ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 December 26; 10(36): 13148-13469

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents Thrice Monthly Volume 10 Number 36 December 26, 2022

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 36 December 26, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 36 December 26, 2022

Contents

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 36 December 26, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Janardhan Mydam, MD, Assistant Professor, Consultant Physician-Scientist, Statistician, Division of Neonatology, Department of Pediatrics, John H. Stroger, Jr. Hospital of Cook County1969 W. Ogden, Chicago, IL 60612, United States. mydamj@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
December 26, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 December 26; 10(36): 13227-13238

DOI: 10.12998/wjcc.v10.i36.13227

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic lymphadenopathy with extrathoracic malignancy

Shi-Jie Li, Qi Wu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Esch M, Germany; Moshref L, Saudi Arabia

Received: July 7, 2022
Peer-review started: July 7, 2022
First decision: October 27, 2022
Revised: November 7, 2022
Accepted: December 5, 2022
Article in press: December 5, 2022
Published online: December 26, 2022

Shi-Jie Li, Endoscopy Center, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing 100142, China

Qi Wu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing 100142, China

Corresponding author: Qi Wu, MD, Chief Physician, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, No. 8 Fucheng Road, Haidian District, Beijing 100142, China. wuqi1973@bjmu.edu.cn

Abstract

BACKGROUND

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of mediastinal and hilar lymph is poorly studied in patients with extrathoracic malignancies.

AIM

To evaluate the value of EBUS-TBNA for the diagnosis of enlarged intrathoracic lymph nodes in patients with extrathoracic malignancies.

METHODS

This was a retrospective study of patients with extrathoracic malignancies who were referred to Peking University Cancer Hospital from January 2013 to December 2018 for EBUS-TBNA due to intrathoracic lymphadenopathy. The specimens were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without a definitive diagnosis. Sensitivity, negative predictive value (NPV) for malignancy, and overall accuracy were calculated. Complications were recorded.

RESULTS

A total of 80 patients underwent EBUS-TBNA and had a final diagnosis, among which 50 (62.5%) were diagnosed with extrathoracic malignancy with intrathoracic lymph nodes metastasis, 14 (17.5%) were diagnosed with primary lung cancer with nodal involvement, and 16 (20.0%) exhibited benign behavior including tuberculosis, sarcoidosis and reactive lymphadenitis or who had benign follow-up. The diagnostic sensitivity, NPV, and accuracy of EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy were 93.8% (n = 60/64), 80.0% (n = 16/20), and 95.0% (n = 76/80), respectively. In the

multivariate analysis, longer short axis of the lymph node (OR: 1.200, 95%CI: 1.024-1.407; P = 0.024) and synchronous lung lesion (OR: 19.449, 95%CI: 1.875-201.753; P = 0.013) were independently associated with malignant intrathoracic lymphadenopathy. No characteristics of the lymph nodes and EBUS-TBNA were associated with the location of malignant intrathoracic lymphadenopathy, and no major complication was observed.

CONCLUSION
EBUS-TBNA is a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy.

Key Words: Endobronchial ultrasound; Intrathoracic lymphadenopathy; Extrathoracic malignancy; Transbronchial needle aspiration; Diagnosis

Core Tip: This was a retrospective study of patients referred to Peking University Cancer Hospital from January 2013 to December 2018 for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) due to intrathoracic lymphadenopathy. The specimens were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without definite diagnosis. Sensitivity, negative predictive value for malignancy, and overall accuracy were calculated. EBUS-TBNA was found to be a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy.

Citation: Li SJ, Wu Q. Endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic lymphadenopathy with extrathoracic malignancy. *World J Clin Cases* 2022; 10(36): 13227-13238
URL: https://www.wjgnet.com/2307-8960/full/v10/i36/13227.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i36.13227

INTRODUCTION

Intrathoracic lymphadenopathy is a common incidental finding by computed tomography (CT) or positron emission tomography (PET)-CT in cases with synchronous or metachronous extrathoracic malignancies[1-3]. In such conditions, the causes of mediastinal or hilar nodal enlargement may be distal metastasis of the extrathoracic lesion, metastasis from a primary lung cancer synchronous with the extrathoracic malignancy, or even benign lesions including tuberculosis, granulomatous inflammation, and reactive changes[3-5]. In all of these situations, pathologic confirmation of the enlarged lymph node is crucial for the proper staging and management of patients[1].

Mediastinoscopy is considered the "gold standard" in nodal evaluation for intrathoracic lymphadenopathy, but it is invasive and requires general anesthesia[6]. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is currently the preferred modality to sample both mediastinal and hilar lymph nodes in primary lung cancer because it is not only minimally invasive but also can be performed under moderate conscious sedation or even under intratracheal surface anesthesia only[7,8]. Tournoy *et al*[9] showed that EBUS-TBNA is a diagnostic test for lung lesions after failed diagnostic bronchoscopy. A number of studies have shown that EBUS-TBNA is of value for the staging of lung cancer, as reviewed by Sehgal *et al*[10]. EBUS-TBNA is also of value for the diagnosis of mediastinal lymphoma[11]. In clinical practice, EBUS-TBNA could be considered the first-line examination for suspicious mediastinal lymph nodes in patients with extrathoracic cancer, preventing surgery in 50% of them[12]; in contrast, the use of EBUS-TBNA in intrathoracic lymphadenopathy in patients with extrathoracic solid organ malignancy is a relatively less investigated topic[13,14].

Therefore, the aim of this study was to evaluate the value of EBUS-TBNA for the diagnosis of enlarged intrathoracic lymph nodes in patients with extrathoracic malignancies.

