



Role of MRI in Treatment Planning of Endometrial CA

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Abstract

Purpose Endometrial carcinoma is a major cause of morbidity and mortality in women. It is the fourth most common cancer in women and its incidence is rising. Clinical examination and endometrial sampling form the mainstay of diagnosis. Magnetic resonance imaging (MRI) due to its superb soft tissue contrast can play an important role in the management of the disease. The present article reviews the role of MRI to exclude mimics, confirm the diagnosis, stage the disease, and in the follow-up of a patient with carcinoma of the endometrium.

Method Using online databases including PubMed and Medline, literature was reviewed to assess the role of MRI to confirm the diagnosis, stage the disease, and follow-up in a patient of carcinoma endometrium. The examples published were taken from a personal file of cases.

Results MRI with newer sequences like dynamic contrast studies and diffusion-weighted imaging can play an important role in excluding mimics, staging, and in the follow-up of the patient.

Conclusion MRI with advanced sequences is the imaging modality of choice in pre- and postoperative evaluation of patients with endometrial carcinoma. It is the most sensitive imaging modality to evaluate myometrial invasion and early involvement of the cervix.

Keywords

- ▶ endometrial CA
- ▶ myometrium
- ▶ MRI

Introduction

Endometrial carcinoma is a major cause of morbidity and mortality in women. It is the fourth most common cancer in women and is the most common gynecological malignancy. Its incidence is rising, especially in metro cities. Globally, it is the sixth most common malignancy with approximately 320,000 cases diagnosed annually.¹ Clinical examination and endometrial sampling form the mainstay of diagnosis. International Federation of Gynecology and Obstetrics (FIGO) staging of endometrial carcinoma is based upon surgical findings. The surgery involves hysterectomy, bilateral salpingo-oophorectomy, nodal dissec-

tion, omental biopsy, and peritoneal washing.² The clinical management, however, is different and not based upon the FIGO staging system. Patients presenting in early stages of the disease may be treated with minimally invasive laparoscopic hysterectomy and salpingo-oophorectomy while more extensive surgery can be reserved for high-risk patients. This decision is highly dependent upon preoperative staging where imaging plays an important role. Magnetic resonance imaging (MRI) can reliably depict the key prognostic factors—depth of myometrial invasion and involvement of cervical stroma.^{3–7} Although it is not part of the FIGO criteria, staging MRI is recommended by the National Cancer Institute of France, the European

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Society of Radiology Guidelines, and the Royal College of Radiologists.^{8–10}

The role of imaging is predominantly in staging the cancer, assessing lymphadenopathy, and thereby deciding the appropriate management. In addition, imaging assists in prognostication of the disease. Postoperative/post-radiotherapy/computed tomography (CT) imaging is also essential to determine the response of treatment and deciding on further management by evaluating for residual or recurrent disease. Here, we present a review of carcinoma endometrium, starting with brief anatomy, major features on MRI, its staging, differential diagnosis, and some common pitfalls.

Endometrial carcinoma takes its origin from the epithelial lining of the uterus. It predominantly affects women in the 55- to 65-year age group. Risk factors include nulliparity, obesity, early menarche, late menopause, high estrogen levels, and drugs like tamoxifen. The most common clinical presentation is abnormal uterine bleeding which occurs early in the disease process, thereby helping in timely detection.

The main role of MRI in carcinoma endometrium is to detect myometrial invasion and cervical involvement which would further correlate with lymph nodal metastasis and grade of the tumor. Dynamic contrast studies and diffusion-weighted imaging (DWI) cannot only improve sensitivity and specificity but also help in differentiating recurrence from postoperative changes. Various authors have reported high sensitivity and specificity of MRI in assessing the locoregional spread—sensitivity of 33 to 100%, a specificity of 44 to 100%, and accuracy of 58 to 100% for deep myometrial invasion; specificity of 82 to 96%, accuracy of 46 to 89% for cervical stromal invasion; and specificity of 88 to 100%, accuracy of 83 to 93% for nodal metastasis.^{11–13} However, internationally there is a difference in opinion about the role of MRI in evaluating these patients. According to the American College of Radiology appropriateness criteria, MRI should be the preferred imaging modality for treatment

planning when available as it allows the best overall assessment of the disease.¹⁴ National Comprehensive Cancer Network advises MRI if cervical invasion is suspected and in pretreatment evaluation of type II endometrial cancer.¹⁵ The European Society of Urogenital Radiology guidelines recommend MRI in high and intermediate risk malignancies, suspected advanced disease, and before node sampling.¹⁰ A multidisciplinary European expert consensus meeting on endometrial cancer advocated the use of MRI in stage I endometrial carcinoma for the assessment of myometrial invasion. MRI is strongly recommended by the National Cancer Institute of France and the Royal College of Radiologists.^{8–10}

There are two histopathological subtypes of endometrial carcinoma. Type I affects younger women with high estrogen levels, presents at an early stage (usually 1 or 2) with vaginal bleeding, and has a good prognosis. These tumors usually arise from epithelial hyperplasia and respond to hormonal therapy. Type II tumors affect women of perimenopausal age, are of higher stage at presentation, and have dismal prognosis. These usually arise from atrophic endometrium and are not hormone sensitive. Tumors originating from the stroma or muscle layer of myometrium are uterine sarcomas.

Adequate clinical history is of utmost importance, followed by transvaginal ultrasound (USG) which is the first imaging modality for screening whenever any patient presents with abnormal vaginal bleeding. In case of postmenopausal females, an endometrial thickness of less than 5 mm is considered normal, 5 to 8 mm is the gray zone, and greater than 8 mm is highly suspicious for malignancy.¹⁶ In the latter case, MRI is the next imaging investigation of choice.

