilla from July 2019 to January 2022 duration were included in our study. **Results**: When the histopathological status of axillary lymph nodes was compared to the histopathology of SLNs it was seen that out of 36 patients, the histopathology of sentinel node was positive in 10 patients (10/36) however the rest of the axilla was positive in 6 cases and negative in 4 cases and the histopathology sentinel node was negative in 26 patients out of 36 cases (26/36) however the rest of the axilla was also negative in 24 cases and positive in 2 cases. **Conclusion:** SLN biopsy using methylene blue dye alone is a highly reliable and predictable technique to stage the axilla in breast cancer patients as this study shown a low false-negative rate (7.69%). This technique may help to avoid complete axillary lymph node dissection in sentinel node-negative patients thereby minimizing the morbidity of axillary lymph node dissection. This study demonstrates that sentinel node localization is possible with methylene blue dye alone.

Key words: Sentinel; Lymph node biopsy; Axilla; Breast carcinoma

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INTRODUCTION

Metastatic spread in breast cancer can occur through two separate pathways through the lymphatic (firstly) and hematogenous. The Greek doctor Hippocrates was the first to describe cancer.[1] Hippocrates was aware of the existence of lymphatic system and described the clinical picture of lymph node metastasis.[2] Sentinel lymph node (SLN) dissection was designed to minimize side effects of lymph node surgery but still offer outcomes of axillary lymph node dissection.[3] SLN biopsy (SLNB) is based on the concept of an orderly pattern of lymphatic drainage from a primary tumor to a regional lymph node basin. The first person known to have used the term sentinel with reference to lymph node was Braithwaite in 1923 who mentioned glands sentinel.[4] In 1970 Kett et al.,

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injected blue dye in the areola of breast and administered contrast medium in the visualized lymphatics to observe the drainage.[5] SLNB in breast cancer was first performed at the John Wayne Cancer Institute in 1991.[6,7] Our study was designed to determine whether SLN resection achieves the same therapeutics outcome as complete axillary dissection but with fewer side effects for node-negative axilla in clinicoradiologically operable breast cancer patients with evaluation of the incidence of lymph node positivity in higher levels of axillary lymph node as primary objective and evaluation of the identification rates of SLN with the usage of blue dye technique alone and its feasibility in tertiary care hospital as a secondary objective.

Aims and objectives

Our study is designed to determine whether sentinel lymph node resection achieves the same therapeutics outcome as complete axillary dissection but with fewer side effects for node negative axilla in clinicoradiologically operable breast cancer patients.

MATERIALS AND METHODS

Duration-based prospective observational study was carried out in the Department of Surgical Oncology with the collaboration of the Department of pathology, at a tertiary care center in government set up. Total of 36 patients of breast cancers with stages T1-T2, N0 with clinically and radiologically negative axilla were included in our study after obtaining written informed consent and detailed clinical history, thorough clinical examination and radiological findings with a duration from July 2019 to January 2022.

Inclusion criteria

a. Patients of early carcinoma of the breast with stage T1 -T2 with clinically and radiologically negative axilla with N0 nodal status
b. Patients with age >18 years of age.

Exclusion criteria

Patients with clinically and radiologically suspicious axillary lymph node, patients having prior breast surgery, patients having a history of blue dye allergy were excluded from our study.

Symptoms were elaborated on in detail. Age, Side, T stage of the tumor, and type of tumor were noted. Axilla was examined for palpable lymph nodes. Only patients who were clinically and radiologically negative for axillary lymph nodes were included in our study. Ultrasound examination of the axilla was done with real-time scanner with a probe head of 7.5 MHz frequency transducer. Axillary lymph nodes were reported at the time of examination as abnormal on the basis of size criteria and morphology (short-axis diameter >10 mm, cortical thickening, and lobulation or loss of the normal hyperechoic hilum). If any patient was found to have axillary lymph nodes with the above-mentioned features on ultrasonogram they were excluded from the study. SLNB was done in all selected patients modified radical mastectomy (MRM) was done with an axilla first approach. After induction of anesthesia, peritumoral injection of 1% Methylene blue dye (4 mL) at the 3, 6, 9, 12 o'clock positions was done (Figure 1). SLNs were looked for after raising the superior flap and opening the clavipectoral fascia, within 15 min from the time of injection (Figures 2 and 3). The stained nodes were removed initially and sent for histopathological examination. MRM was completed along with axillary lymph node dissection in all cases (Figure 4). The excised breast with the axillary tissue was sent for histopathological examination to correlate with the findings of the SLNB. Post-operative specimen of primary tumor was examined under hematoxylin and eosin stain after preparing paraffin sections. Tumor grade, margin, tumor thickness, vascular

