Ultrasound surveillance on detection of nonpalpable supraclavicular recurrence after breast cancer surgery

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Abstract

Aims: To evaluate the clinical utility of supraclavicular scanning for locoregional lymph node (LN) assessment in postoperative screening surveillance using ultrasonography (US) in patients who underwent breast cancer surgery. **Material and methods:** From July 2004 to February 2019, 280 suspicious findings for locoregional recurrence in the lymph node (LRL) on postoperative screening US were detected in 266 asymptomatic patients who underwent breast cancer surgery. Suspicious features of LRL on US included the marked hypoechogenicity, round or irregular shape, eccentric cortical thickening and replacement of the fatty hilum of the LNs. The bilateral breasts, including mastectomy sites, bilateral axillae, internal mammary areas and supraclavicular areas, were included in the scan range of postoperative US. **Results:** Of 280 LNs with suspicious findings for LRL, LRL of supraclavicular LNs was confirmed in 24 LNs according to cytopathology results. Multivariate logistic regression analysis revealed that higher overall staging of primary breast cancer (odds ratio [OR] 2.361 [95% confidence interval (CI) 1.302–4.282]; $p=0.005$), higher N staging of primary breast cancer (OR 3.086 [95% CI 1.479–6.441]; $p=0.003$), older patient age (OR 1.060 [95% CI 1.026–1.095]; $p<0.001$) and breast-conserving surgery (OR 2.253 [95% CI 1.184–4.289]; $p=0.013$) were independently associated with LRL of supraclavicular LNs. Tumor size, nuclear grade, histological type, hormonal receptor status of the primary cancer, and bilateral cancer were not associated with LRL ($p=0.216$, $p=0.205$, $p=0.789$, $p=0.899$, and $p=0.900$, respectively). **Conclusion:** Routine supraclavicular scanning in postoperative screening surveillance using US in breast cancer patients with higher staging could be useful for the detection of LRL of supraclavicular LNs.

Keywords: ultrasonography; lymph nodes; supraclavicular; breast neoplasms; recurrence

Introduction

Breast cancer is the most common cancer and also one of the leading causes of death among women in developing countries [1,2]. Over recent decades, the early detection of and treatment strategies for breast cancer have changed tremendously. As a result, the survival of patients with the breast cancer has been improved significantly [3,4]. However, women with breast cancer who

experience locoregional recurrence after surgery have an increased risk for distant metastasis and poor prognosis, which remains a major problem for postoperative management of those with breast cancer [5-10].

According to the American College of Radiology (ACR) guidelines, ultrasonography (US) is not the recommended modality for postoperative screening in patients with a personal history of breast cancer [11,12]. The false-positive detection rate of locoregional recurrence in lymph nodes (LRL) in postoperative screening surveillance using US has been noted to be high and US is reported as inefficient for evaluating the supraclavicular area due to its time-consuming posture changes and low incidence of supraclavicular LRL [13,14]. Nevertheless, it has been also reported that, postoperative screening surveillance using US has been useful for the early detection of LRL and for diagnosis of postopera-

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tive complications because its scan range can cover the breasts, mastectomy site and locoregional lymph nodes (LNs) [13,15-18]. LRL after mastectomy is relatively uncommon compared with recurrence in the chest wall, but it has been associated with higher rates of simultaneous distant metastases and poor disease-specific survival [19-23]. Among the LRL, isolated supraclavicular LRL could be a curable condition and it has been reported that the early detection of LRL could be helpful in improving prognosis in patients after surgery [13-15,24,25].

Therefore, the present study aimed to evaluate the clinical utility of routine supraclavicular scanning for locoregional LNs assessment in postoperative screening surveillance using US in patients who underwent breast cancer surgery. Furthermore, we also aimed to identify patients who require routine supraclavicular US scanning based on analysis of clinicopathological characteristics of those with supraclavicular LRL detected using US.

Material and methods

Due to the retrospective nature of the present study and the use of anonymized patient data, requirement for informed consent was waived. However, informed consent was obtained for US-guided fine-needle aspiration biopsy (US-FNAB) and surgery from all patients before each procedure. The present study was approved by the institutional review board.