Protocol

The scan should be performed on a high magnetic strength scanner of 1.5 Tesla or more with the patient fasting to

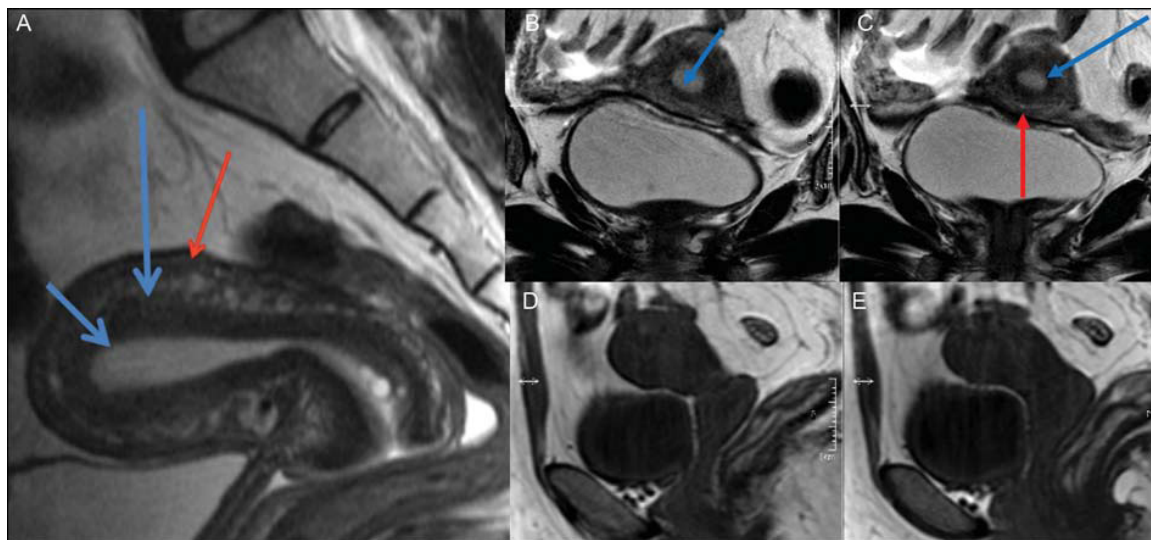


Fig. 1 Sagittal T2 (A), coronal T2 (B, C), and sagittal T1 (D, E) images showing trilamellar anatomy on T2 images—endometrial lining (small blue arrow), junctional zone (long blue arrow), and myometrium (red arrow). On sagittal T1 images, the three zones cannot be differentiated.

reduce bowel motion artifacts, having a partially full bladder, and an empty rectum. There should be a gap of at least 10 days between the biopsy and the MRI examination. For optimal results, it is essential to use appropriate sequences using correct imaging planes to obtain high contrast and spatial resolution. T2-weighted images are obtained in sagittal, axial, and coronal planes. It is important to place axial scans perpendicular to the long axis of the uterus. T1-weighted and DWIs with $b=1,000$ are obtained in the same plane as axial T2 images. DWIs are always evaluated with apparent diffusion coefficient (ADC) images. T2 FATSAT images are also obtained in the axial plane. Three-dimensional dynamic contrast-enhanced (DCE) imaging is performed using gadolinium as the contrast agent. Contrast studies are essential to demonstrate small lesions, for the correct staging of disease, as well as for follow-up of the patients. The pelvic study is followed by screening the whole abdomen in the coronal and axial plane.

Normal Appearance

T1 images cannot differentiate the three zones of the uterus and show signal intensity of skeletal muscle. T2-weighted images are the best to assess the trilamellar anatomy of the uterus (►Fig. 1)—the three zones from the center to outside are hyperintense endometrium, low intense junctional zone, and outermost intermediate signal intensity smooth muscle. Endometrium shows hyperintense signal on T2-weighted images regardless of the hormonal status and age. The thickness, however, varies with age and hormonal status. During menstruation, low intense signal may be seen within the endometrial cavity on T2-weighted images due to blood contents. MRI is the only imaging modality that can demonstrate the junctional zone corresponding to the innermost layer of the myometrium. The low intense signal is a result of the lower water content, higher nucleus-to-cytoplasm ratio, and smaller extracellular space of inner myometrium.^{17,18} Like the endometrium, the thickness of the junctional zone varies with hormonal status and is thickest around the 24th day of the menstrual cycle. However, it usually does not exceed 5 mm. A focal thickness of more than 12 mm suggests

adenomyosis (►Fig. 2). Focal uterine contraction may mimic adenomyoma and has to be kept in mind. The outer myometrium shows intermediate signal which is relatively more in the secretory phase. Postcontrast scans reveal zonal anatomy with endometrium and outer myometrium showing enhancement, and the junctional zone showing less enhancement.

After menopause, there are changes in size as well as in signal intensity patterns. There is a reduction in the size, the endometrium is seen as a thin central stripe of hyperintense signal on T2 images. The differentiation between the junctional zone and myometrium becomes less distinct and may get lost. These changes may not occur if the patient is on external hormonal therapy.

Indications for MR Imaging

MRI is indicated in (1) histologically proven endometrial carcinoma; (2) suspected cancer on USG with vaginal stenosis with no access for biopsy; (3) unequivocal CT/USG; (4) uterine carcinoma of unknown origin; and (5) follow-up, recurrence versus posttreatment changes.

