GYNECOLOGIC ONCOLOGY

# Impact of positron emission tomography/computed tomography in the management of patients with epithelial ovarian carcinoma after treatment

Kaei Nasu · Wakana Abe · Noriyuki Takai ·
Kenichiro Tomonari · Hisashi Narahara

**Abstract**

*Purpose* The aims of this study were to compare the usefulness and reliability of integrated whole-body positron emission tomography/computed tomography (PET/CT) using $^{18}$F-fluorodeoxyglucose (FDG) with those of contrast-enhanced multidetector CT during regular follow-up in patients after initial treatment of ovarian cancer, to assess the impact of FDG–PET/CT on the confirmation of recurrence, restaging, and clinical management of patients, and to determine the incremental information provided by PET/CT.

*Methods* A retrospective review was performed on 19 ovarian cancer patients who underwent a total of 30 FDG–PET/CT and contrast-enhanced multidetector CT scans. The following information was obtained: the clinical information of the patients; the results of FDG–PET/CT and contrast-enhanced multidetector CT, particularly with regard to the impact on the diagnosis of recurrence; information on the localization and number of diseases; and the impact on subsequent clinical management.

*Results* Both FDG–PET/CT and contrast-enhanced multidetector CT had very high sensitivity and specificity for the detection of recurrent ovarian cancer. Contrast-enhanced multidetector CT was considered the more accurate imaging modality for detecting recurrence, whereas FDG–PET/CT was proven more effective for detecting large numbers of small lesions. When comparing the impact on the choice of a management plan, both FDG–PET/CT and contrast-enhanced multidetector CT were found to be significantly effective at predicting the locations of recurrence.

*Conclusions* Both integrated FDG–PET/CT and contrast-enhanced multidetector CT are sensitive surveillance modalities for the detection of recurrent ovarian cancer; the use of both modalities aids decisions on treatment plans and may ultimately have a favorable impact on prognosis. However, contrast-enhanced multidetector CT is recommended for the regular follow-up for ovarian cancer patients after initial treatment.

**Keywords** Epithelial ovarian cancer · Recurrence · FDG–PET/CT · Contrast-enhanced CT · Secondary cytoreductive surgery · Second-line chemotherapy

K. Nasu (✉) · W. Abe · N. Takai · H. Narahara
Department of Obstetrics and Gynecology,
Faculty of Medicine, Oita University,
Idaigaoka 1-1, Hasama-machi,
Yufu, Oita 879-5593, Japan
e-mail: nasu@oita-u.ac.jp

K. Tomonari
Oita Diagnostic Imaging Center, Oita, Japan

## Introduction

Ovarian cancer is the fifth most common cancer among women, accounting for 4.4% of all female malignancies [1]. Approximately 60% of women diagnosed with epithelial ovarian cancer will die of the disease [1]. One of the main reasons for the high fatality ratio among ovarian cancer patients relates to the fact that the majority (65–70%) are diagnosed with advanced disease [1]. Although the histologic forms of ovarian cancer are diverse, epithelial ovarian cancer accounts for 90% of cases, and most of these cases have serous histology. Thorough surgical staging is essential in order to assess the need for adjuvant treatment and to determine prognosis [2]. The standard initial treatment for patients with epithelial ovarian cancer is primary cytoreductive surgery followed by combination

platinum-taxane chemotherapy [2]. Most women respond to primary therapy, with 75% of patients achieving a complete clinical response [2]. Even if the initial response is good, the majority of ovarian cancer patients have persistent disease or ultimately develop recurrent disease, especially in the 2 years following the first-line therapy, and it has been reported that 75% of ovarian cancer patients will experience disease relapse [2]. The pelvis and abdomen are still the most common sites of relapse, whereas isolated lymph node recurrence is a relatively uncommon event.

The surveillance of ovarian cancer patients after initial treatment poses a challenge. Periodic serum cancer antigen (CA) 125 assay, physical examination, and imaging modalities have been employed with different time schedules for the follow-up of asymptomatic patients. Since the anatomic localization of ovarian cancer recurrence is important for subsequent treatment planning and management, conventional morphological imaging modalities including transvaginal ultrasonography, radiography, computed tomography (CT), and magnetic resonance imaging (MRI) have been widely used to evaluate the status of ovarian cancer [3–5]. At present, abdominal CT using contrast media is the imaging modality of choice in these patients. In particular, multidetector CT allows the routine acquisition of sections 0.5–2-mm thick over large volumes, and the data can then be manipulated on an interactive display in multiple planes [4, 5]. Small lesions can be detected more easily in coronal or sagittal reformatted images, which have fewer artifacts than axial images.

