Ovarian cancer recurrence: role of whole-body positron emission tomography using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose

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Abstract. This study was designed to assess the value of whole-body positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) for the diagnosis of recurrent ovarian cancer. Twenty-five patients who had previously undergone surgery for ovarian cancer were imaged using whole-body FDG-PET. During the 4 weeks preceding the PET study, conventional imaging, comprising computed tomography (CT) and magnetic resonance (MR) imaging of the abdomen and/or pelvis, was performed and serum CA125 levels were measured. PET imaging was commenced at 60 min after the intravenous administration of FDG in all patients. PET results were compared with the results of conventional imaging and CA125 levels, and related to pathological findings and clinical follow-up for more than 6 months. FDG-PET showed a sensitivity of 80% (16/20), a specificity of 100% (5/5) and an accuracy of 84% accuracy (21/25) for the diagnosis of recurrent ovarian cancer. The sensitivity, specificity and accuracy of conventional imaging were 55% (11/20), 100% (5/5) and 64% (16/25), respectively. PET could detect recurrent lesions in seven of nine patients in whom conventional imaging was falsely normal, while conventional imaging was true positive in two of four patients with false-negative PET results. The CA125 results showed a sensitivity of 75% (15/20), a specificity of 100% (5/5) and an accuracy of 80% accuracy (20/25). Among the 15 patients with true-positive CA125 results, PET correctly detected abnormal foci of recurrence in 13 patients (86.7%) whereas conventional imaging showed recurrent lesions in only eight patients (53.3%). In conclusion, our preliminary study demonstrates that FDG-PET may be accurate and useful for the detection of tumour recurrence when conventional imaging is inconclusive or negative, especially in patients with abnormal CA125 levels.

Keywords: Recurrent ovarian cancer – Diagnosis – FDG-PET – Conventional imaging – Serum CA125 levels

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Introduction

Ovarian cancers account for most deaths resulting from cancers of the female genital tract. This is primarily because, unlike other common malignant gynaecological neoplasms (cancers of the endometrium and cervix), ovarian cancers present at a relatively advanced stage of disease owing to the lack of an effective early diagnostic test. After completion of initial surgery, patients with advanced ovarian cancer should receive systemic chemotherapy for disease control. In addition, it is essential to monitor such patients carefully during the course of treatment because the incidence of recurrence is relatively high.

The cancer-related antigen 125 (CA125) is an established marker for ovarian cancers, and serial determination of serum CA125 concentrations is the most frequently used method for the detection of asymptomatic recurrences [1, 2, 3]. It is known that elevation of the CA125 level above 35 U/ml indicates tumour recurrence, but a negative CA125 result does not provide absolute assurance of a disease-free state [1]. Furthermore, measurement of CA125 levels provides no localising information about recurrent disease.

Recent progress in diagnostic imaging, especially development of magnetic resonance (MR) imaging and he-

lical computed tomography (CT) with contrast medium, has improved the accuracy in the depiction of recurrent or metastatic lesions of ovarian cancer. These techniques are excellent in characterising lesions once they have attained a size of 1.0–1.5 cm. However, determination of tumour involvement with these morphological imaging techniques is reliant on the location, size and shape of the lesion. In particular, lymph nodes less than 1.0 cm in size cannot be classified as benign or malignant [4, 5]. In the study of Forstner et al. [6], the sensitivity of MR imaging was only 35% when the tumour diameter was smaller than 2 cm while it showed a statistically significant improvement to 82% when the tumour diameter was greater than 2 cm. In this clinical setting, the need for more sensitive and accurate imaging studies is clear.

Positron emission tomography (PET) with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) has emerged as an extremely useful technique in clinical oncology [7, 8, 9, 10, 11]. Particularly since the introduction of whole-body scanning, clinical applications of FDG-PET for tumour staging and monitoring after treatment have been increasing [12, 13, 14]. In contrast to conventional imaging methods, which provide primarily morphological information, PET can yield metabolic information with high-resolution images. Thus, PET may be helpful for detecting small recurrent lesions in patients in whom post-therapeutic alterations in anatomy may make it difficult to interpret conventional imaging studies. To our knowledge, however, the role of FDG-PET in the diagnosis of recurrent ovarian cancer has been addressed in only a limited fashion in previous studies [15, 16, 17, 18, 19]. In this study, we evaluated the role of whole-body FDG-PET for detecting recurrence in patients who had previously undergone surgery for ovarian cancer and compared the clinical value of PET with that of conventional imaging modalities and serum CA125 levels.

