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ORIGINAL ARTICLE

Clinical value of FDG PET/CT in the diagnosis of suspected recurrent ovarian cancer: is there an impact of FDG PET/CT on patient management?

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Abstract
Purpose The aim of this study was to evaluate the clinical value of FDG PET/CT in patients with suspected ovarian cancer recurrence as compared with diagnostic CT, and to assess the impact of the results of FDG PET/CT on treatment planning.
Methods Included in this retrospective study were 60 patients with suspected recurrent ovarian cancer who had previously undergone primary debulking surgery and had been treated with adjuvant chemotherapy. Diagnostic CT and FDG PET/CT imaging were performed for all patients as clinically indicated. The changes in the clinical management of patients according to the results of FDG PET/CT were also analysed.
Results FDG PET/CT was performed in 21 patients with a previously negative or indeterminate diagnostic CT scan, but an elevated CA-125 level, and provided a sensitivity of 95% in the detection of recurrent disease. FDG PET/CT revealed recurrent disease in 19 patients. In 17 of 60 patients, the indication for FDG PET/CT was an elevated CA-125 level and an abnormal diagnostic CT scan to localize accurately the extent of disease. FDG PET/CT scans correctly identified recurrent disease in 16 of the 17 patients, a sensitivity of 94.1%. Moreover, FDG PET/CT was performed in 18 patients with clinical symptoms of ovarian cancer recurrence, an abnormal diagnostic CT scan, but a normal CA-125 level. In this setting, FDG PET/CT correctly confirmed recurrent disease in seven patients providing a sensitivity of 100% in determining recurrence. In four patients, FDG PET/CT was carried out for the assessment of treatment response. Three of four scans were classified as true-negative indicating a complete response. In the other patient, FDG PET/CT identified progression of disease. In total, 45 (75%) of the 60 patients had recurrent disease, in 14 (31.1%) documented by histopathology and in 31 (68.9%) on clinical follow-up, while 15 (25%) had no evidence of recurrent disease. The overall sensitivity, specificity, accuracy, and positive and negative predictive value of FDG PET/CT were significantly superior to those of diagnostic CT (95.5% vs. 55.5%, 93.3% vs. 66.6%, 95% vs. 58.3%, 97.7% vs. 83.3%, 87.7% vs. 33.3%, respectively; p=0.02) in the detection of recurrent ovarian cancer. FDG PET/CT changed the management in 31 patients (51.6%). It led to the use of previously unplanned treatment procedures in 19 patients (61.2%) and the avoidance of previously planned therapeutic procedures in 12 patients (38.8%).
Conclusion Our results confirm that FDG PET/CT is a superior posttherapy surveillance modality for the detection of recurrent ovarian cancer than diagnostic CT imaging. Furthermore, integrated FDG PET/CT was useful specifically in optimizing the treatment plan and it might play an important role in treatment stratification in the future.

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Introduction

Ovarian cancer is the second most common malignancy of the female genital tract and is the leading cause of death from gynaecological cancer. Most patients are asymptomatic, and approximately 75–80% of women with ovarian cancer have tumour spread beyond the ovary at the time of diagnosis [1, 2]. Primary therapy for ovarian cancer initially consists of platinum-based cytotoxic chemotherapy after primary cytoreductive surgery. Even if the overall response rate with primary therapy is about 80%, the majority of patients will ultimately relapse and die of the disease within 5 years of diagnosis [3, 4]. In view of the high probability of relapse, a number of approaches are used to detect recurrent metastatic lesions after initial chemotherapy followed by surgery for ovarian cancer. This clinical follow-up includes physical examination with close surveillance, periodic evaluation of cancer antigen 125 (CA-125) levels, and the use of imaging modalities [5].

Elevation of the serum tumour marker CA-125 has been shown to be a very sensitive indicator of recurrent ovarian disease with an accuracy ranging from 79% to 95%, and such an increase precedes clinically apparent recurrence by an average of 3 to 6 months [6, 7]. However, both benign gynaecological and benign or malignant nongynaecological conditions are known to be related to elevated CA-125 levels, and therefore the CA-125 level does not provide any information about the location of the recurrence. Because the anatomical location of ovarian cancer recurrence is important for subsequent treatment planning and follow-up, the suggestion of ovarian cancer recurrence by rising CA-125 levels is followed by radiological evaluation of patients by computed tomography (CT) and magnetic resonance (MR) imaging to localize the disease [8–11]. CT and MR imaging are of equal value in detecting peritoneal metastases from ovarian cancer [12, 13]. A study by Tempany et al. [14] indicated that the sensitivity of CT and MR imaging for peritoneal disease in women with a pelvic malignancy is 92% and 95%, respectively. Although these anatomical imaging modalities are the mainstay for evaluating patients for possible recurrence of ovarian cancer, they have limitations in the accurate visualization of small intraabdominal disseminated lesions and lymph node metastases, and for differentiating tumour recurrence from postoperative and postradiation changes [8].

Whole-body positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG), which exploits the increased utilization of glucose by malignant cells, is widely used for staging, restaging, evaluating therapy-induced changes and monitoring response to therapy in patients with various cancer [15, 16]. Furthermore, ovarian cancer is usually characterized by a marked increase in FDG uptake, but its usage in the evaluation of primary ovarian masses is limited due to the relatively high rate of false-positive findings [17]. Several studies have shown the benefits of PET [18–20] and integrated FDG PET/CT [21–28] in the detection of recurrent ovarian cancer. This study evaluated the clinical role of whole-body FDG PET/CT in the diagnosis and follow-up of patients with recurrent ovarian cancer according to the additional diagnostic information and subsequent clinical treatment. In addition, the results of FDG PET/CT were also compared with the findings of a diagnostic CT scan for the early detection of recurrence.

