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ORIGINAL ARTICLE

Strategy for the accurate preoperative evaluation of the number of metastatic axillary lymph nodes in breast cancer

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Bedside fine-needle aspiration cytology;
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Summary *Background:* After the ACOSOG Z0011 trial, it became important to evaluate the number of metastatic axillary lymph nodes (LNs) preoperatively. The purpose of this paper is to confirm whether the number of metastases can be accurately diagnosed by preoperative computed tomography (CT), ultrasound sonography (US), and US-guided fine-needle aspiration cytology (FNAC).
Methods: We retrospectively analyzed the axillary LNs finding of preoperative CT/US of 470 breast cancer patients. Metastasis was suspected based on the following findings: LNs with a long-axis diameter of ≥10 mm or a short-axis diameter of ≥5 mm on CT, and LNs with the absence of a fatty hilum, focal cortical thickness or a cortical thickness ≥2 mm on US. We also examined the results of FNAC making a rapid bedside diagnosis (bedside-FNAC) of 162 LNs that were suspected to metastatic based on the US findings.
Results: On CT, all cases with ≥3 LNs with a long-axis diameter of ≥10 mm and a short-axis diameter of ≥5 mm had metastasis. However, there was no relationship between the number of detected LNs and the number of metastases. On US, 75.7% of LNs with the absence of a fatty hilum and all LNs with cortical thickness ≥6 mm had metastasis. The accuracy of bedside-FNAC for suspicious LNs was 100%.

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Conclusions: Although we can pick up LNs that are likely to have metastasis on CT/US, it was impossible to accurately predict the number of metastases on CT/US. However, bedside-FNAC of suspicious LNs could accurately predict the number of metastases.

1. Introduction

The results of the ACOSOG Z0011 trial (Z0011) revealed that women with T1−T2 breast cancer and ≤2 metastases on a sentinel lymph node biopsy (SLNB) did not need to undergo axillary lymph node dissection (ALND), when they underwent breast conservation surgery (BCS), received whole breast radiation, and received the recommended systemic therapy.[1]

Before the Z0011 trial, it was necessary to investigate the presence of positive axillary lymph nodes (LNs) in order to evaluate the need for a SLNB. The 2015 National Comprehensive Cancer Network (NCCN) guidelines recommend that ultrasound sonography (US)-guided fine-needle aspiration cytology (FNAC), which has been reported to be a feasible tool for the preoperative nodal staging of breast cancer, be used to examine suspicious axillary LNs.[2] ALND is performed if metastatic axillary LNs are detected by FNAC. Given the results of the Z0011 trial, our approach to the management of the axilla should be flexible, according to the number of metastatic axillary LNs. Thus, it is necessary to evaluate the number of metastatic axillary LNs in breast cancer patients before surgery.

Clinicians usually examine breast tumors by mammography (MMG), US, computed tomography (CT) and magnetic resonance imaging (MRI). It was reported that conventional MRI was limited in the detection of metastatic LNs <10 mm. Although ultra-small superparamagnetic iron oxide-enhanced MRI (USPIO-MRI) of the axillary LNs was useful for diagnosing metastatic LNs,[3,4] it is not easy to use in clinical practice; thus, the clinical use of MRI for the diagnosis of axillary LNs is difficult. In contrast, US is very convenient and minimally invasive. In Japan, CT can easily be performed in clinical practice; thus, it is generally performed.

In previous studies, metastasis of the axillary LNs was suspected based on a long-axis diameter of ≥10 mm or a short-axis diameter of ≥5 mm on CT,[5–9] or the absence of a fatty hilum, focal cortical thickness, or a cortical thickness of ≥5 mm on US.[10–13] Furthermore, according to the US criteria of some studies using US combined FNAC, the cortical thickness was set at ≥3 mm or 3.5 mm on US[11,14]. Recent studies on axillary LN staging by FNAC have reported that the sensitivity ranged from 6% to 63%, and that the specificity ranged from 96.9% to 100%.[15]

