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The use of indocyanine green to detect sentinel nodes in breast cancer: A prospective study

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Abstract

Background: Although Indocyanine green (ICG) is used to find sentinel nodes (SN) in patients with breast cancer (BC), its role in clinical practice is still debated, and needs a definitive validation to be included in the standard approach to finding sentinel nodes in breast cancer.
Materials and methods: To validate the ICG methods of detecting the SN in BC we have recently concluded a prospective validation trial. Patients with clinically node-negative, invasive early BC scheduled for breast surgery and SN biopsy were included in the trial. All the patients underwent SN detection using both the standard-of-care procedure using radioisotope technetium (99mTc) and the ICG, using the Photodynamic Eye camera. A comparison of the detection rate and the diagnostic accuracy of the two methods was performed to detect the equivalency of the two approaches.
Results: At the end of the enrolment, 301 patients were considered eligible and included in the trial, and 589 nodes were removed. Five hundred and eighty-three nodes (99%) were identified with ICG (median 2 nodes per patient) and 452 (76.7%) were identified with 99mTc (median 2 nodes per patient). A concordance index of 98.75% (CI, 95% = 97.1%–99.5%) was detected. The dosage given ranged from 0.3 to 1.4 ml. ICG was used in all patients eligible for SN biopsy without any significant acute side effects.
Conclusions: The index of concordance between 99mTc and ICG seems to be extremely high, suggesting that ICG could be validated as an alternative method to 99mTc in the detection of SN in BC.

Keywords: Indocyanine green; Sentinel node; Breast cancer surgery

Introduction

Axillary lymph node (LN) status is one of the most important prognostic factors in women with early breast cancer (EBC), and histological examination remains the most accurate method of assessing the spread of disease to these LNs. However, in recent years, axillary LN dissection (ALND) as a staging procedure has been progressively replaced by sentinel LN biopsy (SN biopsy). This is a much less morbid technique, and SN biopsy alone was rapidly accepted as an alternative to ALND for the surgical management of the axilla in patients with node-negative disease.[1–5] New studies have challenged the need for ALND even in patients with limited axillary lymph node metastatic involvement after SN biopsy. This shows that, compared with SN biopsy alone, ALND did not improve survival or reduce loco-regional recurrence, whilst maintaining a significantly higher morbidity.[6–9]

SN biopsy is currently a highly standardized technique and the radioisotope technetium (99mTc) and vital blue dyes are amongst the most widely used enhancers for SN identification, however some limitations in the various

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mapping agents have been highlighted and new methods for sentinel lymph node biopsy are being explored.[10,11]

Indocyanine green, a fluorescent dye, aroused the interest of surgeons as a mapping agent for SN detection,[12] and previous studies in EBC have demonstrated that ICG can be used together with radiolabelled colloid and/or blue dye to identify SNs in EBC.[13–15] A recent meta-analysis on ICG fluorescence-guided SN biopsy in different tumours indicates that this technique is safe and promising for detecting the presence of LN metastases with possible advantages compared to 99mTc.[16] However the number of eligible studies and enrolled patients was limited, and the need for larger and well-designed studies was underlined.[16]

The aim of this study was therefore to compare the performance of ICG and 99mTc, selected as the gold standard for SN mapping,[17–20] in a large number of consecutive EBC patients.

We additionally aimed to evaluate the diagnostic accuracy of a combined ICG-conventional technique, the associated operational times, and the doses appropriate for SN mapping in BC patients.

Methods

The study was approved by the local ethical committee (Eudract registration N°2012-000513-3) and performed in accordance with the ethical standards of the Declaration of Helsinki.

Patient selection

All consecutive potentially eligible patients with clinically node-negative invasive or microinvasive EBC confirmed by core biopsy, each of whom planned to undergo an SN biopsy procedure at Santarcangelo di Romagna Hospital (Rimini, Italy) between July 2012 and December 2013, were invited to participate in this open non-randomized trial. All patients gave written informed consent. Exclusion criteria were neoadjuvant treatment, thyroid dysfunction, renal or hepatic dysfunction, pregnancy, lactation, or known allergy to iodine.