Materials and methods

Patient population. Whole-body FDG-PET scans were performed on 25 patients in the postoperative course following surgery for ovarian cancer (age range, 29–72 years; mean age, 55 years). The 25 patients had the following histopathological tumour types: serous adenocarcinoma (*n*=19), poorly differentiated adenocarcinoma (*n*=2), mucinous adenocarcinoma (*n*=1), clear cell adenocarcinoma (*n*=2) and granulosa cell tumour (*n*=1). The International Federation of Gynecology and Obstetrics tumour stage at initial diagnosis was stage I in six, stage II in one, stage III in 16 and stage IV in two patients. After primary cytoreductive surgery, the patients were treated with the following chemotherapeutic combinations: six patients received cisplatin, adriamycin and cyclophosphamide (6–13 cycles); four patients received carboplatin and etoposide (5–9 cycles); three patients received paclitaxel and carboplatin (3–6 cycles); two patients received cisplatin and etoposide (3 cycles); two patients received paclitaxel and carboplatin (6 cycles); and eight patients received other chemotherapeutic combinations. The time interval between initial diagnosis and PET examination was 4 months to 12 years (median, 14 months), and the interval between the end of chemotherapy and PET was 1 month to 10 years (median, 2.5 months). In 15 of the 25 patients, serum CA125 levels were elevated (>35 U/ml) at the time of PET examination while the other ten patients had normal levels of CA125. These ten patients underwent PET studies because of abnormal findings on conventional imaging and physical examination, elevation of other serum tumour markers, or symptoms such as abdominal distention or general fatigue. All patients provided written informed consent for participation in the study.

PET imaging. All patients fasted for at least 5 h before the PET study. Serum glucose levels measured at the time of FDG injection were normal in all patients. The whole-body PET scanner used was an SHR22000 (Hamamatsu Photonics, K.K., Hamamatsu, Japan) [20]. The SHR22000 scanner permits simultaneous acquisition of 63 transverse planes of 3.6-mm thickness encompassing a 23-cm axial field of view. For attenuation correction for emission data, transmission scans were obtained before FDG injection with five bed positions with a germanium-68 external ring source. Static emission scans were obtained from the upper femur to the head with five bed positions, starting 60 min after intravenous administration of FDG (300–400 MBq), synthesised according to the standard procedure [21]. To minimise the accumulation of FDG activity in the urinary bladder, patients were asked to void just before the start of the emission scan or the urinary bladder was continuously drained by a Foley catheter during the emission scan. Transaxial, coronal and sagittal images were reconstructed by means of a filtered back-projection algorithm with a 128×128 matrix. The average reconstructed x-y spatial resolution was about 3- to 4-mm full-width at half-maximum in-plane.

Conventional imaging. The conventional imaging examinations comprised X-ray computed tomography (CT) and magnetic resonance (MR) imaging. CT imaging was acquired using the CT scanner (ProSeed, General Electric Yokogawa Medical Systems, Tokyo, Japan) before and after administration of non-ionic iodinated contrast medium (100 ml). Images with 10-mm contiguous slices were routinely obtained for the abdomen and/or pelvis. MR imaging was acquired on a 1.5-T MR system (Magnetom Symphony, Siemens, Erlangen, Germany) using a body coil. Transaxial and sagittal T2-weighted fast spin-echo images (TR/effective TE=4,000/80–100) were obtained. Using 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist, Schering, Osaka Japan), transaxial, coronal and sagittal T1-weighted spin-echo images (TR/TE=550/15) were acquired. The fat saturation method was used when needed. The conventional imaging studies were performed within the 4 weeks preceding the PET examination. The findings of conventional imaging were interpreted by experienced radiologists who knew the clinical data but were unaware of the PET results.

Image analysis. PET images were visually interpreted and analysed using all available clinical data and results of other imaging modalities. 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 6 months of the PET examination. Abnormal foci seen on PET that were not verified on 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 6 months of the PET examination. The findings of FDG-PET were compared with those of conventional imaging and serum CA125 levels, and related to histological findings and clinical observation for more than 6 months.

Statistical analysis. The sensitivity, specificity and accuracy of PET imaging, conventional imaging and CA125 levels were compared using the McNemar test of correlated proportions with Yate continuity correction. A two-sided P value<0.05 was considered significant.

