

BRIEF ARTICLE

First endoscopic procedure for diagnosis and staging of mediastinal lymphadenopathy

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Abstract

AIM: To compare a first diagnostic procedure of trans-bronchial needle aspiration (TBNA) with selection of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or TBNA for mediastinal lymphadenopathy.

METHODS: Sixty-eight consecutive patients with mediastinal lymphadenopathy on computed tomography (CT), who required cytopathological diagnosis, were recruited. The first 34 underwent a sequential approach in which TBNA was performed first, followed by EUS-FNA if TBNA was unrevealing. The next 34 underwent a selective approach where either TBNA or EUS-FNA was selected as the first procedure based on the CT findings.

RESULTS: The diagnostic yield of TBNA as the first diagnostic procedure in the sequential approach was 62%. In the selective approach, the diagnostic yield of the first procedure was 71%. There was no significant difference in the overall diagnostic yield, but there were significantly fewer combined procedures with the selective approach.

CONCLUSION: Selecting either EUS-FNA or TBNA as the first diagnostic procedure achieved a comparable diagnostic yield with significantly fewer procedures than performing TBNA first in all patients.

INTRODUCTION

Lung cancer is the commonest cause of mediastinal lymphadenopathy. For non-small cell lung cancer (NSCLC), which accounts for about 80% of lung cancers, mediastinal lymph node enlargement occurs in up to 38% of cases at diagnosis^[1]. As surgical resection of NSCLC offers the best chance of cure in patients without distant metastases, the pathological confirmation of cancer spread to enlarged mediastinal lymph nodes is crucial to staging because this excludes curative surgical resection.

In the approach to suspected lung cancer without distant metastases, the lung mass is the initial target for cytopathological diagnosis. Following a diagnosis of NSCLC, mediastinal staging is the next step. In patients with mediastinal lymphadenopathy however, the mediastinum may be targeted first, even when a lung mass is present. This might achieve simultaneous diagnosis and mediastinal staging of lung cancer with a single procedure.

The esophagus and tracheobronchial tree offer endoluminal access to mediastinal lymph nodes, therefore endoscopic techniques such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and trans-bronchial needle aspiration (TBNA) offer minimally invasive approaches for diagnosis of mediastinal lymphadenopathy.

Although EUS-FNA has a higher accuracy than TBNA, the transbronchial approach is preferred for anterior and right paratracheal lymph nodes. Real-time endobronchial ultrasound-guided TBNA (EBUS-TBNA) is now available but requires expensive specialized equipment and operator training. TBNA does not require specialized equipment and can be performed during the initial diagnostic bronchoscopy^[2-4]. When we evaluated patients with mediastinal lymphadenopathy with bronchoscopy and TBNA, the diagnostic yield for mediastinal lymphadenopathy was 65%^[3].

We have also used EUS-FNA for cases in which TBNA was unrevealing or non-diagnostic, given its higher accuracy^[4]. However, this resulted in subjecting these patients to two diagnostic procedures even though both procedures could be performed in the same outpatient session^[4,5].

We then hypothesized that bronchoscopy with TBNA need not be performed as the first procedure in all cases of mediastinal lymphadenopathy, and that by selecting the appropriate endoscopic procedure based on anatomical access, a higher diagnostic yield could be obtained after the first procedure. This could also result in subjecting the patient to fewer diagnostic procedures. Therefore, in this study, we compared an approach utilizing TBNA as the first diagnostic procedure with one utilizing selection of either EUS-FNA or TBNA.

MATERIALS AND METHODS

Between December 2003 and June 2006, consecutive patients with mediastinal lymphadenopathy on thoracic computed tomography (CT) who presented to, or were referred to our respiratory division for cytopathological diagnosis were recruited for the study. Mediastinal lymphadenopathy was defined as a node larger than 1 cm in its short axis. The institutional review board of our hospital approved the study and informed consent was obtained for all the procedures.

