Value of ultrasound for postoperative surveillance of Asian patients with history of breast cancer surgery: A single-center study

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ABSTRACT

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PURPOSE: To assess the diagnostic performance of postoperative ultrasound (US) for the detection of malignant lesions and to evaluate the role of US in postoperative surveillance of patients with breast cancer history.

MATERIALS AND METHODS: This retrospective study was approved by the institutional review board at our hospital, and informed consent was waived. We studied a total of 392 patients who underwent surgery for breast cancer between January 2000 and December 2002, including 287 mastectomy patients, 104 breast conservation surgery (BCS) patients, and one patient with both mastectomy and BCS. By December 2010, these patients had undergone a total

of 4082 US exams of the remaining breast, chest wall, and regional area for postoperative follow-up, and these ultrasound exams were reviewed. Whether the lesions were final-positive or final-negative was based on cytopathology results, clinical follow-up, and imaging studies, such as breast US or mammogram, during a minimum of 12 months after the procedure. Diagnostic indexes for detecting final-positive lesions were assessed. We also compared the frequency of distant metastases in patients with final-positive lesions and in those without. The 8-year survival rate was assessed.

RESULTS: There were 118 positive US in 93 patients (23.7% of 392 patients). At final diagnosis, 28 final-positive lesions (23.7% of 118 lesions; mean time to surgery 1,275 days; 95%CI for mean 1,102 to 1,721days) were detected in 24 patients (26.7% of 90 patients). There were six false-negative cases in five patients. The detection rate for final-positive lesions was 5.6% per patient (24 of 390 patients) and 1.3% per exam (28 of 4082 exams), and the false-negative rate was 1.3% per patient (5 of 390 patients) and 0.14% per exam (6 of 4082 exams). The sensitivity, specificity, PPV, NPV, and accuracy of follow-up US for final-positive lesion after breast cancer surgery among the 2926 US examinations conducted on 287 mastectomy patients were 91.3% (21 of 23), 98.0% (2840 of 2901), 25.0% (21 of 84), 99.9% (2840 of 2842), and 97.8% (2861 of 2926), respectively. For the 1171 follow-up US exams conducted on 104 BCS patients, the sensitivity, specificity, PPV, NPV, and accuracy of

follow-up US were 20.0% (1 of 5), 97.4% (1136 of 1166), 3.2% (1 of 31), 99.6% (1136 of 1140), and 97.1% (1137 of 1171), respectively. Among mastectomy patients, patients with final-positive lesions showed a higher incidence of distant metastasis than patients without final-positive lesions (7 of 19 patients (36.8%) versus 25 of 269 patients (9.2%), P=0.0009). Among BCS patients, there was no distant metastasis. Among mastectomy patients, the 8-year survival rate was 100% (3 of 3) in patients with only nonpalpable final-positive lesions and 64.5% (20 of 31) in patients with distant metastasis (P=0.1408).

CONCLUSION: Postoperative breast US showed high sensitivity for the detection of malignant lesions in the breast and the regional area, which can be a predictor of distant metastasis in mastectomy patients; however, the role of postoperative breast US in the detection of malignant lesions in BCS patients is unclear.

Key words : breast cancer, postoperative surveillance, ultrasound

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I. INTRODUCTION

The major purpose of postoperative surveillance after breast cancer surgery is the detection of malignant lesions in the breasts and regional lymph nodes. Locoregional failure is associated with an elevated risk of developing distant disease and mortality in patients treated by mastectomy or breast-conserving surgery (BCS) [1, 2]. Early detection of recurrence improves the chance of local disease control and expands opportunities for curative therapy in patients with either mastectomy or BCS [3-5].

A variety of diagnostic tools, such as physical examination, mammography [6, 7], and ultrasonography (US) [3], have been used for detection of malignant lesions after breast cancer surgery. The American Society of Clinical Oncology (ASCO) recommends annual mammography and physical

examination for postoperative follow-up [8]. Although US is not included as recommendation for postoperative follow-up, a few studies regarding postoperative US after breast cancer surgery have reported that postoperative US is helpful for early detection of recurrence in the mastectomy site and regional lymph nodes [3, 9] and metachronous cancer in contralateral breast [10]. However, those studies mostly focused on patients who had lesions detected on US exams [3, 9, 10] and who underwent US exams during a certain study period [3, 4, 9], and the duration of follow-up was not sufficient. The value of postoperative ultrasound for the detection of malignant lesions in patients following breast cancer surgery and the impact of malignant lesions on distant metastasis and survival have not been well established.

The purposes of our study were to assess the diagnostic performance of postoperative US for the detection of malignant lesions and to evaluate the role of US in postoperative surveillance of patients who had undergone preoperative mammography and US for staging of breast cancer.

