Original Article

Role of 18F-FDG PET/CT in the Detection of Ovarian Cancer Recurrence in the Setting of Elevated Tumor Markers


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ABSTRACT

Objectives: To evaluate the diagnostic performance of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with suspected biochemical ovarian tumor recurrence in comparison to contrast enhanced CT.

Patients and Methods: A total of 64 ¹⁸F-FDG PET/CT studies for patients with biochemical suspicious ovarian tumor recurrence were evaluated. Each patient underwent ¹⁸F-FDG PET/CT and Ce-CT scans in the same day. Studies were read independently by one experienced nuclear medicine physician and one experienced radiologist. A four-point score (score 0 = definitely benign, score 1 = probably benign, score 2 = probably malignant and score 3 = definitely malignant) used to assess the presence or absence of recurrence (local, regional or distant).

The final diagnosis of tumor status was made on the basis of subsequent follow-up by ¹⁸F-FDG PET/CT, conventional imaging (CT/MRI) or histopathology whenever possible. Results: Of the 64 studies evaluated, 61 (95%) studies had tumor recurrence and 3 (5%) studies were free based on final diagnosis. ¹⁸F-FDG PET/CT & Ce-CT had sensitivity 97% vs. 87%, specificity 100% vs. 33%, and accuracy 97% vs. 84% respectively. ¹⁸F-FDG PET/CT was significantly more sensitive and more accurate compared to Ce-CT with P-value of 0.07 and 0.02; respectively with no statistical significant difference in accuracy. Conclusions: ¹⁸F-FDG PET/CT is more accurate than Ce-CT in the diagnosis of ovarian tumor recurrence in patients with elevated tumor marker.

Key words: ovarian cancer, elevated tumor markers, 18F-FDG PET/CT, recurrence.

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INTRODUCTION:
Ovarian cancer has a propensity for recurrence after treatment, even after surgery and adjuvant chemotherapy in early-stage tumors. Response rates to this standard primary treatment are approximately 80%, but survival rates are low. Approximately 20% to 30% of patients with early-stage disease and 50% to 75% of patients with advanced disease who obtain a complete response after first-line chemotherapy will ultimately develop a recurrent disease. Most patients with treated ovarian cancer relapse or die within 5 years of diagnosis. Therefore, a close follow-up is essential utilizing non-invasive technique such as tumor marker levels and imaging scans.

While the level of CA-125 has been shown to be a sensitive marker for tumor recurrence and levels may rise 3 to 6 months before there is clinically apparent disease, it does not provide information concerning the size and distribution of the lesions. Levels may also increase in a number of benign conditions, being a non-specific marker for ovarian cancer, and some patients, with relapse of disease, present with normal CA-125 levels.

CT uses morphologic criteria to detect the disease and diagnose metastasis and abnormalities by evaluating the size of the lymph nodes. But sometimes normal-sized lymph nodes may be diseased, while enlarged nodes may be due to inflammation, hence may be free of disease. Moreover, accurate detection of intra-abdominal tumor recurrences may be limited due to difficulties in identifying small tumor deposits and in separating bowel structures from adjacent tumor tissue. Even if the tumor is detected, CT cannot confirm the lesion as tumor recurrence if it is too small. Also metastases from ovarian cancer are unlike most other tumors in that they are primarily peritoneal rather than parenchymal in location. Therefore, they usually occur on the surfaces of the viscera rather than as masses within the viscera. These tumor implants can be miliary and iso-attenuating relative to the viscera at computed tomography (CT), which makes their detection challenging.

FDG-PET/CT imaging for ovarian cancer surveillance has proven useful for detecting early recurrences with a diagnostic accuracy of approximately 80%. Recognized limitations include failure to detect small lesions with all three modalities and misinterpretation of normal physiological abdominal activity on PET. Integrated PET/CT offers the combined benefits of anatomical and functional imaging, and has been used to localize areas of increased FDG uptake with improved sensitivity and specificity. In this work, we sought to explore the possible role of PET/CT using $^{18}$F-FDG compared to Ce-CT for detection of ovarian tumor residual/recurrence when tumor markers are elevated.
PATIENTS AND METHODS:

Patients: This prospective study was conducted in Alfa Scan Radiology Center, during the period from January 2010 to November 2012. The inclusion criteria: patients with pathologically proven ovarian cancer who were treated with initial standard treatments, referred for post-treatment surveillance for detection of residual disease or recurrence. Patients referred for initial staging or with synchronous or past history of other cancers were excluded together with those who lost their follow-up. The study was approved by the Institutional Review Board, and each patient signed a written informed consent form.

