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Comparison of Patent Blue Dye and Technetium-99m Colloid for Sentinel Lymph Node Biopsy in Breast Cancer Patients: A Cross-Sectional Study

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ABSTRACT

Background: To compare the effectiveness of patent blue dye and technetium-99m colloid for sentinel lymph node biopsy (SLNB) in breast cancer patients regarding detection rate, aesthetic outcomes, and complications.
Material and Methods: This cross-sectional study was conducted at Baghdad and Warth hospitals from November 2020 till April 2023. Eighty female patients with breast cancer who underwent breast conservation surgery and SLNB using either patent blue dye or technetium-99m colloid were included. The outcomes of interest were detection rate, overall aesthetic outcome, the symmetry between the breasts and the nipples, shape, and size of the operative breast, appearance of scar, and adverse events.
Results: The mean age of the included patients was 49.45 (23-75). The analysis showed no statistically significant differences between the two groups in any outcomes ($p > 0.05$). The percentage of patients with positive nodes was 22.5% with a higher percentage for patent blue (15%). The majority of patients had good aesthetic outcomes, with scores of 4 (out of 5) for an overall aesthetic outcome, the symmetry between the breasts, the symmetry between the nipples, the shape of an operative breast, the size of the operative breast, and appearance of a scar. No major complications were reported in either group.
Conclusion: Patent blue dye and technetium-99m colloid are both effective and safe tracers for SLNB in breast cancer patients. They have comparable outcomes in terms of recurrence, aesthetics, and complications.
Key words: patent blue dye, technetium-99m colloid, sentinel lymph node biopsy, breast cancer

INTRODUCTION

Breast cancer (BC) is the most prevalent malignancy in women, with a persistently high incidence (1,2). BC poses a significant threat to women's physical and mental health worldwide. However, the advent of primary systemic therapy has revolutionized BC management. With an assured overall therapeutic effect, the focus and future direction of breast surgery is centered on minimizing the extent of the operation and improving patients' quality of life, while maintaining treatment efficacy (2,3).

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The first lymph node to receive drainage directly from a tumor is known as the sentinel lymph node (SLN) (4). The process of SLN biopsy relies on the sequential dissemination of tumor cells from the peri-tumoral area to the lymphatics and then to the sentinel lymph node (SLN), followed by further spread to remote lymph nodes. Clinical identification of these nodes involves the injection of different dyes and radioisotopes into the site followed by surgical removal of the labeled lymph nodes allowing histopathological examination to detect the disease. The identification and biopsy of the SLN can help accurately indicate the status of the lymphovascular invasion (5). In breast cancer patients, when axillary lymph nodes convert from positive to negative after neoadjuvant chemo-therapy, both sentinel biopsy-guided axillary surgery and axillary lymph node dissection without sentinel lymph node biopsy show comparable rates of recurrence (6). Therefore, for breast cancer patients with clinically negative axillary lymph nodes or positive-to-negative conversion following neoadjuvant chemotherapy, utilizing sentinel biopsy-guided axillary operation proves to be a valuable strategy (6,7).

The Sentinel Lymph Node Biopsy (SLNB) procedure involves the injection of either 99mTc-tilmanocept sulfur colloid or blue dye for tracing the sentinel lymph node (SLN), as recommended by the National Comprehensive Cancer Network guidelines for SLN mapping (8).

However, it is important to note that the radio-nuclide approach carries potential hazards due to the radioactive nature of the contrast agent. Additionally, hospitals may face limited access to this agent due to local nuclear use policies as in Iraq. The objective of this study is to analyze the effectiveness of the breast conservation surgery and sentinel lymph node biopsy using the patent blue in comparison with Technitium in terms of recurrence, overall aesthetic appearance, the symmetry between the breasts and the nipples, shape, and size of the operated breast, and the appearance of the scar.

MATERIAL AND METHODS

This is a cross-sectional study conducted at Baghdad and Warith hospitals from November 2020 to April 2023. Eighty female patients with breast cancer were included in this study based on triple assessment (clinical, radiological, and pathological).

The inclusion criteria were female patients between 20-75 years who had breast mass that was unilateral, unifocal, and not multicentric. Resection of the breast tumor was done until negative margins achieved, then dissection of the axilla was done and the stained lymph node or nodes were excised and were sent for frozen section examination, when the result was negative further axillary dissection was done, but when the result was positive we did axillary lymph node dissection.

