



Research article

Accuracy of ultrasound-guided fine-needle aspiration for small cervical lymph nodes: A retrospective review of 505 cases

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ABSTRACT

Purpose: The overall diagnostic value of fine-needle aspiration (FNA) is not as excellent as that of core needle biopsy (CNB). Limited research has investigated small cervical lymph nodes inaccessible to ultrasound-guided CNB due to technical challenges associated with their small size. Therefore, this study aimed to evaluate the accuracy of ultrasound-guided FNA in determining the etiology of small cervical lymph nodes.

Methods: A retrospective analysis was conducted on patients who underwent FNA between May 2018 and May 2021 at our hospital. Cytological, histopathological, and clinical follow-up data were analyzed. The diagnostic yield of FNA was assessed based on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy calculations.

Results: This study included 505 patients, each with a small cervical lymph node under evaluation (total number of lymph nodes: 505). The average maximal diameter of the lymph nodes was 14.6 ± 6.2 mm. According to the Sydney system, the cytology results were as follows: Category I in 26 lymph nodes (5.1 %); Category II in 269 (53.3 %); Category III in 35 (6.9 %); Category IV in 17 (3.4 %); and Category V in 158 (31.3 %). We identified 212 malignant cases (203 metastases and 9 lymphomas) and 293 benign lymph nodes. FNA achieved high sensitivity (88.8 %), specificity (99.6 %), PPV (99.4 %), NPV (91.8 %), and overall accuracy (94.8 %) in determining the etiology of small cervical lymph nodes.

Conclusion: FNA cytology is suitable for small lesions inaccessible by CNB and provides a diagnostic basis for implementing clinically appropriate treatment measures.

1. Introduction

Cervical lymphadenopathy is a common condition with diverse etiologies ranging from benign to malignant [1,2]. Although thorough clinical and imaging evaluations can help identify the underlying cause of cervical lymphadenopathy, a definitive

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pathological diagnosis is imperative. Various methods such as excision biopsy, ultrasound-guided core needle biopsy (CNB), and ultrasound-guided fine-needle aspiration (FNA) are commonly used to evaluate cervical lymphadenopathy [3].

Excision biopsy is the gold standard for pathological diagnosis and is widely used to provide a definitive diagnosis and guide therapy, especially in suspected lymphoma cases; however, it has some limitations in terms of its invasive and time-consuming nature. Moreover, excision biopsy may not be suitable for some patients because of the risks associated with anesthesia, vascular and nerve damage, wound infection, and skin scarring [4]. Recently, ultrasound-guided CNB has gained popularity as a percutaneous sampling technique [5] and is being widely accepted because of its high diagnostic accuracy and ease of operation [6]. However, CNB is performed using an automatic biopsy device with the shortest fixed ejection distance of 15 mm. Consequently, obtaining tissue samples from small suspicious lymph nodes with a maximum diameter of <15 mm situated in close proximity to large cervical vessels is considered impractical. Despite attempts to expand the application of CNB to small lymph nodes, such as manual CNB and CNB assisted by hydrodissection [7,8], limitations to its widespread application persist. CNB requires high technical expertise, which makes broad application difficult. Additionally, even with experienced interventional ultrasound physicians, the high risk of serious complications such as hematoma and nerve damage remains a major concern [4,9]. Furthermore, a few studies have identified lymph node diameter and penetration distance as factors that influence CNB sampling [3,6,7]. The smaller short-axis diameters and shorter penetration distances that are frequently observed in small lymph nodes tend to be associated with lower diagnostic yields owing to the increased likelihood of inadequate samples.

Ultrasound-guided FNA is a safer alternative for small lymph nodes [10], serving as an accurate, quick, and cost-effective procedure with a low complication rate [11]. In cases of malignant lymphadenopathy, the reported diagnostic accuracy of FNA ranges from 79 % to 94.5 % [12,13]. Several studies have compared the efficacy of CNB and FNA and reported that the overall diagnostic value of FNA may not be as excellent as that of CNB [8,14–17]. However, studies that have specifically focused on small cervical lymph nodes that are not approachable by CNB owing to technical difficulties associated with their small size are limited in the literature. Therefore, this study primarily aimed to retrospectively assess the diagnostic accuracy of ultrasound-guided FNA in identifying the underlying causes of small cervical lymph nodes.