Results

Of the 25 patients studied, 20 had tumour recurrence and 5 were free from recurrence. Recurrent disease was histologically proven in eight patients by biopsy (n=2) or operation (n=6) and was confirmed by clinical follow-up in 12 patients. Among these 20 patients, FDG-PET findings were true positive in 16, with one lesion identified in each of three patients and more than two lesions identified in the other 13 patients. These foci of increased FDG accumulation were found in several locations: pelvis (ten patients), abdomen (six patients), liver (three patients) and mediastinum (one patient). At the time of PET examination of these 16 patients, serum CA125 levels were elevated in 13 and falsely normal in three.

Among the 16 patients with true-positive PET results, conventional imaging was true positive in nine patients (Fig. 1) and false negative in the other seven. In one patient, a recurrent liver lesion was correctly detected by CT examination, but MR imaging showed a pelvic mass (2 cm) which was proven to be false positive by the second-look operation. Of the seven patients with false-negative conventional imaging, three received chemotherapy without further imaging examinations because of rapid disease progression and the other four underwent follow-up CT examinations within 2 weeks after PET. Three of the four patients underwent 5-mm slice CT imaging with contrast medium. In two patients, small foci of recurrence in the abdomen were shown by the 5-mm slice CT, corresponding to the abnormal FDG uptake (Fig. 2). In the other patient, however, 5-mm slice CT yielded an equivocal finding and only PET could identify the recurrent lesion in the pelvis, which was confirmed by surgical pathology (Fig. 3). The remaining patient underwent chest CT, which indicated the mediastinal tumour corresponding to the increased FDG uptake on PET. Lymph node metastasis with tracheal invasion was proven by biopsy under bronchoscopic examination.

FDG-PET was false negative in four of the 20 relapsed patients. Serum CA125 levels were abnormal in two patients and were falsely normal in the other two patients. Conventional imaging yielded true-positive results in two of the four patients. One patient showed a cystic tumour with a small solid component on pelvic MR imaging. This patient underwent a second-look operation and the recurrent tumour of ovarian cancer was pathologically diagnosed. The other patient developed disseminated peritoneal disease shown by abdominal CT imaging. PET revealed a hot spot in the neck but no clinical progression was observed within 6 months in the follow-up. Thus, this patient had both false-negative and false-positive results on FDG-PET. The other two patients had false-negative findings on conventional imaging. In one patient, continuously increasing CA125 levels in the follow-up clinically confirmed the presence of recurrent disease. The CA125 level decreased to normal after effective chemotherapy in this patient. In the other patient, conventional imaging and CA125 measurements were negative but serum C-reactive protein was positive (6+) at the time of PET examination. This patient re-

