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

Julie K. Schwarz[1,2], Perry W. Grigsby[1–3], Farrokh Dehdashti[2–4], and Dominique Delbeke[5]

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

For locally advanced cervical cancer, the current literature supports the use of ^{18}F-FDG PET for assessing treatment response 3 mo after the completion of concurrent chemoradiation. ^{18}F-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 ^{18}F-FDG PET for monitoring response during radiotherapy and chemotherapy in the metastatic and neoadjuvant settings. For ovarian masses, the performance of ^{18}F-FDG PET in the detection of borderline tumors is limited, and the presence of physiologic ^{18}F-FDG uptake in normal ovaries of premenopausal women poses another limitation. Preliminary data suggest that the performance of ^{18}F-FDG PET and ^{18}F-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 ^{18}F-FDG PET may be promising for early prediction of response to chemotherapy and for prediction of response after the completion of chemotherapy. ^{18}F-FDG PET and ^{18}F-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 ^{18}F-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

J Nucl Med 2009; 50:64S–73S
DOI: 10.2967/jnumed.108.057257

This article explores the use of ^{18}F-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.

Received Nov. 6, 2008; revision accepted Jan. 13, 2009.
For correspondence or reprints contact: Dominique Delbeke, Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, 21st Ave. S. and Garland, Nashville, TN 37232-2675.
E-mail: dominique.delbeke@vanderbilt.edu

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.

^{18}F-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 ^{18}F-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 ^{18}F-FDG PET after surgery alone for stage I patients and during and after chemotherapy for stage IVB patients.

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

Carcinoma type	Stage	Description
Preinvasive	0	Carcinoma in situ; intraepithelial carcinoma
Invasive	I	Carcinoma strictly confined to cervix
	IA	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
	IA1	Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm
	IA2	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
	IB	Clinical lesions confined to cervix or preclinical lesions greater than stage IA
	IB1	Clinical lesions no larger than 4.0 cm
	IB2	Clinical lesions larger than 4.0 cm
	II	Carcinoma extends beyond cervix but not to pelvic wall; carcinoma involves vagina but not lower third
	IIA	No obvious parametrial involvement
	IIB	Obvious parametrial involvement
	III	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
	IIIA	No extension to pelvic wall
	IIIB	Extension to pelvic wall or hydronephrosis or nonfunctioning kidney
	IV	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
	IVA	Spread of growth to adjacent organs
	IVB	Spread to distant organs

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 ^{18}F-FDG PET for evaluating response after chemoradiation for locally advanced carcinoma of the cervix (*8,9,23*).

Monitoring Response After Chemoradiation

At Washington University in St. Louis, ^{18}F-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 ^{18}F-FDG PET after they completed chemoradiation. Based on posttreatment ^{18}F-FDG PET results, the patients were divided into 3 simple categories. A complete metabolic response was defined as the absence of abnormal ^{18}F-FDG uptake at sites of abnormal ^{18}F-FDG uptake noted on the pretreatment ^{18}F-FDG PET study (Fig. 1). A metabolic partial response was defined as any persistent abnormal ^{18}F-FDG uptake at the known sites (Fig. 2). Progressive metabolic disease was defined as new sites of abnormally increased ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET between 2 and 4 mo (mean, 3 mo) after the completion of chemoradiation for cervical cancer. Posttherapy ^{18}F-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 ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET can provide reliable long-term prognostic information only 3 mo after the completion of therapy. In the future, ^{18}F-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 ^{18}F-FDG PET for monitoring treatment response during the course of radiation therapy for cervical cancer (*23,24*). One advantage of using ^{18}F-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, ^{18}F-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 ^{18}F-FDG PET during radiation therapy for primary tumors, we cannot recommend an optimal timing for performing ^{18}F-FDG PET during therapy. We are enrolling patients in a more systematic study on the use of ^{18}F-FDG PET during radiation therapy for cervical cancer.