For SLNB, 1 ml of patent Blue dye was injected intra-dermally and Subcutaneously at the periareolar margin in the upper outer quadrant of the breast immediately after induction of general anesthesia followed by the gentle massage. Technetium colloid particles were injected as single or two injections in the periareolar region intradermally or subcutaneously 24 hours before surgery. A gamma probe was used to localize the nodes with high radioactivity levels. Any nodes with 10% or more of the hottest node in a patient and any node with at least one blue afferent lymphatic vessel derived from the breast were removed and considered SLNs.

Informed consent was obtained from all patients and their data and privacy were kept secret.

Statistical analysis

Data were collected and analyzed using SPSS v.26. Categorical data were compared using one-way analysis of variance, Pearson's chi-square test, or Fisher's exact test, depending on the data's nature. Continuous Data: Continuous data were compared using independent t-tests. Logistic regression with a backward stepwise model was employed to identify potential risk factors associated with missed detection and false-negative events. P-values were derived from the Wald tests, and odds ratios (OR) were reported with their corresponding 95% confidence intervals (CI). All statistical tests were two-tailed, and the chosen significance level was set at 0.05, indicating a confidence level of 95%.

RESULTS

Regarding the distribution of patients across hospitals, the majority of cases were from Baghdad Hospital, with the highest number of lesions in the upper outer and upper inner sites. Warith Hospital had a smaller number of cases but showed a similar distribution across the sites. When examining the T category, it was found that most patients were classified as T2, followed by T1c and T3. The ER, PR, and HER2 status showed variations among patients, with a higher proportion of positive cases for ER and PR, and a smaller proportion of positive cases for HER2, as shown in *table 1*. The most common patho-

Table 1 - Features of the breast mass.

Variables		Hospital			
		Baghdad		Warith	
		No.	%	No.	%
Site	Upper outer	33	70.21	25	75.75
	Upper inner	10	21.27	4	12.1
	Lower inner	2	4.25	2	6.06
	Lower outer	2	4.25	2	6.06
T	T1c	9	19.14	8	24.24
	T2	34	72.34	23	69.69
	T3	4	8.51	2	6.06
ER	Negative	5	10.63	5	15.15
	Positive	42	89.36	28	84.84
PR	Negative	9	19.14	10	30.3
	Positive	38	80.85	23	69.69
HER2	Negative	40	85.1	27	81.81
	Positive	7	14.89	6	18.18
Re-excision	0	46	97.87	33	100
	1	1	2.12	0	0
DCIS	No	23	48.9	11	33.33
	Yes	24	51	22	66.66
Lymphovascular invasion	No	29	61.7	23	69.69
	Yes	18	38.29	10	30.3
Neoadjuvant chemotherapy	No	26	55.31	21	63.63
	Yes	21	44.68	12	36.36
Level	1	45	95.74	30	90.9
	2	2	4.25	3	9.09
Comorbidity	No	36	76.59	28	84.84
	Yes	11	23.4	5	15.15

logical subtype was ductal carcinoma (DCI), as shown in the *fig. 1*. The mean age of the participants was 49.45 years (SD = 11.70), with ages ranging from 23 to 75 years. The mean size of tumors was 3.06 (SD = 1.15). The masses negative margin had a mean margin score of 0.948 (SD = 0.8263).

About 73.75% of the lesions were grade 2, 21.25% of grade 3, and only 5% of grade 1 as shown in *fig. 2*.

Among the groups, 20% of individuals in each group have comorbidities. Complications such as seroma or infection were observed in 7.5% of the technetium group and 17.5% of the patent blue group. Only one patient who underwent SLN (Sentinel Lymph Node) using patent blue required reoperation. More detailed information about the complications and their management can be found in the *table 2*.

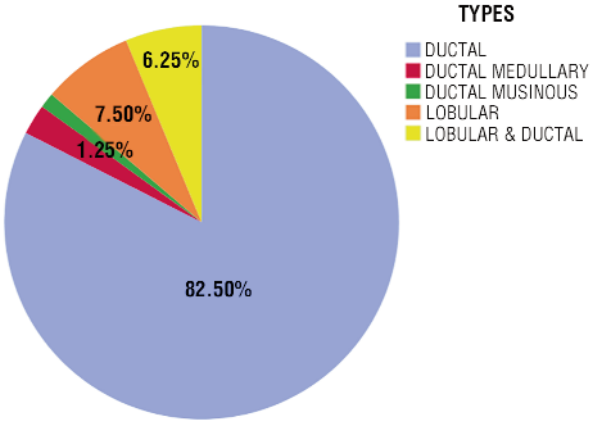

Figure 1 - Pathological subtypes of breast cancer.