MATERIALS AND METHODS

Patients

This study was designed as a single-center retrospective case series study. Data from patients who were referred to Peking University Cancer Hospital (Beijing, China) from January 2013 to December 2018 for EBUS-TBNA due to intrathoracic lymphadenopathy were retrieved from the hospital database. The

study was conducted according to good clinical practice and the Declaration of Helsinki. The protocol was approved by the ethics committee of Peking University Cancer Hospital (No. 2018YJZ72), which waived the need for individual consent.

The inclusion criteria for patients were synchronous or metachronous extrathoracic solid organ malignancy, and available radiological data including from CT or PET-CT scan. The exclusion criteria were synchronous or metachronous lymphoma or leukemia, or follow-up of < 12 mo when no definite diagnosis could be obtained by EBUS-TBNA with/without other interventional procedures including mediastinoscopy or thoracoscopy.

EBUS-TBNA procedures

Before EBUS-TBNA, the target lymph nodes for sampling were selected according to enlarged mediastinal or hilar lymph node with a short axis > 10 mm in thorax CT or maximum standardized uptake (SUV_{max}) value > 2.5 in PET-CT. The lymph node map was determined according to the classification proposed by the International Association for the Study of Lung Cancer[15].

EBUS-TBNA was performed in an outpatient setting using a flexible bronchoscope (BF-UC260F-OL8; Olympus, Tokyo, Japan) by 1 of 2 experienced endoscopists (QW or SJL). First, local anesthesia was applied *via* aerosol inhalation and intratracheal spray of 2% lidocaine. Then, the EBUS scope was introduced, and all reachable lymph node stations were examined. Sampling was performed from mediastinal and hilar lymph nodes that had been previously identified as suspicious by imaging and were able to be accessed by EBUS-TBNA. For each target lesion, real-time punctures were made using a standard 22-gauge needle (ECHO-HD-22-EBUS-O; Cook Medical, Bloomington, IN, United States). Attempts were made to acquire both cytological and histological specimens during sampling, if possible (Figure 1). Major complications (*e.g.*, serious hemorrhage > 100 mL, pneumothorax, and post-procedure infection) that occurred during and/or after surgery were recorded.

Pathological examinations

The cytological samples were prepared as air-dried smears on glass slides and in liquid fixative for thinprep cytological test. They histological specimens were fixed in formalin solution, and immunohistochemistry was performed when necessary (Figure 1).

The specimens obtained from EBUS-TBNA were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without definite diagnosis. In cases of no definite diagnosis, mediastinoscopy, video-assisted thoracic surgery (commonly known as VATS), or repeated EBUS-TBNA was recommended; patients who refused were subject to at least 12 mo of radiological and clinical follow-up every 3 mo. Follow-up was censored on December 31, 2018.

Statistical analyses

SPSS 20.0 software (IBM Corp., Armonk, NY, United States) was used for the statistical analyses. Continuous variables are presented as either means ± SD (normal distribution, Kolmogorov-Smirnov test) or median (minimum-maximum) (non-normal distribution). Categorical variables are presented as numbers and percentages and were analyzed using either the χ^2 test or the Fisher's exact test, as appropriate. Sensitivity for malignancy, negative predictive value (NPV) for non-malignancy, and overall accuracy were calculated. Predictors of malignant lymphadenopathy were modeled using logistic regression (enter method); variables with $P < 0.05$ in univariate analyses were included in multivariate analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 1204 patients who underwent EBUS-TBNA were reviewed. After exclusion of 1124 cases [without known extrathoracic malignancy (n = 1112), with previously or concurrent lymphoma or leukemia (n = 7), with sites of puncture not at the intrathoracic lymph node (n = 3), and with follow-up of less than 12 mo (n = 2)], 80 fulfilled the eligibility criteria (Figure 2). Among the cases included in the study (Table 1), the most common extrathoracic malignancies (65%) were breast, colorectal, and gastric cancers.

Details of the EBUS-TBNA procedures

The 80 included patients had a total of 123 enlarged lymph nodes sampled by EBUS-TBNA (median of one lymph node every patient; range: 1-4). Cytological specimens were successfully acquired from all 80 patients, and histological specimens were available for 74 (92.5%). The paratracheal region was the most common site (42.2%) for puncture (Table 2). The median number of puncture times was two for each lymph node (range: 1-6).

Table 1 Patient characteristics, *n* = 80

Characteristics	*n* (%) or mean ± SD
Age (yr)	58.5 ± 8.8
Male sex	36 (45.0)
Site of the primary extrathoracic malignancy	
Breast	18 (22.5)
Colon	12 (15.0)
Rectal	11 (13.8)
Gastric	11 (13.8)
Renal cell	7 (8.8)
Thyroid	6 (7.5)
Head and neck[1]	5 (6.3)
Endometrial	3 (3.8)
Hepatic cell	2 (2.5)
Other[2]	5 (6.3)
Site of intrathoracic lymphadenopathy	
Mediastinal only	43 (53.8)
Mediastinal and hilar	21 (26.2)
Hilar only	16 (20.0)
Status of the extrathoracic malignancy	
Metachronous	66 (82.5)
Synchronous	14 (17.5)
CT findings	
Intrathoracic nodal enlargement with pulmonary lesion	39 (48.8)
Short axis of the target lymph node in mm	18.1 ± 6.7
PET-CT findings	
Patients with PET-CT examination	49 (61.3)
SUV_{max} of the target lymph nodes	9.2 ± 5.0

[1]Oropharyngeal (*n* = 2), nasopharyngeal (*n* = 1), laryngeal (*n* = 1), and parotid (*n* = 1).
[2]Cervical (*n* = 1), ovarian (*n* = 1), melanoma (*n* = 1), pancreatic (*n* = 1), and prostate (*n* = 1).
CT: Computed tomography; PET: Positron emission tomography; SUV_{max}: Maximum standardized uptake.