Applications After Surgery for Stage I Cancer

Bjurgberg et al. (*25*) reported the interim results of an ongoing prospective study of ^{18}F-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 ^{18}F-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-

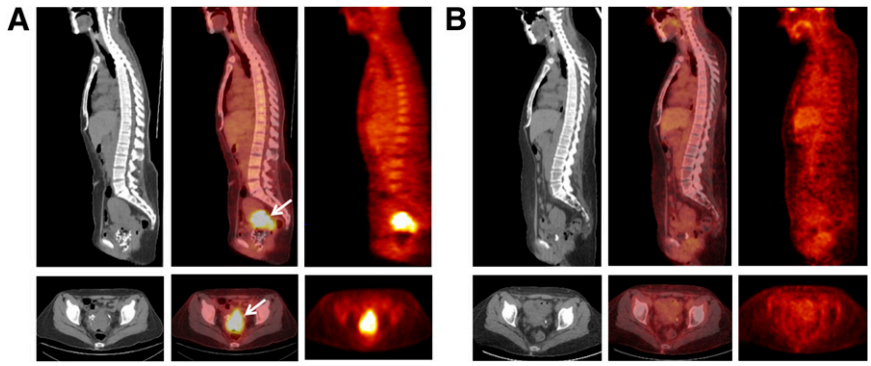

FIGURE 1. ^{18}F-FDG PET of complete metabolic response in 52-y-old woman with newly diagnosed International Federation of Gynecology and Obstetrics stage IVA squamous cell cancer of cervix. (A) At initial staging, sagittal (top) and transaxial (bottom) CT (left), fused PET/CT (middle), and PET (right) demonstrate intense ^{18}F-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]) ^{18}F-FDG uptake within cervix, consistent with complete metabolic response.

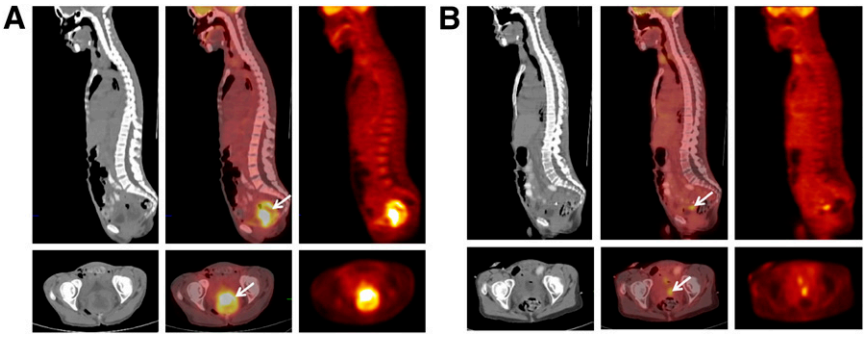

FIGURE 2. ^{18}F-FDG PET of partial metabolic response in 54-y-old woman with newly diagnosed International Federation of Gynecology and Obstetrics stage III squamous cell carcinoma of cervix. (A) At initial staging, sagittal (top) and transaxial (bottom) CT (left), fused PET/CT (middle), and PET (right) demonstrate intense ^{18}F-FDG uptake (SUV, 15.3) 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) show that ^{18}F-FDG uptake has improved but remains focally increased (SUV, 5.4) within residual cervical mass, consistent with partial metabolic response.

rence, 14 mo after surgery. ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET (*26*). After the final course of chemotherapy, ^{18}F-FDG PET demonstrated a complete metabolic response; however, 3 mo later a follow-up ^{18}F-FDG PET examination showed recurrent disease. ^{18}F-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 ^{18}F-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.

