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Near-infrared fluorescence imaging for the prevention and management of breast cancer-related lymphedema: A systematic review

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ABSTRACT

Sentinel lymph node identification by near infrared (NIR) fluorescence with indocyanine green (ICG) is recognized in the literature as a useful technique. NIR fluorescence technology could become key in the prevention and management of lymphedema after axillary dissection for breast cancer. Here, we conducted a systematic review focusing on ICG imaging to improve lymphedema prevention and treatment after axillary surgery.

A systematic literature review was performed using MEDLINE and Embase to identify articles focused on ICG imaging for breast-cancer-related lymphedema (BCRL). Qualitative analysis was performed to summarize the characteristics of reported ICG procedures. In situ tissue identification and functionality assessment based on fluorescence signal were evaluated. Clinical outcomes were appraised when reported.

Studies relating to axillary reverse mapping, lymphography and upper limb supermicrosurgery combined with ICG imaging were identified. We included a total of 33 relevant articles with a total of 2016 patients enrolled. ICG imaging for axillary reverse mapping was safe for all 951 included patients, with identification of arm nodes in 80%–88% of patients with axillary lymph nodes dissection. However, the papers discuss the oncologic safety of the approach and how - regardless of the contrast agent - concerns limit its adoption. ICG lymphography is openly supported in BCRL management, with 1065 patients undergoing this procedure in 26 articles. The technique is reported for lymphedema diagnosis, with high sensitivity and specificity, staging, intraoperative mapping and patency control in lymphaticovenular anastomosis. The substantial advantages/disadvantages of ICG imaging procedures are finally described.

Introduction

The most prevalent cancer in the world is breast cancer, with 266 000 new cases in the US each year (SEER database). In fact, 12.4% of women in the world will have breast cancer. The outcomes for patients with breast cancer are improved if they have access to a full range of treatment options in a multidisciplinary setting [1,2]. Mastectomy and axillary dissection can damage the upper-limb lymphatic system, with undesirable consequences for its ability to remove excess water, proteins and other cell products, leading to their accumulation in the extracellular spaces of the arm and hand [3]. It is a chronic and progressive disorder with internal and external signs of anomalous lymph transport and lymphatic system deficiency. After axillary lymph node dissection (ALND), incidence of lymphedema is between 7% and 49%, and even after sentinel lymph node biopsy there is still a risk of lymphedema in up to 13% of cases [4–7]. Furthermore, when radiotherapy is added to ALND, the risk of lymphedema increases with an odds ratio of 2.74 [8]. Although the majority of lymphedema cases are reported to develop within one year following breast cancer surgery, it can

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develop at any time after surgery. It may be mild to severe and, if left untreated, arm lymphedema has a significant tendency to increase with time, both in terms of the volume of the edema and the stage of tissue fibrosis [9]. For this reasons, efforts have been made to prevent the risk of severe damage to the lymphatic system at the time of surgery, by reducing indication for extensive surgery with axillary sentinel lymph node (SLN) biopsy in routine procedure. Different agents have been used, based on various kinetics, such as blue dye, isotope and more recently indocyanine green (ICG).

Thus, near-infrared (NIR) fluorescence seems to be a useful diagnosis tool for SLN identification in breast cancer surgery and promising results are reported in a hundred articles [10]. In particular, real-time imaging to guide surgical procedures has attracted interest with the development of a new generation of NIR fluorescence devices used in combination with ICG [11]. ICG is a heptamethine cyanine fluorophore, and is the only NIR fluorophore clinically approved by the FDA for ophthalmic angiography, and for determining cardiac output, hepatic function and liver blood flow. These approvals have been in place for several decades but ICG has not yet been granted approval in oncology. Nevertheless, ICG is the most reported fluorescent contrast agent for fluorescence-guided cancer surgery, primarily for liver surgery and SLN identification. ICG is safe to use, with very few side effects and low toxicity [12]. The maximum spectral absorption of ICG is 800 nm (between 780 nm and 805 nm) and its emission peak is at 820 nm, allowing fluorescence imaging without autofluorescence background noise. The fluorescent dye is commonly injected by systemic administration but subcutaneous injection is also successfully reported for fluorescence imaging of lymphatic pathways and lymph nodes [13,14].

With real-time lymphatic pathways highlighting, ICG imaging could answer many expectations to reduce incidence and treat Breast Cancer Related Lymphedema (BCRL) [15]. The purpose of this systematic review is to give a complete overview of the major developments in ICG fluorescence imaging for BCRL to analyse the scope of clinical results and to provide directions for future research.