Material and methods

This retrospective study included 60 patients with suspected ovarian cancer recurrence who had undergone primary cytoreductive surgery and who had undergone FDG PET/CT imaging for diagnosis of recurrence between December 2003 and August 2007 at Dr. Lutfi Kirdar Kartal Education and Research Hospital. FDG PET/CT scans had been performed in all patients for a variety of indications. Indications for FDG PET/CT scans were elevated CA-125 levels and negative or indeterminate diagnostic CT scans, elevated CA-125 levels and abnormal diagnostic CT scans, clinical symptoms and normal CA-125 levels with abnormal diagnostic CT scans and the assessment of treatment response. In addition, the diagnostic CT scan in all patients had also been carried out before FDG PET/CT. The inclusion criteria were histopathologically confirmed diagnosis of ovarian cancer with primary cytoreductive surgery and suspected ovarian cancer recurrence, while exclusion criteria were the presence of a contraindication to FDG PET/CT scanning including a blood glucose level higher than 200 mg/dl and intolerance to FDG PET/CT because of claustrophobia.

Clinical information including age at diagnosis, tumour stage, grade, histopathological type and number of chemotherapy cycles administered, imaging study findings, and serum CA-125 level at the time of FDG PET/CT scan were obtained from the patients' charts after informed written consent had been obtained from each subject included in the study. Serum CA-125 levels were measured with a radioimmunoassay (RIA) method using a CA-125 E-170 kit (Roche Diagnostics, IN). Normal CA-125 values ranged from 0 to 35 U/ml.

All patients were treated with the initial standard treatment for ovarian cancer, and 55 patients (91.6%) received a regimen containing paclitaxel/platinum after primary cytoreductive surgery. The other 5 patients did not receive adjuvant chemotherapy because of the early stage of their disease. The majority of patients had either papillary serous adenocarcinoma (27 patients, 45%) or serous adenocarcinoma (19 patients, 31.6%). The median age was 54 years (range 25 to 77 years). The patient characteristics are summarized in Table 1.

Imaging technique

Chest and abdomen/pelvis diagnostic CT scans were performed using a multislice CT scanner (Siemens Somatom Sensation, 40-slice CT system). Axial images were acquired with 40×0.72-mm collimation before and after intravenous administration of 1 ml/kg (60–100 ml) iomeprol contrast medium, and coronal and sagittal reformations of different thicknesses were obtained using maximum intensity projection and multiplanar reconstruction. For the abdomen and pelvis, images were acquired during the early arterial and portal phases from the xyphoid process to the symphysis pubis, and for the thorax images were obtained from the thoracic inlet to below the surrenal glands.

Table 1 Clinical characteristics of patients with suspected recurrent ovarian cancer

Characteristic	Value
Age (years)	
Median	54
Range	25–77
Stage at diagnosis, *n* (%)	
I	8 (13.3)
II	6 (10)
III	43 (71.7)
IV	3 (5)
Histology, *n* (%)	
Papillary serous adenocarcinoma	27 (45)
Serous adenocarcinoma	19 (31.6)
Clear-cell carcinoma	2 (3.3)
Mucinous adenocarcinoma	5 (8.4)
Endometrioid adenocarcinoma	2 (3.3)
Mixed clear-cell and endometrioid carcinoma	1 (1.7)
Malignant mixed mullerian tumour	1 (1.7)
Transitional cell carcinoma	1 (1.7)
Poorly differentiated adenocarcinoma	2 (3.3)
Grade, *n* (%)	
I	4 (6.7)
II	28 (46.7)
III	28 (46.7)
Initial chemotherapy, *n* (%)	
Paclitaxel/carboplatin	55 (91.6)
No adjuvant therapy	5 (8.4)

The median interval between the diagnostic CT scan and the FDG PET/CT scan was 2 weeks (range 1–4 weeks). The patients fasted for at least 6 h prior to imaging and each patient's blood glucose level was obtained prior to tracer injection. The blood glucose levels of all patients were below 200 mg/dl at the time of injection of FDG. Each patient received 10–15 mCi (370–550 MBq) of FDG intravenously. The patients then rested on a comfortable chair for 1 h to allow FDG biodistribution. For optimal delineation of bowel structures, ingestion of 400–600 ml of contrast material diluted to 2.4% (v/v) with water was started 1 h before CT imaging. The urinary bladder was not catheterized, and no diuretics were administered at this time. Whole-body imaging was acquired 1 h after radiotracer injection, using a Siemens Biograph Duo PET/CT scanner with LSO detectors. First, low-dose CT was performed (140 kV, 50 mA, table speed 22.5 mm/s) without any specific breath-holding instructions. Scanning from the top of the skull through the upper thighs was performed in a single step with the patient in a supine position. CT data were used for attenuation correction (5 mm contiguous axial cuts). Immediately afterwards, a PET emission scan was obtained with the patient in the same position. Six to eight bed positions were used, with an acquisition time of 5 min for each bed position. The PET scan was acquired in three-dimensional mode over the same anatomical regions starting at the level of the mid-thighs. PET image datasets were reconstructed iteratively using the CT data for attenuation correction, and coregistered images were displayed on a workstation.

