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ORIGINAL ARTICLE

Munetaka Takekuma · Makoto Maeda · Takachika Ozawa
Kazuhiko Yasumi · Tatsuo Torizuka

Positron emission tomography with 18F-fluoro-2-deoxyglucose for the detection of recurrent ovarian cancer

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Abstract
Background. Recurrent ovarian cancer is refractory and resistant to treatment in most patients, and no effective treatment for it has been established. Starting a treatment when tumors still consist of micro foci may contribute to improvement of prognosis. Therefore, the early diagnosis of relapse is important.
Methods. Among patients with epithelial ovarian cancer in whom initial treatment achieved remission between April 1998 and December 2003, those patients in whom the cancer-related antigen (CA)125 level was increased during the subsequent follow-up period, or those who showed abnormal computed tomography (CT)/magnetic resonance imaging (MRI) findings despite normal CA125 levels, were examined by 18F-fluoro-2-deoxyglucose – positron emission tomography (FDG-PET). We compared the rates of accurate diagnosis of recurrence achieved using CT/MRI, CA125, and FDG-PET in patients with a definitive diagnosis of relapse.
Results. We investigated 29 patients with epithelial ovarian cancer. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG-PET were 84.6% (22/26), 100% (3/3), 100% (22/22), 42.9% (3/7), and 86.2% (25/29), respectively. These values were higher than the corresponding values obtained using CT/MRI or CA125 levels.
Conclusion. FDG-PET may be very useful for identifying sites of recurrent ovarian cancer, although this procedure had a low NPV because of the high rate of false-negative findings for micro or cystic lesions.

Key words FDG-PET · Recurrent ovarian cancer · CT/MRI · CA125 levels

M. Takekuma (✉) · M. Maeda
Department of Gynecology, Hamamatsu Medical Center, 328 Tomitsukacho, Hamamatsu 432-8580, Japan
Tel. +81-53-453-7111; Fax +81-53-452-9217
e-mail: obgyns-21@hmedc.or.jp

T. Ozawa · K. Yasumi
Department of Pathology, Hamamatsu Medical Center, Hamamatsu, Japan

T. Torizuka
Positron Medical Center, Hamamatsu Medical Center, Hamamatsu, Japan

Introduction

Ovarian cancer is a malignant disease that still has rather poor treatment results. The use of platinum preparations (1980s) and taxane preparations (1990s) has markedly improved the response rate to chemotherapy; however, the recurrence rate of advanced ovarian cancer remains high (60%–70%). Satisfactory treatment results have not yet been achieved.

Recurrent ovarian cancer is refractory and resistant to treatment in most patients, and no effective treatment has been established. Starting a treatment when recurrent tumors are still at the stage of micro foci may improve the prognosis. Therefore, the early diagnosis of relapse is important, and various types of examinations are performed to detect relapses. In clinical practice, the diagnosis of relapse by the measurement of a blood tumor marker (cancer-related antigen [CA]125) level is most commonly applied. Many studies have shown that this procedure is useful.[1–4] Other studies have indicated that the tumor marker level is elevated a few weeks before signs of relapse appear,[5–6] suggesting the reliability of this tumor marker. However, we often encounter patients in whom diagnosis is difficult because diagnostic imaging cannot identify the relapse site, despite an increase in the tumor marker level.

Since April 1998, we have performed 18-F fluoro-2-deoxyglucose positron emission tomography (FDG-PET) in patients with various malignant gynecological tumors, and we have investigated the diagnostic usefulness of this procedure. In this study, we investigated the usefulness of FDG-PET in diagnosing recurrent ovarian cancer in the above patients.

