
Original Article

Analysis of Lymph Node Metastasis Detected by Positron Emission Tomography/Computed Tomography and Contrast-Enhanced Computed Tomography in Patients with Completely Resected Non-Small Cell Lung Cancer — Establishment of Lung Cancer Survey Guideline at E-Da Hospital

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Objectives: Mediastinal lymph node involvement is a prognostic factor for patients with non-small cell lung cancer (NSCLC). Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) and chest contrast-enhanced computed tomography (CECT) are currently most relied on to survey the status of the mediastinal lymph nodes at our hospital. The actual accuracy of these two examinations in interpretation of the mediastinal nodal involvement should be analyzed to improve the clinical application.

Materials and Methods: From February 2007 to May 2011, 102 patients of curatively resected NSCLC were enrolled. The mediastinal lymph nodes were dissected in a systemic approach. They all had pre-operative PET/CT and chest CECT examinations. The reports of the PET/CT and chest CECT were correlated with the pathologic results.

Results: Pathologically, mediastinal lymph node involvement was noted in 31 patients (30.4%). In predicting mediastinal involvement, when PET/CT was correlated with the pathology, the sensitivity, specificity and accuracy were 32.5%, 94.3% and 76.5%, respectively. When chest CECT was correlated with pathology, the sensitivity, specificity and accuracy were 61.3%, 81.7% and 75.5%, respectively. Combining PET/CT and chest CECT, the sensitivity, specificity and accuracy were 100%, 76.1% and 83.3%, respectively.

Conclusions: Since the sensitivity of PET/CT in detecting mediastinal lymph node metastasis in NSCLC is low at our hospital. Chest CECT nodal examination has to be used for augmentation.

Key words: non-small cell lung cancer, fluorodeoxyglucose-positron emission tomography/computed tomography, chest contrast-enhanced computed tomography, lymph node, mediastinum

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Received: December 1, 2014

Accepted: February 27, 2016

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Introduction

In patients of non-small cell lung cancer (NSCLC), mediastinal lymph node status is the major prognostic factor which determines the therapeutic management.¹ Mediastinoscopy is a well known method to interpret the metastasis of mediastinal lymph nodes in NSCLC.² It is put into the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in NSCLC as a pretreatment evaluation. However, it is still not a routine to perform the mediastinoscopy examination in the NSCLC patients due to several reasons, including patient's refusal, physician's reluctance, technical consideration and, most of all, accessibility of the Fluorodeoxyglucose (FDG)-Positron Emission Tomography/Computed Tomography (PET/CT). At E-Da hospital, thoracoscopy is usually used to evaluate the lymph node status at the same time when the operation for curative intent is scheduled. In this situation we have to improve the accuracy of the pre-operative lymph node interpretation. Two image examinations, the PET/CT and chest contrast-enhanced computed tomography (CECT), are routinely used to identify the mediastinal lymph node metastasis. The journal reports of the sensitivity/ specificity/ accuracy in detecting mediastinal lymph node metastasis are in a varied-wide range, being 54.2-84.0%, 81.8-96.8%, and 80.5-95.0%, respectively.³⁻⁶ In addition, the endemic infectious disease in different local area influences the accuracy of the PET/CT and CECT in interpreting the mediastinal lymph node status.^{7,8} Therefore we try to make our own estimation of the accuracy of the PET/CT and CECT in interpreting the mediastinal lymph node metastasis in NSCLC.

Materials and Methods

From February 2007 to May 2011 we retrospectively chart-reviewed all the operated

NSCLC patients, who had the complete resection with either open thoracotomy or video-assisted thoracoscopic approach, in one institutional university-hospital. Among these there were 102 patients who had both the FDG-PET/CT and CECT examinations before the operations. They were enrolled for survey of prediction of mediastinal lymph nodes metastasis. The denotation of the mediastinal lymph node stations and the patient staging conformed to the classification of AJCC (American Joint Committee on Cancer) cancer staging manual, 7th edition.

