Am J Transl Res 2024;16(5):1757-1768
www.ajtr.org /ISSN:1943-8141/AJTR0155471

Original Article

Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic lymphadenopathy in patients with nasopharyngeal cancer

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Received January 16, 2024; Accepted April 24, 2024; Epub May 15, 2024; Published May 30, 2024

Abstract: Objective: This study aimed to assess the efficacy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in detecting intrathoracic lymph nodes in patients with nasopharyngeal carcinoma (NPC). Methods: Retrospective data analysis was conducted on individuals who underwent EBUS-TBNA between June 2015 and June 2022. Patients with NPC and enlarged intrathoracic lymph nodes were included. Specimens were categorized as malignant or non-malignant, with final non-malignancy confirmation procedures, or 12 months of clinical follow-up. Results: Among 97 patients, 59 (60.8%) had NPC with intrathoracic lymph node metastasis, 3 (3.1%) had primary lung cancer involving nodes, and 25 (25.8%) showed benign characteristics. Ten cases (10.3%) were false-negative on initial EBUS-TBNA but confirmed as metastatic on follow-up. For NPC patients with intrathoracic lymphadenopathy, EBUS-TBNA exhibited 86.1% sensitivity (62/72), 71.4% negative predictive value (25/35), and 89.7% accuracy (87/97). Multivariate analysis identified increased lymph node short axis (OR: 1.200, 95% CI: 1.024-1.407; P = 0.041), metachronous NPC (OR: 11.274, 95% CI: 2.289-55.528; P = 0.003), and synchronous lung lesions (OR: 19.449, 95% CI: 1.875-201.753; P = 0.001) as independent predictors of malignant intrathoracic lymphadenopathy. Longer lymph node short axis (OR: 1.305, 95% CI: 1.044-1.631; P = 0.019) was independently associated with EBUS-TBNA accuracy. Conclusion: EBUS-TBNA effectively diagnoses intrathoracic lymphadenopathy in NPC patients.

Keywords: Nasopharyngeal carcinoma, endobronchial ultrasound, intrathoracic lymphadenopathy, transbronchial needle aspiration

Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy of the epithelial cells in the head and neck region and is particularly prevalent in East and South Asia [1, 2]. The primary treatment for NPC is radiotherapy (RT), either alone or in combination with chemotherapy [3]. The 5-year survival rate for these patients after treatment ranges from 80% to 87%, with 5% to 15% experiencing recurrence and approximately 15% to 30% developing distant metastasis [4-6]. NPC cells frequently metastasize to intrathoracic lymph nodes, significantly impacting treatment planning [5]. Distant lymph node metastasis can be detected by conventional imaging methods such as contrast-enhanced computed tomography (CT) scanning and positron emission tomography-computed tomography (PET-CT) [7]. However, these techniques cannot conclusively distinguish between malignant and benign growth. Therefore, they cannot be used for pathological confirmation of suspicious intrathoracic lymph nodes, which is imperative for accurately staging NPC patients.

Video-assisted thoracoscopy (VATS) and mediastinoscopy are frequently used for pathological confirmation of suspicious intrathoracic lymph nodes, depending on their specific location. However, these modalities have a 2% complication rate and require the use of general anesthesia [8]. Recent studies have elucidated that endobronchial ultrasound-guided trans-

https://doi.org/10.62347/GDMG9203

bronchial needle aspiration (EBUS-TBNA) can effectively diagnose lymphadenopathy in the hilar region and mediastinum [9]. It is commonly employed as an initial diagnostic tool for assessing lymphadenopathy in the mediastinum, lung cancer, and extrathoracic metastases [10-12]. Unlike mediastinoscopy, EBUS-TBNA is minimally invasive, allowing for repeated sampling of lymph nodes in the hilar and mediastinal regions. Additionally, EBUS-TBNA can be performed with either mild conscious sedation or intratracheal anesthesia [13, 14]. Real-time imaging during EBUS-TBNA enhances diagnostic accuracy, making it an alternative to conventional needle aspiration [15]. Previous studies have confirmed the diagnostic value and safety of EBUS-TBNA, demonstrating an 88.2% sensitivity in diagnosing intrathoracic metastases post head and neck cancer treatment [16]. Moreover, international clinical practice guidelines recommend EBUS-TBNA [17, 18].

