Interventional Pulmonology

Respiration

Respiration 2009;78:423–431
DOI: 10.1159/000235544

Received: July 24, 2008
Accepted after revision: May 28, 2009
Published online: August 11, 2009

Mediastinal Lymph Node Staging in Potentially Resectable Non-Small Cell Lung Cancer: A Prospective Comparison of CT and EUS/EUS-FNA

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Key Words

Computed tomography · Endoscopic ultrasonography · Endoscopic ultrasound-guided fine needle aspiration · FDG-PET · Lung cancer staging · Mediastinal lymph node · Non-small cell lung cancer

Abstract

Background: Mediastinal lymph node staging (N-staging) is essential to optimize the treatment in non-small cell lung cancer (NSCLC). Transesophageal endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) has recently been introduced as a complementary method. However, in most reports, EUS-FNA has been performed in patients who have demonstrated enlarged lymph nodes (LNs) on CT findings. The yield of EUS/EUS-FNA in patients without enlarged mediastinal LNs by CT has so far only been evaluated in a few reports. ***Aims:*** Our aim was to compare the diagnostic accuracy of CT and EUS with or without EUS-FNA (EUS/EUS-FNA) prospectively, for N-stage in all patients with potentially resectable NSCLC, including patients with and without mediastinal LN enlargement based on CT findings. ***Methods:*** Eighty consecutive patients with potentially resectable NSCLC based on CT findings were enrolled in this prospective comparative study, and underwent EUS/EUS-FNA. ***Results:*** Pathological N-stage was established in 78 patients, while in another 2 cases, malignant pleural effusion was proven by EUS-FNA, and we avoided further N-staging. In the 78 patients, the prevalence of malignant mediastinal LNs was 21%. The accuracy of EUS/EUS-FNA (91%) was significantly higher than that of CT (71%). The negative predictive value of EUS/EUS-FNA was 90%. In addition, EUS-FNA identified 2 patients as N3 disease in 56 patients without mediastinal LN involvement on CT. ***Conclusions:*** EUS/EUS-FNA gave more accurate N-staging in patients with possibly resectable NSCLC than CT, and is thus considered to be useful to determine the optimal treatment strategy.

The annual incidence of lung cancer is more than 1 million worldwide, and it is now the most common malignancy in Japan as well as in Western countries. Mediastinal lymph node (LN) involvement is reported to be present in about one-third of those cases at the time of initial diagnosis, and a mediastinal LN staging (N-staging) of non-small cell lung cancer (NSCLC) is very important in choosing the treatment course [1–3]. CT is the

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standard imaging modality used to define the extent and location of the primary lesion and to detect mediastinal LN enlargement. However, because of its insufficient diagnostic ability, additional imaging modalities have been requested. Recently, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has often been attempted for this purpose [4–6], and transesophageal endoscopic ultrasonography with or without fine needle aspiration (EUS/EUS-FNA) has also been evaluated as a valuable modality [6–21]. However, in most reports, EUS-FNA was performed in the patients who had demonstrated enlarged lymph nodes on the CT findings [7–14]. The yield of EUS/EUS-FNA in patients without enlarged mediastinal LNs by CT has so far been evaluated in only a few reports [18–20]. We therefore compared these 2 modalities simultaneously in both patients with and without mediastinal LN enlargement based on the CT findings.

Patients and Methods

Study Design

This study was a prospective comparative study at 3 tertiary center hospitals: the Gifu University Hospital, the National Hospital Organization Nagara Medical Center, and the National Health Insurance Sekigahara Hospital.

The primary endpoint of this study was to compare the accuracy of CT and EUS/EUS-FNA. Secondary endpoints were the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for predicting the N-staging of CT and EUS/EUS-FNA. These values were also evaluated in FDG-PET for reference.

Sample Size

The accuracy of CT has been estimated to be 67% from previously reported data [6, 11–13, 15]. Since a difference in accuracy by 20% was deemed to be clinically relevant and EUS/EUS-FNA improved accuracy by 20% in a preceding feasibility study (data not shown), we calculated that, with an α-error of 0.05 and a β-error of 0.20, a minimum sample size of 69 patients would be required to show such a difference. Considering the number of patients who might not complete the study, the final number of the enrolled cases was determined to be 80.

