The Role of $^{18}$F-FDG PET in Assessing Therapy Response in Cancer of the Cervix and Ovaries

Julie K. Schwarz, Perry W. Grigsby, Farrokh Dehdashti and Dominique Delbeke

Published online: April 20, 2009.
Doi: 10.2967/jnumed.108.057257

This article and updated information are available at:
http://jnm.snmjournals.org/content/50/Suppl_1/64S

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

*The Journal of Nuclear Medicine* is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

© Copyright 2009 SNMMI; all rights reserved.
The Role of 18F-FDG PET in Assessing Therapy Response in Cancer of the Cervix and Ovaries

Julie K. Schwarz1,2, Perry W. Grigsby1–3, Farrokh Dehdashti2–4, and Dominique Delbeke5

1Department of Radiation Oncology, Mallinckrodt Institute of Radiology, St. Louis, Missouri; 2Washington University School of Medicine, St. Louis, Missouri; 3Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri; 4Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, St. Louis, Missouri; and 5Division of Nuclear Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

For locally advanced cervical cancer, the current literature supports the use of 18F-FDG PET for assessing treatment response 3 mo after the completion of concurrent chemoradiation. 18F-FDG PET can provide reliable long-term prognostic information for these patients and, in the future, may be used to guide additional therapy. Investigational areas include the use of 18F-FDG PET for monitoring response during radiotherapy and chemotherapy in the metastatic and neoadjuvant settings. For ovarian masses, the performance of 18F-FDG PET in the detection of borderline tumors is limited, and the presence of physiologic 18F-FDG uptake in normal ovaries of premenopausal women poses another limitation. Preliminary data suggest that the performance of 18F-FDG PET and 18F-FDG PET/CT is superior to that of CT alone in initial staging, but the sensitivity of both in the detection of carcinomatosis is limited. Preliminary data also suggest that 18F-FDG PET may be promising for early prediction of response to chemotherapy and for prediction of response after the completion of chemotherapy. 18F-FDG PET and 18F-FDG PET/CT are most helpful in the evaluation of patients with suspected recurrent ovarian carcinoma, especially when CA-125 levels are rising and CT findings are normal or equivocal. PET and CT are complementary, and PET/CT should be used when available. Preliminary data suggest that the addition of 18F-FDG PET/CT to the evaluation of these patients changes management in approximately a third and reduces overall treatment costs by accurately identifying patients who will or will not benefit from surgery.

Key Words: therapy response; cancer; cervix; ovary

DOI: 10.2967/jnumed.108.057257

This article explores the use of 18F-FDG PET in cancer of the cervix and ovaries. The topics covered include monitoring of treatment response in cervical cancer after chemoradiation and during radiation, applications after surgery for stage I cervical cancer and during chemotherapy for stage IVB cervical cancer, monitoring of therapy for ovarian cancer, detection of residual ovarian cancer after completion of therapy, surveillance of ovarian cancer, and detection of recurrent or metastatic ovarian cancer.

CERVICAL CANCER

Cervical cancer ranks among the top 3 cancer diagnoses in women worldwide and is a leading cause of cancer-related deaths. In the United States in 2008, 11,070 new diagnoses and 3,870 deaths from this disease are expected (1). Routine screening with cervical cytology (Papanicolaou test) has improved early detection of cervical cancer; however, a significant portion of patients continues to present with advanced disease. In the United States, a review of the Surveillance, Epidemiology and End Results Cancer Statistics Review from 1995 to 2002 found that 43% of patients with newly diagnosed cervical cancer presented with advanced disease (2).

Cervical cancer is staged clinically using the International Federation of Gynecology and Obstetrics system, with stage I representing local disease, stages II–IVA representing locally advanced disease, and stage IVB representing distant metastasis (Table 1). Treatment for cervical cancer is guided by clinical stage: stage I is treated with surgery, stages II–IVA are managed with definitive radiation and chemotherapy, and stage IVB is treated with systemic chemotherapy with or without radiation as indicated for symptom management.

18F-FDG PET has been used in the pretreatment evaluation of patients with cervical cancer and in the routine surveillance of cervical cancer patients after treatment is complete (3,4). This section of the article focuses on the role of 18F-FDG PET in monitoring treatment response after definitive chemoradiation therapy for cervical cancer. A review of the available literature is included for the role of 18F-FDG PET after surgery alone for stage I patients and during and after chemotherapy for stage IVB patients.
Locally advanced cervical cancer is treated with definitive radiation therapy directed to the cervical tumor and lymph node areas at risk along with the concurrent administration of intravenous cisplatin chemotherapy. Using this treatment approach, 5-y overall survival rates reported in the literature range from 67% to 80% (5). In approximately one third of treated patients, disease will ultimately recur after therapy, and most of these recurrences will take place within the first 2 y after therapy. Predictors of disease recurrence include clinical stage and lymph node status at the time of the initial diagnosis and tumor response after therapy is complete (6–9).

