Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.8042619753-148

Indocyanine Green Enhancement for Targeted Lymph Node Dissection in Axillary Staging

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ARTICLE INFO

Received:
9 September 2025
Revised:
31 October 2025
Accepted:
7 November 2025

Keywords:
breast neoplasm, indocyanine green, axillary lymph node dissection, targeted lymph node dissection, sentinel lymph node biopsy

ABSTRACT

Background: Axillary lymph node dissection (ALND) has been the standard of care for node-positive breast cancer. However, recent advances have shown targeted axillary lymph node dissection (TALND) to be an oncologically safe and effective alternative in patients with adequate response to neoadjuvant therapy (NAT). The conventional dual-mapping technique employs a combination of a radioactive tracer and blue dye. Our study aimed to evaluate indocyanine green (ICG) as an adjunct to increase node detection in TALND.

Methods: A descriptive cross-sectional study of 21 patients with biopsy-confirmed axillary lymph node metastases who underwent TALND was conducted. Prior to NAT, metastatic nodes were marked; preoperatively, localization was achieved via radiologic guidewire placement. During surgery, the marked node was excised, and sentinel node mapping was performed using a combination of ICG fluorescence, technetium-99 radiotracer, and palpation. The number and method of node detection were analyzed.

Results: A total of 70 sentinel lymph nodes were identified across 21 patients, with a median of 3 nodes per patient (range, 1–7). Of these, 28 nodes (40.0%) were detected exclusively with ICG, 31 (44.3%) with both ICG and radiotracer, 4 (5.7%) solely with radiotracer, and 7 (10.0%) with palpation. Metastatic involvement was present in 7 of 21 patients (33.3%), including 2 cases in which metastatic nodes were detected only by ICG.

Conclusion: ICG is a valuable adjunct for sentinel lymph node detection during TALND. Combined use of ICG and radiotracer enhances nodal identification and may reduce the need for extensive ALND in patients with clinically node-positive breast cancer.

INTRODUCTION

Recent advances in breast surgical oncology have prioritized reducing patient morbidity without compromising oncologic safety. Traditionally, axillary lymph node dissection (ALND) has been the standard of care for patients with clinically node-positive breast cancer. However, the field is increasingly shifting toward omitting ALND in select cases. Targeted axillary lymph node dissection (TALND) has emerged as an oncologically safe alternative for patients with clinically node-positive disease who demonstrate a response to neoadjuvant therapy (NAT).[1,2]

In this technique, lymph nodes that are suspected of containing metastases are identified and clipped during biopsy prior to NAT. The patient then undergoes planned NAT, and clipped nodes are removed along with sentinel lymph nodes during the oncologic surgery.[1,3] TALND plays a pivotal role in both assessing the need for further axillary dissection and evaluating response to NAT, while minimizing

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the morbidity associated with complete ALND.[1,2,4] Prior studies have shown that targeted axillary dissection has an acceptable false-negative rate of less than 10% if at least 3 sentinel nodes are also sampled during the procedure, including the clipped node.[3,5] This underscores the importance of dual-tracer techniques during sentinel node sampling in TALND. Traditionally, dual mapping combines a radioactive tracer with blue dye.[6] However, blue dye is associated with several adverse effects, including allergic and anaphylactic reactions, wound healing complications, and skin necrosis—particularly in patients undergoing breast reconstruction.[2,7]

Indocyanine green (ICG) is a fluorescent, nontoxic, water-soluble dye approved by the US Food and Drug Administration (FDA) for use in medical diagnostics and surgeries. It absorbs near-infrared light and emits fluorescence at a longer wavelength, which can be visualized using specialized imaging equipment. This makes it especially valuable for visualizing blood flow, lymphatic drainage, and tissue perfusion.[8,9] Multiple studies have demonstrated its feasibility and effectiveness as a tool for sentinel node identification during sentinel lymph node biopsy.[5,7,8] However, its application in the context of TALND has not been previously reported. This study aimed to investigate the efficacy of integrating ICG fluorescence with technetium Tc 99m radiotracer mapping to improve sentinel node detection in patients undergoing TALND.