PET/CT was imaged using the Biograph 6 scanner (Siemens, USA). This system produced transaxial, coronal, and sagittal reconstructions of CT, PET, and fusion PET/CT data for interpretation. The Biograph scanner combined a dual-detector spiral CT scanner (Somatom emotion) and a high-resolution PET scanner with 4.5-mm spatial resolution and 3-dimensional image acquisition. A multimodality computer platform (Syngo, Siemens) was used for image review and manipulation. After the patients had fasted for at least 6 hours, they received 555 MBq (15 mCi) of ¹⁸F-FDG by intravenous injection. The total acquisition time ranged from 25 to 35 minutes per patient. The CT data were used for attenuation correction of PET emission images and for anatomic localization of emission data.⁹ The PET/CT images of all enrolled patients were both taken in the early phase (just after ¹⁸F-FDG injection) and in the delayed phase (about 4 hours after injection). The data were assessed by one single physician of nuclear medicine expert. The maximum standardized uptake value (SUV_{max}) of the primary tumor was measured with a region-of-interest technique and calculated by the software according to standard formulas. The cut point of the SUV_{max} for a malignant tumor was 2.5 in our hospital. When the lymph node was taken as metastasis the following two conditions were incorporated into consideration. One was the

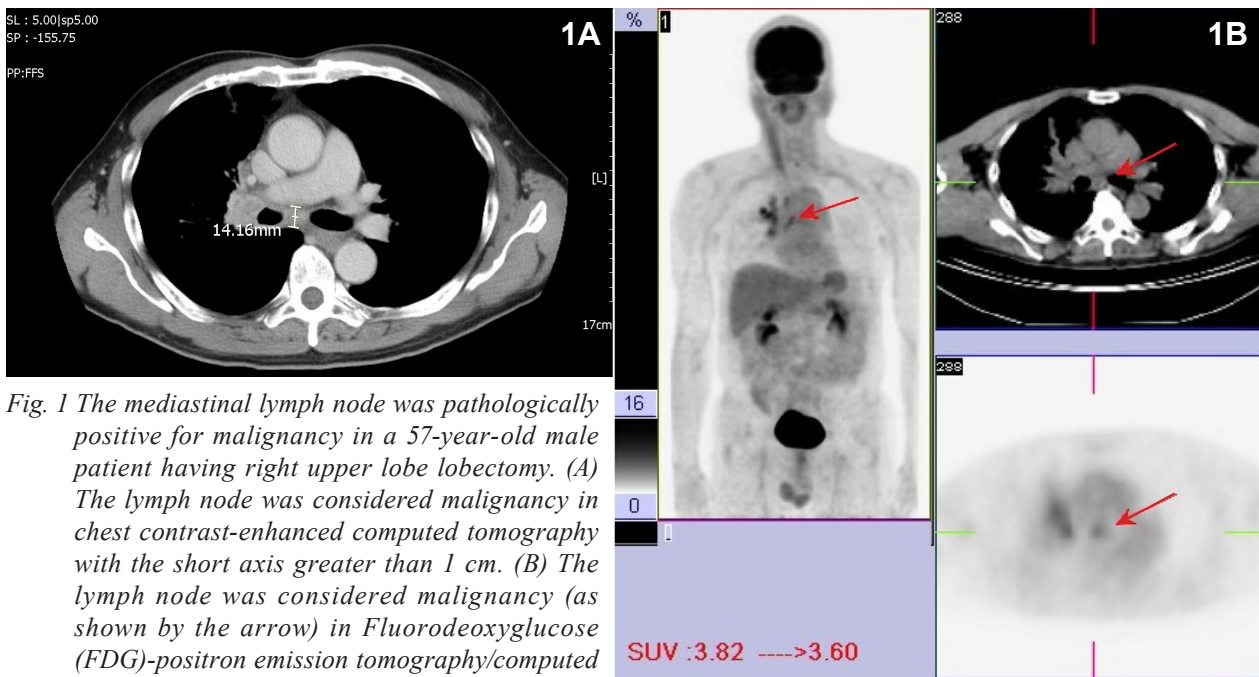


Fig. 1 The mediastinal lymph node was pathologically positive for malignancy in a 57-year-old male patient having right upper lobe lobectomy. (A) The lymph node was considered malignancy in chest contrast-enhanced computed tomography with the short axis greater than 1 cm. (B) The lymph node was considered malignancy (as shown by the arrow) in Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography with the SUV_{max} greater than 2.5.

