Thieme

Indocyanine Green Marking of Axillary Sentinel Lymph Nodes in Early Breast Cancer

Indocyaningrün-Markierung axillärer Sentinellymphknoten beim frühen Mammakarzinom

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ABSTRACT

Introduction
Axillary sentinel lymph node excision (SLNE) in breast cancer patients with clinically node-negative disease may be carried out using different tracers. The standard tracer is technetium colloid (^{99m}Tc). Indocyanine green (ICG) can be used as an alternative. This study aimed to evaluate the clinical usefulness of this fluorescent dye in a standardized setting.

Material and Methods
A prospective, single-center cohort study carried out at the University Gynecological Hospital of Rostock from September 2023 to May 2024 carried out sentinel lymph node marking using only ICG in patients with breast malignancies. The ICG injection was administered immediately after the induction of anesthesia. Detection of the sentinel lymph node (SLN) was done using a laparoscopy system suitable for ICG. The aim was to determine the detection rate (DR) for SLNs marked exclusively using ICG and to record any complications. The costs of using ICG to mark SLNs were compared with those for ^{99m}Tc marking.

Results
During the study period, contraindications against marking with ICG were ascertained for five (3.8%) of 132 patients with planned SLNE. A total of 100 SLNEs were carried out after ICG marking in patients who met the inclusion criteria in the context of the study. A median of two SLNs were resected. The detection rate (DR) for SLNs was 98.0%. SLNs were identified in all obese patients. No serious systemic side effects occurred following ICG injection. Transient skin discoloration in the area around the injection site were observed in eight patients. The direct cost of ICG marking was 62.73 Euros, which was 170.36 Euros lower than the cost of ^{99m}Tc marking.

Conclusion
The detection rate of axillary SLNs marked using ICG is high and the method is cost-effective, has few side effects and can also be used in obese patients. Contraindications

against the administration of ICG are rare. Marking with ICG is a good alternative to the ^{99m}Tc method and offers advantages in terms of costs, logistics, no exposure to radiation, and patient comfort.

ZUSAMMENFASSUNG

Einleitung
Die axilläre Sentinellymphknotenexzision (SLNE) beim klinisch nodal negativen Mammakarzinom kann unter Verwendung unterschiedlicher Tracer durchgeführt werden. Standard ist die Technetiumkolloidmarkierung (^{99m}Tc). Alternativ kann auch Indocyaningrün (ICG) angewendet werden. Ziel dieser Untersuchung war die Prüfung der klinischen Anwendbarkeit dieses Fluoreszenzfarbstoffes in einem standardisierten Setting.

Material und Methoden
In der prospektiven, unizentrischen Kohortenstudie erfolgte die alleinige Sentinellymphknotenmarkierung mit ICG bei Patient*innen mit Malignom der Mamma an der Universitätsfrauenklinik Rostock von September 2023 bis Mai 2024. Die ICG-Injektion erfolgte unmittelbar nach Narkoseeinleitung. Die Detektion des Sentinellymphknotens (SLN) erfolgte mit einem ICG-tauglichen Laparoskopiesystem. Ziel war, die Detektionsrate (DR) ausschließlich mit ICG-markierter SLNs zu ermitteln und Komplikationen zu erfassen. Weiterhin sollten die Kosten für die ICG-Markierung des SLN mit denen der ^{99m}Tc-Markierung verglichen werden.

Ergebnisse
Von 132 Patient*innen mit geplanter SLNE im Untersuchungszeitraum wurden bei 5 (3,8 %) Kontraindikationen gegen eine ICG-Markierung ermittelt. Es wurden 100 SLNE nach ICG-Markierung bei erfüllten Einschlusskriterien im Rahmen der Studie durchgeführt. Im Median wurden 2 SLNs entfernt. Die Detektionsrate (DR) des SLN betrug 98,0 %. Bei allen adipösen Patient*innen war der SLN detektierbar. Es traten keine schwerwiegenden systemischen Nebenwirkungen nach ICG-Injektion auf. Bei 8 Patient*innen wurden vorübergehende Hautverfärbungen im Injektionsgebiet beobachtet. Die unmittelbaren Kosten für die ICG-Markierung betrugen 62,73 Euro und waren 170,36 Euro niedriger als für die ^{99m}Tc-Markierung.