In the posttreatment setting, patients are followed up using physical examination and cervical cytology. There is no reliable serum marker to follow cervical cancer, and interpretation of posttreatment cervical cytology can be difficult because of radiation-related cytologic effects. In the past, no routine posttreatment imaging was used, and recurrent cervical cancer was not diagnosed until symptoms related to disease recurrence developed. Management of large recurrent tumors was difficult and often required extensive surgeries with limited survival benefit (6). The recent literature suggests that early detection of residual or recurrent cervical cancer may improve clinical outcomes for properly selected patients (10,11).

**Monitoring Treatment Response After Chemoradiation**

Jacobs et al. (12) first reported in 1986 that persistent cervical tumor on clinical examination performed 1–3 mo after the completion of therapy was an indicator of poor survival outcome. In 590 patients, 482 patients had no appreciable cervical tumor on posttherapy examination, 72 had persistent disease, and 36 had findings suggestive of disease. Five-year survival outcome was 76% for those with no appreciable tumor, 42% for those with findings suggestive of tumor, and 8% for those with persistent tumor (P < 0.0001).

Physical examination alone can assess the response of gross disease in the cervix but cannot address the issue of residual microscopic tumor in the cervix or of tumor in other sites, including lymph nodes. Unfortunately, cervical cytology (Papanicolaou test) is of limited utility in the posttreatment setting because of radiation-associated cytologic changes (11,13,14). Squamous cell carcinoma antigen is an investigational serum marker, and a decrease in this antigen has been associated with a response to chemoradiation before surgery (15,16). The antigen has been evaluated as part of routine surveillance after definitive radiation, and a persistently elevated level has been associated with disease recurrence (17–19). Additional study will be required to determine whether this marker can be used to reliably predict response immediately after treatment.

Because of rapid tumor volume regression and lack of anatomic detail in the pelvis, CT assessment of cervical tumor response has not been successful. MRI has been used in an investigational setting to monitor cervical tumor treatment response after the completion of therapy, with mixed results (20–22). The current literature supports the use of 18F-FDG PET for evaluating response after chemoradiation for locally advanced carcinoma of the cervix (8,9,23).

---

**TABLE 1. Cervical Cancer Staging System of the International Federation of Gynecology and Obstetrics**

<table>
<thead>
<tr>
<th>Carcinoma type</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinvasive</td>
<td>0</td>
<td>Carcinoma in situ; intraepithelial carcinoma</td>
</tr>
<tr>
<td>Invasive</td>
<td>I</td>
<td>Carcinoma strictly confined to cervix</td>
</tr>
<tr>
<td></td>
<td>IA</td>
<td>Invasive cancer identified only microscopically (all gross lesions, even with superficial staging, are stage IB cancers); invasion is limited to measured stromal invasion with maximum depth of 5.0 mm and no wider than 7.0 mm</td>
</tr>
<tr>
<td></td>
<td>IA1</td>
<td>Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm</td>
</tr>
<tr>
<td></td>
<td>IA2</td>
<td>Measured invasion of stroma greater than 3.0 mm in depth but no greater than 5.0 mm and no wider than 7.0 mm</td>
</tr>
<tr>
<td></td>
<td>IB</td>
<td>Clinical lesions confined to cervix or preclinical lesions greater than stage IA</td>
</tr>
<tr>
<td></td>
<td>IB1</td>
<td>Clinical lesions no larger than 4.0 cm</td>
</tr>
<tr>
<td></td>
<td>IB2</td>
<td>Clinical lesions larger than 4.0 cm</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Carcinoma extends beyond cervix but not to pelvic wall; carcinoma involves vagina but not lower third</td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>No obvious parametrial involvement</td>
</tr>
<tr>
<td></td>
<td>IIB</td>
<td>Obvious parametrial involvement</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Carcinoma has extended to pelvic wall; on rectal examination, there is no cancer-free space between tumor and pelvic wall; tumor involves lower third of vagina; all cases with hydronephrosis or nonfunctioning kidney are included</td>
</tr>
<tr>
<td></td>
<td>IIIA</td>
<td>No extension to pelvic wall</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>Extension to pelvic wall or hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Carcinoma has extended beyond true pelvis or has clinically involved mucosa of bladder or rectum; bullous edema does not permit a case to be allotted to stage IV</td>
</tr>
<tr>
<td></td>
<td>IVA</td>
<td>Spread of growth to adjacent organs</td>
</tr>
<tr>
<td></td>
<td>IVB</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>