The assessment with conventional imaging modalities is generally based on morphological criteria and the size of lesions rather than the actual detection of malignant tissue. Therefore, it has limited value in detecting microscopic and small macroscopic disease, especially small peritoneal lesions using conventional imaging [6, 7]. Moreover, it is difficult to distinguish benign postoperative changes from tumor relapse [8]. Integrated positron emission tomography (PET) and CT (PET/CT) is a new imaging technology which offers the benefits of both functional and morphological imaging. Ovarian cancer is generally characterized by a marked increase in glucose metabolism, which can be exploited as a target for imaging with PET/CT using $^{18}$F-fluorodeoxyglucose (FDG). The potential advantages of PET/CT for patients with ovarian cancer include increased lesion conspicuity, anatomic localization of lesions and differentiation of disease processes from physiologic activity [9]. FDG–PET/CT could enable the detection and localization of metastatic lymph nodes that are not enlarged (i.e., smaller than 1 cm). Recent studies have shown FDG–PET/CT to be useful for the assessment of recurrent ovarian cancer [7, 10].

In this study, we compared the impact of integrated FDG–PET/CT versus contrast-enhanced multidetector CT on the following: (1) detection of ovarian carcinoma recurrence during regular follow-up after initial treatment; (2) restaging of recurrent ovarian cancer; and (3) decision making in the clinical management of recurrent ovarian carcinoma.

## Patients and methods

Between June 2006 and May 2009, two imaging modalities, FDG–PET/CT and contrast-enhanced multidetector CT, were performed a total of 30 times on 19 patients with ovarian cancer during regular follow-up at Oita University Hospital. FDG–PET/CT using a Discovery LS scanner (GE Medical Systems, Milwaukee, WI, USA) and contrast-enhanced multidetector CT using an Aquilion 32 slice system (Toshiba Medical Systems, Tochigi, Japan) were separately performed within a week, and each examination was separately interpreted by experienced radiologists. Serum CA 125 levels were also evaluated.

The patients' characteristics are summarized in Table 1. All the patients had received optimal initial debulking surgery (residual tumor < 1 cm) and conventional platinum-taxane-based chemotherapy as an initial treatment. Ten patients (52.6%) had serous histology and most of the patients (78.9%) were diagnosed as stage III/IV. At imaging analysis, the mean age of the patients was 57.9 years and the mean CA 125 level was 82.9 IU/mL. Six patients (20%) had not experienced recurrence prior to the examination, whereas 15 patients had experienced first-time recurrence and had been treated with second-line therapy. The tumor had recurred more than two times in nine patients. All patients were asymptomatic at the examination.

A CT scan was considered positive if one or several of the following patterns of peritoneal carcinomatosis were visualized in addition to the previously described findings: mesenteric fat infiltration, nodular to bulky tumors in the mesentery or omentum, peritoneal implants along the perihepatic, sub-diaphragmatic, anterior or lateral margin of the peritoneal cavity, bowel wall thickening, and ascites. Nodal involvement was suspected when the small diameter of a lymph node was larger than 10 mm. A CT scan was considered negative if none of the above-mentioned features was found or if there was no significant change when compared to the patient's previous CT scan. A PET/CT scan was considered negative if no abnormal increased FDG focal uptake was visualized. A PET/CT scan was considered positive if one or several abnormal increased FDG focal uptakes were visualized, whatever the CT fusion findings were. Recurrence of the ovarian cancer was