II. MATERIALS AND METHODS

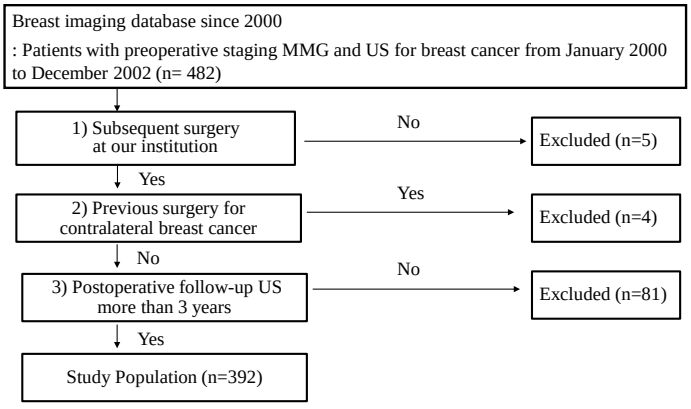
This retrospective study was approved by the institutional review board at our hospital, and informed consent was waived.

1. Patient selection

From a review of our breast imaging database since 2000, we retrieved

482 patients among the 11,880 examinations conducted between January 2000 and December 2002 who met all of the following criteria: had undergone preoperative mammography and US for breast cancer staging at our institution and (b) subsequently underwent surgery for breast cancer (mastectomy or BCS) during this period. We excluded 90 patients, including patients who underwent postoperative follow-up US for less than three years (n=81), had a history of previous surgery for contralateral breast cancer (n=4), or did not undergo surgery at our institution (n=5). Consequently, a total of 392 patients were included in our study (Figure 1). For these 392 patients, we retrospectively analyzed clinical and imaging follow-up data through December 2010.

Figure 1. Flow chart of our study



2. Postoperative treatment

Between 2000 and 2002, the treatment protocol for patients with breast cancer at our institution was as follows. To reduce tumor burden and make surgery possible, preoperative chemotherapy was administered to patients with locally advanced breast cancer or axillary lymph node (LN) metastases. The surgical treatment was total mastectomy or BCS and axillary lymph node dissection. After completion of surgery, adjuvant radiotherapy and appropriate adjuvant chemotherapy or hormone therapy was administered as indicated based on international guidelines.

All patients with invasive carcinoma received axillary clearance, and radiotherapy was administered to the axilla after mastectomy when 10 or more LNs were involved with the metastatic disease. Adjuvant therapy consisted of hormone treatment (tamoxifen for 5 years) and chemotherapy. Patients without axillary LN metastases received cyclophosphamide, methotrexate, and 5-fluorouracil, and patients with axillary LN metastases received 5-fluorouracil, adriamycin, and cyclophosphamide.

3. Postoperative follow-up

At our institution, clinical examination after breast cancer surgery was performed every 6 months for the first 2–3 postoperative years and annually thereafter. Regarding imaging studies, we recommended postoperative breast US every 6 months along with annual mammography for the first 2–3 years

after surgery. Thereafter, annual breast US and mammography were recommended. Despite these recommendations, some of our patients could not or did not follow because of their schedules or distance from the hospital.

When suspicious lesions at the mastectomy bed, remaining bilateral breasts, or in an axillary or supraclavicular LN were diagnosed on US or suspected on clinical examination, or if distant metastasis was suspected on clinical examination or tumor marker testing, further imaging studies, such as a whole-body bone scan, chest computed tomography (CT), neck CT, or positron emission tomography (PET) were performed for the evaluation of distant metastasis.

4. Imaging surveillance

Mammograms were obtained using dedicated equipment (DMR; GE Medical Systems, Milwaukee, WI) before April 2005 and the Selenia Full Field Digital Mammography System (Lorad/ Hologic, Danbury, CT) from May 2005 to the present. Standard craniocaudal and mediolateral oblique views were routinely obtained, and additional mammographic views were obtained as needed. In patients with mastectomy, contralateral breast mammography was performed. In patients with BCS, bilateral breast mammography was performed. Prior to imaging, a radiologist who performed US or a mammography technician verified whether patients had palpable lesions in their breasts, axilla, or neck area. When the women noted palpable lesions, the radiologists checked

the palpable lesions by means of a physical examination and US. After US examination, a dedicated board-certified breast surgeon performed an additional evaluation of the palpable lesions.

US was performed using high-resolution units with 5–10-MHz or 5–12-MHz linear-array transducers (Philips HDI 3000 or 5000; Advanced Technology Laboratories, Bothell, WA). Compound imaging was used in all examinations with the HDI 5000 unit. US was performed by one of 11 full-time, board-certified radiologists with fellowship training (n = 7) or clinical experience (n = 4, including authors M.J.K., E.K.K.), each of whom had 3–10 years of experience in breast imaging and biopsy with US guidance. The procedure was performed with the patient in the supine or lateral position.

In patients with mastectomy, US was performed on the mastectomy bed, ipsilateral chest wall, contralateral breast, and bilateral axillary and supraclavicular LNs. In patients with BCS, US was performed for remaining bilateral breasts and chest wall and bilateral axillary and supraclavicular LN. When a suspicious lesion was found at the remaining ipsilateral or contralateral breast in BCS patients, US-guided core needle biopsy (CNB) was usually recommended. When suspicious axillary or supravlavicular LNs or suspicious lesions in the mastectomy bed were seen on US, US-guided fine needle aspiration biopsy (FNAB) was recommended. Suspicious US findings in the mastectomy bed or the remaining ipsilateral or contralateral breast in BCS patients were defined as follows: American College of Radiology Breast

Imaging Reporting and Data System assessment categories 4 (suspicious abnormality) and 5 (highly suggestive of malignancy). Suspicious findings in the axillary and supraclavicular LNs were defined as follows: marked hypoechogenecity, round or irregular shape, eccentric cortical thickening, replaced fatty hilum and vascularity at the periphery.