Patients

Between July 2004 and February 2019, 20,716 postoperative US screening surveillance examinations were performed in 2,144 women at the authors' institution. Among these 2,144 patients, we included 266 patients that underwent breast cancer surgery, with 280 suspicious findings for LRL on postoperative screening surveillance US in this study. We excluded the patients with suspicious LRL findings found only on computed tomography (CT) or magnetic resonance imaging (MRI) without undergoing postoperative screening surveillance with US, those with local recurrence and with palpable LNs.

A total of 256 patients had suspicious findings for LRL only in one of the axillae, the internal mammary area and the supraclavicular area, 4 patients exhibited suspicious findings in both axillae, the internal mammary area and the supraclavicular area, 4 patients had suspicious findings in both the internal mammary area and the supraclavicular area and 2 patients had suspicious findings for LRL in both axillae and the supraclavicular area. For LRL diagnosis, 262 patients underwent US-FNAB and 4 patients underwent excisional biopsy of the LNs. Pathological characteristics of the patients were categorized retrospectively according to the 8th Edition of the

American Joint Committee on Cancer (AJCC) manual and were reviewed based on histopathological reports by the authors [26]. Among the 112 patients who underwent neoadjuvant chemotherapy before surgery, clinical staging was used instead of pathological staging.

US examinations and US-FNAB procedures

US examinations were performed by 1 of 5 experienced breast radiologists using SONOLINE Antares (Siemens Medical Systems, Issaquah, WA, USA) or Philips iU22 (Philips Healthcare, Best, The Netherlands) or LOGIC E9 (GE Healthcare, Milwaukee, WI, USA) devices equipped with linear-array transducers (7–13 MHz or 5–12 MHz). Postoperative US screening surveillance was performed every 6 months for 5 years after surgery and annually thereafter, while mammography was performed annually.

The scan range of the postoperative US examinations was as follows: both breasts, including mastectomy or breast-conserving surgery site, bilateral axillae, bilateral internal mammary areas and bilateral supraclavicular areas. US examination of the axillary LNs was performed along the axillary artery from the lower axilla to the junction of the axilla and upper arm; for evaluation of the internal mammary LNs, US examination was performed along both sides of the sternum and internal mammary chains; and, finally, for examination of the supraclavicular fossa, the arms were lowered with the chin lifted and the patient supine. US was performed on the both sides of the neck, from the lower margin of the thyroid cartilage to the level of the clavicle. Approximate scanning time was 5 minutes.

Suspicious features of LRL on US included the following: marked hypoechogenicity; round or irregular shape; eccentric cortical thickening; and replacement of the fatty hilum [13]. US-FNAB was recommended for all suspected LRLs found in the axillae, and/or internal mammary areas and/or supraclavicular areas. US-FNAB was performed in LNs with at least one of the above-mentioned suspicious features on US by the same radiologists who evaluated the LNs using US. A 23-gauge needle was used for aspiration using the free-hand technique and each lesion was aspirated at least twice.

Data and statistical analysis

The final diagnosis of LRL was based on pathological results and clinical follow-up. A true-positive finding was defined as an LN with proven malignancy at the subsequent pathological examination. A false-negative finding was defined as an LN that was negative for malignancy at the pathological examination but exhibited an increase in size on the follow-up within 12 months. The positive predictive value (PPV) for each regional LN area was assessed. Furthermore, the association between LRL and

clinicopathological characteristics in patients with suspicious features of LRL on US were also evaluated.

