

# Predicted extracapsular invasion of hilar lymph node metastasis by fusion positron emission tomography/computed tomography in patients with lung cancer

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**Abstract.** Intraoperative detection of hilar lymph node metastasis, particularly with extracapsular invasion, may affect the surgical procedure in patients with lung cancer, as the preoperative estimation of hilar lymph node metastasis is unsatisfactory. The aim of this study was to investigate whether fusion positron emission tomography/computed tomography (PET/CT) is able to predict extracapsular invasion of hilar lymph node metastasis. Between April, 2007 and April, 2013, 509 patients with primary lung cancer underwent surgical resection at our institution, among whom 28 patients exhibiting hilar lymph node metastasis (at stations 10 and 11) were enrolled in this study. A maximum lymph node standardized uptake value of >2.5 in PET scans was interpreted as positive. A total of 17 patients had positive preoperative PET/CT findings in their hilar lymph nodes, while the remaining 11 had negative findings. With regard to extracapsular nodal invasion, the PET/CT findings ( $P=0.0005$ ) and the histological findings (squamous cell carcinoma,  $P=0.05$ ) were found to be significant predictors in the univariate analysis. In the multivariate analysis, the PET/CT findings were the only independent predictor ( $P=0.0004$ ). The requirement for extensive pulmonary resection (sleeve lobectomy, bilobectomy or pneumonectomy) was significantly more frequent in the patient group with positive compared with the group with negative

PET/CT findings (76 vs. 9%, respectively,  $P=0.01$ ). Therefore, the PET/CT findings in the hilar lymph nodes were useful for the prediction of extracapsular invasion and, consequently, for the estimation of possible extensive pulmonary resection.

## Introduction

While accurate preoperative staging of mediastinal and hilar lymph nodes is essential in determining the treatment strategy for patients with non-small-cell lung cancer (NSCLC) (1,2), the accuracy of a preoperative diagnosis for N1 disease is problematic. Clinically diagnosed N1 (cN1) patients have been reported to comprise 19-30% pathologically N0 (pN0), 44-47% pN1 and 17-60% pN2-pN3 cases (3-5). Partly due to the high rate of occult pN2 patients, the cN1 cohort was associated with an unsatisfactory surgical prognosis. Furthermore, unexpected extracapsular invasion of the metastatic hilar lymph nodes often results in extensive surgical resection more often than standard lobectomy, such as pneumonectomy, bilobectomy, or lobectomy with bronchoplasty and angioplasty. Diagnostic clues for the preoperative prediction of extranodal invasion and subsequent extensive surgical resection may be useful in determining the treatment strategy in surgical candidates, particularly those with certain surgical risks or with poor cardiopulmonary reserve. Positron emission tomography (PET) with 2-deoxy-2-(<sup>18</sup>F)fluoro-D-glucose as a tracer (<sup>18</sup>F-FDG-PET) was recently reported to be more effective in detecting tumor involvement of mediastinal and hilar lymph nodes compared with computed tomography (CT) (6-8). However, those reports did not refer to the correlation between the PET findings and the type of lymph node metastasis, i.e., intracapsular or extracapsular, and the required surgical procedure, which was standard lobectomy or an extended resection. The aim of this study was to investigate the ability of fusion PET/CT to predict extracapsular invasion of hilar lymph node metastasis.

## Patients and methods

**Patients.** Between April, 2007 and April 2013, 509 consecutive patients with primary lung cancer underwent surgical

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**Abbreviations:** NSCLC, non-small-cell lung cancer; FDG-PET, 2-deoxy-2-(<sup>18</sup>F)fluoro-D-glucose-positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; SUV, standardized uptake value; IASLC, International Association for the Study of Lung Cancer; OS, overall survival

**Key words:** extracapsular invasion, hilar lymph node, 2-deoxy-2-(<sup>18</sup>F)fluoro-D-glucose-positron emission tomography, lung cancer, surgery