Subjects and methods

Among patients with malignant ovarian tumor in whom initial treatment achieved remission between April 1998 and December 2003, 35 patients were examined by FDG-PET. The criteria for subjects in whom FDG-PET was used were: (1) histologically confirmed epithelial ovarian cancer, and (2) clinical suspicion of having recurrence of the cancer (e.g., serum tumor marker was elevated, but there were no abnormal computed tomography (CT)/magnetic resonance imaging (MRI) findings, or vice versa). The subjects fasted for at least 6 h prior to FDG-PET. About 60 min after the intravenous administration of FDG, PET was performed. To avoid the influence of FDG excretion in urine, patients were asked to void just before the start of the emission scan, or a urethral catheter was inserted into the urinary bladder during examination. Accumulation of FDG was evaluated using the standardized uptake value (SUV). SUV, calculated by correcting the accumulation of FDG by the dose of FDG and body weight, using the formula, SUV = tissue concentration (mCi/g)/injected dose (mCi)/body weight (g), represents tumor activity. In our hospital, tumors with an SUV of 3 or more are judged to be malignant, based on our previous data.

Any foci of FDG uptake that were increased relative to the background and were not located in areas of physiologically increased uptake were considered to be positive for recurrent lesions. Lesions that were detected by PET, but which were not histologically examined, were considered to be true positive if the disease became obvious on clinical observation within 3 months of the PET examination. Abnormal foci seen on PET that were not verified during a follow-up of this duration were considered to be false-positive. When no abnormality was found on PET and when no intervention was performed, the result was considered to be true-negative if no disease was identified by other imaging studies or by clinical observation within 3 months of the PET examination. The findings of FDG-PET were compared with those of conventional imaging and the CA125 levels, and were examined in relation to histological findings and clinical observations for more than 3 months.

In addition, we compared the rate of accurate diagnosis in patients with a definitive diagnosis of relapse to the results obtained with CT/MRI (which was performed simultaneously with FDG-PET), CA125 (normal value; <35 IU/ml), and PET. Written informed consent was obtained from all patients.

Results

Of 35 subjects in whom FDG-PET was performed, we further investigated 29 patients with epithelial ovarian cancer (after having excluded 1 patient with germ cell tumor, 2 patients with sex-cord stromal tumors, 1 patient with ovarian carcinosarcoma, 1 patient with metastatic ovarian cancer, and 1 patient with double cancer). The ages of the 29 subjects ranged from 32 to 75 years, with a mean age of 57.7 years. The FIGO stage was judged as I in 3 patients, III in 21 patients, and IV in 3 patients. The stage was unclear in 2 patients. Furthermore, the histological type in 22 patients suggested serous adenocarcinoma, which was the most common type. The histological type suggested clear cell carcinoma in 3 patients, mucinous adenocarcinoma in 2 patients, and poorly differentiated adenocarcinoma in 2 patients (Table 1). In 23 patients, CA125 levels were increased. In the remaining 6 patients, there was no increase (Table 2), but CT/MRI or hematological data revealed abnormal findings, suggesting relapse.

Table 1. Characteristics (1)

Age (years)	Median 57.7 (32–75)	
FIGO stage	I	3
	III	21
	IV	3
	Unclear	2
Pathology	Serous	22
	Mucinous	2
	Clear cell	3
	Poorly differentiated	2
Elevated CA125	Positive	23
	Negative	6

In 21 of the 23 CA125-positive patients, relapse was clinically confirmed. However, CT/MRI identified the relapse site in only 4 of these 21 patients (patients 1, 2, 3, and 4). In 19 of 21 patients with clinically confirmed relapse, FDG-PET identified the relapse site. In addition, PET identified the relapse site in the 4 patients in whom CT/MRI detected a relapse site. CT/MRI and FDG-PET images for patients 2 and 9 are shown in Figs. 1 and 2, respectively. Patient 2 (Fig. 1) was a representative patient in whom both PET and CT/MRI detected the relapse site. In patient 9 (Fig. 2), FDG-PET showed abnormal accumulation of FDG in the pelvis, and the relapse site could be confirmed; however, there were no abnormal findings for the site on CT/MRI. Furthermore, 2 patients (patients 20 and 21), in whom neither FDG-PET nor CT/MRI identified the relapse site, had peritoneal dissemination of micro lesions.

