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USE OF METHYLENE BLUE DYE TECHNIQUE IN BREAST CANCER SENTINEL NODE BIOPSY – A NOVEL UPDATE

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ABSTRACT

Background: Axillary lymph node dissection (ALND) has been the standard treatment of breast cancer axillary staging in India. The limited facilities of radioisotope tracer and isosulfan or patent blue dye (PBD) have been the major obstacles to perform sentinel node biopsy (SNB) in our country. Hence, we studied the application of 1% methylene blue dye (MBD) alone for SNB to overcome the problem. The study's main goal is to assess the identification rates and negative predictive value (NPV) of SNs in predicting axillary metastases using only 1 percent MBD.

Methods: This prospective study enrolled 108 patients with suspicious malignant lesions or breast cancer stages I–III. SNB was performed using 2–5 cc of 1% MBD and proceeded with ALND. The histopathology results of sentinelnodes (SNs) were compared with axillary lymph nodes (ALNs) for diagnostic value assessments.

Results: There were 96 patients with invasive carcinoma from July 2020 to September 2021 at Dr.D.Y.Patil Hospital and Research Centre , Pimpri , Pune who were included in the final analysis. The median age was 50 (25–69) years, and the median pathological tumor size was 3 cm (1–10). Identification rate of SNs was 91.7%, and the median number of the identified SNs was 2 (1–8). Sentinel node metastasis was found in 53.4% cases and 89.4% of them were macrometastases. The negative predictive value (NPV) of SNs to predict axillary metastasis was 90% (95% CI, 81–99%). There were no anaphylactic reactions, but wefound 2 cases with skin necrosis.

Conclusions: The application of 1% MBD as a single technique in breast cancer SNB has favorable identification rates and predictive values. It can be used for axillary staging, but nevertheless the technique should be appliedwith attention to the tumor size and grade to avoid false negative results.

Keywords: Sentinel node, Breast cancer, Axillary lymph node, Methylene blue dye

BACKGROUND

Breast cancer is one of the most common cancers in India[1]. Axillary lymph node (ALN) metastases is one of the most important prognostic variable[2]. Breast cancer treatments have shifted to conservation therapy in recent years, and sentinel node biopsy (SNB) has been included in minimally invasive breast surgery [3, 7]. Morton et al. [8] work in cutaneous melanoma was a watershed moment in the sentinel node (SN) concept's acceptance. It was quickly adopted to locate SNs in breast cancer patients using isosulfan blue dye or a radioisotope tracer alone. Several studies have been undertaken to verify 1 percent methylene blue dye (MBD) for SNB as an alternative. Simmons [14] was the first surgeon to report the use of 1% MBD in the treatment of breast cancer SNB. Other studies [15–22]also endorsed its usage as well, citing positive outcomes in terms of identification and false negative rates, as well as less allergic problems and cheaper costs. The biggest issue with performing SNB in India is the lack of access to PBD and radioisotope tracer which will be addressed by using MBD alone. The study's main goal is to assess the identification rates and negative predictive value (NPV) of SNs in predicting axillary metastases using only 1 percent MBD.

MATERIALS AND METHODS

Between Jan 2020 and September 2021, 108 patients with a diagnosis or a suspected malignancy of breast were prospectively enrolled at Dr. D.Y. Patil Hospital and Research Centre, Pimpri, Pune. There were two surgeons who took part in the study. Patients with any tumour size (T) and no palpable ALNs (cNo) who had undergone core needle or fine needle aspiration (FNA) biopsy were included. Patients who did not have final pathology results of invasive breast cancer and pregnant women were excluded. The study was authorized by the Hospital's Institutional Review Board, and all patients gave their informed consent.

1 percent MBD was administered at a dose of 2 to 5 cc in a subareolar or peritumoral region. Before lumpectomy, a separate incision in the lower axillary hairline was done to identify SNs. In mastectomy, SNB was performed through the same incision before the breast was removed. Blue nodes or lymph nodes with a lymphatic blue channel were identified as sentinels. ALND levels I–II were followed in all cases. When suspicious level II, axillary lymph node dissection level III was performed. A frozen section would be used to assess an intraoperative SN metastasis if one was available. After the surgery, the histopathological results of all ALNs were gathered.

