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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Sentinel Lymph Node Biopsy Using Indocyanine Green Fluorescence Plus Radioisotope Method Compared With the Radioisotope-Only Method for Breast Cancer Patients After Neoadjuvant Chemotherapy: A Prospective, Randomized, Open-Label, Single-Center Phase 2 Trial

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ABSTRACT

Background. This study aimed to compare the sentinel lymph node (SLN) identification rates for breast cancer patients after neoadjuvant chemotherapy (NAC) between the dual method (DM) of indocyanine green fluorescence (ICG-F) plus a radioisotope (RI) and RI alone.

Methods. This randomized study enrolled 130 patients who received NAC for breast cancer and 122 patients who received SLN biopsy (SLNB) using either DM ($n = 58$) or RI only ($n = 64$). The study compared the identification rate, number of SLNs, and detection time of SLNB.

Results. Among the 122 patients, 113 (92.6%) were clinically node-positive before NAC. The SLN identification rate was 98.3% in the DM group and 93.8% in the RI group ($p = 0.14$). The DM group and the RI group were similar in the average number of SLNs (2.2 ± 1.13 vs. 1.9 ± 1.33; $p = 0.26$) and the time to detection of the first SLN (8.7 ± 4.98 vs. 8.3 ± 4.31 min; $p = 0.30$). In the DM group, transcutaneous lymphatic drainage was visualized by fluorescence imaging for 65.5% (38 of 58) of the patients. The SLN identification rate was 94.7% using ICG-F and 93% using RI ($p = 0.79$). During and after the operation, no complications, including allergic reactions or skin necrosis, occurred.

Conclusions. This study is the first randomized trial to use ICG-F for SLNB in breast cancer patients after NAC. The DM including ICG-F could be a feasible and safe method for SLNB in initially node-positive breast cancer patients with NAC.

Neoadjuvant chemotherapy (NAC) has been a standard treatment for locally advanced breast cancer patients, and 40% to 75% of patients show a pathologic complete response (pCR), including the axillary lymph nodes (ALNs).[1–4] For these patients, sentinel lymph node biopsy (SLNB) could be used to assess the axillary nodal status, resulting in low morbidity including lymphedema, paresthesia, and pain.[3,5–7] However, SLNB after NAC results in clinical issues, including a lower sentinel lymph node (SLN) identification rate (80.1–92.9%) and a higher false-negative rate (FNR) (8.4–15%).[6,8–11] To improve the SLN identification rate and FNR of SLNB after NAC, optimal material SLN mapping has been studied.

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To date, the radioisotope (RI) and blue dye methods are the techniques most widely used to detect SLNB in breast cancer.[12,13] However, these methods have some limitations. The SLNB method using blue dye is reported to be associated with a lower SLN identification rate and a steep learning curve,[14–17] and RI needs an adequate facility for the handling and disposal of isotopes, as well as for legislative requirements.

Indocyanine green fluorescence (ICG-F) has been introduced as a new technique for SLNB.[18] Previously, we reported that ICG-F is a feasible material for SLNB in early breast cancer.[16] In the review by Ahmed et al.,[17] the SLNB identification rates using ICG-F were 93.1–100%. However, no randomized prospective study has investigated SLNB using ICG-F for breast cancer patients after NAC.

This study was designed to compare the rates for SLN identification between the dual-method (DM) of ICG plus RI and RI alone in breast cancer patients with NAC.

METHODS

Study Design

We planned a phase 2, open-label, prospective, single-center, randomized study to compare the rates for SLN identification between DM using a mixture of ICG and RI and the conventional RI-only method for SLNB in breast cancer patients after NAC. The study was approved by the Institutional Review Board at the National Cancer Center of Korea (NCC 2015-0051) according to the Declaration of Helsinki and was registered in ClinicalTrials.gov (NCT 02479997). Before randomization, we explained the content of this study and obtained informed consent from all the patients.

From April 2015 to October 2017, we enrolled 130 breast cancer patients scheduled for curative surgery after NAC. We included women age 18 years or older with clinical stage T0-4, N0-3, or M0 primary invasive breast cancer according to the American Joint Committee on Cancer (AJCC) cancer staging system and an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 who had completed NAC or were planning to undergo NAC (the regimen was decided by the opinion of the patient's medical oncologist).

To evaluate the initial axillary nodal status, all the patients were evaluated using preoperative imaging methods such as sonography for axilla with or without biopsy, breast magnetic resonance imaging, chest computed tomography (CT), or positron emission tomography (PET-CT). However, breast cancer patients with previous breast or axillary surgery, M1 patients with palliative systemic treatment, and patients who were pregnant and had a diagnosis of breast cancer were excluded from this study.

