Original Article

Enhancing Sentinel Lymph Node Localization in Early-Stage Breast Cancer: A Comparative Study of Blue Dye and Combined Blue Dye-Lymphoscintigraphy

Lawrence Raymond Mariano,[1] Eddie Lim, [1,2] and Nicole Patricia Hui[1,3,4]

[1] Department of Nuclear Medicine & PET/CT Center, The Medical City Ortigas, Pasig City [2] Department of Molecular Imaging and Radionuclide Therapy, Rizal Medical Center, Pasig City, [3] Department of Nuclear Medicine, Manila Doctors Hospital, Manila, [4] Department of Nuclear Medicine, ManilaMed (Medical Center Manila), Manila

- Corresponding author: Lawrence Raymond Mariano; lawrencevmariano@gmail.com

ABSTRACT

Objective: To compare the diagnostic performance of blue dye and combined blue dye with lymphoscintigraphy for sentinel lymph node (SLN) localization in early-stage breast cancer patients.
Methods: The researchers retrospectively reviewed 350 patients who underwent SLN biopsy. The patients were divided into two groups: those who received blue dye only ($N = 167$) and those who received a combination method ($N = 183$).
Results: The combined method showed significantly improved sensitivity (97.0% vs. 82.5%), accuracy (96.0% vs. 80.3%), and reduced false negative rates (3.0% vs. 17.5%) compared to blue dye alone ($p < 0.001$). Specificity was comparable between groups (33.3% vs. 34.6%). Compared to blue dye alone, the combined method yielded superior performance in patients with previous excision. For patients who received neoadjuvant therapy, the combined method achieved 100% accuracy and no false negatives, while blue dye alone showed lower accuracy (70.6%). However, the small sample size for this subgroup limits definitive conclusions.
Conclusion: The combined method shows potential benefits in improving SLN localization accuracy, particularly in patients with previous excision. Further research in larger populations is needed to validate these findings further.

Keywords: Sentinel Lymph Node (SLN), breast cancer, blue dye, lymphoscintigraphy, diagnostic accuracy, sensitivity, specificity, false negative rate, neoadjuvant therapy, excision biopsy

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide.[1] In the Philippines, it is the leading cause of cancer mortality and morbidity, with around 27,000 newly diagnosed cases in 2020 alone.[2] An essential aspect in the early management of this disease is axillary lymph node staging. Identification and biopsy of sentinel lymph nodes (SLNs) affect adjuvant treatment decisions and eliminate the need for axillary lymph node dissection (ALND), thus significantly reducing post-operative complications like lymphedema, limitation of shoulder motion, and arm paresthesia.

Several methods can be used to localize sentinel lymph nodes. While more novel techniques, such as indocyanine green fluorescence imaging, are emerging,[3] blue dye injection and lymphoscintigraphy using radioactive colloid are the most commonly utilized in local and global settings. Both agents are preoperatively injected into the breast. Identifying lymph nodes using the blue dye technique has shown good overall efficacy, with identification rates ranging from 95 to 98% and false negative rates of approximately 13%.[4-6] In the same manner, sentinel node localization using lymphoscintigraphy alone has also shown good overall efficacy of 91.4%, with false negative rates of 7.4%. However, the combination of blue dye and radioactive colloid in sentinel node localization shows excellent efficacy, with detection rates approaching 98% to 100%.[7-9]