Imaging Appearance of Endometrial Carcinoma

On T1-weighted precontrast imaging, endometrial carcinoma appears isointense in contrast to hypointense endometrium and is usually difficult to discern. On T2-weighted images, the tumor demonstrates heterogeneous intermediate signal compared with hyperintense endometrium and is mildly hyperintense to normal myometrium (►Fig. 3).^{19,20} However, subtype II may exhibit inhomogeneous morphology with areas of hemorrhage and necrosis and is usually diagnosed with deep myometrial invasion. Detection of myometrial invasion can be challenging in certain cases where there may be associated leiomyomas or adenomyosis, in elderly females where there is myometrial thinning due to uterine involution, when tumor to myometrial contrast is poor, or when the tumor extends to the cornua.²¹ In such

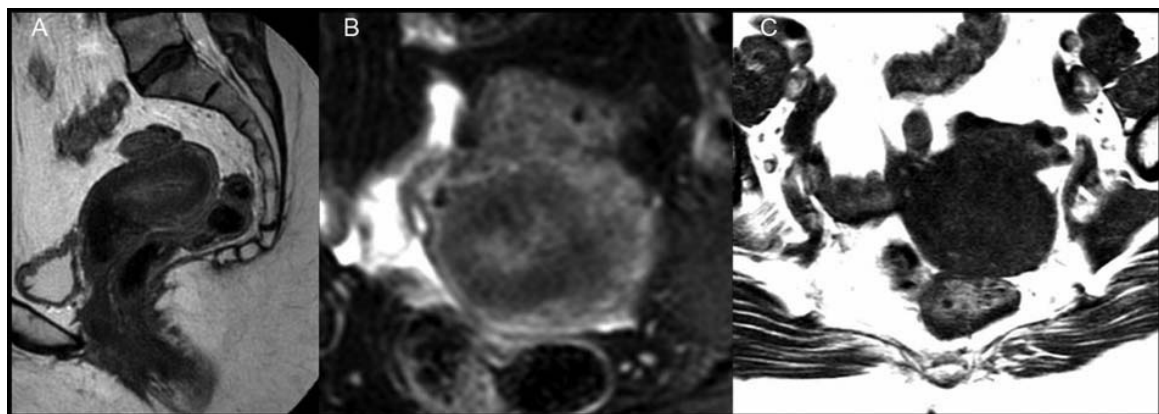


Fig. 2 Sagittal T2 (A), axial T2 (B), and axial T1 (C) images showing diffusely thickened junctional zone—seen as low intense signal on T2 (A, B) images. On T1W images (C) tiny hyperintense foci are seen in the periphery suggestive of adenomyosis.

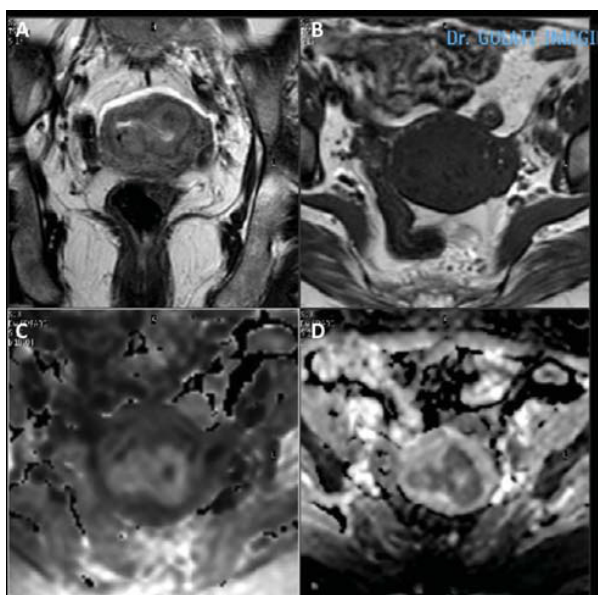


Fig. 3 T2W coronal (A) and T1W axial (B) images showing an isointense mass arising from the endometrium and infiltrating into the myometrium, however, the mass is not extending beyond the serosa—stage IB. Corresponding diffusion-weighted imaging (DWI) (C) and apparent diffusion coefficient (ADC) (D) maps show diffusion restriction.

cases, DCE imaging and diffusion studies prove to be of great help.

On dynamic contrast studies, normal myometrium shows avid enhancement whereas the tumor enhances more slowly and with less avidity than adjacent parenchyma. This distinction is best seen at 120 to 240 seconds of contrast administration, hence is the best time for evaluation of the depth of myometrial invasion.²² Four-minute sequence acquisition is important to assess infiltration into the cervix. T2-weighted sequences in combination with DCE T1 sequences give diagnostic accuracy of up to 98%.^{23–25} Few lesions may be isointense in the equilibrium stage of the dynamic study so it is essential to assess all dynamics.

DWI is functional imaging based upon the Brownian movements of water molecules. In diffusion-weighted sequences, tumoral tissue shows restricted diffusion and shows bright signal on diffusion images and dark signal on ADC maps. The tumor tissue has a significantly lower ADC value ($0.86\text{--}0.98 \times 10^{-3} \text{ mm}^2/\text{s}$) than the normal endometrium ($1.28\text{--}1.65 \times 10^{-3} \text{ mm}^2/\text{s}$); and higher the grade of malignancy, lower the ADC.^{26–28} Many studies in the past have proven the utility of DWI in assessing myometrial and cervical invasion.^{29,30} In a study by Rechichi et al,¹³ diffusion was shown to have higher diagnostic accuracy than DCE in the staging of endometrial carcinoma. In addition, DWI with ADC maps can provide an insight into the histopathology of the tumor, thereby suggesting the aggressiveness of the tumor. With the help of diffusion, mimickers and benign lesions can be easily differentiated. DWI can also play an important role in the detection of pelvic lymph nodes. Malignant nodes show higher diffusion restriction and thus can be easily picked up on DWI sequence. DWI has a

role in posttreatment evaluation as well, as it can accurately distinguish between tumoral recurrence and postradiation inflammatory changes, as both of them would have a similar high signal on T2-weighted sequence.

