Role of positron emission tomography in mediastinal lymphatic staging of non-small cell lung cancer

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Abstract

Objective: Positron emission tomography (PET) is used increasingly in staging of non-small cell lung cancer (NSCLC) as a non-invasive tool. The role of the PET in mediastinal lymphatic staging of NSCLC is not clear. We aimed to demonstrate the efficacy of PET in determining mediastinal lymphatic metastasis by comparing the results of PET with mediastinoscopy.

Patients and methods: We performed PET preoperatively in 170 patients with clinically operable NSCLC between 2004 and 2006. Stations defined as metastasis by PET (SUV<sub>max</sub> > 2.5) were recorded. Mediastinoscopy was performed initially in all patients and a total of 687 stations which can be reached with mediastinoscope were sampled (mean 4.04). Forty-three patients with mediastinal metastasis were referred to the oncology clinic for chemotherapy while lung resection and complete mediastinal lymphatic dissection through thoracotomy was performed in the remaining 127 patients. Involvement of mediastinal lymph nodes was verified to compare the sensitivity and specificity of mediastinoscopy and the related PET results.

Results: Histopathologic classification of the tumors revealed 79 squamous carcinomas and 58 adenocarcinomas. False positivity rate of PET was 26% (95% CI: 14—38), false negativity was 25% (95% CI: 18—33), sensitivity was 74% (95% CI: 63—86), specificity was 73% (95% CI: 66—82) and accuracy was 74% in mediastinal staging. Negative predictive value of mediastinoscopy was 94% (95% CI: 89—98), positive predictive value 100%, sensitivity 84% (95% CI: 74—94), specificity 100% and accuracy was 95%. Conclusion: PET results do not provide acceptable accuracy rates. Mediastinoscopy still remains the gold standard for mediastinal staging of NSCLC, although it cannot reach to all the mediastinal stations.

Keywords: Lung cancer; Staging; Mediastinoscopy; PET

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the common causes of death due to malignancy, and the mediastinal lymph node (MLN) involvement is the most important factor that determines both treatment method and the prognosis [1,2]. Thus, it is crucial to detect the presence of mediastinal lymphatic metastasis preoperatively. Computed tomography of thorax (thorax CT) is the standard non-invasive method to determine the presence of metastatic mediastinal lymph node, which can accurately demonstrate enlarged MLNs. However, it has limited specificity to differentiate metastasis in the enlarged lymph nodes [3]. On the other hand, mediastinoscopy is the gold standard for mediastinal lymphatic staging owing to its perfect sensitivity and specificity, but it has the disadvantage of invasiveness.

Positron emission tomography (PET), which detects the biologic activities of tumor cells, has been increasingly used for several indications in NSCLC patients. Former studies have suggested the superiority of PET over CT in mediastinal lymphatic staging of NSCLC [4—6]. Due to reported excellent results in mediastinal staging, PET, as a non-invasive method, was expected to replace the role of the invasive mediastinoscopy in detection of MLN metastasis and decrease the use of mediastinoscopy [7,8].

We aimed to define the efficacy of PET in detection of MLN metastasis by comparing the mediastinal findings of PET with the histopathologic results obtained by either mediastinoscopy or thoracotomy in patients with clinically operable NSCLC.

2. Materials and methods

We have prospectively evaluated non-small cell lung carcinoma patients diagnosed by tissue biopsy and selected for surgical treatment between 2004 and 2006. Postero—anterior chest X-ray and thorax CT after the administration of...
70 ml of intravenous contrast medium were performed in all patients to assess the localization and size of the tumor and the MLNs. Thorax CT scanned the interval between supraclavicular area and adrenal glands by 7–10 mm slices at deep inspirium. Tumors located at the 1/3 medial side of the hemithorax and in contact with the mediastinal pleura at any level were regarded as 'central' and others were regarded as 'peripheral'. In the analysis of thorax CT for mediastinal lymphatic metastasis, lymph nodes with the shortest diameter exceeding 1 cm were regarded as 'suspected metastasis' and recorded.

Routine biochemical laboratory tests, respiratory function tests, arterial blood gases tests and flexible bronchoscopy were performed in all patients enrolled in the study. Histopathologic diagnosis of all patients was NSCLC based on the biopsies obtained by bronchoscopy, transbronchial fine needle aspiration or transthoracic fine needle aspiration. Whole body scintigraphy, cranial CT or MRI was performed in some patients to exclude the presence of a distant metastasis.

