Preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer: accuracy of integrated positron emission tomography and computed tomography

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Abstract

Objective: To evaluate the accuracy of integrated positron emission tomography with 18F-fluoro-2-deoxy-D-glucose (FDG) and computed tomography (PET/CT) in preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer (NSCLC) and to ascertain the role of invasive staging in verifying positron emission tomography (PET)/computed tomography (CT) results. Methods: Retrospective, single institution study of consecutive patients with suspected or pathologically proven, potentially resectable NSCLC undergoing integrated PET/CT scanning in the same PET 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 bases. Results: A total of 1001 nodal stations (723 mediastinal, 148 hilar and 130 intrapulmonary) were evaluated in 159 patients. Nodes were positive for malignancy in 48 (30.2%) out of the 159 patients (N1 = 17; N2 = 30; N3 = 1) and 71 (7.1%) out of 1001 nodal stations (N1 = 24; N2 = 46; N3 = 1). At univariate analysis, lymph node involvement was significantly associated (p < 0.05) with the following primary tumour characteristics: increasing diameter, maximum standardised uptake value >9, central location and presence of vascular invasion. PET/CT staged the disease correctly in 128 out of 159 patients (80.5%), overstaging occurred in nine patients (5.7%) and understaging in 22 patients (13.8%). The overall sensitivity, specificity, positive and negative predictive values, and accuracy of PET/CT for detecting metastatic lymph nodes were 54.2%, 91.9%, 74.3%, 82.3% and 80.5% on a per-patient basis, and 57.7%, 98.5%, 74.5%, 96.8% and 95.6% on per-nodal-station basis. With regard to N2/N3 disease, PET/CT accuracy was 84.9% and 95.3% on a per-patient basis and on per-nodal-station basis, respectively. Referring to nodal size, PET/CT sensitivity to detect malignant involvement was 32.4% (12/37) in nodes <10 mm, and 85.3% (29/34) in nodes >10 mm. Conclusion: Our data show that integrated PET/CT provides high specificity but low sensitivity and accuracy in intrathoracic nodal staging of NSCLC patients and underscore the continued need for surgical staging.

Keywords: Non-small-cell lung cancer; Lymph node staging; PET/CT

1. Introduction

In patients presenting with localised and clinically resectable non-small-cell lung cancer (NSCLC), intrathoracic lymph node status is the major prognostic factor and determines therapeutic management.

Although computed tomography (CT) is the most commonly used noninvasive modality for the evaluation of primary tumour characteristics (i.e., size, location and extent), a number of reviews and meta-analyses have shown the limited reliability of CT in lymph node staging [1–4].

In recent years, integrated 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography and computed tomography (PET/CT) has been repeatedly reported to improve overall staging of NSCLC patients by allowing the acquisition of co-registered, spatially matched functional and morphological data [5–8]. However, false-positive PET/CT results in nodal staging have been shown in patients with co-existent inflammatory or infectious diseases, while, owing to still suboptimal spatial resolution, PET/CT scanning may be unable to identify metastatic deposits in normal-sized lymph nodes [9–14]. Consequently, the debate continues over the nodal staging algorithm combining integrated PET/CT and invasive procedures.

The primary aim of this study was to investigate the accuracy of integrated PET/CT in preoperative intrathoracic lymph node staging in patients presenting with localised and clinically resectable NSCLC by using surgical and histological methods.
results as reference standards. Our secondary aim was to ascertain the role of invasive staging procedures in verifying integrated PET/CT findings.

2. Patients and methods

2.1. Patient population

From August 2004 to August 2007, 466 consecutive patients underwent surgery (mediastinoscopy, anterior mediastinotomy and/or thoracotomy) for suspected or pathologically proven localised, clinically resectable NSCLC. Before surgery, 159 of these patients (34.1%) had an integrated PET/CT scan performed in 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 conventional diagnostic work-up, 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 within 3 weeks prior to surgery, and all patients provided informed written consent. Patients who had PET/CT performed elsewhere, who received induction chemotherapy and/or radiation therapy, and patients with a PET/CT negative primary tumour were excluded. Patient data were retrospectively collected and analysed from a prospectively compiled electronic database. Main clinical and pathological characteristics of the study population are summarised in Table 1.