2. Methods

2.1. Ethics statement

This study was approved by the Medical Science Research Ethics Committee of Peking University Third Hospital (approval number: M2023383; date of approval: June 4, 2023). Due to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

2.2. Study design and participants

In this retrospective study, we included consecutive patients who underwent ultrasound-guided FNA at our institution between May 2018 and May 2021. The inclusion criteria were as follows: suspicious cervical lymph nodes that were inaccessible for CNB owing to their location or small size, history of initial FNA, no history of lymph node ablation before the study, and sufficient medical records and FNA specimen evaluation findings. The exclusion criteria were as follows: surgical specimens lacking clearly reported locations and history of ablation therapy or radionuclide therapy after FNA.

2.3. Ultrasonic evaluation

Ultrasound examinations and FNA were performed using three commercial ultrasound devices equipped with high-frequency linear array probes: Logic E9 (GE Healthcare, Chicago, IL, USA), Samsung RS80A (Samsung Medison Co., Ltd., Seoul, Korea), and Siemens ACUSON S3000 (Siemens Healthineers, Erlangen, Germany). The following parameters were recorded: lymph node location, lymph node size, lymph node shape, and presence or absence of calcification. The size of lymph node was evaluated based on maximal diameter, the location was classified according to Robbins et al. [18], and the shape was described based on the long/short axis ratio (L/S), where $L/S < 2$ indicated a round shape, and $L/S \geq 2$ indicated an elliptical shape.

2.4. Ultrasound-guided FNA and cytopathology

Ultrasound-guided FNA was performed by interventional ultrasound physicians using a 25 G needle (Hakko, Chikuma, Japan). For each lymph node, 3 or 4 passes were conducted, with each pass consisting of 10–15 to-and-fro needle movements over 5–10 s. Aspirations were performed at different angles and regions using a freehand parallel approach to obtain representative samples. The samples were primarily obtained without suction using a capillary method [7]. The aspirated material was preserved in a vial containing methanol-based preservatives (Cytobrep solution, Cheng Zhi Guang Hui, Beijing, China) and sent to the cytopathology laboratory for centrifugation and staining (SurePath, TriPath Imaging, Burlington, NC, USA).

Cytological findings were reported according to the Sydney system [19], and specimens were categorized as follows: Category I, Inadequate/Insufficient; Category II, Benign; Category III, Atypical undetermined significance/Atypical lymphoid uncertain significance (AUS/ALUS); Category IV, Suspicious; Category V, Malignant. Specimens were grouped into the non-diagnostic (Category I) or diagnostic group (Categories II–V) based on specimen adequacy and diagnostic certainty. In the diagnostic group, patients were further

divided into determinate (benign and malignant lesion reports) and indeterminate (AUS/ALUS and suspicious reports) subgroups [20, 21].

2.5. Clinical data

Clinical, histological, and follow-up ultrasound data were collected from electronic medical records. Patient information (factors such as sex, age, history of cancer, and fever), pathological features (types and results), and follow-up ultrasound findings were extracted.

2.6. Diagnostic criteria

Final benign or malignant diagnoses were based on the following criteria: (1) histopathology after lymphadenectomy or CNB, (2) repeat FNA, (3) clinical assessment with repeat ultrasound performed at least 2 years after the initial FNA, or (4) contact with patients (via phone) without available follow-up information to ascertain outcomes. Lymph nodes were considered benign if they met one or more of the following criteria: (1) benign histopathology after surgery or CNB, (2) benign repeat FNA diagnosis, (3) spontaneous regression or <20 % increase in diameter size on ultrasound performed at least 2 years after the initial FNA, or (4) no report of a malignant cervical lymph node diagnosis when contacted via phone after a minimum of 2 years from FNA.