Table I. Characteristics of the patients with hilar lymph node metastasis (n=28).

| Characteristics                | Number     |
|--------------------------------|------------|
| Age, years                     |            |
| Mean (range)                   | 68 (44-81) |
| Gender                         |            |
| Male                           | 20         |
| Female                         | 8          |
| Smoking habits                 |            |
| Non-smoker                     | 4          |
| Current/former smoker          | 24         |
| Histology                      |            |
| Squamous cell carcinoma        | 11         |
| Adenocarcinoma                 | 12         |
| Others <sup>a</sup>            | 5          |
| Tumor location                 |            |
| Right                          | 13         |
| Left                           | 15         |
| Pathological T stage           |            |
| T1                             | 11         |
| T2                             | 14         |
| T3                             | 3          |
| Surgical procedures            |            |
| Lobectomy                      | 12         |
| Lobectomy with bronchoplasty   | 1          |
| Lobectomy with vascular plasty | 1          |
| Bilobectomy                    | 5          |
| Pneumonectomy                  | 9          |

<sup>a</sup>Small-cell, adenosquamous, large-cell neuroendocrine and pleomorphic carcinomas.

resection at our institution. Among these patients, 28 with pathologically proven hilar lymph node metastasis (at stations 10 and 11), without mediastinal lymph node metastasis and without having received induction therapy, were retrospectively reviewed in this study. All the patients underwent chest and abdominal CT, brain magnetic resonance imaging (MRI) and PET/CT for clinical staging, and were pathologically diagnosed with hilar lymph node metastasis postoperatively. The following parameters were assessed from the medical records: patient gender, age, smoking habits, histological type, tumor location, tumor stage, surgical procedure and prognosis.

This study was reviewed and approved by the Institutional Review Board of Toho University (Tokyo, Japan).

**Treatments and evaluation.** The routine preoperative workup included pulmonary function tests, CT scans of the chest and abdomen, PET/CT, flexible bronchoscopy and brain MRI. To evaluate lymph node metastasis, enhanced chest CT and PET/CT were performed. A team of experienced radiologists reviewed the integrated PET/CT images independently. A lymph node maximum standardized uptake value ( $SUV_{max}$ )

Table II. Characteristics of the metastatic hilar lymph nodes.

| Variables  | Number |
|--|--------|
| Pathological N1 station  |        |
| 10L  | 5      |
| 10R  | 0      |
| 11L  | 10     |
| 11R  | 13     |
| Extracapsular nodal invasion                                     |        |
| Absent   | 14     |
| Present  | 14     |
| Preoperative hilar lymph node PET/CT findings                    |        |
| Positive   | 17     |
| Negative   | 11     |
| PET/CT, fusion positron emission tomography/computed tomography. |        |

of >2.5 was interpreted as positive (9,10). All integrated PET/CT imaging was performed within 4 weeks of surgery. The surgical procedures included standard lobectomy or extensive pulmonary resection, such as bilobectomy, sleeve resection, or pneumonectomy. Systematic lymph node dissection was mandatory for all the patients in this study. Mediastinal lymph node dissection consisted of en bloc resection of all nodes at stations 2R, 4R, 7, 8, 9, 10R and 11R for right-sided tumors, and at stations 4L, 5, 6, 7, 8, 9, 10L and 11L for left-sided tumors. The designation of dissected nodal status was based on the International Association for the Study of Lung Cancer (IASLC) lymph node map (11) and the seventh edition of the TNM staging system (12). The histological classification of NSCLC was based on the WHO classification. The dissected lymph nodes were histologically examined using hematoxylin and eosin staining.