2.2. Integrated PET/CT

Patients were asked to fast for at least 6 h before examination and a serum glucose level below 160 mg dl⁻¹ was ensured. Image acquisition using integrated PET/CT scanner (Discovery ST; GE Medical systems) was performed 60 min after intravenous administration of FDG (4.5—5.5 MBq kg⁻¹). After determining the imaging field, a CT scan (140 kV, tube current 60 mA s⁻¹) was performed and it was used for both anatomical localisation and for calculation of attenuation correction. Then, the PET data were acquired in three-dimensional (3D) mode from the skull base to the pelvic floor in eight to nine 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 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 clinical and stand-alone contrast-enhanced CT results, but blinded to the histological findings. The maximum standardised 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, localised according to the classification scheme of Mountain and Dresler [15], were deemed positive for metastatic spread if they exhibited focally increased FDG uptake higher than the normal background activity, as determined by qualitative analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>112 (70.4)</td>
</tr>
<tr>
<td>Female</td>
<td>47 (29.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>67 ± 8.3</td>
</tr>
<tr>
<td>Range</td>
<td>37—85</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>88 (55.3)</td>
</tr>
<tr>
<td>Left</td>
<td>71 (44.7)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Central (inner 1/3 of lung field)</td>
<td>48 (30.2)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>111 (69.8)</td>
</tr>
<tr>
<td>Tumour diameter (cm)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>Range</td>
<td>1—8</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>38 (23.9)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>100 (62.9)</td>
</tr>
<tr>
<td>Bronchoalveolar</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Carcinoid*</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Other type non-small-cell lung cancer</td>
<td>7 (4.4)</td>
</tr>
<tr>
<td>Grade of differentiation</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>16 (10.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>84 (52.8)</td>
</tr>
<tr>
<td>Poor</td>
<td>59 (37.1)</td>
</tr>
<tr>
<td>Presence of vascular invasion</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>115 (72.3)</td>
</tr>
<tr>
<td>No</td>
<td>44 (27.7)</td>
</tr>
<tr>
<td>Presence of necrosis</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>60 (37.7)</td>
</tr>
<tr>
<td>Focal</td>
<td>58 (36.5)</td>
</tr>
<tr>
<td>Extended</td>
<td>41 (25.8)</td>
</tr>
<tr>
<td>Tumour SUVMAX</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.16 ± 5.23</td>
</tr>
<tr>
<td>Range</td>
<td>2.1—27.0</td>
</tr>
</tbody>
</table>

SD: standard deviation; SUVMAX: maximum standardised uptake value. * Typical n = 8; atypical n = 1.

2.3. Surgery and histopathology

All 159 patients underwent surgical staging. Invasive mediastinal staging procedures were performed in patients (n = 22) 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 patients were excluded from subsequent surgery due to multi-station N2 disease (n = 4) or N3 disease (n = 1). Seventeen patients underwent invasive mediastinal staging procedure followed by thoracotomy during the same surgical session due to non-metastatic mediastinal lymph nodes (n = 7) or N2 minimal disease, defined as single-station, intranodal metastatic deposit (n = 10). Final pathology confirmed absence of mediastinal lymph node involvement in the seven patients with negative mediastinoscopy findings; it also showed multi-station mediastinal lymph node involvement in two out of the 10 patients with positive mediastinoscopy findings. The 137 remaining patients, considered N2 lymph node negative by PET/CT, underwent thoracotomy, pulmonary resection and
involvement was performed on a per-patient basis using chi-
cratered PET/CT were assessed on a per-patient and on a per-
ference standard. Diagnostic characteristics of the inte-
et were determined by using histological results as
positive predictive value and accuracy of integrated PET/
showing satellite tumour nodules in the primary tumour lobe
patients. Pathological review (primary tumour characteristics and
characteristics associated with pathological lymph node
Intrapulmonary lymph node stations (stations 11 and 12)
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
seven patients.

Pathological review (primary tumour characteristics and
node status) was performed by standard techniques, and
and immunohistochemistry was used when appropriate. Pathological TNM staging was performed and disease was
classified as stage IA in 47 patients (29.6%), stage IB in 44
(27.6%), stage IIA in six (3.8%), stage IIB in 28 (T2N1 n = 10;
T3N0 n = 18 [17.6%]), stage IIIA in 31 (T3N1 n = 1; T1N2 n = 5;
T2N2 n = 24; T3N2 n = 1 [19.5%]), stage IIIB in three (1.9%; one
patient had N3 disease and two patients had T4N0 tumours
showing satellite tumour nodules in the primary tumour lobe
of the lung).