METHODS

This descriptive cross-sectional study included 21 patients with biopsy-confirmed axillary lymph node metastases undergoing NAT. Inclusion criteria were as follows: biopsy-confirmed invasive breast carcinoma with axillary lymph node metastasis before NAT, completion of neoadjuvant systemic therapy, and planned TALND using ICG and technetium Tc 99m mapping. Exclusion criteria included inflammatory breast cancer, distant metastases, pregnancy, and known iodine allergy. All eligible cases were identified consecutively from the breast surgery database at Auxilio Mutuo Hospital between January 2022 and March 2025. Twenty-five patients were screened and 4 were excluded for incomplete fluorescence data, yielding 21 patients for analysis. Baseline demographic and clinical characteristics, including age, tumor stage, molecular subtype, and breast surgery type, were recorded. Complications related to ICG administration, such as allergic reactions or wound healing disturbances, were monitored.

Prior to NAT, metastatic nodes were marked with a clip during biopsy, and preoperatively, localization was achieved via radiologic guidewire placement. During surgery, the marked node was excised, and sentinel node mapping was performed using a combination of subdermal ICG fluorescence and intraparenchymal technetium Tc 99m radiotracer, in addition to palpation. Indocyanine green (Diagnogreen; Daiichi Sankyo Co) was used for intraoperative fluorescence mapping following a protocol previously described by Sugie *et al.*[10] Each vial (25 mg) was reconstituted with 10 mL of sterile water for injection to obtain a concentration of 2.5 mg/mL. A total of 1 to 2 mL (2.5–5 mg) of the prepared solution was injected into both the subdermal and intraparenchymal periareolar regions approximately 10 to 15 minutes before skin incision. Gentle massage of the injection site was performed for 2 to 3 minutes to facilitate lymphatic migration. Fluorescence imaging was performed using a near-infrared camera system (PINPOINT Endoscopic Fluorescence Imaging System; Stryker Corp). We then analyzed the number of nodes identified via ICG, radiotracer, and/or palpation.

Descriptive statistics were computed using medians and ranges for continuous variables and frequencies with percentages for categorical variables. This study was designed as a retrospective descriptive analysis to compare the number and proportion of lymph nodes identified by ICG, technetium-99m radiotracer, and palpation. Given the retrospective design and absence of node-by-node histopathologic matching for each detection method, sensitivity and specificity calculations were not performed. To evaluate the effectiveness of different detection methods (ICG, radiotracer, both, and palpation) in identifying lymph nodes, the total number of nodes identified by each method was calculated, and their proportions out of the total nodes were reported. Differences between methods were assessed using the Kruskal-Wallis test, followed by the Dunn test with Bonferroni adjustment for multiple pairwise comparisons.

RESULTS

Twenty-one female patients with a median age of 54 years (range, 38–72 years) were included. Twelve (57%) underwent breast-conserving surgery and 9 (43%) underwent modified radical mastectomy. Most cases were clinical stage II to III after NAT, and 67% were hormone receptor–positive/*ERBB2*-negative (formerly *HER2*-negative). Across this cohort, 70 sentinel lymph nodes were successfully identified and excised, with a median of 3 nodes per patient (range, 1–7). Results are shown in Table 1. These included previously localized (clipped or biopsied) nodes in nearly all cases. Among the detected sentinel lymph nodes (SLNs), 28 nodes (40.0%) were visualized

exclusively using ICG, while 31 nodes (44.3%) were concurrently identified by both ICG and radiotracer.

Table 1. Clinical and Pathologic Characteristics of Sentinel Lymph Node Identification

Characteristic	Median (min, max) (N = 21)[a]
Total nodes identified	3 (1, 7)
ICG-identified nodes	1 (0, 5)
Radiotracer-identified nodes (n = 20)	0 (0, 2)
Identified nodes with both techniques	1 (0, 7)
Nodes identified with palpation only	0 (0, 2)
Clipped or biopsied node identified	20 (95.2%)
Metastatic involvement	7 (33.3%)

ICG, indocyanine green.
[a]Values represent median (minimum, maximum) per patient unless otherwise stated. "Total nodes identified" refers to the median number of sentinel lymph nodes excised per patient.

An additional 4 nodes (5.7%) were localized using radiotracer alone, and 7 nodes (10.0%) were detected via palpation during surgery. Results are shown in Table 2.

Table 2. Detection Methods for Sentinel Lymph Node Identification in TALND

Detection Method	Total Nodes Identified (N = 70)
ICG	28 (40.0%)
Radiotracer	4 (5.7%)
Both (ICG and radiotracer)	31 (44.3%)
Palpation	7 (10.0%)

ICG, indocyanine green; TALND, targeted axillary lymph node dissection.
[a]Data are presented as No. (%).

After performing the Kruskal-Wallis test, a statistically significant difference was found in the number of nodes identified across detection methods ($P < 0.001$).