In five of six CA125-negative patients, relapse was confirmed. In one of these patients, patient 28, it was impossible to detect the relapse, which consisted of peritoneal dissemination of micro lesions, by FDG-PET or CT/MRI. In patient 27, in whom CT/MRI confirmed a cystic lesion, it was impossible to detect the lesion site by FDG-PET. The remaining three patients consisted of one patient with an intraperitoneal tumor, one patient with a pelvic tumor, and one patient with liver metastasis. These lesions were confirmed by both FDG-PET and CT/MRI.

Based on these results, we calculated and compared the rates of consistency of diagnosis by the findings of CT/MRI, CA125, and FDG-PET. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of CT/MRI were 30.8% (8/26), 66.6% (2/3), 88.9% (8/9), 10% (2/20), and 34.5% (10/29), respectively. The sensitivity, specificity, PPV, NPV, and accuracy of

Table 2. Characteristics (2)

Patient No.	Age (years)	Stage	Histology	FDG/PET	CT / MRI	Recurrence
CA125-positive						
1	72	IIIb	Mucinous	+	+	+
2	56	IIIc	Serous	+	+	+
3	53	IIIc	Serous	+	+	+
4	75	IIIc	Serous	+	+	+
5	57	Ic	Serous	+	–	+
6	50	III	Serous	+	–	+
7	54	IIIc	Serous	+	–	+
8	66	IIIc	Serous	+	–	+
9	69	IIIc	Serous	+	–	+
10	54	IIIc	Serous	+	–	+
11	65	IIIc	Serous	+	–	+
12	64	IIIc	Serous	+	–	+
13	47	IIIc	Serous	+	–	+
14	54	IIIc	Poorly diff.	+	–	+
15	58	IV	Serous	+	–	+
16	46	IV	Serous	+	–	+
17	62	IV	Serous	+	–	+
18	68	Unknown	Serous	+	–	+
19	56	Unknown	Serous	+	–	+
20	69	IIIc	Serous	–	–	+
21	60	IIIc	Clear cell	–	–	+
22	47	IIIb	Serous	–	–	–
23	67	IIIc	Serous	–	–	–
CA125-negative						
24	54	III	Serous	+	+	+
25	72	IIIc	Serous	+	+	+
26	63	IIIc	Poorly diff.	+	+	+
27	49	Ic	Clear cell	–	+	+
28	34	Ic	Clear cell	–	–	+
29	32	IIIb	Mucinous	–	+	–

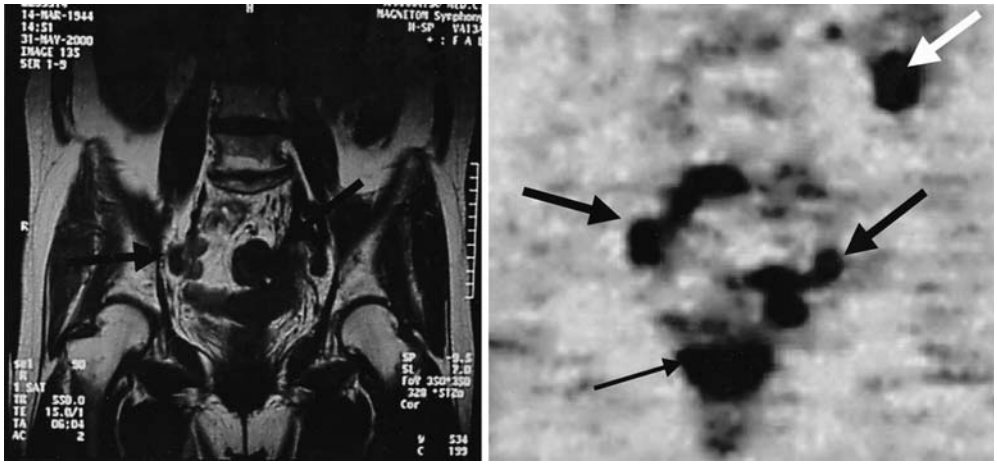

Fig. 1. Magnetic resonance imaging (MRI) and 18F-fluoro-2-deoxy glucose positron emission tomography (FDG-PET) in patient 2. Both PET and MRI detected the relapse site. *Thick black arrows*, relapse site; *narrow black arrow*, bladder; *white arrow*, kidney