Methods and materials

Literature search strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed [16]. A literature review was conducted until December 2018 with no restrictions on publication date, study design, population, type of breast cancer surgery or type of lymphatic surgery by MA and FDL. All titles and abstracts in English were retrieved from the search and screened and assessed for eligibility. Furthermore, the reference lists of the selected papers were reviewed for additional articles. Any discrepancy in the search was discussed between the two authors and consensus was reached following discussion. The search strategy is illustrated in Fig. 1.

Data extraction

The extraction of data was based on study design, type of surgery, number of patients, ICG posology, type of NIR fluorescence camera, imaging protocol and optical signal analysis.

Information sources

The database search included the MEDLINE and Embase databases. clinicaltrial.gov was also used to find relevant sources. Although every attempt was made to eliminate redundancy in the data, we cannot rule out the possibility that one or more individuals may have participated in more than one study.

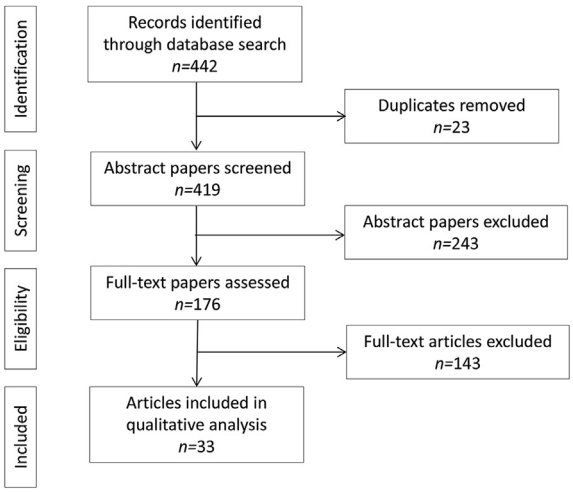

Fig. 1. Systematic record selection.

Inclusion criteria

To be included, studies had to meet the following criteria: (1) use of fluorescence ICG imaging, (2) treatment of breast cancer, (3) breast cancer related lymphedema, (4) *in vivo* data acquisition on human tissues, (5) article in English.

Exclusion criteria

The following studies were excluded: (1) ICG-SLN studies, (2) reviews, letters and comments on articles, (3) abstracts and proceedings.

Assessment of study quality

For the systematic review, all clinical studies were assigned a level of evidence (LOE) adapted from the Oxford Centre for Evidence-Based Medicine, on methodology and study design, and from the Centre for Reviews and Dissemination of the University of York. The assigned levels were LOE1, randomized control trial (1a) and quasi-experimental study (that is, non-randomized control trial, before and after study) (1b); LOE2, cohort study; LOE3, case-control study; LOE4, case series; and LOE5, case report.

Statistical analysis

The paucity of randomized control trials and prevalence of observational studies led to the decision to perform a qualitative synthesis using only descriptive statistics. No assessment of heterogeneity, publication bias or any other statistical assessment was planned.

Results

Study identification and characteristics

We identified 33 relevant articles with a total of 2016 patients enrolled. Most of the series were observational. Based on the definition of cohort studies and case series by Mathes et al. [17] and Dekkers et al. [18], 21% of clinical studies were cohort studies

(LOE2) and 66% were case series (LOE4). Designs were: cohort study (7), case series (22) and case report (4).

Study design and level of evidence

Based on the literature, ICG imaging for BCRL prevention and management was evaluated for three applications after ICG SLN exclusion. The primary outcome in breast cancer surgery was the identification of arm lymph nodes and lymphatic ducts using NIR fluorescence when axillary reverse mapping was achieved during SLN procedure or axillary lymph node dissection. Two cohort studies and five case series reported data on the subject. The second clinical application evaluated was ICG lymphography for diagnosis, mapping and assessment of evolution of BCRL. Three cohort studies and five case series with $n \geq 15$ patients, and one case report patients were reviewed. The last approach described in two cohort studies, twelve case series and three case reports was NIR fluorescence-guided supermicrosurgery to support surgery for patients who were refractory to conservative treatment.