The results of research comparing the two techniques are limited and conflicting. Kim Giuliano and Lyman's systematic review results showed significantly higher SLN identification rates and lower false negative rates when comparing the combination technique to either blue dye or radiotracer alone ($p<0.05$).[10] In another meta-analysis, Liu et al. also found that the identification rate of the combination method was superior to that of using blue dye alone.[11] Finally, Pesek et al. reported a significantly lower false negative rate of using the combination technique (5.9%) versus dye-only (8.6%; $p=0.018$).[12] In contrast, a randomized controlled trial conducted by Gupta and colleagues found that although the combination technique yielded higher sensitivity (83.33%) and specificity (91.67%) than using blue dye alone (sensitivity: 75%, specificity: 95.45%), the difference was not statistically significant ($p>0.05$). False negative rates in this study were also comparable (8.6% vs. 4.3%, $p>0.05$).[13] Similarly, Varghese et al. found no significant difference ($p=0.354$) in the detection rate of blue dye alone (96.5%) and the combination of tracer and dye (98.7%).[14] Significant differences in these studies' design and localization methodology, such as the dose of blue dye or radiotracer and the injection technique, may have contributed to the opposing results.

Both techniques rely heavily on the lymphatic drainage of the breast, so practitioners may encounter difficulty in SLN localization for patients who underwent neoadjuvant chemotherapy or excision biopsy of the same breast. Localization may be more difficult due to fibrosis, fat necrosis, and granulation tissue formation, which may alter lymphatic drainage patterns.[15] For patients with neoadjuvant treatment, Chirappapha et al. found only an 85.71 % detection rate using either blue dye or radiocolloid and false negative rates of 30 - 40 %.[16] When utilizing dye and radiocolloid, Tee et al. found identification rates of 78-93% and false negative rates of 5-20%.[15] Meanwhile, Coskun et al. reported an 83% identification efficiency and 15.7% false negative rate when utilizing blue dye for patients with previous excision biopsy of the same breast.[17] However, published data regarding the combination technique has yet to be reported in this subset of patients. As such, the optimal localization method for these subgroups of patients needs to be studied further.

Objectives

The general objective of this study is to evaluate the comparative effectiveness of sentinel lymph node localization using blue dye alone versus combined blue dye with lymphoscintigraphy in patients diagnosed with breast cancer. Specifically, the study aims to compare the diagnostic accuracy, sensitivity, specificity, and false negative rates of these two localization methods, and to assess for statistically significant differences in these parameters. Furthermore, the research will evaluate whether the performance differences between the two methods vary among patients with and without a history of neoadjuvant therapy. Additionally, the study will determine if there are significant differences in performance between the two methods in patients with a history of excision biopsy of the same breast compared to those without such history. Through these objectives, the study seeks to provide comprehensive insights into the efficacy of these localization techniques in various clinical scenarios, potentially informing best practices in breast cancer management.

Definition of Terms

1. Sentinel lymph node – first lymph node/nodes that receives lymphatic drainage from the tumor
2. Blue dye – chemical agent (PBV, isosulfan blue, or methylene blue) injected near tumor site to identify / stain lymph nodes
3. Lymphoscintigraphy – Nuclear Medicine procedure used to visualize lymphatic drainage of tumor via injection of radioactive colloid
4. Sentinel lymph node biopsy (SLNB) - a surgical procedure performed to assess the presence of cancer cells in lymph nodes; involves the injection of blue dye and/or radioactive colloid that guides the surgeon in localizing the sentinel nodes during surgery
5. Axillary lymph node dissection (ALND) - surgical removal of axillary lymph nodes via incision in the axilla or as part of mastectomy for women with breast cancer

METHODS

Population and Sample

Researchers conducted a retrospective cohort study involving patients who underwent breast sentinel lymph node (SLN) localization through blue dye alone or in combination with lymphoscintigraphy at The Medical City Ortigas from January 1, 2018, to December 31, 2022. They computed sample sizes using G Power software (α = 0.05, power = 0.95). The overall analysis required a minimum of 134 patients, while each subgroup analysis required at least 210 samples (d = 0.5, allocation ratio = 1). Records were then gathered through convenience sampling with the following criteria:

Inclusion and Exclusion Criteria

This study will include patients diagnosed with early-stage breast cancer who underwent surgical procedures with sentinel lymph node (SLN) localization using either blue dye alone or combined with lymphoscintigraphy. To ensure the integrity and completeness of the data analysis, patients with incomplete medical records or missing data necessary for this study will be excluded. This includes, but is not limited to, missing information on localization methods, lymph node status, or other relevant clinical data. By adhering to these inclusion and exclusion criteria, the study aims to maintain a focused and reliable dataset for comparing the effectiveness of the two SLN localization methods in breast cancer patients.

