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FEMALE GENITOURINARY ONCOLOGY SPECIAL FEATURE: REVIEW ARTICLE

MRI of the endometrium - from normal appearances to rare pathology

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ABSTRACT

MRI was recently included as a standard pre-operative diagnostic tool for patients with endometrial cancer. MR findings allow a better risk assessment and ultimately guides the surgical planning. Therefore, it is vital that the radiological interpretation is as accurate as possible. This requires essential knowledge regarding the appropriate MRI protocol, as well as different appearances of the endometrium, ranging from normal peri- and post-menopausal changes, benign findings (*e.g.* endometrial hyperplasia, polyp, changes due to exogenous hormones) to common and rare endometrium-related malignancies. Furthermore, this review will emphasize the role of MRI in staging endometrial cancer patients and highlight pitfalls that could result in the underestimation or overestimation of the disease extent.

INTRODUCTION

Endometrial cancer (EC) is the third most common malignancy in females and the most common gynecological cancer in developed countries. Its increasing incidence is reported to be 13.6 per 100,000 females with a cumulative risk of 1.71% for a diagnosis of EC.[1] The majority of the cases are diagnosed at an early stage (70% stage I) with 5 year survival rate of more than 95%.[2] Whilst post-menopausal females are predominantly affected (75% are >50 years), 4% of the females diagnosed with EC are younger than 40 years and wish to retain their fertility.[3]

Patients with abnormal vaginal bleeding are initially evaluated by transvaginal ultrasound. In post-menopausal patients, a focal or diffuse endometrial thickening of >4 mm is considered suspicious and should by followed by an endometrial pipelle or hysteroscopy and biopsy.[4] Some data suggest a more rigorous threshold of 3 mm thickening to achieve a higher sensitivity (97.5% *vs* 95% for 4 mm thickness).[5]

MRI was recently included as a standard pre-operative diagnostic tool in patients with EC.[6] MRI findings allow a better risk assessment and ultimately guides the surgical planning. Therefore, it is vital that the radiological interpretation is as accurate as possible. This requires essential knowledge regarding the appropriate MRI protocol and the various findings related to endometrium-pathology.

In this review, we will highlight different MRI endometrium appearances, ranging from normal, peri- and post-menopausal changes, benign findings, together with common and rare malignancies.

PATIENT PREPARATION AND MRI PROTOCOL

The quality of the image is improved by optimal patient preparation. Therefore, fasting is recommended 4–6 h prior to MRI examination and urinary bladder and rectal voiding is advised to reduce motion artifacts. Bowel and uterine peristalsis are diminished with antiperistaltic agents (butylscopolamine or glucagon) administered

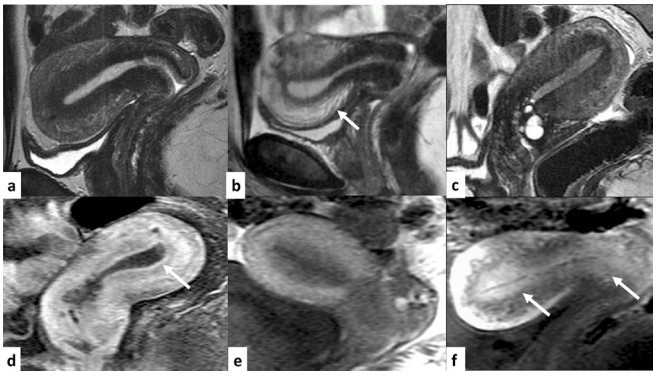
intramuscularly or intravenously at the beginning of the examination. Patients are imaged in supine position by using a pelvic or cardiac multichannel coil. Anterior and posterior fat saturation bands placed along the subcutaneous tissue are useful to reduce near-field artifact.[6–9]

The combination of conventional T_2 weighted sequence (T_2WI) with diffusion (DWI) and dynamic contrast enhanced (DCE) MR imaging provides the "one-stop shop" approach used for patients with EC.[6] The high resolution T_2WI sequences are angled perpendicularly to the endometrium to obtain axial oblique images. A slice thickness of 4 mm and the use of non-fat suppressed sequences is advised.[6] DWI images should be obtained with a minimum of two b values of 0 and 800–1000 s/mm^2 in the same orientation as the sagittal and axial oblique T_2WI. DCE imaging can be used as an adjunct particularly in those patients with total hip replacement when metal artefact limits DW imaging. If appropriate, contrast-enhanced images can be acquired either as a DCE acquisition or as a single phase contrast-enhanced imaging at 2 min 30 sec (best tumor-to-myometrium contrast), depending on the provided clinical history and the radiologist's availability to supervise image acquisition.[6] MRI staging protocol for EC patients should also include a large-field-of-view axial T_1WI and/or T_2WI images of the pelvis and abdomen in order to identify enlarged lymph nodes, hydronephrosis and bone marrow changes.[5,8]

PHYSIOLOGICAL ENDOMETRIUM CHANGES

The normal zonal uterine anatomy is best appreciated on T_2WI sequence, which typically depict the high signal intensity endometrium surrounded by the low signal intensity junctional zone (JZ, inner myometrium) and the intermediate signal intensity myometrium.[8,10]

Figure 1. Physiological uterine changes On T_2WI the endometrium starts to thicken in the late proliferative phase (a), is thickest in secretory phase (b) and thin during menstrual phase (c). Note the decreased JZ thickness and the hyperintense outer myometrium during secretory phase (b, arrow), respectively the ill-defined and irregularly thickened JZ during menstrual phase (c). After contrast administration, there is a characteristic early enhancement of the subendometrial stripe on proliferative phase (d, arrow), early enhancement of outer myometrium in secretory phase (e) and rapid enhancement of endocervical mucosae and JZ in menstrual phase (F, arrows).