Overall, 130 breast cancer patients with NAC were enrolled and randomized evenly to each group. Eight patients withdrew from the study, leaving 122 patients for analysis in the current study (58 in the DM group and 64 in the RI-only group, Fig. 1). These patients received a subareolar injection of either DM including ICG or RI alone for SLN mapping. As the primary outcome, we compared the rates of SLN identification between the two groups, and as the secondary outcome, we evaluated the number of SLNs.

Preparation of DM Agents for SLN Mapping

The agent for DM was prepared, and quality control was performed as described previously.[16] Briefly, we first mixed 1 mL of 111 MBq pertechnetate ([Tc-99 m] $TcO4^{-}$)/NaCl and 1 mg of reduced human serum albumin and then incubated the mixture at room temperature for 10 min. Second, we dissolved 5 mg of human serum albumin and 0.6 mg of ICG in 1 mL of injectable water. The two solutions then were mixed and shaken manually 10 times.

As the ICG-F imaging and display system, we used the previously used fluorescence imaging system[16] (Visual Navigator; SH System, Gwangju, Korea; Fig. 2) consisting of a small charge-coupled device camera with an integrated near-infrared (NIR) light source (energy, 2.4 W; wavelength, 740 nm). A band-path filter (820 nm) was used as the emission filter to collect NIR radiation and reject visible and excitation light.

Methods for Injecting the Materials and Identifying SLNs

In the morning of the day for surgery, the patients were randomized into either the DM or the conventional RI group. Next, 0.3 mL of each agent was injected at the subareolar site, followed by manual massage for 2 min. Then, 30 min after injection, the patients were checked by lymphoscintigraphy, and the surgery was performed within 6 h after the injection. Intraoperatively, ICG-F was checked in the DM group (Fig. 2). All SLNB procedures were performed by three experienced breast surgeons.

The lymph nodes were considered SLNs when we observed either a fluorescent lymph node by NIR imaging (Fig. 2d) or a radioactive lymph node based on the conventional method, including the hottest node and nodes that showed more than 10% of the maximum value as counted by the gamma probe (Navigator; US Surgical, Norwalk, CT, USA). After detection of the SLNs, further axillary

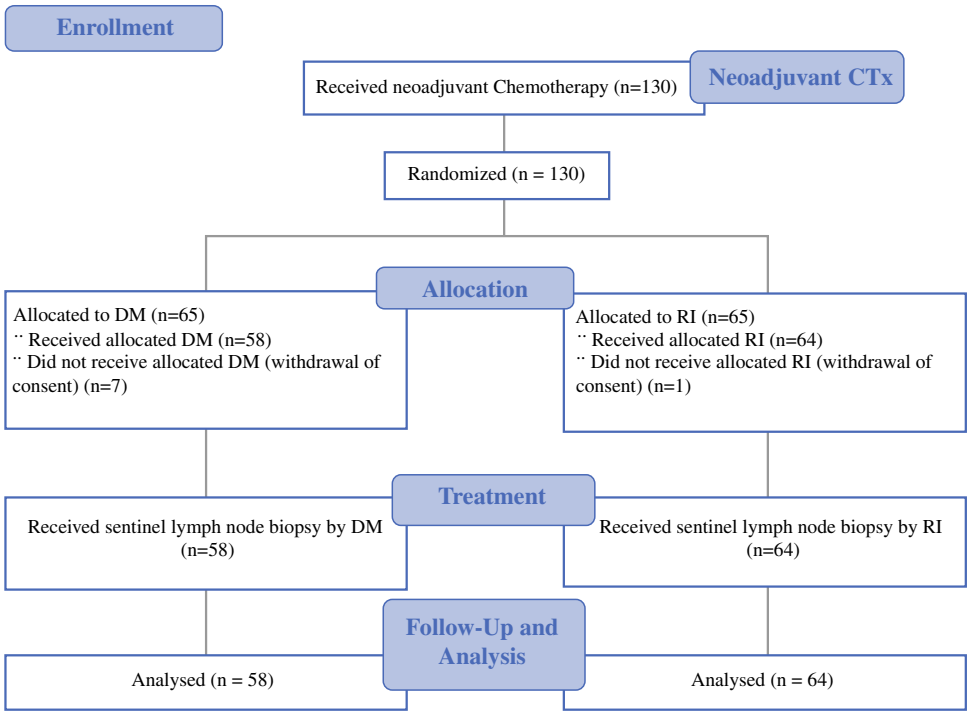

FIG. 1 Consolidated standards of reporting trials (CONSORT) diagram

lymph node dissection (ALND) was performed when SLNs indicated positive malignant cells.