Patients

Eighty consecutive patients with potentially resectable NSCLC, who were referred to our hospitals and met the inclusion criteria below, were enrolled into this study. At our institutions, patients with N2 (stage IIIA) were considered operable, as well as those with stages I and II. These patients underwent lobectomy with complete thoracic lymphadenectomy. The inclusion criteria of this study were: (1) patients with newly diagnosed or suspected NSCLC based on CT and bronchoscopic findings, and (2) the clinical stage was judged to be below T4, any N, M0 according to the TNM subsets [22] based on CT findings. They included both patients with and without swollen mediastinal LNs, and regardless of location of the LNs. Stage-IIIB subjects due to contralateral mediastinal LNs (N3) were also included because if the contralateral LNs were pathologically negative by EUS-FNA, they would be below N3 and thus might be resectable. The exclusion criteria were: (1) patients with poor medical conditions of grades 4 and 5, according to American Society of Anesthesiologists classification; (2) patients with bleeding tendency and coagulopathy, and (3) cases in which the patient refused surgery.

After written informed consent was obtained, the patients underwent EUS/EUS-FNA. FDG-PET was also performed in all patients before EUS/EUS-FNA. In cases eventually diagnosed to be resectable, a surgical operation was performed. If N3 was proven histopathologically by EUS-FNA, surgical procedures were avoided. In cases diagnosed to be N3 (contralateral mediastinal LNs) by CT or FDG-PET but below N3 by EUS/EUS-FNA, a mediastinoscopy was performed just before the surgical operation, and if the result was pathologically negative, a subsequent surgery was performed.

Each institute's review board for human research approved this study protocol. This study was conducted in accordance with the Declaration of Helsinki.

Methods

The CT staging was judged by 2 expert pulmonologists (T.K., F.A.), and the FDG-PET findings were reviewed by an expert radiologist (N.K.). An experienced endosonographer (I.Y.) performed EUS/EUS-FNA. They were blinded to the results of other examinations. The mediastinal LNs were coded according to the American Joint Committee on Cancer staging system [23].

Computed Tomography. All patients underwent a chest and upper abdominal CT. A multi-detector row CT scanner (LightSpeed Ultra, GE Medical Systems, Milwaukee, Wisc., USA) with a detector configuration of 8 × 25 mm was used with a helical pitch of 1.35, and the images were reconstructed from 5-mm-thick images. Scanning was commenced with a delay of 30 and 120 s after 100 ml of non-iodinated contrast medium was administered intravenously at a rate of 2 ml/s. We defined LNs larger than 10 mm across the short axis to be metastatic, except at the subcarinal level where the size for considering an LN to be normal was 12 mm [24].

FDG-PET. This was performed on all patients at the PET Center, Kizawa Memorial Hospital, using GE PET Advance NX/i (GE Medical Systems) with whole-body attenuation. After subjects had fasted for at least 6 h, and their blood glucose levels had been confirmed to be within normal limits, they were injected with an intravenous dose of 5 MBq/kg FDG. The emission study commenced 60 min later, and lasted for 20 min. The FDG uptake in the mediastinal lymph node was examined first, based on visual interpretation, and a standardized uptake value above 3.0 was considered to be positive for a definite localized area in the mediastinum.

EUS/EUS-FNA. We used an electronic linear scanning echoendoscope (GF-UC240P-AL5, Olympus, Tokyo, Japan) equipped with a processor with color Doppler function (SSD-5000, Aloka, Tokyo, Japan). After the patient was sedated using a combination of midazolam and pentazocine, the echoendoscope was advanced to the stomach, and the left adrenal gland, celiac region and left lobe of the liver were observed. The echoendoscope was then gradually withdrawn to the esophagus, and the following regions were evaluated: pulmonary ligament, paraesophageal, subcari-