NEONATAL AND PRE-PUBESCENT UTERUS

The endometrium undergoes distinct morphologic changes over a female's lifetime, governed by hormonal physiology. From birth to menarche, the uterine body is small and zonal anatomy is indistinct. The endometrium generally appears as a thin, T2 hyperintense layer, although up to one-quarter of neonates will have endometrial cavity fluid collections.[11] Endometrial thickness (ET) starts increasing once puberty is reached.[12]

REPRODUCTIVE AND POST-MENOPAUSAL ENDOMETRIUM

As puberty progresses, the endometrial appearance on MRI resembles that seen in adulthood, according to hormonal stimulation through different menstrual cycle phases. The knowledge about various MR appearances of the uterus throughout the menstrual cycle is important for EC staging, to avoid inaccurate upstaging of the disease, particularly since, as per European Society of Urogenital Radiology (ESUR) updated guidelines for the staging of EC MRI staging, scheduling scans according to menstrual cycle is not required.[6]

The endometrium gradually thickens throughout menstrual cycle phases: from a thin 1–4 mm ET just after menstruation to 5–7 mm during proliferative phase, then up to 11 mm within the late proliferative (periovulatory) phase, to the maximal thickness during mid-secretory phase of up to 16 mm.[13,14] However, it maintains high T_2WI signal intensity and uniform appearance up until 24 h prior to menses, when T_2WI signal intensity decreases due to blood products. Blood or layers of shed endometrial tissue of low-signal-intensity may be identified within the uterine cavity, and these can show restricted diffusion on DWI (high signal)/ADC (low signal) sequences that should not be mistaken as cancer.[13,15,16] The JZ does not significantly change in thickness between proliferative and secretory phases but may be indistinct or irregularly thickened during menses, due to uterine peristalsis.[17] On post-contrast imaging, during the proliferative phase, although myometrium shows delayed enhancement, the inner myometrium exhibits early uniform enhancement as a continuous subendometrial stripe.[18]

During the secretory phase, the outer myometrium shows early enhancement and there is delayed endometrial enhancement, whilst during the menstrual phase there is early enhancement of the JZ (Figure 1).[17]

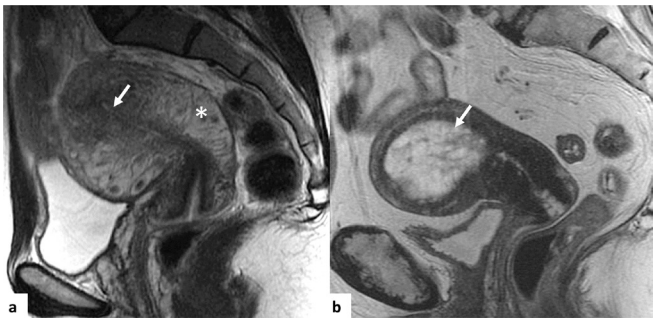
In the post-menopausal female, the endometrium and myometrium atrophy, whilst the JZ may become indistinct. The thickness of the post-menopausal endometrium should take into account whether the patient is on hormonal replacement therapy or tamoxifen. Generally, a thin, homogenous (without any focal thickening) endometrium measuring up to 4 mm is consistent with atrophy and considered as normal, irrespective of whether the patient receives hormonal replacement therapy or not.[19,20] Hormonal replacement therapy on the other hand, may result in endometrial thickening up to 8 mm with variations of up to 3 mm through the month if sequential estrogen/progestin is administered Table 1.[13,21]

Table 1. Physiological endometrial changes

Physiological changes		Relevant MRI features		
		Endometrium	Junctional zone	Outer myometrium
Menstrual cycle phase	Proliferative	• High T2WI SI • Progressively thickening (5–7 mm)	• No significant change on T_2WI (low SI) • Early uniform enhancement of subendometrial layer	• Low T2WI SI • Delayed enhancement
	Secretory	• High T_2WI SI • Progressively thickening (7–16 mm) • Delayed enhancement	• No significant change on T_2WI (low SI) • Early uniform enhancement of subendometrial layer	• Increased T_2WI SI • Early enhancement
	Menstruation	• Thin low-T_2WI SI line (blood products) • Can show restricted diffusion (high DWI and low ADC SI)	• Indistinct or irregularly thickened • Early enhancement	• Indistinct or thinned • Low T_2WI SI
Post menopause		Thin (atrophy)	Indistinct	Atrophied Low T_2WI SI
Pregnancy		Can be mistaken as focally thickened (placenta)	–	–
Oral contraceptives		Thin (atrophy)	Thin or indistinct	Swollen (thick) High T_2WI SI
Tamoxifen		Thick (cystic atrophy)	Can thicken	Can be thinner

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; SI, Signal intensity.

Figure 2. Exogenous hormones During oral contraceptives administration (a), the endometrium is atrophic (arrow) and the myometrium swells and become globular, with high T_2WI SI (*). In contrast, following Tamoxifen treatment (b), one of the spectrum of abnormalities is represented by the endometrium which appears cystically thickened and heterogeneous on T_2WI (arrow). SI, signal intensity.



Endometrial MRI appearance during early pregnancy

MRI may be performed in a patient during early pregnancy only after careful risk/benefit assessment, and without contrast agents, due to theoretical risk to the foetus. However, especially when the patient is not aware of her pregnancy, placenta and/or gestational sac can be mistaken for endometrial pathology (early pregnancy,<10 weeks). The gestational sac in early pregnancy at MRI appears as cystic structure within or near the endometrial cavity, as other fetal features begin to take shape towards the end of the first trimester. It may be small and rather inconspicuous, and the best MRI clue for pregnancy diagnosis is a concomitant corpus luteum cyst, which almost always presents between gestation weeks 5–8 as an ovarian cyst with a thick, enhancing wall.[22] The developing placenta may be seen as an adjacent discoid-shape intermediate to high-SI structure. When the pregnancy test is negative, differentials include retained products of conception or other intracavitary pathology.

Functional endometrial changes due to hormonal therapy administration

Following the administration of oral contraceptives, the endometrium thins and may become atrophic. There is also thinning of the JZ which can become indistinct, whilst the myometrium may exhibit high T_2WI signal intensity, giving the appearance of a globular uterus.[17]

Due to its pro-oestrogenic effects, following tamoxifen administration, there is increased risk of endometrial hyperplasia, polyps and cancer, and these patients need be closely monitored. The endometrium can appear cystically thickened and heterogeneous due to cystic endometrial atrophy caused by endometrial glands obstruction and dilatation, with epithelial atrophy. The amplitude of ET corresponds to the duration of tamoxifen therapy Figure 2.[23]

BENIGN ENDOMETRIAL FINDINGS

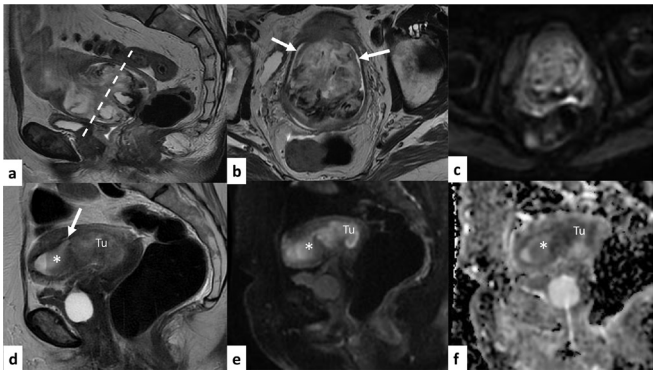
Endometrial hyperplasia (EH)