---
Monitoring Response After Chemoradiation

At Washington University in St. Louis, 18F-FDG PET has been used for more than 10 y to assess response after chemoradiation for carcinoma of the cervix. In total, we have imaged 378 patients with 18F-FDG PET after they completed chemoradiation. Based on posttreatment 18F-FDG PET results, the patients were divided into 3 simple categories. A complete metabolic response was defined as the absence of abnormal 18F-FDG uptake at sites of abnormal 18F-FDG uptake noted on the pretreatment 18F-FDG PET study (Fig. 1). A metabolic partial response was defined as any persistent abnormal 18F-FDG uptake at the known sites (Fig. 2). Progressive metabolic disease was defined as new sites of abnormally increased 18F-FDG uptake. Using these 3 categories, we have found that posttreatment metabolic response is predictive of both cause-specific and progression-free survival after chemoradiation for cervical cancer (8,9,23). Figure 3 shows survival outcomes for 378 patients with posttherapy 18F-FDG PET from our institution.

These results have recently been validated in a prospective cohort study (9). In this study, 92 patients were imaged with 18F-FDG PET between 2 and 4 mo (mean, 3 mo) after the completion of chemoradiation for cervical cancer. Posttherapy 18F-FDG PET showed a complete metabolic response in 65 patients (70%), a partial metabolic response in 15 patients (16%) and progressive disease in 12 patients (13%). The 3-y progression-free survival rates according to metabolic response were 78%, 33%, and 0%, respectively (P < 0.001). A multivariate analysis of factors known to be predictive of outcome after treatment for cervical cancer, including clinical stage, was performed. In this analysis, only posttherapy metabolic response and pretreatment lymph node status (as defined by 18F-FDG PET) predicted progression-free survival. In a subset of patients, salvage therapy was initiated and directed on the basis of 3-mo follow-up 18F-FDG PET results. All these patients were disease-free at the time of the last follow-up (mean follow-up, 50 mo). This study demonstrates that 18F-FDG PET can provide reliable long-term prognostic information only 3 mo after the completion of therapy. In the future, 18F-FDG PET may be used to guide early interventions for patients with less than a complete metabolic response. Our study was performed at a single institution, and it will be important to show that these results are reproducible across imaging centers. One issue will be to use standardized methods to image patients both before and after therapy.

Applications During Radiation Therapy

We are currently studying 18F-FDG PET for monitoring treatment response during the course of radiation therapy for cervical cancer (23,24). One advantage of using 18F-FDG PET during therapy would be to obtain an early readout of tumor metabolic response. On the basis of these results, treatment regimens (including radiation dose and chemotherapy drugs) could be modified for an individual patient. At the moment, 18F-FDG PET studies performed during therapy have been limited to the pelvis and have not addressed the progression of disease at distant sites. Despite promising preliminary data on the use of 18F-FDG PET during radiation therapy for primary tumors, we cannot recommend an optimal timing for performing 18F-FDG PET during therapy. We are enrolling patients in a more systematic study on the use of 18F-FDG PET during radiation therapy for cervical cancer.

Applications After Surgery for Stage I Cancer

Bjurberg et al. (25) reported the interim results of an ongoing prospective study of 18F-FDG PET/CT in the management of cervical cancer patients. The first group consisted of 10 patients with early-stage cervical cancer and only one risk factor related to recurrence: lymphovascular space invasion, depth of invasion greater than 1 cm, tumor larger than 2 cm, or unfavorable histology. These patients did not meet the criteria for adjuvant radiation at that institution and were managed with primary surgery alone. All underwent 18F-FDG PET at 6 mo, on average, after surgery, and all had negative findings. This is not surprising, as local recurrence after primary surgery for early-stage low-risk cervical cancer is rare. With 18 mo of follow-up in the study, only 1 patient had a local recur-

**FIGURE 1.** 18F-FDG PET of complete metabolic response in 52-y-old woman with newly diagnosed International Federation of Gynecology and Obstetrics stage IVA squamous cell cancer of cervix. (A) At initial staging, sagittal (top) and transaxial (bottom) CT (left), fused PET/CT (middle), and PET (right) demonstrate intense 18F-FDG uptake (SUV, 13.3) within large cervical mass. (B) Three months later, after concurrent radiochemotherapy, sagittal (top) and transaxial (bottom) CT (left), fused PET/CT (middle), and PET (right) demonstrate resolution of cervical mass and only mild, diffuse (similar to background [SUV, 2.0]) 18F-FDG uptake within cervix, consistent with complete metabolic response.
rence, 14 mo after surgery. ¹⁸F-FDG PET is not currently indicated for assessing response after surgery for patients with locally confined low-risk cervical cancer.