Surgical technique

Approximately 12–18 h prior to surgery, the enrolled patients underwent the standard-of-care SN procedure using 99mTc. ICG fluorescence-guided SN detection was performed using the Photodynamic Eye® (PDE) Hamamatsu Photonics, Hamamatsu, Japan. ICG PULSION® 25 mg (Pulsion Medical, Inc., Irving, TX, USA) was used, diluted with 5 ml of distilled water (for injection). For all patients, injection with ICG (dose range, 0.4–1.2 ml) was administered under local or general anaesthesia. (Fig. 1). For unicentric cancers, the injection was performed subcutaneously above the tumour site. For multicentric cancers, a periareolar injection was performed (Fig. 2). The time between injection and skin incision was recorded. The incision was performed when the tracer was localised in the axilla (Fig. 3). Dose was selected using an empirical method that was tested on the first 50 patients and then used for all remaining patients. The empirical dose ranged from 0.4 to 1.2 ml according to the patient's body mass index (BMI), breast volume, and tumour site (quadrant).

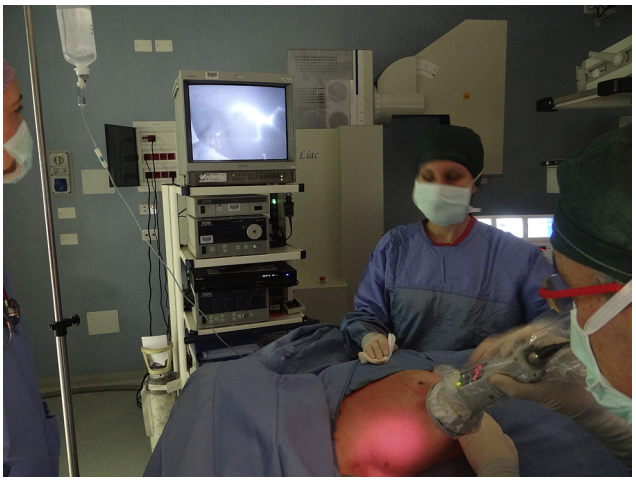

Figure 1. Injection of indocyanine green.

After incision, SNs were localised using an infrared torch PDE; and subsequently removed. The PDE is an infrared light-emitting camera which clearly visualises the lymphatic drainage pathway, and accurately pinpoints the locations of SNs in real time in the operating room. All the SNs that were removed using the PDE were checked with a Scinti-Probe to confirm radioactivity. At the end of the procedure, the Scinti-Probe was placed in contact with the axilla to verify the presence of any remaining radioactive SNs, which had not fluoresced green under

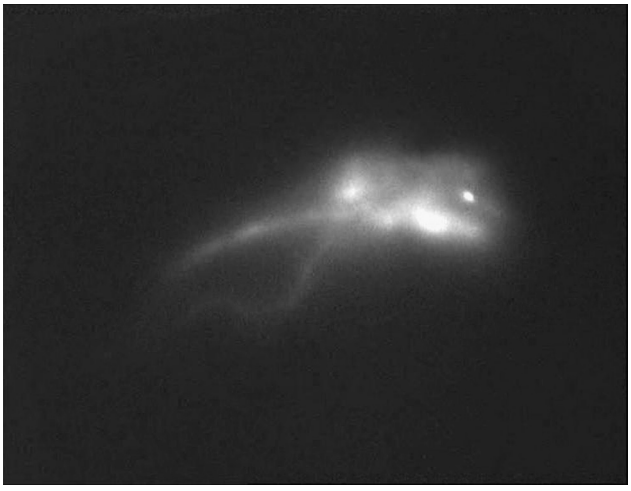

Figure 2. View of indocyanine green after injection.

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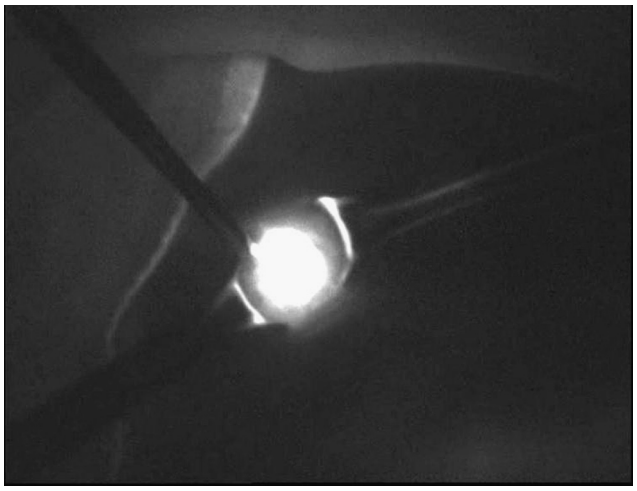

Figure 3. Viewing the sentinel lymph node.

the PDE. When an SN positive for macrometastasis (>2 mm) was identified in this manner, an axillary dissection was performed, irrespective of SN radioactivity.