Statistical comparisons were performed using the independent *t*-test for parametric variables or Pearson's chi-squared test for nonparametric variables. Univariate and multivariate logistic regression analyses were used to identify risk factors predictive for LRL of the supraclavicular area. In the nuclear grade, we grouped G1 into lower nuclear grade, G2 and G3 into higher nuclear grade. In the T stage of the primary cancer, we categorized Tis, T1 and T2 into lower T stage, T3 and T4 into higher T stage. In the N stage of the primary cancer, we categorized N0 and N1 into lower N stage, N2 and N3 into higher N stage. Also, in the overall stage of the primary cancer, we grouped stage 0 and I (IA,IB) into lower overall stage, stage II (IIA,IIB) and stage III (IIIA,IIIB,IIIC) into higher overall stage. The overall stage of the primary cancer was established based on the T and N stages, nuclear grade, and hormonal receptor status. Therefore, multivariate analysis was performed in two models: model 1, containing the overall stage; and model 2, including the T stage, N stage and nuclear grade. Statistical analyses were performed using SPSS version 21 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA), and SAS version 9.2 (SAS Inc, Cary, NC, USA). Differences with $p < 0.05$ were considered to be statistically significant.

Results

Clinicopathological characteristics

Patient demographics and clinicopathological characteristics are listed in Table I. Of the 266 patients with suspicious findings for LRL on postoperative US, 68 (25.6%) patients had a higher N stage and 126 (47.4%) patients had a higher overall stage.

Locations and final diagnosis according to the presence of LRL

Of the 280 suspicious findings for LRL in the 266 patients, 74 LNs in 70 patients were histopathological confirmed as LRL [24 (32.4%) in the supraclavicular fossa (16 in the ipsilateral supraclavicular fossa and the other 8 in the contralateral supraclavicular fossa), 38 (51.4%) LNs in the axilla and 12 (16.2%) LNs in the internal mammary area] (Table II, fig 1). Of the 206 LNs reported to be benign according to histological analysis, no LNs were false-negative at follow-up within 12 months on US, breast MRI and low dose chest CT. The PPV for postoperative US screening surveillance for LRL detection was higher for LNs in the internal mammary areas and those in the supraclavicular fossae compared with those in the axillae.

Table I. Patient demographic characteristics of women with suspicious LRL on postoperative US after undergoing breast cancer surgery

Characteristics	Total (N=266)
Age	59.2 ± 9.3
Primary cancer site	
Unilateral	253 (94.0)
Bilateral	13 (6.0)
Underwent operation method for primary cancer	
Breast conserving surgery	83 (31.2)
Mastectomy	183 (68.8)
Histologic type of primary cancer	
Ductal carcinoma in situ (DCIS)	10 (3.8)
Invasive ductal carcinoma	129 (48.5)
Invasive ductal carcinoma with DCIS	75 (28.2)
Invasive lobular carcinoma	16 (6.0)
Mucinous carcinoma	6 (2.3)
Medullary carcinoma	3 (1.1)
Papillary carcinoma	7 (2.6)
Other type cancer	20 (7.5)
Primary tumor size (mm)	23.4 ± 15.4
Primary cancer stage	
T stage	
Tis	10 (3.7)
T1	118 (44.4)
T2	110 (41.4)
T3	21 (7.9)
T4	7 (2.6)
N stage	
N0	128 (48.1)
N1	70 (26.3)
N2	36 (13.6)
N3	32 (12.0)
Histologic grade	
G1	70 (26.3)
G2	67 (25.2)
G3	129 (48.5)
Hormonal receptor type	
Luminal type cancer (luminal A, luminal B)	98 (36.8)
HER2-positive cancer	109 (41.0)
Triple negative cancer	59 (22.2)
Overall stage of primary cancer	
0	10 (3.8)
I (IA, IB)	130 (48.9)
II (IIA, IIB)	68 (25.5)
III (IIIA, IIIB, IIIC)	58 (21.8)

The results are expressed as mean ± standard deviation or mean (%).

Table II. Results of locations of suspicious for LRL and the final diagnosis on the postoperative US after undergoing breast cancer surgery

Location	Axilla	Internal mammary area	Supraclavicular fossa
Number of suspicious for LRL on US (N=280)	178 (63.6)	22 (7.8)	80 (28.6)
Malignant (N=74)	38 (51.4)	12 (16.2)	24 (32.4)
Benign (N=206)	140 (68.0)	10 (4.8)	56 (27.2)
Positive predictive value (%)	21.3	54.5	28.6

The results are expressed as mean (%). LRL, locoregional recurrence in the lymph node; US, ultrasound.

