Original Article

Specimen number based diagnostic yields of suspicious axillary lymph nodes in core biopsy in breast cancer: clinical implications from a prospective exploratory study

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Background: Ultrasound (US)-guided core needle biopsy (CNB) is widely applied in the pathological diagnosis of suspicious axillary lymph nodes (ALNs) in breast cancer. However, the number of specimens removed during biopsy is currently based on the preference of the individual radiologist. This study aims to analyze the specimen number based diagnostic yields of US guided CNB of suspicious ALNs in breast cancer.

Methods: Core biopsy specimens of suspicious lymph nodes were prospectively obtained from breast cancer patients treated at our hospital between November, 2018, and July, 2019. Four specimens were obtained from each patient and labeled 1–4 in the order they were removed. Each specimen underwent pathological evaluation to determine whether metastasis had occurred. The diagnostic yields of the specimens were calculated and differences in diagnostic accuracy according to the number of specimens were evaluated by McNemar's test.

Results: A total of 167 patients were enrolled, and 139 (83.2%) cases were identified as metastasis by CNB. The diagnostic yields were: 74.2% (specimen 1), 87.8% (specimens 1–2), 91.2% (specimens 1–3), and 94.6% (specimens 1–4). The increases in diagnostic yield from specimen 1 to 1–2 and from specimens 1–2 to 1–4 were significant; however, no significant differences were detected between specimens 1–3 and the first two, or between specimens 1–4 and the first three in this sample size. The lower diagnostic abilities for the first two specimens were associated with shorter long- and short-axis lengths of lymph nodes on US.

Conclusions: Although the second specimen contributed significant diagnostic yield of suspicious axillary lymph nodes in core biopsy in breast cancer, a minimum number cannot be determined by this study. Additional specimens may improve diagnostic yield particularly in patients with small nodes.

Keywords: Breast cancer; axillary lymph node (ALN); ultrasound (US); core needle biopsy (CNB); specimen

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Introduction

Preoperative evaluation of axillary lymph node (ALN) status in patients with non-metastatic breast cancer is crucial in informing clinical decisions on the appropriate type of axillary surgery (1,2). Patients with no clinical evidence of metastatic ALNs upon initial diagnosis are first recommended to undergo sentinel lymph node biopsy (SLNB), while patients with positive ALNs who have not received neoadjuvant therapy before surgery generally undergo ALN dissection (3,4). In general, if ALN metastasis is suspected, specimens should be obtained for pathological diagnosis before surgery, using imaging modalities such as ultrasound (US)-guided core needle biopsy (CNB) or fine needle aspiration (FNA), to determine whether the cancer has metastasized (5-7). US-guided CNB has been demonstrated to have higher sensitivity than FNA and is less operator dependent (8,9). Previous studies have reported the sensitivity of CNB to range from 83.4% to 94% for the diagnosis of metastatic ALNs (8-11). However, the number of core specimens taken during CNB currently depends on the preference of the individual radiologist and has been reported to range from one to six (8,10,12). Obtaining a sufficient but not excessive number of specimens can ensure a good diagnostic performance while shortening the procedure time and minimizing the risk of complications. However, due to a lack of clinical evidence, no consensus on the ideal number of US-guided CNB specimens required to make an adequate pathological diagnosis of ALN status with minimal puncture currently exists. This prospective study therefore aimed to analyze the diagnostic ability of different numbers of US-guided CNB specimens of suspicious ALNs in patients with newly diagnosed breast cancer.

Methods

Patients

All female patients with newly diagnosed non-metastatic breast cancer with ipsilateral abnormal ALN imaging on US between November, 2018, and July, 2019 in Sun Yat-sen Memorial Hospital, were invited to participate in our study. Chest X-ray, abdominal US examination and blood tumor markers test were performed to exclude breast cancer metastases to other organs, further CT/MRI scan would be performed if suspicious finding presents. The inclusion criteria were as follows: (I) female older than 18 years; (II) patients with primary breast cancer; (III) suspicious ALN on US; (IV) received a successful CNB of the suspicious ALN. The exclusion criteria were as follows: (I) patients who could not provide informed consent or for whom CNB was considered unsafe; (II) previous ipsilateral axillary surgery; (III) no metastasis on CNB and no further axillary surgery in our hospital; (IV) CNB based on a false-positive axillary US assessment. Trial Registration: Chinese Clinical Trial Registry (ChiCTR) (http://www.chictr.org.cn), ChiCTR1800020204.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This prospective study was approved by the institutional ethics committee of Sun Yat-sen Memorial Hospital (No. 2018-44). All study participants gave written informed consent, and the data were de-identified.

