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Imaging in the Diagnosis and Treatment of Endometrial Cancer

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Abstract

Ultrasound, sonohysterography (SHG), magnetic resonance imaging, computed tomography (CT), and 18-2-fluorodeoxy-2-deoxy-D-glucose fusion positron emission tomography CT (FDG-PET CT) are tools available for diagnosis, treatment planning, and detection of recurrences post-primary therapy of EC. Transvaginal ultrasound has an established role in screening for cancer in women presenting with postmenopausal bleeding. Sonohysterography allows for diagnosis of focal endocavitary lesions and hysteroscopy planning. For treatment planning, magnetic resonance imaging (MRI) provides the best definition of tumor extent in the central soft tissue pelvis whereas FDG-PET CT is the most accurate modality for detecting lymphadenopathy and distant metastases. Post-primary therapy, CT and FDG-PET CT are both useful in evaluating recurrences with the latter being more sensitive.

Keywords

Female pelvic imaging • Gynecologic cancer imaging • Lymph node imaging • Cancer staging • Pelvic ultrasound

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Introduction

Imaging is employed in the many steps during the diagnosis and treatment of endometrial cancer. Evaluation of abnormal uterine bleeding for tumor detection, defining tumor extent following diagnosis, and post-treatment surveillance, all require imaging. This chapter provides an overview of various imaging modalities used in the

evaluation of endometrial cancer highlighting the strengths and limitations of the various applications.

Ultrasound

Ultrasound has long been known as an effective tool in the evaluation of women with postmenopausal bleeding (PMB) [1–4]. Although transabdominal ultrasound can be used to detect endometrial pathology, limited spatial resolution, patient body habitus, uterine retroflexion, and coexisting conditions such as leiomyomas can make transabdominal endometrial evaluation challenging. The improved resolution afforded by the high-frequency transvaginal ultrasound probe has led to the establishment of transvaginal ultrasound (TVUS) as the initial noninvasive study of choice in evaluating women presenting with postmenopausal bleeding. TVUS demonstrates better image quality than transabdominal ultrasound in 72 % of patients [5] and performs significantly better in evaluating the endometrium in the retroverted uterus [6].

Cancer Detection

In a postmenopausal patient with abnormal vaginal bleeding, the primary role of TVUS is to identify women who need further evaluation for cancer in the form of endometrial biopsy. Endometrial appearance on TVUS is evaluated by thickness and morphology. Normal postmenopausal endometrium is $\leq$5 mm and is homogenous in thickness and echotexture (Fig. 1a). As TVUS demonstrates very high sensitivity and negative predictive value [7] for cancer comparable to other more invasive techniques [8–10] (Table 1), it identifies women who are highly unlikely to have endometrial cancer. Thus, a normal TVUS study can be used to triage patients to diagnostic algorithms that are effective in detecting benign focal causes of PMB, e.g., endometrial polyps or submucosal fibroids.

Endometrial Thickness

Endometrial thickness measurement is an integral part of a TVUS endometrial evaluation. Numerous studies have attempted to establish a size threshold below which endometrial pathology can be excluded with measurements ranging

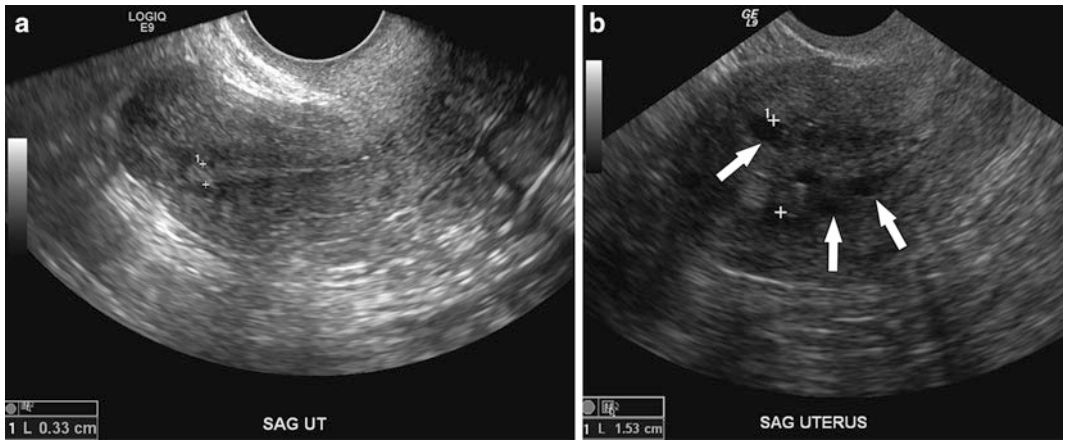

Fig. 1 Transvaginal ultrasound of normal postmenopausal endometrium. Endometrial thicknesses of a patient not on hormone replacement therapy (**a**) and on tamoxifen therapy (**b**) are measured on sagittal images of the uterus. Note that the patient on tamoxifen demonstrates subendometrial cysts (*arrows*) and apparent thickening of the endometrium

Table 1 Diagnostic modalities for endometrial cancer detection

Modality	Sensitivity (%)	Specificity (%)	PPV[a] (%)	NPV[b] (%)
TVUS not on hormone replacement therapy [7]	96	99	57	99
TVUS on hormone replacement therapy [7]	96	77	31	99
Nonfocal biopsy [8]	87	99	82	99
Hysteroscopy [9]	86	99	72	99
Sonohysterography [10]	89	46	16	97

[a]Positive predictive value
[b]Negative predictive value

from 4 to 7 mm [6, 7, 11]. A large meta-analysis including 35 studies with 5,892 women demonstrated that, using a 5 mm threshold to define endometrial thickening, 96 % of women with endometrial cancer had an abnormal TVUS result whereas 92 % of women with any endometrial disease such as cancer, polyp, or hyperplasia had an abnormal TVUS. This threshold of 5 mm is particularly accurate in excluding endometrial disease in symptomatic women on tamoxifen (Table 1). In postmenopausal women with vaginal bleeding, a 10 % pretest probability of endometrial cancer was reduced to a 1 % posttest probability after a normal TVUS [7]. Thus, TVUS is a powerful tool for identifying patients with PMB who are highly unlikely to have endometrial pathology.

While a threshold of $\leq$5 mm endometrial thickness is highly sensitive for detecting endometrial cancer, it is not very specific. Seventy percent of women with postmenopausal bleeding and endometrial thickness >5 mm demonstrate benign pathology [12]. Multiple etiologies for PMB have been reported [13] (Table 2), some of which result in a thickened endometrium. Postmenopausal women on hormonal replacement therapy have a thickened endometrium at baseline as opposed to those who are not on hormone replacement. Patients on sequential hormonal therapy demonstrate greater endometrial thickness than in those on continuous hormonal replacement [14]. Patients on tamoxifen with cystic subendometrial atrophy can also demonstrate apparent abnormal thickening of the endometrium [15] (Fig. 1b).

