The maximum standardized uptake value of fluorodeoxyglucose positron emission tomography of the primary tumour is a good predictor of pathological nodal involvement in clinical N0 non-small-cell lung cancer

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Abstract

OBJECTIVES: Fluorodeoxyglucose positron emission tomography (FDG-PET) plays an important role in the evaluation of resectable non-small-cell lung cancer (NSCLC). However, this modality cannot be used to detect histological nodal involvement, which can result in stage-migration for resectable lung cancer. In this study, we tried to evaluate the possibility of predicting histological nodal involvement in patients with NSCLC using the maximum standardized uptake value (SUVmax) of FDG-PET of the primary tumour instead of that of the lymph nodes.

METHODS: Between February 2008 and September 2011, 898 patients underwent lung cancer surgery at our institute. Among them, we retrospectively analysed 265 patients with clinical N0 NSCLC, who underwent preoperative FDG-PET. The relationships between clinicopathological features, including the findings of FDG-PET and pathological nodal involvement, were investigated. The factors investigated were age, gender, preoperative carcinoembryonic antigen titre, maximum tumour dimension, consolidation/tumour dimension ratio (C/T ratio), SUVmax in the primary tumour and smoking history.

RESULTS: Of the 265 clinical N0 NSCLC patients, 214 (80.8%) had pathological N0 status and 27 (10.2%) and 24 (9.0%) had pathological N1 and N2 disease. In a multivariate analysis, the C/T ratio (P = 0.046) and SUVmax of the primary tumour (P = 0.016) were significant predictors of pathological nodal involvement. With regard to pathological N1–2 disease, the sensitivity, specificity, accuracy and positive and negative predictive values of mediastinal node involvement in patients with NSCLC with an SUVmax for FDG-PET of 10 or more were 49.0, 83.2, 76.6, 41.0 and 87.3%, respectively. Of the 61 patients with NSCLC with an SUVmax for FDG-PET of 10 or more, 25 (41.0%) had pathological N1–2 disease, while only 26 (12.7%) of the remaining 204 patients with an SUVmax for FDG-PET of <10 had nodal disease (P < 0.0001).

CONCLUSIONS: Postoperative nodal status was significantly predicted by the SUVmax of FDG-PET of the primary tumour instead of the lymph nodes themselves. The patients with NSCLC in particular who show strong uptake values of SUVmax in the primary tumour could have occult nodal metastases, and may be indicated for further preoperative modality for an accurate staging.

Keywords: Fluorodeoxyglucose positron emission tomography • Non-small-cell lung cancer • Pathological nodal involvement

INTRODUCTION

Fluorodeoxyglucose positron emission tomography (FDG-PET) plays an important role in evaluating resectable non-small-cell lung cancer (NSCLC). Several authors have reported evidence that supports the clinical value of FDG-PET for lymph node staging in NSCLC [1–4]. However, this modality cannot be used to detect histological nodal involvement, which results in stage migration for resectable lung cancer. In fact, false PET results are not uncommon. In this study, we tried to evaluate the possibility of predicting histological nodal involvement in patients with NSCLC by using the maximum standardized uptake value (SUVmax) of FDG-PET of the primary tumour instead of that of the lymph nodes themselves.
retrospectively analysed 265 patients with clinical N0 (cN0) NSCLC who underwent preoperative computed tomography (CT) scan and FDG-PET, and who received lobectomy or segmentectomy with the systematic evaluation of both hilar and mediastinal lymph nodes. In all patients, the time interval between surgery to CT scan and FDG-PET was <1 month. The staging system for lung cancer was on the basis of the seventh TNM classification of the International Union against Cancer (UICC). Histological findings were determined according to the World Health Organization (WHO) classification. Nodal status was defined preoperatively on the basis of the findings of thoracic thin-section CT and PET scan. The criterion for cN0 was a short-axis of the nodes of <10 mm on the basis of CT and an SUV of <2.5 for nodes on FDG-PET. The cN0 patients did not undergo any type of preoperative invasive mediastinal staging, such as endobronchial ultrasound transbronchial nodal aspiration cytology (EBUS-TBNA) or mediastinoscopy.

In this study, we excluded patients with NSCLC who showed both ground-glass opacity (GGO) with a consolidation/tumour dimension (C/T) ratio of 50% or less, a maximum tumour dimension of 2 cm or less, and those with tumour that could be removed by limited resection. Such small-sized lung cancer on chest CT scan has been reported to show no invasive carcinoma and no lymph node involvement [5, 6]. This is why we enrolled such lesions in randomized controlled trials (Japan Clinical Oncology Group 0804 study) on limited resection for small-sized lung carcinoma. In the JCOG 0804 study, systematic lymph node dissection was not provided if there was no regional lymph nodes metastasis.