However, there is a lack of research exploring the value of EBUS-TBNA in detecting intrathoracic lymph nodes in NPC. Thus, in this study, we retrospectively reviewed data from 97 NPC patients with enlarged intrathoracic lymph nodes who underwent EBUS-TBNA between June 2015 and June 2022 to evaluate the significance of EBUS-TBNA for NPC patients in diagnosing intrathoracic lymphadenopathy.

Materials and methods

Patient selection

We included 97 patients with NPC suspected of intrathoracic lymphadenopathy metastasis from EBUS-TBNA database of Sun Yat-sen University Cancer Center during the follow-up period from June 2015 to June 2022. Inclusion criteria: 1) NPC patients who underwent EBUS-TBNA at our hospital, 2) those with complete clinical and pathological data, and 3) suspected intrathoracic lymphadenopathy metastasis based on contrast-enhanced CT or PET-CT scans. Exclusion criteria: 1) patients with synchronous or metachronous lymphoma or leukemia, and 2) those lacking a conclusive diagnosis within a follow-up period shorter than 12 months.

Ethics statement

This research adhered to proper clinical conduct guidelines and the Helsinki Declaration. Approval for the protocol was obtained from the Ethics Committee of Sun Yat-sen University Cancer Center (B2023-308-01), exempting the need for individual consent.

Data collection

Basic patient information such as age, gender, medical history, and preoperative imaging results was collected from patient records. Intraoperative data, including the EBUS-TBNA operator and number of passes per lymph node, were obtained from medical records. Pathological data were extracted from postoperative and follow-up records.

EBUS-TBNA procedure

Patients were instructed to fast for at least 6-8 hours prior to the procedure, with normal coagulation and platelet function confirmed. Anesthesia was administered locally (2% lidocaine saline solution) or systemically (intravenous). Lymph node maps based on the International Association for the Study of Lung Cancer classification were used [19].

A conventional bronchoscope was used to apply 2% lidocaine saline solution to the mucosa. The Olympus BF-UC260F-0L8 linear ultrasonic bronchoscope (Tokyo, Japan) was then used to examine lymph node sites. This device includes a compact curved ultrasonic probe and a dedicated channel for biopsy needle insertion. Ultrasound images and dimensions of identified lymph nodes adjacent to the airway were documented.

The Olympus 22-gauge puncture needle (NA-201SX-4022) was used for sample aspiration, manipulated reciprocally once successful penetration into the target lesions was confirmed. To ensure adequate sampling, the same site was punctured 2-3 times. Major tissue samples were fixed in 10% neutral buffered formalin, while remaining aspirates and needle passages were used for cytological samples (**Figures 1**, **2**).

No complications related to EBUS-TBNA, such as hemorrhage exceeding 100 mL, pneumothorax, or post-procedure infection, were documented. There was no loss of participants during follow-up or mortality due to unrelated illnesses.