It is important to note that normal endometrial thickness does not exclude endometrial cancer as a cause for postmenopausal bleeding. A study of women with PMB not on tamoxifen showed that half the patients with endometrial cancer had an endometrial thickness between 3 and 4 mm [12]. Thus, even in patients with normal endometrial thickness, persistent or recurrent bleeding should be further evaluated to definitively identify the cause of the symptoms.

Table 2 Common causes of postmenopausal bleeding [13]

Polyps	30 %
Submucosal fibroids	30 %
Endometrial atrophy	8 %
Hyperplasia	4–8 %
Endometrial carcinoma	10 %

Endometrial Morphology

In addition to endometrial thickness, TVUS assesses endometrial morphology. Endometrial morphology can be classified as either focal or diffuse. Diffuse endometrial thickening is often due to hyperplasia or carcinoma (Fig. 2a) and biopsy will usually be adequate to establish a histologic diagnosis. Focal thickening is usually due to "endometrial polyps", which could be benign or malignant (Fig. 2b), and hysteroscopic tissue sampling is often required to establish the diagnosis.

Morphologic features of the endometrium associated with malignancy have been described. They include heterogeneous echotexture, hyperechoic echotexture with irregular borders, and a heterogeneous intraluminal mass. Using these criteria, Weigel et al. concluded that a combined assessment of endometrial thickness and morphology improves detection of endometrial pathology on TVUS [16].

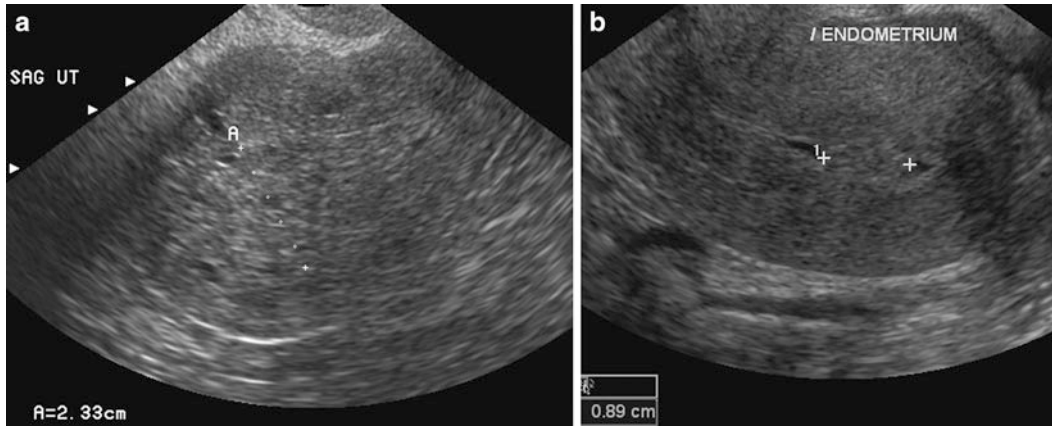

Fig. 2 Transvaginal ultrasound of abnormally thickened endometrium. Sagittal images of the uterus demonstrate diffuse (**a**) and focal (**b**) endometrial thickening (calipers) pathologically confirmed to be endometrial cancer and a benign endometrial polyp respectively

Color Doppler is used in conjunction with TVUS in the evaluation of women with PMB. Presence of Doppler signal within an endometrial lesion eliminates blood clot as a possible etiology. Color Doppler can also assess the pattern of vascularity of an endometrial mass. Malignant lesions are usually broad based with diffuse high level vascularity (Fig. 3a, b) whereas a single feeding vessel in a lesion of relatively low overall vascularity is associated with benign polyps on a stalk (Fig. 3c, d) [16].

As TVUS is used as a first step to triage patients with PMB for tissue sampling, criteria for an abnormal endometrium should be optimized to maximize sensitivity for cancer detection. Thus, all patients with PMB with abnormal endometrial thickness or morphology on TVUS should undergo histological sampling.

Cancer Staging

FIGO staging for endometrial cancer is based on surgery and pathology (Table 3) [17]. Imaging is frequently used for preoperative treatment planning and to estimate prognosis. The high resolution afforded by TVUS readily allows for assessment of the extent of tumor spread within the uterus. However, due to limitations in tissue penetration, neither transabdominal nor transvaginal ultrasound can accurately assess extrauterine spread or nodal involvement by tumor.

To assess the utility of TVUS for tumor staging, accuracies of TVUS in detecting deep myometrial invasion (>50 % myometrial thickness) and cervical extension have been studied [18–23]. In a series of 69 patients, Artner et al. reported high levels of accuracy in detecting deep myometrial invasion (99 %) and cervical extension (96 %) using TVUS [19], although in the latter, TVUS was noted to have missed 3/9 cases of cervical extension. In a study of 90 patients, Sawicki et al. reported slightly lower accuracies of 84 % for myometrial invasion and 86 % for cervical extension [22]. Studies comparing TVUS and magnetic resonance imaging (MRI) have not found comparable TVUS performance in tumor staging with reported accuracies of 68 % [21] and 69 % [20]. This wide range in reported accuracies, likely explained in part by variations in patient body habitus and operator expertise, results in TVUS being a modality whose reliability in tumor staging is difficult to assess.

The technical factors limiting TVUS performance as a staging tool are well understood. TVUS can both under- and overestimate the extent of myometrial tumor invasion. Overestimation can occur when coexisting myometrial

