

Minimally invasive strategy for mediastinal staging of patients with lung cancer

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KEY WORDS

lung cancer,
mediastinum,
staging

ABSTRACT

INTRODUCTION The exclusion of mediastinal involvement in patients with non-small cell lung cancer is essential for choosing an appropriate therapy.

OBJECTIVES The aim of the study was to analyze the ability of a new minimally invasive strategy combining positron emission tomography (PET), endobronchial ultrasound needle aspiration (EBUS-NA), and endoscopic ultrasound needle aspiration (EUS-NA) to exclude mediastinal nodal metastases of non-small cell lung cancer.

PATIENTS AND METHODS In a group of consecutive patients with primary non-small cell lung cancer, the preoperative assessment of mediastinal lymph nodes using PET, EBUS-NA, and EUS-NA. Patients in whom this minimally invasive staging protocol did not confirm mediastinal nodal metastases underwent pulmonary resection with systematic lymph node dissection. The negative predictive values of the combined EBUS-NA/EUS-NA as well as PET/EBUS-NA/EUS-NA were calculated.

RESULTS We analyzed data of 532 patients (367 men and 165 women; mean age, 65 years [range, 30–84 years]). Squamous carcinoma were diagnosed in 276 patients; adenocarcinoma, in 150; large cell carcinoma, in 22; adenosquamous carcinoma, in 40; small cell carcinoma, in 4; carcinoids, in 21; and other histological types, in 19. We performed 421 lobectomies, 55 pneumonectomies, 51 bilobectomies, and 5 sublobar resections. In all patients, systematic lymph node dissection was performed. The mean number of removed lymph nodes was 22. The negative predictive value of EBUS-NA/EUS-NA was 89.8% and of PET/EBUS-NA/EUS-NA—93.2%.

CONCLUSIONS Patients with lung cancer with negative results of PET, EBUS-NA, and EUS-NA are at low risk of mediastinal nodal metastasis. In these patients, invasive mediastinal staging may not be necessary.

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INTRODUCTION Lung cancer is the most common cause of cancer-related deaths. During the 19th century, lung cancer evolved from a rare disease to the most serious oncological problem in the world. The overall 5-year survival rate in Europe is 11.5, and it has not improved significantly over the last 2 decades. The most important issue in choosing an appropriate therapy is reliable staging. In patients with no distant metastases, the involvement of mediastinal nodes is the most important factor. Numerous techniques have been used for this purpose, including imaging, needle biopsies, and invasive

surgical staging. However, the universally accepted staging strategy is still lacking. According to the revised European Society of Thoracic Surgeons (ESTS) guidelines for preoperative mediastinal lymph node staging, primary surgery can be offered to patients with no positive lymph nodes on computed tomography (CT) and positron emission tomography (PET), primary tumor smaller than 3 cm, and the tumor located in the outer third of the lung.¹ However, literature data supporting the use of the minimally invasive regimen in patients with tumors larger than 3 cm and centrally located are scant.

The aim of this study was to assess the value of a minimally invasive strategy, which includes PET scanning, EBUS-NA, and EUS-NA, in mediastinal staging of patients with non-small cell lung cancer, regardless of the size and location of the tumor.

PATIENTS AND METHODS **Clinical question and study setting** It was a prospective cohort study investigating the ability of the minimally invasive strategy combining PET, EBUS-NA, and EUS-NA to exclude mediastinal nodal metastases of non-small cell lung cancer. The study was conducted at the Department of Thoracic Surgery, Jagiellonian University, John Paul II Hospital, in Kraków, Poland.

Patients Between January 2011 and December 2013, all patients suffering from potentially operable lung cancer were included into the study. The inclusion criteria were as follows: confirmed or suspected non-small cell lung cancer, initial clinical stage I-IIIa, general performance status enabling an appropriate lung resection according to the European Respiratory Society / ESTS guidelines.² The exclusion criteria were as follows: restaging after induction chemotherapy, diagnosis of small-cell lung carcinoma, severe coagulation disorders, and lack of the patient's informed consent.

Intervention In all patients, the initial workup included chest radiography, CT, spirometry and diffusing capacity for carbon monoxide, and bronchoscopy. Patients in whom this initial assessment did not reveal distant metastases or severe cardiopulmonary disease fulfilling the criteria of medical inoperability underwent PET-CT and combined transbronchial and transesophageal ultrasound assessment of the mediastinum, referred to as "combined ultrasound" (CUS).