2.7. Statistical analysis

The study’s data presentation followed established conventions, wherein continuous data are expressed as means ± standard deviation and categorical data as counts with corresponding percentages. The diagnostic yield of FNA for benign, suspicious, and malignant cytology was evaluated using key metrics, namely, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

3. Results

3.1. General information

Between May 2018 and May 2021, 589 ultrasound-guided FNAs were conducted. After excluding 63 cases of unclear reported surgical specimen locations, 18 cases of post-FNA ablation therapy, and 3 cases of post-FNA radionuclide therapy, 505 cases remained for analysis (Fig. 1). Therefore, the final analysis included 505 lymph nodes from 505 patients. The average age of the study cohort was 52 ± 16 years (range: 17–86 years). Among these patients, 318 (63.0 %) were females, and 187 (37.0 %) were males (female-to-male ratio of 1.7:1). The mean maximum diameter of the sampled lymph nodes was 14.6 ± 6.2 mm (Table 1). The sampled lymph nodes were located at different levels, as classified according to Robbins et al. [18]: 16 at Level I, 63 at Level II, 88 at Level III, 281 at Level IV, 49 at Level V, and 8 at Level VI. Notably, no complications such as bleeding, infection, nerve damage, or tumor cell seeding were observed during the ultrasound-guided FNA procedure.

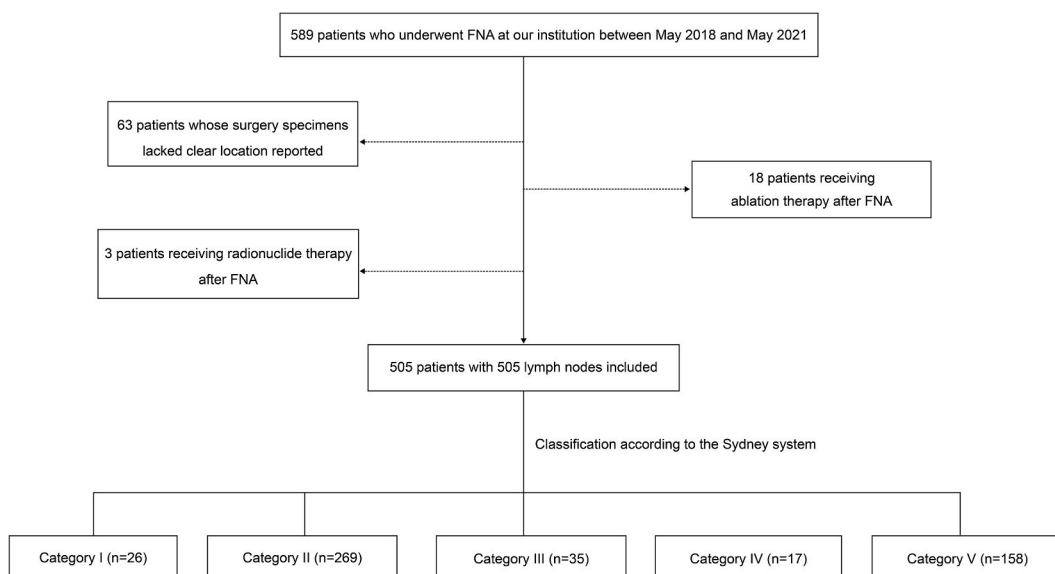


Fig. 1. Flowchart of the inclusion/exclusion criteria for participants FNA, fine-needle aspiration.

3.2. Cytopathological results

The distribution of cytopathological findings among the study participants was as follows: Category I in 26 cases (5.1 %), Category II in 269 (53.3 %), Category III in 35 (6.9 %), Category IV in 17 (3.4 %), and Category V in 158 (31.3 %) (Table 2). Among these cases, 120 patients underwent surgery (n = 107) or subsequent CNB (n = 13) and received a definitive diagnosis based on histopathology. Four patients opted for repeat FNA. In 339 patients, the diagnosis was confirmed through follow-up ultrasound, whereas the remaining 42 patients were contacted via phone to ascertain their diagnostic outcomes (Fig. 2).

