Chapter 8

Cancers of the Male and Female Reproductive Systems

INTRODUCTION

In contrast to many other tumor groups, the role of FDG-PET and PET/CT in gynecological and testicular malignancies is much less clearly defined. There is, however, reliable evidence that FDG-PET does have a useful role in the management of these cancers and, with the introduction of PET/CT, this is likely to advance. FDG-PET experience in gynecological malignancies has, to date, been largely confined to ovarian and cervical carcinoma.

OVARIAN CANCER

Ovarian cancer is associated with late presentation and poor prognosis. At present, the role of FDG-PET has largely been in assessment for recurrent disease and, although the overall numbers reported in the literature are relatively small, the results support the use of FDG-PET. With PET/CT, the investigation is likely to be even more successful, particularly in reducing the number of false-positive reports.

Staging of Disease

There is debate as to the role of PET/CT in initial staging. With surgery considered key in the role of gaining control of tumor burden and the majority of patients receiving adjuvant chemotherapy, PET/CT is not commonly used in preoperative staging. There are currently multicenter trials assessing potential screening modalities for ovarian cancer with view to early detection. If screening for ovarian cancer were to become available, one would anticipate PET/CT becoming an essential tool in patient staging and in directing surgery in earlier, small volume disease. Conventional imaging modalities do not reliably identify small volume disease.

Restaging of Disease

"Second-look" exploratory surgery was originally used in assessment for recurrence, but after studies failed to show any survival benefit, many clinicians have adopted a 'wait-and-see' basis, combined with CT, MRI, U/S and the use of tumor markers—notably Ca125.

Each of these modalities has significant shortcomings in determining disease status. In data reporting the sensitivity and specificity of CT, MRI and U/S in three common sites of metastatic disease, peritoneum, lymph nodes and the liver, none of the three modalities showed sensitivities above 50% in nodal disease, with only ultrasound reporting a sensitivity of >50% in identification of liver lesions. Both CT and MRI identified peritoneal disease with a high degree of sensitivity. Lesions smaller than 2 cm were poorly identified by all modalities. Similarly, while an elevated Ca125 is associated with recurrence in approximately 80% of patients, in up to 33% of patients, recurrent disease is associated with normal Ca125 levels.

The current primary indication for FDG-PET/CT in ovarian cancer is where there is suspicion of recurrent disease, either clinically or, more frequently, where Ca125 is elevated and/or rising but conventional imaging has been negative.

Assessment of Treatment Response

As with the other tumor groups, response to therapy is likely to be an emerging indication, as the number of second-line chemotherapy drugs increases. This is not currently standard practice with many fundamentals (e.g., timing of scans and prognostic benefit have not yet established).

Top Tip

PET/CT enhances detection rates when used as an adjunct to conventional imaging modalities.
Key indication is when elevated/rising CA125 levels with normal CT/MRI.

Issues with Scan Interpretation

Ovarian uptake of FDG is not always pathological. It is seen in relation to ovulatory activity, so a relevant history should always be obtained. Another issue is the limitations in identifying local and early disease.

THE UTERINE CARCINOMAS

In contrast to ovarian cancer, the uterine carcinomas (i.e., endometrium and cervix) tend to present earlier and have much better survival rates. Although studies have shown that FDG does accumulate in endometrial cancers, PET/CT is not currently routinely used in management of these tumors. There is growing evidence that FDG-PET and PET/CT does contribute to patient management in cervical cancers.

CARCINOMA OF THE CERVIX

Both CT and MR are used to stage carcinoma of the cervix. The limitation of this structural staging is often, as is the case for all tumors, the arbitrary 1 cm cut off for differentiation of malignant from benign disease. It is now accepted that small nodes can harbor disease and large nodes may only be reactive. As lymph node staging is fundamental in the management of cervical cancer both in terms of survival and treatment, accurate assessment of nodal involvement is required.

Staging

PET performs particularly well in detection of distant metastases and paraaortic disease, at least as well as CT and MR in pelvic nodal disease, and less well in local disease. This is attributed to the high levels of excreted activity in the bladder. In early disease, FDG-PET outperformed MRI.

Nodal metastases are common and seen in almost 20% of patients with Stage Ib disease (outside cervix, upper two-thirds of the vagina may be involved, but not as far as the pelvic wall) and more than 60% of patients with stage III disease (disease to the pelvic wall and/or lower one-third of the vagina). Given the decreased survival rates associated with paraaortic nodal disease, PET/CT is being increasingly used to assess disease in these nodes.