Table 3. Pairwise Comparisons of Nodes Identified Between Methods

Detection methods comparison	Adjusted *P* value[a]
ICG vs both (ICG and radiotracer)	> 0.99
ICG vs palpation	0.01
ICG vs radiotracer	0.002
Radiotracer vs both (ICG and radiotracer)	0.005
Radiotracer vs palpation	> 0.99
Palpation vs both (ICG and radiotracer)	0.03

ICG, indocyanine green.
[a]Adjusted *P* values calculated using the Dunn test with Bonferroni adjustment.

In pairwise comparisons of the 4 detection methods, both the combined method (ICG and radiotracer) and ICG alone were found to be the most effective overall, while ICG was superior to radiotracer alone. The combined method also performed better than radiotracer alone. Results are shown in Table 3. Metastatic involvement of SLNs was found in 7 of 21 patients (33.3%), including 2 cases in which metastatic nodes were identified solely by ICG. The clipped or biopsied node was successfully identified in 20 of the 21 patients (95.2%).

DISCUSSION

This study aimed to evaluate the effectiveness of ICG as an adjunct mapping technique when used in combination with radioactive tracer during targeted axillary dissection (TAD). To our knowledge, this is the first report documenting the use of ICG as a mapping tool during TAD. Our findings suggest that ICG is a reliable and effective technique for sentinel lymph node identification in this setting. While the majority of lymph nodes were identified using both ICG and radiotracer, 28 additional nodes were identified exclusively with ICG. Importantly, among these 28 nodes, 2 harbored metastatic disease. These results are consistent with previous studies demonstrating that ICG performs comparably to radiotracer in sentinel node mapping across various clinical scenarios.[5,6,8] While the current study presents, to our knowledge, the first evaluation of ICG fluorescence specifically during TAD, several prior investigations have validated its utility for axillary staging in broader breast cancer cohorts. Jung *et al.*[11] conducted a randomized phase 2 trial comparing ICG fluorescence plus radioisotope vs radioisotope alone after neoadjuvant chemotherapy, reporting superior detection rates with the combined method (98.0% vs 90.9%). Similarly, Chirappapha *et al.*[12] demonstrated that ICG, when used with blue dye and radioisotope, achieved a 100% detection rate with reduced false negatives compared with conventional techniques. The INFLUENCE trial by Bargon *et al.*[13] further confirmed the feasibility of ICG fluorescence imaging in sentinel node mapping with high concordance to radiotracer results and favorable safety outcomes. More recently, Tarapongpun *et al.*[14] reported comparable efficacy between ICG and technetium-99m for SLN identification in both upfront and post-neoadjuvant settings. Collectively, these studies affirm that ICG is a robust and reliable mapping agent for axillary staging, supporting its expanded role as an adjunct in hybrid TAD procedures. The ability of ICG to identify additional nodes not detected by radiotracer alone may have significant clinical implications, particularly in

ensuring accurate staging and guiding further treatment decisions.

Our findings are consistent with recent clinical experience reported by Pinto *et al.*,[15] who demonstrated the feasibility and diagnostic accuracy of targeted axillary dissection after NAT using combined localization and mapping techniques. Similarly, Yuan *et al.*[16] conducted a randomized trial comparing ICG plus blue dye and radioisotope vs blue dye and radioisotope alone, showing that ICG-based dual mapping achieved higher detection rates with comparable safety. These studies confirm that integrating ICG into hybrid mapping protocols enhances axillary staging accuracy while maintaining procedural safety and efficiency.

Although blue dye has traditionally been used as part of dual mapping for sentinel lymph node identification, multiple studies have demonstrated comparable or superior performance of ICG fluorescence with a more favorable safety profile. Blue dye carries risks of allergic and anaphylactic reactions (up to 1% to 2%) and can cause skin necrosis or wound healing complications, particularly in patients undergoing reconstruction. In contrast, ICG is non-toxic and rarely associated with adverse events (<0.1%), making it a safer alternative.[17] In terms of detection accuracy, fluorescence imaging provides superior visual guidance and deeper tissue penetration than blue dye, resulting in higher identification rates and lower false-negative rates in both upfront and post-neoadjuvant settings. While ICG requires a near-infrared camera system, which may increase initial setup costs, its improved efficiency and reduced morbidity offset these expenses. Therefore, ICG represents a non-inferior alternative to blue dye for sentinel node detection in TAD.