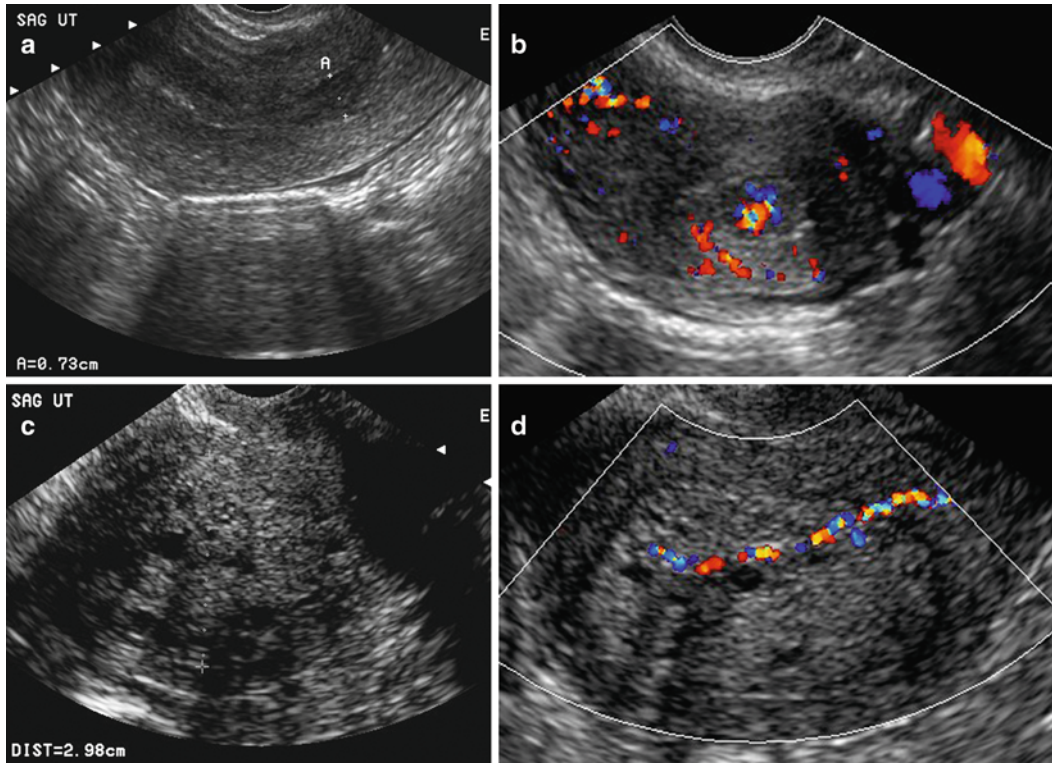

Fig. 3 Doppler ultrasound of abnormally thickened endometrium. Grey scale (**a** and **c**) and color Doppler (**b** and **d**) transvaginal ultrasound evaluation demonstrate a diffusely elevated vascularity of the thickened endometrium typical for cancer (**a** and **b**) and a single feeding vessel in an endometrium of overall low vascularity characteristic of a polyp (**c** and **d**)

Table 3 FIGO staging of endometrial cancer

Stage I			Tumor confined to the corpus uteri
	IA		No or less than half myometrial invasion
	IB		Invasion equal to or more than half of the myometrium
Stage II			Tumor invades the cervical stroma, but does not extend beyond the uterus
Stage III			Local and/or regional spread of the tumor
	IIIA		Tumor invades the serosa of the corpus uteri and/or adnexae
	IIIB		Vaginal and/or parametrial involvement
	IIIC		Metastases to pelvic and/or para-aortic lymph nodes
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV			Tumor invades bladder and/or bowel mucosa, and/or distant metastases
	IVA		Tumor invasion of bladder and/or bowel mucosa
	IVB		Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

processes, e.g., adenomyosis, leiomyomas, or endometrial cavity distension from tumor or hematometra, are present. Underestimation is usually seen in cases of microscopic invasion or lymphovascular invasion.

Intrauterine sonography involving transcervical insertion of a high-frequency microtip probe has also been used as a staging tool. Probe placement does not require cervical dilatation or anesthesia. Improved accuracies for depth of

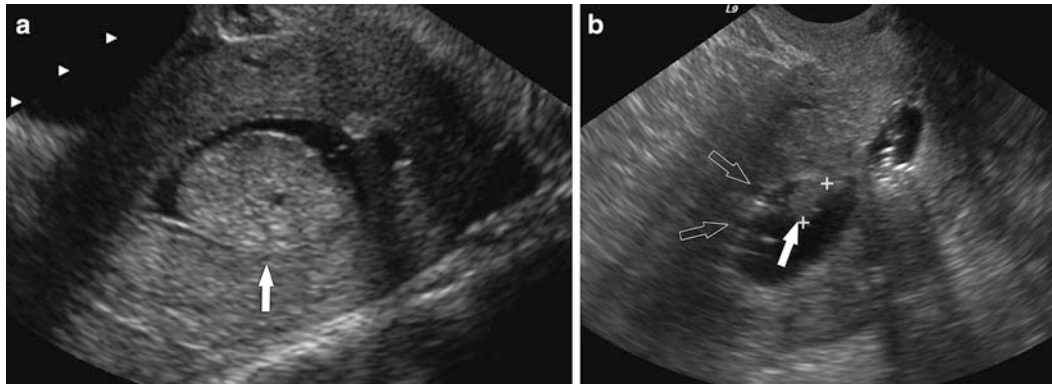

Fig. 4 Sonohysterography of abnormally thickened endometrium. Sagittal images of the uterus after intracavitary saline infusion delineate a polyp (**a**) with a narrow base of attachment (*arrow*) to the posterior fundal wall. Evaluation of the tamoxifen endometrium (**b**), same patient as in Fig. 1b demonstrates a polyp (*solid arrow*) originating from the anterior uterine body and the subendometrial location of the cysts (*clear arrows*) both accounting for the apparent thickening seen on transvaginal ultrasound

tumor invasion when compared to TVUS have been reported [23] in a single series of 48 patients.

Sonohysterography

Sonohysterography (SHG) is a minimally invasive procedure in which saline is instilled in the uterine cavity prior to TVUS through a catheter positioned in the cervical canal. The saline separates the two walls of the uterus facilitating sonographic evaluation of the endometrium. Endometrium suspicious for hypertrophy or malignancy demonstrates irregularities in thickness or echotexture or a broad-based poorly marginated endoluminal mass. Benign endometrium is characterized as either normal, i.e., homogeneous echotexture or uniform thickness, or demonstrating a polyp, i.e., a smoothly marginated pedunculated endoluminal mass (Fig. 4a).

SHG is recommended when TVUS cannot adequately assess the endometrium. In patients with non- or poor visualization of the endometrium with TVUS, usually due to fibroids or adenomyosis, SHG can delineate the endometrial cavity. It is also extremely useful in assessing patients with postmenopausal bleeding on tamoxifen, many of whom demonstrate apparent endometrial thickening on TVUS due to cystic subendometrial atrophy [24]. As SHG can discriminate between endometrial and subendometrial processes, an endometrial lesion, e.g., polyp or cancer, can be visualized separate from the subendometrial tamoxifen-related changes after the instillation of saline (Fig. 4b).

SHG accurately identifies endometrial pathology with reported sensitivities of 89–98 % and specificities of 46–88 % (Table 1) [10, 25]. As with TVUS, SHG demonstrates higher sensitivity than specificity, thereby a highly reliable negative predictive value. While SHG is more sensitive than TVUS in detecting focal endometrial pathology, there is no data to suggest that SHG is more sensitive in cancer detection when the endometrium has been adequately visualized with TVUS. Thus, based on the current evidence, the primary role of SHG in evaluating patients with postmenopausal bleeding should be to identify etiologies other than cancer (Table 2).

SHG is recommended in patients with abnormal endometrial thickness on TVUS or with persistent PMB only after a nonfocal endometrial biopsy has proven negative for cancer [26]. As SHG demonstrates a sensitivity for endometrial pathology comparable to that reported for hysteroscopy (Table 1), and it represents a less invasive alternative in evaluating patients with a negative biopsy.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is primarily used for defining tumor extent for treatment planning and estimation of prognosis. The inherent soft tissue resolution and multiplanar imaging capability of MRI make this technique an effective modality for assessing disease extent within the pelvis. MRI plays only a limited role in cancer detection to evaluate patients with cervical or vaginal stenosis where adequate assessment of the endometrium is precluded with TVUS or biopsy.