Sequential approach

During the first 16 mo of the study period, we employed a sequential approach for which bronchoscopy with TBNA was performed as the first diagnostic procedure, with or without other conventional bronchoscopic techniques. If TBNA was unrevealing on rapid on-site cytopathological evaluation (ROSE), EUS-FNA was performed immediately after TBNA, during the same session. Details of this approach and the results of the first 20 patients have been described when we explored the one-stop approach to mediastinal lymphadenopathy^[4,5].

Selective approach

From April 2005, we employed a selective approach for which either EUS-FNA or TBNA was performed as the first diagnostic procedure. This was selected based on the predominant location of the lymphadenopathy on CT. If either the esophageal or transbronchial approach could access the nodes, the pulmonologist was left to

decide which procedure he deemed most appropriate. In general, TBNA was selected mainly for patients with right paratracheal lymphadenopathy, whereas EUS-FNA was the preferred option for left paratracheal lymphadenopathy. Subcarinal lymph nodes could be approached by either procedure. If TBNA was selected as the first diagnostic procedure, EUS-FNA remained a subsequent option.

TBNA, EUS-FNA and ROSE

Bronchoscopy was performed by experienced pulmonologists using standard flexible videobronchoscopes (Olympus Optical Co. Ltd., Tokyo, Japan). Premedication with pethidine and atropine and sedation with midazolam were optional, while all patients received topical anesthesia with xylocaine. TBNA was performed blind with a Wang 22-gauge (MW 222) cytology needle (Bard Endoscopic Technologies, Billerica, MA, USA) at sites of mediastinal lymph node enlargement based on review of the CT scan. TBNA was performed before other conventional bronchoscopic procedures to avoid contamination.

EUS-FNA was performed as previously described using the curved linear array echoendoscope (GF-UC30P; Olympus) by experienced gastroenterologists^[6]. Patients received topical anesthesia with xylocaine and sedation with a combination of midazolam and pethidine.

ROSE was employed to determine the adequacy of the needle aspirates. The aspirated material was blown onto a slide using the direct smear technique^[7]. The smears were either air-dried and stained with Diff-Quik (American Scientific Products, McGraw Park, IL, USA) or fixed immediately in 95% ethanol and stained with Papanicolaou stain. Solid particles were fixed in formalin, routinely processed, and made into cell blocks for histological examination. The air-dried smears for Diff-Quik staining were reviewed immediately by an experienced cytotechnician. Endoscopists were then advised as to the need for additional needle aspirates (up to a maximum of six passes).

Diagnostic yield

The final cytopathological diagnoses were made based upon analysis of the aspirated material by experienced cytopathologists. The diagnostic yield of TBNA was the number of patients in whom a definite diagnosis was made by TBNA over the total number of patients subjected to TBNA. The diagnostic yield after the first procedure was the number of patients in whom a definite diagnosis was made after the first procedure over the total number of patients. The overall diagnostic yield for each approach was the number of patients in whom a definitive diagnosis was made by needle aspiration over the total number of patients. When a diagnosis could not be made by either procedure, the final diagnostic categories were determined by review of further tests and clinical assessments.