nal, lower paratracheal, subaortic and upper paratracheal [25]. After the initial orientation, LNs larger than 5 mm across the short axis were intended for FNA. This size criterion was defined because, in our experience, it is difficult to obtain pathological materials by EUS-FNA from LNs smaller than 5 mm. If multiple LNs were detected at the same level (region), then FNA was performed on the largest LN, that showed a round shape, a homogeneous hypoechoic image, and sharp distinctive borders [26, 27]. However, when it was difficult to choose only 1 LN, then 2 LNs would be punctured. The puncture was made using either a 22-gauge or 19-gauge needle (EchoTip, Wilson-Cook, Winston-Salem, N.C., USA). Since there are no pathologists on-site at our institutions, pathological samples were obtained in all levels of the LNs, and were sent to pathologists thereafter. If pleural effusion was detected by EUS, then the fluid was obtained by FNA and was immediately sent to the pathologist. If the cytopathological assessment of the fluid showed malignancy, we avoided further FNA for N-staging. The cytopathological results of FNA samples were classified into positive, suspicious and negative, and only positive was defined as 'positive for metastasis'.

Data Analysis

The final pathological N-staging was determined from results of mediastinoscopy, thoracoscopy, open surgery or EUS-FNA. The N-staging was divided into the following 3 categories: N0/N1, N2 and N3. We calculated the accuracy and its 95% CI, and performed comparisons using the MacNemar's test, with a p value of less than 0.05 considered to indicate a significant difference. The sensitivity, specificity, PPV, and NPV were calculated after counting the number of true positives, true negatives, false positives and false negatives according to each modality. The number of false positives was counted as the number of patients with a higher N-stage in comparison to the final diagnosis, and the number of false negatives was counted as the number of patients with a lower N-stage compared to the final diagnosis. The software program used was the JMP, version 7 (SAS Institute, Cary, N.C., USA).

Results

Eighty patients were enrolled in this study between March 2004 and February 2006. Their baseline characteristics are outlined in table 1. They included 49 patients without any mediastinal LNs (N0), 10 patients with N1, 18 patients with N2 and 3 patients with N3 on CT findings. All patients had undergone bronchoscopy, and 45 patients had been proven to have NSCLC, with a histological diagnosis of adenocarcinoma in 33, squamous cell carcinoma in 11 and adenosquamous carcinoma in 1. However, the remaining 35 patients showed negative biopsies or normal bronchoscopic findings.

Following enrollment, FDG-PET and EUS were performed in all patients as shown in figure 1. EUS did not detect any mediastinal LNs larger than 5 mm in 14 patients, and their N-stage was judged as N0/N1. EUS detected LNs larger than 5 mm in 66 patients and, simultaneously, a small amount of pleural effusion in 2 patients. Cytopathological samples of the effusion were obtained by EUS-FNA and showed malignancy. These 2 patients were judged as non-resectable, and FNA for N-staging was avoided. Thus, EUS-FNA was performed in the remaining 64 patients for N-staging. The locations of the punctured LNs were level 2L in 3, level 2R in 2, level 4L in 36, level 4R in 5, level 5 in 2, level 7 in 57 and level 8 in 5 patients. In the right lower paratracheal region (level 4R), it is difficult to image the whole area due to the scatter from the air-filled trachea. However, bending the endoscope's tip upward thus makes it somewhat easier to assess the area, and it therefore becomes possible to assess at least the area around azygos arch (fig. 2). The subaortic region (level 5) can be assessed by EUS, but the puncture of LN at this location is often difficult because this site is far from the esophagus and adjacent to the aortic arch and the pulmonary artery. However, whether the puncture approach is possible or not depends on the size and the location of LN. We attempted to carry out FNA here only in cases in which the puncture could be safely per-

Table 1. Baseline characteristics of the enrolled patients

Patients		80
Age (median, range), years		69 (45–82)
Gender, n		
Women		27
Men		53
General condition (ASA classification), n		
Grade 1		59
Grade 2		20
Grade 3		1
CT findings		
Locations of primary tumor		
Right	upper	35
	middle	6
	lower	14
Left	upper	15
	lower	10
Largest diameter of primary tumor (median, range), mm		26 (10–80)
T-staging		
T1		42
T2		34
T3		4
N-staging		
N0		49
N1		10
N2		18
N3		3

