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Brief Communication

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Feasibility of Ultrasound-Guided Localization for Clipped Metastatic Axillary Lymph Nodes After Neoadjuvant Chemotherapy in Breast Cancer Patients: A Pilot Study

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

We present our initial experience of ultrasound (US)-guided localization of clipped metastatic axillary lymph nodes (LNs) following neoadjuvant chemotherapy (NAC). We evaluated US visibility and the successful excision rate of clipped LN after NAC in 29 consecutive patients with breast cancer. US-guided localization of clipped nodes was performed in 22 patients on the day of surgery, while seven patients underwent surgery without localization. The clips were identified in all patients with residual metastatic LNs and 6 of 12 (50%) patients without residual metastatic LNs on US. Six patients without visible clips underwent US-guided localization at the presumed previous clip insertion site. The successful excision rate of 22 LNs with localization was 100% (even though 3 of them were non-sentinel LNs) and 57% (4/7) without localization. Regardless of the presence of visible residual metastatic LNs on US after NAC, successful excision of the clipped LN with US-guided localization is feasible.

Keywords: Breast Neoplasms; Lymph Node Excision; Neoadjuvant Therapy; Ultrasonography

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has been increasingly used in patients with operable breast cancers [1]. The reported nodal pathologic complete response (pCR) rate ranges from 40% to 74% after NAC in patients with clinically node-positive breast cancer. The indications for sentinel lymph node biopsy (SLNB) have been extended and SLNB has become an alternative to axillary lymph node dissection (ALND), with reduced patient morbidity [2-6]. However, achieving a sufficiently low false-negative rate (FNR) in SLNB is a primary concern. Currently, the FNRs of SLNB after NAC varies between 9% to 21% [7-9]. To reduce the unacceptably high FNR of SLNB, the concept of targeted axillary dissection (TAD) has emerged, which removes biopsy-proven metastatic lymph nodes (LNs) in addition

Author Contributions

Conceptualization: Kim H, Ko EY; Data curation: Kim H, Ko EY, Lee JE, Cho SY; Formal analysis: Kim H, Ko EY, Han BK, Ko ES, Choi JS, Cho SY; Investigation: Kim H, Ko EY, Han BK, Ko ES, Choi JS, Cho SY; Methodology: Kim H, Ko EY, Han BK, Ko ES, Choi JS, Lee JE, Cho SY; Resources: Lee JE; Software: Ko ES; Supervision: Ko EY; Validation: Ko EY, Han BK, Choi JS, Lee JE; Visualization: Kim H; Writing - original draft: Kim H; Writing - review & editing: Ko EY.

to sentinel lymph nodes (SLNs) [10]. Studies on TAD reported that 9%–24% of clipped LNs are not SLNs, resulting in an FNR reduction to 1.4% [11-13]. For TAD, tissue marker insertion in histologically confirmed metastatic LNs is required prior to the initiation of NAC. Biopsy markers, referred to as metallic clips, usually made of stainless steel or titanium, or ultrasound (US)-visible metallic clips with an associated bioresorbable material that absorbs water over time, have been utilized for marking biopsy-proven metastatic axillary LNs [14]. For successful TAD, preoperative US-guided localization and postoperative specimen mammography (MG) of the clipped LN are needed, as well as SLNB, after the completion of NAC. Several methods are used for clipped LN localization, including wire localization, tattooing, and other types of non-wire localization, such as radar reflectors, magnetic seeds, and radioactive seeds. Regardless of the type of localization, the methods for visualization and targeting of clipped LNs under US guidance are almost identical. Although studies have reported the feasibility of the US-guided localization of clipped LNs, few have described in detail the US-guided procedures and the feasibility of visualizing clipped LNs on US after NAC. Here, we present our initial experience of the feasibility of US-guided localization of clipped LNs after NAC.

