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Seminars in
ULTRASOUND
CT and MRI

Imaging and Staging of Endometrial Cancer

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Endometrial carcinoma is the most common female pelvic malignancy in the United States. Although endometrial cancer is staged according to the International Federation of Gynecology and Obstetrics surgical system, early and accurate diagnostic assessment of disease status of gynecologic malignancies is important for optimal treatment planning and outcome prediction. Preoperative imaging may assist in evaluation of local extent and detection of distant metastatic disease guiding the optimal course of treatment. Several imaging techniques such as transvaginal ultrasound, computed tomography, and magnetic resonance imaging have been used as tools for preoperative staging of endometrial cancer. Positron emission tomography/computed tomography and more recently, positron emission tomography/magnetic resonance imaging have also been used in the management of endometrial cancer.

Cross-sectional imaging, especially MRI, may detect gross myometrial invasion or extension of tumor to the cervical stroma which can alter management. Imaging studies can also evaluate the presence of lymph nodal involvement, and detect local and distant metastatic disease at diagnosis. Additionally, imaging also plays a role in the monitoring of treatment and surveillance of the patients for detection of early recurrent disease.

In this article, we will review the imaging and staging of endometrial cancer.

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Introduction

Endometrial cancer (EC) is the most frequent cancer of the female genital tract in developed countries. Approximately 61,880 new cases are expected in the United States and 12,160 deaths are estimated to occur in 2019.[1]

Epidemiology and Risk Factors

Most patients diagnosed with EC are postmenopausal women with a mean age at diagnosis of 68 years old.[2] However, up to 15% of cases may occur in premenopausal women.[3] Risk factors for EC include conditions promoting increased exposure to unopposed estrogen such as hormonal replacement therapy, obesity, nulliparity, and tamoxifen therapy.[4] Although most endometrial cancers are thought to be sporadic, some hereditary cases are caused by germline mutations. The most common genetic syndrome associated with EC is Lynch syndrome.[4]

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Clinical Presentation and Diagnosis

Endometrial carcinoma typically presents with abnormal uterine bleeding in postmenopausal women and the diagnosis is confirmed based upon the results of evaluation of an endometrial biopsy, endometrial curettage, or hysterectomy specimen.[4]

Pathology

EC arises from the epithelial lining of the uterine cavity. Traditionally, EC has been classified based on clinical and hormonal features, into 2 subtypes with distinct clinical, pathological, and histological behavior. Type I EC are mainly low grade, estrogen-dependent, hormone-receptor-positive adenocarcinomas with endometrioid morphology and are often referred as endometrioid endometrial cancers and account for approximately 85% of all EC usually diagnosed at an early stage and characterized by a good prognostic. Type II EC is characterized by nonendometrioid subtypes such as serous, clear-cell, and undifferentiated carcinomas. They generally are high-grade, hormone-receptor negative, and have poor prognosis.[5] EC are histologically classified according the World health Organization classification system, and are divided into subgroups: endometrioid that

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accounts for 80% of cases, serous that accounts for 10%, clear cell (<6%), mixed cell adenocarcinoma and other rare types.[6] Recently, molecular studies have obtained promising results to provide important information for prognosis and for predicting response to novel therapies. The Cancer Genome Atlas Research Network identified 4 distinct EC molecular subtypes: the Polymerase e (POLE) ultra-mutated tumors, the microsatellite instability hypermutated tumors, the copy-number low microsatellite stable, and the copy-number high serous-like subgroups.[6-9]

Prognosis

Due to early symptoms, most women with EC are diagnosed at an early stage with uterine-confined tumors and consequently better prognosis. Despite the overall favorable prognosis, some women have aggressive neoplasms. The most important prognostic factors in EC include tumor grade, histological type, depth of myometrial invasion, tumor size, lymphovascular invasion, and lymph node status.[10] EC typically spreads by invasion of the myometrium into the cervix, or via the fallopian tubes to the ovaries or trans-serosal spread to bladder or bowel.[10]

Staging

EC is staged according to the International Federation of Gynecology and Obstetrics system (Table 1).[11] Stage I reflect EC that are confined to the uterine corpus. They are further divided into stage IA (no or less than 50% myometrial invasion) and IB (equal to or more than 50% of myometrial invasion). Tumors that invades cervical stromal but does not extend beyond the uterus are defined as stage II. Stage III represents tumor that spread beyond the uterus but not outside the true pelvis. They are further divided in stage IIIA (invade the uterine serosa and/or adnexa), stage IIIB (parametrium and/or vaginal involvement), and stage IIIC1 (positive pelvic nodes) and IIIC2 (positive paraaortic lymph nodes). Stage IVA includes tumors with extension to the bladder or bowel and stage IVB tumors with distant metastases.[11]

