Surgery Today (2025) 55:172–179
https://doi.org/10.1007/s00595-024-02981-0

ORIGINAL ARTICLE

Diagnostic accuracy of sentinel lymph node biopsy and wire localized clipped node biopsy after neoadjuvant chemotherapy in node-positive breast cancer

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Received: 25 January 2024 / Accepted: 13 June 2024 / Published online: 27 December 2024

Abstract

Purpose The optimal method for axillary staging in patients with initially node-positive breast cancer after NACT remains unclear.

Methods We conducted a prospective, single-center trial to investigate the diagnostic performance of sentinel lymph node biopsy (SLNB) combined with wire localized lymph node biopsy (WLNB) of the clip-marked node as an axillary staging technique in patients with node-positive breast cancer after neoadjuvant chemotherapy (NACT).

Results A total of 233 patients were enrolled, 208 of whom were included in the analysis. The IR of SLNB and WLNB alone were 63.0% and 70.7%, respectively. The identification rate (IR) of targeted axillary dissection (TAD) was 87.5%. The FNR of and NPV were 6.9% (95% confidence interval [CI]:2.0–11.8%) and 92.0% (95% CI 86.3–97.7%), respectively, for the TAD procedure, 17.1% (95% CI 8.2–25.6%) and 83.3% (95% CI:74.7–91.9%) for SLNB alone, and 6.7% (95% CI:1.5–12.0%) and 90.6% (95% CI:83.5–97.7%) for WLNB alone.

Conclusions The diagnostic performance of TAD using wire localization was similar to that of the procedure performed using radioactive seed localization. (Clinical Trial Registration: NCT03715686).

Keywords Neoadjuvant chemotherapy · Targeted axillary dissection · Clipped node · Lymph node positive breast cancer

Introduction

Neoadjuvant chemotherapy (NACT) is an established treatment for locally advanced breast cancer and is increasingly being used in patients with early-stage breast cancer [1]. With the increasing efficacy of modern systemic treatment, nodal pathologic complete response (pCR) rates have been reported to range from 35 to 68%, depending on the tumor subtype, and approach 70–80% among patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors [2].

Patients with no axillary disease remaining after NACT are unlikely to benefit from axillary lymph node dissection (ALND) and may experience complications from the procedure. However, the feasibility and accuracy of sentinel lymph node biopsy (SLNB) after NACT remain controversial. Studies have shown that NACT can alter lymphatic drainage pathways, resulting in a lower SLN identification rate (IR) and a higher false-negative rate (FNR) [3]. Three prospective studies (ACOSOG-Z1071, SENTINA, and SN-FNAC) evaluated SLNB in node-positive patients after NACT. The overall false negative rate was 12.6–14.2%, which was higher than the prespecified threshold of 10% [4–6]. Subsequent subgroup analyses of these trials showed that the use of dual tracers, retrieval of more than 2 SLNs, and immunohistochemistry can reduce the FNR to below

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10%. However, these results were based on subgroup analyses, which lack definitive power.

Studies using clips to mark biopsied nodes showed that the clipped node is 1 of the SLNs in only approximately 75% of cases [7–9]. Therefore, in approximately 1 in 4 cases, the clipped node was not removed along with the SLNs, which could partially explain the high FNR after NACT. In an unplanned subgroup analysis of the ACOSOG Z0171 trial, an FNR of 6.8% was found if the clip was located in 1 of the SLNs, while the FNR was 14.3% if the clip was not found and 19.0% if the clip was found within the ALND specimen [7]. Caudle et al. reported that localizing and removing the clipped node in addition to SLNs resulted in an FNR of 2.0% [8]. Following this observation, the concept of targeted axillary dissection (TAD) was introduced and is currently endorsed by international guidelines [10].

Clinical trials are ongoing to identify the optimal method for staging the axilla in a neoadjuvant setting. However, there is great heterogeneity across studies in terms of patient selection and technical aspects of the procedure. Our goal was to provide sound evidence for the feasibility and diagnostic performance of TAD (SLNB and/or wire localization of the clipped node) in node-positive breast cancer patients after NACT.