METHODS

Patients

This retrospective study was approved by the Institutional Review Board and Ethics Committee of Samsung Medical Center, which waived the requirement for informed consent (IRB No. 2021-04-181). Between March and September 2020, 29 consecutive breast cancer patients who underwent NAC after clip insertion for biopsy-proven metastatic axillary LN underwent breast cancer surgery. All the patients underwent staging US of the axilla before starting NAC. Fine-needle aspiration (FNA) or core-needle biopsy (CNB) was performed on the most suspicious LN. In cases with several similarly suspicious LNs, we performed FNA or CNB for the lower medially located level I LN, which is the most suspicious SLN.

US-guided clip insertion for biopsy-proven metastatic axillary LN

US-guided clip insertion was performed by one of the seven radiologists with 1–26 years of experience in breast imaging. We used iU22 (Philips Advanced Technology Laboratories, Bothell, USA), Aixplorer US (SuperSonic Imagine, Aix-en-Provence, France), or RS80A system (Samsung Medison Co., Ltd., Seoul, Korea) with 12–5-MHz, 15–4-MHz, or 3–12-MHz linear array transducers. For clip insertion, we identified the metastatic LNs (previously confirmed by FNA or CNB) among all visible suspicious LNs on US and deployed a US-visible titanium marker (UltraClip® Dual-Trigger Breast Tissue Marker, Ultrasound-enhanced Ribbon; Bard Biopsy Systems, Tempe, USA) at the cortex of the LN using a coaxial biopsy needle (TruGuide™; Bard Biopsy Systems) under US guidance after local anesthesia. We then confirmed the location of the clip using axillary view MG.

Preoperative US-guided localization of clipped axillary LN

One of the seven radiologists who performed clip insertion performed US-guided preoperative localization of the clipped LN on the day of surgery. Localization of the clipped LN was performed consecutively with localization of a clip within the primary breast cancer in the same room. Together, both procedures required < 30 minutes per patient to complete. Using the previous US images of clip insertion in the same patient position, the surrounding structures and distance from the skin were located and the same LN was identified. Wire

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localization was performed using a hooked wire (Accura™ Breast Localization Needle; Argon Medical Devices, TX, USA) under US guidance. Post-localization axillary view MG was performed to confirm the location of the wire and clip. In cases with tattooing localization, 0.3–0.5 mL of charcoal tracer (Charcotrace™; Phebra, Lane Cove West, Australia) was injected at the clip site and along the needle tract to the skin. MG with a fiducial marker on the skin of the tattooing site was then performed to confirm the location of the tattooing site and the clip.

When the clip was not identifiable on US, US-guided localization was performed at the presumed clip site in the same patient position by referring to the US images taken at the time of clip insertion, and measuring the distance from the skin and surrounding structures.

Axillary surgery and pathological correlation

The clipped LNs and the SLNs were surgically excised using TAD. SLNB was performed using the dual tracer technique with technetium-99m sulfur colloid diluted in normal saline solution and vital blue dye (0.8% indigo carmine). Radiolabeled colloid was injected 2–6 hours before the scheduled surgery, 5 mL of 0.8% indigo carmine was injected peri-areolarly, and the breast was massaged for 5 minutes. A handheld gamma probe was used to detect radioactive axillary LN. All radioactive and/or blue LNs were excised as suspected SLNs. In this way, the removed LNs were classified and marked as SLNs or non-SLNs, and specimen MG was taken to confirm the retrieval of the clipped LN. If the clip was seen in the SLN specimen, the clipped LN was confirmed to be the SLN. The pathologist was also asked to state whether a clip was present in the specimen classified as an SLN. A single pathologist (SYC) retrospectively reviewed the specimens to determine whether the clipped LN was an SLN and whether residual metastasis was present. The total number of retrieved LNs and residual metastatic LNs was recorded in the pathology reports.