Table 1 International Federation of Gynecology and Obstetrics Staging System for Endometrial Cancer, 2009[12]

FIGO Stage	Treatment
Stage IA	Tumor confined to the uterus, no invasion or invasion of less than one-half of the myometrial thickness.
Stage IB	Tumor confined to the uterus with invasion of more than one-half of the myometrial thickness.
Stage II	The tumor invades the cervical stroma but does not extend beyond the uterus.
Stage IIIA	The tumor invades the uterine serosa or adnexa.
Stage IIIB	Vaginal and/or parametrial involvement.
Stage IIIC	The tumor has spread to pelvic or para-aortic lymph nodes.
Stage IIIC1	Pelvic lymph node involvement.
Stage IIIC2	Para-aortic lymph node involvement (with or without pelvic nodes).
Stage IVA	Tumor invasion of the bladder and/or bowel mucosa.
Stage IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes.

The 5-year survival rates for EC vary according to the stage at diagnosis. In patients with tumors localized to the uterus, the 5-year survival rate is ≥95%, but it decreases when the disease has spread beyond the uterus, with rates of 69% in patients with regional metastasis and rates of 17% in women with distant metastatic disease.[12]

Imaging

Ultrasound (US) is usually the first examination performed in women with history of vaginal bleeding. Transvaginal US is performed with a dedicated vaginal probe using high frequencies. Normal and abnormal endometrial findings can be readily identified at transvaginal US. In premenopausal patients, the endometrium demonstrates a wide spectrum of appearances throughout menarche secondary to physiologic and hormonal changes. The normal postmenopausal endometrium should appear thin, homogeneous, and echogenic.[13] Although there is some controversy regarding endometrial thickness with menopause, most authors considered 5 mm the upper limit of normality for endometrial thickness in postmenopausal women.[14] Transvaginal US measurement of the endometrium should be performed at the thickest point in the sagittal plane. The cut-off value for endometrium thickness of 5 mm has a sensitivity of 96% and a specificity of 61% in the diagnosis of EC in postmenopausal women with abnormal uterine bleeding (Fig. 1).[15]

Additional US imaging features suggestive of endometrial carcinoma include heterogeneity, focal thickening, irregular endometrial margins, a polypoid mass in the endometrial cavity (Fig. 2), intrauterine fluid collection, and frank myometrial invasion (Fig. 3).[16] The value of Doppler and color Doppler US

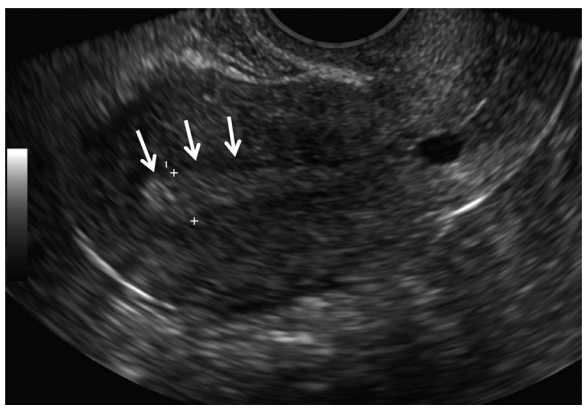

Figure 1 75-year-old female with postmenopausal bleeding. (A) Transvaginal sagittal ultrasound image of the uterus demonstrates a thickened homogeneous endometrium measuring 9 mm cm (arrows). Note regular endometrial-myometrial border with no signs of invasion (arrows). Endometrial biopsy was performed with the diagnosis of endometrial cancer.

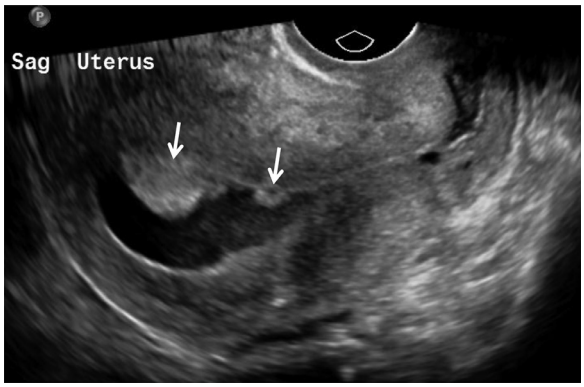

Figure 2 68-year-old female with postmenopausal bleeding. Transvaginal sagittal ultrasound image of the uterus demonstrates a distended endometrial cavity with fluid and 2 solid echogenic lesions (arrows) arising from the endometrium measuring 2.0 cm and 1.1 cm. Patient was submitted to hysterectomy that confirmed endometrial cancer.

in distinguishing benign from malignant endometrial disease is controversial and a biopsy should be obtained for confirmation of the diagnosis. Although, transvaginal US is excellent in determining the endometrial thickens, US is limited in the evaluation of the depth of myometrial invasion by the EC.[17]

