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Utility of ^{18}F-FDG PET/CT in follow-up of patients with low-grade serous carcinoma of the ovary

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HIGHLIGHTS

- PET/CT may impact clinical management in the setting of low-grade serous carcinoma in approximately 30% of patients.
- PET/CT may be a useful tool in the detection of low-grade serous carcinoma recurrence.
- Total lesion glycolysis may predict poorer overall survival after recurrence.

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ABSTRACT

Objective. Ovarian low-grade serous carcinoma (LGSC) is a rare and indolent tumor. The utility of ^{18}F-FDG PET/CT in monitoring patients with LGSC has not been established. We assessed the accuracy and clinical impact of ^{18}F-FDG PET/CT in patients with ovarian LGSC after initial treatment.

Methods. A retrospective analysis was performed on patients with ovarian LGSC who had undergone ^{18}F-FDG PET/CT scans during follow-up after primary treatment. The impact of ^{18}F-FDG PET/CT on the management plan was assessed. The sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT findings in the detection of recurrence were calculated. Total lesion glycolysis (TLG) was determined to assess metabolic activity of tumors. Potential prognostic factors for disease-free and overall survival after recurrence were assessed.

Results. Forty-eight patients were included in the analysis, 39 with recurrent disease and 9 without recurrence. A total of 91 ^{18}F-FDG PET/CT scans were performed, and 30% of these (27/91) had an impact on the management plan. Sensitivity, specificity, and accuracy in the detection of LGSC recurrence were 94%, 100%, and 97%, respectively, for ^{18}F-FDG PET/CT; 89%, 95%, and 93%,respectively, for CT; and 68%, 89%, and 73%, respectively, for serum CA-125. There was no significant difference in sensitivity between PET/CT and CT. Survival after recurrence was poorer in patients with a TLG value greater than 67.7 g.

Conclusions. ^{18}F-FDG PET/CT may provide useful information during the follow-up of patients with LGSC after initial treatment. TLG may be a predictor of survival after recurrence.

Introduction

Ovarian carcinoma is the second most common gynecological malignancy in the United States and the most lethal; it accounted for nearly 15,500 deaths in the United States in 2012 [1]. Ovarian carcinoma is a heterogeneous disease including several distinct tumor subtypes. The serous subtype accounts for approximately 60% to 80% of ovarian cancer cases [2]. A two-tier grading system—low-grade and high-grade—for invasive ovarian serous carcinoma has been described [3]. Low-grade serous carcinoma (LGSC) accounts for fewer than 10% of ovarian serous carcinomas [4]. LGSC has different clinical behavior from high-grade serous carcinoma and is characterized by young age at diagnosis and prolonged overall survival [5].

Computed tomography (CT) and measurement of serum tumor marker antigen 125 (CA-125) are currently standard surveillance modalities in patients with ovarian cancer [6]. However, CA-125 poorly correlates with objective response and radiographic imaging, such as CT scans, does not often provide accurate information due to desmoplasia,

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calcification and fibrosis frequently associated with LGSC tumor nodules [7]. Since metabolic function may better discriminate active from treated tumor, we hypothesized that nuclear imaging, including ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), would be a useful surveillance tool in patients diagnosed with and treated for LGSC.

Materials and methods

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center and was performed in compliance with the Health Insurance Portability and Accountability Act. The Institutional Review Board waived the requirement for informed consent. We retrospectively reviewed the database of the Department of Gynecologic Oncology and Reproductive Medicine at MD Anderson and identified 71 consecutive patients with ovarian LGSC who were referred to our institution for treatment or follow-up between January 2002 and December 2011. Twenty-three patients were excluded because they had not undergone PET/CT during follow-up (n = 10); had another active malignancy (n = 2); or had visited our institution only once to obtain a second opinion (n = 11). The remaining 48 patients were included in this study. Tumor specimens from all the patients were obtained from referring institutions, and diagnosis was confirmed as LGSC by an expert gynecologic pathologist at MD Anderson. PET/CT scans were performed at the primary physician's discretion during follow-up after initial treatment.

^{18}F-FDG PET/CT

For PET/CT imaging, patients were required to fast for 6 h before ^{18}F-FDG administration to achieve a blood glucose level of less than 120 mg/dl. ^{18}F-FDG (185–370 MBq/injection; 5–10 mCi/injection) was administered intravenously, and then patients rested in a quiet room. Sixty minutes after ^{18}F-FDG administration, imaging was performed. Integrated PET/CT systems were used to acquire imaging data (Discovery ST, STe, or RX; GE Healthcare). PET/CT was performed in accordance with guidelines published by the National Cancer Institute [8].