Methods

Study design

The current study was a prospective, single-center investigator-initiated trial. The primary objective was to investigate the diagnostic accuracy of SLNB combined with wire localized node biopsy (WLNB) of the clipped node as an axillary staging technique in node-positive breast cancer patients after NACT, comparing the results with the gold standard: the pathological analysis of specimens obtained by ALND. The secondary objective was to determine the diagnostic accuracy of SLNB and WLNB. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the institutional review board. Written informed consent was obtained from all patients. The trial was registered on ClinicalTrials.gov website NCT03715686. This study followed the Standards for Reporting the Diagnostic Accuracy (STARD) Reporting Guidelines.

Eligibility criteria

Patients with core needle biopsy-confirmed invasive breast cancer who were 18 years of age or older were eligible for inclusion in this study. Other eligibility criteria included clinical stage T1-4N1-2M0, age $\leq$ 70 years, and World Health Organization performance status 0–1. Nodal positivity was confirmed using either fine-needle aspiration cytology or core-needle biopsy before NACT. Patients with positive infraclavicular or supraclavicular lymph nodes and patients with metastatic disease were ineligible. Other exclusion criteria included inflammatory breast cancer, previous chemotherapy or radiation therapy, and other concurrent illnesses (e.g., active infection, heart failure, or other significant illnesses) that might influence treatment tolerability.

Axillary ultrasound and clip insertion

All patients included in the study underwent an ultrasound examination of the axilla as well as the infraclavicular and supraclavicular areas at the time of initial staging. If more than one suspicious lymph node was found in the axilla, the largest of these nodes was defined as the index node and a biopsy was performed on this node. Ultrasonographic variables of lymph node morphology were recorded in detail to avoid subsequent clip insertion in different nodes. After nodal positivity was confirmed by pathology, the clip was inserted into the biopsied node in a separate procedure. An ultra-clip dual trigger breast tissue marker (Bard Peripheral Vasular, Inc., AZ, USA) was used to mark the biopsied node.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy was administered according to national and institutional guidelines. Sequential anthracycline- and taxane-based regimens are generally recommended. Typically, HER2-negative tumors were treated with 4 cycles of EC (epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2) in a dose-dense schedule (every 2 weeks), after which the patients switched to paclitaxel (80 mg/m^2) every week for 12 weeks. For HER2-positive tumors, HER2-targeted therapy (trastuzumab with or without pertuzumab) was administered concurrently with paclitaxel.

Axillary surgical treatment

The TAD procedure in our study consisted of both the SLNB and WLNB procedures. One of the 13 dedicated breast surgeons in our unit performed this procedure. For SLNB, a single tracer, the Tc-99 m radioisotope, was used. On the day of surgery, after the patient underwent general anesthesia, the surgeon performed an axillary ultrasound and identified the lymph node marked with the clip, with the patient's ipsilateral arm abducted at 90°, mimicking the position of the arm during axillary surgery. Occasionally, the assistance of a radiologist was necessary to locate the clip. Subsequently, a localization wire was percutaneously deployed under ultrasound guidance to facilitate surgical removal. During SLNB, all radioactive lymph nodes with a radioactive count that

was ≥ 10% of the ex vivo count of the hottest node were defined as sentinel lymph nodes. The study protocol requires specimen radiography of the resected wire-localized node (WLN). Radiography of the SLN and axillary dissection specimens was performed in cases where the clip was not identified in the WLN. If the clip could not be identified within the WLN, WLNB was regarded as a failure, regardless of whether the clip and WLN were not detected at all or if the clip was found in a non-WLN lymph node during ALND. After SLNB and WLNB, ALND was performed in all patients.

Ultrasonography and histopathological evaluation

Ultrasonographic complete remission (rCR) in the axilla after NACT was defined as the absence of suspicious features in the clipped node and other non-clipped nodes compared with baseline ultrasound.

SLNs and WLNs were processed separately from the ALND specimens. Paraffin-embedded SLNs and WLNs were serially sectioned at 2-mm intervals and stained with hematoxylin and eosin (HE). If no metastasis was detected, a further immunohistochemical (IHC) analysis was performed. SLNs were considered positive for any size and number of metastases, including micrometastases and isolated tumor cells (ITCs), according to the AJCC 8th edition. Nodes from ALND were dissected and stained with hematoxylin and eosin (H&E). Intraoperative pathological examinations were not performed.

Statistical analysis

The sample size was calculated using the PASS 11 software program based on a 2-sided, 1-sample log-rank test. Assuming an axillary pCR rate of 40%, a total sample size of 230 (which includes 127 subjects with residual axillary disease and considers a 5% dropout rate) achieves 91% power to detect a change in sensitivity from 0.9 to 0.97, using a 2-sided binomial test. The 2-sided target significance level was set at $P < 0.05$.

