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Indocyanine Green Is a Safe and Effective Alternative to Radioisotope in Breast Cancer Sentinel Lymph Node Biopsy regardless of Patient Body Mass Index

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Keywords
Indocyanine green · Body mass index · Sentinel lymph node biopsy · Breast cancer

Abstract
Introduction: A recent meta-analysis [Lancet Oncol. 2010;11:908–909] has confirmed high sensitivity of indocyanine green (ICG) fluorescence mapping for sentinel node detection in early breast cancer. Concerns have previously been raised regarding the efficacy in patients with high body mass index (BMI). ***Materials and Methods:*** All consecutive patients undergoing sentinel lymph node biopsies (SLNBs) for early breast cancer in NHS Tayside were included in a prospective audit of surgical and pathology findings. All patients included in the study received dual injection of patent blue dye and ICG. Approval was obtained from the local Caldicott guardian for collection and use of personal data. ***Results:*** Of 239 cases, all were female patients of mean age 62 years (range 27–93). In 4.2% (10/239) of cases, neither blue dye nor ICG was present in the axilla. Of the remaining 229 SLNB cases in this series, surgeons documented retrieval of 451 nodes, with a mean surgical nodal count per case of 1.97 (range 1–5) and pathological nodal count of 2.15 (range 0–7). Eighty three cases were performed in patients with BMI 30–39.9 and 21 cases with BMI ≥40, with nodal detection rates of 96.4% (80/83) and 95.2% (20/21), respectively, in these groups of patients. Twenty percent (48/229) of cases had nodal metastases on histopathology. ***Conclusions:*** This is a large single-center study which demonstrates the safety and accuracy of the combined ICG and blue dye technique for SLNB in breast cancer. This is represented by nodal detection rates and node positivity rates which are comparable to previous multicenter studies of standard SLNB regardless of BMI.

Introduction

Axillary surgery in the form of sentinel lymph node biopsy (SLNB) is widely acknowledged as a key component in the staging and assessment of overall prognosis of early breast cancer. Equal therapeutic outcomes have been proven between pathologically node-negative patients receiving either the traditionally extensive axillary lymph node dissection or SLNB [1, 2].

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The dual localization technique using blue dye (BD) and radioisotope (RI) has been promoted as the optimal and standard practice for SLNB [3]. However, there are disadvantages with the use of RI, including cumulative radiation exposure to healthcare workers and problems with surgical waste disposal. There are also considerable financial burdens and logistical issues associated with the need for a nuclear medicine department and patients traveling to different sites to ensure the correct timing of injections [4]. The recent COVID-19 pandemic has heightened some of these issues.

Indocyanine green (ICG) is a nonradioactive tracer which generates molecular fluorescence in the lymphovascular system. Light is absorbed at a near-infrared range [5], and the illuminated subcutaneous lymphatic network can be seen in real time on a monitor passing from the nipple into the axilla with the use of an infrared camera which filters out wavelengths below 820 nm [4–6], providing a valuable dimension to SLNB.

Multiple feasibility studies in recent years have studied and proven the efficacious use of ICG in the localization of sentinel lymph nodes [7–10]. However, concerns have been raised about the ability of ICG to detect nodes in patients with higher body mass index (BMI) [8] and the aforementioned studies did not have high numbers of patients with BMI over 30.

The objective of this study was to determine the accuracy and safety of ICG when used in combination with BD in SLNB. The study also aimed to assess the effect of BMI on nodal detection. Data were collected to investigate the following: (1) the sentinel lymph node localization rate, defined as the proportion of cases in whom this technique resulted in successful uptake of either tracer to nodes; (2) nodal detection rates for each tracer, defined as how many nodes retrieved by the surgeon were reported as containing either ICG and/or BD; (3) the node positivity rates, defined as confirmation of metastatic disease on histopathology.

