# 14

# PET and PET/CT Imaging in Testicular and Gynecologic Cancers

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Tumors of the testes and gynecologic malignancies are important cancers with significant morbidity, and the role of imaging is vital. Although testicular cancer is not common, it is increasing in incidence and is a cancer of relatively young men. Ovarian, uterine, and cervical cancer are among the most common tumors in women, with high morbidity and mortality rates. There are early screening tests for cervical cancer but, despite this, mortality from this tumor remains significant. Ovarian cancer is a problem as it often presents in late stage. In all three, outcome is dependent on stage at diagnosis and imaging plays a crucial role in assessment. Following initial treatment, appropriate posttreatment evaluation and timely additional therapy can decrease morbidity from unnecessary further treatment or can lead to cure when residual tumor is detected. Imaging techniques have been fundamental in this process, and positron emission tomography (PET) is developing an important role in pretreatment assessment and in assessing early response to therapy. This chapter considers the role of imaging in the management of these tumors.

## Testicular Cancer

Testicular cancer (seminoma and nonseminoma, NSGCT) is a relatively rare tumor affecting only 1% of men, but it is the commonest tumor in young males (aged 15–35) and its incidence is increasing (1). The two tumor types differ in their biologic behavior and potential for metastases so that treatment also differs. The overall prognosis for these tumors is good.

### Diagnosis and Tumor Staging

Most testicular cancers present as an asymptomatic lump in the testes, and urgent orchidectomy is performed. The basic histologic distinction is between seminoma and nonseminomatous germ cell tumor (NSGCT), although the histology can be complex and 10% of patients have mixed tumors (2). The tumors spread to the paraaortic region initially, although hematogenous spread is more common in NSGCT and metastases are seen in the lung, brain, liver, and bone. At diagnosis all patients should be staged by clinical examination and computed tomography (CT) scans of the chest and abdomen and pelvis. Tumor markers should be measured as they provide prognostic information, allow monitoring of treatment response and assessment of recurrence (3, 4). In addition, histologic factors in the tumor such as the presence of blood vessel invasion by the primary tumor, the percentage of embryonal cancer, and involvement of the rete testes (in seminoma) provide prognostic information. All these data are used to stage the patient. There are many staging systems. One of the most common is the Marsden System (Table 14.1) (5).

On the basis of staging investigations, patients with NSGCT are classified as low or high risk for metastatic disease, and treatment regimens are based on this stratification. Low-risk patients may be observed or treated with two courses of chemotherapy followed by surveillance, and both these regimens have good cure rates (4, 6). The factors influencing staging, however, have proven to be unreliable for absolute determination of risk for metastases in any individual. Because of advances in chemotherapy, cure is now possible for the majority of patients with minimal metastatic disease. Accordingly, there has been a need to reevaluate the treatment strategies that are currently being used to minimize chemotherapy toxicity by accurately differentiating the patients who have metastatic disease from those who do not. Further concerns have been raised over the long-term effects of chemotherapy on the cardiac system and the precipitation of second malignancies (7). If tumor spread could be reliably assessed, some patients with NSGCT stage I (no evidence of metastases) could be clinically observed rather than undergo prophylactic chemotherapy. Of the patients initially classified as stage I, 20% to 30% have lymph

**Table 14.1.** Staging of testicular cancer.

| Stage | Description |
|---|---|
| I | No evidence of metastases |
| IM | Rising concentrations of serum markers with no other evidence of metastases |
| II | Abdominal node metastases |
| A | =2 cm in diameter |
| B | 2–5 cm in diameter |
| C | =5 cm in diameter |
| III | Supradiaphragnatic nodal metastasis |
| M | Mediastinal |
| N | Supraclavicular, cervical, or axillary |
| O | No abdominal node metastasis |
| ABC | Node stage as defined in stage II |
| IV | Extralymphatic metastasis |
| Lung | |
| L1 | =3 metastases |
| L2 | =3 metastases, all =2 cm in diameter |
| L3 | =3 metastases, one or more =2 cm in diameter |
| H+, Br+, Bo+ | Liver, brain, or bone |

*Source:* From Horwich A. Testicular Cancer. In: Horwich A, ed. Oncology: A Multidisciplinary Textbook. London: Chapman & Hall 1995:485–498.

nodes at retroperitoneal lymph node dissection and therefore need further treatment. Overall, as many as 50% are understaged and 25% overstaged by currently available techniques. Eventually, 20% of these patients will relapse whereas 50% of patients who have been classified as high risk on the basis of prognostic factors and therefore sent for treatment do not relapse (4).

In seminoma, conventional practice has been to perform retroperitoneal radiotherapy even in stage I disease, and about 15% of patients at presentation have disease confined to the abdomen. Retroperitoneal and pelvic radiotherapy is a common practice and has a good rate of achieving local control. Even so, 15% of clinical stage I relapse and 20% to 30% of patients with seminoma will relapse at distant sites (8).

## *Imaging Procedures in Tumor Staging*

Anatomic staging techniques including CT, ultrasound, and lymphangiography have all been used to stage testicular cancer. The most widely used now is CT, which is routinely performed as part of the initial staging protocol. All staging procedures have limitations, and even for CT false-negative rates of 59% have been reported. The false-negative rates for lymphangiography and ultrasound are 64% and 70%, respectively (9). The diagnosis of nodal metastases by CT is based on detection of nodal enlargement, with a 1-cm upper limit for normal lymph node size. Before nodal enlargement, the entire volume of a lymph node may be replaced by malignant cells, whereas a large lymph node may contain only benign reactive cells. As a result, the false-positive rate of CT is also high at 40% (10). This inaccuracy has led to search for more-accurate imaging methods including metabolic imaging with PET.

Because of the ability of $^{18}$F-2-deoxy-D-glucose (FDG)-PET to detect metabolically active disease without reliance on size criteria, FDG-PET imaging has the potential to identify small-volume disease in a lymph node that is normal in size; this may have a direct effect on patient management. In stage I tumor, more accurate classification of patients as high or low risk would avoid unnecessary treatment and morbidity. In stage II and III tumor, where prognosis is based on many factors including nonvisceral disease and tumor markers, accurate classification may determine whether radiotherapy/chemotherapy or surgery should be used to treat patients.

At diagnosis, FDG-PET can clearly identify more sites of disease in patients with established metastatic disease than seen on CT (11, 12). This finding will have minimal effect on initial management if the patient is to receive chemotherapy based on traditional staging. In a few cases, it has identified unsuspected visceral or bone disease and therefore altered management (11).

There are only a few studies that have addressed the issue of improving the initial staging using PET, and these include between 31 and 50 patients (11–15). The sensitivity ranged between 70% and 87% and the specificity between 94 and 100%. The three major initial studies (11, 13, 14) confirmed overall better sensitivity, positive predictive value (PPV), and negative predictive value (NPV) for PET than for CT. Both CT and PET missed small (approximately 1 cm) retroperitoneal lymph node metastases (13).