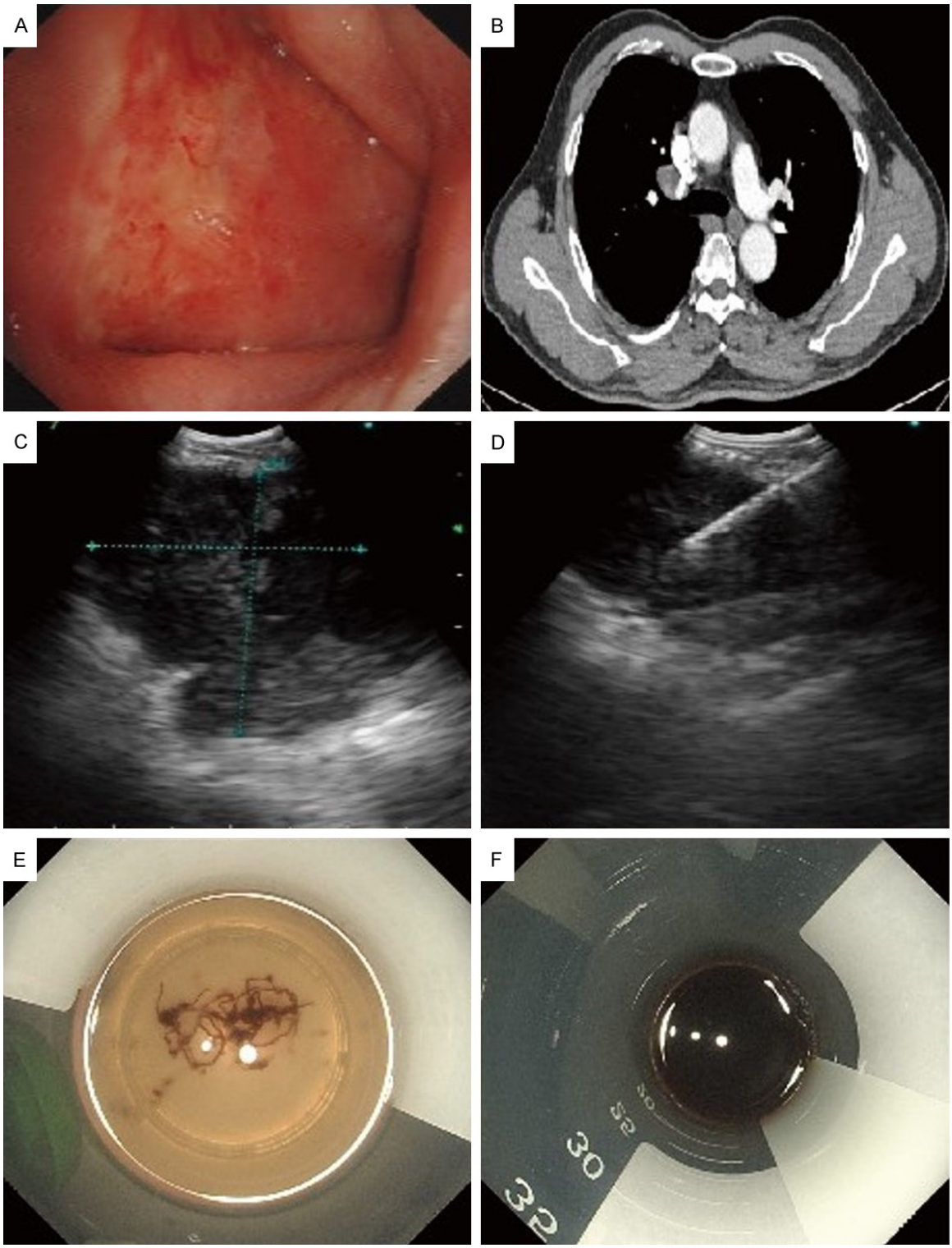

Figure 1. The diagnosis of nasopharyngeal carcinoma (NPC) with suspected intrathoracic metastases was confirmed in a 62-year-old patient through endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). A. Nasopharyngoscopy only revealed fibrosis and scarring changes in the nasopharyngeal mucosa. B. A chest computed tomography (CT) scan showed enlargement of the subcarinal lymph node. C. Localization and measurement of the subcarinal lymph node using EBUS. D. Real-time EBUS-TBNA with the needle positioned inside the lymph node. E. Aspiration of tissue samples during EBUS-TBNA. F. Retrieval of liquid-based cytology specimens during EBUS-TBNA.

