


Intraoperative palpation of sentinel lymph nodes can accurately predict axilla in early breast cancer

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Abstract

Recent randomized trials have shown that completion axillary lymph node dissection (ALND) is not required in all patients with a positive sentinel lymph node (SLN) who will receive radiation therapy. Although routine intraoperative pathologic assessment (IPA) becomes unnecessary and less indicated by breast surgeons in the United States and some European countries, it is still widely used all around the world. In this prospective study, the feasibility of intraoperative nodal palpation (INP) as opposed to IPA of the SLN has been analyzed. Between March 2014 and June 2015, 305 patients with clinical T1-2/ N0 breast cancer from two different breast clinics (cohort A; [n = 225] and cohort B; [n = 80]) who underwent any breast surgery with sentinel lymph node biopsy (SLNB) were included in this study. Surgeons evaluated the SLNs by manual palpation before sending for IPA, and findings compared with the final pathology. The positive predictive values (PPV) of INP and IPA were 81.8% and 97.9%, respectively, whereas the negative predictive values (NPV) of INP and IPA were 83% and 92.4%. The accuracies of INP and IPA were 82.6% and 94.1%, respectively. If patients with SLNB including micrometastasis were also considered in the final pathologic assessment (FPA) (–) group that would not require a further axillary dissection, the revised NPV of INP and FPA were found to be 92.6% and 98.1%, respectively. The revised accuracy of INP also found to be increase to 86.9%. Our study, which is the only prospective one about palpation of dissected SLNs in the literature, suggests that INP can help to identify patients who do not need ALND, which encourages omitting IPA in cT1-2 N0 breast cancer.

KEYWORDS

axillary lymph node dissection, breast cancer, intraoperative nodal palpation, intraoperative pathologic assessment, sentinel lymph node

1 | INTRODUCTION

Milestone studies such as National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32¹ and others^{2,3} demonstrated that there was no difference in locoregional disease control and survival rates

between axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB). However, there can be some morbidity such as lymphedema, limitation of arm movement, numbness or paresthesia, seroma, prolonged pain, and wing scapula depending on ALND.⁴

Such complications would also significantly affect the patient's quality of life. With the inclusion of the SLNB concept, complication rates due to ALND were greatly reduced and similar survival rates have been achieved.^{5,6}

Axillary nodal status has traditionally been the most important factor in staging breast cancer.⁷ SLNB has been used in most centers for patients with clinically negative axilla and has gained acceptance as a predictor of axillary lymph node status with a reported accuracy of 95%-100%.^{8,9} If the sentinel lymph node (SLN) is positive and contains metastatic tumor cells, 13%-60% of patients will have positive non-sentinel axillary nodes.^{8,10,11} The sensitivity and accuracy of intraoperative pathologic assessment (IPA) of SLNs have been reported to range from 36.0% to 93.3% and 83.2% to 96.0%, respectively.^{8,12,13}

With implementation of the American College of Surgeons Oncology Group (ACOSOG) Z0011 data, along with other randomized trials that showed completion ALND is not required in all patients with a positive SLN, routine IPA has recently become unnecessary in dedicated breast centers.¹⁴⁻¹⁶ After Z0011, surgeons were less likely to perform intraoperative nodal assessment (26% vs 69%, $P = 0.001$), which resulted in decreased median operative times for patients who were SLN-negative at the MD Anderson Cancer Center.¹⁷ This concept is accepted by many of the breast surgeons and unit in the United States and European countries. Although intraoperative assessment of sentinel lymph nodes has become less necessary in the post-Z11 era, surgeons continue to request IPA. Therefore, we sought to determine the accuracy of INP vs IPA.