Staging of Endometrial Carcinoma

FIGO staging is commonly used for staging endometrial carcinoma. It was formulated in 1988 and revised in 2009. It is primarily staged surgico-pathologically. The modified 2009 FIGO staging system has given a boost to the role of imaging in endometrial carcinoma. The new system combines superficial invasion (less than 50% myometrial thickness) and disease confined to the endometrial cavity as stage IA, whereas invasion of the outer half of the myometrium is classified as stage IB. The definition of stage II changed with the removal of cervical mucosal involvement as a determinant of upstaging, keeping only cervical stromal invasion to define stage II. It is not possible to assess mucosal involvement on MRI but the involvement of cervical stroma can be assessed on MRI thereby improving the accuracy of MR staging. Table 1 summarizes the 2009 FIGO system and its corresponding MRI findings.

Stage I

This is an early stage of cancer where the tumor is limited to the corpus uteri. It is further subdivided into A and B depending on the depth of myometrial infiltration. The tumor is seen as a hypoenhancing mass having intermediate signal on T2, with a hyperintense and enhancing endometrium surrounded by a T2 hypointense junctional zone. In stage IA, there can be either focal or diffuse thickening of the endometrium with or without infiltration of the junctional zone. If the depth of infiltration of the myometrium is less than 50%, it is classified as stage A (► Fig. 4) and as stage IB if it is equal to or more than 50% (► Fig. 5). In stage IB, there is definite disruption of the junctional zone with marked infiltration of the myometrium. Both T2 and postcontrast images should be evaluated for determining the depth of invasion.

Stage II

There is direct invasion of the cervical stroma with no extension outside the uterus. In this stage, approximately 50 to 67% of patients will have either involvement of lymph nodes or extrauterine disease.^{31,32} The intermediate to T2 hyperintense mass will invade the internal os to enter into the endocervical canal and infiltrate the T2 hypointense stroma (► Figs. 6 and 7).

Stage III

There is locoregional spread of the tumor. It has been divided into A, B, and C. In IIIA, there is extension of the mass to the serosa of corpus uteri or the adnexae (► Fig. 8). On MRI, there will be disruption of the outer thin myometrial wall and extension of the mass beyond the serosa. Deposits in the ovaries can also be identified. In IIIB, there is involvement of the vagina or parametrium which can be well appreciated on

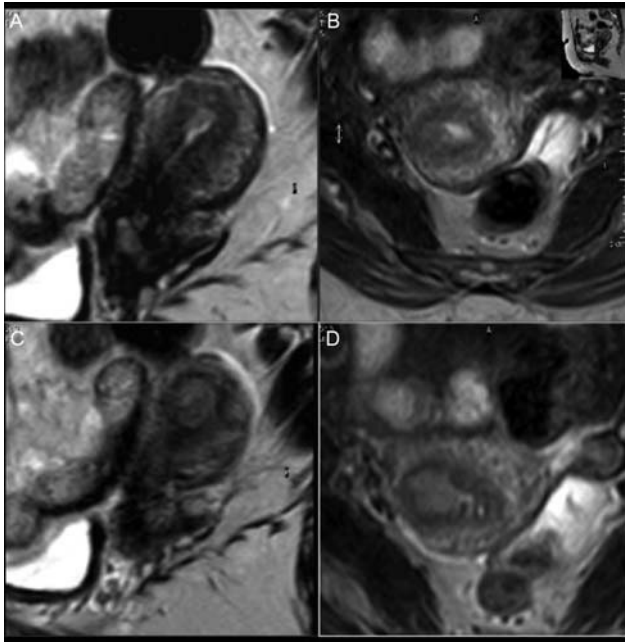


Fig. 4 T2W sagittal (A, C) and axial (B, D) images show endometrial mass infiltrating into the superficial myometrium invading less than 50% of the myometrium—stage IA.

T2 or on post-gadolinium T1 images (►Fig. 9). There can be direct extension or skip lesions. In IIIC, there is lymph nodal involvement. When pelvic nodes are involved, it is classified as IIIC1 and when paraaortic nodes are involved it is IIIC2 (►Fig. 10). This depends on the part of uterus involved, as the middle and lower uterine segments drain into pelvic nodes whereas the cornua and fundus drain into the common iliac and paraaortic nodes. Nodal involvement can be diagnosed

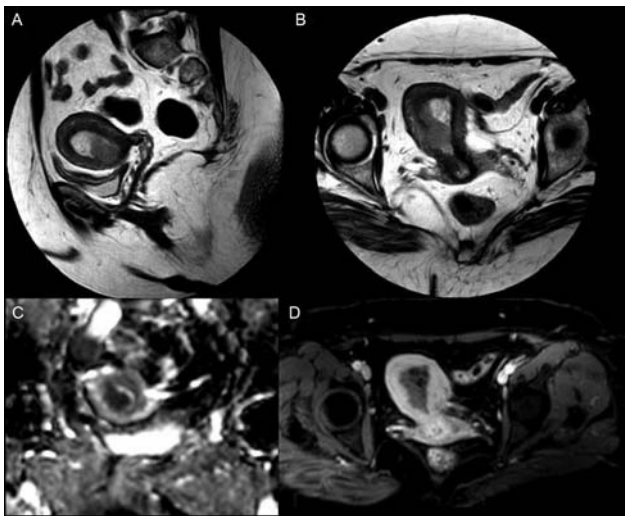


Fig. 5 Sagittal (A) and axial (B) T2W images showing an iso- to mildly hyperintense mass in the lower uterine body arising from the endometrium and infiltrating into the myometrium. More than 50% myometrial invasion is seen with an intact serosa. Apparent diffusion coefficient (ADC) map (C) shows the mass to be highly hypointense suggestive of diffusion restriction. Postcontrast image (D) shows the map to be hypoenhancing as compared with the myometrium—stage IB.