In Japan, the sensitivity of FNAC is higher than that in other countries, and the results of FNAC are considered to be reliable.[16] Thus, the diagnosis of suspicious axillary LNs by FNAC is clinically important for detecting metastatic axillary LNs. Indeed, in our hospital, FNAC is performed at the bedside (bedside-FNAC) to rapidly diagnose suspicious axillary LNs. Some studies that have investigated bedside-FNAC have reported that it is adequate in 95.6% of cases[17] and that a definitive diagnosis was made in 91.2% of cases, with adequacy improving from 78% to 96%[18]

Thus, we retrospectively examined subjects with CT, US and FNAC (using bedside-FNAC). The purpose of this study was to confirm whether the number of axillary metastases can be accurately diagnosed based on the preoperative CT, US, and FNAC findings. Based on this study, we would like to develop a strategy that allows for the accurate evaluation of the number of metastatic axillary LNs before surgery.

2. Methods

This study was performed at Mie University Hospital and was approved by the Ethical Review Board of Mie University Hospital.

2.1. Case selection

We analyzed 470 consecutive patients who had been diagnosed with breast cancer and who received operation (SLNB or ALND) at Mie University Hospital between March 2013 and December 2014. We excluded the CT and US images of patients who had received neoadjuvant chemotherapy (NAC) in order to avoid any possible bias.

2.2. The evaluation of metastatic axillary lymph nodes using CT

We investigated CT images that were obtained at our hospital or other hospitals after the diagnosis of breast cancer. The CT devices differed among the hospitals, and the slice thickness interval ranged from 1.25 to 5 mm. We analyzed 444 patients' CT images; 26 that had been obtained in other hospitals could not be analyzed at our hospital. We investigated the number of LNs with 1) a long-axis diameter of ≥10 mm; and 2) a short-axis diameter of ≥5 mm (Fig. 1), and determined the percentage of LNs that were positive for metastasis as well as the number of detected LNs. There were cases in which contrast CT could not be performed; however, in cases in which contrast agent was used, the contrast effect was not considered.

2.3. The evaluation of metastatic axillary lymph nodes using US

We investigated the US images obtained at our hospital using an ultrasound diagnostic system (APLIO XG SSA-790A; Toshiba Medical Systems Corp., Tochigi, Japan, LOGIQ E9; GE Healthcare Japan, Tokyo, Japan). We analyzed the US images of 470 patients. We compared the shape of the surgically-removed LNs with the LNs detected on the preoperative US images under low magnification. For 11 of the 470 LNs, the shape of the surgically-removed LNs differed from the preoperative US images under low magnification. This suggested

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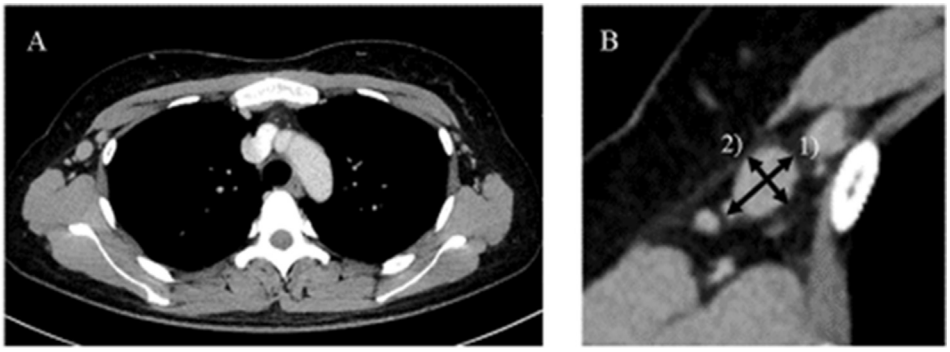

Figure 1 The shape of the lymph nodes on computed tomography (A). The long-axis diameter (B-1) and short-axis diameter (B-2) of the lymph node.

that metastatic LNs were overlooked on preoperative US images. We therefore analyzed the US images of 459 patients because the shape of the surgically-removed LNs was consistent with their preoperative US images.