Statistical analysis

The radioactive tracer was treated as a gold standard and was assumed to capture at least 97% of the LNs.

To demonstrate the equivalence between the 2 methods with a margin of 5%, assuming an alpha error of 5% and a power of 80% we planned to assess at least 260 nodes of BC patients. The detection rate of the 2 methods was compared using the chi-square test, assuming an alpha error of 5% as the index of statistical significance. The clinical correlation between the number of removed LNs and BMI, and between the doses and the time interval between injection and SN removal were assessed using the Student *T*-test, assuming an alpha error of 5% as the index of statistical significance. The correlation between the number of removed LNs and breast size, was assessed using the Kruskal–Wallis non-parametric test assuming an alpha error of 5% as the index of statistical significance.

Results

Patient characteristics

From July 2012 to December 2013, the ICG plus 99mTc method was used to find SNs in 301 consecutive cases of female BC. The median patient age was 59 years (range 35–90 years). One hundred and forty-three patients had cancers of the left breast and 158 had cancers of the right breast. Two hundred and thirty-eight patients (79.1%) underwent breast-conserving surgery (quadrantectomy) and 63 (20.9%) underwent mastectomy (41 with simultaneous breast reconstruction). Local anaesthesia was employed in 36 cases (12%) and general anaesthesia was employed in 265 cases (88%). The median tumour size was 14.6 mm (6–90 mm). In 49 cases (16.5%), the tumour was larger than 30 mm. In 257 cases (86.5%) the cancer was unifocal and in 40 cases (13.5%) it was multifocal. In 12 cases, the patient had undergone previous ipsilateral quadrantectomy with SN biopsy. In only one of these cases, the SN was not found; this was most likely a result of previous surgery, and it was necessary to perform an axillary dissection.

Technical aspects and comparison data

The time from the injection of ICG and skin incision was 3–15 min (median, 4 min), and the nodes were removed in 5–30 min (median, 10 min). The median dose of ICG was 0.8 ml, and 95% of patients received a dose of 0.5–1.0 ml. There was no significant correlation between the removal of a smaller number of ICG-positive LNs (1 or 2) versus a greater number of positive LNs (>2 LNs) and ICG dose ($p = 0{,}86$), BMI ($p = 0.37$), breast size ($p = 0.75$), or the time interval between injection and SN removal ($p = 0.15$) (Table 1).

Identification of SNs was successful in 297 of the 301 subjects using ICG fluorescence imaging, or the combination of ICG fluorescence imaging with radioactive guidance. In 4 patients, SNs were not found and axillary dissection was performed. In the remaining 297 patients, at least one SN was identified using ICG. However, only 287 patients (95.4%) had at least 1 SN that was identified

Table 1
Characteristics of the patients according to BMI.

BMI	Numb	Dose/ml ICG (median)	Time/min injection – incision (median)	Number LNs hot removed (median)	Number LNs fluorescent removed (median)	Detection rate ICG	Detection rate 99mTc
<20	18	0.5	2	2	1	18/18 100%	18/18 100%
20–25	174	0.6	4	2	2	172/174 98.9%	166/174 95.4%
26–30	58	0.7	4	2	2	57/58 98.3%	55/58 94.8%
>30	51	0.9	4	2	2	50/51 98%	48/51 94.1%

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with 99mTc. The difference met the statistical requirement for significance (ICG vs. 99mTc, chi-squared test $p < 0.05$) (Table 2).

A total of 589 SNs (range, 1–5 per patient) were resected. Of these SNs, 98.7% were ICG fluorescent (95% CI, 97.1%–99.5%). Five hundred and eighty-three SNs (99%) were identified using ICG (median, 2 nodes per patient: range 0–5) and 458 SNs (77.7%) were identified using 99mTc (median, 2 nodes per patient: range 0–5), 452 nodes (76.7%) were both fluorescent (positive for ICG) and hot (positive for 99mTc), 131 nodes (22.3%) were fluorescent but cold (negative for 99mTc), and 6 (1%) were not fluorescent (negative for ICG) but hot. Overall, ICG identified more SNs per patient than did 99mTc (1.94 SNs per patient vs. 1.62 SNs per patient; Table 3). Seventy metastatic nodes were found in 46 patients (15.5%). Fifty-five of 70 metastatic nodes (84.5%) were fluorescent and hot, 15 (21.4%) were fluorescent but cold, and none were hot but not fluorescent (Table 4). Forty-six total axillary dissections were performed.