Statistical analysis

Descriptive statistics are presented as mean \pm SD. Discrete

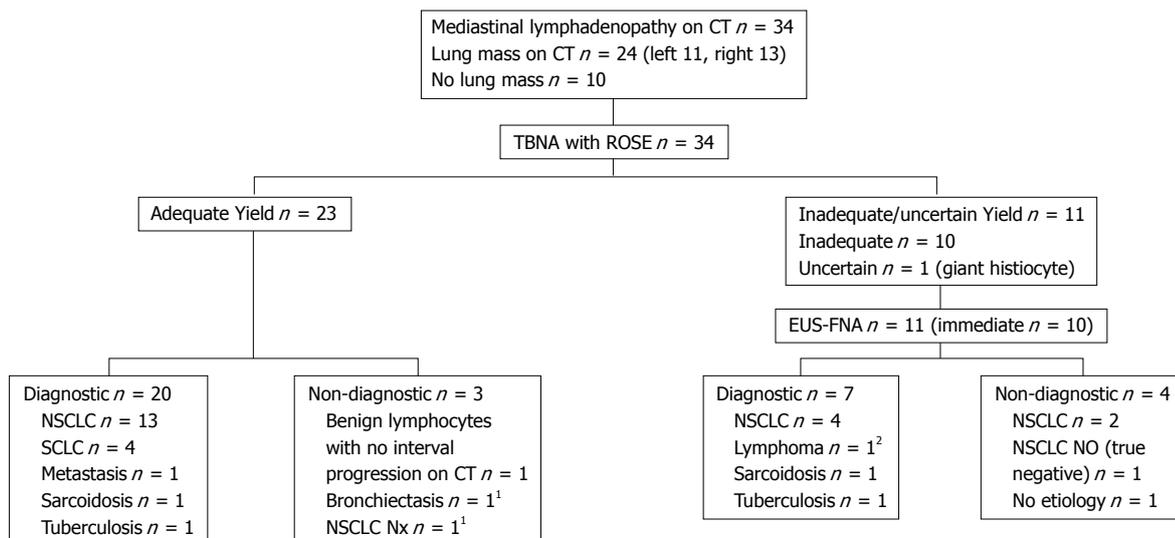


Figure 1 The sequential approach. ¹False positive TBNA with ROSE; ²False negative TBNA with ROSE. CT: Computed tomography; TBNA: Transbronchial needle aspiration; ROSE: Rapid on-site cytopathological evaluation; NSCLC: Non-small cell lung cancer; EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration.

variables were analyzed with χ^2 test and $P < 0.05$ was defined as statistically significant.

RESULTS

Sixty-eight consecutive patients with mediastinal lymphadenopathy on CT were recruited during the study period. The main indication for CT was suspected malignancy ($n = 58$). Other indications included suspected pulmonary embolism ($n = 4$), pyrexia of unknown origin ($n = 2$), suspected aortic dissection ($n = 1$), investigation of weight loss ($n = 1$), suspected sarcoidosis ($n = 1$), and follow-up of non-Hodgkin's lymphoma ($n = 1$).

The baseline characteristics and diagnostic categories of the sequential group ($n = 34$) and the selective group ($n = 34$) were similar (Table 1).

Results of the sequential approach are shown in Figure 1. TBNA was performed at the following mediastinal sites according to regional lymph node map definitions as described by Mountain *et al*^[8]: 4R in 10 patients, 7 in 24 patients, and 4L in 7 patients. The TBNA obtained adequate specimens in 23 of the 34 patients. In the remaining 11 patients, TBNA with ROSE showed the specimens to be inadequate or unrevealing, thus, EUS-FNA was performed immediately after bronchoscopy, at lymph node stations 7 (seven patients), 4L (10 patients) and 4R (one patient). Some patients had TBNA or EUS-FNA performed at more than one lymph node station. When the final cytopathological results were analyzed, TBNA with ROSE was falsely negative in one patient. In another patient, TBNA with ROSE showed a giant histiocyte and a decision was made to proceed with EUS-FNA. The final cytopathological diagnosis for both specimens returned as granulomatous inflammation. Results of the first 20 patients with this approach have been described previously^[4].

Results of the selective approach are shown in Figure 2. TBNA was performed in 22 patients in the following mediastinal sites: 4R (six patients) and 7 (19 patients).