Arm lymph node identification by NIR fluorescence imaging

Since the introduction of SLN biopsy, indication for extensive ALND has been reduced, thereby reducing the incidence of arm lymphedema. However, ALND cannot be avoided in all patients with invasive breast cancer [19] and a meta-analysis showed that patients with ALND have incidence of lymphedema that is four times higher than that of patients with SLN [20]. Several studies have shown promising results of sparing arm nodes on reducing the incidence of lymphedema after ALND [21]. In 2007, axillary reverse mapping (ARM) was proposed by Thomson et al. [22] and Nos et al. [23] to identify and preserve arm lymphatic drainage during ALND. Based on the theory that the arm and the breast each have specific paths of lymphatic drainage, the ARM nodes are identified by subcutaneous or intradermal injection of tracer into the arm prior to surgery, followed by a brief massage and elevation of the arm. The tracer then diffuses through the lymphatic ducts to the axillary lymph nodes draining the arm [24]. Initial investigators used blue dye to identify the ARM nodes but showed low detection rates (61%–71%) of ARM nodes. Moreover, it was difficult to identify lymphatic networks [22,23]. In addition, an inconvenience of blue dye injection was that staining at the injection site could persist over months. Furthermore, some surgeons are not keen to use blue dye given that hypersensitivity reactions are observed in up to 2% of cases [23]. To improve the identification rate of ARM nodes and to prevent persistent blue staining at the injection site, ARM node detection using radioisotope injection and gamma probe has been described [25]. However, the use of radioisotope alone does not enable the visualization of the lymphatic ducts, yet the purpose of ARM procedure is to preserve the lymphatic pathway.

First described by Noguchi et al. [26], NIR fluorescence imaging combined with ICG injection has since been reported in the breast oncological setting for ARM node identification and lymphatic visualization (Fig. 2) in two cohort studies and five case series (Table 1). Among the studies, we noticed variation in the volume of subcutaneously injected ICG and in injection sites [27–30]. The fluorescence technique was always safe with ICG injection to be given at anaesthesia time to more than 2 h before surgery [28]. Given that a lack of standardization of the protocol and the optimal dose of ICG to be injected, an objective comparison of the clinical results is not possible. In practice, no side effects were reported, and only a transitory green stain at the injection site (which disappeared within 10 days) was described by Noguchi et al. [31]. For a total of 951 patients, authors showed that ARM nodes can be identified in 80%–88% of patients using NIR fluorescence during ALND, and to a lesser extent during SLN incision (21%–50%) (Table 1). Tausch et al. reported failure to detect ARM nodes outside of the axilla or when there was a high tumour burden in the axilla [32]. Moreover metastatic lymph nodes that limit ICG dye diffusion could also partly explain ARM node identification rate. The difference between ALND and SLN for ARM node identification may be explained by a reported localization of fluorescent ARM nodes mainly between the axillary vein and the second intercostobrachial nerve and close to the anterior edge of the latissimus dorsi muscle regardless of the contrast agent injected, as described by Ikeda et al. [33]. In terms of number of ARM nodes identified by fluorescence, we noted variation in the studies that we examined from 1.2 to 7.2 (Table 1). Higher numbers of identified lymph nodes might be explained by a long delay between ICG injection and axillary dissection, with diffusion of fluorescent dye along the subsequent lymph nodes. Not only the fluorescence technique was useful for detecting the ARM lymph nodes but also the lymphatic ducts (in 63%–86% of cases in ALND) [31]. Difference in the visualization of the lymphatic ducts in the axilla may be related to the delay between the ICG injection and the lymphatic ducts imaging. In practice, when the drug-light interval increases, this delay may result in one lower rate of lymphatic vessels visualization. Besides, Foster et al. compared injection of blue dye and ICG for ARM node mapping and they reported better visualization of lymphatic pathways with ICG (39.1% vs 60.9%) [29].

The authors CM and AC are breast specialists with a long experience in breast oncological surgery. They first used ICG for sentinel lymph node biopsy: the technique is considered easy to perform, intuitive, with a short learning curve [34]. No more operative time is necessary. Transposition of the same procedure to perform axillary reverse mapping was the natural progression of surgical skills. They conducted a recent clinical trial (NCT02994225) in which ARM node detection and excision were fast and in the surgery time procedure, simple and available for almost 99% of patients. Training procedure is short (two patients) and surgeons get experienced after only few procedures for selecting fluorescent lymph node from lymphatic leak and vessels around axillary and thoracic veins. Most of the clinical studies used the handheld PDE (photodynamic eye, Hamamatsu Photonics) fluorescence imaging system (Table 1). Given that a new generation of NIR cameras with more sensitive detectors is now available, the quality of lymphatic mapping using ICG may increase in a near future.