Schlussfolgerung
Die ICG-Markierung axillärer SLNs ist mit hoher DR kostengünstig und nebenwirkungsarm auch bei adipösen Patient*innen durchführbar, Kontraindikationen gegen eine ICG-Applikation sind selten. Sie stellt eine Alternative zur ^{99m}Tc-Methode mit Vorteilen hinsichtlich Kosten, Logistik, fehlender Strahlenbelastung und Patient*innenkomfort dar.

Introduction

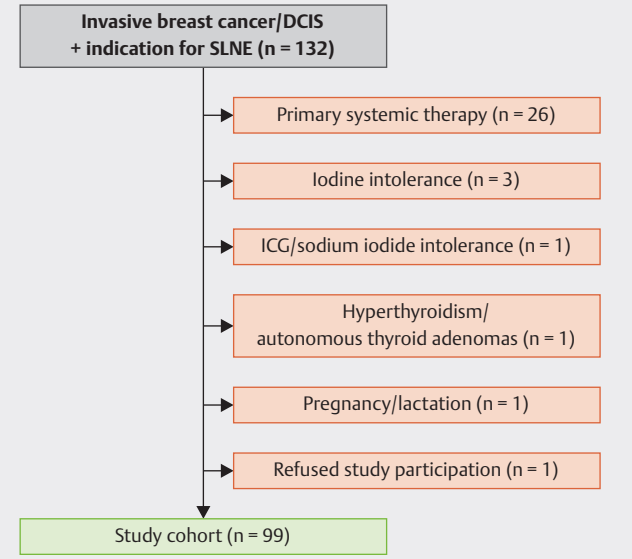
In Germany, more than 70 000 breast carcinomas are newly diagnosed every year [1]. At the time of diagnosis, 76 % of affected patients have no axillary lymph node metastases [2]. Axillary lymph node status is considered an important classic prognostic factor for early breast cancer [3]. Axillary sentinel lymph node excision (SLNE) to determine node status is recommended in cases with clinically node-negative invasive breast cancer and cases undergoing a mastectomy for ductal carcinoma in situ (DCIS) [4]. At the beginning of the 21 st century, this became the standard approach, as it offered the same level of oncological safety [5] as complete axillary lymph node dissection (ALND) but resulted in a lower postoperative morbidity (lymphedema, reduced quality of life, numbness/pain in the arm) [6]. Different tracers are injected into the breast, depending on the marking procedure. After they have been transported along the lymphatic pathways, they make targeted detection of sentinel lymph nodes (SLN) possible. The standard approach recommended in Germany is to mark the SLN using technetium colloid (^{99m}Tc) [7]. A meta-analysis of more than 8000 patients already carried out in 2006 was able to confirm a detection rate (DR) for SLNs using ^{99m}Tc marking of 96.0 % and a false negative rate (FNR) of 7.0 %, although this meta-analysis also included studies with dual SLN marking (^{99m}Tc and blue dye) [8]. Radionuclide marking requires cooperation with a nuclear medicine department (NMD) to inject the tracer and, in some cases, this even necessitates the patient being transported to the NMD as well as precise planning of the time of surgery due to the limited half-life of ^{99m}Tc. One alternative, rated as + by the Gynecological Oncology Working Group (AGO) [7] which makes it possible to bypass these logistical challenges, is to use indocyanine green (ICG) to mark SLNs. ICG is a water-soluble, metabolically neutral, tricarbocyanine dye which fluoresces under near-infrared light. The ICG is injected by the surgeon immediately prior to surgery. A meta-analysis of ten studies found a high DR for SLNs after ICG marking which was comparable to that found for radionuclide marking [9]. It should be noted, however, that in most of the studies published to date, ICG marking was done in addition to conventional marking (radionuclide or blue dye) and was not carried out by itself. Moreover, different doses of ICG and different camera systems were used [10].