5. Postoperative survival

For evaluation of patient survival, we reviewed clinical records of our institution and survival data of included patients, obtained from the National Cancer Center Registry [11]. We investigated survival for at least 8 years after surgery, as well as the time and cause of death.

6. Data analysis

Locoregional recurrence (LRR) was defined as recurrence in the mastectomy bed, LN recurrence in the ipsilateral axilla or supraclavicular area in both mastectomy and BCS patients. Ipsilateral breast tumor recurrence (IBTR) was defined as recurrence in the ipsilateral remaining breast in BCS patients. Contralateral malignancy was defined as recurrence in the contralateral normal breast in both mastectomy and BCS patients. The lesions suspicious for recurrence, as outlined above, were considered positive on US surveillance (US-positive). Distant metastasis was defined as evidence of breast cancer in any part of the body, except in the mastectomy bed, remaining breast

parenchyma, and ipsilateral axillary or supraclavicular LN areas. LN recurrence in the contralateral axilla and supraclavicular area was considered distant metastasis, which was also considered positive on US surveillance.

The final diagnoses of LRR, IBTR, and contralateral breast malignancy were divided into final-positive or final-negative lesions based on cytopathology results, clinical follow-up, and imaging studies, such as breast US or mammogram, performed for at least 12 months after the procedure. The presence of distant metastasis was based on cytopathology results of the metastatic lesion, if available, or on clinical findings and further imaging studies. True-positives were defined as final-positive lesions among US-positive lesions. A false-positive was defined as a detected suspicious lesion on US that was revealed to have no evidence of recurrence on cytopathologic examination or within 12 months of follow-up. A false-negative was defined as no evidence of a suspicious lesion on scheduled US but final-positive identified with or without palpation within 12 months.

Detection rate of malignant lesion was defined as the total number of cases with final-positive lesions during US surveillance divided by the number of individuals in the population and was assessed on the basis of the patients and the examinations. The false-negative rate was calculated as the cases with false-negatives divided by the number of individuals in the population and was assessed per patient and per examination. Diagnostic indexes, such as sensitivity, specificity, accuracy, positive predictive value (PPV), and negative

predictive value (NPV), were determined for US surveillance using the patient data and the examination data.

To assess the diagnostic performance of US surveillance, our study population of 392 patients was divided into two groups, patients with mastectomy and those with BCS. We divided the mastectomy patients into two groups, patients with final-positive and patients without, for comparison of the frequency of distant metastases. In patients with BCS, two groups were divided according to the presence or absence of final-positive lesions, and the frequency of distant metastases was compared.

The mean interval between surgery and detection of a US-positive lesion and final-positive lesion was assessed, and patients were divided into two groups with a cut-off of three years after surgery. For the evaluation of the effect of US on prognosis, the 8-year survival rate of patients was analyzed with patients divided into two groups, patients with nonpalpable final-positive lesions only and patients with distant metastasis, for each surgical method. In survival analysis, subsequent distant metastases that occurred beyond 6 months from final-positive diagnosis were still classified as the final-positive only because the analysis was to evaluate the delayed impact of final-positive only lesion on survival. The overall survival for these groups was estimated. Patients with contralateral breast malignancy were excluded from the survival analysis because of the possibility of bias.

Statistical comparisons were performed using a $\chi 2$ test or Fisher exact

test for nonparametric variables and *t* test for parametric inference. Statistical significance was assigned to *P* values less than 0.05. Data were analyzed using software (SAS System for Windows, version 9.0; SAS Institute, Cary, NC).

III. RESULTS

1. Diagnostic values of postoperative US

During the study period, a total of 392 patients underwent 4110 postoperative US exams (2925 exams in mastectomy patients, 1185 exams in BCS patients and 15 exams in a patient with both mastectomy and BCS), with a range of 4-19 exams per patient (mean 10.4 exams; median 10 exams). Among the 392 patients, 287 (73.2%) underwent mastectomy only, 104 (26.5%) underwent BCS, and one (0.3%) underwent mastectomy for one breast and BCS for the other breast. The last patient was included in both the mastectomy and the BCS group for data analysis. Therefore, the mastectomy group consisted of 288 patients, and the BCS group was made up of 105 patients. The mean age of patients at the time of surgery was 48.0 years (range, 21–73 years; median, 48 years). The mean US follow-up period for each patient was 92 months (range, 36 to 128 months, and median period 94 months).