**Table 1** Patients' characteristics

| Variable | n |
|---|---|
| Number of patients | 19 |
| Number of examinations with FDG–PET/CT and enhanced CT images | 30 |
| Mean age (range), years | 57.9 (32–78) |
| Mean CA 125 (range), IU/mL | 82.9 (4.9–1,265) |
| Recurrence at examination ($n = 30$) | |
| No | 6 (20.0%) |
| 1 | 15 (50.0%) |
| ≥2 | 9 (30.0%) |
| Stage at diagnosis ($n = 19$) | |
| I | 4 (21.1%) |
| II | 0 (0%) |
| III | 13 (68.4%) |
| IV | 2 (10.5%) |
| Histology ($n = 19$) | |
| Serous | 10 (52.6%) |
| Endometrioid | 3 (15.8%) |
| Clear cell | 4 (21.1%) |
| Mucinous | 1 (5.3%) |
| Undifferentiated | 1 (5.3%) |
| Residual disease after initial debulking surgery ($n = 19$) | |
| Optimal | 19 (100%) |
| Suboptimal | 0 (0%) |

**Table 2** Comparison of CA 125, PET/CT, and contrast-enhanced CT results and final diagnosis

| | CA 125 | PET/CT | Enhanced CT | Final diagnosis |
|---|---|---|---|---|
| Positive | 9 | 18 | 21 | 22 |
| True positive | 8 | 18 | 21 | – |
| False positive | 1 | 0 | 0 | – |
| Negative | 21 | 12 | 9 | 8 |
| True negative | 7 | 8 | 8 | – |
| False negative | 14 | 4 | 1 | – |
| PPV (%) | 11.1 | 100 | 100 | – |
| NPV (%) | 33.3 | 66.7 | 88.9 | – |
| Sensitivity (%) | 36.4 | 81.8 | 95.5 | – |
| Specificity (%) | 87.5 | 100 | 100 | – |

*PPV* positive predictive value, *NPV* negative predictive value

confirmed by surgery or the subsequent clinical course of the patients.

In all 19 of these patients, subsequent clinical management was planned based on the results of FDG–PET/CT and contrast-enhanced multidetector CT.

## Results

Among the total of 30 images, 22 resulted in a diagnosis of recurrence. The results of the CA 125 assay, FDG–PET/CT analysis, and contrast-enhanced multidetector CT analysis are given in Table 2 along with the final diagnosis. When the normal CA 125 levels were defined as below 35 IU/mL, the positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity of the CA 125 assay were 11.1, 33.3, 36.4, and 87.5%, respectively. The PPV, NPV, sensitivity, and specificity of FDG–PET/CT were 100, 66.7, 81.8, and 100%, respectively. The PPV, NPV, sensitivity, and specificity of contrast-enhanced multidetector CT were 100, 88.9, 95.5, and 100%, respectively. As shown in Table 3, false-negative diagnosis from FDG–PET/CT occurred in two cases with peritoneal lesions of serous papillary adenocarcinoma, one case with a

peritoneal lesion of clear cell adenocarcinoma, and one case with a single inguinal lymph node metastasis of mucinous adenocarcinoma. A false-negative diagnosis from contrast-enhanced multidetector CT occurred in a single case of pelvic lymph node metastasis of serous papillary adenocarcinoma. Contrast-enhanced multidetector CT was considered the most accurate imaging modality.

Among the total of 30 analyses, FDG–PET/CT yielded 18 positive imagings, whereas contrast-enhanced multidetector CT gave 21 positive imagings (Table 4). Contrast-enhanced multidetector CT tended to detect a greater number of both peripheral peritoneal lesions and lymph node involvements. In cases of positive imaging, FDG–PET/CT tended to detect a greater number of small lesions than contrast-enhanced multidetector CT (Tables 5, 6).

Finally, the impact of FDG–PET/CT and that of contrast-enhanced multidetector CT on the choice of management plan were compared (Table 7). In most of the 30 imaging analyses, the management plans obtained from FDG–PET/CT results were similar to those based on the contrast-enhanced multidetector CT results. Nine of 11 patients (81.8%) in whom surgery was recommended by both PET/CT and contrast-enhanced CT findings achieved the complete resection of the recurrent tumor. Two patients in whom surgery was recommended by contrast-enhanced CT findings, but not by PET/CT findings, achieved the complete resection. There was no patient in whom surgery was recommended by PET/CT findings only.

