

Sentinel Lymph Node Identification for Breast Cancer Patients Using Fluorescence Navigation with Indocyanine Green: Early Experience at Lampang Hospital

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Abstract

Background: Breast cancer is the most common malignancy among women. Axillary lymph node status is a key determinant of prognosis and treatment decisions. Although axillary lymph node dissection (ALND) provides accurate staging and regional control, it is associated with higher morbidity. Sentinel lymph node biopsy (SLNB) has therefore become the standard approach for axillary staging and avoiding unnecessary dissection. Indocyanine green (ICG) has recently been used as an alternative technique for sentinel lymph node localization via fluorescence imaging. This study presents a case series using ICG fluorescence navigation in breast cancer surgery.

Objective: To describe surgical techniques and clinical outcomes of SLN detection using ICG in breast cancer patients.

Materials and Methods: From June 2022 to June 2024, 18 breast cancer patients underwent SLNB with ICG fluorescence navigation at Lampang Hospital. All patients had been diagnosed with breast cancer. These 18 patients included clinically node-negative cases and node-negative-to-positive patients (N1 to N0) who received neoadjuvant systemic treatment and underwent SLNB (dual mapping: standard isosulfan blue dye with ICG).

Results: Eighteen cases underwent sentinel lymph node biopsy (SLNB) using dual mapping with standard isosulfan blue dye and ICG for localization. No adverse events occurred from intraoperative use of ICG or blue dye. All lymph nodes visualized with either fluorescence or dye were excised. In total, we removed 75 lymph nodes across 18 procedures. ICG identified seventy nodes, while only 29 were detected with blue dye. On average, the ICG method detected 3.88 sentinel lymph nodes (SLNs) (range: 2-8), resulting in a detection rate of 100%. In comparison, only 1.61 SLNs (range: 0-4) were identified, with an identification rate of 88.88%.

Conclusion: Fluorescence-guided SLNB with ICG is safe and highly effective, improving detection rates compared to dye alone. This method enhances lymphatic mapping and supports surgical training for both surgeons and residents.

Keywords: Breast cancer, Indocyanine green, blue dye, Sentinel lymph node biopsy

INTRODUCTION

Breast cancer is the most common malignancy among women. Breast cancer cells primarily spread through the axillary lymphatic system. Consequently, axillary lymph node involvement is crucial for disease prediction and prognosis and guides local, regional, and systemic treatment decisions. A procedure employed to determine nodal staging and regional control is axillary lymph node dissection (ALND). However, this proce-

dures is linked to more complications, such as pain, paresthesia, lymphedema, shoulder joint stiffness, seroma formation, and brachial plexus injuries.^{1,2}

Sentinel lymph nodes (SLNs) are the first lymph nodes to receive drainage from primary breast cancer. The standard method for assessing axillary lymphatic status when there is no clinical or radiological evidence of metastasis is the sentinel lymph node biopsy (SLNB). It is linked to lower morbidity com-

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pared to axillary lymph node dissection (ALND).¹ Recent studies indicate that SLNB is acceptable when used with a dual technique in a post-chemotherapy setting, concerning both the detection rate and the false-negative rate.³⁻⁷ The commonly used method for locating SLNs combines radioisotopes (RI) and blue dye.

RI offers high detection rates for SLNs. Still, it requires specialized detection equipment, exposure to radioactivity, limited availability, high cost, no real-time tracing, and special hospital preparations. Blue dye-guided SLNB is easy to perform and cost-effective.⁸ However, surgeons need experience to develop the skills needed to achieve a high success rate. Using only blue dye results in a lower identification rate (IR) and a higher false negative rate (FNR), which are linked to a substantial risk of anaphylactic reactions and skin necrosis.⁹⁻¹¹

In developing countries like Thailand, radioisotopes are only available at high-volume centers or in medical schools with nuclear medicine departments. Some clinical limitations of RI have led to the development of an alternative tracer technique using a fluorescent dye, indocyanine green (ICG).¹²

