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Research Article

ULTRASOUND GUIDED METHYLENE BLUE DELINEATED EXCISION OF BREAST CANCER ALONG WITH FLUORESCEIN AND METHYLENE BLUE GUIDED SENTINEL NODE BIOPSY

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Abstract: ***Introduction:*** Sentinel lymph node biopsy is central to axillary staging in early breast cancer, but radioisotope-based mapping requires specialized infrastructure and increases procedural cost. Ultrasound-guided methylene blue tumour delineation combined with fluorescein–methylene blue sentinel node mapping may provide an accessible alternative.**Objectives:** To evaluate the feasibility and cost-effectiveness of the combined technique, determine its diagnostic accuracy against final axillary lymph node status, and assess dye-related adverse events.**Materials and Methods**: This cross-sectional observational study included 36 patients with T1–T2 breast cancer and a clinically node-negative axilla at Subharti Medical College and Chhatrapati Shivaji Subharti Hospital, Meerut. Tumours were delineated using ultrasound-guided methylene blue injection, while sentinel lymph nodes were identified using fluorescein and methylene blue. Excised nodes underwent histopathological examination. Feasibility was assessed using a five-point Likert scale, and safety was evaluated by recording adverse events.**Results:** The mean age was 52.2 ± 6.59 years. Sentinel lymph nodes were identified in all patients; two nodes were retrieved most frequently in 18 patients (50.0%). Comparison with final axillary status yielded 10 true-positive, 23 true-negative, three false-negative, and no false-positive results. Sensitivity was 76.9%, specificity 100%, positive predictive value 100%, negative predictive value 88.5%, and diagnostic accuracy 91.7% ($\chi^2 = 24.5$, $p < 0.001$). No complication occurred in 31 patients (86.1%); recorded events were minor and self-limiting. Mean visualization, cost-effectiveness, and overall feasibility scores were 4.58, 4.97, and 4.64, respectively. The procedural cost was ₹13,120 per patient.**Conclusion:** The combined technique was feasible, safe, affordable, and diagnostically useful for axillary staging, although the false-negative findings warrant validation in larger studies.

Keywords: Breast cancer, sentinel lymph node biopsy, fluorescein, methylene blue, ultrasound-guided excision, axillary staging, feasibility, cost-effectiveness.

INTRODUCTION

Early breast cancer management requires complete tumour excision and reliable assessment of axillary nodal status. The sentinel lymph node is the first draining node from the tumour-bearing breast; its histopathology therefore estimates regional spread in patients with T1–T2 disease and a clinically node-negative axilla. Accurate localization is also essential during breast-conserving surgery because inadequate delineation may leave involved margins, whereas excessive excision may impair cosmesis. Methylene-blue–based near-infrared imaging of resected breast tissue demonstrated tumour-visualization feasibility, but achieved a sensitivity of 0.63 and positive predictive value of 0.79.[1]

Standard sentinel lymph-node biopsy commonly combines radio-colloid with blue dye, but nuclear-medicine dependence, cost and logistical requirements restrict access in many Indian hospitals. In an Indian prospective validation study, fluorescein plus methylene blue achieved a 95.4% identification rate and 6.3% false-negative rate, comparable with radio-colloid plus methylene blue.[2] Methylene blue alone showed sensitivity of 91.67%, specificity of 96.67% and negative predictive value of 96.67%.[3] Fluorescein combined with methylene blue produced a 92.9% detection rate and 7.5% false-negative rate without observed local or systemic reactions.[4] A meta-analysis showed that indocyanine-green fluorescence identified sentinel nodes more effectively than blue dye, supporting fluorescence-guided axillary mapping.[5]

Indian randomized evidence found fluorescein–methylene blue non-inferior to technetium-99m–methylene blue, with identification rates of 89.0% and

90.9%, respectively, and lower cost.[6] Methylene blue can itself fluoresce in the near-infrared spectrum, although clinical visualization was limited and concentration-dependent.[7] Indocyanine green combined with methylene blue achieved higher detection and accuracy than methylene blue alone,[8] while another comparison reported detection rates of 98.5% versus 91.5%.[9] Ultrasound-guided injection of methylene blue at sonographically defined tumour margins has also been described to facilitate margin-directed lumpectomy.[10] Evaluating this combined, affordable approach at Subharti Medical College, Meerut is therefore justified to determine its feasibility, diagnostic accuracy, safety and cost-effectiveness in early breast cancer.