Technique

MRI protocols for imaging patients with endometrial cancer include triplane T2-weighted fast spin echoimages of the pelvis, axial sagittal dynamic gadolinium-enhanced fat-saturated T1-weighted images, and triplane post-contrast fat-saturated T1-weighted images. For purposes of tumor staging, gadolinium should be routinely administered as it is necessary to accurately define the extent of tumor spread in the uterus and adjacent organs [27]. Diffusion-weighted imaging is increasingly being adopted as it aids in delineating the primary tumor and in detecting lymphadenopathy [28, 29]. Finally, as uterine cancer may present with para-aortic adenopathy in the absence of pelvic adenopathy, one sequence of a staging exam, typically an axial T1-weighted or a single shot fast spin echo coronal T2-weighted, should be dedicated to evaluate retroperitoneal adenopathy and to assess hydronephrosis. The study is performed with a phased array body coil in either a 1.5 T or 3.0 T magnet. To decrease artifact from bowel motion, patients may be asked to fast for 4–6 hours prior to imaging and glucagon may be administered.

Cancer Detection

The normal endometrium is isointense on T1-weighted images, very hyperintense on T2-weighted images, and enhances more slowly than the myometrium after dynamic gadolinium administration. Endometrial pathology, including cancer, appears as intermediate signal (between bright endometrium and dark myometrium) on T2-weighted images (Fig. 5a) and, after dynamic gadolinium administration, enhances faster than normal endometrium but slower than the

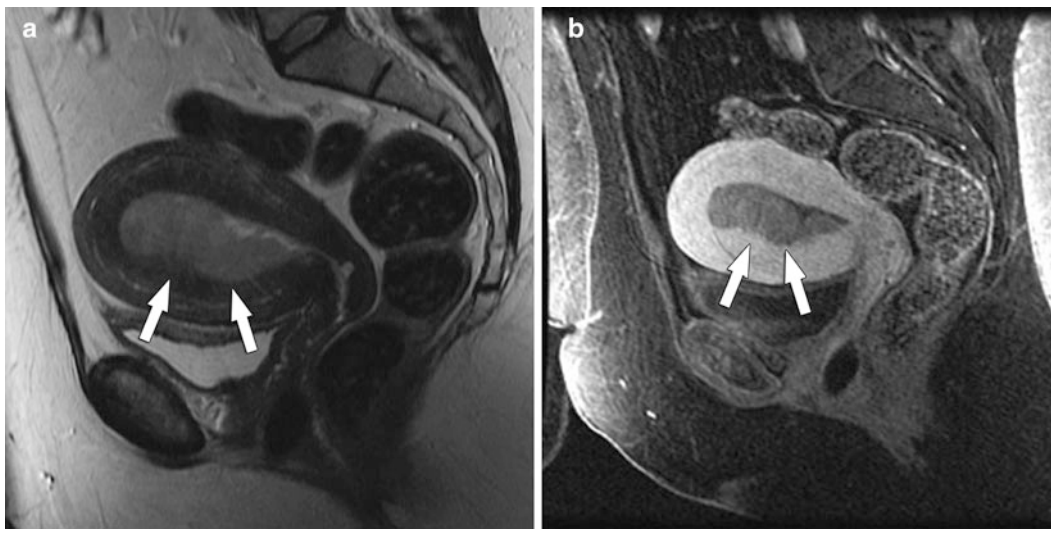

Fig. 5 Magnetic resonance imaging (MRI) of endometrial cancer. Sagittal FSE (fast spin echo) T2-weighted (**a**) and post-gadolinium T1-weighted fat-saturated (**b**) images of the uterus demonstrate a mass (*arrows*) extending throughout the endometrial cavity, which is of intermediate grey T2 signal and enhances with gadolinium more avidly than normal endometrium. Note that the cancer does not enhance as avidly as normal myometrium

hypervascular myometrium (Fig. 5b). Blood clots can be distinguished from endometrial pathology as they often demonstrate portions that are T1 hyperintense and minimal or no enhancement with gadolinium. However, in the absence of tumor extension outside the endometrial cavity, MRI cannot discriminate cancer from other endometrial pathologies such as hyperplasia or polyps [30]. Thus, endometrial lesions identified on MRI require histology for definitive diagnosis.

Cancer Staging

The initial step in endometrial cancer therapy is usually hysterectomy and bilateral salpingo-oophorectomy for those patients with presumed stages I–III disease. Surgery can also include resection of the pelvic and para-aortic lymph nodes to assess for metastases, which is only performed in patients with a primary tumor demonstrating high-risk features for lymph. These are high-grade histology (grade 3 endometrioid, serous papillary or clear cell adenocarcinomas), tumor size >2 cm, deep (>50 % thickness) myometrial invasion, or cervical stromal invasion [31]. The latter three features are best assessed preoperatively with MRI. Meta-analysis has demonstrated that contrast-enhanced MRI performs better than noncontrast MRI, CT, or US in detecting myometrial invasion [27]. In a multicenter audit of 775 cases over a 12-month period in the UK, MRI demonstrated sensitivity and specificity of 77 % and 88 %, respectively, in detecting deep myometrial invasion; 42 % and 97 %, respectively, in detecting cervical stromal invasion; and 64 % and 96 % in diagnosing pelvic lymphadenopathy [32].

As MRI is the most effective imaging modality to define the extent of tumor, it is used to evaluate endometrial cancer patients for lymphadenectomy, radical hysterectomy, and medical hormonal therapy for fertility preservation. In patients with comorbidities that preclude surgery, MRI is used to both stage and plan fields for primary radiotherapy.

Myometrial Invasion

Assessment of myometrial invasion with MRI requires evaluation of both T2-weighted and post-gadolinium administration images. Any disruption or irregularity of the myometrial junctional zone by an isointense mass on T2-weighted images is diagnostic of myometrial invasion. An intact junctional zone with a sharp tumor-myometrium interface suggests a non-invasive malignancy. MRI detects deep myometrial invasion with reported accuracies of 74–91 % (Fig. 6) [33, 34]. When compared side-by-side to TVUS, MRI demonstrates similar