We investigated the number of LNs with 1) the absence of a fatty hilum (Fig. 2A), 2), focal cortical thickness (Fig. 2B), and 3) a cortical thickness of $\geq$2 mm (Fig. 2C) and determined the percentage of the detected LNs that were positive for metastasis.

2.4. Validity of FNAC

One hundred sixty-two suspicious (based on the US results [with the absence of a fatty hilum, focal cortical thickness or a cortical thickness of $\geq$2 mm]) LNs were subjected to FNAC with 22-gauge needles using a freehand technique under US guidance. Seven breast surgeons performed FNAC; their experience in preoperative diagnostic and interventional breast imaging with FNAC was $<$5 years (n = 2), 5—10 years (n = 2), $>$10 years (n = 3).

Bedside-FNAC was performed at our hospital. All specimens were subjected to modified Giemsa staining with Diff-Quik® (Sysmex, Kobe, Japan) and hematoxylin and eosin (H&E) staining. The Diff-Quik method helped to obtain a rapid bedside diagnosis and the ultimate cytological diagnosis was made after the evaluation of H&E-stained specimens by two cytopathologists with experience over 10 years in cytology. FNAC was performed after evaluating a sufficient amount of lymphocytes. If an inexperienced doctor performed FNAC and cells were not obtained, then a more experienced surgeon reperform the procedure. In 2010, 3.9% of the specimens obtained by bedside-FNAC in our hospital inadequate.[19]

When $\geq$2 abnormal nodes were identified in the axilla, FNAC was performed on the LNs for which there was the highest degree of suspicion based on the cortical thickness and the size of the LNs. In addition, the examination was finished when 2 metastasis-positive LNs were identified. Then, if no metastasis was detected in the LN, FNAC was performed on LNs in which the degree of suspicion was the second highest.

2.5. Histopathological examinations

When LNs were found to be positive by FNAC, ALND was performed. When LNs were found to be negative by FNAC, SLNB was performed. If the sentinel lymph node (SLN) had macrometastasis ($>$2 mm), ALND was also performed. If the SLN had micrometastasis ($\leq$2 mm), several LNs surrounding the SLN were picked up and $\geq$4 LNs were sampled.

Each LN was sliced into 2 mm sections and stained with H&E. The pathologist performed nodal staging according to the TNM staging system of the American Joint Committee on Cancer (Chicago, IL, USA), seventh edition.[20] When very small deposits of "isolated" tumor cells were found in a LN ($\leq$0.2 mm or 200 cells), the nodal staging of the case was classified as N0 (i+), which was considered to be a negative final pathologic result.

2.6. Statistical analyses

The statistical analyses were performed using the SPSS software program (ver. 23. IBM SPSS, Chicago, IL, USA). The differences between LNs with focal cortical thickness and

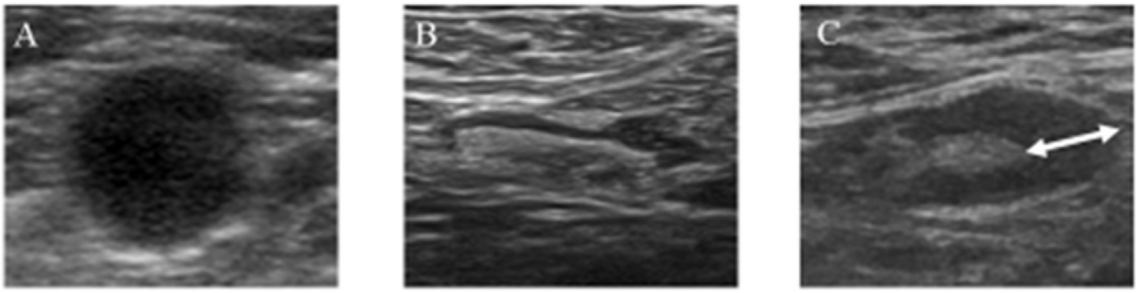

Figure 2 The shape of the lymph nodes on ultrasound sonography. A lymph node with the absence of a fatty hilum (A), a lymph node with focal cortical thickness (B), the cortical thickness of the lymph node (C).