Technically, the routine use of radioisotope Tc^{99m} to identify SLNs could be combined with ICG ARM procedure to preserve the lymphatic system of the arm when ALND is required. Both methods could be complementary and not competitive when radioisotope and blue dye are also injected for SLN procedures. Despite the promising results, there are some aspects that need to be considered before fluorescence ARM procedure can be used in routine clinical practice in the surgical oncology setting. Recent reviews have discussed the oncologic safety of ARM procedures, independent of the injected tracer (blue dye, radioisotope and ICG), as the major issue for technique adoption [35,36]. To date, predictors for metastatic ARM node are poorly studied but a recent meta-analysis by Han et al. of 24 prospective studies reported a metastatic rate of ARM nodes of 16.9% (95% CI, 14.2%–20.1%) [36]. Ikeda et al. showed (in 98 patients followed for up to 3 years after ALND and ICG ARM procedure) that patients with metastatic ARM nodes identified using fluorescence were significantly more affected by lymphedema than patients with ARM nodes without involvement (42% vs 13%) [30]. At last, Noguchi et al. [37] and Schunemann et al. [38] studied the link between the clinical status of lymph nodes, pNx and ARM node involvement. The reviewing of published clinical results argues for the contraindication of ARM procedure for patients with clinically node positive due to oncological concern. They

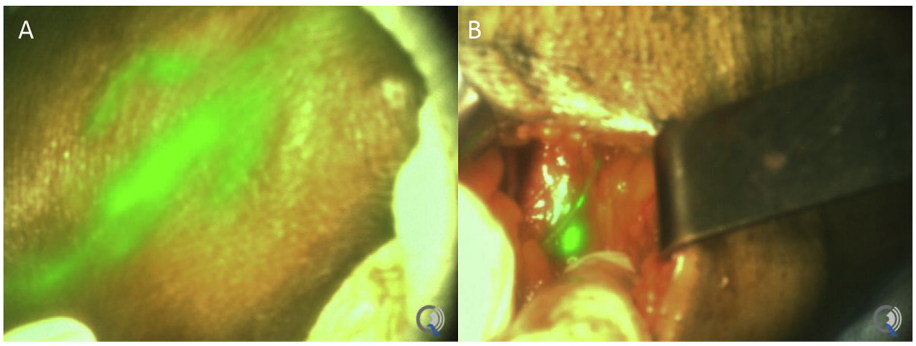

Fig. 2. A. Fluorescence signal in a lymphatic pathway of the arm after subcutaneous ICG injection in the interdigital space for axillary reverse mapping (ARM). B. Fluorescence signal in the ARM node during axillary lymph node dissection for breast cancer. Images acquisition with Spectrum camera (Quest, Middenmeer, the Netherlands).

Table 1
Clinical studies reporting ICG fluorescence imaging during the axillary reverse mapping procedure..

Authors	Number of patients	ICG administration	Imaging system	Number of cases with ARM node identification	Number of ARM nodes identified	Cases with fluorescence imaging of lymphatic pathways (%)	Study design	LOE
Noguchi [26]	20	0.1 ml (0.25 mg) inner side of the wrist	PDE	In SLNf: 6/12 (50%) In ALND: 7/8 (88%)	1.2 2.7	42% 63%	Case series	4
Noguchi [31]	131	0.1 ml (0.25 mg) inner side of the wrist	PDE	In SLNf: 42/97 (43%) In ALND: 29/34 (85%)	1.7 5.3	19% 76%	Case series	4
Ikeda [33]	60	0.5–1 ml (5 mg) at the upper inner ipsilateral arm	PDE	In ALND: 48/60 (80%)	1.6	76% without prior SLN 86% with prior SLN	Case series	4
Ikeda [30]	98	0.5–1 ml (5 mg) at the upper inner ipsilateral arm	PDE	In ALND: 80/98 (82%)	1.6 LED- 1.9 LED+	83%	Case series	4
Sakurai [28]	327	0.15 ml subcutaneously into the interdigital area	PDE	In SLNf: 77/372 (21%) (SLN = ARM node)	NA	32%	Cohort study	2
Noguchi [27]	292	0.1 ml (0.25 mg) inner side of the wrist	PDE	In SLNf: 90/292 (31%)	7.2	22%	Cohort study	2
Foster [29]	23	0.5–3 mg/ml medial aspect of the proximal arm at the intermuscular groove	SPY	In SLNf: 8/23 (35%) and 7/23 (31% after SLN resection)	NA	61%	Case series	4

ICG: Indocyanine Green, ARM: axillary reverse mapping, SLNf: sentinel lymph node field, ALND: axillary lymph node dissection, LED: lymphedema, LOE: level of evidence.

proposed the ARM procedure for patients with cN0 and SLN-positive, when the arm node is not the SLN, as arm node involvement is reported in most cases from cN1. Only randomized controlled studies can determine whether the ARM technique is secure and may reduce lymphedema when ARM nodes are preserved in ALND with a selected population, as proposed by Parks et al. [39].