**Statistical analysis.** Univariate data analysis was conducted using Pearson's Chi-squared test and multivariate analysis was conducted using logistic regression (backward stepwise). Differences were considered to be statistically significant when  $P < 0.05$ . Overall survival (OS) was defined as the time from the date of surgery until the date of the last follow-up or death. Disease-specific survival was defined as the time from the date of surgery until the date of the last follow-up. Patients who remained alive or who had succumbed to a cause other than lung cancer, were censored for disease-specific survival analysis. Survival curves were prepared using the Kaplan-Meier method and were compared univariately using the log-rank test. All the statistical analyses were performed using JMP 11.0 software (SAS Institute Inc., Cary, NC, USA).

## Results

**Patient characteristics.** The 28 patients with hilar lymph node metastasis were predominantly male (71%) and smokers (86%). The most common tumor types were squamous cell carcinoma in 11 (39%) and adenocarcinoma in

Table III. Univariate analysis for factors associated with PET/CT findings in hilar lymph node metastasis.

| Variables                                  | Hilar lymph node PET/CT findings |          | P-value |
|--|----------------------------------|----------|---------|
|  | Positive                         | Negative |         |
| Mean age, years                            | 69                               | 66.5     | 0.47    |
| Gender                                     |                                  |          | 0.11    |
| Male                                       | 14                               | 6        |         |
| Female                                     | 3                                | 5        |         |
| Smoking habits                             |                                  |          | 0.12    |
| Non-smoker                                 | 1                                | 3        |         |
| Current/former smoker                      | 16                               | 8        |         |
| Tumor location                             |                                  |          | 0.93    |
| Right                                      | 9                                | 6        |         |
| Left                                       | 8                                | 5        |         |
| Pathological T stage                       |                                  |          | 0.59    |
| T1   | 6                                | 5        |         |
| T2-3                                       | 11                               | 6        |         |
| Pathological N1 station                    |                                  |          | 0.29    |
| No. 10                                     | 2                                | 3        |         |
| No. 11                                     | 15                               | 8        |         |
| Histology                                  |                                  |          | 0.29    |
| Non-SCC                                    | 9                                | 8        |         |
| SCC  | 8                                | 3        |         |
| Extracapsular invasion                     |                                  |          | 0.001   |
| Present                                    | 13                               | 1        |         |
| Absent                                     | 4                                | 10       |         |
| Surgical procedures                        |                                  |          | 0.01    |
| Lobectomy                                  | 4                                | 8        |         |
| Extensive pulmonary resection <sup>a</sup> | 13                               | 3        |         |

<sup>a</sup>Lobectomy with bronchoplasty or vascular plasty, bilobectomy, or pneumonectomy. PET/CT, fusion positron emission tomography/computed tomography; SCC, squamous cell carcinoma.

12 patients (43%). The surgical procedures performed were standard lobectomy in 12 (43%) and extensive pulmonary resection in 16 patients (57%). Of the patients receiving extensive pulmonary resection, 2 underwent plasty of the bronchus or pulmonary artery (Table I).

**Characteristics of hilar lymph nodes.** The metastatic N1 station was station 10 in 5 (18%) and station 11 in 23 patients (82%). Extracapsular invasion of the hilar lymph node was detected in 14 patients (50%) (Table II).

**PET/CT visual assessment analysis.** A total of 17 patients (60%) had positive hilar lymph node findings on PET/CT and the remaining 11 had negative findings (Table III). The rate of extracapsular invasion was significantly higher in the patient group with positive PET/CT findings (13/17, 76%) compared

Table IV. Univariate analysis for factors predictive of extracapsular nodal invasion.

