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Fine-needle aspiration cytology versus core needle lymph node biopsy in axillary staging of breast cancer

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Abstract

Background: Axillary lymph node status is an extremely important prognostic factor in evaluating and managing recently diagnosed breast cancer patients. So, preoperative evaluation of the lymph nodes in breast cancer patients with minimally invasive methods is of significant concern. Ultrasonography is the main modality used for this purpose, with advantages including the ability to help to guide the biopsy. This study aimed to compare ultrasound-guided fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) in their ability to detect metastatic disease in the axillary lymph nodes, as well as to estimate the accuracy of preoperative ultrasound-guided axillary lymph node biopsy for staging in patients with breast cancer.

Results: In total, 108 cases were included in the study, and 55.6% (60 cases) had metastases. The sensitivity for FNAC was 83.3%, and the specificity was 100%. The sensitivity for CNB was 100% and the specificity was 100%. The negative predictive value for FNAC was 81.5%, and that for CNB was 100%. The positive predictive value was 100% for both methods.

Conclusions: CNB biopsy shows higher sensitivity and accuracy than FNAC in the characterization of benign and malignant lymph nodes. FNAC is a suitable substitute when a smaller node is encountered, a node in an inaccessible site, or even an uncorrectable bleeding diathesis of the patient.

Keywords: Fine-needle aspiration, Core needle biopsy, Axillary lymph node staging, Ultrasound, Breast cancer

Background

When assessing and treating patients with recently discovered breast cancer, the status of the axillary lymph nodes is a critical prognostic indicator. Axillary lymph node dissection has long served as the gold standard for diagnosis and staging. However, axillary lymph node dissection can result in some postoperative problems, such as arm lymphedema, discomfort, reduction in shoulder range of motion, and arm weakness. Axillary lymph node dissection also yields negative results in more than 80% of patients with T1 stage cancer after the spread mammographic screening [1–3].

Consequently, node dissection has been replaced with sentinel lymph node biopsy (SNB) of axillary lymph nodes. But still some practical problems must be overcome. For instance, pathologists must make quick decisions based on the analysis of frozen sections, radiotracer dispersion that may be sluggish or inaccurate, to avoid wasting important operating theater time and necessitating a second surgery. Therefore, sentinel lymph node biopsy could be skipped and axillary dissection, which is the default method of management for the most of

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node-positive cases, can be performed if nodal positivity could be demonstrated and documented before surgery [4, 5].

Ultrasonography, computed tomography, and magnetic resonance imaging are three minimally invasive modalities of preoperative assessment of axillary lymph node condition in breast cancer patients that are gaining popularity. The primary imaging technique utilized for this purpose is ultrasound (US), which has benefits such as the ability to assist in biopsy guidance [4–6].

Lately, some randomized clinical trials in early breast cancer patients reported the necessity for SNB when ultrasound-guided fine-needle aspiration cytology (FNAC) of suspicious lymph nodes is negative [7–9].

FNAC is valuable for evaluating metastatic disease, with a wide range of sensitivity (44 to 100%). This wide range of sensitivity is likely due to patient selection, and additionally, FNAC is considered to be an operator-dependent technique, requiring both the assistance of skilled cytologists and the operator's experience. Another meta-analysis reported that both procedures offer good accuracy, with each breast center having the option of using either one [10–12].

Our study aimed to compare the accuracy of ultrasound-guided FNAC and CNB in the detection of metastatic axillary lymph nodes in breast cancer patients.

Methods

This prospective study included patients who attended our hospital in the period between October 2018 and October 2021. The inclusion criteria were recently diagnosed patients with breast cancer, regardless of whether lymph nodes are suspicious or not. The exclusion criteria were a) Patients who had previously undergone axillary surgery. b) Patients with metastatic disease and not planned for axillary surgery. c) Patients with a preoperative diagnosis of a benign lesion or ductal carcinoma in situ. d) Patients with severe uncorrectable bleeding diathesis. e) Patients refused to sign consent.

The study comprised 108 patients who met the inclusion requirements. The research was carried out with the Ethical Committee of the Faculty of Medicine's approval (approval no. 17100609) and with the approval of a clinical trial (NCT03681418). Each participant provided written consent after being fully informed.

Techniques for US examination of the axilla

Axillary ultrasound was done using a high-frequency (5–12 MHz) linear-array probe. The patient lay in an oblique supine position. The hand was above the head, and the arm was abducted and externally rotated.

It was crucial to employ low wall filter settings and low-velocity settings when utilizing the color Doppler to identify abnormal cortical blood flow. While preventing color noise artifact, the color gain was sufficient enough to discern minor flow.