Applications During Chemotherapy for Stage IVB Cancer

Using ¹⁸F-FDG PET to monitor response to chemotherapy alone is investigational, and the current literature is limited to case reports. Dose et al. published a report of a single patient with recurrent metastatic cervical cancer treated with primary chemotherapy and monitored with posttreatment ¹⁸F-FDG PET (26). After the final course of chemotherapy, ¹⁸F-FDG PET demonstrated a complete metabolic response; however, 3 mo later a follow-up ¹⁸F-FDG PET examination showed recurrent disease. ¹⁸F-FDG PET has also been used in an investigational setting to monitor response after neoadjuvant chemotherapy with planned surgical resection (27). In a series of 3 patients from Japan, tumor ¹⁸F-FDG uptake, as measured by standardized uptake value (SUV), MRI tumor volume, and pathologic response on the surgical specimen, was compared. In that study, SUV appeared to be more closely linked to pathologic results than to changes in MRI tumor volume; however, these results should be interpreted with caution because of the extremely small sample size and a nontraditional approach to patient management.

Summary

For locally advanced cervical cancer, the current literature supports the use of ¹⁸F-FDG PET for assessing treatment response 3 mo after the completion of concurrent chemoradiation. ¹⁸F-FDG PET can provide reliable long-term prognostic information for these patients and, in the future, may be used to guide additional therapy. Investigational areas include the use of ¹⁸F-FDG PET for monitoring response during radiotherapy and chemotherapy in the metastatic and neoadjuvant settings.

OVARIAN CANCER

Ovarian cancer is the leading cause of death from gynecologic cancer in the West. The American Cancer Society estimates that, in the United States, approximately 21,650 new cases of ovarian cancer are diagnosed each year and approximately 15,520 patients die of this disease each year. Ovarian cancer represents 1.5% of new cases of cancer and 3% of all cancer deaths annually in the United States. Surgery followed by chemotherapy is the most common treatment. The overall survival at 1 and 5 y is 75% and 45%, respectively. The 5-y survival is 92% for the localized stage, but only 19% are detected at this stage; 71% are detected when there is regional spread, and 30% are detected when there are distant metastases (1).

Nearly 90% of ovarian cancers are epithelial in origin and arise from the cells on the surface of the ovary. The remaining 10% are germ cell and stromal tumors. Ovarian cancer typically has vague symptoms that are often ignored, and the disease is therefore usually diagnosed at an advanced stage. Prognosis is strongly related to the stage of disease at diagnosis. Although early-stage disease has a good prognosis, advanced disease carries a poor prognosis. Ovarian cancer spreads early by implantation on both the
been accepted as useful imaging modalities for preoperative at the time of primary debulking. CT and MRI have
ovarian lesions using PET is currently not recommended. Ovarian cancer is typically staged by exploratory laparotomy when there is focal 18F-FDG uptake in the region of the ovaries it is essential to correlate the focal 18F-FDG uptake in the pelvis with anatomic and morphologic findings on CT or MRI scans to avoid false-positive diagnoses. Because most PET is presently performed on PET/CT scanners, CT is usually available (33), and because primary ovarian cancers can be missed, characterization of ovarian lesions using PET is currently not recommended. Ovarian cancer is typically staged by exploratory laparotomy at the time of primary debulking. CT and MRI have been accepted as useful imaging modalities for preoperative staging of ovarian cancer. 18F-FDG PET may be useful as an adjunct to diagnostic CT for staging ovarian cancer (34–36). More data are needed to better define the role of PET in the initial staging of ovarian cancer. Surgical exploration remains the standard of reference for the initial staging of ovarian cancer.

Monitoring of Therapy
Standard treatment of advanced ovarian cancer includes aggressive cytoreductive surgery followed by platinum- or taxane-based chemotherapy. Despite an often initial good response to this therapy, most patients will subsequently die of progressive disease (37). Neoadjuvant chemotherapy followed by surgical debulking has been used to improve outcome. This, however, can be achieved only in patients with complete or nearly complete response to neoadjuvant therapy (38).

