

# Usefulness of transbronchial needle aspiration for initial lung cancer staging

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## KEY WORDS

mediastinum,  
non-small cell lung  
cancer staging,  
transbronchial needle  
aspiration

## ABSTRACT

**INTRODUCTION** Besides radiological methods (especially positron emission tomography combined with computed tomography), endoscopic techniques including transbronchial needle aspiration (TBNA) of mediastinal lymph nodes play an important role in lung cancer staging, thus having a significant effect on further patient management.

**OBJECTIVES** The aim of the study was to investigate the diagnostic value of blind TBNA in staging of lung cancer, using systematic mediastinal lymph node dissection (SLND) at thoracotomy as a confirmatory test.

**PATIENTS AND METHODS** Patients with lung cancer and enlarged mediastinal lymph nodes on computed tomography scans underwent TBNA. Non-small cell lung cancer (NSCLC) patients with negative TBNA or with single-level N2 disease underwent thoracotomy with appropriate pulmonary resection and with SLND.

**RESULTS** In 84 lung cancer patients, 166 TBNA were performed. Metastatic lymph node involvement was identified in 57 patients (67.9%). There were 10 patients (11.9%) with small cell lung cancer. Of the 74 NSCLC patients, TBNA revealed metastases in 48 (64.9%). Twenty-four TBNA-negative patients (32.4%) and 4 patients (5.4%) with single-level N2 disease underwent pulmonary resection with SLND. In 8 of 28 operated patients (28.6%), N2 metastatic nodes were identified. The per-patient analysis showed the sensitivity of TBNA to be 81.5%, specificity – 100%, accuracy – 86.5%, and negative predictive value (NPV) – 66.7%.

**CONCLUSIONS** Our results suggest that TBNA may be a useful method for initial NSCLC staging in patients suspected of N2-3 disease. Positive TBNA in 1 station only should not be considered as a true single-level N2 disease, because of a relatively low NPV for TBNA.

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**INTRODUCTION** Recent data indicate that only 20% of non-small cell lung cancer (NSCLC) patients have a local disease at the time of diagnosis, while 26% to 38% have mediastinal lymph node involvement. A complete mediastinal staging is important for patient management, so it is essential to determine eligible candidates for lung resection. Positron emission tomography combined with computed tomography (PET-CT) is the most accurate and widely used noninvasive

method of lung cancer staging. Although its sensitivity ranges from 79% to 96%, specificity – 83% to 92%, positive predictive value (PPV) – 79% to 90%, and negative predictive value (NPV) – 93% to 95%, PET-CT does not provide histological diagnosis and is relatively expensive.<sup>1,2</sup>

Transbronchial needle aspiration (TBNA) is the basic, safe endoscopic procedure that may be performed during a routine bronchoscopy. TBNA enables to perform the biopsy of mediastinal or

hilar lymph nodes for cytological and even histological diagnosis, which is necessary for accurate lung cancer staging.<sup>3-5</sup> The specificity of TBNA in identification of mediastinal masses is very high (96%–100%). Sensitivity varies from 20% to 89%, because the technique is highly operator-dependent, but also due to variable prevalence in the presented trials, which might have biased the reports. Also, these studies do not provide sufficient data on the NPV of TBNA, as it is not clearly defined which confirmatory surgical tests were used. Numerous studies indicate that TBNA provides a possibility for non-invasive lung cancer staging during initial bronchoscopic assessment.<sup>4</sup> For patients with discrete mediastinal lymph node enlargement and no distant metastases, an invasive confirmation of the radiographic stage is recommended, regardless of PET-CT results. Many invasive techniques for confirmation of the N2-3 node status are suggested as useful methods (mediastinoscopy [MS], endoscopic ultrasound-guided fine needle aspiration [EUS-FNA], TBNA, endobronchial ultrasound-guided transbronchial needle aspiration [EBUS-TBNA]). Their use depends on the availability of personnel with appropriate skills. The result of histological examination of the sample that was obtained using needle technique and shows no malignancy should always be further confirmed by MS, regardless of PET-CT findings.<sup>6,7</sup>

The aim of the study was to assess the diagnostic value of blind TBNA for lung cancer staging using systematic mediastinal lymph node dissection (SLND) during thoracotomy as a confirmatory test.

**PATIENTS AND METHODS** A blind TBNA was performed in consecutive lung cancer patients with enlarged mediastinal lymph nodes. Negative results of TBNA were verified by SLND in patients who underwent pulmonary resection or, in the case of bulky nodes, by MS. This prospective cohort diagnostic study was conducted in the Endoscopy Unit, Department of Thoracic Surgery, John Paul II Hospital, Kraków, Poland.

