Follow-up papers - Thoracic oncologic


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Abstract

Objectives: F18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT), which allows differentiation between malignant and benign lesions based on difference in tissue glucose metabolism, has become increasingly important in lung cancer diagnosis. This study examined the clinical value of FDG-PET/CT in a large number of patients with non-small cell lung cancer (NSCLC) after potentially curative surgery. Methods: Four hundred and ninety FDG-PET/CT of 241 patients (143 males and 98 females; age range 38–87 years; mean 68.0 years) between May 2006 and February 2008 were retrospectively evaluated. All the 241 patients had undergone potentially curative surgery for NSCLC > 6 months before FDG-PET/CT and their pathologic stages were stage I and II according to the tumor-node-metastasis (TNM) classification. A final diagnosis of recurrence was confirmed by histologic or cytologic examination of the disease or by clinical and radiologic follow-up image analysis. Confirmation of recurrence-free status was based on a clinical and radiologic image analysis follow-up period of at least 12 months with no evidence of active malignancy. The diagnostic performance of FDG-PET/CT was evaluated. Details of false results and incidental detection of diseases other than recurrent lung cancer by FDG-PET/CT was also analyzed. Results: Recurrences were confirmed in 35 (15%) patients, and 206 patients (85%) had no evidence of recurrence. FDG-PET/CT correctly diagnosed recurrence in 34 of 35 patients and provided true negative findings in 198 of 206 patients who had no evidence of recurrence (sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 97%, 96%, 96%, 81%, and 99%, respectively), indicating a high diagnostic performance. However, one patient had false negative studies and eight patients had false positive studies; misdiagnosis was more frequently in intrathoracic sites associated with postoperative changes. Malignancies other than recurrence were detected in nine of all 241 patients (4%) including five second primary lung cancers. Conclusions: The present study demonstrated the high diagnostic performance of FDG-PET/CT in detecting recurrences in a large group of patients with NSCLC after potentially curative surgery. FDG-PET/CT is useful not only for diagnosis of recurrence but also for detection of other diseases. © 2010 Published by European Association for Cardio-Thoracic Surgery. All rights reserved.

Keywords: Positron emission tomography; Lung neoplasms; Follow-up studies

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in the Western world [1], and non-small cell lung cancer (NSCLC) accounts for ~85% of the cases. Surgery remains the best treatment for NSCLC, if curative resection is expected. Unfortunately, many patients who undergo potentially curative surgery eventually develop recurrences. Although no conclusive data support the survival benefits of earlier detection of recurrence or start of treatment for recurrent disease, early and accurate diagnosis of recurrence is important for selection of optimal therapy.

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F18-fluorodeoxyglucose positron emission tomography (FDG-PET) has become increasingly important in the diagnosis of lung cancer. FDG-PET allows differentiation between malignant and benign lesions based on differences in glucose metabolism between normal and cancer tissues [2, 3]. Previous studies have demonstrated that FDG-PET is more accurate than computed tomography (CT) for the diagnosis and staging of NSCLC [4, 5]. The main disadvantage of FDG-PET is the poor quality of the anatomic information. To overcome this disadvantage of FDG-PET, new imaging systems using integrated FDG-PET/CT were developed recently.

Several groups reported the high diagnostic performance of the FDG-PET in suspected recurrence after definitive treatment [6–9]. Recently, Takenaka and co-workers [10]...
directly compared diagnostic capabilities of FDG-PET/CT and standard radiologic examination for assessment of recurrence in 92 postoperative NSCLC patients. In their series, 12 patients with recurrent lung cancer were included and they concluded that FDG-PET/CT can be used for assessment of postoperative recurrence in NSCLC patients with accuracy as good as that of standard radiological examinations. However, clinical study which includes large number of patients has not been conducted so far. In the present study, the diagnostic performance of FDG-PET/CT in large scale patients with NSCLC after potentially curative surgery was evaluated retrospectively. Details of false results and incidental detection of diseases other than recurrent lung cancer by PET/CT was also analyzed.

2. Patients and methods

2.1. Patient eligibility

In our hospital, FDG-PET/CT was performed in NSCLC patients after potentially curative surgery generally when the patient meets the following criteria. (1) New clinical symptoms or signs are observed. (2) Recurrence is suspected based on new abnormal or equivocal findings by conventional imaging modalities. (3) Elevation of serum tumor markers is observed. Serum tumor markers are routinely checked every 3–6 months after surgery. (4) Even if there are no unfavorable postoperative events, FDG-PET/CT is performed as a routine medical checkup approximately 12, 24 and 36 months after surgery or when the patient desires to undergo FDG-PET/CT.