One limitation of these studies was that not all patients had histologic confirmation of findings on PET and assessment of true negativity or positivity. Albers et al. (14) had histopathology results in some patients and found 70% sensitivity and a 100% specificity in a study of 37 patients. They concluded that PET was useful in stage II tumors to correctly diagnose the false positives that were seen on CT but was not useful in stage I tumor because, among 15 patients with stage I NSGCT, PET identified only 4 of 6 patients with pathologically involved lymph nodes negative on CT. Even with the limitation of low sensitity for detection of small-volume disease, the use of PET could significantly improve management of stage I NSGCT patients. Although there are no studies regarding the performance of integrated PET/CT imaging for staging of testicular tumors, precise localization of FDG-avid nodes can guide biopsy to these specific lymph nodes, even if normal by size criteria, and further improve staging.

Understaging with imaging is of most concern in NSGCT because patients with true stage I tumor could be followed by surveillance only. Lassen et al. (15) performed a prospective analysis of 46 patients with stage I tumor

after a normal CT and tumor markers who underwent FDG PET imaging. All patients underwent routine follow-up with repeated CT and tumor marker evaluation; 22% (10/46) relapsed, of whom 7 of 10 had positive initial PET scans, which gave a negative predictive value of 92% for PET compared to that of 78% for conventional imaging. The authors concluded that PET was superior to conventional staging ($P = 0.06$) in stage I NSGCT with the potential to improve patient management.

To fully define if PET may be useful in staging, large-scale prospective studies are needed in which patients are followed until relapse or until abnormalities found on PET and CT are biopsied. If it can be confirmed that PET has the suggested improved sensitivity for occult disease, then it could significantly improve the current management of patients with stage I NSGCT. Studies have been started including the Medical Research Council (MRC)-funded TE22 Trial in the U.K. to further address this problem.

## Tumor Recurrence

Patients with metastatic disease must be monitored to detect relapse at a time when salvage treatment would have the best chance of cure or disease control. Patients must be followed for several years clinically, biochemically with serum tumor markers, and radiologically.

Following treatment, patients with metastatic disease frequently have residual masses and the treatment of these remains difficult. When the mass contains persistent tumor, immediate further treatment is indicated. Often the mass contains merely necrosic or fibrous tissue, in which case no further treatment is indicated and the patient may be observed. In the case of NSGCT, such masses may also contain mature teratoma differentiated (MTD), which is a benign tumor. Such masses need to be removed because there is a risk of malignant tumor recurrence, but the procedure can be delayed and undertaken later at a time when the patient is less likely to experience surgical morbidity from recent chemotherapy. CT imaging is the standard method of monitoring these patients, and by this means it is not possible to determine whether the residual mass contains any active tumor.

Determination of tumor markers is the second important procedure in the follow-up of patients with testicular cancer because a detectable level of such markers may indicate residual or recurrent tumor. Serum tumor markers are not sufficiently sensitive or specific to determine tumor presence or absence reliably and cannot indicate the anatomic site of any tumor that is present (16, 17).

### *PET Imaging in Tumor Recurrence*

Functional imaging techniques, including imaging with radiolabeled antibodies ($^{67}$gallium and $^{201}$thallium), have been used to assess disease presence but with variable results (18–20). FDG-PET potentially has the ability to detect small-volume tumors in solitary residual masses, to identify a specific mass as the site of relapse in patients with multiple masses, to detect other unsuspected sites of tumor, and to determine the site and extent of disease in patients with raised tumor markers.

### *Residual Masses*

Several studies have focused on the ability of PET to determine which patients should undergo resection of residual masses following treatment (12, 21–23). Initially, Stephens et al. (21) studied 30 patients with NSGCT who had residual masses after chemotherapy. PET was able to differentiate viable tumor from fibrosis/necrosis or MTD but could not differentiate these nonmalignant lesions from each other. Hain et al. (22) evaluated 70 patients with FDG-PET posttreatment (47 for assessment of residual masses). FDG-PET had sensitivity and specificity of 88% and 95%, respectively, for detecting residual tumor in masses, as well as high PPV and NPV, 90% and 96%, respectively. Most studies confirmed the improved PPV and accuracy of PET over CT (23). Hain et al. (22) and Cremerius et al. (23) each had one case of histologically proven MTD that had low uptake; both these masses were in the chest. Cremerius postulated that this may have been the result of tissue attenuation differences between the chest and other organs. However, not all intrathoracic MTDs were found to be positive in the study by Hain et al. (21).

The sensitivity, specificity, and predictive values of PET for active tumor allow a sufficient degree of certainty in distinguishing active tumor from nonactive tumor to allow early intervention in patients with active disease. However, PET could not differentiate MTD from fibrosis or necrosis. MTD has the potential to become malignant and must eventually be resected. Resection may be delayed and performed electively at a later time when the patient has recovered from the effects of chemotherapy/radiotherapy.

Analysis of PET data by standard uptake value (SUV) determination has been used in an effort to improve diagnosis of residual masses. Stephens et al. (21) found that recurrent NSGCT had a higher SUV (mean, 8.81) than MTD (mean, 3.07) and necrosis/fibrosis (mean, 2.86). Patients with an SUV greater than 5 were 75 times more likely to have persistent tumor. Cremerius et al. (23) also considered SUV analysis and found seminoma to have a higher SUV than NSGCT, although their results for NSGCT were affected by their considering MTD as tumor in their analysis. MTD has been successfully differentiated from fibrosis or necrosis with PET using kinetic rate constants, and this approach needs further evaluation (24).

In seminoma, detection of active disease is even more important because treatment is more difficult. The value

of surgical removal is uncertain, and there is no advantage to be gained from radiotherapy after chemotherapy (25). Cremerius et al. (23) found, in a study of 42 posttreatment PET scans (seminoma and NSGCT), that FDG-PET had a 90% sensitivity for detection of residual tumor in seminoma, and these high values were confirmed by Hain et al. (22). De Santis et al. (26) published the largest study, including 51 patients with seminomas and postchemotherapy residual masses. PET detected residual tumor in all masses greater than 3 cm and in 95% of masses less than 3 cm, with PPVs and NPVs of 100% and 96%, respectively, for PET versus 37% and 92%, respectively, for CT. They concluded that PET was the best predictor of residual tumor and should be used as a standard investigation in this group of patients with seminomas and residual masses after therapy.

Two problems emerged in the studies of residual masses. First, FDG-PET can miss some small-volume active disease. Hain et al. (22) had two false-negative studies, both of which are of concern as they involved small numbers of malignant cells in large masses otherwise containing MTD. Cremerius et al. (23) had one patient with a 15-mm lymph node containing tumor that was missed on PET and CT, but they did not indicate whether the nodes contained only a small number of malignant cells or were entirely replaced by tumor. FDG-PET may therefore have an undefined detection limit that varies with tumor type. It is also possible that the uptake time may be important for detecting malignant testicular cancer, as is the case for sarcoma and breast cancer (27, 28). Cremerius et al. and Hain et al. (22, 23) both found false-negative studies within 2 weeks of chemotherapy, suggesting that it would be appropriate to wait more than 2 weeks after chemotherapy to perform a PET study. Overall, the numbers of false-negative PET studies were small and the NPV was high.