Image analysis

The diagnostic CT images were interpreted by an experienced radiologist who had no knowledge of the FDG PET/CT findings. Recurrent viable tumour on the diagnostic CT images was identified by the presence of a highly contrast-enhanced, predominantly solid lesion in the ovarian region. Relapse of disease were also identified as areas of abnormal contrast enhancement in the pelvis and the abdomen. The diagnosis of lymph node involvement by neoplastic disease on the diagnostic CT images was based on morphological criteria. The presence of distant metastases was also evaluated.

All FDG PET/CT images were analysed by an expert nuclear medicine physician who had knowledge of the diagnostic CT findings. Attenuation-corrected PET images, CT scans and coregistered PET/CT images were interpreted using a dedicated image fusion workstation and a final consensus was reached in all patients. Any foci of increased FDG uptake except for areas of physiologically increased uptake, corresponding to a CT abnormality (tissue or lymph node) were considered to be positive for recurrent lesions.

Suspicious CT findings were evaluated as negative if they did not correspond to an area of increased FDG uptake.

Maximum standardized uptake values (SUVmax) ranged from 4.5 to 26 (mean 10.9±6). SUV values greater than 3.0 have previously been considered to be indicative of malignant lesions [27, 29].

Follow-up

A final diagnosis of recurrence was obtained from the results of histopathological examination after surgery, second-look laparotomy or biopsy, or clinical follow-up of at least 6 months. Clinical recurrence was defined as the detection of recurrent disease by contrast-enhanced diagnostic CT or a continuously rising CA-125 level to a value greater than twice the nadir within 6 months of the FDG PET/CT scan. Recurrent disease detected more than 6 months after the FDG PET/CT scan was interpreted as a new recurrence. For the assessment of treatment response following chemotherapy, a complete response was defined as the disappearance of all measurable disease, a partial response as a decrease of at least 30% in the tumour volume, and progressive disease as a more than 20% increase in tumour volume or any new sites of disease according to RECIST criteria [30].

Statistical analysis

The sensitivity, specificity, accuracy, and positive predictive values (PPV) and negative predictive value (NPV) for tumour detection of FDG PET/CT scans were calculated using the McNemar test of correlated proportions with Yates' continuity correction. For the purposes of statistical analysis, a true-positive lesion was a lesion seen on FDG PET/CT images and found to be positive for tumour tissue on histological examination or clinical follow-up. A false-positive lesion was a lesion seen on FDG PET/CT images but found to be negative for tumour tissue on histological analysis or clinical follow-up. A true-negative lesion was defined as one that was not seen on FDG PET/CT images and the results of histopathological examination were negative for tumour or clinical follow-up was negative. A false-negative lesion was a lesion that was missed on image analysis, but was found to be positive for malignancy on histopathological analysis or clinical follow-up. The analyses were performed using SPSS 13.0 (SPSS, Chicago, IL) software. CA-125 levels were compared using the Mann-Whitney *U*-test. The significance of differences among the results of FDG PET/CT and diagnostic CT were determined using the chi-squared test. Receiver operating characteristics (ROC) analysis was performed for the detection of the SUVmax cut-off value that showed a recurrent lesion. All p values were two-sided in tests and p values less than or equal to 0.05 were considered to be statistically significant.

Results

This retrospective evaluation included 60 patients who had undergone FDG PET/CT and diagnostic CT imaging for suspected recurrent ovarian cancer or to assess treatment response following chemotherapy. Overall, 45 of the 60 patients (75%) developed recurrent disease during follow-up (median 27.5 months, range 7–89 months). Of the 45 patients with recurrent disease, 14 (31.1%) were documented as having recurrence by pathological examination after surgical biopsy, while in 31 (68.9%) recurrence was confirmed on clinical follow-up as previously defined.

The indications for and results of the FDG PET/CT scans, mean SUVmax values, mean sizes of lesions and the sites of recurrence are summarized in Table 2. In 21 of 60 patients (35%), the FDG PET/CT scan was performed because of an elevated CA-125 level and negative or indeterminate diagnostic CT scan. The median time to the FDG PET/CT scan after completion of initial treatment was 7.5 months (range 2–40.5 months). The median CA-125 level at the time of the FDG PET/CT scan and the mean SUVmax value were 208 U/ml (range 58–3,936 U/ml) and 8.7±3.4 (range 5.2–20.4), respectively. Of these 21 FDG PET/CT scans, 19 (90.4%) correctly revealed recurrent disease. The mean size of the lesions was 3.2±1.12 cm. In six patients, recurrence was confirmed by histopathology and in 13 patients, on clinical follow-up for a median of 30.6 months (range 13.8–81 months) after the FDG PET/CT scan. The FDG PET/CT scan was true-positive in these 19 patients. However, the FDG PET/CT scan was false-negative in one patient, as recurrent disease was detected on clinical follow-up within 6 months of the FDG PET/CT scan. Following the FDG PET/CT scans, five patients underwent surgical cytoreduction, and then received chemotherapy. The other 15 patients were treated with chemotherapy alone. However, the FDG PET/CT scan was false-positive in the remaining one patient. No recurrent disease was detected in this patient during 6 months of follow-up. She was not given any therapy. The overall sensitivity, accuracy, and PPV of FDG PET/CT in determining recurrent ovarian cancer in this setting were 95%, 90.4% and 95%, respectively. The specificity and NPV were not applicable due to absence of patients with true-negative findings.