EH is defined as abnormal proliferation of endometrial glands with increase of gland-to-stroma ratio.[24] Its prevalence rises with age and is mainly related to chronic endometrial stimulation

by oestrogens of both endogenous and exogenous origin.[25] The main clinical manifestation of EH is post-menopausal bleeding, although occasionally, patients are asymptomatic. According to the 2014 WHO system classification, EH is classified as EH without atypia or atypical hyperplasia/endometrioid intraepithelial neoplasia.[26] EH diagnosis is important due to the higher risk of developing EC.[27] It is generally accepted that in symptomatic post-menopausal females, an ET of >4 mm is considered abnormal and requires a biopsy.[28]

In cases where the endometrial cavity is not properly evaluated by ultrasound, MRI is recommended for further evaluation. On sagittal T_2WI, EH appears as a thickening of the endometrium, iso/hypointense to the normal endometrium; however, T_2WI appearance is non-specific.[29] Some recent studies assessed the possible added value of DWI/ADC in characterizing endometrial pathologies.[30–32] Both benign and malignant endometrial lesions may show restricted diffusion, with lower ADC values for the latter group. An ADC value of 0.9–1 have been proposed as a cut-off and is particularly helpful in cases when hysteroscopy and biopsy are not possible.[33,34] Benign and malignant lesions may enhance, thereby the role of contrast agents in clinical practice lies more in staging and therapeutic management.[35]

Figure 3. Benign endometrium pathology – polyp and hematoma. A 48-year-old patient with vaginal bleeding. On T_2WI arising from the endometrial cavity, there is a heterogeneous, polypoid mass with intralesional cysts and hemorrhagic changes (a). The mass is protruding into the cervical canal and is surrounded by fluid (b, arrows). The polyp is high SI on DWI due to T2 shine through secondary to hemorrhage / edema. ADC (not shown) demonstrated no restricted diffusionl (c). Pathology revealed a benign pedunculated endometrial polyp. A 53-year-old patient referred after a positive Papanicoloau test for cervical cancer. On T_2WI the tumor (Tu) is located in the cervix without gross invasion into the lower uterine segment but it is abutting the internal cervical os (a, arrow) causing stenosis with fluid and blood retention (haematometra) into the endometrial cavity. Compared with the fluid, the hyperacute hemorrhage (*) has a low-T2 SI with a corresponding high-DWI SI (e) and low ADC values (e). ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; SI, signal intensity.



ENDOMETRIAL POLYP (EPS)

The majority of EPs are benign, characterized by focal, disorganized proliferation of stromal and glandular components protruding into the endometrial cavity. They are commonly benign but some may be malignant. EPs have a pedunculated or broad-based stalk with central thick-walled vessel. Up to 25% of females may be diagnosed with EPs in their lifetime, particularly during perimenopausal phase.[36] EPs can also cause abnormal bleeding or be completely asymptomatic, their growth being dependent on hormonal stimulation. Increased malignancy risk has been reported for EP associated with vaginal bleeding and post-menopausal status.[37]

In cases of inconclusive transvaginal ultrasound and sonohysterography, MRI could be used as a problem-solving method.[36,38,39] On T_2WI, EPs usually appear hypo/isointense compared to normal endometrium, surrounded by hyperintense fluid; occasionally a stalk with central fibrous stalk, intralesional cysts (20–55%) and hemorrhage (9–35%) are seen.[29,31,35,36,38] EPs do not show restricted diffusion and have various appearances post-contrast enhancement. They may exhibit a rapid and persistent enhancement while, on delayed phase, EPs are hypointense compared to adjacent endometrium.[30,31,40] Differential diagnosis include submucosal polypoid adenomyomas and malignancy. The former are difficult to differentiate from sessile polyps even though, submucosal adenomyoma are more hypointense on T_2WI with a higher frequency of cystic and hemorrhagic components.[29,36] On the other hand, malignant neoplasms are usually characterized by myometrial invasion, restricted diffusion and early enhancement on dynamic post-contrast (DCE) images Figure 3a–c.[35,38]

INFECTIONS

Endometritis refers to acute inflammation of the endometrium mainly observed in the post-partum setting (in particular after cesarean section), and retained products of conception.[41] MRI may show a thickened endometrium with intracavitary fluid and possible hematoma, the latter with hyperintense signal intensity on pre-contrast T_1WI. The endometrial cavity may also exhibit signal void due to the presence of gas and a diffuse endometrial enhancement after contrast administration.[29,41–43]

INTRAUTERINE HEMATOMA (IUH)

IUH is caused by a wide variety of conditions such as pregnancy, post-delivery and post-uterine artery embolization.[29,42,44–46] Ultrasound and CT are usually used to detect acute conditions. On MRI, IUH has hyperintense appearance on unenhanced T_1WI and intermediate/hyperintense signal intensity on T_2WI, the latter sometimes mimicking a solid mass Figure 3d–f.[29,47]

MALIGNANT ENDOMETRIUM PATHOLOGY

Classification

There are two main clinicopathological endometrial carcinoma (EC) subtypes. Type I (80–85%) is estrogen-dependent, affects younger patients and has a good prognosis. Type II (10–15%) is not estrogen driven, affects older females, behaves more aggressively and has a poorer prognosis (5 year survival rate of 40%).[4,48–50] Most cases of EC are sporadic, although 5% have a

Table 2. Dichotomous classification of endometrial carcinoma types

	Type I	Type II
Frequency	Frequent (85%)	Rare (15%)
Associated clinical features	Metabolic syndrome: obesity, hyperlipidemia, hyperglycemia Polycystic ovary syndrome Hyperoestogenism, nulliparity	None
Age of onset	Pre-menopausal <50 y	Post-menopausal >50 y
Estrogen dependent	Yes	No
Precursor lesion	Endometrial hyperplasia	Endometrial intraepithelial carcinoma
Histology	Endometrioid	Non-endometrioid • Serous • Clear cell • Undifferentiated • Carcinosarcoma Endometrioid
Tumor grade	Low (I, II)	High (III)
Genetics	• TP53 rare • PTEN mutation (75–85%) • PIK3CA mutation (50–60%) • PIK3R1 mutation (40–50%) • KRAS mutation (20–30%)	• TP53 mutation (35–90%) • PTEN mutation (<19%) • PIK3CA mutation (18–45%) • PIK3R1 (<12%) • KRAS mutation (<17%)
Surrogate marker approach – ESGO/ESTRO/ESP	• POLE • MMRd • NSMP	• p53 abnormal
Clinical course	Early initial stage (70%) Slow growing Local recurrence	Advanced initial stage (60%) Rapid progression Aggressive behavior Abdominal and lymphatic recurrence
Prognosis	Good (OS 80% at 5 y) - POLE Intermediate – MMRd and NSMP cancers	Poor (OS 40% at 5 y)

OS, Overall survival.

hereditary component linked to hereditary non-polyposis colon cancer (HNPCC, Lynch syndrome) and a higher proportion of Type II cancers.[51,52]

Histologically, Type I is a Grade 1 or 2 endometrioid adenocarcinoma and Type II includes Grade 3 endometrioid adenocarcinoma and other rare etiology such as clear-cell carcinoma, undifferentiated serous carcinoma and carcinosarcoma Table 2.