The most suspicious node was selected for the biopsy. If all axillary lymph nodes had a normal or similar appearance, the lymph node located at the lowest axilla was selected because it was most probably to be the sentinel node.

Fine-needle aspiration cytology (FNAC) technique

First, the indications and technique of the procedure were mentioned to the patient. In addition, potential complications were discussed, including minor bleeding and infection in the area after the procedure. Then, they were asked to sign an informed consent.

Slides were labeled and arranged, and a suitable fixative (95% alcohol) was made accessible. Next, sterilization was performed on the axillary region, and anesthesia was applied with a 3- or 5-ml syringe of 2% lidocaine.

FNAC was performed with a 22-gauge needle on a 5-mL syringe. The plunger was pulled a ½ mL to apply some negative pressure. Then, under US guidance the needle was directed accordingly to enter the node at its thickest portion of the cortex. The plunger was retracted to create more negative pressure, and short, rapid strokes in various directions (fan-shaped movements) were applied to cause the dislodgement of cells. The aspiration and retraction of the plunger should be undone before the removal of the needle. Between 6 and 20 passes (minimum 2–3 passes) were usually made before the needle was removed or as soon as any material or blood was seen in the hub of the needle. Then the puncture site was compressed with sterile gauze to stop bleeding, and an aid bandage was applied.

After removal of the needle, the aspirate was expelled forcefully onto 2–4 clean dry slides without delay to avoid clotting of the blood within the hub. The needle was detached from the syringe and the plunger was pulled back fully, the needle was reattached and the material was expelled quickly again. Minimal pressure is exerted on the two opposing slides, this pressure should be gentle but firm and uniform to avoid mechanical trauma, create a thin, uniform smear, and retain the morphology of lymphoid cells, which are fragile and easily crushed. Two aspiration samples were performed from the selected lymph node. The smears were processed by wet preparations with 95% ethanol and stained by Papanicolaou stain.

Core needle biopsy (CNB) technique

A radiologist with 22 years of expertise conducting biopsies performed by the core Tru-cut needle. The biopsy needle was semi-automated. This needle can collect a

sample without moving the needle tip from its initial position, allaying worries about injury of nearby axillary vessels, nerves, or other tissues. The axillary core biopsy carried other hazards of bleeding and infection. However, the risk of bleeding and nerve injury can be easily avoided in almost all cases by being aware that the nerves travel alongside the axillary vessels.

The indications and technique of the procedure were mentioned to the patient. In addition, potential complications were discussed, including bleeding and infection in the area after the procedure. Then, they were asked to sign an informed consent. Laboratory evaluation of patient coagulation profile had been checked before the procedure.

The approach to the lymph node was from inferolateral to superomedial direction, if possible, to avoid injury to major vessels and muscles. The targeted lymph node should have been visualized clearly at ultrasound scanning. Color Doppler ultrasound was used to determine if there were large vessels around it, and determine the best approach at the time. After the site of the puncture and the needle approach had been determined, a local anesthetic was injected superficially and then deeply using a 5 ml syringe of 2% lidocaine. The biopsy needle 18- or 16-gauge × 10 cm, according to the size of the lymph node, was then advanced manually under ultrasound guidance with the bevel pointing up to aid penetration. The needle's tip and the targeted lymph node should have been visualized in the same imaging plane but if not or if it seemed that the angle of the needle would miss the target, the angle was adjusted accordingly. Two to three samples were routinely obtained from the node and preserved in a 10% formalin solution for histologic studies which will be embedded in paraffin after fixation. The samples were then cut and stained with Hematoxylin and Eosin. The puncture site was compressed with sterile gauze to stop bleeding and an aid bandage was applied. The specimen must contain a component that tends to sink to the bottom of the container of either white (typically pathogenic) or brown tan (lymph node tissue).

Statistical analysis

Data were collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20). Quantitative data were expressed as mean ± standard deviation (SD) while Nominal data were given as a number (*n*) and percentage (%).

The accuracy of CNB and FNAC in the diagnosis of malignant axillary LNs was determined by the receiver operator characteristics (ROC) curve. The confidence level was kept at 95%; hence, the *P* value was considered significant if less than 0.05.

Results

The age of enrolled patients ranged from 23 to 82 years (mean was 46.09 ± 11.88 years). A Tru-cut needle biopsy was done in only 36 (33.3%) patients, while all patients were subjected to fine-needle aspiration cytology (FNAC).

Nature of the lymph node based on the final histopathology (*N* = 108)

It was found that the majority (55.6%) of lymph nodes were malignant while 48 (44.4%) of nodes had benign features based on the final histopathological evaluation.