Case 1

This patient had a diagnosis of stage IIa cancer of the cervix, and it was assumed that she had been successfully treated with surgical resection and pelvic lymphadenectomy. A follow up PET/CT scan was performed to assess possible small paraaortic nodal involvement demonstrated on CT. The nodes were not significantly enlarged by conventional size criteria.

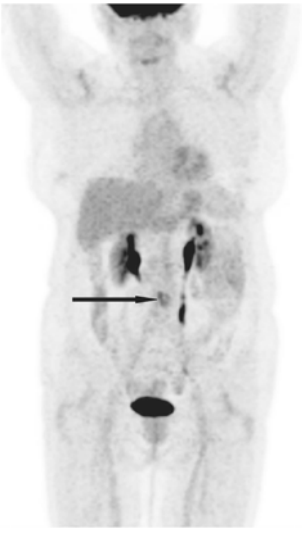

FIGURE 8.1. Low-grade midline FDG uptake.

Figure 8.1 is the whole body MIP that reveals a low-grade focus of FDG uptake in the midline (arrow). Figure 8.2 is an axial view through this low-grade uptake, and it reveals a mesenteric metastatic deposit (arrow). No abnormal nodal uptake was demonstrated within any paraaortic nodes. The referring clinician and surgeon were not convinced of this finding and it was agreed to reimage the patient in six months. A follow-up PET/CT (Figure 8.3) was carried out six months later. It revealed significant disease progression in the interval since the original PET scan. Notice the increased intensity of FDG uptake in the original lesion (arrow) during the six-month interval.

Restaging

FDG-PET has been shown to be superior over conventional imaging in detection of recurrent disease. This is important as further treatment options may be available for those who have relapsed and improved survival rates using FDG-PET for restaging have been reported. PET-CT, particularly where conventional imaging is normal, is likely to be even more beneficial than PET only.

Case 2

This case is a patient with a stage Ib cervical cancer treated with radiotherapy and a PET/CT was carried out to assess response to

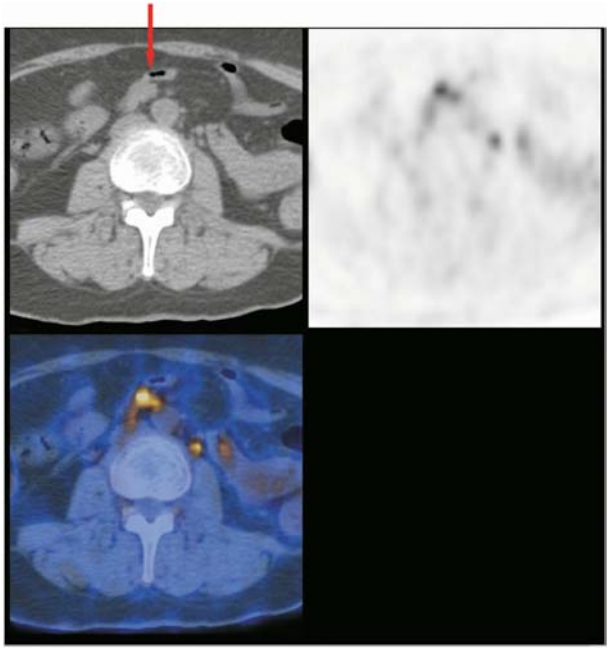

FIGURE 8.2. Axial image demonstrating a focal mesenteric met.

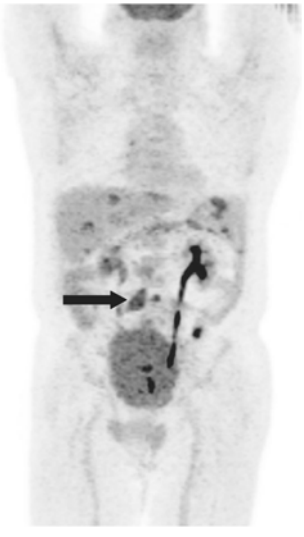

FIGURE 8.3. Multiple sites of peritoneal and hepatic disease.

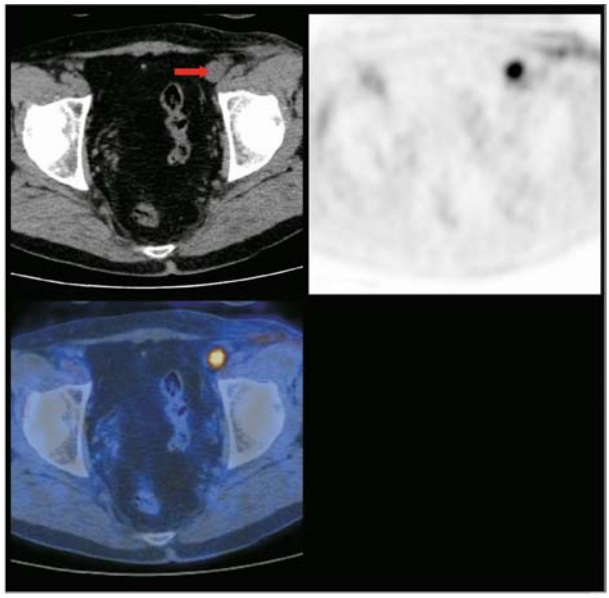

FIGURE 8.4. Left external iliac FDG positive node.