ICG is a water-soluble, near-infrared tricarbo-cyanine fluorescent dye. In 1959, the FDA approved its use for measuring cardiac output, hepatic function, and eye perfusion. It absorbs light around 780 nm and emits at 830 nm through a laser imaging device.¹³ We can perform sentinel node identification intraoperatively by injecting ICG dermally or subdermally, along with real-time lymphangiography using near-infrared fluorescence imaging, allowing surgeons to directly visualize lymphatic pathways in the axilla.¹²⁻¹⁴

More evidence supports SLN detection by ICG in early breast cancer. Previous research using ICG alone or combined with blue dye shows it is safe and reports IR exceeding 90%. Multiple meta-analyses have shown that ICG-based SLN detection achieves a high success rate in identifying SLNs.¹⁵⁻¹⁹ This method improves axillary status and offers a useful alternative to RI.

Fluorescence navigation using ICG for SLNB is a novel technique practiced at Lampang Hospital, where it has been implemented for two years. However, no thorough evaluation of surgical outcomes has been reported. This study aims to demonstrate the operative technique and the results achieved with this approach for SLN detection in breast cancer patients.

MATERIALS AND METHODS

Patient selection

This case series included 18 patients who underwent fluorescence-guided SLNB with ICG and isosulfan blue at Lam-

pang Hospital between June 2022 and June 2024. All patients were diagnosed with breast cancer; Some patients were axillary lymph node-negative, and some cases changed from lymph node positive to negative (N1 to N0) in patients who received neoadjuvant systemic treatment. We performed a core needle biopsy to confirm the breast cancer diagnosis, while the axillary diagnosis was made through fine needle aspiration of the axillary lymph node. Patients whose axillary lymph nodes turned negative after receiving neoadjuvant treatment underwent repeat mammograms with ultrasound before surgery to confirm that the positive lymph nodes had disappeared. The exclusion criteria included patients who were pregnant, breastfeeding, or had a history of hypersensitivity to ICG and iodine compounds.

Materials

The SLN tracer utilizes 3 mL of isosulfan blue injection with a concentration of 1% (Pharmaceutical Unit, Chiang Mai University, Chiangmai, Thailand), along with 25 mg of ICG (Daiichi Sankyo Pharmaceutical, Tokyo, Japan), which was diluted in 10 mL of sterile water to reach a concentration of 2.5 mg/mL, using 2 mL for injection. ICG fluorescence was detected with a near-infrared (NIR) camera system (LIGHT VISION, SHIMADZU, Kyoto, Japan) (**Figure 1**). When the fluorescent substance ICG is excited with NIR light (780 nm), it emits NIR light of a longer wavelength (peak WL: 820 nm) as fluorescence.

Operative procedure

SLNB was performed prior to mastectomy or wide excision for primary breast cancer as follows.

1. After anesthesia, 3 mL of 1% isosulfan blue was injected subdermally into the four quadrants of the periareolar area, and the breast was then gently massaged for 10 minutes.
2. After painting and draping, 2 mL of ICG (Diagnogreen) was injected subdermally into the four quadrants of the periareolar area, followed by a 10-minute massage.
3. The NIR camera system was used to identify fluorescent nodes, and the operating room's lights were turned off to visualize lymphatic channels better.
4. The visibility of the lymphatic vessels through the skin helped in precisely locating the skin incision. Make a small cut below the hairline; usually, you can identify this spot by where the subcutaneous lymphatic fluorescence stops in the skin. (**Figure 2**).
5. The dissection proceeded until we reached the cla-

vi-pectoral fascia, which was then opened to access the axilla. Carefully perform dissection along the blue or fluorescence green lymphatic channels to locate the sentinel node. Precise manipulation and careful dissection during SLN identification help reduce lymphatic injury and prevent fluorescent dye contamination of the axilla.

6. Blue nodes, fluorescent nodes, or palpable nodes were removed and sent to the pathologist for metastasis analysis via intraoperative frozen section (Figure 3). Finally, a permanent pathological diagnosis is made through postoperative H&E staining.

Treatment

After obtaining SLNs, breast surgery, whether breast-conserving surgery or mastectomy, was performed based on the previous multidisciplinary team decision and the patient's preference. Following the operation, patients received treatment according to the clinical practice guidelines for breast cancer.

