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Axillary Reverse Mapping Using Indocyanine Green and Concurrent Sentinel Lymph Node Biopsy in Breast Cancer Patients with or without Neoadjuvant Systemic Treatment

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Abbreviations:
ARM: axillary reverse mapping;
SLNB: sentinel lymph node biopsy;
SLN: sentinel lymph node;
NST: neoadjuvant systemic treatment;
ALND: axillary lymph node dissection;
ICG: Indocyanine Green;
BMI: Body Mass Index;
NIR: near-infrared;
NSLN: non-sentinel lymph nodes;
FFPE: Formalin-Fixed and Paraffin-Embedded;
IHC: immunohistochemistry;
H&E: hematoxylin and eosin;
SD: standard deviation;
HER2: human epidermal growth factor receptor 2;
NSM: Nipple-Sparing Mastectomy;
SSM: Skin-Sparing Mastectomy;
DTI: direct-to-implant.

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Rezumat

Cartografierea axilară retrogradă cu verde de indocianină concomitent cu identificarea și biopsia de ganglion santinelă la paciente cu neoplasm mamar, cu sau fără tratament sistemic neoadjuvant

Introducere: tehnica de cartografiere axilară retrogradă a fost dezvoltată pentru a încerca prezervarea drenajului limfatic al membrului superior cu scopul de a scădea riscul de apariție a limfedemului brațului după chirurgia axilară în cancerul mamar.
Material şi Metode: acest studiu prospectiv a inclus 57 de paciente cu cancer mamar la care s-a efectuat biopsie de ganglion santinelă şi cartografiere axilară retrogradă. Ganglionul santinelă a fost identificat cu ajutorul unui trasor radioactiv. Ganglionii care colectează limfa de la nivelul brațului au fost identificați cu verde de indocianină, printr-un sistem optic care utilizează lumină în domeniul infraroşu apropiat. Toți ganglionii santinelă au fost examinați histopatologic intraoperator. Dacă ganglionii santinelă au fost invadați, a fost luată în considerare continuarea disecției axilare. Ganglionii cu fluorescență au fost prezervați dacă nu au avut şi semnal radioactiv semnificativ.
Rezultate: ganglioni fluorescenți au fost identificați la 53 de paciente (92.94%). Ganglioni santinelă cu fluorescență au fost observați la 19 paciente, 5 netratate şi 14 tratate neoadjuvant şi rata de suprapunere a fost de 33.33%. Pacientele cu tratament neoadjuvant au avut o probabilitate mai mare de a avea ganglioni santinelă cu fluorescență ($p = 0.015$) comparativ cu cele operate de primă intenție. Dintre cele 20 de paciente cu ganglioni santinelă invadați, 13 au avut suprapunere, 5 fără tratament preoperator şi

8 tratate neoadjuvant. Dintre pacientele cu suprapunere şi ganglioni santinelă fluorescenți pozitivi, 7 paciente, toate tratate neoadjuvant, au avut ganglioni fluorescenți printre ganglionii excizați suplimentar.
Concluzie: cartografierea axilară retrogradă la pacienții cu cancer mamar cu indicație de biopsie de ganglioni santinelă permite efectuarea unei chirurgii axilare supraselective cu scopul de a reduce morbiditatea. La pacienții operați de primă intenție, în toate cazurile de suprapunere, ganglionii santinelă cu fluorescență au prezentat metastază carcinomatoasă şi niciun alt ganglion fluorescent nu a fost invadat. Ratele de suprapunere au fost mai mari la pacientele care au efectuat tratament sistemic neoadjuvant.

Cuvinte cheie: cartografiere axilară retrogradă, verde de indocianină, biopsie de ganglion santinelă, tratament sistemic neoadjuvant

Abstract

Background: the axillary reverse mapping (ARM) procedure aims to preserve the lymphatic drainage structures of the upper extremity during axillary surgery for breast cancer, thereby reducing the risk of lymphedema in the upper limb.
Material and Methods: this prospective study included 57 patients with breast cancer who underwent SLNB and ARM. The sentinel lymph node (SLN) was identified using a radioactive tracer. The ARM nodes were identified using indocyanine green with a near-infrared imaging system. All SLNs were examined intraoperatively. If the SLN was metastatic, further surgery was considered. The identified ARM nodes were preserved unless they coincided with the SLN.
Results: ARM nodes were visualized in 53 patients (92.94%). Crossover between SLN and ARM nodes was observed in 19 patients, 5 untreated and 14 who received neoadjuvant systemic treatment (NST), resulting in an overall crossover rate of 33.33%. Patients who received NST were more likely to show SLN-ARM crossover ($p = 0.015$) compared to those who underwent upfront surgery. Of the 20 patients with positive SLNs, 13 had crossover, 5 untreated and 8 received NST. In patients with positive SLN-ARM nodes, additional invaded ARM nodes were identified 7 patients, all of whom received NST.
Conclusions: using ARM in patients undergoing SLNB allows a supraselective approach to axillary surgery, aiming to reduce morbidity. In cases where patients underwent upfront surgery all SLN-ARM nodes were found to be metastatic and none of the other fluorescent nodes that were removed showed signs of invasion. The crossover rates are higher in patients with neoadjuvant treatment.

Key words: axillary reverse mapping, indocyanine green, sentinel lymph node biopsy, neo-adjuvant systemic treatment

Introduction

Axillary surgery for breast cancer has evolved from radical procedures to more selective approaches. Axillary lymph node dissection (ALND) was once a mandatory part of radical mastectomy, aimed at achieving regional control of the disease and improving survival rates (1). Over time, its role shifted from being primarily therapeutic to serving mainly as a staging procedure, as the status of axillary lymph nodes is the most important independent prognostic and predictive factor for breast cancer patients (2). However, ALND is associated with significant morbidity, particularly arm lymphedema, which can occur at rates ranging from 6% to 49% (3).

To address these issues, sentinel lymph node biopsy (SLNB) was developed to evaluate the status of axillary lymph nodes, thereby avoiding unnecessary ALND and minimizing complications that can arise from ALND (4,5).

The sentinel lymph node (SLN) is the first lymph node or group of nodes that receive lymphatic drainage from the tumor. Therefore, the SLN is the first that could potentially contain metastatic tumor cells. The status of the SLN can accurately reflect the status of all nodes in the regional basin (6,7).

SLNB has become the standard method for staging the axilla in node-negative patients with breast cancer (8). SLNB is also considered safe for patients who are clinically node-negative at the time of surgery following neoadjuvant systemic treatment (NST), even if they had previously confirmed node-positive disease before treatment (9,10).

There are various techniques for detecting SLNs, including 99mTc radiotracer, blue dye, superparamagnetic iron oxide tracer and more recently, indocyanine green (ICG). The dual technique using both a radiotracer and ICG is a safer alternative to the method that employs a radiotracer and blue dye. It demonstrates high identification rates and may ultimately become the gold standard method (11). Following NST, it is recommended to use a dual technique for mapping and to remove at least three lymph nodes to reduce false negative rates (12).

However, there is a 2-7% risk of developing lymphedema in patients who undergo only SLNB. Removing more than five lymph nodes can result in a higher incidence of lymphedema in the ipsilateral arm (13). Additional risk factors include a high body mass index (BMI), undergoing mastectomy, postoperative infections, lacking regular physical activity, vigorous, repetitive or excessive upper body exercise and radiation therapy or chemotherapy (14,15).

Several methods to reduce lymphedema after ALND and/or SLNB have been developed. One such procedure is axillary reverse mapping (ARM), which has been evaluated in various research studies (16-20). This method is based on the hypothesis that the lymphatic pathways of the arm and breast are separate, suggesting that the lymph nodes draining the arm are not involved in breast cancer. And so, by identifying and preserving the lymphatic pathway that drains the arm, the risk of developing lymphedema can be reduced (16, 20). However, it is important to note that anatomical interconnections exist between the lymph nodes that drain the upper extremity and those that drain the breast (21,22).