US and biopsy

Preoperative axillary US was performed at the same time as breast US, in line with routine practice in our center. All axillary US examinations and biopsies were performed by one of three dedicated breast radiologists (Y.H., R.G., and F.T.L.), who each have 5–10 years' experience in breast radiology and interventions.

Each examination was performed using a high-resolution US unit (S2000/S1000/Oxana 2; Siemens, Erlangen, Germany; or HS70A; Samsung, Hongcheon-gun, South Korea) with a high-frequency linear transducer. Real-time US was performed and interpreted by the same radiologist, according to usual practice in our center (13). Real-time scanning can help true cortical thickening of a lymph node to be distinguished (14) and has been used in previous studies (15,16). During scanning, special attention was given to the axillary tail area (17,18).

Suspicious ALNs were identified on US according to the following criteria, based on published studies: cortical thickening (>3 mm) or an eccentric cortex; compression or displacement of the fatty hilum; a round or irregular shape; no circumscribed margin; and non-hilar blood flow to the cortex (14,17-20). The differences in US features between suspicious and contralateral ALNs were also an important reference (14). Lymph nodes that did not meet any of these criteria were assessed as negative. The original report documented the detailed features and representative images were obtained.

Patients with abnormal lymph nodes subsequently underwent CNB, patients without abnormal nodes directly underwent SLNB. If more than one abnormal node was

present, the most suspicious node was selected for CNB at the discretion of the radiologist performing the procedure. A core biopsy instrument with a 22-mm throw (Bard Max-Core; Bard Biopsy Systems, AZ, USA) was used to obtain a 14-gauge CNB from the target ALN. The peripheral cortex was targeted specifically, and color Doppler US was used to avoid any large vessels (17). For each lymph node, 4 core specimens (labeled specimens 1–4 in the order of removal) longer than 5 mm and including solid tissue containing no macroscopic fat were removed from different angles, which is the usual practice in our center. All US images of CNB-negative cases were reviewed retrospectively in a non-blinded fashion by all three dedicated breast radiologists to determine if the original axillary US assessment might have been falsely positive.

Histopathological evaluation

The four CNB specimens from the same lymph node were stained immediately with tissue marking dye in four different colors (red, blue, green and black, respectively; Davidson Marking System; Bradley Products, MN, USA) and then placed into 10% neutral formalin. The specimens were stained with the different colored dyes at random, and the pathological diagnosis was not affected by the color of the dye (21). After fixation, the specimens were processed, as closely as possible and without overlap, into a single paraffin block, according to standard protocols (22). Uniform pressure was put on the specimens with a tamper so that all four were embedded in the paraffin at the same depth. One microtome section level (encompassing all four cores) was then subjected to standard histopathological examination using hematoxylin-eosin (HE) staining (22,23). If suspicious cells of uncertain nature were identified, immunohistochemical staining was carried out using the broad-spectrum cytokeratin antibody AE1/3 (FLEX Monoclonal Mouse Anti-Human Cytokeratin, Clone AE1/AE3, Ready-to-Use, Dako, CA, USA). The pathologists were blinded to the order of the colors. The four core specimens for each case were evaluated for the presence of metastasis by two pathologists (J.J.Z. and J.J.Y.), who made their diagnoses independently. A positive pathological diagnosis was considered when macro-metastasis or micro-metastasis was present in the ALN, while the presence of isolated tumor cells represented a negative result. Patients with negative CNB results subsequently underwent SLNB to confirm the ALN status (*Figure 1*).