Table 1 Baseline characteristics and diagnostic categories of study population n (%)

Variables	Sequential approach	Selective approach	P value
No. of patients	34	34	
Male/female	24/10	25/9	
Age (mean \pm SD, yr)	64.7 \pm 11.2	65.1 \pm 12.7	
Mass on CT	24	23	
Right-sided/left-sided,	13/11	12/11	
No. of patients undergoing			
TBNA	34 (100)	22 (65)	< 0.001
TBNA and EUS-FNA	11 (32)	2 (6)	< 0.05
Diagnostic yield (%)			
First procedure	62	71	0.6
TBNA	62	73	0.6
Overall	79	73	0.8
Diagnostic categories			
Malignancy	26	28	
NSCLC/SCLC	22/3	21/7	
Benign tumor	8	6	
Sarcoid/tuberculosis	2/2	1/1	

CT: Computed tomography; TBNA: Transbronchial needle aspiration; NSCLC: Non-small cell lung cancer; EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration.

EUS-FNA was performed as a first diagnostic procedure in 12 patients at lymph node stations 7 (12 patients), 4L (five patients) and 2R (one patient, Figure 3). In contrast to the sequential approach for which all 34 patients had TBNA performed first, 35% (12/34) of patients in the selective approach had EUS-FNA performed first, while the remaining 65% (22/34) had TBNA performed first. In the selective approach, TBNA was performed only for right paratracheal and subcarinal stations, whereas EUS was performed predominantly in the left paratracheal and subcarinal stations.

The diagnostic yield of TBNA as the first diagnostic test was 62% in the sequential approach, while the diagnostic yield of the first diagnostic procedure in the selective approach was 71%. The diagnostic yield of

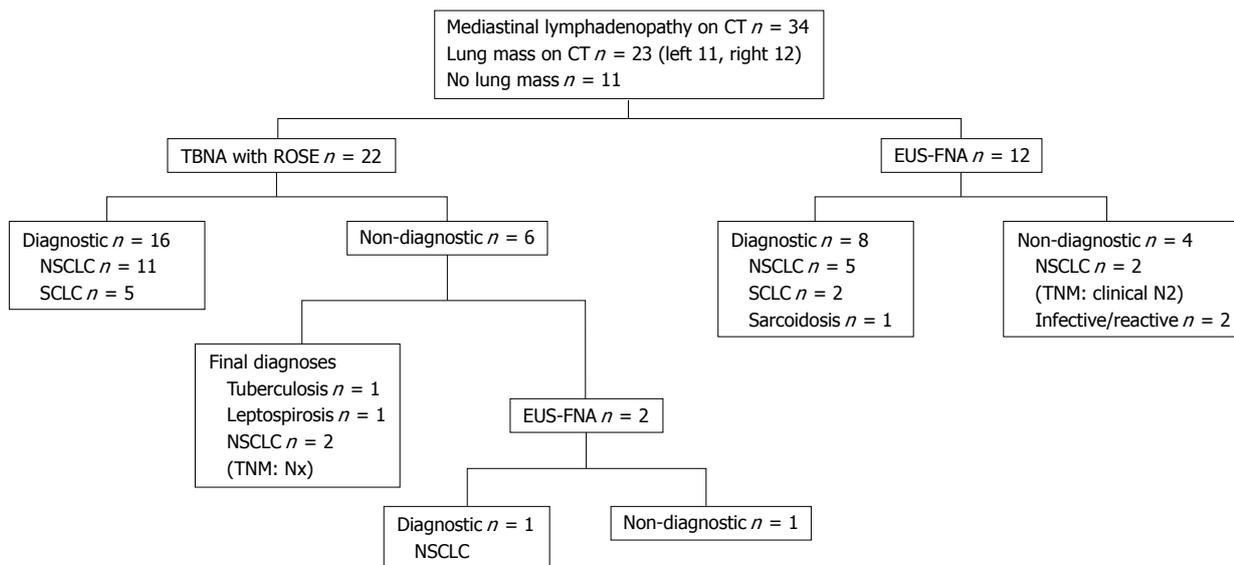


Figure 2 The selective approach.



Figure 3 CT showing right paratracheal lymphadenopathy that was sampled by EUS-FNA.