The current study aimed to determine the DR of axillary SLNs after marking with ICG alone in patients with breast malignancies in the context of a standardized administration scheme using a laparoscopy system suitable for ICG which was available in our institution. The secondary goals of the study were to determine the rate of ICG-associated complications and to compare the costs of ICG marking with those of ^{99m}Tc marking.

Material and Methods

Patient cohort

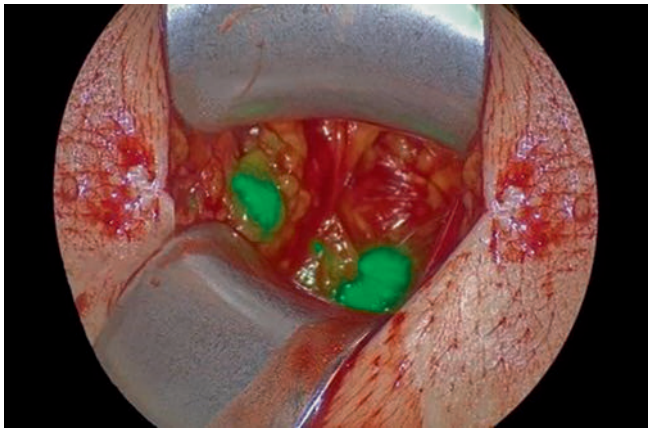
Patients with an initial diagnosis of invasive breast cancer or ductal carcinoma in situ (DCIS) diagnosed in the University Gynecology Hospital of Rostock between 09/2023 and 05/2024 whose primary surgical therapy required planned axillary SLNE were included in this single-center prospective cohort study after giving their written informed consent. The indication for SLNE was based on the recommendations of the AGO Breast Commission which applied at the time of recruitment into the study. This means that SLNE was indicated in patients with clinically node-negative disease, unless the patient had inflammatory or distant metastatic breast cancer, was scheduled for breast-conserving surgery for DCIS, or had already undergone SLNE or ALND in the context of prior disease [7]. Based on the results of the SOUND study [11] and even before this approach was included in the AGO recommendations, postmenopausal patients with breast-conserving surgery were offered the option to forego SLNE if they had an invasive hormone-receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative tumor with a maximum diameter of 2 cm. Exclusion criteria for the study were contraindications for ICG administration (iodine, sodium iodide, or ICG intolerance, hyperthyroidism, autonomous thyroid adenomas), primary systemic therapy, age < 18 years, pregnancy, lactation, and previous axillary surgery (▶ **Fig. 1**). The Rostock University Medicine Ethics Committee approved the study (A2022–0161).



▶ **Fig. 1** Flow diagram of the study. DCIS = ductal carcinoma in situ; SLNE = sentinel lymph node excision; ICG = indocyanine green.

Marking and detection of SLNs

25 mg ICG powder (Verdye, Diagnostic Green GmbH, Aschheim-Dornach, Germany) was dissolved in 10 ml distilled water to result in a finished solution containing 2.5 mg ICG per ml. After anesthesia induction and positioning of the patient, 1 ml of the solution was injected 2–5 times subcutaneously/intradermally into the craniolateral quadrant of the breast planned for surgery. Unused amounts of the solution were protected against light, temporarily stored, and used for other ICG-marking procedures performed on the same day. The surgical site was then disinfected and covered with sterile surgery drapes. The time between injection and the start of SLNE should be at least 5 minutes and maximally 60 minutes. The study protocol did not stipulate whether to start with breast surgery or with SLNE. The access path to the axilla was also not specified, with access possible either through a separate skin incision performed in the anterior axillary line or, if this was possible due to the location of the tumor or the type of breast surgery, from the direction of the breast. The video-endoscopy systems IMAGE1 S CONNECT, Optik HOPKINS 0° or Rubina 30° with fluorescence imaging (Karl Storz, Tuttlingen, Germany) were used to detect the SLN (▶ **Fig. 2**).



▶ **Fig. 2** Intraoperative imaging of two sentinel lymph nodes marked with indocyanine green using a near-infrared camera.

Recorded complications

Potential injection-related complications (hematoma, skin discoloration, allergic reaction) were recorded immediately postoperatively by the surgeon using a standardized protocol. All participants in the study were contacted by telephone four weeks postoperatively and specifically asked about postoperative complications in the breast or axilla (persistent skin discoloration, skin necrosis, seroma, wound infection, hematoma). If complications persisted, the patient was again contacted by telephone four weeks later.