Statistical analysis

The primary outcome was diagnostic yield based on the number of CNB specimens (specimen number-specific yield). The secondary outcome was the correlation between the diagnostic ability of the first two specimens and clinical and US characteristics. Specimen number-specific sensitivity (diagnostic yield), specificity, accuracy, and positive and negative predictive values were calculated for CNB. Cases were finally defined as positive if metastasis was found in the lymph nodes (either by CNB or subsequent surgical biopsy). True-positivity of combined CNB specimens was defined as any of the combined cores presenting a positive diagnosis.

All statistical analyses were performed using SPSS, version 19 (IBM, Chicago, IL, USA). McNemar's test was used to evaluate significant differences between the specimen number-specific yields of CNB with respect to the final result. Continuous and categorical variables were evaluated by independent samples *t*-test and χ^2 test, respectively. $P<0.05$ was considered to indicate a significant difference.

Results

Patient characteristics

Between November, 2018, and July, 2019, 192 female patients with newly diagnosed breast cancer and ipsilateral abnormal ALN imaging on US were initially recruited. Twenty-five patients were excluded due to undergoing ipsilateral axillary surgery (n=15), having no available data on pathological diagnosis for each CNB specimen (n=4), having a negative CNB result but no subsequent open surgery performed in our hospital (n=4), or having a negative CNB result based on a false-positive US assessment pre-CNB (n=2). Finally, 167 patients (mean age: 50.2± 10.4 years, range, 26–88 years) with 167 CNBs were included in the analysis (*Figure 2*). *Table 1* shows the patients' demographic information and characteristics. No severe CNB-related complications were observed. Four patients experienced transient sharp pain, which was controlled by extra local anesthesia. Two patients experienced bleeding, which was stopped by direct compression.

Of the 167 eligible and evaluable patients, 139 (83.2%) were identified as positive for lymph node metastasis by CNB. Among these patients, 109 cases were diagnosed as metastasis based on the first specimen, 129 cases based on the first two specimens, 134 and 139 cases based on