EUS-FNA was 67% (8/12). The overall diagnostic yield of the sequential approach was 79% (27/34) and that of the selective approach was 74% (25/34). There was no significant difference in the overall diagnostic yields. Significantly fewer combined diagnostic procedures (6% *vs* 32%, $P < 0.05$) were required with the selective approach. The yield of TBNA was higher with the selective approach (73%) as compared to the sequential approach (62%). There were no complications with either TBNA or EUS-FNA, or damage to the bronchoscopes or endoscopes.

DISCUSSION

The present study compared a diagnostic approach utilizing TBNA as the first diagnostic procedure with one in which EUS-FNA or TBNA was selected as the first procedure. The selection was based on whether the optimal anatomical approach was transesophageal or transbronchial. We found a higher diagnostic yield after the first diagnostic procedure with the selective approach, and this translated to a significant reduction in the number of diagnostic procedures performed.

The transesophageal and transbronchial routes to the mediastinum are complementary. The transesophageal approach has limited access to the right paratracheal nodes, therefore, the endobronchial route offers better access, as shown by Herth *et al*⁹. Therefore, the procedure of choice for right paratracheal lymphadenopathy with the selective approach was TBNA, unless CT showed a peri-esophageal location of these nodes that was easily accessed by EUS-FNA (Figure 3). Harrow *et al*¹⁰ also have shown that the right paratracheal and subcarinal locations are predictors of a positive aspirate with TBNA. With the selective approach, TBNA was limited to these two locations, and the yield of TBNA improved from 62% to 73%.

Although mediastinoscopy remains the diagnostic standard for the mediastinal staging of lung cancer, with a sensitivity of 80%-85%, this invasive surgical procedure requires general anesthesia and has a morbidity and mortality rate of 2% and 0.08%, respectively^[11]. In contrast, both TBNA and EUS-FNA are minimally invasive and can be performed in the outpatient setting under local anesthesia and sedation. EUS-FNA permits real-time visualization of needle sampling and has been shown to be highly accurate in the mediastinal staging of lung cancer, as well as in the diagnosis of mediastinal lymphadenopathy of unknown etiology^[6,12-18].

The development of EBUS-TBNA for mediastinal lymph nodes has lagged behind EUS-FNA by more than a decade^[19,20]. As such, the new convex-probe EBUS is still not as widely available as EUS. Wallace *et al*^[21] have suggested that the use of ultrasound-guided needle sampling of mediastinal lymph nodes in patients with suspected lung cancer, whether by EUS or EBUS, is superior to conventional TBNA. By combining EUS-FNA and EBUS-TBNA, they have achieved a near-complete medical mediastinoscopy, thus reinforcing the complementary nature these procedures^[22].

Our aim was not to achieve comprehensive staging of the mediastinum in the setting of lung cancer, but

rather, to demonstrate that, with appropriate selection of the first endoscopic procedure, a higher diagnostic yield could be obtained. This would mean that EUS-FNA could be selected as the first procedure, rather than routinely subjecting all patients to bronchoscopy. Indeed, a recent meta-analysis has suggested that EUS-FNA is the diagnostic test of choice for mediastinal lymphadenopathy^[23]. In addition, the transesophageal route may be better tolerated as compared to the transbronchial route, with less coughing and the absence of obstruction of the needle by cartilaginous rings.

Most studies with EUS-FNA for mediastinal evaluation have been performed in patients only after confirmation of the diagnosis of NSCLC. Singh *et al*^[24], however, have demonstrated that EUS-FNA may be performed as the first diagnostic procedure for suspected lung cancer. In the setting of mediastinal lymphadenopathy in NSCLC, this diagnostic procedure also has enabled simultaneous mediastinal staging. Thus, besides showing that bronchoscopy need not be the first diagnostic procedure in patients with suspected lung cancer, they also have demonstrated that diagnosis and staging of lung cancer need not be performed sequentially or require multiple procedures. This highlights a paradigm shift where mediastinal staging is no longer performed only after confirming the diagnosis of NSCLC.