Consecutive patients who underwent FDG-PET/CT between May 2006 and February 2008 in our hospital were evaluated retrospectively. Patients were eligible for this study if they had undergone potentially curative surgery for NSCLC >6 months before a follow-up. FDG-PET/CT and their pathologic stages were stage I and II according to the tumor-node-metastasis (TNM) classification. Patients were excluded from analysis if recurrence had been already confirmed by either biopsy or conventional imaging modalities before FDG-PET/CT. Patients who had another primary cancer at the time of surgery or diabetes mellitus were also excluded.

A total of 243 patients with 493 FDG-PET/CT studies were entered, however, two patients were lost to follow-up and excluded from the analysis. The final analysis included 241 patients (Table 1) with 490 FDG-PET/CT studies. Two FDG-PET/CTs were performed in 155 patients and three FDG-PET/CTs in 47 patients. The time interval between initial surgery and first FDG-PET/CT ranged from 6 to 215 months (median 25 months). The major histopathological cancer type was adenocarcinoma followed by squamous cell carcinoma (SCC) and other miscellaneous types (Table 1). The pathological stage after surgery according to the 1997 update of TNM classification was stage IA in 122 patients, IB in 61, IIA in 17, IIB in 41. The majority of patients underwent surgery alone as the primary treatment, though some underwent radio- or chemoradiotherapy followed by surgery, or surgery followed by adjuvant chemotherapy (Table 1).

PET/CT was performed for some unfavorable postoperative events in 78 patients (suspected recurrence in nine patients based on onset of new clinical symptoms/signs, suspected recurrence in 31 patients based on new abnormal or equivocal findings by conventional imaging modalities, and suspected tumor recurrence in 38 patients due to high serum tumor markers). Table 2 provides more details of the reasons for performing FDG-PET/CT for suspected recurrence of the disease. In contrast, FDG-PET/CT was performed as a routine postoperative medical checkup in the remaining 163 patients. In 132 patients (81%) of this group, FDG-PET/CT was performed 6–36 months after surgery.

2.2. FDG-PET/CT imaging

Patients were asked to fast, except for glucose-free oral hydration, for at least 5 h before the injection of 18F-FDG (3.5 MBq/kg body weight). After injection of the tracer, patients were kept lying comfortably on the bed. No urinary bladder catheterization was performed and no oral muscle relaxants were administered. Whole-body PET/CT fusion scanning was performed 1 h after the injection, using a PET/CT system (Discovery LS, General Electric Medical Systems; Biograph Duo LSD, Siemens-Asahi Medical Technologies). PET, CT, and fused PET/CT images were available for review, displayed in axial, coronal, and sagittal planes. The FDG uptake of tumor was visually compared with that of the surrounding tissue in areas devoid of prominent artifacts and overlapping increased FDG uptake organs.

### Table 1: Clinical characteristics of the patient population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143</td>
</tr>
<tr>
<td>Female</td>
<td>98</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>Mean</td>
<td>68.0</td>
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<tr>
<td>Range</td>
<td>38–87</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>176</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>48</td>
</tr>
<tr>
<td>Other histopathological types*</td>
<td>17</td>
</tr>
<tr>
<td>Pathologic stage after surgery**</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>122</td>
</tr>
<tr>
<td>IB</td>
<td>61</td>
</tr>
<tr>
<td>IIA</td>
<td>17</td>
</tr>
<tr>
<td>IIB</td>
<td>41</td>
</tr>
<tr>
<td>Initial treatment</td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>183</td>
</tr>
<tr>
<td>Induction radio- or chemoradiotherapy followed by surgery</td>
<td>5</td>
</tr>
<tr>
<td>Surgery followed by adjuvant chemotherapy</td>
<td>53</td>
</tr>
<tr>
<td>Interval between surgery and PET/CT (months)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td>6–215</td>
</tr>
</tbody>
</table>

*Other histopathological types of NSCLC include adenosquamous carcinoma, large cell carcinoma.