Statistical analysis

We collected the patients' demographic and histopathological data, including procedure details such as SLNB time, the number of ICG-stained lymph nodes (LNs), the number of blue LNs, and LN metastasis status. The study aimed to assess the clinical accuracy of ICG-guided fluorescence imaging for SLN detection in breast cancer patients, specifically examining whether combining ICG with blue dye is better than using blue dye alone for SLN detection. We calculated the detection rate by dividing the number of cases with at least one successfully identified, mapped lymph node by the total number of mapping procedures performed. We used SPSS Statistics Version 22.0 for data analysis and reported categorical data as numbers and percentages. For continuous data, we reported the mean and standard deviation if the data were normally distributed. If the data were non-normally distributed, it was reported as the median, along with the lowest and highest values.

RESULTS

Eighteen cases underwent SLNB with both isosulfan blue and ICG localization methods. No adverse events related to the intraoperative use of ICG or isosulfan blue occurred, regardless of dosage. The mean age was 51.28 years (range: 38-72). Patients' body mass index (BMI) ranged from 17.90 to 31.64, with a mean of 24.29. The most common primary site of breast cancer was the upper-outer quadrant (55.55%; $n = 10$), followed by the upper-mid (11.11%; $n = 2$), lower-inner (11.11%; $n = 2$),

and central (11.11%; $n = 2$) regions, as well as the upper-inner (5.56%; $n = 1$) and lower-outer (5.56%; $n = 1$) regions. Among the 18 cases, 2 were grade I, 8 were grade II, and 8 were grade III. Additionally, one case had a Tis lesion, 4 had T1 lesions, 12 had T2 lesions, and one had a T3 lesion (Table 1).

Table 1 Patient characteristics

Characteristics	n (%)
Age, years	
Range	38-72
Median	50.5
Mean $\pm$ standard deviation	51.28 $\pm$ 10.89
≥ 50 years old	9 (50)
< 50 years old	9 (50)
BMI, kg/m² (n = 18)	
Mean $\pm$ standard deviation	24.29 $\pm$ 3.80
< 18.5,	1 (5.56)
18.5-25	9 (50.00)
25-30	7 (38.88)
> 30	1 (5.56)
Tumor size	
Tis	1 (5.56)
T1	4 (22.22)
T2	12 (66.66)
T3	1 (5.56)
Histological grade	
I	2 (11.11)
II	8 (44.44)
III	8 (44.44)
Tumor location	
Upper-outer	10 (55.55)
Upper-mid	2 (11.11)
Upper-inner	1 (5.56)
Lower-outer	1 (5.56)
Lower-inner	2 (11.11)
Central position	2 (11.11)
Operative procedure	
Breast-conserving surgery	6 (33.33)
Mastectomy	12 (66.67)
Pathology	
Invasive ductal carcinoma	17 (94.44)
Ductal carcinoma in situ	1 (5.56)
Estrogen receptor	
Negative	16 (88.89)
Positive	2 (11.11)
Progesterone receptor	
Negative	13 (72.22)
Positive	5 (27.78)
HER-2	
Negative	5 (27.78)
Positive	10 (55.55)
Negative Equivocal	3 (16.67)

All fluorescing or blue dye-stained lymph nodes (LNs) were collected. In total, we removed 75 lymph nodes across 18 procedures. ICG identified seventy nodes, whereas blue dye

detected only 29 (see **Table 2**). The ICG detected an average of 3.88 sentinel lymph nodes (SLNs) (range: 2-8), with a detection rate of 100%. In contrast, only 1.61 SLNs (range: 0-4) were identified using isosulfan blue, resulting in an identification rate of 88.88% (**Table 3, Figure 4**). Metastases (macro/micrometastases) were found in 13 nodes, all showing blue and fluorescent features. Eight patients had at least one positive node (42.10%).