The current study aimed to determine the identification rates for SLNs and ARM nodes. It also sought to assess the overlap rates between SLNs and ARM nodes. Additionally, the study aimed to evaluate the metastatic involvement of ARM nodes in clinically node-negative patients, both with and without neoadjuvant systemic treatment. The ultimate goal was to establish when these nodes can be preserved to achieve a supraselective surgery with a low morbidity rate.

Material and Methods

Patients

This observational, prospective research was conducted by a single surgical team and included patients diagnosed with breast cancer who underwent surgery between February 15 and October 15, 2024.

The inclusion criteria comprised women aged 18 years and older, confirmed to have breast cancer, and scheduled for breast surgery with SLNB. Patients who had known contraindications to ICG were excluded.

Patients who met the inclusion criteria underwent an ARM procedure using ICG. Ethics approval was obtained for this study and all participants provided their written informed consent.

Surgical Technique

Sentinel lymph node biopsy with a radioactive tracer and axillary reverse mapping with indocyanine green were performed simultaneously on all patients.

All patients received a periareolar or peritumoral injection of 5-200 MBq of sodium pertechnetate (99mTc) labeled nanocolloidal human serum albumin (Nanoscan®, RADIOPHARMACY Laboratory Ltd, Hungary) on the day before or in the morning of the surgery. Afterward, all patients underwent preoperative lymphoscintigraphy for sentinel lymph node identification.

All patients received an intradermal injection of 3 mL (25 mg/10 mL) of indocyanine green solution (Verdye®, Diagnostic Green, Germany) in the upper and inner region of the ipsilateral arm. The injection was administered using a 5 mL syringe with a 25-gauge needle. This procedure took place on the operating table after anesthesia and just prior to the breast surgery (*Fig. 1*). Following the injection, local massage was applied for 5 minutes. The fluorescence signal was detected as it flowed from the upper extremity to the axilla using a near-infrared (NIR) imaging system (IMAGE1 S™ Rubina®, KARL STORZ, Germany) (*Fig. 2*). The axillary incision was performed 10 to 20 minutes after the injection. A continuous assessment of the surgical field was performed with the NIR camera throughout the surgical exploration. The axillary lymph nodes and lymphatics that received indocyanine green appeared as fluorescent spots and streams (*Fig. 3*). The fluorescent lymph nodes are referred to as ARM nodes.

Sentinel lymph node identification was conducted using a gamma-detecting probe (Europrobe 3.2®, Eurorad, France). Nodes that emitted radioactive signals were classified as "hot" (*Fig. 4*). The sentinel lymph node (SLN) was identified as the node with the highest radioactivity counts, while supplementary sentinel lymph nodes were defined as any node that exhibited at least 10% of the highest radioactivity counts. In some cases, non-sentinel lymph nodes (NSLNs) were also excised, including biopsied and clipped nodes before neoadjuvant treatment and macroscopic suspicious lymph nodes.

The removed SLNs were sent for intra-

Figure 1. Intraoperative aspect during ARM – injection site of the ICG solution (**A**) and local massage (**B**)

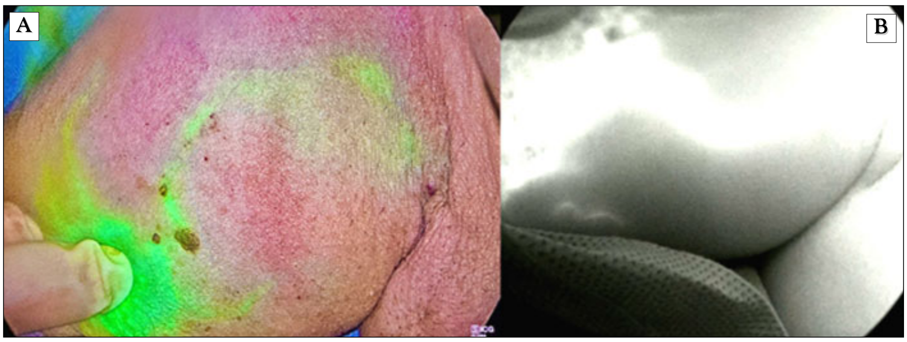

Figure 2. Intraoperative aspect during ARM – migration of ICG to the axilla in overlay mode (**A**) and monochromatic mode (**B**)

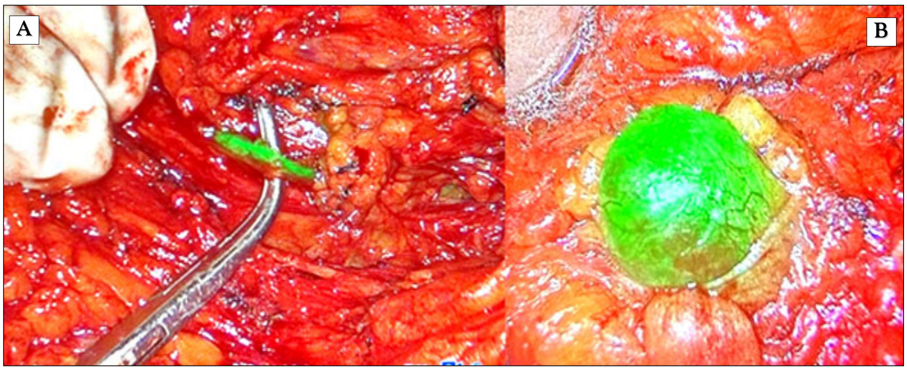

Figure 3. Intraoperative aspect during ARM - lymphatic vessel (**A**) and lymph node (**B**)

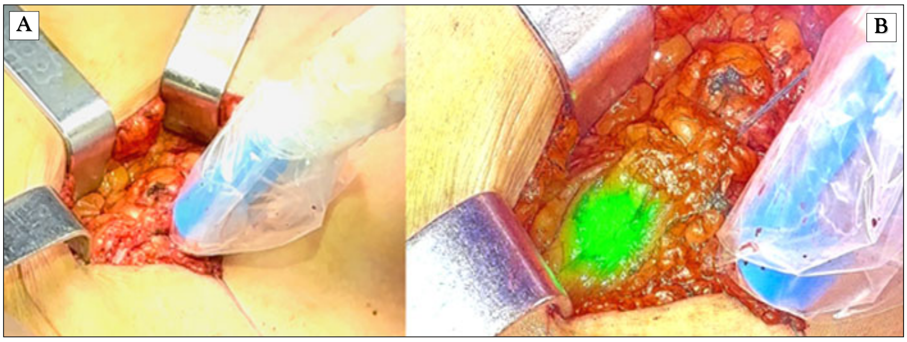

Figure 4. Intraoperative aspect during ARM: sentinel lymph node identification with gamma probe (**A**), sentinel lymph node identification with gamma probe and ARM node identification with NIR imaging system in overlay mode (**B**)

operative histopathological examination. When SLNs were negative, the identified ARM nodes were preserved unless they were the same as the SLN or exhibited macroscopic suspicion. When SLNs were positive, additional surgery was considered This decision took into account the neoadjuvant systemic treatment, the number of removed lymph nodes, the tumoral burden and the presence of macroscopic modified lymph nodes in the axilla. Further surgery performed ranged from additional biopsy to ALND.

The axillary lymph node dissection's superior, medial, and lateral boundaries were defined by the axillary vein, the chest wall, and the anterior edge of the latissimus dorsi muscle, respectively. Fluorescent nodes (ARM nodes) located in this area were also removed and sent separately for pathological evaluation when ALND was performed. The ARM nodes outside this area were preserved.

The number of nodes removed from each patient - categorized as fluorescent, hot, both, or neither - was documented. This data enabled the calculation of overlap rates between SLNs and ARM nodes and the invasion rates for all excised ARM nodes.