3.3. Final diagnoses

Based on the reference standards of histological diagnoses from surgery and CNB, cytology results of repeat FNA, and follow-up ultrasound or phone findings, 212 lymph nodes were diagnosed to be malignant, whereas the remaining 293 were benign. The risk of malignancy (ROM) associated with each category is shown in Table 3.

Among the 26 patients with inadequate or insufficient cytology results, 7 underwent subsequent excision (n = 6) or CNB (n = 1). Among these 7 patients, lymph nodes were confirmed to be malignant in three cases: two cases of papillary thyroid carcinoma metastases and one case of lung adenocarcinoma metastasis. In the remaining four specimens, all patients were diagnosed with papillary thyroid carcinoma; however, postoperative pathology confirmed that the suspicious lymph nodes were benign. Of the remaining 19 patients with inadequate or insufficient cytology results, 1 was diagnosed with lung cancer metastasis during the phone follow-up. During the two-year follow-up period, the remaining 18 enlarged lymph nodes decreased in size and were ultimately considered benign.

Among the 35 cases in the diagnostic group with AUS/ALUS cytology results, there were 32 cases of AUS and 3 cases of ALUS. Of the 32 AUS cases, the lymph nodes in 21 cases were eventually diagnosed as benign, while those in the remaining 11 were ultimately diagnosed as malignant. Of the 21 patients with benign lesions in the AUS group, 14 had a history of tumors and 7 had no known history of tumors. In this AUS group, 5 patients underwent lymphadenectomy, whereas the remaining 16 patients were followed up through ultrasound examinations or phone communication. Of the 11 patients with malignant lesions in the AUS group, 8 had metastatic lymph nodes: papillary thyroid carcinoma was the primary tumor in four cases (with three cases of diffuse sclerosing papillary carcinoma), lung cancer in two cases, and gastric cancer and breast cancer in one case each. The final diagnosis of lymphoma was established in three other patients. Among the three cases of ALUS, the lesion in one case was diagnosed as papillary thyroid carcinoma metastasis, whereas those in the other two cases were confirmed to be benign.

Of the total 505 cases, 42.0 % (212 cases) were diagnosed with malignant lymphadenopathy, with 203 cases of metastases and 9 cases of lymphoma. Among the cases of malignant lymphadenopathy, the most common primary site of malignancy was the thyroid (44.3 %, 90/203), followed by the lungs (26.6 %, 54/203), female reproductive system (7.9 %, 16/203), breast (7.4 %, 15/203), gastrointestinal tract (7.4 %, 15/203), and other sites (6.4 %, 13/203). Ultrasound-guided FNA successfully detected 82.1 % (174/212) of the malignancies, including 16 cases of Category IV and 158 of Category V. In our study, only one false-positive case was classified as Category IV (Suspicious), wherein the patient presented with a thyroid nodule in the right lobe, accompanied by lymphadenopathy in the ipsilateral supraclavicular region. The FNA specimen from the cervical lymph node initially raised suspicion of metastatic lesions originating from differentiated tumors originating from the thyroid follicular epithelium. However, subsequent pathological analysis of the surgical specimen revealed that the thyroid nodule was a microinvasive follicular carcinoma, whereas the cervical lymph nodes were confirmed to be benign.

Among the nine cases of lymphoma, the initial cytological findings were distributed as follows: Category II in three patients, Category III in three patients, Category IV in two patients, and Category V in one patient. Of the three patients misdiagnosed as benign, one reported progressive lymph node enlargement during ultrasound follow-up and underwent surgical resection. The remaining two patients had a previous history of tumor involvement (breast cancer and diffuse large B-cell lymphoma each), and the cytological morphology in these two cases did not support metastasis or high-grade lymphoma. For the three cases classified as AUS, although a diagnosis of lymphoma was not made, appropriate recommendations were provided, highlighting the limitations of simple cytological morphology in distinguishing between reactive proliferation and low-grade lymphohematopoietic tumors. The lesions in two cases classified to be suspicious showed highly suggestive cytological morphology of lymphoma but lacked definitive diagnosis and classification. In Category V, the FNA results indicated a high-grade malignancy without specific differentiation among poorly

Table 1
Baseline characteristics of all participants and lymph nodes.