FDG PET/CT scans were carried out in 17 patients due to an elevated CA-125 level and an abnormal diagnostic CT scan for treatment planning to localize accurately the extent of disease. The median interval between initial treatment and the FDG PET/CT scan was 8.3 months (range 2.5–26.4 months). The median CA-125 level at the time of the FDG PET/CT scan and the mean SUVmax value were 137.6 U/ml (range 38–3,199 U/ml) and 9.7±3.7 (range 5.1–15.7), respectively. In 16 of 17 patients (94.1%), the FDG PET/CT scan correctly

Table 2 Number of patients with positive FDG PET/CT findings, number of patients with confirmed recurrence or progression of disease, mean SUVmax values, the size of lesions and the sites of recurrence in relation to the indications for the FDG PET/CT scan

Indication	No. (%) of patients	No. (%) positive by FDG PET/CT (true or false)	No. (%) with confirmed recurrence or progression	SUVmax (mean ± SD)	Lesion size, mean ± SD (cm)	Sites of recurrence
Elevated CA-125 level and negative or indeterminate CT scan	21 (35)	20 (95.2)	19 (90.4)	8.7±3.4	3.2±1.2	Liver, peritoneum, omentum, lung, retroperitoneal lymph nodes, vaginal stump
Elevated CA-125 level and abnormal CT scan	17 (28.3)	16 (94.1)	16 (94.1)	9.7±3.7	3.5±1.9	Liver, peritoneum, omentum, lung, retroperitoneal lymph nodes, left cervical lymph node, spleen, vaginal stump
Clinical symptoms and normal CA-125 level with abnormal CT scan	18 (30)	7 (38.8)	7 (38.8)	8.4±3.2	1.6±1.0	liver, peritoneum, omentum, gallbladder, coeliac lymph nodes, retroperitoneal lymph nodes, uterus
Assessment of treatment response	4 (6.7)	1 (25)	1 (25)	NA	NA	Retroperitoneal lymph nodes

NA not applicable.

identified recurrent disease. The mean size of the lesions was 3.5±1.9 cm. Recurrence was documented by pathology in six patients and on clinical follow-up for a median of 24.4 months (range 6.9–80 months) in ten patients. The FDG PET/CT scan was classified as true-positive in these patients. After the FDG PET/CT scan, surgical cytoreduction was performed successfully in four patients. The other 12 patients were treated with recurrence chemotherapy alone. In the remaining one patient, the FDG PET/CT scan was false-negative because recurrent disease was detected during a 6-month clinical follow-up following the FDG PET/CT scan. She was treated with recurrence chemotherapy. The overall sensitivity, accuracy and PPV for FDG PET/CT in the detection of recurrent disease among patients with an increased CA-125 level and abnormal diagnostic CT scan were 94.1%, 94.1% and 100%, respectively. The specificity and NPV were not applicable because of the lack of patients with false-positive and true-negative findings.

FDG PET/CT scans were performed because of clinical symptoms of ovarian cancer recurrence, but normal CA-125 level and abnormal diagnostic CT scan in 18 patients. In this setting, the median time to the FDG PET/CT scan after completion of initial treatment was 6 months (range 3–48.4 months). The mean SUVmax value was 8.4±3.2 (range 4.5–11.8). Of these 18 FDG PET/CT scans, 7 (38.8%) correctly indicated recurrent disease. The mean size of lesions was 1.6±1.0 cm. In two patients recurrence was confirmed by histopathology and in five patients, by clinical follow-up for a median of 26.9 months (range 7–71.4 months). FDG PET/CT scans were true-positive in these seven patients. Following FDG PET/CT scans, two of seven patients underwent surgical cytoreduction and then received chemotherapy. The other five patients were treated with chemotherapy alone. FDG PET/CT scans were classified as true-negative in the other 11 patients. The overall sensitivity, specificity, accuracy, PPV and NPV for FDG PET/CT in the detection of recurrent disease in this setting were 100%, 100%, 100%,100% and 100%, respectively.

In the remaining 4 of the 60 patients, FDG PET/CT scan was performed for the assessment of treatment response following chemotherapy. The median time between completion of treatment and the FDG PET/CT scan was 2.6 months (range 1.6–6 months). Three of four scans were classified as true-negative and the fourth as true-positive. In this patient, the FDG PET/CT scan correctly confirmed progression of disease during the 6-month follow-up period. She was treated with recurrence chemotherapy alone. A complete response was obtained in the other three patients as determined by FDG PET/CT without recurrence within 6 months. The FDG PET/CT results in relation to indications are summarized in Table 3.

A total of 60 FDG PET scans were carried out in the patients described above. The overall patient-based sensitivity, specificity, accuracy, PPV, and NPV of FDG PET/CT in determining recurrent ovarian cancer were 95.5%, 93.3%, 95%, 97.7% and 87.5%, respectively. The median CA-125 level at the time of FDG PET/CT imaging was 116 U/ml (range 6–3,936 U/ml) in patients with a true-positive scan and 13 U/ml (range 10–38 U/ml) in patients with a true-negative scan. This difference was statistically significant ($p<0.001$).