2.4. Data analysis

The sensitivity, specificity, positive predictive value,
negative predictive value and accuracy of integrated PET/CT
in the assessment of intrathoracic lymph node involve-
ment were determined by using histological results as
reference standard. Diagnostic characteristics of the in-
tegrated PET/CT were assessed on a per-patient and on a per-
nodal-station basis. Univariate analysis for primary tumour
characteristics associated with pathological lymph node
involvement was performed on a per-patient basis using chi-
square χ² test, Fischer’s exact test, unpaired t-test, and
analysis of variance (ANOVA) where appropriate. All other
data were analysed for significance using the χ² test or
Fischer’s exact test. A probability value of <0.05 was
considered statistically significant. Statistical analysis was
carried out with StatSoft version 6.1 software.

3. Results

Histological typing of the primary tumour showed
adenocarcinoma in 100 patients (62.9%), squamous cell in
38 (23.9%) and other NSCLC cell types in 21 (13.2%). A total of
1001 nodal stations were biopsied and histologically
evaluated in 159 patients. The mean number of nodal
stations examined per-patient was 6.3 (±1.2) and the mean
number of lymph nodes dissected per-patient was 28.9
(±13.3). At pathologic staging, 111 of the 159 patients
(69.8%) had no lymph node involvement, 17 (10.7%) were
found to have N1 disease, 30 (18.9%) N2 disease (single-
station 20, multi-station 10) and one (0.6%) N3 disease. Skip
metastasis in mediastinal lymph nodes was recognised in 23
patients. At univariate analysis, primary tumour charac-
teristics that had significant predictive value with regard to
pathological lymph node involvement were: increasing
maximum diameter (p = 0.039), SUVmax >9 (p = 0.033),
central location (p = 0.004) and presence of vascular
invasion (p = 0.0001). On the other hand, site of disease,
histology, grade of differentiation and presence of necrosis
showed no statistical significance in relation to pathological
lymph node involvement.

PET/CT correctly identified 102 out of 111 patients (91.9%)
who did not have metastatic lymph node involvement on
histological analysis. N1 disease was correctly detected by
PET/CT in 12 of 17 patients (70.6%) with pathologically
proven disease. N2/N3 disease was correctly determined by
PET/CT in 14 of 31 patients (45.2%) with positive results on
histological analysis. PET/CT falsely understaged 22 patients
(13.8%). Of these patients, one patient was understaged from
N3 to N2, two patients from N2 to N1, 14 from N2 to N0 and
five from N1 to N0. The causative factors for understaging
were sub-centimetre metastatic deposits in 17 patients and
inability of the PET/CT to distinguish between large central
tumours and adjacent mediastinal or pulmonary lymph nodes
in five patients. PET/CT falsely overstaged nine patients
(5.7%): two patients from N0 to N1 and seven from N0 to N2.
Overslapping was due to inflammatory conditions (n = 6) and
silicoanthracosis (n = 3). Integrated PET/CT showed an
overall sensitivity of 54.2%, a specificity of 91.9%, a positive
predictive value of 74.3%, a negative predictive value of
82.3% and an accuracy of 80.5% for the detection of
intrathoracic nodal metastases on a per-patient basis
(Table 2).

Out of 1001 nodal stations histologically evaluated, 71
proved to be positive for malignancy. PET/CT correctly
identified 41 metastatic lymph node stations (57.7%; 19 N1,
22 N2). False-negative results were obtained in 30 nodal
stations (five N1, 24 N2, one N3), and false-positive results in
14 (five N1, nine N2). Table 3 shows the correlation between
N staging with PET/CT and pathological N stage. The overall
sensitivity, specificity, positive and negative predictive
values and accuracy of PET/CT for detecting intrathoracic
lymph node involvement were 57.7%, 98.5%, 74.5%, 96.8%
and 95.6%, respectively, on a per-nodal-station basis
(Table 4). The most common lymph node station for occult
metastatic involvement was in the subcarinal level (8 out of
30 [26.6%]) followed by right upper and lower paraotracheal
and hilar levels (four each out of 30).

The short-axis diameter of the 71 pathologically proven
metastatic lymph node stations ranged from 3 to 37.5 mm,
with a mean value of 10.4 ± 4 mm. Of these 71 lymph node
stations, 37 (52.1%) were less than 10 mm in short-axis
diameter. The size of the 41 lymph node stations that yielded
true positive results on PET/CT ranged from 7.5 to 37.5 mm,
with a mean value of 13.1 ± 5.3 mm. Twelve (29.3%) of the 41
true positive lymph node stations at PET/CT were less than
10 mm in short-axis diameter. The size of the 30 lymph node
stations that yielded false-negative results on PET/CT ranged

Table 2
Contingency table for PET/CT in identifying intrathoracic lymph node (LN) involvement.