A. Patients with mastectomy

Among the 288 mastectomy patients, there were 85 US-positive lesion in 67 patients (23.3%, mean time to surgery, 1369 days; 95% CI for mean 1193

to 1544 days); 16 cases (18.8% of 85 US) had lesions in the mastectomy bed, 40 (47.1%) had lesions in the contralateral breast, 26 (30.6%) had lesions in the regional LNs, and three (3.5%) had contralateral axilla LN. Fifty-two patients (77.6% of 67 patients) had only one lesion during follow-up US exam, 13 patients (19.4%) had two lesions, one patient (1.5%) had three lesions, and one patient (1.5%) had four lesions. Among the 85 US-positive lesions, 31 lesions were detected within three years after surgery (time to surgery; mean 572 days, median 555 days, range 177-945 days), and the remaining 54 lesions were detected after three years (time to surgery; mean 1808 days, median 1685 days, range 1080-3324 days). Aside from three lesions, all of the 85 positive US were pathologically confirmed (Table 1). One patient was lost to follow-up without cytopathologic confirmation or imaging study; however, the National Cancer Registry revealed that she was free from distant metastasis. The second patient had a lesion within a lesion in the mastectomy bed that was decreased in size on follow-up US, and these two lesions were considered benign. The third patient had a lesion in the mastectomy bed that decreased in size after radiation therapy and that was considered LRR. Of the 82 positive US exams with pathologic results, 21 lesions (25.6% in 82) in 19 patients including two palpable lesions were ultimately classified as final-positives at final diagnosis (Table 2, mean time to surgery, 1336 days; 95% CI for mean 945 to 1726 days); there were ten LRRs (12.2%) in nine patients (six cases of malignant masses in the mastectomy site and four cases of metastatic ipsilateral regional LNs), ten

contralateral cancers (12.2%) in nine patients, and one contralateral LN metastasis (1.2%) in one patient. One patient had a suspicious lesion in the ipsilateral axilla that was confirmed as leiomyosarcoma, and 14 exams from her were excluded from US surveillance analysis because this was not related to breast cancer. Two patients had two final-positive lesions on US. The first patient had two suspicious lesions in the contralateral breast. The second patient had suspicious lesions in the mastectomy bed and regional LNs on a separate US. Among 21 final-positive lesions, nine lesions occurred within three years of surgery (time to surgery; mean 632 days, median 686 days, range 177-891 days), and the remaining 12 lesions were detected after three years (time to surgery; mean 1426 days, median 686 days, range 1142-2904 days). The mean sizes of local recurrence in the mastectomy bed, LN recurrence, contralateral malignancy, and contralateral axillary LNs were 15 mm (range, 6–30 mm), 9.4 mm (range, 8–10 mm), 9.75 mm (range, 4–20 mm), and 7 mm, respectively. Locations and the final diagnoses of US-positive in mastectomy patients are shown in Table 1. There were two false-negatives in two patients (Table 3). In one of the patients, contralateral malignancy was detected by palpation within one year after a negative scheduled US. The other patient had no detected lesion on prior scheduled US, but a metastatic LN in the ipsilateral neck area was revealed by palpation and subsequent US performed after five months.

Table 1. Locations and the final diagnoses of US-positive lesions.

Location	Number of cases	Malignant	Benign
Mastectomy	84	22 (26.2%)	62 (73.8%)
Mastectomy bed	16	6 (37.5%)	10 (62.5%)
Contralateral breast	40	10 (25.0%)	30 (75.0%)
Regional lymph node			
Ipsilateral axillary fossa	25	5* (20.0%)	20 (80.0%)
Ipsilateral supraclavicular area	0	0	0
Contalateral axilla or supraclavicular lymph nodes	3	1 (33.3%)	2 (66.7%)
BCS	32	1 (3.1%)	31 (96.9%)
Ipsilateral breast	14	1 (7.1%)	13 (92.9%)
Contlateral breast	10	0 (0%)	10 (100%)
Regional lymph node			
Ipsilateral axillary fossa	5	0 (0%)	5 (100%)
Ipsiltaral supraclavicular area	1	0**(0%)	1 (100%)
Contalateral axilla or supraclavicular lymph nodes	2	0 (0%)	2 (100%)

* One lymph node confirmed as leiomyosarcoma was not included.

** One lymph node confirmed as a metastatic lesion from ovarian cancer was not included.

Table 2. Clinical findings and locations of final-positive lesions.