The diagnostic CT scan was performed in all patients before the FDG PET/CT scan. In total 60 diagnostic CT scans were compared with FDG PET/CT scans. The diagnostic CT scans were carried out because of an elevated

Table 3 FDG PET/CT results in the detection of recurrent ovarian cancer in relation to indications for the FDG PET/CT scan

Indication	No. (%) of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Median CA-125 level (U/ml)	Median follow-up (months)
Elevated CA-125 level and negative or indeterminate CT scan	21(35)	95	NA	95	NA	90.4	208	30.6
Elevated CA-125 level and abnormal CT scan	17(28.3)	94.1	NA	100	NA	94.1	137.6	24.4
Clinical symptoms and normal CA-125 level with abnormal CT scan	18(30)	100	100	100	100	100	13.4	26.9

CA-125 level in 38 patients. Of these 38 CT scans, 18 (47.3%) correctly revealed recurrent disease and the diagnostic CT was true-positive in these patients. However, the diagnostic CT scan was classified as false-negative in the remaining 20 patients. The overall sensitivity, accuracy and positive PPV of diagnostic CT in determining recurrent ovarian cancer in this setting were 47.3%, 47.3% and 100%, respectively. The specificity and NPV were not applicable due to the lack of patients with true-negative findings. In 18 patients, the diagnostic CT scan was performed because of clinical symptoms of ovarian cancer recurrence with a normal CA-125 level. Of these 18 diagnostic CT scans, 8 (44.4%) correctly indicated recurrent disease. In these 8 patients the diagnostic CT scans were true-positive. In the remaining ten patients the scan was classified as false-positive. The overall sensitivity, accuracy and PPV of diagnostic CT in the detection of recurrent disease in the setting of clinical symptoms of ovarian cancer recurrence, but normal CA-125 level were 100%, 44.4% and 44.4%, respectively. The specificity and NPV were not applicable due to the lack of patients with true-negative findings. Four patients underwent a diagnostic CT scan for the assessment of treatment response following chemotherapy. Three scans were true-negative and the fourth was classified as true-positive. The results of the diagnostic CT scans were confirmed by FDG PET/CT after a median of 2 weeks (range 1–4 weeks). The results of the diagnostic CT scan in relation to the indications are summarized in Table 4.

The overall sensitivity of the diagnostic CT scan in the detection of tumour recurrence was 55.5% and the specificity was 66.6%. In addition, the overall accuracy, PPV, and NPV were 58.3%, 83.3% and 33.3%, respectively. The scanning study and tumour marker analysis in the 60 patients indicated higher sensitivity, specificity, accuracy, PPV, and NPV with FDG PET/CT than with the diagnostic CT scans ($p=0.02$). Table 5 summarizes the results of FDG PET/CT and the diagnostic CT scans for all patients.

The ROC analysis indicated that an FDG-PET/CT SUVmax cut-off value of 5.6 accurately indicated the presence of recurrence with a sensitivity and specificity of 85.7% (95% CI 71.5–94.6%) and 50% (95% CI 10.8–98.7%), respectively (AUC 0.554; Fig. 1). In the majority of patients ($n=37$), the SUVmax cut-off value was greater than 5.6. The FDG PET/CT scan revealed recurrent disease in 36 of these 37 patients. There was no significant difference with respect to the SUVmax cut-off value in the detection of recurrent disease ($p=0.29$).

In this study, we found that FDG PET/CT had a high impact on patient management and care. The further diagnostic or treatment plan was changed in 31 patients (51.6%), and in 19 (61.2%) of these 31 patients with an elevated CA-125 level, a negative or indeterminate diagnostic CT scan, and no clinical symptoms of recurrent disease, FDG PET/CT indicated the presence of suspected recurrent lesions. They were then treated with previously unplanned surgery or recurrence chemotherapy. The other

Table 4 The results of the diagnostic CT scan in the detection of recurrent ovarian cancer according to the indications for the diagnostic CT scan

Indication	No. (%) of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Elevated CA-125 level	38 (63.3)	47.3	NA	100	NA	47.3
Clinical symptoms and normal CA-125 level	18 (30)	100	NA	44.4	NA	44.4

NA not applicable.

Table 5 Comparison of the results of the FDG PET/CT and the CT scans

Performance	FDG PET/CT	CT
True-positive (*n*)	43	25
True-negative (*n*)	14	10
False-positive (*n*)	1	5
False-negative (*n*)	2	20
Sensitivity (%)	95.5	55.5
Specificity (%)	93.3	66.6
PPV (%)	97.7	83.3
NPV (%)	87.5	33.3
Accuracy (%)	95	58.3

12 (38.8%) of these 31 patients with an abnormal diagnostic CT scan were revealed to have lesions with physiological or inflammatory uptake of FDG which led to cancellation of a previously planned diagnostic procedure and chemotherapy.

Figure 2 shows FDG PET/CT images of a patient with recurrent ovarian cancer in the pelvis, as well as liver, spleen and peritoneal metastases. Figure 3 shows FDG PET/CT images of a 69-year-old woman with ovarian cancer and multiple metastases in the liver, gallbladder and coeliac lymph node.

Discussion

Despite rigorous efforts to improve diagnosis and treatment, ovarian cancer remains the leading cause of death from gynaecological cancer. Although the initial response to therapy is good, 5-year survival for advanced disease is very poor because of the high rate of recurrence [31]. Therefore, early detection of recurrent disease is very

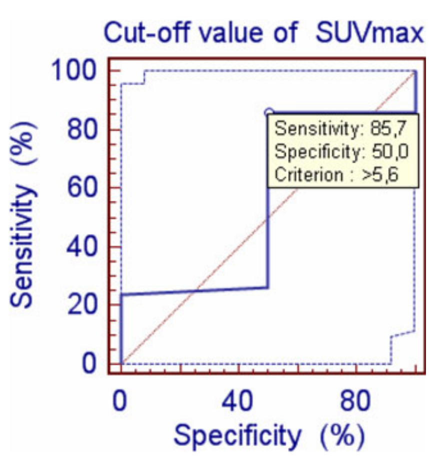

Fig. 1 ROC curve shows the SUVmax cut-off value during FDG PET/CT that was indicative of recurrence

important for prognosis. Although, conventional imaging modalities including CT and MR imaging are the mainstay in detecting recurrence of ovarian cancer, they have some limitations including a low accuracy in detecting small disseminated lesions such as peritoneal carcinomatosis, and mesenteric and omental recurrences, despite elevation in the level of the tumour marker CA-125 [10, 14]. Although, the sensitivity of spiral CT has been shown to be 85–93% for the detection of peritoneal metastases, the sensitivity is only 25–50% in patients with peritoneal implants of 1 cm or less in diameter [32].

