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Analysis of Subcarinal Lymph Nodes in (Suspected) Non-Small-Cell Lung Cancer after a Negative Transbronchial Needle Aspiration – What's Next?

A Preliminary Report

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For editorial comment see p. 555

Key Words
Endoscopic ultrasound-guided fine needle aspiration · Non-small-cell lung cancer · Staging · Transbronchial needle aspiration

Abstract
Background: Transbronchial needle aspiration (TBNA) of subcarinal lymph nodes (LN) has a variable yield. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has demonstrated a high accuracy in the analysis of enlarged subcarinal LN. ***Objective:*** To assess the diagnostic accuracy of EUS-FNA in the analysis of enlarged subcarinal LN previously staged tumor negative by TBNA. ***Methods and Patients:*** In this retrospective study, we included all patients with (suspected) lung cancer and enlarged (>1 cm on CT) subcarinal LNs staged tumor negative by TBNA, who were subsequently staged by EUS-FNA. In addition, surgical-pathological information had to be available in those cases in which EUS-FNA was tumor negative. ***Results:*** Subcarinal LN metastases were assessed by EUS-FNA in 10 of 14 patients (71%). In 1 patient granulomas without necrosis were found. The remaining 3 patients staged tumor negative by both TBNA and EUS-FNA had reactive LN tissue, which was confirmed by surgical-pathological staging. Sensitivity, specificity and diagnostic accuracy of EUS in analyzing TBNA-negative LNs was 100% in all. ***Conclusions:*** In patients with (suspected) lung cancer and enlarged subcarinal LNs staged tumor negative by TBNA, additional staging by EUS-FNA confirmed subcarinal LN metastasis in 71% of the patients. These data suggest that for the analysis of the subcarinal LNs the real-time controlled technique of EUS-FNA is superior to the 'blind' technique of TBNA.

Introduction

Determination of mediastinal lymph node (LN) metastases usually excludes surgical intervention in patients with (suspected) lung cancer. Regional LN metastases often spread to the subcarinal LN, which can be punctured transcarinally during bronchoscopy [1]. Harrow et al. [2] reported a sensitivity of 89% using transbronchial needle aspiration (TBNA) of the subcarinal LNs, and in another study TBNA proved mediastinal tumor spread in

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50 of the 80 patients with lung cancer and enlarged subcarinal LNs, thus preventing further invasive staging [3]. The false-negative rate of TBNA however is high, as was demonstrated in a study on 23 lung cancer patients with enlarged LN who were staged tumor negative by TBNA, but who all had mediastinal metastases [4]. The main drawback of TBNA is the 'blind' way of aspirating LN [5] making it highly operator dependent [6, 7] and resulting in a limited use in daily practice. Both a US (1991) and a UK (2002) based survey revealed that only 12 respectively 27% of bronchoscopists used TBNA [8, 9].

The minimally invasive technique of transesophageal endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is increasingly performed for lung cancer staging [10].

An ultrasound transducer incorporated on top of an endoscope enables the investigator to visualize and puncture mediastinal LN under real-time ultrasound guidance, being in contrast to the 'blind' TBNA. EUS-FNA can detect and biopsy LN as small as 5 mm, and especially the subcarinal LNs can be visualized very well from the esophagus. The procedure is well tolerated, safe, has a high diagnostic accuracy (89–95%) for the analysis of mediastinal LNs [11–14] and has been shown to have a major impact on patient management [12].

We hypothesized that EUS-FNA with real-time aspiration of LNs might be valuable in analyzing enlarged subcarinal LN judged tumor negative by TBNA. In this retrospective study, we reviewed EUS-guided biopsies of subcarinal LNs in patients with (suspected) non-small cell lung cancer (NSCLC) previously staged tumor negative by TBNA.

Patients and Methods

Study Design

In our department, EUS-FNA is one of the staging options for patients with NSCLC and is also frequently used for the primary diagnosis of patients with mediastinal lesions. For the purpose of this study, we retrospectively analyzed patients with (suspected) lung cancer and enlarged subcarinal lymph nodes (short axis >1 cm on CT) staged tumor negative by TBNA, who underwent further staging by EUS-FNA. Surgical-pathological data had to be available in case EUS-FNA was tumor negative. Data were obtained from the EUS-FNA database of the Endoscopic Ultrasound Center of the Department of Pulmonary Medicine of the Leiden University Medical Center (LUMC). The study was approved by the Ethical Committee of the LUMC.

TBNA

Patients undergoing either flexible or rigid bronchoscopy with TBNA with either 19- or 22-gauge needles were included. A CT scan of the chest was available to the bronchoscopists prior to TBNA. Prior to the investigation, informed consent was obtained. Flexible bronchoscopy was performed under local anesthesia, rigid bronchoscopy under general anesthesia.