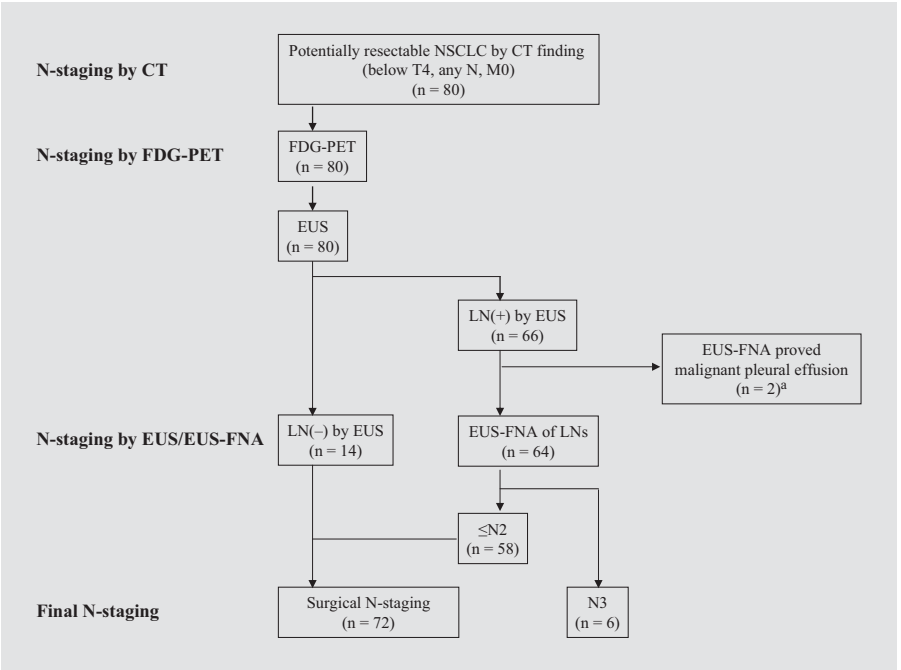

Fig. 1. Structure of the process to reach final pathological diagnosis. NSCLC = Non-small cell lung cancer; LN = lymph node. [a] Avoided N-staging by EUS-FNA and final N-staging.

formed (fig. 3). The mean number of LN stations sampled per patient was 1.7: the LN was punctured at single station in 27, two stations in 29, three stations in 7, and four stations in 1 patient. Multiple LNs were punctured at the same stations in 11 patients, thus a total of 121 LN samples were obtained. The median short axis of the LNs was 7 mm (5–26 mm). The mean number of needle passes was 1.3 (range 1–3). The pathological results were positive in 14 LNs, negative in 107 LNs, and suspicious in none. Thus, 6 patients were diagnosed to be N3 by pathological assessment of FNA samples, while others were ≤N2 (fig. 1). There were no lesions suspected of liver metastasis on the EUS in any patient. However, a mass was detected in the left adrenal gland in 2 patients, and the FNA diagnosis was adenoma in both cases. After excluding 6 patients with N3 disease and 2 patients with malignant pleural effusion, the remaining 58 patients were scheduled to undergo surgery (fig. 1).

In LN(–) patients with EUS, 4 have been suspected to be N3 based on the CT or FDG-PET, and they underwent mediastinoscopy with or without thoracoscopy. Fortunately, N3 was ruled out in all 4 patients, and subsequent surgical operations were thus performed in all LN(–) patients by EUS (fig. 1).

After surgery in a total of 72 patients, 67 were diagnosed to have NSCLC, with a histological diagnosis of adenocarcinoma in 46, squamous cell carcinoma in 18 and adenosquamous carcinoma in 3. Five patients were diagnosed to have benign diseases, tuberculosis in 3 and inflammatory pseudotumor in 2. However, these 5 patients with a final diagnosis of benign diseases were also included in the assessment of N-staging. As a result, the final data analysis was assessed in 78 patients.

