Incidence of occult mediastinal node involvement in cN0 non-small-cell lung cancer patients after negative uptake of positron emission tomography/computed tomography scan

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Abstract

Objective: This study sought to assess the real incidence of pN2 among patients with non-small-cell lung cancer (NSCLC) (cN0) with negative mediastinal uptake of 2-deoxy-2-(18F)-fluoro-o-glucose (FDG). Methods: During 30 consecutive months (January 2007–May 2009), all patients with NSCLC scheduled for surgery in our unit had a preoperative FDG positron emission tomography (PET)/computed tomography (CT) in our institution, after a dedicated chest CT (n = 259). Only patients with both FDG-PET/CT and negative dedicated chest CT scan (N1 and N2 nodes <1 cm) were prospectively included (n = 125). Patients with cT1/cN2/cN3 and patients who had undergone preoperative chemo-radiotherapy were excluded. No invasive surgical staging was carried out in this group and curative resection plus systematic mediastinal dissection was performed except in the event of unexpected oncological contraindication. All variables were collected prospectively and, when pathological information was obtained, all the cases were carefully reviewed. Results: Mediastinal assessment by FDG-PET/CT, negative predictive value (NPV) was 85.6%, confidence interval (CI): [77—91]; false negatives (FNs) for mediastinal lymph nodes involvement was 14.4% (18 cases). The ph2 stations most frequently involved were: 4R (six cases), seven (six cases) and five (five cases). Multiple-level pN2 occurred in six (4.8%) cases. Occult (pN2) lymph nodes were more frequent in women (p < 0.01), adenocarcinoma (p < 0.05) and pN1 (p < 0.05). Pathological N2 prevalence for pN1 was 34 (27.7%). Considering pathological staging as the gold standard, the agreement was 70% and 47.5% for stage IA and IB (Kappa's index: 0.72 and 0.76) and, in all patients, 47% (Kappa's index: 0.27). In general, down-staging is more frequent than up-staging. Conclusions: Mediastinal assessment of NSCLC by FDG-PET/CT showed a considerable incidence of FNs. NPV is lower than previously reported and the preoperative mediastinal staging by 18FDG-PET/CT may jeopardise accurate staging for early stage NSCLC patients.

Keywords: Mediastinal metastases; Lung cancer; PET; Staging

1. Introduction

The treatment of lung cancer is guided by correct clinical staging. The ability to make informed treatment decisions in patients with lung cancer is heavily dependent on accurate disease staging. In particular, the ability to correctly identify patients with potentially curable (early stage I–II) non-small-cell lung cancer (NSCLC) is a crucial management goal [1–3]. The unforeseen involvement of mediastinal lymph nodes in lung cancer patients is the most important prognostic factor in the absence of distant metastases [2,4]. Some randomised studies have suggested that neoadjuvant therapy prior to surgery is best for patients with IIIA stage based on mediastinal lymph node disease [5,6]. All these reasons make particularly important the preoperative mediastinal staging of cancer in potentially surgical candidates.

Prior to the era of positron emission tomography (PET) with F-18-fluorodeoxyglucose, thoracic computed
tomography (CT) and cervical mediastinoscopy, sometimes routinely performed, were the conventional staging methods for mediastinal disease. Thus, the implementation of PET in the treatment algorithm reduces the number of surgical staging in 65% of cases due to the high negative predictive value (NPV) [7]. Negative nodes after PET scan and chest CT scan make it possible to proceed directly to the thoracotomy, without any further investigations [3,8,9].

Recently, PET combined with thoracic CT (2-deoxy-2-(18F)-fluoro-o-glucose (18F-FDG)-PET/CT) has shown a similar NPV (82—98%), improving the anatomical information in lymph node localization. False negatives (FNs) of FDG-PET/CT in mediastinal staging are expected in less than 10%, whether or not this tool is implemented following the European Society Thoracic Surgeons (ESTS) guidelines recommendations. However, a few studies have reported a higher incidence of occult mediastinal metastases after negative uptake of FDG-PET/CT scan [10,11]. In a recent meta-analysis, the post-test probability for N2 disease of 21% was found in patients with PET negative nodes >16 mm [12]. In cN1 or central tumours after CT and FDG-PET/CT, patients largely seem to accept that invasive surgical staging is needed [1,9]. The real incidence of occult lymph nodes metastases in cN0 after dedicated CT scan plus FDG-PET/CT remains unclear without studies that focus on this particular issue.