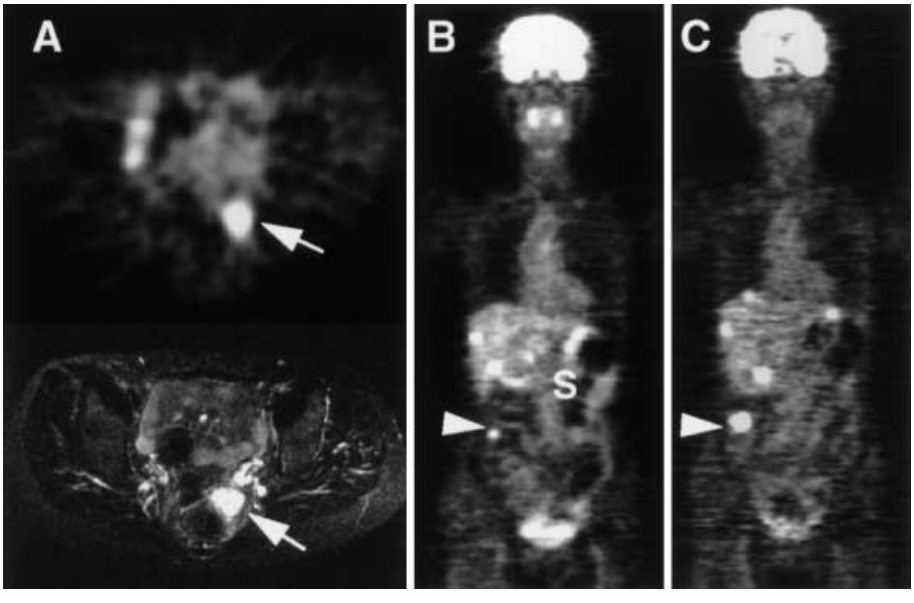

Fig. 1. A FDG-PET showed abnormal FDG uptake in the pelvis (*arrow*), corresponding to a hyperintense lesion on the T2-weighted MR image. Serum CA125 level was 130 U/ml. After radiation therapy, the pelvic tumour disappeared and the CA125 level normalised. Three months later, however, the CA125 level had risen again to 160 U/ml. **B** Whole-body coronal FDG-PET image showed multiple hot spots in the liver and abdomen (*arrowhead*), suspicious for tumour recurrence. Physiological uptake in the stomach was observed (*S*). **C** One month later, the activities of the hot spots in the liver and abdomen (*arrowhead*) had apparently increased

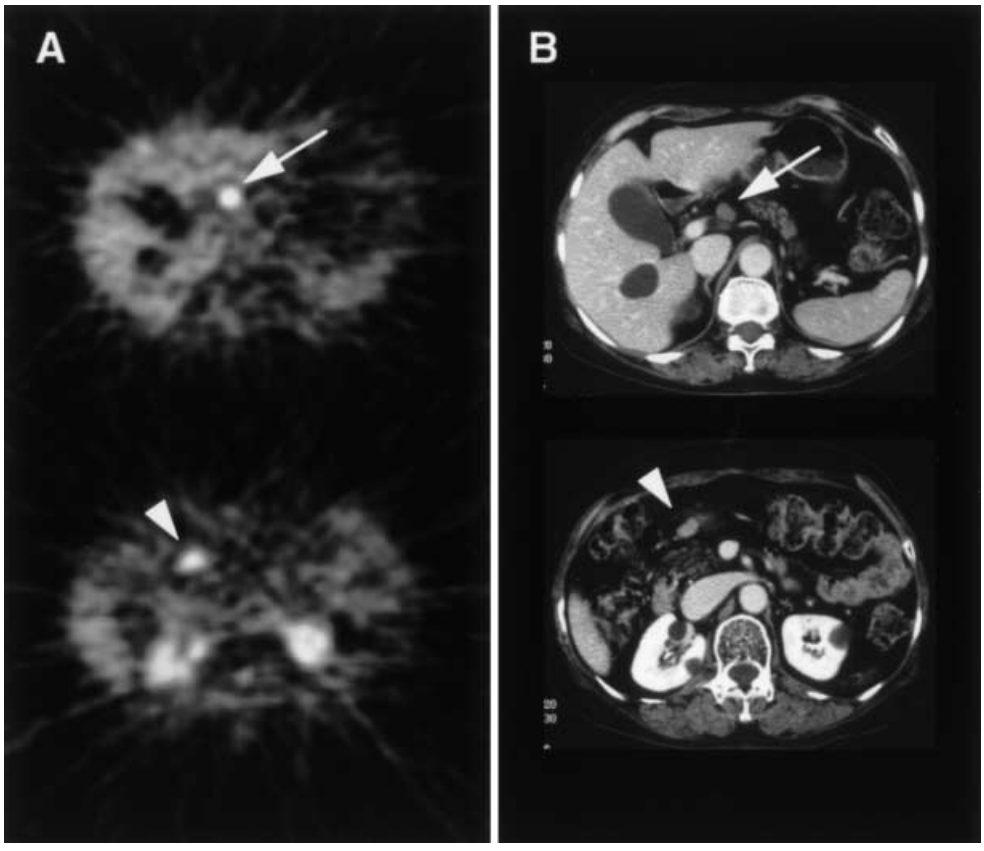

Fig. 2. A FDG-PET images showed two hot lesions in the abdomen (*arrow* and *arrowhead*). **B** Contrast-enhanced 5-mm slice CT images revealed two small tumours in the abdomen (*arrow* and *arrowhead*), corresponding to the intense FDG uptake. Recurrent tumours of ovarian adenocarcinoma were histologically proven by the second-look operation. Cystic lesion was seen in the right lobe of the liver