Data analysis

We retrospectively reviewed the medical records, imaging studies, and pathology reports to collect data, including patient age, pathologic diagnosis, subtypes, clinical stage, use of preoperative localization, method of localization of clipped LNs, identification rate and associated factors for indentification of clipped LN or clips on preoperative localization US, whether specimen MG was taken, successful excision rate and associated factors for successful excision of clipped LN, type of breast and axillary surgery, number of retrieved LNs and residual metastatic LNs, and the match between the clipped LN and SLN.

RESULTS

The clinicopathological characteristics of the patients are presented in **Table 1**. The mean age was 48.4 ± 10.3 years. All patients were diagnosed with invasive ductal carcinoma, with 75.9% at stage IIB or higher. Of the patients in this study, 44.8% had human epidermal growth factor receptor 2 (HER2)-enriched breast cancer, 24.1% had triple-negative breast cancer, and 31% had estrogen-receptor-positive and HER2-negative breast cancer. In total, 9 (31.0%) of the 29 patients presented with pCR in the breast lesion, and 17 (58.6%) of the 29 patients presented with pCR in the axillary LN. HER2-enriched breast cancers showed the highest pCR rate (46.2% [6/13] in the breast lesions and 84.6% [11/13] in the axillary LNs), followed by triple-negative breast cancers (42.9% in both breast and axillary lesions).

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Table 1. Patient clinicopathological characteristics (n = 29)

Characteristics	Values
Age (yr)*	48.4 ± 10.3
Tumor subtype	
Luminal A	1 (3.4)
Luminal B HER2–	8 (27.6)
Luminal B HER2+	6 (20.7)
HER2+	7 (24.1)
Triple-negative	7 (24.1)
Breast pathologic complete response	
Luminal A	0/1 (0)
Luminal B HER2–	0/8 (0)
Luminal B HER2+	1/6 (16.7)
HER2+	5/7 (71.4)
Triple-negative	3/7 (42.9)
Axilla pathologic complete response	
Luminal A	0/1 (0)
Luminal B HER2–	3/8 (37.5)
Luminal B HER2+	6/6 (100)
HER2+	5/7 (71.4)
Triple-negative	3/7 (42.9)

Unless otherwise specified, data represent the numbers of lesions with percentages in parentheses.
HER2 = human epidermal growth factor receptor 2.
*Values represent means ± standard deviation.

Table 2. Median number of metastatic LNs according to the surgery type in the breast and axilla

Type of axilla surgery	Type of breast surgery			
	BCS (n = 18)		TM (n = 11)	
	Metastatic LNs	Retrieved LNs	Metastatic LNs	Retrieved LNs
SLNB (n = 19)	0	5	0	4
ALND (n = 10)	2	19	5	19

LN = lymph node; BCS = breast conserving surgery; TM = total mastectomy; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection.

Furthermore, 18 (62.1%) of the 29 patients underwent breast-conserving surgery (BCS), while 11 (37.9%) underwent total mastectomy (TM) (**Table 2**). Among the patients who underwent BCS, 16 (88.9%) of 18 underwent preoperative localization of the axillary clips, while only 6 (54.4%) of 11 patients who underwent TM underwent preoperative localization of the axillary clip. For the axilla, 19 (65.5%) patients underwent SLNB only, nine patients underwent ALND after SLNB, and one patient underwent direct ALND. Among the patients who underwent SLNB only, 17 showed axillary pCR and two showed only one residual metastatic LN. The median number of retrieved SLNs was five (range, 2–7).

A flowchart of the clipped LNs is presented in **Figure 1**. Among the 29 patients, 22 underwent US-guided localization of the clipped LN before surgery, while seven patients underwent surgery without localization. Of the 22 patients who underwent preoperative localization, 10 showed residual metastatic LNs on US, with the clip identifiable in all cases, and a successful retrieval rate of 100%. In 12 cases without residual metastatic LN on preoperative localization US, the clip was identified in only 50% (**Figure 2**). However, regardless of the clip visibility, all 22 clipped LNs were successfully retrieved, which corresponded to a successful excision rate of clipped LN with localization of 100% (**Figure 3**).