therapy. Figure 8.4 reveals an abnormal left external iliac node with focal FDG uptake. The node was removed and revealed metastatic cells. The patient received further consolidation radiotherapy and underwent pelvic lymphadenectomy.

Treatment Planning

In addition to patients with advanced (Stage III, IV) disease where radiotherapy is the primary treatment, a significant number of patients receive postoperative radiotherapy to the pelvis. Given the paramount importance of determining paraaortic disease status and the superiority of FDG-PET over CT and MRI in assessment of paraaortic disease, PET-CT is being increasingly used to guide therapy planning. If the study is positive, radiotherapy fields will be modified.

Response to Treatment

At present there are no guidelines as to the role of PET in assessing response to treatment.

Top Tip
Presence/absence of paraaortic disease has high prognostic significance.
PET/CT "best" imaging modality for paraaortic disease.
PET/CT outperforms conventional imaging for distant disease.

Issues with Scan Interpretation

The issues with interpreting scans is that the differentiation of physiological ureteric activity from paraaortic nodal disease can be difficult in some cases. In additions, there are limitations in the detection of local disease because of high activity in bladder.

TESTICULAR NEOPLASMS

Most testicular neoplasms (95%) are germ cell tumors. These are subdivided into seminoma and nonseminomatous germ cell tumors (NSGCT). The NSCGCT group includes teratomas of varying degrees of differentiation, tumors containing mixed cell lines of teratomas, and mixed tumors with both teratoma and seminoma components. The division reflects the different treatments and outcomes. The other 5% of testicular neoplasia includes lymphoma, and metastases. This section is confined to germ cell tumors.

Initial management for all germ cell testicular tumors is surgical, with radical inguinal orchidectomy the procedure of choice. The key prognostic markers are histological subtype, tumor extension to the spermatic cord, invasion of local vessels and the serum level of the tumor markers α-fetoprotein (AFP) and human chorionic gonadotrophin-β (HCG).

Top Tip
Prognostic indicators include:
Histology
Tumor extension
AFP level
HCG level

Pure seminomas may have a modest elevation of HCG, but AFP levels should be normal. Elevated AFP is seen in about 70% of teratomas, with elevated HCG in about 50% of the cases. These markers reflect different cell lines and accordingly do not necessarily respond in the same way to chemotherapy.

Staging of Disease

With advances in treatment, a growing number of patients will be cured and great emphasis is placed on accurate initial staging. Sensitive assays of tumor markers contribute greatly to staging, as does imaging such as CT and MRI. Both PET and PET/CT provide an increase in conventional diagnostic accuracy. FDG-PET has positive and negative predictive values superior to those reported for conventional imaging in staging, including early disease.

FDG-PET however is not considered a reliable tool for disease evaluation in mature teratoma differentiated (MTD).

Restaging of Disease

PET/CT has positive and negative predictive values superior to those reported for conventional imaging in restaging. This is particularly important in those patients for whom there are no available tumor markers to provide an early and sensitive indication of relapse. PET and now PET/CT also has a key role when tumor markers are rising and conventional imaging has been unrewarding.

Case 3

This case is a patient who had a PET/CT scan to restage disease extent following a rise in tumor markers. He had previously undergone an orchidectomy for a testicular seminoma.

The MIP view (Figure 8.5) shows a focus of uptake in the left hemipelvis which could represent activity within the distal left ureter. The axial view through this focus demonstrate small volume recurrent disease in a small left common iliac node (Figure 8.6).

Treatment Planning

Early stage seminomas have high cure rates associated with surgery and radiotherapy, with more advanced disease showing good response rates to chemotherapy. There is debate about the role of radiotherapy in early disease and, as a significant number of pure seminomas are not associated with abnormal tumor markers, PET/CT may have a role in treatment planning where

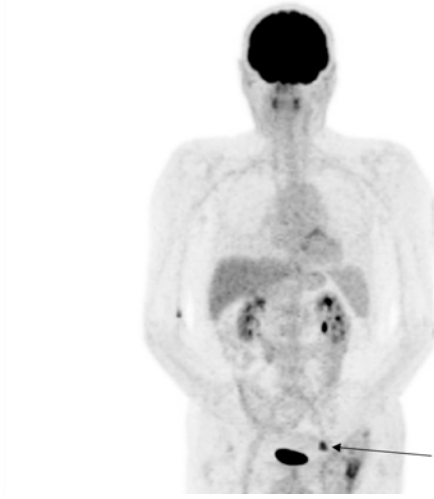

FIGURE 8.5. MIP image demonstrating a left sided pelvic focus of uptake.

