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Endobronchial ultrasound-guided transbronchial needle aspiration and cervical mediastinoscopy for mediastinal staging of non-small cell lung cancer: a retrospective comparison study

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Background: Invasive mediastinal lymph node staging is essential to resectable non-small cell lung cancer (NSCLC) patients. This retrospective study aimed to compare the diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) against cervical mediastinoscopy (CMS) in radiologically enlarged mediastinal lymph nodes.

Methods: Retrospective data were collected from January 2009 to March 2016. Suspected lung cancer patients with enlarged mediastinal lymph nodes (short axis ≥10 mm), underwent EBUS-TBNA or CMS for invasive mediastinal staging were enrolled. Substantial radical resection with systematic mediastinal lymphadenectomy (SML) was used as the gold standard. Mediastinal lymph nodes diagnostic comparison and N staging analysis were conducted in this study.

Results: Fifty-five patients received EBUS-TBNA and one hundred and ninety patients received CMS were included into the analysis set. In per case analysis, no significant differences were seen between EBUS-TBNA and CMS in N staging accuracy (83.6% *vs.* 78.9%, P=0.444). EBUS-TBNA had significantly higher sensitivity than CMS (82.4% *vs.* 47.6%, P=0.039) in malignant lymph nodes diagnosis. In lymph nodes diagnosis comparison (station #2, #4 and #7), both EBUS-TBNA and CMS showed high diagnostic sensitivity, specificity and accuracy (82.4% *vs.* 94.7%, P=0.130; 97.4% *vs.* 100%, P=0.173; 98.8% *vs.* 92.9%, P=0.025; respectively), CMS had slightly better diagnostic accuracy rate than EBUS-TBNA. Malignant lymph nodes had longer short axis than benign nodes (mean 14.2 *vs.* 6.5 mm, P<0.001). In lymph nodes with a short axis ≥15 mm, the malignant rate was 48.8%. More complications and injuries were found in patients receiving CMS.

Conclusions: For clinically suspected lung cancers with enlarged mediastinal lymph nodes, both EBUS-TBNA and CMS are favorable invasive mediastinal staging options. EBUS-TBNA may be preferred for its higher malignant diagnostic sensitivity and fewer complications.

Keywords: Non-small cell lung cancer (NSCLC); endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); cervical mediastinoscopy (CMS); mediastinal lymph nodes staging

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Introduction

Accurate mediastinal lymph nodes staging is essential for non-small cell lung cancer (NSCLC) patients who are potential candidates for radical surgical resection. Mediastinal staging is the most important factor that affects patient's treatment strategy and prognosis (1). Common staging methods include non-invasive and invasive staging. Non-invasive methods are imaging-based, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and PET-CT scans, which had poor sensitivity and specificity (2). For patients with potential resectable NSCLC, invasive methods are indispensable for mediastinal lymph nodes staging (N-staging) (3-5).

Transbronchial needle aspiration (TBNA) guided by endobronchial ultrasound (EBUS) was first introduced to clinical practice in 2002, and soon, physicians had found that linear probe EBUS-guided TBNA increased the yield of mediastinal lymph nodes diagnosis (6,7), which changed the practice of bronchoscopic biopsy of the mediastinum. Generally, TBNA had a sensitivity of around 50–60% in invasive staging(3). Guided by the linear probe of real-time EBUS, the sensitivity can be improved up to 85% (6,7). Recently research had indicated that the yield of EBUS-TBNA for mediastinal lymph node staging in lung cancer had increased to 90% or higher (8-16).

In past decades, mediastinoscopy had generally been considered a favorable option for invasive mediastinal staging (17,18). EBUS-TBNA had been developing rapidly and recommended for NSCLC mediastinal staging by clinical practice guidelines (19,20). Derived from an imaging modality that is capable of detecting lymph nodes using a probe, EBUS-TBNA has satisfactory sensitivity and specificity in pathological results by invasive needle aspiration and fewer injuries compared to mediastinoscopy (8-14).