EUS-FNA

All patients underwent EUS-FNA with sampling of at least the subcarinal LN. The EUS examinations were performed with a Pentax FG 34 UX echo-endoscope with an electronic curved linear array ultrasound transducer with an adjustable ultrasonic frequency of 5, 7.5 or 10 MHz in combination with a Hitachi EUB 6,500 ultrasound scanner. All EUS-FNA investigations were performed in a standardized way [15] on an outpatient basis in the LUMC, with the patient under conscious sedation using midazolam. Prior to the investigation, informed consent was obtained. After introduction, the echo-endoscope was advanced into the distal esophagus and then slowly withdrawn while making circular movements. Anatomical landmarks such as the inferior vena cava, right and left atria, azygos vein, main pulmonary artery and aorta were identified. If present, LNs were described and numbered according to the regional LN classification [16]. LNs were biopsied with a 22-gauge needle (type Hancke/Vilmann) under real-time US guidance with monitoring of the needle during insertion and aspiration. Specimens were judged for adequacy during the procedure after the application of a May-Grünwald diff quick staining.

Surgical-Pathological Staging

Subcarinal LNs staged tumor negative by EUS-FNA were surgically biopsied or resected, except in those patients in whom EUS-FNA established an alternative diagnosis.

Results

Patients

Fourteen patients (8 males and 6 females; mean age 64 years, range 44–82 years) with suspected (n = 8) or proven (n = 6) NSCLC with enlarged subcarinal LNs on CT who were staged tumor negative by transcarinal needle aspiration were retrospectively selected from the EUS-FNA database of the LUMC in the period from January 1999 to December 2003. Patient characteristics and results are shown in table 1.

TBNA

TBNA was performed by flexible (n = 11) and rigid bronchoscopy (n = 3) using 22- and 19-gauge needles, respectively. TBNA was performed by nine different investigators. Representative LN tissue was obtained in 6 patients. The mean number of needle passes was 3 (range 1–7). No complications, such as fever, occurred during or after TBNA. In 5/14 (36%) patients on-site cytology was available during the procedure.

Table 1. Patient characteristics and results

No./Sex/Age	PA	TCNA/n	EUS/n	OP
1/M/68	ad	–/3	–/4	+ (obduction)
2/M/67	?	–/2	ns/2	
3/M/62	ns	–/2	ns/2	
4/M/59	sq	–/4*	+/2	+ (MS, Thor)
5/F/57	?	+/2	sc/2	
6/M/57	?	+/3	ns/3	
7/F/64	sq	+/2	+/2	+ (MS)
8/M/52	?	–/4	ad/2	
9/M/44	?	+/4	ad/ 1	
10/F/78	?	–/3	ad/4	
11/F/75	sq	+/7*	sq/2	
12/F/ /81	sq	–/1*	sq/3	
13/M/58	?	+/2	gr/3	
14/F/70	?	–/1	ad/2	

No. = Study patient number; PA = histology of the primary lung tumor; ? = suspected lung cancer; n = number of needle passes; OP = histology of the subcarinal LN; ad = adenocarcinoma, sq = squamous cell carcinoma; ns = large cell carcinoma; sc = small cell lung carcinoma; gr = granulomas; + = LN tissue; – = no LN tissue; * = 19-gauge needle (all other biopsies: 22 gauge); MS = mediastinoscopy; Thor = thoracotomy.

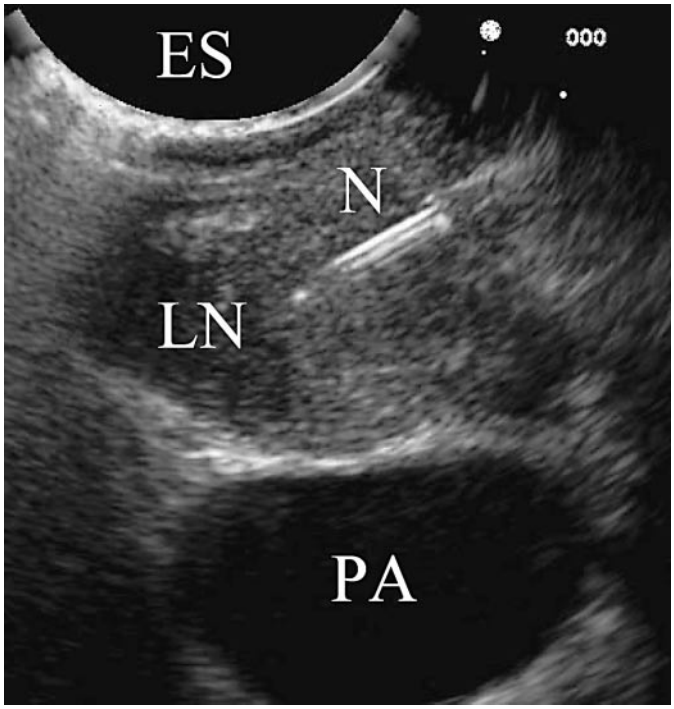

Fig. 1. Real-time EUS-FNA of a subcarinal LN. Es = Esophagus; LN = lymph node; PA = pulmonary artery, N = needle.