Table 2 Number of SLNs identified (n = 18)

SLN identification (nodes)	Number of SLNs identified	
	ICG	Blue dye
0	0	2
1	0	8
2	2	4
3	5	3
≥ 4	11	1
Average	3.88	1.61

Table 3 Diagnostic effectiveness of ICG and blue dye in identifying SLNs in breast cancer patients

Variables	ICG (%)	Blue dye (%)
Total number of SLNs	70	29
SLN detection rate	100 (18/18)	88.88 (16/18)
Difference (ICG - blue dye)	2.27	
Total number of metastatic nodes	13	

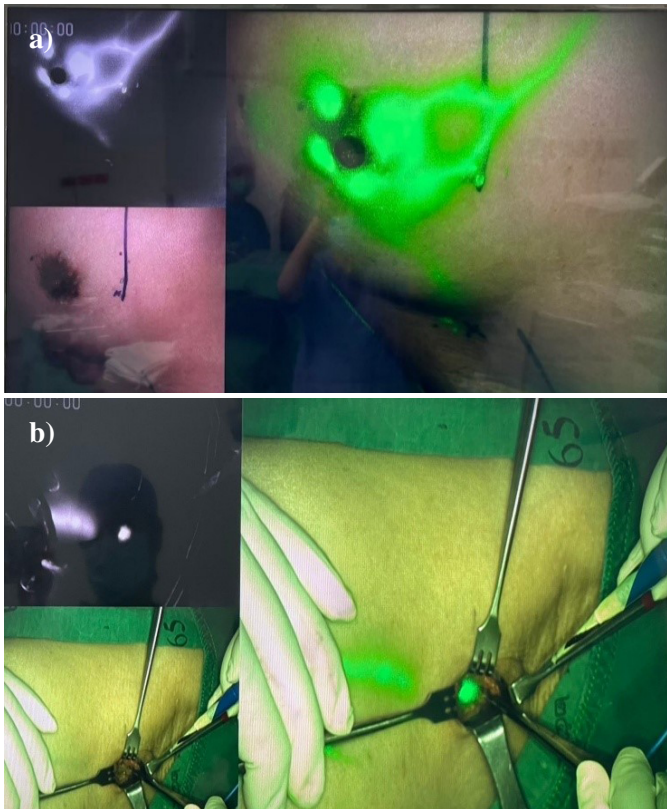


Figure 2 ICG imaging. A Transcutaneous lymphography is used to detect the SLN after injection of ICG. b) ICG fluorescence in the lymph node



Figure 1 Near-infrared (NIR) camera system

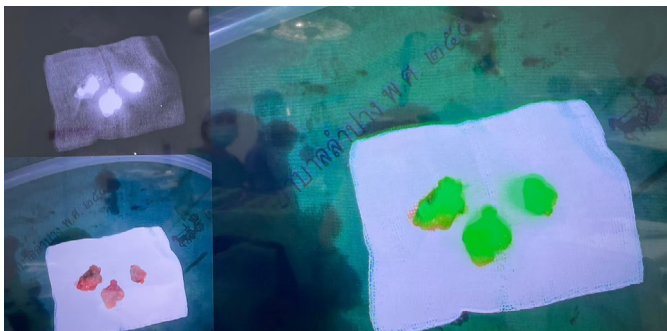


Figure 3 SLNs development status under ICG and Isosulfan blue

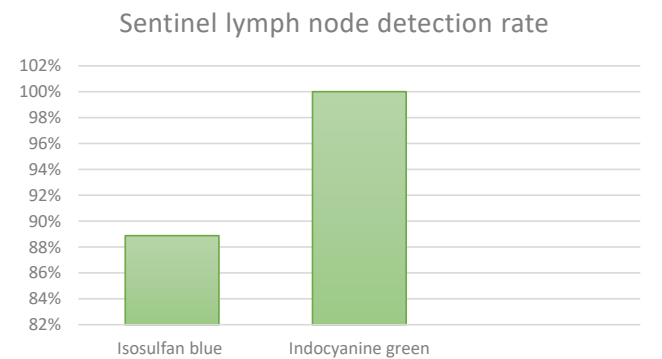


Figure 4 Graph of sentinel lymph node detection rates via each method: Isosulfan blue and Indocyanine Green

DISCUSSION

The most significant prognostic and predictive factor in managing breast cancer is the axillary lymph node status, which affects the choice of adjuvant systemic therapy and radiotherapy.²⁰ Common methods for sentinel node biopsy include the radiocolloid technique, the blue dye procedure, or a combination of the two.