ICG imaging in lymphedema mapping and staging

Diagnosis and staging of lymphedema are usually based on patients' reported experiences (for example, pain and heaviness), characteristic physical findings (for example, mobility, arm volume and arm circumference) and standard lymphoscintigraphy with the injection of radioisotope-labelled colloids into the interdigital space to monitor the lymphatic flow along the limb using a gamma camera. Lymphoscintigraphy is the gold standard but it is time-consuming and expensive, requiring licensing and a nuclear medicine department. In addition, its poor spatial resolution makes detailed analysis of the lymphatic ducts impossible [40]. ICG fluorescence imaging of the lymphatic pathway of the upper limb was first described by Yamamoto et al. for the diagnosis of lymphedema without exposure to radiation [41].

ICG lymphography for lymphedema mapping and staging has been described in BCRL, in three cohort studies, five case series and one case report [42], corresponding to data from 449 patients (Table 2). The protocols used in the studies that we evaluated show slight differences to each other but ICG was typically injected subcutaneously into the web spaces of the hand and then the fluorescent dye diffusion was measured in the lymphatic ducts from the hand to the axilla (Table 2). Fluorescence imaging of lymphatic ducts can be conducted from multiple angles, in real-time and in a user friendly way. A temporary green stain at the injection sites is reported after two weeks [43]. Mihara et al. reported sensitivity and specificity of 100% for ICG lymphography for secondary lymphedema [44]. Moreover, the results of a study by Akita et al. suggested that ICG lymphography could be useful for detecting lymphatic disorder before clinical symptoms, such as arm volume change, thereby increasing the chance of disease regression by compression therapy at an early stage [45]. In practice, for lymphatic vessels of the healthy limb, a fluorescent linear pattern is usually observed a few minutes after dye injection. In the case of lymphedema, Yamamoto et al. established a severity staging system, the arm dermal backflow (ADB) stage, to classify ICG data into five stages (I to V) [41]. The ADB stage is qualitatively subdivided into three categories, ordered splash, stardust and finally diffuse. When many patterns are visible on the arm, the most severe pattern is selected for the final diagnosis. However, ICG lymphography cannot be used to detect lymph vessels at a depth of more than 1 cm below the skin surface [44]. In addition, Zaleska et al. reported that ICG diffuses rapidly through the lymphatic wall and then may combine with tissue proteins, resulting in inaccurate pictures of lymphatics [46]. In terms of quantitative measurement, Yamamoto et al. proposed two parameters to assess lymphatic function with the determination of ICG velocity (i.e dye diffusion distance from the injection point divided by time) and the transit time after subcutaneously ICG injection in 15 patients with BCRL [47]. In the future, real-time ICG lymphatic flow imaging during

Table 2
Clinical studies (with $n \geq 15$ patients) on ICG lymphography for diagnosis and staging of breast cancer-related lymphedema.

Authors	Patients selection	ICG administration	Imaging time	Image information	Study design	LOE
Yamamoto [41]	Secondary unilateral UE-LED after breast resection and ALND ± radiotherapy	0.1 ml ICG 0.25% injected subcutaneously into the bilateral upper extremities at the second web space of the hand and the ulnar border of the palmaris longus tendon at the level of the wrist	Immediately after injection	First UE-LED classification by ADB stage	Case series	4
Mihara [44]	Secondary unilateral UE-LED, ISL stage 1, without dropout	0.2 ml ICG 0.5% injected intracutaneously into the bilateral second interdigits	Few minutes after injection	100% specificity for ICG, MRI, CT and LSc and 100% sensitivity for ICG and MRI with unaffected limb as control.	Case series	4
Yamamoto [47]	Secondary unilateral UE-LED after mastectomy and ALND	0.1 ml 0.25% ICG injected subcutaneously into the second web space of the hand	Immediately after injection	Description of quantification parameters based on ICG signal	Case series	4
Akita [45]	Breast cancer surgery ± ALND or SLN	0.3 ml ICG injected subcutaneously into the first web space of the dorsal aspect of the hand	1 h after injection	Observation of lymphatic dysfunction with ICG, before arm volume changes	Prospective cohort study	2
Tashiro [83]	UE-LED after tumour resection	0.2 ml ICG 0.5% intracutaneously injected into the second interdigits of the hand and the ulnar border of the palmaris longus tendon at the level of the wrist	15–24 h after injection	Imaging of accessory lymphatic pathways in axillary region and UE with ICG	Case series	4
Zaleska [46]	UE-LED stage II to IV, post inflammatory, post traumatic, post-surgery (mastectomy)	0.2 ml 0.5% ICG injected subcutaneously into the second and fourth interdigital spaces of the hand	Few minutes after injection	Description of clinical data provided by ICG lymphography	Retrospective cohort study	2
Zaleska [49]	UE-LED after mastectomy	0.2 ml 0.5% ICG injected subcutaneously into the second and fourth interdigital spaces of the hand	Few minutes after injection	Imaging of fluid flow by ICG lymphography to support manual drainage	Case series	4
Qin [84]	Suspicion of unilateral UE-LED	0.1 ml ICG 0.25% injected into the distal arm at three separate sites: two interdigital injections and one injection in the volar wrist	After injection and again 6 h after	Diagnostic accuracy of bioimpedance spectroscopy in comparison with ICG lymphography as reference procedure	Retrospective cohort study	2