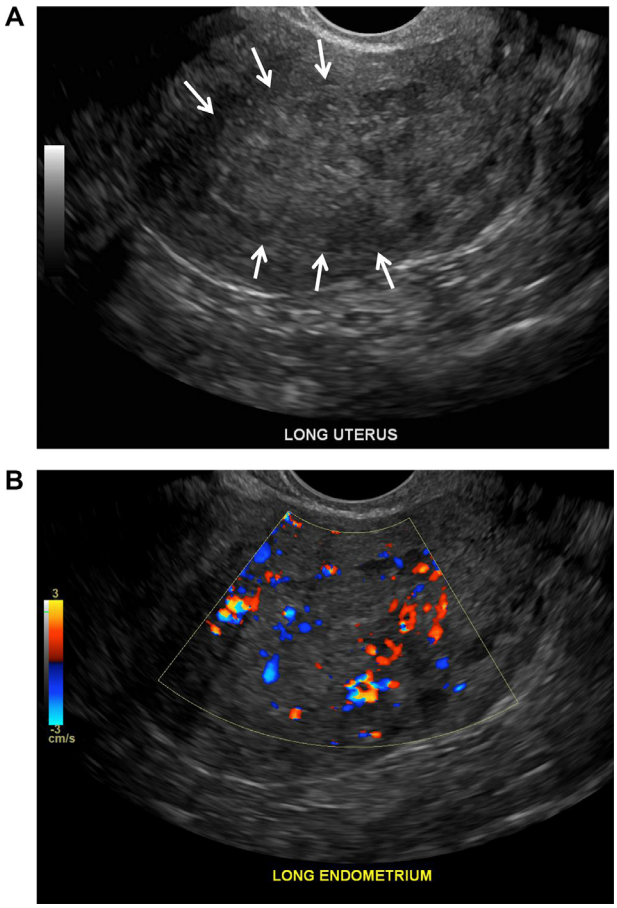

Figure 3 72-year-old female with postmenopausal bleeding. (A) Transvaginal sagittal ultrasound image of the uterus shows a markedly thickened and heterogeneous endometrium (arrows) measuring 24 mm with ill-defined anterior border (arrows) and no clear separation from the myometrium. Note some vascularity in the color Doppler US (B). At hysterectomy endometrial cancer with myometrial invasion was confirmed.

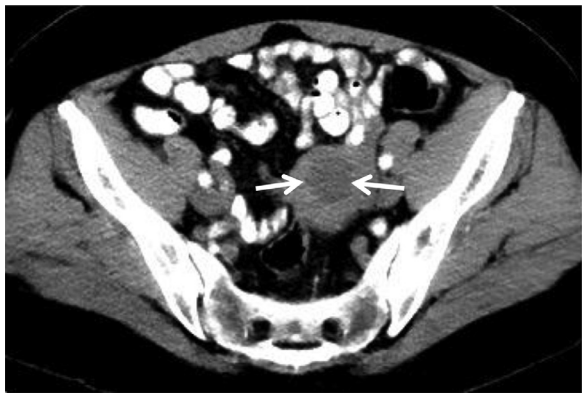

Figure 4 75-year-old female with endometrial cancer Axial enhanced computed tomography image showing a uterus with a thicken hypodense endometrium (arrows).

Computed tomography (CT) is generally not used for initial diagnosis of endometrial carcinoma. EC may appear on CT as a dilated hypoenhancing endometrial cavity (Fig. 4) associated or not with enhancing solid nodules.[18] CT has a low sensitivity (83%) and a low specificity (42%) in evaluating myometrial involvement as well as in assessing cervical stromal invasion.[19] CT is useful in the evaluation of more advanced disease with extrauterine spread, lymphadenopathy, and metastatic disease beyond the pelvis (Fig. 5). The most common sites of metastatic disease are the lymph nodes, ovaries, and lungs.[20]

Magnetic resonance imaging (MRI) is considered the most accurate imaging technique for preoperative assessment of endometrial cancer due to its excellent soft tissue contrast resolution. EC usually appears hypo- to isointense on T1-weighted images, and hyperintense or heterogeneous on T2-weighted images, relative to normal endometrium, and enhances after IV contrast injection. EC has restricted diffusion demonstrating high signal intensity on DW Images and low signal intensity on the apparent diffusion coefficient maps.[21]