Genomic and molecular data support this dichotomous classification that have become an integrated part of the pathologic evaluation. Type I carcinomas are preferentially associated with genetic alteration in PTEN, KRAS, CTNNB1, PIK3CA and MLH1 genes, while Type II carcinomas typically harbour TP53 mutations. Limitations of this dichotomous model exist, as 25% of high grade endometrioid carcinoma express mutated TP 53 and behave like serous carcinomas.[53] The considerable molecular heterogeneity of EC was addressed by The Cancer Genome Atlas (TCGA) Research working group, introducing not two, but four molecular subtypes: (1) POLE (ultramutated tumors), (2) microsatellite unstable tumors, (3) high copy-number tumors with mostly TP53 mutations, (4) the group without any of these alterations.[54]

A surrogate marker approach using three immunohistochemical markers (p53, MSH6 and PMS2) and one molecular test (POLE mutation analysis) is clinically feasible in identifying the molecular-based TCGA groups, and particularly relevant for adjuvant treatment recommendation in high-grade/high-risk EC.[55] POLE tumors have excellent prognosis, the p53-abdnormal group exhibits poor prognosis and the remaining two groups have an intermediate prognosis.

FIGO staging is a surgical and pathological system following hysterectomy, bilateral oophorectomy, lymphadenectomy and peritoneal washings.[56] Although FIGO stage correlates with prognosis, pre-operative imaging staging is essential to tailored treatment since such radical surgery may not be suitable for all EC patients. Therefore, MRI has an essential role in stratifying patients with EC.

MRI recommendations

It is widely acknowledged that MRI is the best imaging technique for pre-operatively evaluate of EC patients, in terms of cervical and myometrial invasion depth, factors that correlate with the tumor grade, presence of lymph node metastases and overall survival.[6,57]

Table 3. MRI recommendations in endometrial cancer

Society,Year	MRI Recommendation	Level/strength of recommendation OR Appropriateness criteria
ACR, 2014	**Initial staging or pretreatment;** assessment of local tumour extension for all grades **Assessment of lymph node and distant metastasis** - low-grade tumour (type I, Grade 1–2) - high grade tumour (type I, Grade three and type II) **Surveillance** for asymptomatic patients with - low- intermediate- and high-risk **Post-therapy evaluation of clinically suspected recurrence**	Usually appropriate May be Appropriate Usually Appropriate Usually Not Appropriate Usually appropriate
ESMO,2016	**Optional preoperative workup imaging** - Low risk (type I, Grade 1–2) *4.3:* In clinical stage I, Grade 1 and 2: At least one of the three following tools should be used to assess myometrial invasion if LND is considered: Expert ultrasound and/or MRI and/or intra operative pathological examination - Intermediate- high and high-risk (type I Grade 3; type II) Other imaging methods (thoracic, abdominal and pelvic CT scan, MRI, PET scan or ultrasound) should be considered to assess ovarian, nodal, peritoneal or metastatic disease **Fertility sparing treatment** *2.4:* Pelvic MRI should be performed to exclude overt myometrial invasion and adnexal involvement. Expert ultrasound can be considered as an alternative	IVA IVC IIIB
ESUR,2019	**MRI is recommended to stage endometrial cancer** - Type I, Grade 1–2 Select patients with Stage IA disease who are at low risk for lymph node metastases and would not benefit from lymphadenectomy - Type I, Grade 3 AND Type II Assess the presence of extra uterine spread to facilitate treatment planning **MRI is recommended to facilitate patient selection prior to fertility-sparing management**	NR ** NR**
NCCN, 2020	**Initial workup** – Non-fertility sparing treatment - to establish the origin of the tumour (endocervical versus endometrial) AND to assess local disease extent - Type I – only if suspected or gross cervical involvement (endometrioid histology) OR suspected extrauterine disease - Type II – to all patients to asses local disease extent AND if extrauterine disease is present – Fertility sparing treatment - to exclude myoinvasion AND assess local disease extent **Follow-up/Surveillance** – Fertility sparing treatment - repeat pelvic MRI for patients with persistent endometrial carcinoma after 6 months of failed medical therapy **Suspected recurrence/Metastasis** - whole body PET/CT and/or abdominal/pelvic MRI	IIA IIA IIA
ESGO/ ESTRO/ ESP, 2020	**Pre-operative mandatory work-up includes** - expert transvaginal or transrectal ultrasound or pelvic MRI **Depending on clinical and pathologic risk, additional imaging modalities to asses ovarian, nodal, peritoneal, and other sites of metastatic disease** - thoracic, abdominal and pelvic CT scan, MRI, PET scan, or ultrasound **Fertility-sparing candidates** -Pelvic MRI to assess the extension of the disease	IV C IV C III B

ACR, American College of Radiologists; ESGO/ ESTRO/ESP, European society of gynaecological oncology/European society for radiotherapy and oncology/European society of pathology; ESMO, European society of medical oncology; ESUR, European society of urogenital radiology; LND, Lymph node dissection; NCCN, National comprehensive cancer network; NR, Not reported.
[a]Recommendations based on >80% agreement among experts.