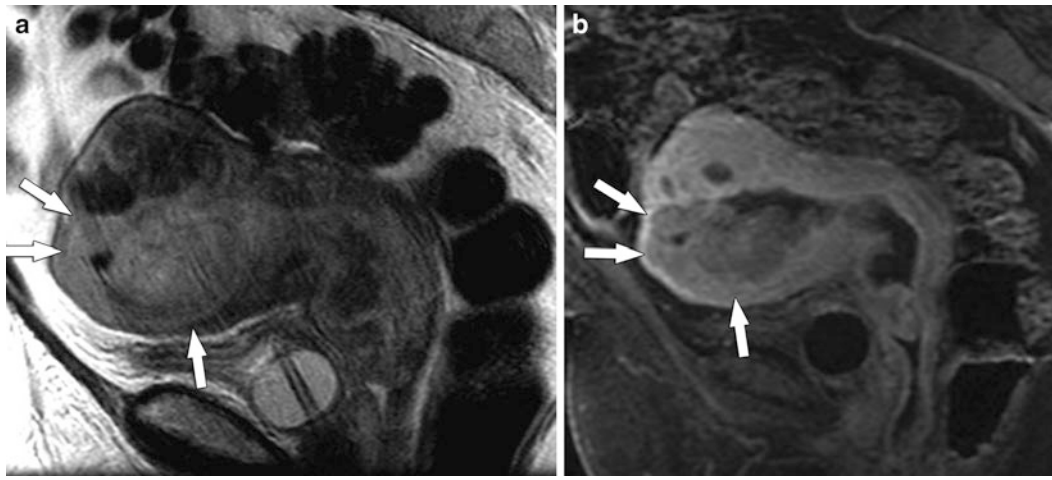

Fig. 6 MRI evaluation of the depth of myometrial invasion. Sagittal FSE T2-weighted (**a**) and post-gadolinium T1-weighted fat-saturated (**b**) images of the uterus demonstrate a cancer with invasion of >50 % myometrial depth (*arrows*). Imaging findings were confirmed by pathologic examination

accuracies with noncontrast imaging [33] but higher accuracies when gadolinium is administered [35].

Typically, errors occur in over- rather than underestimating the extent of myometrial tumor invasion [36]. Coexisting myometrial conditions, such as leiomyomas or thinned myometrium due to atrophy or endometrial canal distention, can decrease the accuracy of MRI in assessing tumor invasion. In patients with adenomyosis who demonstrate a thickened junctional zone, an indistinct junctional zone on T2-weighted images corresponds to myometrial invasion only in 22 % of cases. With gadolinium administration, accuracy is reported to increase considerably to 92 % [37].

Cervical Invasion

Tumor extending into the cervix appears as widening of the internal os and the endocervical canal. Disruption of the cervical stroma is seen as loss of the "fibrous" black line around the cervix seen on T2-weighted images (Fig. 7). While accuracies using MRI are reported to be as high as 92 % [38], sensitivity may be lower as microscopic cervical invasion can be missed.

Extrauterine Spread

Disruption or irregularity of the outer layer of the myometrium indicates extrauterine spread. There may be direct extension of the tumor to serosa or adnexa (Stage IIIA) (Fig. 8a). The ovaries can also be involved by discrete metastases. While gross tumor extension into the vaginal tissue (Stage IIIB) can be seen on gadolinium-enhanced images, mucosal vaginal involvement is more readily established by direct visualization and biopsy.

Extension into the bladder or rectum is best determined on gadolinium-enhanced sagittal images and can be corroborated on axial imaging (Fig. 8b). Loss of the normal fat plane between the tumor and the bladder or rectum indicates invasion (Stage IVA). While this finding signifies tumor invasion of the bladder or rectal serosa, it does not necessary imply mucosal involvement, which is more accurately assessed by endoscopic visualization and biopsy.

Lymph Nodes

As a cross-sectional imaging modality, MRI enables detection of pelvic and retroperitoneal lymphadenopathy (Stage IIIC). Typically endometrial cancer spreads to regional pelvic nodes,

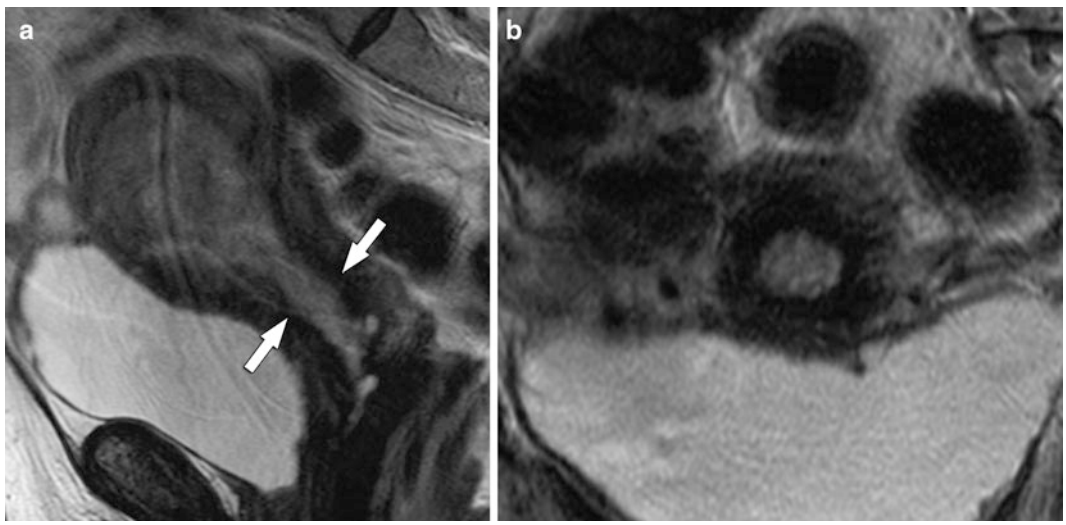

Fig. 7 MRI evaluation of cervical invasion. Sagittal FSE T2-weighted image of the uterus (**a**) demonstrates a mass involving the endometrial cavity and the endocervical canal (*arrows*). A long-axis oblique FSE T2-weighted image of the cervix (**b**) reveals no evidence of gross stromal or parametrial invasion by tumor. Imaging findings were confirmed by pathologic examination

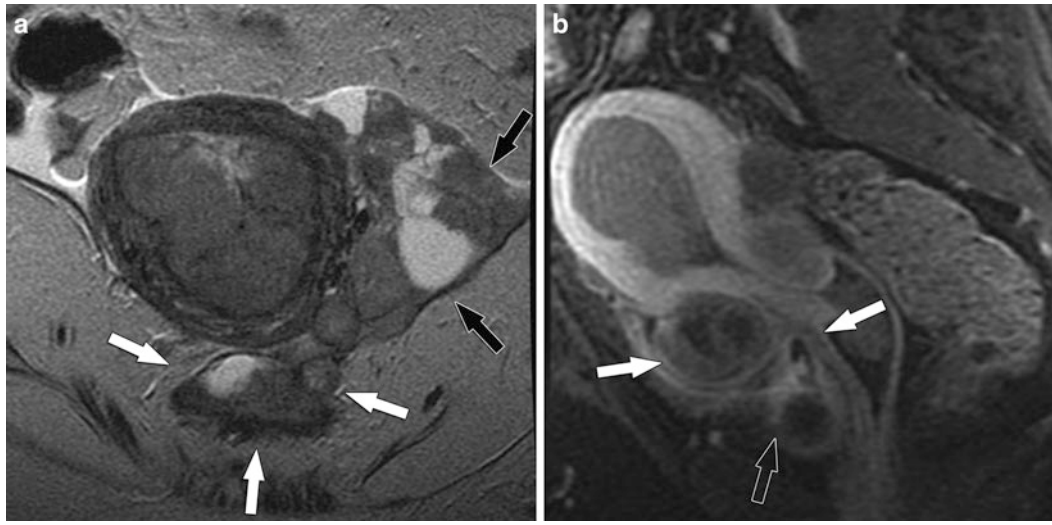

Fig. 8 MRI evaluation of extrauterine spread. Axial FSE T2-weighted image of the uterus (**a**) shows cancer involving the endometrial cavity with metastasis to the left ovary (*black arrows*). Tumor implants in the cul-de-sac (*white arrows*) are also noted. Sagittal post-gadolinium T1-weighted image with fat saturation (**b**) illustrates a Foley catheter balloon in a collapsed bladder (*black arrow*) and tumor involving the bladder dome and trigone, respectively (*white arrows*). Imaging findings were confirmed by pathologic examination biopsy