The TAD procedure was considered successful if at least 1 lymph node (SLN and/or WLN) could be identified. The identification rate (IR) was defined as the number of successful procedures divided by the total number of patients in whom the procedure was attempted. FNR was defined as the number of FN divided by the total number of patients with residual axillary disease (FN/ [FN + TP]). NPV was defined as the number of TN divided by the total number of patients with a negative test result (TN/ [TN + FN]). All analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). All statistical tests were 2-sided, and *P*-values of < 0.05 were considered statistically significant. Descriptive analyses were used to calculate the identification rates for the different procedures. Contingency tables were constructed to determine the FNRs and NPVs for different parameters.

Results

Between September 2018 and February 2022, 233 patients provided informed consent and were enrolled in the study. 25 patients were later excluded, and 208 patients underwent SLNB and WLNB followed by completion of ALND (for details, see the study flowchart, Fig. 1). The median age was 51 years (27–69 years), and 165 patients (79.3%) had T1-2 tumors. The approximated breast cancer subtype was derived from estrogen and progesterone receptors and the HER2 status. and used to classify cases into the following categories: HER2-positive, triple-negative (estrogen and progesterone receptors and HER2 negative), and hormone receptor (HR)-positive and HER2-negative. The most frequent tumor subtypes were HR-positive and HER2-negative (105/208). The patient and tumor characteristics are summarized in Table 1. The overall rate of axillary pCR (ypN0) was 44.2% (92 208; 95% CI 37.5–51.0%). The axillary pCR rate differed by subtype: 18.1% (19 of 105; 95% CI 10.7–25.5%) for HR-positive/HER2-negative, 80.8% (59 of 73; 95% CI 71.8–89.8%) for HER2-positive breast cancer, and 46.7% (14 of 30; 95% CI 28.8–64.6%) for triple-negative breast cancer (chi-square = 68.77, $P < 0.001$). Among the 116 patients with nodal non-pCR, residual disease was only found in the biopsied SLNs and/or WLNs in 38 patients (32.8%), and additional residual disease was found in the ALND specimen in 78 patients (67.2%).

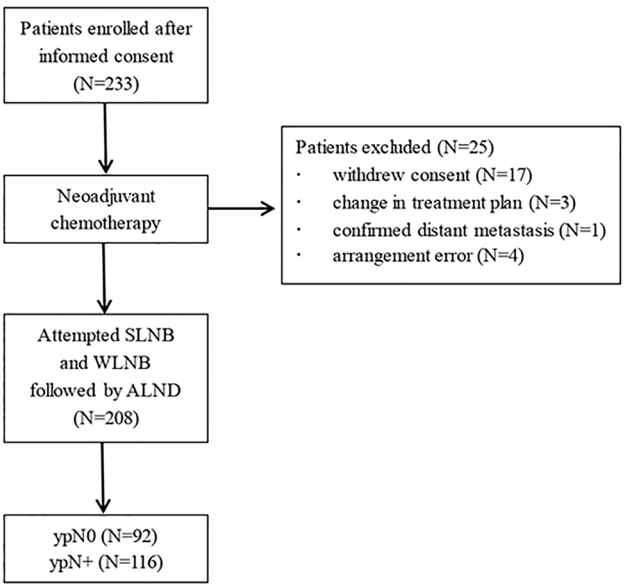

Fig. 1 Study flowchart

Table 1 Patient and tumor characteristics

Characteristic	No. (%)
Median age (range)	51 (27–69)
Tumor type	
IDC	195 (93.8)
ILC	6 (2.9)
Others	7 (3.4)
T stage	
T1–2	165 (79.3)
T3–4	43 (20.7)
Initial clinical stage	
II	150 (72.1)
III	58 (27.9)
Surgery	
BCT	58 (27.9)
Mastectomy	150 (72.1)
Method of pretreatment lymph node biopsy	
Core needle biopsy	182 (87.5)
Fine needle cytology	26 (12.5)
Subtype	
HR + /HER2-	105 (50.5)
HER2 +	73 (35.1)
TNBC	30 (14.4)
Lymph node status after NACT	
Nodal pCR	92 (44.2)
Node positive	116 (55.8)
Nodal ultrasound response evaluation after NAC	
Node positive	120 (57.7)
Node negative	88 (42.3)
Number of SLNs retrieved	
1–2	64 (30.8)
≥ 3	67 (32.2)
Visualization failure	77 (37.0)

HR hormone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *pCR* pathologic complete response

SLNB

SLNB was successful in 131 of 208 patients (63.0%). The median number of SLNs that were removed was 3. In 12 patients, no residual axillary disease was found in the SLN(s), while residual axillary disease was found in WLNB and/or completion ALND. This yielded an FNR of 17.1% (12 of 70; 95% CI 8.2–25.6%) and an NPV of 83.3% (60 of 72; 95% CI 74.7–91.9%) (Table 2).