All the removed lymph nodes were submitted for formalin-fixed, paraffin-embedded (FFPE) histopathology and immunohistochemistry (IHC) analysis.

Histopathology Assessment

During surgery, each sentinel lymph node was sliced into 5-µm-thick frozen sections (at 3 to 6 levels) The frozen sections were examined histologically immediately after hematoxylin and eosin (H&E) staining.

The remaining tissue samples from the SLNs and the tissue samples containing the other removed lymph nodes were fixed in 10% formalin and cut into 4 µm-thick serial sections at 250 µm intervals. Serial sections were stained with H&E and histopathologically examined. Then, the sections were stained with a murine monoclonal anti-cytokeratin antibody for IHC analysis. This analysis confirmed metastatic node involvement and identified additional positive nodes. In positive nodes, the expression of ER, PR, HER2 and Ki-67 were also studied by IHC.

The pathology report included the number of lymph nodes examined, as well as how many were not involved or containing isolated tumor cells (<0.2 mm in size), micrometastasis (0.2–2 mm in size), or macrometastasis (>2 mm in size). Lymph nodes that contained micrometastases or macrometastases were classified as positive (pN1 or pN1mi) and the IHC profile was also mentioned. In contrast, nodes that contained isolated tumor cells were considered negative [pN0(i+)].

Outcomes

Primary outcomes were the identification rate for SLNs and fluorescent nodes, the number of SLNs, the rate of SLN-ARM crossover, fluorescent nodes and additional lymph nodes removed and the number of metastatic SLNs, ARM nodes and additional lymph nodes removed. The outcomes were reported for the entire patient sample, with analysis also considering the two groups (patients with and without neoadjuvant systemic treatment) to assess the impact of neoadjuvant therapy.

Group Definition

Two groups were defined for the analysis of SLN-ARM node crossover and metastasis rates: the upfront surgery group and the neoadjuvant systemic treatment group. The upfront surgery group consisted of patients with a multidisciplinary committee indication for surgical intervention as the primary method of treatment, while the NST group included patients with an indication for neoadjuvant systemic treatment followed by surgery.

Statistical Analysis

Continuous variables were presented as median and mean values, along with their standard deviation (SD), while dichotomous and categorical data were expressed as frequencies with corresponding percentages. The t-test was utilized to compare the means of continuous variables between the two groups. For categorical variables, the Chi-squared test was employed to compare the proportions between the two groups. Results with a p-value of $\leq .05$ were deemed statistically significant. Statistical analysis was conducted using IBM SPSS Statistics, version 29.0.2.0.

Results

This study included 57 patients, ages 35 to 76, with a median of 49 (mean age 51.81 ± 1.349). Four were classified as underweight, 28 had normal weight, 13 were overweight, 7 had class 1 obesity, 4 had class 2 obesity, and 1 had class 3 obesity. Of them, 33 patients were post-menopausal, while 24 were pre-menopausal.

The diagnosis of breast cancer was established by histopathological and IHC examination. In most cases, the diagnosis was made through a core-needle biopsy of the tumor, accounting for 44 cases (77.2%). Six cases (10.5%) were diagnosed by core-needle biopsies of both the breast tumor and axillary adenopathy, three cases (5.3%%) by biopsies of two different breast tumors, and two cases (3.5%) by biopsies of three breast tumors. Only one patient (1.8%) had occult breast cancer, with the diagnosis confirmed through a core-needle biopsy of the axillary adenopathy. In one instance (1.8%), the diagnosis was established by prior excisional biopsy of the tumor.

The tumor sizes were categorized as follows: T1 in 13 patients (22.9%), T2 in 34 patients (59.5%) and T3 in 10 patients (17.6%). Twenty-nine (17.5%) patients were luminal B, 15 (26.3%) luminal A, 10 (17.5%) human epidermal growth factor receptor 2 (HER2) positive and 3 (4.8%) triple-negative. The TNM staging and IHC profiles are described in *Table 1*.

Twenty-eight patients had an indication from the multidisciplinary committee for upfront surgery.

The other 29 received neoadjuvant systemic treatment, because of the locally advanced stage or because of the aggressive tumor

Table 1. TNM staging and immunohistochemistry-type characteristics in the groups

Characteristic	Upfront surgery group (N = 28)	NST group (N = 29)
Tumor size, N (%)		
T1	11 (19.29%)	2 (3.5%)
T2	15 (26.31%)	19 (33.33%)
T3	2 (3.50%)	8 (14.03%)
Lymph node status, N (%)		
N0	28 (49.12%)	14 (24.56%)
N1	0	15 (26.31%)
TNM stage, N (%)		
IA	11 (19.29%)	2 (3.5%)
IIA	15 (26.31%)	13 (22.8%)
IIB	2 (3.50%)	8 (14.03%)
IIIA	0	6 (10.52%)
IHC type, N (%)		
Luminal A	13 (22.8%)	2 (3.5%)
Luminal B	11 (19.29%)	18 (31.57%)
HER2 positive	3 (5.26%)	7 (12.28%)
Triple negative	1 (1.75%)	2 (3.50%)

NST: neoadjuvant systemic treatment,; HER2: human epidermal growth factor receptor 2

profiles. Of those, 18 patients had their tumors marked with a radiopaque clip before NST and twelve achieved a complete clinical and imaging response of the breast tumor.

A total of 15 patients were clinically node-positive at the time of the diagnosis. Among these, 11 underwent core-needle biopsy, which confirmed in 8 cases the lymph node metastasis. Four of them had the confirmed lymph node marked with a radiopaque clip. All clinically node-positive patients had a complete clinical and imagistic response of the axilla and were eligible for SLNB.

Twenty-seven patients (47.4%) underwent breast-conserving surgery (BCS), with one patient treated using the oncoplastic round block technique.

The other 30 patients (52.6%) underwent mastectomy, with or without immediate breast reconstruction. These included 12 nipple-sparing mastectomies (NSM) and four skin-sparing mastectomies (SSM). Immediate breast reconstruction was performed in 16 patients, accounting for 53.33% of those who had a mastectomy. Among them, 11 patients had direct-to-implant (DTI) procedures, with nine implants placed prepectoral. One implant was positioned partially retropectoral and partially covered by a deepithelialized dermal flap, while another was partially retropectoral and covered by Sergyn mesh Additionally, five patients underwent a two-stage reconstruction (3 with retropectoral and 2 with prepectoral placed tissue expanders). One patient had a previous breast augmentation and underwent NSM while preserving the breast implant.

Two patients with genetic mutations opted for a contralateral risk-reducing mastectomy, one of whom had immediate breast reconstruction.

All fifty-seven patients underwent SLNB and ARM. All 28 patients who underwent surgery as their initial treatment were clinically node-negative. Of those who received NST, 14 were initially clinically node-negative, while 15 showed a complete axillary response after the treatment.

SLNs were identified in all cases. The average number of SLNs identified through lymphoscintigraphy was 1.67 ± 0.08 (median 2, range 1 - 3). A total of 189 SLNs were removed, with an average of 3.32 ± 0.211 (range 1 to 8).

During the intraoperative examination, 41 patients had histologically negative SLNs, 18 from the upfront surgery group and 23 from the NST one. Sixteen patients (28.07%) were found to have SLNs with metastasis. Among these, 10 patients had upfront surgery and 6 received NST. For the 16 patients with positive SLNs identified during the frozen

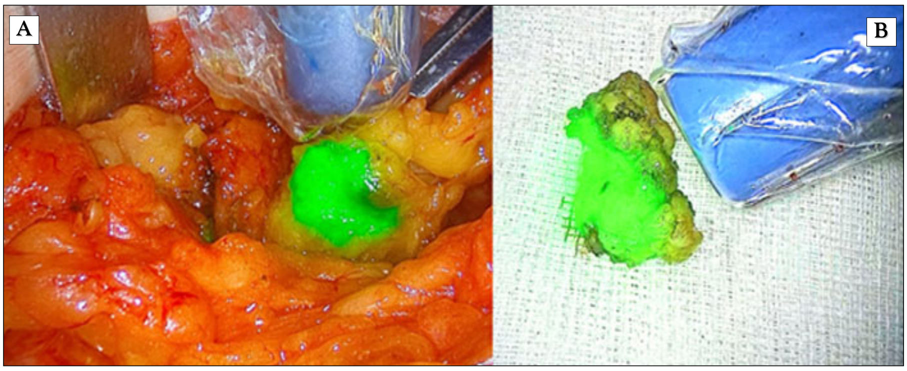

Figure 5. Intraoperative aspect during ARM: fluorescent sentinel lymph node (**A**) and specimen (**B**)

section analysis subsequent surgery was considered, which ranged from additional lymph node biopsies to ALND.