PET/CT Imaging Protocol

The $^{18}$F-FDG PET/CT scans were acquired using a Philips Gemini Time-of-Flight PET/CT machine equipped with LYSO crystals (Philips, Holland). The patients were instructed to fast for at least 6 hours before imaging and their blood glucose level was measured at the time of the tracer injection and was less than 160 mg/dl. A dose of 0.1-0.14 mCi/Kg was injected intravenously and adjusted according to patient’s weight. For the optimal delineation of bowel structures, 400–600 ml of diluted mannitol solution was administered 1 hour before CT imaging. Approximately 60 minutes after tracer administration, a low-dose CT scan (5-mm contiguous axial cuts) was obtained in a 64 integrated multi-slice CT machine, from the skull base to the mid-thigh. The acquisition was obtained in a helical mode, using 120 kV, 60mAs, and a 512 x 512 matrix size, acquiring a field of view (FOV) of 700 mm in 22.5 seconds. The first CT scan was used for attenuation correction. Immediately after the low-dose CT, an emission PET scan was acquired in a three-dimensional mode over the same anatomical regions starting from the skull vertex to the level of the mid-thigh. The acquisition time was 2 minutes per bed position in 9 bed positions, with a one-slice overlap at the borders of the FOV. Finally, a diagnostic CT was acquired using 120 kV, 300 mAs, and a 512 x 512 matrix size. The acquired FOV was 500 mm using dose automatic modulation in the Z direction. The radiation exposure dose from low-dose CT was in average 3.37 milli Gray (mGy) while that for diagnostic CT was 11.48 mGy.

After completion of acquisition, the images were reconstructed with a standard iterative algorithm, and then the reconstructed CT attenuation-corrected PET images, low dose CT images and Ce-CT images were transferred to the viewing stations for reviewing in axial, coronal, and sagittal planes and in a maximum-intensity-projection (MIP) three-dimensional cine mode using the manufacturer’s review station (Brilliance, Philips, Holland). Semi-quantitative analysis of the 18F-FDG uptake in the suspected lesions was carried out by calculating the maximum standardized uptake values of each lesion using a rounded region of interest tool and a systematic
slice by slice search for the most intense voxel within a given lesion.

**Data Interpretation:**
The fused PET/CT and Ce-CT images were separately interpreted by a team of one nuclear medicine physician and one radiologist with knowledge of aim of the study.
For each study, 11 sub-sites were evaluated for the presence or absence of abnormality and recorded in a special database. A four-point score was used to describe the possibility of malignancy for each sub-site: score 0 = definitely benign, score 1 = probably benign, score 2 = probably malignant and score 3 = definitely malignant. The sub-sites were: local tumor site, peritoneum, pelvic LNs, abdominal LNs, mediastinal LNs, cervical LNs, liver, lung, bone, brain and other sites (pleura, muscles, adrenal glands).

**Follow up:**
The final diagnosis of the presence or absence of recurrent/residual disease was made on the basis of subsequent follow-up by conventional imaging (CT/MRI), tumor markers, PET/CT and/or clinical follow-up of at least 6 months or histopathological findings obtained during surgery or biopsy whenever possible.
Clinical recurrence was defined as the detection of recurrent disease by subsequent PET/CT, Ce-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.

**Statistical analysis:**
Study-based and site based analyses were employed. True positive (TP), true negative (TN), false positive (FP) and false negative (FN) readings were identified based on subsequent clinical/imaging/histopathological validation. Diagnostic performance parameters were calculated in the form of sensitivity, specificity, PPV, NPV and accuracy. The non-parametric McNemar test was used to evaluate the statistical significance of the differences in sensitivity and specificity (A two-sided p value <0.05 was considered significant) while Receiver’s Operating Characteristics (ROC) analysis was used to compare the accuracy.
Quantitative data were summarized and expressed as mean ± SD, median (range), whereas qualitative data were expressed as frequencies and percentages. The analyses were carried out using the SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA), (MedCalc, Ostend, Belgium), and Microsoft Excel (Microsoft, USA) softwares.
RESULTS:

Patients: A total of 64 studies from 55 patients with ovarian cancer were eligible for this study. The general characteristics of the 55 patients enrolled in this study were summarized in (Table 1). The median age was 54 year (range: 13-76) with the majority of the patients having epithelial tumors (89.1%).

