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^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography is useful in postoperative follow-up of asymptomatic non-small-cell lung cancer patients

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Abstract

OBJECTIVES: Postoperative follow-up and surveillance after curative resection for non-small-cell lung cancer (NSCLC) patients are generally performed. However, there is no consensus on the best programme at this time. The aim of this study was to evaluate the diagnostic capability of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in postoperative NSCLC patients without clinical and radiological evidence of recurrence, as a follow-up and surveillance programme.

METHODS: Between January 2005 and April 2010, a total of 101 NSCLC patients underwent potentially curative operations and follow-up FDG-PET/CT was performed in patients without clinical and radiological evidence of recurrence at least once a year in principle. A total of 233 FDG-PET/CT studies were entered and retrospectively reviewed.

RESULTS: Eighteen (18%) asymptomatic patients had recurrent diseases and 22 recurrent sites were confirmed. Of 22 recurrent sites, recurrence was diagnosed by histological examination in 9 (41%) sites and by imaging examination in 13 (59%) sites. FDG-PET/CT correctly diagnosed recurrence in 17 of the 18 (94%) patients and 21 of the 22 (95%) recurrent sites. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 94.4, 97.6, 89.5, 98.8 and 97.0%, respectively. On the other hand, in 3 patients, other diseases were detected and treated appropriately. Post-recurrence therapies were performed in all patients with recurrence, but 4 (22%) patients died of the original diseases. The median post-recurrence survival was 25.2 months, and the 1- and 2-year post-recurrence survival rates were 83.3 and 69.6%, respectively.

CONCLUSIONS: FDG-PET/CT is a useful tool that has high capability to detect recurrences in asymptomatic NSCLC patients after a potentially curative operation. However, a large-scale multi-institutional randomized control trial may be needed to ascertain the benefit of surveillance with FDG-PET/CT.

Keywords: Positron emission tomography/computed tomography • Non-small-cell lung cancer • Asymptomatic patients • Recurrence • Follow-up and surveillance

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide [1]. For most non-small-cell lung cancer (NSCLC) patients at an early stage (stages I and II) and selected patients at a locally advanced stage (stage IIIA), curative resection was the most appropriate treatment for a cure. However, even if curative resection could be achieved for them, the risk of recurrence was high, as several reports have indicated that recurrence rates ranged from 30 to 75% [2–6].

Although postoperative follow-up and surveillance after curative resection for NSCLC patients are generally performed, there is no consensus on the best program. While there are some guidelines for follow-up and surveillance in NSCLC patients treated with curative intent therapy, American College of Chest Physicians (ACCPs) guidelines recommend as Grade 1C that chest computed tomography (CT) should be performed every 6 months for 2 years as an imaging study [7]. On the other hand, European Society for Medical Oncology (ESMO) guidelines note the lack of evidence that surveillance of asymptomatic patients following curative intent therapy is needed and do not recommend routine imaging studies [8]. However, several retrospective studies have demonstrated that asymptomatic patients at recurrences detected by intensive surveillance had a better prognosis than symptomatic patients [5, 6]. Therefore, early detection of recurrences by intensive follow-up

and surveillance may improve survival in postoperative asymptomatic NSCLC patients.

In recent years, positron emission tomography (PET) and CT using ^{18}F-fluorodeoxyglucose (FDG) have been widely used as a metabolic imaging tool for NSCLC patients. Several studies have also more recently proved the effectiveness of FDG-PET/CT for the diagnosis of intrathoracic and extrathoracic staging in NSCLC patients [9, 10]. ACCP guidelines recommend as Grade 1B that FDG-PET/CT should be performed as a non-invasive diagnostic tool [11]. On the other hand, the necessity of performing FDG-PET/CT for surveillance in postoperative NSCLC patients is controversial. ACCP guidelines do not recommend FDG-PET/CT for surveillance at this time [11]. However, recent studies have demonstrated the usefulness of FDG-PET/CT for the detection of postoperative recurrence in NSCLC patients [12–17].

In this study, we evaluated the diagnostic performance of FDG-PET/CT in asymptomatic NSCLC patients after a potentially curative operation, retrospectively.