Patients were suggested to have preoperative PET imaging in order to support primary diagnosis, search for presence of distant metastasis or mediastinal lymphatic metastasis and informed about the costs of the examination. Patients consented for the examination were included in the study and PET imaging was performed in four separate centers. CT-fusion PET scanner (Siemens PET ECAT ART + multi-slice CT fusion) was used for 45 patients, 6-slice multi-detector CT integrated high-resolution PET-CT scanner (Siemens Biograph LSO HI-RES PET/CT) was used for 125 patients. At least 4 h of fasting and adequate hydration was arranged before the examination. Fasting blood glucose levels of the patients were determined; and 296–703 MBq FDG18 was administered intravenously if values were below 150 mg/dl (Flouro-deoxy glucose). Patients were taken to a comfortable environment for 45–90 min and whole body PET imaging was carried out after this resting period. Images acquired to detect mediastinal lymphatic metastasis were visually evaluated. In the visual evaluation, mediastinal foci apart from normal biodistribution that show increased FDG uptake relative to background and adjacent tissues were considered as 'suspected metastasis'. SUVmax, values of primary tumor and the mediastinal lymph nodes, if involved, were recorded in the PET reports. Upper and lower paratracheal lymph nodes at the right and left sides were combined as right and left paratracheal region, subaortic and para-aortic lymph nodes were combined as aortopulmonary region, subcarinal, paraesophageal and pulmonary ligament nodes were combined as inferior mediastinal region in order to overcome the disadvantage of low spatial resolution of PET imaging. After the evaluation of the PET images, patients with the following criteria were excluded from the study:

1. Patients with distant metastasis,
2. Patients who cannot tolerate or who have rejected the surgical procedure.

Cervical mediastinoscopy was performed within 30 days after PET imaging in all patients to avoid the risk of time interval affecting the mediastinal metastasis results. Patients were placed supine and after induction of general anesthesia, skin was incised for 3–5 cm just above the jugular notch to reach the pretracheal fascia. Fascia was incised to introduce mediastinoscope. Stations number 2R, 4R, 2L, 4L and 7 were routinely explored. Extended mediastinoscopy was performed through the same incision if lymph nodes with pathologic size were detected at aortopulmonary region (station number 5–6) by thorax CT and involvement of these lymph nodes was confirmed by PET in the patients with tumor localized at the left upper lobe. Identified lymph nodes were sampled for histopathologic examination. Patients were referred to the oncology department for neoadjuvant or other non-surgical treatments when metastasis was detected in the MLN samples examined by experienced pathologists. If no metastasis was observed by mediastinoscopy, systematic sampling of lymph nodes by thoracotomy and pulmonary resection if possible, was performed.

Out of 173 patients, three patients were excluded from the study: one patient because the time interval between PET and mediastinoscopy exceeded 1 month (PET revealed findings of suspected metastasis in the colon and colonoscopy was performed), one patient that systematic mediastinal lymph node sampling could not be performed on and one patient who refused thoracotomy after mediastinoscopy. Remaining 170 patients formed the study group.

Necessary variables of thorax CT, PET, mediastinoscopy and thoracotomy to evaluate mediastinal lymphatic metastasis were recorded in a database and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positivity (FP), false negativity (FN) and accuracy rates of each for detection of MLN metastasis were calculated with 95% confidence intervals. 95% confidence intervals for proportions are calculated according to the efficient-score method (corrected for continuity) described by Newcombe [9].

Data were analyzed using 'SPSS for Windows 11.5 (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA)' statistics software. Mann–Whitney U-test, chi-square test and Fisher’s exact tests were used for comparison of the parameters. p Values less than 0.05 were accepted as significant.

3. Results

The study group consisted of 155 males and 15 females and mean age was 59.3 ± 9 (range 35–84). Histopathologic tumor type was squamous carcinoma in 79 patients (46.5%), adenocarcinoma in 58 patients (34%), adenosquamous carcinoma in 10 patients (5.9%), pleomorphic carcinoma in six patients (3.5%), large cell carcinoma in four patients (2.3%), and unclassified NSCLC in 13 patients (7.6%).