**Patients** The inclusion criteria were as follows: confirmed or suspected lung cancer, enlarged mediastinal lymph nodes on CT scan (>10 mm in short axis), and the general condition allowing appropriate pulmonary resection. The exclusion criterion was lack of consent. The study was approved by the local ethics committee and informed consent was obtained from all patients.

**Intervention** After a careful analysis of the CT scans, bronchoscopy was performed under local anesthesia and intravenous sedation (fentanyl 0.05–0.1 mg and midazolam 1–5 mg). The BF 1T180 videobronchoscopes (Olympus Medical Systems Corporation, Tokyo, Japan) with a 3.0 mm working channel were used. The biopsy was performed using NA-411D-1521 (21g/15mm)

(Olympus Medical Systems Corporation, Tokyo, Japan). In each patient 1 to 3 nodal stations were punctured and 2 to 4 passes were performed in each station. The preferred biopsy method was the “pushing” technique.

The cytological smear was performed and fixed using 96% ethanol. The standard hematoxylin-eosin staining was used and the specimen was sent to a histopathology laboratory. In patients with bulky nodes on CT scans and TBNA-negative results, MS was performed. In other NSCLC patients with negative TBNA, an appropriate pulmonary resection with SLND was performed.

The Mountain-Dresler lymph node classification was used.<sup>8</sup>

**Statistical analysis** The sensitivity, specificity, accuracy, PPV, and NPV (including 95% confidence interval) were calculated using the GraphPad InStat 3.05 software (GraphPad Software, San Diego, California, United States). The bootstrap method was used (Statistica™, Statsoft Inc., United States) to compare the diagnostic values of different medical tests. The level of significance was set at  $P < 0.05$ .

**RESULTS** Between January 2009 and October 2009, 84 lung cancer patients were recruited to the study and 166 mediastinal nodal stations were biopsied. A cytological diagnosis of metastatic lymph node involvement was made in 57 patients (67.9%). In the examined group, there were 74 patients with NSCLC and 10 with small cell lung cancer (SCLC). The biopsy was technically successful in 136 cases (81.9%). In the final analysis, only the patients with NSCLC were studied. There were 20 women and 54 men at the mean age of  $65 \pm 8$  years (range: 42–78 years).

The cytological diagnosis of SCLC was confirmed by TBNA in 9 patients (15 biopsies) in the following stations: 2R – 2 biopsies, 4R – 4, 4L – 5, and 7 – 4. In 1 patient (2 stations: 2R – 1 biopsy and 4R – 1), the result of biopsy of SCLC was negative, which was confirmed by MS.

In 74 NSCLC patients, 149 biopsies were performed in the following stations: 7 – 63 biopsies, 4R – 59, 4L – 20, and 2R – 7 (TABLE 1).

The cytological examination of the smear revealed metastatic nodal involvement in 48 of 74 NSCLC patients (64.9%) (44 patients had double- or multilevel N2-3 disease and 4 had single-level N2 disease).

Among the 26 TBNA-negative patients, the MS was performed only in 2 patients with bulky nodes on CT scans and revealed nodal metastases in both in station 4R (2 patients) and station 7 (1 patient).

Twenty-eight patients, including 24 TBNA-negative patients (32.4%) and 4 patients (5.4%) with single-level N2-TBNA disease, underwent an appropriate pulmonary resection with SLND. In 8 of these 28 patients, N2 metastatic nodes were found: in 6 patients in 7 stations accessible

**TABLE 1** Characteristics of 74 patients with non-small cell lung cancer and mediastinal adenopathy, including clinical TNM staging and the localization of the tumor

	Number of patients, n	Percentage, %
M/F	54/20	73/27
mean age $\pm$ SD, yrs	65 $\pm$ 8 (range, 42–78)	
definite diagnosis of NSCLC based on TBNA	48	64.9
clinical TNM stage		
(T1N2M0) IIIA	4	5.4
(T2N2M0) IIIA	41	55.4
(T3N2M0) IIIA	19	25.7
(T4N2M0) IIIB	8	10.7
(T2N3M0) IIIB	1	1.4
(T4N3M0) IV	1	1.4
side of the primary tumor		
right side	53	71.6
RUL	29	39.1
RML	5	6.8
RLL	12	16.2
CR	7	9.5
left side	21	28.4
LUL	8	10.8
LLL	9	12.2
CL	4	5.4

Abbreviations: CL – central left, CR – central right, F – female, LLL – left lower lobe, LUL – left upper lobe, M – male, NSCLC – non-small cell lung cancer, RLL – right lower lobe, RML – right middle lobe, RUL – right upper lobe, TBNA – transbronchial needle aspiration, SD – standard deviation, TNM – tumor, node, metastasis

for TBNA (station 4R in 5 patients and 7 in 2) and in 2 patients in stations inaccessible for TBNA and MS: aortopulmonary window (station 5 in 1 patient) and prevascular (station 3A in 1 patient).