Comparison of CT and EUS/EUS-FNA

The raw data of the N-staging in the 78 patients, including 73 NSCLC and 5 benign cases, based on CT, FDG-PET and EUS/EUS-FNA are shown in figure 4 and table 2. As summarized in tables 3 and 4, the accuracies of CT and EUS/EUS-FNA were 71% (95% CI 60–80%) and 91% (83–96%), respectively. There was a significant statistical difference between EUS/EUS-FNA and CT ($p = 0.0003$). The sensitivity, specificity, PPV and NPV of CT were 27, 81, 25 and 82%, respectively, and those of EUS/EUS-FNA were 56, 100, 100 and 90%, respectively. For reference purposes, the accuracy, sensitivity, specificity, PPV and NPV of FDG-PET were 77, 25, 90, 40 and 82%.

As shown in figure 4, EUS-FNA found 2 patients to have N3 disease among the 56 patients in whom mediastinal LNs were not detected on CT and FDG-PET. In addition, EUS-FNA correctly denied mediastinal LN involve-

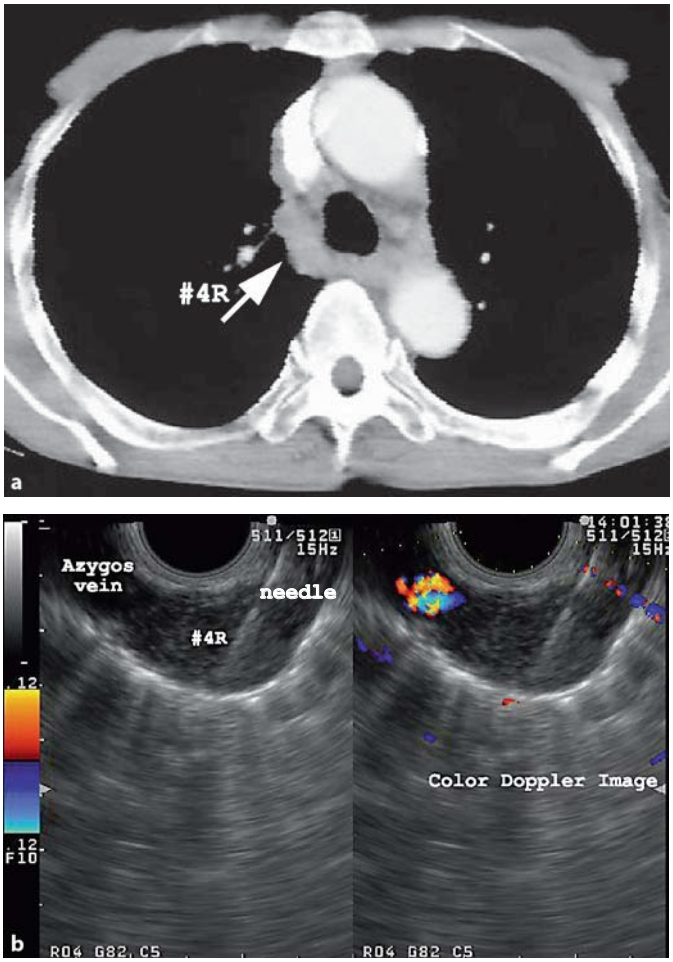

Fig. 2. A case of NSCLC with lymph node swelling at level 4R. **a** The contrast-enhanced CT image shows an enlarged lymph node just above the azygos arch (arrow). **b** EUS-FNA was performed on the lymph node. The left image is a fundamental image and the right image is an image with color Doppler function.