Currently, minimally invasive needle techniques, like EBUS-TBNA, have been increasingly accepted as the first choice for mediastinal disease diagnosis. However, only few comparison studies were focused on mediastinal lymph nodes staging of NSCLC by EBUS-TBNA and cervical mediastinoscopy (CMS) methods (7,14). So, we conducted this retrospective study to compare the diagnostic yield of malignant mediastinal lymph nodes and N staging of EBUS-TBNA and CMS in clinical suspected lung cancer with enlarged mediastinal lymph nodes.

Methods

A total of 248 patients underwent EBUS-TBNA and 303 patients underwent CMS between January 2009 and March 2016 in the Sun Yat-sen University Cancer Center. The inclusion criterion of the final analysis set included clinical suspected lung cancer, which was based on symptoms, smoking history, or other characteristics; with enlarged mediastinal lymph nodes (short axis ≥10 mm) based on enhanced CT; patients should not receive any anti-cancer treatment. Clinical/radiologic evidence of stage IV or N3 lung cancer, or other mediastinal masses (e.g., thymoma, lymphoma) before the EBUS-TBNA or CMS were excluded. Patients with pathological confirmed NSCLC, and underwent substantial surgical resection with systematic mediastinal lymphadenectomy (SML) were included in the analysis set. The sizes of all lymph nodes (max axis and minor axis) were measured and recorded according to enhanced CT scan images. To be qualified in per lymph node station diagnosis yield comparison, the enlarged mediastinal lymph nodes were confined in station #2, #4 and #7 in both EBUS-TBNA and CMS groups. Radical resection and SML were considered as the gold standard in this study. Consecutive patients were included into this retrospective study in single center. Invasive mediastinal staging methods (whether EBUS-TBNA or CMS) were decided mainly by surgeon according to patients' clinical characteristics (age, lesions on CT scan, complication diseases, performance status, etc.). Both EBUS-TBNA and CMS were conducted by specialized physicians, and an independent review board of Sun Yat-sen University Cancer Center approved the data collection and analysis (Approved number: B2017-101-01).

EBUS-TBNA

EBUS-TBNA was performed as a separate procedure before radical resection and SML. After airway examination with conventional bronchoscopy, EBUS-TBNA was performed under conscious sedation. An ultrasound probe (BF-UC260F-OL8; Olympus) was inserted into the trachea with a flexible bronchoscope. TBNA biopsies were performed using a dedicated 22-gauge needle (NA-201SX-4022, Olympus) (21). After the procedure, rapid on-site evaluation (ROSE) was conducted for cytological smears using the collected samples at first, the remain samples would be used for Thinprep cytologic test,

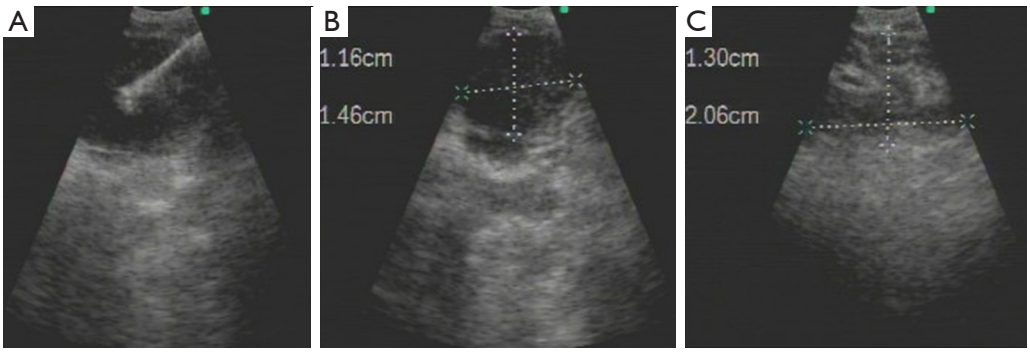

Figure 1 Ultrasound images of EBUS-TBNA. (A) The TBNA procedure; (B) suspected benign lymph node; (C) suspected malignant lymph node. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

histological examination would be performed using the fresh tissue sample, immunohistochemistry was necessary in some cases. Quality control: sample adequacy was decided by endoscopy physician and pathologist, the puncture was performed at most 4 times. Large quantity of lymphocytes would be considered as representative. NSCLC lymph node metastasis, highly suspicious cancer cell would be diagnosed positive. Negative results should be no malignant cells found in cytological or histological examination. Non-diagnostic sample included blood clots, necrotic tissue, mucus, etc. (*Figure 1*).