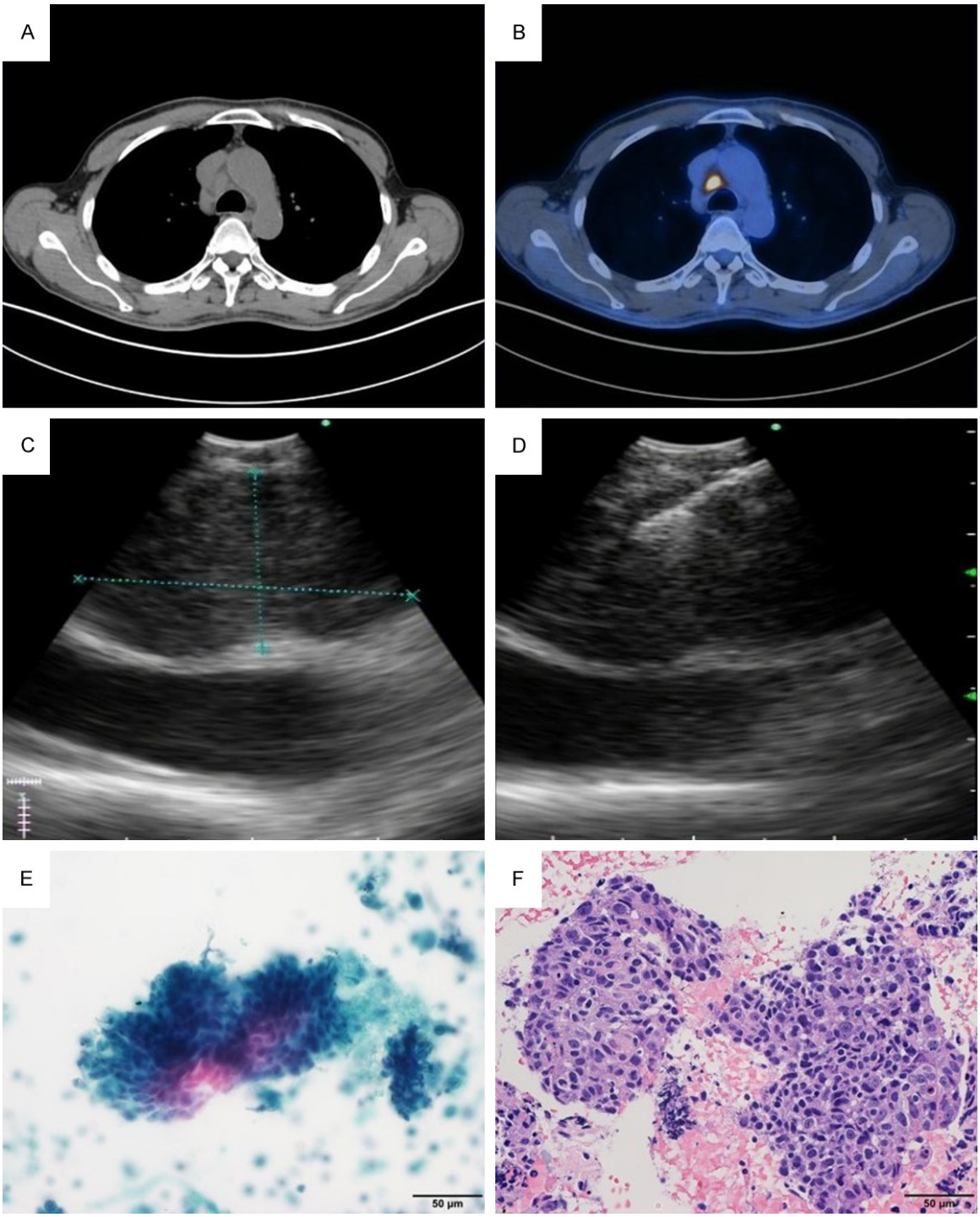

Figure 2. Representative CT, positron emission tomography-computed tomography (PET-CT), and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) images of a 54-year-old patient with nasopharyngeal carcinoma (NPC) and suspected intrathoracic metastases. A. A chest CT examination revealed an enlarged right lower paratracheal lymph node. B. PET-CT demonstrated significant enhancement of the lymph node. C. Localization and measurement of the right lower paratracheal lymph node using EBUS. D. Real-time EBUS-TBNA with the needle positioned inside the lymph node. E. Cytology showing clusters of malignant epithelial cells (Papanicolaou staining ×40). F. Histology displaying NPC metastasis (hematoxylin-eosin staining ×40).

Pathological examination

On-site cytological evaluation was not performed during the procedure. Two pathologists independently diagnosed the samples and reached a consensus afterward. The pathology samples were categorized as malignant, non-malignant, or indeterminate. Due to the lack of on-site cytological analysis, the adequacy of cellular quantity in tissue samples could not be assessed. Therefore, EBUS-TBNA was used to determine if each sampling region had been sufficiently evaluated.

Samples were diagnosed as positive for cancer if the presence of malignant tumor cells was confirmed by immunohistochemistry. Patients without a definitive diagnosis were advised to undergo mediastinoscopy, VATS, or repeat EBUS-TBNA. Those who declined these procedures were monitored clinically and radiologically for at least 12 months.

Outcome measures

NPC cases with intrathoracic lymph node metastasis identified through EBUS-TBNA were classified as positive. Negative findings of EBUS-TBNA were validated through alternative biopsy methods such as thoracoscopic surgery, repeated EBUS-TBNA, or mediastinoscopic surgery. Patients ineligible for surgical biopsy were monitored every three months for at least one year using bronchoscopy and imaging techniques. Stable or reduced dimensions of intrathoracic masses or thoracic lymph nodes over a 12-month period were classified as true negatives, while indications of advancement led to follow-up EBUS-TBNA or surgical biopsy. Patients with metastatic NPC confirmed by alternative biopsy methods during the one-year follow-up were classified as false negatives, while those without confirmation were considered true negatives.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (for normally distributed data, assessed using the Kolmogorov-Smirnov test) or median with interquartile range (for non-normally distributed data). Categorical variables were reported as numbers and percentages and analyzed using the χ^2 test or Fisher's exact test.