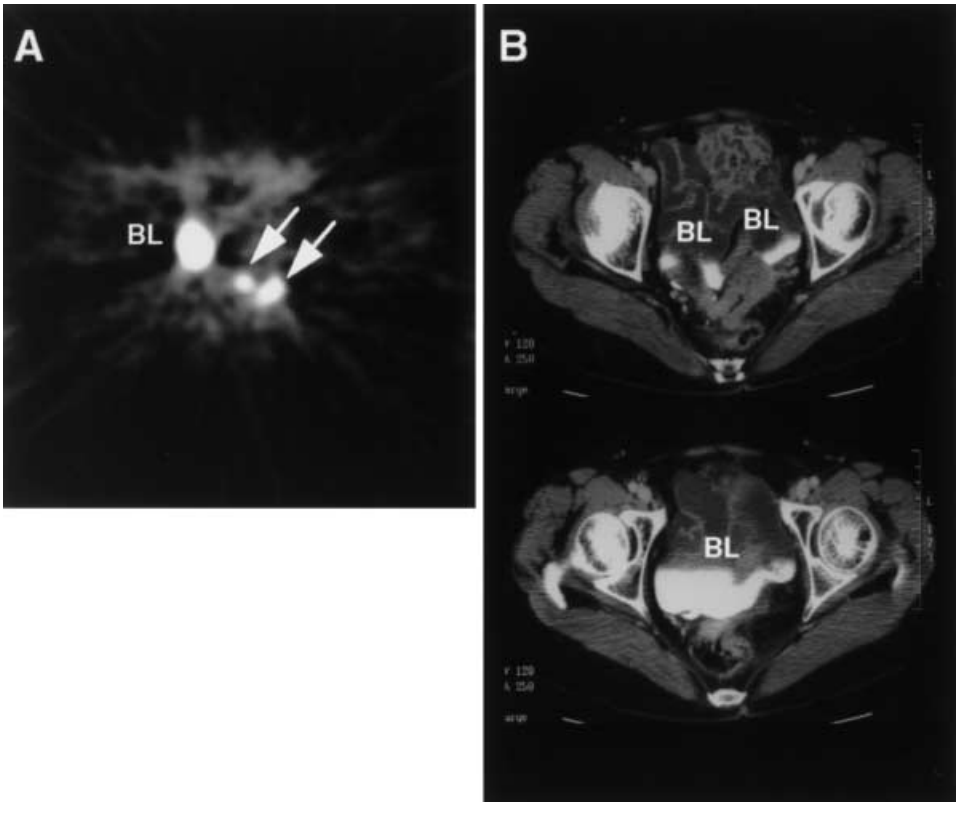

Fig. 3. A FDG-PET showed abnormal foci of increased FDG uptake in the pelvis (*arrows*). *BL*, Physiological uptake by the urinary bladder. **B** Corresponding contrast-enhanced 5-mm slice CT images did not show tumour lesions, although the bowel seemed to be dilated, with mild wall thickening. Surgical histology revealed recurrent tumours of ovarian adenocarcinoma. *BL*, Urinary bladder filled with contrast medium

fused treatment and developed peritonitis carcinomatosa 2 months after PET. Histological diagnosis at initial surgery was clear cell carcinoma, which was an aggressive type of ovarian cancer.

In the remaining five patients, PET results were true negative because no recurrent disease was identified by other imaging modalities or by clinical observation for 8–35 months (median, 15 months) after PET. Conventional imaging and CA125 levels were also true negative in these five patients, although CA19-9 levels were elevated in two patients at the time of PET.

Table 1 shows the results of FDG-PET, conventional imaging and determination of serum CA125 levels for the diagnosis of recurrent ovarian cancer in the 25 patients. FDG-PET showed a sensitivity of 80%, a specificity of 100% and an accuracy of 84% for the detection of recurrent tumours, if one patient with both false-negative and false-positive PET findings was included in false-negative category. The sensitivity, specificity and accuracy of the conventional imaging were 55%, 100% and 64%, respectively, if one patient with true-positive CT and false-positive MR imaging was included in the true-positive category. The sensitivity, specificity and accuracy of CA125 were 75%, 100% and 80%, respectively. PET and CA125 showed higher accuracy than conventional imaging, although the differences were not significant (P=0.070 and 0.117, respectively).

Figure 4 depicts the combined performance of PET, conventional imaging and serum CA125 level in predicting the presence or absence of recurrent disease in the 25 patients. In 12 patients (48%), all three parameters accurately predicted the presence (n=7) or absence (n=5) of tumour recurrence. In six patients (24%), the PET result and CA125 level correctly demonstrated the presence of recurrence whereas conventional imaging alone was falsely normal. On the other hand, in one patient (4%), conventional imaging and CA125 level were true positive and only PET was incorrect. Among 15 patients with true-positive CA125 results, PET correctly detected abnormal foci of recurrence in 13 (86.7%) while conventional imaging showed recurrent lesions in only eight (53.3%). None of the three parameters was correct in one patient (4%).