Localization of the tumor was right lung in 85 patients (50%), left lung in 85 patients (50%) and upper lobes in 115 patients (58 right + 57 left). Tumor was located in the central part in 26% of the patients. Thorax CT revealed MLNs with pathologic size in 57 patients, and no enlarged MLN was observed in 113 patients. Metastasis was detected by mediastinoscopy or thoracotomy.
in 15 of 113 patients with no findings of MLN metastasis, (false negative n = 15/113) and metastasis could not be shown by mediastinoscopy or thoracotomy in 21 of 57 patients that had suspected MLN metastasis by thorax CT (false positive n = 21/57). These findings indicate that thorax CT has a sensitivity of 70% (95% CI: 58—83), and a specificity of 82% (95% CI: 76—89), PPV of 63% (95% CI: 51—76), NPV of 86% (95% CI: 80—93), accuracy rate of 78% for detection of MLN metastasis.

PET reported MLN involvement in 101 patients and no MLN involvement in 69 patients. Metastasis was detected by mediastinoscopy or thoracotomy in 13 of 101 patients reported as no MLN involvement by PET (false negative n = 13/101). MLN metastasis was demonstrated by mediastinoscopy in eight patients (number 4L in two patients, 4R in two patients, both 4R and 7 in two patients and 5 in one and 7 in one patient) or thoracotomy in five patients (number 8 in three patients, 5 in one patient and 4R in one patient). MLN metastasis was detected by thoracotomy or mediastinoscopy in 38 of 69 patients that PET suggested MLN metastasis, and no metastasis was detected in the remaining 31 patients (false positive n = 31/69). These findings indicate that PET has a sensitivity of 74% (95% CI: 63—86) and a specificity of 73% (95% CI: 66—82), PPV of 55% (95% CI: 43—67), NPV of 87% (95% CI: 80—94), accuracy rate of 74% for detection of MLN metastasis.

Mediastinoscopy sampled a total of 687 stations (mean 4.04, range 2—7). In 127 of the patients MLN metastasis was not detected, whereas mediastinal lymphatic metastasis was detected in 43 patients. Thoracotomy was performed in the patients negative for MLN metastasis. During thoracotomy lobectomy was performed in 94 patients (74%), sleeve lobectomy was performed in nine patients (7%) pneumonectomy was performed in 22 patients (17.3%) together with lymph node dissection; explorative thoracotomy and only lymph node sampling was performed in two patients (1.5%). Thoracotomy revealed metastasis in lymph node number 8 in four patients, in 4R in two patients, in number 7 in one patient and in number 6 in one patient, among 127 patients who were supposed to be negative in mediastinoscopy (mediastinoscopy false negative n = 8/127). These findings indicate that mediastinoscopy has a sensitivity of 84% (95% CI: 74—94), specificity of 100%, PPV of 100%, NPV 94% (95% CI: 89—98), accuracy rate of 95% for detection of MLN metastasis. When only stations of 2R, 2L, 4L, 4R and number 7 that can be reached by standard cervical mediastinoscopy are included in the calculation, standard cervical mediastinoscopy has a sensitivity of 93% (95% CI: 86—100), specificity of 100%, PPV of 100%, NPV of 98% (95% CI: 95—100), FN 6% (95% CI: 2—11), FP 0% and accuracy rate of 98%.

N2 or N3 was detected in 51 of 170 patients (30%) clinically assessed as operable after mediastinoscopy and thoracotomy.

MLN metastasis was detected in 22 of 58 adenocarcinoma patients (38%), and 17 of 79 squamous carcinoma patients (21%). Incidence of MLN metastasis was significantly higher in adenocarcinoma patients (p < 0.05).

When PET results were compared to postoperative pathologic examination results, staging of PET for lymph node metastasis was accurate in 93 patients (55%), lower in 33 patients (20%), higher in 44 patients (25%). When nodal stages of PET were compared to histopathologic nodal stages, MLN was detected in six of 80 patients (7.5%) staged as N0 by PET, in seven of 21 patients (33%) staged as N1 by PET, in 38 of 69 patients (55%) staged as N2 or N3 by PET (Table 1). MLN metastasis was significantly higher in the patients reported as N1 by PET compared to patients reported as N0 by PET (p < 0.05).

Accuracy of PET showed no difference for tumor type, tumor size, tumor location or its peripheral or central localization (p > 0.05).

Out of 31 false positive MLN reported by PET, 22 were reactive hyperplasia, three were chronic granulomatous inflammation, and six were necrotizing granulomatous inflammation. One of these patients with MLNs had a history of tuberculosis and one patient had a history of diabetes. Tumor localization in patients with false positive PET reports was peripheral in 19 patients (61%) and central in 12 patients (39%). Histopathologic type of tumor was squamous carcinoma in 14 patients (45%) and adenocarcinoma in 10 patients (32%). MLNs with pathologic diameter were detected in 14 by thorax CT among these patients.