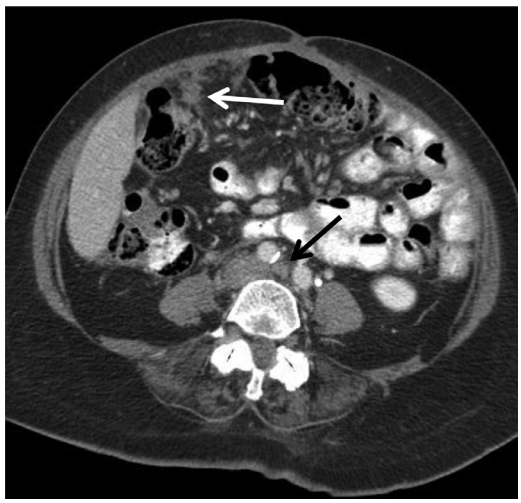

Figure 5 66-year-old female with endometrial cancer. Axial enhanced computed tomography image shows soft tissue nodules in the anterior peritoneum suggestive of peritoneal carcinomatosis (white arrow) and metastatic retroperitoneal lymph node (black arrow). (Color version of figure is available online.)

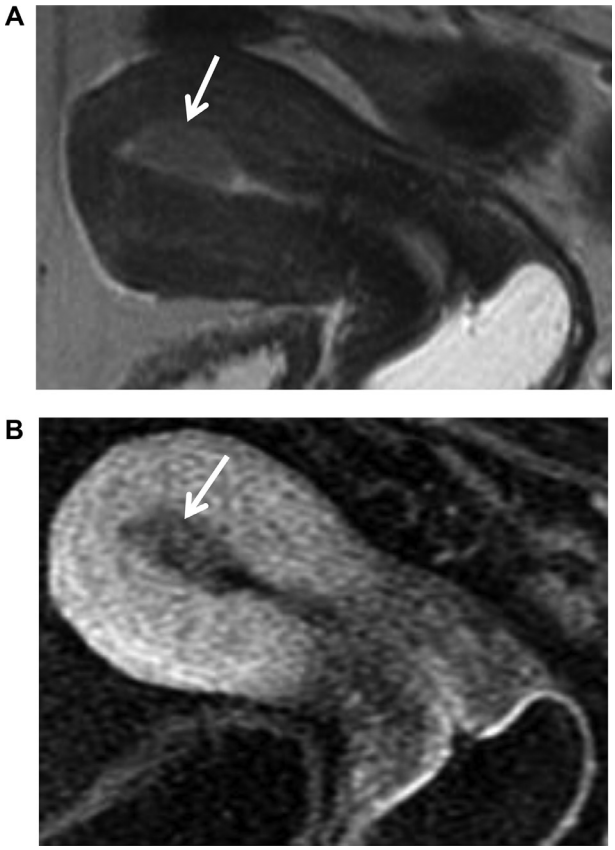

Figure 6 64-year-old female with endometrial cancer. (A) Sagittal T2-weighted image shows a polypoid mass (arrow) distending the endometrial cavity. It is a hypovasculat tumor (arrow) presenting less enhancement than the adjacent myometrium in the sagittal post contrast T1-weighted image (B). It is a Stage IA endometrial cancer with less than 50% myometrial invasion.

One of the most important aspects of EC staging is the depth of myometrial invasion. Stage IA indicates tumors with no or less that 50% invasion of the myometrial thickness (Fig. 6). Stage IB represents tumors with more than 50% of myometrial thickness invasion. The presence of myometrial invasion is suggested by an irregular interface and/or loss of the normal endometrium-myometrium interface. Sagittal T2-weighted image delineates the uterine anatomy and is a useful tool in the assessment of the depth of myometrial invasion. However, some limitations include the uterine anatomy distorted by leiomyomas, presence of adenomyosis and when the tumor involved a cornu of the uterus. In these cases, the use of dynamic contrast-enhanced MR images are of particular value to improve the delineation of the tumor margins and for assessing the depth of myometrial invasion because EC will enhance less than the myometrium (Fig. 7). Dynamic contrast-enhanced and T2-weighted images have together an accuracy of 98% for assessing myometrial invasion.[22] Additionally, DWI has been increasingly employed as an assessment tool of the myometrial invasion (Fig. 7). Diffusion-weighted imaging (DWI) is particularly useful in patients who cannot receive intravenous contrast injection of gadolinium-based contrast agent and in evaluating the depth of myometrial invasion in the setting of concurrent adenomyosis.[23] Meta-analysis showed similar pooled sensitivity for DWI s dynamic contrast enhanced (DCE)-MRI, and specificity did not significantly differ between them in the evaluation of depth of myometrial invasion.[24] A more recent meta-analysis by Deng et al. confirmed similar diagnostic performance of DWI vs DCE-MRI and they also found that combined T2WI and DWI were superior to either DWI or DCE-MRI alone.[25]

The presence of cervical stromal invasion but with no extension beyond the uterus represents stage II disease. T2 and DCE MR images are useful in the assessment of cervical stromal invasion with a diagnostic accuracy of approximately 90% (Fig. 8).[26]