**Stage of disease was defined according to the 1997 update of TNM criteria established by UICC.

PET/CT, positron emission tomography-computed tomography; NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis.
FDG-PET/CT study was defined as false positive. When a patient with negative studies was later confirmed to have recurrence, the FDG-PET/CT study was defined as false negative. When a patient with negative study was confirmed to have no recurrence, the FDG-PET/CT study was defined as true negative. Among the patients who present with lung nodules, differentiation between recurrent lung cancer and second primary lung cancer were conducted based on criteria of Martini and Melamed [11]. Patients with a site of increased FDG uptake, which is considered to be other diseases than recurrent lung cancer, underwent diagnostic procedure for the site. Diseases other than recurrent lung cancer are diagnosed by clinical course or serial radiologic imaging or biopsies if possible.

3. Results

3.1. Clinical outcome

The time interval between initial surgery and latest follow-up in the present series ranged from 11 to 229 months (median 44 months), and the time interval between FDG-PET/CT and latest follow-up ranged from 2 to 34 months (median 19 months). At the end of the follow-up period, recurrences were confirmed in 35 (15%) patients, while 206 patients (85%) had no evidence of recurrence. Recurrence after treatment was as follows: lung metastasis in 11 patients, pleuritis carcinomatosa in 5, surgical margin recurrence in 2, mediastinal lymph node recurrence in 11, brain metastasis in 2, bone metastasis in 3, liver metastasis in 1. Representative case is shown in Figs. 1 and 2.

3.2. Performance of FDG-PET/CT study in diagnosis of recurrence

PET/CT correctly diagnosed recurrence in 34 of 35 patients and gave true negative findings in 198 of 206 patients who had no evidence of recurrence. Therefore, the performance indices of FDG-PET/CT for diagnosis of

![Fig. 1. A 57-year-old man with mediastinal lymph node recurrence after potentially curative resection of adenocarcinoma. Contrast-enhanced CT performed 10 months after surgical resection showed a right upper paratracheal node (arrow). The short axis diameter was 8 mm. CT, computed tomography.](image-url)
Finally diagnosed with non-specific FDG uptake in distant organs. Two patients were finally diagnosed with other diseases (multiple myeloma and desmoid tumor of the chest wall).

3.4. Detection of other diseases by FDG-PET/CT studies

PET/CT studies detected 50 diseases other than recurrent lung cancer in 45 of 241 patients (19%). Twelve patients undertook treatment for the disease, which is detected by PET/CT studies. In nine patients (4%), malignancies were detected. Second primary lung cancer was detected in five patients. Four of these five patients underwent potentially curative surgery and one patient underwent definitive chemoradiotherapy. Malignancies other than lung cancer detected are as follows: one gastric cancer which was subsequently resected, one thyroid cancer which was resected, one pancreatic cancer which was treated by chemotherapy, and one multiple myeloma which was treated by chemotherapy. Two benign tumors detected by PET/CT were resected, one desmoid tumor of the chest wall and one teratoma of ovary.

4. Discussion

The present study retrospectively examined the diagnostic performance of FDG-PET/CT for recurrence in large-scale patients with NSCLC after potentially curative surgery. The results [sensitivity (97%), specificity (96%), and NPV (99%)] of FDG-PET/CT for recurrence demonstrated in the present study are as high as those in earlier studies summarized in Table 3 [6–10, 12, 13]. Although the tested patients were included not only for some reasons of recurrence-suspected events but also for medical routine checkup, the high diagnostic performance was obtained regardless of the reason for the examination. The PPV (81%) demonstrated in the present study is relatively low compared with earlier studies because of the false positive FDG-PET/CTs in our study discussed below.

Several groups reported that FDG-PET accurately differentiate recurrent cancer from benign inflammatory process in patients with clinically suspected recurrence [7, 9]. However, previous studies have some limitations, such as inclusion of patients with residual tumors after palliative treatment or patients with small cell lung cancer, or limited number of patients. The present study included the largest

![Fig. 2. FDG-PET/CT of the patient shown in Fig. 1 performed during the same period demonstrated high uptake of FDG (SUV<sub>max</sub> = 3.5) within the right upper paratracheal node (arrow). This site was interpreted malignant and this FDG-PET/CT study was interpreted as positive. Radiologic follow-up analyses revealed that this case was true positive for the FDG-PET/CT study and radiation therapy was performed. FDG-PET/CT, F18-fluorodeoxyglucose positron emission tomography-computed tomography; SUV, standard uptake value.](https://academic.oup.com/icvts/article-abstract/10/6/1009/773130)
number of patients with NSCLC after potentially curative surgery and is the first to examine the value of FDG-PET/CT as a routine medical checkup during follow-up.