Patient number / Lesion number/ Age (year) at US	Type of surgery	Location	Time to surgery (day)		Palpability	Distant metastasis
1 / 1/ 60	Mastectomy	Axilla	555	TP[1]	Palpable	No
2 / 2/ 68	Mastectomy	Contralateral	716	TP	Nonpalpable	No
3/ 3/ 53	Mastectomy	Mastectomy bed	1184	TP	Nonpalpable	Yes
4/ 4/ 64	Mastectomy	Mastectomy bed	1452	TP	Nonpalpable	No
5/ 5/ 52	Mastectomy	Mastectomy bed	686	TP	Nonpalpable	Yes
5/ 6/ 54	Mastectomy	Axilla	1400	TP	Nonpalpable	Yes
6/ 7/39	Mastectomy	Contralateral	177	TP	Nonpalpable	No
7/ 8/62	Mastectomy	Contralateral	736	TP	Nonpalpable	No
8/ 9/51	Mastectomy	Contralateral	1142	TP	Nonpalpable	No
9/ 10/45	Mastectomy	Axilla	1643	TP	Nonpalpable	No
10/ 11/53	Mastectomy	Contralateral	1457	TP	Nonpalpable	No
11/ 12/53	Mastectomy	Mastectomy bed	2904	TP	Palpable	Yes
12/ 13/39	Mastectomy	Axilla	545	TP	Nonpalpable	Yes
12/ 14/40	Mastectomy	Contralateral	941	FN[2]	Nonpalpable	Yes
13/ 15/49	Mastectomy	Contralateral	1297	TP	Nonpalpable	No
13/ 16/49	Mastectomy	Contralateral	1297	TP	Nonpalpable	No
14/ 17/47	Mastectomy	Contralateral	546	TP	Nonpalpable	No

15/ 18/65	Mastectomy	Mastectomy bed	2472	TP	Nonpalpable	No
16/ 19/39	Mastectomy	Axilla	840	TP	Nonpalpable	Yes
17/ 20/70	Mastectomy	Mastectomy bed	1184	TP	Nonpalpable	Yes
18/21/56	Mastectomy	Contralateral axilla	891	TP	Nonpalpable	Yes
19/22/47	Mastectomy	Ipsiltaeral supraclavicular fossa	3205	FN	Nonpalpable	Yes
20/23/57	Mastectomy	Contralateral	2904	TP	Nonpalpable	No
21/ 24/69	BCS[3]	Ipsilateral	1080	FN	Nonpalpable	No
22/25/26	BCS	Contralateral	2161	FN	Nonpalpable	No
22/ 26/27	BCS	Ipsilateral	2368	FN	Nonpalpable	No
23/ 27/53	BCS	Ipsilateral	2024	TP	Nonpalpable	No
24/ 28/60	BCS	Ipsilateral	1715	FN	Palpable	No

[1]TP= true positive

[2]FN= false negative

[3] BCS= breast-conserving surgery

Table 3. False negative US results for final-positive lesions.

Patient number / Lesion number/ Age (year) at US	Type of surgery	Location	Time to surgery (day)	Detection	Distant metastasis
12/ 14/40	Mastectomy	Contralateral	941	Palpation	Yes
19/22/50	Mastectomy	Ipsiltaeral axilla	3205	US	Yes
21/ 24/69	BCS[1]	Ipsilateral	1080	PET-CT	No
22/25/26	BCS	Contralateral	2161	Mammography	No
22/ 26/27	BCS	Ipsilateral	2368	US[2]	No
24/ 28/60	BCS	Ipsilateral	1715	Palpation	No

[1] BCS= breast-conserving surgery

[2] Scheduled US exam performed six months before was negative in this patient.

The detection rate of malignant lesions, including one contralateral malignancy, was 7.0% among the patients (20 of 287 patients) and 0.8% among the exams (23 of 2926 exams). The false-negative rate on US was 0.7% among the patients (2 of 287 patients), 0.07% among the exams (2 of 2926 exams), and 10.0% among the final-positives during surveillance (2 of 20).

The sensitivity, specificity, PPV, NPV, and accuracy of follow-up US for lesion detection after breast cancer surgery were 95.0% (19 of 20), 75.3% (221 of 267), 30.3% (20 of 66), 99.5% (220 of 221), and 83.6% (240 of 287) in

the 287 patients and 91.3% (21 of 23), 98.0% (2840 of 2901), 25.0% (21 of 84), 99.9% (2840 of 2842), and 97.8% (2861 of 2926) for the 2926 US examinations, respectively.

B. Patients with BCS

Among the 105 patients with BCS, there were 33 positive US in 26 patients (24.7%, mean time to surgery, 1049 days; 95% CI for mean 664 to 1434 days); 14 were in the ipsilateral remaining breast, 10 in the contralateral breast, six in regional LNs, and two in contralateral LNs (Table 1). Twenty-two patients had only one lesion during follow-up US exam, two patients had two lesions, one patient had three lesions, and one patient had four lesions. Among the 33 US-positive lesions, 23 were detected within three years of surgery (time to surgery; mean 443 days, median 353 days, range 121-1042 days), and the remaining 10 lesions were detected after three years (time to surgery; mean 2623 days, median 2835 days, range 1394-3288 days). All of the 33 positive US cases were pathologically confirmed, except one case that was lost to follow-up at our hospital but was alive without distant metastasis according to the National Cancer Center Registry. Of the 32 positive US with pathologic results, one US-positive lesions (3.1%, time to surgery, 2024 days) revealed IBTR. No LN recurrences were revealed, but one ipsiltaeral neck LN was confirmed as a metastatic LN from ovarian cancer. Fourteen exams from this patient were excluded from analysis of US surveillance. The mean size of the IBTR was 8

mm (range, 6–10 mm).