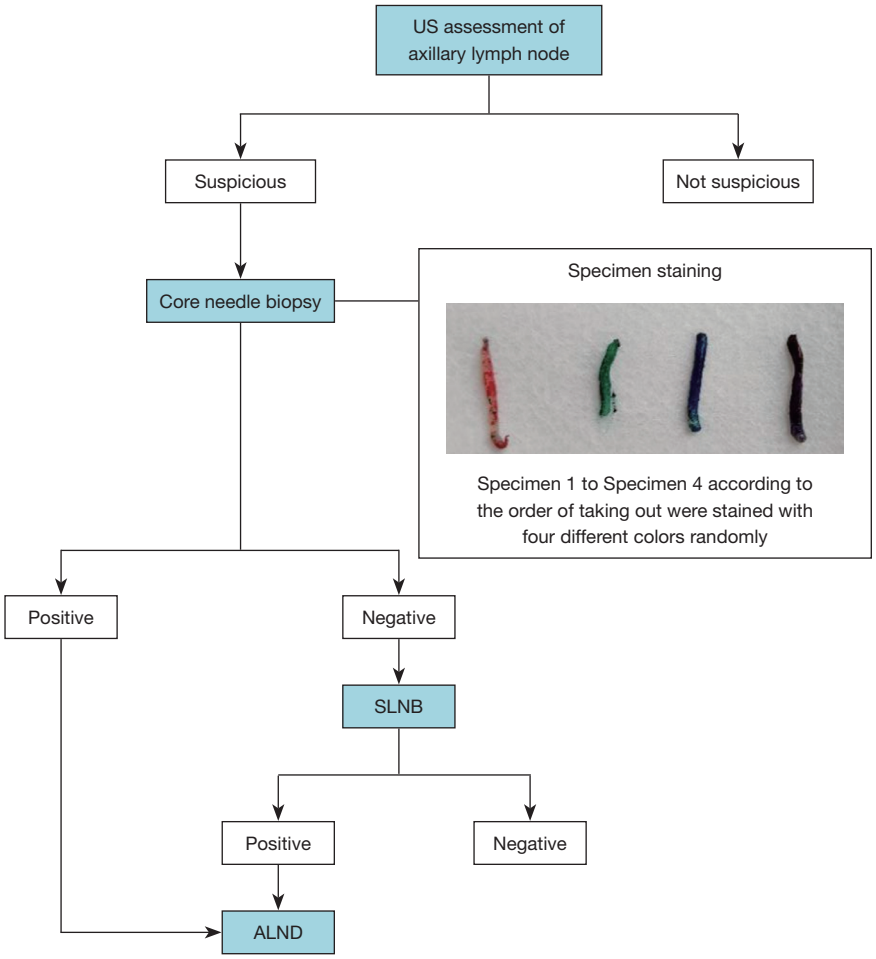

Figure 1 Algorithm for axillary staging. US, ultrasound; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

the first three and all four specimens, respectively. Of the 139 patients, 124 underwent open surgery and 79 received preoperative neoadjuvant chemotherapy (NAC).

Of the 28 (16.8%) patients with a CNB-negative diagnosis, 17 were assigned directly to open surgery, 6 of whom were identified with positive lymph nodes. The remaining 11 of the 28 patients underwent NAC followed by open surgery, and 2 patients were finally identified with positive lymph nodes (*Figure 2*).

Specimen number-specific diagnostic performance

The diagnostic performance according to the number of specimens is shown in *Table 2*. Metastasis was detected in 438 (74.5%) of the 588 CNB specimens obtained from the 147 patients who were ultimately found to have positive ALNs. The sensitivity of specimens 1, 2, 3, and 4 was 74.2% (109/147), 76.2% (112/147), 71.4% (105/147), and 76.2% (112/147), respectively. No significant differences were detected between the four specimens in terms of sensitivity (all P>0.05). The sensitivity of the first two specimens [1–2] was significantly higher than that of the first specimen (87.8% *vs.*74.2%, P<0.001). Albeit no significant differences were detected between the sensitivity of the first three specimens [1–3] versus the first two [1–2], or between all four specimens [1–4] versus the first three [1–3] (91.2% *vs.* 87.8% and 94.6% *vs.* 91.2%, respectively, both P=0.06). The sensitivity of all four specimens [1–4] was significantly higher than that of the first two [1–2] (94.6% *vs.* 87.8%, P=0.002). The specificity was 100% for all specimens, with no CNB false-positive cases.