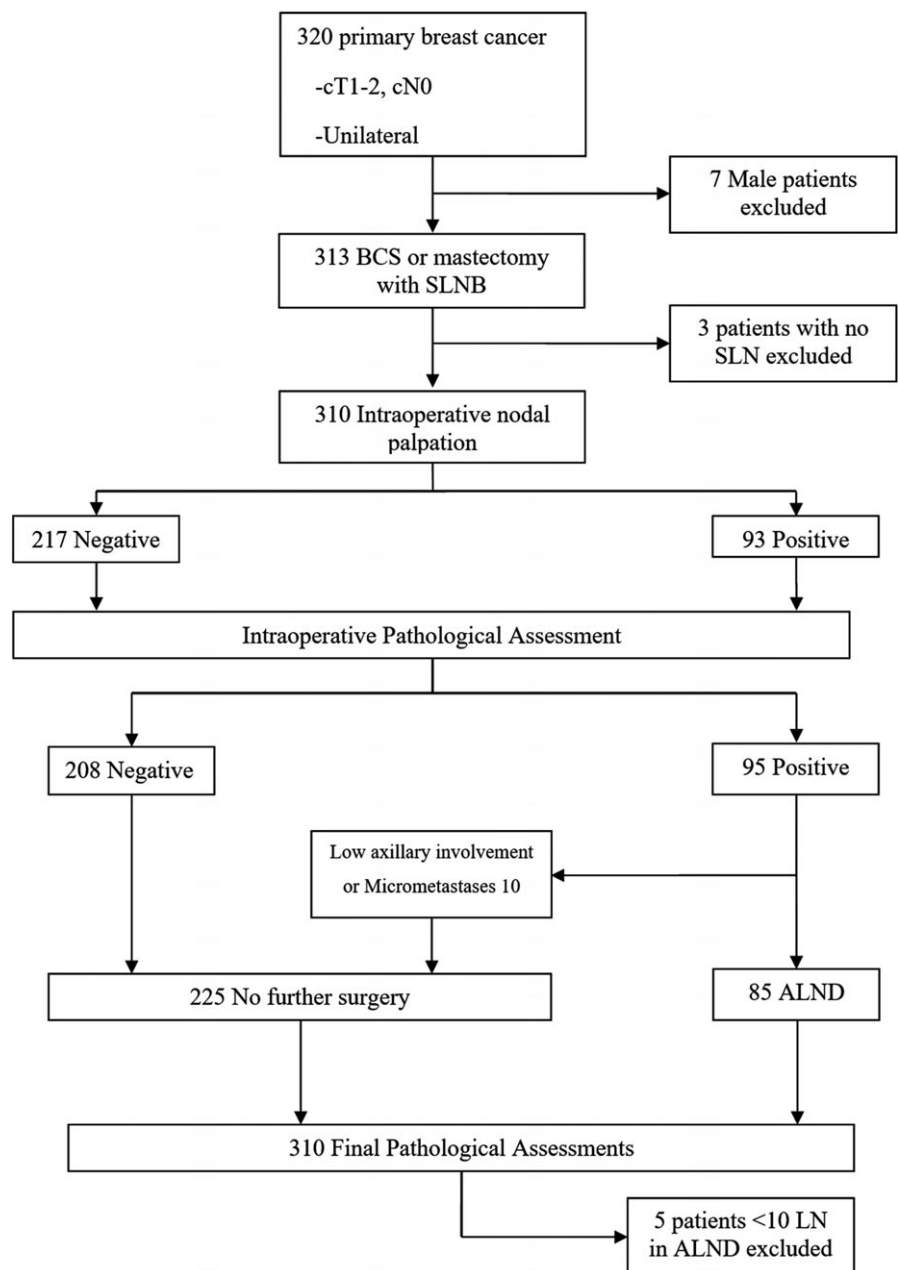


FIGURE 1 Profile schema of the study. ALND: axillary lymph node dissection; BCS: Breast conserving surgery; LN: Lymph node; SLN: Sentinel lymph node; SLNB: Sentinel lymph node biopsy

2 | MATERIALS AND METHODS

2.1 | Patient selection and clinical evaluation

Between March 2014 and June 2015, a total of 320 patients with clinical T1-2/N0, unilateral breast cancer from two different breast clinics (cohort A; [n = 233] and cohort B; [n = 87]) underwent breast conserving surgery (BCS) or mastectomy with SLNB. Three patients were male in cohort A and four in cohort B. These patients were excluded from the study. Two patients from cohort A and one patient from cohort B were also excluded from the study because of the absence of SLN detection after subareolar injection of isosulfan blue. Patients who underwent ALND with fewer than 10 lymph nodes dissected in the final pathology were also excluded from the study (cohort A, n = 3; cohort B, n = 2). Three hundred five patients were eligible for the study. This study was approved by both local ethics committees of Istanbul University, Istanbul Faculty of Medicine, and Bezmialem Vakıf University, Faculty of Medicine, respectively.

Preoperative clinical evaluation was performed by physical examination and radiologic assessment. Clinical staging was determined according to the American Joint Committee on Cancer (AJCC) Breast Cancer Staging 7th edition. Patients who were clinically > T2 and/or axillary positive were excluded from the study (Figure 1).