MATERIALS AND METHODS

Study Design: A cross-sectional observational study was conducted to evaluate the feasibility, diagnostic accuracy, safety, and cost-effectiveness of ultrasound-guided methylene blue delineated excision of breast cancer combined with fluorescein- and methylene-blue-guided sentinel lymph node biopsy.

Study Setting: The study was carried out in the Department of General Surgery, Subharti Medical College and associated Chhatrapati Shivaji Subharti Hospital, Meerut, Uttar Pradesh, India.

Study Population: Patients with early breast cancer of T1–T2 stage and a clinically node-negative axilla presenting to the Surgery outpatient, inpatient, or emergency services during the study period were considered eligible.

Sample Size: A total of 36 patients fulfilling the eligibility criteria were included.

Inclusion Criteria: Patients with T1–T2 early breast cancer, a clinically node-negative axilla, and willingness to participate after providing written informed consent were enrolled.

Exclusion Criteria: Patients with a known allergy to methylene blue or fluorescein, pregnant or lactating women, and those unwilling to provide informed consent were excluded.

Data Collection and Investigations: Demographic, clinical, imaging, operative, cost, and histopathological data were recorded in a predesigned proforma. Ultrasound-guided methylene blue was used for tumour delineation, while fluorescein and methylene blue guided sentinel lymph-node identification and excision. Diagnostic accuracy was assessed against final axillary nodal status, feasibility using a five-point Likert scale, and safety by recording dye-related adverse events.

Ethical Consideration: Approval was obtained from the Institutional Ethics Committee of Subharti Medical College, Meerut. Written informed consent was obtained from every participant. Participation was voluntary and confidentiality was assured.

Statistical Analysis: Data were entered in Microsoft excel and analyzed using suitable statistical software. Continuous variables were reported as mean ± standard deviation and categorical variables as frequencies (percentages). Chi-square test, independent-samples t-test and Pearson correlation analysis were used as appropriate. Diagnostic performance was reported using sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy.

RESULTS

Table 1: Distribution of the Number of Sentinel Lymph Nodes Identified

Frequencies of Sentinel Nodes		
Sentinel Nodes	**Counts**	**% of Total**
1	11	30.6%
2	18	50.0%
3	7	19.4%

As shown in Table 1, the most frequently identified was two sentinel lymph nodes in 18 patients (50.0%), followed by one node in 11 patients (30.6%), and three nodes in 7 patients (19.4%) proving successful sentinel-node identification in all participants.

Table 2: Comparison of Sentinel Lymph Node Pathology with Final Axillary Lymph Node Status

Contingency Tables			
Final Axillary LN			
SLN Pathology	**Negative**	**Positive**	**Total**

Negative	23	3	26	
Positive	0	10	10	
Total	23	13	36	

χ^2 Tests			
	Value	**df**	**p**
χ^2	24.5	1	<.001
N	36		

As shown in Table 2, sentinel lymph node pathology correctly identified 23 node-negative and 10 node-positive cases, with three false-negative results and no false-positive findings. A significant association was observed with final axillary lymph node status ($\chi^2 = 24.5$, $p < 0.001$).

Table 3: Distribution of Intraoperative Complications

Frequencies of Intraoperative Complications				
Intraop Complications	**Adverse Events**	**Counts**	**% of Total**	**Cumulative %**
None	**None**	31	86.1%	86.1%
	Skin mark	1	2.8%	88.9%
	Skin tattoo	1	2.8%	91.7%
	Urine color	3	8.3%	100.0%

As shown in Table 3, 31 patients (86.1%) experienced no intraoperative complication. Low incidence of minor adverse events was suggested by transient urine discoloration in 3 patients (8.3%) and skin marking and skin tattooing in 1 patient (2.8%).