As for other tumors, CT and MRI are limited in detecting response early after the initiation of therapy because anatomic response takes time. Limited data are available regarding the role of 18F-FDG PET or PET/CT to monitor therapy (Table 2).

Avril et al. (39) demonstrated a significant correlation between changes in tumor tracer uptake after the first and third cycles of chemotherapy, but not with conventional clinical or CA-125 response criteria. A higher rate of complete tumor resections was achieved in metabolic responders (defined as ≥20% reduction in SUV after the first cycle and ≥50% after the third cycle) than in nonresponders, and macroscopically tumor-free surgery was achieved in 33% of metabolic responders, compared with only 13% of nonresponders. Metabolic responders had a longer median overall survival than did nonresponders. By using a threshold for decrease in SUV from baseline of 20% after the first cycle, median overall survival was 38.3 mo in metabolic responders, compared with 23.1 mo in metabolic nonresponders. At a threshold of 55% decrease in SUV after the third cycle, median overall survival was 38.9 mo in metabolic responders, compared with 19.7 mo in nonresponders.

Nishiyama et al. (40) demonstrated that 18F-FDG PET–derived parameters, including SUV and percentage change, have the potential to predict response to chemotherapy or chemoradiotherapy in patients with advanced gynecologic cancer (uterine cancer, n = 13; ovarian cancer, n = 8). Based on histopathologic analysis of the specimens obtained at surgery, 10 patients were found to be responders and 11 to be nonresponders. SUV after therapy in responders was significantly lower than that in nonresponders (P < 0.005). When an arbitrary SUV of 3.8 was taken as the cutoff for differentiating between responders and nonresponders, 18F-FDG PET showed a sensitivity of 90%, a specificity of 63.6%, and an accuracy of 76.2%. The percentage change was significantly higher in the responders than in the nonresponders (P < 0.0005). When an arbitrary percentage change of 65% is taken as the cutoff for differentiating between responders and nonresponders, 18F-FDG PET showed a sensitivity of 90%, a specificity of 81.8%, and an accuracy of 85.7%.

Detection of Residual Disease After Completion of Therapy
CT and MRI are limited in distinguishing residual tumor from necrosis or fibrosis. Therefore, second-look laparotomy has sometimes been recommended after initial debulking surgery and first-line chemotherapy. In the absence of disease, additional chemotherapy is not necessary. If disease is present, reductive surgery is performed, followed by adjuvant chemotherapy. Negative findings on second-look surgery are a good prognostic indicator; however, the 5-y recurrence rate afterward approaches 50% (41).

Several studies have compared the performance of 18F-FDG PET with second-look laparotomy (Table 3). In a prospective series of 22 patients with a complete biochemical, clinical, and radiologic response, PET showed a poor 10% sensitivity and 42% specificity, because of its limited ability to detect small malignant lesions (42). In a retrospective study of 21 patients evaluated 1 mo before second-look surgery (43), both 18F-FDG PET and CT had a low sensitivity for detecting recurrence in a lesion-based analysis (36% vs. 54%). 18F-FDG PET had lower detection rates than did CT for small lesions of 3–7 mm. 18F-FDG PET/CT was evaluated in a series of 31 patients, 17 of whom showed persistent cancer on subsequent second-look surgery (44). Integrated PET/CT detected persistent ovarian carcinoma with a high positive predictive value. The overall lesion-based sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were 78%, 75%, 77%, 89%, and 57%, respectively. Patient-based
sensitivity and specificity were 53% and 86%, respectively. In the detection of tumors, a size threshold could be set at 0.5 cm, as this was the largest diameter of a lesion missed at PET/CT.

A study by Kim et al. (45) compared the prognosis of 55 patients evaluated either by 18F-FDG PET or second-look laparotomy after cytoreductive surgery and adjuvant chemotherapy. PET had a prognostic value similar to that of second-look surgery. There was no significant difference in progression-free interval (28.8 vs. 30.6 mo) or disease-free interval in the PET-negative group (40.5 vs. 48.6 mo). Kurosaki et al. (46) demonstrated that the prognosis (2-y survival) of patients with positive 18F-FDG PET findings was less favorable than that of patients with negative findings. However, over the mean extended observation period of about 2.5 y, no significant difference was seen between the 2 groups. Elevated serum CA-125 levels were more useful than 18F-FDG PET findings for evaluating the prognosis of ovarian cancer during postoperative follow-up. The 2-y survival rate for patients with normal CA-125 levels (100%) was significantly higher (P = 0.025) than that for patients with elevated CA-125 levels (47%); however, there was no significant differ-