Stage III represents tumor with local or regional spread beyond the uterus. MRI is used to evaluate extrauterine disease extending beyond the serosa or to the adnexal region (stage IIIA), and vaginal and/or parametrial involvement (stage IIIB) (Fig. 9). In stage IIIC, the tumor has spread to lymph nodes and is further divided into stage IIIC1 when there is pelvic lymph node involvement and stage IIIC2 when there is para-aortic lymph node involvement (with or without pelvic nodes) (Fig. 10). The incidence of nodal metastatic involvement correlates with depth of invasion: 3% if less than 50% myometrial invasion and 46% if greater than 50%.[27] Additional risk factors for lymph nodes metastases include presence of high-risk histologic subtypes, lymphovascular space invasion, and cervical stroma invasion. Lymph node metastases distribution is also influenced by EC tumor location. The middle and lower parts of the uterus drain into the parametrium and the paracervical and obturator lymph nodes, while the upper part of the uterus drains into the common iliac and para-aortic lymph nodes. MRI has a sensitivity of 44% and specificity of 98% in the detection of lymph node metastases.[28]

Stage IV represents tumors that are locally advanced or have distant metastases (Fig. 11). It is further divided in stage IVA with tumoral invasion of the bladder and/or bowel mucosa and stage IVB when there is distant metastases and/or inguinal lymph nodes involvement.[29]

Positron emission tomography (PET)/CT allows for simultaneous acquisition of anatomical and metabolic information. The EC shows intense fluorodeoxyglucose (FDG) uptake with reported mean standardized uptake value of 11.2 ± 5.9 (Standard Deviation).[30] However, PET/CT scan has little value in detection and initial stage of early stage disease due to limited spatial resolution, as well as, physiologic uptake of FDG in premenopausal women and in other benign conditions such as endometrial hyperplasia, polyps, and adenomyosis.[31] PET/CT has an increasing importance in preoperative assessment of metastatic lymphadenopathy and distant metastatic disease in patients with EC.[32] In a meta-analysis, the reported overall pooled sensitivity, specificity, and accuracy of PET/CT in the detection of lymph node metastases were 72%, 94%, and 94%, respectively.[33] However, one of the limitations of PET/CT is the size of the lymph node of less than 5 mm.

PET/CT has high sensitivity and specificity (100% and 96%) for detecting distant metastases in the abdomen and extra-abdominal regions in high-risk patients with EC.[34,35] PET/CT also play an important role in the surveillance of patients. Post-therapeutic changes can be difficult to differentiate from recurrent