Data collection

In this study, researchers utilized multiple data sources to gather comprehensive patient information. They accessed electronic records through the ArcusAir patient database and Laboratory Information System (LIS) to collect patient demographics, medical history, operative reports, and histopathological data. Additionally, they reviewed hard copies of histopathologic records from 2018 to 2022 to ensure completeness. The data gathered from these sources included patient demographics (age and sex), medical history (focusing on neoadjuvant therapy and previous breast surgery), tumor characteristics (laterality, size, and histology), the specific localization technique used (blue dye alone or combined with lymphoscintigraphy), the number of submitted lymph nodes and non-nodal tissues, and the lymph node status (positive or negative) for both localization methods. This thorough data collection approach aimed to provide a comprehensive dataset for analyzing the comparative effectiveness of the two sentinel lymph node localization techniques in breast cancer patients.

Data management

All collected data were de-identified using the patient's surgical pathology (SP) number and stored securely in a password-protected Microsoft Excel spreadsheet. Data was categorized based on the localization method (blue dye vs. combined). Researchers categorized the data based on the localization method used (either blue dye or combined) as "blue dye positive and/or radiotracer positive," "radiotracer positive only," "blue dye positive only," or "blue dye and radiotracer negative" based on their histopathologic and radiotracer findings.

Data privacy and confidentiality

All patient data were anonymized using the surgical pathology (SP) number, a unique identifier only accessible within the Department of Laboratory Medicine and Anatomic Pathology. No other personal identifiers were collected or stored. Data was stored securely in a password-protected Microsoft Excel spreadsheet on the principal investigator's computer. A strong password and two-factor authentication restrict access to the computer.

This study was conducted strictly with the Data Privacy Act of 2012 (RA 10173) and the ethical guidelines established by the Declaration of Helsinki. The Medical City Institutional Review Board (IRB), through the hospital's Clinical and Translational Research Institute (CTRI), approved the study before data collection began. The Department of Laboratory Medicine and Anatomic Pathology also obtained written permission for data access.

Analysis

The researchers used descriptive statistics to analyze patient demographics, tumor characteristics, and the distribution of localization methods employed. They created two-by-two tables for each group (blue dye and combined localization). The rows represented the tissue's localization status (positive/negative) based on the specific method used (blue dye or combined). The columns distinguished between lymph nodes (confirmed by histopathology) and non-nodal tissues.

Based on these tables, values for true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results were acquired. Diagnostic performance was then evaluated through the calculation of accuracy [*TP+TN/TP+TN+FP+FN*], sensitivity [*TP/TP+FN*], specificity [*TN/TN+FP*], and false negative rates [*FN/FN+TP*]. These values were analyzed and compared using a Chi-square analysis for statistically significant differences with a 95% confidence interval ($p<0.05$). The researchers also conducted subgroup analyses to compare the performance of the localization methods in two specific patient groups: those who received neoadjuvant therapy before surgery and those with a history of prior excision biopsy.

RESULTS

Demographics and Distribution

The researchers included a total of 350 female patients diagnosed with early-stage breast cancer in this study. They excluded data from 65 patients because of missing information. While this exclusion could have led to overestimating or underestimating calculated values, the researchers believe it will not significantly impact the analysis. The ages ranged from 28 to 88 years, with a mean of 54.8 years. The majority (*N* = 270) were ≥ 45 years old, while the remainder (*N* = 80) were younger. The right breast (*N* = 180) was affected more frequently than the left (*N* =151), with a small proportion (*N* = 19) having bilateral involvement. A total of 17 patients had undergone neoadjuvant chemotherapy, and 97 patients had previous surgical excision before SLN localization (Table 1).