**Preoperative evaluation**

The clinical records of each patient were reviewed to determine the following values: age, gender, histological findings, C/T ratio in the primary tumour on preoperative CT scan, preoperative carcinoembryonic antigen (CEA) titre, SUVmax in the primary tumour, clinical stage and smoking status. For the smoking status, we used categories of pack-years. All CT scans were reviewed. A contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. In addition, the major tumour was evaluated preoperatively by thin-section helical CT scan with a field of view of 15–20 cm. The lung was photographed with a window level of 500 to 700 H and a window width of 1000–2000 H as a ‘lung window,’ and with a window level of 30–60 H and a window width of 350–600 H as a ‘mediastinal window’. The consolidation component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as an area of a slight, homogenous increase in density that did not obscure the underlying vascular markings. Minimally-invasive lung cancer was tentatively defined as a tumour in which the ratio of the maximum diameter of consolidation to the maximum tumour diameter (C/T ratio) was <0.5, which would indicate a tumour with a wide GGO area. Thus, we considered the C/T ratio (≥0.5, <0.5) in our investigation.

**Statistical analysis**

Statistical analyses were performed using SPSS 10.0 software (SPSS, Inc., Chicago, IL, USA). For the comparisons of pathological nodal involvement and the clinical factors, categorical and continuous variables were analysed by the chi-square test and unpaired t-test, respectively. Statistical analysis was performed with uni- and multivariate analyses using logistic regression analysis. The factors investigated were age, gender, histological findings (adenocarcinoma vs others), maximum tumour dimension, C/T ratio (≥0.5 vs <0.5), preoperative CEA titre, maximum SUVmax in the primary tumour and smoking status (pack-years, ≥20 vs <20). The factors that were potentially associated with false results in the univariate analysis were also evaluated by a multivariate analysis. P-values of <0.05 were considered to be significant.

In addition to the above analyses, the diagnostic efficacy of FDG-PET according to four cut-off values of SUVmax in the primary tumour (≥3, ≥5, ≥7 and ≥10) was calculated with respect to sensitivity, specificity, accuracy and positive and negative predictive value (PPV and NPV) for the patients with pathological N1–2 disease. We added a supplementary explanation that these cut-off values, especially 5, 7 and 10, of SUVmax in the primary tumour were found as prognostic factors or relapse-factors of NSCLC here and there in several previous reports from Cerfolio et al. [7] and Downey et al. [8]. Therefore, we determined these cut-off values including 5, 7 and 10 in this study.

**RESULTS**

One hundred and fifty-nine (60.0%) of the patients were men and 106 (40.0%) were women (Table 1). The median age was 68 years, with a range of 35–89 years. One hundred and fifty-two patients had a smoking history. Among them, 133 patients were heavy smokers of >20 pack-years. Histological findings were as follows; adenocarcinoma in 202 (75.5%), squamous cell carcinoma in 51 (19.2%), large cell neuroendocrine carcinoma in seven (2.6%), adenosquamous carcinoma in three (1.1%) and other in two (0.8%). Clinical staging was IA (T1aN0M0, T1bN0M0) in 191 (72.1%), IB (T2aN0M0) in 50 (18.9%), IIA (T2bN0M0) in nine (3.4%), IIB (T3N0M0) in 13 (4.9%) and IIIA (T4N0M0) in two (0.7%). In clinical IIB, the main tumour invaded the parietal pleura, chest wall and superior vena cava. Similarly, in clinical IIIA, the main tumour directly invaded the trachea. Among all of the clinical N0 NSCLC patients, 214 (80.8%) had pathological N0 status and 51 (20.1%) had pathological nodal involvement. The median SUVmax in the primary tumour was 3.8, with a range of 0.6–44.1. The median maximum tumour dimension and preoperative CEA titre were 23.0 mm (range 5–96 mm) and 2.9 (range 0.4–80.5), respectively.

The correlation between clinicopathological features including the findings by FDG-PET and pathological nodal involvement were investigated (Table 2). No significant correlations were seen between clinicopathological features and pathological nodal involvement, except for histological findings, maximum tumour dimension, C/T ratio and SUVmax in the primary tumour. Among the 201 patients with adenocarcinoma, only 32 (15.9%) had pathological nodal involvement, while 19 (29.7%) of the remaining 64 with non-adenocarcinoma had pathological nodal involvement (P = 0.019). Among the 45 patients with a C/T ratio <0.5, only one (2.2%) had pathological nodal involvement, while 50 (22.7%) of the remaining 220 with a C/T ratio ≥0.5 had pathological nodal involvement (P < 0.001). There were significant differences in maximum tumour dimension and SUVmax in the primary tumour between pathological N0 and N1–2 (P = 0.012
The univariate analysis revealed four factors that may be associated with pathological nodal involvement in clinical N0 NSCLC. Histological findings, maximum tumour dimension and C/T ratio (>0.5) on the preoperative CT scan and SUVmax of the primary tumour were all significant predictors (P = 0.018, 0.014, 0.012 and <0.001) (Table 3). Preoperative CEA titre did not predict pathological nodal disease in this study (P = 0.081).