Materials and Methods

Study Design and Patient Selection

Data were collected prospectively for consecutive patients undergoing SLNB in NHS Tayside over 14 months between May 2020 and June 2021. Approval was obtained from the local Caldicott guardian for collection and use of personal data. The study was conducted in a single institution, and all procedures were carried out by one of five surgeons.

Sentinel Lymph Node Biopsy

All patients received dual injection of BD (2 mL 2.5% Patent Blue Vby SALF) and ICG (0.8–2 mL 0.5% Verdye by Diagnostic Green, distributed by KIMAL PLC) in the subareolar region after induction of anesthesia with subsequent breast massage. Subcutaneous lymphatics were visualized using an infrared camera (SPY-PHI Photodynamic Eye Camera, Stryker Corporation, USA) [4] to guide placement of the axillary incision, and the fluorescence allowed navigation within the axillary space. All excised nodes were examined ex vivo for fluorescence. The number of sentinel nodes harvested for each patient was recorded numerically by surgeons and whether they were blue, fluorescent, or both. Surgeons were also asked to record any additional palpable nodes excised and to note if allergic reactions occurred.

Histopathology

Sentinel lymph nodes were serially sectioned at 2–3 mm intervals and subsequently stained with hematoxylin and eosin. Metastases were categorized as macrometastases (>2 mm in size), micrometastases (>0.2 mm; ≤2 mm in size or <0.2 mm within the lymph node parenchyma), and isolated tumor cells (≤0.2 mm).

Statistics

Mann-Whitney U test was used to compare the continuous variable of BMI. χ^2 test was used to compare the nodal uptake of the tracers for the various BMI categories [11].

Results

Patients

A total of 238 female patients underwent SLNB during the study period. The data of 231 patients (239 cases) were included in the analysis as shown in Figure 1. The mean age of the patients was 62 years (range 27–93), with a mean BMI of 29.6 kg/m^2 (range 16.7–53.5). One potential serious allergic reaction was documented post-induction of anesthesia. The indications for SLNB performed are summarized below as shown in Table 1.

Sentinel Lymph Node Localization Rate

In 10 cases, surgeons reported no blue nor fluorescent dye was present in the axilla. These cases were converted to axillary node sampling and excluded from further analysis. In 1 further case, the node retrieved was documented by the surgeon to be both blue and fluorescent, but no node was present on histopathology examination. Therefore, the sentinel lymph node localization rate was 95.4% (228/239).

Nodal Detection Rates for Tracer Type

Of the 229 cases in whom at least one of the nodes had some form of dye uptake, therefore designated as true sentinel nodes, surgeons documented a total of 451 nodes retrieved. The mean number of nodes retrieved per case of 1.97 (range 1–5). 82 were palpable nonsentinel nodes