In 4 patients (5.4%), lymph node dissection at thoracotomy showed double-level N2 disease with a partial involvement of metastatic nodes.

The per-patient analysis showed the sensitivity of TBNA to be 81.5%, specificity – 100%, accuracy – 86.5%, PPV – 100%, and NPV – 66.7%.

The diagnostic yield of TBNA for the nodes accessible for TBNA (subcarinal and paratracheal) is presented in **TABLE 2**.

The diagnostic yield of TBNA in nodal stations accessible for TBNA (subcarinal and paratracheal) was statistically higher than for all groups of mediastinal lymph nodes ( $P = 0.01$ ). Also NPV was statistically higher in lymph nodes accessible for TBNA ( $P = 0.01$ ).

Sensitivity and NPV of blind TBNA was statistically higher in group 7 than in group 4R ( $P = 0.046$  and  $P = 0.023$ , respectively). We did not observe

similar differences between group 7 and group 4L ( $P = 0.161$  and  $P = 0.161$ ).

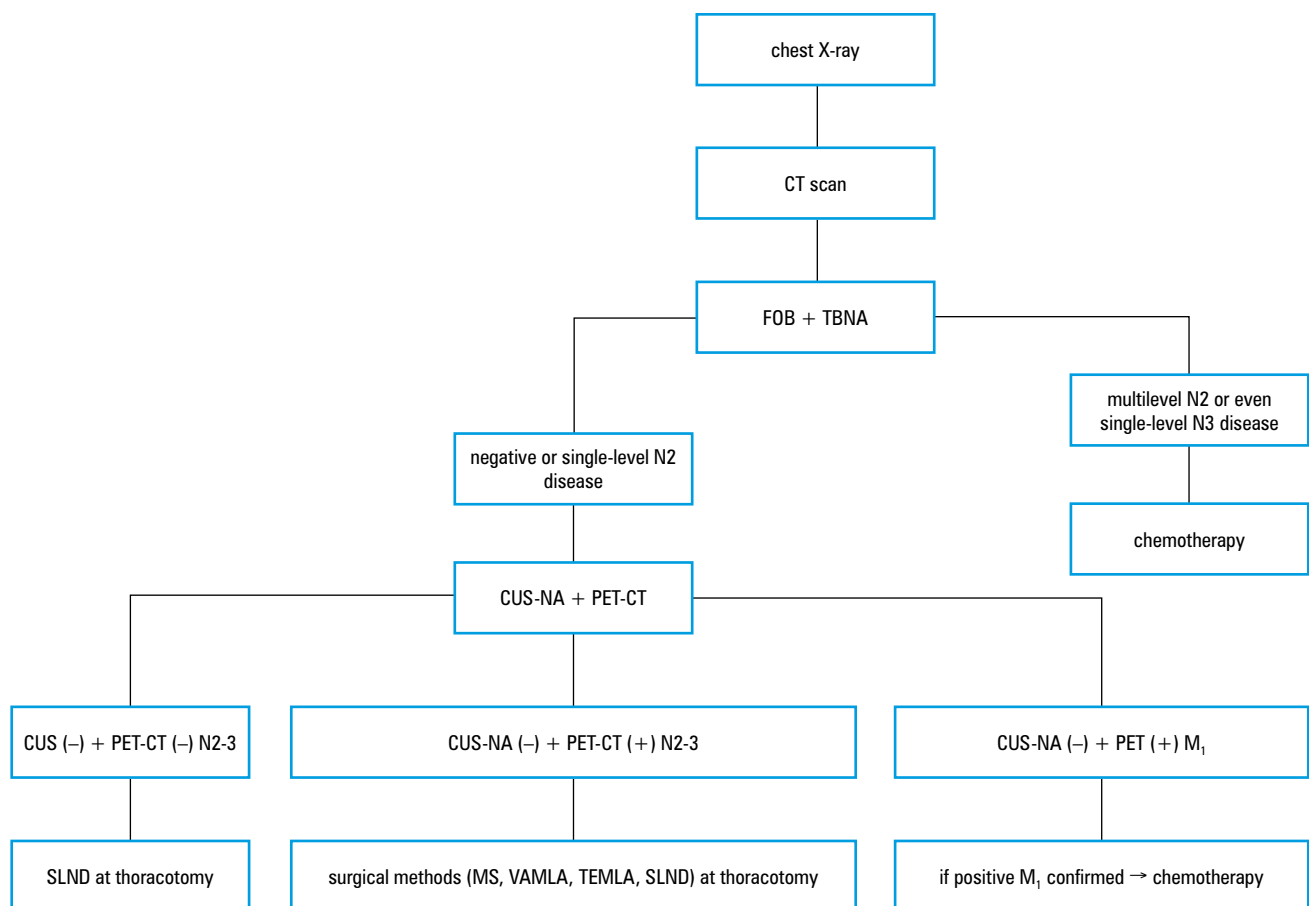
No complications after TBNA were observed (small bleeding from the site of puncture was not considered a complication).