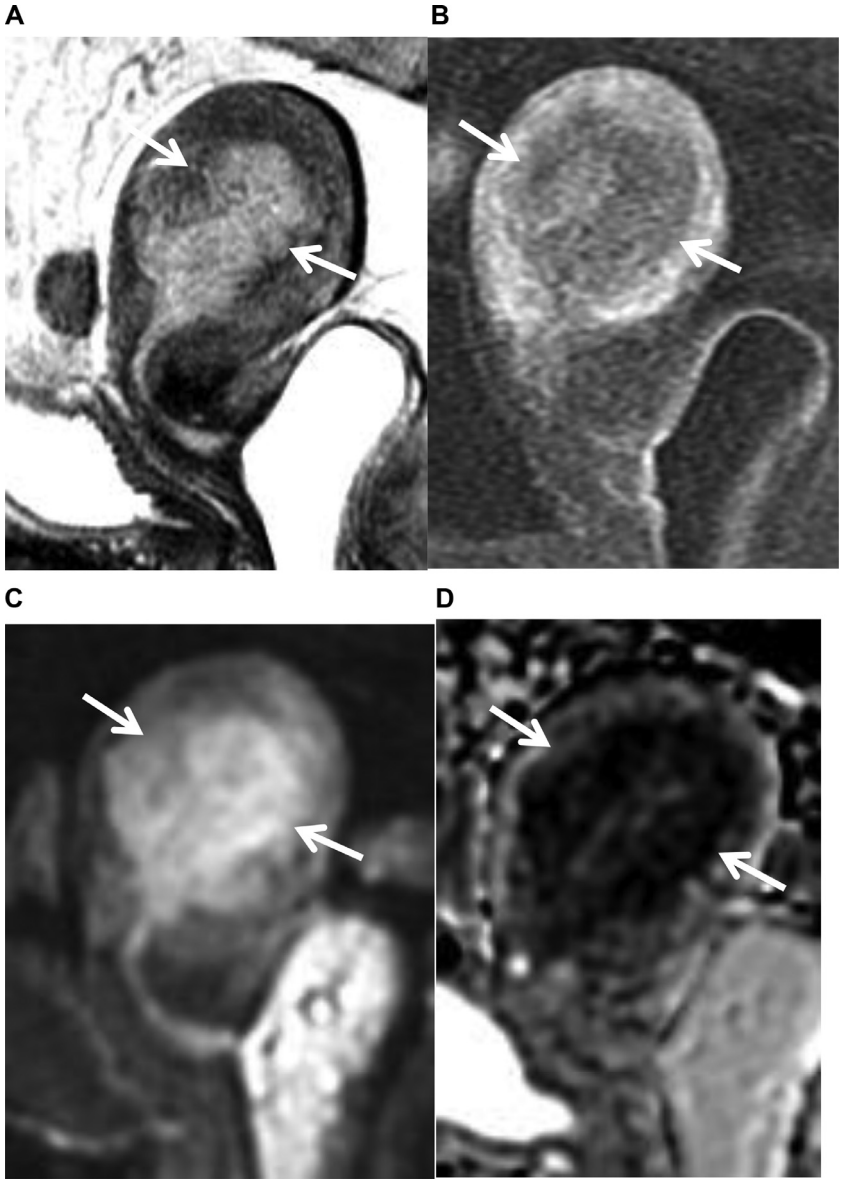

Figure 7 65-year-old female with endometrial cancer. (A) Sagittal T2-weighted, sagittal postcontrast T1-weighted image (B), (C) DWI and ADC map (D) images show a large irregular mass (arrows) distending the endometrial cavity with more than 50% myometrial invasion. It is a Stage IB endometrial cancer with more than 50% myometrial invasion.

disease on CT, as they can have a similar morphological appearance. Viable tumor is more likely to demonstrate hypermetabolism and thus can be differentiated from post-therapeutic change, and FDG-PET can be used in this setting. The reported sensitivity, specificity, and accuracy of PET/CT in detecting recurrent disease in patient with EC is 95%, 91%, and 97%, respectively.[33]

Recently introduced PET/MR scanners acquire MR and PET data either simultaneously or sequentially adding the strengths of PET in detecting nodal and distant metastatic disease to the strengths of MRI in local staging of patients with EC.[36]

It has been shown that PET/MRI is valuable in preoperative evaluation of patients with EC. In a direct comparison of fused PET/MR imaging, MR imaging and PET/CT data, PET/MR imaging and MR imaging alone were both more accurate for local staging of endometrial cancer than PET/CT (accuracy of 80% vs 60%).[37] Queiroz et al. reported that PET/MRI is superior to PET/CT for tumor delineation but no significant differences were found in the detection of regional lymph node metastases and abdominal metastases.[38] A recent systematic review of the literature, suggest that PET/MRI are comparable in the detection of local lymph node and distant metastases, with PET/MRI being superior at local staging and determining the local extent of tumors.[39] PET/MRI is also valuable in the assessment of oncologic treatment response.[40]

In patients with suspected recurrent pelvic cancer, PET/MRI correctly identified more patients with cancer recurrence than MRI alone with superior diagnostic accuracy and diagnostic confidence ($P \leq 0.01$).[41] Future directions for this rapidly developing PET/MRI technology, with investigation of new positrons tracers as well as novel MR imaging tracers are likely to make PET/MRI a very important tool in the preoperative staging and surveillance of patients with EC.[42]