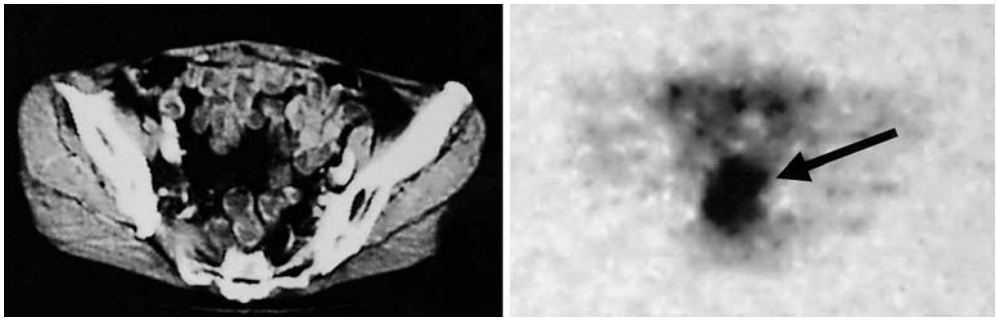

Fig. 2. MRI and FDG-PET in patient case 9. FDG-PET showed abnormal accumulation of FDG in the pelvis, showing, the relapse site. *Black arrow*, relapse site

Table 3. Results of FDG-PET, CT/MRI, and measurement of serum CA125 levels for the diagnosis of recurrent ovarian cancer

	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
FDG-PET	22	4	3	0	84.6	100	100	42.9	86.2
CT/MRI	8	18	2	1	30.8	66.6	88.9	10	34.5
CA125	21	5	1	2	80.8	33.3	91.3	16.7	75.9

TP, true-positive; FN, false-negative; TN, true-negative; FP, false-positive; PPV, positive predictive value; NPV, negative predictive value

CA125 were 80.8% (21/26), 33.3% (1/3), 91.3% (21/23), 16.7% (1/6), and 75.9% (22/29), respectively. The corresponding values for FDG-PET were 84.6% (22/26), 100% (3/3), 100% (22/22), 42.9% (3/7), and 86.2% (25/29), respectively, and these values were the highest among those for the three methods (Table 3).

Discussion

During the past 20 to 30 years, the development of noninvasive tomography with good resolution, such as that performed with CT/MRI devices, has markedly advanced, and the clinical usefulness of these methods has been demonstrated. However, these methods have limitations: the morphological abnormalities of foci alone are detected, and it is impossible to clarify functional changes. PET facilitates the evaluation of physiological/biochemical changes, but not the evaluation of the morphology of foci. In this regard, PET may be a diagnostic imaging procedure that is basically different from CT/MRI. The usefulness of PET in various fields has been reported.

Recently, PET has been widely applied in studies of malignant tumors. In particular, many studies have shown the usefulness of FDG-PET.[7–9] In FDG-PET, tissue glycometabolism is visualized. This procedure facilitates the identification of malignant tumor sites and provides semiquantification (SUV) of tumor activity, although the resolution is poor. It also facilitates qualitative diagnosis, which cannot be obtained by conventional diagnostic imaging procedures. In this study, we investigated the usefulness of FDG-PET for diagnosing recurrent ovarian cancer. Generally, recurrent ovarian cancer has been diagnosed by performing invasive procedures such as a second-look operation (SLO) and by imaging procedures such as CT/MRI, or by measuring tumor markers such as CA125. However, the rate of false-positive findings by SLO is approximately 50%, and some studies have found that SLO does not influence the survival rate; further, the usefulness of SLO is controversial.[10–15] Currently, recurrent ovarian cancer is mainly diagnosed based on CT/MRI findings and the level of CA125, as noninvasive examinations.