value of the SUV_{max} in the lymph node. When the SUV_{max} of the lymph node was similar to that of the main malignant mass and higher than the normal background activity,^{1,10} it was considered as metastasis. The other was that when the SUV_{max} had increased value in the delayed phase (dual-time-point PET/CT image technique),^{11,12} it was also considered as metastasis if the SUV_{max} was in the range of borderline.

Chest CECT was imaged on a 16 slices scanner (KV 120, mA 150-420; General Electric Company, BrightSpeed Elite, USA). The lymph node was considered to be malignant in CECT when the short axis of the lymph node was greater than 1 cm.^{12,13} The data were assessed by one single radiologist expert.

The mediastinal lymph nodes were dissected in a systemic approach according to the European Society of Thoracic Surgeons (ESTS) guidelines.¹⁴ In the right thoracic cavity, these included the lymph node stations 2, 3, 4, 7, 8, and 9, and in the left thoracic cavity, the lymph node stations 5, 6, 7, 8, and 9.

The prediction reports of the PET/CT, CECT were correlated with the pathologic

results. Furthermore we integrated the PET/CT and CECT data into the combination data in which the mediastinal status was considered positive for metastasis when either one of the examinations was positive (Fig. 1 and 2). This study was approved by the Institutional Review Board to use the patients' records, and the patients' confidentiality was strictly maintained.

The authors had no financial interests related to the materials in the manuscript.

Results

There were 47 female and 55 male patients with mean age of 60.8 ± 8.8 years. There were 79 adenocarcinomas (77.5%), 18 squamous cell cancers (17.6%) and 5 other cell types (adenosquamous and large cell carcinoma) (4.9%). The main tumors were located in the right upper lobe in 34 patients (33.3%), right middle lobe in 9 (8.8%), right lower lobe in 18 (17.6%), left upper lobe in 25 (24.5%), and left lower lobe in 16 (15.7%). Most of the patients were of single lobectomy with exception of three bilobectomy and one pneumonec-

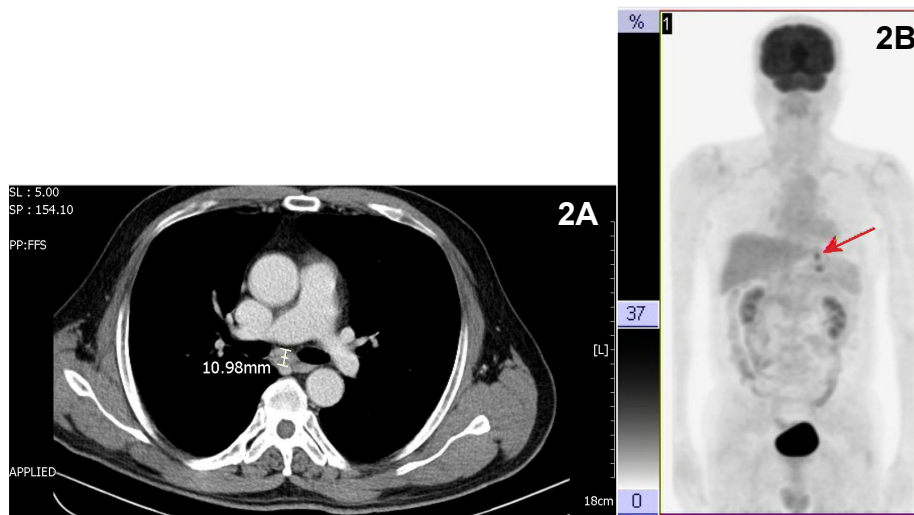


Fig. 2 The mediastinal lymph node was pathologically positive for malignancy in a 62-year-old male patient having left lower lobe lobectomy. (A) The lymph node was considered malignancy in chest contrast-enhanced computed tomography with the short axis greater than 1 cm. (B) The lymph node was not considered malignancy in Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography. Only the main tumor (as shown by the arrow) had the SUV_{max} greater than 2.5.

tomy. There had 43 patients in pathologic stage I (42.2%), 14 in stage II (13.7%), 34 in stage III (33.3%), and 11 in stage IV (10.8%). Among the stage IV patients, 9 patients had brain metastasis and 2 had different lobe metastasis in the ipsilateral site.

