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Review Article

Using magnetic resonance tomography as an imaging method for pre-operative evaluation of early-stage endometrial cancer

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Summary

Endometrial cancer is one of the most common gynecological malignancies, especially in high-income regions of the world, and its incidence rates have continued to increase over the past decade. Its staging is surgical, with treatment planning based on the FIGO stage and histological subtype and grade. Imaging is obligatory in the diagnostic work-up process in order to allow more tailored treatment. Magnetic resonance tomography is the preferred imaging modality that may be used to aid in the preoperative risk stratification, surgical planning and individualized therapy.

Key words: Endometrial carcinoma, FIGO staging, magnetic resonance tomography, pre-operative staging

Introduction

Endometrial cancer is the 6th most common cancer in females and the 17th most common cancer overall, with 417 367 new cases and 97 370 deaths in 2020 (Sung et al. 2021). Its incidence rates increased over the past decades, mainly affecting postmenopausal women and today, the average age of diagnosis is 60 years (Mazidimoradi et al. 2024). The highest are reported for North America, Europe, Micronesia/Polynesia, and Australia/New Zealand, while the lowest are those from Africa and South Central Asia (Sung et al. 2021) (Fig. 1).

The main risk factors are age, increased exposure to estrogen caused by nulliparity, estrogen-producing tumors, hormone replacement, tamoxifen therapy, obesity, diabetes, and Lynch syndrome (Wise et al. 2016; Karageorgi et al. 2010). The aging and obese female population worldwide is growing, so the incidence of endometrial cancer is expected to increase (Europe 2022). Approximately 90% of these females complain of abnormal vaginal bleeding, and 75% are with stage I of the disease (limited to the uterus) at diagnosis (Manfredi et al. 2005). However, the standard surgical treatment includes pelvic and paraaortic lymph node dissection because actually, about 15% of these patients with early-stage tumors may already have lymph node metastases (Mariani et al. 2008; Abu-Rustum et al. 2009). The other 85% of these patients will have undergone unnecessary lymphadenectomy, which could be

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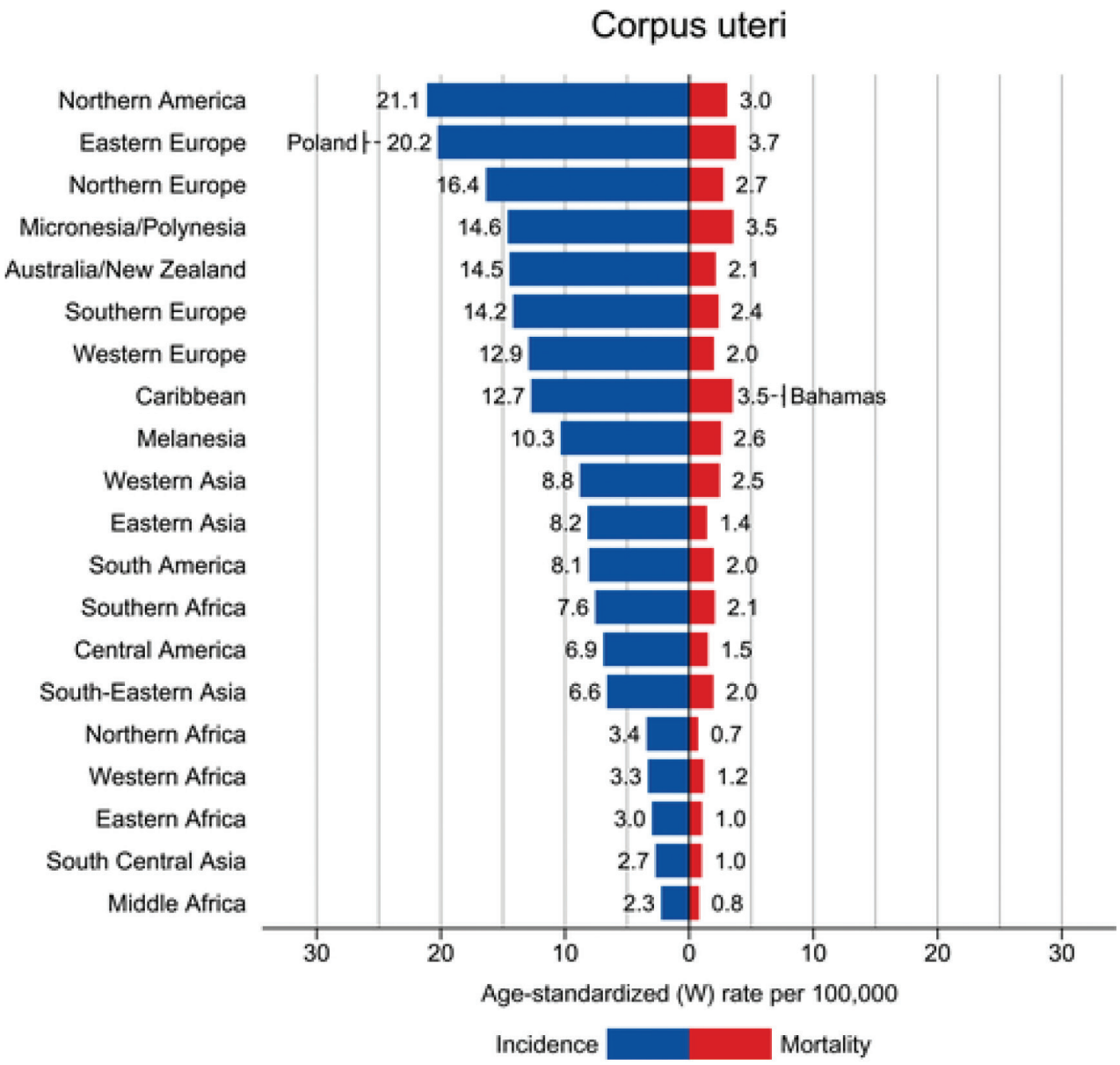