Specimen MG was performed in 15 (68.2%) of the 22 cases with localization to confirm the clip retrieval. In 7 (31.8%) cases with no MG specimen, successful clipped LN retrieval was confirmed by pathology reports and follow-up chest computed tomography (CT) scans. In cases without preoperative localization of the clipped LNs, the clipped LNs were successfully

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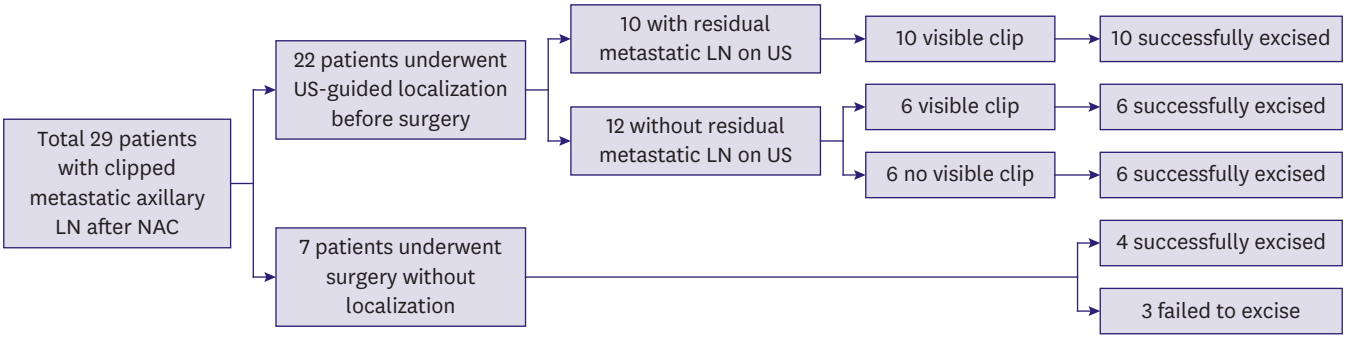

Figure 1. Flowchart of the process for clipped LNs.
LN = lymph node; NAC = neoadjuvant chemotherapy; US = ultrasound.