2.2 | Surgical and intraoperative palpation procedure

After induction of general anesthesia, isosulfan blue and/or radio-colloid was injected to the deep subareolar tissue. All dissected sentinel and non-SLNs were palpated by the primary surgeon and their predictions were recorded separately for all dissected nodes at that time. There were seven different breast-specific surgeons in cohort A and three in cohort B. Even though it is a subjective evaluation, SLNs were accepted as positive for metastasis according to stiffness (different from fatty lymph node), hardness, non-homogenous rough nodularity. If any of the dissected lymph nodes suspicious in the INP, it was considered as positive; otherwise negative. At the same time, rest axillary tissue checked manually for any other metastatic lymph nodes. Following INP, the lymph nodes were sent for IPA. If the result was positive, axillary lymph node dissection was performed. However, if the result was negative, suspicious (atypical cell groups, isolated tumor cells [ITC]), or low involvement of isolated nodes (low metastatic volume or ratio according to breast-specific pathologist assessment) no further axillary dissection was performed. Subsequent to SLNB, BCS or mastectomy was decided depending on patient and tumor characteristics.

2.3 | Intraoperative pathologic assessment of sentinel lymph nodes

Sentinel lymph nodes were sent to the pathology laboratory directly from the operating room during the operation. All sentinel lymph

nodes were dissected and routinely examined with touch imprint cytology. The slides were stained with hematoxylin and eosin (H and E). If there were not enough cells on the slide, scrape cytology was performed. Frozen section was used occasionally when there was still a doubt of metastasis after scrape cytology.

2.4 | Final pathologic assessment

Tissues were fixed with 10% formalin for 24–48 hours at room temperature. Samples from the sentinel lymph nodes were placed in embedding cassettes. After standard tissue processing (nearly 10 hours) in a tissue processor, samples were embedded in paraffin and sectioned using a microtome. Five to ten 4- μ m-thick serial sections were floated on the surface of a 37°C water bath with a brush and picked up on glass slides. Finally, the slides were placed in a 65°C oven for 20 minutes before undergoing the standard hematoxylin and eosin staining process. We routinely examine sentinel lymph nodes with serial sections. Four sections are prepared for each half of the sentinel lymph node. The third section is stained with pancytokeratin and the others are stained with H and E.

2.5 | Data collection and statistical analysis

In this prospective multicenter study, patients' data were collected on a specific study datasheet. All data including INP findings were collected prospectively and compared with the IPA and final pathologic assessment (FPA) results. Statistical analyses were performed using SPSS 17.0 for Windows software (SPSS Inc, Chicago, IL, USA). Descriptive statistical methods (median, number, and percentage) were used for analyzing the demographic data. INP and IPA data were compared with FPA findings, and χ^2 analyses were used to assess for differences. All *P*-values were two-sided, and *P* < 0.05 was considered to indicate statistical significance.

3 | RESULTS

Patient characteristics including demographic data and descriptive analyses are shown in Table 1. The median age was 52 years (range, 19–90 years). Of the 305 patients, 248 (81.3%) underwent BCS, and 57 (18.7%) underwent mastectomy. SLNB was performed using isosulfan blue injection in 275 patients (90.2%), radio-colloid injection in six patients (2%), and a combined technique in 24 patients (7.8%). The median time for IPA was 31 minutes (range, 14–59 minutes). Eighty patients underwent ALND (26.2%). FPA revealed that 109 of 305 patients had positive SLNs (35.7%).

The positive predictive value (PPV) of INP and IPA was 81.8% and 97.9%, whereas negative predictive value (NPV) of INP and IPA was 83% and 92.4%. The accuracy of INP and IPA was 82.6% and 94.1% (Table 2). Other analysis comparing INP and FPA was also shown in Table 2. Of 37 INP negative but FPA positive patients, 21 (56.8%) were found to have micrometastasis in SLNB. Of those, 12 (57.1%) were also IPA negative. ALND was performed in 12 patients (32.4%), and none had three or more metastases; only one had