| Variables                        | Extracapsular nodal invasion |           |                      |
|----------------------------------|------------------------------|-----------|----------------------|
|                                  | HR                           | 95% CI    | P-value <sup>a</sup> |
| Age, years                       |                              |           |                      |
| <70                              | 1                            |           |                      |
| ≥70                              | 0.42                         | 0.09-1.91 | 0.25                 |
| Gender                           |                              |           |                      |
| Female                           | 1                            |           |                      |
| Male                             | 2.03                         | 0.38-10.9 | 0.4                  |
| Smoking habits                   |                              |           |                      |
| Non-smoker                       | 1                            |           |                      |
| Current/former smoker            | 3.5                          | 0.32-39.1 | 0.28                 |
| Tumor location                   |                              |           |                      |
| Right                            | 1                            |           |                      |
| Left                             | 1.33                         | 0.30-5.91 | 0.14                 |
| Hilar lymph node PET/CT findings |                              |           |                      |
| Negative                         | 1                            |           |                      |
| Positive                         | 32.5                         | 3.12-337  | 0.0005               |
| Pathological T stage             |                              |           |                      |
| T1                               | 1                            |           |                      |
| T2-3                             | 1.35                         | 0.29-6.18 | 0.7                  |
| Pathological N1 station          |                              |           |                      |
| No. 10                           | 1                            |           |                      |
| No. 11                           | 1.64                         | 0.23-11.7 | 0.62                 |
| Histology                        |                              |           |                      |
| Non-SCC                          | 1                            |           |                      |
| SCC                              | 4.88                         | 0.93-25.6 | 0.05                 |

<sup>a</sup>P-values derived from logistic regression analysis. HR, hazard ratio; CI, confidence interval; PET/CT, fusion positron emission tomography/computed tomography; SCC, squamous cell carcinoma.

with that in the group with negative PET/CT findings (1/11, 9%) (P=0.0005). Extensive pulmonary resection was performed more frequently in the patient group with positive PET/CT findings (13/17, 76%) compared with the group with negative PET/CT findings (3/11, 27%) (P=0.01).

**Analysis of extracapsular invasion of hilar lymph nodes.** The univariate analysis identified two factors as significant predictors of extracapsular nodal invasion, namely the PET/CT and histological findings (P=0.0005 and 0.05, respectively) (Table IV). In the multivariate analysis, the PET/CT findings were the only independent predictor (P=0.0004) (Table V).

**Survival pattern analysis.** A total of 3 patients (11%) succumbed during the postoperative period (pneumonia, 2 patients; and acute exacerbation of interstitial pneumonia, 1 patient). Follow-up was performed for all the patients. The median follow-up time was 39.5 months (range, 0-80 months). The 5-year OS rate was 82 vs. 38% in the patient groups with positive vs. negative

Table V. Multivariate analysis for factors predictive of extracapsular nodal invasion.

| Variables       | HR  | 95% CI   | P-value <sup>a</sup> |
|-----------------|-----|----------|----------------------|
| PET/CT findings |     |          |                      |
| Negative        | 1   |          |                      |
| Positive        | 39  | 4.2-1217 | 0.0004               |
| Histology       |     |          |                      |
| Non-SCC         | 1   |          |                      |
| SCC             | 6.5 | 0.75-142 | 0.09                 |

<sup>a</sup>P-value derived from logistic regression analysis. HR, hazard ratio; CI, confidence interval; PET/CT, fusion positron emission tomography/computed tomography; SCC, squamous cell carcinoma.

PET/CT findings, respectively (Fig. 1). The difference between the two groups was not statistically significant ( $P=0.123$ ). The 5-year disease-specific survival rate was 100 vs. 50% in the patient groups with positive vs. negative PET/CT findings, respectively (Fig. 2). The difference between the two groups was not statistically significant ( $P=0.055$ ), although the group with positive PET/CT findings tended to have a better prognosis compared with the group with negative findings.

## Discussion

The presence of pN1 disease may unavoidably lead to changes in the surgical approach. A recent study reported that extensive pulmonary resection was required in 41% of patients with cN1 disease. Therefore, it is crucial to predict the potential extracapsular invasion of hilar lymph node metastasis preoperatively. The main findings of the present study were as follows: i) PET/CT was a significant predictor of extracapsular invasion in cases with hilar lymph node metastasis and ii) extensive pulmonary resection was required in 76% of the patients with positive hilar lymph node metastasis on PET/CT.