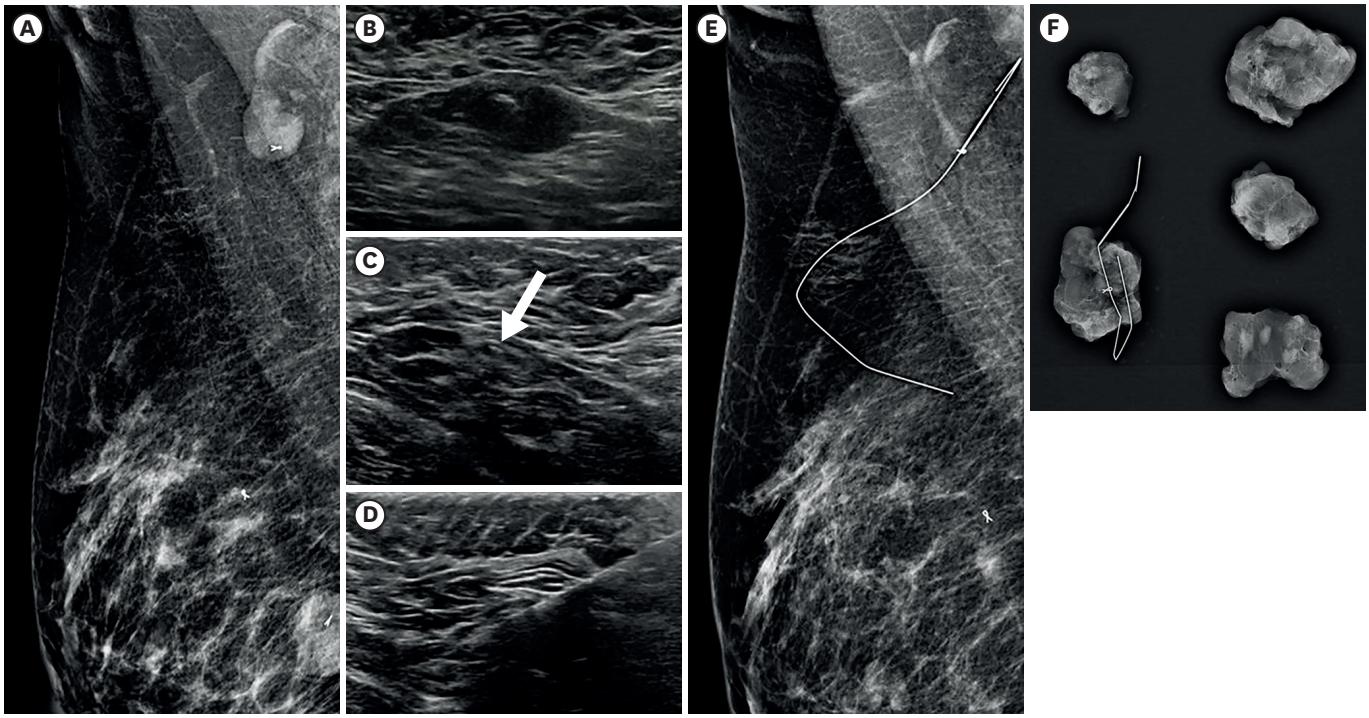

Figure 2. A 36-year-old woman with right breast cancer and ipsilateral axillary metastatic LN. The patient underwent clip insertion before NAC. (A, B) The clip was deployed at an axillary LN which was proven to be metastatic by fine-needle aspiration and confirmed by MG. (C) After NAC, the LN greatly reduced in size such that no suspicious features remained, and it appeared as a small benign LN (arrow) that was difficult to distinguish from the surrounding fat. (D) The clip was identified, and wire localization was performed. (E, F) Subsequent MG showed the successful placement of the wire on the clip, while subsequent specimen MG confirmed the retrieval. The clipped LN was proven to be the SLN, and pathological examination showed no residual metastasis.
LN = lymph node; NAC = neoadjuvant chemotherapy; MG = mammography; SLN = sentinel lymph node.

excised in only 4 (57.1%) of the 7 cases. In the other three patients, clipped LNs were not included in the MG specimen of two patients, whereas one patient did not undergo specimen MG. The pathology reports did not indicate the presence of clipped LNs.

In total, 21 (80.8%) of the 26 retrieved clipped LNs were SLNs, while 5 (19.2%) LNs were not. Among the four clipped LNs that were successfully excised without localization, two were non-SLNs. All cases of residual metastasis were detected in the SLNs or clipped LNs of patients who underwent localization of the clipped nodes.