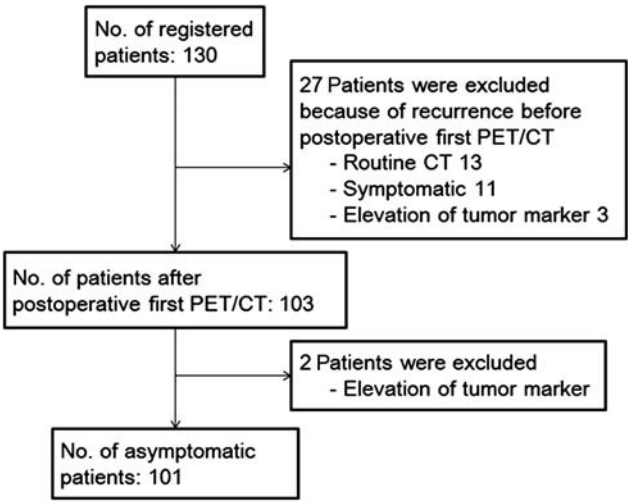

Figure 1: Flow diagram of this study.

MATERIALS AND METHODS

Patients

In our hospital, a follow-up FDG-PET/CT was performed in NSCLC patients who had no clinical and radiological evidence of recurrence after a potentially curative operation at least once a year in principle. In this study, patients were excluded if they had FDG-PET/CT when recurrence was suspected on the basis of symptoms or results of other imaging modalities or elevation of tumor markers. FDG-PET/CT was performed in patients from whom informed consent was obtained after we provided detailed explanations about the expected effects, cost and radiation exposure of FDG-PET/CT.

Between January 2005 and April 2010, 130 consecutive NSCLC patients were registered. However, 27 patients were excluded because recurrences were detected before the first postoperative FDG-PET/CT owing to routine CT in 13, appearance of symptoms in 11 and elevation of tumor markers in 3. First, postoperative FDG-PET/CT was performed in 103 patients. However, subsequently, 2 were excluded because recurrences were detected by elevation of tumor markers. Finally, 101 asymptomatic patients (59 males and 42 females; mean age: 67.4 years) with 233 FDG-PET/CT studies were entered and retrospectively reviewed (Fig. 1).

Table 1 shows the characteristics of patients. The histological type of lung cancer was adenocarcinoma in 76 patients, squamous cell carcinoma in 20, large cell carcinoma in 3 and others in 2. The pathological stage of tumors according to the 7th edition of the American Joint Committee on Cancer and the International Union Against Cancer TNM classification [18] was Stage 0 in 1 patient, IA in 65, IB in 9, IIA in 11, IIB in 4 and IIIA in 11, respectively. In all cases, complete resection could be performed. Surgical procedures were pneumonectomy in 3 patients, lobectomy in 84, segmentectomy in 6 and partial resection with sufficient margin in 8. Sixty-eight patients underwent surgery alone as initial treatment. Two patients underwent neoadjuvant chemoradiotherapy followed by surgery and 31 underwent surgery followed by adjuvant chemotherapy. The time interval between initial surgery and latest follow-up was 44.7 ± 15.5 months (range 14.9–77.6 months). The time interval between initial surgery and first FDG-PET/CT was 17.1 ± 6.3 months (range 3–35 months). During the follow-up period, the mean number of times that FDG-PET/CT was performed per patient was 2.3 ± 1.2 times (range 1–times).

Table 1: Characteristics of the patients

No. of patients	101
Age, years (range)	67.4 (31–85)
Sex	
Male	59
Female	42
Histology	
Adenocarcinoma	76
Squamous cell carcinoma	20
Large cell carcinoma	3
Others	2
Pathological stage	
0/IA/IB	1/65/9
IIA/IIB	11/4
IIIA	11
Initial treatment	
Surgery alone	68
Neoadjuvant chemoradiotherapy followed by surgery	2
Surgery followed by adjuvant chemotherapy	31
Interval between surgery and PET/CT, months (range)	17.1 (3–35)
Follow-up duration, months (range)	40.1 (11.6–74.5)
No. of times PET/CT were performed (range)	2.1 (1–6)

Follow-up examination

Follow-ups were conducted for 5 years along the planned schedule. These included physical examination, chest radiograph, tumor marker, chest CT, FDG-PET/CT and brain magnetic resonance imaging (MRI). Tumor marker was routinely checked every 3–6 months. Either chest CT or FDG-PET/CT was alternately performed every 6 months for the first 3 years. Furthermore, FDG-PET/CT was performed every 12 months for the next 2 years. In addition, brain MRI was routinely performed every 12 months even if there were no unfavorable events.