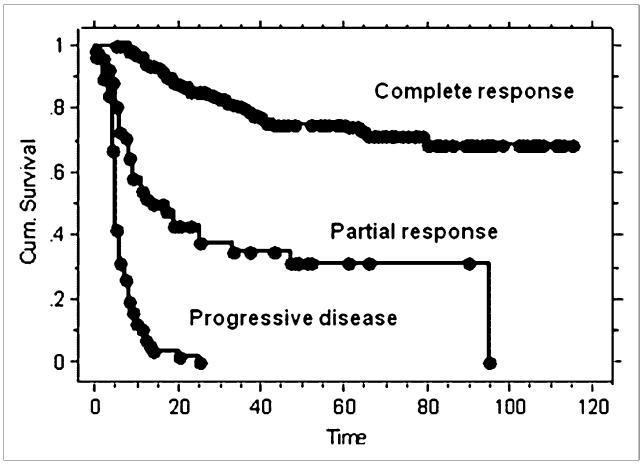

FIGURE 3. Kaplan–Meier curves showing survival outcome based on follow-up posttherapy ^{18}F-FDG PET in 378 patients: 269 patients had complete metabolic response, 52 had persistent abnormal ^{18}F-FDG uptake, and 57 had new sites of disease (log-rank P value < 0.0001 for all plots).

Summary

For locally advanced cervical cancer, the current literature supports the use of ^{18}F-FDG PET for assessing treatment response 3 mo after the completion of concurrent chemoradiation. ^{18}F-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 ^{18}F-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

parietal and the visceral peritoneum before spreading through the lymphatics and involving the inguinal, pelvic, paraaortic, and mediastinal lymph nodes. The serum tumor marker CA-125 is elevated in nearly 80% of patients with advanced ovarian cancer. This tumor marker is widely used to assess the effectiveness of therapy and to detect tumor recurrence. Abnormal marker levels often precede clinical and radiologic signs of disease recurrence.

^{18}F-FDG PET has been shown to be limited in the diagnosis of cancer of the ovaries (*28–35*). Physiologic ^{18}F-FDG uptake observed in the ovaries of women of reproductive age even after hysterectomy is reasonably common and may be mistaken for pathologic uptake. However, as it is not easy to determine the hormonal cycle in these women, when there is focal ^{18}F-FDG uptake in the region of the ovaries it is essential to correlate the focal ^{18}F-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. ^{18}F-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 ^{18}F-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 ^{18}F-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 after therapy, ^{18}F-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, ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET and CT had a low sensitivity for detecting recurrence in a lesion-based analysis (36% vs. 54%). ^{18}F-FDG PET had lower detection rates than did CT for small lesions of 3–7 mm. ^{18}F-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

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

Author	Year	Number of patients	Criteria for response on PET	Outcome measure	Design	*P*
Avril (*39*)	2005	33	20% decrease in SUV after first cycle	Overall survival	Prospective study	0.008
			55% decrease in SUV after third cycle	Overall survival		0.005
Nishiyama (*40*)	2008	21	SUV after completion, <3.8	Detection of responders: sensitivity 90%, specificity 64%, accuracy 76%	Retrospective study	<0.005
			>65% change in SUV between baseline and after completion	Detection of responders: sensitivity 90%, specificity 82%, accuracy 86%		

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 ^{18}F-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 ^{18}F-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 ^{18}F-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 3. ^{18}F-FDG PET Compared with Second-Look Laparotomy for Ovarian Carcinoma

Author	Year	Number of Patients	Modality	Sens	Spec	Acc	PPV	NPV	Design	Outcome	*P*
Rose (*42*)	2001	22 with complete clinical response	PET: lesion-based	10%	42%	NA	NA	NA	Prospective: compared with second-look surgery	NA	NA
Cho (*43*)	2002	21	PET + CT						Retrospective: compared with second-look surgery	NA	NA
			Lesion-based	58%	99%	92%	97%	92%			
			Patient-based	100%	92%	95%	92%	100%			
			PET								
			Lesion-based	36%	100%	89%	95%	88%			
			Patient-based	81%	90%	86%	90%	82%			
			CT								
			Lesion-based	54%	100%	82%	97%	92%			
			Patient-based	100%	90%	95%	92%	100%			
Sironi (*44*)	2004	31 (15 patients with CA-125 > 35 U/mL)	PET/CT: lesion-based	78%	75%	77%	89%	57%	Prospective study	NA	NA
			PET/CT: patient-based	53%	86%						
Kim (*45*)	2004	55	PET	NA	NA	NA	NA	NA	Randomized: ^{18}F-FDG PET vs. second-look surgery	Progression-free survival	NS
Kurosaki (*46*)	2006	18	PET ± CA-125 high/normal	NA	NA	NA	NA	NA	Retrospective study	2-y survival	0.025