UE-LED: upper extremity-lymphedema, ALND: axillary lymph node dissection, ICG: indocyanine green, ADB: arm dermal backflow, LOE: Level of evidence, ISL: International Society of Lymphology, Lsc: lymphoscintigraphy, SLN: sentinel lymph node.

massage for decongestive lymphatic therapy could indicate to the therapist the compression force to apply to the tissues to move the lymphatic fluid [48–50].

NIR fluorescence-guided lymphatic surgery

The quality of fluorescence images, and the suitability and safety of ICG lymphography have persuaded surgeons to support lymphatic surgery. Lymphaticovenular anastomosis (LVA) and lymph node transfer (LNT) are now proposed to patients who are refractory to conservative treatment. Intraoperative ICG imaging for physiological reconstructive surgery has been reported for a total of 616 patients: two cohort studies, twelve case series (of which four included less than 15 patients [51–54]) and three were case reports [55–57] (Table 3).

LVA corresponds to an anastomosis created between the lymphatic and venous system to improve lymphatic flow [58,59]. In practice, ICG can be injected for preoperative staging and again for intraoperative mapping of superficial lymphatic ducts with good spatial resolution of images. First, individual lymphatic ducts can be detailed quickly by the NIR fluorescence signal and guide surgeons in real-time to mark (with a pen) appropriate lymphatic pathways and incision sites [60]. As a consequence, operative time are usually reduced with fluorescence-guided supermicrosurgery [55]. In ICG-guided LVA, regions in which linear patterns are visible are generally advised for microsurgery, as incisions in these areas are likely to reveal appropriate, typically nonsclerotic, lymphatic vessels, particularly in patients with early-stage lymphedema [61]. However, Yang et al. pointed out that an incorrect ICG injection could fail to detect some functional lymphatic ducts [53]. Then, imaging with handheld NIR fluorescence camera can be completed using intraoperative NIR fluorescence microscopy for dissection guidance thanks to high-resolution fluorescence signal from lymphatic vessels [52,62]. Finally, ICG diffusion inside the vein can be used as an aid to control intraoperative anastomosis patency. After the surgery, regression of lymphedema severity can be monitored by reproducible ICG lymphography without side effects over months [63]. For repeatable ICG lymphography, Chen et al. mentioned the importance of a standardized protocol (posology and camera) and the need to use the same distance between the camera and the limb at each imaging session [63]. Studies showed a reduction in arm volume of between 33% and 61% after 12 months and 38% after 3 years in patients treated by ICG-guided LVA [60,64]. In the literature, the long-term impact of ICG administration on the skin layers and on the components of lymphatic vessels and lymph nodes has not yet been studied but such data would be valuable for patients with lymphedema. Then, the repeated intradermal or subcutaneous ICG injection should not be prescribed, today, to patients with advanced lymphedema. The follow up of patients with early stage of lymphedema by ICG lymphography may be proposed with precautions.

However, when patients had only critical patterns of the ICG lymphography staging (that is, stardust and diffuse ADB), LVA is less satisfactory [52]. In cases of severe lymphedema, surgeons may not find suitable lymphatic ducts for LVA. Thus, LNT can be proposed to reduce symptoms of lymphedema [65]. Namely, LNT is indicated to reconstruct the damaged or missing lymphatic tissue [66]. Lymph nodes are harvested from a donor site and transferred as a free flap to the lymphedematous limb [65,66]. For instance, few studies have described intraoperative ICG imaging to demonstrate lymph collecting in recipient sites by subdermal injection of fluorescent dye (0.3ml–0.6 ml) proximal to the flap [67] or by injection of 0.05 ml ICG directly into the lymph nodes [68].