FDG PET has emerged as an extremely useful technique in clinical oncology [33, 34]. Recently, PET has shown sensitivity, specificity and diagnostic accuracy, especially in combination with CT, comparable to or higher than conventional imaging and in comparison to tumour markers in various solid cancers including ovarian cancer [29, 35, 36]. The usefulness of concurrent FDG PET/CT for posttherapy surveillance of patients with ovarian cancer has been investigated in several studies [21–28, 37–39]. In these studies, the sensitivity, specificity, and accuracy of patient-based analyses were 73–100%, 40–100%, and 63–100%, respectively, whereas those of lesion-based analyses were 41–78%, 75–95%, and 72–77%, respectively [21–28].

Our study demonstrated the feasibility of using FDG PET/CT for the diagnosis of tumour recurrence in patients with previously treated ovarian cancer, equivocal imaging findings, or increased CA-125 levels. In a recent prospective study in 97 patients, the utility of FDG PET/CT for the evaluation of a pelvic mass of unknown origin with postsurgical histopathological follow-up was investigated, and the sensitivity and specificity of FDG PET/CT in the diagnosis of a malignant pelvic tumour were found to be 100% and 93%, respectively [40]. Other studies evaluating FDG PET/CT in suspected recurrent ovarian cancer have also shown promising results. The sensitivity and specificity of FDG PET/CT in these studies were 83–95% and 71–100%, respectively [26, 37, 41]. In our study, the FDG PET/CT results were in agreement with those of other previously reported trials [5, 26–28].

In addition, the superiority of PET/CT over CT in detecting recurrent ovarian cancer has also been reported. Torizuka et al. [42] evaluated the usefulness of PET in the diagnosis of recurrent ovarian cancer in patients who had previously undergone surgery. PET showed a sensitivity of 80% whereas conventional imaging had a sensitivity only 55%. Sironi et al. found that FDG PET/CT has a sensitivity and specificity in detecting persistent ovarian cancer of 78% and 75%, respectively [21]. Hauth et al. [23] compared enhanced FDG PET/CT with FDG PET and enhanced diagnostic CT alone in 19 patients. They found that the patient-based sensitivity of FDG PET/CT was 100%, whereas that of enhanced CT was 73%. In addition,