In the present study, one patient had a false negative FDG-PET/CT study. The recurrence site was pleuritis carcinomatosa and the standard uptake value (SUV) of the lesion was low (1.2). Previous reports described the diagnostic limitations of FDG-PET in detection of brain metastasis [14]. Detection of tumors with modest increases in glucose metabolism is difficult because of the high rate of physiologic glucose metabolism in normal brain tissue. Our results demonstrated diagnostic limitations for FDG-PET/CT in detecting early intrathoracic recurrences, for example plural lesions, which could be interpreted as postoperative change. On the other hand, eight patients have false positive FDG-PET/CT studies. Even in six of these eight patients, the final diagnosis was clinically or pathologically non-specific or FDG uptake by benign inflammatory or reactive process. Generally, the inflammatory process is known as the main cause of false findings on FDG-PET [15]. In particular, false results are not unusual during the period of up to six months after the end of treatment due to FDG uptake in irradiated tissues and postsurgical inflammatory changes [7, 8, 16]. Although FDG-PET/CT studies within the first six months after surgery were excluded in this study, inflammatory changes were the main reason for the false positive studies. On the other hand, several studies used SUV cut-off of 2.5 to differentiate malignant from benign lesions [7, 17]. In the present study, four false positive cases were identified in which SUV was >2.5. This finding indicates that SUV is not reliable even after >6 months postsurgical follow-up period.

The present study also demonstrated a high NPV of FDG-PET/CT in a large number of patients (199 FDG-PET/CT negative patients) during a follow-up period of sufficient length (at least 12 months). Therefore, in conjunction with the high NPV, we propose that conventional imaging modalities, with the exception of brain MRI, can be omitted if the result of FDG-PET/CT study is negative in patients with NSCLC after potentially curative surgery. A recent report of Takenaka and co-workers could support our proposal. They directly compared diagnostic capabilities of FDG-PET/CT and conventional imaging modalities (combination of chest and abdominal CT, bone scintigraphy, and brain MRI) for assessment of recurrence in 92 postoperative NSCLC patients. They concluded that FDG-PET/CT can be used for assessment of postoperative recurrence in NSCLC patients with accuracy as good as that of conventional imaging modalities. However, no patient with brain metastasis was included in their study. Brain MRI is considered an appropriate modality for detecting brain metastasis of lung cancer [14]. Thus, the combination of FDG-PET/CT and brain MRI may represent a suitable replacement of conventional imaging modalities. We recommend brain MRI for patients who undergo FDG-PET/CT according to the criteria described in Patients and methods in this communication.

Nevertheless, the FDG-PET/CT has certain limitations; limitation related to the detection of recurrent lesions of intrathoracic pleura or those with low SUVs described above, and cost. The cost of the combination of FDG-PET/CT and brain MRI is higher than that of the combination of chest and abdominal CT, bone scintigraphy, and brain MRI (~100,000 yen vs. 65,000 yen) [18]. After considering these limitations, whether FDG-PET/CT could be used routinely as an alternative to the combination of conventional imaging modalities during the postoperative follow-up period need to be investigated.

Unfortunately, the main limitations of the present study were the lack of evaluation of the impact of FDG-PET/CT on management of patients and patient selection bias, both of which are related to the retrospective nature of the study. Keidar et al. [12] prospectively evaluated the impact of FDG-PET/CT on the management of suspected recurrent lung cancer. They reported that FDG-PET/CT modified the management (i.e. eliminated the need for previously planned diagnostic procedures, resulted in initiation of previously unplanned treatment or changed the previously planned therapeutic approach) of 29% of the patients. In the present study, however, we believe that FDG-PET/CT could be a potential alternative to the combination of conventional imaging modalities during the postoperative course in patients with NSCLC after potentially curative surgery.

5. Conclusions

The present study demonstrated the high diagnostic performance of FDG-PET/CT in detecting recurrences in a large group of patients with NSCLC after potentially curative surgery. FDG-PET/CT is useful not only for diagnosis of recurrence but also for detection of other diseases.

References