The factors that were potentially associated with false results in a univariate analysis, histological findings, maximum tumour dimension and C/T ratio (>0.5) on preoperative CT scan and SUVmax of the primary tumour, were also evaluated by a multivariate analysis. The multivariate analysis showed that both the C/T ratio (>0.5) on preoperative CT scan and SUVmax of the primary tumour were independent predictive factors for pathological nodal involvement (P = 0.046 and 0.016) (Table 4).

The sensitivity, specificity, accuracy, PPV and NPV of pathological N1–2 disease are shown in Table 5. Among patients with NSCLC who had an SUVmax for FDG-PET of 10 or more, the sensitivity, specificity, accuracy, PPV and NPV of mediastinal node involvement were 49.0, 83.2, 76.6, 41.0 and 87.3%, respectively. In patients with an SUVmax in the primary tumour of 10 or more, the PPV was higher than those in the three other populations (>3, ≥5 and ≥7). Among the 61 patients with NSCLC who had an SUVmax for FDG-PET of 10 or more, 25 (41.0%) had pathological N1–2 disease, while only 26 (12.7%) of the remaining 204 patients with an SUVmax for FDG-PET of <10 had nodal disease (P < 0.0001).

**DISCUSSION**

Pathological nodal involvement is a very important prognostic factor in patients with potentially resectable NSCLC. Several authors have reported that induction chemotherapy and chemoradiotherapy followed by surgery could provide pathological down-staging and better long-term survival in patients with N2 disease [9–11]. Therefore, the accurate preoperative evaluation of mediastinal nodes is important for planning NSCLC treatment [11].
In Japan, the conventional clinical staging regimen for NSCLC does not include FDG-PET. CT scan is routinely used for preoperative diagnosis and locoregional staging for lung cancer. The clinical criterion of mediastinal lymph node involvement is a short dimension of 10 mm or more on CT scan. A diagnosis of hilar lymph node involvement requires the presence of swollen soft tissue on CT scan. Thus, the clinical diagnosis of lymph node is on the basis of lymph node enlargement. However, obstructive pneumonia, atelectasis, infection by nontuberculous mycobacteria and interstitial pneumonia can also cause swollen lymph nodes [1]. On the other hand, a metastatic node can appear to have a normal size. These conditions could lead to false-positive and false-negative results, which could result in stage-migration of resectable lung cancer [2–4, 12].

FDG-PET is now widely used for the clinical staging of NSCLC [7, 11, 13–17]. The first approved indications for the staging of NSCLC by the use of FDG-PET were reported in the 1990s [18]. Since 2001, the combination of PET and CT) has rapidly eclipsed stand-alone PET [19]. Furthermore, it has been reported that the diagnostic value of PET-CT for the preoperative staging of NSCLC was superior to that of CT alone [1, 7, 15–20]. Previous randomized trials have proven that PET-CT is significantly more accurate and more sensitive for the staging of NSCLC than the conventional staging regimen [21]. Additionally, the addition of PET-CT examination has been shown to reduce the frequency of futile thoracotomies. However, PET-CT examination was not associated with improved overall survival in patients with NSCLC [21]. Previous reports have shown that potential lymph node involvement may not be detected by FDG-PET. In our study, 51 (19.2%) of 265 patients with clinical N0 NSCLC had pathological lymph node involvement, which was comparable to the findings in previous reports (5.7–25%) [2–4, 7]. This population, especially those with N2 disease, could receive futile thoracotomies and show reduced overall survival in each clinical stage.

Several authors have reported that CEA titre, maximum tumour size, C/T ratio and tumour disappearance rate (TDR) on HRCT scan were each good clinical predictors of pathological nodal involvement [22, 23]. In addition, these factors could also be prognostic determinants for NSCLC [24].

In this study, the C/T ratio on preoperative CT scan significantly predicted pathological nodal involvement. However, preoperative CEA titre was not a significant predictor.

In this study, in a univariate analysis, histological findings predicted pathological nodal involvement. In particular, squamous cell carcinoma was seen in many cases of pathological N1–2 disease, compared with adenocarcinoma. Eighteen (35.3%) of 51 patients with squamous cell carcinoma had pathological N1–2 disease, while only 32 (15.8%) of 202 patients with adenocarcinoma had pathological N1–2 disease. Thirty nine (76.4%) of 51 patients with squamous cell carcinoma were heavy smokers (>40 pack-years). Their lungs were subjected to emphysematous change and this was believed to be the basis of poorly differentiated carcinoma. All of the cases of squamous cell carcinoma were invasive carcinoma with a C/T ratio of ≥0.5 on preoperative CT scan. Additionally, the median SUVmax of primary squamous cell carcinoma was 11.0, with a range of 2–25.5. Thus, clinical N0 squamous cell carcinoma had a high potential for pathological nodal disease in this study. Further studies on squamous cell carcinoma will be needed in the future.