Figure 1. Region-Specific Incidence and Mortality Age-Standardized Rates for Uterine Corpus Cancer in 2020. Rates are shown in descending order of the world (W) age-standardized incidence rate, and the highest national age-standardized rates for incidence and mortality are superimposed (Source - GLOBOCAN 2020).

associated with significant complications such as chronic lymphedema and lymphocele. (Bhosale et al. 2016). These figures show why it is important to evaluate different possibilities to determine patients at high risk for nodal metastatic disease correctly.

Tumor stage and grade, histology, the depth of myometrial infiltration, lymph vascular space invasion, and lymph node metastases are the most important factors that correspond with the disease's prognosis and overall survival (Sahin et al. 2018). In most cases, the preliminary diagnosis with histology subtype and grade can be determined with biopsy (Dijkhuizen et al. 2000). Magnetic resonance tomography is valuable for assessing deep myometrial invasion, cervical stromal involvement, and lymph node spread of the disease (Concin et al. 2021).

Methods

A comprehensive computer literature search was performed to identify articles on the diagnostic use of magnetic resonance tomography for pre-operative staging of endometrial cancer. PUBMED database from 2019 to 2024 was searched with keywords: endometrial carcinoma, FIGO staging, MRI, and pre-operative staging. The reference lists of included studies and review articles were searched manually.

Histopathology and staging systems

Since 1988, endometrial cancer has been staged according to the FIGO staging system. The staging system was revised over the years (Frei and Kinkel 2001). Histopathology is crucial for the prognosis of endometrial cancer, and the revised FIGO staging system is mainly based on it (Berek et al. 2023). After biopsy, risk group sorting according to the WHO Classification of Tumors (5^{th}) edition and FIGO grading of endometrial cancer is required for suitable therapy planning (Concin et al. 2021). The histological tumor types according to these are: endometrioid carcinoma (grade 1 and 2 are considered low grade, and grade 3 carcinomas -high-grade); serous carcinoma; clear cell carcinoma; mixed carcinoma; undifferentiated carcinoma; carcinosarcoma; other rare carcinomas (mesonephric-like); gastrointestinal mucinous type carcinoma. They are also divided into non-aggressive types (low-grade endometrioid carcinoma) and aggressive types (high-grade endometrioid carcinoma and the rest of the above-listed carcinomas). The latest FIGO staging system for endometrial cancer was published in 2009 (Fig. 2).