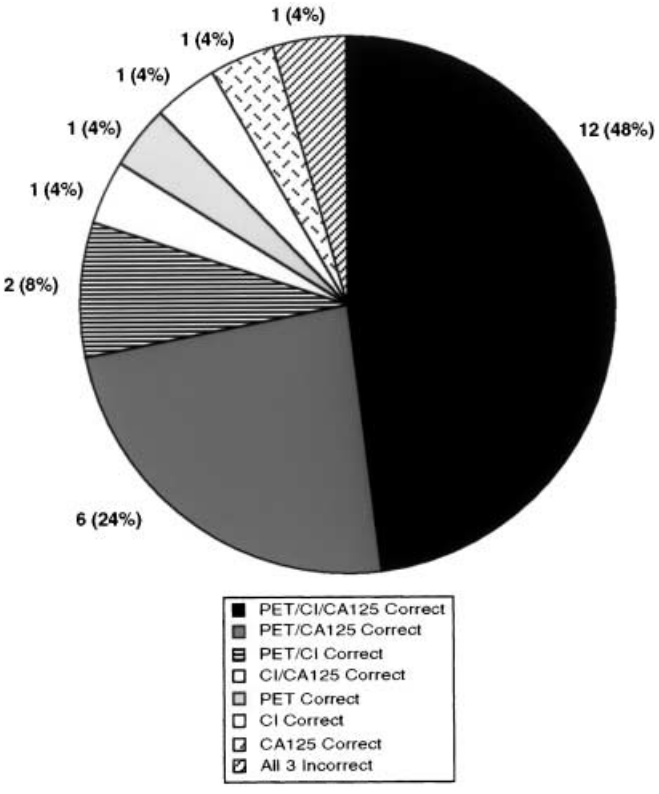

Fig. 4. Graph showing the combined performance of PET, conventional imaging (*CI*) and CA125 level in determining tumour recurrence in 25 patients with treated ovarian cancer

Discussion

Ovarian cancer continues to present a challenge in clinical oncology. Its frequency is rising, and ovarian cancer has become the second most common gynaecological malignancy. Despite rigorous efforts to improve diagnosis and therapy, ovarian cancer remains the leading cause of death from gynaecological cancer [22]. Clinical treatment of patients with ovarian cancer has traditionally included initial surgical staging and aggressive cytoreduction, followed by a variety of adjuvant chemotherapy regimens. Although the initial response to therapy is

Table 1. Results of FDG-PET, conventional imaging and measurement of serum CA125 levels for the diagnosis of recurrent ovarian cancer in 25 patients

	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)	Accuracy (%)
FDG-PET	16	4	5	(1)[a]	80	100	84
Conventional imaging[c]	11	9	5	(1)[b]	55	100	64
CA125	15	5	5	0	75	100	80

TP, True positive; FN, false negative; TN, true negative; FP, false positive

[a] One patient with both FN and FP findings is included in the FN category

[b] One patient with both TP and FP findings is included in the TP category

[c] CT and MRI

good, 5-year survival for advanced disease is only 17% because of the high rate of recurrence [23].

Our study demonstrated the feasibility of using FDG-PET for the diagnosis of tumour recurrence in patients with previously treated ovarian cancer. For the detection of recurrent disease, the sensitivity and accuracy of PET were superior to those of conventional imaging (80% vs 55% and 84% vs 64%, respectively), although the differences were not significant. PET was able to detect recurrent tumours in seven of nine patients in whom conventional imaging was falsely normal. Three of these patients underwent 5-mm slice CT with contrast medium after PET. In two of them, 5-mm slice CT showed small foci of recurrence in the abdomen, corresponding to abnormal FDG uptake (Fig. 2); however, it may be difficult to classify such small tumours as benign or malignant based solely on criteria related to tumour size on CT. In the remaining patient, the 5-mm slice CT result was equivocal and only PET could detect the recurrent lesion in the pelvis, which was proven by surgical pathology (Fig. 3). Because PET indicates regional metabolic abnormalities, PET could identify recurrent ovarian cancer in tissues that appeared normal anatomically on CT imaging and allowed the differentiation of recurrent disease from postoperative changes.

