Evaluation of integrated positron emission tomography and computed tomography accuracy in detecting lymph node metastasis in patients with adenocarcinoma vs squamous cell carcinoma†

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Received 5 March 2012; received in revised form 28 April 2012; accepted 17 May 2012

Abstract

OBJECTIVES: The aim of our study was to analyze the specificity and sensitivity of integrated positron emission tomography and computed tomography (PET/CT) in detecting nodal metastasis according to histology (adenocarcinoma vs squamous cell carcinoma), and to identify the factors related to false-negative findings.

METHODS: A retrospective, single-institution review of 353 consecutive patients with suspected or pathologically proven, potentially resectable non-small-cell lung cancer (NSCLC) who had integrated PET/CT scanning at the same centre. Lymph node staging was pathologically confirmed on tissue specimens obtained at mediastinoscopy and/or thoracotomy. Statistical evaluation of PET/CT results was performed on a per-patient and per-nodal-station basis.

RESULTS: A total of 2286 nodal stations (1643 mediastinal, 333 hilar and 310 intrapulmonary) were evaluated. Adenocarcinoma was the final diagnosis in 244 patients and squamous carcinoma in 109 patients. Nodes were positive for malignancy in 80 (32.8%) of 244 patients with adenocarcinoma (N1 = 31; N2 = 48 and N3 = 1) and in 32 (29.3%) of 109 with squamous carcinoma (N1 = 21 and N2 = 11). PET/CT in the adenocarcinoma group had a sensitivity, specificity and accuracy of 53.8, 91.5 and 79.1%, and in the squamous cell group, of 87.5, 81.8 and 83.5%, respectively in a per-patient analysis. In the analysis for N2 disease on a per-patient basis, the sensitivity, specificity and accuracy were 38.8, 97.4, and 85.7% for the adenocarcinoma group and 81.8, 91.8 and 90.8% in the squamous cell group. In the adenocarcinoma group, the mean diameter of false-negative lymph nodes was 7 mm (standard deviation [SD] ± 2.5 mm) compared with the diameter of true-positive lymph nodes of 12.5 (SD ± 4 mm; P < 0.00001). In the squamous cell group, the mean diameter of false-negative lymph nodes was 7.4 mm (SD ± 2.8 mm) compared with the diameter of true-positive lymph nodes of 14.7 (SD ± 6 mm; P < 0.005). In the adenocarcinoma group, false-negative lymph nodes were statistically correlated with the presence of vascular invasion and in the squamous cell group only with the maximum standardized uptake value (SUVmax) < 5.4.

CONCLUSIONS: The sensitivity of PET/CT in detecting nodal metastasis in patients with adenocarcinoma is too low to avoid any further invasive staging procedure. Ultrasound-guided needle biopsy or mediastinoscopy is still necessary in staging patients undergoing lung resection for adenocarcinoma.

Keywords: PET/CT · Adenocarcinoma · Squamous cell carcinoma · Lymph node staging · Accuracy

INTRODUCTION

The accurate staging of patients with early-stage non-small-cell lung cancer (NSCLC) is important as mediastinal lymph node involvement in these patients is the most important prognostic indicator and determinant of treatment modality [1]. Invasive mediastinal staging using cervical mediastinoscopy has been the gold-standard method for many years. The emergence of integrated positron emission tomography and computed tomography (PET/CT) using 18F-fluoro-2-deoxy-D-glucose (FDG) has significantly improved the accuracy of lung cancer diagnosis and staging using noninvasive means. Its routine use for preoperative staging of surgical patients with known or suspected NSCLC is now recommended [2]. It is widely accepted that patients with no mediastinal nodal involvement at PET/CT need not undergo invasive staging before surgery. Patients with positive mediastinal nodes at PET/CT should, however, have this confirmed by invasive

†Presented at the 19th European Conference on General Thoracic Surgery, Marseille, France, 5–8 June 2011.
The value of integrated PET/CT in detecting nodal metastases has been verified by comparing the results of PET/CT with the pathology results obtained at cervical mediastinoscopy and/or thoracotomy [4, 7]. This has shown good correlation between PET/CT and histopathology results. However, occult mediastinal nodal metastases occur in 10–15% of cases [3, 4]. No comparison has been made between results on the accuracy of PET/CT with the histological tumour subtype in NSCLC.