FIGO Stage	Description
IA	Tumor confined to uterine corpus, <50% myometrial invasion
IB	Tumor confined to uterine corpus, >50% myometrial invasion
II	Tumor invades cervical stroma but does not extend beyond the uterus
IIIA	Invasion of uterine serosa and/or adnexa
IIIB	Tumor involves vagina and/or parametrium
IIIC1	Metastases to pelvic lymph nodes
IIIC2	Metastases to para-aortic lymph nodes, with or without pelvic nodal involvement
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal nodes

Figure 2. The FIGO staging system for endometrial cancer, 2009.

Since then, many clinical trials have been completed. New treatment approaches and prognostic and survival information corresponding to the surgico-pathological findings have been reported. Also, molecular factors with underlying molecular alterations have been researched. Therefore, the FIGO Committee on Women's Cancer suggested some necessary changes. According to Berek et al. (2023) the goals of the new staging system are to determine the prognostic groups better and to create substages to accomplish a better-tailored treatment (Table 1).

If available, molecular profiling allows better prediction of the prognosis of the disease and treatment options, especially for high-grade endometrioid carcinoma (Bosse et al. 2018). It is divided into a good prognosis group (POLEmut in early-stage disease) and a poor prognosis group (p53 abnormal) (Fig. 3).

Table 1. 2023 FIGO staging of the endometrium (Berek et al. 2023).

Stage	Description
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e., low-grade endometroid, with invasion of less than half of the myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease:
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium and with no or focal LVSI
IC	IC
	Aggressive histological type is limited to a polyp or confined to the endometrium.
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI*d* of non-aggressive histological types
IIC	Aggressive histological type with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis:
	IIIA1 Spread to the ovary or fallopian tube (except when meeting stage IA3 criteria)
	IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum:
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria
	IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both:
	IIIC1 Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	III C1ii Macrometastasis
	III C2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	III C2i Micrometastasis
	III C2ii Macrometastasis
Stage IV	Spread to the bladder and/or intestinal mucosa and/or distance metastases
IV A	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IV B	Abdominal peritoneal metastasis beyond the pelvis
IV C	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Figure 3. FIGO endometrial cancer stage with molecular classification (Berek et al. 2023).

This is a good opportunity for prognostic risk-group stratification, which may also contribute to the staging/prognosis scheme and adjuvant treatment. Molecular profiling is important and valuable, especially within high-grade endometrioid carcinoma, as it allows distinguishing a good prognosis group (POLEmut) from a bad prognosis group (p53abn).

Factors for recurrence in early-stage cases such as age, high-grade tumor, and depth of myometrial invasion were established by the PORTEC-1 trial and then were validated by Gynecologic Oncology Group (GOG) study 99 (Creutzberg et al. 2000; Keys et al. 2004). These factors show interconnection, so G1 and G2 tumors tend to be less invasive with not-so-frequent lymph vascular space invasion, and G3 tumors are deeply invasive and with more common lymph vascular space invasion (Das et al. 2014). A study found that patients older than 60 with lymph vascular space invasion had a higher frequency of local and regional recurrence. However, progesterone receptor status and deeper myometrial invasion substantially influenced the disease's distant spread (Zhang et al. 2013). Therefore, pre-operative evaluation of myometrial and lymph vascular space invasion depth is important for tailoring surgical treatment. The depth of myometrial invasion divides stage I of the FIGO staging system into Ia (no or less than 50%) and Ib (more than 50%), so it directly impacts the treatment (Andreano et al. 2014).