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those without focal cortical thickness were assessed using Fisher's exact tests. *P* values of <0.05 were considered to indicate statistical significance.

3. Results

3.1. The patient and tumor characteristics

In this continuous study, all patients were women (median age, 56 years; range 27—87 years). The T stages were classified as follows: Tis (n = 125), T1mic (n = 8), T1a (n = 38), T1b (n = 77), T1c (n = 138), T2 (n = 76), T3 (n = 6) and T4 (n = 2). The histological types of the cases of invasive carcinoma were invasive ductal carcinoma (n = 295), invasive lobular carcinoma (n = 23), mucinous carcinoma (n = 16) and other specific type (n = 11).

Thirty-one patients underwent ALND without SLNB. SLNB was performed in 439 patients; sampling was added in 12 cases involving patients with micrometastasis, while ALND was added in 38 cases involving patients with macrometastasis.

3.2. The evaluation of metastatic axillary lymph nodes using CT

1) Long-axis diameter $\geq$10 mm

Table 1A shows the cases in which axillary LNs with a long-axis diameter of $\geq$10 mm were found. Among the patients with one node with a long-axis diameter of $\geq$10 mm, only 14.6% of the patients had metastasis, while only 24.6% of the patients with two such nodes had metastasis. In contrast, 73.3% of the patients with $\geq$3 such nodes had metastasis. However, there was no relationship between the number of such LNs detected on CT and the number of metastases (Fig. 3A). That is, there were cases in which multiple metastases were identified, even if one such LN was detected, and among the cases in which $\geq$3 such detected, some patients had one or two metastases.

Table 1A Evaluation of metastatic axillary lymph nodes by computed tomography (CT). Findings for axillary lymph nodes with a long-axis diameter of $\geq$10 mm.
N: The number of lymph nodes detected on CT.

		Axillary lymph nodes				Total
		Metastatic		Non-metastatic		
Number of nodes with a long-axis diameter of $\geq$10 mm	N = 0	22	(15.2%)	123	(84.8%)	145
	N = 1	32	(14.6%)	187	(85.4%)	219
	N = 2	16	(24.6%)	49	(75.4%)	65
	N $\geq$ 3	11	(73.3%)	4	(26.7%)	15
	Total	81		363		444

2) Short-axis diameter $\geq$5 mm

Table 1B shows the cases in which axillary LNs with a short-axis diameter of $\geq$5 mm were found. Among the cases in which one node had a short-axis diameter of $\geq$5 mm, only 14.6% had metastasis; furthermore, only 25.4% the patients in whom two nodes had a short-axis diameter of $\geq$5 mm, had metastases. In contrast, 72.0% of the patients in whom $\geq$3 nodes had a short-axis diameter of $\geq$5 mm, had metastasis. However, as with the long-axis diameter, there was no relationship between the number of such LNs detected on CT and the number of metastases (Fig. 3B).

Table 1B Evaluation of metastatic axillary lymph nodes by computed tomography (CT). Findings for axillary lymph nodes with short-axis diameter of $\geq$ 5 mm.
N: The number of lymph nodes detected on CT.

		Axillary lymph nodes				Total
		Metastatic		Non-metastatic		
Number of nodes with a short-axis diameter of $\geq$5 mm	N = 0	18	(11.4%)	140	(88.6%)	158
	N = 1	29	(14.6%)	169	(85.4%)	198
	N = 2	16	(25.4%)	47	(74.6%)	63
	N $\geq$ 3	18	(72.0%)	7	(28.0%)	25
	Total	81		363		444