The aim of our study was to define the sensitivity and specificity of PET/CT in detecting mediastinal nodal metastases according to the tumour histological type (adenocarcinoma vs squamous cell carcinoma), to identify the factors related to false-negative findings and to ascertain the role of invasive staging in verifying PET/CT results.

MATERIALS AND METHODS

Patient population

This is a retrospective review of 413 consecutive patients who underwent surgery (mediastinoscopy, anterior mediastinotomy and/or thoracotomy) for suspected or pathologically proven localized, clinically resectable NSCLC over a 6-year period between August 2004 and January 2010.

Patients who had PET/CT performed elsewhere, who received induction chemotherapy and/or radiation therapy, those with a PET/CT-negative primary tumour and those with histological types other than adenocarcinoma and squamous cell carcinoma were excluded. A total of 353 patients were eligible for our study.

All 353 patients had an integrated PET/CT scan performed at the same PET Centre with the same integrated scanner to complete the disease staging, and were enrolled in this study. In addition to integrated PET/CT, all enrolled patients had a conventional diagnostic workup, including a thorough history and physical examination, laboratory tests, spirometry, chest X-ray, contrast-enhanced brain, chest and upper abdomen CT, and bronchoscopy. Integrated PET/CT was performed no more than 3 weeks prior to surgery, and all patients provided informed written consent. Patient data were retrospectively collected and analyzed from a prospectively compiled electronic database.

Integrated PET/CT

Patients were asked to fast for at least 6 h before the examination and a serum glucose level below 160 mg/dl was ensured. Image acquisition using an integrated PET/CT scanner (Discovery ST; GE Medical systems) was performed 60 min after intravenous administration of FDG (3.5–4.5 MBq/kg). After determining the imaging field (CT scout view), a CT scan (140 kV, tube current 60 mAs) was performed, and it was used for both anatomical localization and for the calculation of attenuation correction.

Then, the PET data were acquired in the three-dimensional mode from the pelvic floor to the skull bases in 6–8 bed positions. The acquisition time for PET was 3 min per bed position. Coronal, sagittal and transverse data sets were reconstructed. Co-registered scans were displayed by using the dedicated software (Advantage 4.2; GE Healthcare) and integrated PET/CT data sets were prospectively evaluated in consensus by two nuclear medicine physicians (E.P. and V.A.) who were aware of the clinical and stand-alone contrast-enhanced CT results, but blinded to the pathological findings. The maximum standardized uptake value (SUVmax) of the primary tumour was measured with a region-of-interest technique and calculated by the software according to standard formulas.

Pulmonary and mediastinal lymph node stations, localized according to the classification scheme of the 7th edition TNM staging [8], were deemed positive for metastatic spread if they exhibited focally increased FDG uptake higher than the normal background activity, as determined by qualitative analysis.

Surgery and histopathology

All 353 patients underwent surgical staging. Invasive mediastinal staging procedures were performed in patients (n = 41) considered N2/N3 lymph node positive by PET/CT. Cervical mediastinoscopy was used to sample stations 2R, 4R, 2L, 4L and 7, and anterior mediastinotomy was used to sample stations 5 and 6. Five (1.2%) patients were excluded from subsequent surgery due to multistation N2 disease (n = 4) or N3 disease (n = 1). Thirty-six (10.2%) patients underwent invasive mediastinal staging procedure followed by thoracotomy because of non-metastatic mediastinal lymph nodes (n = 13) or minimal N2 disease, defined as single-station, intranodal metastatic deposit (n = 16); seven were false negative at mediastinoscopy. The 312 remaining patients, considered N2 lymph node negative by PET/CT, underwent thoracotomy, pulmonary resection and complete thoracic lymphadenectomy. Overall, pulmonary resections included pneumonectomy (n = 24), bilobectomy (n = 10), lobectomy (n = 302) and segmentectomy (n = 12). At thoracotomy, complete thoracic lymphadenectomy was routinely performed, which consisted of en bloc resection of all lymph nodes that were accessible in the mediastinum and hilum. Intrapulmonary lymph nodes (stations 11 and 12) were removed in the resected lung specimen. At the subcarinal level, the contralateral mediastinal lymph nodes, lying on the opposite main stem bronchus, were removed in 62 patients.