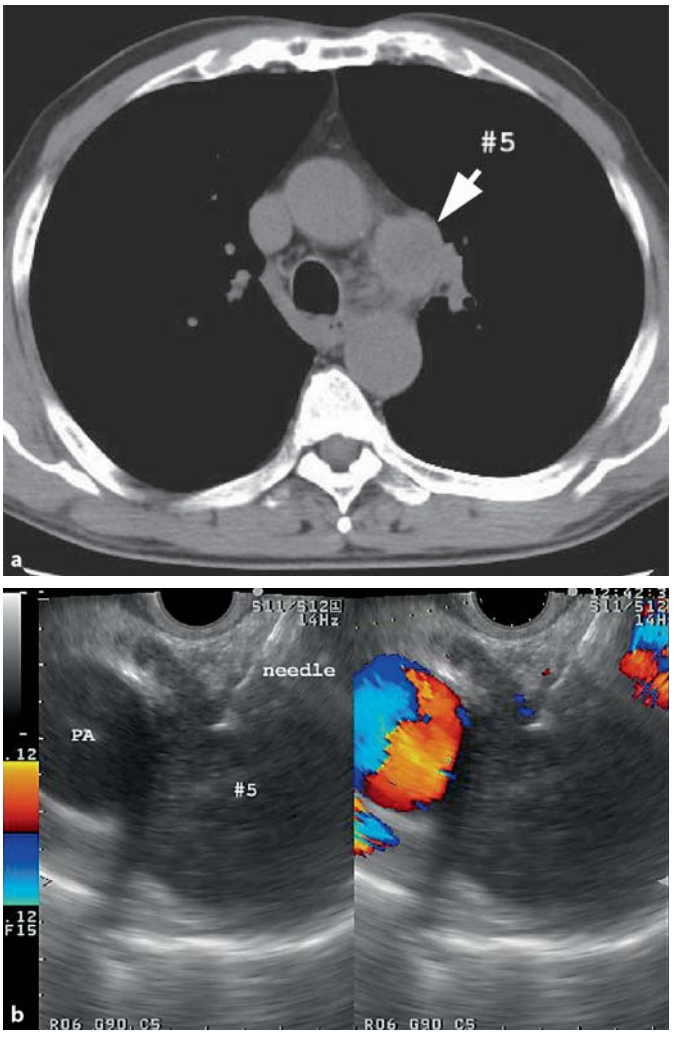

Fig. 3. A case of NSCLC with lymph node swelling at level 5. **a** The CT image shows an enlarged lymph node at level 5 (arrow). **b** EUS-FNA was performed on the lymph node. PA = Right pulmonary artery.

ment in 13 of 22 patients who had been suspected of having mediastinal LN involvement on either CT or FDG-PET.

On the other hand, 7 patients were false-negative by EUS-FNA in this study. The positive LN was not detected by EUS in 4 patients: the location was at level 4R (pretracheal) in 3 and at level 6 in 1. In the remaining 3 patients, although the LNs were punctured, the pathological results were negative.

Complications

Mediastinal hematoma occurred in 1 (1.5%) of 66 patients who underwent EUS-FNA, but it resolved after a conservative treatment of fasting and bed rest. The surgical operation for NSCLC was performed 7 days later as scheduled.

Discussion

CT is currently recommended to evaluate the N-stage of NSCLC, but its diagnostic accuracy is not sufficient [5]. FDG-PET has also been used for this purpose recently, and several studies demonstrated FDG-PET to be significantly superior to CT [4, 6]. However, FDG-PET still has

Table 2. Mediastinal lymph node staging by CT, FDG-PET and EUS/EUS-FNA

		Final diagnosis		
		N0/N1	N2	N3
CT	N0/N1	51	5	2
	N2	9	4	4
	N3	2	1	0
FDG-PET	N0/N1	56	6	3
	N2	1	4	3
	N3	5	0	0
EUS/EUS-FNA	N0/N1	62	7	0
	N2	0	3	0
	N3	0	0	6

Table 3. Comparison of CT, FDG-PET, and EUS/EUS-FNA to the final diagnosis

Tests	True positive	True negative	False positive	False negative
CT	4	51	12	11
FDG-PET	4	56	6	12
EUS/EUS-FNA	9	62	0	7

Data represent number of patients. True positive = number of patients with identical N-stage in malignant lesions; true negative = number of patients with identical N-stage in benign lesions; false positive = number of patients with a higher N-stage compared to the final diagnosis; false negative = number of patients with a lower N-stage compared to the final diagnosis.