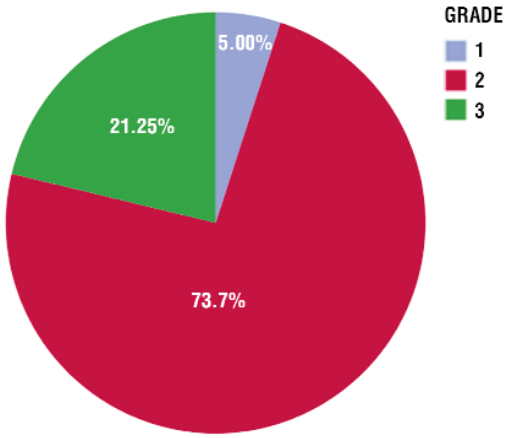

Figure 2 - The pathological grades of excised lesions.

Table 2 - The prevalence of comorbidities and complications and their treatment

Variables		Type of Sentinel	
		Technetium	Patent Blue
		No. (%)	No. (%)
Comorbidity	No	32 (80)	32 (80)
	Yes	8 (20)	8 (20)
Complications	No	37 (92.5)	33 (82.5)
	Seroma	1 (2.5)	5 (12.5)
	Seroma and deep wound infiltration	0	1 (2.5)
	Surgical site infiltration	2 (5)	1 (2.5)
Treatment	Antibiotics	2 (2)	1 (2.5)
	Aspiration	1 (2.5)	5 (12.5)
	Reoperation	0	1 (2.5)
	No	37 (92.5)	33 (82.5)

Table 3 shows the outcome of the SLN biopsy which revealed comparable outcomes for an overall aesthetic outcome, the symmetry between the breasts, the symmetry between the nipples, the shape of the operative breast, the size of the operative breast, and the appearance of the scar quantified according to patients' opinion, mammography nurses and surgeon's opinion. The percentages of patients with different outcomes were similar between the technetium and patent blue groups, with no statistically significant differences observed ($p > 0.05$) in any of the evaluated categories.

Evaluation metrics

In summary, both Technetium and Patent Blue are highly accurate methods for sentinel node detection, with similar outstanding specificity and Positive Predictive Value. However, Patent Blue exhibited a marginally better sensitivity. These metrics provide valuable insights for clinicians and researchers when selecting appropriate methods (*table 4*).

DISCUSSION

The American College of Surgeons Oncology Groups (ACOSOG) Z0011 Study demonstrated that there was no statistically significant distinction in local recurrence-free survival among patients who underwent breast-conserving surgery and avoided axillary lymph node dissection (ALND) at 6.3 years and 9.25 years of follow-up, in comparison to patients treated with ALND. A recent meta-analysis encompassing many trials found no significant differences in survival or recurrence rates among patients who underwent ALND, sentinel lymph node biopsy (SLNB), or axillary radiotherapy (RT).

Table 3 - The percentage of positive nodes and the aesthetic outcomes

Positive nodes and outcomes		Type of Sentinel				P-value
		Technetium		Patent Blue		
		No.	%	No.	%	
Overall Aesthetic outcome	Mammography nurses	8	20	7	17.5	0.775
	Surgeon's opinion	32	80	33	82.5	
Symmetry between breast	Mammography nurses	9	22	6	15	0.390
	Surgeon's opinion	31	77.5	34	85	
Symmetry between nipple	Patients' opinion	1	2.5	0	0	0.361
	Mammography nurses	7	17.5	11	27.5	
	Surgeon's opinion	32	80	29	72.5	
The shape of the operative breast	Patients' opinion	1	2.5	0	0	0.591
	Mammography nurses	9	22.5	10	25	
	Surgeon's opinion	30	75	30	75	
Size of operative breast	Mammography nurses	6	15	13	32.5	0.066
	Surgeon's opinion	34	85	27	67.5	
Appearance of scare	Unspecific	0	0	1	2.5	0.431
	Patients' opinion	3	7.5	2	5	
	Mammography nurses	6	15	14	35	
	Surgeon's opinion	31	77.5	23	57.5	

Table 4 - Evaluation metrics for SLNB using patent blue or technetium.