Overall, 20 out of the 57 patients (35.08%) had positive SLNs following FFPE and IHC analysis. In total, 189 SLNs were removed, of which 32 lymph nodes were found to have metastases, with a mean of 1.6 (± 0.15, range 1-3) reported in the postoperative histopathologic report.

ARM nodes were visualized in 53 patients (92.94%). A total of 26 SLNs removed showed fluorescence (1.37 ± 0.114, range 1-2). Crossover SLN-ARM nodes (*Fig. 5*) was noted in 19 patients (33.33%), 5 from the upfront surgery group and 14 from the NST group. Crossover rates were much higher in the NST group (48.27%) compared to the untreated group (17.85%).

A chi-square test of independence was conducted to assess the relationship between neoadjuvant systemic treatment and crossover between the arm and breast lymphatic circulation. The results indicated a significant relationship between these variables, χ^2 (1, N = 57) = 5.932, p = .015. Patients who received neoadjuvant systemic treatment were more likely to exhibit SLN-ARM overlap (*Table 2*).

The number of ARM nodes excised during SLNB for patients receiving neoadjuvant systemic treatment was with 0.546 (95%, CI [0.197, 0.894], p < .001) higher than the number for untreated patients.

Out of the 26 SLNs with fluorescence examined, 18 were found to have metastasis (1.38 ± 0.14, range 1-2). Thirteen patients had SLN-ARM nodes with metastasis, five of them were from the upfront surgery group and eight from the NST one. Among the 19 patients with crossover, 13 had a positive SLN-ARM: five of them were untreated patients and eight received neoadjuvant systemic treatment.

From the 41 patients with negative SLNs after extemporaneous examination, non-sentinel lymph nodes were surgically removed in 20 patients (7 from the upfront surgery group, 13 from the NST group).

The mean number of NSLNs removed in these patients was 3.45 ± 0.69, with a range of 1 to 12 nodes (median 2, sum 69). Metastatic NSLNs were found in 3 of 20 (15.00%) patients. Among these 3 patients, there were 5 (1.67 ± 0.67, range 1-3) metastatic nodes which represented 7.28% of all NSLNs excised

Table 2. Contingency table for the relationship between neoadjuvant systemic treatment and the crossover of SLN-ARM nodes

	Neoadjuvant systemic treatment		Total
	Yes	No	
SLN-ARM node crossover			
Yes	14 (24.6%)	5 (8.8%)	19 (33.3%)
No	15 (26.3%)	23 (40.4%)	38 (66.7%)
Total	29 (50.9%)	28 (49.1%)	57 (100.0%)

SLN: sentinel lymph node, ARM: axillary reverse mapping in these patients. All three patients were from the NST group.

One patient from the upfront surgery group had a positive SLN at the FFPE and IHC examination. In this case, one negative NSLN without fluorescence was removed.

In 7 patients with negative SLNs, 22 (3.14 ± 0.63, range 1-5) fluorescent non-sentinel lymph nodes were removed. Among these, 5 NSLN-ARM nodes tested positive for metastasis (1.5 ± 0.267, range 1-3). Notably, in all 3 patients with NSLN metastasis, at least one of those also had fluorescence. All these patients were from the NST group and one did not have SLN-ARM crossover.

For the 16 patients with positive SLNs after the frozen section further surgery was considered, ranging from additional biopsy to ALND. After subsequent surgery, 133 lymph nodes were removed, with an average of 8.31 nodes per patient (± 0.99, range 4-15). Out of the total lymph nodes, 30 were determined to be involved, with a mean of 3.75 (± 0.79, range 1-7). Only eight (50%) of the 16 patients had positive lymph nodes after subsequent surgery. Two of them were from the upfront surgery group and the other six were from the NST-group.

Thirteen out of the 16 patients had additional fluorescent nodes removed (81,25%). Among the 133 lymph nodes removed, 47 showed fluorescence, with a mean of 3.62 (± 0.45, range 1-6). Out of these, 20 lymph nodes were found to have metastases, with a mean of 2.50 (± 0.50, range 1-5). All 8 patients with positive additional removed lymph nodes had at least one with fluorescence. Two of them were from the upfront surgery group and both had SLN-ARM crossover. The other six were from the NST-group, 4 with and 2 without SLN-ARM crossover.

In total, 390 (7.33 ± 0.51, range 1-19) lymph nodes were excised, 67 out of which were positive (3.15 ± 0.436, range 1-8). From all 57 patients included in the study, 23 patients (41.95%) had positive nodes. Sixteen of them had a metastatic SLN at frozen section and 4 patients had a metastatic SLN after post-operative evaluation. Another 3 patients had metastatic NSLNs.

From all the patients included in the study, ARM nodes were excised in 47.36% of them (27 patients). Among these, 13 patients had positive ARM nodes, representing 48.14% of the patients with removed ARM nodes. There were 43 positive nodes (2.42 ± 0.299, range 1-6), representing 45.26% of the total of 95 ARM nodes removed (3.53 ± 0.354, range 1-6).

There was a significant difference in the total number of ARM nodes invaded between patients who received neoadjuvant chemotherapy and those who did not ($t(34.966) = 2.996$, $p = <.001$). Patients who underwent neoadjuvant systemic treatment had an average of 0.925 more fluorescent nodes excised, with a 95% confidence interval of (0.298, 1.552) (*Table 3*).

In the four patients (7.01%) where no fluorescent nodes were identified, only SLNB was performed, suggesting that the ARM

Table 3. Independent t-test for the influence of neoadjuvant systemic treatment on the number of removed SLN-ARM nodes

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Significance (two-sided p)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Number of removed ARM-SLN nodes	Equal variances assumed	17.048	<.001	3.124	55	.003	.546	.175	.196	.896
	Equal variances not assumed			3.150	45.971	.003	.546	.173	.197	.894

SLN: sentinel lymph node, ARM: axillary reverse mapping

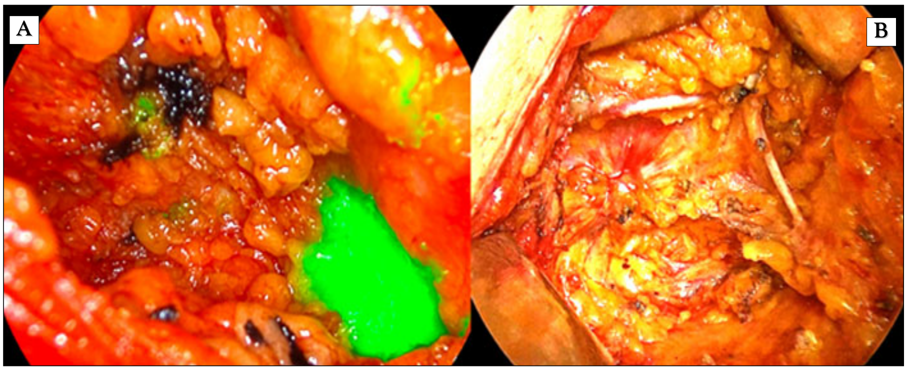

Figure 6. Intraoperative aspect during ARM- inspection of the axilla after the axillary surgery: residual fluorescent nodes (**A**), no fluorescence observed in the (**B**)

pathway is probably located on a deeper layer than the SLNs. Three of them were from the upfront surgery group and one from the NST one. In 26 other patients (45.61%) no ARM nodes were removed. Another eleven patients (19.28%) had residual ARM nodes in the axilla. These three patient groups, representing 71.92% (41 patients) of the study sample, presumably have a low risk of lymphedema.