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

Author	Year	Number of patients	Modality	Sens	Spec	Acc	PPV	NPV	Design	Change of management
Smith (*57*)	1999	Simulation study	PET	NA	NA	NA	NA	NA	Simulation analysis of cost with and without PET	Decrease of unnecessary surgery from 70% to 5%
Bristow (*51*)	2003	22 with rising CA-125 and equivocal CT	PET/CT for detection of tumor > 1 cm	83%	NA	82%	94%		Prospective study	Complete cytoreduction to no gross residual tumor: 72%
Havrilesky (*47*)	2005	10 studies between 1966 and 2003	PET	90%	86%	NA	NA	NA	Review	NA
			CT	68%	58%					
			PET when CA-125 high	94%	80%	NA	NA	NA		NA
			PET when CA-125 normal	54%	73%	NA	NA	NA		NA
Ruiz (*49*)	2005	17 studies between 1972 and 2003	PET	94%	65%	NA	NA	NA	Metaanalysis	NA
Simcock (*52*)	2006	55 for surveillance or suspicion of relapse	PET/CT	NA	NA	NA	NA	NA	Prospective	58%
Garcia (*50*)	2007	80 for suspicion of relapse	PET	87%	79%	85%	92%	68%	Retrospective study	NA
			CT	53%	82%	61%	89%	39%		
			CA-125	58%	94%	67%				
Mangili (*53*)	2007	32 for suspicion of relapse	PET/CT; CT	NA	NA	NA	NA	NA	Retrospective study	44%
Chung (*54*)	2007	77	PET/CT	93%	97%	94%	98%	91%	Retrospective study	25%
Kitajama (*56*)	2008	132	PET/contrast-enhanced CT	79%	91%	85%	NA	NA	Retrospective study	39%
			PET/unenhanced CT	74%	91	83%	NA	NA		NA
			Contrast-enhanced CT	61%	85%	73%	NA	NA		NA
Soussan (*55*)	2008	29	PET/CT	NA	NA	NA	NA	NA	Questionnaire	33%