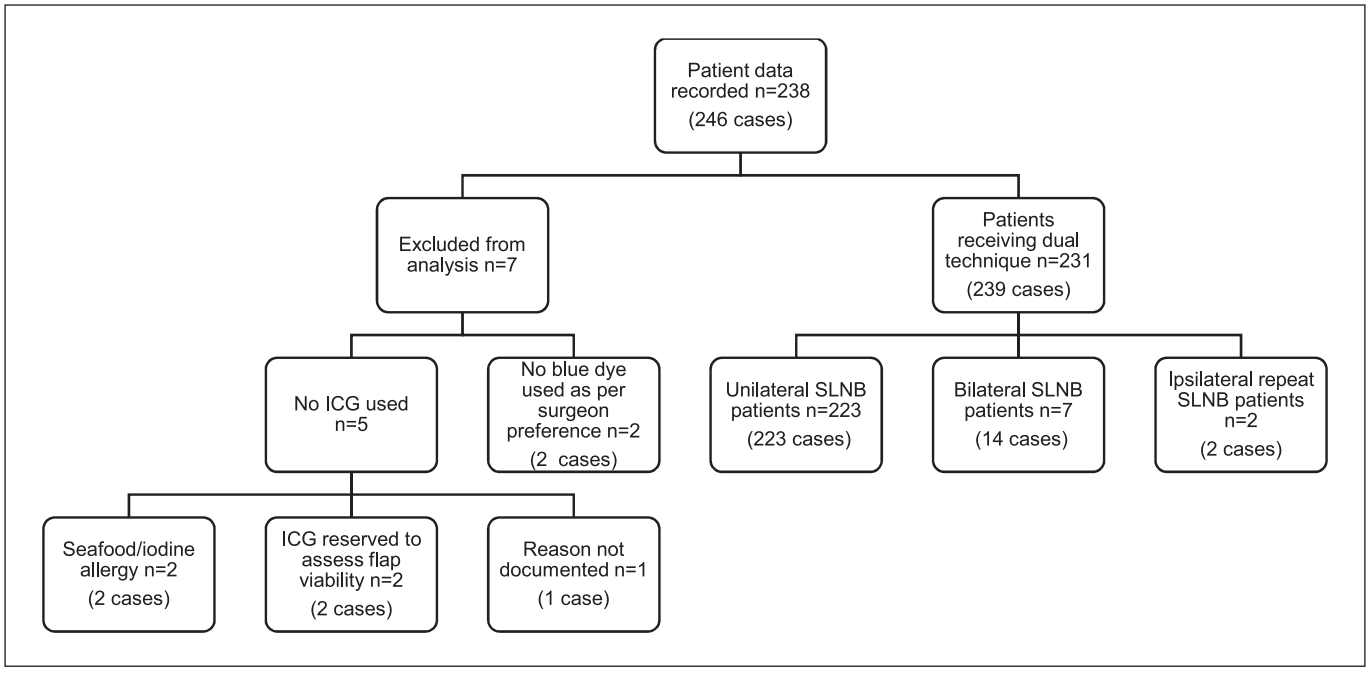

Fig. 1. Flow diagram showing the number of patients and cases studied, total 239 cases included in study.

Table 1. Indications for SLNB

Type of procedure	Cases, *n*	Sentinel node successfully localized, *n*
Primary SLNB	208	202*
SLNB-targeted axillary dissection	24	21
SLNB post-NET	2	2
Repeat SLNB for failed SLNB	2	1
Repeat SLNB for previous ipsilateral breast cancer	3	2
Total	239	228

* In one case, the node was reported by the surgeon as blue and fluorescent but no node was found on histopathology, deemed an unsuccessful primary SLNB.

and were excluded from the nodal detection rate calculation as shown in Table 2. 98.6% of all reportedly harvested nodes were fluorescent compared to only 85.1% of nodes being blue.

Nodal Detection Rates by Patient BMI

In our case series, 227 cases had uptake of ICG to nodes, and 12 did not, of whom 10 had no uptake of any tracer, and 2 had uptake of BD only. There was successful uptake of ICG at the full range of BMIs including BMI over 40 as shown in Figure 2, with no significant difference between the various BMI categories, χ^2 (3, N = 235) = 0.17, p = 0.9822. We compared the BMIs of patients who had uptake of ICG to nodes (n = 227, mean 29.5 kg/m^2 [range 16.7–53.5]) versus no uptake of ICG (n = 12, mean 30.3 kg/m^2 [range 20.6–42.7]), and there was no significant difference (z = −0.50; p = 0.617).

Node Positivity Rates

Histopathology revealed a total of 492 nodes retrieved with a mean 2.15 nodes per case for the 229 cases. The number of nodes ranged from zero to 7, as in one case no node was found on histopathology. 20.9% (48/229) of cases contained at least one sentinel node with disease

Table 2. Reported rate of uptake of each tracer per node retrieved by surgeon

Uptake of tracer in each node retrieved	Nodes reported by surgeons documented on sheet (n = 451)	Nodal detection rates, % (n = 369)
Both fluorescent and blue	309*	83.5 (308/369)*
Fluorescent only	55	98.6 (364/369)
Blue only	5	85.1 (314/369)
Nonblue, non-ICG (deemed nonsentinel)	82	N/A

* In one case, the node was reported by the surgeon as blue and fluorescent but no node was found on histopathology.