Pathology of lymph nodes

EBUS-TBNA diagnosed intrathoracic nodal metastasis from extrathoracic malignancy in 47 (58.8%) patients, and intrathoracic lymphadenopathy due to primary lung cancer in 13 (16.3%) patients (including 8 Lung adenocarcinomas, 3 Lung squamous carcinomas, and 2 small cell lung cancers). Regarding the 9 patients with benign diagnosis, sarcoidosis was diagnosed in 3, caseous granulomatosis with suspected tuberculosis in 3, and non-caseating granulomatous inflammation in 3. For the last 3, the inflammation was clinically inconsistent with sarcoidosis because of negative fungal and mycobacterial cultures. All 3 refused further interventional procedures, and after a median follow-up of 15 (14-19) mo, clinical and radiological results suggested benign behavior (all enlarged lymph nodes remained stable).

EBUS-TBNA found normal lymph node tissue or non-specific tissue for pathologic diagnosis in 11 (13.8%) patients. Six of them received surgical intervention (four mediastinoscopy procedures and two VATS procedures) to obtain pathologic results. Reactive change was found in 2 patients, tuberculosis was found in 1, squamous carcinoma of lung with hilar lymph node metastasis in 1, rectal cancer lung metastasis with nodal involvement in 1, and renal cell cancer with mediastinal nodal involvement in 1. The remaining 5 patients who refused surgical intervention received periodical clinical and radiologic follow-up. One patient had progressive lymphadenopathy that was clinically considered metastasis from extrathoracic malignancy (colon cancer) and accepted the recommendation of systemic

Table 2 Primary extrathoracic malignancy site and the final pathologic result of the intrathoracic lymphadenopathy

Extrathoracic malignancy	*n* (%)	Location			EBUS			Surgery			Follow-up	
		Paratracheal	Subcarinal	Hilar and lobar	ETM LNM	PLC LNM	Benign	ETM LNM	PLC LNM	Benign	FO	ETM LNM
Breast cancer	18 (22.5)	12	8	8	11	3	2	-	-	1	1	-
Colon cancer	12 (15.0)	8	4	4	7	3	-	-	-	-	1	1
Rectal cancer	11 (13.8)	4	2	8	7	3	-	1	-	-	-	-
Gastric cancer	11 (13.8)	7	5	6	6	2		-	-	1	1	-
Renal cell cancer	7 (8.8)	6	4	2	6	-	-	1	-	-	-	-
Thyroid cancer	6 (7.5)	6	2	2	1	2	3	-	-	-	-	-
Head and neck cancer[1]	5 (6.3)	3	3	2	3	-	-	-	1	1	-	-
Endometrial cancer	3 (3.8)	1	2	2	2	-	1	-	-	-	-	-
Hepatic cell cancer	2 (2.5)	1	1	0	2	-	-	-	-	-	-	-
Other[2]	5 (6.3)	4	2	4	2	-	2	-	-	-	1	-
Total	80 (100.0)	52	33	38	47	13	9	2	1	3	5	

[1]Oropharyngeal cancer (*n* = 2), nasopharyngeal cancer (*n* = 1), laryngeal cancer (*n* = 1), and parotid cancer (*n* = 1).
[2]Cervical cancer (*n* = 1), ovarian cancer (*n* = 1), melanoma (*n* = 1), pancreatic cancer (*n* = 1), and prostate cancer (*n* = 1).
EBUS: Endobronchial ultrasound-guided transbronchial needle aspiration; ETM: Extrathoracic malignancy; FO: Favorable outcome; LNM: Lymph node metastasis; PLC: Primary lung cancer.

chemotherapy by multidisciplinary team. The remaining 4 patients showed a favorable outcome (1 was stable and 3 showed regressive lymphadenopathy) during a median follow-up of 16 (13-18) mo.

Diagnostic accuracy

Ultimately, 50 (62.5%) patients were diagnosed with extrathoracic malignancy with intrathoracic lymph nodes metastasis and 14 (17.5%) with primary lung cancer with nodal involvement; the remaining 16 (20.0%) patients exhibited benign behavior including tuberculosis, sarcoidosis and reactive lymphadenitis, or who had benign follow-up. The diagnostic sensitivity, NPV, and accuracy of EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy were 93.8% (*n* = 60/64), 80.0% (*n* = 16/20), and 95.0% (*n* = 76/80), respectively.

Predictors of malignant lymphadenopathy

Univariate analyses revealed that longer short axis of the lymph node and synchronous lung lesion were associated with the presence of metastatic lymphadenopathy (*P* = 0.003 and *P* = 0.001, respectively). In the logistic regression multivariate model, longer short axis of the lymph node (OR: 1.200, 95%CI: 1.024-1.407) and synchronous lung lesion (OR: 19.449, 95%CI: 1.875-201.753) were independently associated with malignant intrathoracic lymphadenopathy (*P* = 0.024 and *P* = 0.013, respectively; Table 3).

Univariate analyses demonstrated that no characteristics of the lymph nodes themselves and EBUS-TBNA were associated with the yield of malignant intrathoracic lymphadenopathy (Table 4).