PET/CT datasets for eligible patients were reviewed for this study. Two reviewers (S.T., H.A.M.) experienced in PET/CT interpretation measured the highest metabolic activity within the tumor (maximum standard uptake value; SUV_{max}) and total lesion glycolysis (TLG), using an Advantage workstation (GE Healthcare). While SUV_{max} reflects only the highest point of metabolic activity within the tumor, it is hypothesized that TLG could better reflect tumor metabolic activity by taking into account the activity in the entire tumor. The SUV was defined as measured activity concentration (Bq/ml) multiplied by lean body mass (kg) divided by injected activity (Bq). TLG was defined as the average metabolic activity within the tumor multiplied by the tumor volume, with a threshold of 45% SUV_{max} in the volume of interest [9]. In the case of multiple recurrent lesions, the highest TLG was used for the analysis. For the patients who had PET/CT performed at an outside institution, available raw imaging data were obtained and input into an Advantage workstation, and SUV_{max} and TLG were defined by radiologists at our institution.

Evaluation of recurrence

On PET/CT, a positive finding was defined as a lesion diameter of more than 10 mm or a lesion diameter of 10 mm or less with FDG uptake. An SUV_{max} value of 2.0 g/ml was used as a cut-off between positive and negative findings. FDG activity only in areas of the physiologic tracer distribution and absence of sites of increased uptake were considered negative findings. On conventional CT, a positive finding was defined as a lesion more than 10 mm in diameter or with other signs of malignancy, such as central necrosis, characteristic shape (e.g., spherical lymph nodes), or abnormal contrast enhancement. Both PET/CT and conventional CT were performed within one month at the diagnosis of recurrence and were performed at physician's discretion during follow-up. For CA-125 measurement, a CA-125 value greater than 35 U/ml was considered a positive finding. Serum CA-125 values had to have been obtained within 1 month of the confirmation of recurrence.

All PET/CT scans from follow-up of patients were correlated with histopathologic findings and/or subsequent imaging findings. PET/CT findings of recurrence were considered true-positive if they corresponded with histopathologically detected recurrence or with subsequent imaging findings positive for recurrence performed within 6 months after PET/CT. PET/CT findings were considered true-negative if they indicated no recurrence and subsequent imaging studies also showed no evidence of disease for at least 6 months after the initial PET/CT scan. The same parameters were used for CT scan.

The sensitivity, specificity, and accuracy of PET/CT, conventional CT, and CA-125 in the detection of recurrent disease were calculated using region-by-region comparison. For each imaging report, recurrences were divided into three regions: abdomen, pelvis, and distant site. For example, in the case of recurrent lesions in the pelvis and mediastinum, a patient was considered to have two regions positive. If a patient had no recurrence, a patient was considered to have all three regions negative.

Impact of PET/CT on management plans

The impact of PET/CT on management plans was assessed. If the results of PET/CT prompted a change from one modality to another (e.g., from chemotherapy to surgery) or prompted changes in chemotherapy (e.g., regimen changes, dose changes, cessation, or a switch from chemotherapy to hormonal therapy), PET/CT was considered to have had an impact on management plans. For example, if CT revealed a suspicious lesion and subsequent PET/CT performed within one month confirmed a positive lesion and prompted a change in treatment then the PET/CT was considered to have had an impact on the management plan.

Statistical analysis

Statistical analyses were performed with S-PLUS 7.0 for Windows (Insightful Corp., Seattle, WA). Differences in performance between PET/CT and CT were compared with the McNemar test. Progression-free survival (PFS) and overall survival (OS) from the date of the first recurrence were calculated. Recurrence was defined as confirmation of recurrence by pathological or radiological diagnosis. For PFS, progressive disease and death were considered events. Patients who were alive at the last follow-up were recorded as censored. The Kaplan–Meier method and a log-rank test were used to compare OS and PFS after recurrence stratified by various potential prognostic factors. The optimal cut-off point of TLG for PFS was determined using the methods described by Williams et al. [10]. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Of the 48 patients in the study, 47 had primary surgery and 1 had neoadjuvant chemotherapy as initial treatment. Thirty-nine patients had recurrence. As the diagnosis of recurrence, 22 patients (56%) were detected by imaging studies, nine patients (23%) had an increasing CA-125 level, seven patients (18%) were symptomatic, and one patient (3%) had an abnormality detected by a pelvic examination. The median interval from initial treatment to disease recurrence was 29.2 months (range, 5.3–311.0). Thirty-four patients had recurrence in the abdomen, pelvis, or both. Five