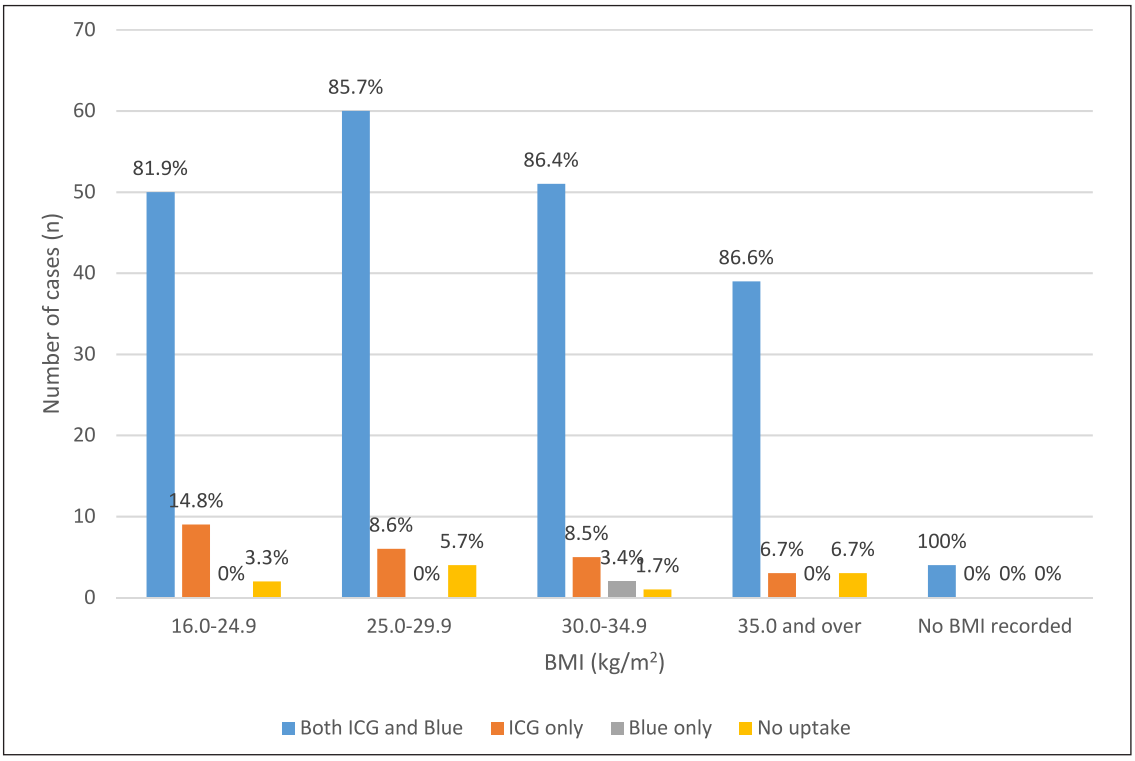

Fig. 2. Nodal tracer uptake by patients' BMI. Percentage of cases for each tracer type for each range of BMI shown above each column (p = NS).

present, with 36 of these positive cases containing macrometastases. Of the 23 cases in which only fluorescent dye was taken up, 9 cases were positive for metastases. Conversely, of the 2 cases in which only BD was taken up, there were no positive nodes identified.

Neoadjuvant Treatment Cases

Of the 231 patients, a total of 62 patients (26.41%; 65 cases) received preoperative treatment including NAC in 24 patients (24 cases), neoadjuvant endocrine therapy (NET) in 35 patients (38 cases), and window of opportunity studies in 3 patients (3 cases). Window of opportunity studies refers to research studies which use the time period between a diagnostic biopsy and surgical excision to examine the action of various pharmacological or other types of agents on tumor biology.