We conducted this prospective study to assess the real incidence of pN2 among the clinically staged cN0 NSCLC patients with negative mediastinal uptake of FDG. Secondly, we sought to evaluate whether the strategy of avoiding invasive staging when there is negative mediastinal uptake of FDG-PET/CT is appropriate in this group.

2. Methods

2.1. Study design

This study has been performed between January 2007 and May 2009 in a tertiary hospital. Since the beginning of the study, all the NSCLC patients who were potentially candidates for thoracic surgery had a dedicated chest CT scan and an FDG-PET/CT. Both investigations were independently assessed by two radiologists and a nuclear medicine specialist. This study was designed to mimic the routine clinical pathway in our hospital (Fig. 1), approved by the ethics committee and the institutional review Board of the hospital. The target condition of this study is the metastatic disease in mediastinal lymph nodes undetected by non-invasive methods. Following the ESTS guidelines for mediastinal surgical staging when the chest CT scan and FDG-PET/CT were considered negative for mediastinal disease, a thoracotomy with anatomical pulmonary resection plus systematic mediastinal dissection (gold standard (GS)) was carried out by a consultant thoracic surgeon as Keller previously described and as recommended by the ESTS guidelines [9,13]. Chest CT scan, FDG-PET/CT and thoracotomy were performed within a month.

2.2. Eligibility of patients

Patients included were histologically diagnosed with NSCLC, clinically staged as cN0 and met the oncological and functional criteria for resectability. The exclusion criteria were enlarged lymph node in CT scan or PET-CT (short-axis: >1) or 18FDG uptake in PET-CT at N1, N2 or N3 stations. Patients who had undergone surgical treatment previously, patients who had undergone neo-adjuvant therapy or patients who, for logistical reasons, had had a CT scan or PET in another unit were also excluded. Allergy to iodine contrast and hyperglycaemia >160 mg dl$^{-1}$ on the day PET was performed were excluded. The clinical tumour, node, metastasis (TNM) staging was performed based on the 1997 International System for Staging Lung Cancer [2].

2.3. Chest CT scan

Chest CT scans were acquired at one breath-hold with maximum inspiration during the injection of a 100 cm$^3$ bolus of intravenous iodiodate contrast agent, from the lung apices through the upper abdomen, by using a standard 64-slice multidetector CT (MDCT) protocol (Somatom Sensation 64, Siemens Medical Solutions, Germany). From each dataset different series were obtained with 4- to 5-mm-thick axial and coronal reconstructions. The criterion of CT definition for suspected metastasis of the lymph node was a short-axis diameter of 1.0 cm or larger.

2.4. 18 Fluoro-2-deoxy-d-glucose PET-CT scan

FDG-PET/CT scans were performed using a PET/CT (Biograph, Siemens) with an ECAT EXACT HR+ Bi4Ge3 O12
(BGO) PET and a helicoidal CT scanner (Somatom, Emotion). Patients had fasted for 4 h before PET acquisition and blood glucose had to be less than 160 mg dl⁻¹ before injection of 0.1 MBq kg⁻¹ of 18F-FDG. Intravenous injection using a venous line (to prevent extravasation) was followed by a period of 60 min, during which patients remained in a quiet room. No muscle relaxants were administered. Patients were allowed to breathe normally during PET and CT acquisitions. During acquisitions, patients were in the supine position with their arms raised above their head. Whole-body PET data were acquired in three-dimensional (3D) mode and for 5 min per bed position. PET images were reconstructed both with CT data for attenuation correction and without CT-based attenuation correction. Interpretation of PET data was carried out by one nuclear physician prior to surgical treatment. A region of interest (ROI) in 3D around the tumour was placed manually in transaxial, sagittal and coronal slices to include the whole volume of the lesion. The standardised uptake value (SUV) was calculated based on the measured activity, decay-corrected injected dose and patient body weight. Results were considered negative when no mediastinal localised area showed higher visual or maximum SUV uptake than the mediastinal background, and positive otherwise.

2.5. Statistical analysis

Statistical analyses were carried out with the computer programme package SPSS version 13 (SPSS Inc., Chicago, IL, USA). Qualitative variables were compared with the χ² statistical test or Fisher’s exact test where appropriate, with a significance taken at level p < 0.05. All values in the text and tables are given as mean ± SD. The raw frequency of agreement was used to compare clinical against pathological stages and to assess the agreement. Kappa’s index was used to determine the agreement.