Currently, there are different approaches and recommendations of American College of Radiologists (ACR), National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO) and European Society of Urogenital Radiology (ESUR) regarding the use of MRI for EC patients Table 3.[6,57–59]

The ACR endorses MRI as the modality of choice for the staging of both types of EC and imaging assessment of recurrence or treatment response. Furthermore, MRI is appropriate for assessing lymph node involvement and distant metastasis.[58] The NCCN guidelines recommend MRI for initial assessment of all

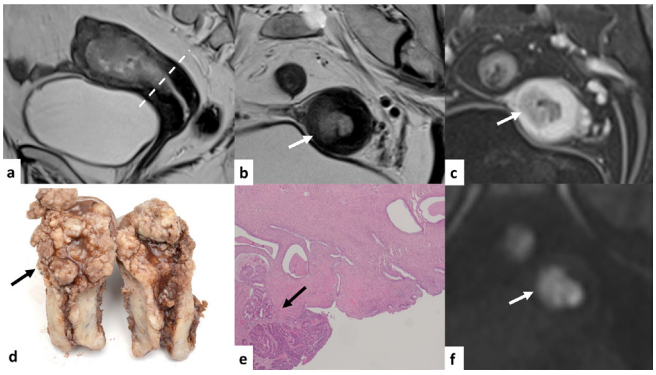
Type II EC patients and only for suspected cervical involvement or extrauterine disease for Type I EC patients.[59]

The updated ESMO guidelines advise for MRI only as an optional pre-operative work-up imaging method in institutions where the lymph node dissection (LND) is tailored according to the stratification of patients into low-, intermediate and high-risk groups.[60,61] Low-risk patients, with Type I tumors and myometrial invasion of less than 50% do not benefit from LND, which is therefore no longer recommended in this group. Several recent prospective trials support the recommendation and show no survival benefit after LND for patients with early stage Grade 1–2 endometrioid carcinoma.[62–64] For high-risk patients with high grade tumors or non-endometrioid carcinomas, the MRI is recommended by the ESMO guidelines in order to assess the extra uterine extent of the disease and facilitate treatment planning.

The updated ESUR guidelines endorse the ESMO guidelines and recommends MRI first, for initial staging of EC, with an imaging protocol tailored based on the risk of lymph node metastases and to facilitate patient selection prior to fertility sparing management.[6] Therefore, in Grade 1–2 endometrioid adenocarcinoma cases MRI helps to identify patients with Stage IA disease who would not benefit from lymphadenectomy, whilst in patients with Grade 3 endometrioid adenocarcinoma or non-endometrioid carcinoma, MRI is focused more on detecting extrauterine spread, thus facilitating treatment planning.

ESGO/ESTRO/ESP guidelines include pelvic MRI as a mandatory pre-operative work-up for all EC patients together with family history, inventory of co-morbidities and geriatric assessment.[54]

Figure 4. "One stop-shop" approach. A 66-year-old patient with vaginal bleeding. On T_2WI there is an intermediate-SI endometrial tumour (a), which interrupts the low-SI of cervical stroma (b, arrow). On DCE (c) the normal enhancement of cervical stroma is disrupted by the hypoenhancing tumor (arrow) which has restricted diffusion on DWI (f, arrow). The gross examination of the surgery specimen is showing the solid tumor (d, arrow). The pathology revealed endometrioid adenocarcinoma involving the cervical stroma (e), consistent with FIGO Stage II. DCE, dynamic contrast enhanced; DWI, diffusion-weighted imaging; SI, signal intensity.



Regardless of the guidelines, the role of MRI in EC patients can be summarized as follows: 1) establish the tumor's origin and 2) assess the local extent of the disease, including the depth of myometrial invasion.

For the majority of the patients, the origin of the tumor is established through clinical examination and histologic evaluation of biopsy specimens. However, in a limited number of cases, it is difficult to confidently establish the tumor's origin for various reasons that include unusual morphologic patterns, mixed-type histologic findings, inadequate samples or discordant readings at different institutions.[65] Differentiating between endometrial and cervical origin before surgery is critical as it has major implications for patient management. On MRI, the origin is subjectively established by the location where the tumor seems to be centered or based on the location of the bulk (>50% of the tumor mass, in cases where the tumor extends across the corpus or cervix). Most ECs are treated with simple hysterectomy and bilateral oophorectomy, while cervical cancer patients undergo simple or radical hysterectomy in early stages and a combination of chemo- and radiotherapy in advanced stages.[60,66,67] MRI has been proved useful in this clinical scenario, with an accuracy of 85–88% in correctly attributing the cancer origin to the corpus or cervix.[65]

MRI has a reported accuracy of 85–93% in delineating the extent of the EC and is the imaging modality of choice to determine the depth of myometrial invasion pre-operatively.[66,68] The latter is the most important morphologic prognostic factor, correlating with tumor grade, presence of lymph node metastases and overall survival.[69,70] Special attention should be given to the eligibility criteria prior to the fertility-sparing treatment for patients with Grade 1 EC who desire fertility preservation. In this scenario, the tumor must be endometrium-confined, with a smooth tumor-to-JZ interphase on T2, DWI and a continuous early enhancement stripe of the subendometrial layer on DCE. Thereby, MRI is confirming the absence of myometrial and cervical stroma invasion, ovarian metastases and the absence of lymphadenopathy.[6,71]

Rad-path correlation of endometrium-related malignancies

On T_2WI, EC appears as a thickened endometrium or soft tissue mass, occupying the endometrial cavity and shows hyperintense signal intensity when compared to hypointense myometrium, and intermediate–low signal intensity relative to hyperintense normal endometrium. Small tumors may not be associated with endometrial thickening or can have a similar signal-intensity with that of normal endometrium. In these cases, DWI and contrast-enhanced sequences are particularly helpful. On DWI, the tumor is hyperintense at the high b value (800, 1000), with a corresponding hypointense signal on the ADC map. On dynamic multiphase contrast material-enhanced (DCE) images, the tumor shows an early enhancement compared with normal endometrium and on later phases it appears hypointense, relative to the myometrium Figure 4.

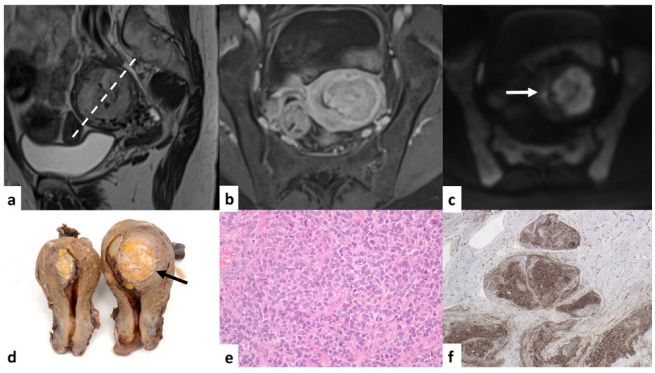
Table 4. Histological classification of endometrium-related malignancy

Primary endometrial tumors	Secondary endometrial tumors
Epithelial tumors Endometrial carcinomas • Endometrioid • Serous • Clear cell • Neuroendocrine Mixed cell adenocarcinoma Undifferentiated carcinoma Dedifferentiated carcinoma	• GU: ovarian cancer • GI: colon, gastric, rectum cancer • Breast cancer: most often lobular type • Melanoma
Mesenchymal tumors Endometrial stromal tumors • Low/high grade endometrial stromal sarcoma • Undifferentiated uterine sarcoma • Uterine tumor resembling ovarian sex cord tumor	
Mixed epithelial and mesenchymal tumors Adenomyoma/ Atypical polypoid adenomyoma Adenosarcoma Carcinosarcoma	
Lymphoid and myeloid tumors Lymphomas – most often non-Hodgkin type Myeloid neoplasm	

The above-mentioned MRI features are common to all endometrium tumor types, despite their pathological and immunohistochemical differences Table 4.