## *Rising Tumor Markers*

The presence of tumor markers is an important prognostic factor in testicular cancer, and tumor markers are used in the routine monitoring and follow-up of patients. Rising markers may be the first indicator of disease recurrence (29). However, they are neither sensitive nor specific for tumor detection, and marker-negative relapse may occur even where the initial tumor was marker positive. Also, some patients with residual masses posttreatment may show modest elevation of markers even though the masses contain no active tumor (30), and a return of markers to normal posttreatment does not guarantee disease remission (16, 17).

There are two groups of patients with recurrent or residual disease in whom elevated tumor markers are diagnostically problematic. In patients with elevated markers and no residual masses, the anatomic location of recurrent disease may be difficult to determine, and in patients with elevated markers and residual masses, it may not be apparent which, if any, of the known masses contain active disease.

Cremerius et al. (23) found that adding PET imaging to tumor marker determination improved sensitivity and NPV of markers, but adding the tumor marker determination to PET imaging was of little value. However, tumor marker determination was not available for all patients. Hain et al. (22) had marker information for all 70 patients who underwent PET imaging. They found that in patients with raised tumor markers, including those with a resid-

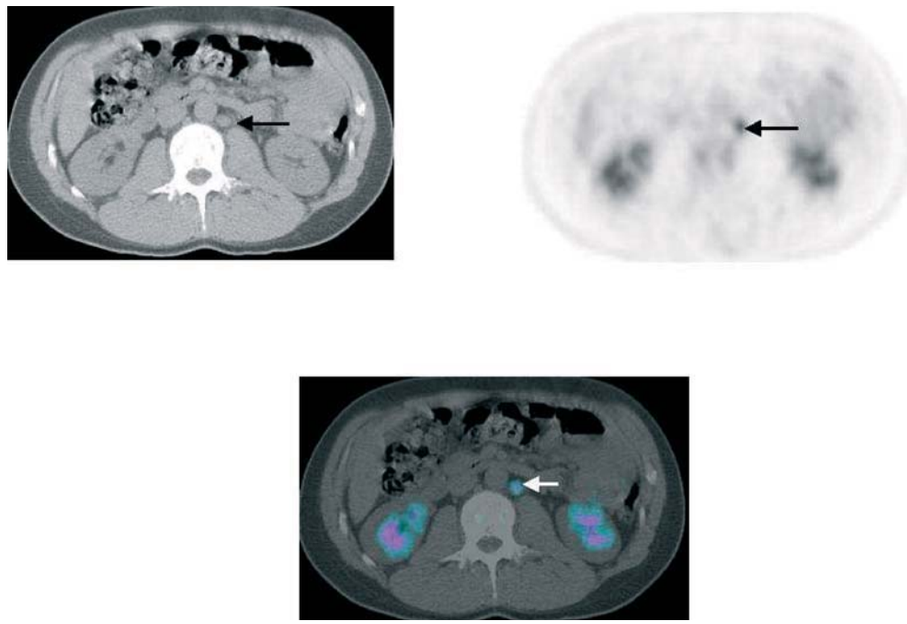


**Figure 14.1.** A 33-year-old man with a history of testicular cancer 18 months previously presented with rising tumor markers. There was no evidence of disease on conventional imaging. PET/CT imaging revealed a $^{18}$F-2-deoxy-D-glucose (FDG)-avid lymph node lying close to the L2 vertebra, as shown on the transaxial images of CT (*top left*), PET (*top right*), and PET/CT fusion images (*lower*).

ual mass, PET identified the site of disease in all patients but 1. In the group with raised tumor markers and no residual masses, PET demonstrated the tumor in all patients (Figure 14.1). In the group with raised tumor markers and residual masses, there was one false positive. Negative PET scans in the presence of raised tumor markers presented more of a problem as there were 5 patients with false-negative findings in this group. In 3 of these cases, all imaging was normal and subsequent PET scans were the first studies to identify the site of recurrence. This finding suggests that, in the presence of raised tumor markers and negative imaging findings, the most appropriate follow-up procedure is repeating the PET study.

These findings have important implications for the management of patients. Hain et al. (22) found that the ability of PET to find unsuspected disease resulted in management changes in 57% of patients. Management changes involved changes from local therapy–radiotherapy/surgery to chemotherapy or surveillance (Figure 14.2). Many of their patients had had multiple recurrences and had chemotherapy-resistant tumor, and here local control of active sites may be the only chance of cure. In the first relapse, determination of whether there are one or multiple sites will help to determine the type of consolidation treatment.

### *Predicting Response to Treatment*

In other tumors, for example, lymphoma and breast (31–33), PET can predict the response to chemotherapy early during the course and predict long-term outcome. Bokemeyer et al. (34) have evaluated the value of FDG-PET imaging compared to tumor markers and CT/MR in 23 patients with relapsed testicular cancer after two or three cycles of induction chemotherapy before high-dose chemotherapy. The outcome of high-dose chemotherapy was correctly predicted by PET/CT scan/serum tumor marker in 91%, 59%, and 48% of patients, respectively. In those patients who showed response to induction chemotherapy according to CT scans or serum tumor marker evaluation, a positive PET study correctly predicted treatment failure. In addition, PET identified patients most likely to achieve a favorable response to subsequent high-dose chemotherapy. It was suggested that FDG-PET is a valuable addition to the prognostic model of low-, intermediate-, and high-risk patients, particularly in the low and intermediate groups, for further selection of patients who would benefit from high-dose chemotherapy (Figure 14.3).

## Cervical Cancer

Cervical carcinoma is one of the most common cancers in women (35). About 80% are squamous cell carcinomas and about 20% adenocarcinomas, in addition to other rare types of tumors. Cervical carcinoma can be detected early in the course of the disease with screening Pap smears and biopsy when appropriate. The International