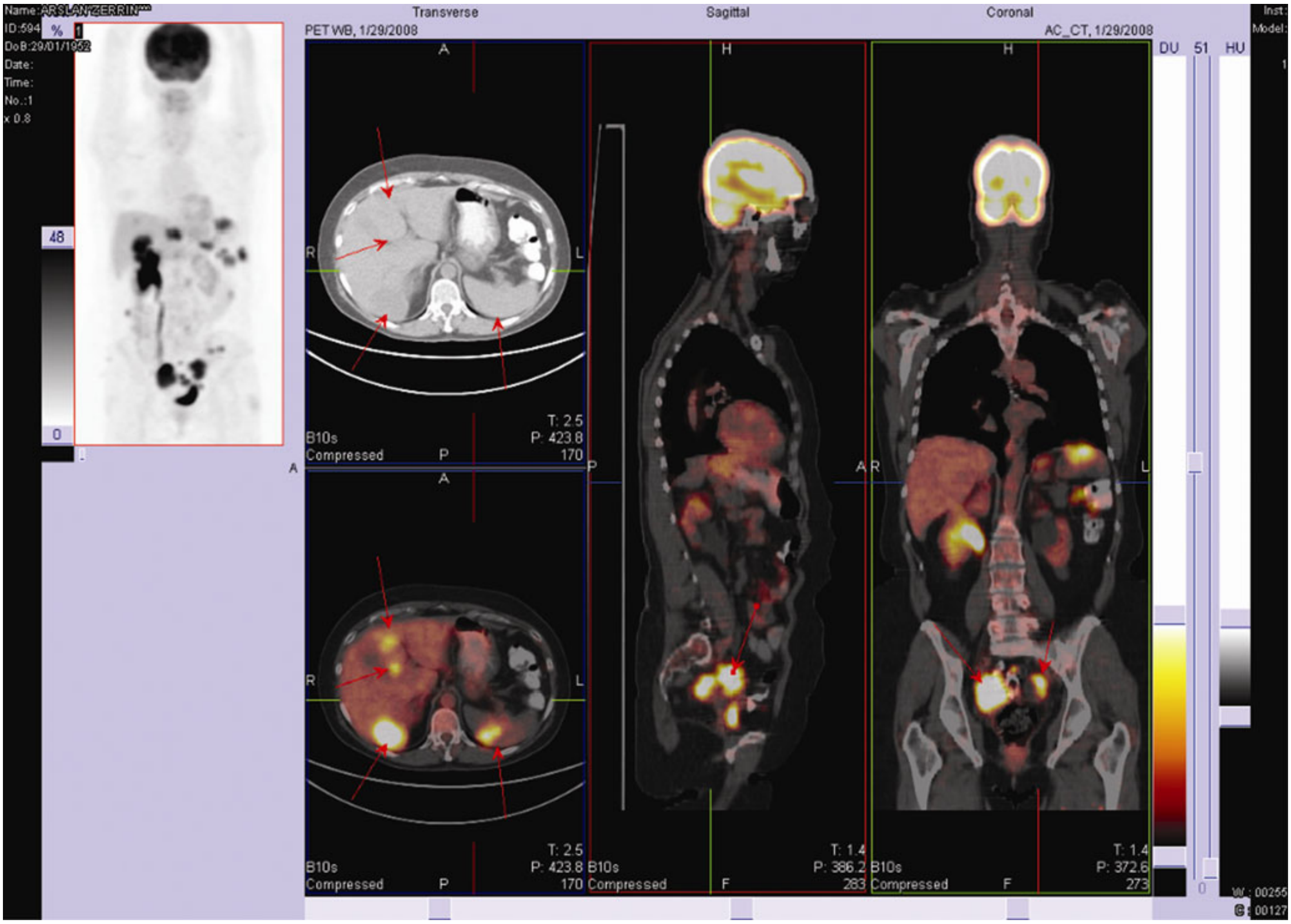

Fig. 2 FDG PET/CT images in a 56-year-old woman with ovarian cancer. The scan was performed because of an elevated CA-125 level (59 U/ml) and an abnormal diagnostic CT scan for treatment planning to localize accurately the extent of disease.. The images show metastases in the pelvis, liver, spleen and peritoneum. She was treated with recurrent chemotherapy and a partial response was obtained

Thrall et al. [26] found that enhanced FDG PET/CT had a sensitivity and specificity of 95% and 100%, respectively, in 39 patients, but they did not compare FDG PET/CT with another conventional imaging modality. Sebastian et al. [28] compared enhanced FDG PET/CT with enhanced CT alone for sites in the chest and abdomen in 51 patients with suspected recurrent ovarian cancer. They found that FDG PET/CT was more accurate than CT with less interobserver variability. In our study, we also compared enhanced FDG PET/CT with enhanced diagnostic CT in the detection of suspected recurrent ovarian cancer. The results of FDG PET/CT were significantly better than those of diagnostic CT in a patient-based comparison (p=0.02). However, there were no patients with a true-negative result in some groups. This may have influenced our results because of the small sample size of our study with respect to indications.

We performed the FDG PET/CT scan because of an elevated CA-125 level with a negative or indeterminate diagnostic CT scan in 21 patients. Our results compare favourably with those of the study by Thrall et al. [26] in which 39 patients with ovarian cancer were evaluated by FDG PET/CT. FDG PET/CT had the greatest utility in the setting of suspected ovarian cancer recurrence, especially in patients with an elevated CA-125 level and negative conventional imaging. In addition, Thrall et al. concluded that FDG PET/CT is specifically helpful in optimizing the selection of patients for site-specific treatment. In a study including 56 women with an increased CA-125 level (66 FDG PET/CT scans) all patients except one had positive FDG PET/CT scans [43].

FDG PET/CT had the greatest utility in patients with clinical symptoms of ovarian cancer recurrence but a normal CA-125 level and abnormal diagnostic CT scan. In this setting, 18 patients underwent FDG PET/CT, which correctly identified recurrent disease in 7 (38.8%) . In the other 11 patients, FDG PET/CT was true-negative. The sensitivity and specificity of FDG PET/CT in this category were 100% and 100%, respectively.

The ability to identify the extent and correct location of disease in recurrent ovarian cancer is important for the