## Discussion

The importance of debulking in recurrent ovarian cancer was demonstrated in a retrospective data analysis [2]. It has been suggested that only those patients in whom a macroscopic tumor-free resection could be achieved could

**Table 3** Characteristics of false-negative cases

| Case no. | Result of imaging study | | Histology | Sites of recurrent tumor (largest size) |
|---|---|---|---|---|
| | PET/CT | Contrast-enhanced CT | | |
| 1 | False negative | Positive | Serous | Subphrenic peritoneum (14 mm) |
| | | | | Pelvic peritoneum (20 mm) |
| 2 | False negative | Positive | Serous | Pelvic peritoneum (8 mm) |
| 3 | False negative | Positive | Mucinous | Inguinal lymph node (25 mm) |
| 4 | False negative | Positive | Clear cell | Upper abdominal mesenterium (10 mm) |
| 5 | Positive | False negative | Serous | Pelvic peritoneum (8 mm) |

**Table 4** Comparison of disease location detected by PET/CT and contrast-enhanced CT

| | PET/CT | Enhanced CT |
|---|---|---|
| Positive imaging | 18 | 21 |
| Peripheral lesions | | |
| Abdominopelvic | 10 | 13 |
| Extra-abdominopelvic | 1 | 1 |
| Lymph node involvement | | |
| Abdominopelvic | 8 | 9 |
| Extra-abdominopelvic | 2 | 3 |

**Table 5** Distribution of lesions detected by PET/CT and contrast-enhanced CT

| | PET/CT | Enhanced CT |
|---|---|---|
| Positive imaging | 18 | 21 |
| 1 | 6 | 7 |
| 2 | 2 | 1 |
| 3–5 | 0 | 5 |
| >5 | 10 | 8 |

**Table 6** Comparison of the number of lesions detected by PET/CT and contrast-enhanced CT

| | |
|---|---|
| PET/CT > contrast-enhanced CT | 4 (18.2%) |
| PET/CT = contrast-enhanced CT | 11 (50.0%) |
| PET/CT < contrast-enhanced CT | 7 (31.8%) |

**Table 7** Comparison of the management plans chosen based on PET/CT and contrast-enhanced CT

| PET/CT | CT | Final plan | Number of patients |
|---|---|---|---|
| Surgery | Surgery | Surgery | 11 |
| Chemotherapy | Chemotherapy | Chemotherapy | 7 |
| Chemotherapy | Observation | Chemotherapy | 1 |
| Observation | Observation | Observation | 8 |
| Observation | Surgery | Surgery | 2 |
| Observation | Chemotherapy | Chemotherapy | 1 |

benefit from surgery in terms of overall survival [2]. Regarding these aspects of patient management, accurate and early diagnosis of recurrence and disease location is important for determining the most appropriate therapy for recurrent ovarian cancer. For this purpose, it is necessary to find a diagnostic tool to select patients who benefit from surgery and to identify those who are better off with primary systemic therapy, preferentially as an interdisciplinary approach involving radiologists, gynecologists, and medical oncologists. Physical examination with or without ultrasound, CT, MRI, and serum CA 125 assay has been utilized for the surveillance of these patients. However, because it is difficult to diagnose disease using these modalities, there has been increasing interest in the use of FDG–PET/CT for recurrent ovarian cancer. Prior studies have shown that small-volume disease (<2 cm) can be missed on anatomic imaging due to the widespread location of metastases on visceral surfaces [3, 11]. Studies with FDG–PET/CT in ovarian cancer indicated that this technique is particularly useful for the diagnosis of recurrence when CA 125 levels are rising and conventional imaging is inconclusive or negative [9, 10, 12–16].

In this study, we compared the impact of integrated FDG–PET/CT versus contrast-enhanced multidetector CT on the following: (1) detection of ovarian carcinoma recurrence during regular follow-up after initial treatment; (2) restaging of recurrent ovarian cancer; and (3) decision making in the clinical management of recurrent ovarian

carcinoma. It was demonstrated that both FDG–PET/CT and contrast-enhanced multidetector CT had very high sensitivity and specificity for the detection of recurrent ovarian cancer. Contrast-enhanced multidetector CT was considered the most accurate imaging modality for detecting recurrence. On the other hand, FDG–PET/CT was shown to detect a larger number of small lesions. When comparing the impact on the decision of management plan, both FDG–PET/CT and contrast-enhanced multidetector CT provided significant information on the location of recurrent disease.