Pathological evaluation after surgical treatment is the golden standard for the final staging of endometrial cancer. The staging surgical procedure is a total hysterectomy with bilateral salpingo-oophorectomy, with observation of intraabdominal structures (Koskas et al. 2021). Lymphadenectomy is an essential part of the surgical staging, although some clinical trials do not show significant overall survival improvement, especially in stage I disease (Benedetti Panici et al. 2008; Kitchener et al. 2009).

Low-risk disease features determined by the National Comprehensive Cancer Network (NCCN) include less than 50% myometrial infiltration, tumor size not more than 2 cm, and well/moderately differentiated histology type (Abu-Rustum et al. 2023). The optimal selection of high-risk for advanced disease patients who would benefit from extensive surgical intervention (e.g., lymphadenectomy) and the prevention of overtreatment in low-risk patients are the main clinical challenges, especially since lymphadenectomy has a reported complication rate of up to 17% (Nougaret et al. 2015).

American College of Radiology (ACR) appropriateness criteria recommend MRI as a modality of choice for treatment planning because it provides the best assessment of endometrial cancer. The National Comprehensive Cancer Network (NCCN) guidelines, as well as The European Society of Urogenital Radiology (ESUR) guidelines, also recommend MRI as a pre-treatment method in suspected local and lymph node spread of the disease (Amin et al. 2020).

The use of magnetic resonance tomography

Magnetic resonance tomography is valuable in the pre-operative assessment of endometrial cancer because it can provide detailed local-regional imaging and, therefore, evaluation of the depth of myometrial invasion, which correlates with tumor grade, lymph node metastasis, and patients' prognosis (Nougaret et al. 2015).

Conventional MRI

At least 1.5T magnet strength is needed to ensure adequate quality.

Usually, two perpendicular T2-weighted acquisitions are performed, angled along the short and long axes of the uterine body. In these T2-weighted images, the tumor has medium-to-low intensity, and the normal endometrium is hyperintense. At the same time, the myometrium's inner part has a low signal, and the outer part demonstrates medium intensity (Pintican et al. 2021). T1-weighted acquisitions after applying an intravenous contrast agent, with a delay of 2 min±30 sec, may be optimal for the assessment of myometrial infiltration: the tumor is hypointense, while the myometrium is hyperintense due to higher vascularization (Kinkel et al. 2009). Other acquisitions perpendicular to the axis of the endocervical canal may be made to evaluate the involvement of cervical tumors. Axial and/or coronal images up to the kidneys are useful for evaluating retroperitoneal lymph nodes and hydronephrosis/hydroureter (Meissnitzer and Forstner 2016), (Fig. 4).

Diffusion-weighted MRI

Diffusion-weighted magnetic resonance imaging (DWI) evaluates the Brownian motion of water in tissues. It is restricted in biological tissues by interactions with cell membranes and macromolecules. Usually, the Brownian motion is restricted in tumors because of increased tissue cellularity, so it can be quantified by calculating the apparent diffusion coefficient (ADC) (Tanaka et al. 2018). DWI has been used in addition to conventional magnetic resonance tomography in the pre-operative approach to endometrial cancer for determining the depth of myometrial invasion as well as the stage and grade of the disease, especially if MRI contrast agents are contraindicated for the patient (Seo et al. 2013; Woo et al. 2014). Endometrial cancer is usually hyperintense in high b-value images – high diffusion-weighted, while on ADC maps, it is hypointense, with lower ADC values compared to normal endometrium and endometrial polyps (Sala et al. 2013; Ytre-Hauge 2019; Pintican et al. 2021). In that way, DWI can help to distinguish benign from malignant lesions (Fig. 5).