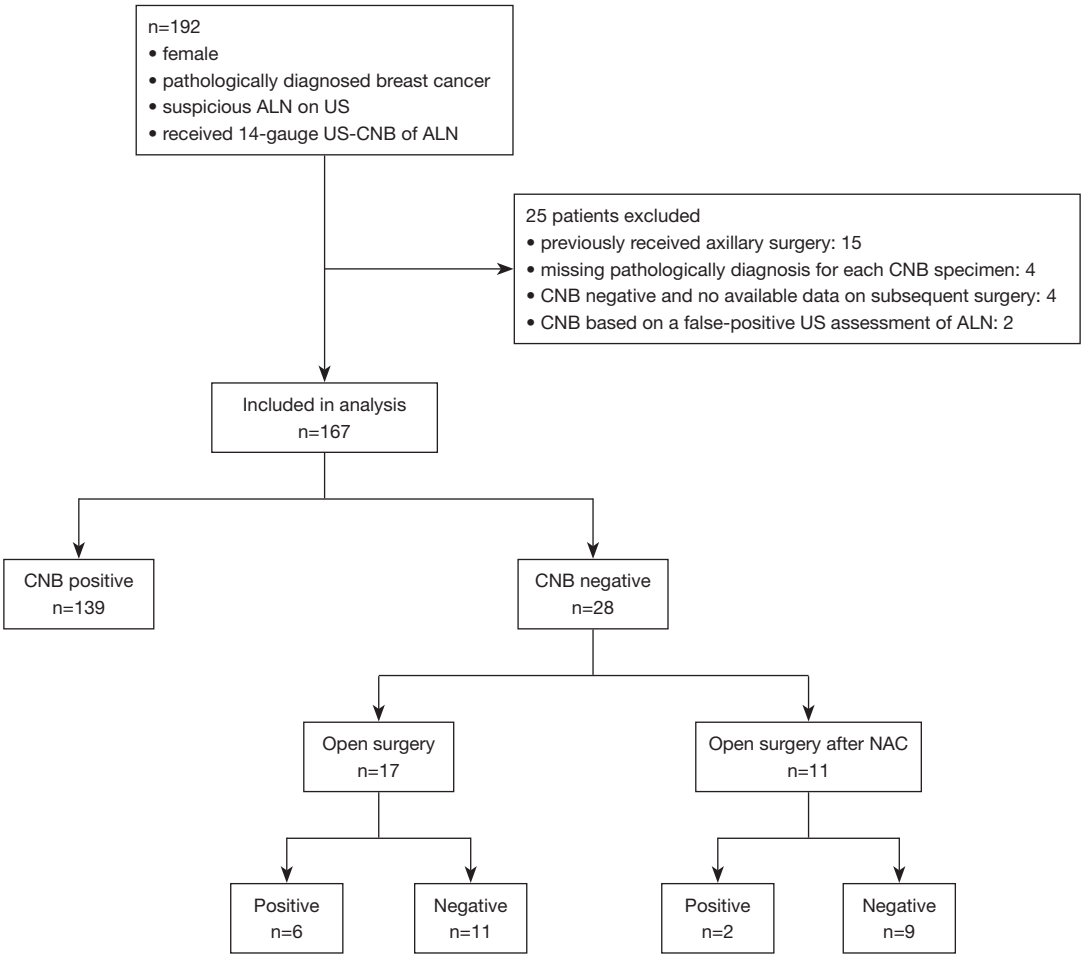

Figure 2 Flowchart of patients. ALN, axillary lymph node; US, ultrasound; CNB, core needle biopsy; NAC, neoadjuvant chemotherapy.

Predictors of requirement for two more CNB specimens

Among the 147 cases finally diagnosed as ALN-positive, shorter long- and short-axis lengths of the targeted lymph node on US were associated with a false-negative diagnosis based on the first two specimens (both P<0.001). *Figure 3* shows a representative case. Other characteristics on US (tumor size, number of suspicious ALNs, shape and margin of the ALN, cortex, hilar status, and blood flow of the ALN), the patient's age, tumor characteristics obtained by preoperative biopsy (pathology type, grade, hormone receptor, Ki67, and HER2 status), and N stage after surgery had no significant effect (all P>0.05) (*Table 3*). Due to the relatively small number of false-negative results based on the first two specimens (18 cases), further multivariable analysis was not performed.

Discussion

This study found that the second specimen contributed significant diagnostic yield of suspicious axillary lymph nodes in core biopsy in breast cancer and additional cores may improve diagnostic yield particularly in patients with small nodes.

US-guided biopsy plays a pivotal role in the preoperative identification of breast cancer and ALN involvement (5). Approximately 50% of breast cancer patients with ALN metastasis can be identified preoperatively by US combined with US-guided biopsy if ALN was assessed as abnormal (24). US-guided CNB has a lower false-negative rate (FNR) than FNA and has been proved to be safe (8,9); consequently, CNB has replaced FNA as the clinically preferred diagnostic method (18), and the most suspicious

