Evaluation of the role of indocyanine green in mapping of axillary sentinel lymph node biopsy

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Background
Axillary lymph nodes (LNs) are known to be the most important prognostic factor for recurrence and survival in the management of patients with early breast cancer. Blue dye and radioactive isotopes are the most widely used tracers in the mapping of axillary sentinel node (SN) biopsy. These tracers still have several drawbacks. Indocyanine green (ICG) has the potential for guiding SN biopsy.
Patients and methods
A total of 35 patients with early breast cancer, clinically and radiologically node negative, underwent SN biopsy with combined ICG and patent blue (PB) dye for localization of SNs. The obtained lymph nodes were histopathologically investigated.
Outcomes
This study aimed to assess the feasibility of using ICG for SN biopsy, to calculate the detection rate, and to assess the safety of ICG dye.
Results
The mean age of the patients was 51.94 years. The detection rate of SN depending on ICG was 100 and 91% depending on the PB dye visualization. Of 129 SNs dissected from the 35 recruited patients, a mean of 2.31 ± 1.23 nodes/patient were seen in case of SN detection by the PB dye and a mean of 3.69 ± 0.72 nodes/patient in case of SN detection by ICG (P<0.001). No complications or adverse actions were recorded in all patients.
Conclusion
This study demonstrated that ICG is a feasible technique for SN biopsy with a high detection rate and can be used safely.

Keywords:
sentinel node biopsy, indocyanine green, breast cancer

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Introduction

Breast cancer has surpassed lung cancer as the most frequently diagnosed cancer. It is fifth cause of cancer-related deaths worldwide. Female breast cancer accounts for ~24.5% of all cancer cases and 15.5% of cancer deaths [1]. Incidence rates of breast cancer have increased in the last decade. This may be due to the growth of population, aging, increased prevalence of risk factors, and mammography screening detections [2,3]. Strategies of management of breast cancer are always heading to the least invasive and the most esthetic, keeping in mind the oncological safety [4–6].

The nodal status, or the axillary lymph node (LN) involvement, was reported to be the most substantial prognostic factor; therefore, it is regularly assessed during the management of breast cancer. Early detection of breast cancer is associated with a better prognosis and a significantly reduced percentage of axillary LN involvement [7]. Surgical de-escalation strategies in breast cancer recommend sentinel node (SN) biopsy in patients with clinically negative nodes (cN0) [8]. The SN biopsy has an equivalent diagnostic accuracy as axillary LN dissection but with significantly reduced complication rates [9–11].

The idea behind the SN technique is to transport a tracer from a certain area of interest to the catching LN group, like what metastases do [12]. The typical technique of SN biopsy includes periareolar or interstitial injection of radioactive Technetium99m (Tc99m) colloid, blue dye, or a combination of both [13,14].

The use of radioactive colloids has high detection rates, but it has several disadvantages, such as exposure

to radioactivity (the patient, surgeons, and medical staff), limited availability, elevated cost, no real-time tracing, and the need for special hospital preparations [15]. On the contrary, blue dyes [isosulfan blue, patent blue (PB) V, and methylene blue] are relatively safe, easy to handle, and cost-effective, but they have lower detection rates and high false-negative rates, they cannot be seen via skin or fat, they have a long learning curve, and they can cause allergic reactions and skin complications [16–18].

The indocyanine green (ICG) was suggested as a tracer for SN biopsy. It is a water-soluble molecule with a hydrodynamic diameter of 1.2 nm. When exposed to the light of the wavelength of 800 nm, it shows fluorescence. This specific wavelength is present in the near-infrared spectrum of light [19–21]. Being one of the safest medical dyes [22], it is used in many medical applications like liver function tests, cardiac output tests, retina angiography, intraoperative cholangiography, lymphatic mapping, and testing the viability of intestinal stumps [23–27].

Outcomes

This study was designed to assess the feasibility of using ICG/NIR light in SN biopsy, to define the detection rate of SN with ICG when compared to the PB dye, and to assess the safety of the technique.

Patients and methods

This was a prospective study. It included 35 patients with early breast carcinoma who presented to the Breast Surgery Clinic in El-Demerdash Hospital and Ain-Shams University Specialized Hospital (ASUSH) eligible for SN biopsy from November 2021 to June 2022.

The study was approved by the Research Ethics Committee (REC), General Surgery Department, Ain-Shams University (IRB 00006379). All patients received information about surgical technique and risks of the operation and other options for treatment. All patients participated in this study after signing an informed consent and medical photography consent.

Inclusion criteria were being a female patient from 20 to 80 years old, with early breast cancer (T1-2, N0, M0), diagnosed with invasive ductal carcinoma, invasive lobular carcinoma, or ductal carcinoma in situ. Axillary LNs should have been clinically and radiologically negative with no previous axillary surgery or radiotherapy. Excluded patients were those who had hypersensitivity to iodine or were pregnant or lactating.