Table 4: Feasibility Scores and Correlation Between Procedural Feasibility Parameters

Correlation Matrix				
Parameters	**Statistical measure**	**Visualization Ease (1–5)**	**Cost-Effectiveness (1–5)**	**Overall Feasibility (1–5)**
Visualization Ease (1–5)	Pearson's *r*	—		
	df	—		
	p-value	—		
Cost-Effectiveness (1–5)	Pearson's *r*	0.418	—	
	df	34	—	
	p-value	0.011	—	
Overall Feasibility (1–5)	Pearson's *r*	0.934	0.185	—
	df	34	34	—
	p-value	<0.001	0.281	—

Descriptive			
Statistical parameter	**Visualization Ease (1–5)**	**Cost-Effectiveness (1–5)**	**Overall Feasibility (1–5)**
Number of patients	36	36	36
Mean	4.58	4.97	4.64
Standard error	0.108	0.0278	0.0988
95% CI, lower limit	4.36	4.92	4.44
95% CI, upper limit	4.80	5.03	4.84
Median	5.00	5.00	5.00
Standard deviation	0.649	0.167	0.593
Interquartile range	1.00	0.00	1.00
Minimum	3	4	3
Maximum	5	5	5
Skewness	−1.32	−6.00	−1.45
Standard error of skewness	0.393	0.393	0.393
Kurtosis	0.663	36.0	1.21

Descriptive			
Statistical parameter	**Visualization Ease (1–5)**	**Cost-Effectiveness (1–5)**	**Overall Feasibility (1–5)**
Standard error of kurtosis	0.768	0.768	0.768

As shown in Table 4, mean scores for visualization ease, cost-effectiveness, and overall feasibility were 4.58, 4.97, and 4.64, respectively. Visualization ease correlated strongly with overall feasibility ($r = 0.934$, $p < 0.001$) and moderately with cost-effectiveness ($r = 0.418$, $p = 0.011$), whereas cost-effectiveness was not significantly related to overall feasibility.

Table 5: Association of Surgical Margin Status with Sentinel Lymph Node Pathology

Contingency Table			
	SLN Pathology		
Margin Status	**Negative**	**Positive**	**Total**
Clear	**23**	**6**	**29**
Close	**3**	**4**	**7**
Total	**26**	**10**	**36**

	χ^2 Tests		
	Value	**df**	**p**
χ^2	3.74	1	0.053
N	36		

As shown in Table 5, clear surgical margins were achieved in 29 patients (80.6%), while 7 patients (19.4%) had close margins. Close margins were more frequent among sentinel lymph node–positive cases; however, the association did not reach statistical significance ($\chi^2 = 3.74$, $p = 0.053$).

DISCUSSION

Among 36 patients, one sentinel lymph node was identified in 11 (30.6%), two nodes in 18 (50.0%), and three nodes in 7 (19.4%), making two-node retrieval the most frequent finding. This pattern indicates successful sentinel-node identification in every patient. Valiveru et al. (2020)[2] Average yield of 3.5 ± 1.8 nodes Yang et al. (2023)[9] Average yield of 3.1 nodes with dual tracers and 2.6 nodes with methylene blue alone. 3.8 nodes/patient was reported by Xu et al. (2022)[8] and the median of four (range two to seven) by Hermansyah et al. (2021)[3]. Thus, overall identification was satisfactory, although the nodal yield was lower than in these reports.