Table 4 Imaging for nodal metastases

	Sensitivity (%)	Specificity (%)
CT endometrial [41]	28–64	78–94
MRI endometrial [40, 41]	59–72	93–97
PET-CT endometrial [41, 53]	74–77	93–100

but it can metastasize to abdominal nodes without involvement of pelvic nodes. Consequently, pelvic MRI for endometrial cancer staging includes view images from the pelvic floor to the renal hilum to assess for retroperitoneal as well as pelvic sidewall lymphadenopathy. Size and morphology have traditionally been used as criteria for suscipious lymphadenopathy with oval nodes greater than 1 cm in the short axis labeled as concerning for malignant disease [39]. These morphologic criteria yield moderate sensitivity (59–72 %) but very high specificity (93–97 %) in detecting lymph node metastases (Table 4) [40, 41]. Diffusion-weighted imaging, an MRI technique that improves lesion detection, clearly aids in detection of positive nodes (Fig. 9). However, whether the technique improves differentiation of benign from malignant nodes beyond the more conventional size criteria is still under investigation [29, 42].

Computed Tomography

Computed tomography (CT) does not play a role in primary tumor detection or in defining tumor spread in early stage intrauterine disease. In patients with suspected advanced disease, it can be used to evaluate nodal (Stage IIIC) and distant metastases (Stage IVB) should integrated 2-[18F]-fluoro-2-deoxyglucose positron emission tomography-CT (FDG-PET CT), a more accurate modality for this purpose, not be available. Compared to MRI, with a resolution sometimes compromised by bowel or patient motion, contrast-enhanced CT more reliably detects distant parenchymal metastases, peritoneal implants, and malignant ascites [43] (Fig. 10). CT performs comparably to MRI in detecting lymphadenopathy, as both modalities rely on morphologic criteria of >1 cm short axis diameter for a lymph node to be considered positive.

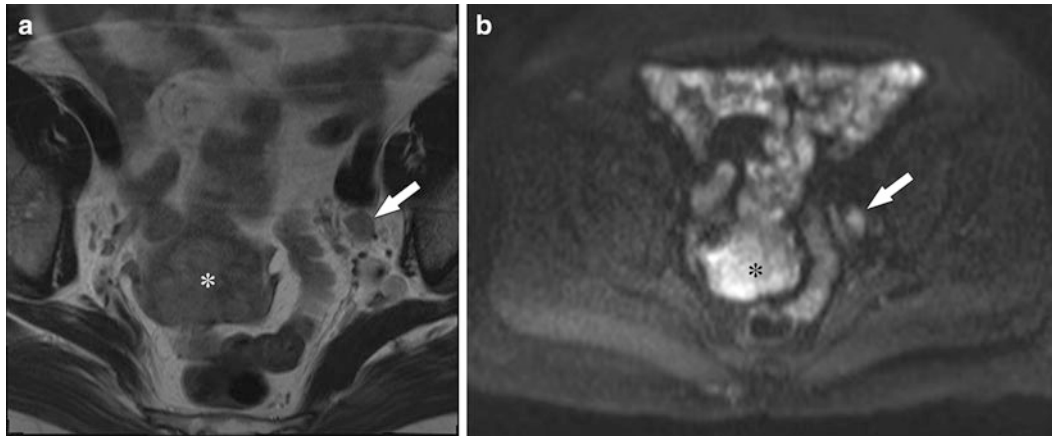

Fig. 9 MRI evaluation of nodal involvement. Axial FSE T2-weighted (**a**) and diffusion-weighted images (**b**) of the pelvis reveal an abnormally enlarged 1.8 × 1.1 cm left obturator node (*arrow*) shown to be involved by tumor by pathologic examination

Reported ranges of sensitivity and specificity of CT in detecting lymph node metastases are 28–64 % and 78–94 %, respectively (Table 4) [41].

Because of its multiplanar and greater tissue-specific imaging capabilities, MRI performs better than CT in staging early disease (Stages I and II) and in evaluating tumor invasion into adjacent organs (Stage IVA) [27, 44–46]. A side-by-side comparison of both modalities found that CT demonstrates 83 % sensitivity and 42 % specificity while MR demonstrates 92 % sensitivity and 90 % specificity in detecting myometrial invasion. Moreover CT demonstrates 25 % sensitivity and 70 % specificity while MR demonstrates 86 % sensitivity and 97 % specificity in detecting cervical invasion [47].

Integrated 2-[18F]-Fluoro-2-Deoxyglucose Positron Emission Tomography and Computed Tomography

Imaging Technique

Positron emission tomography (PET) with the radioactive glucose analog 18-2-fluorodeoxy-2-deoxy-D-glucose (18-FDG) has proven to be a powerful tool for cancer staging and detection of tumor recurrence. Cells with elevated glycolysis avidly take up this glucose analog. 18-FDG is phosphorylated to 18-FDG-6P, which is trapped in tumor cells that are relatively deficient in glucose-6-phosphatase during the time interval in which images are acquired. Following a $\geq$6 h fast, patients are injected with the 18-FDG (average dose, 555 MBq [15 mCi]). A low radiation dose CT is first obtained for attenuation correction of the PET scan. PET images from the neck to the pelvis are then obtained 45–60 min after intravenous injection of the tracer, followed by a diagnostic quality CT exam with or without the administration of intravenous contrast. Increased 18-FDG uptake can be detected on PET images corresponding to tissue with increased metabolic activity, such as in neoplastic or inflammatory conditions.