Clinical characteristics	
Age (years), mean ± SD	52.4 ± 16.1
Female, n (%)	318 (63.0 %)
History of cancer, n (%)	370 (73.3 %)
History of fever, n (%)	35 (6.9 %)
Ultrasound characteristics	
Maximum diameter (mm), mean ± SD	14.6 ± 6.2
Round shape (L/S < 2), n (%)	304 (60.2 %)
Presence of calcifications, n (%)	124 (24.6 %)

SD: standard deviation; L/S: long/short axis ratio.

Table 2
Number of cases and corresponding proportions for the FNA diagnostic category.

FNA diagnostic category	Cases (n, (%))
Category I (Inadequate/Insufficient)	26 (5.1 %)
Category II (Benign)	269 (53.3 %)
Category III (AUS/ALUS)	35 (6.9 %)
Category IV (Suspicious)	17 (3.4 %)
Category V (Malignant)	158 (31.3 %)

FNA: fine-needle aspiration; AUS/ALUS: atypical undetermined significance/atypical lymphoid uncertain significance.

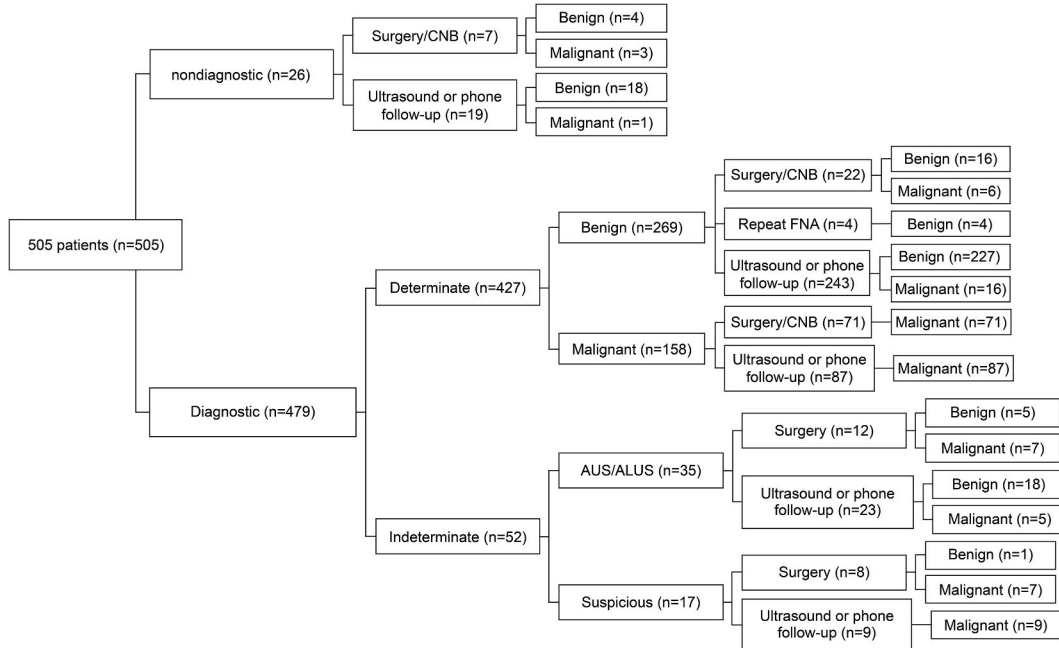


Fig. 2. Outcomes of the FNA for 505 small cervical lymph nodes FNA, fine-needle aspiration; CNB, core needle biopsy; AUS/ALUS, atypical undetermined significance/atypical lymphoid uncertain significance.

Table 3
Analysis of ROM.