TABLE 1 Sociodemographic profile (n =350).

Characteristics	***n***	**Frequency**
Age		
< 45 years old	80	22.9 %
≥ 45 years old	270	77.1 %
Laterality		
Right	180	51.4 %
Left	151	43.1 %
Bilateral	19	5.5 %
Neoadjuvant Therapy		
None	333	95.1 %
Present	17	4.9 %
Previous Excision		
None	253	72.3 %
Present	97	27.7 %
Histologic Type		
Invasive Ductal Carcinoma	232	66.3 %
Ductal Carcinoma In-Situ	55	15.7 %
Invasive Lobular Carcinoma	12	3.4 %
Papillary, mucinous, tubulolobular, apocrine	51	14.6 %
Tumor Size		
< 1 cm	56	16.0 %
≥ 1 cm	225	64.3 %
No residual carcinoma	67	19.7 %
Localization Method		
Blue Dye Only	167	47.7 %
Blue Dye + Lymphoscintigraphy	183	52.3 %

Overall Performance of Localization Techniques

Five hundred fifty-two tissues were localized using blue dye alone, and 577 tissues were submitted for analysis following combined blue dye and lymphoscintigraphy (Table 2). For blue dye alone, the sensitivity was 82.5%, specificity was 34.6%, false negative rate was 17.5%, and diagnostic accuracy was 80.3%. Compared to blue dye alone, the combined method significantly improved the sensitivity (97.0%, p<0.001), reduced the false negative rate (3.0%, p<0.001), and increased the diagnostic accuracy (96.0%, p<0.001). However, the specificity remained comparable (33.3%) between the two methods (Table 3).

TABLE 2 Tissue counts by localization method.

Localization Method	Color	SLN	Non-Nodal
All patients			
Blue Dye (n=552)	Blue	434	17
	Not Blue	92	9
Blue Dye with Lymphoscintigraphy (n=577)	Hot and/or Blue	542	12
	Not Hot, Not Blue	17	6
Patients with Neoadjuvant Chemotherapy			
Blue Dye (n=17)	Blue	12	0
	Not Blue	5	0
Blue Dye with Lymphoscintigraphy (n=23)	Hot and/or Blue	23	0
	Not Hot, Not Blue	0	0
Patients with Previous Excision			
Blue Dye (n=147)	Blue	111	1
	Not Blue	33	2
Blue Dye with Lymphoscintigraphy (n=174)	Hot and/or Blue	165	5
	Not Hot, Not Blue	2	2

TABLE 3 Diagnostic performance of localization methods in all patients.

	Dye Only	Dye with Lymphoscintigraphy	Chi-square Value	*p*-value
Sensitivity	82.5 %	97.0 %	62.6	<0.0001[a]
Specificity	34.6 %	33.3 %	0.008	0.93
False Negative Rate	17.5 %	3.0 %	62.6	<0.0001[a]
Diagnostic Accuracy	80.3 %	95.0 %	57.0	<0.0001[a]

a = Significant at $p<0.001$

Performance in Subgroups

In patients with neoadjuvant chemotherapy (N = 17), the combined method achieved 100% sensitivity, specificity, and accuracy, with a 0% false negative rate, compared to 70.6% accuracy and 70.6% sensitivity with blue dye alone (Table 4). However, due to the small sample size in this subgroup, statistical comparisons were not possible.

TABLE 4 Diagnostic performance of localization methods in patients with neoadjuvant chemotherapy.