Table 1 Patient characteristics for the total cohort

Variable*	No. (%)
Age, median [IQR], years	51 [43–57]
US tumor size	
T1	21 (12.8)
T2	90 (54.9)
T3	53 (32.3)
US no. of suspicious LN	
≤3	101 (62)
≥4	62 (38)
US long-axis of LN, cm	
≤1	24 (14.5)
1–2	79 (47.9)
>2	62 (37.6)
US short-axis of LN, cm	
≤1	88 (53.3)
>1	77 (46.7)
US shape of LN	
Regular	152 (92.1)
Irregular	13 (7.9)
US margin of LN	
Not circumscribed	6 (3.6)
Circumscribed	159 (96.4)
US cortex of LN	
No thickening	5 (3.0)
Thickening	160 (97.0)
US hilum of LN	
Normal	18 (10.9)
Compressed or displaced	147 (89.1)
US blood flow of LN	
Without NHBF	113(68.5)
NHBF	52 (31.5)
Tumor pathology‡	
Invasive ductal cancer	135 (80.8)
Other	32 (19.2)
Tumor grade‡	
I	1 (0.9)
II	39 (36.1)
III	68 (63.0)
Hormone receptor status‡	
Positive	104 (73.2)
Negative	38 (26.8)
Ki67 status‡¦	
High	107 (74.8)
Low	36 (25.2)
HER2 status‡	
Positive	51 (39.8)
Negative	77 (60.2)
N stage‡	
N0	44 (28.9)
N1	48 (31.6)
N2	34 (22.4)
N3	26 (17.1)

Values in parentheses are percentages unless indicated otherwise. *, some data are missing; ‡, data were obtained from surgery specimens; ¦, cut-off point 14%. IQR, interquartile range; US, ultrasound; LN, lymph node; NHBF, nonhilar blood flow; HER2, human epidermal growth factor receptor 2.

node was usually selected for CNB considering the cost of biopsy instruments and the risk of complications. To the best of our knowledge, however, a consensus regarding the ideal number of specimens that should be obtained by US-guided CNB for abnormal ALNs in breast cancer patients has yet to be reached. Obtaining a sufficient but not excessive number of specimens carries the advantages of shortening the procedure time, minimizing complications, and ensuring a good diagnostic performance.

Previous studies have reported numbers of core specimens taken during CNB ranging from one to six, depending on the preference of the individual radiologist (8,10,12). Although Macaskill *et al.* (12) analyzed the diagnostic accuracy based on the number of specimens,

Table 2 Diagnostic performance of different numbers of specimens for evaluating axillary lymph node metastasis

Measure	Specimen 1 (%)	Specimen 1–2 (%)	Specimen 1–3 (%)	Specimen 1–4 (%)
Sensitivity	74.2 (109/147) (66.3–81.0)	87.8 (129/147) (81.3–92.6)	91.2 (134/147) (85.4-95.2)	94.6 (139/147) (89.6–97.6)
Specificity	100% (20/20) (83.2–100)	100% (20/20) (83.2–100)	100% (20/20) (83.2–100)	100% (20/20) (83.2–100)
Negative predictive value	34.5 (20/58) (22.5–48.1)	52.6 (20/38) (35.8–69.0)	60.6 (20/33) (42.1–77.1)	71.4 (20/28) (51.3–86.8)
Positive predictive value	100% (109/109) (96.7–100)	100% (129/129) (96.7–100)	100% (134/134) (96.7–100)	100% (139/139) (96.7–100)
Accuracy	77.3 (129/167) (70.9–83.7)	89.2 (149/167) (84.5–93.4)	92.2 (154/167) (88.1–96.3)	95.2 (159/167) (92.0–98.4)

Data in parentheses are numbers used to calculate percentages, and data in brackets are 95% confidence intervals.

