



Is Indocyanine Green Superior to Blue Dye in Sentinel Lymph Node Biopsy for Early Breast Cancer: A Comparative Analysis

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Date of Submission: 01-03-2026

Date of Acceptance: 10-03-2026

ABSTRACT

Background/Objective: Breast biopsy and analysis of sentinel lymph nodes (SLNs) accurately predict tumor status in the affected basin and help in avoiding unnecessary axillary lymph node dissection, which is associated with remarkable morbidity risk. Blue dye and radioisotope are the most widely used mapping agents, but non-radioactive tracers of comparable accuracy warrant further investigation. This study aimed to investigate utilization of indocyanine green (ICG) fluorescence in sentinel node localization compared with blue dye and to assess the incremental value of ICG.

Methods: A total of 100 patients with early breast carcinoma clinically node negative patients sentinel lymph node biopsy (SLNB) (40 cases: 38 unilateral and 1 bilateral) with blue dye and ICG given for 50 cases each for localization. The obtained fluorescence images of the lymphatic system were investigated.

Results: Total 142 lymph nodes removed in which 97 identified by ICG, but only 45 were identified by blue dye. The ICG method identified an average of 1.94 SLNs in 97 of 50 cases with a detection rate of 94%, but only 0.9 SLN per case with blue dye. On comparing the detection rate by ICG and blue dye we attained P value of 0.002 [Table 6] which is statistically significant, confirming that ICG is better than blue dye in SLNB.

Conclusion: This study demonstrated the accuracy and safety of ICG for SLNB and its superiority to blue dye method in SLN localization. Therefore, ICG fluorescence method is safe and effective in breast clinical settings, wherein blue dye is used.

KEY WORDS: Early breast carcinoma, Indocyanine green, Blue dye, Sentinel lymph node biopsy

I. INTRODUCTION

Early-stage breast cancer is defined as any form of the disease that has not spread beyond the breast tissue or adjacent lymph nodes. This is consistent with TNM phases (T1-2, N0, and M0). It is associated with a 5-year survival rate of 99%. Adjuvant radiation therapy is typically administered to individuals with ESBC following breast-conserving surgery¹.

One of the most significant prognostic indicators for women with early-stage breast cancer is the state of the axillary lymph nodes. The gold standard for identifying whether metastatic spread to the lymph node has taken place is the sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) is the first lymph node to directly discharge from a tumor. The scope and radicality of oncologic surgery may change if the SLN is detected and examined pathologically².

In 1960, Gould recorded the first time SLN biopsy was used in a therapeutic setting. "A frozen segment of a lymph node taken during a total parotidectomy that looked normal turned out to be histologically positive, he said, prompting the surgeon to undertake a comprehensive neck dissection³. SLN biopsy has also been demonstrated to be helpful in patients with penile cancer. Cabanas showed that a tumor first drains to the SLN. These results provide verifiable evidence that tumor cells follow a certain anatomical pathway and proliferate in a systematic manner.

For patients with breast cancer, Giuliano was the first to recommend injecting isosulfan blue into the tumor site during SLN biopsy. Identification of the SLN became simpler with the appearance of radioisotopes. Three randomized controlled trials demonstrated that SLN biopsy was



an oncologically safe treatment for patients with early-stage breast cancer⁴.

Sentinel lymph node (SLN) biopsies can be safely and successfully detected using indocyanine green (ICG) fluorescence. Before near-infrared fluorescence imaging technology was developed, Motomura et al. employed ICG as a visible dye in daylight and achieved an identification rate of up to 73.8%⁵. None of our patients had local toxicity or systemic adverse effects after receiving an ICG periareolar injection. This outcome is in line with earlier studies that concluded ICG to be a dye that is reasonably safe and has a low rate of morbidity. ICG possesses both lipophilic and hydrophilic qualities because it is composed of two polycyclic components, each of which has a sulfate group linked to it. ICG is cleared more quickly and allows for more intraoperative examinations because it has a shorter half-life in humans than fluorescein.

Methylene blue is a low molecular weight dye that has a relatively low retention rate in SLN and migrates quickly into and out of the lymphatics. About 70% to 98% of SLN can be identified using methylene blue dye. However, the possibility of skin necrosis is one of the main drawbacks of methylene blue (MB) dye⁶.