FNA diagnostic category	Cases (n)	Malignant cases (n)	ROM (%)
Category I (Inadequate/Insufficient)	26	4	15.4
Category II (Benign)	269	22	8.2
Category III (AUS/ALUS)	35	12	34.3
Category IV (Suspicious)	17	16	94.1
Category V (Malignant)	158	158	100
Total	505	212	

ROM: risk of malignancy; FNA: fine-needle aspiration; AUS/ALUS: atypical undetermined significance/atypical lymphoid uncertain significance.

differentiated cancer, invasive lymphoma, and high-grade sarcoma.

Benign lymphadenopathy constituted 58.0 % (293/505) of all cases, and ultrasound-guided FNA provided an accurate diagnosis in 84.3 % (247/293) of these cases. The most common benign condition was reactive hyperplasia, followed by normal lymph nodes, granulomatous inflammation, necrotizing lymphadenitis, and tuberculosis. A total of five patients were finally diagnosed with tuberculosis, and their FNA findings were reported to be benign in Category II. Cytological morphology in three cases displayed inflammatory granuloma, which is strongly suggestive of tuberculosis, whereas that in the remaining two cases indicated benign lesions. Fortunately, all patients received timely and appropriate treatment without any delays.

3.4. Accuracy of ultrasound-guided FNA

We conducted a comprehensive analysis to evaluate the diagnostic accuracy of ultrasound-guided FNA in patients with benign, suspicious, or malignant cytopathology. To determine the accuracy, we compared the cytology results obtained through ultrasound-guided FNA with the diagnoses established through surgical examination, CNB, repeat FNA, or follow-up examination. For small cervical lymph nodes, the following metrics were used to determine the accuracy of ultrasound-guided FNA: sensitivity (88.8 %), specificity (99.6 %), PPV (99.4 %), NPV (91.8 %), and overall accuracy (94.8 %) (Table 4).

4. Discussion

In this study, we primarily and thoroughly explored the diagnostic effectiveness of FNA in assessing small cervical lymph nodes that are inaccessible to CNB, aiming to provide valuable insights into the diagnosis of conditions in the field of lymphadenopathy and to enhance our understanding of the utility of FNA in such specific clinical scenarios.

We conducted ultrasound-guided FNA procedures in 505 patients to assess small cervical lymph nodes. The rate of non-diagnostic specimens (according to Sydney System Category I) was 5.1 %, which was lower than the rates of inadequate sampling specimens reported in previous studies (range: 10%–15 %) [22–28]. Category I specimens cannot be diagnosed due to factors such as scant cellularity, extensive necrosis, or technical limitations [19]. Although there is no consensus on the minimum number of cells required for a satisfactory lymph node sample, the presence of a polymorphous lymphoid population or obvious malignant cells is typically considered sufficient to deem the sample adequate [29]. In this study, the proportion of Category I specimens is attributed to the standardization of FNA techniques by experienced interventional ultrasound physicians, as the skill and expertise of the FNA operator can influence specimen adequacy [30]. On-site evaluation of FNA samples is a potential strategy to enhance diagnostic yield; however, its benefits and cost-effectiveness require further investigation [31,32].

Regarding the diagnostic performance of ultrasound-guided FNA for small cervical lymph nodes, we observed a sensitivity of 88.8 %, specificity of 99.6 %, PPV of 99.4 %, NPV of 91.8 %, and overall accuracy of 94.8 %. Notably, the specificity and PPV were high, which is consistent with the findings of previous research [11,23,25,32]. The high specificity reaffirms the broad applicability of FNA when metastatic disease is suspected, potentially reducing the need for more invasive interventions in patients with cancer.

In the current study, ultrasound-guided FNA demonstrated moderate sensitivity. Among the 22 false-negative cases, 19 cases were of metastases and 3 were of lymphomas. While most lymphadenopathy cases are attributed to infections or benign conditions, “benign” or “malignant negative” FNA results do not definitively exclude the possibility of malignancy in patients with unexplained lymph node enlargement. Therefore, CNB or excisional biopsy should be considered in such cases, based on the clinical findings to further evaluate and establish a definitive diagnosis.