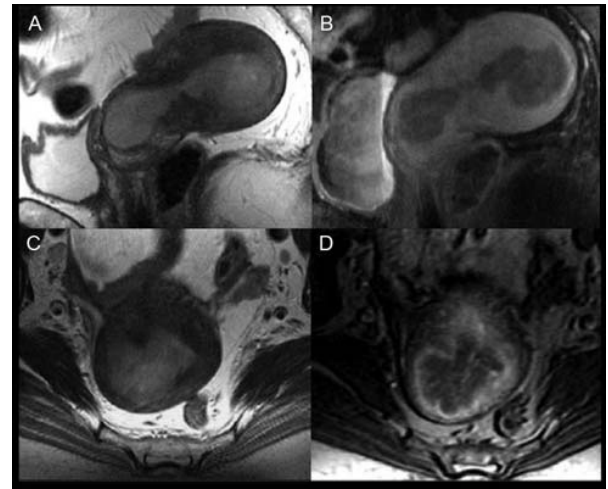


Fig. 6 T2W sagittal (A), axial (B), postcontrast sagittal (C), and axial (D) images showing an irregular endometrial mass infiltrating deep into the myometrium and cervical stroma—stage II.

based on morphology on T2-weighted images, or functionally by DWI.

Pelvic Lymph Node Assessment

Pelvic lymph node assessment is of utmost importance as that would determine the management and prognosis of the patient. Characteristics of metastatic nodes include—short axis diameter greater than 10 mm, rounded shape with irregular margins, contrast enhancement, restricted diffusion, and the presence of extranodal soft tissue (►Fig. 11). However, these criteria, especially size, have their limitations. The nodes may show these changes when there is superadded inflammation or infection, and not metastasis.

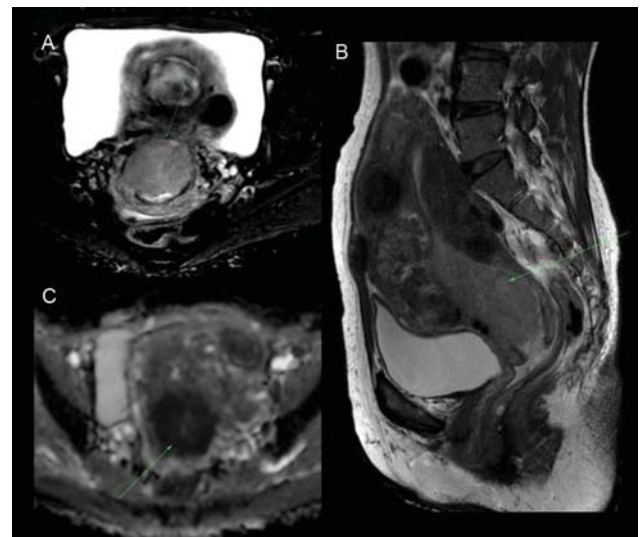


Fig. 7 Short tau inversion recovery (STIR) axial (A) and sagittal T2W (B) images showing a large polypoidal isointense endometrial mass projecting into the endometrial cavity and into the cervical canal which is dark on apparent diffusion coefficient (ADC) image (C) signifying marked diffusion restriction—stage II. T2W hypointense intramural fibroids are also seen.