Figure 1: Peritumoural injection of methylene blue dye

Figure 2: Blue node identified during the operative procedure

Figure 3: Blue stained node along with perilymphatic fat

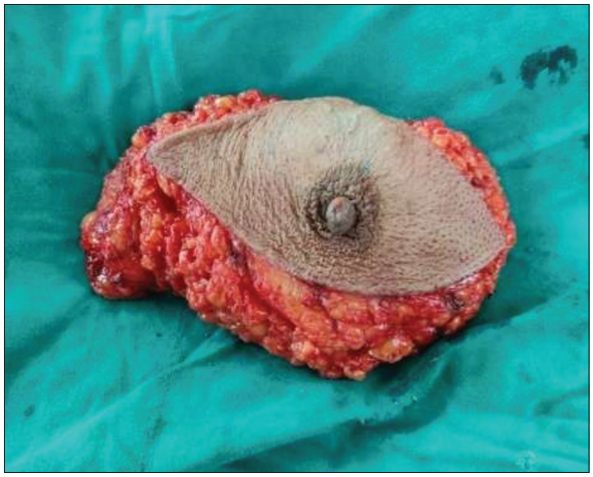

Figure 4: Modified radical mastectomy specimen

invasion, lymphatic invasion, and pathological T stage were noted. Lymph nodes of axilla were separately noted such as number of nodes harvested at each level and nodes positive for blue dye. Lymph nodes were bisectioned along the long axis and each lymph node half was examined after fixing and staining.

RESULTS

A total of 36 patients of breast cancers with stages T1-T2, N0 with clinically and radiologically negative axilla were included in our study of which majority 36% of the subjects were in 41–50 years of age group followed by 25% of the subjects were <40 years, 19.4% of the subjects were more than 60 years and 19.4% of the subjects were in 51–60 years age group. In our study right-sided lesions which were 50% were equal to left-sided lesions which were also 50%. The most common site involved was upper outer quadrant (UOQ) which was 69.4% followed by lower inner quadrant (LIQ) was 13.9%, Lower outer Quadrant was11.1% and upper inner quadrant (UIQ) was 5.6%. Majority 70% of the subjects had T2 staging and 30% of the subjects had T1 staging. According to histopathology of sentinel node, 27.8% of the subjects were positive and 72.2% of the subjects were negative for SLN. 70% of the subjects had 1 sentinel node positive, 20% of the subjects had 4 sentinel node positive, 10% of the subjects had 6 sentinel node positive. According to histopathology of axilla, 22.2% of the subjects were positive and 77.8% of the subjects were negative for axillary lymph node. When the histopathological status of axillary lymph nodes was compared to the histopathology of SLNs it was seen that out of 36 patients the histopathology of sentinel node was positive in 10 patients (10/36) however the rest of the axilla was positive in 6 cases and negative in 4 cases and the histopathology sentinel node was negative in 26 patients out of 36 cases (26/36) however the rest of the axilla was also negative in 24 cases and positive in 2 cases.

The sensitivity, specificity values were 75% and 85.71% respectively. The positive predictive value, negative predictive values were 60% and 92.31%, respectively. There are only 2 clinicoradiologically node-negative patients out of 36 in which histopathology of SLN was positive but the axillary lymph nodes were negative this may be due to skip metastasis or the false negative rate which was 7.69% in our study. Among the subjects who had left-sided lesion, 27.8% of the sentinel node became positive and 72.2% of them were negative while among the subjects who had right side lesion, 27.8% of the sentinel node were positive and 72.2% of them were negative. In the subjects who had LIQ position, 40% of the sentinel node were positive and 60% of them were negative while among the subjects who had LOQ position. Fifty percent of the sentinel node were positive and 50% of them were negative. In this way among the subjects who had UIQ position, 0% of the sentinel node were positive and 100% of them were negative. In the subjects who had UOQ position, 24% of the sentinel node were positive and 76% of them were negative. Among the subjects who had T1 lesion, 18.2% of the sentinel node were positive and 81.8% of them were negative. Among the subjects who had T2 lesion, 32% of the sentinel node were positive and 68% of them were negative.