The prevalence of metastases in mediastinal lymph nodes was 77.4%.

**DISCUSSION** TBNA is a well-established bronchoscopic technique, which allows for tissue sampling from mediastinal lymph nodes, submucosal and peripheral lesions.<sup>9–12</sup> The first biopsy of mediastinal lymph nodes through the carina was performed in 1949 by Schieppati<sup>13</sup> using a rigid bronchoscope. In 1983, Wang et al.<sup>14</sup> for the first time reported diagnostic utility of TBNA in lung cancer staging. TBNA allows to perform a biopsy of several nodal stations including 2R, 2L, 4R, 4L, 7, 10R, 10L and 11R, 11L. The diagnostic yield of blind TBNA ranges from 20% to 89%<sup>11,15–21</sup> and is highly dependent on the operator's experience.<sup>22–24</sup>

**TABLE 2** The diagnostic yield of transbronchial needle aspiration calculated on per-biopsy basis

Lymph node station	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
7 – subcarinal	95.2	100	96.8	100	91.3
2R – right upper paratracheal	83.3	100	85.7	100	50.0
4R – right lower paratracheal	84.1	100	88.1	100	68.2
4L – left lower paratracheal	100	100	100	100	100



**FIGURE** Proposed diagnostic flow-chart for non-small cell lung cancer staging including transbronchial needle aspiration.

Abbreviations: CT – computed tomography, CUS-NA – combined ultrasound needle aspiration, FOB – fiberoptic bronchoscopy, MS – mediastinoscopy, PET-CT – positron emission tomography combined with CT, SLND – systematic mediastinal lymph node dissection, TBNA – transbronchial needle aspiration, TEMPLA – transcervical extended mediastinal lymphadenectomy, VAMLA – video-assisted mediastinal lymphadenectomy

In our study, the results of blind TBNA were verified by MS or SLND at thoracotomy. The biopsy was technically successful in 136 cases (81.9%), and the overall sensitivity and accuracy of TBNA calculated per patient was high – 81.5% and 86.5%, respectively. It is because TBNA was performed by 3 experienced bronchoscopists and the prevalence of metastases in mediastinal lymph nodes in the whole study was 77.4%.

The diagnostic yield of TBNA for the nodes accessible for TBNA was statistically higher than for all lymph nodes. Sensitivity and NPV was statistically higher in group 7 than in 4R. The NPV of blind TBNA in lymph node stations other than group 7 was low (7 – 91.3% vs. 2R – 50% and 4R – 68.2%). There was no similar difference between groups 7 and 4L.

In 10 NSCLC patients (13.5%), the result of blind TBNA was false negative. In 2 of these patients, MS revealed metastases in station 4R (2 patients) and station 7 (1 patient). In 8 of 28 patients who underwent lung resection, metastatic nodes were found not only in stations accessible for TBNA (station 4R in 5 patients and station 7 in 2) but also in stations inaccessible for TBNA and MS: aortopulmonary window (station 5 in 1 patient) and prevascular (station 3A in 1 patient).

In the present study, NPV calculated per patient was relatively low – 66.7%. A low NPV of blind TBNA in the majority of nodal stations diminishes its value in complete and accurate lung cancer staging in patients with NSCLC and is an indication for further diagnostic procedures, including other invasive methods such as EBUS-TBNA, EUS-FNA, and if negative – MS. Nevertheless, blind TBNA seems to be a useful method for initial NSCLC staging in patients suspected of N2-3 disease. The results of our study also prove that a positive TBNA in 1 station should not be considered as a true single-level N2 disease, because of a relatively low NPV.