One hundred and thirty-one LNs were collected using ICG (cold for 99mTc), of which 15 (corresponding to 12 patients) had a metastatic biopsy. Six of the 12 patients actually had a true benefit from ICG, since the other 6 patients already had a hot 99mTc node and metastatic biopsy.

In summary ICG was the only tracer to highlight at least one SN in 10 patients (Table 5), and thereby prevented the removal of the entire axilla. In another 6 patients ICG identified a metastatic node that was cold at 99mTc examination. Overall, the use of ICG provided an advantage in 16 cases (5.3%) without a significant increase of acute complications. There were no allergic reactions. In the 30 days following surgery, 9 of the 277 patients (3.2%) developed seromas and 7 of the 277 patients (2.5%) developed paraesthesia.

Discussion

Assessment of axillary LN status remains a very important step for evaluation of prognosis and selection of adjuvant treatment in early BC, despite the increasing importance of biological characterization and acknowledgement of tumour heterogeneity in treatment choice.[21]

The transition from ALND to SN biopsy represents an important step forward in the bid to minimise the morbidity of surgical BC treatment and the technique is well standardized, reproducible, with high detection rate and diagnostic accuracy.[1–5,17–19] Technetium-labelled nanocolloid and/or blue dye represent the more frequently used enhancers for SN mapping, but despite its clinical effectiveness, the procedure has drawbacks partially related to the characteristics of these agents.[11]

The use of isosulfan blue dye for SN biopsy is associated with a significant number of allergic reactions, some of which are life-threatening.[10]

Methylene blue dye is an accurate and cost-effective single agent for SN mapping in EBC.[10,22,23] It has a low risk of allergy, few side effects (blue discolouration of urine, stool and skin), and local effects at the injection site are temporary and benign. However, it can cause skin necrosis if improperly injected[24] and is generally avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, thalassaemia or drepanocytosis, because it may aggravate methemoglobinaemia or precipitate haemolytic anaemia.[25]

Technetium-colloid is more expensive, cumbersome (requiring time-consuming preoperative preparation and increased operating time), and demands specific logistical arrangements due to regulations regarding handling of radioactive material, therefore limiting the number of hospitals which is permitted to use radioactive tracers.[25]

Indocyanine green is a promising tracer which, after being administered intradermally, flows to the sentinel node and additionally, unlike blue dye, it is visible in infrared light through the skin. The medical use of ICG began in 1950, but in recent years there has been renewed interest in the use of ICG for SN detection for a variety of cancers, including BC, melanoma, gastric cancer, colon cancer, and cancer of the vulva.[16,28,29]

Near-infrared (NIR) fluorescence emission from ICG is undetectable by human eyes and an appropriate intraoperative detection system is required to produce real-time images with a high signal-to-background ratio (SBR); current fluorescent imaging devices enable visualized and real-time lymphography. Detection with ICG can be

Table 3
Number of sentinel lymph nodes (SN) found for patient.

SN	ICG	99mTc
0	4	14
1	107	168
2	112	88
3	62	21
4	9	6
5	7	4

Table 2
Patients with SN positive and negative for 99mTc and ICG.

	99mTc positive	99mTc negative	Total
ICG positive	287 (95.34%)	10 (3.33%)	297 (98.67%)
ICG negative	0	4 (1.33%)	4 (1.33%)
Total	287 (95.34%)	14 (4.66%)	301 (100%)

Sentinel nodes positive and negative for 99mTc ICG*.

Table 4
Metastatic nodes positive and negative for (99)technetium-colloid (Tc) and indocyanine green (ICG).

	Tc negative	Tc positive	Total
ICG negative	/	0	0
ICG positive	15 (6 patients)	55 (40 patients)	70 (46 patients)

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Table 5
Patients with SN cold for 99mTc.

Patient	Age	Surgical procedure	Multifocality	Tumor dimension mm.	Num SN fluorescent (positive at ICG)	Metastatic SN	Metastatic node/ALND	Previous surgery breast/axilla
QR	50	Mastectomy	No	55	0	X	23/23	No
LR	62	Mastectomy	Yes	18	0	X	8/25	No
LM	59	Mastectomy	No	10	0	X	0/15	Yes (quadr. + SN)
CA	64	Quadrantectomy	No	7	0	X	0/14	No
CA	86	Mastectomy	No	35	1	1	3/19	No
PM	81	Quadrantectomy	No	5	2	0	X	No
CE	75	Quadrantectomy	No	14	2	2	8/30	No
BE	45	Quadrantectomy	No	15	1	0	X	No
LV	46	Quadrantectomy	No	12	3	0	X	No
BA	59	Quadrantectomy	No	12	2	0	X	No
KR	70	Mastectomy	No	50	2	0	X	No
VE	65	Mastectomy	Yes	15	3	0	X	No
CF	41	Mastectomy	Yes	10	3	0	X	No
MM	51	Mastectomy	Yes	30	2	2	20/20	No

performed in the operating theatre immediately after the induction of general anaesthesia and without any discomfort for the patient. Local anaesthesia may be performed in cases without complications.