<table>
<thead>
<tr>
<th>PET/CT (+)</th>
<th>Intrathoracic LN Involvement (+)</th>
<th>Intrathoracic LN Involvement (−)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT (+)</td>
<td>26</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>PET/CT (−)</td>
<td>22</td>
<td>102</td>
<td>124</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>111</td>
<td>159</td>
</tr>
</tbody>
</table>
Table 3
Per-nodal-station results of PET/CT and histologic analyses.

<table>
<thead>
<tr>
<th>Lymph node station*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>TP</td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

from 3 to 15 mm, with a mean value of 7.8 ± 2.7 mm. Twenty-five (83.3%) of thirty false-negative lymph node stations were less than 10 mm in short-axis diameter. In fact, PET/CT was successful in identifying 29 of 34 (85.3%) metastatic lymph node stations measuring ≥10 mm in short-axis diameter, and 12 of 37 (32.4%) metastatic lymph node stations measuring <10 mm in short-axis diameter.

In view of the central importance of mediastinal lymph node involvement for therapeutic decision making in patients with localised NSCLC, a subset per-patient analysis was performed in which N0 disease and N1 disease were combined in order to evaluate PET/CT diagnostic efficacy in the detection of mediastinal nodal metastasis. This resulted in a sensitivity of 45.2%, a specificity of 94.5%, a positive predictive value of 87.7%, and an accuracy of 84.9% of PET/CT for the detection of mediastinal nodal metastasis. As shown in Table 3, the most common location for mediastinal lymph node disease was the subcarinal station (13 out of 47 [27.6%]), followed by the lower paratracheal station (10 out of 47 [21.3%]). The highest rate of PET/CT inaccuracy among mediastinal lymph node stations was in station 3, followed by station 5, 7 and 4. The highest incidence of both false-positive and false-negative PET/CT results was in station 7 (3 out of 9 [33.3%] and 8 out of 25 [32%], respectively). Finally, 21 (84%) of the 25 false-negative mediastinal lymph node stations were less than 10 mm in short-axis diameter. Of these 21 lymph node stations, 19 (90.5%) were in patients with adenocarcinoma. These patients showed higher small-sized mediastinal nodal metastatic rates than those with other NSCLC cell types did.

Table 4
Per-nodal-station diagnostic efficacy of PET/CT.

<table>
<thead>
<tr>
<th>Nodal station*</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.3</td>
<td>98.8</td>
<td>66.7</td>
<td>95.3</td>
<td>94.4</td>
</tr>
<tr>
<td>2</td>
<td>40.0</td>
<td>97.5</td>
<td>75.0</td>
<td>95.1</td>
<td>93.3</td>
</tr>
<tr>
<td>3</td>
<td>66.7</td>
<td>95.1</td>
<td>57.1</td>
<td>96.7</td>
<td>92.3</td>
</tr>
<tr>
<td>4</td>
<td>66.7</td>
<td>100.0</td>
<td>100.0</td>
<td>96.9</td>
<td>97.1</td>
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<td>5</td>
<td>38.5</td>
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<td>62.5</td>
<td>94.6</td>
<td>92.9</td>
</tr>
<tr>
<td>6</td>
<td>50.0</td>
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<td>100.0</td>
<td>96.8</td>
<td>96.9</td>
</tr>
<tr>
<td>7</td>
<td>9.0</td>
<td>100.0</td>
<td>99.2</td>
<td>99.2</td>
<td>99.2</td>
</tr>
<tr>
<td>N2 (n = 696)</td>
<td>47.8</td>
<td>98.6</td>
<td>71.0</td>
<td>96.4</td>
<td>95.3</td>
</tr>
<tr>
<td>10</td>
<td>75.0</td>
<td>97.7</td>
<td>80.0</td>
<td>97.9</td>
<td>95.3</td>
</tr>
<tr>
<td>11 – 12</td>
<td>87.5</td>
<td>98.4</td>
<td>77.8</td>
<td>99.2</td>
<td>98.5</td>
</tr>
<tr>
<td>N1 (n = 278)</td>
<td>79.2</td>
<td>98.0</td>
<td>79.2</td>
<td>98.0</td>
<td>96.4</td>
</tr>
<tr>
<td>N3 (n = 27)</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>96.3</td>
<td>96.3</td>
</tr>
</tbody>
</table>

PPV: positive predictive value; NPV: negative predictive value.