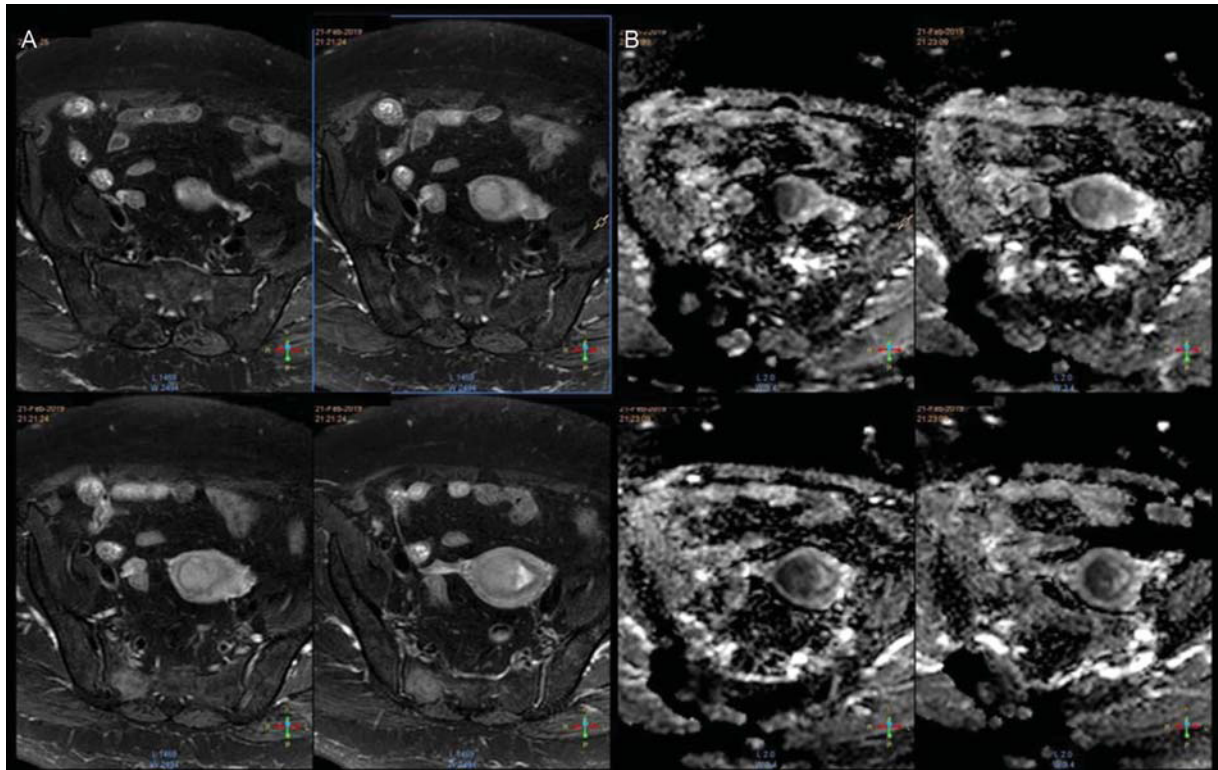


Fig. 8 Axial T2-weighted images (A) showing a heterogeneous soft tissue mass filling the endometrial cavity showing mildly hyperintense signal on T2 images with low intense signal on apparent diffusion coefficient (ADC) images (B) suggestive of diffusion restriction. The mass shows full-thickness infiltration of the myometrium with extension to serosa near the right cornu, well seen on ADC images—stage IIIA.

In such cases, the distinction can be made with ADC calculation which will be lower for metastatic nodes. The studies have shown a good correlation between depth of myometrial invasion with nodal metastasis which increases from 3% when the depth of tumor is less than 50% of myometrial

thickness to 46% when more than 50% of myometrial thickness is involved.^{33–35}

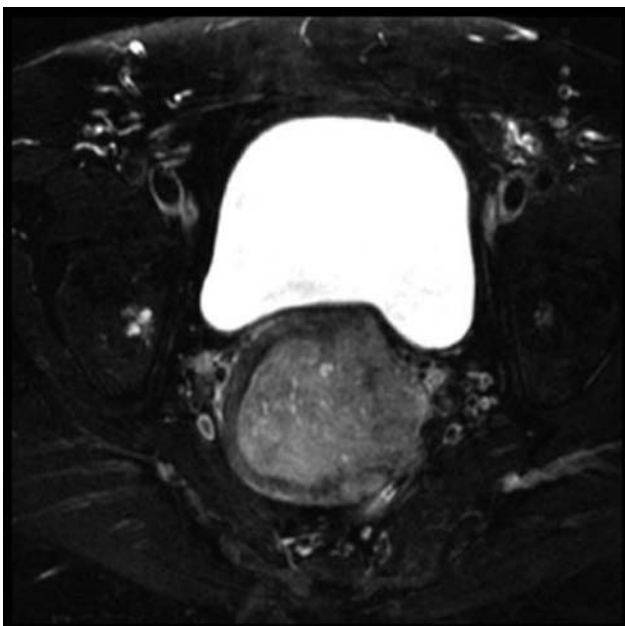


Fig. 9 Axial short tau inversion recovery (STIR) image showing a large endometrial soft tissue mass showing full-thickness myometrial invasion with extension to the left parametrium—stage IIIB.

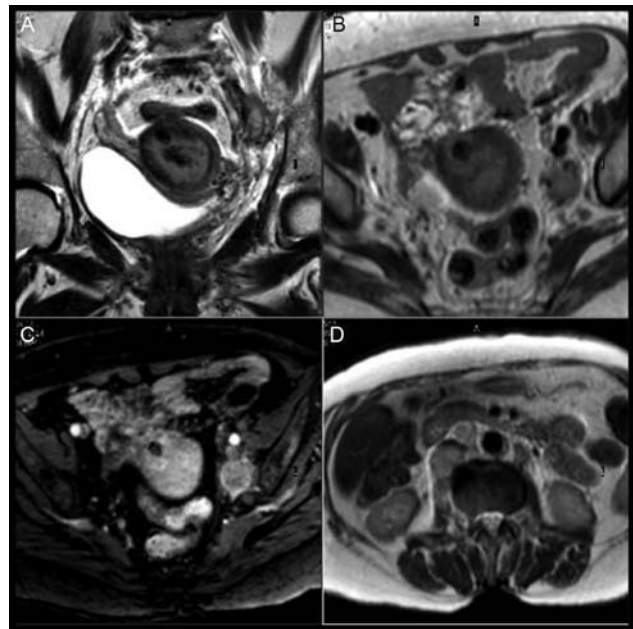


Fig. 10 T2W coronal (A) and T1W axial (B) image depicting an endometrial mass extending to the serosa, short tau inversion recovery (STIR) axial (C) image shows enlarged left internal iliac node, T2W axial (D) image shows enlarged aortocaval node—stage IIIC2.