3. Results

During the period of this study, 259 patients with potentially operable NSCLC were assessed by chest CT scan and an FDG-PET/CT. Among these, 125 patients clinically staged cN0 were enrolled prospectively in this study (Table 1). There were 105 male and 20 female patients, with a mean age of 66.5 ± 10.0 years (range: 41–83 years). Operative mortality occurred in three (2.4%) patients. Causes of death were myocardial infarction (one case), postoperative pneumonia and bronchial fistula (two cases). Major or minor complications occurred in 38 (31.2%) patients. Among the major complications that did not lead to death, pneumonia occurred in 12 (9.6%) cases, pleural empyema in two (1.6%) and pulmonary embolism in one (0.8%).

FDG-PET-CT and chest CT scan mediastinal FN was noted in 18 cases (Table 2). The prevalence of N2 FN was 14.4% and NPV was 85.6% CI [77–91]. Twelve cases showed only one pN2 station affected and six cases (4.8%) presented a multiple pN2 level. Metastatic involvement of mediastinal lymph nodes was present in 28 (4.5%) stations out of 613 station explored by thoracotomy and systematic mediastinal dissection. The most frequently station involved was R4 (six cases) and 7 (six cases) (Table 3).

The relative risk of factors that predict unsuspected N1 and N2 disease are shown in Table 4. In our study, 34 (27.2%) patients had pN1 disease. Among these, 11 (32.3%) patients were pN1 and pN2 (p < 0.0001) and seven out of 18 (38.8%) were considered skip pN2 metastases (Tables 4 and 5). Station 5 was the most frequent skip pN2 metastasis (three cases), followed by station 7 (two cases). No risk factors were detected for pN1 FN among the studied. Tumour SUV (7.69 ± 34.7) uptake was unrelated with pN1 or pN2 detection.

Unsuspected pN2 risk factors detected in this group of patients are depicted in Table 4. Female sex, adenocarcinoma and pN1 overcome independent risk factors for FN-pN2 in 18FDG-PET-CT (p < 0.05). However, no other variables were associated to occult pN2 such as clinical staging (cTNM), primitive tumours SUV, location of the tumour (lobe location: central or peripheral) or size, clinical characteristics of the patients (age, chronic obstructive pulmonary disease (COPD), diabetes, etc.) or others.
Taking pathological staging as the gold standard, the percentage of accurate diagnosis by clinical stages was at its height in stage IA (70% of 47 pIA; Kappa index: 0.72) followed by IB (47.5% of 61 pIB; Kappa index: 0.76). General agreement was 49% (Kappa index: 0.27) (Table 6).

4. Discussion

NSCLC carries a dreadful prognosis for most of the patients. In the absence of distant metastases, the mediastinal lymph node involvement is the most important prognostic factor, followed by the tumour size and its characteristics related to the surrounding structures [4,14]. Earlier-stage patients have a better chance of long-term survival and radical surgery remains the best treatment available in these cases. TNM stages from IA to IIB are widely considered to be suitable surgical candidates [3]; however, controversy continues to surround the role of the surgery for pN2 patients [4].

Various authors suggest that patients with metastatic involvement of mediastinal lymph nodes have a poor chance of survival and should not be offered surgical resection as a first-line therapy. However, to date, a few multicentric studies have been carried out to address the more appropriate algorithm for IIIA patients and particularly with unforeseen pN2. Despite the controversy surrounding them, chemotherapy and radiotherapy were employed as induction therapies, both individually and in combination, in order to improve the prognosis or the chance of resectability in tumours a priori non-surgically treated [5,6].

Thus, careful mediastinal staging is essential, and chest CT and cervical mediastinoscopy have been the traditional gold standards. FDG-PET/CT recently has become an important non-invasive tool in mediastinal staging for NSCLC, with a low rate of FNs reported initially [8,15]. After the implementation of the FDG-PET/CT in the algorithm, several authors have agreed to proceed straight to the thoracotomy, thus avoiding other mediastinal staging tools such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), endobronchial ultrasound (EBUS) of surgical staging [9]. Surgical staging procedures have been reduced by 65% with the consequent saving in terms of cost and morbidity for the patients [7].

However, a few studies have raised concerns about the underestimation of N2 disease when FDG-PET/CT and chest CT results are negative. Al-Sarraf et al. found 16% of occult mediastinal metastases out of 153 patients clinically staged cN0 or cN1 [10]. Other authors have reported an even higher FN rate [16,17].

With regard to the N1 problem, in the author’s opinion, when a N1 disease is suspected after a chest CT or FDG-PET/CT, a further mediastinal lymph node investigation must be carried out. The unsuspected mediastinal lymph node-

### Table 2

Characteristics of FDG-PET/CT false negative patients.