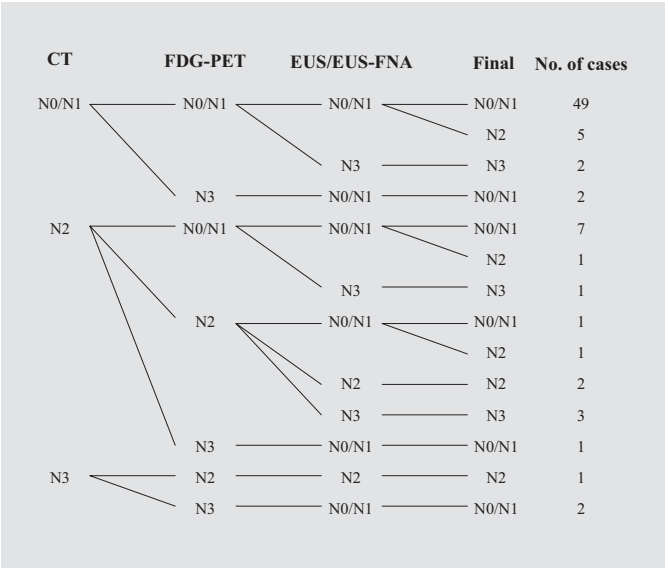

Fig. 4. The raw data of the N-staging in the 78 patients based on the CT, FDG-PET and EUS/EUS-FNA findings.

a problem of false-positive and false-negative results. Therefore, current guidelines describe that NSCLC patients with suspected LN involvement should undergo tissue sampling for pathological confirmation before surgical interventions [1–3]. For this aim, transbronchial needle aspiration (TBNA) has been sometimes attempted, but the procedure is not easy and the diagnostic yield is not sufficient [28, 29]. Recent surgical and mediastinoscopic techniques for N-staging, such as transcervical extended mediastinal lymphadenectomy (TEMLA) and video-assisted mediastinoscopic lymphadenectomy (VAMLA), have become more accurate [30, 31], but these procedures are still invasive, costly and require general anesthesia, as well as a long time and substantial manpower.

Transesophageal EUS is generally performed on an outpatient basis. It delivers a high-resolution image by itself and, furthermore, enables simultaneous tissue sampling. In the last decade, many studies have evaluated the usefulness of EUS-FNA in the N-staging of NSCLC with promising results, and several comparative studies revealed that EUS-FNA was superior to CT [6, 11–13, 15]. However, in most reports, EUS-FNA was performed in the patients who had demonstrated enlarged lymph nodes on the CT findings [11–13].

Eloubeidi et al. [21] compared the diagnostic ability of EUS-FNA to that of FDG-PET and CT. In their study, 104 consecutive patients with suspicious LNs based on CT or FDG-PET were prospectively evaluated by EUS-FNA. They concluded that EUS-FNA was more accurate and had a higher positive predictive value than CT or FDG-PET in confirming the posterior mediastinal involvement. However, as the authors described, a limitation of their study was that the subjects were patients with suspicious LNs either on CT or on FDG-PET only, and they did not evaluate patients who were CT and FDG-PET negative. On the other hand, another study reported that EUS-FNA detected mediastinal involvement in 42% of patients whose CT findings were falsely negative [15].

Therefore, in our study, EUS was attempted on all patients with possibly resectable NSCLC, regardless of the N-staging results based on CT or FDG-PET. As a result,

Table 4. Comparison of diagnostic results of CT, FDG-PET, and EUS/EUS-FNA

Tests	Accuracy	Sensitivity	Specificity	PPV	NPV
CT	71 (60–80)	27 (11–52)	81 (70–89)	25 (10–49)	82 (71–90)
FDG-PET	77 (66–85)	25 (10–49)	90 (80–95)	40 (17–69)	82 (72–90)
EUS/EUS-FNA	91 (83–96)*	56 (33–77)	100 (94–100)*	100 (70–100)*	90 (81–95)

Data are presented as % (95% CI). * Rate is significantly higher than those of CT and FDG-PET.

our study included 56 patients who were CT and FDG-PET negative, and EUS-FNA proved N3 disease in 2 patients among them. On the other hand, EUS-FNA correctly ruled out mediastinal LN involvement in 13 of 22 patients who had been suspected of having mediastinal LN involvement on CT. Taken together, our study demonstrated the accuracy of EUS/EUS-FNA (91%) to be significantly superior to that of CT (71%). It illustrates that EUS/EUS-FNA should be added for the preoperative N-staging of patients with potentially resectable NSCLC.