### TABLE 2. 18F-FDG PET for Monitoring Response of Advanced Ovarian Carcinoma to Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Criteria for response on PET</th>
<th>Outcome measure</th>
<th>Design</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avril (39)</td>
<td>2005</td>
<td>33</td>
<td>20% decrease in SUV after first cycle 55% decrease in SUV after third cycle</td>
<td>Overall survival</td>
<td>Prospective study</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall survival</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Nishiyama (40)</td>
<td>2008</td>
<td>21</td>
<td>SUV after completion, &lt;3.8 &gt;65% change in SUV between baseline and after completion</td>
<td>Detection of responders: sensitivity 90%, specificity 64%, accuracy 76%</td>
<td>Retrospective study</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

---

### TABLE 3. 18F-FDG PET Compared with Second-Look Laparotomy for Ovarian Carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Modality</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Design</th>
<th>Outcome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose (42)</td>
<td>2001</td>
<td>22 with complete clinical response</td>
<td>PET: lesion-based</td>
<td>10%</td>
<td>42%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Prospective: compared with second-look surgery</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cho (43)</td>
<td>2002</td>
<td>21</td>
<td>PET + CT</td>
<td>58%</td>
<td>100%</td>
<td>99%</td>
<td>92%</td>
<td>92%</td>
<td>Retrospective: compared with second-look surgery</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sironi (44)</td>
<td>2004</td>
<td>31 (15 patients with CA-125 &gt; 35 U/mL)</td>
<td>PET/CT: lesion-based</td>
<td>78%</td>
<td>75%</td>
<td>77%</td>
<td>89%</td>
<td>57%</td>
<td>Prospective study</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PET/CT: patient-based</td>
<td>53%</td>
<td>86%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim (45)</td>
<td>2004</td>
<td>55</td>
<td>PET</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Randomized: 18F-FDG PET vs. second-look surgery</td>
<td>Progression-free survival</td>
<td>NS</td>
</tr>
<tr>
<td>Kurosaki (46)</td>
<td>2006</td>
<td>18</td>
<td>PET ± CA-125 high/normal</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Retrospective study</td>
<td>2-y survival</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Sens = sensitivity; Spec = specificity; Acc = accuracy; PPV = positive-predictive value; NPV = negative-predictive value; NA = not available; NS = not significant.
ence ($P = 0.20$) between $^{18}$F-FDG PET–positive cases (53%) and –negative cases (83%). Presently, these data are insufficient to recommend that $^{18}$F-FDG PET be used to replace second-look laparotomy.

**Surveillance**

In approximately 20%–30% of patients with early-stage disease and 50%–75% of those with advanced disease who obtain a complete response after first-line chemotherapy, disease will ultimately recur and will more frequently involve the pelvis and abdomen. Few formal guidelines exist on the surveillance of these patients, and there is no agreement in the literature about the type and timing of examinations to perform. Moreover, the objective of follow-up is unclear, as recurrent epithelial ovarian cancer continues to be a therapeutic dilemma, with almost all relapsed patients eventually dying of their disease. The follow-up of asymptomatic patients generally includes a complete clinical history, measurement of the serum cancer antigen CA-125 level, physical examination, and often ultrasound examination. Additional radiologic imaging techniques are usually performed when symptoms or signs appear.

**Detection of Recurrent or Metastatic Disease**

Follow-up of ovarian cancer relies on serial CA-125 measurements. However, CA-125 does not localize cancer recurrence, and a negative level does not rule out recurrent cancer. Detection of recurrent ovarian cancer can be prob-