CMS

CMS conducted in this analysis was mostly performed as a part of lung cancer radical resection. Whether substantial surgeries continue or not depended on frozen pathology analysis and the surgeons' decisions. If the frozen pathology analysis indicated N2 or N3 nodes positive, surgery would generally be ceased, and patients received neoadjuvant therapy or other treatments, unless the surgeon had other indications to continue. If N1 nodes positive (in EBUS-TBNA group) or all nodes negative, the surgeon would generally continue with the radical resection and SML in resectable cases or cease surgery in medical inoperable cases.

According to the regional lymph node staging of lung cancer by the IASLC 2009 criteria, EBUS-TBNA was able to reach N2 nodes including superior mediastinal nodes (stations #1 highest mediastinal, #2 upper paratracheal, #3 retrotracheal and #4 lower paratracheal), inferior mediastinal nodes (stations #7 subcarinal), and N1 nodes including hilar (#10), interlobar (#11), and part of lobar (#12). EBUS-TBNA cannot reach #3 pre-vascular, #5 sub-aortic, #6 para-aortic, #8 paraesophageal, #9 pulmonary ligament, and #13 segmental, #14 subsegmental lymph nodes. The lymph nodes of CMS are fewer, it only includes N2 nodes #1 highest mediastinal, #2 upper paratracheal, #4 lower paratracheal and #7 subcarinal (19,22-24).

Statistical analyses

Statistical analyses were performed using SPSS v13 statistical software (USA). Continuous variables were expressed as means and standard deviations, and comparisons were performed with *t* tests. Categorical variables are summarized as count and percent. Pearson Chi-square test or Fisher's exact test, as appropriate, was used for comparing proportions. McNemar's test was used for evaluating agreement between the two procedures. A two-tailed p value of 0.05 indicated statistical significance.

Results

The study flowchart is shown in *Figure 2*. In total, 103 and 274 clinical suspected lung cancer patients with indication for mediastinal lymph nodes staging received EBUS-TBNA or CMS. Two hundred and forty-five patients met the inclusion criterions and enrolled into analysis set, 55 patients in EBUS-TBNA group and 190 patients in CMS group, respectively. Seven patients (6.8%) in EBUS-TBNA group were excluded for non-diagnostic sample, standard cytological examinations were conducted in the biopsied lymph nodes in these patients, 5 were diagnosed as necrotic tissue, 2 were blood clots. Two patients underwent both EBUS-TBNA and CMS, and were included in both groups.