FDG-PET/CT protocol and image interpretation

Patients were required to fast for 6 h and avoid strenuous work or exercise for 24 h before PET/CT. Sixty minutes after the intravenous injection of FDG (3.7 MBq/kg body weight), PET/CT was performed with an Aquiduo (Toshiba Medical Systems, Tokyo, Japan). Patients were imaged from the skull base to the mid-thigh level. The technical parameters used for the CT scan were a detector row configuration of 16 × 1.25 mm, a helical pitch of 15, a gantry rotation speed of 0.5 s, peak voltage of 120 kVp, a tube load of 50 mA and slice thickness of 2 mm. An emission scan was acquired immediately following the CT scan for 2 min per bed position in a 3D mode. The images were usually reconstructed using ordered subset expectation maximization selecting 4 iterations and 12 subsets, a 128 × 128 matrix and post-smoothing with an 8-mm Gaussian filter. The reconstructed spatial resolution after smoothing was 9.2 mm.

Abnormal FDG uptake was defined as greater than the background activity in surrounding normal tissue excluding physiological uptake sites. Regions of interest were placed on visible uptake sites and standardized uptake values (SUVs) were calculated as follows:

SUV = decay-corrected activity (kBq)/tissue volume (ml)/injected-FDG activity (kBq)/body weight (g). The maximum SUV (SUVmax) was used to minimize the partial volume effect and ensure the reproducibility of measurements. FDG-PET/CT was analysed by consensus among several chest surgeons while referring to reports made by several experienced nuclear medicine physicians.

Diagnosis of recurrence

The presence of recurrence was determined on the basis of results of imaging examination, assessment of tumor markers and physical examination in a comprehensive manner. When clinically feasible, the diagnosis of recurrence was histologically confirmed by biopsy, surgery or fine-needle aspiration cytology (FNAC) in principle. If the lesions suspected of recurrences could not be confirmed histologically, they were diagnosed as recurrences when they became larger during follow-up periods or decreased in size after treatment. On the other hand, when the lesions suspected of recurrences did not change in size during follow-up periods or treatment periods, they were diagnosed as non-recurrences.

Statistical analysis

All values are expressed as mean ± standard deviation. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were used for the evaluation of recurrence with FDG-PET/CT. Statistical analyses were performed using Student's *t*-test with SPSS software (Version 11.0.1, SPSS). $P<0.05$ was considered to be statistically significant.

RESULTS

Recurrence

Table 2 shows the details of patients with recurrence. At the end of the follow-up period, 18 (18%) asymptomatic patients had recurrent diseases and 22 recurrent sites were confirmed (Table 2). Recurrent sites were as follows: mediastinal lymph node in 6 patients, lung in 5, hilar lymph node in 4, pleuritis carcinomatosa in 3, surgical margin in 2, supraclavicular lymph node in 1 and axillary lymph node in 1. Of 22 recurrent sites, recurrence was diagnosed by histological examination in 9 (41%) sites and by imaging examination in 13 (59%) sites. The median disease-free interval was 25.6 ± 9.5 months (range 3–42 months). According to pathological stage, 11 patients in Stage I and 7 in Stage IIIA had recurrences.

Results of FDG-PET/CT for the diagnosis of recurrence and other diseases

Table 3 shows the results of FDG-PET/CT for diagnosis of recurrence. FDG-PET/CT correctly diagnosed recurrence in 17 of the 18 (94%) patients and 21 of the 22 (95%) recurrent sites. In 19 of the 21 (90%) recurrent sites, higher FDG uptakes were recognized. In 2 patients (Cases 8 and 17 in Table 2) with lung metastasis, FDG uptakes were not recognized because the recurrent sites, the sizes of which were 3 and 5 mm, were too small. However, the nodules were gradually enlarged in follow-up CT examinations for several months and were diagnosed as metastases, and the patients could receive appropriate therapies.