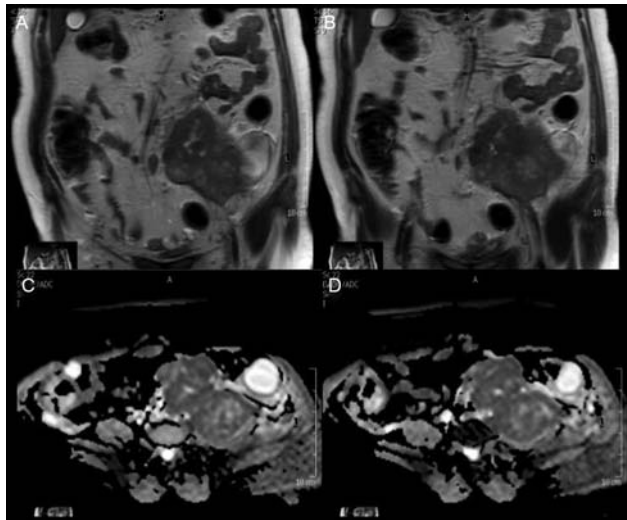


Fig. 11 Coronal (A, B) and axial apparent diffusion coefficient (ADC) images (C, D) showing an irregular lobulated heterogeneous soft tissue mass in the left pelvic region demonstrating iso- to hyperintense signal on T2, and low intense signal on ADC images suggestive of metastatic nodal mass in a follow-up case of endometrial carcinoma.

Stage IV

This is the advanced stage where there is an infiltration of bowel/bladder mucosa (IVA) or there is distant metastasis (IVB).

Uterine versus Cervical Carcinoma

Most of the time it is not difficult to differentiate endometrial from cervical carcinoma based on clinical history and examination. However, at times the distinction is not clear even on histology which is essential as the management and prognosis of the two groups varies.

Bhosale and colleagues³⁶ in a retrospective study found that MRI can differentiate cervical from endometrial carcinoma, with a sensitivity and specificity of 88 and 88%, respectively, in endometrial carcinoma; and sensitivity and specificity of 75 and 93%, respectively, in cervical carcinoma. The key features to differentiate the two were the epicenter of the mass and enhancement pattern in dynamic contrast imaging. Cervical carcinomas were epicentered to the cervix and showed early enhancement as compared with the cervical stroma and endometrial carcinoma showed epicenter in the uterus, showing late enhancement as compared with endometrium and myometrium. Bourgioti et al found seven statistically important criteria to distinguish the two—location of the tumor, early enhancement on dynamic contrast imaging, tumor rim enhancement, depth of myometrial invasion, cervical stromal integrity, intracavitary mass, and retained endometrial secretions.³⁷ They also designed a scoring system based on these criteria to distinguish the two in cases where histology is indeterminate.

Mimics of Carcinoma Endometrium

Four conditions may mimic endometrial carcinoma—submucosal leiomyoma/fibroid, endometrial hyperplasia, adeno-

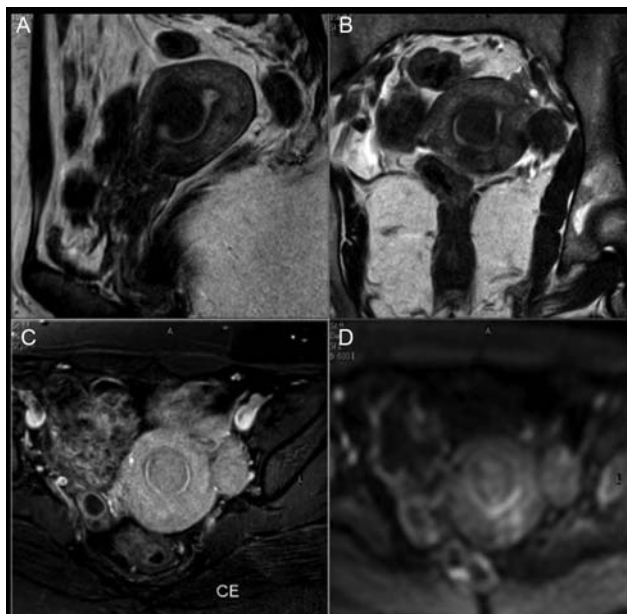


Fig. 12 T2W sagittal (A) and coronal (B) images showing a markedly hypointense mass in submucosal location projecting into the endometrial cavity which demonstrates enhancement equal to the myometrium on the postcontrast image (C) and no diffusion restriction (D)—likely submucosal fibroid. Proved on histopathology.

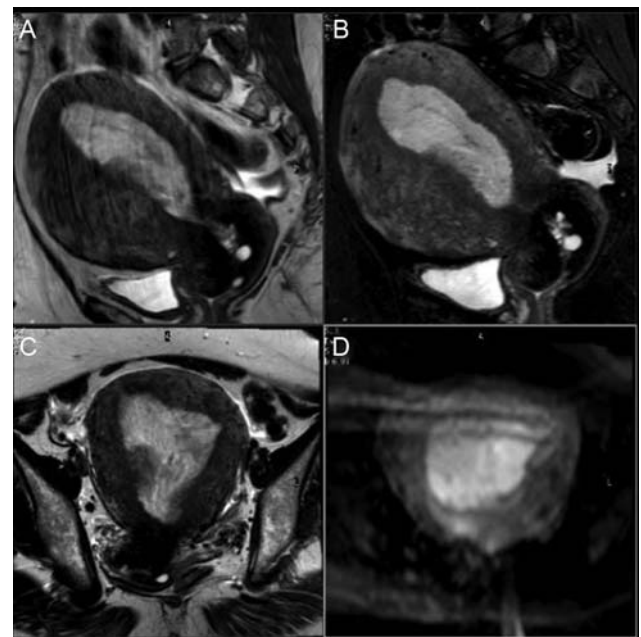


Fig. 13 T2W sagittal (A), axial (B), short tau inversion recovery (STIR) sagittal (C), and axial diffusion-weighted imaging (DWI) (D) images depicting markedly thickened endometrium with no myometrial invasion or diffusion restriction. Proved endometrial hyperplasia on histopathology.