There were four false-negative cases in three patients (Table 3). The first patient had metastatic ipsilateral axillary LNs detected by PET/CT within one year after a negative US that showed no lesion in the axillary area. The second patient had two false-negative lesions. She had undergone previous BCS on the left breast and had microcalcifications in her right breast on mammography performed 663 days after prior scheduled US (2161 days after initial surgery), but US performed on the same day revealed no focal lesion. Microcalcification seen on mammography was confirmed as ductal carcinoma in situ by subsequent excisional biopsy, thus she underwent left partial mastectomy. However, six months after the second operation (2368 days after initial operation), follow-up US showed suspicious microcalcification in her right breast, which was confirmed as ductal carcinoma in situ on subsequent vacuum-assisted core biopsy. The third patient had a palpable lesion in the remaining ipsilateral breast within one year after a negative US. This lesion was confirmed as invasive ductal carcinoma via US-guided core biopsy. All these four false-negative lesions were confirmed by biopsy. detection rate of final-positive lesions were 3.8% of the patients (4 of 104 patients) and 0.4% of the exams (5 of 1171 exam), and the false-negatives on US occurred in 2.9% of the patients (3 of 104 patients), 0.3% of the examinations (4 of 1171 exams), 75.0% of the patients with IBTR (3 of 4), and 80.0% of the detected malignancies (4 of 5).

The sensitivity, specificity, PPV, NPV, and accuracy of follow-up US for final-positive lesions in the 104 patients who had undergone BCS were 25.0% (1 of 4), 77.0% (77 of 100), 4.2% (1 of 24), 96.3% (77 of 80), and 75.0% (78 of 104), respectively. The sensitivity, specificity, PPV, NPV, and accuracy of follow-up US for final-positive lesion for the 1171 follow-up US were 20.0% (1 of 5), 97.4% (1136 of 1166), 3.2% (1 of 31), 99.6% (1136 of 1140), and 97.1% (1137 of 1171), respectively.

In total, final-positive lesions were detected in 5.6% of patients (24 of 390 patients) and 1.3% of the exams (28 of 4082 exams). US resulted in a false-negative rate of 1.3% among the patients (5 of 390 patients) and 0.14% among the exams (6 of 4082 exams). The sensitivity, specificity, PPV, NPV, and accuracy of follow-up US for final-positive lesions after breast cancer surgery in the 390 patients were 83.3% (20 of 24), 81.1% (297 of 366), 23.3% (21 of 90), 98.7% (296 of 300), and 81.3% (317 of 390), respectively. When evaluated on the basis of the exams (4082 follow-up US), the sensitivity, specificity, PPV, NPV, and accuracy of follow-up US for final-positive lesions were 78.6% (22 of 28), 97.7% (3961 of 4054), 19.1% (22 of 115), 99.8% (3961 of 3967), and 97.6% (3983 of 4082), respectively.

2. Distant metastasis

Among the 23 patients with final-positive lesions in both breasts and

regional LNs, seven (30.4%) had distant metastases, whereas only 8.9% (33 of 369) of patients without final-positive lesions had distant metastases (P=0.0032). According to type of surgery, patients with mastectomy, patients with final-positive lesions showed a higher incidence of distant metastasis compared to patients without final-positive lesions (7 of 19 patients (36.8%) versus 25 of 269 patients (9.2%), P=0.0009). In patients with BCS, patients with final-positive lesions did not show a significantly higher incidence of distant metastasis than patients without final-positive lesions (0 of 4 patients (0%) versus 8 of 101 patients (7.9%), P=0.7129) because no distant metastases were revealed in patients with IBTR and contralateral malignancy.

3. Postoperative survival

Based on the survival data from our institution and the National Cancer Center Registry, there were 12 deaths among the 288 patients with mastectomy. In patients with BCS, there were four deaths among 105 patients. Two deaths (one in a mastectomy patient and one in a BCS patient) were not due to breast cancer, and these were excluded from the survival analysis. Among the patients with mastectomy, eight patients with final-positive lesions in the contralateral breast only and one patient with a false-negative lesion were excluded from the survival analysis. The eight-year survival rate was 100% (3of 3) in patients with only nonpalpable final-positive lesions detected on US, which was the same as that of patients with neither final-positive lesions nor distant metastasis (243of

243) and 64.5% (20 of 31) of that among patients with distant metastasis (P=0.5430). Among seven patients classified with final-positive lesions only, one had a final-positive lesion and subsequent distant metastasis after 18 months but was still alive. In patients with BCS, the eight-year survival rate was 100% (1 of 1) in patients with final-positive lesion only and 62.5% (5 of 8) in patients with distant metastasis (P=0.7077).

IV. DISCUSSION

Postoperative surveillance in breast cancer has focused on the early detection of potentially treatable relapse, resulting in a beneficial effect on survival [3, 12]. ASCO recommends regular clinical examinations and mammography to meet this aim by ASCO [8]. US is preferred in cases of suspicious lesions discovered after clinical examination or in cases in which lesions cannot be thoroughly evaluated because of postoperative or postradiotherapy changes. Also, US can provide much more information about deeper tissues and a more accurate characterization of suspected lesions than physical examinations and allows for immediate intervention for tissue diagnosis of suspicious lesions [9, 13, 14]. Previous studies report that postoperative US has higher sensitivity (91%) than physical examination (79%) [13], and the US detection rate for occult LRR is 1.7% [4].