<table>
<thead>
<tr>
<th>n</th>
<th>Age/sex</th>
<th>cTNM/pTNM</th>
<th>Localisation</th>
<th>Histology</th>
<th>Pathological station (pN2)</th>
<th>pN1</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>53/M</td>
<td>T2N0M0/T2N2N0</td>
<td>RUL</td>
<td>Squamous carcinoma</td>
<td>R4</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>43/F</td>
<td>T2N0M0/T2N2M1</td>
<td>RUL</td>
<td>Adenocarcinoma</td>
<td>R4, R2, R8</td>
<td>11</td>
</tr>
<tr>
<td>25</td>
<td>74/F</td>
<td>T1N0M0/T1N2N0</td>
<td>LUL</td>
<td>Adenocarcinoma</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>38</td>
<td>62/M</td>
<td>T1N0M0/T2N2N0</td>
<td>LUL</td>
<td>Adenocarcinoma</td>
<td>6</td>
<td>12, 13</td>
</tr>
<tr>
<td>42</td>
<td>77/M</td>
<td>T2N0M0/T2N2N0</td>
<td>RLL</td>
<td>Adenocarcinoma</td>
<td>R4, R8, R9</td>
<td>10, 11</td>
</tr>
<tr>
<td>48</td>
<td>71/F</td>
<td>T2N0M0/T2N2N0</td>
<td>RUL</td>
<td>Adenocarcinoma</td>
<td>R4, R2</td>
<td>11</td>
</tr>
<tr>
<td>58</td>
<td>52/M</td>
<td>T1N0M0/T1N2N0</td>
<td>LUL</td>
<td>Squamous carcinoma</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>64/M</td>
<td>T2N0M0/T2N2N0</td>
<td>RUL</td>
<td>Squamous carcinoma</td>
<td>R4</td>
<td>11, 12</td>
</tr>
<tr>
<td>62</td>
<td>70/M</td>
<td>T3N0M0/T3N2N0</td>
<td>LUL</td>
<td>Adenocarcinoma</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>54/M</td>
<td>T3N0M0/T3N2N0</td>
<td>LUL</td>
<td>Squamous carcinoma</td>
<td>5, 6</td>
<td>11</td>
</tr>
<tr>
<td>91</td>
<td>41/F</td>
<td>T1N0M0/T1N2N0</td>
<td>LUL</td>
<td>Adenocarcinoma</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>49/M</td>
<td>T2N0M0/T4N2N0</td>
<td>RUL</td>
<td>Adenocarcinoma</td>
<td>R4, R2, 7</td>
<td>12</td>
</tr>
<tr>
<td>103</td>
<td>74/F</td>
<td>T1N0M0/T1N2N0</td>
<td>RLL</td>
<td>Adenocarcinoma</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>78/F</td>
<td>T2N0M0/T2N2N0</td>
<td>LLL</td>
<td>Adenocarcinoma</td>
<td>L9</td>
<td>12</td>
</tr>
<tr>
<td>112</td>
<td>72/F</td>
<td>T2N0M0/T2N2N0</td>
<td>LUL</td>
<td>Adenocarcinoma</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>74/M</td>
<td>T2N0M0/T2N2N0</td>
<td>LLL</td>
<td>Squamous carcinoma</td>
<td>L8, 7</td>
<td>10</td>
</tr>
<tr>
<td>122</td>
<td>64/F</td>
<td>T2N0M0/T2N2N0</td>
<td>ML</td>
<td>Adenocarcinoma</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>60/M</td>
<td>T1N0M0/T1N2N0</td>
<td>LID</td>
<td>Adenocarcinoma</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

RUL: right upper lobe; ML: median lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe.

### Table 3

Surgically explored mediastinal station related to tumour location.

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>Stations explored</th>
<th>pN2</th>
<th>pN1</th>
<th>pN2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>R2</td>
<td>R4</td>
<td>7</td>
</tr>
<tr>
<td>RUL</td>
<td>52</td>
<td>(41.5%)</td>
<td>11</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>ML</td>
<td>5</td>
<td>(4%)</td>
<td>25</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>RLL</td>
<td>23</td>
<td>(18.5%)</td>
<td>115</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>LUL</td>
<td>30</td>
<td>(24%)</td>
<td>144</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>LLL</td>
<td>15</td>
<td>(12%)</td>
<td>75</td>
<td>12.5</td>
<td>3</td>
</tr>
</tbody>
</table>

RUL: right upper lobe; ML: median lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe.
involvement rate after pN1 is 35% in our study. This prevalence rate precludes proceeding directly to curative surgery in cases of N1 suspicion as the ESTS guideline recommends [9]. The limitation of PET, with regard to anatomical location of lymph nodes making it difficult to distinguish between hilar and mediastinal, appears to be addressed by the PET-CT integration [16,18]. The value of FDG-PET/CT when the sparing of invasive procedures for mediastinal staging is assessed remains unclear. Anatomical information is useful if surgical or other procedures must be carried out; however, we recommend mediastinal invasive staging if any N1 lymph node is abnormal after CT or FDG-PET/CT.