EC is arising from the epithelial cells of the endometrium, being a subtype of epithelial tumors of the uterine corpus, together with serous, clear cell and mucinous carcinoma as well as the rarer undifferentiated/dedifferentiated carcinoma. Furthermore, DWI/ADC values are not useful in predicting the histology or grade in EC patients.[72–74]

Figure 5. Low-grade endometrial stromal sarcoma. A 56-year-old with vaginal bleeding. On T_2WI, there is a heterogeneous endometrial mass with nodular borders (a, arrow), avid enhancement after contrast administration (b) and restricted diffusion on high b-value (c, arrow). The gross examination of the surgery specimen is showing the solid tumour (d, arrow). The pathology revealed well-differentiated endometrial stromal cells (e) that were strongly immunoreactive to CD10 (f) in consistence with a low-grade endometrial stromal tumor.

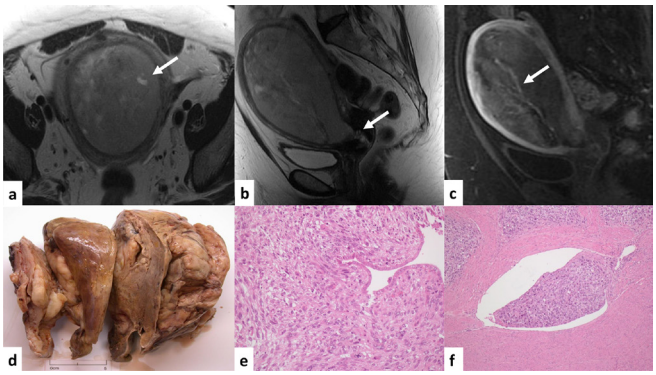


Malignancy may occur also in the stromal endometrial glands, thus being included in the group of mesenchymal uterine tumors with three types of endometrial stromal sarcomas (low grade, high grade and undifferentiated) that account for <1% of all primary endometrial tumors.[75] On MRI, endometrial stromal tumors appear as multinodular masses with irregular borders and nodular extension into the myometrium, ligaments, fallopian tubes, ovaries and along the vessels. The T2 low SI bands, seen at the site of myometrial invasion represent the preserved myometrial bundles. Compared with endometrioid type, stromal tumors tend to have a higher T2 SI and a more avid and heterogeneous enhancement Figure 5.[76–79]

The endometrium may host mixed epithelial and mesenchymal tumors in which the epithelial component is benign and the stromal component is malignant. Adenosarcoma has the highest incidence for peri- and post-menopausal females, with a better survival rate, compared to other sarcomas of the uterus.[79] On MRI, adenosarcoma typically presents as a polypoid, heterogeneous mass occupying the endometrial cavity which may protrude into the cervical canal. On T_2WI, the presence of small hyperintense cystic spaces are observed within the mass, reflecting the glandular epithelial components, while DCE may show an enhancing tumor stalk Figure 6.[80]

Lymphoid and myeloid infiltration of the endometrium is particularly rare. The ovaries are most commonly affected, followed by cervix, uterine corpus, vulva and fallopian tubes.[81] Nearly all cases are non-Hodgkin's lymphomas, with diffuse large B-cell type being the most common subtype. However, when lymphoma develops during pregnancy, involvement of reproductive organs is common. In these cases, the MRI examination is unable to show any suggestive diagnostic features.[82]

Figure 6. Adenosarcoma with sarcomatous overgrowth. A 72-year-old patient with vaginal bleeding. On T_2WI, there is a heterogeneous endometrial mass, with cystic spaces included (a, arrow) which distends the endometrial cavity and protrudes into the cervical canal (b, arrow). The tumor exhibits an enhancing stalk after contrast administration (c, arrow). The gross examination of the surgery specimen is showing the polypoid tumor (d). The pathology revealed a biphasic tumor with mixed glands and abundant stroma (e) with lymphovascular invasion (f) corresponding to an adenosarcoma with sarcomatous overgrowth.



Uterine metastases originate more frequently from genital sites and typically affect the myometrium rather than endometrium. Uterine metastases originating from outside the genital tract are rare and originate from gastrointestinal (44.5%) and breast (42.9%, lobular type most common) malignancies, as well as lung (4.8%) and cutaneous melanoma (3.2%).[83] Figure 7 EC is usually isointense relative to normal endometrium on T1, whereas melanoma metastases typically exhibit a hyperintense

Figure 7. Endometrial metastasis. A 78-year-old patient with previous extralevator abdominoperineal excision of rectum with en bloc posterior vaginectomy and resection of coccyx for rectal cancer. On sagital (a), coronal (b) and axial (c) T_2WI the recurrent rectal tumor (Tu) is seen with restricted diffusion on DWI (f). The tumor is abutting superiorly the uterus, cervix and urinary bladder and invades the perineum and rectus abdominals flap inferiorly and urethra and urinary bladder anteriorly. The endometrial cavity is distended by fluid and soft tissue (d, arrow), the latter with restricted diffusion (e, arrows) suggesting malignancy. The pathology revealed an endometrial metastasis from the recurrent rectal cancer. DWI, diffusion-weighted imaging.

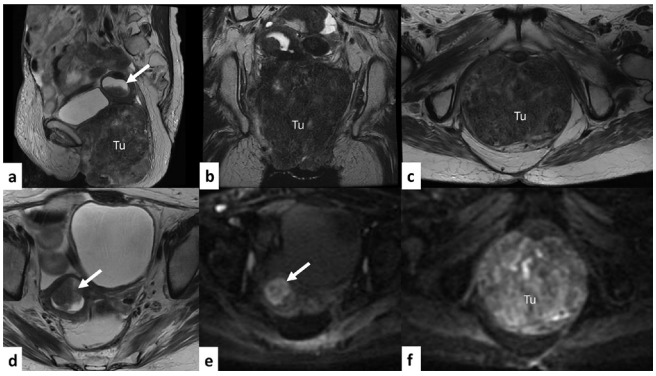
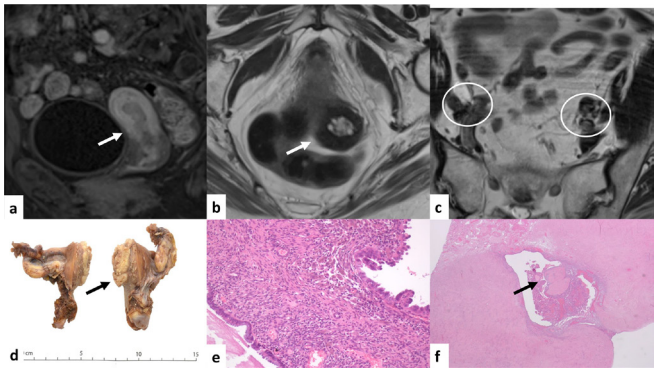