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

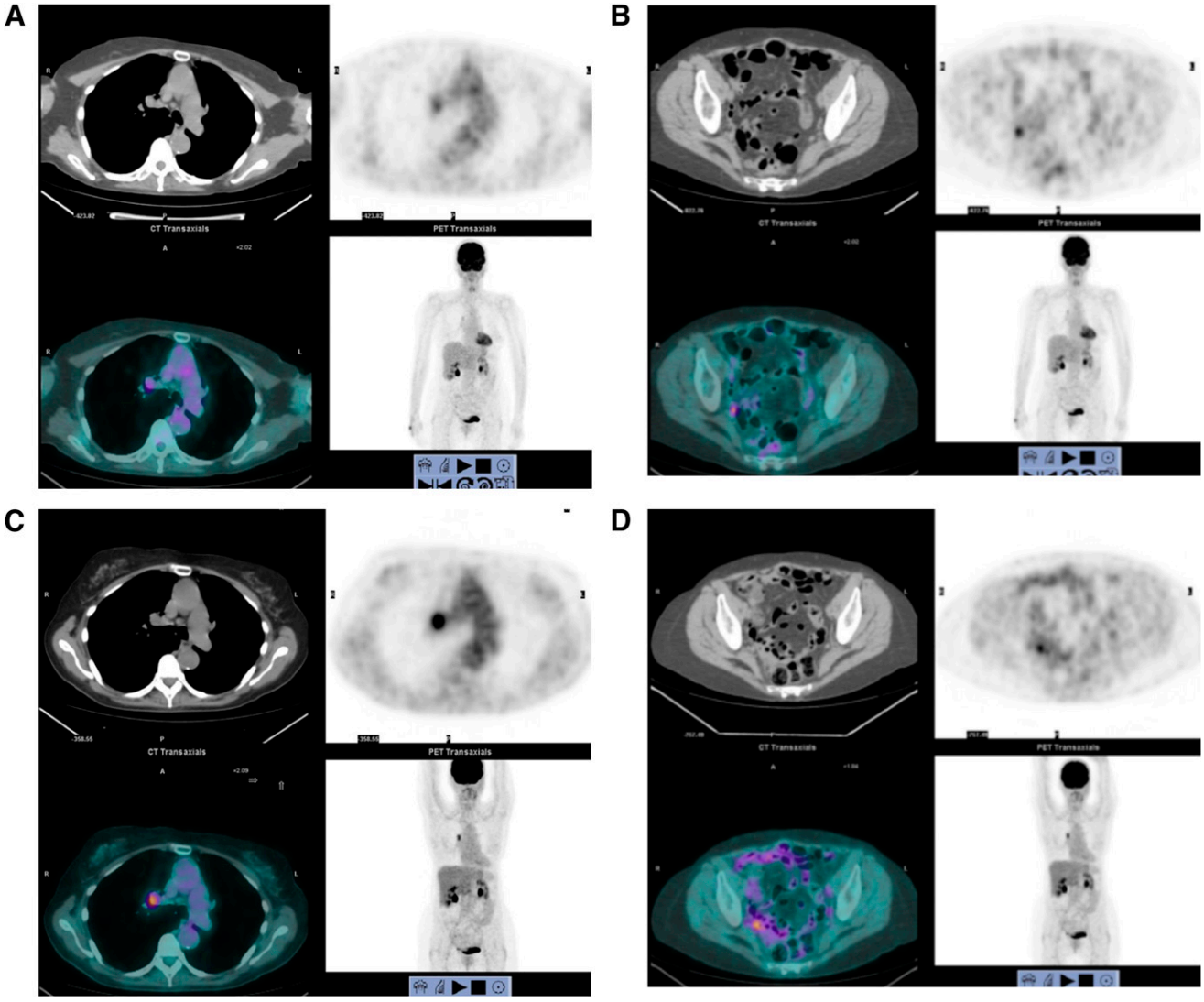

FIGURE 4. A 68-y-old woman presented with rising CA-125 levels and normal findings on CT. (A and B) At restaging, transaxial PET/CT slice through chest (A) demonstrates moderate (same as blood pool) ^{18}F-FDG uptake in right hilum, corresponding to 1.6-cm lymph node, consistent with metastasis; transaxial 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.

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 ^{18}F-FDG PET, CT, and CA-125 for the detection of recurrence in patients with suspicion of relapse demonstrated superior performance for ^{18}F-FDG PET. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of ^{18}F-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, ^{18}F-FDG PET was positive and relapse was confirmed. Furthermore, ^{18}F-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). ^{18}F-FDG PET and ^{18}F-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 ^{18}F-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, ^{18}F-FDG PET/CT changed the management in 58% of patients (*52*). In addition, ^{18}F-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 ^{18}F-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 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 ^{18}F-FDG PET. Evaluation of patients with ^{18}F-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 ^{18}F-FDG PET positivity, intratumor microvessel density, and mitotic activity has been demonstrated. Microvessel density was the strongest parameter in predicting positive tumor recurrence on ^{18}F-FDG PET (*58*). There was no significant correlation between ^{18}F-FDG PET positivity and Ki-67 or p53.

Summary

For ovarian masses, the performance of ^{18}F-FDG PET in the detection of borderline tumors is limited, and the presence of physiologic ^{18}F-FDG uptake in normal ovaries of premenopausal women poses another limitation. Preliminary data suggest that the performance of ^{18}F-FDG PET and ^{18}F-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 ^{18}F-FDG PET may be promising for early prediction of response to chemotherapy and for prediction of response after the completion of chemotherapy.