True-negative findings were found in 80 of the 82 (98%) patients who had no evidence of recurrence. False-positive results were found in 2 patients. In 1 patient, left supraclavicular lymph nodes were enlarged, with higher FDG uptakes, but they were diagnosed as benign inflammatory processes by FNAC (Fig. 2A). In another patient, a left lung nodule appeared with higher FDG uptake, but it later disappeared spontaneously (Fig. 2B and C) on short-term follow-up CT. A false-negative result was found in 1 patient (Case 11 in Table 2) with pleuritis carcinomatosa. While she received left lower lobectomy for adenocarcinoma at Stage IA, a small amount of ipsilateral pleural effusion was recognized, but FDG uptake was not recognized at pleura on routine FDG-PET/CT. However, subsequently, pleural effusion increased and the diagnosis was confirmed by aspiration cytology.

The sensitivity, specificity, PPV, NPV and accuracy of FDG-PET/CT for diagnosis of recurrence were 94.4, 97.6, 89.5, 98.8 and 97.0%, respectively.

Furthermore, other diseases could be detected in 3 patients. These were as follows: prostate cancer in 1 patient, colon polyps in 1 and pancreatic tumor in 1 (Table 3). These patients received appropriate treatment.

Figure 3 shows the relationship between number of times and each number of the presence or the absence of findings on FDG-PET/CT. In the first and second examinations, some positive findings were recognized in 10 of the 101 (9.9%) patients and 9 of 74 (12.2%), respectively. In contrast, after the third examinations, they were recognized in only 2 of the 58 (3.6%) patients. A higher trend was observed in the first and second examinations although there was no significant difference ($P = 0.149$).

Post-recurrence therapy and outcome

Surgery was performed in 2 patients. One patient (Case 8 in Table 2) received left S6 segmentectomy for ipsilateral solitary

Table 2: Details of postoperative asymptomatic patients with recurrence

Case	Age (years)	Sex	Histology/stage	DFI (m)	Recurrent site	SUVmax	Treatment	PRS (m)	Outcome
1	64	F	Ad/IA	30	Surgical margin	2.6	RT	48	Alive
2	64	M	Ad/IA	35	Hilar lymph node	18.0	CRT	10	Dead
					Pleura	8.1			
3	69	F	Sq/IIIA	17	Lung	2.9	CT	52	Alive
					Mediastinal lymph node	5.1			
4	54	M	Ad/IIIA	29	Mediastinal lymph node	3.5	CRT	42	Alive
5	81	F	LC/IA	31	Hilar lymph node	2.2	CT	36	Dead
6	69	M	Ad/IIIA	3	Hilar lymph node	3.4	CT	17	Dead
7	31	F	Ad/IIIA	30	Mediastinal lymph node	3.7	CRT	31	Alive
8	66	F	Ad/IA	10	Lung (solitary)	Not measured	Surgery	47	Alive
9	74	M	Ad/IA	30	Lung (solitary)	2.1	Surgery	16	Dead[a]
10	74	M	Ad/IIIA	18	Mediastinal lymph node	6.8	CRT	20	Dead
11	59	F	Ad/IA	28	Pleura	–	CT	27	Alive
12	60	F	Ad/IA	24	Surgical margin	2.0	RT	26	Alive
13	67	M	Ad/IIIA	22	Mediastinal lymph node	4.0	CRT	24	Alive
14	68	F	Ad/IA	21	Mediastinal lymph node	5.0	CRT	26	Alive
15	62	M	Ad/IB	42	Lung	6.2	CRT	5	Alive
16	73	F	Ad/IA	37	Hilar lymph node	9.8	CT	9	Alive
					Axillary lymph node	6.2			
					Pleura	8.0			
17	63	F	Ad/IA	30	Lung	Not measured	CT	15	Alive
18	67	M	Ad/IIIA	24	Supraclavicular lymph node	4.7	CT	3	Alive

DFI: disease-free interval; PRS: post-recurrence survival; Ad: adenocarcinoma; Sq: squamous cell carcinoma; LC: large cell carcinoma; RT: radiation therapy; CRT: chemoradiotherapy; CT: chemotherapy.
[a]Due to other disease.