Cost analysis

To compare the cost of SLN marking using ^{99m}Tc or ICG, the prices which applied during the investigation period including statutory value-added tax were used. For the ICG marking, the costs of consumable materials (injection cannula, syringe and ICG solution) per SLNE were calculated. For the ^{99m}Tc marking of the SLN, the costs of the nuclear medicine specialist per SLN marking and the transportation costs to the nuclear medicine department were

analyzed per patient. In addition, the difference in costs between ^{99m}Tc and ICG marking and the cost of upgrading an existing laparoscopy tower to include the required ICG endoscopy technology (manufacturer information dated 12/2022) was calculated, including how many SLNEs were needed until the purchase price would be recouped, based on the option of carrying out up to three SLNEs with ICG marking per day (i.e., including the cost of purchasing 3 lenses).

Statistical analysis

Statistical analysis was done using SPSS software, version 27 (IBM, Armonk, NY, USA). Descriptive analysis was used to characterize the study cohort and surgical parameters, with qualitative data summarized as absolute or relative frequencies and quantitative parameters as mean (± standard deviation) or median (minimum – maximum).

Results

Patient cohort

During the investigation period, axillary SLNE was indicated in 132 of 325 (40.6 %) patients with a first diagnosis of invasive breast cancer or DCIS. No SLNE was carried out in 193 (59.4 %) patients first diagnosed with breast malignancy in the investigation period for the following reasons: distant metastasis, n = 22; clinically suspicious axillary lymph node, n = 39; breast-conserving surgery for DCIS, n = 30; postmenopausal patients with breast-conserving surgery and invasive HR-positive, HER2-negative tumor with a diameter of < 2 cm, n = 62; ongoing primary systemic therapy, n = 34; other reasons, n = 6. A total of 33 patients with an indication for SLNE were excluded from the study (primary systemic therapy, n = 26/19.7 %; known intolerance of iodine/sodium iodide/ICG, n = 4/3.0 %; pre-existing thyroid disease, n = 1/0.8 %; pregnancy/lactation, n = 1/0.8 %; refused study participation, n = 1/0.8 %), which left 99 patients as the study cohort (▶ **Fig. 1**). In one female patient with bilateral breast cancer, SLNE was carried out on both sides, meaning that a total of 100 SLNEs were available for evaluation. Three patients (3.0 %) were male; 26 patients (26.3 %) were obese (▶ **Table 1**). Lymph node metastases were confirmed in
18 cases (18.0 %) (▶ **Table 2**). ALND was carried out in 7 (7.0 %) patients (2 × because of non-detection of the SLN, 5 × because of metastases in the SLN). In five cases (5.0 %), the indication for SLNE was in the context of a mastectomy for DCIS; in 95 cases (95.0 %) the indication was made in the context of invasive breast cancer (▶ **Table 2**). Prior operations of the affected breast were for tumor resection of benign findings in four (4.0 %) cases and breast-conserving surgery for malignancy in two (2.0 %) patients. A separate skin incision in the axilla was used as the access pathway for SLNE in 85 (85.0 %) cases; in 15 cases (15.0 %), the axillary fossa was opened from the side of the breast.

▶ **Table 1** Clinical characteristics of the studied patient cohort (n = 99).

Parameter	n (%)
Mean age, years (± SD)	62.6 (± 12.6)
Mean BMI, kg/m^2 (± SD)	26.8 (± 5.6)
Obesity classification of the WHO	
Underweight (BMI < 18.5 kg/m^2)	2 (2.0)
Normal weight (BMI 18.5–24.9 kg/m^2)	42 (42.4)
Overweight (BMI 25.0–29.9 kg/m^2)	29 (29.3)
Obese class I (BMI 30.0–34.9 kg/m^2)	16 (16.2)
Obese class II (BMI 35.0–39.9 kg/m^2)	6 (6.1)
Obese class III (BMI ≥ 40 kg/m^2)	4 (4.0)
Sex	
Female	96 (97.0)
Male	3 (3.0)
Synchronous bilateral breast cancer	
Yes	1 (1.0)
No	98 (99.0)
Menopausal status (medical history)	
Pre-/perimenopausal	23 (23.2)
Postmenopausal	70 (70.8)
Not specified	3 (3.0)
Not applicable (male)	3 (3.0)