All patients were subjected to triple assessment (clinical assessment, radiological assessment, and core needle biopsy), after confirming the diagnosis of breast cancer. Metastatic workup and preoperative workup were done. All cases were discussed in the multidisciplinary team weekly meeting.

All surgeons were well trained on SN biopsy procedures. After induction of general anesthesia, sterilization of the operative site and draping were done. Subcutaneous periareolar injection of 3 ml (in concentration of 3 mg/ml) of PB solution (Patent Blue V, S.A.L.F. S.p.A. Laboratorio Farmacologico, Cenate Sotto, Italy), followed by a gentle massage of the breast for 10 min, was done. This was followed by subcutaneous injection of 2.5 ml (in concentration of 2.5 mg/ml) of ICG (Verdye, Diagnostic Green, Aschheim-Dornach, Germany) periareolarly at 3, 6, 9, and 12 o'clock positions.

The SN biopsy was performed before breast surgery. Approximately 5 min after injection of the ICG, a small incision is done below the hair line; usually this site can be marked by the point of cut-off subcutaneous lymphatic fluorescence from the skin. Then, the dissection was continued till we reach the clavi-pectoral fascia, which was opened to approach the axilla.

At that time, operation room lights were turned off. With the help of an ICG visualization system, the SN biopsy procedure was done. The system used was the IMAGE 1 S camera system, HOPKINS NIR/ICG scope, and D-LIGHT P light source, Karl Storz Endoskope, Tuttlingen, Germany (Figs 1 and 2).

During SN dissection, careful manipulation and fine dissection helped to minimize injury of lymphatics and contamination of axilla by fluorescent dye. Tissues that appeared fluorescent under the NIR light and/or blue dye stained were excised (Figs 3 and 4). All excised tissues were sent for frozen section.

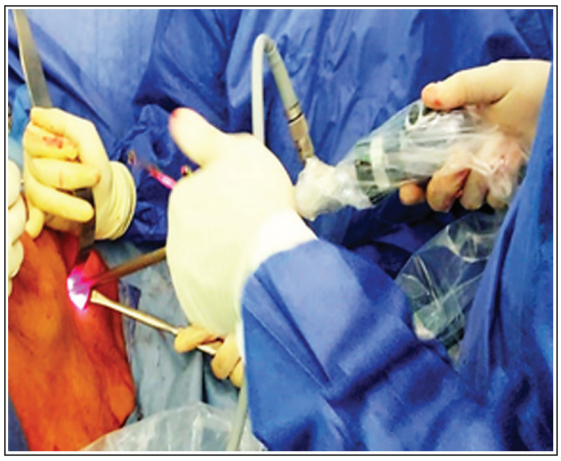
After SNs were obtained, breast surgery, either breast-conserving surgery or mastectomy, was done according to the previous multidisciplinary team decision and patient desire.

Collected data were revised, coded, and exported to IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., New York, USA. The quantitative data were presented as mean, SDs, and ranges, and the Wilcoxon test and the Spearman correlation coefficients tests were used for comparison. The qualitative variables were presented as numbers and percentages and the χ^2 test was used for comparison.

Figure 1

The near-infrared/indocyanine green system.

Figure 2



Using the near-infrared light in the axilla.

Results

The 35 recruited patients were subjected to a combined application of PB dye and ICG dye. The mean age of the patients was 51.94 ± 4.9 years, and it ranged from 43 to 63 years old. The mean BMI was 27.2 ± 2.58 kg/m^2, and it ranged between 22 and 32 kg/m^2. A total of 25 (71.4%) patients were free from any comorbidities (Table 1). The tumor characteristics are presented in Table 2.

The mean time from ICG injection to all SNs excision was 19.23 ± 2.30 min (range, 15–25 min). Lymphatic fluorescence, along the lymphatic vessels, was observed in 30 (85.7%) patients (Fig. 5). There was no correlation between the number of SN detected and fluorescence lymphangiography.

The LNs were detected in 32 (91.4%) patients by visualizing the PB dye, whereas all of the patients (100%) had detected LNs by the ICG/NIR. A total number of 129 LNs were dissected from the 35 recruited patients, with a mean of 2.31 ± 1.23 nodes/patient in case of SN detection by the PB dye and a mean of 3.69 ± 0.72 nodes/patient in case of SN detection by ICG/NIR (Table 3).