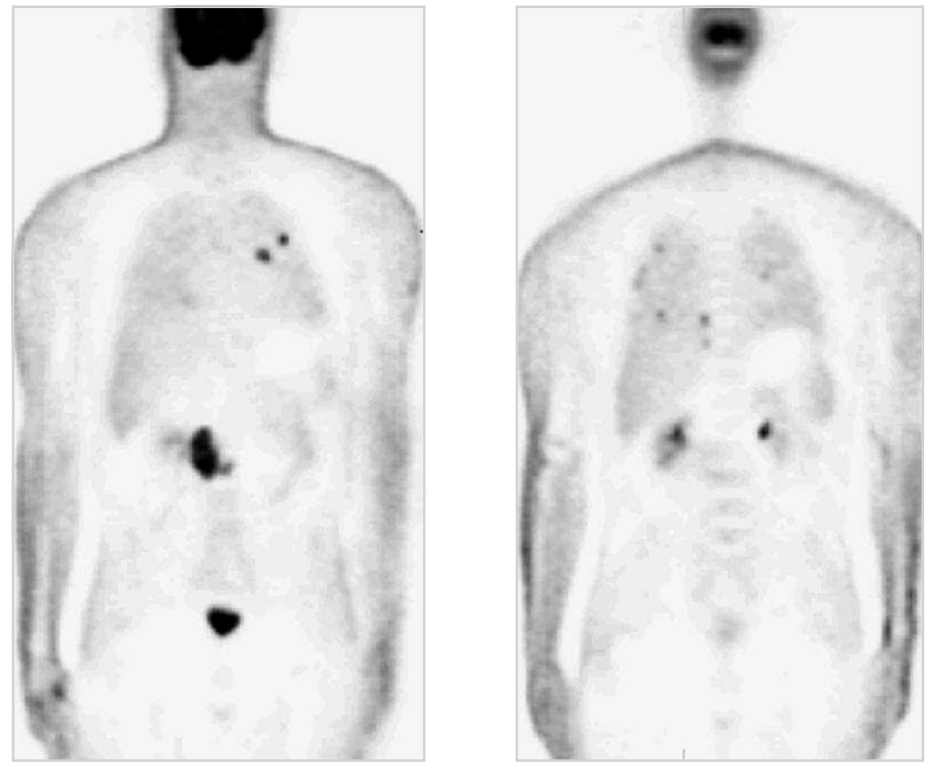
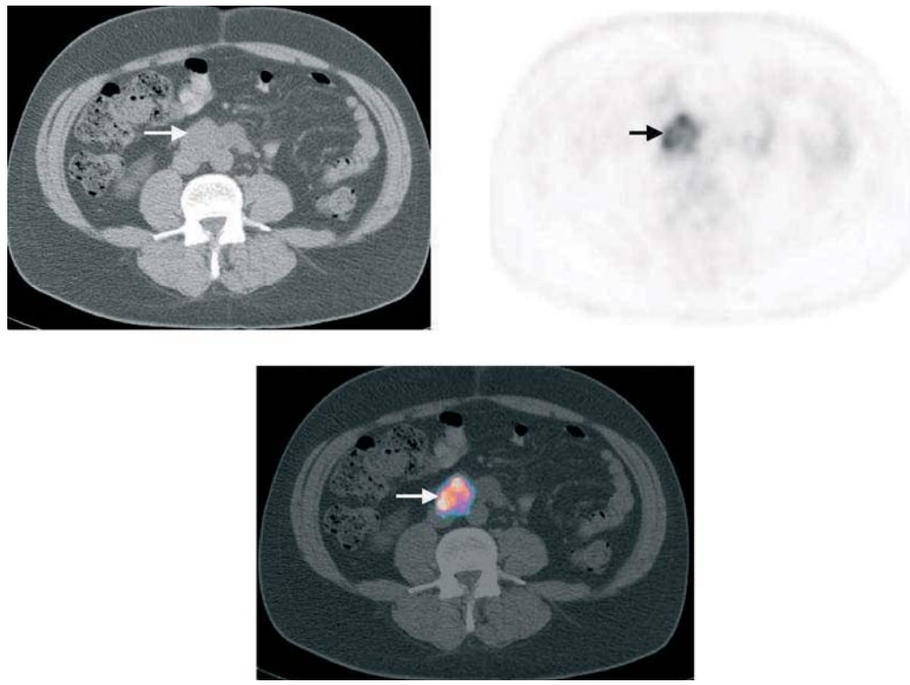


**Figure 14.2.** FDG-PET image in a patient with a history of testicular cancer and a right para-aortic residual mass on CT and rising markers. He was being considered for laparotomy as definitive treatment if this was the only site of disease. CT of the abdomen and chest was otherwise normal although he previously had lung metastases. He was referred for a PET scan to exclude other sites of disease and thereby enable surgery. The images show increased uptake in the known mass as well as disease in the lungs and mediastinum, which directly altered the patient's management.



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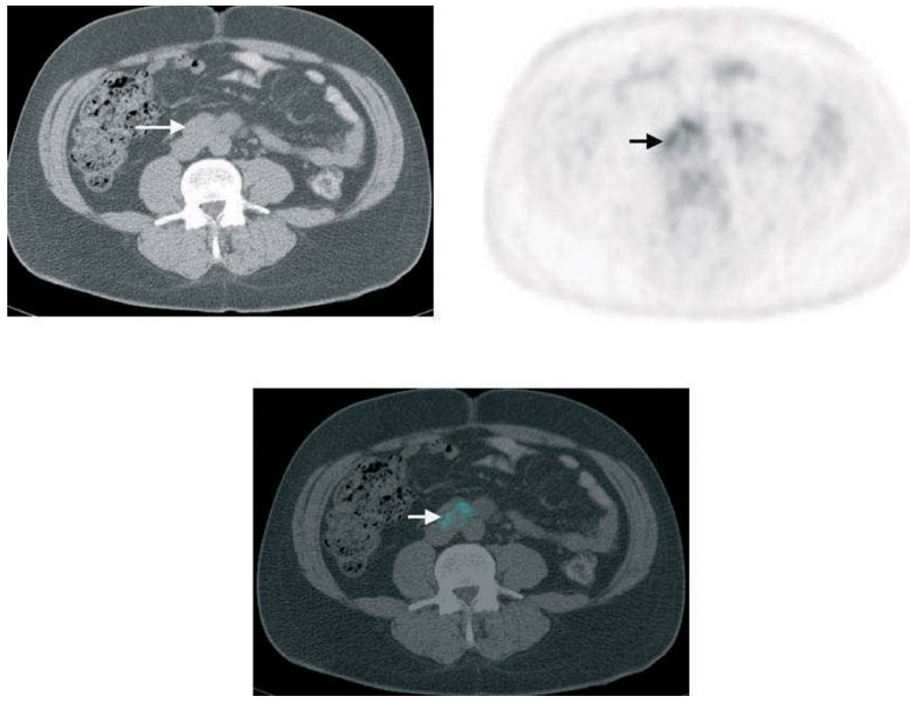

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**Figure 14.3.** (**a**) A patient with known metastatic testicular cancer had an FDG-PET scan performed before chemotherapy. The transaxial images of CT (*top left*), PET (*top right*), and PET/CT fusion image (*lower*) showed an FDG-avid nodal lesion (*arrows*). (**b**) One week later, following chemotherapy, there has been a rapid decrease in uptake in the tumor (*arrows*), indicating an early response to chemotherapy. The patient responded well to the current course of chemotherapy.

Federation of Gynecology and Obstetrics (FIGO) (36) has defined a staging system for carcinoma of the cervix that uses a combination of clinical and radiologic findings (Table 14.2). Although prognosis is related to stage, other factors are important in determining prognosis, including the extent of lymph node involvement. For example, in patients with stage IB tumor (tumor confined to the cervix), the finding of tumor-positive lymph nodes is associated with a decrease in survival, from 85% to 95% to 45% to 55% (37–40).