Safety of the EBUS-TBNA procedure

No major complications occurred during the EBUS-TBNA procedures. Twelve (15.0%) patients experienced transient hypoxemia and all recovered after immediate increase of oxygen flow.

DISCUSSION

EBUS-TBNA for the diagnosis of mediastinal and hilar lymph is poorly studied in patients with extrathoracic malignancies. This study's evaluation of the value of EBUS-TBNA for the diagnosis of enlarged intrathoracic lymph nodes in patients with extrathoracic malignancies suggested that the procedure is simple and accurate for diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy. Moreover, there were no complications.

Table 3 Risk factors of being malignant for intrathoracic lymphadenopathy

Covariates	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Sex				
Female	1			
Male	1.720 (0.727-4.071)	0.217		
Age (yr)				
≤ 60	1			
> 60	1.647 (0.696-3.900)	0.257		
Size of sampled lymph node	1.113 (1.036-1.196)	0.003	1.200 (1.024-1.407)	0.024
Site of lymphadenopathy				
Mediastinal and hilar	1			
Mediastinal only	1.244 (0.528-2.932)	0.617		
Hilar only	6.788 (0.819-56.257)	0.076		
Status of synchronous lung lesion				
Without	1		1	
With	8.082 (2.292-28.501)	0.001	19.449 (1.875-201.753)	0.013
Status of synchronous ETM				
Synchronous	1			
Metachronous	1.057 (0.629-1.776)	0.834		
SUV_{max} of sampled lymph node	0.987 (0.887-1.098)	0.806		

ETM: Extrathoracic malignancy; SUV_{max}: Maximum standardized uptake.

With the rapid development of cancer therapies, overall survival of patients has improved significantly[16]. Regular follow-up and surveillance are essential and, unfortunately, the detection of intrathoracic lymphadenopathy is not uncommon, due in part to improvements in imaging technologies. Up to 30% of extrathoracic malignancies may lead to intrathoracic lymph node metastasis[17]. The most common solid malignancies responsible include breast, colorectal, head and neck, melanoma, kidney, and stomach cancers[14,18,19]. This study showed that breast, colorectal, gastric, and renal cell cancers accounted for 73.4% (59/80) of the extrathoracic malignancies in our patients; of note, however, differences in other cancer types might simply be due to the differences in cancer types treated at our hospital.

Primary lung cancer with nodal involvement accounts for the majority of mediastinal and hilar lymphadenopathy cases[20], but Mehta *et al*[13] showed a high frequency of benign diagnoses. EBUS-TBNA is considered safe and feasible for tissue sampling with access to both mediastinal and hilar lymph nodes, which is recommended by both the American College of Chest Physicians and European Society of Thoracic Surgeons in primary lung cancer[7,8]. In a meta-analysis that included nine studies and 1066 patients, EBUS-TBNA had pooled sensitivity of 90%, accuracy of 96%, and NPV of 93% for mediastinal staging[21]. EBUS-TBNA also showed an acceptable diagnostic ability in determining intrathoracic lymphadenopathy with extrathoracic malignancy. In a meta-analysis of six studies (553 patients) by Yang *et al*[17], EBUS-TBNA provided pooled sensitivity of 85%, accuracy of 85%, and negative likelihood ratio of 16%. The present study revealed sensitivity, accuracy, and NPV of 93.8%, 95.0%, and 80.0%, respectively, by EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy, in accordance with a previous study[17]. As intrathoracic metastasis always indicates an advanced stage of the primary extrathoracic malignancy, early and accurate identification of the nature of the lymph node is important for staging, treatment strategy, and prognosis. Considering the promising diagnostic value of EBUS-TNBA, the procedure could be recommended as the first diagnostic procedure for mediastinal and hilar lymphadenopathies seen in extrathoracic malignancies.

Regarding granulomatous lymphadenitis, the diagnostic yield of EBUS-TBNA seems efficacious. A meta-analysis of 15 studies with 553 patients found that the pooled diagnostic accuracy for sarcoidosis was 79% by EBUS-TBNA[22]. Concerning tuberculous lymphadenitis diagnosis, in a meta-analysis of 14 studies with 684 patients, EBUS-TBNA showed a pooled diagnostic yield of 80%[23]. In regard to EBUS-TBNA for non-caseating granulomatous, more attention should be paid. Sanz-Santos *et al*[14] reported a

Table 4 Factors influencing endobronchial ultrasound-guided transbronchial needle aspiration accuracy in intrathoracic malignant lymphadenopathy, *n* = 94