Table 3: PET/CT findings and recurrence characteristics

No. of PET/CT positive findings	21
No. of recurrence (sites)	18 (22)
PET/CT true positive	17 (21)
Local recurrence (20 sites)	
Mediastinal lymph node	6
Lung	5
Hilar lymph node	4
Pleura	2
Surgical margin	2
Supraclavicular lymph node	1
Distant metastasis (one site)	
Axillary lymph node	1
PET/CT false positive ($n = 2$)	
Supraclavicular lymph node	1
Lung	1
PET/CT false negative ($n = 1$)	
Pleura	1
Other diseases ($n = 3$)	
Prostate cancer	1
Pancreatic tumor	1
Colon polyp	1

PET/CT: positron emission tomography/computed tomography.

lung metastasis after left upper lobectomy. Another patient (Case 9 in Table 2) received right lower lobectomy for contralateral solitary lung metastasis after left lower lobectomy. On the other hand, 16 patients received non-surgical therapy: 7 were treated with chemoradiotherapy, 7 with chemotherapy and 2 with radiotherapy. Of 18 patients with recurrence, 4 (22%) died of original diseases, 1 (6%) died of other disease and 13 (72%) are still alive. The median post-recurrence survival was 25.2 ± 15.0 months (range 3–52 months), and the 1- and 2-year post-recurrence survival rates were 83.3 and 69.6%, respectively.

DISCUSSION

In recent years, studies have reported the diagnostic usefulness of FDG-PET/CT in postoperative NSCLC patients [12–17]. It was indicated that the capability for the assessment of postoperative recurrence with FDG-PET/CT was better than that with standard radiological examinations [14, 17]. In this study, we could demonstrate good results [sensitivity (94.4%), specificity (97.6%), PPV (89.5%), NPV (98.8%), accuracy (97.0%)] for the diagnosis of recurrences with FDG-PET/CT in asymptomatic NSCLC patients after a potentially curative operation. In fact, the diagnostic results were as high as those in previous studies [12–15]. However, in these studies [12–15], patients with various clinical symptoms and elevation of tumor markers were also included. Furthermore, while Cho and Lee [16] demonstrated the usefulness of FDG-PET/CT as a follow-up tool in asymptomatic postoperative patients in whom recurrences were not suspected, the diagnostic capability, in terms of the sensitivity, specificity and so on, was not evaluated. Therefore, to our knowledge, this study is the first to show that FDG-PET/CT was performed as a planned follow-up tool in asymptomatic patients, and diagnostic usefulness was evaluated including the sensitivity, specificity, PPV, NPV and accuracy. Furthermore, this study showed that some positive findings could be detected more frequently in the first and second FDG-PET/CT, but after that, the numbers decreased. Several reports indicated that most recurrences occurred during the initial 2 years after operation [5, 6]. Therefore, we think that, in particular, it is meaningful and feasible to check the whole body with FDG-PET/CT periodically.