Figure 8. EC clear cell type – microscopic disease. A 62-year-old patient with vaginal bleeding. The endometrial tumor shows less than 50% myometrial invasion on DCE (a, arrow), with no cervical invasion (b, arrow), or ovarian involvement (c, circles) on T_2WI, hence a corresponding imaging FIGO Stage IA. The gross examination of the surgery specimen is showing the solid endometrial tumor (d, arrow). The pathology revealed endometrial carcinoma with clear cell type invading the cervical stroma (e) and ovary (f, arrow shows the micrometastasis <2 mm) corresponding to a final FIGO Stage III A. In this case, MRI under staged the EC. DCE, dynamic contrast enhanced; EC, endometrial cancer.



signal on T1; all other endometrial metastases resemble common MRI findings of EC.[84]

MRI staging pearls and pitfalls

The diagnostic performance of MRI depends on understanding the possible pitfalls that may result in over- or under staging of the EC. There are two major types of pitfalls, technique- and staging-related.

The first category resembles technical artifacts (motion or metal artifacts), inadequate slice thickness >4 mm, improper slice orientation (in cases of retroverted, laterodeviated uterus), limited spatial resolution in depicting microscopic disease. Figure 8 Adequate patient preparation, the use of antiperistalsis agents and proper axial oblique plane limit technical pitfalls.

The second category implies benign endometrial lesions and rare endometrium-malignancy that may mimic EC together with specific stage-related pitfalls: Table 5

Stage I – Tumor invasion of < 50% of the myometrial thickness indicates a Stage IA tumor, while invasion of ≥ 50% of the myometrial thickness indicates a Stage IB tumor. Several pitfalls have been reported for making the evaluation of myometrial invasion to be challenging.[6,85] Physiological uterine contractions (notably during menstruation), can cause transient focal myometrial thickening of low T_2WI SI. If caught adjacent to an EC at MRI staging, a transitory uterine contraction should not be mistaken as myometrial invasion and repeating the sequence or assessing the localizer sequences thoroughly can prevent that misinterpretation pitfall. The presence of leiomyomas, adenomyosis or a thin

Table 5. MRI staging pearls and pitfalls

FIGO staging with corresponding MRI findings	MRI diagnostic accuracya	Pitfalls	Pearls
I – Assess depth of myometrial invasion (MI) IA <50% IB > 50%	55–89%	Over/underestimate the depth of MI in case of: • Poor tumor-myometrium contrast • Thin myometrium due to involution OR compression from a polypoid mass • Tumor extension into cornua • Leiomyoma, adenomyosis	• Use late DCE images (2.5 min) • Use DWI/ADC map – for tumour margins
II – Identify cervical stromal invasion	90–92%	• Cervical inflammation/oedema • Tumor extension into cervical canal • Poor tumor—myometrium contrast	• Correlate with DWI and DCE - > if negative don't report • Should be staged as IA/IB. • DWI/ADC may help to improve the delineation of the tumor margins
III – locoregional spread IIIA-serosa or ovarian involvement; IIIB – vagina IIIC- pelvic/para-aortic lymph nodes	90%	• Concomitant benign ovarian pathology • Questionable serosa deposits • Concomitant primary ovarian tumor • Inflammatory lymphadenopathy	• Dark T2/Dark DWI: benign pathology? • Check DWI for small serosa deposits • Complex solid-cystic mass - > suggest primary pathology • Report if >10 mm, round/spiculated nodes; if uncertain recommend PET/CT
IV – Identify extrauterine spread IVA – Bladder/rectum invasion IVB – Peritoneal deposits	–	• Bladder edema • Questionable peritoneal implants - "Misty mesentery"	• Check for mucosal invasion. • Check DWI for small peritoneal deposits
Applicable in any stage disease	–	• Microscopic disease • Rare endometrium malignancy	• Limited MRI spatial resolution • Check for T2 cystic spaces, enhancing stalk, hyperintense T1

DWI, diffusion-weighted imaging.
[a]According to reference 69, 71

endometrium (post-menopause, cornua region) may result in under- or overestimation of myometrial invasion. In such cases, an intact low signal intensity JZ on T2 and a continuous subendometrial band of enhancement on early phases DCE practically exclude myometrial invasion. DWI/ADC map may help delineate the tumor margins especially in cases of small or isointense tumors or where DCE images are not available.

Stage II – The carcinoma directly invades the cervical stroma. The hyperintense T2 cervical stroma inflammation or oedema may lead to upstaging. If there is no associated DWI/ADC and a normal enhancement of cervical mucosa is observed in the delayed phase (2.5 min), cervical stroma invasion should be excluded Figure 9.[86]

Stage III – Stage IIIA is defined by the tumor invasion of the uterine serosa or ovaries. A concomitant primary ovarian tumor or a benign adnexal mass may be interpreted as a locoregional spread of EC. A primary tumor is suspected when a complex solid-cystic mass with enhancement or restricted diffusion is noted (Figure 10). In cases where a solid tumor with low SI on T2 and low SI on DWI (dark T2, dark DWI) is observed, a benign ovarian tumor should be diagnosed.[10]Figure 11d–f.

Stage IIIB includes vaginal or parametrial involvement and IIIC is for cases which have pelvic and para-aortic lymphadenopathy. To avoid missing vaginal drop metastases, image the entire vagina down to the perineum on T_2WI and DWI. Similarly, whole abdominal and pelvic axial T_1 or T_2WI should be obtained to ensure all lymph node regions are evaluated.