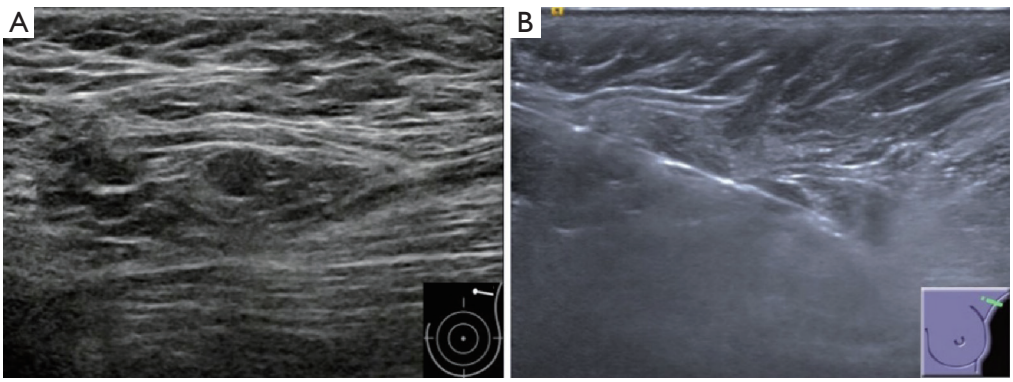

Figure 3 Invasive ductal carcinoma in a 73-year-old woman with a negative result of axillary lymph node CNB but two lymph nodes metastases after surgery. (A) Gray-scale US image of the ipsilateral axilla shows a small (0.7×0.5 cm) suspicious lymph node with an absent fatty hilum. (B) US image obtained post-firing of CNB shows that the needle passes the lymph node precisely, but the visualization of needle may be caused by the artifact from partial volume effects. CNB, core needle biopsy; US, ultrasound.

their study was based on a very small sample size. In the present study, 74.2% (109/147) and 87.8% (129/147) of ALN metastases were diagnosed in the first and first two specimens, respectively, compared with 81.8% (45/55) and 96.4% (53/55), respectively, reported by Macaskill *et al.* (12). Moreover, the diagnostic yield of the first three specimens in their study was 100% (55/55), compared with 91.2% (134/147) in our study. Furthermore, Macaskill *et al.*'s study included only 55 CNB-positive cases with three cores per node, and the other 55 cases were CNB-negative. The apparent differences between our results and those of Macaskill *et al.*'s study may be due to the lower US sensitivity, the smaller sample number of their study, and the different calculation methods used. Five cases were diagnosed with metastasis based on the fourth specimen in our study, with an overall sensitivity for all four specimens of 94.6% (139/147), which was slightly higher than the sensitivity reported in a previous meta-analysis (88%) (9), but similar to that in a study by Abe *et al.* (94%, 64/68) (10).

In this study, the increase (13.6%) in diagnostic sensitivity from specimen 1 to specimen 1–2 was significant, which was similar to the increase reported by Macaskill *et al.* (12). Meanwhile, no significant differences were detected between the sensitivity of specimen 1–3 versus specimen 1–2, or between specimen 1–4 versus specimen 1–3, probably due to insufficient statistical power to detect the differences. Therefore, these nonsignificant findings should be interpreted with caution, further studies with larger sample size are needed to confirm these findings.

Among the preoperative US features and tumor characteristics, shorter long- and short-axis lengths of the suspicious lymph node were associated with the lower diagnostic yields of the first two specimens. This may be related to the difficulty in targeting smaller lesions, which

Table 3 Preoperative patient characteristics and N stage after surgery in the specimens 1–2 true-positive and false-negative groups

Variable*	Specimens 1–2		P value
	True-positive (n=129), No. (%)	False-negative (n=18), No. (%)	
Age (years)	50.3±10.3	51.7±11.2	0.59
US tumor size			0.93
T1	18 (14.2)	2 (11.1)	
T2	70 (55.1)	10 (55.6)	
T3	39 (30.7)	6 (33.3)	
US no. of suspicious LN			0.53
≤3	72 (56.7)	11 (64.7)	
≥4	55 (43.3)	6 (35.3)	
US long-axis of LN, cm			<0.001
≤1	11 (8.7)	7 (38.9)	
1–2	58 (45.7)	9 (50.0)	
>2	58 (45.7)	2 (11.1)	
US short-axis of LN, cm			<0.001
≤1	51 (40.2)	17 (94.4)	
>1	76 (59.8)	1 (5.6)	
US shape of LN			0.37
Regular	114 (86.4)	18 (100)	
Irregular	13 (13.6)	0 (0)	
US margin of LN			1.00
Circumscribed	121 (95.3)	18 (100)	
Not circumscribed	6 (4.7)	0 (0)	
US cortex of LN			0.42
No thickening	3 (2.4)	1 (5.6)	
Thickening	124 (97.6)	17 (94.4)	
US hilar of LN			0.36
Normal	8 (6.3)	2 (11.1)	
Compressed or displaced	119 (93.7)	16 (88.9)	
US blood flow of LN			0.93
Without NHBF	86 (67.7)	12 (66.7)	
NHBF	41 (32.3)	6 (33.3)	
CNB tumor pathology			0.60
Invasive ductal cancer	104 (80.6)	16 (88.9)	
Others	25 (19.4)	2 (11.1)	
CNB tumor grade			1.00
II	54 (67.5)	6 (66.7)	
III	26 (32.5)	3 (33.3)	
CNB hormone receptor status			0.17
Positive	73 (73.0)	14 (93.3)	
Negative	27 (27.0)	1 (6.7)	
CNB Ki67 status‡			0.07
High	97 (98.0)	12 (85.7)	
Low	2 (2.0)	2 (14.3)	
CNB HER2 status			1.00
Positive	39 (41.9)	3 (37.5)	
Negative	54 (58.1)	5 (62.5)	
N stage			0.17
N0	24 (21.1)	0 (0)	
N1	41 (36.0)	7 (38.9)	
N2	28 (24.6)	6 (33.3)	
N3	21 (18.4)	5 (27.8)	