This study compares the use of indocyanine green and blue dyes for sentinel lymph node biopsy detection in cases with early breast cancer.

II. METHODOLOGY

Patients:

The approach entails carrying out a cross-sectional study at a Tertiary Teaching Hospital connected to Dr. NTRUHS for a period of 18 months. The purpose of the study is to examine the use of ICG and Blue dye techniques for the detection of sentinel lymph nodes in clinically and radiologically node-negative early stage breast cancer. Based on the formula's computations, a sample size of 100 cases will be included. We will include patients with clinically and radiologically confirmed early-stage breast cancer that are node negative. However, those with distant metastatic tumors, inflammatory breast cancer, lymph node positive, tumors larger than 5 cm, prior axillary

surgery, and iodine or ICG hypersensitivity were not included. Patients with tumor size > 5cm, clinically or radiologically proven malignancy, inflammatory breast carcinoma, distant metastatic tumors, previous axillary surgery and who are hypersensitive to indocyanine green or methylene blue were excluded from study.

Sentinel lymph node biopsy:

ICG and blue dye were administered at random to the 100 subjects. Following the administration of anesthesia and the draping and disinfection of the surgical site, they received periareolar injections of 1 mL blue dye (2 mg/mL) and 1–2 mL ICG (2.5 mg/mL). To improve the absorption of blue dye and ICG, the surrounding breast tissue was then gently squeezed and rubbed for roughly five minutes. The ICG near infrared analyzer equipment was used to trace the fluorescent signals of subcutaneous lymphatic flow, and the skin was marked with the lymphatic streams. The ICG near infrared analyser was then placed over the operating field for a real-time image-guided biopsy after a transverse skin incision was performed in the lymphatic basin. For additional examination, all lymph nodes that had been dye- or fluorescence-stained were collected and tallied.

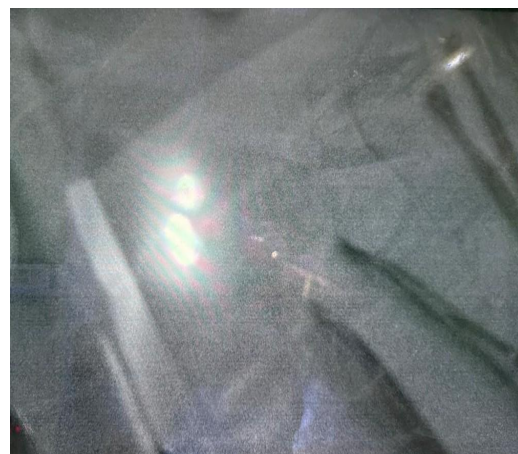


Figure 1: Dissected ICG positive sentinel lymph nodes

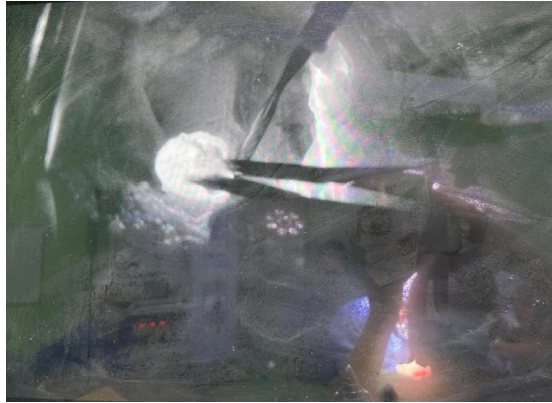


Figure 2: Radioactive ICG detected sentinel lymph node under gamma probe



Figure 3: Hot / blue lymph node being dissected

Statistical analysis:

SPS software version 20 and Microsoft Excel 2010 will be used for statistical analysis, and descriptive statistics will be displayed as percentages and Mean \pm SD (Min-Max). The sensitivity and specificity of the predictors will be ascertained by analyzing the Receiver Operating Characteristic (ROC) curve, and statistical significance will be evaluated using chi-square tests. The p-value will be deemed statistically significant if it is less than 0.05.