Stage IV – Stage IVA disease is indicated when the tumor extends into the bladder or rectum associated with mucosal invasion. A common pitfall is bullous edema being a sign of tumor invading the subserosal or muscular layer, but does not infer a diagnosis of Stage IV disease. In Stage IVB, distant metastases are noted: lymphadenopathy above renal hilum or inguinal region, malignant ascites or peritoneal deposits Figure 12.[8,10]

CONCLUSIONS

MRI has reliably been used routinely in the pre-operative setting for treatment stratification and has now also recently been officially recognised and included by European and American guidelines as a pre-operative tool in the management of EC patients. Therefore, it is mandatory that all radiologists are familiar with various endometrial appearances on MRI, including peri- and post-menopausal changes and benign pathology. Rare

Figure 9. Staging pitfalls: low contrast tumor-myometrium and upstaging. A 73-year-old patient with vaginal bleeding. There is polypoid endometrial tumor isointense with the myometrium on T_2WI (a, b), which makes difficult to appreciate the myometrial invasion. On DWI, the tumor's margins are better delineated (arrows). The normal low-SI of the cervical stroma is disrupted by the tumor on T_2WI (d, arrow) with a corresponding high-DWI SI (e, arrow) suggestive of cervical invasion. The pathology revealed endometrial serous carcinoma involving >50% of the myometrial thickness and marked cervical mucosa inflammation (f), corresponding to a FIGO Stage Ib. DCE (not available) can avoid this pitfall. DCE, dynamic contrast enhanced; DWI, diffusion-weighted imaging; SI, signal intensity.

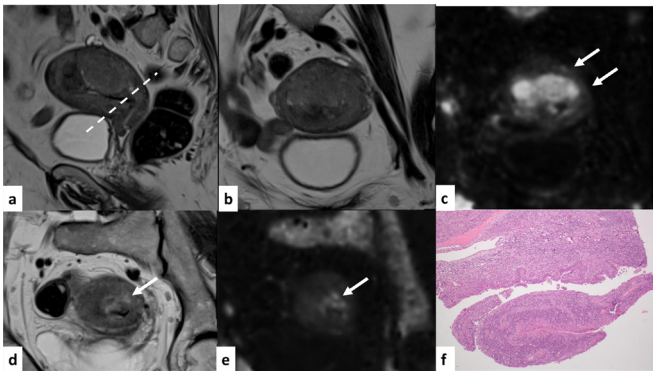


Figure 10. EC serous carcinoma – FIGO III A. A 78-year-old patient with vaginal bleeding. On T_2WI, there is a polypoid mass within the endometrial cavity (a, b) with restricted diffusion on DWI (c). Note the adjacent leiomyoma (*) with characteristic low-T_2WI SI. The left ovary has intermediate-T_2WI SI associated with high-DWI SI (c, arrow); the appearance is suspicious for involvement of the left ovary. The gross examination of the surgery specimen (d) shows the endometrial tumor (arrow heads), the leiomyoma (*) and the left adnexa (arrow). The pathology revealed endometrial serous carcinoma (e) disseminated to the left ovary (f), corresponding to a FIGO Stage III A. DWI, diffusion-weighted imaging; SI, signal intensity.

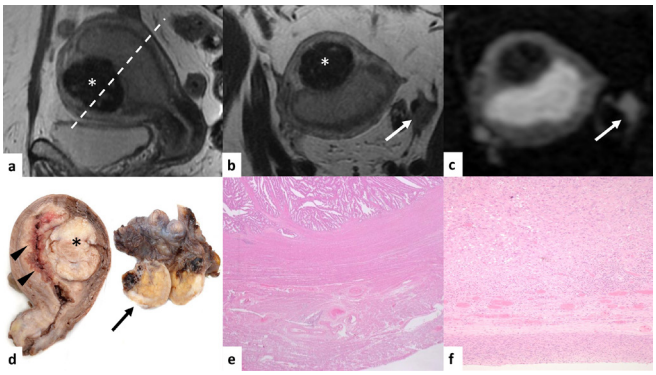
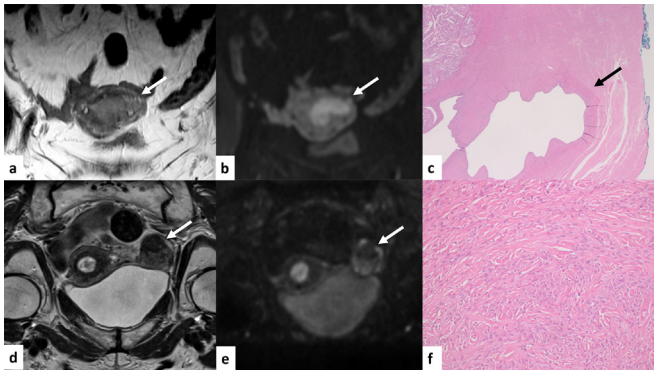
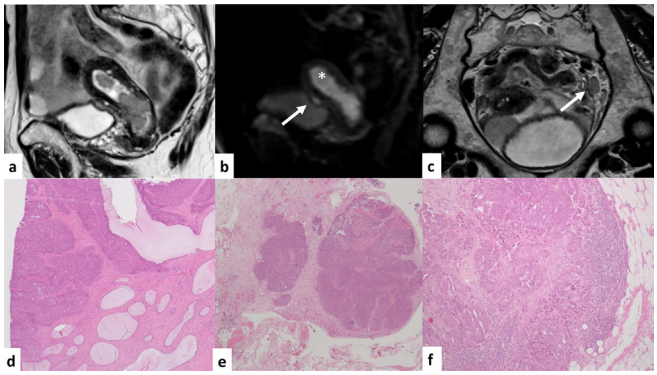


Figure 11. Staging pitfalls: uterine cornua and benign ovarian mass There is a polypoid endometrial tumor abutting the left uterine cornua on T_2WI (a, arrow), invading >50% of the myometrial thickness as suggested by DWI (b, arrow), corresponding to a FIGO Ib stage. The pathology revealed endometrioid adenocarcinoma with <50% myometrial invasion (c, arrow), in consistence with a FIGO Ia stage. In this case, MRI over staged the EC. A 71-year-old patient with mixed high grade endometrial carcinoma with a concomitant left ovarian mass with low-T2 SI (d, arrow) and low-DWI SI (e, arrow), highly suggestive of benign disease. Pathology revealed spindle cells in a whorled arrangement in consistence with an ovarian fibroma (f). DWI, diffusion-weighted imaging; EC, endometrial cancer.



malignancies found within the endometrium may mimic EC and sometimes have suggestive MRI features. Various MRI pitfalls may under- or overestimate the extent of the EC, having significant impact on staging.

Figure 12. Mixed high grade EC – FIGO IVB. A 71-year-old patient with vaginal bleeding. On T_2WI (a) there is a heterogeneous endometrial mass with restricted diffusion (b,*) associated with a suspicious left internal-iliac lymph node (c, arrow). The DWI is easily highlighting a tumor deposit between the bladder and uterus (b, arrow). The pathology revealed endometrioid and serous high grade endometrial cancer (d), involving the peritoneum (e) and left lymph node (f), consistent with a mixed EC, FIGO Stage IVB. DWI, diffusion-weighted imaging; EC, endometrial cancer.



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