EUS-FNA

The mean size of the subcarinal lymph nodes was 23 mm (15–50 mm). In 10 of 14 patients (71%), EUS-FNA confirmed subcarinal LN metastases: adenocarcinoma (n = 4), large cell carcinoma (n = 2), squamous cell carcinoma (n = 2), giant cell carcinoma (n = 1) and a small cell lung cancer (n = 1). In 1 patient, the aspirate contained granulomas without necrosis compatible with sarcoidosis; in 2 patients reactive LN tissue and in 1 patient inadequate material was obtained. The mean number of needle passes was 3 (range 1–4). EUS-FNA was performed by two investigators. No complications, such as fever, occurred during or after EUS-FNA. In 12/14 patients (86%), aspirates were judged for adequacy during the procedure.

Surgical-Pathological Staging

In the 3 patients staged tumor negative by both TBNA and EUS-FNA, the subcarinal LNs contained reactive LN tissue on surgical-pathological examination (mediastinoscopy, n = 1; thoracotomy, n = 1, and obduction, n = 1).

Analysis

We assumed that none of the biopsies was false positive due to the fact that none of the primary tumors were directly adjacent to the biopsied subcarinal LNs, and all tumor-positive EUS-FNA aspirates contained multiple clusters of malignant cells. The positive predictive value, negative predictive value, sensitivity, specificity and diagnostic accuracy of EUS-FNA in analyzing subcarinal LNs previously staged tumor negative by TBNA were all 100%.

Discussion

EUS-FNA assessed subcarinal LN metastases in 10/14 patients (71%) previously staged tumor negative by TBNA. Sensitivity, specificity and diagnostic accuracy of EUS-FNA in analyzing subcarinal LNs in this case series was 100%.

In only 6 of 14 patients (43%), TBNA contained representative LN tissue. A possible explanation for the low yield in our study was the low mean size of the subcarinal LN of 23 mm. Increasing LN size is a major determinant of TBNA yield [2, 17]. It has been shown that the quality of aspirates among non-diagnostic TBNA procedures was suboptimal in 25% or unsatisfactory in 8% of the cases

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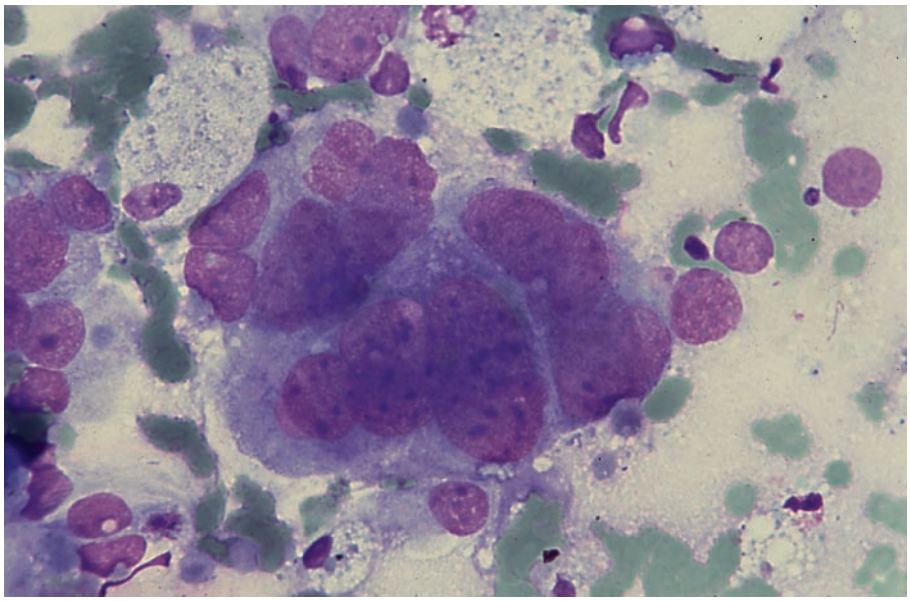

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Fig. 2. 'Blind' transcarinal needle aspiration during bronchoscopy.
Fig. 3. EUS-FNA of a subcarinal LN demonstrating giant cell carcinoma.