III. RESULTS

Total of 100 patients early breast carcinoma with clinical node negativity were underwent sentinel lymph node biopsy with ICG and blue dye for localization, none of them experienced adverse effects or complications

related to intraoperative use of ICG and blue dye regardless of dose. Majority of them were in the age group of 41 – 50 years with 3% followed by 51 – 60 years age group with 2%. other cases fall under age group of 61 - 70 years with 17%, 31 - 40 years with 11%, 71 – 80 years with 5%, 81 – 90 years with 2% in decreasing order in our institution. 58 cases were having right sided breast carcinoma, 42 cases were left sided breast carcinoma with 58% and 42% of sample size respectively. 55 cases were having upper outer quadrant lump [55%], upper inner quadrant lump in 27 cases [27%], lower outer quadrant lump in 7 cases [7%], central quadrant lump in 6 cases [6%], lower inner quadrant lump in 5 cases [5%].

In the ICG given cases out of 50, in 47 cases sentinel lymph nodes were detected with 94% detection rate. In blue dye given cases 33 out of 50 cases detected sentinel lymph nodes with 66% detection rate. Out of 50 ICG given cases, no sentinel lymph nodes were identified in 3 cases, total of 97 sentinel lymph nodes were identified in 47 detected cases, 1 lymph node each was detected in 18 cases, 2 lymph nodes each in 14 cases, 3 lymph nodes each in 11 cases and ≥ 4 lymph nodes in 4 cases. Out of 50 blue dye given cases, no sentinel lymph nodes were detected in 17 cases. Total of 45 sentinel lymph nodes were identified in 3 detected cases, 1 lymph node each in 24 cases, 2 lymph nodes each in 6 cases, 3 lymph nodes each in 3 cases. Average number of lymph nodes detected by ICG is 1.94 per case and with blue dye 0.9 per case.

Out of 80 sentinel lymph node detected cases by both the dye methods, 58.75% detection rate by ICG and 41.25% detection rate by BLUE DYE. On comparing detection rates of ICG and BLUE DYE, p value is 0.002 which showed strong significance indicating that ICG is better than BLUE DYE in detection of sentinel lymph node biopsy in clinically and radiologically node negative early breast carcinoma.



Table 1: Distribution of Age

Age group	No of cases	Percentage
31 - 40	11	11.00%
41 – 50	36	36.00%
51 – 60	29	29.00%
61 – 70	17	17.00%
71 – 80	5	5.00%
81 - 90	2	2.00%
TOTAL	100	100%

Table 2: Laterality of Early Breast Carcinoma with clinically node negative

Diagnosis	Frequency	Percentage
Carcinoma left breast	42	42.00%
Carcinoma right breast	58	58.00%

Table 3: Distribution based on quadrant involved

Quadrant	No of cases	Percentage
Upper Outer	55	55.00%
Upper Inner	27	27.00%
Lower Outer	7	7.00%
Lower Inner	5	5.00%
Central	6	6.00%
Total	100	100%

Table 4: detection rate of cases by each dye

	ICG	Percentage	BLUE DYE	Percentage
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Total no of cases	50	100%	50	100%
SLNs detected cases	47	94.00%	33	66.00%

Table 5: lymph node detection rate by each dye

No of sentinel lymph nodes	No of lymph nodes Identified by each dye	
	ICG DETECTED	BLUE DYE DETECTED
0	3	17
1	18	24
2	14	6
3	11	3
≥4	4	0
Total	97	45
Average no of lymph nodes	1.94 [97/50]	0.9[45/50]

Table 6: comparison of detection rate with ICG VS BLUE DYE

			DYEGIVEN		Total	P-VALUE
			BLUE DYE	ICG		
NO OF LN DETECTED	NO	Count	17	3	20	0.002
		% within NO OF LN NOT DETECTED	85.00%	15.00%	100.0%	



	YES	Count	33	47	80
		% within NO OF LN DETECTED	41.25%	58.75%	100.0%
Total		Count	50	50	100
		Percentage	50.0%	50.0%	100.0%

IV. DISCUSSION

The first lymph node to discharge from the main tumor is the sentinel lymph node. The prognosis of early breast cancer is significantly influenced by the status of axillary lymph nodes, which can change the therapeutic approach depending on their positive. Serious complications such as acute pain, paresthesia, decreased shoulder joint mobility, ipsilateral arm lymphedema, numbness, and recurrent hospitalization are linked to axillary lymph node dissection⁷. By performing sentinel lymph node biopsy in patients with early breast cancer who are clinically and radiologically node negative, we can prevent needless axillary lymph node dissection, as it has been established in the literature that sentinel lymph node biopsy negative cases do not require axillary lymph node dissection⁸.