PET/CT is most beneficial for identifying the presence of metastatic disease. PET/CT relies on the hypermetabolic nature of cancer cells for preferential uptake of the radiolabeled glucose analogue  $^{18}\text{F}$ -FDG. The fusion of PET and CT simultaneously provides anatomical and functional information, thus improving localization accuracy. Preferential uptake of  $^{18}\text{F}$ -FDG in the lymph nodes may be quantified by the SUV. In the mediastinum, high SUV cut-off values identifying malignant lymph nodes increase the chances of false-negative results, thus leading to the current recommendation of an SUV of 2.5 as the criterion for the classification of a node as positive (9,13). Using an SUV of 2.5 as the threshold, the resulting sensitivity, specificity and negative predictive value were reported to be 89, 84 and 96%, respectively (9).

Imaging tests, such as PET-CT, have been used for the clinical diagnosis of the nodal status during staging. Previous randomized trials have demonstrated that PET/CT is significantly more accurate and more sensitive for the staging of NSCLC compared with the conventional staging regimen (14). The pooled sensitivity and specificity of PET for identifying mediastinal lymph node metastasis were reported to be

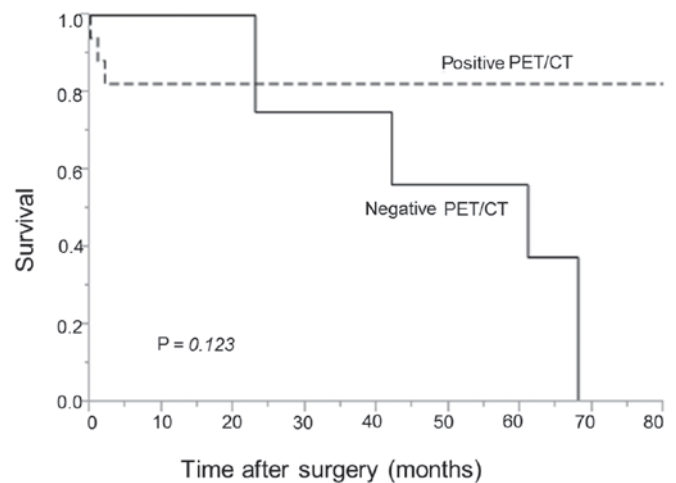


Figure 1. The 5-year overall survival rate was 82 vs. 38% in the patients with positive vs. negative hilar lymph node findings on PET/CT, respectively. There was no significant difference between the two groups ( $P=0.123$ ). PET/CT, fusion positron emission tomography/computed tomography.

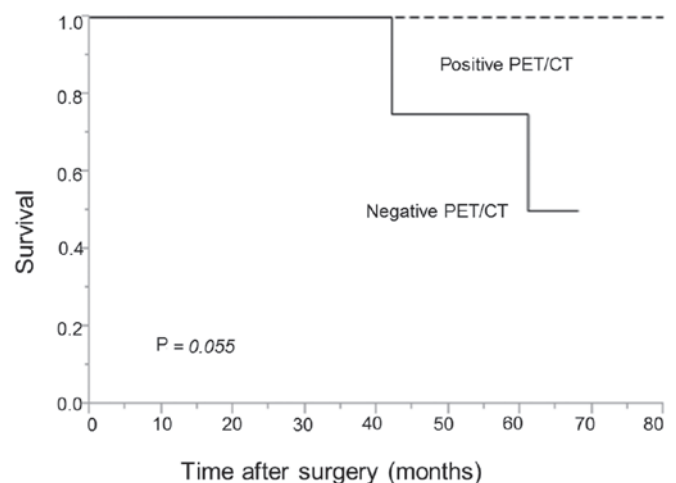


Figure 2. The 5-year disease-specific survival rate was 100 vs. 50% in the patients with positive vs. negative hilar lymph node findings on PET/CT, respectively. The patients with positive PET/CT findings tended to have a better prognosis ( $P=0.055$ ). PET/CT, fusion positron emission tomography/computed tomography.