Many studies have shown that CT/MRI and the tumor marker CA125 are useful for evaluating recurrent ovarian cancer. Meden et al.[16] reported that, for diagnosing recurrent ovarian cancer, the sensitivity and specificity of CT were 70% and 65%, respectively, and that the sensitivity and specificity of CA125 were 55% and 100%, respectively. In our study, the sensitivity, specificity, and accuracy of FDG-PET for the diagnosis of recurrent ovarian cancer were 84.6% (22/26), 100% (3/3), and 86.2% (25/29), respectively, as shown in Table 3. These values were the highest of those among the three examinations/parameters evaluated here, i.e., FDG-PET, CT/MRI, and CA125. Torizuka et al.[17] also reported that FDG-PET was more useful than CT/MRI and CA125 for diagnosing ovarian cancer recurrence. Yen et al.[18] investigated the usefulness of FDG-PET, CT/MRI, and CA125 in 24 patients in whom recurrent ovarian cancer was suspected, and the sensitivity, specificity, and accuracy of FDG-PET were 90.9%, 92.3%, and 91.7%, respectively, similar to our results. The sensitivity of CT/MRI was 90.9%, and the specificity of CA125 was 76.9%. These values were higher than our results (30.8%, 33.3%). This may have been because of bias in patient selection in our study; namely, these lower values in our study may have resulted from the fact that we performed PET in patients in whom CA125 levels were high, but in whom CT/MRI could not identify the relapse site, or in patients in whom CT/MRI suggested relapse, but in whom there were no increases in the CA125 level, making the diagnosis of relapse difficult. Thus, the values we obtained for CT/MRI and CA125 were lower than the values in the literature. Therefore, we cannot simply compare FDG-PET to CT/MRI and CA125. However, in this study, it was difficult to diagnose relapse using conventional examinations (CT/MRI and tumor markers, including CA125) in all patients, as described above. So, considering the sensitivity, specificity, and accuracy of FDG-PET, as shown in Table 3, and the limitations of the current diagnosis of recurrent ovarian cancer, FDG-PET may be very useful for identifying recurrent ovarian cancer sites.

Treatment for recurrent ovarian cancer has not been established; however, some studies have reported the usefulness of a second debulking surgery[19,20] or the usefulness of intraperitoneal chemotherapy,[21,22] depending on the relapse site, tumor volume, and number of lesions. Thus, earlier diagnosis increases the range of choices of treatment. Zimny et al.[5] reported that FDG-PET facilitated the diagnosis of relapse 6 months earlier, on average, than CT/MRI and CA125; thus, FDG-PET may also be useful for the early diagnosis of relapse. In addition, FDG-PET facilitates systemic investigation, and is also useful for detecting remote metastasis. In our study, in patient 5, lung metastasis was detected by FDG-PET, although it was impossible to detect it by CT/MRI.

However, although FDG-PET shows excellent PPV, its NPV is low.[5,23] This is because the rate of false-negative

findings for micro or cystic lesions is high. In this study, 4 patients (patients 20, 21, 27, and 28) showed false-negative findings on FDG-PET. Patient 27 showed a recurrent cystic tumor on MRI, but no accumulation of FDG on FDG-PET. Also, patients 20, 21, and 28 showed ascites only on MRI / CT, but, as with patient 27, no accumulation of FDG on FDG-PET. In such patients, the rate of accurate diagnosis by FDG-PET is low, which may be a diagnostic limitation. However, with a change in the radioactive substances used, PET can facilitate the visualization not only of glycometabolism but also of protein/nucleic acid synthesis, bone metabolism, blood flow, and oxygen consumption. Thus, the above limitation will likely be conquered in the near future.

The 5-year survival rate of patients with ovarian cancer has shown no improvement. Various studies have investigated the usefulness of surgical therapy, chemotherapy, and radiotherapy for patients with ovarian cancer. The rate of accurate diagnosis by diagnostic imaging procedures should be further improved. In the future, morphological and biological diagnostic imaging, for identifying the relapse site and evaluating the treatment response will be essential. FDG-PET may play an important role in such imaging.

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