DISCUSSION

The status of the axillary lymph node remains the most important predictor of survival in women with invasive breast cancer which is used for making treatment decision. Various methods of predicting axillary lymph node status have been described including clinical assessment, radiological, and operative procedures. Axillary lymph node dissection was earlier considered to be the gold standard

for predicting the axillary lymph node status which may be associated with significant morbidity. SLNB has emerged as an effective diagnostic tool in staging axillary disease. The major advantage of SLNB is the lower complication rate compared with axillary lymph node dissection. The present study was conducted to assess the feasibility of SLN localization using methylene blue dye alone.[6,7] Although number of patients included was small (n=36) it was comparable to studies done by Krag et al.,[8] (n=22) Borgstein et al.,[9] (n=33), Pijpers et al.,[10] n=34, Ikeda et al.,[11] n=29), Motta et al.,[12] (n=54), Bassi et al.,[13] (n=40).

In our study, 36 patients were evaluated with a median age of 47 years and the study group was similar to what is reported in literature. In this study, both right (50%) and left (50%) sides were equally affected. The most common site involved was UOQ which was 69.4% followed by LIQ was 13.9%, lower outer Quadrant was 11.1% and UIQ was 5.6%. The UOQ (75%) were the most common side and site of tumor location in a study by Altan Ozdemir et al.,[13] the study by Mukherjee et al.,[14] UOQ 44% was the most common site of tumor. In our study, majority 69.4% of the subjects had T2 and 30.6% of the subjects had T1 and it is compared with study conducted by Kollis et al., in which Clinical tumor status includes T2 70%, and T1 20%. In this study, clinical characteristics did not affect sentinel node identification except tumor grade and it was similar to the results observed by Nano et al.,[15] who studied clinical and histological factors associated with sentinel node identification. 70% of the subjects had 1 sentinel node positive, 20% of the subjects had 4 sentinel node positive, 10% of the subjects had 6 sentinel node positive.

According to histopathology of axilla 22.2% of the subjects were positive for axillary lymph nodes and 77.8% of the subjects were negative for axillary lymph nodes. When the histopathological status of axillary lymph nodes was compared to the histopathology of SLNs it was seen that out of 36 patients the histopathology of sentinel node was positive in 10 patients (10/36) however the rest of the axilla was positive in 6 cases and negative in 4 cases and the histopathology sentinel node was negative in 26 patients out of 36 cases (26/36) however the rest of the axilla was also negative in 24 cases and positive in 2 cases. The sensitivity, specificity values were 75% and 85.71%, respectively. The positive predictive value, negative predictive values were 60% and 92.31%, respectively. The accuracy rate was 83.33%. Sensitivity was 75% which means the ability of a SLNs to identify correctly all those who have the disease. Specificity was 85.7% which means the ability of a SLNs to identify correctly those who do not have the disease.

This study is compared with the study conducted by Krag et al.,[8] in 1998 in which 443 patient was there and sensitivity was 89%, positive predictive value was 100%, negative predictive value was 96% and false-negative rate was 11% with accuracy of 97%. This study was also compared with the study carried by Canavese et al.,[16] in 2009 with a sample size of 202 in which the sensitivity was 77%, negative predictive value was 91.1%, and accuracy was 93%.

The result of our study (sensitivity - 75%, specificity - 85.7%, ppv- 60%, npv- 92.3%, and accuracy - 83.3%) was also compared with the A Sentinella –GIVOM,[17] a randomized clinical trial on SLNB versus axillary lymph node dissection in breast cancer carried out in July 2004, in which the sensitivity was 80%, negative predictive value was 91.1% and accuracy was 80%. Sentinel node identification was higher in the age group of <50 years. Patient age was inversely correlated with the ability to identify the SLN. This finding has been reported previously and may be related to the inability of the blue dye to be taken up by the lymphatic system when injected into the fat-replaced postmenopausal breast Altan Ozdemir et al., studied 32 patients with a median age of 50. Mukherjee et al.,[14] evaluated 27 patients with a median age of 43. Among the subjects aged <50 years 40% of the sentinel node became positive and 60% of them became negative. Among the subjects aged more than 50 years 12.5% of the sentinel node became positive and 87.5% of them became negative. P=0.113, there was no statistically significant difference found between age and Sentinel node. Among the subjects who had left side lesion, 27.8% of the sentinel node became positive and 72.2% of them became negative. Among the subjects who had right side lesion, 27.8% of the sentinel node became positive and 72.2% of them were negative. P=1.00, there was no statistically significant difference found between side and sentinel node. Among the subjects who had LIQ position, 40% of the sentinel node were positive and 60% of them were negative while among the subjects who had LOQ position, 50% of the sentinel node were positive and 50% of them were negative. In this way among the subjects who had UIQ position, 0% of the sentinel node were positive and 100% of them were negative. Among the subjects who had UOQ position 24% of the sentinel node were positive and 76% of them were negative. P=0.512, there was no statistically significant difference found between position and Sentinel node. Among the subjects who had T1 lesion, 18.2% of the sentinel node were positive and 81.8% of them were negative. Among the subjects who had T2 lesion, 32% of the sentinel node were positive and 68% of them were negative. P=0.209, there was no statistically significant difference found between T staging and Sentinel node.