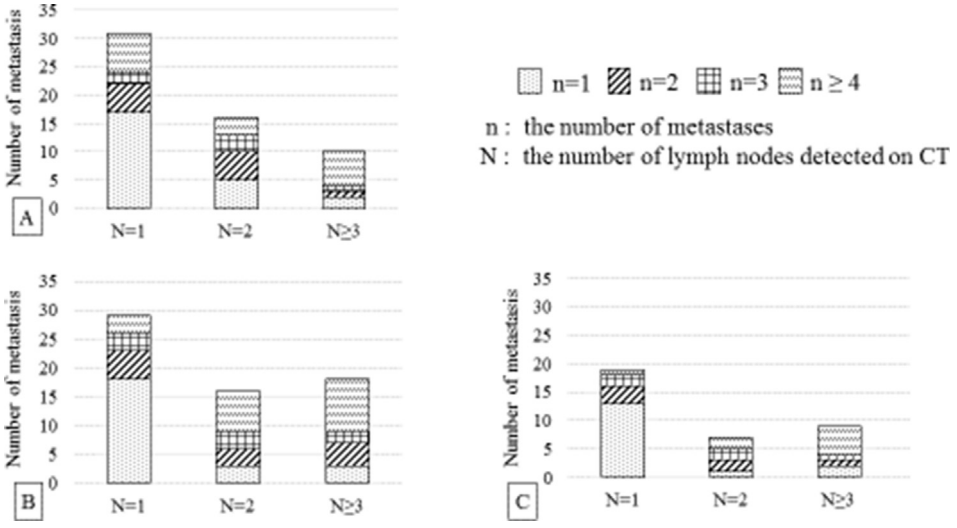

Figure 3 The relationship between the number of metastases and the lymph nodes detected on computed tomography; long-axis diameter of $\geq$10 mm (A), short axis diameter of $\geq$5 mm (B) and a long-axis diameter of $\geq$10 mm and a short axis diameter of $\geq$5 mm (C).

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3) Long-axis diameter ≥10 mm and short-axis diameter ≥5 mm

Table 1C shows the cases in which the axillary LNs had a long-axis diameter of ≥10 mm and a short-axis diameter ≥5 mm. Among these patients in whom only one node met this criterion, 14.7% had metastasis. In contrast 40.6% of the patients in whom two LNs met this criterion and 100% of the patients in whom ≥3 nodes met this criterion had metastases. However, there was no relationship between the number of such LNs detected on CT and the number of metastases (Fig. 3C).

The results of 1−3) showed that findings of ≥3 LNs with a long-axis diameter of ≥10 mm and/or a short-axis diameter of ≥5 mm on CT could be used to identify cases in which LN metastasis could be strongly suspected. However, Fig. 3 shows that there was no relationship between the number of such LNs on CT and the number of metastases.

3.3. The evaluation of metastatic axillary lymph nodes using US

1) Absence of a fatty hilum

Table 2A shows the finding for the axillary LNs with absence of a fatty hilum. Among the 459 cases, the absence of a fatty hilum in an axillary LN was only detected in 37 cases (8.1%); however, LN metastasis was observed in 28 of these cases (75.7%).

Table 1C Evaluation of metastatic axillary lymph nodes by computed tomography (CT). Findings for axillary lymph nodes with a long-axis diameter of ≥ 10 mm and a short-axis diameter of ≥ 5 mm.
N: The number of lymph nodes detected on CT.

		Axillary lymph nodes				Total
		Metastatic		Non-metastatic		
Number of nodes with a long axis diameter of ≥10 mm and a short-axis diameter of ≥5 mm	N = 0	30	(13.9%)	186	(86.1%)	216
	N = 1	29	(14.7%)	158	(80.2%)	197
	N = 2	13	(40.6%)	19	(59.4%)	32
	N ≥ 3	9	(100.0%)	0	(0.0%)	9
	Total	81		363		444

Table 2A Findings for axillary lymph nodes with the absence/presence of a fatty hilum. Evaluation of metastatic axillary lymph nodes by US. US: ultrasound sonography.

		Axillary lymph nodes				Total
		Metastatic		Non-metastatic		
Fatty hilum	Absent	28	(75.7%)	9	(24.3%)	37
	Present	45	(10.7%)	377	(89.3%)	422
	Total	73		386		459

2) Focal cortical thickness

We analyzed 422 US images (37 cases with the absence of a fatty hilum were excluded). Table 2B shows the findings for the axillary LNs with focal cortical thickness. The possibility of metastasis in LNs with focally cortical thickening was only 29.7%; however, the possibility of metastasis in LNs without focally cortical thickness was as low as 8.8%. There was a significant difference between the LNs with focal cortical thickness and those without focal cortical thickness ($p = 0.0006$).