---

**TABLE 4. $^{18}$F-FDG PET for Detection of Recurrence of Ovarian Carcinoma**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Modality</th>
<th>Sens</th>
<th>Spec</th>
<th>Acc</th>
<th>PPV</th>
<th>NPV</th>
<th>Design</th>
<th>Change of management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith (57)</td>
<td>1999</td>
<td>Simulation study</td>
<td>PET</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Simulation analysis of cost with and without PET</td>
<td>Decrease of unnecessary surgery from 70% to 5%</td>
</tr>
<tr>
<td>Bristow (51)</td>
<td>2003</td>
<td>22 with rising CA-125 and equivocal CT</td>
<td>PET/CT for detection of tumor $&gt; 1$ cm</td>
<td>83%</td>
<td>NA</td>
<td>82%</td>
<td>94%</td>
<td>Prospective study</td>
<td>Complete cytoreduction to no gross residual tumor: 72%</td>
<td></td>
</tr>
<tr>
<td>Havrilesky (47)</td>
<td>2005</td>
<td>10 studies between 1966 and 2003</td>
<td>PET</td>
<td>90%</td>
<td>86%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Review</td>
<td>NA</td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td>CT PET when CA-125 high</td>
<td>68%</td>
<td>58%</td>
<td>94%</td>
<td>80%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PET when CA-125 normal</td>
<td>54%</td>
<td>73%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz (49)</td>
<td>2005</td>
<td>17 studies between 1972 and 2003</td>
<td>PET</td>
<td>94%</td>
<td>65%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Metaanalysis</td>
<td>NA</td>
</tr>
<tr>
<td>Simcock (52)</td>
<td>2006</td>
<td>55 for surveillance or suspicion of relapse</td>
<td>PET/CT</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Prospective study</td>
<td>58%</td>
</tr>
<tr>
<td>Garcia (50)</td>
<td>2007</td>
<td>80 for suspicion of relapse</td>
<td>PET</td>
<td>87%</td>
<td>79%</td>
<td>85%</td>
<td>92%</td>
<td>68%</td>
<td>Retrospective study</td>
<td>NA</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td>CA-125</td>
<td>53%</td>
<td>82%</td>
<td>61%</td>
<td>89%</td>
<td>39%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mangili (53)</td>
<td>2007</td>
<td>32 for suspicion of relapse</td>
<td>PET/CT; CT</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Retrospective study</td>
<td>44%</td>
</tr>
<tr>
<td>Chung (54)</td>
<td>2007</td>
<td>77 PET/CT</td>
<td>93%</td>
<td>97%</td>
<td>94%</td>
<td>98%</td>
<td>91%</td>
<td>Retrospective study</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Kitajama (56)</td>
<td>2008</td>
<td>132 PET/contrast-enhanced CT</td>
<td>79%</td>
<td>91%</td>
<td>85%</td>
<td>NA</td>
<td>NA</td>
<td>Retrospective study</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>PET/unenhanced CT</td>
<td>74%</td>
<td>91%</td>
<td>83%</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast-enhanced CT</td>
<td>61%</td>
<td>85%</td>
<td>73%</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soussan (55)</td>
<td>2008</td>
<td>29 PET/CT</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Questionnaire</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

Sens = sensitivity; Spec = specificity; Acc = accuracy; PPV = positive-predictive value; NPV = negative-predictive value; NA = not available.
lematic, particularly in the setting of a rising CA-125 level and negative or equivocal findings on conventional imaging. Several studies, summarized in Table 3, have shown that $^{18}$F-FDG PET is superior to conventional imaging and CA-125 measurements in detecting recurrent ovarian cancer. $^{18}$F-FDG PET can detect recurrence earlier than conventional imaging. A review by Havrilesky et al. (47) of the published literature between 1966 and 2003 showed that PET had a pooled sensitivity and specificity of 90% and 86%, respectively, in patients with clinical suspicion of recurrent ovarian cancer, compared with 68% and 58%, respectively, for conventional imaging and 81% and 83%, respectively, for CA-125 measurements. Some studies comparing $^{18}$F-FDG PET with second-look surgery after completion of therapy were included (42,43). The performance of PET was better when CA-125 was elevated and conventional imaging findings were negative (94% sensitivity and 80% specificity) than when both CA-125 and conventional imaging findings were negative (54% sensitivity and 73% specificity). Menzel et al. (48) suggested that PET should be restricted to patients with CA-125 levels above 30 U/mL. A metaanalysis published in 2005 identified 17 articles published between 1972 and 2003 evaluating the accuracy of $^{18}$F-FDG PET for detection of

![FIGURE 4](https://example.com/figure4.png)

**FIGURE 4.** A 68-y-old woman presented with rising CA-125 levels and normal findings on CT. (A and B) At restaging, transaxial PET/CT slice through chest (A) demonstrates moderate (same as blood pool) $^{18}$F-FDG uptake in right hilum, corresponding to 1.6-cm lymph node, consistent with metastasis; transaxial PET/CT slice through focus of $^{18}$F-FDG uptake in right lower quadrant (B) demonstrates moderate $^{18}$F-FDG uptake in 0.5-cm right serosal implant, consistent with metastasis. This lesion was identified on CT retrospectively because of $^{18}$F-FDG uptake. (C and D) Three months after chemotherapy, transaxial PET/CT slice through chest (C) demonstrates more intense (greater than blood pool) $^{18}$F-FDG uptake in right hilar lymph node and slight increase in size, consistent with progressive disease; transaxial PET/CT slice through pelvis (D) demonstrates more intense $^{18}$F-FDG uptake in right serosal implant, consistent with progressive disease.
in a change of management for 39% of patients and affected the management of 12% of patients diagnosed by enhanced CT alone and 2% of patients diagnosed by PET/unenhanced CT.