From the pathologic results, the mediastinal lymph nodes were involved (N2 disease) in 31 patients (30.4%). The average number of mediastinal lymph nodes removed during the operations and the average number of malignant nodes were 20.1 ± 11.6 and 1.4 ± 3.6 , respectively. The average number of lymph node stations approached in the mediastinum was 4.0 ± 1.2 . There were 7 patients (6.9%) who had malignant lymph node involvement in station 2, 7 patients (6.9%) in station 3, 17 patients (16.7%) in station 4, 7 patients (6.9%) in station 5, 1 patient (1.0%) in station 6, 12 patients (11.8%) in station 7, 3 patients (2.9%) in station 8, and 1 patient (1.0%) in station 9. The relationship between the location of the tumor and the lymph node involvement was shown in Table 1.

The PET/CT reported positive uptake

Table 1. The relationship between the location of the tumor and the pathologic lymph node involvement.

Lobe [#]	Station [*]								Total
	2	3	4	5	6	7	8	9	
RUL	4	5	6	1	0	3	1	1	21
RML	1	1	2	0	0	1	0	0	5
RLL	1	0	3	0	0	3	0	0	7
LUL	0	1	3	5	1	3	0	1	14
LLL	1	0	3	1	0	2	2	0	9
Total	7	7	17	7	1	12	3	2	56

* Station: Lymph node station designation. The denotation of the mediastinal lymph node stations conformed to the classification of AJCC (American Joint Committee on Cancer) cancer staging manual, 7th edition.

[#] Lobe: The resected lobe designation; RUL: Right upper lobe; RML: Right middle lobe; RLL: Right lower lobe; LUL: Left upper lobe; LLL: Left lower lobe

of the lymph nodes in the mediastinal area in 17 patients (16.7%). From the PET/CT report, there were no patients who had malignant lymph node involvement in station 2, 1 patient (1.0%) in station 3, 12 patients (11.8%) in station 4, 7 patients (6.9%) in station 5, no

patient in station 6, 5 patients (4.9%) in station 7, 1 patient (1.0%) in station 8, and no patient in station 9. Comparing the pathologic results with the PET/CT results in prediction of positive lymph node metastasis, the sensitivity, specificity and the accuracy was 32.5%, 94.3% and 76.5%, respectively (Table 2).

The CECT reported abnormal lymph nodes in the mediastinal area in 46 patients (45.1%). From the CECT report, there were 1 patient (1.0%) who had malignant lymph node involvement in station 2, 6 patients (5.9%) in station 3, 23 patients (22.5%) in station 4, 9 patients (8.8%) in station 5, no patient in station 6, 7 patients (6.9%) in station 7, no patient in station 8, and no patient in station 9. Comparing the pathologic results with the CECT results in prediction of positive lymph node metastasis, the sensitivity, specificity and the accuracy was 61.3%, 81.7% and 75.5%, respectively (Table 2).

Table 2. The profile of the results of the sensitivity, specificity and accuracy of Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT), chest contrast-enhanced computed tomography (CECT) and combination in comparison with the pathologic results.

	Mediastinal nodes
Pathology	
Total No./per person	20.1 ± 11.6
Malignancy No./per person	1.4 ± 3.6
Positive rate	6.5% ± 15.3%
PET/CT	
Sensitivity	32.5%
Specificity	94.3%
Accuracy	76.5%
CECT	
Sensitivity	61.3%
Specificity	81.7%
Accuracy	75.5%
PET/CT & CECT*	
Sensitivity	100.0%
Specificity	76.1%
Accuracy	83.3%

* PET/CT & CECT: Integrate PET/CT and chest CECT image reports

Table 3. Correlation of the sensitivity, specificity and accuracy of the combination of PET/CT and chest CECT with the pathologic results in each anatomic lymph node station.