3) Cortical thickness ≥2 mm

As noted above, we analyzed 422 US images (37 cases with the absence of a fatty hilum were excluded). Table 3 shows the positive predictive value (PPV) for each increment of cortical thickness. Metastasis was detected in approximately 30% of cases with a cortical thickness of

Table 2B Findings for axillary lymph nodes with and without focal cortical thickness. Evaluation of metastatic axillary lymph nodes by US.

		Axillary lymph nodes				Total
		Metastatic		Non-metastatic		
Cortical thickness	Focal	11	(29.7%)	26	(70.3%)	37
	Not focal	34	(8.8%)	351	(91.2%)	385
	Total	45		377		422

Table 2C Findings for the US criteria. Criteria: the absence of a fatty hilum, focal cortical thickness and cortical thickness of ≥2 mm in diameter. Evaluation of metastatic axillary lymph nodes by US.

		Axillary lymph nodes				Total
		Metastatic		Non-metastatic		
Criteria met	Any	61	(38.4%)	98	(61.6%)	159
	None	12	(4.0%)	288	(96.0%)	300
	Total	73		386		459

Table 3 The positive predictive value for each diameter of cortical thickness.

		Axillary lymph nodes		
		Metastatic	Non-metastatic	Positive predictive value
Diameter of cortical thickness	<2 mm	8	291	2.7%
	≥2 mm	36	87	29.3%
	≥3 mm	22	31	41.5%
	≥4 mm	11	14	44.0%
	≥5 mm	7	7	50.0%
	≥6 mm	5	5	100.0%

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≥2 mm, and the rate of metastasis increased as the cortex thickened; all LNs with a cortical thickness of ≥6 mm were metastatic. We also investigated the diameter of the LNs but detected no relationship between the diameter and the presence of metastatic LNs.

4) The absence of a fatty hilum, focal cortical thickness or a cortical thickness of ≥2 mm

We examined the cases with any of the abovementioned findings (absence of a fatty hilum, focal cortical thickness or cortical thickness ≥2 mm); the accuracy is shown in Table 2C. Although the possibility of metastasis, when any finding was present, was only as high as 38.4%; the possibility of metastasis was only 4% when no findings were present.

3.4. The evaluation of metastatic axillary lymph nodes by bedside-FNAC

Bedside-FNAC was performed in 162 cases in which metastasis was suspected based on the US findings.

Table 4 shows the findings regarding the accuracy of bedside-FNAC. Among 162 patients who underwent bedside-FNAC, 61 patients (37.7%) had metastasis; the accuracy of preoperative bedside-FNAC was not high in our US criteria. However, all of the cases in which metastasis was detected by bedside-FNAC were found to be positive for metastasis in the final pathology. In addition, among the cases in which metastasis was not detected by preoperative bedside-FNAC, metastasis detected by a pathological examination in only 22 cases (17.9%). This finding indicated that bedside-FNAC could accurately diagnose the presence of LN metastasis using.

4. Discussion

SLNB has long been performed in breast cancer patients with no preoperative metastasis to the axillary LNs. SLNB has helped to reduce the number of patients who undergo unnecessary ALND and suffer from after-effects of ALND, such as lymphedema, neuropathies, seroma and restriction in shoulder mobility.[21,22] Furthermore, the Z0011 trial[1] showed that women who underwent BCS, and in whom ≤2 metastases were detected by SLNB, did not need to undergo ALND.

Table 4 Evaluation of metastatic axillary lymph nodes with bedside-FNAC. FNAC: fine-needle aspiration cytology. The accuracy of FNAC.

		Axillary lymph nodes		Total
		Metastasis	Non-metastasis	
FNAC	Positive	39	0	39
	Negative	22	101	123
	Total	61	101	162

Sensitivity: 63.9%, Specificity: 100%.
Positive predictive value: 100%, Negative predictive value: 82.1%.