There were only 2 clinicoradiologically node negative patients out of 36 in which histopathology of SLN was positive but the axillary lymph nodes were negative this

may be due to skip metastasis or the false negative rate which was 7.69% in our study. Either isosulfan blue or methylene blue can be used as a dye in SLNB. Methylene blue is cheaper, more easily obtainable, and is a dye with fewer complications as compared to isosulphane blue. Hypersensitivity reactions which may also be fatal are reported at a rate of 0.6–2.5% following isosulfan blue injection. Skin necrosis, if injected intradermally, fat necrosis, and fibrosis over the injection site are among complications of methylene blue. However, in the present study, no such complications related to methylene blue were encountered. In studies conducted in our country isosulphane blue was often preferred. In the literature, there are many studies showing that methylene blue can be used safely and with high success as an alternative to isosulphane blue.

Simmons et al., have identified the SLN in 104 of 112 patients by using methylene blue and reported that SLN represented axillary status in 96.9% of patients. Bleesing et al., compared isosulfan blue and methylene blue, and found the accuracy rate as 88.5% with isosulfan blue and as 92.7% with methylene blue. In this study also sentinel node identification with blue dye alone was 100%.

In comparison other studies have reported sentinel node identification, with methylene blue dye alone, ranging from 65 to 94% (Blessing et al., Simmons et al., Nour,),[18] slightly improved rates with a combination of both radioactive colloid and blue dye (94–100%) (Table 1).

Our results indicate that SLNB can reliably predict the axilla status such that when the sentinel node is negative for metastases, axillary dissection can be safely omitted. A recent survey on SLNB distributed by the American Society of Breast Diseases Rapid Response Panel demonstrates that SLNB is considered to be the standard of care by 85% of the members who responded. It has been suggested that surgeons should demonstrate an SLN identification rate of more than or equal to 90% and a false-negative rate of <5% before they offer SLNB without completion axillary dissection.[19] However, before SLNB becomes the undisputed standard of care, randomized trials will have to show no difference in axillary recurrence and overall survival between SLNB alone and SLNB followed by axillary dissection in patients with negative sentinel node(s). Blue dye along with Tc99m mapping theoretically increases the accuracy of test but from various validation studies it was clear that the blue dye technique alone can be used when Tc99m mapping facility is not available.

Table 1: Sentinel lymph node identification with blue dye/combination methods

Study/author	Cases	SN identification rate (%)	FN rate (%)
Canavese (2009)[16]	202	97.1	6.5
Krag (1998)[8]	443	91.0	11.0
Tafra (2001)	529	87.0	13.0
SNAC	1080	94.5	5.5
NSABP-B32	5611	97.1	9.8
Almanac[2]	803	96.1	6.7
ACOSOG Z010	5283	98.7	0.3
Sentinella/GIVOM[17]	697	95.0	6.7
This study	36	100	7.69

Limitations of the study

The limitations of this study were the inclusion of small number of patients due to COVID 19 pandemic situation & consideration of micrometastasis not as per AJCC 8th edition so further study including more number of patients with consideration of micrometastasis as per AJCC 8th edition is required in future.

CONCLUSION

SLNB using methylene blue dye alone is a highly reliable and predictable technique to stage the axilla in breast cancer patients as this study showed a low false-negative rate (7.69%). This technique may help to avoid complete axillary lymph node dissection in sentinel node-negative patients thereby minimizing the morbidity of axillary lymph node dissection. This study demonstrates that sentinel node localization is possible with methylene blue dye alone.

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Authors Contribution:
AMT- Conceptualized and designed the study and collection of clinical data; **ASV-** Collection of surgical data; **BSM-** Collection and revision of pathological data and carried out the statistical analyses and prepared the tables and Figures; and all authors have contributed equally in writing the manuscript. All authors read and approved the final manuscript.

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