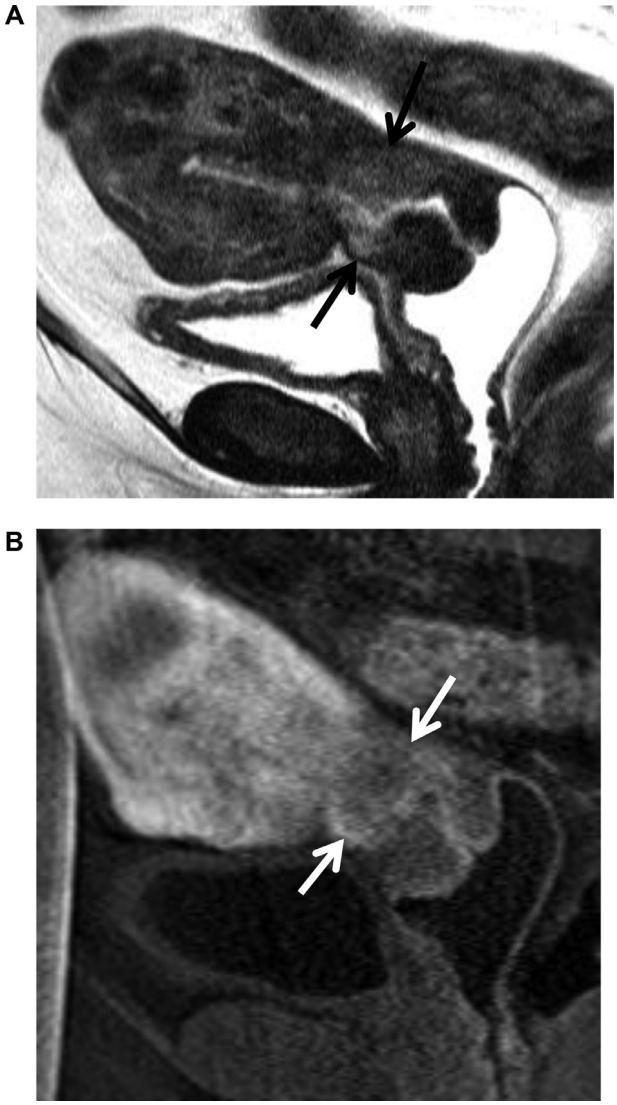

Figure 8 77-year-old female with endometrial cancer. (A) Sagittal T2-weighted image, and sagittal postcontrast T1-weighted image (B) images show an ill-defined enhancing mass in the lower uterine segment measuring approximately 3.2 × 3.1 cm (arrows) with more than 50% of myometrial invasion. It invades the superior cervix but there is no extension beyond the uterus indicating stage II disease.

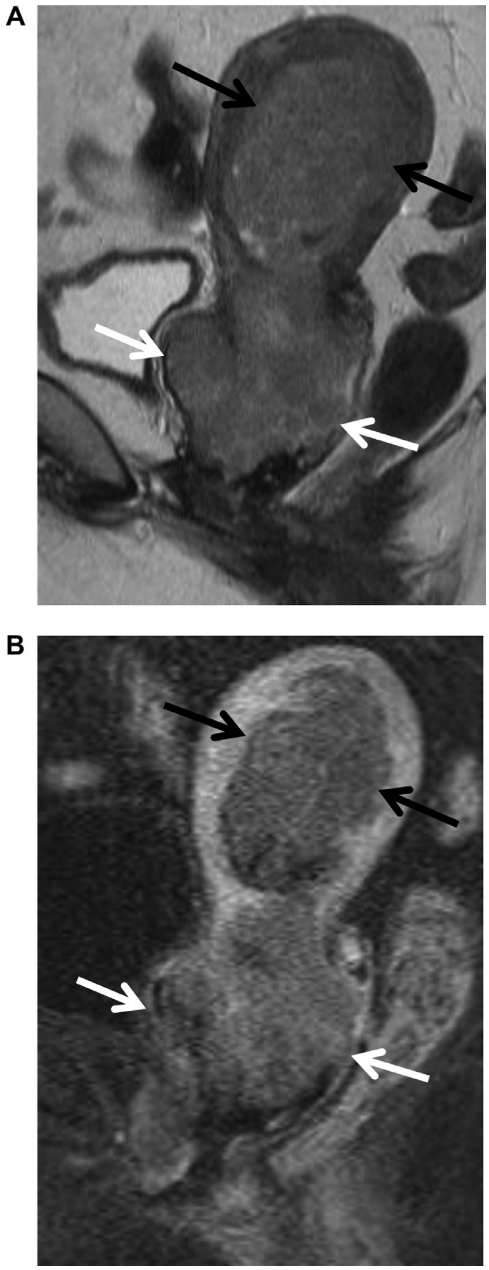

Figure 9 70-year-old female with endometrial cancer. (A) Sagittal T2-weighted image, and sagittal postcontrast T1-weighted image (B) show a large mass within the endometrial cavity (black arrow) that extends into the cervix measuring 10.8 × 4.0 cm involving the anterior and posterior vaginal walls (white arrows) and extending into the middle third of the vagina indicating stage IIIB. (Color version of figure is available online.)

Treatment

The standard treatment for EC confined to the uterus is total hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy with sentinel lymph node sampling enables identification of lymph node positive patients who need adjuvant treatment. Adjuvant radiotherapy is used for stage I-II patients with high risk factors and stage III lymph node negative patients.[43] Adjuvant radiotherapy may be used in selected patients with cervical or vaginal involvement. In advanced disease, a combination of surgery with radiotherapy and/or chemotherapy is used.[44]

Recurrence

Recurrent disease is defined as tumor regrowth and/or the appearance of distant disease after treatment. Although the overall prognosis for patients with EC is relatively good, local, and distant recurrences can occur after surgical treatment of the primary EC especially in high-risk patients.[45] Approximately 25%-30% of patients with advanced disease and poor prognostic factors may develop recurrent disease.[46] Early detection of recurrent disease is critical for establishing a therapeutic strategy with curative intent.[47]

The overall median time to recurrent disease is 13 months with the majority of the cases of occurring within 24 months after primary surgery.[46] The most frequently observed sites of