[7]. Education and experience have shown to improve the yield of TBNA significantly [6, 7]; to achieve acceptable TBNA results, an estimated training period of around 50 procedures is recommended [6]. In contrast, only 1 of the 14 EUS-guided biopsies revealed inadequate material. We are well aware that this study describes a selected group of non-diagnostic results of transcarinal needle aspiration. As patients from different hospitals were included, we are not aware of the number of TBNA procedures which were diagnostic, and therefore nothing about the yield of TBNA can be said. All bronchoscopists who performed TBNA were trained in this procedure, but the experience varied widely amongst the different investigators, as TBNA procedures performed by pulmonary fellows were also included. A recent study performed by (supervised) pulmonary fellows demonstrated a TBNA yield of 60%, suggesting that even less-experienced investigators can obtain a high yield [17].

An advantage of EUS-FNA is the real-time visualization of the needle insertion (fig. 1) and monitoring during the whole procedure, which in our experience provides a huge advantage, compared to the 'blind' fashion of TBNA (fig. 2). Although the diagnostic accuracy of 100% in this study is promising and consistent with other studies [10–14], we are well aware that the sample size is small. From our experience of more than 400 EUS-FNA procedures for mediastinal analysis, we learned that subcarinal metastases can be missed by EUS-FNA even despite adequate biopsies. In a large recent retrospective study about the yield of TBNA, a total of 166 patients were included in the diagnosis of mediastinal lesions covering a timespan of 9 years [17]. Only 25 of them underwent TBNA of the subcarinal LN, which resulted in 15 tumor-positive (60%) and 10 tumor-negative results. In that respect, the 14 TBNA-negative patients for LN 7 described in this preliminary report is not that small. In addition, we included only patients in whom a final diagnosis of the subcarinal LN was available – important information which lacks in most other studies.

Part of the discrepancy between TBNA and EUS-FNA may be explained by the fact that 86% of the EUS-FNA aspirates were examined for adequacy (fig. 3), in contrast to only 36% of the TBNA procedures, while on-site cytology was not available in all hospitals. The average number of needle passes by both techniques, however, was the same (n = 3). It has been shown that there is a plateau in the yield of TBNA after seven aspirates, and it is suggested that at least four samples are taken [18].

The failure to position the needle exactly in the target lesion is regarded as the leading cause of the variable yield in TBNA [5]. To facilitate needle monitoring, it has been suggested to perform CT-fluoroscopy-guided TBNA in patients with a previously non-diagnostic 'blind' TBNA. Disadvantages are the radiation exposure and the reported inadequate needle positioning of up to 40% [19]. Recently, endobronchial ultrasound (EBUS)-guided TBNA has been proposed as a new technique to increase the yield of TBNA [20, 21]. In these studies, however, the ultrasound probe was only used to localize the target LN. The actual TBNA was performed after removal of the US

probe making real-time-guided procedure impossible. The development of bronchoscopes with real-time EBUS-guided FNA may overcome this problem.

In contrast to CT fluoroscopy and EBUS, EUS-FNA enables real-time needle monitoring. The average sensitivity of 93% and specificity of 98% of EUS-FNA in mediastinal LNs are high [10–14]; however, most studies are performed in selected patients with enlarged LNs, which are accessible by EUS-FNA. EUS-FNA is particularly suited to sample subcarinal LNs (No. 7), the aortopulmonary window (No. 5) and those LNs located paraesophageal in the lower mediastinum (No. 8) and the ligamentum pulmonale (No. 9). Paratracheal LNs (No. 2, 4 right and left) can only be visualized if they are situated lateral to the trachea due to the intervening air of the trachea. In our opinon, only 4L is easily identified. As far as N2/N3 staging is concerned, TBNA is most commonly performed analyzing subcarinal or paratracheal LNs. Currently, the only prospective study (abstract) between EUS-FNA and TBNA suggests that EUS-FNA is more accurate [22].

As patients with suspected lung cancer undergo a bronchoscopy anyway, a TBNA should be considered in those patients with enlarged subcarinal LNs in order to maximize the diagnostic yield [23, 24]. If further analysis of a subcarinal LN is needed after bronchoscopy with a non-diagnostic TBNA, EUS-FNA should be considered as the next diagnostic procedure. Its real-time needle monitoring, safety and high diagnostic accuracy in assessing subcarinal metastases may reduce the need for further invasive staging procedures.

In conclusion, this study demonstrates that EUS-FNA has a high yield in confirming subcarinal LN metastases after previously tumor-negative TBNA. EUS-FNA may qualify as the diagnostic tool of choice to analyze subcarinal LN. Future (prospective) studies comparing TBNA, EUS-FNA, EBUS-FNA and mediastinoscopy in the analysis of mediastinal LNs are needed in order to improve staging strategies for (suspected) NSCLC.

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