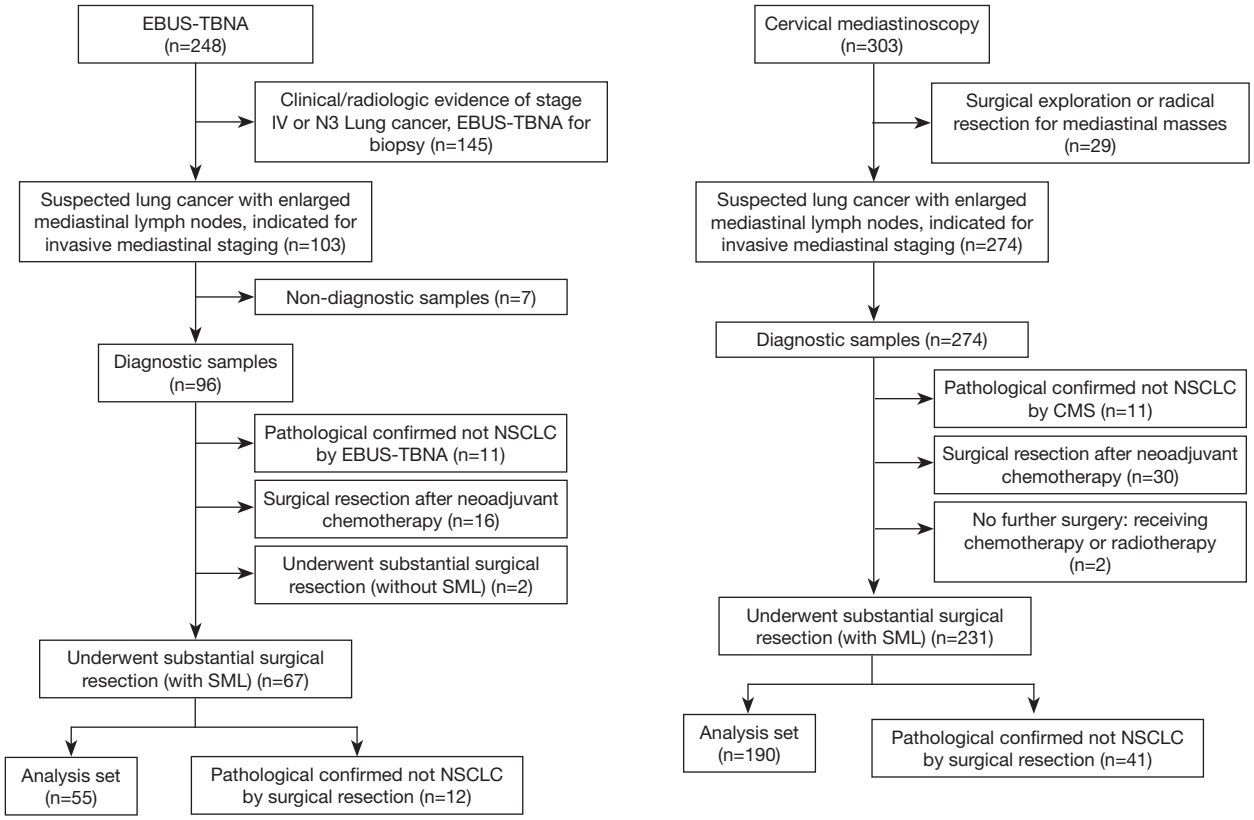

Figure 2 Study flowchart. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; NSCLC, non-small cell lung cancer; CMS, cervical mediastinoscopy; SML, systematic mediastinal lymphadenectomy.

Patient demographics were shown in *Table 1*, basic characteristics were balanced in two groups. Three hundred and six mediastinal lymph nodes met the criterion and enrolled into the comparison, 62 and 244 nodes were biopsied by EBUS-TBNA and CMS respectively. The average number of nodes per case were 1.13 and 1.28, respectively.

Mediastinal lymph nodes diagnosis and N staging yield comparison

The results were showed in *Table 2*. Fifty-five patients underwent surgical resection and SML after EBUS-TBNA examination. Forty-six patients had consistent pathological confirmed N staging results from both TBNA and surgery. Nine patients showed a disagreement of N stage with SML, and three patients had positive lymph nodes exceed diagnostic range of EBUS-TBNA (1 node in #5, and 2 nodes in #13). One patient had #4 positive but SML indicated a negative result. Five patients were missed diagnosed, EBUS suggested negative but SML indicated positive (1 nodes in #2, #4 and #7 each) in 3 patients, 2 patients were missed because of small nodes (1 node in #4 and #7 each, short-axis <10 mm). One hundred and ninety patients underwent radical surgery substantially after CMS, 150 patients had consistent results, 33 patients with positive lymph nodes metastasis exceed CMS's diagnostic range (1 node in #5; 2 nodes in #6, #8 and #9 respecively;19 in #10, 13 in #11, 6 in #12, 20 in #13), and 7 patients were with missed diagnosis, CMS suggested negative but SML indicated positive (2 nodes in #7 and 1 in #4) in 3 patients,4 patients were missed for small nodes (1 node in #2 and #7 each, 2 nodes in #4, short-axis <10 mm).