Adequacy of sampling of FNAC and Tru-cut needle biopsy

In this study, inadequate sampling was observed in 2 (1.9%) cases with Tru-cut needle biopsy and 4 (3.7%) cases with FNAC (Fig. 1).

Accuracy of FNAC in identifying malignant axillary lymph nodes

FNAC was done in all cases, after the exclusion of the four cases with inadequate sampling, a total of 104 cases were analyzed in Tables 1 and 2. All malignant lesions according to final histopathology were accurately diagnosed by FNAC with exception of 10 cases where FNAC considered them benign lesions (Fig. 2).

Based on ROC curve analysis, it was found that FNAC has 83.3% sensitivity and 100% specificity for the diagnosis of metastatic axillary lymph nodes with an overall accuracy of 91.4% and the area under the curve was 0.92 (Fig. 3).

Accuracy of Tru-cut needle biopsy in identifying malignant axillary lymph nodes:

A Tru-cut needle biopsy was done in only 36 cases, after the exclusion of the two cases with inadequate sampling, a total of 34 cases were analyzed in Tables 3 and 4. All malignant and benign lesions according to final histopathology were accurately diagnosed by the Tru-cut biopsy (Figs. 4 and 5).

Based on ROC curve analysis, it was found that Tru-cut has 100% sensitivity and 100% specificity for the diagnosis of metastatic axillary lymph nodes with an overall accuracy of 100% and the area under the curve was 1 (Fig. 6).

Discussion

The necessity for subsequent surgical operations can be reduced by performing axillary staging by percutaneous preoperative biopsy, and the choice to proceed to the next step can then be made accordingly.

In our study, out of 108 total patients, 60 of them (55.6%) were having metastatic axillary lymph nodes,

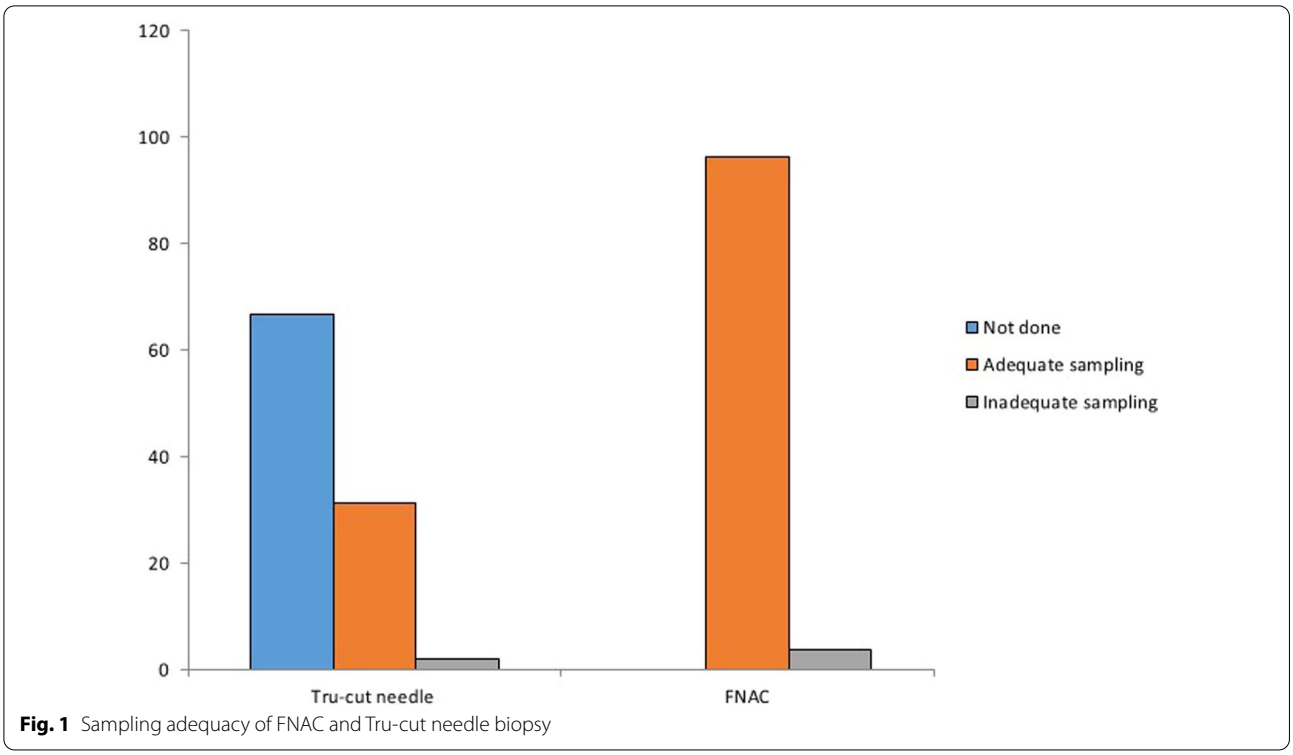

Fig. 1 Sampling adequacy of FNAC and Tru-cut needle biopsy

Table 1 Cross-tabulation between results of FNAC and final histopathology

FNAC	Histopathology		Total
	Malignant	Benign	
Malignant	50	0	50
Benign	10	44	54
Total	60	44	104