CT has been the most common modality, and the use of intravenously administered contrast agents and a thinner slice thickness are generally recommended. Conventional CT is of limited value in the detection of recurrence, with a 36% false-positive rate, sensitivities as low as 40–60%, and a specificity of 87% [8, 17] owing mainly to failure in detecting microscopic and small macroscopic disease. Recent advances in CT technology with the availability of multidetector row scanners and multiplanar images have the potential to improve the visualization of small lesions on curved surfaces throughout the whole body [4]. It has been demonstrated that helical multidetector CT yields a higher sensitivity (85–93%) for peritoneal metastases compared with conventional CT (64–79%) [3, 8, 11]. Limitations are mainly due to a low accuracy in detecting small disseminated lesions, such as peritoneal carcinosis, and mesenteric and omental recurrences [6]. In the present study, one of the most recently developed multidetector CT system with contrast enhancement was used to assess recurrence. Contrast-enhanced multidetector CT imaging had a sensitivity of 95.5% and specificity of 100%, which were superior to those obtained from FDG–PET/CT.

Many previous studies have reported that integrated PET/CT, which merges the metabolic information from FDG–PET with the anatomical information from CT, appeared superior to conventional imaging modalities, whose sensitivity is relatively low for small lesions, especially when post-treatment changes (surgical scars or postradiation fibrosis) made image interpretation difficult [11, 12, 18, 19]. In this regard, the biochemical features of malignant tissues have been employed as a valid parameter to distinguish between metabolically active tissue and the presence of scars. The sensitivity, specificity, and accuracy of FDG–PET/CT for recurrent ovarian cancer are 73–100, 40–100, and 63–100%, respectively, in most series, and these values are often higher than those of CT [9, 10, 12–16], although the diagnostic reliability of FDG–PET/CT for peritoneal lesions <1 cm is still unsatisfactory [9, 13, 14, 19]. It has also been reported that this diagnostic procedure offers less satisfactory results in the evaluation of retro-peritoneal disease [13]. However, $^{18}$FDG–PET/CT may be useful to disclose unusual supra-diaphragmatic spreading of the disease and may be very helpful for treatment planning, especially for the selection of patients suitable for secondary surgical cytoreduction [10, 14–16].

It has also been demonstrated that PET/CT can provide important additional information for deciding the clinical management plan for recurrent ovarian cancer, because of the higher incidence of multiple lesions detected on FDG–PET/CT compared to conventional imaging modalities [14–16, 20]. Chung et al. [14] showed retrospectively that PET/CT imaging modified the diagnostic or treatment plan in 25% of patients. Simcock et al. [20] demonstrated

prospectively that PET/CT altered the distribution of the disease in 61% of patients, and led to a significant change in the management in 57% of patients. Mangili et al. [15] described that clinical management was changed in 44% of patients when PET/CT information was added to the CT follow-up findings. Mansueto et al. [21] also demonstrated that the introduction of PET/CT in the early detection of recurrent ovarian cancer was cost-effective and allowed to redirect the clinical management toward more appropriate therapeutic choices.

In summary, our present study shows that FDG–PET/CT, as well as contrast-enhanced multidetector CT, is a useful tool for the clinical follow-up of ovarian cancer after first-line therapy, which is consistent with previous reports. PET/CT can assist treatment planning by predicting resectability and by localizing tumor tissue for subsequent treatment modalities. However, the detection of microscopic lesions remains challenging with the currently available PET and PET/CT systems. Improving the spatial resolution and sensitivity of PET/CT scanners, and developing new, more specific radioactive tracers may help to overcome this limitation in the future. On the other hand, recent advances in CT technology with the availability of multidetector row scanners and multiplanar images have the potential to improve the visualization of lesions on curved peritoneal surfaces such as the diaphragm and pelvis. As demonstrated in this study, the use of the most recently developed multidetector CT system with contrast enhancement can achieve satisfactory images of recurrent lesions with high sensitivity, specificity, and accuracy similar to those of the images obtained from FDG–PET/CT. At present, contrast-enhanced multidetector CT is recommended for the regular follow-up for ovarian cancer patients after initial treatment. FDG–PET/CT should be utilized to decide the optimal management plan for the recurrent ovarian cancer detected by conventional imaging modalities.

**Conflict of interest statement** None.

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