WLNB

WLNB was successful in 147 of the 208 patients (70.7%) (Fig. 2). In the remaining patients, it was difficult to correctly locate the clipped node with preoperative US-guided wire location. The localization wire was not deployed in 9 patients (4.3%) because of the inability to identify the clip with ultrasound. A localization wire was deployed in 52 patients (25.0%), but radiography failed to locate the clip within the WLN. In 6 patients, no residual axillary disease was found in the WLNB, whereas residual axillary disease was found in the SLN(s) and/or completion ALND. This yielded an FNR of 6.7% (6 of 89; 95% CI 1.5–12.0%) and an NPV of 90.6% (58 of 64; 95% CI 83.5–97.7%) (Table 2).

TAD (SLNB and/or WLNB)

TAD was successful in 182 of 208 patients (at least one SLN and/or WLN was identified), resulting in an identification rate of 87.5%. In 7 patients, no residual axillary disease was found in the SLN(s) or WLNB, whereas residual axillary disease was found in the completed ALND. This yielded an FNR of 6.9% (7 of 101; 95% CI 2.0–11.8%) and an NPV of 92.0% (81 of 88; 95% CI:86.3–97.7%) (Table 2). Both SLNB and WLNB were successful in 96 of 208 patients (46.2%), and the wire-localized node was also an SLN in 76 of 96 patients (79.2%). In 2 patients, no residual axillary disease was found in the SLN(s) or WLNB, whereas residual

Table 2 Identification rates, false negative rates and negative predictive values of SLNB, WLNB and the combined procedure (TAD)

	IR		FNR		NPV	
	%	95% CI	%	95% CI	%	95% CI
SLNB	63.0 (131/208)	56.4–69.6	17.1 (12/70)	8.2–25.6	83.3 (60/72)	74.7–91.9
WLNB	70.7 (147/208)	64.5–76.9	6.7 (6/89)	1.5–12.0	90.6 (58/64)	83.5–97.7
TAD (SLNB and/or WLNB successful)	87.5 (182/208)	83.0–92.0	6.9 (7/101)	2.0–11.8	92.0 (81/88)	86.3–97.7
SLNB and WLNB both successful	46.2 (96/208)	39.4–53.0	3.4 (2/58)	0.1–8.1	95.0 (38/40)	88.2–99.9

SLNB sentinel lymph node biopsy, *WLNB* wire localized lymph node biopsy, *TAD* targeted axillary dissection

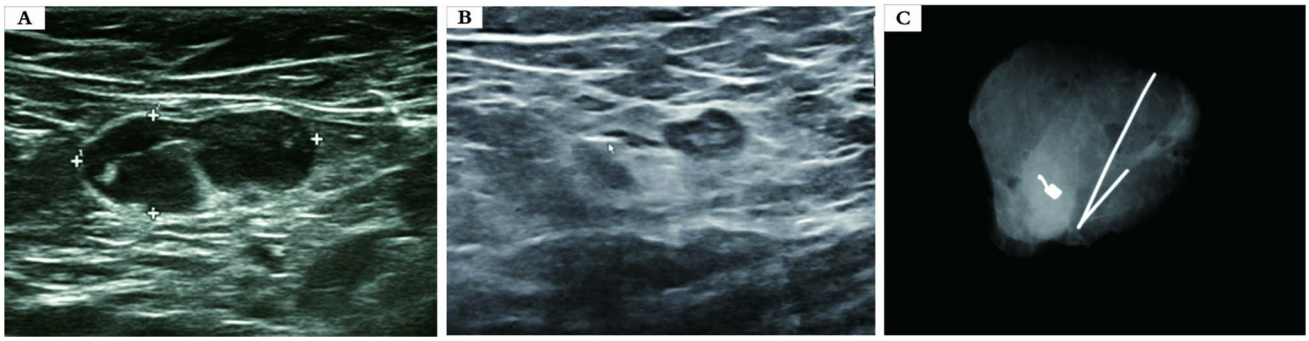

Fig. 2 Ultrasonographic images of lymph nodes before and after neoadjuvant chemotherapy (NACT) and intraoperative radiography showing both the clip and the localization wire from the same patient. **A** Ultrasonographic image of a metastatic lymph node confirmed by pathology before NACT. **B** Ultrasonographic images of the same lymph node after neoadjuvant chemotherapy Arrow indicates the clip. **C** Intraoperative radiography showing both the clip and the localization wire