Values in parentheses are percentages unless indicated otherwise. *, some data are missing; ‡, cut-off point 14%. IQR, interquartile range; US, ultrasound; LN, lymph node; NHBF, non-hilar blood flow; CNB, core needle biopsy; HER2, human epidermal growth factor receptor 2.

introduces a greater possibility of sampling error (25,26). Although longitudinal (along the needle) imaging post-firing was used to ensure that the needle passed the lesion, determining this may be subjective and could be affected by partial-volume effects towards the periphery of the lymph node, which has a greater influence in small lesions (26). Visualization by another image in the orthogonal plane before the removal of the needle, as well as validation by three-dimensional US, may help to evaluate the post-firing

needle placement more precisely (26-28). Therefore, in cases with small ALNs at CNB, more specimens are needed to make an accurate diagnosis.

CNB with four specimens failed to achieve a diagnosis in 8 cases (FNR 5.4%, 8/147) that were subsequently confirmed as metastasis after surgery. These false-negative results may be attributable to two main reasons. First, CNB did not precisely target the metastatic deposits in the suspicious ALN, in which case increasing the number of specimens might elevate the possibility of a positive diagnosis by CNB. Second, the ALN targeted by CNB was not the SLN and was non-metastatic; therefore, obtaining more specimens would not reduce the FNR. Previous studies found that only 64–78% of lymph nodes that underwent CNB corresponded with the SLNs removed at surgery (29,30). Precise targeting of the SLN guided by a gamma-probe, contrast-enhanced US, or elastography imaging is a promising method for reducing the CNB FNR (31-33). The negative predictive value of CNB with four specimens in the study was 71.4% (20/28), which suggests that further management of CNB-negative axilla should not be abandoned. Similar to our results, a recent meta-analysis reported that one in four women with a US-guided biopsy-"proven" negative axilla had a positive result after SLN biopsy (24). However, US combined with needle biopsy could serve as a potential alternative to SLN biopsy for axillary staging in selected patients (34,35).

This study had several limitations. First, this is an exploratory study and we didn't define the statistical power and calculate the required sample size due to limited published data, therefore, cautions should be made in interpreting the non-significant findings of specimen 3/4. Second, we did not compare the CNB-sampled and surgically removed ALNs, which creates uncertainty as to how many of the eight lymph nodes from patients with CNB FNRs ultimately had metastasis. Third, 11 of 28 patients with CNB-negative results underwent surgery after NAC, 9 of whom had no evidence of lymph node metastasis; however, some of these patients may have benefitted from NAC and were subsequently mistaken as true-negative cases.

Conclusions

In conclusion, although the second specimen contributed significant diagnostic yield of suspicious axillary lymph nodes in core biopsy in breast cancer, the current findings do not provide data to indicate how many more than two specimens are sufficient. Additional specimens may improve diagnostic yield particularly in patients with small nodes. Further studies with pre-defined statistical power requirement are needed to confirm this observation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1030). The authors have no conflicts of interest to declare.

Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Sun Yat-sen Memorial Hospital (No. 2018-44). Written informed consent was obtained from all study participants.

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