74 and 85%, respectively (15). However, the sensitivity and specificity of PET for identifying hilar lymph node metastasis were only 48.5 and 80.2%, respectively (10). Furthermore, it is more difficult to discriminate N1 involvement and primary tumors *per se* using imaging alone, particularly when the primary tumor is very close in proximity to the N1 nodes involved. Therefore, tissue confirmation is recommended to determine whether lymph node metastasis is truly present. Hilar lymph nodes have recently become accessible by means of endobronchial ultrasound (16). However, extracapsular invasion of hilar lymph node metastasis is difficult to diagnose using endobronchial ultrasound.

The present study identified PET/CT as a significant predictor of extracapsular invasion of hilar lymph node metastasis in the multivariate analysis ( $P=0.0005$ ). Shin *et al* (17) reported that the presence of extracapsular nodal invasion



detected by both CT and PET/CT was more frequent in the cN1-pN1 group compared with the cN0-pN1 group, resulting in a poorer surgical outcome. Although PET/CT is reported to be less sensitive for identifying hilar lymph node metastasis, we found it to be useful for identifying extracapsular invasion of hilar lymph node metastasis.

Regarding surgery, Watanabe *et al* (3) reported that extensive pulmonary resection was required in 41% of patients with cN1 disease. Moreno *et al* (18) reported that pneumonectomy was required in 40% of surgically treated T3<sub>>7 cm</sub> N1 NSCLC patients. The postoperative mortality rate for surgical resections in lung cancer was recently found to have significantly improved (19); thus, preoperative detailed cardiopulmonary function tests should be mandatory to reduce surgical morbidity and mortality. In the present study, extensive pulmonary resection was required in 53% of the patients with hilar lymph node metastasis. Furthermore, extensive pulmonary resection was required in 76% of the patients with positive hilar lymph node metastasis on PET/CT ( $P=0.003$ ). It may be deduced from our findings that such patients are more likely to require extensive pulmonary resection, as hilar lymph node metastasis with extracapsular invasion is very close in proximity to the bronchus and pulmonary arteries.

As regards prognosis, there was no significant difference in OS or disease-specific survival rates between the positive and negative PET/CT groups in our study. However, the positive PET/CT group tended to have a better prognosis in terms of disease-specific survival ( $P=0.055$ ), exhibiting a 100% disease-specific survival rate at 5 years. The positive PET/CT group displayed a high rate of extracapsular invasion (76%) and required extended surgical resection. While the presence of extracapsular invasion may indicate poor survival (17), the positive PET/CT group exhibited favorable outcomes, probably due to the beneficial effect of extended surgical resection on curability. Even with extracapsular involvement, sufficient therapy by extensive surgical resection may result in an acceptable surgical outcome. Preoperative meticulous evaluation of pulmonary and cardiac function tests should be mandatory for patients with positive hilar lymph node findings on PET/CT to assess the possibility of extended resection.

This study had several limitations. As our data were retrospectively collected and reviewed, there were some intrinsic drawbacks. In addition, although all the patients had pN1 disease, the study population comprised a heterogeneous group of subjects. In this study, the CT size criterion for metastatic lymph nodes, i.e., a short-axis diameter of  $>1$  cm on a transverse CT image, was not implemented, the reason being that the hilar lymph nodes were difficult to distinguish from blood vessels in certain patients examined without the use of intravenous contrast medium.

In conclusion, we retrospectively reviewed the clinical and pathological characteristics of patients with hilar lymph node metastasis following surgical resection for NSCLC. The PET/CT findings were a significant predictor of extracapsular invasion of hilar lymph node metastasis. Extensive pulmonary resection was required in patients with positive hilar lymph node metastasis on PET/CT, resulting in acceptable surgical outcomes, despite a relatively high postoperative mortality rate. Thus, meticulous preoperative evaluation of pulmonary and cardiac function test should be mandatory for patients with

PET/CT positive hilar lymph node for determining potential extensive pulmonary resection.

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