BMI = body mass index; SD = standard deviation; WHO = World Health Organization

Detection rate of ICG-marked SLNs

After the injection of a mean of 2.9 (± 0.9) ml of ICG solution and a mean time of 22.5 (± 8.7) minutes between the injection and the start of the SLNE, at least 1 SLN was detected intraoperatively in 98.0 % of cases (98 of 100 SLNEs). One of the patients with an undetected SLN (female, 60 years old, BMI 20.0 kg/m^2) had a mixed invasive ductal and invasive lobular, retromammary, HR-positive, HER2-negative breast carcinoma with a diameter of 36 mm and no axillary lymph node metastases on ALND (pT2 pN0 cM0 R0, G2). The volume of injected ICG solution was 4 × 1 ml and the time between injection and SLNE was 20 minutes; the patient underwent mastectomy without reconstruction. The second patient (female, 61 years old, BMI 25.2 kg/m^2) had a craniolateral invasive ductal, triple-negative breast carcinoma with a diameter of 9 mm and also no lymph node metastases (pT1 b pN0 cM0 R0, G2). This patient underwent breast-conserving surgery during which 3 × 1 ml ICG was administered, and SLNE was performed 40 minutes after injection through a separate axillary skin incision.

Complications after ICG marking of the SLN

In 11 (11.0 %) cases with ICG marking, the surgeon reported green discoloration of the skin around the site of injection immediately intraoperatively (▶ **Fig. 3**). No other complications occurred immediately after injection. Postoperatively, five patients (5.2 %) had hematoma, six (6.3 %) had a seroma and two (2.1 %) had wound

▶**Table 2** Tumor and surgical characteristics of the performed sentinel lymph node excision (n = 100).

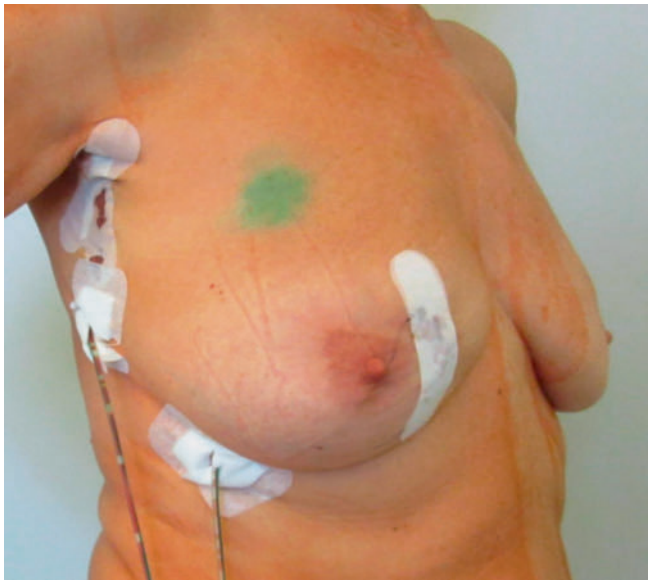
Parameter	n (%)
Prior breast surgery	
Yes	6 (6.0)
No	94 (94.0)
Oncoplastic breast surgery	
Yes	6 (6.0)
No	91 (91.0)
Not applicable (SLNE alone)	3 (3.0)
Tumor type	
Invasive ductal	60 (60.0)
Invasive lobular	21 (21.0)
Mixed invasive ductal/lobular	7 (7.0)
Other invasive tumor	7 (7.0)
DCIS	5 (5.0)
Tumor biology	
HR+/HER2−	83 (83.0)
HR+/HER2+	2 (2.0)
HR−/HER2+	2 (2.0)
HR−/HER2−	8 (8.0)
Not applicable (DCIS)	5 (5.0)
Histological grading	
1	13 (13.0)
2	74 (74.0)
3	8 (8.0)
Not applicable (DCIS)	5 (5.0)
Mean Ki-67, % (± SD)	**15.1 (± 12.8)**
Tumor location	
Craniolateral	36 (36.0)
Craniomedial	24 (24.0)
Caudolateral	9 (9.0)
Caudomedial	10 (10.0)
Central	12 (12.0)
Multicentric	9 (9.0)
Breast surgery	
Breast-conserving	59 (59.0)
Mastectomy	38 (38.0)
SLNE alone	3 (3.0)
Median number of SLNs detected intraoperatively (min–max)	**1 (0–4)**
Median number of histologically confirmed SLNs (min–max)	**2 (0–9)**
SLN histology	
pN0(sn)	81 (81.0)
pN1mi(sn)	2 (2.0)
pN1(sn)	13 (13.0)
pN2(sn)	2 (2.0)
Not specified	2 (2.0)
pT stage	
pTis	5 (5.0)
pT1	49 (49.0)
pT2	44 (44.0)
pT3	1 (1.0)
pT4	1 (1.0)
pN stage	
pN0	82 (82.0)
pN1mic	2 (2.0)
pN1	13 (13.0)
pN2	3 (3.0)
pN3	0 (0.0)