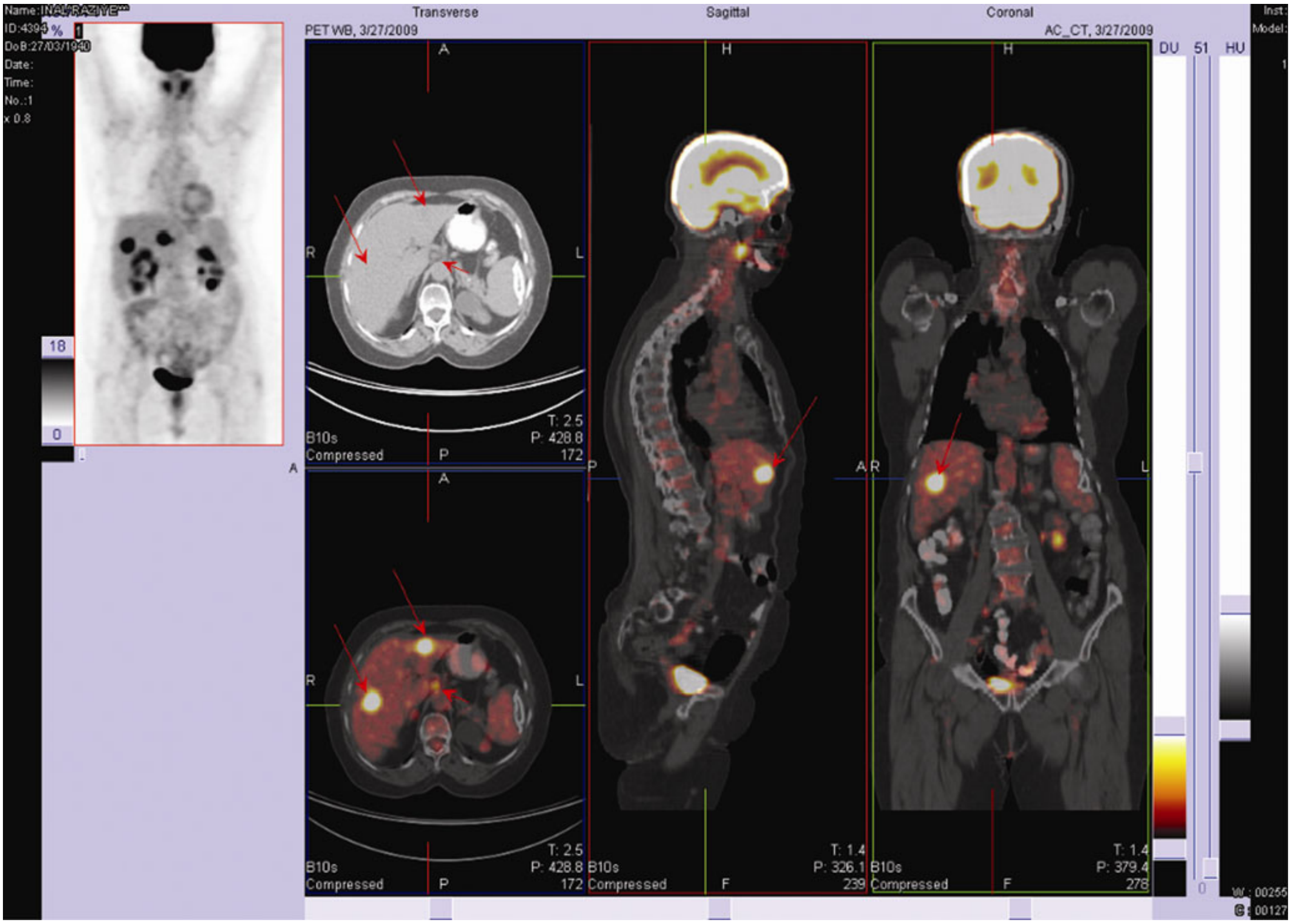

Fig. 3 FDG PET/CT images in a 69-year-old woman with ovarian cancer. The scan was performed because of the presence of clinical symptoms of recurrence. She had a normal CA-125 level but abnormal diagnostic CT scan. The images show metastases in the liver, gallbladder and coeliac lymph node. The patient received recurrence chemotherapy, but progressive disease was subsequently detected

selection of subsequent therapeutic modalities. In a study by Mangili et al. [25], FDG PET/CT was compared with CT for the detection of ovarian cancer recurrences. A change in the clinical management was observed in 44% of the patients when FDG PET/CT information was added to conventional follow-up findings. Chung et al. [27] also investigated the role of FDG PET/CT in the assessment of suspected recurrent ovarian cancer and found that FDG PET/CT modified the diagnostic or treatment plan in 24.7% of patients. FDG PET/CT led to previously unplanned therapeutic procedures in 11 (57.9%) patients and to the avoidance of previously planned diagnostic procedures in 8 patients. Simcock et al. studied 34 patients with suspected recurrent ovarian cancer and found that FDG PET/CT led to a change in the management of 58% of the patients [43].

In our study, the management of 51.6% of patients was changed after comparing the FDG PET/CT scan with the diagnostic CT scan for detecting ovarian cancer recurrence. Of the 31 patients, 19 (61.2%) with an elevated CA-125 level and a negative diagnostic CT scan, and no clinical symptoms of recurrent disease, were found to have suspected recurrent lesions on FDG PET/CT. They were subsequently treated with previously unplanned surgery or chemotherapy. All patients in this setting had true-positive FDG PET/CT scans. However, 12 (38.8%) patients with an abnormal diagnostic CT scan were found to have lesions with physiological or inflammatory uptake of FDG on FDG PET/CT. In these patients a previously planned diagnostic procedure or chemotherapy was then cancelled. A recent prospective multicentre study [44] in 90 patients, evaluating the impact of FDG PET/CT on suspected recurrent ovarian cancer found that FDG PET/CT altered management in close to 60% of patients, detected more sites of disease than abdominal and pelvic CT, and was also superior in detecting nodal, peritoneal, and subcapsular liver disease. Our results are thus in accordance with those reported previously with regard to modifications to planned treatment.

Changes in glucose metabolism have been suggested to precede alteration in tumour size and to accurately reflect treatment response in various tumour types [45]. We carried out an FDG PET/CT scan in four patients for the assessment of treatment response after completion of chemotherapy. FDG PET/CT was specifically useful in patients in whom the disease was not clearly confirmed by diagnostic CT imaging, but the correct evaluation of treatment response with FDG PET/CT may have been difficult due to the small sample size in our study. The higher accuracy of FDG PET/CT in identifying recurrent disease is also associated with a higher ability to monitor treatment response.

The ROC analysis showed that an FDG PET/CT SUVmax cut-off value of 5.6 accurately indicated the presence of recurrent lesions. With this cut-off value the sensitivity and specificity for the presence of recurrence were 85.7% and 50%, respectively (AUC 0.554). There was no significant difference with the respect to the SUVmax cut-off value in the detection of recurrent disease ($p=0.29$). It may be associated with low specificity of SUVmax cut-off value of in ROC analysis. The AUC is close to 0.5 which is not good enough, and it seems that the cut-off value has low specificity.

In conclusion, our results confirm that FDG PET/CT is a better modality for posttherapy surveillance for the detection of recurrent ovarian cancer than diagnostic CT imaging in all settings including in patients with an elevated CA-125 level and a normal or abnormal diagnostic CT scan. FDG PET/CT might also be useful for the assessment of treatment response following chemotherapy. Furthermore, our results, together with those in the literature, indicate that integrated FDG PET/CT allows optimization of the treatment plan and might play an important role in treatment stratification. Future studies will need to address the impact of FDG PET/CT on the survival of patients and clinical patient management in relation to its cost effectiveness.

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