Data expressed as frequency

Table 2 Accuracy of FNAC in identifying malignant axillary lymph nodes

Indices	Value
Sensitivity	83.3%
Specificity	100%
Positive predictive value	100%
Negative predictive value	81.5%
Accuracy	90.4%
Area under curve	0.92
P value	< 0.001

and 48 (44.4%) showed benign axillary lymph nodes according to the postoperative final histopathological evaluation. FNAC was performed in all 108 patients, while Tru-cut core needle biopsy was applied to 36 patients (33.3%); this was because either the lymph nodes were small for sampling with Tru-cut needle or they were showing no morphological criteria for malignancy at ultrasound examination, especially those with very thin even cortex, as axillary metastases are typically subcapsular which always the aimed site for sampling.

In this study, we found that preoperative biopsy by either FNAC or CNB is simple, safe, and well tolerated. Our results showed that there were no fatal procedural complications; only 5.5% of the cases developed minimal complications including hematomas which seem to be more common with CNB or bruises and ecchymosis at the site of needle puncture. However, the rate of complications was very low and even if they happened, it seems to be minor and can be managed easily. These results were in agreement with different previous studies which also reported no serious complications at all regarding FNAC and CNB [5, 13].

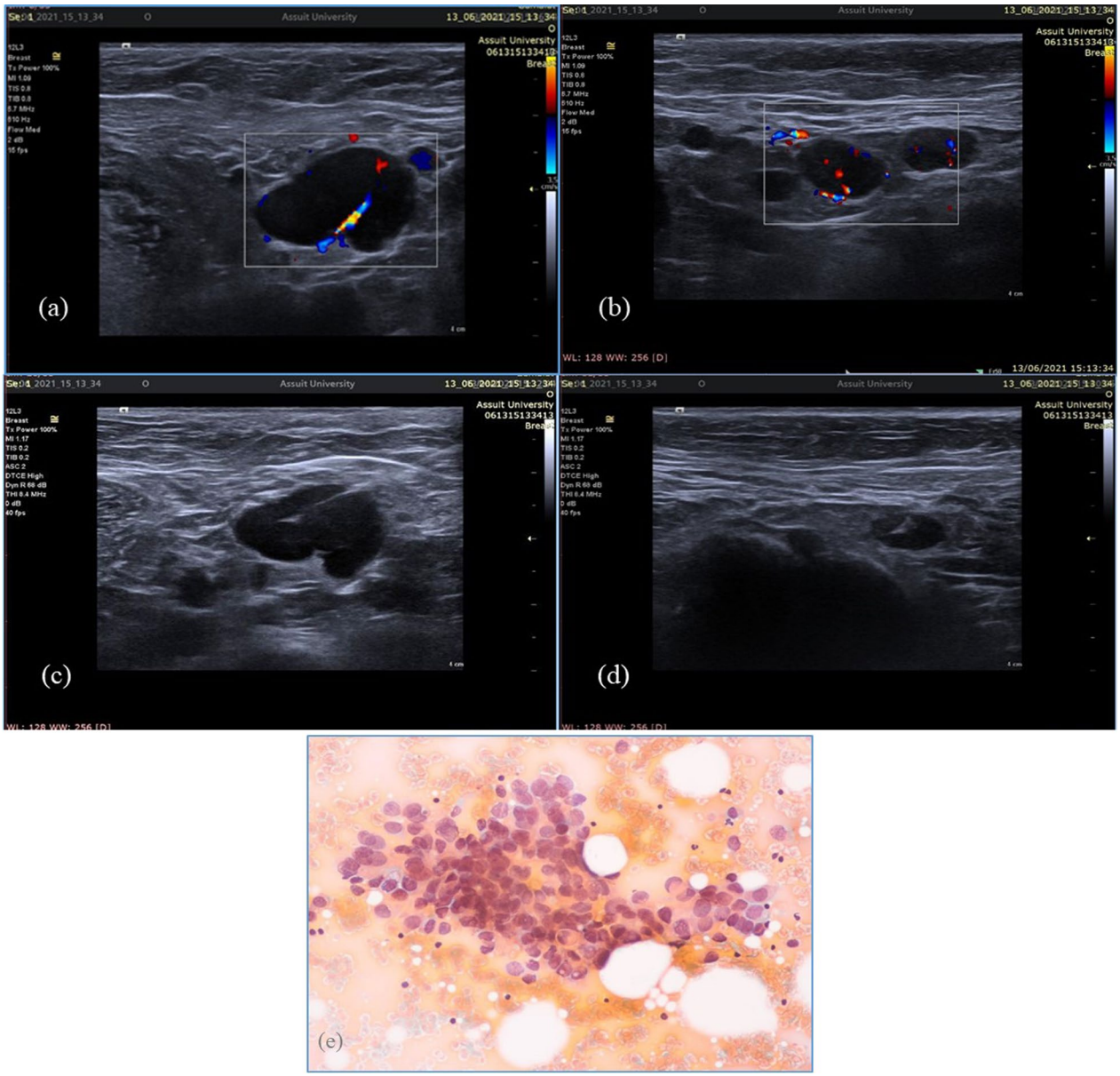

Fig. 2 An 48-year-old female patient, presented with breast cancer, and underwent fine-needle aspiration cytology from the most two suspicious lymph nodes, Tru-cut needle biopsy didn't obtain in this case as suspicious lymph nodes were multiple and small in size, The final cytological evaluation showed metastatic lymph nodes harboring malignancy. **a**, **b** Axillary ultrasound with Doppler shows multiple suspicious lymph nodes, the largest was oval in shape and measures about 21 × 12 mm, with effaced hilum. The other nodes are round in shape the and largest of them measuring about 10 × 9 mm. On color Doppler, the lymph nodes showed both hilar vascular flow in addition to some cortical non-hilar blood flow at the periphery. **c**, **d** show FNA needle arrows while traversing the cortex of both lymph nodes, in which histopathological analysis revealed metastatic malignant cells of both aspirated nodes. **e** Photomicrograph of the largest lymph node cytology smear: clusters of malignant epithelial cells on hemorrhagic (Papanicolaou stain, 400X)