The endobronchial ultrasound needle aspiration (EBUS-NA) was performed using a BF-UC160F-OL8 videobronchoscope (Olympus Medical Systems Corporation, Tokyo, Japan) with an EU-C60 7.5-MHz ultrasound processor. For the biopsy, a cytological 40-mm 22-gauge needle (NA-201SX-4022, Olympus Medical Systems Corporation) was used.

The endoscopic ultrasound needle aspiration (EUS-NA) was performed using a GF-UCT160-OL5 videogastroscope (Olympus Medical Systems Corporation) with an EU-C60 7.5-MHz ultrasound processor. For the biopsy, a cytological 80-mm 22-gauge needle (NA-200H-8022, Olympus Medical Systems Corporation) was used.

During CUS, a needle biopsy of all mediastinal nodes of 5 mm or more on the short axis and of all PET-positive nodes, regardless of their size, was performed. The cytological smear of all biopsies was performed and fixed using ethanol (96%). Samples from each lymph node station were prepared separately. The standard hematoxylin and eosin staining was used. The technique

of the procedure was described elsewhere.³ All procedure-related complications were recorded.

In patients with contradictory results of PET and CUS, the result of CUS was used for the final clinical staging. All patients with the final clinical stage of I-IIIa underwent an appropriate lung resection with mediastinal dissection according to the ESTS guidelines.⁴ The results of the final pathological examination of the surgical specimens were used for the calculation of a negative predictive value (NPV).

Assessed variables The primary variable was the NPV of CUS and that of the combination of PET and CUS. The secondary variable was the complication rate of the staging procedure.

Statistical analysis As the descriptive statistics, mean values were used. The NPV was determined using the Statistica™ (Statsoft Inc., Tulsa, Oklahoma, United States). The level of significance was set at a *P* value of 0.05 or lower.

RESULTS A total of 696 patients were enrolled to the study. In 164 of these patients, a cytological analysis of the CUS-NA specimen confirmed mediastinal nodal involvement. In the remaining 532 patients, an appropriate lung resection with a systematic lymph node dissection was performed. The group consisted of 367 men and 165 women. The mean age was 65 years (range, 30–84 years). The most common locations of the tumor were upper lobes: left in 135 patients, and right in 134 patients. Other locations included the right lower lobe in 88 patients, left lower lobe in 80 patients, middle lobe in 24 patients, right central lobe in 42 patients, and left central lobe in 29 patients (TABLE 1).

The most common histological type was squamous cell carcinoma (*n* = 276), followed by adenocarcinoma (*n* = 150), adenosquamous carcinoma (*n* = 40), and large cell carcinoma (*n* = 22). In 24 patients who underwent surgery with the initial cytological finding of "malignant cells" without specific diagnosis or without cytological confirmation, the carcinoid was finally diagnosed in 21 patients, of whom 4 had small-cell lung cancer. Other histological types were diagnosed in 19 cases (TABLE 2).

There were 421 lobectomies, 55 pneumonectomies, 51 bilobectomies, and 5 sublobar resections performed. During all procedures, a systematic nodal dissection was performed according to the ESTS guidelines. The mean number of lymph nodes resected was 22. Regarding the N2 nodes, the NPV calculated for CUS alone was 89.8%. However, when CUS and PET were assessed together, the NPV was 93.2%.

There were no complications related to the use of CUS. Although the NPV of the PET alone was very high (93%), its positive predictive value was only 21%.

TABLE 1 Location of the primary tumor

Location of the tumor	Number of patients
RUL	134
RML	24
RLL	88
RC	42
LUL	135
LLL	80
LC	29

Abbreviations: LC, left central; LLL, left lower lobe; LUL, left upper lobe; RC, right central; RLL, right lower lobe; RML, right middle lobe

TABLE 2 Histological type of the tumor in the study group

Type of the tumor	Number of patients
squamous	276
adenocarcinoma	150
mixed (adenosquamous)	40
large cell carcinoma	22
carcinoid	21
small cell carcinoma	4
other	19

DISCUSSION The high sensitivity and NPV of EBUS-NA and EUS-NA have been confirmed by numerous studies published in the last decade. Several meta-analyses were performed that showed the sensitivity of EBUS-NA to range between 88% and 93%,⁵⁻⁹ and of EUS—between 83% and 89%.^{5,9,10} CUS was introduced in 2005 by Wilmann et al,¹¹ and several papers published since then have confirmed its sensitivity and NPV to be higher than those of any other minimally invasive strategies. One meta-analysis assessed the diagnostic yield of the CUS and found its sensitivity to reach 91% and NPV—96%.⁹ The diagnostic yield of the CUS is reportedly significantly higher than that of either EBUS-NA or EUS-NA alone.¹² All these data are consistent with the results of our study, which showed the NPV of the CUS to reach 89.8%.