Predictive factors of malignant lymphadenopathy were identified through univariate logistic regression, and significant variables ($P < 0.05$) were included in the multivariate regression model. Statistical analyses were performed using SPSS software version 27.0 (IBM Corp., Armonk, NY, United States), with $P < 0.05$ considered statistically significant.

Results

Baseline characteristics

A total of 5,437 individuals underwent EBUS-TBNA at our institution from June 2015 to June 2022. After excluding 5,340 cases that did not meet the inclusion criteria (5,019 without an NPC diagnosis, 43 with previous or concurrent lymphoma or leukemia, and 215 with puncture sites outside the intrathoracic lymph node or incomplete information), 97 patients were selected for the study (**Figure 3**). The study cohort comprised 75 males and 22 females, with ages ranging from 18 to 73 years and an average age of 48.3±11.7 years. Approximately 79.4% of the enlarged lymph nodes within the thoracic cavity were detected in the mediastinal and hilar areas, with confirmation often through CT or PET-CT imaging (**Table 1**). A total of 108 lymph nodes were punctured in these patients via EBUS-TBNA, averaging one lymph node sampled per individual. To obtain samples for pathological diagnosis, each lymph node was punctured one to seven times, with an average of three punctures per node. The short diameters of the lymph nodes ranged from 5 to 45 mm, with an average diameter of 16.6 mm (**Table 1**).

Results of EBUS-TBNA

EBUS-TBNA identified intrathoracic nodal metastasis in 59 (60.8%) patients and diagnosed intrathoracic lymphadenopathy caused by primary lung adenocarcinomas in 3 (3.09%) patients. Negative EBUS-TBNA results were observed in 35 (36.1%) patients, of whom 25 (25.7%) showed no radiological changes during the minimum 12-month follow-up period. Ten (10.3%) cases were initially false-negative, with non-specific or normal lymph node tissues noted in pathological examination. One of these cases was later diagnosed through surgical intervention elsewhere. The remaining 9 patients had clinically interpreted lymphade-

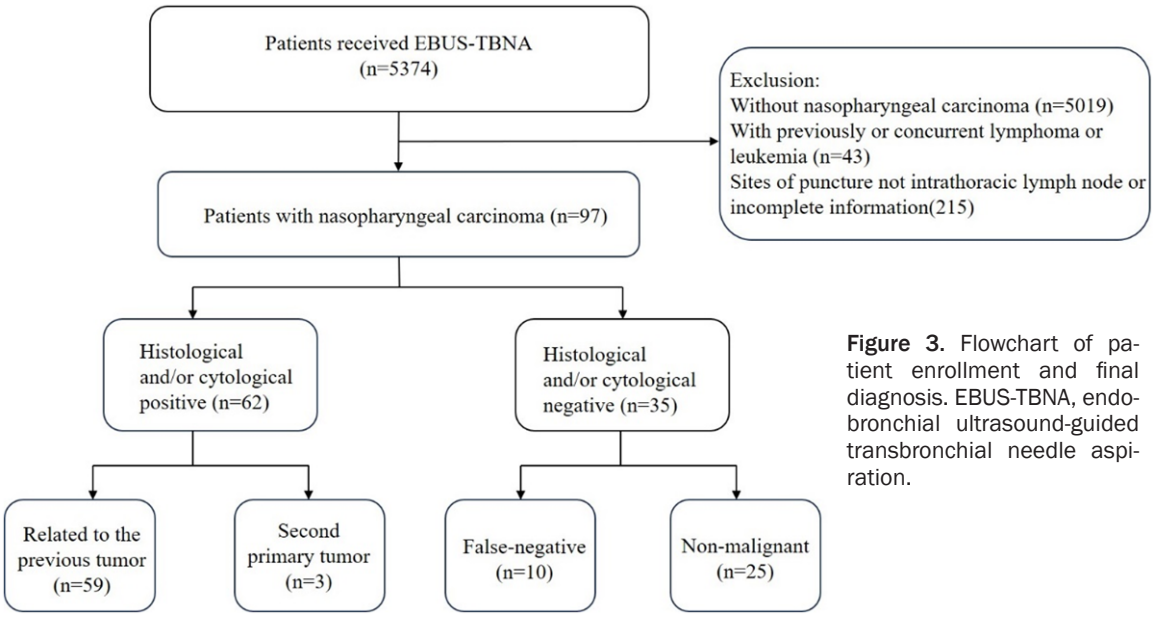

Figure 3. Flowchart of patient enrollment and final diagnosis. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Table 1. The general characteristics of patients and samples