Statistical Analysis

The sample size was calculated for a superiority design, assuming an SLN identification rate of 80% for the RI-only group (control) in the initially node-positive breast cancer patients with NAC[19] and an SLN identification rate of 95% in the DM group (case). To detect a 15% difference in the identification rate, this study required 58 patients, with a one-sided type 1 error rate of 10% and a power of 81%. Considering a 10% dropout rate, we planned to enroll 65 patients per group.

The baseline characteristics and SLNB results were summarized as means ± standard deviations for continuous variables and frequencies (%) for categorical variables. Comparison of the distribution between the RI and DM groups was performed using the Chi square test, Fisher's exact test, and the *t* test. The *z* test and Barnard exact test were used to verify the difference in rates of SLN identification between the two groups. For additional confirmation, the SLN identification rates of each method were compared only with those of the DM group.

As the primary end point of the study, the difference in SLN identification rates between the RI and DM groups was considered statistically significant at a one-sided *p* value lower than 0.1. The number of SLNs and time to detection of the first SLN were considered to be the secondary end points and regarded as statistically significant at a one-sided *p* value lower than 0.05. The remaining results were considered significant at a two-sided *p* value lower than 0.05. The time to detection of the SLN was defined as the time from the skin incision to the extraction of the first SLN, a method we previously reported.[16] All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Regarding the evaluation of each method's safety, all patients were followed up to evaluate the complications of skin color changes and necrosis until 3 months after the operation

RESULTS

Clinicopathologic Characteristics of the Study Population

The study enrolled and randomized 130 patients. Of these 130 patients, 122 were analyzed in this study (58 in the DM group and 64 in the RI group). The clinicopathologic characteristics are summarized in Table 1. The mean age was 49.9 years in the DM group and 47.8 years in the RI group ($p = 0.23$).

Among the 122 patients, 113 (92.6%) were clinically node-positive before NAC, and all the patients with clinical N0 stage ($n = 9$) were in the RI-only group. No differences were found in the histopathologic factors, including clinical T stage, N stage, hormone receptor positivity, and human epidermal growth factor receptor 2 (HER2) positivity, between the two groups.