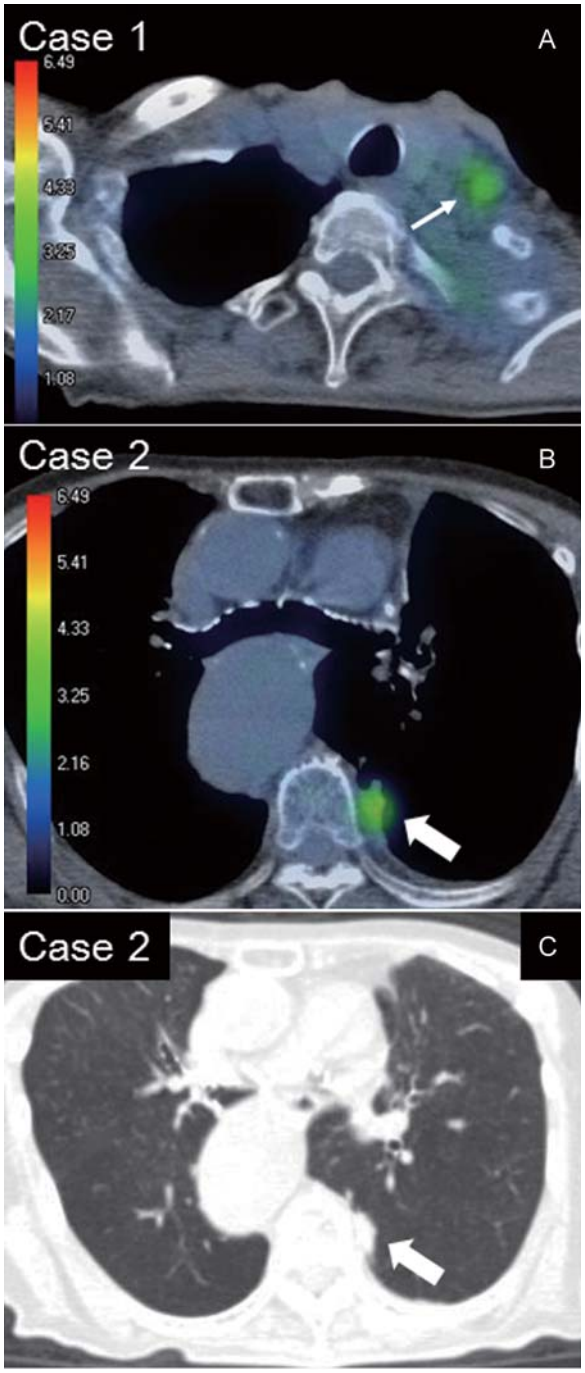

Figure 2: Two false-positive cases. (Case 1; **A**) A 64-year old female with benign inflammatory enlarged lymph node after segmentectomy of the left upper division for adenocarcinoma with Stage IA. FDG-PET/CT showed a higher FDG uptake (SUVmax = 4.1) within the left supraclavicular lymph node (arrow). The diagnosis was confirmed by FNAC. (Case 2; **B** and **C**) A 79-year old female with a benign inflammatory lung nodule after left upper lobectomy for adenocarcinoma with Stage IA. FDG-PET/CT showed a higher FDG uptake (SUVmax = 4.5) within the left lung nodule (thick arrows). It was observed and diagnosed as a benign inflammatory change because it disappeared spontaneously on chest CT after 3 months.

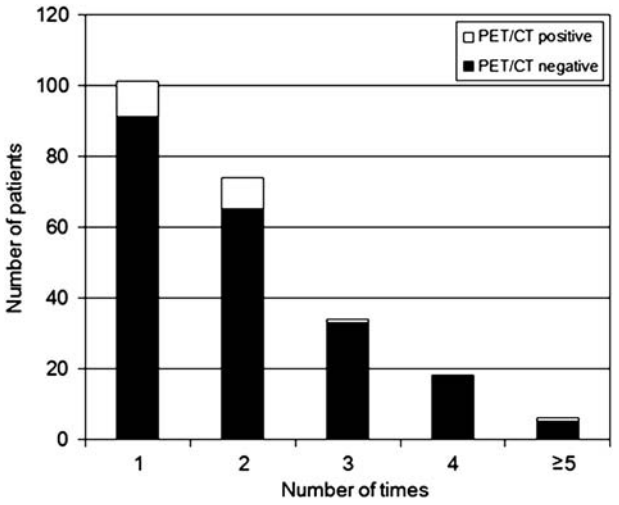

Figure 3: Relationship between number of times and each number of the presence or the absence of findings on FDG-PET/CT. One false-positive case and 2 other diseases were included in positive findings of the first examination. In addition, 1 false-positive case and 1 other disease were included in positive findings of the second examination.