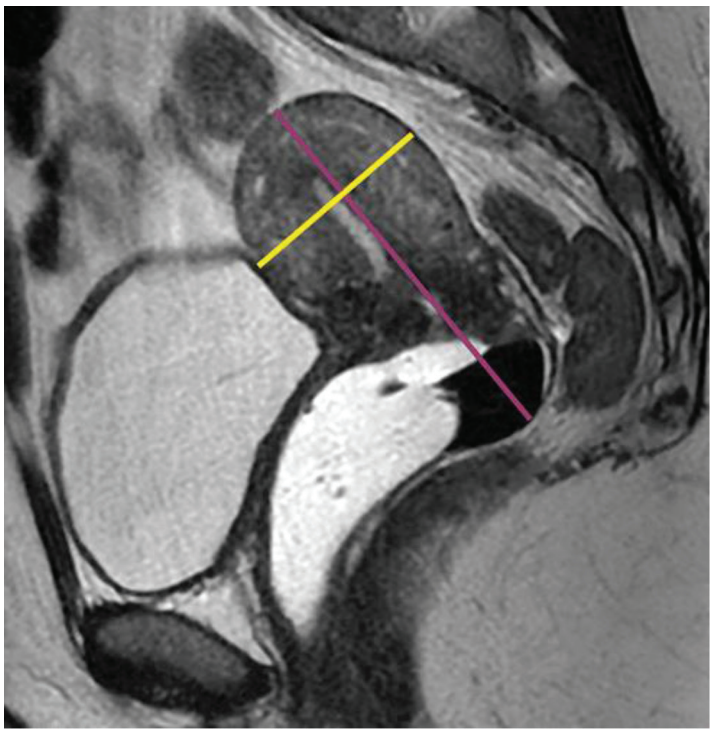

Figure 4. MRI plane for endometrial cancer assessment. Sagittal T2-weighted high-spatial-resolution small-field-of-view MR images should be obtained. Coronal high-spatial-resolution T2-weighted MRI is planned parallel to the long axis of the endometrial cavity (purple line). The axial oblique T2-weighted sequence is planned perpendicular to the long axis of the endometrial cavity (yellow line) - (Maheshwari et al. 2022).

Dynamic contrast-enhanced MRI (DCE-MRI)

This technique represents a function, so tissue perfusion and vascular permeability may be measured (Ytre-Hauge 2019). This technique allows the evaluation of the enhancement of the subendometrial zone (best seen at 35–45s after contrast medium administration) and is useful for fertility-preserving strategies as it is valuable for assessment of the myometrial infiltration – smooth enhancement seen as thin layered enhancement between endometrium and myometrium denies myometrium infiltration (Fujii et al. 2015). DCE-MRI can also be used to assess another important prognostic factor – cervical stromal invasion, if the image acquisition is delayed at 4–5 min after contrast administration (Nougaret et al. 2019).

Many studies compare DWI and DCE-MRI for pre-treatment staging of endometrial cancer, with various results. One larger meta-analysis showed that DWI and DCE-MRI have an equivalent diagnostic capacity, but T2 weighted imaging with DWI combination is superior to them (Deng et al. 2015).

MR spectroscopy (MRS)

MRS is a functional imaging technique that quantifies particular tissue metabolites to obtain biochemical information. It may differentiate benign from malignant lesions, and even more, some studies have reported MRS-measured choline, lipids, and lactate in endometrial cancer to be associated with particular phenotypes (Ytre-Hauge 2019). MRS may be used preoperatively to reveal the metabolic characteristics of the whole tumor (Zhang et al. 2022).