Metric	Technetium	Patent Blue
Sensitivity	0.83	0.91
Specificity	1	1
Accuracy	97.5%	97.5%
Positive Predictive Value	1	1
Negative Predictive Value	0.97	0.96

However, the meta-analysis did observe a higher incidence of local complications in patients treated with ALND, thus breast conservation surgery is preferred over ALND (9,10).

In this study, 80 patients underwent sentinel lymph node biopsy with 40 of them using technetium and 40 of them using patent blue dye. It is known that the dual-modality method, which combines the use of technetium-99m (Tc)-labeled nanocolloid and blue dye (BD) injections in the peritumoral or periareolar region, is the most commonly employed technique for identifying sentinel lymph nodes (11). In a meta-analysis involving over 9,000 patients, the dual-modality technique demonstrated a false-negative rate of 5.9 percent, compared to 8.6 percent for dye-only techniques and 7.4 percent for tracer-only techniques (12-14). However the use of dual modality faces multiple difficulties related to the cost and complications they cause. In this study the detection rate of SLN using patent blue was 7.83% with 5.75% for technetium, however, this was not statistically significant between the two groups.

This study compared the outcome of two mapping techniques and evaluated its cosmetic effect in multiple aspects including overall aesthetic appearance, symmetry between the breasts and the nipples, the shape and size of the operated breast, and the appearance of the scar. The findings suggest a good outcome with no significant difference between both methods. Multiple articles reported that the combined treatment of breast-conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) offers several benefits to patients. It provides a favorable cosmetic result (15,16). Studies have also shown that a significant proportion of patients, ranging from 70% to 93%, find the cosmetic outcome of breast-conserving therapy (BCT) including irradiation acceptable (17,18).

The participants in this study did not experience any complications related to the tracer used. However, the radioisotope method that utilizes radioactive technetium (99mTc) has limitations, mainly associated with cost and organizational requirements. The use of patent blue dye carries the risk of anaphylactic shock and the potential for persistent tattoos, which are considered undesirable. Consequently, many teams have opted to discontinue the dual detection method due to these concerns (19,20).

In this study, the upper outer quadrant was the most common site in 70 to 75% which agrees with the literature (21). In this study, 40 participants were selected for each group to assess the success rate of different mapping methods, highlighting the importance of experience in achieving optimal performance (22). Previous studies have also shown that the success rate of sentinel lymph node identification depends on the experience of the medical team (23-26). Studies found that surgeons typically require around 40 cases to become proficient in this procedure. This finding is consistent with a literature review by Sanidas et al., which indicated that specialized center surgeons achieve reliable proficiency in SLNB after 20-30 cases, while those in community hospitals may require up to 60 cases (22).

In a study by Douek et al. (27), involving 160 patients, the mean detection rate was 95.0%. On the other hand, Ghilli et al. (28) conducted research with 193 patients and reported an impressive mean DR of 99.0%, Thill et al. (29) contributed valuable insights with their study of 150 patients. They found a commendable mean detection rate of 97.3% per patient. Rubio et al. (30), in their study encompassing 120 patients, reported a mean detection rate of 95.7% per patient.

Being a developing country, the profound financial burden on the health management system is significant due to the increasing population, with over 50% being females who are at high risk of breast carcinoma. Therefore, researching this critical issue cost-effectively is crucial. This study demonstrates the advantages of using blue dye in a population that cannot afford expensive medical equipment and has less equipped hospitals. The use of blue dye provides good accuracy rates without the need for complicated and expensive devices such as the Gamma camera and frozen sections, which are unavailable in most hospitals.

The major limitations in this study are that the long-term effect of breast conservation surgery and sentinel lymph node biopsy was not evaluated clearly and patients were not followed up for a while. The accuracy and the predictive value of Sentinel lymph node biopsy were not investigated against Axillary Lymph Node Dissection.

CONCLUSION

Patent blue dye and technetium-99m colloid are

both effective and safe tracers for SLNB in breast cancer patients. They have comparable outcomes in terms of recurrence, aesthetics, and complications.

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Ethical statement

This study was approved by the Ethics Committee of Baghdad Hospital (333 in 22/10/2022).

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