^{18}F-FDG PET and ^{18}F-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 ^{18}F-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

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58:71–96.
2. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) cancer statistics review, 1975-2002. Available at: http://seer.cancer.gov/csr/1975_2002/. Accessed January 21, 2009.
3. Gold MA. PET in cervical cancer: implications for 'staging,' treatment planning, assessment of prognosis, and prediction of response. *J Natl Compr Canc Netw.* 2008;6:37–45.
4. Grigsby PW. The role of FDG-PET/CT imaging after radiation therapy. *Gynecol Oncol.* 2007; 107(1, suppl 1):S27–S29.
5. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol.* 2004;22:872–880.
6. Sommers GM, Grigsby PW, Perez CA, et al. Outcome of recurrent cervical carcinoma following definitive irradiation. *Gynecol Oncol.* 1989;35:150–155.
7. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol.* 2001;19:3745–3749.

8. Grigsby PW, Siegel BA, Dehdashti F, Rader J, Zoberi I. Posttherapy [^{18}F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol.* 2004;22:2167–2171.
9. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA.* 2007;298:2289–2295.
10. Hong JH, Tsai CS, Lai CH, et al. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys.* 2004;60:249–257.
11. Bodurka-Bevers D, Morris M, Eifel PJ, et al. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. *Gynecol Oncol.* 2000;78:187–193.
12. Jacobs AJ, Faris C, Perez CA, Kao MS, Galakatos A, Camel HM. Short-term persistence of carcinoma of the uterine cervix after radiation: an indicator of long-term prognosis. *Cancer.* 1986;57:944–950.
13. Shield PW, Daunter B, Wright RG. Post-irradiation cytology of cervical cancer patients. *Cytopathology.* 1992;3:167–182.
14. Chien CR, Ting LL, Hsieh CY, Lai MS. Post-radiation Pap smear for Chinese patients with cervical cancer: a ten-year follow-up. *Eur J Gynaecol Oncol.* 2005;26:619–622.
15. Ferrandina G, Macchia G, Legge F, et al. Squamous cell carcinoma antigen in patients with locally advanced cervical carcinoma undergoing preoperative radiochemotherapy: association with pathological response to treatment and clinical outcome. *Oncology.* 2008;74:42–49.
16. Scambia G, Benedetti Panici P, Foti E, et al. Squamous cell carcinoma antigen: prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. *J Clin Oncol.* 1994;12:2309–2316.
17. Micke O, Prott FJ, Schafer U, Tangerding S, Potter R, Willich N. The impact of squamous cell carcinoma (SCC) antigen in the follow-up after radiotherapy in patients with cervical cancer. *Anticancer Res.* 2000;20:5113–5115.
18. Esajas MD, Duk JM, de Bruijn HW, et al. Clinical value of routine serum squamous cell carcinoma antigen in follow-up of patients with early-stage cervical cancer. *J Clin Oncol.* 2001;19:3960–3966.
19. Forni F, Ferrandina G, Deodato F, et al. Squamous cell carcinoma antigen in follow-up of cervical cancer treated with radiotherapy: evaluation of cost-effectiveness. *Int J Radiat Oncol Biol Phys.* 2007;69:1145–1149.
20. Hricak H. Cancer of the uterus: the value of MRI pre- and post-irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:1089–1094.
21. Mayr NA, Taoka T, Yuh WT, et al. Method and timing of tumor volume measurement for outcome prediction in cervical cancer using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys.* 2002;52:14–22.
22. Boss EA, Massuger LF, Pop LA, et al. Post-radiotherapy contrast enhancement changes in fast dynamic MRI of cervical carcinoma. *J Magn Reson Imaging.* 2001;13:600–606.