Among 36 patients, sentinel lymph node pathology was negative in 26 and positive in 10, whereas final axillary status was negative in 23 and positive in 13. There were 23 true-negative, 10 true-positive, three false-negative, and no false-positive cases, with a significant association between both findings ($\chi^2 = 24.5$, $df = 1$, $p < 0.001$). This is equivalent to a sensitivity of 76.9%, specificity of 100% and a false negative rate of 23.1%. The sensitivity and specificity were respectively 91.67% and 96.67% (Hermansyah et al., 2021)[3]. Xu et al. (2022)[8] reported a sensitivity of 92.7% and false negatives of 7.3% . However, Valiveru et al. (2020)[2] and Li et al. (2021)[4] have reported lower false-negative rates of 6.3% and 7.5% respectively, which means that these studies had a better diagnostic performance.

Among 36 patients, 31 (86.1%) experienced no intraoperative complication, while five (13.9%) developed only minor adverse events. Skin marking occurred in 1 patient (2.8%), skin tattooing in 1 (2.8%), and transient urine discoloration in 3 (8.3%); no severe allergic reaction was recorded. The good safety profile was in accordance with Li et al. (2021)[4] who reported no local or systemic adverse reactions and with Zhang et al. (2019)[1] who reported no serious adverse events after methylene blue administration. Clinical support for fluorescein–methylene blue was provided by Khadka et al. (2022)[6] and Valiveru et al. (2020)[2] but no detailed frequencies of adverse events were reported. Therefore, direct numerical comparison is limited, but the recorded events were infrequent, mild, and self-limiting.

Among 36 patients, mean visualization ease, cost-effectiveness, and overall feasibility scores were 4.58±0.649, 4.97±0.167, and 4.64±0.593, with medians of 5.00, respective 95% CIs of 4.36–4.80, 4.92–5.03, and 4.44–4.84, and ranges of 3–5, 4–5, and 3–5. Visualization ease correlated strongly with overall feasibility ($r=0.934$, $p<0.001$) and moderately with cost-effectiveness ($r=0.418$, $p=0.011$), whereas cost-effectiveness and overall feasibility were not significantly related ($r=0.185$, $p=0.281$). The high ratings are in agreement with findings of Khadka et al. (2022)[6] and Valiveru et al. (2020)[2] who promoted low-cost fluorescein-methylene blue mapping. Budner et al. (2022)[7] reported only 51% fluorescent sentinel-node visibility, which means poorer visualization performance in the near-infrared assessment.

Among 36 patients, surgical margins were clear in 29 (80.6%) and close in 7 (19.4%). Of 26 sentinel lymph node–negative cases, 23 (88.5%) had clear and 3 (11.5%)

had close margins; among 10 sentinel lymph node–positive cases, 6 (60.0%) had clear and 4 (40.0%) had close margins. The association approached but did not reach statistical significance (χ^2=3.74, df=1, p=0.053). Similarly, Kataria et al. (2024)[10]. Methylene blue boundary marking with ultrasound guidance was described as a convenient technique to confirm tumour-free lumpectomy margins. Zhang et al. (2019)[1] reported a sensitivity of 63% and positive predictive value of tumour visualization with methylene-blue fluorescence of 79%. The numerical results are limited to directly compare as Khadka et al. (2022)[6] and Valiveru et al. (2020) [2] dealt with nodal identification and not margin clearance.

CONCLUSION

Ultrasound-guided methylene blue delineated excision combined with fluorescein–methylene blue guided sentinel lymph node biopsy was feasible and clinically acceptable for early breast cancer with a clinically node-negative axilla. Sentinel lymph nodes were identified in all 36 patients, with two nodes retrieved most commonly. Comparison with final axillary lymph node status showed 76.9% sensitivity, 100% specificity, 100% positive predictive value, and 88.5% negative predictive value, although three false-negative cases indicate the need for careful pathological assessment and continued validation. Most patients had no complications and the adverse events documented were minor and self limiting with no severe allergic reaction. Clear surgical margins were achieved in 80.6% of patients, supporting the utility of ultrasound-guided tumour delineation. The uniform procedural cost of ₹13,120 and high feasibility scores suggest that this combined technique may offer a practical, safe, and affordable alternative in hospitals where radioisotope-based mapping is unavailable.

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