Tumor localization was peripheral in 82 and central in 19 of total 101 patients reported as negative for mediastinal metastasis by PET. Histopathologic type of tumor in this group was squamous carcinoma in 52 patients, adenocarcinoma in 34 patients and other types in the remaining 15 patients. MLN metastasis was detected in 13 (13%) of these patients. Localization of tumor in this false negative group of patients was peripheral in nine patients (9/82; 11%) and central in four patients (4/19; 21%). False negative rates for central tumors were higher than peripheral tumors although this difference was not statistically significant (p > 0.05). Histopathologic type of tumors in patients with false negative results after mediastinal examination was adenocarcinoma in nine patients (69.2%), squamous carcinoma in four patients (30.8%) demonstrating a statistically significant difference (p < 0.05).

When stepped analysis is performed to thorax CT and PET findings, no involvement was detected by PET in 12 patients out of 57 patients that had pathologic lymph nodes detected by thorax CT, and metastasis was detected in five of these 12 patients by mediastinoscopy or thoracotomy. Mediastinoscopy or thoracotomy showed no metastasis in 14 patients out of 45 patients that thorax CT detected pathologic MLNs and reported as metastasis by PET (Fig. 1). These results indicate that PET has a sensitivity of 86% (95% CI: 75—97), specificity of 33% (95% CI: 13—53), PPV of 68% (95% CI: 55—82), NPV of 59% (95% CI: 30—86), accuracy rate of 66% for the patients reported suspected MLN metastasis by CT examination.

When 572 mediastinal lymph node areas arranged as right, left paratracheal, inferior mediastinal and para-aortopulmon-

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The prognostic marker for NSCLC without distant metastasis is the most important criterion to decide the treatment and accurate as the presence of mediastinal lymphatic metastasis.

4. Discussion

PET results were found true positive for 49 stations, true negative for 428 stations, false positive for 75 stations, and false negative for 20 stations. Therefore, PET had a sensitivity of 71% (95% CI: 60–82), specificity of 85% (95% CI: 82–88), PPV of 39% (95% CI: 31–48), NPV of 96% (95% CI: 94–97) and accuracy rate of 83% in terms of stations.

Thorax CT is the most readily and frequently performed non-invasive method but metastasis cannot be found in 40% of the lymph nodes denoted as pathologic size in thorax CT, and 15–20% of the MLNs that have not reached to pathologic size in CT may be metastatic. Thus, efficacy of thorax CT staging to be low compared to mediastinoscopy.

Mediastinoscopy has the best sensitivity and specificity rates but is an invasive method with the disadvantages of morbidity and mortality, though very low. Mediastinoscopy is reported to have sensitivity above 80% and NPV above 90% in almost all of the studies in the literature. Although reported morbidity and mortality rates are as low as 1% and 0.008%, respectively, the disadvantage of invasiveness persists.

Imaging-guided fine needle biopsies have gained popularity in the hope of replacing mediastinoscopy in recent years. But these methods can be used only in some selected patients and also contain some degree of morbidity albeit low.

Consequently, none of these modalities seem to be ideal for mediastinal staging of NSCLC, and various combinations of these methods are employed for a reliable mediastinal staging. A sensitive, specific and non-invasive method to demonstrate MLN metastasis sounds very attractive. But the selected method must be applicable to all patients, have a high sensitivity for the patients with no suspected metastasis, high specificity for the patients with suspected metastasis and a high accuracy rate for all patient groups.

When these objectives were considered, PET was introduced with very encouraging results. Studies comparing the efficacy of thorax CT and PET to demonstrate MLN metastasis implemented between 1990 and 2000 proved PET to be superior to thorax CT. Accuracy of PET to demonstrate MLN metastasis was reported as 93–100% in the study of Scott et al. and Sasaki et al. in 1996. PET was believed to replace mediastinoscopy as a non-invasive method with its high accuracy rate. Studies performed in the following years did not confirm these early good results. For example, in a study by Gonzalez-Stawinski et al. published in 2003 including 202 patients, PET was reported to have a sensitivity of 64%, specificity of 77%, PPV of 44%, and NPV of 88% to detect MLN metastasis and in the study of Reed et al., accuracy was 61%, specificity was 84%, PPV was 56%, and NPV was 87%.