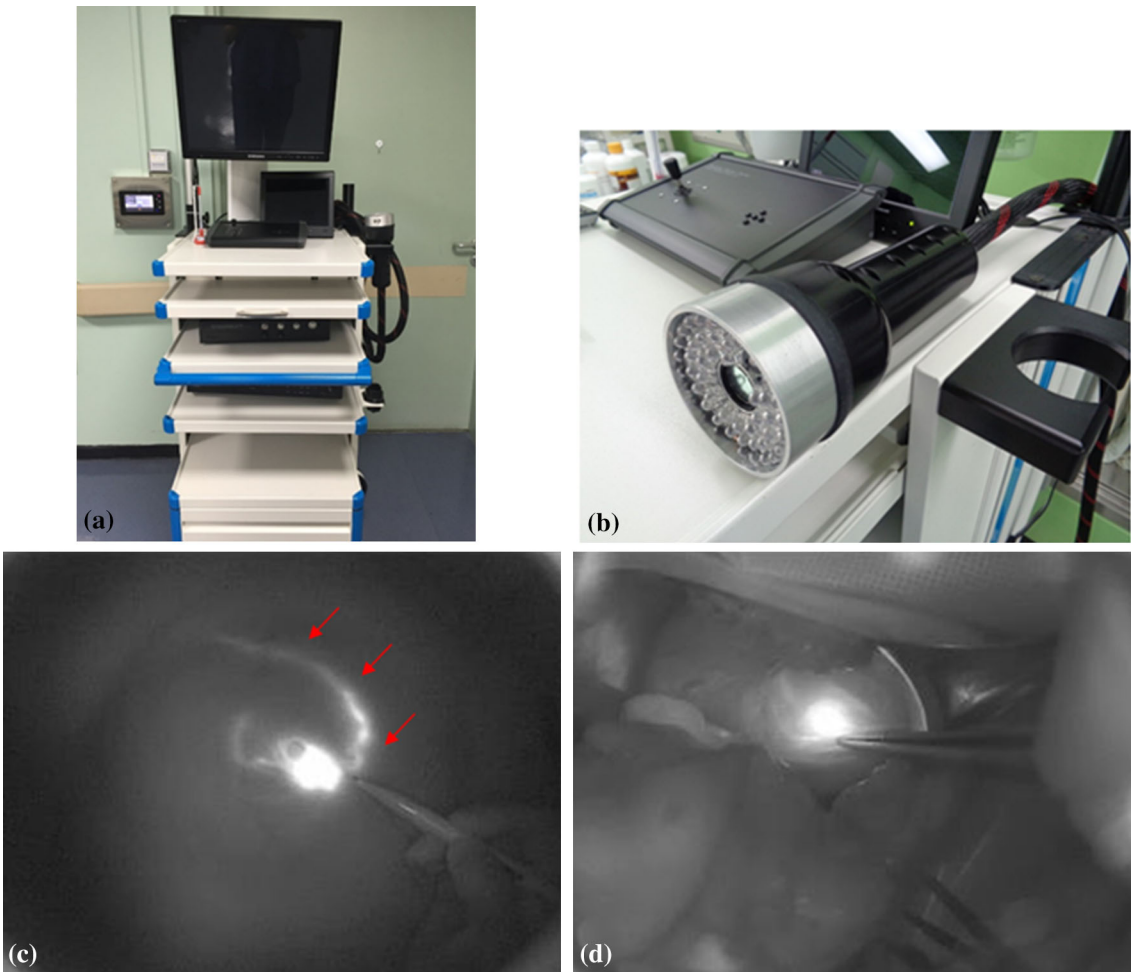

FIG. 2 Near-infrared fluorescence imaging system (**a** Visual Navigator and **b** portable handy instrument) and transcutaneous lymphatic track (**c** *arrows* and **d** SLN detected by fluorescence)

For 47 patients (38.5%), pCR was achieved in both the tumor and the lymph nodes. For 53 patients (43.4%), pCR was shown in the tumor, and for 78 patients (70.3%), pCR was shown in the lymph nodes. The pCR rates were similar between the two groups. The rates of breast-conserving surgery after NAC were respectively 74.4% and 75.0% ($p = 0.91$). Additional ALND was received by 44 patients (36.1%), 34.5% in the DM group and 37.5% in the RI-only group.

Primary and Secondary Outcomes

The SLN identification rate was 98.3% in the DM group and 93.8% in the RI group ($p = 0.14$) (Table 2). Regarding the rates for identification of two or more SLNs, no significant difference was found between the two groups (70.2% vs. 60.0%, respectively; $p = 0.12$). The average number of SLNs in the DM group was similar to that in the RI group (2.2 ± 1.13 vs. 1.9 ± 1.33, respectively; $p = 0.26$). In the two groups, the time to detection of the first SLN (8.7 ± 4.98 vs. 8.3 ± 4.31 min, respectively; $p = 0.30$) and the total time for SLNB (11.4 ± 5.59 vs. 10.1 ± 5.30 min, respectively; $p = 0.11$) were similar.

Because all of the initially node-negative patients ($n = 9$) were randomized into the RI-only group, we reanalyzed the SLN identification rates for the clinically node-positive patients (58 in the DM group and 55 in the RI group). No difference was found in the SLN identification rates (57 [98.3%] vs. 51 [92.7%], respectively; $p = 0.11$].

SLN Identification Rates by ICG-F Only in the DM Group

In the DM group, transcutaneous lymphatic drainage (Fig. 2c) was visualized by fluorescence imaging in 65.5% (38 of 58) of the patients. When we evaluated and compared the SLN identification rates by ICG-F and by RI in the DM group, 94.7% were detected by ICG-F and 93.0% by RI ($p = 0.79$, Table 3). Among 30 patients with a