Recently, very promising methods in lung cancer staging have been introduced, namely EBUS-TBNA and EUS-FNA, which allow to perform a biopsy in real-time conditions<sup>25-30</sup> and are characterized by high sensitivity and, more importantly, high and reliable NPV (EBUS-TBNA: 88%–95% and 85%–96%,<sup>25,31-33</sup> EUS-FNA: 71%–100% and 73%–79%,<sup>34-36</sup> respectively). The importance of EBUS-TBNA and EUS-FNA in lung cancer staging has been confirmed in several studies and is now widely accepted.<sup>6,25,31,37-40</sup> Because EBUS is not designed for a detailed assessment of the bronchial tree, the examination

should be preceded by standard videobronchoscopy. Gaining skill and experience in endobronchial ultrasound imaging and biopsy is more time-consuming than in conventional bronchoscopy and requires proper training. Actually, EBUS and EUS are expensive and not widely available techniques. According to our data, it seems reasonable to perform TBNA for initial NSCLC staging as the first invasive procedure, but if negative, a combined ultrasound needle aspiration (CUS-NA), including EBUS-TBNA and EUS-FNA, should be performed (FIGURE). Moreover, it seems controversial whether MS accessing only 5 of 13 mediastinal stations is an appropriate confirmatory test for CUS-NA. At present, many centers replace more invasive surgical techniques with new endoscopic techniques.<sup>7,25,27,31,32,36</sup>

To conclude, TBNA may be a useful method for initial NSCLC staging in patients suspected of N2 disease. Positive TBNA in 1 station only should not be considered as a true single-level N2 disease, because of a relatively low NPV.

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# Przydatność przezoskrzelowej biopsji igłowej we wstępnej ocenie stopnia zaawansowania raka płuca

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## SŁOWA KLUCZOWE

ocena stopnia  
zaawansowania  
niedrobnokomórko-  
wego raka płuca,  
przezoskrzelowa  
biopsja igłowa,  
śródpierście

## STRESZCZENIE

**WPROWADZENIE** Techniki endoskopowe, w tym przezoskrzelowa biopsja igłowa (*transbronchial needle aspiration – TBNA*) węzłów chłonnych śródpierścia, odgrywają, obok metod radiologicznych (zwłaszcza zintegrowanej pozytronowej tomografii emisyjnej i tomografii komputerowej), istotną rolę w ocenie stopnia zaawansowania raka płuca (*staging*), mając ogromny wpływ na dalsze postępowanie.

**CELE** Celem badania była ocena wartości diagnostycznej „ślepej” TBNA węzłów chłonnych śródpierścia w *stagingu* raka płuca przy wykorzystaniu operacyjnej limfadenektomii śródpierścia (*mediastinal lymph node dissection – SLND*), wykonywanej podczas torakotomii jako test weryfikacyjny.

**PACJENCI I METODY** U chorych na raka płuca i z powiększonymi węzłami chłonnymi śródpierścia w badaniu TK wykonywano TBNA. Chorych na niedrobnokomórkowego raka płuca (NDRP) z ujemnym wynikiem TBNA lub 1-poziomym zajęciem węzłów chłonnych śródpierścia kwalifikowano do anatomicznej resekcji mięszu płuca z limfadenektomią.

**WYNIKI** U 84 chorych z rakiem płuca wykonano 166 TBNA. Zmiany przerzutowe w węzłach chłonnych stwierdzono u 57 chorych (67,9%). U 10 chorych (11,9%) rozpoznano drobnokomórkowego raka płuca. Wśród 74 chorych na NDRP stwierdzono metodą TBNA zmiany przerzutowe u 48 chorych (64,9%). U 24 chorych z ujemnym wynikiem TBNA (32,4%) i u 4 chorych (5,4%) z 1-poziomym zajęciem węzłów chłonnych śródpierścia wykonano resekcję mięszu płuca z SLND. U 8 spośród 28 zoperowanych chorych stwierdzono cechę N2 (28,6%). Analiza w przeliczeniu na pacjenta wykazała czułość TBNA – 81,5%, swoistość – 100%, dokładność – 86,5% i wartość predykcyjną ujemną (*negative predictive value – NPV*) – 66,7%.

**WNIOSKI** Wyniki badań wskazują, że TBNA może być użyteczną metodą we wstępnej ocenie stopnia zaawansowania raka płuca u chorych podejrzanych o przerzuty w węzłach chłonnych śródpierścia N2-3. Dodatni wynik TBNA tylko w jednej stacji węzłów chłonnych śródpierścia nie powinien być rozważany jak faktycznie 1-poziomowe N2, ze względu na relatywnie niską wartość NPV dla TBNA.

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