TABLE 1 Patient demographic characteristics and surgical procedure

	n	%
Median age (range, min-max)	52 (19-90)	
Age (years)		
<50	125	41
≥50	180	59
Menopausal status		
Premenopausal	112	36.7
Postmenopausal	193	63.3
SLNB procedure		
Isosulfan blue	275	90.2
Radio-colloid	6	2
Combined	24	7.8
Surgery type		
BCS	248	81.3
Mastectomy	57	18.7
Tumor type		
Invasive ductal carcinoma	246	80.7
Invasive lobular carcinoma	15	4.9
Mixed (Ductal and Lobular)	21	6.9
Other	23	7.5
Pathologic tumor size		
pTis	11	3.6
pT1	139	45.6
pT2	146	48.2
pT3	8	2.6
Pathologic lymph node involvement		
pN0	207	67.9
pN1	76	24.9
pN2	15	4.9
pN3	7	2.3
Number of dissected SLNs		
1	115	37.7
2	93	30.5
3	47	15.4
4	30	9.8
5	20	6.6
Number of dissected non-SLNs		
0	218	71.5
1	50	16.4
2	25	8.2
≥3	12	3.9
Median number of SLNs (range, min-max)	2 (1-5)	
Median time of IPA (range, min-max)	31 (14-59)	
ALND		
Yes	80	26.5
No	225	73.5

(Continues)

TABLE 1 (Continued)

	n	%
Positive SLN in FPA		
Yes	109	35.7
No	196	64.3
Size of the largest SLN metastases (including ITC)	n = 116	%
Macrometastases	80	69
Micrometastases	29	25
ITC	7	6

ALND, axillary lymph node dissection; BCS, breast conserving surgery; FPA, final pathologic assessment; IPA, intraoperative pathologic assessment; ITC, isolated tumor cells; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

extracapsular involvement with a diameter of 4 mm (Table 3). Three patients had micrometastasis in only one lymph node. To assess the results in an unbiased manner, these 12 patients were discussed in the multidisciplinary tumor board as they only had SLNB not ALND. Only 1 of 12 patients was agreed for ALND. This patient had a T1 multicentric tumor with lymphovascular invasion, grade 3, human epidermal growth factor receptor-2 (HER2-neu) score 3+, high Ki-67 score (>20%), and 1 of 3 SLNs was positive. More importantly, decision was made due to young age (31 years old) and she underwent mastectomy with ALND. Besides, four patients with macrometastasis in FPA (also IPA positive) were also discussed in tumor board and no further axillary surgery decided. In conclusion, of 217 INP negative patients, it is decided that only one patient (0.5%) actually needed further axillary surgery meaning that our prediction rate for INP negative group is 99.5%.

Again, in this INP negative but FPA positive group, ALND was not performed in 7 of 16 patients with macrometastasis. Of these seven patients, IPA was negative in 3. All three had one SLN involved with a metastasis <5 mm. The remaining four patients with IPA positivity also only had one SLN involved with metastasis <5 mm. Therefore, in the subgroup of INP (-) patients, the management of axillary treatment did not differ even though they had a positive FPA and/or a macrometastasis in SLNB because of the small size of the metastases.

Eighty patients underwent ALND. The indications for ALND were metastasis in ≥3 lymph nodes, macrometastasis with extranodal involvement of two SLNs, clinical suspicion of non-SLN involvement accompanied with SLN involvement, and patients that are not planned to receive whole breast irradiation (WBI) represented with positive SLNs. Of 80 patients who underwent ALND, 11 had only micrometastasis in FPA. Furthermore, all of these patients have only 1 involved lymph node which we can conclude that these patients actually do not need completion ALND.

If patients with SLNB including micrometastasis were considered as in the FPA (-) group, the revised PPV and NPV of INP and FPA were found as 72.7% and 92.6%, respectively. Thus, we can correctly predict almost 93% of the patients with negative axilla. The revised accuracy also found to increase up to 86.9% (Table 4).

TABLE 2 Statistical analyses of intraoperative nodal palpation and intraoperative pathologic assessment compared with final pathological assessment

	FPA (+) (n = 109)	FPA (-) (n = 196)		FPA (+) (n = 109)	FPA (-) (n = 196)
INP (+) (n = 88)	72	16	IPA (+) (n = 95)	93	2
INP (-) (n = 217)	37	180	IPA (-) (n = 210)	16	194
Sensitivity		66.06%	Sensitivity		85.32%
Specificity		91.84%	Specificity		98.98%
PPV		81.82%	PPV		97.89%
NPV		82.95%	NPV		92.38%
Accuracy		82.62%	Accuracy		94.10%
FNR		33.94%	FNR		14.68%
FPR		8.16%	FPR		1.02%

FNR, false negativity rate; FPA, final pathologic assessment; FPR, false positivity rate; INP, intraoperative nodal palpation; IPA, intraoperative pathologic assessment; NPV, negative predictive value; PPV, positive predictive value.