The accuracy rate for N staging in EBUS-TBNA was 83.6% (46/55 cases) versus 78.9% (150/190 cases) in CMS (P=0.444), with no statistically significant differences. EBUS-TBNA had significant higher sensitivity (65.2% *vs.* 40.3%, P=0.039) in mediastinal malignant lymph nodes diagnosis, with also higher missed diagnosis rate (9.1% *vs.* 3.7%, P=0.148) than CMS. EBUS-TBNA also had a wider

Table 1 Patients' characteristics in the analysis set

Characteristics	EBUS-TBNA (n=55)	CMS (n=190)
Age	56 [35–72]	59 [32–78]
Sex		
Male	36 [65]	111 [58]
Female	19 [35]	79 [42]
Smoking history		
Smoker (mean of smoking index)	21 [38–268.5]	71 [37–213.7]
Non-smoker	34 [62]	119 [63]
ECOG PS		
0	45 [82]	154 [81]
1	10 [18]	36 [19]
Pathology		
Adenocarcinoma	37 [67]	150 [79]
Squamous carcinoma	9 [16]	18 [9]
Adenosquamous carcinoma	2 [4]	6 [3]
Others*	7 [13]	16 [8]
Enlarged lymph nodes biopsy**		
Average per case	1.13 [62]	1.28 [244]
Mean short-axis mm	14.6 [10–25]	14.5 [10–28]

Data are shown as mean [rang] or number [percentage]; *, others included large cell carcinoma, large cell neuroendocrine carcinoma, sarcomatoid carcinomas, lymphoepithelioma-like carcinoma, pleomorphic adenoma and mucoepidermoid carcinoma; **, with short axis ≥10 mm.

diagnostic range, the exceeding rate was significantly lower than CMS (5.5% *vs.* 17.4%, P=0.028).

Comparison of lymph nodes station diagnosis yield

Lymph nodes station #2, #4 and #7 were in the diagnostic range of both EBUS-TBNA and CMS, which made it comparable to evaluate the diagnosis yield of enlarged lymph nodes (short-axis ≥10 mm in CT scan). The results were showed in *Table 3*, both EBUS-TBNA and CMS had very high levels and no statistically difference was found in diagnosis sensitivity and specificity (82.4% *vs.* 94.7%, P=0.130; 97.4% *vs.* 100%, P=0.173; respectively) of these 3 mediastinal lymph nodes station. The diagnostic accuracy was also at very high level; however, CMS was slightly better than EBUS-TBNA (98.8% *vs.* 92.9%, P=0.025).

The description of lung cancer lymph nodes

The sizes of all the lymph nodes dissected in SML were measured according to previous CT scan and described in *Table 4*. Short-axis of malignant lymph nodes were significantly longer than benign lymph nodes (mean 14.2 *vs.* 6.5 mm, P<0.001). The results also indicated that for the detection of malignant lymph nodes with short axis ≥15 mm, CMS had better diagnostic yield than EBUS-TBNA (100% *vs.* 80%, P=0.012). Malignant rate of lymph nodes was elevated in accordance with the minor axis, and reached as high as 48.8% when minor axis ≥15 mm.

Safety

There were 4 complications (1.6%, 4/248) that occurred in EBUS-TBNA examination. Two patients had a severe cough, and two patients experienced an oxygen saturation decrease during the process and were not able to complete the TBNA. Seven complications (2.3%, 7/303) were observed in CMS. Six patients had recurrent laryngeal nerve or vessel injury, and one patient suffered from a post-operative infection. Generally, the complication rate was low in both invasive examinations. When CMS was conducted as a part of surgical resection, complications were difficult to assess.

Discussion

Over the past decade, interest had been drawn towards exploring the roles of EBUS-TBNA in lung cancer mediastinal lymph node staging, not only by ultrasound specialists, but also by thoracic surgeons. A prospective, crossover trial to compare the diagnostic yield of EBUS-TBNA and CMS was conducted by Ernst in 2008, and the results indicated that the yield of N staging accuracy was not different between two methods, but the sensitivity of EBUS-TBNA in lymph node station diagnosis was higher than that of CMS (25). Several systemic reviews also concluded that the pooled sensitivities of EBUS-TBNA and CMS had no significant differences, and both exhibited equally high diagnostic accuracy for mediastinal staging of lung cancer (20,26).