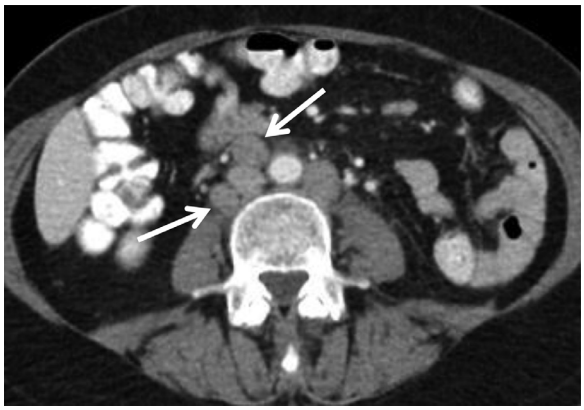

Figure 10 68-year-old female with endometrial cancer. Axial CT image shows enlarged para-aortic lymph nodes that were biopsied with the diagnostic of metastatic disease in the para-aortic lymph nodes indicating stage IIIC2.

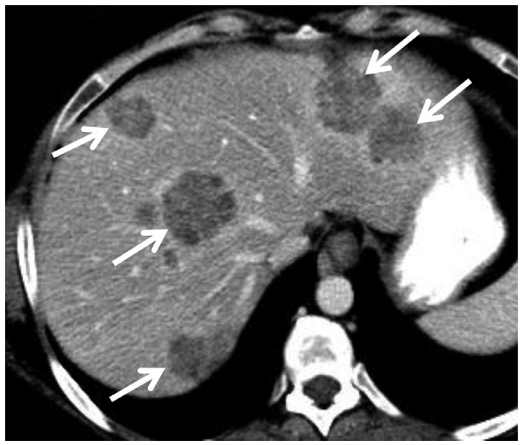

Figure 11 76-year-old female with endometrial cancer. Axial CT image shows bilobar hepatic metastases (arrows) characterizing stage IV disease.

relapse are pelvic and para-aortic lymph nodes, vagina, peritoneum, and lungs.[46] The most common site for recurrent EC within the vagina is the vaginal apex.[48]

The use of MRI with DCE images and DWI aids in the detection of recurrent tumor and differentiation from postsurgical changes, postradiotherapy soft-tissue thickening an inflammation from recurrent disease.[49] On FDG-PET, recurrent tumor appears as a focal area of increased uptake (Fig. 12).[50] PET can help in detecting recurrence in the pelvis as well as metastatic spread to extrapelvic locations such as the lungs and abdomen. FDG-PET/CT has a sensitivity of 90%-100%, a specificity of 78%-93%, and an accuracy of 87%-96% in the detection of recurrent disease in EC patients.[31,51,52]

The treatment for recurrent EC depends on the anatomic location of the recurrence. Recurrent endometrial cancer occurring at the vaginal cuff may be successfully treated with external beam radiation or brachytherapy. The 5-year cure rate for patients with isolated recurrence at the vaginal apex is reported to be about 40%-60%.[53] In some cases, isolated pelvic recurrences can be treated with pelvic exenteration. Patients with systemic disease can be treated with chemotherapy or hormonal therapy.[54]

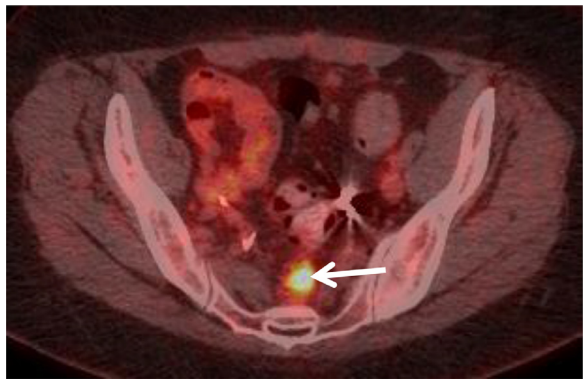

Figure 12 78-year-old female with endometrial cancer surgically treated with hysterectomy 16 months ago. FDG-PET/CT image shows a 1.7 cm soft tissue nodule with focal FDG uptake (arrow) in the presacral region that was biopsied with the diagnostic of recurrent disease.

Conclusion

Cross-sectional imaging plays an essential role in the evaluation of the patients with endometrial cancer. Imaging can identify the primary tumor, assess the presence of lymphadenopathy, demonstrate local and distant advanced disease, provide guidance for radiation ports, monitor treatment response, and post-treatment surveillance to detect recurrent disease. Due to its excellent soft tissue contrast, MRI has become the standard for imaging uterine malignancies; providing good definition of the primary lesion and its extrauterine extension. PET/CT and more recently PET/MRI are also being used in the evaluation of endometrial cancer patients. In summary, imaging provides a comprehensive assessment of local and distant disease contributing to a better management of patients with endometrial cancer.

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