**Table 14.2.** Staging of cervical cancer.

| Stage | Description |
|---|---|
| I | Confined to the uterus |
| IA | Invasion carcinoma diagnosed only by microscopy |
| IB | Clinically visible lesions confined to the cervix or lesions more than 5 mm and with 7 mm or greater horizontal spread |
| II | Tumor invades beyond the uterus but not to pelvic wall or lower third of vagina |
| IIA | Without parametrial invasion |
| IIB | With parametrial invasion |
| III | Tumor extends to pelvic wall and/or involves lower one-third of vagina and/or causes hydronephrosis or nonfunctioning kidney |
| IIIA | Tumor involves lower third of the vagina, no extension to pelvic wall |
| IIIB | Tumor extends to pelvic wall, and/or causes hydronephrosis or nonfunctioning kidney |
| IV | Cancer has spread to the bladder, rectum, or outside the pelvis |
| IVA | Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis |
| IVB | Distant metastases |

*Source:* Reprinted from FIGO Committee on Gynaecological Oncology: Benedet JL, Bender H, Jones H III, Ngan HYS, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. Int J Gynecol Obstet 2000;70:209–262. Copyright © 2000, with permission from International Federation of Gynecology and Obstetrics.

## Tumor Staging

### *Imaging Procedures in Tumor Staging*

Definition of lymph node status is important. Currently, the best methods for defining the status of lymph nodes are lymphangiography, CT, and MRI scanning. As these procedures are not widely available, FIGO has not included them to the staging criteria (36). Lymphangiography has been widely used in the past for assessment of lymph nodes but suffers from technical problems and may have high false-positive rates (41–43), as well as false-negative findings because of nonopacification in lymph nodes that are totally replaced by tumor (44). The problem in lymph node staging by anatomic imaging using CT or MRI is the need to use anatomic criteria for tumor detection. As with other tumors, small (less than 1 cm) lymph nodes may contain tumor and enlarged (greater than 1 cm) lymph nodes may be reactive; this results in sensitivities as low as 34% (45) for detection of lymph node metastases by CT and sensitivity and specificity for MR of 38% to 89% and 78% to 99%, respectively (44–47). Attempts have been made to improve the results in MR by contrast enhancement and by the use of circular polarized phased-array coil, but without success (47). A meta-analysis of studies that evaluated lymphangiography, CT, and MR showed that all perform similarly with regard to detection of lymph node metastases. The less-invasive nature of CT/MR as well as the extra anatomic information provided on tumor extent has made the imaging procedures preferable (44).

These problems with conventional imaging have led to evaluation of FDG-PET as an alterative for the staging of cervical carcinoma and for the evaluation of lymph nodes in particular. Several studies that have examined the performance of PET imaging compared either CT or MRI for initial staging of patients with cervical cancer diagnosed both at early and at more-advanced stages (48–53). Overall, the sensitivity for FDG-PET imaging ranged from 83% to 100% and the specificity from 89% to 100%. This sensitivity for CT/MR in the same studies ranged from 50% to 73%. In studies where PET was evaluated in patients with negative CT/MR (48, 50, 51), the sensitivity and specificity of PET for detection of metastases were 83.3% to 85.7% and 94.4% to 96.7%, respectively. There was some difference between studies in early- and late-stage disease.

Rose et al. (48) studied a group of 32 patients with stage IIb–IVA cervical cancer presurgery and used PET to evaluate pelvic and paraaortic lymph nodes that were negative by CT. In 17 patients who underwent pelvic nodal resection, PET detected nodal metastases in 11 of 17 patients, with no false-positive or false-negative results. Rose et al. (48) analyzed the data according to identification of pelvic and paraortic disease. FDG-PET was less effective in the paraaortic region. Overall, PET in the paraaortic region had a PPV of 75% and NPV of 92%, with positive PET indicating a relative risk of 0.9 for paraaortic metastasis.

Reinhardt et al. (49) compared PET and MRI in patients with stage IB–IIA disease. On a patient-by-patient basis, the PPV for nodall staging by PET and MRI was 100% and 67%, respectively. However, this difference was not found to be statistically significant. These investigators also evaluated the detection of nodal metastases on a site-by-site basis and found PPV for PET and MRI as 90% and 64%, respectively ($P$ less than 0.05; Fischer exact test). Unlike Rose et al. (48), they found some false-negative PET results in the pelvis and speculated that the difference in the two studies may have resulted from patient selection, with Rose et al. (48) studying more patients with advanced disease.

On the basis of the difference in PPV for detection of metastatic lymph nodes by PET and MRI (90% and 64%, respectively), FDG-PET was considered useful for planning patient management. Any patient with positive lymph nodes by PET, regardless of findings by MRI, should undergo treatment of the involved nodal region, either by extended-field radiotherapy or surgical clearance (49). On the basis of this, it can be concluded that more patients would benefit from the use of FDG-PET in the staging procedure.

Both Rose et al. (48) and Reinhardt et al. (49) reported cases of enlarged lymph nodes by conventional imaging that were merely reactive, and a negative PET finding in

these patients was also useful to the managing clinican. As in testicular cancer, such negative results may mean that more-limited treatment is required, thereby avoiding unnecessary morbidity.

Miller and Grisgsby (54) have evaluated the usefulness of tumor volume measurement with PET in patients with advanced cervical cancer treated by radiation therapy. They concluded the following: (1) tumor volume can be accurately measured by PET; (2) tumor volume separates patients with a good prognosis from those with a poorer prognosis; (3) a subset of patients with relatively small tumors and no lymph node involvement does remarkably well; and (4) tumor volume does not correlate with the presence of lymph node disease.

The same group of investigators (55) have evaluated a treatment planning method for dose escalation to the paraaortic lymph nodes based on PET with intensity-modulated radiotherapy (IMRT) for cervical cancer patients with paraaortic lymph node involvement. They subsequently determined the guidelines regarding the selection of appropriate treatment parameters (56).

Miller et al. (57) developed a simple, rapid, and highly reproducible system for visual grading of characteristics of the primary tumor in patients with cervical cancer at the time of diagnosis. This approach allowed separation of patients with a poor prognosis from those who will do well, thus providing a new tool for accurate estimation of prognosis. In addition, as this did not correlate with lymph node status, it provides a potentially independent predictor of outcome. Singh et al. (58) evaluated the outcome of patients with FIGO clinical stage IIIb cervical carcinoma as a function of site of initial regional lymph node metastasis as detected by FDG-PET. They concluded that the cause-specific survival in this group was highly dependent on the extent of lymph node metastasis as identified on FDG-PET.

The performance of FDG-PET imaging for evaluation of patients with cervical carcinoma pre- and postradiotherapy allows predicting reponse to treatment and overall outcome. Grisgby et al. (59) studied 152 patients with cervical cancer who underwent radiotherapy and/or chemotherapy with pre- and posttreatment FDG-PET imaging. The 5-year survival of patients with negative FDG-PET posttherapy was 80%, whereas patients with positive FDG-PET scans (at previous or new sites) had a 5-year survival of 32%. They concluded that persistent or new FDG uptake on the posttherapy scan was the most significant prognostic factor for developing metastatic disease and for predicting death from cervical cancer.