To evaluate the results of PET imaging, hypermetabolic FDG uptake was considered as the presence of metastatic MLNs. PET has shown a sensitivity of 74%, specificity of 73%, PPV of 55%, NPV of 87% accuracy rate of 74%, which proved the overall efficacy of PET for mediastinal staging to be low compared to mediastinoscopy.

This difference in support of mediastinoscopy compared to PET, is present despite the disadvantage of mediastinoscopy not to reach all mediastinal stations. During standard cervical mediastinoscopy, due to technical reasons, mediastinoscope cannot reach the lymph nodes in aortic and inferior mediastinal regions. Still, accuracy rate of mediastinoscopy to reveal MLN metastasis is higher than PET. When only lymph nodes in the range of mediastinoscopy are considered, PET was reported to have a sensitivity of 84%, specificity of 89%, PPV of 79%, and NPV of 93% to demonstrate MLN metastasis. In our study PET showed a sensitivity of 74%, specificity of 73%, PPV of 55%, NPV of 87% accuracy rate of 74%, which proved the overall efficacy of PET for mediastinal staging to be low compared to mediastinoscopy.
However major deficiencies of the studies that report very low false negative rates can be listed as implementation of the study in terms of mediastinal lymph node stations, inclusion of patients other than NSCLC, i.e. inclusion of benign diseases, and lower than expected N2 rates of the selected patient groups. Studies based on MLN-stations may lead to some bias. For example, if only one false negative is obtained by PET from four mediastinal regions performed to detect MLN metastasis, this will be recorded as three true negatives and one false negative in a station-based study. But if the same situation is reconsidered based on the patient, PET has to be recorded as only one false negative. When results of our study are analyzed for stations, NPV is 96% and PET accuracy rate is 85%, but if patient-based analysis is performed NPV decreases to 87%, and accuracy rate decreases to 74%. Presence of N2 in the patients clinically considered to be operable is reported to be between 30% and 37% [3]. In our study this ratio was determined as 30%. Inclusion of less than expected patients with N2 and a patient population of predominantly early stages would certainly decrease false negative rates. Thus patient inclusion criteria of the study should be carefully reviewed.

Although overall efficacy of PET is lower compared to mediastinoscopy to demonstrate MLN metastasis, we searched for patient groups where PET could potentially replace mediastinoscopy through some subgroup analysis. In these analyses:

- Localization at right or left lung, or peripheral or central has no effect on the accuracy of the PET. But central lung carcinomas have a higher rate of MLN metastasis thus mediastinoscopy must be considered.
- When patients reported to have lymphatic metastasis in hilar-interlobar region (N1) are compared to patients reported to have with no intrathoracic lymphatic involvement (N0) by PET, MLN metastasis was significantly higher (p < 0.05) in patients supposed to be N1 (7.5% vs 33%). Thus mediastinoscopy indication is supported for patients that are reported to be N1 by PET.
- Another analysis was performed for the patients having radiologically detected enlarged lymph node. In the literature, incidence of N2 determined by mediastinoscopy or thoracotomy is reported to be 20–30%, if MLNs larger than 1.6 cm are detected by thorax CT and no involvement is reported by PET [21,22]. In our study, metastasis was detected in 41% of the patients that pathologic MLNs was observed radiologically and reported to have no involvement by PET. Thus, the accuracy rate of PET was observed to decrease significantly in patients with the possibility of N2 by radiological methods (from 76% to 66%). As stated by many studies in the literature [4,10,21] we also recommend performing mediastinoscopy without a preceding PET examination in all patients assigned as N2 by radiological methods.

- There was no difference for accuracy of PET according to histological tumor type but, for all the patients in the group, adenocarcinoma cell type had a higher incidence of MLN metastasis compared to squamous carcinoma. When patients reported to have no MLN metastasis by PET are analyzed, most of the patients with false negative results had cell type of adenocarcinoma (9/13). Thus we believe that mediastinoscopy should be performed in patients with adenocarcinoma even though no involvement is reported for MLN metastasis by PET.

We believe that early results of PET reported for mediastinal staging in the initial studies would be decreased to reasonable levels just like the excellent results of thorax CT for mediastinal staging that were reported in the first years regressed to rational levels by time. Although PET sounds attractive, it does not provide enough accuracy in mediastinal staging of NSCLC compared to mediastinoscopy. Mediastinoscopy still continues to be the gold standard for the mediastinal staging of NSCLC. To obtain better results in mediastinal staging of NSCLC, all available invasive and non-invasive methods should be used together.

References