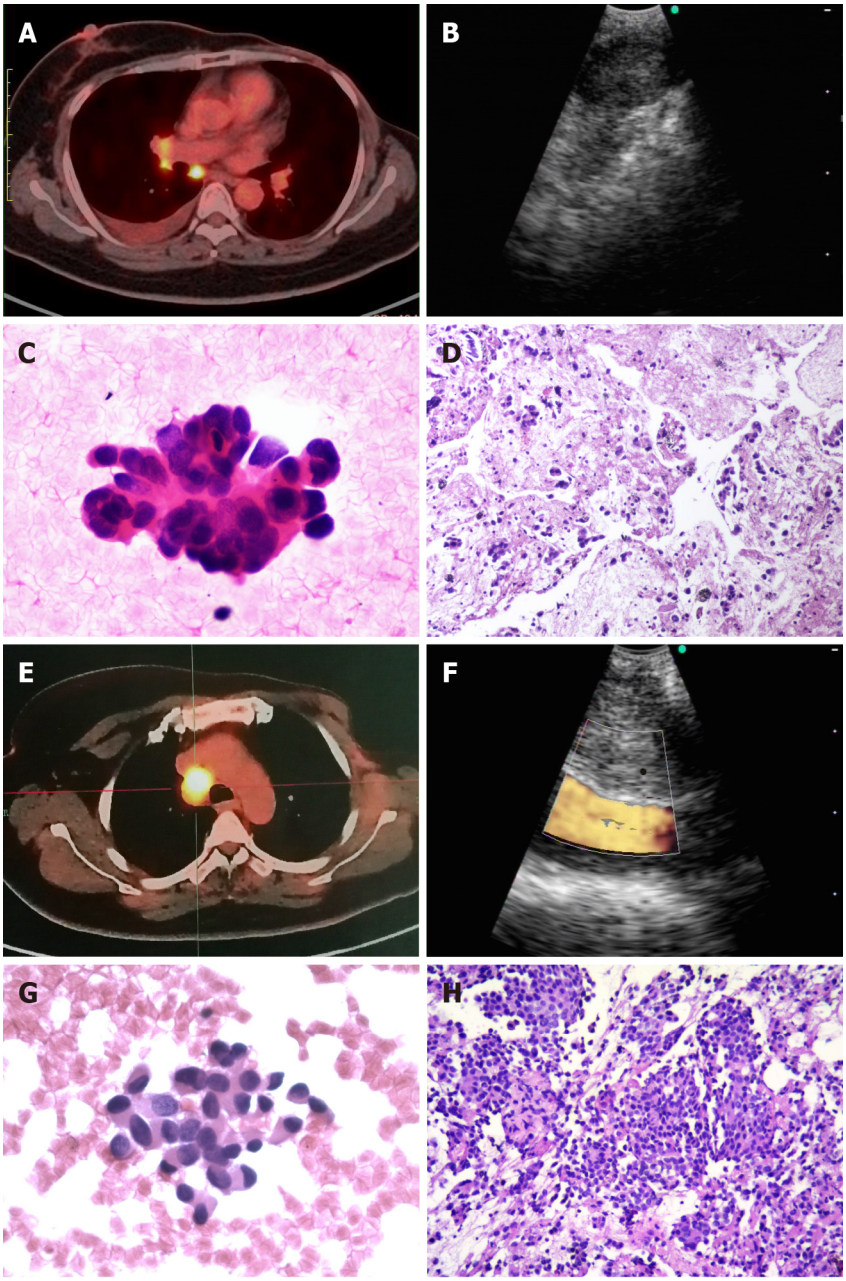
Covariates	Accurate number, *n* (%)	Univariate analysis OR (95%CI)	*P* value
Sex			
Female	46 (92.0)	1	
Male	41 (93.2)	1.783 (0.310-10.246)	0.571
Age (yr)			
≤ 60	47 (92.2)	1	
> 60	40 (93.0)	1.702 (0.296-9.785)	0.551
Location of sampled lymph node			
Hilar	27 (93.1)	1	
Paratracheal	36 (92.3)	2.000 (0.312-12.815)	0.465
Subcarinal	24 (92.3)	2.667 (0.260-27.381)	0.409
Determination of target lymph node			
PET-CT and CT	52 (90.0)	1	
CT only	35 (97.2)	3.365 (0.377-30.052)	0.277
Size of short axis in sampled lymph node in mm	18.9 ± 7.0	1.093 (0.975-1.248)	0.191
SUV_{max} of sampled lymph node	8.8 ± 5.1	0.877 (0.753-1.015)	0.077
Number of passes per lymph node, times, median (range)	2 (1-5)	2.097 (0.691-6.253)	0.193
Histological specimen acquired			
No	7 (87.5)	1	
Yes	80 (93.0)	2.286 (0.233-22.387)	0.478
Operator of EBUS-TBNA			
Dr. LSJ	70 (92.1)	1	
Dr. WQ	17 (94.4)	1.124 (0.133-11.085)	0.863

Data are presented as *n* (%) or mean ± SD, unless otherwise indicated. CT: Computed tomography; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; PET-CT: Positron emission tomography-computed tomography; SUV_{max}: Maximum standardized uptake.

case of non-caseating granulomatous detected by EBUS-TBNA that was diagnosed with lymphoma after 6 mo of follow-up. Kitamura *et al*[24] reported that 6% of patients with thoracic malignancy may have sarcoid-like reactions in non-metastatic lymph nodes. The present study found 3 patients with tuberculosis and 3 with sarcoidosis, but we could not obtain specimens for the 3 granulomatous cases and their benign behavior was merely determined through follow-up. These results suggest that in the case of the possibility of undiscovered malignancy, all granulomatous lymphadenitis cases diagnosed by EBUS-TBNA without obvious infection or sign of sarcoidosis should be followed with more attention or surgical interventions should be advised. Evison *et al*[25] suggested that for suspicious mediastinal and/or hilar lymph nodes but negative EBUS-TBNA, follow-up rather than resampling could be an appropriate approach.

The radiologic diagnosis of nodal involvement is mostly based on morphologic changes such as increase in size, coexistence of pulmonary lesions on CT scans, and lymph nodes > 2 cm in short axis [26]. In this study, both univariate and multivariate regression suggested that the diameter of the lymph node and synchronous lung lesion can be malignancy indicators. As intrathoracic lymph node metastasis is relatively common in primary lung cancer[4], patients with a history of extrathoracic malignancy, exhibiting intrathoracic lymphadenopathy combined with lung lesion, should be distinguished between distal metastasis and extrathoracic lesion and between intrathoracic metastasis and lung cancer. In such conditions, EBUS-TBNA may provide help in pathologic evidence acquisition.