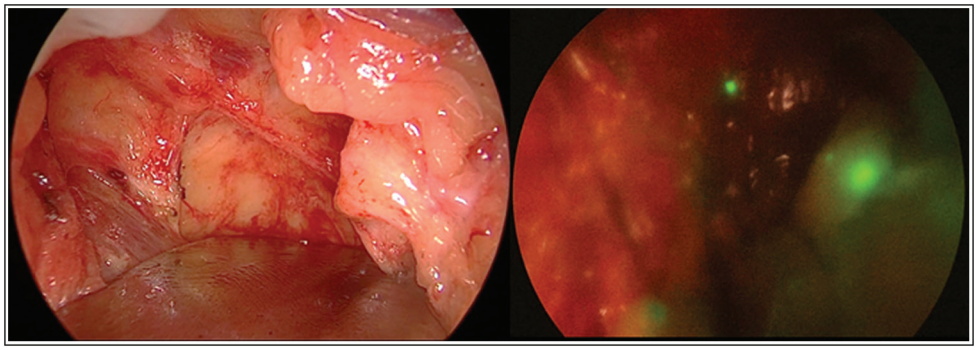
A single LN with tumor deposits was detected in five (14.3%) patients, whereas two LNs with tumor deposits were found in a single (2.9%) patient, and 29 (82.9%) had no LNs with tumor invasion. The relation between the dye and detection of positive SNs is presented in Table 4.

The correlation of SNs detected by BP stain and ICG fluorescence with age, BMI, and size of the mass is illustrated in the Table 5. No adverse effects from the dyes used were detected in any of the patients.

Discussion

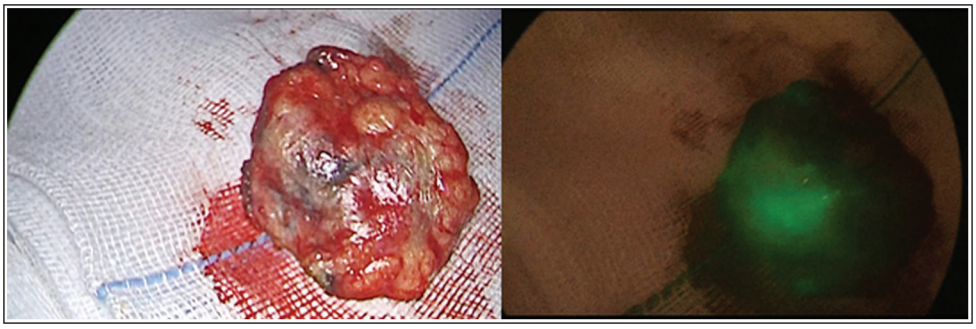
Breast cancer is a growing threat. The forecasted number of breast cancer cases, based on the available

Figure 3



A sentinel node under the white light and the near-infrared light.

Figure 4



Under the white light the sentinel node showed the blue dye, and under the near-infrared light, the node showed florescence.

Table 1 Demographic data and characteristics of the studied patients

	Total no.=35 [*n* (%)]
Age (years)	
Mean±SD	51.94±4.90
Range	43–63
Comorbidities	
Free	25 (71.4)
Positive	10 (28.6)
DM	5 (14.3)
HTN	6 (17.1)
IHD	1 (2.9)
BMI (kg/m^2)	
Mean±SD (range)	27.20±2.58 (22–32)
Breast cup size	
B	6 (17.1)
C	18 (51.4)
D	11 (31.4)

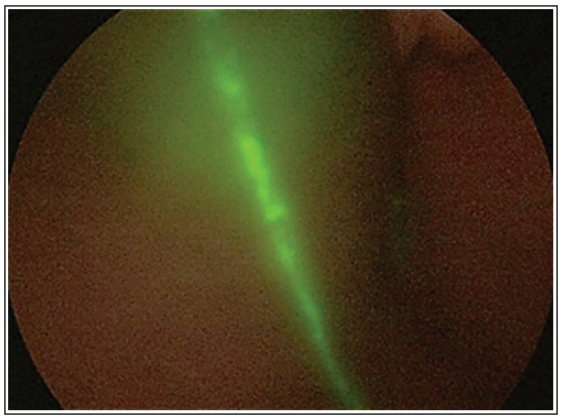
DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.

Table 2 Tumor characteristics

	Total no.=35 [*n* (%)]
Laterality of mass	
Right	12 (34.3)
Left	23 (65.7)
Site of the mass	
UOQ	17 (48.6)
LOQ	7 (20.0)
UIQ	4 (11.4)
LIQ	4 (11.4)
Central	3 (8.6)
Size of the mass (cm)	
Mean±SD	2.73±0.87
Range	1.5–4.5
Radiological assessment of the axilla	
Free	25 (71.4)
Nonspecific lymphadenopathy	10 (28.6)
Histopathological type	
IDC	29 (82.9)
ILC	4 (11.4)
DCIS	2 (5.7)

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LIQ, lower-inner quadrant; LOQ, lower-outer quadrant; UIQ, upper-inner quadrant; UOQ, upper-outer quadrant.