* Lymph node stations were localised according to the classification scheme of Mountain and Dresler [15].

4. Discussion

In patients with localised and clinically resectable NSCLC, presence and extent of intrathoracic lymph node involvement dictate treatment strategy. Specifically, in the presence of mediastinal lymph node involvement, minimal N2 disease, defined as single-station, intranodal metastatic deposit, does not per se preclude surgery as a primary therapy. On the other hand, factors known to be associated with a dismal prognosis rendering initial resection unrewarding include multi-station nodal disease, extra-capsular invasion and bulky lymphadenopathy.

Since the 1960s, cervical mediastinoscopy has been extensively used in the mediastinal lymph node staging of potential candidates to thoracotomy. Specificity and false-positive rates of mediastinoscopy can be assumed to be 100% and 0%, respectively, while in a review of more than 6500 patients undergoing mediastinoscopy between 1985 and 2003, the average sensitivity of mediastinoscopy to detect mediastinal lymph node involvement was approximately 80%
and the average false-negative rate was approximately 10% [16]. False-negative results mainly occur in lymph node stations that are not reachable by mediastinoscopy, although the yield of the technique is also surgeon dependent [17]. In recent years, transbronchial [18] and transoesophageal [19] ultrasound-guided needle biopsy techniques have provided a valuable adjunct for the evaluation of mediastinoscopic ‘blind spots’. Besides being unable to completely stage the mediastinum, mediastinoscopy has several shortcomings including invasiveness, risk of morbidity and mortality and cost. As a consequence, several imaging techniques have been employed as a guide to enable the most efficient use of mediastinoscopy.

Lately, the role of integrated PET/CT has been investigated as a noninvasive staging modality in patients with NSCLC. In the early literature, integrated PET/CT showed substantially higher accuracy in overall tumour staging over CT and PET interpreted separately [5–8]. By allowing the simultaneous registration of spatially matched metabolic and anatomic data, PET/CT was thought to be particularly helpful in identifying metastatic deposits in normal-sized lymph nodes and for distinguishing between hyperplastic lymph nodes and enlarged metastatic lymph nodes. However, subsequent studies which focussed on the diagnostic accuracy of PET/CT in mediastinal lymph node staging and used stringent ascertainment methods of PET/CT findings, have yielded far-from-ideal sensitivity, specificity and accuracy of PET/CT for nodal staging [9–14,20] (Table 6).

Our study confirms the limited ability of integrated PET/CT to correctly identify the actual intrathoracic lymph node stage in patients with potentially resectable NSCLC. Out of a series of 159 consecutive patients, 154 of whom (96.8%) underwent lung resection with systematic pulmonary and mediastinal lymph node dissection, 22 patients (13.8%) were falsely understaged and nine (5.7%) were falsely overstaged. All performance characteristics of integrated PET/CT turned out to be well below the threshold of 95% at which the test could replace invasive staging procedures [14].

Clinicopathological factors that have been identified as being associated with incorrect PET/CT staging (whether understaging or overstaging) include a number of conditions [21,22]. Limitations of spatial and anatomic resolution remain the main causative factors for false-negative results of PET/CT. In a study with 150 patients with stage T1 NSCLC [11], PET/CT identified malignant involvement only in 20 (38%) of 52 pathologically proven metastatic lymph node stations measuring <10 mm in short-axis diameter. Similarly, in a study with 143 patients with stage T1 NSCLC, Yi and co-workers [12] reported that, in 12 (80%) of 15 PET/CT false-negative results, helical CT showed visible lymph nodes with a mean short-axis diameter of 5.5 mm. In the current study, PET/CT was successful in identifying only 12 (32.4%) of 37 metastatic lymph node stations measuring <10 mm in short-axis diameter, and 25 (83.3%) of 30 false-negative lymph node stations were less than 10 mm in short-axis diameter. Interestingly enough, similar results were reported by Nomori and co-workers [23] and by Takamochi and co-workers [24] who used PET alone. However, in these cases, N2 minimal disease is found which might not influence clinical decisions.

On the other hand, previous or concomitant inflammatory and infectious conditions are mainly responsible for false-negative results of PET/CT. Indeed, in the present study, a false-positive rate of 25.7% in intrathoracic nodal staging was observed in spite of the extremely low incidence of granulomatous disease in our region. In contrast with the findings of some reports [11,12], PET/CT appeared limited in the predictive value in confidently identifying advanced disease in potential candidates to surgical resection. However, since false-positive results are calculated on small numbers in our series, one should use caution when interpreting the positive predictive value of integrated PET/CT.