We believe that, in the diagnostic approach to the mediastinum, the transesophageal and transbronchial routes are complementary rather than competing. Instead of pitting TBNA against EUS-FNA, this study emphasizes that the complementary value of these endoscopic approaches is best exploited by appropriate procedure selection. Thus, when either EUS-FNA or TBNA was selected as the first procedure, the diagnostic yield increased from 62% to 71%, thereby significantly reducing the need for additional procedures. Targeting the mediastinum first to enable simultaneous diagnosis and staging, and optimizing the yield of the first diagnostic procedure may lead to fewer delays in the treatment of lung cancer patients. Devbhandari *et al*^[25] have reported that a negative initial bronchoscopy in suspected lung cancer resulted in significant delays in diagnosis and treatment. In that study, initial bronchoscopy was diagnostic in less than 50% of cases.

The present study had several limitations. Firstly, this was not a randomized trial and the patient population was small. However, they were consecutive patients with similar baseline characteristics and diagnostic categories (Table 1). Secondly, a definitive diagnosis could not be made in all cases because some patients and their referring physicians declined further invasive surgical sampling. However, the aim of this study was to determine the diagnostic yield of the sequential and selective approaches rather than the accuracy of either endoscopic procedure. Thirdly, conventional TBNA was employed rather than EBUS-TBNA. This was because at the time of the study, EBUS-TBNA was not available at our center.

Three practical clinical points are highlighted here. Firstly, the cytopathological diagnosis of mediastinal lymphadenopathy may be achieved in the majority of

patients utilizing widely available endoscopic techniques. Secondly, targeting the mediastinum first may establish simultaneously diagnosis as well as mediastinal staging for patients with NSCLC. Finally, appropriate selection of the first diagnostic procedure may optimize the yield and minimize the number of procedures required for the diagnosis and/or staging of mediastinal lymphadenopathy. Thus, with the availability of EUS-FNA, bronchoscopy may no longer be required in selected patients with suspected lung cancer.

Endoscopic techniques are becoming essential high-utility tools in the investigative approach to the mediastinum. With the rapid evolution of newer endoscopic techniques, the physician's diagnostic armamentarium is likely to expand. The question of which is the most appropriate initial diagnostic procedure for mediastinal lymphadenopathy, given what is available, will become even more important. While awaiting further studies comparing the different emerging endoscopic techniques and combination of techniques, we suggest that the optimal diagnostic approach for mediastinal lymphadenopathy depends on selection of the most appropriate initial diagnostic procedure.

COMMENTS

Background

In the absence of distant metastasis, mediastinal staging remains crucial for determining prognosis and therapy of non-small cell lung cancer. An approach to patients with mediastinal lymphadenopathy regardless of whether a lung mass is present, is to target the mediastinum first. This may achieve simultaneous diagnosis and mediastinal staging with a single procedure, in the event of diagnosis of lung cancer, which is the commonest cause of mediastinal lymphadenopathy.

Research frontiers

The transbronchial and transesophageal routes allow minimally invasive endoscopic needle sampling of mediastinal lymph nodes. These endoscopic procedures may be done under sedation in contrast to the gold standard mediastinoscopy, which requires general anesthesia.

Innovations and breakthroughs

Minimally invasive mediastinal staging with endoscopic ultrasound-guided fine-needle aspiration and blind or endobronchial ultrasound guided transbronchial-needle aspiration may be a substitute for mediastinoscopy.

Applications

Not all patients require all three procedures, therefore, appropriate initial procedure selection may be important in the diagnostic approach to mediastinal lymphadenopathy, because only a single procedure may be diagnostic in the majority of cases.

Peer review

This is a very interesting topic for the readers of *World Journal of Gastroenterology*.

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