DCIS = ductal carcinoma in situ; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; max = maximum; min = minimum; SD = standard deviation; SLN = sentinel lymph node; SLNE = sentinel lymph node excision

infection in the axilla. A total of 96 of 99 patients (97.0 %) were successfully contacted by telephone four weeks postoperatively. Of these patients, eight (8.3 %) reported persistent skin discoloration at four weeks after injection. When these patients were contacted again four weeks later, no skin discoloration was visible in any of the patients.

Cost comparison of ICG and ^{99m}Tc marking

The mean cost of axillary SLN marking with ^{99m}Tc per SLNE at the University Gynecology Hospital of Rostock was 233.09 Euros during the study period and the mean cost of ICG-based SLN marking was 62.73 Euros. This results in a difference of 170.36 Euros. If existing laparoscopy towers are upgraded with ICG technology, the costs incurred by switching from marking with ^{99m}Tc to marking with ICG would be recouped after 324 SLNEs.



▶ **Fig. 3** Skin discoloration in the right breast on the first postoperative day after breast-conserving surgery with axillary sentinel lymph node excision (invasive ductal breast cancer on the right side, pT2 $pN0_{(0/1\ sn)}$ cM0 R0, G2).

Discussion

The current prospective study demonstrates the feasibility of axillary SLNE using only the fluorescent dye ICG for marking. The study showed a high DR for SLN after marking with ICG. This confirms the results of earlier, prospective, randomized studies in which the DRs were just as high as those reported after marking with ^{99m}Tc [12, 13] and higher than after marking with blue dye alone [14]. However, those studies did not compare SLN marking using ICG alone with the results of other tracers; instead, marking with ICG was always done in combination with ^{99m}Tc or blue dye and compared with the results for ^{99m}Tc or blue dye alone. There are currently no randomized studies which compare the DR of SLNs in breast cancer patients using ICG alone with other marking methods. Similarly, in contrast to our study, the non-randomized cohort studies which reported DRs of more than 95 % for SLN after marking with ICG administered ^{99m}Tc in addition to ICG [15, 16, 17, 18, 19, 20]. Only two studies investigated marking with ICG alone. A retrospective cohort analysis reported a DR of 94.4 % in 36 patients where SLN marking was carried out using ICG alone [21]. A second prospective cohort study of 184 patients reported a DR of 98.4 % [22]. These results were confirmed in our study but using higher ICG doses, a different injection technique and a different camera system. In our study, neither of the patients in whom the SLN was not detected were obese. The reportedly poorer detection of ICG in obese patients because of a maximum penetration depth of 2 cm [23], especially in patients with a BMI of 40 kg/m^2 [24], was not replicated in our study. Moreover, our study shows that an approach to reduce scarring by not performing a separate axillary skin incision does not negatively affect the DR of SLN, even after marking with ICG alone. When dissecting ICG-marked SLNs, it is important to be aware that cutting lymphatic pathways may result in a broader diffusion of ICG into the surrounding tissue, making it more difficult to identify the SLN [25].