The utility of serum CA125 measurements has been established in follow-up of ovarian cancer, and an elevated CA125 (>35 U/ml) level is a strong indication of residual or recurrent tumour [1, 2]. In our study, the CA125 result showed a high accuracy of 80% (20/25) and a positive predictive value of 100% (15/15), but the negative predictive value was relatively low (50%, 5/10). Our findings support the results of Rubin et al. [3], who demonstrated that residual or recurrent tumours of ovarian cancer were found at second-look laparotomy in 18 (62.1%) of 29 patients in whom CA125 levels were normal. Therefore, CA125 is most useful when elevated, but normal values cannot exclude the presence of active disease. Furthermore, CA125 values provide no information concerning the size and distribution of recurrent disease, which may influence the prognosis of patients with ovarian cancer [2]. In this setting, PET has the advantage of providing a high-resolution image of the whole body. Our study demonstrated that PET correctly indicated abnormal foci of recurrence in 13 (86.7%) of 15 patients with elevated CA125 levels and detected recurrent disease in three of five patients with false-negative CA125 results. By contrast, conventional imaging predicted recurrence in only eight (53.3%) of the 15 patients in whom CA125 levels were truly abnormal. Thus, in the follow-up of patients with ovarian cancer, PET may be more accurate and useful than conventional imaging for detecting tumour recurrence, especially when CA125 levels are elevated.

Despite these favourable results, PET has some limitations in the diagnosis of macroscopic or microscopic disease recurrence. Of four patients with false-negative PET findings in our study, one had cystic recurrent disease which was detected by MR imaging and confirmed by surgical histology. Thus, caution must be exercised in respect of possible cystic recurrent tumours at the time of PET examination because they may not show increased FDG uptake and may be easily missed. In one patient, peritoneal disseminating disease was shown by abdominal CT imaging. In the remaining two patients, conventional imaging was also false negative; however, a rising CA125 level or the development of peritonitis carcinomatosa during follow-up suggested the presence of recurrence, probably microscopic disseminating disease. Previous studies have discussed the difficulties in the diagnosis of microscopic peritoneal involvement by recurrent ovarian cancer using PET as well as other imaging techniques [15, 17]. Karlan et al. [15] evaluated FDG-PET in the diagnosis of recurrence in 12 patients who underwent second-look laparotomy. All six patients with positive PET findings had histologically proven recurrent ovarian cancers whereas five of the other six, in whom PET was negative, showed microscopic foci of disease at laparotomy. Rose et al. [17] correlated PET findings with second-look laparotomy in 22 patients with ovarian or peritoneal carcinoma who had achieved complete clinical and radiological remission after chemotherapy. They reported that, in 13 patients with persistent disease, PET accurately predicted only one of nine sites with macroscopic disease and none of four sites with microscopic disease.

Although PET cannot substitute for invasive second-look laparotomy for the detection of very small lesions, our and other studies suggest that it may play a non-invasive and significant role in the management of patients with ovarian cancer. It was previously demonstrated that FDG-PET was accurate in detecting lymph node metastasis (86.4%) and peritoneal carcinomatosis (85%) in ovarian cancer, but the PET results were not compared with conventional imaging findings [19]. In the study of Nakamoto et al. [18], who studied 24 patients with treated ovarian cancer, FDG-PET provided additional information in ten patients when findings of conventional imaging were negative or inconclusive; the diagnostic accuracy of conventional imaging (73.3%) was consequently improved to 94.4% when it was combined with PET. In our results, FDG-PET correctly identified the presence of recurrence in seven of nine patients in whom conventional imaging was falsely normal. One may assume that PET could be performed before conventional imaging in the surveillance of patients at high risk of developing recurrence, because anatomical imaging yields less accurate results. Although FDG-PET is more expensive and needs more equipment than conventional imaging, if PET can eliminate other unnecessary examinations and help physicians to choose the best treatment, it will have a clear impact on the therapeutic management of patients. Further studies will be necessary to optimise FDG-PET imaging in the follow-up of patients with ovarian cancer.

In conclusion, our preliminary study demonstrates the feasibility of whole-body FDG-PET for the diagnosis of recurrent ovarian cancer. Metabolic imaging with PET may provide additional and clinically relevant information when conventional imaging is inconclusive, especially in patients with elevated CA125 levels.

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