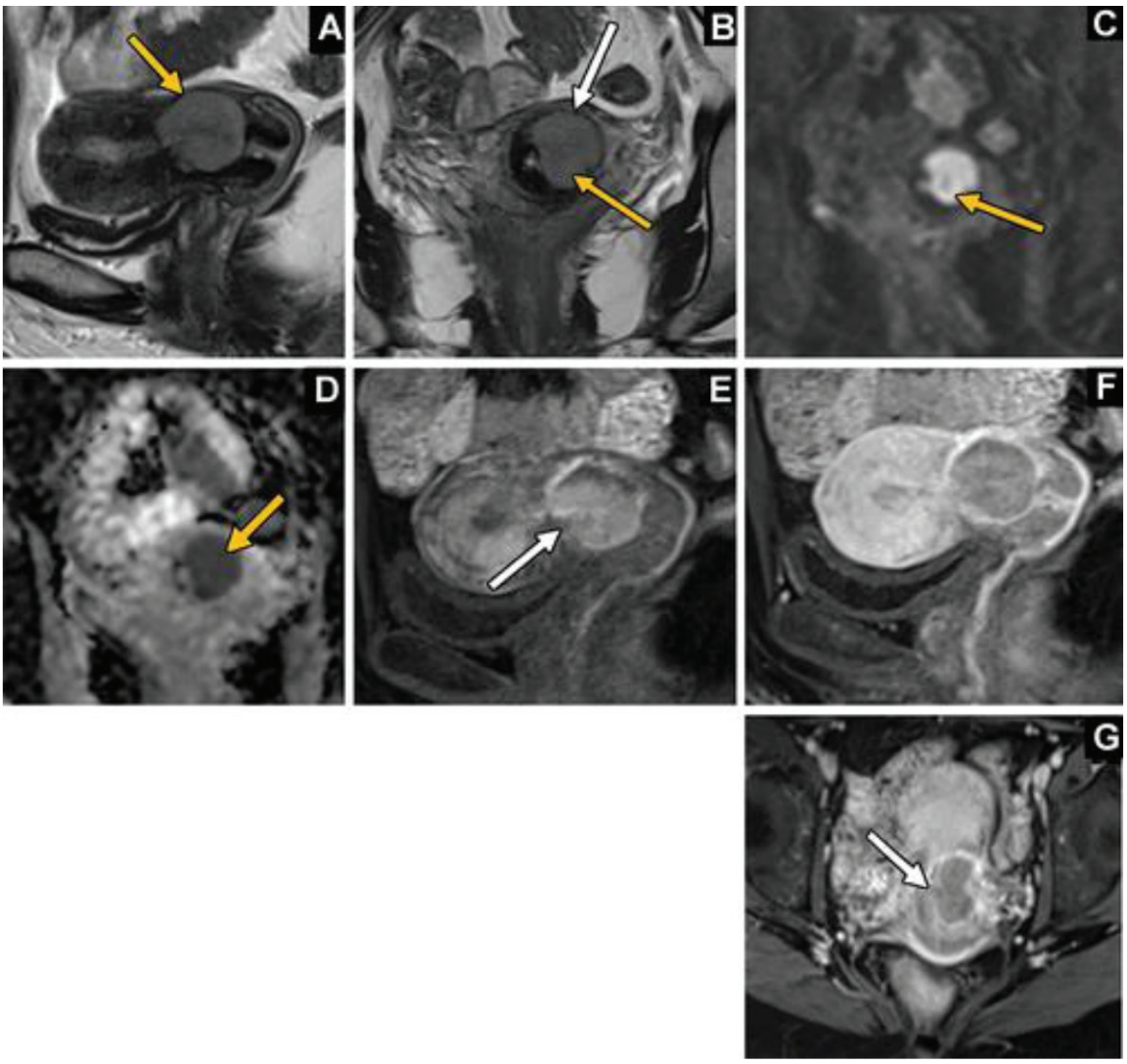

Figure 5. MRI sequences and key signal intensity characteristics of endometrial carcinoma. **A, B.** Sagittal (**A**) and coronal (**B**) T2-weighted MR images demonstrate endometrial cancer involving the lower uterine segment (gold arrow), which is associated with typical T2-intermediate signal intensity relative to the normal T2-hyperintense endometrium and mild T2 hyperintensity relative to the myometrium. Cervical stromal invasion is also evident, disrupting the normal T2-hypointense cervical stroma (white arrow in **B**). **C, D.** Coronal diffusion-weighted MR image (**C**) and ADC map (**D**) demonstrate the hyperintense signal of the tumor on the high-*b*-value image (arrow in **C**) and marked hypointense signal on the ADC map (arrow in **D**). Postcontrast imaging demonstrates characteristic hypoenhancement relative to the myometrium. **E–G.** Sagittal postcontrast T1-weighted fat-suppressed MR images obtained in the early phase (30–40 seconds) (**E**), equilibrium phase (2.5 minutes) (**F**), and axial delayed phase (4–5 minutes) (**G**) demonstrate mildly interrupted subendometrial enhancement anteriorly on the early phase image (arrow in **E**), which is indicative of superficial myometrial invasion. On the equilibrium phase image (**F**), during which tumor-to-myometrial contrast is maximal, compression of the myometrium is demonstrated, but no deep myometrial invasion is present. The axial delayed phase MR image (**G**) re-demonstrates cervical stromal invasion (arrow). Surgical pathologic analysis confirmed superficial myometrial and cervical stromal invasion (Maheshwari et al. 2022).