Figure 5



Subcutaneous lymphatic fluorescence.

data, in the Egyptian population in the year 2040 exceeds 40 000 cases [28]. There has been significant progress in breast cancer diagnosis and management in the last decades [29,30].

The SN biopsy techniques depending on the radioactive colloids or blue dyes are difficult procedures with long learning curve. On the contrary, ICG/NIR fluorescence-guided SN biopsy enables direct visualization of lymphatics and LNs, which enables an easier learning curve [31] and the evasion of complications that may result from unnecessary dissection.

In our study, both PB and ICG/NIR detection rates were similar to the earlier reported studies; the detection rates ranged from 78 to 92% with the PB and from 97 to 100% with ICG/NIR [32–35]. The higher detection rates of the ICG dye promote it to be a better tracer for SN biopsy procedure [35–38]. In all patients with observed subcutaneous lymphatic fluorescence spread (85.7%), the direction of the spread was toward the axilla. It was helpful to determine the site of the axillary incision.

Studies showed that extraction of only one SN had a high risk to have a false negative result, whereas

Table 3 Dissected nodes/patient and relation to the detection dye

Number of intraoperative SNs	PB stained [*n* (%)]	ICG fluorescent [*n* (%)]	Test value	*P* value
0	3 (8.6)	0	26.794¤	<0.001*
1	6 (17.1)	0		
2	9 (25.7)	0		
3	12 (34.3)	16 (45.7)		
4	4 (11.4)	14 (40.0)		
5	1 (2.9)	5 (14.3)		
Total	81	129		
Mean±SD	2.31 ± 1.23	3.69 ± 0.72	−4.432≠	<0.001*
Range	0–5	3–5		

ICG, indocyanine green; PB, patent blue; SNs, sentinel nodes. ¤χ^2 test. ≠Wilcoxon signed ranks test. *Significant.

Table 4 Detection rate of positive sentinel nodes and positive patients by both dyes

	By BP	By ICG	*P* value
Patients having SNs invasion	5/6 (83.3)	6/6 (100.0)	0.296
SNs showing invasion	5/7 (71.43)	7/7 (100.0)	0.126

ICG, indocyanine green; PB, patent blue; SNs, sentinel nodes.

Table 5 Correlation between detected sentinel node and age, BMI and mass size using both dyes

	Number SNs stained by PB		Number SNs stained by ICG	
	r	*P* value	*r*	*P* value
Age (years)	0.188	0.279	0.064	0.715
BMI (kg/m^2)	−0.187	0.281	−0.187	0.282
Size of the mass	−0.672	0.000*	−0.081	0.642

Significant Spearman correlation coefficient.

increasing the number of removed SNs, within limits, increased the accuracy and decreased the false-negative rates [35,39,40]. The mean number of SNs removed under the guidance of PB was 2.31 ± 1.23 nodes. On the contrary, under the guidance of ICG/NIR, 3.69 ± 0.72 nodes were removed (P<0.001). Based on our results, ICG/NIR had a better detection rate of pathologically positive nodes than the PB dye. This helps in better assessment of axillary status. Similar results were previously reported [41,42].

The lymphatic function declines with age, which may decrease the SN detection rate [34], but our study revealed that ICG/NIR detection rate was not affected by the increase in age (P=0.715). Liu *et al.* [38] reported similar results. Obesity may also reduce the SN recognition rate, and layers of fat may obscure the visualization of the SN or may also hinder the lymphatic drainage [43]. However, our study suggests that the fluorescence method can effectively overcome the effect of obesity on SN detection (P=0.282).

The combined application of PB dye and ICG dye was superior to PB alone, but the blue dye was helpful in identifying the SN when contamination of the axilla by ICG occurs. The ICG contamination of the axilla is the fluorescence of all the operative field of the axilla. It happens after rough blunt dissection leading to disruption of the lymphatics. This increases the difficulty to identify the SNs by ICG/NIR fluorescence. Contamination does not happen with fine manipulation and sharp dissection [44].

None of our patients experienced any form of local or systemic adverse events. This finding was correlated to previous studies [45,46]. In general, ICG is one of the safest medical dyes. Although a few case reports reported anaphylactic reactions owing to the iodine component, the exact pathophysiology was undetermined [47].

Conclusion

The ICG fluorescence technique is a feasible method for the identification of sentinel LNs. The ICG fluorescence method permits a high detection rate of SNs and transcutaneous identification of lymphatic flow pathways with high safety and with no adverse effects from ICG. This technique has a great potential as an alternative method for the traditional SN biopsy using the radioactive agents or the blue dyes.

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Nil.

Conflicts of interest

No conflict of interest.

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