Pathological review (primary tumour characteristics and lymph node status) was performed by standard techniques, and immunohistochemistry was used when appropriate. Pathological TNM staging, according to the 7th edition, was performed and disease was classified as stage IA in 95 patients (27%), stage IB in 97 (27.5%), stage IIA in 45 (12.7%), stage IIB in 35 (9.9%), stage IIIA in 79 (22.3%), stage IIIB in 1 (0.3%); 1 patient had N3 disease) and stage IV in 1 (N2 positive and metastatic pleural effusion).

Data analysis

Continuous data are reported with medians and ranges, while categorical data are reported with counts and percentages. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of integrated PET/CT in the assessment of intrathoracic lymph node involvement were determined by using histological results as the reference standard. Sensitivity was defined as a positive PET/CT result in a patient with lymph node metastases at subsequent histological examination, i.e. true positive; specificity was defined as a negative PET/CT result in patients with no nodal metastases at histology, i.e. true negative.
Accuracy of PET/CT was defined as the proportion of all the patients who had true values (i.e. true positive and true negative mediastinal nodal disease). Diagnostic characteristics of integrated PET/CT were assessed on a per-patient basis and on a per-nodal-station basis. Univariate analysis of data was performed using the \( \chi^2 \) test, log-rank test, Fisher’s exact test, unpaired \( t \)-test and analysis of variance where appropriate. A \( P \)-value < 0.05 was considered statistically significant. All analyses were conducted using the SPSS (SPSS Inc., Chicago, IL, USA) software package.

RESULTS

Between August 2005 and January 2010, a total of 353 patients with suspected or proven adenocarcinoma or squamous cell carcinoma were considered eligible for this study and had an integrated PET/CT scan done as part of the staging prior to surgery. They subsequently had a mediastinoscopy and/or thoracotomy for NSCLC resection and had a diagnosis of adenocarcinoma or squamous cell carcinoma confirmed. Patients with other pathological types (\( n = 64 \)) or who did not have surgery (mediastinoscopy and/or thoracotomy) were excluded.

Baseline characteristics of the study population are summarized in Table 1. The median age of patients with adenocarcinoma was 66.3 years (range 37–86) compared with 68.6 years for squamous (range 45–84; \( P = 0.01 \)). Thirty-two percent of adenocarcinoma patients were female (79 of 244) compared with 15% (16 of 109) in the squamous cell carcinoma group (\( P = 0.0005 \)).

Lymph node and primary tumour characteristics

Adenocarcinoma was the final diagnosis in 244 patients and squamous carcinoma in 109. A total of 2286 nodal stations (1643 mediastinal, 333 hilar and 310 intrapulmonary) were evaluated. The median number of lymph nodes resected as part of the systematic nodal dissection was comparable between the two groups of patients (adenocarcinoma 27 [range 6–103]; squamous cell carcinoma 31 [range 11–67]; \( P = 0.13 \)). The median number of lymph node stations resected was 6 (range 2–10) for patients with adenocarcinoma and 7 (range 3–9) for squamous cell carcinoma. Nodes were positive for malignancy in 80 (32.8%) of adenocarcinoma patients and 91 of 109 (83.5%) of squamous carcinoma patients. One thousand and sixty nodal stations in the adenocarcinoma group and 718 in the squamous cell group were resected respectively. One hundred and thirty and 43 lymph node stations in adenocarcinoma and squamous cell groups respectively were positive for metastasis. In the adenocarcinoma group, 63 (4.0%) nodal stations were false negative and 67 (4.3%) nodal stations were true positive and 6 (0.8%) and 37 (5.1) in the squamous cell group, respectively (\( P = 0.0001 \)).