In our study, we retrospectively analyzed suspected lung cancer patients with enlarged mediastinal lymph nodes who underwent EBUS-TBNA or CMS for invasive mediastinal staging, using SML as the reference standard. Our results also indicated that both EBUS-TBNA and

Table 2 Per case comparison of mediastinal lymph nodes diagnosis and N staging yield of EBUS-TBNA and CMS in NSCLC

Comparison	Rate, % (No./SML)		P value*
	EBUS-TBNA	CMS	
N staging accuracy yield comparison			
N0	96.9 (31/32)	100 (123/123)	0.206
N1	75.0 (6/8)	0.0 (0/29)	<0.001
N2	60.0 (9/15)	71.1 (27/38)	0.52
N staging accuracy	83.6 (46/55)	78.9 (150/190)	0.444
Mediastinal malignant lymph nodes diagnosis yield comparison			
Sensitivity	65.2 (15/23)	40.3 (27/67)	0.039
Specificity	96.9 (31/32)	100 (123/123)	0.206
Positive predictive value	93.8 (15/16)	100 (27/27)	0.372
Negative predictive value	79.5 (31/39)	75.5 (123/163)	0.596
Exceed diagnostic range**	5.5 (3/55)	17.4 (33/190)	0.028
Missed diagnosis***	9.1 (5/55)	3.7 (7/190)	0.148

*, P values were calculated using Pearson Chi-square test or Fisher's exact test; **, exceed diagnostic range: the malignant lymph nodes were beyond CMS reaching area, confirmed by substantial SML; ***, one patient EBUS biopsy showed positive but SML suggested negative, excluded from missed diagnosis. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; CMS, cervical mediastinoscopy; NSCLC, non-small cell lung cancer; SML, systematic mediastinal lymphadenectomy.

Table 3 The diagnosis yield comparison of mediastinal malignant lymph node stations at #2, #4 and #7 of EBUS-TBNA and CMS in NSCLC

Station	Accuracy, % (No./SML)			Sensitivity (malignant), % (No./SML)			Specificity (benign), % (No./SML)		
	EBUS-TBNA	CMS	P value*	EBUS-TBNA	CMS	P value*	EBUS-TBNA	CMS	P value*
All	92.9 (52/56)	98.8 (241/244)	0.025	82.4 (14/17)	94.7 (54/57)	0.130	97.4 (38/39)	100 (187/187)	0.173
#2	92.3 (12/13)	100 (55/55)	0.191	83.3 (5/6)	100 (11/11)	0.353	100 (7/7)	100 (44/44)	1.000
#4	89.5 (17/19)	98.8 (84/85)	0.085	66.7 (2/3)	94.7 (18/19)	0.260	93.8 (15/16)	100 (66/66)	0.195
#7	95.8 (23/24)	98.1 (102/104)	0.469	87.5 (7/8)	92.6 (25/27)	0.553	100 (16/16)	100 (77/77)	1.000

*, P values were calculated using Pearson Chi-square test or Fisher's exact test. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; CMS, cervical mediastinoscopy; NSCLC, non-small cell lung cancer; SML, systematic mediastinal lymphadenectomy.

Table 4 The description of malignant rate in different sizes of mediastinal lymph nodes in non-small cell lung cancer

Short-axis (mm)	Malignant rate (%, No./SML)	EBUS-TBNA yield (%, No./SML)	CMS yield (%, No./SML)	SML results	P value*
<5	1.1 (6/563)	–	–	–	–
5–9	3.1 (36/1,158)	–	–	–	–
10–14	10.1 (18/179)	100 (8/8)	70 (7/10)	–	0.216
≥15	48.8 (62/127)	80 (12/15)	100 (47/47)	–	0.012
14.2±6.3 [10–28]	–	–	–	Malignant lymph nodes	<0.001
6.5±3.2 [10–25]	–	–	–	Benign lymph nodes	<0.001

*, P values were calculated using Pearson Chi-square test or Fisher's exact test. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; CMS, cervical mediastinoscopy; SML, systematic mediastinal lymphadenectomy.