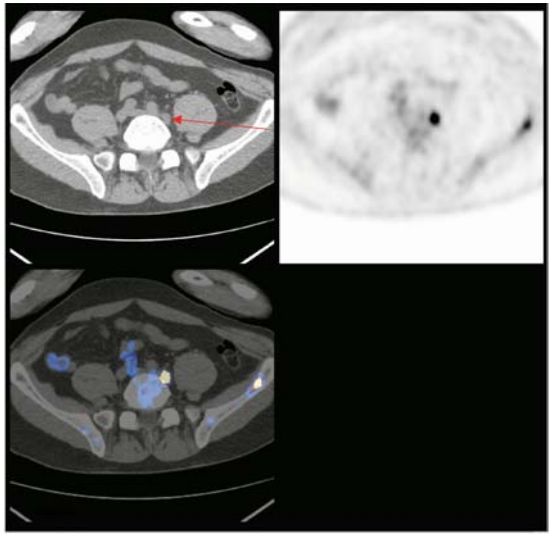

FIGURE 8.6. Axial image demonstrating uptake in a left common iliac node representing recurrent disease.

more conservative treatment of early stage disease (i.e., surgery only is being offered). In NSGCT, chemotherapy is the mainstay of treatment and as such, FDG-PET has not played a significant role in treatment planning.

Assessment of Treatment Response

Structural imaging does not characterize the nature of residual masses or residual lymphadenopathy. FDG-PET and PET/CT allows assessment of metabolic activity still regarded as "abnormal" on conventional imaging.

Top Tip
High positive predictive value for recurrent disease
Useful with rising tumor markers and normal CT and/or MRI
Useful in the assessment of residual lymphadenopathy

Issues with Scan Interpretation

The issues in interpreting scans are that FDG-PET is *not* reliable in MTD and there is difficulty in differentiating physiological ureteric activity from paraaortic nodal disease.

STAGING OF TESTICULAR CANCER

TABLE 8.1. TNM Classification and Stage Grouping

DEFINITION OF TNM

Primary Tumor (T)

The extent of primary tumor is usually classified after radical orchiectomy, and for this reason, a *pathologic* stage is assigned.

*pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histologicscar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
PT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
PT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion

TABLE 8.1. *Continued*

Note: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional nodal or pulmonary metastasis
M1b	Distant metastasis other than to non-regional lymph nodes and lungs

Serum Tumor Markers (S)

SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × N* **AND** hCG (mIu/ml) < 5000 **AND** AFP (ng/ml) < 1000
S2	LDH 1.5–10 × N **OR** hCG (mIu/ml) 5000–50,000 **OR** AFP (ng/ml) 1000–10,000

TABLE 8.1. *Continued*

S3	LDH > 10 × N **OR** hCG (mIu/ml) > 50,000 **OR** AFP (ng/ml) > 10,000

*N indicates the upper limit of normal for the LDH assay.

STAGE GROUPING

Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1–3
Stage II	Any pT/Tx	N1–3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
Stage IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
Stage IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
Stage IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-New York, www.springeronline.com.

TABLE 8.2. TNM Classification and Stage Grouping

DEFINITION OF TNM

The definitions of the T categories correspond to the stages accepted by FIGO. FIGO stages are further subdivided by histologic grade of tumor—for example, Stage IC G2. Both systems are included for comparison.

Primary Tumor (T) (Surgical-Pathologic findings)

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor

TABLE 8.2. *Continued*

Tis	0	Carcinoma *in situ*
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium
T1b	IB	Tumor invades less than one-half of the myometrium
T1c	IC	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades cervix but does not extend beyond uterus
T2a	IIA	Tumor limited to the glandular epithelium of the endocervix. There is no evidence of connective tissue stromal invasion
T2b	IIB	Invasion of the stromal connective tissue of the cervix
T3	III	Local and/or regional spread as defined below
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor asT4)

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis pelvic and/or para-aortic nodes

Distant Metastasis (M)

MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes; excludes metastasis to vaginal pelvic serosa, or adnexa)

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0

TABLE 8.2. *Continued*

Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IV	Any T	Any N	M1

Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-New York, www.springeronline.com.