Pathological Examination

The sentinel nodes were sectioned at a thickness of no more than 2 mm and in a straight line parallel to the long axis. The remaining SNs were formalin fixed and stained with hematoxyline-eosin in paraffin sections. The tumours were histologically identified and graded using the World Health Organization's (WHO) Histological Classification of Breast Tumors. Two pathologists reviewed all specimens at Dr. D. Y. Patil Hospital and Research Centre, Pimpri, Pune . Luminal A (ER+ and/or PR+, HER2, and histological grade 1 or 2), luminal B (ER+ and/or PR+, HER2+; or ER+ and/or PR+, HER2 and grade 3), triple negative (ER, PR, HER2), and HER2+ (ER, PR, HER2+) were the molecular subtypes for invasive cancer. The 7th edition of the American Joint Committee on Cancer (AJCC) manual was used to stage.

Statistical analysis

Descriptive data were presented in the table of frequency. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were calculated using CAT maker. Diagnostic values were reported with 95% confidence of interval (CI). We used SPSS version 16.0 to manage the data.

RESULTS

Patient characteristics

We enrolled 108 patients prospectively. 12 patients with a FNA biopsy result of suspected breast cancer were eliminated as final HPE turned negative for malignancy.

The median age was 50 years (range 25–69 years). Stage I 9(9.4%), stage II 64 (66.7%), and stage III 23 (23.9%) cases. The pathological tumour size was 3 (1–10) cm on average. The most prevalent result was invasive carcinoma of no particular type (NST) 71 (74 percent), followed by invasive lobular carcinoma (ILC) 11 (11.5 percent)

Table 1. The characteristics of patients

Patient characteristics		Number	Percentage
Age (years)	Median (range)	96	50 (25–69)
Tumor size	Median (range)	96	3 (1–10)
Pathology	NST	71	74.0
	ILC	11	11.4
	Others	14	14.6
Molecular subtypes	Luminal A	38	39.6
	Luminal B	24	25.0
	HER2 positive	10	10.4
	Triple negative	24	25.0
Surgery	Mastectomy	60	62.5
	BCS	36	37.5

Sentinel node biopsy and pathological examination

In 88 cases, we were able to find SNs. Peritumoral injections used in 29 (30.2%) patients, while subareolar injections used in 67 (69.8%). The median number of SNs identified was two (1–8), whereas the median number of ALNs was eleven (5–27). 41showed no metastases. 4 had metastases in non-sentinel nodes (NSNs) hence, the patients without lymph node metastases was 37(42%). SN metastases were found in 47 (53.4%) of the patients, while macrometastases was found in 42 (89.4%)

Table 2. Sentinel node characteristics of patients with positivemetastases (n = 47)

SN characteristic		Number	Percentage
Positive SN count	1–2	43	91.5
	>2	4	8.5
Metastasis type	Macrometastases	42	89.4
	Micrometastases	5	10.6
Patients with SNs onlymetastasis count		22	46.8
Patients with SN and NSN metastasis count		25	53.2

43 (91.5%) of SN metastases were diagnosed in 1–2 SNs, while 4 (8.5%) metastases were observed in more than 2 SNs. We found 25 patients (53.2%) with extra metastatic deposits in NSNs. As a result, the metastases occurred in SNs only is 22 (46.8%) of the individuals. The instances with positive SNs are included in Table 2. The SNs found metastases in 47 of

51 patients, with a Sensitivity of 92 percent (95 percent CI, 85–100 percent) and 4 NSN metastases in the SN negative group, with an NPV of 90 percent (95 percent CI, 81–99 percent). The median pathological tumour size in all four cases that failed to predict ALN metastases was 4 cm, with two patients in stage IIB and the others in stage IIIA. Three patients (75%) had grade 3 invasive carcinoma. The false negative patients are listed in Table 3.