PET-CT is widely used in cancer staging and distant metastasis detection. Generally, a SUV_{max} value > 2.5 could be clinically correlated with the risk of malignancy, and a SUV_{max} value > 6.3 is considered malignant with sensitivity and specificity of 70.6% and 83.3%, respectively[27]. In the present study, no



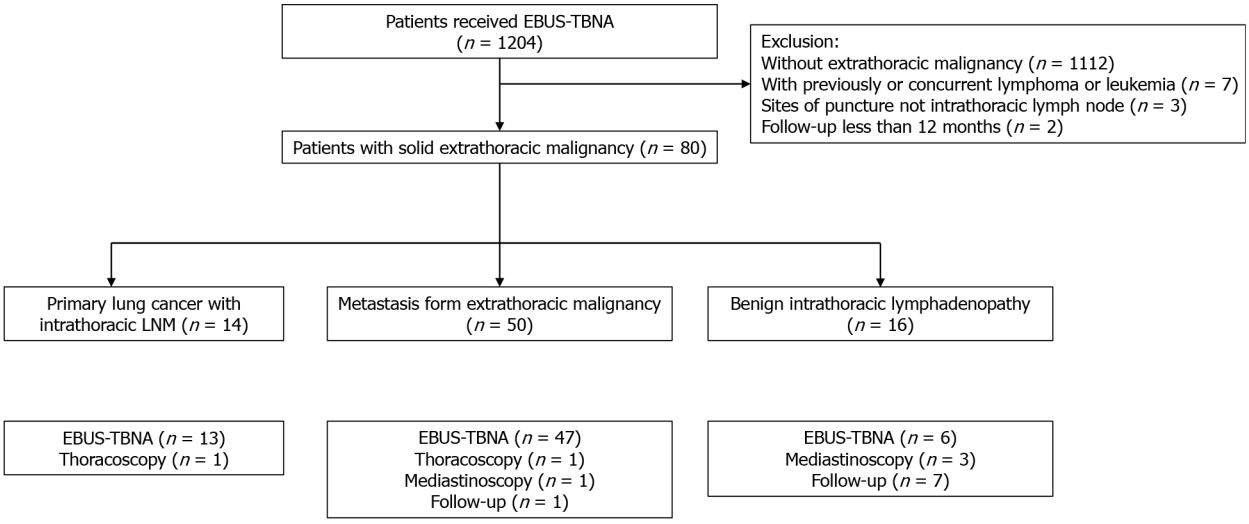
DOI: 10.12998/wjcc.v10.i36.13227

Figure 1 Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal lymphadenopathy in patients with history of resected breast cancer. A-D: Female (F)/age: 49 yr, left breast cancer resected 6 yr prior; A: Positron emission tomography-computed tomography (PET-CT) showed subcarinal region lymph node enlarged with maximum standardized uptake (SUV_{max}) value of 8.1 and right pleura effusion; B: Endobronchial ultrasound (EBUS) scanning for the subcarinal region lymph node; C: Cytology showed adenocarcinoma cells. Hematoxylin and eosin (H&E) staining 40 × 10; D: Histology showed pulmonary adenocarcinoma, H&E staining 40 × 10; E -F: F/age: 45 yr, left breast cancer resected 3 yr prior; E: PET-CT showed right lower paratracheal region lymph node enlarged with SUV_{max} value of 8.8; F: EBUS scanning for the right lower paratracheal region lymph node; G: Cytology showed adenocarcinoma cells; H: Histology showed breast cancer metastasis, H&E staining 40 × 10).

significant relationship was found between the SUV_{max} value and the presence of malignancy. This may be due to the possibility that increased SUV_{max} values can also be seen in benign pathologies involving inflammation such as sarcoidosis and infectious disease[5]. Moreover, not all patients in our study underwent PET-CT, which may have also caused data bias.

As with other interventional procedures, the high diagnostic yield of EBUS-TBNA is associated not only with lesion-related factors such as size, location, and metabolic activity but also with procedure-related factors such as the operator's experience, number of passes, and number of lymph nodes sampled[28]. In this study, none of the above factors showed a significant relationship with accurate diagnosis in malignancy. That may be caused by mixture of multiple lesion categories.

This study had a couple of limitations. First, it was a retrospective study, which intrinsically has a certain selection bias. Second, several cases without definite diagnosis by EBUS-TBNA did not have histological confirmation. In the future, a well-designed prospective study should overcome the



DOI: 10.12998/wjcc.v10.i36.13227

Figure 2 Patient flowchart by endobronchial ultrasound-guided transbronchial needle aspiration findings, follow-up, and final diagnosis.
EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; LNM: Lymph node metastasis.

limitations above.

CONCLUSION

In conclusion, EBUS-TBNA is a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy. Its application resulted in no major complications.

ARTICLE HIGHLIGHTS

Research background

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an established technique for the diagnosis of mediastinal and hilar lymphadenectasis in primary lung cancer, but is poorly studied in patients with extrathoracic malignancies.

Research motivation

Regular follow-up and surveillance are essential in cancer patients, and the detection of intrathoracic lymphadenopathy in those with extrathoracic malignancies is not uncommon. EBUS-TBNA is recommended for tissue sampling both in mediastinal and hilar lymph nodes in lung cancer. Data on the usefulness of this technique in patients with extrathoracic malignancies remain limited.