Diagnostic Measure	Dye Only	Dye with Lymphoscintigraphy	Chi-square Value	*p*-value
Sensitivity	70.6 %	100 %	N/A[a]	N/A[a]
Specificity	N/A[a]	100 %		
False Negative Rate	29.4 %	0.0 %		
Diagnostic Accuracy	70.6 %	100 %		

a= Cannot be computed

Patients who underwent previous excision biopsy ($N = 97$) performed significantly better with the combined method than blue dye alone. The combined method achieved a sensitivity of 98.8% and an accuracy of 96.0%, while blue dye alone had a sensitivity of 77.1% and an accuracy of 76.9% ($p<0.0001$). Additionally, the combined method significantly reduced the false negative rate (1.2%) compared to blue dye alone (22.9%, $p<0.0001$). Specificity remained comparable between the groups (Table 5).

TABLE 5 Diagnostic performance of localization methods in all patients with previous excisions.

Diagnostic Measure	Dye Only	Dye with Lymphoscintigraphy	Chi-square Value	*p*-value
Sensitivity	77.1 %	98.8 %	36.5	<0.0001[a]
Specificity	66.7 %	28.6 %	1.3	0.26
False Negative Rate	22.9 %	1.2 %	36.5	<0.0001[a]
Diagnostic Accuracy	76.9 %	96.0 %	26.1	<0.0001[a]

a= Significant at $p<0.001$

DISCUSSION

The combined blue dye and lymphoscintigraphy method demonstrated significantly higher sensitivity, lower false negative rate, and comparable specificity compared to blue dye alone for SLN localization overall ($p<0.001$). In patients with previous excision, the combined method showed superiority with significantly higher sensitivity, accuracy, and lower false negative rate than blue dye alone ($p<0.001$). For patients receiving neoadjuvant therapy, the combined method achieved 100% accuracy and no false negatives, while blue dye alone showed lower accuracy (70.6%) and a higher false negative rate (29.4%). However, the small sample size in this subgroup limits definitive conclusions.

For the blue dye group in the current study, detection accuracy and specificity values were lower than previously reported in the literature, with an 80.3% detection rate and 34.6% specificity as opposed to the expected values of 95-98% and 95%, respectively.[3-5] However, the calculated sensitivity of 82.5% and false negative rate of 17.5% seem almost to parallel the 87% sensitivity and 13% false negative rates reported by Li et al.[18] On the other hand, the combination technique yielded a higher sensitivity of 97% than the expected 83.3%, and a detection rate of 95% that is comparable to the 98% detection rate in reported previous literature.[8-9,13] The false negative rate of 3.0% in this study is lower than the 4.34% reported by Pesek et al. and is within the recommended false negative rate of less than 5.0% by the American Society of Breast Surgeons.[12,18]

While both localization techniques demonstrate adequate detection accuracy and sensitivity for SLN detection, as shown by values in this study and previous literature, the combination of dye and radiotracer is more advantageous in higher detection rate and sensitivity and significantly lower false negative rates. This coincides with findings from previous meta-analyses regarding the significantly greater detection accuracy and lower false negative rates of the combination technique.[10-12] In our research, however, this technique also showed greater sensitivity than the dye-only method (95% vs 80%). This finding differs from previous literature, reporting no significant difference between the two.[10-14] Meanwhile, the specificity of both techniques was comparable and consistent with previous findings by Gupta et al.[13]

The results of the subgroup analysis demonstrate a particular advantage of using blue dye and lymphoscintigraphy for patients who underwent prior excision biopsy or surgery before SLN localization. This study reveals a novel finding not previously reported in the existing literature. For the neoadjuvant therapy subgroup, results from the combination technique may be comparable with findings by Tee et al., who found a 78-93% identification rate and a 30-40% false negative rate when using blue dye to localize sentinel nodes in these patients (70.6% and 29.4% in the current study, respectively).[15] Our study yielded a much higher accuracy of 100% and no false negative cases, although the small sample size for this sub-analysis may still limit the interpretation of these values. Regarding neoadjuvant chemotherapy, the more effective localization method remains a topic for further investigation.