Predictive factors of the supraclavicular LRL

Table III summarizes the results of univariate and multivariate analysis for predictive factors for supraclavicular LRL. In the univariate analysis, age ($p=0.004$), undergoing breast-conserving surgery ($p=0.043$), higher overall stage of the primary cancer ($p=0.015$), higher N stage of the primary cancer ($p=0.002$), and higher nuclear grade ($p=0.01$) were independently associated with supraclavicular LRL, respectively. Primary breast cancers with nuclear grade G3 were more likely to have LRL than were those with nuclear grade G1 ($p=0.002$). However, bilaterality, histological type, higher T stage, and hormonal receptor status of the primary cancer were not significantly associated with supraclavicular LRL ($p=0.900$, $p=0.789$, $p=0.216$, $p=0.899$, respectively).

The multivariate analysis was performed using two models. In model 1, older patient age (odds ratio [OR] 1.060 [95% confidence interval (CI) 1.026–1.095]; $p<0.001$), undergoing breast-conserving surgery (OR 2.253 [95% CI 1.184–4.289]; $p=0.013$), and higher overall stage of the primary cancer (OR 2.361 [95% CI 1.302–4.282]; $p=0.005$) were independent predictive factors for LRL of supraclavicular LNs. In model 2, older patient age (OR 1.059 [95% CI 1.022–1.098]; $p=0.001$), undergoing breast-conserving surgery (OR 3.209 [95% CI 1.538–6.692]; $p=0.002$), and higher N stage of the pri-

mary cancer (OR 3.086 [95% CI 1.479–6.441]; $p=0.003$) were independent predictive factors for LRL of supraclavicular LNs. However, the nuclear grade of the primary cancer was not significantly associated with LRL of supraclavicular LNs on multivariate analysis ($p=0.205$).

Discussion

The present study focused on the presence of supraclavicular LRL in patients who underwent breast cancer surgery, which was independently associated with higher N stage and the higher overall stage of the primary breast cancer. Our results suggested that supraclavicular LRL was approximately 3 times (OR 3.086) more likely to occur in patients with higher N stages or 2.5 times (OR 2.361) more likely to occur in those with higher overall stages. However, in our univariate model and two multivariate models, higher T stage, nuclear grade and hormonal receptor status did not reach statistical significance in association with supraclavicular LRL in patients who underwent breast cancer surgery.

We found that, if supraclavicular LRL was suspected on routine postoperative US screening surveillance, it was very likely to be identified as LRL after histological examination. In other words, the PPV of the US surveillance for supraclavicular LRL was high. Therefore, we

Fig 1. A 57-year-old female patient underwent right breast conserving surgery in 2008: a) and b) a 9 mm-sized irregularly shaped hypoechoic mass was noted at the right 9:00 direction on the preoperative US images. The mass was confirmed as invasive ductal carcinoma and the stage of that was T1bN0 and overall stage IA; c) after 10 years, on the postoperative screening US surveillance, there was an enlarged LN in the right supraclavicular area, which was suspicious for LRL and confirmed as metastatic lymphadenopathy by core needle biopsy. The subtype was same as that of the primary cancer.

Table III. Univariate and multivariate logistic regression analysis for predicting LRL of supraclavicular lymph nodes