A comparison of the material costs for FNAC and CNB yielded favorable results for FNAC.

In this study, we found that the specimens obtained by FNAC were insufficient for cytology in 3.7% of the cases, whereas the materials obtained by CNB were inadequate for the histological assessment in 1.9% of cases. The fault regarding FNAC was due to insufficiency of the aspirated amount of material or overly bloody samples, and for CNB was because of insufficient fragmented acquired cores.

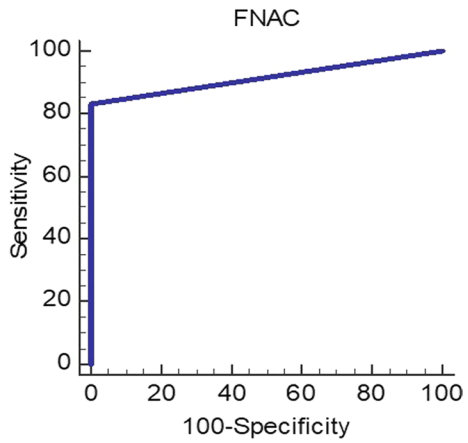

Fig. 3 ROC curve for the accuracy of FNAC in identifying malignant axillary lymph nodes

Table 3 Cross-tabulation between results of Tru-cut biopsy and final histopathology

Tru-cut biopsy	Histopathology		Total
	Malignant	Benign	
Malignant	24	0	24
Benign	0	10	10
Total	24	10	34

Data expressed as frequency

Table 4 Accuracy of Tru-cut needle biopsy in identifying metastatic axillary lymph nodes

Indices	Value
Sensitivity	100%
Specificity	100%
Positive predictive value	100%
Negative predictive value	100%
Accuracy	100%
Area under curve	1
P value	< 0.001

Our results showed that CNB was more sensitive than FNAC in the detection of axillary lymph node metastasis with a sensitivity of 83.3% for FNAC and 100% for CNB (after exclusion of inadequate samples). The sensitivity of both FNAC and CNB in our study were higher than in the following studies: A retrospective assessment by Rao et al. [14] compared the diagnostic efficacy of FNAC and CNB in distinct patient groups, comparing a group of 22 patients who underwent FNAC to a different group of 25 patients who underwent CNB. CNB and FNAC had sensitivities of 82% and 75%, respectively. And Houssami et al. [11] reported in meta-analysis a sensitivity of 72.2% for FNAC in 24 studies and a sensitivity for core biopsy of 83.3% in 4 studies. Also, Rautiainen et al. [13] reported sensitivities for FNAC and CNB of 72.5% and 88.2%, respectively, of 51 total cases. Ganott et al. [15] showed FNAC sensitivity of 78.6% and CNB of 87.1% in 70 patients. Our study also showed that sensitivity of both FNAC and CNB increased remarkably if different FNAC passes and different core passes were taken. But in all previous studies, CNB showed higher sensitivity than FNAC with different percentages.