Smith et al. (57) used a simulation analysis to compare the cost of managing recurrent ovarian cancer with and without the use of 18F-FDG PET. Evaluation of patients with 18F-FDG PET decreased unnecessary laparotomies from 70% to 5% of patients. Cost savings per patient ranged from $1,941 to $11,766.

A positive correlation between 18F-FDG PET positivity, intratumor microvessel density, and mitotic activity has been demonstrated. Microvessel density was the strongest parameter in predicting positive tumor recurrence on 18F-FDG PET (58). There was no significant correlation between 18F-FDG PET positivity and Ki-67 or p53.

Summary

For ovarian masses, the performance of 18F-FDG PET in the detection of borderline tumors is limited, and the presence of physiologic 18F-FDG uptake in normal ovaries of premenopausal women poses another limitation. Preliminary data suggest that the performance of 18F-FDG PET and 18F-FDG PET/CT is superior to that of CT alone in initial staging, but the sensitivity of both in the detection of carcinomatosis is limited.

Preliminary data also suggest that 18F-FDG PET may be promising for early prediction of response to chemotherapy and for prediction of response after the completion of chemotherapy.

18F-FDG PET and 18F-FDG PET/CT are most helpful in the evaluation of patients with suspected recurrent ovarian carcinoma, especially when CA-125 levels are rising and CT findings are normal or equivocal. PET and CT are complementary, and PET/CT should be used when available.

Preliminary data suggest that the addition of 18F-FDG PET/CT to the evaluation of these patients changes management in approximately a third and reduces overall treatment costs by accurately identifying patients who will or will not benefit from surgery.

REFERENCES


recurrence in patients with ovarian cancer. The overall sensitivity and specificity were 94% and 65%, respectively, with few false-negative results (49).

A direct comparison of 18F-FDG PET, CT, and CA-125 for the detection of recurrence in patients with suspicion of relapse demonstrated superior performance for 18F-FDG PET. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 18F-FDG PET were 87%, 79%, 85%, 92%, and 68%, respectively, compared with 53%, 82%, 61%, 89%, and 39%, respectively, for conventional imaging and 58%, 94%, and 67%, respectively, for CA-125 measurements (50). In 23 of 55 patients with positive serum CA-125 levels but negative conventional imaging findings, 18F-FDG PET was positive and relapse was confirmed. Furthermore, 18F-FDG PET was positive and relapse was confirmed in 11 of 55 patients with negative serum CA-125 levels and negative conventional imaging findings.

The most recent studies have evaluated integrated PET/CT and have included the impact on patient management (Table 4). 18F-FDG PET and 18F-FDG PET/CT may be especially useful for the selection of patients with late recurrent disease who may benefit from secondary cytoreductive surgery (51). A prospective study of 22 patients with elevated CA-125 and negative or equivocal CT findings evaluated the ability of PET to detect macroscopic disease that can potentially be resected surgically. PET/CT patient-based accuracy was 82% for lesions greater than 1 cm. The authors suggested that only patients harboring recurrent tumors 1 cm or greater would benefit from surgical exploration and, thus, that 18F-FDG PET/CT could identify these candidates. A 72.2% complete rate of secondary cytoreductive surgery was achievable in this series (51). In a subsequent prospective study of 56 patients with suspicion of recurrent ovarian cancer, 18F-FDG PET/CT changed the management in 58% of patients (52). In addition, 18F-FDG PET/CT identified a subgroup of patients with apparently localized disease or no definite evidence of disease who had an improved survival, compared with patients having systemic disease. Integrated PET/CT had an impact on management in 44% of patients in a retrospective review of 32 patients, and PET/CT detected tumor relapse in a higher percentage of patients than could CT (53). The impact on management has been confirmed in a larger series of patients (54), including a questionnaire-based study that showed PET/CT allows a better restaging than does CT and induces a change in clinical management in over one third of patients with suspected ovarian carcinoma recurrence based on increased CA-125 levels (55). Figure 4 illustrates the example of a patient in whom 18F-FDG PET/CT detected recurrence and later also documented progressive disease with therapy.

When PET/enhanced CT is compared with PET/unenhanced CT, the performance of the former is slightly superior and both are significantly superior to enhanced CT alone (56). The findings of PET/enhanced CT resulted

728 THE JOURNAL OF NUCLEAR MEDICINE • Vol. 50 • No. 5 (Suppl) • May 2009