CMS had similar diagnostic accuracy in N staging (83.6% and 78.9%). However, EBUS-TBNA had better diagnostic sensitivity than CMS in mediastinal malignant lymph nodes. Most of the disagreement in N staging of CMS group were malignant lymph nodes beyond the diagnostic range, mostly happened in N1 station; for those within the range, the missed diagnosed rate was very low (3). The disagreement of EBUS-TBNA in N staging was more balanced. So, one advantage for EBUS-TBNA in NSCLC mediastinal lymph nodes diagnosis and N staging is the wider diagnostic range, which allows the physician to explore both N2 and N1 (such as hilar, interlobar, and lobar) lymph nodes station. Combined EBUS with esophageal ultrasound (EUS), the diagnostic range could reach the aortopulmonary (#5), paraesophageal (#8) and inferior pulmonary ligament (#9) nodes to accomplish complete endoscopic staging of the N2 mediastinal lymph nodes staging (5,27).

However, in EBUS-TBNA, the pathology sample collected by lymph nodes needle aspiration is less excessive, mostly for cytology only. CMS is performed mainly by lymph nodes resection, provide both cytology and histology samples, which can significantly decrease the missed diagnostic rate (3). The higher missed diagnosis rate could be seen in lymph nodes station #2, #4 and #7 diagnosis yield comparison, the diagnostic accuracy was higher in CMS group. Our results remain consistent with prior reports' conclusions (3,10-16,25). Also, CMS has significant higher diagnostic yield in lymph nodes ≥15 mm in our study. The high false negative rate in EBUS-TBNA could largely attribute to inadequate sample. But, the results are less convincible because of small cohort size, large-scale sample studies are needed to confirm that results. CMS operation requires inpatient care and general anesthesia, and is associated with complications such as nerve and vessel damage. EBUS-TBNA has fewer complications and less damage to patients, and could be operated in a clinic with topical anesthesia (28-30).

Our study suggests that EBUS-TBNA might be preferred in diagnosis of enlarged lymph nodes in suspected lung cancer, however, there are still concerns about EBUS-TBNA, and CMS clearly retains an important role. One of the concerns is the false negative rate of EBUS-TBNA, previous report has suggested a false negative rate as high as 24% (nearly 10% in our study), which is commented that needle-based biopsy is not as reliable as surgical resection for less abundant sampling (3,17). Another concern is the high non-diagnostic rate of EBUS-TBNA, which is reported as high as 25.8% (6.7% in our study, 7/105), could arouse a diagnostic bias and clinical confusions.

So, the appropriate practice, which is also suggested by the guideline, is EBUS-TBNA and followed by CMS. EBUS-TBNA can be easily repeated without the technical difficulties, combination examination is reasonable (20,31). Clinical suspected NSCLC will be mediastinal staged by radiology at first, EBUS-TBNA will be performed to confirm the malignant nodal involvement, and negative results should be corroborated by CMS. Based on these results, physician could make decisions of substantial radical resection or neoadjuvant chemotherapy or other treatments.

Limitation

We recognize various limitations of the present study. This is a retrospective cohort study, perspective randomization is not available. So, selection bias (EBUS-TBNA or CMS) does exist and may affect the results. Also, there is inherent investigator bias in deciding went on or cease surgery after frozen pathology results of CMS, so the surgery rate in CMS group is higher than EBUS-TBNA group. Interpersonal bias might be small as the basic characteristics are balanced in both groups.

Conclusions

The results of our study suggest that the diagnostic accuracy for EBUS-TBNA and CMS are similar, but EBUS-TBNA had better malignant diagnostic sensitivity and fewer complications, which indicates that in clinical suspected lung cancer patients with enlarged mediastinal lymph nodes, EBUS-TBNA is preferred for invasive mediastinal nodal staging.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the independent review board of Sun Yat-sen University Cancer Center (approved number: B2017-101-01) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consents were exempted in this retrospective study.

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