Concurrent FDG-PET and diagnostic CT scanning are necessary for accurate staging of endometrial cancer. Analysis of fused PET-CT images minimizes errors in lesion detection and localization. As FDG physiologically localizes to bowel and urine, and as endometrial cancer metastasizes to retroperitoneal lymph nodes and peritoneal surfaces, normal tracer can be reliably distinguished from tumor only with precise anatomic mapping on CT images. When PET images

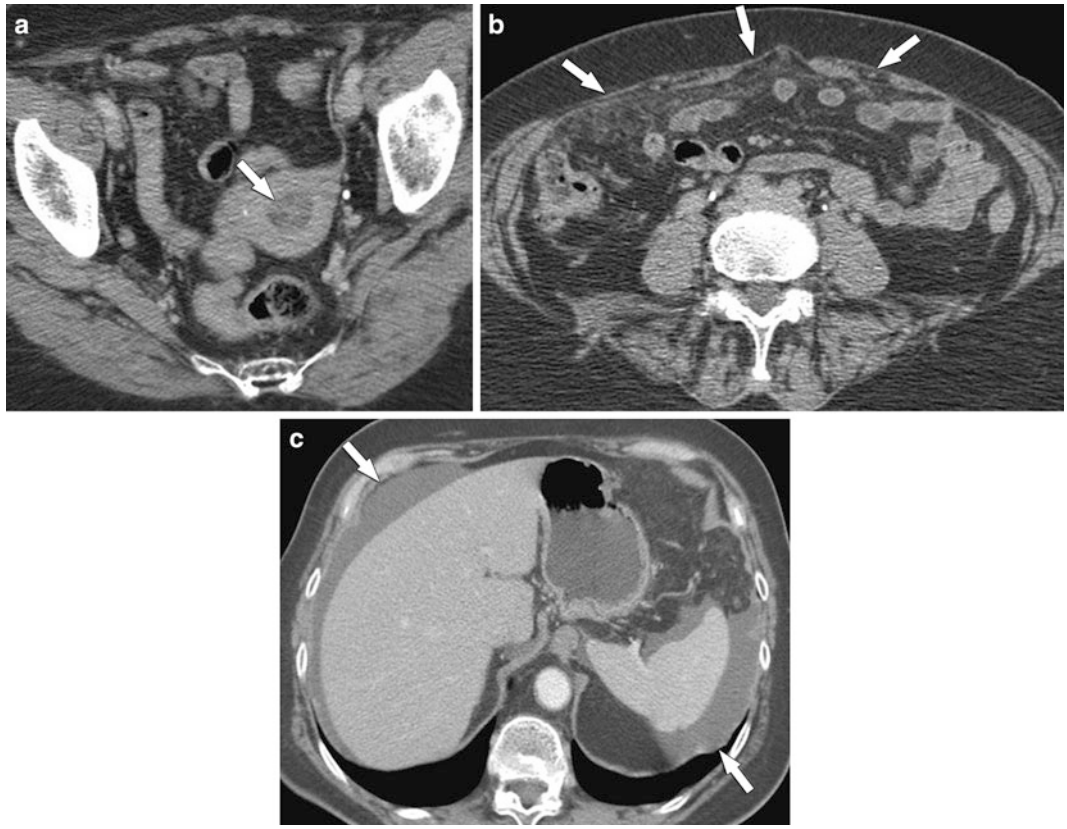

Fig. 10 Computed tomography (CT) of advanced endometrial cancer. Axial contrast-enhanced image through the pelvis (**a**) demonstrates an enhancing mass (*arrow*) enlarging the endometrial cavity. Image through the mid-abdomen above the iliac crests (**b**) reveals omental carcinomatosis (*arrows*). Image of the upper abdomen at the level of the liver (**c**) shows ascites (*arrows*). Pathologic evaluation demonstrated a clear cell endometrial cancer

are interpreted in the absence of a concurrent diagnostic CT, physiologic tracer activity can be mistaken for pathology, resulting in false positive (Fig. 11), and tumor can be misinterpreted as normal physiologic activity, resulting in false negative [48, 49]. Finally small metastases below the threshold of resolution of PET (approximately <8 mm) such as peritoneal carcinomatosis are missed if only PET images are evaluated.

Cancer Detection

Most endometrial cancers are abnormally hypermetabolic on PET-CT; low grade endometrial cancers can demonstrate little to no FDG uptake [50]. Most importantly, nonmalignant endometrium can demonstrate increase tracer avidity and be mistaken for cancer. In premenopausal patients, endometrial evaluation on PET-CT should be correlated with menstrual history, as the endometrium can exhibit FDG uptake during the proliferative phase and menses. In addition, infection (e.g., endometritis) and benign processes (e.g., polyps) can also exhibit tracer avidity [51]. However, in postmenopausal patients, increased endometrial tracer uptake should elicit clinical evaluation and, if appropriate, biopsy to exclude cancer.

Cancer Staging

In patients with known high-grade cancer or suspected extrauterine disease, FDG-PET CT and MRI represent complementary imaging tools for staging. While MRI is the best modality to assess extent of tumor spread in soft tissues of

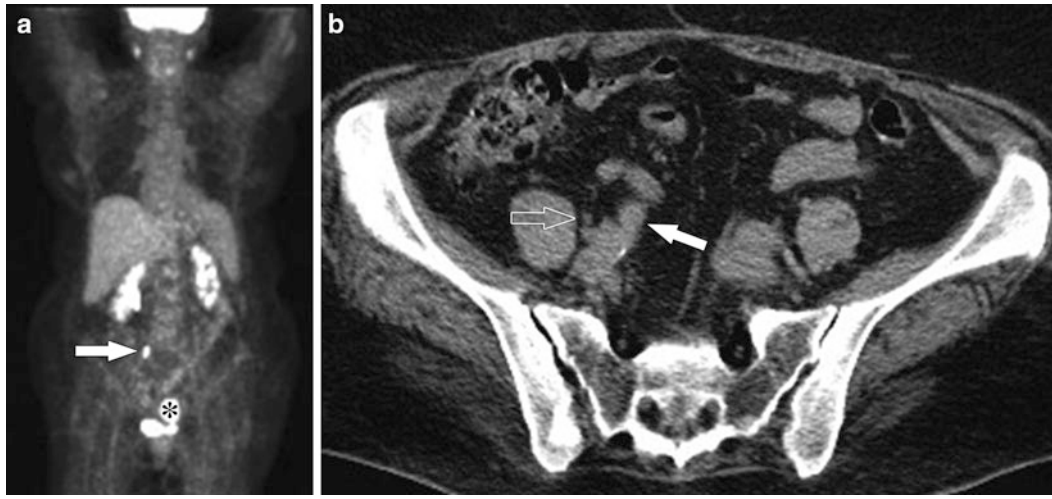

Fig. 11 PET-CT without diagnostic CT resulting in false positive lymphadenopathy. Coronal PET image demonstrates FDG avid uterine tumor (*asterisk*) and a right pelvic focus of tracer (*arrow*) interpreted as a lymphadenopathy (**a**). Diagnostic CT performed 5 days later demonstrates a 1.2 × 1.0 cm right common iliac node (*arrow*) thought to correspond to the FDG-avid right pelvic focus located adjacent to the ureter (**b**). Surgical resection of the node, confirmed on postoperative CT (not shown), revealed no tumor. The FDG-avid focus likely represented urine in the ureter

the central pelvis, PET-CT is preferred to assess for lymphadenopathy and distant metastases [52].