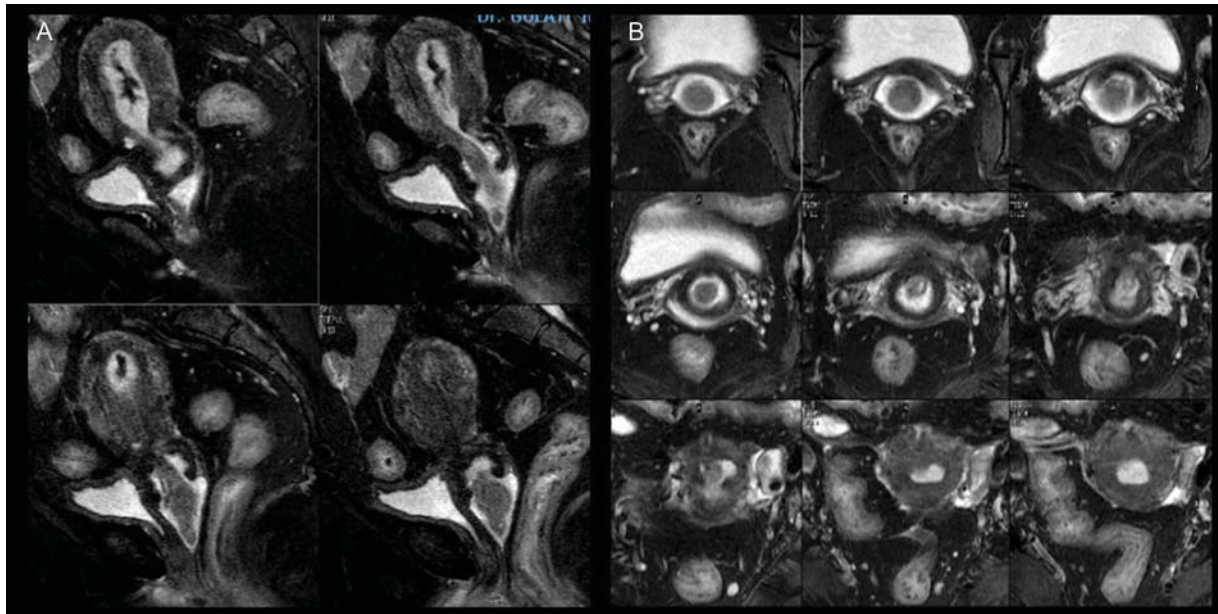


Fig. 14 Multiple short tau inversion recovery (STIR) sagittal (A) and axial (B) images showing an oval soft tissue lesion in the cervico-endometrial canal projecting into the cervix with a stalk attached to the endometrium anteriorly (arrow)—likely a polyp. Proven on histopathology.

myosis, and polyp. Properly performed and evaluated MRI using T2-weighted imaging, DCE, and DWI can differentiate all these confidently.

A submucosal leiomyoma seen as a subendometrial mass at times may mimic endometrial carcinoma (►Fig. 12). MRI can differentiate between the two confidently based on T2-weighted imaging, dynamic contrast studies, as well as DWI. Submucosal fibroid shows low intense signal on T2 images with dynamic contrast following the enhancement pattern of the myometrium (except areas of necrosis/degeneration and calcification) and shows no restriction of diffusion which is in contrast to endometrial carcinoma which shows intermediate signal on T2, lesser enhancement on delayed (120–180 seconds) scans, and no restriction of diffusion.

Endometrial hyperplasia is an abnormal proliferation of endometrial glands and stroma, defined as a diffuse smooth thickening of more than 10 mm (►Fig. 13). It includes non-neoplastic entities—simple and complex hyperplasia without atypia, and precancerous complex endometrial hyperplasia with atypia. DWI with ADC maps can help in differentiating between the two with diffusion restriction seen in endometrial carcinoma. Çavuşoğlu et al in their study found ADC values of endometrial cancer to be significantly lower than in endometrial hyperplasia— $0.88 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{s}$ for endometrial cancer versus $1.78 \pm 0.27 \times 10^{-3} \text{ mm}^2/\text{s}$ for endometrial hyperplasia/benign lesions with a cutoff value of $1.18 \times 10^{-3} \text{ mm}^2/\text{s}$.³⁸ Similar results have been published by Fujii et al, Shen et al, and Takeuchi et al.^{30,39,40} MRI can help in identifying the onset of malignant transformation with DWI by demonstrating areas of diffusion restriction which were not there earlier.

Adenomyosis is ectopic endometrial tissue in the myometrium, some considering it on the spectrum of endome-

triosis. MRI is the modality of choice to diagnose adenomyosis as this is the best modality to evaluate the junctional zone. A thickened T2 low intense junctional zone is diagnostic of the condition. On T1 images there may be seen foci of hyperintense signal indicating foci of menstrual hemorrhage into ectopic endometrial tissue.

Endometrial polyps are masses projecting into the endometrial cavity (►Fig. 14). Transvaginal sonography is an excellent tool to assess endometrial polyps. On MRI the polyps show iso- to low intense signal relative to endometrium on T2 images with no diffusion restriction. Dynamic contrast scans will show rapid enhancement with a persistent strong enhancement or gradually increasing enhancement. Central fibrous core showing low intense signal on T2 images is another feature commonly seen.⁴¹ These features can help distinguish endometrial polyps from other endometrial lesions

Conclusion

MRI is an excellent imaging modality at depicting the trilamellar uterine anatomy. It should be the modality of choice in assessing endometrial cancer for tumor size, extension, myometrial invasion, parametrial/cervical invasion, as well as metastatic lymph node enlargement. It can differentiate the malignancy from the mimics like endometrial hyperplasia, submucosal fibroid, polyp, and endometrial hyperplasia. It can differentiate postoperative changes from recurrent/residual disease.

Conflict of Interest

None declared.

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