axillary disease was found in the completed ALND. This yielded an FNR of 3.4% (2 of 58; 95% CI 0.1–8.1%) and an NPV of 95.0% (38 of 40; 95% CI 88.2–99.9%) (Table 2).

An axillary ultrasound examination was performed in all patients before the initiation of treatment and after NACT. An ultrasonographic complete response of the lymph nodes was observed in 88 patients (42.3%). The final pathological examination revealed an axillary pCR in 43 of 88 patients (48.9%; 95% CI 38.5–59.3%). The diagnostic performance of TAD according to tumor subtype, number of SLNs retrieved, and nodal ultrasound response evaluation after NAC was calculated and is shown in Table 3.

Discussion

Our results indicate that the diagnostic accuracy of SLNB combined with WLNB is comparable to that of the RISAS trial. For patients with at least 1 SLN and/or WLN identified, the FNR was 6.9%, which is below the clinically acceptable threshold of 10%. No additional use of radioactive seeds was involved in our TAD method, making it ideal for institutions with limited access to radioactive seeds.

The management of the axilla in patients with breast cancer has evolved dramatically in recent years toward less invasive surgery. Conventional SLNB was less reliable in the post-NACT era. Targeted removal of biopsy-proven positive lymph node has been shown to increase the accuracy of nodal evaluation, and different methods of marking and localizing of the index node have been studied [8, 11]. Recently, the results of a prospective multicenter RISAS trial have been published [12]. The marked MARI nodes and SLNs were removed and examined, followed by ALND. The FNR of the RISAS procedure was 3.5% and the NPV was 92.8%. Although these results are promising, radioactive 125-iodine seeds are a radiation source and strict radioactive material handling and disposal regulations are major drawbacks to radioactive seed localization in many countries worldwide. A simple alternative may be wire localization of the clipped node. Wire localization is a straightforward and

Table 3 Identification rate and accuracy of the TAD procedure by subgroup

	IR		FNR		NPV	
	%	95% CI	%	95% CI	%	95% CI
Subtype						
HR + /HER2−	88.6 (93/105)	82.5–94.7	6.7 (5/75)	1.0–12.4	78.3 (18/23)	61.5–95.1
HER2 +	87.7 (64/73)	80.2–95.2	9.1 (1/11)	0.1–26.1	98.1 (53/54)	94.5–99.9
TNBC	83.3 (25/30)	70.0–96.6	6.7 (1/15)	0.1–19.4	90.1(10/11)	72.5–99.9
Number of SLNs retrieved						
1–2	–	–	11.1 (4/36)	0.8–21.4	87.5 (28/32)	76.0–99.0
≥ 3	–	–	2.9 (1/34)	0.1–8.5	97.1 (33/34)	91.5–99.9
Nodal ultrasound response evaluation after NACT						
Node positive	90.0 (108/120)	84.6–95.4	7.7 (5/65)	1.2–14.2	89.6 (43/48)	81.0–98.2
Node negative	84.1 (74/88)	76.5–91.7	5.6 (2/36)	0.1–13.1	95.0 (38/40)	88.2–99.9

HR hormone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *NACT* neoadjuvant chemotherapy

safe technique that is routinely used for targeted removal of non-palpable breast lesions. Previous studies have employed wire localization and reported high clipped node identification and removal rates [13–16]. However, most of the existing studies were retrospective in design and included only a limited number of patients. Many of these studies aimed to report the feasibility and initial experiences with TAD but not the accuracy of the procedure; only a few studies have performed complementary ALND as the gold standard, which enables the calculation of the FNR and NPV [15, 17, 18]. The FNR is an important measure of accuracy; it is essential that an acceptably low FNR is demonstrated before TAD becomes the standard procedure. A high NPV is also important, because leaving the residual tumor behind may lead to undertreatment of the axilla. Moreover, studies have shown that some non-pCR patients may benefit from additional adjuvant treatment with capecitabine or trastuzumab emtansine (T-DM1) [19, 20], and missing any residual disease can negatively affect their outcomes.