The nodal detection rate in patients who received NAC and NET was 87.5% (21/24) and 100% (35/35), respectively. The percentage of patients with positive nodes who received NAC was 25.0% (6/24) and 28.9% (11/38)

in NET cases. Evidence of nodal scarring or downstaging was seen in 11.3% of cases (7/62), of whom 3 had received NAC and 4 had received neoadjuvant letrozole.

Discussion

The data presented from our study reflect the introduction of the ICG-BD technique at a high-volume single-center practice and are one of the largest prospective studies undertaken. We report a sentinel lymph node localization rate of 95.4% for ICG-BD technique, which is comparable to previous smaller studies of this technique [4, 12, 13] and is favorable when compared to the outcomes for standard RI-BD dual technique of 94% [14].

Included in this study series are 2 patients who required repeat SLNB as no nodes were found from their first SLNB on histopathology. The first patient's initial SLNB was performed alongside a localized (Magseed) wide local excision of the ipsilateral breast and occurred outside the study period. Their repeat SLNB revealed neither blue nor ICG, so axillary node sampling was performed. Of note, all four nodes harvested were negative for cancer metastases. The second patient's initial SLNB documented a both blue and fluorescent "node." The subsequent repeat SLNB successfully retrieved a node which was fluorescent only with no BD. This node was negative for cancer metastasis. The first case was performed near the beginning of the study time period, likely reflecting a short learning curve associated with this technique. Failure of the second attempt could be attributed to possible disruption of the lymphatic pathways caused by the first surgery.

One patient in this case series was documented to have a potential serious allergic reaction. The patient had become tachycardic and hypotensive following injection of both the ICG and BD after induction of anesthesia. The Medicines and Healthcare products Regulatory Agency (MHRA) estimated that the incidence of serious allergic reactions with the use of Patent Blue V is 1/1,000 on the basis of a clinical trial [15]. This is in contrast to Verdye ICG which carries less than a 1/10,000 risk of anaphylaxis as reported in the MHRA Summary of Product Characteristics [16]. In this patient, serum tryptase levels confirmed likely anaphylaxis. Although we could not be certain of the cause, the above data show that BD is more likely to have been the culprit.

ICG appears to have outperformed BD in our series, with the nodal detection rate for ICG of 98.6% (364/369), consistent with existing literature which showed nodal detection rates between 97 and 100% [8, 12, 17]. We demonstrate a nodal detection rate for BD of 85.1% (314/369); previously reported rates were between 83 and 93% [8, 17]. We provided opportunity for feedback from the surgeons about this dual technique in the free text box on our data collection sheets. There were no comments to suggest that the concurrent use of both tracers affected either the fluorescent signal or the identification of the blue color of the nodes. The significance of this superiority of ICG is also emphasized by the higher rate of node positivity in those that had only ICG uptake (9 of 23 cases), with none of the BD only cases (0 of 2 cases) containing metastasis. However, these results were not statistically significant when subjected to a Fisher's exact test ($p = 0.52$). We suspect this was due to our relatively small sample size and should be studied further.

Previous studies have demonstrated that ICG results in higher nodal yields compared to BD or RI [18, 19]. Our mean nodal yield of 2.1 per case in this series is reassuringly comparable to the average of 2.3 nodes in the study performed by Sugie et al. [17]. There is increasing evidence in the context of SLNB post-neoadjuvant therapy that a higher nodal yield is in fact more accurate and may be advantageous rather than avoided [20–22].

A hypothetical disadvantage to ICG is that it has a lower tissue penetration capacity compared to RI as the fluorescent imaging is known to be possible to a subcutaneous depth of 1.0–2.0 cm [8, 12, 23]. This could mean worse performance in obese patients, and a previous study reported that nodal detection with ICG was difficult with BMI >40, although there were only 3 patients in that study's subgroup [8]. In our series, there were very few cases of failed ICG uptake and there were no significant differences in success with the range of patient BMIs. In particular, we note that among patients with BMI ≥40, 19 had positive ICG uptake and only 1 had no ICG or BD uptake. We would therefore suggest that in real-world practice, ICG is effective in patients across the BMI spectrum, including those with BMI over 40.