Future perspectives in breast cancer related lymphedema management with optical tools

With the prolongation of patients' survival thanks to early diagnosis and modern tools, lymphedema management is becoming a major health problem following cancer treatment. Despite the value of ICG as a contrast agent for lymph node

Table 3
Clinical studies (with $n > 15$ patients) on ICG lymphography-guided supermicrosurgery for breast cancer-related lymphedema.

Authors	Number of patients	ICG administration	Injection and Imaging times	Imaging System	Applications	Study design	LOE
Chang [60]	65	0.01–0.02 ml ICG into each finger	Intraoperative: immediately after injection	PDE	Identification of functioning lymphatic vessels	Case series	4
Chen [63]	21	0.1 mL 0.25% ICG intradermal into the second and third web spaces of the hand	Preoperative: 6 h after injection 3, 6, 9 months after surgery	SPY elite system	Staging and mapping	Case series	4
Gennaro [85]	40	0.1 mL ICG subcutaneously at the second web space of the hand and the ulnar border of the palmaris longus tendon at the level of the wrist.	Preoperative: ND One year after surgery	PDE	Preoperative: Staging and mapping Postoperative: Patency of anastomosis	Case series	4
Gentileschi [86]	16	0.1 ml ICG intradermal into the second web space of the hand and at the ulnar border of the palmaris longus tendon at the level of the wrist (both hands)	Day before: Immediately after injection Intraoperative: 2x just after injection	PDE	Day before: Identification of functioning lymphatic vessels During surgery: Functioning of selected vessels Functioning of anastomosis	Case series	4
Winters [64]	29	ND	Intraoperative: 2x ND	PDE	Functioning of selected vessels Functioning of anastomosis	Case series	4
Engel [87]	124	ICG into the second and fourth web spaces of both hands	Preoperative: ND Intraoperative: ND	ND	Preoperative: Staging and (if LVA is possible) mapping During surgery: Functioning of anastomosis	Retrospective cohort study	2
Akita [88]	189	ND	6 months after surgery	ND	Lymphedema staging	Retrospective cohort study	2
Visconti [89]	37	0.2 mL ICG 5 mg/ml intradermal	Day before: Immediately after injection Intraoperative: ND	PDE IR 800(microscope Zeiss)	Day before: Staging and identification of functioning lymphatic vessels Intraoperative: Functioning of anastomosis	Case series	4
Seki [61]	30	0.1 ml ICG 0.25% intradermal into the second web space of both hands, at the anterior border of the styloid process of both radii, and at the anterior border of the styloid process of both ulna	Preoperative: 2 h after injection	ND	Identification of functioning lymphatic vessels	Case series	4
Khan [90]	27	0.1–0·2 ml of ICG 5 mg/ml injected in the second web space of the hand and the ulnar border of the hand (both hands)	Intraoperative: Immediately after injection	PDE	Identification of functioning lymphatic vessels Functioning of anastomosis	Case series	4

LOE: Level of evidence, LVA: lymphaticovenular anastomosis, ND: not described.

identification and management of BCRL, the dye is used 'off-label' for these applications (it is not FDA approved for these applications), limiting its adoption by medical centers. Intradermal or subcutaneous injection of ICG is not associated with an increase in adverse events or intra- or postoperative complications (for example, wound healing or tissue retraction). ICG imaging is however limited to superficial layers and cannot provide data for high body mass index patients. Then, the lymphatic vasculature is a complex network and some preclinical studies highlight a possible physiological state perturbation of lymphatic function when an exogenous agent such as ICG is introduced [69]. Intraluminal pressure might also be modified by injection of such exogenous agents [70]. Table 4 presents final pros and cons for ICG imaging in BCRL prevention and management.

Although there is reasonable data to suggest that ICG can guide the surgeons in ARM procedure to preserve lymphatic network and in supermicrosurgery to identify lymphatic ducts, the post-operative function of lymphatic vessels must be correlated to any improvements in hard clinical end-points through RCTs. The 2016 consensus document of the international society of lymphology reaffirms the importance of lymphoscintigraphy as current standard imaging. The document reports also the increasing use of ICG lymphography in medical centers and the superficial lymphatic imaging by ICG which is critical for proper assessment of arm lymphatic flow (Table 4). The authors argue on the interest in combining imaging methods to add scientific rigor to the analysis of patients outcomes and encourages research in near-infrared fluorescence imaging field based on valuable randomized trials. For instance, identification of functioning lymphatic vessels was the most challenging step in the LVA procedure until the introduction of ICG imaging with handheld cameras for lymphatic mapping and selection of incision sites.

Table 4
Pros and Cons of NIR fluorescence Indocyanine Green imaging in prevention and management of breast cancer related lymphedema.