We noted that patients with both successful SLNB and WLNB, those with HER2-positive tumors, and those with complete ultrasonographic nodal remission had high NPVs (95% or higher). The negative predictive value is affected by both the false-negative and population positivity rates. From an oncological safety perspective, a low FNR is essential if the lymph node positivity rate is high. However, if the lymph node positivity rate is low, then the required FNR may be more flexible. For these patients, the risk of leaving any residual tumor behind after a negative TAD is very low: approximately 1 in every 50 patients for the HER2-positive subtype, approximately 1 in every 20 patients for those in whom both SLNB and WLNB are successful, and those with ultrasonographic nodal complete remission. Based on our observations, we believe that these patients are appropriate candidates for TAD after NACT.

The present study adopted a similar design to that of the RISAS trial but used wire localization to retrieve clip-marked nodes. The FNR and NPV of our TAD procedure, which consisted of the removal of the clipped node with wire localization together with the SLNs, were similar to those of the RISAS trial. However, the identification rate of WLN (70.7%) in our study was significantly lower in comparison to the identification rate of MARI nodes in the RISAS trial (94.1%). Similar low IRs were reported in previous studies using wire localization [18, 21, 22]. Together with our results, a similar identification rate of approximately 70% was observed across studies using wire localization, which was lower than the IR of approximately 90% obtained using radioactive seeds. The lower IR raises concerns regarding clip visibility after NACT, and the non-visibility of the clip after NACT is regarded as a major technical pitfall in this practice [18]. Adjustments in the technique and the implementation of new clip devices with better sonographic visibility are of great importance. Some researchers have turned to alternative marking methods, and the use of wire-free and radiation-free localization devices has shown promising results [23–26].

Our study had several strengths and limitations. One of the strengths of this study was the standardization of treatment procedures. The design of the study allowed the evaluation of the FNR and NPV. We used strict criteria to confirm the successful retrieval of clipped nodes. Our overall SLNB identification rate of 63.0% was lower than that reported in other studies that reported SLNB in node-positive patients after NACT. We acknowledge that if we had used a dual-tracer method, our IR would have been higher. It has recently been clarified that a dual-tracer method should be used after NACT to minimize false negatives and non-IRs when sampling the axilla [27]. However, when the current study was designed, the use of blue dye was considered optional [5]. This study was also limited to a single comprehensive cancer institution with dedicated breast surgeons with considerable expertise in ultrasonography. In our study, the wires were placed under ultrasound guidance in the operating room after general anesthesia. This eliminates the discomfort of the patient while wearing the wire and minimizes the risk of potential wire displacement. Studies reported high successful identification rates usually have the localization wires placed by experienced radiologists before surgery [16, 17]. This involves extra scheduling with radiologists and will increase the overall cost and impact workflow, especially in high-volume centers such as ours. The issue of interobserver variability may also be considered a limitation and is difficult to overcome; however, it may increase the generalizability of these results in a real-world environment. Finally, the actual dropout rate in our study was higher than that expected. We performed a post hoc power analysis, and the post hoc power of the study was 0.863, which may be considered acceptable.

In conclusion, the diagnostic performance of TAD using wire localization was similar to that of the procedure performed using radioactive seed localization. TAD using wire localization is recommended in institutions with limited access to radioactive seeds. There are some technical difficulties associated with clip visualization after NACT, but we believe these technical difficulties should not preclude its clinical use, because it can potentially spare patients from the default treatment of ALND.

Author contributions WXG, ZQJ, HYJ, OYT, and FZQ were involved in the study design, data collection and analysis, interpretation of results, manuscript writing, and the decision to submit the manuscript. HL and ZN performed the ultrasound, interpreted the ultrasonographic results, wrote the manuscript, and decided to submit the manuscript. LYQ, WTF, XYT, and LJF were involved in study design, manuscript writing, and the decision to submit the manuscript.

Funding This work was supported by Capital's Funds for Health Improvement and Research (Code: 2018-2-2152) and Beijing Hospitals Authority Clinical Medicine Development of Special Funding (Code: YGLX202334).

Data availability The datasets generated and/or analyzed in this study can be made available upon reasonable request. Please contact the corresponding author for additional information.

Declarations

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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