The value of PET-CT in lung cancer staging is also well recognized. Regarding the mediastinal nodal metastases, a recent meta-analysis has shown its NPV of 93%,¹³ which corresponds well with our results. Besides mediastinal staging, PET-CT has the advantage of enabling the diagnosis of unsuspected distant metastases or second malignancy. Including PET-CT in the staging algorithm is recommended both by the American College of Chest Physicians⁹ and by the ESTS.¹ However, owing to its very low positive predictive value, it cannot be used as the sole modality if its results are positive.

However, reliable data regarding the collective diagnostic yield of the minimally invasive staging strategy including PET and CUS are lacking. In the present study, including the largest original

series in the literature, we have shown that the routine use of the combination of PET-CT and CUS results in improved ability to exclude mediastinal nodal metastases of lung cancer, with the NPV of this combined approach reaching 93.2%.

In conclusion, the routine use of CUS is a safe and minimally invasive staging strategy in lung cancer. Adding PET-CT to CUS increases the NPV of the staging workup. Patients with lung cancer in whom the results of mediastinal lymph node staging with PET as well as the results of CUS are negative are at low risk of mediastinal metastases. In these patients, invasive mediastinal staging may not be necessary.

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Minimalnie inwazyjna strategia oceny śródpiersiowych węzłów chłonnych u chorych na raka płuca

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SŁOWA KLUCZOWE

ocena
zaawansowania, rak
płuca, śródpiersie

STRESZCZENIE

WPROWADZENIE Wykluczenie zajęcia węzłów chłonnych śródpiersia u chorych na niedrobnokomórkowego raka płuca ma kluczowe znaczenie dla wyboru właściwego leczenia.

CELE Celem badania była ocena zdolności nowej minimalnie inwazyjnej strategii polegającej na połączeniu pozytonowej tomografii emisyjnej (*positron emission tomography* – PET), biopsji cienkoigłowej pod kontrolą ultrasonografii przezoskrzelowej (*endobronchial ultrasound needle aspiration* – EBUS-NA) i biopsji cienkoigłowej pod kontrolą ultrasonografii przezprzetykowej (*endoscopic ultrasound needle aspiration* – EUS-NA) do wykluczenia przerzutów niedrobnokomórkowego raka płuca w węzłach chłonnych śródpiersia.

PACJENCI I METODY W grupie kolejnych chorych na pierwotnego niedrobnokomórkowego raka płuca zastosowano przedoperacyjną ocenę węzłów chłonnych śródpiersia obejmującą PET, EBUS-NA i EUS-NA. U chorych, u których ten minimalnie inwazyjny protokół badania nie potwierdził przerzutów w węzłach śródpiersia, wykonywano resekcję miąższu płucnego z systematyczną limfadenektomią. Obliczono wartość predykcyjną wyniku ujemnego dla połączenia EBUS-NA z EUS-NA oraz dla połączenia PET z EBUS-NA i EUS-NA.

WYNIKI Analizą objęto dane 532 pacjentów (367 mężczyzn i 165 kobiet; średni wiek: 65 lat [zakres: 30–84]). U 276 chorych rozpoznano raka płaskonabłonkowego, u 150 – gruczołowego, u 22 – wielkokomórkowego, u 40 – gruczołowo-płaskonabłonkowego, u 4 – drobnokomórkowego, u 21 – rakowiaka, a u 19 – inne typy histologiczne. Wykonano 421 lobektomii, 55 pneumonektomii, 51 bilobektomie i 5 mniejszych resekcji. U wszystkich chorych wykonano systematyczną limfadenektomię śródpiersiową. Średnia liczba usuniętych węzłów chłonnych wyniosła 22. Wartość predykcyjna wyniku ujemnego dla EBUS-NA/EUS-NA wyniosła 89,8%, a dla PET/EBUS-NA/EUS-NA – 93,2%.

WNIOSKI U chorych na raka płuca z negatywnym wynikiem badania PET, EBUS-NA i EUS-NA, ryzyko wystąpienia przerzutów w węzłach chłonnych śródpiersia jest małe. W tej grupie chorych inwazyjna diagnostyka śródpiersia może nie być konieczna.

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