The nature of the combination procedure may explain these findings. This technique utilizes two localization agents (blue dye and radiotracer) instead of just one. This approach increases the number of tissues identified, including those positive for both agents (blue dye and radiotracer positive), those positive only for blue dye (blue dye positive only), and those positive only for the radiotracer (radiotracer positive only). This comprehensive identification leads to a higher true positive rate, as evidenced by the significantly improved sensitivity and detection accuracy for sentinel lymph nodes (SLNs). Additionally, it reduces the number of false negative results. The study also highlights a noteworthy finding: the specificity of both techniques was significantly lower than values reported in previous literature. This discrepancy might be explained by the limited number of non-nodal tissues excised by the surgeons during the procedures. Their experience and skill likely influenced this decision (26 tissues for blue dye; 18 tissues for combination). A larger sample size of non-nodal tissues could improve the specificity of the results. This small number of non-SLN samples tends to underestimate the specificity of both methods.

Data gathered in this study are subject to some limitations. Currently, no standardized methods or thresholds consider tissues blue-stained or radiotracer positive. As such, subjective interpretation of slight staining and minimal tissue counts may significantly alter the yield of sentinel nodes. Convenience sampling and small sample sizes in subgroup analyses that do not meet the minimum required to achieve power may also limit generalizability to the broader population. Lastly, the retrospective design limits establishing causality between localization methods and outcomes.

Considering the significant advantages and limitations, the combined method shows promise as the preferred technique for SLN localization in most patients, including those with previous breast excision. Further research is needed to investigate the combined method's efficacy in more extensive, diverse populations and with standardized protocols to strengthen these findings and address limitations.However, it is crucial to acknowledge the limitations of this study, including convenience sampling and small subgroup sizes, which limit the generalizability of findings to the broader population. The need for standardized protocols for blue dye interpretation and gamma probe count thresholds warrants further investigation. The study underscores the need for further research to solidify these findings. First, conducting similar studies with more extensive and diverse patient populations would strengthen the generalizability of the results. Second, implementing standardized protocols across studies would ensure consistency and allow for more robust data comparison. Finally, researchers should specifically investigate the efficacy of the combined localization method in patients who received neoadjuvant chemotherapy before surgery. This targeted investigation would provide valuable insights into the technique's performance in this patient group.

CONCLUSION

This study compared the diagnostic performance of blue dye alone and combined blue dye with lymphoscintigraphy for sentinel lymph node (SLN) localization in breast cancer patients. The results demonstrated that the combined method significantly improved the localization of true lymph node tissue (sensitivity) and the non-identification of non-nodal tissue (diagnostic accuracy), as well as reduced the risk of missing nodal tissues (false negative rate). These findings were particularly evident in patients who had undergone previous excision of the affected breast tissue.

Based on these results, the combined method of blue dye and lymphoscintigraphy shows promise as a potentially preferred technique for SLN localization in most patients undergoing surgery for early-stage breast cancer, especially those with prior excision. This approach can potentially improve the accuracy of surgical procedures and patient outcomes. Although cautious interpretation and further research are still necessary, the current study suggests that the combined blue dye and lymphoscintigraphy method offers potential advantages for SLN localization compared to blue dye alone.

DATA AVAILABILITY STATEMENTS

The authors can make the gathered data underpinning this article's conclusions accessible upon request without unnecessary restriction. The authors cannot publicly share the data to protect ethical considerations and participant privacy. However, they can make it available upon reasonable request with approval from the institutional ethics committee.

ETHICS STATEMENT

The Ethics Review Board/Committee of The Medical City Ortigas approved thestudy. The researchers conducted the study using local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the provision of written informed consent for the retrospective analysis of de-identified patient data.

AUTHORS CONTRIBUTION

LRM, conceptualization, literature review, protocol writing and editing; data collection, data analysis, manuscript writing, and editing; EL, conceptualization, protocol review and editing, manuscript review and editing; NPH, conceptualization, protocol review and editing, supervision

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The authors declare no conflicts of interest related to commercial or financial relationships.

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