Table 3: Characteristics of patients with false negative SN (n = 4)

Patient characteristics		Number	Percentage
Age (years)	Median (range)	4	44 (35–59)
Tumor size	Median (range)	4	4.0 (3.0–6.0)
Pathology	NST	4	100.0
Molecular subtypes	Luminal B	3	75.0
	Triple negative	1	25.0
Tumor grade	2	1	25.0
	3	3	75.0

Unidentified sentinel nodes

In eight patients, the SNs were not found. The patients were 54 years old on average (range 36–67 years), with a median tumour size of 2.8 (1.5–5.0) cm. There were 2 (25%) grade 1 invasive carcinomas, 3 (37.5%) grade 2 invasive carcinomas, and 3 (37.5%) grade 3 invasive carcinomas. Two individuals (25%) had lymph node metastases, whereas the others were negative.

Complications

After 5 cc of peritumoral injection, two patients developed skin necrosis surrounding the injection site. They were both mastectomies, with one having a breast reconstruction. The wounds on these patients were successfully treated with conservative methods. All of the patients had no systemic anaphylactic symptoms.

DISCUSSION

SNB has superseded ALND in terms of axillary staging, and the paradigm of early breast cancer management has shifted toward conservation treatments [27, 28]. The majority of breast cancer cases in our nation are in locally advanced stages, compared to developed countries [29]. This is why ALND has become a standard procedure among our surgeons. Since the improvement in our national health care insurance, we have been expecting to treat patients in the early stages, and this circumstance will push us to promote SNB. Although the combined technique is supported by the standard for lymphatic mapping [13, 30], restricted access to radioisotope tracers, PBD, and nuclear medicine facilities have become our roadblocks.

Several publications [17, 21, 31] used 1 percent MBD to tackle the problem of PBD limitation, with favourable results [17, 21, 31]. When compared to other studies that used MBD [14–17, 19–21], our research's identification rate of 92 percent was satisfactory. In their randomised controlled study in cutaneous melanoma, Liu et al. confirmed our findings. They discovered that MBD was just as good as isosulfan blue dye at detecting SNs [32]. Our study's median SN number of two nodes was comparable to research that indicated finding

two to three SNs to reduce the false negative rate [33–37].
The fact that 53 percent of metastatic foci were detected in SNs and nearly half (47 percent) of them were only confined to SNs were the next key findings from our investigation. Approximately half of patients with SN metastases did not have positive NSNs, according to early SNB reports in breast cancer [38, 39]. The ability of a nomogram to forecast NSN metastases [40–43] would be extremely useful in this scenario. The Z0011, IBCSG 23-01, and AMAROS trials [44–46] have provided new insights about omitting ALND after positive SNs.
Patients with a small tumour, BCS goals, and full breast radiation are the appropriate indications, according to the studies. Because it was found in this study that we had a larger median tumour size, 24 percent of cases were in stage III, 89 percent MAC in SNs, and mastectomy was more common than BCS, these selection criteria did not meet the majority of our patient characteristics. Because we had 91 percent of patients with 1–2 metastases in SNs, the POSNOC study is expected to provide more evidence for avoiding ALND following positive SNs [47], especially in mastectomy, which accounts for the bulk of our patients.
The reported NPV in this study was 90%, while Canavese et al. reported a virtually identical result (91.1%) in a randomised study [48].
This study had several limitations. First, we only included clinically node negative patients but we did not perform ALN biopsy if the axillary ultrasound found suspicious lymph nodes. Ultrasound-guided axillary lymph node biopsy will select patients with true negative lymph nodes before surgery. Second, blue nodes or non-bluenodes with lymphatic blue channels were the only criteria for SNs. We did not try to find the non-blue suspicious nodes as SNs. These could have reduced our NPV results, especially in cases with high grade and bigger tumor size that could have alternated MBD into the false SNs.

CONCLUSION

SNB in breast cancer can be performed with just 1% MBD, according to this study. It can be used in clinical situations where performing the normal combination technique is difficult or when PBD is not accessible. The following are key variables to consider: first, with high-grade and larger tumour sizes, surgeons should not be satisfied with merely finding blue nodes. To avoid misleading negative results, non-blue suspicious lymph nodes must be checked. Second, when using MBD alone, a better understanding of the SN anatomic position in the axilla is critical to increasing the identification rate. SNB using MBD alone can be a safe, cost effective and simple alternate in resource poor center.

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