As compared with 99mTc, ICG has different possible advantages:

1) Organisational: involvement of a nuclear medicine department is not necessary; the use of radioactive material is reduced, and waste disposal is a less substantial issue.
2) Social: patients no longer need to have 99mTc or other radioactive material injected at a nuclear medicine department (on the morning of or the day before surgery). Further, the ICG technique can be performed in the operating room immediately after the induction of general anaesthesia and without any discomfort to the patient.
3) Operative: when radio-guided occult lesion localisation (ROLL) is combined with SN biopsy, SN detection with ICG avoids the superposition of 2 radioactive tracings at the injection site, favouring tumour detection.

Ahmed et al. in their systematic review found that ICG was significantly better than blue dye in terms of improved SN identification in EBC, while there was no statistically significant difference between ICG and radiocolloid.[11] Recently Ballardini et al. expanded our knowledge about the performance of ICG as a mapping agent for SN biopsy in EBC with their study in a large series of patients.[30] The ICG method detected 99.6% of all SNs, and concordance with 99mTc was as high as 93.5%, suggesting that ICG could be used alone to reliably identify SNs.[30]

However, ICG is also associated with some drawbacks as compared with 99mTc. ICG's small molecular size means it can identify a higher number of SNs, leading to the removal of a larger number of nodes; after ICG injection and before skin incision, it is necessary to wait for ICG to migrate to the axilla (ca. 3–10 min). Detection of fluorescent SNs is more difficult in patients who are obese, although this is also true of 99mTc mapping[14] and it requires specialized training. Lastly ICG cannot be used in patients with iodine allergy, because it contains iodine. Further, there is no consensus regarding the appropriate ICG dose or the optimal time between injection and skin incision.[16] The SN detection rate and the number of LNs that are removed could both be improved by identifying the optimal ICG dose and injection-incision interval.

Our study, which represents at present the largest analysis of ICG in EBC, builds upon the existing debate. Identification rate of SN with ICG was 98.67%. Overall, 98.7% (95% CI, 97.1%–99.5%) of the removed 99mTc positive sentinel nodes were ICG fluorescent, a finding that is consistent with the previous literature, and suggests that the ICG technique is feasible and not inferior to the 99mTc technique.[6–8,15,16,24,26,27,30,31] As compared with 99mTc, ICG identified a higher number of SNs. It is worth noting that some of these excess SNs (12 SNs, corresponding to 2%) were positive for metastases, an observation already suggested by other authors.[33] Although our study was designed to demonstrate the equivalence of ICG compared to 99mTc, data seem to suggest that ICG improves detection rate by a statistically significant amount compared to 99mTc (ICG = 98.6%; 99mTc = 95.34%).

Indeed, we could not confirm a difference in the SN detection rate according to BMI as previously reported.[34]

The power of the data presented here is limited by the empirical method used to determine ICG dose. We assumed that the doses used in previous experiences[30,32] could be reduced and tailored to patients characteristics in order to reduce the number of removed nodes. However within the

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dosages used (0.4–1.2 ml) the number of removed nodes was identical.

Amongst the limitations of this study was its design as a non-blind cohort trial: a potential source of bias; however a double-blind study was unfeasible. The identification rate of SN with ICG leads to the removal of a larger number of nodes, with possible side effects, and in the absence of a medium-long term follow-up there is limited information about the real incidence of arm lymphoedema.

In conclusion, we believe that ICG could be a promising technique for SN detection in BC. The method seems reproducible, safe, eliminates exposure to ionizing radiation and is potentially cost-saving, despite requiring specialist training. Additionally it could be an option for breast cancer centres with no nuclear medicine supply. Furthermore, we suggest that the detection technique outlined in this paper, which combines ICG with 99mTc in specific cases, is the best way of implementing the ICG method without exposing patients to additional risks during the learning process.

Conflict of interest statement

The authors certify that they have no financial or other conflicts of interest regarding the material discussed in the manuscript.

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