TABLE 1 Baseline characteristics of the study population

Characteristics		Total (n = 122) n (%)	ICG-F+RI (n = 58) n (%)	RI only (n = 64) n (%)	p value
Mean age (years)		48.8 ± 9.95	49.9 ± 10.20	47.8 ± 9.68	0.23[a]
Histologic types	DCIS	1 (0.82)	0 (0)	1 (1.56)	0.86[b]
	IDC	118 (96.72)	56 (96.55)	62 (96.88)	
	ILC	2 (1.64)	1 (1.72)	1 (1.56)	
	Mucinous	1 (0.82)	1 (1.72)	0 (0)	
Breast surgery	BCS	91 (74.59)	43 (74.14)	48 (75.00)	0.91[c]
	Mastectomy	31 (25.41)	15 (25.86)	16 (25.00)	
Axillary surgery	SLNB+ALND	44 (36.07)	20 (34.48)	24 (37.5)	0.73[c]
	SLNB only	78 (63.93)	38 (65.52)	40 (62.5)	
Clinical T stage	0–2	85 (69.7)	42 (72.41)	43 (67.19)	0.53[c]
	3,4	37 (30.3)	16 (27.59)	21 (32.81)	
Clinical N stage	0,1	66 (54.1)	30 (51.72)	36 (56.25)	0.62[c]
	2,3	56 (45.9)	28 (48.28)	28 (43.75)	
Pathologic stage	pCR	47 (38.52)	27 (46.55)	20 (31.25)	0.08[c]
	Non pCR	75 (61.48)	31 (53.45)	44 (68.75)	
Pathologic T stage	pCR	53 (43.44)	29 (50.00)	24 (37.50)	0.16[c]
	Non pCR	69 (56.56)	29 (50.00)	40 (62.50)	
Pathologic N stage	pCR	78 (70.27)	39 (62.24)	39 (60.94)	0.47[c]
	Non pCR	44 (29.73)	19 (32.76)	25 (39.06)	
ER	Negative	62 (50.8)	32 (55.17)	30 (46.88)	0.36[c]
	Positive	60 (49.2)	26 (44.83)	34 (53.13)	
PR	Negative	70 (57.4)	33 (56.9)	37 (57.81)	0.92[c]
	Positive	52 (42.3)	25 (43.1)	27 (42.19)	
HER2	0,1	55 (45.1)	25 (43.1)	30 (46.88)	0.68[c]
	2,3	67 (54.9)	33 (56.9)	34 (53.13)	

ICG-F indocyanine green fluorescence, *RI* radioisotope, *DCIS* ductal carcinoma *in situ*, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *BCS* breast-conserving surgery, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *T* tumor, *N* nodal, *pCR* pathologic complete response, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[a] t test

[b] Fisher's exact test

[c] Chi square test

TABLE 2 Sentinel lymph biopsy results in both groups

Characteristics	ICG-F+RI (n = 58) n (%)	RI only (n = 64) n (%)	p Value
SLN identification rate	57 (98.3)	60 (93.8)	0.14[a]
Rate for identification of 2 or more SLNs	40 (70.2)	36 (60.0)	0.12[b]
Mean time to first SLN (min)	8.7 ± 4.98	8.3 ± 4.31	0.31[c]
Mean total time for SLNB (min)	11.4 ± 5.59	10.1 ± 5.30	0.11[c]
Mean no. of SLNs identified per patient	2.2 ± 1.13	1.9 ± 1.33	0.26[c]
Mean average time for each SLN (min)	6.3 ± 4.09	6.2 ± 3.85	0.44[c]

ICG-F indocyanine green fluorescence, *RI* radioisotope, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy

[a] Barnard exact test

[b] z test

[c] t test

TABLE 3 SLN identification rate for ICG-F and RI in the DM group

Characteristics	ICG-F *n* (%)	RI *n* (%)	*p* Value
First SLN group ($n = 57$)	54 (94.7)	53 (93.0)	0.79
Second SLN group ($n = 30$)	29 (96.7)	25 (83.3)	0.11
Third SLN group ($n = 5$)	5 (100)	5 (100)	–

ICG-F indocyanine green fluorescence, *RI* radioisotope, *SLN* sentinel lymph node

second SLN, 96.9% underwent SLN detection by ICG-F and 83.3% underwent SLN detection by RI ($p = 0.11$) (Table 3).

Comparison of the Adverse Effects

Regarding the evaluation of each method's safety for SLN mapping, no patient showed any adverse reaction or complication related to the preoperative injection for SLN mapping. All the patients tolerated the procedure well without any allergic reaction. During 3 months after the operation, no wound or injection-site complications occurred, including skin staining or skin necrosis.

DISCUSSION

To our knowledge, this is the first report of a randomized study to compare the SLN identification rates between DM including ICG-F and the conventional RI-only method for breast cancer patients who received NAC. The results showed that the SLN identification rate using DM with ICG-F was similar to that of the RI-only method. In addition, the identification rate for ICG alone in the dual method (DM) exceeded that for RI alone, although the difference was not statistically significant (94.7% vs. 93.8%).