23. Lin LL, Yang Z, Mutic S, Miller TR, Grigsby PW. FDG-PET imaging for the assessment of physiologic volume response during radiotherapy in cervix cancer. *Int J Radiat Oncol Biol Phys.* 2006;65:177–181.
24. Schwarz JK, Lin LL, Siegel BA, Miller TR, Grigsby PW. 18-F-fluorodeoxyglucose-positron emission tomography evaluation of early metabolic response during radiation therapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2008;72:1502–1507.
25. Bjurberg M, Kjellen E, Ohlsson T, Ridderheim M, Brun E. FDG-PET in cervical cancer: staging, re-staging and follow-up. *Acta Obstet Gynecol Scand.* 2007;86:1385–1391.
26. Dose J, Hemminger GE, Bohuslavizki KH. Therapy monitoring using FDG-PET in metastatic cervical cancer. *Lancet Oncol.* 2000;1:106.
27. Yoshida Y, Kurokawa T, Kawahara K, et al. Metabolic monitoring of advanced uterine cervical cancer neoadjuvant chemotherapy by using [F-18]-fluorodeoxyglucose positron emission tomography: preliminary results in three patients. *Gynecol Oncol.* 2004;95:597–602.
28. Schroder W, Zimny M, Rudlowski C, Bull U, Rath W. The role of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in diagnosis of ovarian cancer. *Int J Gynecol Cancer.* 1999;9:117–122.
29. Whiteford MH, Whiteford HM, Yee LF, et al. Usefulness of FDG-PET scan in the assessment of suspected metastatic or recurrent adenocarcinoma of the colon and rectum. *Dis Colon Rectum.* 2000;43:759–767.
30. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of mucinous neoplasms: correlation of FDG uptake with histopathologic features. *AJR.* 2000;174:1005–1008.
31. Short S, Hoskin P, Wong W. Ovulation and increased FDG uptake on PET: potential for a false-positive result. *Clin Nucl Med.* 2005;30:707.
32. Kim SK, Kang KW, Roh JW, Sim JS, Lee ES, Park SY. Incidental ovarian ^{18}F-FDG accumulation on PET: correlation with the menstrual cycle. *Eur J Nucl Med Mol Imaging.* 2005;32:757–763.
33. Lerman H, Metser U, Grisaru D, Fishman A, Lievshitz G, Even-Sapir E. Normal and abnormal ^{18}F-FDG endometrial and ovarian uptake in pre- and postmenopausal patients: assessment by PET/CT. *J Nucl Med.* 2004;45:266–271.
34. Kitajima K, Murakami K, Yamasaki E, et al. Diagnostic accuracy of integrated FDG-PET/contrast-enhanced CT in staging ovarian cancer: comparison with enhanced CT. *Eur J Nucl Med Mol Imaging.* 2008;35:1912–1920.
35. Drieskens O, Stroobants S, Gysen M, Vandenbosch G, Mortelmans L, Vergote I. Positron emission tomography with FDG in the detection of peritoneal and retroperitoneal metastases of ovarian cancer. *Gynecol Obstet Invest.* 2003;55:130–134.
36. Turlakow A, Yeung HW, Salmon AS, Macapinlac HA, Larson SM. Peritoneal carcinomatosis: role of ^{18}F-FDG PET. *J Nucl Med.* 2003;44:1407–1412.
37. Chan JK, Cheung MK, Husain A, et al. Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol.* 2006;108:521–528.
38. Chan YM, Ng TY, Ngan HY, Wong LC. Quality of life in women treated with neoadjuvant chemotherapy for advanced ovarian cancer: a prospective longitudinal study. *Gynecol Oncol.* 2003;88:9–16.
39. Avril N, Sassen S, Schmalfeldt B, et al. Prediction of response to neoadjuvant chemotherapy by sequential F-18-fluorodeoxyglucose positron emission tomography in patients with advanced-stage ovarian cancer. *J Clin Oncol.* 2005;23:7445–7453.
40. Nishiyama Y, Yamamoto Y, Kanenishi K, et al. Monitoring the neoadjuvant therapy response in gynecological cancer patients using FDG PET. *Eur J Nucl Med Mol Imaging.* 2008;35:287–295.