Research objectives

In this study, we describe our experience with the use of EBUS-TBNA in patients with extrathoracic malignancies due to intrathoracic lymphadenopathy.

Research methods

The results of the sample acquired by EBUS-TBNA were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without definite diagnosis. Sensitivity, negative predictive value (NPV) for malignancy, and overall accuracy were ca-lculated. Complications were recorded.

Research results

The diagnostic sensitivity, NPV, and accuracy of EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy were 93.8% (n = 60/64), 80.0% (n = 16/20), and 95.0% (n = 76/80), respectively. Longer short axis of the lymph node (P = 0.024) and synchronous lung lesion (P = 0.013) were independently associated with malignant intrathoracic lymphadenopathy. No major complication was observed.

Research conclusions

EBUS-TBNA is a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy. Its application resulted in no major complications.

Research perspectives

This retrospective study demonstrates that EBUS-TBNA is effective and safe for diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy. Additional prospective studies are warranted to establish standards for higher diagnostic yield.

ACKNOWLEDGEMENTS

We thank Zhong-Hu He for his generous help with the data analyses.

FOOTNOTES

Author contributions: Li SJ and Wu Q carried out the studies; Li SJ performed the analyses and collected the data; Li SJ drafted the manuscript; Wu Q conceived and designed the study; All authors approved the final draft submitted.

Supported by The Wu Jieping Medical Foundation Special Fund for Clinical Research, No. 320.6750.2021-04-71; Open Research Fund of NHC Key Laboratory of Prevention and Treatment of Central Asia High Incidence Diseases, No. KF202101; and Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences, No. 2020-PT330-003.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Peking University Cancer Hospital (Approval No. 2018YJZ72).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: Contact lishijie@bjmu.edu.cn to obtain the anonymized dataset.

Country/Territory of origin: China

ORCID number: Shi-Jie Li 0000-0003-4914-0832; Qi Wu 0000-0002-1309-7054.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **Munden RF**, Carter BW, Chiles C, MacMahon H, Black WC, Ko JP, McAdams HP, Rossi SE, Leung AN, Boiselle PM, Kent MS, Brown K, Dyer DS, Hartman TE, Goodman EM, Naidich DP, Kazerooni EA, Berland LL, Pandharipande PV. Managing Incidental Findings on Thoracic CT: Mediastinal and Cardiovascular Findings. A White Paper of the ACR Incidental Findings Committee. *J Am Coll Radiol* 2018; **15**: 1087-1096 [PMID: 29941240 DOI: 10.1016/j.jacr.2018.04.029]

2 **Frank L**, Quint LE. Chest CT incidentalomas: thyroid lesions, enlarged mediastinal lymph nodes, and lung nodules. *Cancer Imaging* 2012; **12**: 41-48 [PMID: 22391408 DOI: 10.1102/1470-7330.2012.0006]

3 **Nin CS**, de Souza VV, do Amaral RH, Schuhmacher Neto R, Alves GR, Marchiori E, Irion KL, Balbinot F, Meirelles GS, Santana P, Gomes AC, Hochhegger B. Thoracic lymphadenopathy in benign diseases: A state of the art review. *Respir Med* 2016; **112**: 10-17 [PMID: 26860219 DOI: 10.1016/j.rmed.2016.01.021]

4 **Shroff GS**, Viswanathan C, Carter BW, Benveniste MF, Truong MT, Sabloff BS. Staging Lung Cancer: Metastasis. *Radiol Clin North Am* 2018; **56**: 411-418 [PMID: 29622076 DOI: 10.1016/j.rcl.2018.01.009]

5 **Larici AR**, Glaudemans AW, Del Ciello A, Slart RH, Calandriello L, Gheysens O. Radiological and nuclear medicine

imaging of sarcoidosis. *Q J Nucl Med Mol Imaging* 2018; **62**: 14-33 [PMID: 29190998 DOI: 10.23736/S1824-4785.17.03046-1]

6 **McNally PA**, Arthur ME. Mediastinoscopy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [PMID: 30521284]

7 **Silvestri GA**, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**: e211S-e250S [PMID: 23649440 DOI: 10.1378/chest.12-2355]

8 **De Leyn P**, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, Turna A, Van Schil P, Venuta F, Waller D, Weder W, Zielinski M. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014; **45**: 787-798 [PMID: 24578407 DOI: 10.1093/ejcts/ezu028]

9 **Tournoy KG**, Rintoul RC, van Meerbeeck JP, Carroll NR, Praet M, Buttery RC, van Kralingen KW, Rabe KF, Annema JT. EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. *Lung Cancer* 2009; **63**: 45-49 [PMID: 18514365 DOI: 10.1016/j.lungcan.2008.04.004]

10 **Sehgal IS**, Agarwal R, Dhooria S, Prasad KT, Aggarwal AN. Role of EBUS TBNA in Staging of Lung Cancer: A Clinician's Perspective. *J Cytol* 2019; **36**: 61-64 [PMID: 30745743 DOI: 10.4103/JOC.JOC_172_18]

11 **Dhooria S**, Mehta RM, Madan K, Vishwanath G, Sehgal IS, Chhajed PN, Prakash G, Gupta N, Bal A, Agarwal R. A Multicenter Study on the Utility of EBUS-TBNA and EUS-B-FNA in the Diagnosis of Mediastinal Lymphoma. *J Bronchology Interv Pulmonol* 2019; **26**: 199-209 [PMID: 31238329 DOI: 10.1097/LBR.0000000000000552]