Mediastinal node station*	Sensitivity	Specificity	Accuracy
2	28.6%	100%	95.1%
3	28.6%	95.8%	91.2%
4	68.8%	80.2%	78.4%
5	100%	95.8%	96.1%
6	0%**	100%**	99.0%
7	25%	93.3%	85.3%
8	0%#	99.0%#	96.1%
9	0%##	100%##	98.0%

* The denotation of the mediastinal lymph node stations and the patient staging conformed to the classification of AJCC (American Joint Committee on Cancer) cancer staging manual, 7th edition.

** There was only one case having positive pathologic finding in lymph node station 6, which was falsely presented as negative in combination of PET/CT and chest CECT.

There were three cases having positive pathologic finding in lymph node station 8, which were all falsely presented as negative in combination of PET/CT and chest CECT.

There were only two cases having positive pathologic finding in lymph node station 9, which were all falsely presented as negative in combination of PET/CT and chest CECT.

Combining the results of the PET/CT and CECT (the combination data), the mediastinal nodes were positive for malignancy in 46 patients (45.1%). From the combination data, there were 7 patients (6.9%) who had malignant lymph node involvement in station 2, 11 patients (10.8%) in station 3, 34 patients (33.3%) in station 4, 11 patients (10.8%) in station 5, 1 patient (0.1%) in station 6, 18 patients (17.6%) in station 7, 4 patients (3.9%) in station 8, and 2 patients (2.0%) in station 9. Comparing the pathologic results with the combination results in prediction of positive lymph node metastasis, the sensitivity, specificity and the accuracy was 100%, 76.1% and 83.3%, respectively (Table 2). The sensitivity, specificity and accuracy of PET/CT and chest CECT combination in each anatomic lymph node station is shown in Table 3.

Discussion

The extent of mediastinal lymph node dissection during surgery is controversial and there is no consensus about the total number of the lymph nodes having to be removed during complete resection.¹⁴ The International Staging Project on Lung Cancer by The International Association for the Study of Lung Cancer (IASLC) recommended at least removing three mediastinal nodal stations in a systemic fashion, and at least removing six lymph nodes in the mediastinal/hilar area to define nodal staging accurately.^{15,16} In some of the published papers, an average of 20 lymph nodes were removed for systemic lymph node dissection.¹⁷ We performed complete resection in all cases, in compliance with the European Society of Thoracic Surgeons (ESTS) guidelines,¹⁴ in a systematic fashion. For a complete nodal dissection of the left upper mediastinum, division of the ligamentum arteriosus allowing mobilization of the aortic arch and removal of the paratracheal (station 4L) lymph nodes was recommended in ESTS guidelines.¹⁴ However, it was not routinely done in our practice to avoid injuring the left recurrent laryngeal nerve.

From the report of Jemal et al., mediastinal lymph node involvement was found in 26% of newly diagnosed lung cancer patients, and extrathoracic metastases were found in 49%.¹⁸ From the SEER 1999-2006 data, regional lymph node spreading was found in 22% of lung cancers. Mediastinoscopy is the standard method to survey the mediastinal lymph node status in NSCLC. However, not all mediastinal nodes are accessible by mediastinoscopy.¹⁹ Nodes in the subaortic window and in the left anterior mediastinum (usually along the phrenic nerve) cannot be reached by conventional mediastinoscopy, nor can the inferior or posterior subcarinal lymph nodes.¹⁹ Obviously, nodes along the esophagus and in the inferior

pulmonary ligament are not accessible either.¹⁹ Therefore thoracoscopic node sampling before curative operation is adapted to replace the mediastinoscopy in some hospitals, including ours.