However, we must also mention that EUS/EUS-FNA has a limitation, namely, the imperfect false-negative rate, which was seen in 7 cases (9%) in our study. This is likely to have resulted from both sampling error due to LNs with micrometastases and the visual inability in the anterior mediastinum. The mean number of needle passes was 1.3 (range 1–3) per lesion in our study, and the number of needle pass was only once in 88 of the 121 lesions, including the 3 false-negative cases. These data may indicate that repeated needle passes can reduce the false-negative rate, as reported in a previous paper [32]. Regarding the inaccessibility of the pretracheal area, we could not detect by EUS the pretracheal LNs in 3 patients, and they resulted in false negatives. Therefore, in cases with suspected LNs in the pretracheal area based on CT or FDG-PET, another option should be added to investigate such involvement. For this purpose, an endobronchial ultrasound-guided TBNA (EBUS-TBNA), which is capable of providing pathological information from the anterior tracheal and hilar regions, has recently been introduced. A combined approach with both EUS-FNA and EBUS-TBNA may thus make it possible to achieve near-complete minimally invasive mediastinal N-staging in patients with suspected NSCLC [33–36]. However, the anterior mediastinum (level 3A) is still inaccessible even using EBUS or mediastinoscopy. For this area, another option, such as thoracoscopy and TEMLA, should therefore be considered [3, 30].

In addition, this study has several other limitations. First, contralateral LN positive (N3) by EUS-FNA was defined as N3 on the final N-staging because the diagnosis was based on the pathological findings and surgical N-staging was thus considered to be ethically unacceptable in this situation. Therefore, a false positive of EUS-FNA could not be detected in this setting, which is probably advantageous for EUS-FNA and related to its high PPV.

Second, our study population included all potentially resectable NSCLC patients, because the aim of this study was to prospectively evaluate the diagnostic accuracy of CT and EUS/EUS-FNA in this setting. For this aim, we did not set limits on N-stage by CT findings. However, N-staging was N0/1 in the final diagnosis of 62 (79%) of 78 patients. Therefore, such a low prevalence of mediastinal involvement might influence the assessment of the diagnostic results, and the presence of only small LNs probably influenced the low sensitivity of CT (27%) in our study. In fact, the short axis of the LNs finally diagnosed as positive was smaller than 10 mm in 12 (75%) of 16 patients with mediastinal involvement. In addition, EUS-FNA should be able to detect smaller LNs than CT or FDG-PET, but the sensitivity of EUS/EUS-FNA in our study (56%) was still lower than that described in previous reports [10]. This may be due to the fact that our subjects included the patients regardless of location of the LNs, while most of previous studies included only patients who were most likely to have LNs accessible by the procedure. Indeed, 4 of 7 false-negative patients had positive LNs at levels inaccessible by EUS.

Third, our inclusion criteria did not require a pathological confirmation of NSCLC. The pathological diagnosis by bronchoscopy is often difficult, especially in small lesions. Therefore, we included all patients suspected of having potentially resectable NSCLC on the CT findings to avoid any selection bias in this step. As a result, our data analysis included 5 patients who were finally diagnosed to have benign diseases. This resulted in

the specificity and the PPV of CT being lower, because all of them had enlarged mediastinal LNs and were counted as false positives. On the other hand, EUS-FNA correctly diagnosed the LNs as either malignant or benign. This situation was thus considered to be advantageous for EUS-FNA.

In conclusion, EUS/EUS-FNA is a more accurate procedure than CT, and should be added as a tool for the preoperative N-staging of NSCLC. However, it also has a limitation since some locations remain inaccessible, therefore a complementary method is thus considered to be necessary to achieve complete N-staging in patients with potentially resectable NSCLC.

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