In this study, we could detect not only recurrences but also other diseases. This is an advantage of the use of FDG-PET/CT. In fact, recurrences were detected in 18 of the 101 postoperative asymptomatic patients. Furthermore, three other diseases could also be detected and treated appropriately. However, ESMO guidelines note the lack of evidence about the necessity of surveillance for postoperative asymptomatic patients and do not recommend routine imaging studies [8]. In contrast, several reports indicated that asymptomatic patients at recurrences could have significantly longer survival by the intervention of appropriate treatment compared with symptomatic patients [5, 6]. In previous studies [5, 6], post-recurrence survival was about 20 months in asymptomatic relapsing patients, which is the same as ours (25.2 months). These data were significantly better than those of symptomatic relapsing patients. Judging from these findings, early detection of recurrences by intensive follow-up and surveillance as well as appropriate treatment may improve survival in asymptomatic relapsing patients. Therefore, planned FDG-PET/CT may have substantial importance for postoperative asymptomatic patients.

In this study, the PPV (89.5%) was as high as those in previous studies [12, 15]. We think that this value is acceptable. In 2 false-positive cases, although the enlargement of supraclavicular lymph nodes and the appearance of lung nodules were recognized owing to active inflammatory processes, both could be diagnosed as benign by FNAC and short-term follow-up CT. Generally, the inflammatory process is known as the main cause of false-positive findings on FDG-PET/CT [19]. Therefore, it is necessary to confirm aggressively by histological examination if possible, as we could accomplish in 9 (41%) of the 21 recurrent sites.

On the other hand, we could also confirm two recurrences of the surgical margin accurately despite diagnostic difficulty due to postoperative changes. Bruzzi and Munden [20] indicated that PET/CT may be able to distinguish recurrence from the parenchymal scarring, distortion of bronchovascular anatomy, pleural thickening and mediastinal fibrosis commonly seen on conventional imaging after initial treatment [20]. We were of the opinion that accurate diagnosis would be achieved owing to the advantage of FDG-PET/CT as a metabolic imaging tool.

This study demonstrated high NPV (98.8%). A false-negative result was found in only 1 case with pleuritis carcinomatosa. This result was the same as in previous studies [13, 15]. Schafller *et al.*

[21] reported that in 92 patients, the specificity (76%) and PPV (67%) of FDG-PET/CT in the detection of pleural malignancies were relatively low, and indicated the diagnostic difficulty. We think that this limitation of diagnostic capability is compelling and our data are also acceptable.

This study had certain limitations. First, it was retrospective and, as a result, a patient selection bias was introduced. In addition, it was single-arm, which meant that the diagnostic capability was not compared with any other imaging modalities. However, in this study, we purely evaluated the diagnostic capability of the detection of recurrence with FDG-PET/CT in postoperative asymptomatic patients and could show the usefulness in a large number of patients ($n = 101$). Furthermore, we could observe for a long median follow-up period (44.7 months) and improve post-recurrence survival by the early detection of recurrences. However, we need to note that the recurrence rate is relatively low (18%) compared with those in previous reports [2–6] because of the selection of asymptomatic patients.

Secondly, all recurrent sites were recognized in intrathoracic or cervical fields. Therefore, it was possible to detect them adequately with only chest CT. However, although almost all cases were incidentally intrathoracic recurrences in this study, we believe that the capability to detect not only extrathoracic metastases but also other diseases is a major advantage of FDG-PET/CT.

Thirdly, radiation exposure of patients from FDG-PET/CT is high. Brix *et al*. [22] investigated the radiation exposure of patients who underwent FDG-PET/CT at four German hospitals and reported that the effective dose of PET/CT was ∼25 mSV and ∼3 times as high as that of conventional CT (7.0 mSV) [23]. This value is very high, although examination by PET/CT occurs only once per year. Furthermore, cancer risks associated with CT studies are also indicated [24], so radiation exposure is a considerable problem.

Fourthly, in Japan, the cost of FDG-PET/CT is higher than that of chest-enhanced CT (∼1120 US dollars vs ∼180 US dollars) [25].

In conclusion, FDG-PET/CT is a useful tool that has a high capability of detecting recurrences in asymptomatic NSCLC patients after a potentially curative operation. However, a large-scale multi-institutional randomized control trial may be needed to ascertain the benefit of surveillance with FDG-PET/CT, including cost-effectiveness and post-recurrence survival in postoperative patients.

Conflict of interest: none declared.

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