	Univariate analysis		Multivariate analysis model 1		Multivariate analysis model 2	
	Crude odds ratio	p value	Adjusted odds ratio	p value	Adjusted odds ratio	p value
Age (years)	1.043 (1.013 – 1.074)	0.004	1.060 (1.026 – 1.095)	<0.001	1.059 (1.022 – 1.098)	0.001
Unilateral / bilateral cancer						
Unilaterality	Reference					
Bilaterality	0.926 (0.282 – 3.046)	0.900				
Surgery						
Mastectomy	Reference		Reference		Reference	
Breast conserving surgery	1.765 (1.017 – 3.062)	0.043	2.253 (1.184 – 4.289)	0.013	3.209 (1.538 – 6.692)	0.002
Histologic type	1.080 (0.615 – 1.897)	0.789				
Overall stage						
Stage 0 and I (IA, IB)	Reference					
Stage II (IIA, IIB) and III (IIIA, IIIB, IIIC)	2.011 (1.146 – 3.528)	0.015	2.361 (1.302 – 4.282)	0.005		
T stage						
Tis, T1, and T2	Reference					
T3 and T4	0.488 (0.157 – 1.521)	0.216				
N stage						
N0 and N1	Reference				Reference	
N2 and N3	2.660 (1.415 – 5.000)	0.002			3.086 (1.479 – 6.441)	0.003
Nuclear grade		0.010				0.205
G1	Reference				Reference	
G2	2.632 (1.065 – 6.502)	0.036			1.348 (0.498 – 3.652)	0.557
G3	3.483 (1.553 – 7.811)	0.002			2.097 (0.861 – 5.110)	0.103
Hormonal receptor status		0.899				
Luminal type	Reference					
HER2-positive type	1.020 (0.537 – 1.936)	0.952				
Triple-negative type	1.183 (0.555 – 2.522)	0.663				

found that US was a reliable modality for the evaluation of the supraclavicular LN. Moreover, we could identify whether patients had a high potential for supraclavicular LRL using staging of the primary breast cancer. In cases for which the high-stage primary breast cancer is confirmed on the imaging evaluation before neoadjuvant chemotherapy or on the final surgical pathology, postoperative US screening surveillance for the supraclavicular areas must be carefully realized. Furthermore, we may expect that postoperative routine US scanning of the supraclavicular area would improve patient prognosis by enabling early detection of supraclavicular LRL.

Many previous studies have reported that younger age is a significant risk factor for locoregional recurrence of breast cancer [27-32]. Unlike previous studies investigating age, we demonstrated that older age was also independently associated with supraclavicular LRL. While most previous studies compared young age and old age as subgroups, we set the age as a continuous

variable. In addition, the mean age of our study population was somewhat higher than in other studies [32]. In our study group, older patients tended to have a higher stage of primary cancer and that could explain the association between the older age and the supraclavicular LRL. In addition, there was also an independent association between supraclavicular LRL and previous breast-conserving surgery, unlike other studies [33,34]. Patients undergoing mastectomy are more likely to have a higher stage of primary cancer than are those undergoing breast-conserving surgery and this may be interpreted as a result of the association between supraclavicular LRL and higher staging of the primary breast cancer. The precise association between supraclavicular LRL and age and breast-conserving surgery should be determined through further larger-scale studies.

There were several limitations to our study. First, the retrospective design of the study. We excluded patients who underwent postoperative screening surveillance

using CT or MRI without US and those with palpable lesion(s) in the locoregional areas; thus, selection bias was inevitable. Second, patients who underwent neoadjuvant chemotherapy underwent clinical staging instead of pathological staging. The exact pathological staging was unknown; therefore, this may have affected the outcome. Third, a small number of cases with LRL (n=74), especially with supraclavicular LRL (n=24), was analyzed. Fourth, we did not evaluate interobserver variability in the US interpretation for LRL. Fifth, we focused only on supraclavicular LRL not internal mammary LRL. However, the incidence of internal mammary LRL was relatively lower than that of axillary or supraclavicular LRL in a previous study [35] and also in our study. Therefore, the effect of excluding internal mammary LRL on the results of our study is believed to be minimal. Finally, clinicopathological factors were compared between true positive – histologic confirmed LRL – and false positive – histologic confirmed negative for malignancy – groups. The false positive group did not represent the non-LRL group.

In **conclusion**, in patients who underwent breast cancer surgery, the higher overall stage of primary breast cancer and the higher N stage of primary breast cancer are predictive factors of supraclavicular LRL. And routine US supraclavicular scanning is useful for the detection of supraclavicular LRL in breast cancer patients with a higher stage.

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Conflict of interest: none

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