The tumour size was limited to that which tended to be associated with lymph node involvement. This was the reason why we excluded small-sized lung carcinoma that showed pure GGO with both a C/T ratio of 50% or less and a maximum tumour dimension of 2 cm or less on chest CT scan. On the other hand, including patients with tumour as small as 5 mm might also impact on this analysis, therefore these very small tumours were at the detection limit of this method.

Additionally, the clinical strategy for pathological N2 disease is controversial. As noted above, pathological N2 patients with clinical N0 NSCLC might be subjected to futile thoracotomies. On the other hand, the presence of pathological N1 disease could lead to unavoidable changes in. For example, it may become necessary to convert usual lobectomy to bilobectomy, sleeve lobectomy or double sleeve lobectomy. Therefore, an accurate staging for resectable NSCLC is very valuable for not only patients but also surgeons. In this study, in all of the cases of pathological N1–2 disease among clinical N0 NSCLC patients, the main tumour showed a strong uptake value of SUVmax, compared with pathological N0 disease (Table 5). The PPV of

### Table 4: Multivariate analysis for factors that predicted pathological nodal involvement

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological findings, non-adenocarcinoma</td>
<td>1.001</td>
<td>1.458–2.186</td>
<td>0.99</td>
</tr>
<tr>
<td>Tumour sizea (mm)</td>
<td>1.005</td>
<td>0.980–1.030</td>
<td>0.72</td>
</tr>
<tr>
<td>C/T ratio, ≥0.5</td>
<td>7.950</td>
<td>1.034–61.128</td>
<td>0.046</td>
</tr>
<tr>
<td>SUVmax in the primary tumour</td>
<td>1.085</td>
<td>1.015–1.159</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*P-value in logistic regression analysis.

aContinuous variable.

CI: confidence interval; SUVmax: maximum standardized uptake value.

### Table 5: The correlation between SUVmax in the primary tumour and pathological N1–2 disease in overall patients

<table>
<thead>
<tr>
<th>SUVmax</th>
<th>cN0</th>
<th>cN0–pN1–2</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>155</td>
<td>46</td>
<td>90.1</td>
<td>49.1</td>
<td>57.0</td>
<td>29.7</td>
<td>95.5</td>
</tr>
<tr>
<td>≥5</td>
<td>114</td>
<td>36</td>
<td>70.6</td>
<td>64.9</td>
<td>64.9</td>
<td>31.6</td>
<td>90.1</td>
</tr>
<tr>
<td>≥7</td>
<td>89</td>
<td>31</td>
<td>60.9</td>
<td>69.7</td>
<td>70.1</td>
<td>34.8</td>
<td>88.6</td>
</tr>
<tr>
<td>≥10</td>
<td>61</td>
<td>25</td>
<td>49.0</td>
<td>83.2</td>
<td>76.6</td>
<td>41.0</td>
<td>87.3</td>
</tr>
</tbody>
</table>

SUVmax: maximum standardized uptake value; PPV: positive predictive value; NPV: negative predictive value.
pathological N1–2 disease with clinical N0 NSCLC that showed an SUVmax in the primary tumour of 10 or more was 41.0%. On the other hand, the PPV of pathological N1–2 disease that showed an SUVmax in the primary tumour of ≥3, ≥5 or ≥7 were 29.7, 31.6 and 34.8%, respectively. In the case of an SUVmax in the primary tumour of 10 or more, over 40% of clinical N0 patients could have occult nodal metastasis. Meanwhile, it was previously reported that the patients without an enlarged lymph node and a PET-negative mediastinum may proceed directly to surgery [16]. Moreover, it was reported that radical lymphadenectomy could be omitted in patients with stage I NSCLC tumour <1 cm or SUVmax 2.0 [25]. However, each of these studies was retrospective and did not consider SUVmax of the primary tumour. On the basis of the results of our study, further preoperative modality such as EBUS-TBNA or mediastinoscopy could be considered for the accurate clinical staging of patients with NSCLC, and particularly in those who show a strong uptake value of SUVmax.

In conclusion, the pathological nodal status in clinical N0 NSCLC was significantly predicted by SUVmax for FDG-PET of the primary tumour instead of the lymph nodes themselves. In particular, patients with NSCLC who show a strong uptake value of SUVmax could have occult pathological nodal metastases, and may be indicated for a further preoperative modality for accurate clinical staging. For these reasons, FDG-PET is a feasible modality for the clinical staging of NSCLC.

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