PET-CT demonstrates 74–77 % sensitivity and 93–100 % specificity in the detection of lymphadenopathy from endometrial cancer [40, 53]. PET-CT allows for the detection of tumor involvement in lymph nodes that measure <1 cm in short axis, i.e., the size threshold for morphologic assessment of lymphadenopathy (Fig. 12). Thus, in lymph node evaluation, PET-CT demonstrates increased sensitivity when compared to CT or MRI without loss of specificity. Detection of FDG-avid nodes allows for surgical planning and histologic confirmation. Nevertheless, because PET-CT is still suboptimal to detect micrometastases, staging lymphadenectomy is performed in patients with primary tumors with high-risk features even when PET-CT is negative.

In patients with high-grade histology, PET-CT is the most accurate imaging test to determine the complete extent of tumor spread. It images the whole body and detects lymph node and osseous metastases with greater sensitivity than CT. Thus, it is the preferred exam to evaluate stage IV disease that would triage a patient away from the unnecessary morbidity of a large-scale staging operation [54].

Imaging Post-primary Therapy

Most patients are cured following primary treatment. However, 20–25 % of patients develop recurrence, usually within the first 3 years. Most common sites are lymph nodes and vagina. Recommended algorithms for postoperative surveillance include clinical history, pelvic examination, and vaginal cytology. However, detection of recurrence based on clinical and laboratory findings is suboptimal as 20 % of patients present with asymptomatic metastases [55]. Hence, imaging is used as an adjunct to evaluate for clinically occult recurrence.

FDG-PET CT is the preferred modality to evaluate recurrence post-therapy. Whole-body PET or integrated PET-CT demonstrate 92–93 % sensitivity and 93–100 % specificity in detecting recurrent disease [56, 57]. A study measuring the added value of FDG-PET in addition to CT or MRI for

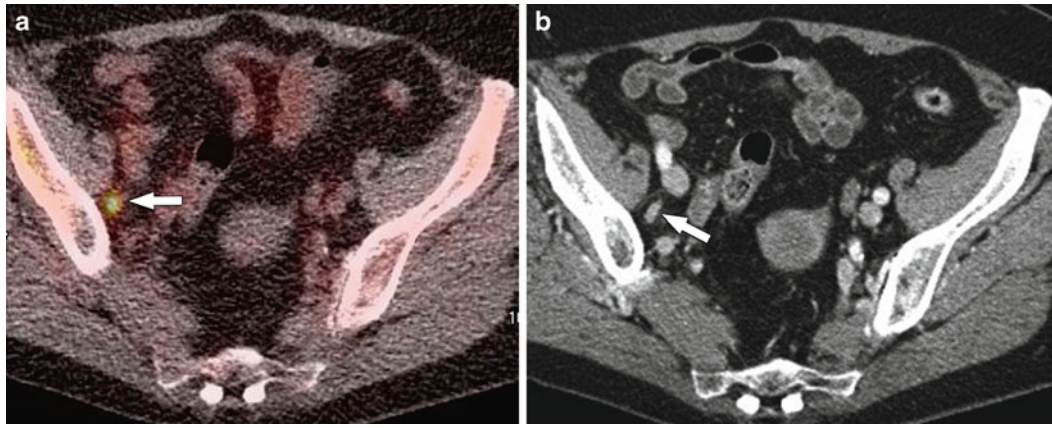

Fig. 12 Fusion PET-CT of endometrial cancer detecting lymphadenopathy. Fusion FDG-PET image (**a**) of a patient with endometrial cancer demonstrates abnormal tracer uptake (*arrow*) in the right pelvic sidewall which on concurrent diagnostic CT (**b**) corresponds to a 1.0 × 0.9 cm right obturator (*arrow*) node. Tumor involvement of the node was confirmed with surgical resection and pathologic evaluation

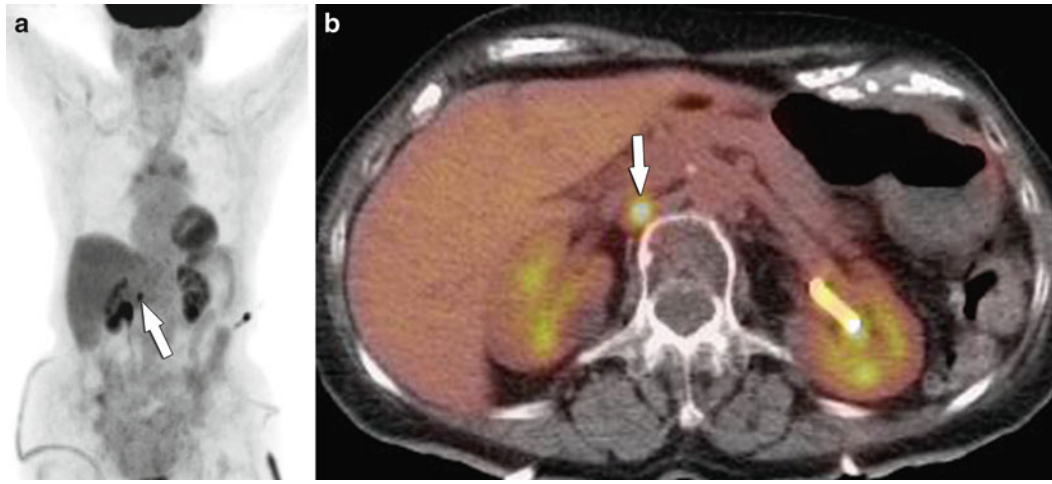

Fig. 13 Fusion PET-CT detecting endometrial cancer recurrence. Coronal FDG-PET image (**a**) of a patient with a history of Grade 2 endometrial cancer and primary therapy 1 year ago demonstrates a focus of abnormal tracer uptake (*arrow*) medial to the right kidney. Fusion PET-CT image (**b**) reveals a corresponding 1.0 × 0.8 cm retrocaval node which was not identified as abnormal on a standard CT examination 7 days before. Tumor involvement of the node was confirmed with a biopsy

post-therapy surveillance found that FDG-PET had better diagnostic performance (accuracy 93.3 %) compared to combined conventional imaging (accuracy 85 %) and tumor markers (accuracy 83.3 %) [57] (Fig. 13). Additionally, as PET-CT affords whole-body evaluation of metastases, it serves to identify patients who would not be candidates for loco-regional therapy. In patients with recurrent tumor confined to the pelvis, MRI is used to plan salvage surgery or radiotherapy.

Conclusions

- In detecting endometrial cancer, TVUS has a well-defined role in the evaluation of patients presenting with postmenopausal bleeding. It

is recommended as the initial test to select patients for biopsy as it demonstrates a high negative predictive value.
- Once the diagnosis of endometrial cancer is confirmed, MRI is the best modality to delineate the intrauterine tumor and its spread into adjacent pelvic organs.
- In patients with suspected extrauterine disease, integrated FDG-PET CT is more accurate than MRI or CT to detect lymph node, intraperitoneal, thoracic, and bony metastases.
- Optimal test performance for PET-CT requires that diagnostic quality CT images be acquired concurrently with the PET scan.
- Following treatment, PET-CT is the most accurate modality to assess for recurrence.

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