PROS	CONS
Suitable for intraoperative imaging	No FDA approval for the three described procedures
Real-time imaging of lymphatic vessels and Identification of lymph nodes	Limited to superficial tissue imaging
Safe (1/10000 allergy risk)	Limited data for high BMI patients
Short learning curve	Unknown long-term impact of repeated ICG administration in the tissues
High-resolution	No RCTs with hard clinical endpoints to prove the benefits.
Low invasiveness	Temporary green tattoo at injection sites
Low cost and no need of specialized medicine department for dye injection (in comparison with isotopic method)	

ICG administration routes described in the 33 clinical studies listed were heterogeneous in both ARM procedure, ICG lymphography and ICG guided supermicrosurgery: intradermal (ID) (ie. into the dermis, just below the epidermis), subcutaneous (SC) (i.e into the adipose tissue layer just below the epidermis and dermis) and intracutaneous injection (IC) (i.e into the skin, indeed, it is unclear as to whether it was ID or SC). We must point out that ID and SC will lead to different results if the lymphatic vessels function has to be evaluated. Comparison between two and one injection to view the lymphatic vascular network has not been yet evaluated in the literature. A procedure including two injections (using the same administration route) is more likely adapted for the mapping of the lymphatic vascular network (and more precise than a single injection). Guidelines about fluorescence imaging in BCRL are needed to setup reference protocol for ICG administration according to the application to be considered. Then the time interval between the administration of ICG and the imaging may be short if the physician only needs to look at the lymphatic network but may become longer for lymphatic vessels functional assessment with a significant impact on the operative time.

There is a need for substantial evidence regarding the effect of the fluorescence procedures on the incidence of lymphedema when ICG ARM node is preserved, the benefit of ICG lymphography to conservative treatment with a long-term follow-up on lymphedema index scores, and the impact of ICG imaging for LVA on surgery times (skin incisions and dissections) and anastomosis patency. Fluorescence imagers are relatively expensive but one device can be used across a general surgery department for other applications such as SLN mapping [34], flap perfusion assessment and endocrine surgery [71,72]. Another point is that ICG imaging may be efficient but an optical method with deeper imaging, a higher spatial resolution and real-time information would be optimal. In consequence, new optical tools are under development for lymph node and lymphatic vessel imaging, and when possible by label-free techniques. Among them, NIR II fluorescence, optical coherence tomography (OCT) [70] and photoacoustic imaging [73,74] have shown promising results in preclinical studies. First, recent animal studies report imaging at greater depths than previous studies and with comparable spatial resolution when specific fluorescent dyes are illuminated in the NIR II spectrum (from 1000 nm to 1700 nm). Vascular fluorescence imaging in the NIR II window is significantly improved due to less light scattering in tissues and a higher signal-to-noise ratio at these longer wavelengths [75,76]. Interestingly, ICG also exhibits a fluorescence signal in NIR II [75] and this novel approach could be evaluated for deep lymphatic imaging [77]. Then, identification of the ICG ARM node could be combined with *in situ* OCT imaging to determine the lymph node status and to decide its surgical preservation [78]. OCT based on low-coherence interferometry works in a similar manner to conventional ultrasound but uses light instead of sound waves [79]. *Ex vivo* OCT imaging of lymph nodes has already shown promise [80,81] and, combined with Doppler capabilities, lymph flow, lymphatic vessel contraction and lymph valve dynamics, can also be followed at high resolution, enabling the refinement of quantitative imaging to better understand lymphatic function [70]. Finally, Photoacoustic imaging (PAI) uses ultrasound for image acquisition, while photons are used for signal generation [82]. Few preclinical studies have described the use of this technology to image lymphatic systems but PAI imaging has been demonstrated to a depth of 5 mm and at a resolution of 110 μm [73,74].

Conclusion

NIR fluorescence imaging is gaining interest in breast surgery, mainly for SLN identification but also for ARM node identification in axillary lymph node dissection and supermicrosurgery following BCRL. At present, it is not possible to conclude on its advantages over standard clinical techniques but the contribution of multidimensional real-time imaging that does not use a radiolabelled probe could undoubtedly provide new possibilities for BCRL prevention and management. Other non-invasive optical techniques to enable surgeons to accurately visualize the lymphatic system and flow (such as OCT, Doppler OCT and photoacoustic imaging) are also evolving rapidly, with intraoperative applications expected in the future.

Conflict of interest statement

The authors whose names Muriel Abbaci, Angelica Conversano, Frederic de Leeuw, Corinne Laplace-Builhé and Chafika Mazouni are listed certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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