Table 1: General characteristics of the patients with possible recurrent ovarian cancer enrolled in the work.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>55</td>
<td>100%</td>
</tr>
<tr>
<td>Range of Age</td>
<td>54</td>
<td>13-76 Years</td>
</tr>
<tr>
<td>Pathologic Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>49</td>
<td>89.1%</td>
</tr>
<tr>
<td>Non-epithelial</td>
<td>6</td>
<td>10.9%</td>
</tr>
<tr>
<td>Timing of PET/CT after Therapy</td>
<td>8</td>
<td>0.25-36 Month’s</td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>5</td>
<td>7.8%</td>
</tr>
<tr>
<td>Surgery + CTh</td>
<td>53</td>
<td>82.8%</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>4</td>
<td>6.3%</td>
</tr>
<tr>
<td>Neoadjuvant CTh + Surgery + CTh</td>
<td>2</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

CTh = Chemotherapy

Diagnostic performance:

Table 2: Diagnostic performance of PET/CT and Ce-CT in patients with suspected recurrent ovarian cancer & elevated tumor markers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ce-CT</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>True Positive</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>True Negative</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>False Positive</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87%</td>
<td>97%</td>
</tr>
<tr>
<td>Specificity</td>
<td>33%</td>
<td>100%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>11%</td>
<td>60%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>84%</td>
<td>97%</td>
</tr>
</tbody>
</table>
Table 3: Differences in sensitivity, specificity and accuracy between Ce-CT and PET/CT on study-basis for patients with suspected recurrent ovarian cancer & elevated tumor markers.

<table>
<thead>
<tr>
<th>Modality</th>
<th>PET/CT</th>
<th>Ce-CT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FN</td>
<td>TP</td>
<td>TN</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Difference in sensitivity by Mc Nemar’s test.
<sup>b</sup> Difference in specificity by Mc Nemar’s test.
<sup>c</sup> Difference in area under the curve (AUC) by ROC curve analysis.

Fig.1: ROC-Analyses of the difference in accuracy between Ce-CT & combined PET/CT on study-basis in patients with suspected recurrent ovarian cancer & elevated tumor markers.
Fig. 2: PET/CT results in patients with suspected recurrent ovarian cancer & elevated tumor marker in relation to Ce-CT results

Fig. 3: A 40-year old patient, with serous adenocarcinoma, underwent surgical resection followed by chemotherapy & presented with elevated CA-125 7 months later. Fused PET/CT (a & b) showed FDG-avid peritoneal foci in left iliac fossa (a) and deep in the pelvic cavity along serosa of sigmoid colon (b) as well as FDG-avid right external iliac lymph node (not shown). All these lesions were missed on Ce-CT (c&d).
Ce-CT and PET/CT were concordantly TN in 1/3 studies (Table 3). PET/CT excluded disease in 2 FP studies by Ce-CT with no statistically significant difference in-between. Both modalities were TP in 52 studies (Table 3). Additionally PET/CT diagnosed disease in 7/8 FN results by Ce-CT with marginal statistically difference

\( P = 0.07 \). The difference of the overall accuracy as proved by ROC analyses (Fig.1) was statistically significant \( (P=0.02) \). PET/CT truly diagnosed recurrent disease in 7/9 studies with normal/equivocal Ce-CT and excluded disease in 2/55 studies with abnormal Ce-CT (Fig.2).