Characteristics	Value
Age, years	
Mean ± SD	48.3±11.7 (18-73)
Gender, n (%)	
Male	75 (77.3)
Female	22 (22.7)
Site of intrathoracic lymphadenopathy, n (%)	
Mediastinal only	15 (15.5)
Mediastinal and hilar	77 (79.4)
Hilar only	5 (5.1)
Status of NPC, n (%)	
Synchronous	15 (15.5)
Metachronous	82 (84.5)
Computed tomography (CT) findings, n (%)	
Intrathoracic nodal enlargement with pulmonary lesion	46 (47.4)
Short axis of the target lymph node in mm	16.6±6.8
Positron emission tomography-computed tomography (PET-CT) findings, n (%)	
Patients with PET-CT examination	38 (39.2)
SUVmax of lymph nodes	11.2±6.5
Number of passes per lymph node, times, median (range)	3 (1-7)

SUV, standardized uptake value.

nopathy as metastatic NPC, leading to systemic chemotherapy recommendations (**Figure 3**; **Table 2**).

Ultimately, 69 (71.1%) patients were diagnosed with NPC and intrathoracic lymph node metastasis, with 3% showing nodal involvement in primary lung cancer. The remaining 25 (25.8%) patients had benign conditions like sarcoidosis, tuberculosis, and reactive lymphadenitis. For patients with intrathoracic lymphadenopathy, EBUS-TBNA demonstrated 86.1% diagnostic sensitivity (62/72), 89.7% accuracy (87/97), and 71.4% negative predictive value (NPV,

Table 2. Pathological diagnosis of overall lymph node station sampled by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (n = 108)

Lymph node station	Case	Histological positive (n)	Cytological positive (n)	Total positive (n)	Total positive (%)
Mediastinal lymph nodes					
#2L	2	1	1	1	50
#2R	2	1	0	1	50
#4L	5	1	1	1	20
#4R	24	15	14	15	62.5
#7	45	31	26	31	68.9
Hilar lymph nodes					
#10L	7	4	3	4	57.1
#10R	10	5	5	5	50
#11L	2	1	0	1	50
#11R	11	6	6	6	54.5
Total	108	65	56	65	60.2

Table 3. Factors associated with malignant intrathoracic lymphadenopathy

Covariates	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex				
Female	1			
Male	0.784 (0.294-2.092)	0.627		
Age (years)				
≤ 60	1			
> 60	0.480 (0.161-1.426)	0.186		
Size of sampled lymph node	1.213 (1.090-1.350)	< 0.001	1.116 (1.005-1.240)	0.041
Site of lymphadenopathy				
Mediastinal and hilar	1			
Mediastinal only	0.498 (0.167-1.487)	0.211		
Hilar only	1.935 (0.215-17.435)	0.556		
Status of synchronous lung lesion				
Without	1		1	
With	9.625 (3.071-30.165)	< 0.001	9.750 (3.071-30.165)	0.001
Status of synchronous nasopharyngeal carcinoma (NPC)				
Synchronous	1		1	
Metachronous	12.316 (3.602-42.109)	< 0.001	11.274 (2.289-55.528)	0.003

25/35). We also compared the effectiveness of EBUS-TBNA with PET-CT in 38 NPC patients using an standardized uptake value (SUV) max threshold of ≥ 2.5 to distinguish malignant cases [13]. In these patients, the accuracy of EBUS-TBNA was 81.6% (31/38) compared to 65.8% (25/38) for PET-CT (Supplementary Table 1).