There are some technical aspects of PET scanning for cervical cancer that need to be considered. Because of the close proximity to the bladder and the excretion of tracer in the urine, it has been thought by some investigators that problems in interpretation could arise from activity in the ureters and image artifact from the bladder. Most reported studies used continuous bladder irrigation and some also used preimaging hydration. Some have used vigorous hydatrion and furosemide as well (60). Others investigators have not found these patient manipulations to be necessary (49). Sugawara et al. (52) imaged patients pre- and postvoid without patient interventions and found 100% sensitivity for tumor detection on postvoid images. With integrated PET/CT imaging, precise localization of FDG uptake should facilitate the differentiation of physiologic urine activity from pathologic activity in tumor.

## Tumor Recurrence

### *Imaging Procedures in Tumor Recurrence*

There are limited data on the place of FDG-PET imaging in recurrent cervical cancer. Studies have focused particularly on patients without radiologic evidence of recurrence (also called asymptomatic or disease free). Three studies (61–63) have shown sensitivity ranging from 80% and 90.3%, with specificity from 76.1% to 100%, which is of particular value when other imaging is normal or equivocal. Ryu et al. (62) evaluated PET in different body regions and found that the sensitivity of PET imaging was high in mediastinal, hilar, and scalene lymph nodes and in liver and spine, but was relatively low in lungs and retrovesical and paraaortic lymph nodes.

In patients with documented (also called symptomatic) recurrence, PET imaging may also be of value (61, 64). Unger et al. (61) evaluated 21 PET scans in women symptomatic of recurrence and found PET to have a sensitivity of 100% and a specificity of 85.7%. Lai et al. (64) prospectively examined 44 patients with recurrent disease and compared restaging with PET and CT/MR. PET imaging was superior to CT/MR in the overall detection of lesions and in the identification of metastatic disease. In addition, PET altered management in 55% of patients. They concluded that in patients with recurrence who are candidates for salvage treatment by CT/MR crtiteria, adding PET imaging significantly reduced unnecessary salvage therapies. Yen et al. (65) defined a prognostic scoring system using PET for patients with recurrent cervical cancer that allowed ranking patients into three groups. They concluded that, using this risk score, FDG-PET may offer maximal benefits by selecting appropriate recurrent cervical cancer patients for salvage therapy with precise restaging information.

As with other tumors, timing of the acquisition of the PET images postadministration of FDG may be important, and a distribution period of 1 h for FDG may not be optimal (27, 28). Ma et al. (66) studied patients with primary and recurrent cervical cancer at 40 min and 3 h after injection of FDG. On the 3-h-delayed images, additional lower paraaortic lymph nodes were detected, and some FDG-avid lesions at 40 min demonstrated decreased FDG uptake at 3 hours, allowing classifying them as benign.

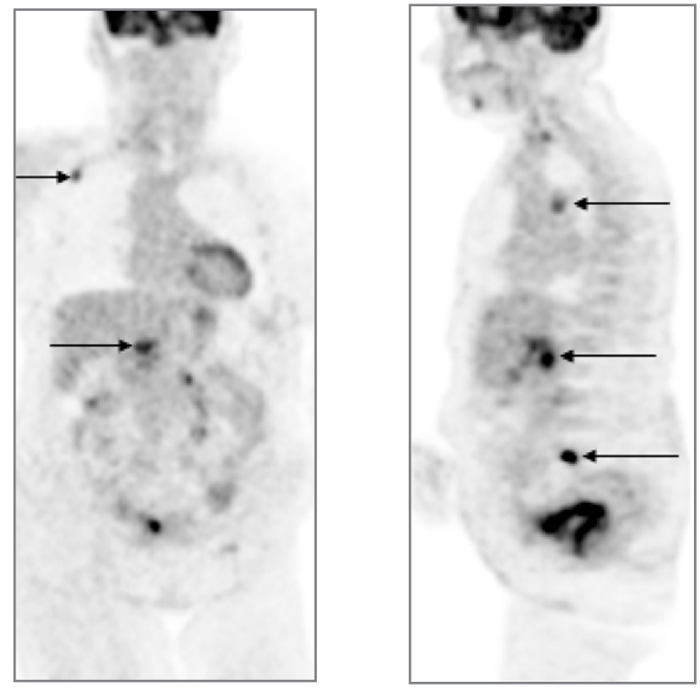

**Figure 14.4**. A 79-year-old women with carcinoma of the cervix and known involvement of the left ureter was treated with surgery and radiotherapy and considered to be cured. Nine years later, she presented with gross hematuria. CT showed a complex mass at the vaginal vault, and the biopsy was negative. A PET was performed to assess local and possible metastatic disease. The coronal (*left*) and sagittal (*right*) FDG-PET images showed widespread metastases (*arrows*) including the right pectoral region, the lung hilum, the porta hepatis, and retroperitoneal lymph nodes in the abdomen. Biopsy confirmed metastatic disease.

When cervical cancer recurs, PET imaging may also be useful in differentiating tumor from fibrosis after surgery or radiotherapy, a common problem with anatomic imaging. The ability to coregister images from different imaging modalities using software package or integrated PET/CT systems (Figure 14.4) provides fusion images allowing identification of FDG-avid anatomic lesions and guidance of biopsies. Further studies need to be done to define the role of integrated PET/CT imaging compared to PET alone role in patients with cervical cancer.

$^{11}$C-Methionine has been used to successfully to image cervical carcinoma although, because of physiologic uptake of tracer, correlation with anatomic imaging is required (67). It is possible that this procedure may find a place imaging the difficult-to-manage patient.

## Ovarian Carcinoma

Ovarian cancer has a high mortality. The tumor may be asymptomatic until quite late (68), and there are no readily available screening tests similar to those that are available for detection of cervical cancer. At primary diagnosis, accurate staging is an important in determinig the prognosis (69), but no imaging modality has as yet provided accurate staging information. The FIGO staging system is presented in Table 14.3 (36). In recurrent disease, early detection and detection of peritoneal carcinomatosis are important for appropriate selection of patients for second-line salvage therapy. Similar to testicular

**Table 14.3.** Staging of ovarian cancer.

| Stage | Description |
|---|---|
| I | Tumor confined to ovaries |
| IA | Tumor limited to one ovary, with the capsule, no tumor on surface, no malignant cells in ascites or peritoneal washings |
| IB | Tumor limited to both ovaries, but otherwise as above |
| IC | Tumor limited to one or both ovaries with any of the following capsule ruptured, tumor on surface, positive malignant cells in ascites or peritoneal washings |
| II | Tumor involves one or both ovaries with pelvic extension |
| IIA | Extension/implants in uterus and/or tubes, no malignant cells in ascites or peritoneal washings |
| IIB | Extension to other pelvic organs, no malignant cells in ascites or peritoneal washings |
| IIC | Either IIA or IIB, with malignant cells in ascites or peritoneal washings |
| III | Tumor involves one or both ovaries with microscopically confirmed peritoneal metastases outside the pelvis and/or regional lymph node metastases |
| IIIA | Microscopic peritoneal metastases beyond the pelvis |
| IIIB | Macroscopic peritoneal metastases beyond the pelvis 2 cm or less in diameter |
| IIIC | Peritoneal metastasis beyond the pelvis more than 2 cm in diameter and/or regional lymph node metastases |
| IV | Distant metastases beyond the peritoneal cavity |

*Source:* Reprinted from FIGO Committee on Gynaecological Oncology: Benedet JL, Bender H, Jones H III, Ngan HYS, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. Int J Gynecol Obstet 2000;70:209–262. Copyright © 2000, with permission from International Federation of Gynecology and Obstetrics.

cancer, ovarian cancer does have a biochemical marker in CA-125, and this has been useful in the monitoring of patients after treatment. CA-125 levels can, however, be falsely elevated in a number of conditions, and in early-stage disease it is elevated in fewer than half the patients (70).