The results of the Z0011 trial have further underscored the importance of determining the number of metastases in the axillary LNs. In some cases, the number of metastatic axillary LNs should be determined before surgery. These cases are described below. In the future, if ≤ two metastatic axillary LNs are accurately identified before NAC, patients who undergo BCS will be able to subsequently undergo SLNB. According to current clinical practice, if a patient undergoes total mastectomy, it is enough to only identify one metastatic LN preoperatively. However, depending on the response to NAC, a considerable number of patients who require total mastectomy before NAC can undergo BCS. Thus, in such cases, even when just two metastatic LNs are detected before NAC, ALND would be required because only one metastatic LN would be examined before NAC, and no other suspicious metastatic LNs would be examined. As stated above, in such cases, the number of metastatic axillary LNs must be identified before surgery.

In the present study, we successfully determined new criteria that were either strongly or only slightly suggestive of metastatic axillary LNs. The detection of ≥3 LNs (long-axis diameter ≥10 mm and short-axis diameter ≥5 mm) on CT and the presence of LNs with a cortical thickness of ≥6 mm in diameter on US was associated with a 100% possibility of metastatic axillary LNs. These findings are very important for determining the subsequent axillary operation.

The CT criteria that we established in this study for predicting the number of metastatic axillary LNs may prove very useful in clinical practice, as they were based on findings from multiple facilities, independent of the slice thickness interval. Thus, all clinicians can reference these criteria, regardless of the CT device that is used.

In contrast, the presence of LNs with focal cortical thickness or a cortical thickness of ≥2 mm in diameter on US only suggested an approximately 20—30% possibility of metastasis. In some previous studies, the cut-off cortical thickness was set ≥3 mm or 3.5 mm in diameter[11,14]; these cut-off points resulted in a PPV of 61% to 85%. However, in our present study, we found no significant difference in the PPV between cortical thicknesses of ≥2 mm and ≥3 or 3.5 mm. On the other hand, a significant difference in the PPV was observed between the cortical thicknesses of <2 mm and ≥2 mm.

Therefore, we established the following US criteria in the present study: the presence of LNs with the absence of a fatty hilum, focal cortical thickness or a cortical thickness of ≥2 mm in diameter. The PPV was low, especially with regard to the diameter of the cortical thickness, because we set the criteria ≥2 mm in diameter rather than ≥6 mm in diameter.

However, in order to accurately evaluate the number of metastatic axillary LNs before surgery, we have to select more LNs that meet the criteria, even if the accuracy of these criteria is not so high. In addition, we need to investigate the presence of metastasis by performing bedside-FNAC in one of each suspicious LNs.

As noted above, there were some cases in which we could more accurately identify the number of metastatic axillary LNs before surgery. In such cases, even if one LN was found to be metastatic, we have to examine other LNs

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that meet the criteria in order to find other metastatic LNs. Thus, it is very important to recognize the presence of metastasis at the very moment of performing FNAC. For this reason, we place high value on the performance of bedside-FNAC.

Furthermore, the performance of bedside-FNAC will help to make a definitive diagnosis, as we will be able to ensure that a reliable amount of lymphocytes have been collected.

This method is associated with a limitation: in order to effectively use bedside-FNAC with the US criteria, it is necessary for the physician to master accurate FNAC techniques. In addition, since a rapid diagnosis is performed by Diff-Quik® staining, it is necessary for cytopathologists to become familiar with the performance of this staining method.

In conclusion, the use of FNAC in combination with US/CT facilitates the accurate diagnosis of the number of metastatic LNs. In addition, the performance of bedside-FNAC will help in the development of a strategy for accurately evaluating the number of metastatic axillary LNs before surgery. The accurate evaluation of the number of metastatic axillary LNs will play a very important role in individualized treatment for breast cancer.

Conflicts of interest

Non −financial conflicts of interests. The authors declare no conflicts of interest in association with the present study.

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