TABLE 3 Characteristics of patients with conflicting palpation and pathology findings

Patient characteristics	n = 37	%
Micrometastases		
Yes	21	56.8
No	16	43.2
IPA		
+	21	56.8
-	16	43.2
ALND		
Yes	12	32.4
No	25	67.6
ALND positivity (n = 12)		
<3	12	100
≥3	0	0

ALND, axillary lymph node dissection; IPA, intraoperative pathological assessment; ITC, isolated tumor cells.

4 | DISCUSSION

In the last decade, randomized studies have been designed to answer the question as to whether it was possible to avoid ALND in patients with low axillary involvement at SLNB by omitting ALND in selected patients.^{15,18–21} First, in the ACOSOG Z0011 trial, patients with clinical T1-2 N0 breast cancer with one to two positive SLNs who underwent BCS followed by tangential WBI were randomly selected to undergo either completion ALND or no further surgery.¹⁴ At a median follow-up of 6.3 years, there was no difference in locoregional recurrence, overall survival (OS), and disease-free survival (DFS) rates. In the IBCSG 23-01 trial, similarly, no significant difference was found in DFS, OS, and cumulative incidence rates between the no-ALND and ALND-group in patients with one or more micrometastatic (≤ 2 mm) sentinel nodes and tumor of maximum 5 cm in diameters at a median follow-up of 5 years.¹⁵ Finally, in the recently published AMAROS trial, Rutgers et al concluded that ALND and axillary radiotherapy after a positive SLN provided

excellent and comparable axillary control for patients with T1-2 primary breast cancer and no palpable lymphadenopathy after a median follow-up of 6.1 years.¹⁶ In the 2014 American Society of Clinical Oncology clinical practice guideline update, the concept of omitting ALND in a specific group of patients with low-risk axillary involvement was therefore described for patients treated with BCS, WBI, and adjuvant systemic treatment.²²

To evaluate the impact of Z0011 on the surgical practice of members of the American Society of Breast Surgeons (ASBrS), a survey was sent by email to 2759 surgeons and 849 responded.²³ The authors emphasized that ASBrS respondents had embraced Z0011 and had changed their practice, omitting ALND in patients with one or two positive SLNs who would undergo WBI. Caudle et al¹⁷ similarly found that after Z0011, surgeons were more likely to perform ALND on patients with larger tumors (2.2 vs 1.5 cm, $P = 0.09$), lobular histology ($P = 0.01$), fewer SLNs (1 vs 3, $P = 0.09$), larger SLN metastasis size (4 vs 2.5 mm, $P = 0.19$), extranodal extension present (20% vs 6%, $P = 0.16$), or a higher probability of positive non-SLNs ($P = 0.03$). Surgeons were less likely to perform IPA in the post-Z0011 cohort (26% vs 69%, $P < 0.001$), which resulted in decreased median operative times for patients who were SLN-negative (79 vs 92 minutes, $P < 0.001$). They concluded that Z0011 results had significantly impacted practice by decreasing rates of ALND, use of IPA, and operative times. Even though IPA less likely to be performed in the United States, it is still being used by one-fourth of the breast surgeons.¹⁷ Adoption of Z0011 still is not that high in other countries all around the world including Turkey. In an unpublished data of the survey about breast surgical practice of the surgeons in Turkey which is conducted by our clinic ("Practice changes among breast surgeons in Turkey after the results of axilla positive trials") revealed that 60% of the breast surgeons and only 20% of the surgeons performing breast surgery besides other procedures adopted Z0011 approach. Hereby, we want to set an alternative and time-saving method for the exact need for intraoperative evaluation of the SLNs.

The most negative effect of intraoperative assessment of SLNB is prolonged operation times. Although there can be differences between clinics and the number of SLNs removed, IPA extends

TABLE 4 Statistical analysis for intraoperative nodal palpation and final pathologic assessment with micrometastases in sentinel lymph node biopsy considered as final pathologic assessment (-)

	FPA (+) (n = 80)	FPA (-) (n = 225)		FPA (+) (n = 80)	FPA (-) (n = 225)
INP (+) (n = 88)	64	24	IPA (+) (n = 95)	76	19
INP (-) (n = 217)	16	201	IPA (-) (n = 210)	4	206
Sensitivity		80.00%	Sensitivity		95.00%
Specificity		89.33%	Specificity		91.56%
PPV		72.73%	PPV		80.00%
NPV		92.63%	NPV		98.10%
Accuracy		86.89%	Accuracy		92.46%
FNR		20.00%	FNR		5.00%
FPR		10.67%	FPR		8.44%