Chest CECT is an essential examination for NSCLC. The accuracy of detecting mediastinal lymph node metastasis by CECT was reported to be 38% for N2 disease and 69% for all lymph node stations.^{20,21} Previous investigators have reported a 67-95% accuracy for CECT in the evaluation of mediastinal nodal metastases from non-small-cell lung cancer.⁶ Lymph node size (short-axis diameter: malignant, ≥ 10 mm; benign, < 10 mm) on CECT is a key criterion in characterizing mediastinal nodes. However, up to 21% of nodes < 10 mm have been reported to be malignant and up to 40% of nodes > 10 mm have been reported to be benign.²² Malignant nodes usually have no calcification or show similar attenuation to mediastinal great vessels. Benign nodes show calcification (stippled, central nodular, laminated, popcorn-like, and diffuse) or higher attenuation than mediastinal great vessels.²³

The PET/CT is used to evaluate the mediastinal lymph node status because it is non-invasive, and it can access all the mediastinal structures. It has shown acceptable results in previous reports for detecting mediastinal metastatic nodes in patients with non-small cell lung cancer, with sensitivity of 84% (95% CI, 0.49-0.66) and specificity of 89% (0.83-0.93).^{20-21,24} In our study the lymph node was considered to be malignant in PET/CT when the SUV of the lymph node was similar to that of the main mass, and when the SUV had increased value in the delayed phase.^{1,10-11} In one study the SUV_{max} of a normal hilar lymph node was considered not greater than 3.0 and the lesion-to-background ratio also less than 3.0.²⁵ It is reasonable that the SUV_{max} of 3.0 is the cut value to distinguish malignancy from a benign lesion.²⁶ In our study we used SUV_{max} of 2.5 as a reference cutoff value of malig-

nancy. Nevertheless, the sensitivity of 32.5% in our PET/CT seems inferior to that from other reports.^{20-21,24} Therefore, our PET/CT reports are likely to give false negative results. The low pathologic positive rate (6.5%) of mediastinal spreading in our study indicated that this study population was a highly selected group. Those who had the obvious mediastinal node spreading were excluded from the curative operations. We also hypothesized that the endemic chronic tuberculosis infection in Taiwan could cause false-positive results in many PET/CT mediastinal surveys. Another explanation is that the small-sized lymph node tumors (micrometastasis) could reveal false negative findings on PET/CT scan. The different definition of positive cut-off values of the PET/CT in all the reported papers was also speculated to render different sensitivity. And we used dual time point PET/CT imaging in all cases, which was also different from other report.²⁴ Obviously, when compared with PET alone, nodal staging appeared to be significantly more accurate with PET/CT.²⁸ FDG is not a cancer-specific agent, and false positive findings in benign diseases have been reported. Infectious diseases (mycobacterial, fungal, bacterial infection), sarcoidosis, radiation pneumonitis and post-operative surgical conditions have shown intense uptake on PET scan. On the other hand, tumors with low glycolytic activity such as adenomas, bronchioalveolar carcinomas, carcinoid tumors, low grade lymphomas and small-sized tumors have been reported to show false negative findings on PET scan. Furthermore, in diseases located near the physiologic uptake sites (heart, bladder, kidney, and liver), FDG-PET should be complemented with other imaging modalities to confirm results and to minimize false negative findings.⁷ This led us to combining the CECT with the PET/CT to thoroughly evaluate the mediastinal lymph nodes, which could improve the sensitivity to 100.0%.

We combined the “OR” results of PET/

CT and CECT in calculation of the sensitivity/specificity/accuracy as mentioned above in the Materials and Methods section. Therefore, the sensitivity increased but the specificity decreased, which was clearly shown in Table 3. When applying the data in Taiwan the recommendations are as follows. If both the results of PET/CT and CECT are negative, benign lymph node should be considered. If both the results of PET/CT and CECT are positive, malignant lymph node should be considered. If one of the results of PET/CT and CECT is positive, exploration sampling of the lymph node should be considered before the curative operation.

In conclusion, the sensitivity of the PET/CT in detecting mediastinal lymph node metastasis in NSCLC is low. It is therefore mandatory to integrate chest CECT to evaluate the mediastinal lymph node status.

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