In contrast, fluorescence was not observed in the axilla at the end of axillary surgery in 10 cases (17.54%). Additionally, in 6 patients (10.52%), only some of the identified ARM nodes were preserved because these nodes were located outside the area of the ALND (*Fig. 6*).

No adverse reactions related to ICG were identified, including allergic reactions or skin necrosis at the injection site. Postoperatively, all of the patients experienced temporary green staining at the injection site, which disappeared within 7 to 14 days.

Disscussion

Breast cancer surgery-related lymphedema of the ipsilateral arm is a common morbidity that can occur after axillary dissection. It has a negative impact on the quality of life due to discomfort, pain, decrease in upper limb function and impaired aesthetic aspect. For these patients, managing and concealing an enlarged arm is sometimes even more difficult than dealing with an amputated breast (23,24).

While sentinel lymph node biopsy involves less sacrifice of the arm's lymphatic system compared to axillary lymph node dissection, the risk of developing lymphedema after SLNB is still present. It is estimated to be 2-7% (25). This risk can increase depending on additional factors, such as BMI, type of breast surgery, postoperative infections, systemic treatment and radiotherapy (26-28).

The ARM procedure was developed to try to preserve the lymphatic drainage structures of the upper extremity during axillary surgery, in order to avoid lymphedema (29-32).

In this study, ICG was used for the ARM procedure. No allergic reactions occurred, and the skin discoloration on the upper inner limb lasted only between one and two weeks. Several mapping techniques are available for identifying lymph nodes, including blue dye, radioisotope, and ICG (33-38). Radioactive tracers, like technetium-99m, can lead to unwanted radiation exposure, and some hospitals may not have access to them, while blue dyes can cause permanent skin markings and frequent allergic reactions (39). Indocyanine green has emerged as a viable alternative.

ICG is a dye that was developed in 1955 for photographic purposes. It was approved for medicinal use in 1959, and its applications rapidly expanded in various medical specialties thereafter (40-42). Today, it is commonly used in breast cancer surgery for multiple techniques, including ARM (43). Although ICG has some limitations, such as the restricted 2 cm penetration depth of NIR light, which can complicate lymph node identification, it is a water-based solution that moves quickly through the lymphatic system. This characteristic facilitates high-resolution, real-time imaging (39). Another advantage of ICG is that it is a non-ionizing substance, and allergic reactions following systemic injection are rare, occurring in fewer than 1 in 10,000 cases (40).

ICG mapping is considered a safe and effective alternative to traditional blue dye or radioisotope mapping methods (44,45). This imaging technique has a very high sensitivity for identifying ARM nodes and enables the evaluation of the crossover between SLNs and ARM nodes (46). This technique does not require special preparation or imaging before the surgery, just patient history to evaluate the allergic risk. Preoperative cutaneous testing is not recommended (40).

A disadvantage of this technique is the devices that are required and the costs associated with it. Most of the clinical studies use handheld fluorescence imaging systems, such as the Photo Dynamic Eye (PDE, Hamamatsu Photonics KK, Hamamatsu, Japan) and SPY imaging system (Novadaq Technologies, Inc, Toronto, Canada). However, a laparoscopic camera with an infrared filter may be used so that images can be seen on a high-definition monitor. This is available in most of the hospitals, but requires repetitive turning off and on of the lights in the operating room (30,47).

ARM was initially described for patients undergoing axillary lymph node dissection. Blue dye was injected into the arm to identify and preserve the lymphatic drainage pathways. Initial studies indicated that none of the ARM nodes were metastatic, which prompted the use of this technique to preserve these nodes (16,20). Subsequent research has demonstrated that node-preserving surgery in the ARM significantly reduces the incidence of lymphedema (36,48-50).

However, later studies have suggested the potential metastatic involvement of ARM nodes. The observed rates of this involvement ranged from 14% to 43% (51). Data indicates that metastatic ARM nodes can occur not only in patients with high pathological axillary staging (pN2 and pN3) but also in those with low pathological axillary staging (pN1) (52,53).

The ARM procedure has been tested on patients undergoing sentinel lymph node biopsy, too (19). In the present study, all patients also underwent SLNB with radioactive tracer and ARM using indocyanine green.

This study included both patients who had an indication for upfront surgery and patients who underwent neoadjuvant systemic treatment. When introduced, SLNB was performed only in clinically node-negative patients undergoing upfront surgery. However, SLNB is now also indicated for patients who receive NST and show a clinical and imaging complete response in the axilla (54). Given the increasing frequency of NST and the high success rates associated with it, the majority of these patients are now recommended for SLNB (55).

In this study, a radioactive tracer (99mTc-nanocolloidal) was injected into the periareolar or peritumoral area, the day before or on the morning of the procedure. Numerous studies have demonstrated that the injection site does not significantly impact the identification of SLNs in breast cancer (56-58). Several 99mTc-based agents have been used for SLN detection in breast cancer. It is widely agreed that a radiocolloid provides the best balance between rapid lymphatic drainage and strong retention in the SLNs (56,59). Generally, SLNs can be visualized within 1 to 2 hours post-injection, and patients should be in the operating room within 2 to 30 hours after colloid injection. If surgery is scheduled for the early morning, injection and imaging can be safely performed the afternoon before the procedure. Alternatively, the injection can be done on the morning of the surgery (56,60). There is currently no consensus on the appropriate dose to administer. The recommended total injected dose is 5 to 30 MBq for surgeries scheduled on the same day and up to 150 MBq if the injection is administered the afternoon before surgery (56, 61). In cases with non-identification sentinel lymph nodes when the radioactive signal is not detected preoperatively, ICG can serve as a backup method for SLN identification.

Before the breast surgery, after the anesthesia, a 3 ml injection of ICG solution was injected into the medial aspect of the ipsilateral upper arm. The literature indicates that the timing of the ICG injection varies. In some studies, ICG is injected more than two hours before surgery, while in others it is administered immediately after anesthesia and before breast surgery (18,30,62).

Additionally, there is a variation in the volume of subcutaneously injected ICG, ranging from 0.1 to 3 mL of a 2.5 mg/mL ICG solution. Injection sites also differ, being performed subcutaneously in the interdigital area, on the inner side of the wrist or the medial aspect of the proximal arm in the intermuscular groove (18,19,30,46,62,63). Some authors suggest elevating the arm after ICG injection to enhance lymphatic drainage, particularly when the injection is administered at a more distal site (30).

This study employed a gamma-detecting probe to identify sentinel lymph nodes. The SLN was defined as the node exhibiting the highest radioactivity count. The threshold for the removal of additional SLNs was established at 10% of the highest recorded radioactivity count. It is widely accepted to excise all nodes with a radioactive count of 10% or more of the hottest node. However, recent data suggest that the "40% rule" or the "hottest two" rule may serve as viable alternatives (64). Using the ARM technique, it is possible to preserve fluorescent lymphatic channels and lymph nodes, even if they register a low radioactive signal that falls below the previously mentioned threshold. However, our primary objective is to remove all "hot" lymph nodes first, and only afterward focus on sparing the fluorescent nodes.

An average of 3.32 sentinel lymph nodes were removed in our study, with a range of 1 to 8 nodes. The literature generally reports that the number of SLNs ranges from one to thirteen, with an average of 2.9 (65).