41. Rubin SC, Randall TC, Armstrong KA, Chi DS, Hoskins WJ. Ten-year follow-up of ovarian cancer patients after second-look laparotomy with negative findings. *Obstet Gynecol.* 1999;93:21–24.
42. Rose PG, Faulhaber P, Miraldi F, Abdul-Karim FW. Positive emission tomography for evaluating a complete clinical response in patients with ovarian or peritoneal carcinoma: correlation with second-look laparotomy. *Gynecol Oncol.* 2001;82:17–21.
43. Cho SM, Ha HK, Byun JY, Lee JM, Kim CJ, Nam-Koong SE. Usefulness of FDG PET for assessment of early recurrent epithelial ovarian cancer. *AJR.* 2002;179:391–395.
44. Sironi S, Messa C, Mangili G, et al. Integrated FDG PET/CT in patients with persistent ovarian cancer: correlation with histologic findings. *Radiology.* 2004;233:433–440.
45. Kim S, Chung JK, Kang SB, et al. [^{18}F]FDG PET as a substitute for second-look laparotomy in patients with advanced ovarian carcinoma. *Eur J Nucl Med Mol Imaging.* 2004;31:196–201.
46. Kurosaki H, Oriuchi N, Okazaki A, et al. Prognostic value of FDG-PET in patients with ovarian carcinoma following surgical treatment. *Ann Nucl Med.* 2006;20:171–174.
47. Havrilesky LJ, Kulasingam SL, Matchar DB, Myers ER. FDG-PET for management of cervical and ovarian cancer. *Gynecol Oncol.* 2005;97:183–191.
48. Menzel C, Dobert N, Hamscho N, et al. The influence of CA 125 and CEA levels on the results of ^{18}F-deoxyglucose positron emission tomography in suspected recurrence of epithelial ovarian cancer. *Strahlenther Onkol.* 2004;180: 497–501.
49. Ruiz-Hernandez G, Delgado-Bolton RC, Fernandez-Perez C, Lapena-Gutierrez L, Carreras-Delgado JL. *Rev Esp Med Nucl.* 2005;24:161–173.
50. Garcia-Velloso MJ, Jurado M, Ceamanos C, et al. Diagnostic accuracy of FDG PET in the follow-up of platinum-sensitive epithelial ovarian carcinoma. *Eur J Nucl Med Mol Imaging.* 2007;34:1396–1405.
51. Bristow RE, del Carmen MG, Pannu HK, et al. Clinically occult recurrent ovarian cancer: patient selection for secondary cytoreductive surgery using combined PET/CT. *Gynecol Oncol.* 2003;90:519–528.
52. Simcock B, Neesham D, Quinn M, Drummond E, Milner A, Hicks RJ. The impact of PET/CT in the management of recurrent ovarian cancer. *Gynecol Oncol.* 2006;103:271–276.
53. Mangili G, Picchio M, Sironi S, et al. Integrated PET/CT as a first-line re-staging modality in patients with suspected recurrence of ovarian cancer. *Eur J Nucl Med Mol Imaging.* 2007;34:658–666.
54. Chung HH, Kang WJ, Kim JW, et al. Role of [^{18}F]FDG PET/CT in the assessment of suspected recurrent ovarian cancer: correlation with clinical or histological findings. *Eur J Nucl Med Mol Imaging.* 2007;34:480–486.
55. Soussan M, Wartski M, Cherel P, et al. Impact of FDG PET-CT imaging on the decision making in the biologic suspicion of ovarian carcinoma recurrence. *Gynecol Oncol.* 2008;108:160–165.
56. Kitajima K, Murakami K, Yamasaki E, et al. Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent ovarian cancer: comparison with integrated FDG-PET/non-contrast-enhanced CT and enhanced CT. *Eur J Nucl Med Mol Imaging.* 2008;35:1439–1448.
57. Smith GT, Hubner KF, McDonald T, Thie JA. Cost analysis of FDG PET for managing patients with ovarian cancer. *Clin Positron Imaging.* 1999;2:63–70.
58. Cho SM, Park YG, Lee JM, et al. ^{18}F-fluorodeoxyglucose positron emission tomography in patients with recurrent ovarian cancer: in comparison with vascularity, Ki-67, p53, and histologic grade. *Eur Radiol.* 2007;17:409–417.