Predictors of malignant lymphadenopathy

The univariate regression model revealed that metastatic lymphadenopathy was significantly associated with a longer lymph node short axis, metachronous NPC, and synchronous lung lesions (P < 0.001 for all). Additionally, longer lymph node short axis (OR: 1.116, 95% CI: 1.005-1.24; P = 0.041), metachronous NPC (OR: 11.274, 95% CI: 2.289-55.528; P = 0.001), and synchronous lung lesions (OR: 9.75, 95% CI: 3.071-30.165; P = 0.003) were independent predictors of intrathoracic lymphadenopathy in the multivariate regression model (**Table 3**). We also conducted a univariate logistic regression analysis using clinical and lesion data to iden-

Table 4. Factors influencing the accuracy of endobronchial ultrasound-guided transbronchial needle aspiration for intrathoracic malignant lymphadenopathy

Covariates	Accurate number, n (%)	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value
Sex					
Female	19 (95)	1			
Male	46 (82.1)	4.130 (0.494-34.548)	0.191		
Age (years)					
≤ 60	56 (84.8)	1			
> 60	9 (90)	1.607 (0.183-14.115)	0.669		
Location of sampled lymph node					
Hilar	16 (88.9)	1			
Paratracheal	19 (79.2)	0.475 (0.081-2.787)	0.410		
Subcarinal	30 (88.2)	0.938 (0.155-5.686)	0.944		
Determination of target lymph node					
PET-CT and CT	18 (66.7)	1			
CT only	47 (95.9)	3.937 (1.034-14.987)	0.044	2.275 (0.501-10.324)	0.287
Size of short axis in sampled lymph node in mm	17 (8-45)	1.366 (1.090-1.712)	0.007	1.305 (1.044-1.631)	0.019
Number of passes per lymph node, times, median (range)	3 (1-7)	1.445 (0.751-2.782)	0.270		
Operator of EBUS-TBNA					
Senior doctors	33 (91.7)	1			
Junior doctors	32 (80)	0.364 (0.088-1.494)	0.161		

PET-CT, positron emission tomography-computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

tify factors influencing the diagnostic precision of EBUS-TBNA for intrathoracic malignant lymph nodes. As shown in **Table 4**, longer lymph node short axis and CT examination alone prior to EBUS-TBNA were identified as potential risk factors (P = 0.007 and P = 0.044, respectively). Multivariate analysis further indicated that an increased lymph node short axis (OR: 1.305, 95% CI: 1.044-1.631) was the sole determinant of the diagnostic precision of EBUS-TBNA.

Discussion

In recent years, the overall survival of patients diagnosed with NPC has significantly improved due to advances in treatment modalities. However, the presence of intrathoracic nodal metastasis adversely affects the prognosis of NPC patients. Conventional diagnostic techniques, such as CT and PET-CT imaging, have limited accuracy in detecting malignant growth within the mediastinum. Moreover, routine pathological examination cannot distinguish between primary and metastatic tumors. Over the past few years, minimally invasive imaging techniques like mediastinoscopy and thoracoscopy have been gradually replacing thoracotomy biopsy procedures for thoracic examination to reduce collateral trauma and postoperative complications. However, these novel imaging modalities also have drawbacks, including the need for prolonged general anesthesia, an increased risk of postoperative complications, higher medical expenses, and potential surgical scarring [21, 22]. These limitations can hinder accurate diagnosis of intrathoracic metastases, leading to unfavorable long-term outcomes and missed salvage opportunities.

Convex probe EBUS was developed in 2002 for staging lymph nodes in pulmonary malignancies, incorporating an ultrasonic probe and a small puncture biopsy needle. EBUS-TBNA has been recommended by the American College of Chest Physicians and European Society of Thoracic Surgeons for obtaining samples from mediastinal and hilar lymph nodes in primary lung cancer cases [23, 24]. Endosonographic biopsy is considerably safer compared to invasive surgical examination, with a low complication rate of 0.36% and no reported deaths [25, 26]. However, there are reports indicating that EBUS-TBNA can lead to bleeding, infections, collapsed lungs, and perforations [26], although we did not observe any such complications in our follow-up records. Based on our study findings and prior research, EBUS-TBNA can be considered a safe technique for sampling intrathoracic lymph nodes.