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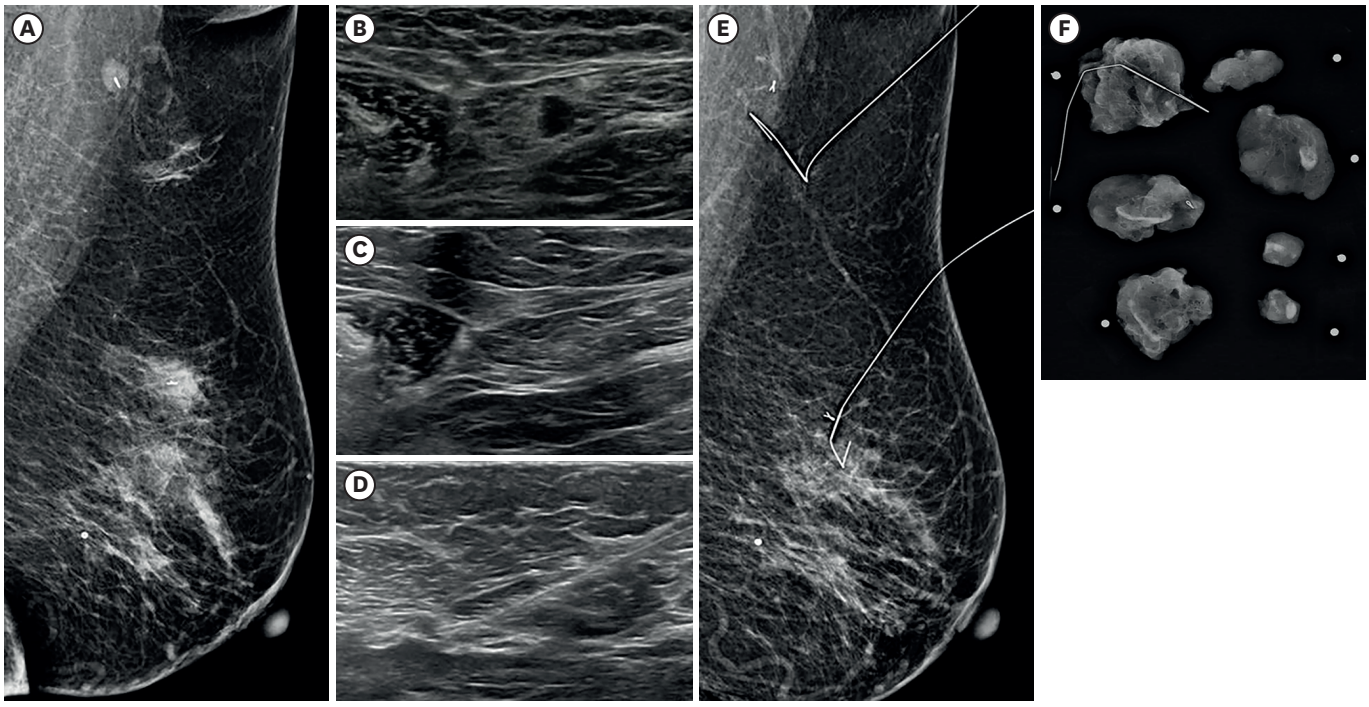

Figure 3. A 72-year-old woman with left breast cancer and ipsilateral axillary metastatic LN. The patient underwent clip insertion before NAC. (A, B) Initially, the clip was deployed at the small axillary LN which was proven to be metastatic by fine-needle aspiration and confirmed by MG. (C) After NAC, the LN size decreased such that it, as well as the echogenic clip, was difficult to identify. (D) By referring to previous US images at the time of clip insertion, wire localization was performed at the presumed clip-inserted site, which showed similar surrounding structures. (E) Subsequent MG showed that the wire did not exactly match the clip but was located nearby. (F) Subsequent specimen MG confirmed the successful retrieval of the clipped LN, which was confirmed as the SLN. Pathological analysis showed no residual metastasis.
LN = lymph node; NAC = neoadjuvant chemotherapy; MG = mammography; US = ultrasound; SLN = sentinel lymph node.

DISCUSSION

In our study, regardless of the visibility of the residual metastatic LNs or clips on US, all clipped LNs were successfully retrieved by TAD with US-guided localization. However, only 57.1% of the clipped LNs were successfully retrieved without localization. This result emphasizes the importance of preoperative US localization of clipped LNs. Plecha et al. [15] also reported a significantly higher rate of clipped LN removal in patients who underwent US-guided wire localization (97.3%) than in those who did not (79.4%).