Ultrasound, CT, and MR imaging have all been used in the assessment of ovarian cancer, both for assessment of adnexal masses and for detection of recurrent disease. Ultrasound has been used in primary disease but lacks specificity (71). CT and MR are not accurate for defining small-volume primary disease. Even in recurrent tumor, the sensitivity of CT has been reported to be 40% to 93% (72–74) and, because of its low NPV (45%–50%) (75, 76), CT cannot replace second-look laparotomy. Much recent work had focused on FDG uptake in both primary and recurrent disease.

## Diagnosis and Tumor Staging

### *Imaging Procedures in Tumor Staging*

In the evaluation of primary disease, FDG-PET can identify tumor with high sensitivity and specificity (both, 90%). However, PET fails to detect small stage I cancers and tumors that are histologically borderline for malignancy (77, 78). False-positive FDG uptake may be seen in some benign lesions, including ovarian endometriosis and corpus luteal cysts (79). SUV evaluation of lesions has been performed and, although an SUV greater than 7.9 is a strong indicator of malignancy (79), it does not improve diagnostic accuracy, especially in the differentiation of benign from borderline tumors (77). These studies have all been performed at early imaging times, and it remains to be seen whether delayed scanning permits better differentiation of benign from malignant, as seen in other tumors (27, 28). $^{11}$C-Methionine was found to be less dependent on tumor type (80). Physiologic uptake was a limiting factor for staging, but there may be potential for imaging with this tracer, especially when combined with FDG.

PET, MRI, and ultrasound have been compared for the evaluation of adnexal masses in several studies (78, 81, 82) as well as MR versus PET after identification of a mass on ultrasound (83). Generally, ultrasound was more sensitive than PET or MR but less specific (77, 80). Grab et al. (78) concluded that the best specificity without loss of sensitivity was obtained when all three were combined. However, because negative PET and MRI findings did not exclude stage I or borderline disease, ultrasound was the most appropriate screening tool in the diagnosis of ovarian cancer. Furthermore, it was concluded that any mass that was suspected of being malignant on ultrasound evaluation required surgical evaluation.

Adding an FDG-PET study to the preoperative assessment of patients at diagnosis improves the accuracy of staging. Yoshida et al. (84) found that in 15 patients CT agreed with pathology in 53% whereas CT and FDG-PET agreed in 87%.

## Tumor Recurrence

### *Imaging Procedures in Tumor Recurrence*

FDG-PET may be more useful in recurrent disease and restaging than in primary ovarian cancer. Many small studies have combined groups with suspected recurrence and unsuspected recurrence and compared PET versus conventional imaging and tumor markers. The overall sensitivity and specificity of PET was in the range of 80% to 100% (85–89). PET did, however, miss lesions less than 1cm and microscopic metastatic disease (77). PET was most valuable when conventional imaging was negative or equivocal and tumor markers were raised, with a sensitivity ranging from 87% to 96% (85, 86) (Figure 14.5). The abnormalities on PET preceded those on conventional imaging where markers were raised by as much as 6 months, which reflects a similar situation as described by Hain et al. (22) in testicular cancer and Valk et al. (90) for raised CEA in colorectal cancer. PET may have an important role in monitoring these patients after initial treatment.

Integrated PET/CT imaging is becoming more available, and Makhija et al. (91) reported findings on eight patients, six with ovarian and two with fallopian tube tumors, after cytoreductive therapy. Five of the eight patients had recurrrent disease identified on PET/CT imaging whereas CT alone was negative. Bristow et al. (92) studied a larger group of 22 patients more than 6 months after initial therapy. All patients presented with rising CA-125 and negative or equivocal CT and underwent PET/CT imaging followed by surgery. They found that combined PET/CT imaging was valuable, with overall patient-based sensitivity, specificity, and accuracy of 83%, 75%, and 82%, respectively, and lesion-based sensitivity, specificity, and accuracy of 60%, 95%, and 72%, respectively. Although promising, as suggested by Pannu et al. (93) following their study, a larger trial is necessary to judge the impact of PET/CT on clinical practice.

The treatment of ovarian cancer is limited by the inability to diagnose early peritoneal tumor spread. Many patients undergo second-look laparotomy, which is not without morbidity, because imaging is not sufficiently sensitive for detection of peritoneal tumors. The appropriate use of salvage chemotherapy also depends on accurate assessment of disease extent. Anatomic imaging modalities have been poor at imaging peritoneal carcinomatosis. Results with PET for detection of peritoneal carcinomatosis have been conflicting. Rose et al. (94) found that PET had a sensitivity and specificty of 10% and 42%, respectively, suggesting little value. Later studies (95, 96) have been more favorable. Kim et al. (96) found that there