In our study, 20.9% (48/229) of cases were positive for nodal metastases. These node positivity rates are comparable with our previously published node positivity rates comparing RI-BD SLNB with axillary node sampling [24]. In this series, there were higher rates of node positivity in those that had uptake of ICG only (39.1%) compared with BD only (0%). We would therefore caution against use of BD only on the basis of this series.

Two patients were not given ICG due to a history of seafood or iodine allergy. In fact, iodine allergies should not be synonymized to shellfish allergies. This is because it is actually the noniodinized proteins in shellfish which are responsible for seafood allergies [25]. Moreover, patients with

known allergies to macromolecular iodide or iodine containing compounds can be given ICG as ICG contains the compound salt sodium iodide rather than iodine alone [26]. However, caution may need to be exercised when administering ICG to hyperthyroid patients as the iodide compound can be synthesized to form thyroid hormones [27].

Limitations

This was a single-center study representing our local practice. As all harvested nodes were placed in a combined specimen pot, we were unable to identify precise node positivity rates according to whether individual nodes were fluorescent, blue, or both.

We did not have sufficient numbers of patients who had undergone neoadjuvant therapy in this series to conclusively study this group but found the technique to be successful in these cases.

We are aware that our patients are predominantly white Caucasians. Further study is recommended to ensure representation of different ethnic backgrounds and skin tones.

Conclusion

This prospective observational study confirms the accuracy and safety of the dual ICG and BD technique for SLNB in early breast cancer patients regardless of BMI. The results from this study show comparable sentinel node identification rates and node positivity rates to other studies of dual tracer techniques. Furthermore, nodal yields were satisfactory and not excessive. ICG consistently outperformed BD when nodal detection rates were compared and was successful at detection in patients with a broad range of BMI.

Statement of Ethics

Ethical approval was not required for this study in accordance with local and national guidelines. Approval was obtained from the local UK Caldicott Guardian Council for collection and use of personal data to enable us to audit service improvement. Written informed consent was not required from participants for this study. This was also decided by the local UK Caldicott Guardian council.

Conflict of Interest Statement

We, Samantha Ng, Vassilis Pitsinis, Emad H. Elseedawy, Douglas Brown, Alessio Vinci, Benjamin A. Jones, and E. Jane Macaskill, the authors of "Indocyanine green is a safe and effective alternative to radioisotope in breast cancer sentinel lymph node biopsy regardless of patient body mass index," have no conflicts of interest to declare. We confirm that we have no known current or potential competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We, Samantha Ng, Vassilis Pitsinis, Emad H. Elseedawy, Douglas Brown, Alessio Vinci, Benjamin A. Jones, and E. Jane Macaskill, the authors of "Indocyanine green is a safe and effective alternative to radioisotope in breast cancer sentinel node biopsy regardless of patient body mass index," hereby declare that we have no involvement with any financial sponsors throughout this study. We did not receive any sources of funding which has impacted or influenced the study design, the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Author Contributions

Samantha Ng, Vassilis Pitsinis, Emad H. Elseedawy, Douglas Brown, Benjamin A. Jones, Alessio Vinci, and E. Jane Macaskill all contributed to the data acquisition of this study. E. Jane Macaskill contributed substantially to the conception and design of this study, and ensured quality control of data and algorithms. E. Jane Macaskill and Samantha Ng conducted data analysis and interpretation and performed the statistical analyses in this study. All named authors participated in the preparation and critical revision of this manuscript. All authors have given their final approval of this version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Samantha Ng at samantha.ng@lanarkshire.scot.nhs.uk upon reasonable request.

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