However, previous studies regarding postoperative US have some limitations. First, information about whether preoperative whole breast

evaluation other than mammography, such as US or magnetic resonance imaging (MRI), was performed is not presented in most studies. Second, most of the previous studies investigated the value of US covering only a specific part of the mastectomy, regional LNs, or contralateral breast [3, 9, 10]. However, in the clinical setting, it is difficult to perform postoperative US focused on a specific part of the abovementioned area. Thus, an evaluation of the value of postoperative US for the detection of malignant lesions in mastectomy sites, the remaining breast, and regional LNs is needed. Third, the study populations in previous studies consist of heterogeneous patient groups because they included patients with postoperative breast US exam within a certain study period. Therefore, the patients have variable postoperative periods (range, 7-300 months) [3, 4, 9, 10]. Also, because previous studies included patients who underwent surgery at different institutions, the protocol for preoperative evaluation and follow-up varied even between patients within the same study. The study periods of previous studies range from 1 to 4 years, and the number of examinations is approximately double the number of patients (the ratio of exam frequency per patient, 1.36 to 2.19), which is insufficient to assess incidence and prevalence rates.

The cancer detection rates in our study, especially per the patients (5.6% per patient and 1.3 % per exam), were much higher than those (1.2 to 1.7% per patient and 0.7 to 1.1 per examination) in the previous literature, and this can be attributed to our long study period (median follow-up duration of 94 months)

and a median exam frequency of ten exams. Additionally, the US examination included both the breast area and regional LN area. Based on these characteristics of our study, the cancer detection rate can be expected to be at least five times higher among the patients and two times higher for the exams than those reported in previous studies. However, our results seemed to be at the lower margin or lower than the expected values (6.0 to 8.5 % per patient and 1.4 to 2.2% per exam). There are some potential reasons for this discrepancy. The first is that all of our cases had undergone whole breast US as part of the preoperative evaluation, and we rarely observed final-positive lesions within two years. Another reason is that they might include cases within the period when LRR is highly prevalent. We included consecutive examinations that occurred over the course of 8-10 years for each patient, while the previous studies only included the examinations performed within a certain period. Nevertheless, our observed detection rate was still higher than the 0.35% to 0.46% cancer detection rate with screening breast US, which supports the rationale for postoperative US surveillance [15-20].

In patients with mastectomy, the PPV rate of a positive US was 25.0% (21 of 84) when evaluated per exam; 37.5% were in the mastectomy bed, 25.0% in the contralateral breast, and 20.0% in the regional LNs. The PPV of our study was at the lower margin of those in previous studies that had shorter follow-up periods, which report PPVs ranging from 25.4% to 57.1% [3, 4, 9, 10]. We did not investigate the statistical significance of the difference of PPV in each evaluated

area or PPV according the period from breast cancer operation. However, in patients with BCS, the PPV of the US examination was 3.2% (7.1% (1 of 14), 0% in the contralateral breast and regional LNs), which is much lower than the results of a previous study [4]. One possible explanation is that final-positive lesions occurred less commonly in BCS patients (5 of 105 patients) than in mastectomy patients (23 of 288 patients). PPV in the patient group with lower prevalence has been shown to be lower than in high-risk patient groups [19]. Moreover, 71% of positive US in patients with BCS (23 of 32) occurred within three years, but none turned out to be final-positive lesions. Another possible explanation is that US has limited utility in evaluation of IBTR in BCS patients. Shin et al. [4] reported four IBTRs near conserving scars in BCS patients, but another four false-negative local recurrence cases were observed in the ipsilateral breast. The false negative rate of IBTR in Shin's study was 50%, and the false negative rate in our study was 75% (3 of 4 IBTR). Based on these two results, the false negative rate of IBTR seemed to be higher than that of LRR in another regional area.

ASCO recommends annual mammography for postoperative surveillance, which has a sensitivity of 44.5-67% [13, 21], and patients with recurrence detected on mammography with a negative physical exam or without symptoms show better survival than patients with symptoms [12]. Although our study investigated the value of US in postoperative surveillance, the role of mammography should not be underestimated. Two of six false-negative cases in

our study were detected on mammography as microcalcifications. This was consistent with a previous study, which reported that 40% of false-negative IBTR cases present as microcalcifications on mammography [4]. Moreover, mammography performed prior to US exam might be helpful for the detection of some true-positive cases, although the additional value of mammography was not specifically analyzed in this retrospective study.

Recently, the role of postoperative surveillance of MRI has been concerned because of wide range of examined area. For example, IBTR in BCS patients is known to be difficult to detect on mammogram due to postoperative architectural distortion [22]. Therefore, the utility of different modalities, such as US or MRI, has been investigated. However, our study suggested that the role of US in postoperative surveillance for the detection of IBTR in BCS patients remains unclear because US detected only one of five final-positive lesions. Future studies with MRI or contrast-enhanced digital mammography are needed; however, MRI also has limitations, such as insufficient evaluation for regional LNs particularly in the supraclavicular fossa.