PET/CT results

PET/CT staged the disease correctly in 193 of 244 (79.1%) of adenocarcinoma patients and 91 of 109 (83.5%) of squamous cell carcinoma patients. One thousand five hundred and sixty eight nodal stations in the adenocarcinoma group and 718 in the squamous cell group were resected respectively. One hundred and thirty and 43 lymph node stations in adenocarcinoma and squamous cell groups respectively were positive for metastasis. In the adenocarcinoma group, 63 (4.0%) nodal stations were false negative and 67 (4.3%) nodal stations were true positive and 6 (0.8%) and 37 (5.1) in the squamous cell group, respectively (\( P = 0.0001 \)).

The sensitivity, specificity and accuracy were 53.8, 91.5 and 79.1% in the adenocarcinoma group and 87.5, 81.8 and 83.5% in the squamous cell group in a per-patient analysis (Tables 3 and 4). The sensitivity, specificity and accuracy were 51.5, 98.6 and 94.7% in the adenocarcinoma group and 86, 97.5 and 96.8% in the squamous cell group in a per-nodal analysis (Tables 5 and 6). PET/CT had lower sensitivity (53.8 [43/80] vs 87.5% [28/32]; \( P = 0.0005 \)) and accuracy (79.1 [193/244] vs 83.5% [91/109]; \( P = 0.2 \)) and higher specificity (91.5 [105/164] vs 81.8% [63/77]; \( P = 0.02 \)) in adenocarcinoma patients compared with squamous cell carcinoma patients.
Under-staging occurred in 37 (15.2%) and four (3.7%) patients, and over-staging in 14 (5.7%) and 14 (12.8%), in adenocarcinoma and squamous cell, respectively. There was a higher proportion of false-negative mediastinal lymph nodes at PET/CT in the adenocarcinoma group (37 of 244) compared with the squamous group (four of 109, \(P = 0.006\)).

In the analysis for N2 disease on a per-patient basis, the sensitivity, specificity and accuracy were 38.8, 97.4 and 85.7% for the adenocarcinoma group and 81.8, 91.8 and 90.8% in the squamous group (Tables 7 and 8). The sensitivity was significantly lower and the specificity significantly higher in the adenocarcinoma group compared with the squamous cell group (\(P = 0.01\) and 0.03, respectively).

Patients or primary tumour characteristics were analyzed to evaluate if they might affect the number or proportion of false-negative metastatic lymph node in the two groups.

In the adenocarcinoma group, the N1/N2 node false-negative rate was not associated with any statistically significant difference in sex, age, side of primary tumour, location of tumour (central vs peripheral), median tumour SUV\(_{\text{max}}\), tumour T stage or visceral pleural invasion of tumour, histological subtype, tumour grade or presence of tumour necrosis. There was, however, a statistically significant prevalence of vascular invasion of the tumour (17 of 37) in false-negative N1/N2 nodes at PET/CT compared with negative patients (\(P = 0.008\)).

In the squamous cell group, the N1/N2 node false-negative rate was only significantly correlated with a tumour SUV\(_{\text{max}}\) < 5.4, \(P = 0.02\); all the other characteristics, previously analyzed, did not significantly correlate with the false-negative rate.

In the analysis of lymph node size, the mean diameter of the false-negative lymph nodes in the adenocarcinoma group was 6.5 compared with 12.0 mm of true-positive lymph nodes (\(P < 0.001\)). Only three of 63 (4.8%) false-negative lymph node stations had a diameter \(\geq 10\) mm and only 19 of 63 (30.1%) true-positive lymph node stations had a diameter <10 mm.

In the squamous cell group, the N1/N2 node false-negative rate was less than the positive metastatic lymph node: 7.4 vs 14.7 mm of true positive nodes (\(P = 0.005\)). In this group, two (33.3%) of the six false-negative lymph node stations had a diameter \(\geq 10\) mm and only five (13.5%) of the 37 true-positive lymph node stations had a diameter <10 mm.
**DISCUSSION**

Integrated PET/CT scanning is an important tool in the staging of patients with early NSCLC and guides the selection of surgical candidates. For many years, cervical mediastinoscopy was the only tool available for mediastinal lymph node staging. Whereas, it remains the ‘gold standard’ method [2, 5, 7], the noninvasive nature of PET/CT makes it particularly attractive. Perhaps, the most important attributes of PET/CT in screening for mediastinal lymph node metastases are its high specificity and negative predictive value, which are consistently reported as being >90% [4, 5, 9–11]. Because of its low sensitivity, however, patients with negative mediastinal disease on PET/CT should undergo invasive staging to confirm lymph node metastases [2, 4, 5, 9–11].