FNR, false negativity rate; FPA, final pathologic assessment; FPR, false positivity rate; INP, intraoperative nodal palpation; IPA, intraoperative pathologic assessment; NPV, negative predictive value; PPV, positive predictive value

operation time approximately 30 minutes. In addition, high load pathology clinics, such as those in universities or state hospitals, are also engaged with this unnecessary procedure thereby causing additional costs to the hospitals. Canvase et al investigated whether omitting intraoperative staging of the SLN in patients with T1-N0 breast cancer was feasible and convenient.²⁴ T2 patients all received SLN staging on IPA as a reference group. Of 395 T1-N0-patients, 118 patients who were T1a-T1b whose SLN was not analyzed at surgery, 12 (10.2%) were recalled for ALND. In the group of 258 patients who were T1c, 112 received SLN analysis on IPA and 146 did not. Overall, the rate of recall for ALND was 11.6%, compared with 8.4% in T2-patients. The median time for IPA of SLN was 30 minutes, which is comparable with the findings of our study as "31 minutes". This approach has been more cost-effective because the institution decreased its operational times and realized a 9.6% cost saving, as compared with the standard procedure as expected.

The sensitivity and accuracy of IPA of the SLN have been reported to range from 36.0% to 93.3%, and 83.2% to 96.0%, respectively.^{8,12,13} The accuracy of IPA in our series was 94.1%, which is similar to the published literature.^{8,12,13} The revised accuracy of INP improved to 87% when micrometastasis was considered in the FPA negative group, which could be considered a clinically feasible rate. IPA is less effective in the detection of micrometastasis.²⁵ The sensitivity ranges between 10% and 52%.²⁶⁻²⁹ Almost half of cases with micrometastasis were not detected with IPA in our study, similar to the published literature.³⁰ Further analyses considering micrometastasis in the FPA negative group also showed that we only would have an error margin of approximately 7% in INP (-) group due to our revised NPV as 93%. In the INP (+) group, however, the revised error margin was 27% due to the revised PPV as 73%. Besides, of the 217 patients with INP (-), completion ALND was decided only for one patient (0.5%), and this rate is very low when we compare with decision rates of completion ALND in the literature.²³ Therefore, it seems to be more appropriate to send SLNs to IPA in the INP (+) group.

Current concept in breast cancer treatment is systematic and locoregional treatment incorporated with biological tumor behavior. BCS followed by WBI therapy effectively prevent axillary recurrence

in clinically node negative breast cancer patients which may contain certain micrometastasis or low tumor burden macrometastasis.^{14,15} This concept mainly depending on dedicated imaging of the axilla, preoperatively axillary palpation which detect overt axillary metastasis and may be more importantly INP. ALND rarely advised in cases which adjuvant treatment (Radiation field, systemic treatment choices) decision will be affected.

To assess the reproducibility of our study, patients from 2 different cohorts were included into our study. Even though there might be some variations in experiences between surgeons in these 2 different breast clinics, the findings regarding NPV, PPV, and accuracies were almost comparable between the 2 cohorts. However, it should be kept in mind that almost all of the surgeons who participated in this study are dedicated breast surgeons. Therefore, it might be useful to investigate surgeons from general surgery clinics who are not dedicated breast surgeons to assess the feasibility and reproducibility of this study in future.

5 | CONCLUSION

Axillary lymph node dissection is still being used in many clinics around the world. At our institution, ALND was omitted in the majority of patients with micrometastatic disease before the results of the Z0011 trial were released. However, after the Z0011 trial, our indications to omit ALND have been widened even though we still send SLNs for IPA. In this study, which is the only prospective study about palpation of dissected SLNs in the literature, our results suggest that in patients with clinically node-negative early-stage disease, there is no need to send SLNs to IPA, especially in the INP negative group. Whether to perform ALND according to FPA results together with other prognostic factors especially biology, age and systemic treatment could be therefore decided in Multidisciplinary Breast Conferences with the radiation oncologist and medical oncologist. This approach seems to be more time-saving, more cost-effective and can prevent unnecessary ALND due to positive IPA results which patients mostly contain small volume of metastasis (ITC, micrometastasis or most of palpation negative macrometastasis) in experienced breast clinics.

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CONFLICT OF INTEREST

None.

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