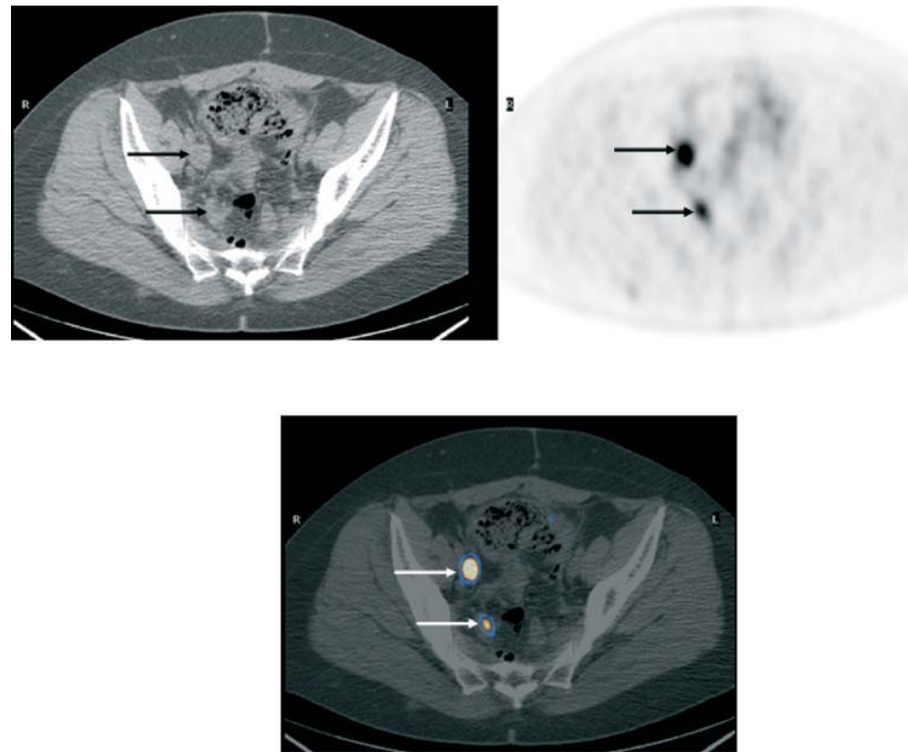

**Figure 14.5.** A 40-year-old woman was diagnosed with ovarian cancer 20 months earlier and was treated with radical surgery including hysterectomy, bilateral salpingo-oophorectomy, and anterior resection with end-colostomy. Postoperatively she had a right pelvic abscess that had resolved. She was found on routine follow-up to have a rising CA-125 tumor marker. Magnetic resonance imaging (MRI) was stable without evidence of recurrence. The transaxial images of CT (*top left*), PET (*top right*), and PET/CT fusion image (*lower*) showed FDG-avid lesions in the pelvis that were proven to be recurrent disease.

was no statistical signficance in the progression and disease-free interval between patients evaluated with PET or second-look laparotomy. These data suggest that PET imaging could replace second-look laporotomy for evaluation of patients with ovarian cancer, especially those at high risk. One early study (97) evaluated the cost-effectiveness of PET in managing patients with recurrent ovarian cancer. Using Monte Carlo simulation analysis, FDG-PET imaging was found to reduce unnecessary invasive surgical staging, leading to cost savings of $US 1,941–11,766 per patient.

In assessing metastatic disease, the use of half-body scans may also facilitate identification of extrapelvic suspected or unsuspected disease. Some authors have speculated on the use of PET to monitor response to chemotherapy (77), an application that has been demonstrated in other tumors, for example, breast and testicular cancers (32–34).

## Uterine Cancer

Cancer of the uterine body (endometrial) is the most common gynecologic cancer but, in contrast to cervical cancer, it occurs predominantely in postmenopausal women. Endometrial cancer metastasizes predominently by hematogenous spread and is associated with the tumor marker CA-125. Endometrial cancer has been shown to be FDG avid (Figure 14.6) but has been less studied with FDG-PET than cervical cancer. There are no published data on the use of PET in initial staging. Two studies (98, 99) that examined its use in recurrent disease found that PET altered management in 30% to 35% of patients, often by detecting clinically and radiologically unsuspected extrapelvic metastases. Saga et al. (99) compared the performance of PET, CT/MRI, and tumor markers in the follow-up of postoperative patients with endometrial cancer. They reported a sensitivity, specificity, and accuracy of 100%, 88%, and 93% for PET, 85%, 86%, and 85% for CT/MRI, and 100%, 71%, and 83% for tumor markers.

Endometrial cancer has been imaged with $^{11}$C-methionine with success. The physiologic accumulation of methionine in the pelvis provided some confusion and therefore correlative imaging would always be required (100). The use of FDG-PET for diagnosing uterine sarcoma has been reported (101). Given the avidity of FDG in soft tissue sarcoma (27), this result is not surprising.

## Vulval Cancer

Primary vulvar cancer is less common than the other gynecologic tumors. It commonly spreads via the groin lymph nodes, and their status is important for treatment decisions and prognosis. There is one study evaluating FDG-PET imaging for staging of vulvar cancer. All the primaries were FDG avid, and PET was sensitive for detection of extranodal metastases but relatively insensitive for detection of inguinal lymph node involvement (102). This limitation is related to the inabilty of PET imaging to

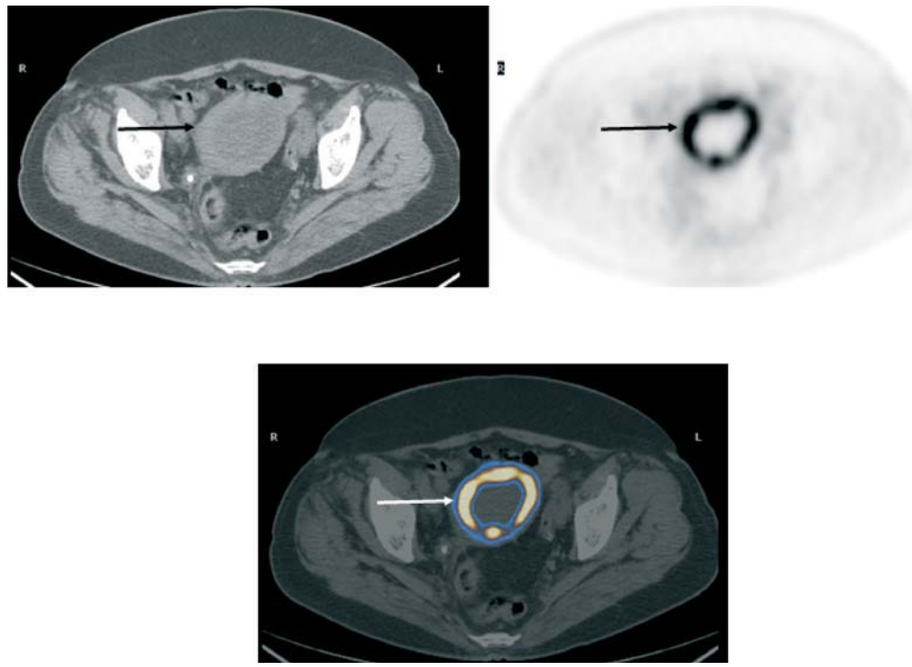

**Figure 14-6.** A 61-year-old women with stage IV endometrial cancer had completed chemotherapy and radiotherapy and was being considered for surgery. PET/CT imaging was performed to exclude metastatic disease. There was no evidence of disease outside the uterus. The transaxial images of CT (*top left*), PET (*top right*), and PET/CT fusion image (*lower*) showed persistent FDG uptake in the primary endometrial tumor indicating residual tumor.

detect microscopic metastases, as reported in studies comparing sentinel lymph node biopsy and PET in patients with melanoma and head and neck cancer (103, 104).

## Conclusions

In testicular cancer, PET is particularly useful for detection of viable tumor in posttreatment residual masses and for localization of marker-positive relapse. In both testicular and gynecologic cancer, PET can also be used to identify primary tumors and metastatic disease, and it can be used in surveillance for tumor recurrence. Investigations regarding the role of PET in these tumors have been increasing, but larger studies are needed to define the role of PET in the staging of cancer of the testis and ovary and in the evaluation of cancer of the cervix.

The role of FDG-PET is likely to be extended with the use of integrated PET/CT to assist in localizing disease with a view to guide biopsy. Further assessment of its role in determining and predicting response to treatment may have direct effects and benefits for individual patient management.

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