In this study, the most common location for mediastinal lymph node disease was the subcarinal station, followed by the lower paratracheal station. In agreement with the findings reported by Cerfolio and co-workers [7], PET/CT proved to be less accurate in the subcarinal station, where the highest incidence of both false-positive and false-negative PET/CT results was found. These data underline the need for a thorough lymph node dissection in the subcarinal level.

Finally, in the detection of mediastinal nodal metastasis, PET/CT specificity, negative predictive value and overall accuracy improved unsubstantially at the cost of lowered sensitivity and positive predictive value. Indeed, as a consequence of the low prevalence of pathologically proven mediastinal lymph node involvement in our series [24], the false-negative rate decreased from 17.7% to 12.3% while the false positive rate increased from 25.7% to 33.3%.

Table 6

<table>
<thead>
<tr>
<th>First author [reference]</th>
<th>No. of patients</th>
<th>No. of T.tomy</th>
<th>No. of LN stations</th>
<th>Prev (%)</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerfolio [9]</td>
<td>383</td>
<td>295</td>
<td>N/A</td>
<td>30</td>
<td>76</td>
<td>64</td>
<td>47</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>Kim [11]</td>
<td>150*</td>
<td>135</td>
<td>3.8</td>
<td>23</td>
<td>47</td>
<td>100</td>
<td>100</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Yi [12]</td>
<td>141*</td>
<td>132</td>
<td>3.2</td>
<td>24</td>
<td>56</td>
<td>100</td>
<td>100</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Lee [13]</td>
<td>126</td>
<td>101</td>
<td>4^d</td>
<td>22.2</td>
<td>86</td>
<td>81</td>
<td>56</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td>Melek [20]</td>
<td>170^c</td>
<td>127</td>
<td>4^d</td>
<td>30</td>
<td>74</td>
<td>73</td>
<td>55</td>
<td>87</td>
<td>74</td>
</tr>
<tr>
<td>Present series</td>
<td>159</td>
<td>154</td>
<td>4.5</td>
<td>19.5</td>
<td>45</td>
<td>94</td>
<td>67</td>
<td>88</td>
<td>85</td>
</tr>
</tbody>
</table>

No. of T.tomy: number of patients undergoing thoracotomy and systematic lymphadenectomy; no. of LN stations: mean number of mediastinal lymph node stations examined per-patient; Prev: prevalence of N2/N3 disease; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; Acc: accuracy; N/A: not available.

* Include only patients with stage T1 non-small-cell lung cancer.

† Mean number of lymph node stations sampled per-patient in 629 patients undergoing surgical mediastinal lymph node biopsy during the study period.

‡ 125 patients had integrated PET/CT and 45 had routine PET.

§ Mean number of lymph node stations sampled per-patient at mediastinoscopy.
Some limitations apply to this study. First, the retrospective nature of this single institution study might have introduced biased information. Second, because our series includes only potential candidates to surgical resection, PET/CT sensitivity and accuracy might have been underestimated. Third, we included patients with serum glucose levels up to 160 mg dl\(^{-1}\) which could have impaired FDG uptake in metastatic lymph nodes. Fourth, there may have been a verification bias in which surgeons were aware of PET/CT results. However, 154 out of 159 patients underwent pulmonary resection and systematic pulmonary and mediastinal lymph node dissection with removal of both normal-appearing and abnormal-appearing lymph nodes. Finally, although 1001 lymph node stations were examined in 159 patients, false-negative and false-positive PET/CT findings were calculated on relatively small numbers. This must be duly considered when interpreting the data.

In conclusion, both the published literature and our experience underline the sustained need for tissue confirmation of a positive PET/CT result in the evaluation of mediastinal lymph node involvement in patients with clinically resectable NSCLC in order to determine whether patients are candidates for potentially curative surgery or for protocols involving induction therapy. On the other hand, the spatial resolution of PET/CT remains inadequate to rule out sub-centimetre lymph node metastasis and does not obviate the need for invasive staging procedures such as mediastinoscopy in patient cohorts with a higher likelihood of mediastinal lymph node involvement (in primis, patients with central tumours, adenocarcinoma histology, PET/CT hilar N1 disease and CT mediastinal N2 disease) [16,20,22].

While new detector modules with higher spatial and temporal resolution and sensitivity are developed along with improvements in image reconstruction capabilities [25], further investigation is warranted to determine more precisely the actual benefit of integrated PET/CT implementation in the staging algorithm in patients with clinically resectable NSCLC.

References