Our study showed that the specificity of both FNAC and CNB was 100%. So, it is acceptable to proceed with axillary lymph node dissection if percutaneous biopsy methods reveal malignancy.

FNAC was able to accurately diagnose the negative lymph nodes with no false positive results, which aligned with most of the previous studies [14, 16]. However, regarding the malignant nodes, FNAC accurately diagnosed 50 out of 60 cases as true positive, with 10 cases (16.7%) diagnosed as false negative. This was close to Rao et al. [14] who reported 17% false-negative cases. Krishnamurthy et al. [16] reported 11.6% false-negative cases, a finding less than that in our study. Koelliker et al. [17] found false-negative findings in 24%, a higher result than ours. While CNB was able to accurately diagnose both negative and metastatic lymph nodes.

Regarding those 10 false-negative cases, after evaluating their cytology and analyzing the number of lymph nodes that harbored malignancy among all dissected lymph nodes, we found that roughly 60% of the false-negative results were probably due to a failure to identify the sentinel LN by using the US regardless of our effort to choose the most suspicious lymph node with the high probability of being the sentinel lymph node. That can be overcome by ultrasound identification of the sentinel lymph node by using a gamma probe, fluorescence imaging, or contrast agent which will lead to better results regarding this point. About 40% were likely due to insufficient scanty aspirated cells, this can be tried to be avoided by increasing the number of aspirations and taking multiple entries and passes from different cortical areas, in addition to an immediate assessment of sample suitability by a pathologist on-site. However, after all, this is taken into consideration, false negative results still can be seen with small metastatic deposits.

Conclusions

CNB biopsy shows higher sensitivity and accuracy than FNAC in differentiation between benign and malignant lymph nodes. FNAC is a good alternative when a smaller node is encountered, a node in an inaccessible