Although FNA cytology is sensitive in detecting metastatic lymph nodes, its diagnostic utility is limited in lymphoma cases. Distinguishing between reactive and malignant lymphoid proliferation is particularly challenging in lymph node FNA, with specific difficulties noted in differentiating between low-grade lymphoma and reactive hyperplasia [24,33]. Further excisional biopsy is recommended for patients with malignant clinical considerations. As in our study, lymphomas were detected in only 1.8 % (9) of cases, and this low incidence is possibly attributed to the preference for more invasive diagnostic methods, such as CNB or excisional biopsy, when there is a clinical or radiological suspicion of lymphoproliferative disease. As a result, the condition in cases wherein lymphomas were identified through cytology were primarily those without any prior clinical suspicion of lymphoproliferative disease or those requiring exclusion of metastatic disease owing to a history of previous carcinoma.

Tuberculous lymphadenitis is a benign cause of unexplained cervical lymphadenopathy and requires prompt and accurate anti-tuberculosis treatment for patients [34,35]. Although clinical evaluation and imaging studies can offer valuable clues, definitive diagnosis relies on microbiological, cytopathological, or histological examinations [36]. However, the sensitivity and accuracy of FNA for detecting tuberculous lymphadenitis are not reported to be particularly high [12].

FNA rarely leads to complications such as bleeding, infection, nerve damage, or tumor cell seeding. In our series of 505 cases with lymph node involvement, no complications were observed, highlighting the safety and reliability of FNA.

This study has some limitations, including being a single-center study with a retrospective design. Furthermore, most malignant and benign lymph nodes lacked further pathological confirmation, leading to reliance on ultrasound and follow-ups via phone as part

Table 4
Diagnostic accuracy of ultrasound-guided FNA for small cervical lymph nodes.

Variables	Ultrasound-guided FNA
True-positive cases (a) (n)	174
False-positive cases (b) (n)	1
False-negative cases (c) (n)	22
True-negative cases (d) (n)	247
Sensitivity $[a/(a+c)]$ (%)	88.8
Specificity $[d/(b+d)]$ (%)	99.6
PPV $[a/(a+b)]$ (%)	99.4
NPV $[d/(c+d)]$ (%)	91.8
Diagnostic accuracy $[(a+d)/(a+b+c+d)]$ (%)	94.8

FNA: fine-needle aspiration; PPV, positive predictive value; NPV, negative predictive value.

of the reference standard. This approach could potentially lead to misclassification, particularly of indolent malignancies that might not have been definitively identified. Hence, our results should be interpreted with caution. Future investigations with larger sample sizes and prospective designs are needed for more robust and conclusive findings.

5. Conclusion

Ultrasound-guided FNA is a minimally invasive method of evaluating lymphadenopathy. To our knowledge, this is the first study specifically focused on the value of FNA in small cervical lymph nodes that are not approachable by CNB because of the technical barriers owing to their small size or difficult accessibility. The results have shown that ultrasound-guided FNA with high sensitivity (88.8 %), specificity (99.6 %), and overall accuracy (94.8 %) is effective and reliable in determining the etiology of these small cervical lymph nodes. It can serve as a viable alternative to CNB and will be widely accepted by clinicians and pathologists. Nevertheless, further research with larger and more diverse cohorts remains essential to validate and extend our findings and enhance diagnostic accuracy and patient care.

Ethics approval

This study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee (Approval No. M2023383; date of approval June 4, 2023).

Informed consent

The requirement for informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

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Availability of data and materials

The datasets collected and/or analyzed during this study are available from the corresponding authors upon reasonable request.

CRedit authorship contribution statement

Ying Fu: Writing – original draft, Investigation, Conceptualization. **Chang Liu:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Minglei Ren:** Data curation. **Tingting Du:** Data curation. **Yihua Wang:** Data curation. **Fang Mei:** Methodology, Formal analysis. **Ligang Cui:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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