It is technically difficult to correctly localize clipped LNs under US guidance when the response to chemotherapy is excellent, and the metastatic LNs shrink to normal size after NAC. In some cases, the clip may even be displaced into the perinodal fatty tissue, which renders it difficult to distinguish the clip from the echogenic line of the surrounding tissues [16]. Hartmann et al. [17] reported that clipped LNs after NAC were visible on US in 83.3% (25/30), wire localization was possible in 80% (24/30), and clipped nodes were identified in the surgical specimens in 70.8% (17/24) of cases. In our study, 72.7% (16/22) of the clipped LNs were visible on US. However, localization was performed in all 22 cases regardless of the visibility of the clipped LNs on US, with successful retrieval in 100% of cases. The visibility of clipped LNs after NAC in our study was slightly lower than that reported by Hartmann et al. [17]. The higher pCR rate of metastatic axillary LNs in our study (58.6% vs. 46.7%) may have increased the difficulty of detecting clipped LNs after NAC.

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Previous studies have reported that 16.7%–28.0% of clipped LNs were not visible on US after NAC, which made US-guided localization of the clipped LNs unfeasible [16,17]. Although 27.3% of the clipped LNs were not visible on US after NAC in this study, we performed localization in these cases by referring to the US images taken at clip insertion, measuring the distances from the skin, and considering the surrounding structures, including the degree of arm elevation. We performed localization at a nearby site, even if it was not at the exact location. We attributed the 100% successful retrieval rate of the clipped LNs to these efforts.

Studies reporting difficulties in identifying clipped LNs on US after NAC have rarely described procedures taken in detail or explained the method of localization. Kim et al. [18] overcame the difficulty of localization by using fluoroscopy and cone-beam CT during wire localization. However, in addition to extra radiation, patients with a clip in the breast lesions for BCS must visit multiple locations for preoperative localization, including an appointment for US-guided or MG-guided localization for the breast clips, and another appointment for fluoroscopy and/or CT for the localization of the axillary clips. As many patients scheduled to undergo TAD were also scheduled for BCS, we attempted to perform US-guided localization on the same day.

There were two cases in which US-guided wire localization failed initially but was successful on the second attempt. In both cases, no residual suspicious LNs or clips were visible via US. We attempted wire localization at the estimated site by referring to previous US images. However, the axillary view MG taken after wire localization showed an incorrect wire position. The second attempt was successful, likely because the clip location could be more precisely estimated by using the location of the inserted wire in the MG and US as a reference. In one case, tattooing was the preferred method. The clipped LN was located deep in the axillary fossa, and the axillary view MG did not include the shrunken clipped LN. We performed tattooing localization, and specimen MG after excision confirmed the retrieval of the clipped LN. Five of the seven patients who did not undergo preoperative localization of the axillary clipped LN were scheduled for TM. In the TM, the lower axillary LNs were easily included in the surgical specimens. Since FNA- or CNB-proven metastatic LNs are usually located in the lower medial portion at level I of the axilla, successful retrieval without localization can be performed. However, three of the seven clipped LNs without preoperative localization could not be retrieved, two of which were TM cases. Therefore, although the surgical field may appear to include the clipped LN in the axilla, preoperative localization is recommended, unless the residual clipped LN is palpable. The three cases in which we failed to retrieve the clipped LNs without preoperative localization showed no residual metastases in SLNB, and thus, we did not proceed with further axillary surgery.

Our study has some limitations. First, the number of included cases was small, as this study aimed to describe our initial experience. Our successful retrieval rate of clipped LNs in patients with preoperative localization, regardless of the US visibility of the residual clipped LN, may differ if we had performed a larger number of procedures. Further prospective studies with larger numbers of patients are needed. Second, this was a single-center study that included all Korean women, mostly in their 5th or 6th decades, although the age range was 29–72 years. These results may vary across countries and populations. Another limitation was that the US-guided localization of the clipped LN was performed by seven radiologists with various experiences. The US visibility of clipped LNs may have differed between the radiologists. Conversely, the results of the procedures performed by heterogeneous practitioners were equally excellent, which increased the strength of this study.

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In conclusion, US-guided preoperative localization is essential for the successful excision of clipped axillary LNs. Regardless of the presence of visible residual metastatic LNs after NAC on US, successful excision of clipped LNs with US-guided localization is feasible.

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