Either technetium labelled sulfur colloid and blue dye combination, isosulfan blue, fluorescence, or magnetic particles were used for sentinel lymph node biopsies. Numerous research in the literature that used both individual dye methods and combination techniques demonstrated that the latter could lead to a lower rate of false positives. Indocyanine green has been used more frequently in SLNB lately, either alone or in conjunction with methylene blue, which has increased the lymph node detection rate^{9,10}.

The study objective was to compare the detection rate of ICG and Blue dye methods for sentinel lymph node biopsy with histopathological examination in lymph node negative early breast carcinoma specimens. The study comprised of 100 patients, 50 were given ICG and 50 were given blue dye. The detection rate of ICG and Blue dye were calculated.

The study showed comprehensive analysis of the breast tumor characteristics like age distribution, laterality, staging, quadrant involved and average number of lymph nodes detected by each dye and superiority of ICG over blue dye in sentinel lymph node biopsy in node negative early breast carcinoma. In our study total of 100 cases with lymph node negative early breast carcinoma were taken, in which 50 cases were given ICG and 50 cases blue dye majority fall under age range of 41 – 50 followed by 51 – 60 years [Table 1] and my results were almost similar to previous study done by J.lin et al¹.

Based on the laterality in our study right sided breast carcinoma presentation is more than the left sided [Table 2] which is inconsistent with the study done by Guo et al¹¹. And majority of the patients showed involvement of upper outer quadrant with 55 cases [55%] followed by upper inner quadrant 27 cases [27%] [Table 3] which is similar to the study done by Guo et al¹¹. In our study of sentinel lymph node biopsy in node negative early breast carcinoma in which ICG and Blue dye were given in 50 cases each, with significant number of sentinel lymph node detected cases by ICG than blue dye with 94% and 66% respectively [Table 4] which is comparable to the study done by Wang et al^{12,13}. Maximum number of lymph nodes detected by ICG than blue dye with 97 lymph nodes and 45 lymph nodes respectively with significant average of 1.94 per case by ICG and 0.9 per case by blue dye [Table 5] which is consistent to the study done by J.lin et al¹.

Overall detection rate of sentinel lymph nodes in clinically and radiologically node negative early breast carcinoma by ICG was 58.75% and with blue dye was 41.25%. On comparing the



detection rate by ICG and blue dye we attained P value of 0.002 [Table 6] which is statistically significant, confirming that ICG is better than blue dye in SLNB. Our results were almost similar to the study done by J.lin et al and Wang et al with P values of 0.001 and <0.05 respectively^{1,13}.

ICG's greater visibility when seen by high-resolution near-infrared equipment may be the cause of its enhanced sensitivity. While its effects on prognosis are unknown, several studies have indicated that high ALND raises the risk of upper limb postoperative problems¹⁴. Consequently, more clinical research ought to be carried out to determine any possible advantages for patients. There were various restrictions on the current investigation. First of all, the sample size was limited, and neither the combination approach nor the exclusion criteria eliminated individual variance. Second, rather than continuing to look for further blue nodes, surgeons may decide to stop the treatment once all fluorescent nodes have been found. This could lead to an overestimate of blue staining's effectiveness and an overestimation of ICG's accuracy¹⁵.

This study demonstrated the high detection rate and superiority of ICG in identifying SLNs in breast cancer patients. In the absence of radioactive agents, ICG fluorescence can be employed in place of MB or radioisotope and should be utilized in hospitals.

V. CONCLUSION

As long as ICG fluorescence imaging is better than blue dye, the study assessed its application in sentinel lymphnode biopsy of early-stage breast cancer with clinically and radiologically node-negative illness. In clinical situations when blue dye is utilized, ICG is more effective and has a much higher sentinel lymph node detection rate. Additionally, ICG use in early-stage breast cancer will reduce needless ALND and its morbidity. The study's limitation is the absence of combination technique data, which is necessary because this technique may produce better outcomes than the ICG alone method.

Ethical consideration:

Informed consent was obtained from the patient for publication of the case report.

Author contributions:

K V Charishma led in the conceptualization and writing of the first draft. All other authors contributed equally to reviewing and editing the original draft.

Conflict of interest:

There is no conflict of interest amongst the authors.

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