An important issue is that crossover between SLNs and ARM nodes can occur (48, 66,67). In our study, the axillary surgery was performed 10 to 20 minutes after the ICG injection. Crossover between SLNs and ARM nodes was detected in 19 out of 57 cases, resulting in an overall rate of 33.3%. This finding is higher than what has been reported in the literature, where crossover rates range from 8.7% to 18.9%, with only one study reporting a rate of 27% (18,46,68,69,70). Patients with SLN-ARM node crossover are at an increased risk of developing lymphedema after SLNB (13,36).

This discrepancy may be attributable to the fact that some patients in our study underwent neoadjuvant systemic treatment. Taking this into consideration, the crossover rates were 17.85% for those in the upfront surgery group and 48.27% for those in the NST group. The higher crossover rates may be related to the assumption that NST causes anatomical changes in the lymphatic pathways due to factors like tumor cell destruction, inflammation, fibrosis, or blockage from necrosis. The rates reported in our study align with existing literature on the topic for the untreated group, but are higher than those reported after NST. Only one study specifically examined the ARM procedure on patients after NST, reporting a crossover rate of 36.5% (71).

It has been suggested that the ARM procedure may be oncologically safe for clinically node-negative patients (46, 66, 72-74). In this study, all patients with SLN-ARM node crossover from the upfront surgery group had at least one metastatic fluorescent SLN. Among the patients with positive SLNs who did not experience crossover in this group, no other excised ARM nodes were found to be positive. This suggests that for the SLN-positive patients without overlap in the upfront surgery group, if further axillary surgery is necessary, the fluorescent nodes can potentially be preserved. These findings align with existing literature, where two studies determined that ARM nodes, which do not coincide with SLNs, may be preserved when further surgery is necessary for SLN-positive patients (68, 72). However, further studies are needed to confirm these findings.

In this study, the metastatic rate of the fluorescent SLNs was 27.58% in the NST group. Moreover, patients with positive SLNs from this group without crossover had additional fluorescent lymph node with metastasis. On this matter, there are contradictory opinions in the literature. A study including clinically node-positive patients who underwent neoadjuvant systemic therapy reported a metastasis rate of 5.7% of fluorescent SLNs, with all cases being classified as luminal-type tumors. The authors discussed these findings in the context of precision medicine, when up to 80% of selected patients with triple-negative or HER-2 positive breast cancer achieve pathologic complete response rates after NST. They argued that it is reasonable to consider preserving axillary lymph nodes in this specific subpopulation without compromising oncologic safety (71). However, another study on patients with node-positive breast cancer recommends that suspicious ARM nodes should be removed, particularly in NST and clinicopathologically node-positive patients before NST (62).

In the 16 cases where a positive SLN was identified during frozen section examination, further surgical intervention was considered. As the literature states, for some patients, it may be possible to avoid axillary dissection, thereby reducing the risk of complications associated with axillary surgery without negatively impacting survival outcomes (75-79). According to the results of the IBCSG 23-01 trial, SLNs that contain micrometastases (less than 2 mm) do not require ALND (75). Furthermore, based on findings from the ACOSOG Z0011 trial, additional axillary surgery is not recommended for patients with T1 or T2 tumors and 1 to 2 positive SLNs who undergo breast-conserving surgery without prior neoadjuvant systemic therapy and will receive whole-breast radiation therapy (76). The SENOMAC trial also indicates that omitting ALND is safe for node-negative breast cancer patients with T1-T3 tumors who have one or two SLNs with macrometastases and will receive adjuvant systemic treatment and radiation therapy (79).

In terms of technical details, during the inspection of the axilla after the sentinel lymph node biopsy (SLNB) procedure, the integrity of the lymphatic drainage could only be confirmed by visualizing fluorescence within the axilla. Achieving complete visualization of the axillary operative field using a NIR optical system is often challenging due to the limited exposure offered by a small incision (71).

The primary goal of this procedure is to reduce upper limb lymphedema following breast cancer surgery. As the current study had a short follow-up period and did not include lymphedema assessment as an outcome, the authors plan to conduct a study with a longer follow-up time to assess the effectiveness of this procedure. Various studies have reported lymphedema rates after ARM ranging from 0% to 4% for SLNB and between 2.4% and 30.7% for ALND (40,49,50,69,80-82).

However, these studies often employ varying definitions of lymphedema and different measurement methodologies, generally exhibiting low levels of evidence. Additionally, several factors can influence the rates of lymphedema (83).

Axillary reverse mapping has been studied for over a decade since its introduction. However, several issues remain unresolved, particularly concerning crossover rates with sentinel lymph nodes, the indication of ARM node sparing in the case of positive SLN, especially in clinically node-positive patients, and the lack of predictive factors for ARM node involvement. Despite these challenges, ARM has the potential to reduce lymphedema rates. Furthermore, combining the ARM with lympho-venous anastomosis techniques could yield even greater benefits (84).

The study has as limitations the limited sample size, short follow-up period and patient heterogeneity, with the inclusion of both patients who received neoadjuvant systemic treatment and those who did not, regardless of their initial oncological stage. One upside of the study is that all surgeries were conducted by a single surgical team led by a principal surgeon with over 40 years of experience in surgical oncology and 25 years in performing sentinel lymph node biopsies. This consistency helps eliminate variations in technique. Another advantage of this study is that only two other studies have addressed SLNB and ARM using indocyanine green for patients following neoadjuvant systemic treatment. Notably, this is the only study that directly compares SLNB and ARM performed during upfront surgery and after neoadjuvant systemic treatment.

Conclusions

Axillary reverse mapping in patients undergoing sentinel lymph node biopsy enables a supraselective approach to axillary surgery in breast cancer. This technique is valuable, feasible and oncologically safe, as it allows the preservation of axillary drainage of the upper limb and may potentially prevent lymphedema. However, it can also help identify patients who may be at risk of developing lymphedema in the future. Notably, in patients who underwent upfront surgery, in all cases of SLN-ARM node crossover, the nodes were found to be metastatic. In this category of patients, no other invaded ARM nodes were found in patients without SLN-ARM node crossover. This observation raises the possibility of sparing ARM nodes in SLN-positive patients.

Crossover rates are higher in patients who have received neoadjuvant treatment, possibly due to anatomical changes in the lymphatic pathways caused by NST. In this category of patients, metastatic ARM nodes were also found in patients without SLN-ARM node crossover.

Further research on larger patient populations, along with multicenter studies and long-term follow-up, are necessary to validate the indication of preserving ARM nodes and the effectiveness of this method in reducing lymphedema rates.

Conflict of Interest and Source of Funding

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Ethical Statement

All procedures involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

References

1. Halsted WS. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. Ann Surg. 1907;46(1):1–19.
2. Yoshihara E, Smeets A, Laenen A, Reynders A, Soens J, Van Ongeval C, et al. Predictors of axillary lymph node metastases in early breast cancer and their applicability in clinical practice. Breast. 2013;22(3):357–61.
3. Noguchi M, Miwa K, Michigishi T, Yokoyama K, Nishijima H, Takanaka T, et al. The Role of Axillary Lymph Node Dissection in Breast Cancer Management. Breast Cancer. 1997;4(3):143–53.
4. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
5. Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg. 2010;251(4):595–600.
6. Dogan NU, Dogan S, Favero G, Köhler C, Dursun P. The Basics of Sentinel Lymph Node Biopsy: Anatomical and Pathophysiological Considerations and Clinical Aspects. J Oncol. 2019;2019:3415630.
7. Cousins A, Thompson SK, Wedding AB, Thierry B. Clinical relevance of novel imaging technologies for sentinel lymph node identification and staging. Biotechnology Advances. 2014;32(2):269–79.
8. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2014;32(13):1365–83.
9. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455–61.
10. Boileau JF, Poirier B, Basik M, Holloway CMB, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol. 2015;33(3): 258–64.
11. Nguyen CL, Zhou M, Easwaralingam N, Seah JL, Azimi F, Mak C, et al. Novel Dual Tracer Indocyanine Green and Radioisotope Versus Gold Standard Sentinel Lymph Node Biopsy in Breast Cancer: The GREENOR-BLUE Trial. Ann Surg Oncol. 2023;30(11):6520–7
12. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609–18.
13. Isik A, Soran A, Grasi A, Barry N, Sezgin E. Lymphedema After Sentinel Lymph Node Biopsy: Who Is at Risk? Lymphat Res Biol. 2022;20(2):160–3.
14. Greene AK, Zurakowski D, Goss JA. Body Mass Index and Lymphedema Morbidity: Comparison of Obese versus Normal-Weight Patients. Plast Reconstr Surg. 2020;146(2):402–7.
15. Armer JM, Ostby PL, Ginex PK, Beck M, Deng J, Fu MR, et al. ONS GuidelinesTM for Cancer Treatment-Related Lymphedema. Oncol Nurs Forum. 2020;47(5):518–38.
16. Thompson M, Korourian S, Henry-Tillman R, Adkins L, Mumford S, Westbrook