The standard method for early breast cancer patients has been SLNB, and ALND could be avoided even for patients with one or two positive metastatic SLNs based on the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial.[20] However, the role of SLNB in patients receiving NAC remains debatable because of its lower identification rate and higher FNR resulting from the fibrotic changes in the axillary lymph nodes (LNs) and lymphatic channels during NAC.[21] Previous meta-analyses of SLNB after NAC reported identification rates of 89.6% and 90.9% and FNRs of 8.4% and 10.5%, respectively.[8,9]

In a French prospective multicenter study (GANEA study) comprising clinically node-negative and node-positive patients before NAC, the identification rates were reported to be respectively 94.6% and 81.5%, and the FNRs were respectively 9.4% and 15%.[22] The SENTINA study showed an identification rate of 99.1% for patients with SLNB before NAC and 80.1% for patients with clinically node-negative breast cancer after NAC, with an FNR of 14.2%.[10] In a prospective multicenter SN FNAC study of 153 biopsy-proven node-positive breast cancer patients, the identification rate was 87.6%, and the FNR was 8.4%.[11] In the ACOSOG Z1071 (Alliance) trial with biopsy-proven disease, SLNs were identified in 92.9% of the patients with an FNR, 31.5% of the patients with only one SLN, and 12.6% of the patients with two or more SLNs.[6] In our study, the SLN identification rate after NAC was 95.9% (117 of 122 patients), 93.75% in the RI group and 98.28% in the DM group, although most of the patients (92.6%) were clinically node-positive before receiving NAC and underwent SLNB after NAC.

The methods for SLN mapping were reported to have an impact on the SLN identification rates in previous studies of the NAC setting. The SENTINA study found that combined RI and blue dye had a better SLN detection rate than RI alone.[10] In the ACOSOG Z1071 study, the DM with RI and blue dye was shown to improve the SLN identification rates significantly, with an identification rate of 93.8% using the DM and only 88.9% when a single agent was used (91.4% in the RI-only group vs. 78.6% in the blue dye-only group).[23] Thus, the authors recommended the DM or RI-only method rather than the blue dye-only method for optimal SLN mapping after NAC.

For cancer patients in the NAC setting, ICG-F has been studied as a new SLN mapping strategy.[17,24,25] In a previous systematic review study, using the ICG-F was significantly better than using the blue dye, and similar to using RI for SLN identification (blue dye: OR, 18.37; 95% CI, 8.63–39.10 vs. RI: OR, 0.81; 95% CI, 0.03–24.29). The use of ICG-F provides a visual dimension to SLNB that complements RI and avoids problems of anaphylaxis and tissue staining with blue dye. In a study to evaluate the lymphatic pathway and location of SLNs using ICG-F before and after NAC, the locations of the SLNs were not affected by NAC, although the lymphatic pathways were changed by NAC.[24]

This is the first randomized study to use DM including ICG-F for breast cancer patients after NAC. The study findings show the feasibility of ICG-F because the SLN identification rate using DM with ICG-F tended to be higher than that of RI-only (98.3% vs. 94.7%), and the identification rate for ICG alone in the DM exceeded that for RI alone, although the difference was not statistically significant (94.7% vs. 93.8%).

Our study had some limitations. Although the SLN identification rate for DM including ICG-F was greater than the expected identification rate (95%) and higher than that of the RI-only group, we failed to demonstrate

statistical significance in this study. This might have been because the sample of this study was relatively small. To calculate the sample size, we selected 80% as the expected SLN identification rate in the RI group according to previous NAC reports.[6,10,22] However, this study finally identified SLNs in 93.8% of the RI-only group. For the next phase of this multicenter, randomized trial (phase 3), we need to consider an improved SLN identification rate for the RI-only group. In this study, we could not perform axillary LNs biopsy for all the patients before NAC and evaluated only clinical LN metastasis using sonography, PET-CT, and breast MRI. Moreover, we did not calculate the FNR of the SLNs because ALND was determined by the SLN results. Although concerns exist about FNR for SLNB after NAC, a Korean study reported that SLNB-guided axillary surgery showed prognosis similar to that of ALND without SLNB for patients with the clinical conversion of axillary LNs from positive to negative after NAC.[7] This study was focused only on evaluating the optimal SLN-mapping material to improve the SLN identification rate for breast cancer patients after NAC.

In conclusion, this study demonstrated that SLNB using DM including ICG-F was comparable with the conventional RI method for breast cancer patients after receiving NAC. Although we could not obtain statistical significance for the superiority of DM in SLNB, we showed that DM could be a feasible method for SLN mapping in clinically node-positive breast cancer patients after NAC, and that using ICG-F only was comparable with using RI alone.

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DISCLOSURE There are no conflicts of interest.

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