12 **Fournier C**, Hermant C, Gounant V, Escarguel B, Thibout Y, Lachkar S, Raspaud C, Vergnon JM. Diagnostic of mediastinal lymphadenopathy in extrathoracic cancer: A place for EBUS-TBNA in real life practice? *Respir Med Res* 2019; **75**: 1-4 [PMID: 31235451 DOI: 10.1016/j.resmer.2019.03.001]

13 **Mehta RM**, Biraris P, Patil S, Singla A, Kallur K, Gasparini S. Utility of EBUS-TBNA in PET-positive mediastinal lymph nodes in subjects with extra-thoracic malignancy. *PLoS One* 2019; **14**: e0213437 [PMID: 30856231 DOI: 10.1371/journal.pone.0213437]

14 **Sanz-Santos J**, Cirauqui B, Sanchez E, Andreo F, Serra P, Monso E, Castellà E, Llatjós M, Mesa M, Ruiz-Manzano J, Rosell R. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of intrathoracic lymph node metastases from extrathoracic malignancies. *Clin Exp Metastasis* 2013; **30**: 521-528 [PMID: 23196318 DOI: 10.1007/s10585-012-9556-3]

15 **Rusch VW**, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P; Members of IASLC Staging Committee. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009; **4**: 568-577 [PMID: 19357537 DOI: 10.1097/JTO.0b013e3181a0d82e]

16 **Chen W**, Sun K, Zheng R, Zeng H, Zhang S, Xia C, Yang Z, Li H, Zou X, He J. Cancer incidence and mortality in China, 2014. *Chin J Cancer Res* 2018; **30**: 1-12 [PMID: 29545714 DOI: 10.21147/j.issn.1000-9604.2018.01.01]

17 **Yang B**, Li F, Shi W, Liu H, Sun S, Zhang G, Jiao S. Endobronchial ultrasound-guided transbronchial needle biopsy for the diagnosis of intrathoracic lymph node metastases from extrathoracic malignancies: a meta-analysis and systematic review. *Respirology* 2014; **19**: 834-841 [PMID: 24935652 DOI: 10.1111/resp.12335]

18 **Navani N**, Nankivell M, Woolhouse I, Harrison RN, Munavvar M, Oltmanns U, Falzon M, Kocjan G, Rintoul RC, Janes SM. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: a multicenter study. *J Thorac Oncol* 2011; **6**: 1505-1509 [PMID: 21792077 DOI: 10.1097/JTO.0b013e318223c3fe]

19 **Tertemiz KC**, Alpaydin AO, Karacam V. The role of endobronchial ultrasonography for mediastinal lymphadenopathy in cases with extrathoracic malignancy. *Surg Endosc* 2017; **31**: 2829-2836 [PMID: 27770251 DOI: 10.1007/s00464-016-5293-z]

20 **Detterbeck FC**, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**: e78S-e92S [PMID: 23649455 DOI: 10.1378/chest.12-2350]

21 **Dong X**, Qiu X, Liu Q, Jia J. Endobronchial ultrasound-guided transbronchial needle aspiration in the mediastinal staging of non-small cell lung cancer: a meta-analysis. *Ann Thorac Surg* 2013; **96**: 1502-1507 [PMID: 23993894 DOI: 10.1016/j.athoracsur.2013.05.016]

22 **Agarwal R**, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. *Respir Med* 2012; **106**: 883-892 [PMID: 22417738 DOI: 10.1016/j.rmed.2012.02.014]

23 **Li W**, Zhang T, Chen Y, Liu C, Peng W. Diagnostic Value of Convex Probe Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Mediastinal Tuberculous Lymphadenitis: A Systematic Review and Meta-Analysis. *Med Sci Monit* 2015; **21**: 2064-2072 [PMID: 26177653 DOI: 10.12659/MSM.894526]

24 **Kitamura A**, Takiguchi Y, Kurosu K, Takigawa N, Saegusa F, Hiroshima K, Nakajima T, Tanabe N, Nakatani Y, Yoshino I, Tatsumi K. Feasibility of cytological diagnosis of sarcoidosis with endobronchial US-guided transbronchial aspiration. *Sarcoidosis Vasc Diffuse Lung Dis* 2012; **29**: 82-89 [PMID: 23461069]

25 **Evison M**, Crosbie PA, Morris J, Martin J, Barber PV, Booton R. A study of patients with isolated mediastinal and hilar lymphadenopathy undergoing EBUS-TBNA. *BMJ Open Respir Res* 2014; **1**: e000040 [PMID: 25478187 DOI: 10.1136/bmjresp-2014-000040]

26 **Brufau BP**, Cerqueda CS, Villalba LB, Izquierdo RS, González BM, Molina CN. Metastatic renal cell carcinoma: radiologic findings and assessment of response to targeted antiangiogenic therapy by using multidetector CT. *Radiographics* 2013; **33**: 1691-1716 [PMID: 24108558 DOI: 10.1148/rg.336125110]

27 **Kandemir Z**, Sentürk A, Ozdemir E, Yildirim N, Hasanoğlu HC, Keskin M, Türkölmez S. The evaluation of hypermetabolic mediastinal-hilar lymph nodes determined by PET/CT in pulmonary and extrapulmonary malignancies: correlation with EBUS-TBNA. *Turk J Med Sci* 2015; **45**: 1234-1242 [PMID: 26775376]

28 **Muthu V**, Sehgal IS, Dhooria S, Prasad KT, Gupta N, Aggarwal AN, Agarwal R. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: Techniques and Challenges. *J Cytol* 2019; **36**: 65-70 [PMID: 30745744 DOI: 10.4103/JOC.JOC_171_18]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com