Unlike Ketchedjian et al. [19], we do not recommend further mediastinal investigation in central tumours unless resectability is compromised. In our study, we did not find significant differences between central and peripheral tumours in the pN1 or pN2 disease. The prevalence of pN1 and pN2 is similar in central and peripheral tumours, irrespective of tumour size or histology, and we only recommend a surgical staging if the tumours' SUV may disguise an affected interlobar or mediastinal lymph node. In addition, small mediastinal lymph nodes may result negative in FD-GPET/CT being under the threshold of the investigation capacity precisely due to their size, <1 cm.

Irrespective of sex differences in the relative risk of lung cancer in smokers, lung cancer appears to be a biologically different disease in women. In Spain, the predominant histology is adenocarcinoma and the prevalence of NSCLC is similarly growing annually in other countries [20]. For women with lung cancer, curative resection appears to offer a better survival rate compared to men [21]. However, in our practice, the percentage of women with mediastinal lymph node involvement at diagnosis, even in early stages, was higher than percentages that have been reported for men [22]. Only 20–25% of lung carcinomas in Spanish women are tobacco related [20].

Conversely, FDG-PET/CT and chest CT scan correctly staged nearly 50% of the patients [16]. Lopez-Encuentra et al. considered a similar rate of accuracy of clinical staging compared with pathological staging in the pre-FDG-PET/CT
era, being much more accurate in the early stages of IA-IB than in advanced stages. In general, down-staging is more frequent than up-staging; however, the crucial issue is the unexpected pN2 in previously cN0- or cN1-staged patients [23].

Despite the poor results of FDG-PET/CT for mediastinal staging, there are many reasons for requesting this investigation preoperatively. In the first place, FDG-PET/CT provides good staging to rule out metastatic disease. The rate of detection of unexpected M1 disease by PET scanning has been reported as 1—8% in patients with clinical stage I disease and 7—18% in patients with clinical stage II disease [18,24]. This leads to a better selection of patients and spares them a useless thoracotomy. In our opinion, all patients with clinical IA—IIIB lung cancer being treated with curative intent should undergo PET scanning for mediastinal and extrathoracic staging. Nevertheless, careful individual assessment, taking into consideration several variables (e.g., cTNM, histology, tumours size, N1 disease) should be carried out when there is negative mediastinal uptake of FDG-PET. Adenocarcinoma [10,16], cN1 [9,18] and currently smoking patients [25] have been identified as being at risk factor of mediastinal involvement in the early stages of NSCLC.

Secondly, FDG-PET is the best non-invasive tool for mediastinal staging, despite the pitfalls detected in the latest studies. In patients with an abnormal result on FDG-PET/CT scans, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumour. Thirdly, FDG-PET/CT may provide accurate anatomical information for SUV deposit location, making it easier to select the more appropriate invasive staging method.

In conclusion, in our environment we consider very carefully whether to proceed directly to the thoracotomy in all patients with negative mediastinal uptake of FDG-PET-CT. Considering the accurate preoperative staging of NSCLC patients as an applicable quality standard in practice, we believe that the FN rate after this investigation makes it unreliable for mediastinal staging. Further mediastinal investigations may be necessary in these patients, and invasive procedures should be performed, in particular, in female patients and in the event of adenocarcinoma histology. However, the authors are entirely aware of the limitation of this study and the unanswered questions regarding the prognosis, most appropriate multimodality treatment or how the algorithm will change in this ‘new subgroup’ of minimal pN2 disease patients in the future. Even more, the role of surgical staging, EBUS-FNA and EUS-FNA must be determined in a multidisciplinary meeting, assessing the pitfalls, weaknesses and accessibility of the different methods [18]. In T1 < 1 cm, cN0 patients’, invasive staging might be avoided; however, further studies are necessary to draw solid conclusions even in this atypical group. Conversely, we only recommend surgical staging in poor-risk surgical candidates, in patients in whom there is a reasonable risk of mediastinal invasion, in patients who have been rescued surgically after neo-adjuvant treatment or when less invasive methods are not available or their results are not validated.

References