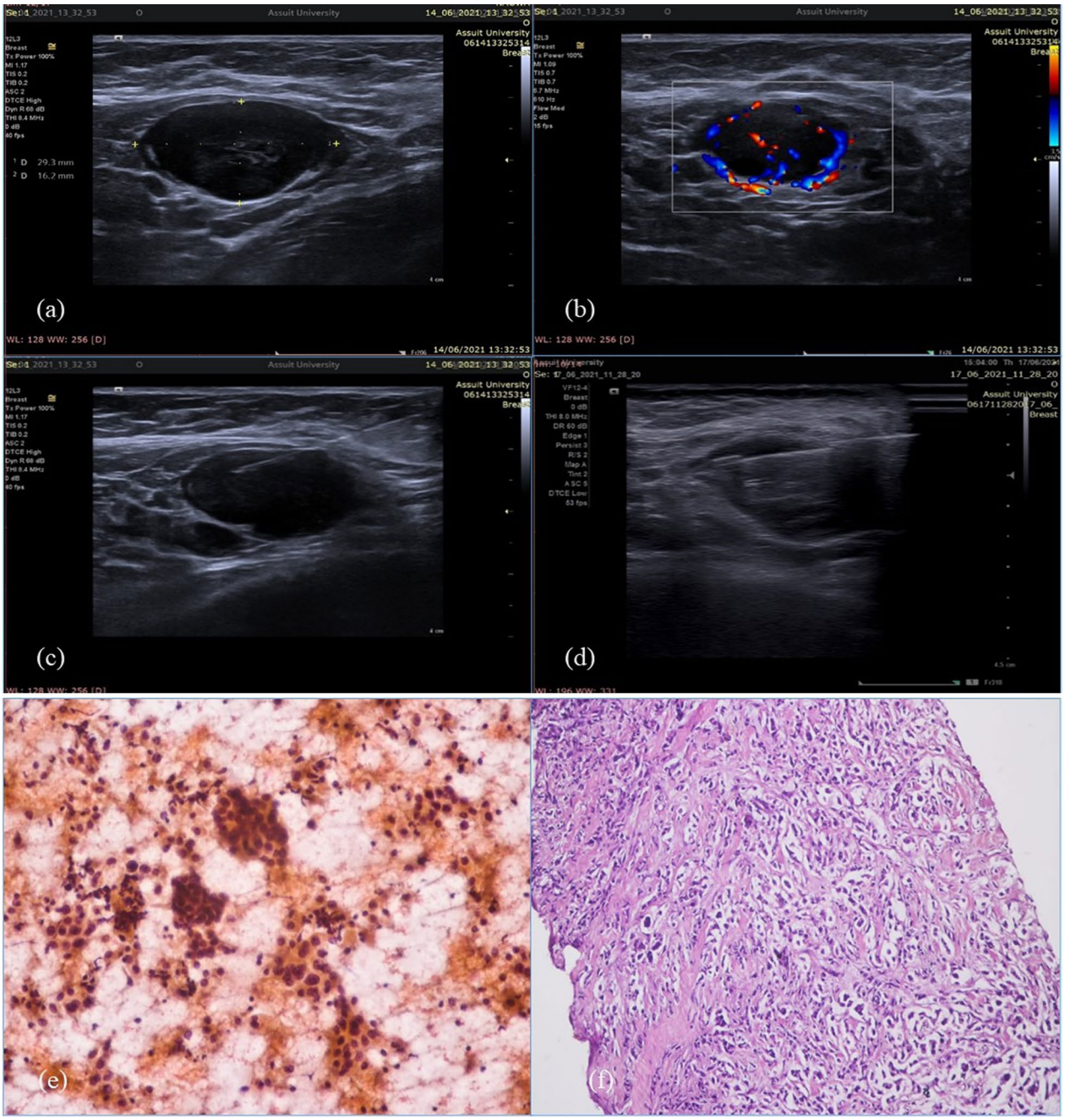

Fig. 4 An 42-year-old female patient presented with breast cancer, the freehand technique was used and under ultrasound guidance, FNAC & core biopsy were obtained simultaneously, and the final histopathological evaluation showed metastatic lymph nodes harboring malignancy. **a** Axillary gray-scale ultrasonographic image demonstrates a suspicious lymph node, measuring 30 × 16 mm. It is oval in shape with effaced hilum. **b** Doppler US image shows that the lymph node has both hilar vascular flow as well as prominent cortical non-hilar blood flow at the periphery. **c** Needle pass during FNAC in the cortical region of the lymph node. **d** Needle pass during Tru-cut biopsy of the lymph node from cortical regions. **e** Photomicrograph of a lymph node cytology smear: multiple clusters of malignant epithelial cells on the lymphoid background (Papanicolaou stain, 400X). **f** Photomicrograph of tissue section of metastatic ductal carcinoma in the lymph node. Many nests and cords of neoplastic cells are separated by desmoplastic stroma (Hematoxylin and Eosin stain, 200X)