In our series, the accuracy of PET/CT at staging was comparable in adenocarcinoma and squamous cell carcinoma groups. The sensitivity and specificity were, however, different between adenocarcinoma and squamous cell groups. This may have to do with the fact that the false-negative lymph nodes <10 mm were significantly higher in the adenocarcinoma group.

In keeping with published reports, we found that primary tumour SUV\(_{\text{max}}\) was higher in squamous cell carcinoma than in adenocarcinoma [12, 13]. Squamous cell carcinoma has been reported to have a higher degree of expression of transmembrane glucose transporters (GLUT-1 and GLUT-3) and the same molecules facilitate uptake of FDG [14–16]. This may account for the higher median tumour SUV\(_{\text{max}}\) that we observed for squamous cell carcinoma, an observation we have previously noted [4]. We also found a higher proportion of squamous cell carcinomas to have a higher grade than adenocarcinoma. A higher tumour grade has been reported to correlate with tumour SUV\(_{\text{max}}\) [12, 15].

Of course, tumour location is important in determining the likelihood of overt and occult mediastinal nodal disease with centrally located tumours more likely to present with lymph node metastases [17, 18]. Although our study showed a higher proportion of centrally located squamous cell carcinomas (48 vs 14% for adenocarcinomas, \(P < 0.001\)), there were more false-negative PET/CT nodes in adenocarcinoma than in squamous cell carcinoma.

The pattern of lymph node metastases in adenocarcinoma can be different from that in squamous cell carcinoma and can explain the difference in sensitivity and specificity. Whereas, the latter occurs by direct drainage to adjacent regional nodes, adenocarcinoma metastases can be found in more distant nodes (mediastinal without hilar involvement, for instance)—the so-called skip metastases [4, 19]. This may account for the higher incidence of occult nodal metastases that we observed in the adenocarcinoma group with consequent higher false-negative rates.

Moreover, the diameter of the false-negative adenocarcinoma nodes was less than that in the squamous cell carcinoma group, and the number of false-negative lymph nodes <10 mm was higher than that in the squamous cell carcinoma group, meaning these nodes were below the spatial resolution of PET/CT.

In the adenocarcinoma group, the sensitivity was significantly lower compared with the squamous cell group for detecting intrathoracic lymph node metastasis. This is probably related to the prevalence of micrometastasis in adenocarcinoma that we have previously reported [4]. According to our results, the mediastinal staging with a negative PET/CT in the squamous cell group may be avoided; only the squamous tumour in our series with a low SUV\(_{\text{max}}\) showed an increase risk of false-negative metastatic lymph nodes.

In the adenocarcinoma group, according to our results, invasive mediastinal staging is still needed to ascertain mediastinal disease to provide better treatment to patients with adenocarcinoma. We did not identify any specific subgroup of adenocarcinoma patients at higher risk of false-negative metastasis lymph node. Most patients presented with metastasis in normal-sized lymph nodes, but also, these patients could probably benefit from neoadjuvant treatment.

In conclusion, this report is a retrospective study on a large homogeneous population that confirms the low sensitivity and accuracy of PET/CT in detecting mediastinal lymph node metastasis in patients with adenocarcinoma. Invasive mediastinal staging is still considered the gold standard in discovering mediastinal nodal involvement and selecting patients for neoadjuvant treatment. Recently, with the introduction of EBUS and EUS, the number of cervical mediastinoscopies has decreased, but invasive mediastinal staging is still required, due to the suboptimal spatial resolution of PET/CT in normal-sized lymph nodes.

Further prospective studies to better identify specific subgroups of patients at higher risk of false-negative lymph node metastases and to understand the role of PET/CT in the preoperative diagnostic algorithm in patients with NSCLC are needed.

**Conflict of interest:** none declared.

**REFERENCES**