Only a few patients are unsuitable for ICG marking due to contraindications. No serious complications such as allergic reactions occurred in our study. This confirms the observation that intolerance reactions are very rare (0.002 %) [26]. It should be noted, however, that when an intradermal/subcutaneous injection of ICG is administered at a dosage of 5–12.5 mg and a concentration of 2.5 mg/ml, as was done in our study, skin discoloration around the injection site occurred in 8.3 % of patients and this persisted for several weeks postoperatively. This has not been previously described in other studies. The amount of ICG used and the ICG concentration corresponds to the amount recommended in the literature of > 2 ml and < 5 mg/ml for an optimal DR [27]. If necessary, drainage of the fluorescent dye from the skin may be expedited by carrying out local massage immediately after the injection, which could avoid the unwanted skin discoloration effect. But ultimately, all skin discolorations were only transient.

The immediate cost of marking is lower when ICG is administered compared to marking with ^{99m}Tc. Detection of axillary SLNs using conventional ICG-compatible laparoscopic technology is possible. If the technology is already available, the administration of ICG is cheaper than radionuclide marking. If an existing laparoscopy tower needs to be upgraded to be capable of detecting ICG, more than 300 SLNEs with ICG marking need to be performed to recoup the purchase costs. Because of the importance of ICG for marking SLNs in gynecological malignancies [28, 29], many gynecology departments already have this laparoscopic technology, which requires a near-infrared camera system. In addition to the lower costs, ICG marking of SLN also offers logistical advantages compared to using ^{99m}Tc. As the injection is done by the surgeon immediately preoperatively, the time of surgery can be planned independently from the nuclear medicine department. Whether this additionally results in cost savings due to optimization of logistical processes is not a question that this current study can answer. Direct benefits for patients include no exposure to radiation, no need to be transported to the nuclear medicine department, and the fact that ICG is only injected after the induction of anesthesia (avoids pain). One disadvantage of using ICG to mark SLNs irrespective of the tumor entity is that this constitutes an off-label use and patients must be explicitly informed about this.

The advantage of this study is its prospective study design which allowed a standardized investigation into the use of ICG alone according to a previously specified protocol and any complications to be recorded several weeks postoperatively. The limitations of this study are its single-center design and that it was not possible to determine the FNR after ICG marking as treatment was carried out in accordance with current guidelines and ALND was therefore not carried out in all patients. Whether tattooing in the area of the ICG injection site leads to changes in the lymphatic drainage pathways was not part of this investigation. Initial data about the possible impact of lymphatic drainage were only published after the study planning phase had been completed [30] and this question needs to be investigated in future studies. A direct comparison between marking with ICG alone and standard marking with ^{99m}Tc with regards to the DR, the number of

resected SLNs and the duration of surgery is not possible in the context of this study design. Based on the current analysis, comparing the use of ICG with the use of superparamagnetic iron oxide (SPIO) to mark SLNs [7], an approach that has been recommended by the AGO, is only indirectly possible. On the one hand, the SPIO method is not in use in the hospital where the study was carried out; on the other hand, there are no studies which directly compare the two methods. A review reported a pooled DR of 97.4% when SPIO was used [31]. This is comparable with the DR for ICG found in our study.

Conclusion

ICG can be used to mark axillary SLNs in cases with breast malignancy and has a high DR using the technique described here. ICG can be used irrespective of whether the patient is obese but patients must be informed that using ICG for marking is an off-label use. Pre-existing contraindications against the use of ICG are rare but must be inquired into. While patients should be informed about possible transient skin discoloration in the area around the site of injection, serious systemic complications are rare. Marking with ICG is less expensive than marking with ^{99m}Tc and offers advantages both with regards to logistical processes and with regards to the lower burden on patients. Especially in view of the fact that ^{99m}Tc is sometimes in short supply, the administration of ICG in a standardized setting represents a cost-efficient alternative for almost all patients for whom axillary SLNE is indicated and also offers logistical benefits, but in Germany this still constitutes an off-label use.

Conflict of Interest

The authors declare that they have no conflict of interest.

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