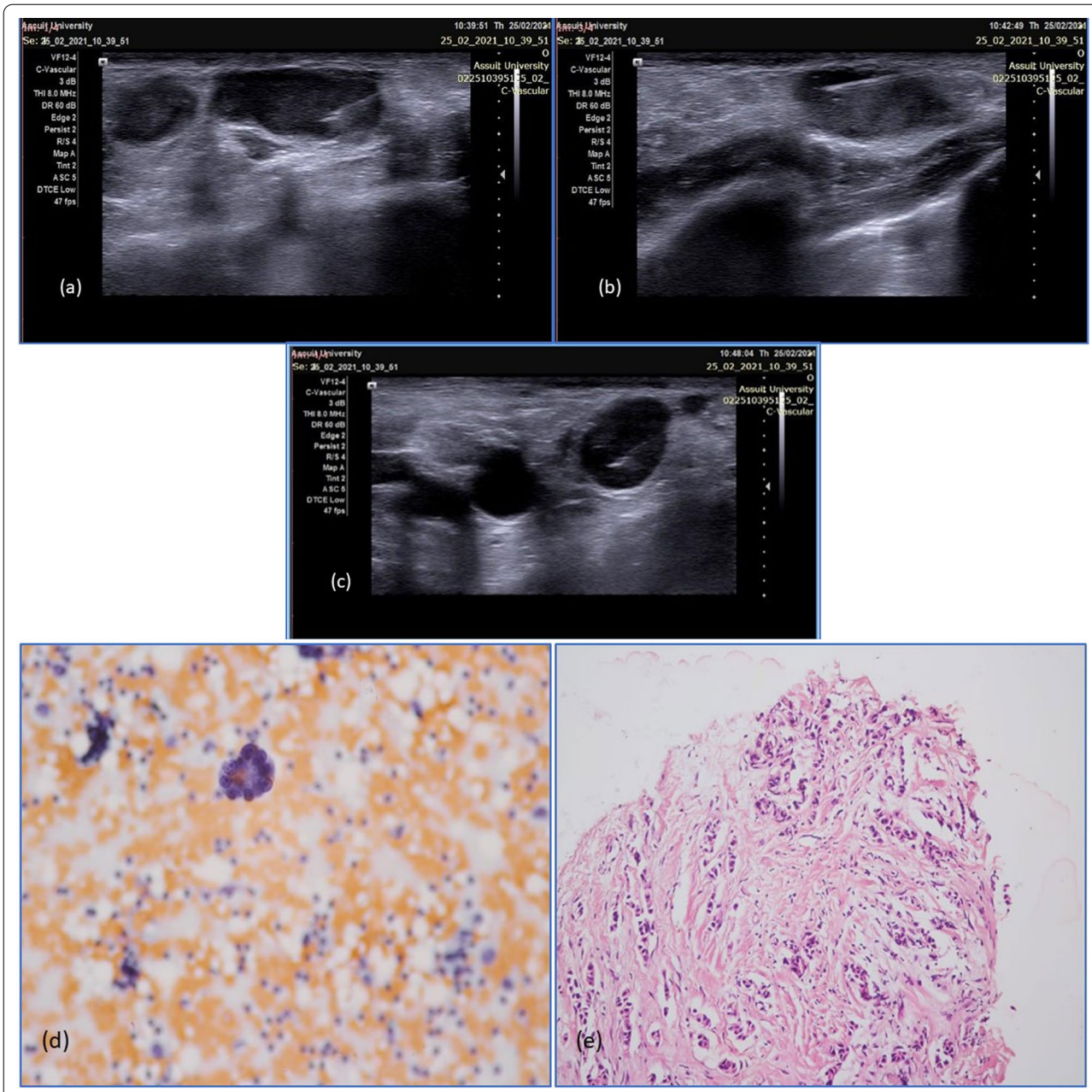

Fig. 5 An 43-year-old female patient presented with breast cancer, FNAC and CNB were obtained simultaneously from the largest and most suspicious node and another FNAC aspirate was obtained from another suspicious lymph node. The final histopathological evaluation showed metastatic lymph nodes harboring malignancy. **a**, **b** axillary ultrasound showed multiple suspicious lymph nodes, the largest was oval in shape and measures about 23 × 8 mm, with loss of its hilum, FNAC and CNB were obtained from this node. **c** another smaller round node was seen measuring about 15 × 10 mm, in which FNAC was also taken from this node, all obtained biopsies were containing malignant metastatic cells. **d** Photomicrograph of a lymph node cytology smear: a single acinus of malignant ductal carcinoma on the lymphoid background (Papanicolaou stain, 400X). **e** Photomicrograph of tissue section of metastatic ductal carcinoma in the lymph node. Many nests and cords of neoplastic cells are separated by desmoplastic stroma (Hematoxylin and Eosin stain, 200X)

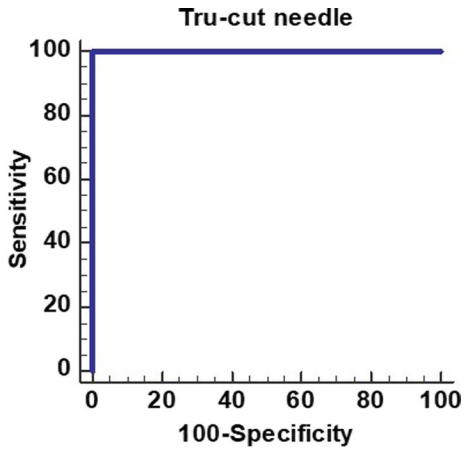

Fig. 6 ROC curve for the accuracy of Tru-cut needle biopsy in identifying malignant axillary lymph nodes

location, or even an uncorrectable bleeding diathesis of the patient.

Abbreviations
ALND: Axillary lymph node dissection; SNB: Sentinel lymph node biopsy; US: Ultrasonography; FNAC: Fine-needle aspiration cytology; CT: Computed tomography; CNB: Core needle biopsy.

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Author contributions
MK and MA designed the research. MK performed the research; and wrote the manuscript. HM, MA and MM analyzed the collected data. HM, MA, MM and OM revised data and manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Available on request with the corresponding author.

Declarations

Ethics approval and consent to participate
The study was conducted after approval of the Ethical Committee of Faculty of Medicine, (Approval Number 17100609) and after Clinical Trial Approval (NCT03681418). Informed written consent was obtained from each participant.

Consent for publication
All patients included in this study gave a written informed consent to publish the data contained in this study.

Competing interests
The authors declare that they have no competing interests.

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