In a meta-analysis, EBUS-TBNA demonstrated a 96% accuracy rate, 90% sensitivity, and 93%

NPV in the staging of mediastinal cancer [27]. Previous studies have also reported that EBUS-TBNA can diagnose intrathoracic metastases of extrathoracic malignancies with sensitivities ranging from 83.3% to 93.3% [10, 28, 29]. Consistent with these findings, the sensitivity, accuracy, and NPV of EBUS-TBNA for detecting intrathoracic metastases of NPC in our study were 86.1%, 89.7%, and 71.4%, respectively. Given that intrathoracic metastases suggest advanced primary NPC, prompt and accurate determination of lymph node nature is crucial for appropriate staging and treatment planning. Based on our results, EBUS-TBNA is recommended for the initial diagnosis of NPC mediastinal and hilar lymphadenopathies.

In our study cohort, pathological examination confirmed 65 malignant lesions detected by EBUS-TBNA in 62 patients. Additionally, histological examination provided a definitive diagnosis for nine lesions with negative cytological smear results. Similarly, Vaidya et al. demonstrated a higher diagnostic sensitivity of histological examination compared to cytological smears (85% vs. 65%) [30]. However, Tian et al. showed that cytology smears provided a conclusive diagnosis for 11 patients with negative histological results [31]. Furthermore, another study indicated that results from EBUS-TBNA were more reliable for cytological assessment than histological evaluation, with a success rate of 81.9% versus 68.4% [32]. These discrepancies can be attributed to the use of different tissue preparation techniques. Therefore, combining standard cytological methods with histological analysis can yield the most informative outcomes.

In our cohort, 59 patients received a final diagnosis of intrathoracic lymphadenopathy metastasis of primary NPC, and the majority of these cases underwent concurrent platinum-based chemoradiotherapy. The remaining three patients were diagnosed with primary lung adenocarcinoma, requiring a different treatment approach. Thus, EBUS-TBNA can not only effectively prevent treatment delays in cases of recurrence but also avoid unnecessary therapy in patients with a history of cancer who develop a second primary tumor.

Radiological identification of nodal involvement primarily relies on morphological features such as size increase, pulmonary involvement on CT scans, and lymph nodes measuring over 2 cm in the shorter axis [33]. Our study revealed that lymph node size, concurrent lung abnormalities, and metachronous NPC can independently predict intrathoracic lymph node metastasis. Additionally, intrathoracic lymphadenopathy and a lung lesion may indicate primary lung cancer. Therefore, distinguishing between a primary lung tumor and intrathoracic lymph node enlargement in patients with a history of NPC is crucial, and EBUS-TBNA can provide valuable pathological evidence in such cases.

The diagnostic success of EBUS-TBNA is influenced by the number of attempts, operator expertise, and the quantity of sampled lymph nodes [34]. We observed a significant association between the larger width of the lymph node's shorter axis and the diagnostic accuracy of EBUS-TBNA. Moreover, lesion size may impact diagnostic accuracy, as evidenced by Marchand et al., who reported slightly reduced sensitivity for smaller nodes (< 10 mm) compared to larger nodes (> 20 mm), although overall sensitivity exceeded 95% [35]. Additionally, Chen et al. noted a direct correlation between lymph node dimensions and biopsy positivity rate ($P = 0.021$), highlighting challenges in sampling small lesions due to breathing motions [36].

There were several limitations in this study that need addressing. Being retrospective, the study was susceptible to selection bias as patients undergoing EBUS-TBNA were selected based on clinical criteria. Moreover, the study was conducted at a single site with a limited sample size. Although our hospital's EBUS database is the largest in South China, with around 36,566 initially diagnosed NPC patients from 2015 to 2022, only 97 met the inclusion criteria after almost 7 years of data retrieval. Notably, only a small number of NPC patients (28 cases) were included in the two previous studies by other investigators [37, 38]. There is a lack of expanding research on the differential diagnosis of intrathoracic lymphadenopathy in NPC patients using EBUS-TBNA. Fortunately, a significant percentage of patients in our group (46 out of 97) underwent EBUS-TBNA after 2020, indicating growing awareness of its benefits for NPC patients with suspected intrathoracic lymph nodes.

In conclusion, EBUS-TBNA accurately diagnoses suspected intrathoracic lymph nodes in NPC patients and guides subsequent treatment. Importantly, no significant complications were observed related to its implementation.

Acknowledgements

We thank all the patients for their participation.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Diagnostic value of EBUS-TBNA and PET-CT in detecting intrathoracic lymphadenopathy of NPC patients

	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
EBUS-TBNA	81.6	72	100	100	65
PET-CT	65.8	100	0	65.8	0

EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; PET-CT, positron emission tomography/computed tomography; PPV, positive predictive value; NPV, negative predictive value.