PET/MRI

This hybrid technique merges the metabolic information from PET with the high soft-tissue contrast of MRI. It is useful in endometrial cancer staging because PET can assess for local-regional and distant spread of the disease, while MRT is better at local tumor evaluation (Tarcha et al. 2023).

Current understanding

The Society of Abdominal Radiology presented a Uterine and Ovarian Cancer Disease-Focused Panel recommending a detailed MRI protocol (Nougaret et al. 2019) (Fig. 6).

MRI Technique	Pulse Sequence	FOV (cm)	Section Thickness (mm)	Matrix
Coronal T2WI	SSFSE or TSE	36–40	6, skip 0.5–1 mm	256 × 256
Sagittal T2WI (no fat saturation)	TSE or FSE	24–26	4	256 × 256
Sagittal DWI (best right after sagittal T2WI)	DWI (50, 500,1000)	28–32	4	80–128 × 80–128
Axial oblique T2WI Perpendicular to long axis of uterus	TSE or FSE	24–26	3–4, skip 0.5 mm	256–320 × 256–320
Axial oblique DWI, perpendicular to long axis of uterus	DWI (50, 500, 1000)	28–32	4	80–128 × 80–128
Axial T1WI and T2WI (perineum to top of L5)	TSE or FSE	30–34	5, skip 1 mm	256–320 × 256–320
Sagittal precontrast and postcontrast T1WI	3D GRE	28	4	256 × 192
Axial oblique postcontrast T1WI at 180 seconds	3D GRE	28	3–4	256–320 × 192–224
Axial delayed postcontrast T1WI (perineum to renal hila)	3D GRE	28	6	256 × 192

Figure 6. MRI protocol for imaging endometrial cancer by the Society of Abdominal Radiology Uterine and Ovarian Cancer Disease-Focused Panel, 2022. (FOV – field of view, FSE – fast spin-echo, GRE – gradient-echo, SSFSE – single-shot fast spin-echo, T1WI – T1-weighted imaging, TSE – turbo spin-echo, T2WI – T2-weighted imaging).

Many studies evaluate the reliability of modern magnetic resonance tomography techniques such as diffusion-weighted, contrast-enhanced, and dynamic MRT for pre-operative staging of endometrial cancer. Most of these studies discuss the sensitivity and specificity of the method for detecting myometrial infiltration of 50% or greater, cervical stromal involvement, and lymph node metastasis. The high sensitivity reduces false negative results and helps to avoid incomplete staging in patients who can benefit from lymphadenectomy. In their study, Luomaranta et al. (2015) measured a sensitivity of 80.7% of MRT in detecting deep myometrial involvement – a negative predictive value of 89.5%, considering it is not enough to avoid lymphadenectomy in patients with no or superficial myometrial involvement. They proposed that a negative result should be confirmed by, for example, intraoperative frozen section analysis (Luomaranta et al. 2015).

Conclusion

The use of magnetic resonance tomography has gained interest over the past decades for the assessment of high-risk features of endometrial cancer, such as deep myometrial invasion, cervical stromal involvement, and lymph node metastasis. Pre-operative evaluation of these key prognostic factors in early-stage patients is needed for tailored surgical treatment. However, the pre-operative evaluation of these variables is still a challenge. Further research on the MRT technique and how it corresponds to histopathology is clinically needed in order to allow more tailored treatment for endometrial cancer patients in a world in which the incidence of the disease is expected to increase.

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