Many studies show that SLNB can be guided by fluorescence after ICG injection, with ICG movement through lymphatic vessels visualized transcutaneously. Depending on the traditional technique (radioactive colloids or blue dyes), the SLN biopsy techniques are complicated procedures with long learning curves. In contrast, ICG/NIR fluorescence-guided SLN biopsy enables direct transcutaneous visualization of lymphatics. This approach offers a gentler learning curve and helps avoid complications from unnecessary dissection.¹²⁻¹⁴

This case series assessed the effectiveness of ICG and blue dye techniques for identifying sentinel lymph nodes (SLN) within the same patient group. The results show that subareolar ICG injections allow safe SLN biopsy, with no allergic reactions or adverse events. ICG showed better SLN localization than blue dye (100% versus 88.88%). The ICG detection rate in this series (100%) is similar to rates reported in previous studies. A meta-analysis by Sugie and Ikeda with 1736 patients reported a detection rate between 88.6% and 100%.¹⁸ The detection rate for blue dye is lower than that of ICG (88.88%) because blue dye has a larger molecule than ICG. Most patients in this series received neoadjuvant chemotherapy before surgery, which caused fibrosis in the lymphatic channels and disrupted lymphatic flow.

A systematic review and meta-analysis by Thongvito-komarn S et al. comparing Indocyanine Green fluorescence with blue dye or radioisotope for detecting sentinel lymph nodes in breast cancer analyzed 30 studies from January 2000 to October 2019. The results showed a statistically significant difference in SLN detection rate between ICG and blue dye (OR, 6.73; 95% CI, 4.20-10.78). However, ICG and RI did not differ significantly.¹⁷

Kitai T et al. reported the detection rate of SLNs using ICG fluorescence navigation in breast cancer. Sentinel nodes were successfully identified in 17 of 18 cases, with a detection rate of 94%.⁸

Takemoto N et al. conducted a retrospective study comparing ICG alone versus a combination of indigo carmine blue dye with ICG fluorescence imaging for SLNB in breast-conserving therapy for stage IIA or smaller breast cancer. Results from 202

patients showed that the combined ICG and indigo carmine group had a significantly higher SLN detection rate than ICG alone (96.4% vs. 83.7%; $p = 0.003$).¹²

Lin J et al. compared indocyanine green (ICG) fluorescence with blue dye for sentinel node detection and evaluated the additional benefit of ICG in 39 cases of breast cancer. The ICG detection rate was significantly higher than that of blue dye (97.5% vs. 70%, $p = 0.001$).¹³

Chirappapha et al. conducted a prospective cohort study assessing SLNB after neoadjuvant therapy in breast cancer patients, utilizing blue dye, radioisotope (RI), and ICG. The detection rates were 95.23% for ICG and 85.71% each for blue dye and RI. Combining ICG with blue dye increased the detection rate to 100%.⁷

In the SENTINA trial, the identification rate was 80.1%, with a false negative rate (FNR) of 14.2%. The FNR decreased to 12% when the radioisotope was combined with isosulfan blue. If more than three sentinel lymph nodes are present, the FNR is 7.3%.⁵ In the ACOZOG Z1071 trial, the identification rate reached 92.7%, with an FNR of 12.6%; using the dual technique lowered the FNR to just 8.6%. When more than three sentinel lymph nodes were identified, the FNR was 9.1%.⁶

In this case series, we used a dual technique for SLNB, combining isosulfan blue dye and ICG in the same patients. ICG fluorescence for lymphatic mapping achieves a high success rate in detecting SLNs and improves mapping when combined with the dye method, as demonstrated in previous studies.^{7,12,15-18,21}

A limitation of this study is that it is a case series reporting only our experience using ICG as a tracer for lymphatic mapping in breast cancer surgery at a single center. The study population was small, which makes the results less reliable than those of other studies. Future studies should use randomized or prospective methods to ensure reliability and clinical applicability.

CONCLUSION

Fluorescence-guided lymphatic mapping with ICG was safe, showed a high detection rate, and improved mapping efficiency when combined with the dye method. The breast cancer patient experienced no complications from the extended axillary dissection. Importantly, both surgeons and residents can improve their sentinel lymph node biopsy skills.

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