KC, et al. Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. Ann Surg Oncol. 2007;14(6):1890–5.
17. Tummel E, Ochoa D, Korourian S, Betzold R, Adkins L, McCarthy M, et al. Does Axillary Reverse Mapping Prevent Lymphedema After Lymphadenectomy? Ann Surg. 2017;265(5):987–92.
18. Sakurai T, Endo M, Shimizu K, Yoshimizu N, Nakajima K, Nosaka K, et al. Axillary reverse mapping using fluorescence imaging is useful for identifying the risk group of postoperative lymphedema in breast cancer patients undergoing sentinel node biopsies. J Surg Oncol. 2014;109(6):612–5.
19. Foster D, Choy N, Porter C, Ahmed S, Wapnir I. Axillary reverse mapping with indocyanine green or isosulfan blue demonstrate similar crossover rates to radiotracer identified sentinel nodes. J Surg Oncol. 2018;117(3):336–40.
20. Nos C, Lesieur B, Clough KB, Lecuru F. Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection. Ann Surg Oncol. 2007;14(9):2490–6.
21. Suami H, Heydon-White A, Mackie H, Czerniec S, Koelmeyer L, Boyages J. A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for patients with breast cancer-related lymphoedema. BMC Cancer. 2019;19(1):985.
22. Pavlista D, Eliska O. Relationship between the lymphatic drainage of the breast and the upper extremity: a postmortem study. Ann Surg Oncol. 2012;19(11):3410–5.
23. Rockson SG. Addressing the unmet needs in lymphedema risk management. Lymphat Res Biol. 2006;4(1):42–6.
24. Rockson SG, Rivera KK. Estimating the population burden of lymphedema. Ann N Y Acad Sci. 2008;1131:147–54.
25. Wijaya WA, Peng J, He Y, Chen J, Cen Y. Clinical application of axillary reverse mapping in patients with breast cancer: A systematic review and meta-analysis. Breast. 2020;53:189–200.
26. Sener SF, Winchester DJ, Martz CH, Feldman JL, Cavanaugh JA, Winchester DP, et al. Lymphedema after sentinel lymphadenectomy for breast carcinoma. Cancer. 20015;92(4):748–52.
27. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis: A Randomized Clinical Trial. JAMA. 2011;305(6):569–75.
28. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303–10.
29. McEvoy MP, Ravetch E, Patel G, Fox J, Feldman S. Prevention of Breast Cancer-Related Lymphedema. Clin Breast Cancer. 2021;21(2):128–42.
30. Abbaci M, Conversano A, De Leeuw F, Laplace-Builhé C, Mazouni C. Near-infrared fluorescence imaging for the prevention and management of breast cancer-related lymphedema: A systematic review. Eur J Surg Oncol. 2019;45(10):1778–86.
31. Noguchi M. Axillary reverse mapping for breast cancer. Breast Cancer Res Treat. 2010;119(3):529–35.
32. Han C, Yang B, Zuo WS, Zheng G, Yang L, Zheng MZ. The Feasibility and Oncological Safety of Axillary Reverse Mapping in Patients with Breast Cancer: A Systematic Review and Meta-Analysis of Prospective Studies. PLoS One. 2016;11(2):e0150285.
33. Noguchi M, Miura S, Morioka E, Ohno Y, Yokoi-Noguchi M, Nakano Y, et al. Is axillary reverse mapping feasible in breast cancer patients? Eur J Surg Oncol. 2015;41(4):442–9.
34. Hirche C, Murawa D, Mohr Z, Kneif S, Hünerbein M. ICG fluorescence-guided sentinel node biopsy for axillary nodal staging in breast cancer. Breast Cancer Res Treat. 2010;121(2):373–8.
35. Sugie T, Kassim KA, Takeuchi M, Hashimoto T, Yamagami K, Masai Y, et al. A novel method for sentinel lymph node biopsy by indocyanine green fluorescence technique in breast cancer. Cancers (Basel). 2010;2(2):713–20.
36. Boneti C, Korourian S, Bland K, Cox K, Adkins LL, Henry-Tillman RS, et al. Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy. J Am Coll Surg. 2008;206(5):1038–42; discussion 1042-1044.
37. Gandhi SJ, Satish C, Shanmuga Sundaram P, Subramanyam P, Vijaykumar DK. Axillary reverse mapping using 99mTc-SC: a case illustration. Clin Nucl Med. 2014;39(10):e428-430.
38. Yoon KH, Lim SM, Koo B, Kim JY, Park HS, Park S, et al. Conserving the lymphatics from the arm using fluorescence imaging in patients with breast cancer at high risk of postoperative lymphedema: a pilot study. Gland Surg. 2020;9(3):629–36.
39. Suami H, Heydon-White A, Mackie H, Czerniec S, Koelmeyer L, Boyages J. A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for patients with breast cancer-related lymphoedema. BMC Cancer. 2019;19(1):985.
40. Alander JT, Kaartinen I, Laakso A, Pätilä T, Spillmann T, Tuchin VV, et al. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging. 2012;2012:940585.
41. Coufal O, Fait V. Use of indocyanine green and the HyperEye system for detecting sentinel lymph nodes in breast cancer within a population of European patients: a pilot study. World J Surg Oncol. 2016;14(1):299.
42. Zelken JA, Tufaro AP. Current Trends and Emerging Future of Indocyanine Green Usage in Surgery and Oncology: An Update. Ann Surg Oncol. 2015; 22 Suppl 3:S1271-1283.
43. Dip F, Boni L, Bouvet M, Carus T, Diana M, Falco J, et al. Consensus Conference Statement on the General Use of Near-infrared Fluorescence Imaging and Indocyanine Green Guided Surgery: Results of a Modified Delphi Study. Ann Surg. 2022;275(4):685–91.
44. Benya R, Quintana J, Brundage B. Adverse reactions to indocyanine green: a case report and a review of the literature. Cathet Cardiovasc Diagn. 1989;17(4):231–3.
45. Jung SY, Kim SK, Kim SW, Kwon Y, Lee ES, Kang HS, et al. Comparison of sentinel lymph node biopsy guided by the multimodal method of indocyanine green fluorescence, radioisotope, and blue dye versus the radioisotope method in breast cancer: a randomized controlled trial. Ann Surg Oncol. 2014;21(4):1254–9.
46. Noguchi M, Noguchi M, Ohno Y, Morioka E, Nakano Y, Kosaka T, et al. Feasibility study of axillary reverse mapping for patients with clinically node-negative breast cancer. Eur J Surg Oncol. 2016;42(5):650–6.
47. Sorrentino L, Sartani A, Pietropaolo G, Bossi D, Mazzucchelli S, Truffi M, et al. A Novel Indocyanine Green Fluorescence-Guided Video-Assisted Technique for Sentinel Node Biopsy in Breast Cancer. World J Surg. 2018; 42(9):2815–24
48. Boneti C, Korourian S, Diaz Z, Santiago C, Mumford S, Adkins L, et al. Scientific Impact Award: Axillary reverse mapping (ARM) to identify and protect lymphatics draining the arm during axillary lymphadenectomy. Am J Surg. 2009;198(4):482–7.
49. Casabona F, Bogliolo S, Valenzano Menada M, Sala P, Villa G, Ferrero S. Feasibility of axillary reverse mapping during sentinel lymph node biopsy in breast cancer patients. Ann Surg Oncol. 2009;16(9):2459–63.
50. Tausch C, Baege A, Dietrich D, Vergin I, Heuer H, Heusler RH, et al. Can axillary reverse mapping avoid lymphedema in node positive breast cancer patients? Eur J Surg Oncol. 2013;39(8):880–6.
51. Ponzone R, Cont NT, Maggiorotto F, Cassina E, Mininanni P, Biglia N, et al. Extensive nodal disease may impair axillary reverse mapping in patients with breast cancer. J Clin Oncol. 2009;27(33):5547–51.
52. Nos C, Kaufmann G, Clough KB, Collignon MA, Zerbib E, Cusumano P, et al. Combined axillary reverse mapping (ARM) technique for breast cancer patients requiring axillary dissection. Ann Surg Oncol. 2008;15(9):2550–5.
53. Choi JE, Jeon YS, Kang SH, Lee SJ. Preservation of Lymphatic Drainage of Arm during Axillary Procedure in Breast Cancer Patients. Journal of Breast Cancer. 2009;12(3):179–85.
54. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455–61.
55. Provenzano E. Neoadjuvant Chemotherapy for Breast Cancer: Moving Beyond Pathological Complete Response in the Molecular Age. Acta Med Acad. 2021;50(1):88–109.
56. Giammarile F, Alazraki N, Aarsvold JN, Audisio RA, Glass E, Grant SF, et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and

sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging. 2013;40(12):1932–47.
57. Nieweg OE, Estourgie SH, van Rijk MC, Kroon BBR. Rationale for superficial injection techniques in lymphatic mapping in breast cancer patients. J Surg Oncol. 2004;87(4):153–6.
58. Noguchi M, Inokuchi M, Zen Y. Complement of peritumoral and subareolar injection in breast cancer sentinel lymph node biopsy. J Surg Oncol. 2009;100(2):100–5.
59. Lyman GH, Giuliano AE, Somerfield MR, Benson AB, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23(30):7703–20.
60. De Cicco C, Cremonesi M, Luini A, Bartolomei M, Grana C, Prisco G, et al. Lymphoscintigraphy and radioguided biopsy of the sentinel axillary node in breast cancer. J Nucl Med. 1998;39(12):2080–4.
61. Gray RJ, Pockaj BA, Roarke MC. Injection of (99m)Tc-labeled sulfur colloid the day before operation for breast cancer sentinel lymph node mapping is as successful as injection the day of operation. Am J Surg. 2004; 188(6):685–9.
62. Noguchi M, Inokuchi M, Yokoi-Noguchi M, Morioka E, Haba Y. The involvement of axillary reverse mapping nodes in patients with node-positive breast cancer. Eur J Surg Oncol. 2023;49(10):106937.
63. Ikeda K, Ogawa Y, Kajino C, Deguchi S, Kurihara S, Tashima T, et al. The influence of axillary reverse mapping related factors on lymphedema in breast cancer patients. Eur J Surg Oncol. 2014;40(7):818-23.
64. Xu L, Yang J, Du Z, Liang F, Xie Y, Long Q, et al. Redefining Criteria to Ensure Adequate Sentinel Lymph Node Biopsy With Dual Tracer for Breast Cancer. Front Oncol. 2020;10:588067.
65. Yi M, Meric-Bernstam F, Ross MI, Akins JS, Hwang RF, Lucci A, et al. How many sentinel lymph nodes are enough during sentinel lymph node dissection for breast cancer? Cancer. 2008;113(1):30–7.
66. Noguchi M, Noguchi M, Nakano Y, Ohno Y, Kosaka T. Axillary reverse mapping using a fluorescence imaging system in breast cancer. J Surg Oncol. 2012;105(3):229–34.
67. Rubio IT, Cebrecos I, Peg V, Esgueva A, Mendoza C, Cortadellas T, et al. Extensive nodal involvement increases the positivity of blue nodes in the axillary reverse mapping procedure in patients with breast cancer. J Surg Oncol. 2012;106(1):89–93.
68. Noguchi M, Inokuchi M, Yokoi-Noguchi M, Morioka E. The involvement of axillary reverse mapping nodes in patients with clinically node-negative breast cancer. Breast Cancer. 2022;29(2):209–15.
69. Ochoa D, Korourian S, Boneti C, Adkins L, Badgwell B, Klimberg VS. Axillary Reverse Mapping: Five Year Experience. Surgery. 2014;156(5): 1261–8.
70. Ikeda K, Ogawa Y, Komatsu H, Mori Y, Ishikawa A, Nakajima T, et al. Evaluation of the metastatic status of lymph nodes identified using axillary reverse mapping in breast cancer patients. World J Surg Oncol. 2012; 10:233.
71. Tasdoven I, Balbaloglu H, Erdemir RU, Bahadir B, Guldeniz Karadeniz C. Triple mapping for axillary staging after neoadjuvant therapy: Axillary reverse mapping with indocyanine green and dual agent sentinel lymph node biopsy. Medicine (Baltimore). 2022;101(52):e32545.
72. Deng H, Chen L, Jia W, Chen K, Zeng Y, Rao N, et al. Safety study of axillary reverse mapping in the surgical treatment for breast cancer patients. J Cancer Res Clin Oncol. 2011;137(12):1869–74.
73. Han JW, Seo YJ, Choi JE, Kang SH, Bae YK, Lee SJ. The Efficacy of Arm Node Preserving Surgery Using Axillary Reverse Mapping for Preventing Lymphedema in Patients with Breast Cancer. J Breast Cancer. 2012;15(1): 91–7.
74. Gobardhan PD, Wijsman JH, van Dalen T, Klompenhouwer EG, van der Schelling GP, Los J, et al. ARM: axillary reverse mapping - the need for selection of patients. Eur J Surg Oncol. 2012;38(8):657–61.
75. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297–305
76. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg. 2016;264(3):413–20.
77. Bartels SAL, Donker M, Poncet C, Sauvé N, Straver ME, van de Velde CJH, et al. Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial. J Clin Oncol. 2023;41(12):2159–65.
78. Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017;43(4):672–9.
79. de Boniface J, Filtenborg Tvedskov T, Rydén L, Szulkin R, Reimer T, Kühn T, et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med. 2024;390(13):1163–75.
80. Kuusk U, Seyednejad N, McKevitt EC, Dingee CK, Wiseman SM. Axillary reverse mapping in breast cancer: a Canadian experience. J Surg Oncol. 2014;110(7):791–5.
81. Connor C, McGinness M, Mammen J, Ranallo L, Lafaver S, Klemp J, et al. Axillary reverse mapping: a prospective study in women with clinically node negative and node positive breast cancer. Ann Surg Oncol. 2013;20(10): 3303–7.
82. Tummel E, Ochoa D, Gallagher K, Betzold R, Adkins, L, Korourian S, et al. Axillary reverse mapping: redefining axillary surgery. Ann Surg Oncol. 2014; 21(Suppl 1):S8.
83. Parks RM, Cheung KL. Axillary reverse mapping in N0 patients requiring sentinel lymph node biopsy - A systematic review of the literature and necessity of a randomised study. Breast. 2017;33:57–70.
84. Nguyen CL, Dayaratna N, Graham S, Azimi F, Mak C, Pulitano C, et al. Evolution of Indocyanine Green Fluorescence in Breast and Axilla Surgery: An Australasian Experience. Life (Basel). 2024;14(1):135.