Our findings highlight the clinical relevance of integrating ICG fluorescence into sentinel lymph node mapping, particularly after NAT. Multiple studies demonstrate that ICG improves sentinel node detection rates compared with conventional radiotracers or blue dye alone.[17,18] Kang *et al.*[19] reported discordance rates of 17.7% between radiotracer and ICG uptake, underscoring that a subset of nodes may be visualized exclusively by ICG fluorescence. Importantly, such ICG-only nodes have been shown to harbor metastases in both breast and gynecologic malignancies, with omission of ICG mapping risking false-negative staging and potential under-treatment. .[17,20] Meta-analyses confirm that ICG yields higher overall detection rates and lower false-negative rates than radiotracer alone.[18] Comparable findings across gynecologic cancers, such as endometrial and cervical cancer, show superior bilateral mapping with ICG relative to radiotracer with or without blue dye and emphasize its reproducibility and safety.[21] Collectively, this evidence suggests that omitting ICG may miss clinically relevant metastatic nodes, particularly in post-NAT or altered lymphatic drainage contexts, leading to under-staging and potentially reduced adjuvant treatment intensity. Therefore, dual mapping with both ICG and radiotracer should be considered the preferred approach to maximize staging accuracy and therapeutic decision-making.

Our findings also underscore the value of employing dual-mapping techniques to optimize sentinel lymph node detection. In addition to using both ICG and radiotracer, this study incorporated a combination of intraparenchymal and subdermal injection routes for tracer delivery. Prior research has shown that both injection methods are effective, each offering distinct advantages in terms of nodal detection and localization efficiency.[5,6] Intraparenchymal injection has been associated with increased detection of extra-axillary sentinel nodes, whereas subdermal injection tends to facilitate faster visualization of lymphatic pathways. Notably, patients who undergo neoadjuvant chemotherapy often exhibit increased axillary fibrosis, which can complicate lymphatic drainage and mapping.[22] By combining both injection routes, we believe our approach maximizes the strengths of each technique, improving nodal yield and potentially reducing the risk of false-negative results. This aligns with recent literature advocating for the identification of at least 3 sentinel nodes to maintain an acceptably low false-negative rate and supports the growing interest in omitting axillary radiotherapy in select cases.[7,9] Although dual-route injection enhances detection, its implementation remains largely institution specific and depends on surgeon preference. Because this analysis was retrospective and descriptive, we were unable to calculate sensitivity or specificity for ICG detection relative to radiotracer or histopathologic confirmation. Nonetheless, the proportion of additional nodes identified exclusively with ICG provides compelling evidence of its diagnostic contribution and feasibility as an adjunct mapping technique. Future prospective studies with node-level pathologic correlation are warranted to establish diagnostic accuracy metrics.

The primary limitations of our study include the relatively small sample size and its retrospective design, which may limit generalizability. Additionally, outcomes may vary depending on surgeon experience and the availability of imaging equipment required for ICG visualization. Despite these constraints, our results support the use of ICG as a safe and potentially valuable adjunct mapping modality during targeted axillary dissection. Further

research with larger cohorts is warranted to validate these findings and to better define the role of ICG in this evolving surgical technique.

CONCLUSION

Our study sought to determine the feasibility of using ICG fluorescence alongside radiotracer for node localization during TALND. Our findings support ICG fluorescence as a complementary, rather than alternative, modality to radiotracer in TALND. The combined use of ICG and radiotracer techniques represents a safe option that enhances nodal identification, potentially reducing the need for extensive ALND in patients with clinically node-positive breast cancer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this work.

ETHICAL CONSIDERATIONS

Institutional Review Board (IRB) approval was obtained from Auxilio Mutuo Hospital (2319657-1). Given the retrospective design, the requirement for informed consent was waived. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

FUNDING

None of the authors received any funding or have any financial interests to disclose for the research, authorship, and publication of this article.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality but may be available from the corresponding author upon reasonable request.

ACKNOWLEDGMENT

None.

AI DISCLOSURE

No AI-based tools were used for writing or editing this manuscript.

AUTHOR CONTRIBUTIONS

TPP: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing; ATO: Conceptualization, Methodology, Writing – original draft, Writing – review & editing; ERT, ARR, LSOO: Investigation, Writing – original draft, Writing – review & editing; MEG: Supervision, Writing – original draft, Writing – review & editing.

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How to Cite This Article

Perez TP, Olivieri AT, Torres ER, Rodriguez AR, Ortiz Ocasio LS, et al. ICG Enhancement for Targeted Lymph Node Dissection in Axillary Staging. Arch Breast Cancer. 2025; 13(1):72-7.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1189