**DISCUSSION:**

The usefulness of concurrent FDG PET/CT for post-treatment surveillance of patients with ovarian cancer has been investigated in several studies (12-15) the overall reported sensitivity, specificity and accuracy of patient-based analyses were 73-100%, 40-100% and 63-100% respectively. In this work, 64 cases represented with elevated tumor markers; 9 with normal/equivocal Ce-CT and 55 with abnormal Ce-CT (Fig. 2). According to the final status, 61/64 studies were positive for residual/recurrence. The sensitivity, specificity and accuracy for PET/CT were 97%, 100% and 97% respectively compared to 87%, 33%, 84% respectively by Ce-CT. There was statistically significant difference in accuracy \( (P=0.02) \). Although PET/CT had higher sensitivity and specificity, there was marginal difference in sensitivity \( (P=0.07) \). Although the difference in percentage of specificity was high (100% for PET/CT and 33% for Ce-CT); however, this difference was obtained from a very small group of patients \( (n = 3) \) who were truly disease-free on final follow-up. PET/CT showed no false positive results while Ce-CT mis-diagnosed 2 of them as having disease. It is assumed that patients with high tumor markers had a high pre-test probability of residual/recurrence disease, given that 95% of patients proved to have disease on follow-up with only 3 TN studies yielding 60% NPV; hence, negative PET/CT results should be taken cautiously. Among 9 studies with elevated tumor markers and normal/equivocal Ce-CT, PET/CT was TP in 7 studies, FN in one study and TN in another study. PET/CT identified unsuspected disease in 7 studies (78%); 3 studies with normal sized lymph nodes and 4 studies with small peritoneal nodules missed by Ce-CT (16-19). This emphasizes the added value of PET/CT in this study. The only FN PET/CT study in this sub-group proved to have abdominal recurrence (peritoneal metastases) on second-look laparotomy (SLL) 3 months later (Figure 3). This could be explained by the inherent limitation of resolution of PET/CT for detection of miliary peritoneal metastases < 5mm. Among 55 studies with elevated tumor markers and abnormal Ce-CT, PET/CT correctly confirmed residual/recurrence in 52 studies, excluded disease in 2
studies (2 TN) and missed residual/recurrence disease in one study (1 FN). One TN patient referred 1 month after initial standard treatment (Surgery+ CTH) where Ce-CT showed 2.8 cm hepatic focal lesion and considered as positive for residual disease. The lesion remained stable over a period of 15 months upon second Ce-CT and PET/CT studies with normalization of CA-125 level, thus excluding the presence of residual disease. The second TN study in this subgroup was in a patient with perihepatic hypodense peritoneal nodule that was remained stable for 9 months upon second PET/CT imaging. Due to the narrow time interval between primary standard treatment and PET/CT, it was expected that morphological changes takes time more than metabolic changes explaining the inability of Ce-CT in differentiating between residual active disease and necrosis/fibrosis. (20-23) The FN PET/CT study in this sub-group had a 7-mm pulmonary nodule in Ce-CT that was confirmed to be metastatic on follow-up and the patient received CTH with subsequent resolution of nodule and normalization of tumor marker level. Generally, the diagnostic performance indices of combined PET/CT come in line with those reported in literature. (24-27) However, the sensitivity of Ce-CT is generally higher than others reported in literature. (24, 25, 28, 29) In our work, Ce-CT was performed using a diagnostic-level high-dose 64-slice machine for the whole body simultaneously with PET/CT and interpreted using volume images rather than reconstructed 3-5 mm slices. Most of the other studies were retrospective studies, CT was not performed on the same setting and contrast enhancement is not mentioned clearly in their methods. Also some authors correlated PET/CT with conventional imaging other than CT. This work suffers some limitations; firstly, lack of histopathologic correlation of all the sites of abnormal $^{18}$FDG uptake. The confirmation of all the sites would not have been ethical solely for the purpose of validation of PET/CT findings. Secondly, impact of PET/CT on change of management and cost-effectiveness of PET/CT versus Ce-CT was not feasible in current study. Data collection about the planned treatment before and after Ce-CT could not be reached. Lastly, semi-quantitative parameters as SUV and metabolic tumor volume that may have prognostic significant were beyond the scope of this study. Advantages of this study include prospective design with relatively large number of patients that was performed using simultaneous Ce-CT & PET/CT protocol with uniform interpretation criteria.

REFERENCES:


27. Sari O, Kaya B, Kara PO, Gedik GK, Celik C, Ozbek O, Serdengecti M. The role of FDG-PET/CT in ovarian cancer patients with high tumor markers or suspicious lesion on contrast-enhanced CT in evaluation of