Many studies have shown that patients with malignant lesions, such as LRR or IBTR, have higher risk of distant metastasis [23-26]. Some reports show that the overall survival of patients with only LRR is higher than that of patients with distant metastasis [9, 27]. In our study, mastectomy patients with only final-positive lesions had a similar eight-year survival rate to that of patients without final-positive lesions, which supports the recommendation that patients

with final-positive lesions should be treated aggressively only if combined with distant metastasis. Therefore, meticulous evaluation for distant metastasis should be considered if a malignant lesion is detected on US. However, there was no significant difference in eight-year survival between patients with only final-positive lesions and patients with distant metastasis. Our results could be due to several factors. First, the number of patients in our study was relatively small, which could result in a failure to achieve statistical significance. Second, the eight-year survival rate of patients with distant metastasis was relatively higher than that of previous studies [9, 27], which may be a result of our exclusion of patients who underwent postoperative US surveillance for less than three years. Among the excluded patients, there may have been patients who had distant metastasis in the early postoperative period. Therefore, future studies regarding the indications for postoperative US among high-risk patients are needed.

Although the number of patients in each group was too small to reach a concrete conclusion, our study population was a relatively homogeneous patient group that was followed for a longer period than in previous studies, and thus our results might present a more reliable estimate of the survival impact of malignant lesions detected on US. Although previous studies report that early detection of US-detected LRR may improve survival, our study suggests that the long-term survival benefit of malignant lesions detected on US warrants further investigation.

Our study had several limitations. First, our study population consisted of only patients who underwent postoperative US surveillance and did not include patients without US surveillance. Comparison between a group of patients with US surveillance and a group without US surveillance that are treated with the same protocol, including preoperative US and subsequent surgery, may clarify the value of US surveillance. Large prospective randomized trials to obtain direct evidence are costly and require extensive resources. Second, our study included both mastectomy and BCS patients, and the number of BCS patients was relatively small. The number of final-positive lesions detected on US exam was too small, with only one IBTR, to perform meaningful survival analysis. Third, we did not investigate clinical data such as preoperative staging, which could affect the methods of postoperative surveillance.

V. CONCLUSION

In conclusion, postoperative breast US showed high sensitivity for the detection of malignant lesions in the breast and associated breast region, which can be a predictor of distant metastasis in mastectomy patients; however, the role of postoperative breast US for the detection of malignant lesions in BCS patients remains unclear.

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ABSTRACT(IN KOREAN)

아시아인 유방암 환자의 수술 후 감시에서 초음파 검사의 가치 : 단일 기관 연구

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서 영 주

목적: 유방암 수술 후 환자들을 대상으로 하여, 수술 후의 연속적 추적 초음파 검사의 악성 병변 발견에서의 진단적 가치를 알아보고, 수술 후 초음파의 역할을 평가한다.

대상 및 방법: 2000년 1월부터 2002년 12월까지 본원에서 유방암 수술 전 유방촬영술 및 초음파를 시행한 환자들 중 본원에서 수술 받은 환자들 392명이 연구 대상으로 포함되었다. 2010년 12월까지 이 환자들은 총 4082번의 수술 후 초음파 검사를 시행하였다. 악성 병변의 최종 진단은 세포병리학적 진단 또는 1년 이상의 임상/영상적 추적 관찰을 바탕으로 이루어졌다. 대상 환자들을 악성 병변이 있는 환자들과 없는 환자들 두 군으로 나누어 두 군

간의 원격 전이 비율을 비교하였다. 또한 8년 생존률을 평가하였다.

결과: 총 392명의 환자 중 93명의 환자에서 118번의 초음파 검사가 양성 소견이었으며, 최종 진단에서 24명의 환자에서 28개의 악성 병변이 진단되었다. 5명의 환자에서 총 6개의 위음성 병변이 발견되었다. 악성 병변의 발견율은 5.6% (390명 환자 중 24명), 1.3% (4082 검사 수 당 28 번), 악성 병변 진단의 민감도, 특이도, 양성예측율, 음성예측율은 각각 91.3%, 98.0%, 25.0%, 99.9%였다. 유방 전절제술을 시행한 환자 군에서, 악성 병변이 있는 환자들이 없는 환자들보다 원격 전이의 비율이 높았으나 (36.8% 대 9.2%, P=0.0009), 유방보존술을 시행한 환자에서는 원격 전이가 발견되지 않았다. 유방 전절제술 환자군에서, 8년 생존률은 악성 병변만 있는 환자에서 100% (3명 중 3명), 원격 전이가 있는 환자에서 64.5% (31명 중 20명)였다 (P=0.5430).

결론: 수술 후 추적초음파는 유방과 주위 구역의 악성 병변의 진단에 민감도가 높은 검사이며, 유방 전절제술을 시행한 환자에서 초음파에서 발견된 악성 병변은 원격 전이의 예측인자이지만, 유방보존술을

시행한 환자에서는 수술 후 초음파의 역할이 불분명하다.

핵심되는 말: 유방암, 수술 후 감시, 초음파