Imaging Recommendations for Diagnosis, Staging, and Management of Uterine Cancer

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Introduction

Tumors of the uterine corpus include epithelial tumors, mesenchymal tumors, mixed epithelial and mesenchymal, miscellaneous tumors (neuroendocrine or germ cell), lymphoid, myeloid and secondary tumors.1,2 The American Joint Committee on Cancer (AJCC) staging system has classified uterine cancers into two groups: corpus uteri (uterine carcinomas and carcinosarcoma) and corpus uteri (sarcomas).3 Out of these, endometrial cancer is the most common and is classified histologically into Type I and Type II. Definitive diagnosis is usually made through endometrial biopsy or dilatation and curettage; however, pre-operative...
Radiological imaging is required to stage the disease and to tailor patient’s management. The treatment comprises surgical staging and adjuvant radiotherapy and/or chemotherapy depending on the final surgico-pathological stage.

**Risk Factors and Etiopathogenesis**

Long-term estrogen excess (exogenous or endogenous) is postulated to have a causative effect on Type I cancers. Early menarche, late menopause, nulliparity, anovulatory states (polycystic ovary syndrome) and estrogen only hormonal therapy are causes of prolonged estrogen exposure. The other risk factors include obesity, diabetes mellitus, Lynch syndrome, Cowden syndrome, tamoxifen therapy, and previous pelvic irradiation. Most patients present at an early stage and are associated with a good prognosis, which depends on several factors, including the clinical stage, depth of myometrial invasion, histological grade, cell type, lymphovascular invasion, nodal status, and patient age. In contrast, Type II cancers have a worse prognosis and risk factors include Black race, older age, and lower body mass index.

**Epidemiology, Clinical Presentation in India and Global**

There has been an increase in the incidence and prevalence of cancers in female population worldwide. Though breast and carcinoma cervix are the most common causes of morbidity and mortality, carcinoma of the uterine corpus continues to pose a significant concern. It is the sixth most common cancer with detection of 417,000 new cases and 97,000 deaths, as per GLOBOCAN 2020. Uterine malignancies are predominantly seen in developed countries as compared with the developing countries; however, the incidence shows a rising trend in both due to an increase in the prevalence of associated risk factors such as excess body weight and diabetes. The National Cancer Registry of India showed heterogeneous distribution of cancers in India with breast and carcinoma cervix being the most common since 2012. It had projected the risk of uterine corpus in 26,514 patients in 2020 with cumulative risk of 1 in 190, indicating its potential risk. GLOBOCAN 2020 showed 16,413 new cases of carcinoma uterine corpus, with 6,385 deaths, estimating its 5-year prevalence of 6.56 per 100,000 in Indian population.

**Imaging Referral Guidelines**

**Endometrial Carcinoma**

Endometrial carcinoma is staged surgically according to the joint 2017 International Federation of Gynecology and Obstetrics (FIGO)/Tumour, Node, Metastasis (TNM) classification system. The staging procedure includes total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy, unless the patients desire fertility sparing surgery (and are candidates for the same). Imaging serves as an adjunct in the treatment stratification of endometrial carcinoma. According to the NCCN guidelines, the initial imaging workup varies according to the treatment offered. For Non-Fertility Sparing treatment, pelvic contrast-enhanced magnetic resonance imaging (CEMRI) is recommended (to establish origin of tumor as endometrial versus endocervical and local disease extent evaluation). In early stages, evaluation with transvaginal sonography can be done followed by MRI as an optional modality. Chest X-ray is the baseline evaluation, to be followed by non-contrast computed tomography (NCCT) chest in case of any abnormality. CECT chest and abdomen (including pelvis) is recommended for metastatic evaluation in high-grade carcinomas (poorly differentiated endometrioid, clear cell, serous, undifferentiated carcinoma, and carcinosarcoma) and PET/CT (neck/chest/abdomen/pelvis/groin) can be done in select cases. In case of postoperative incidental finding of endometrial cancer or incompletely staged cancer with...
uterine risk factors (tumor > 2 cm, high-grade carcinomas, invasion > 50% myometrium, cervical stromal involvement and LVSI), CECT chest and abdomen is suggested to evaluate for metastatic disease. Additional imaging can be considered based on the clinical concern for metastases (delay in presentation or treatment, abnormal physical exam finding, abdominal or pulmonary symptoms, bulky uterine tumor and vaginal or extrauterine disease).

For Fertility-Sparing treatment, CEMRI pelvis is preferred to exclude any myoinvasion and assess the local disease extent. If MRI is contraindicated, transvaginal ultrasound pelvis can be considered. Chest X-ray is the baseline evaluation to be followed by non-contrast computed tomography (NCCT) chest in case of any abnormality. If metastasis is suspected in select patients, PET/CT (neck/chest/abdomen/pelvis/groin) is recommended. Additional imaging can be considered based on the clinical concern for metastases.

Uterine Sarcoma

Uterine sarcomas may be diagnosed after total/supracervical hysterectomy (SCH) or after biopsy/myomectomy and the imaging workup varies accordingly. For the initial workup of patients with incidental finding of uterine sarcoma or incompletely resected uterus/adnexa, CEMRI abdomen and pelvis is recommended with non-contrast CT chest for metastatic disease. In cases of SCH, suspicious tumor fragmentation, myomectomy, or intraperitoneal morcellation local tumor extension and residual disease is to be evaluated with pelvic MRI. PET/CT (neck/chest/abdomen/pelvis/groin) is recommended to clarify ambiguous findings. Additional imaging can be considered based on the clinical concern for metastases (as in case of endometrial carcinoma).

Clinical/Diagnostic Workup Excluding Imaging

The clinical presentation is usually abnormal uterine bleeding in premenopausal women and postmenopausal bleeding in the elderly age group. A detailed history including use of hormones, tamoxifen use, diabetes mellitus, and family history is essential followed by a complete systemic and gynecological examination. Endometrial and endocervical sampling is required to make a definitive diagnosis and endocervical curetage is done before endometrial aspiration. Endometrial biopsy is done with endometrial aspiration using devices such as Pipelle or a fine Karman's cannula. In women with inadequate or negative sampling and strong suspicion of malignancy, hysteroscopy and directed biopsy is advised.

The preoperative laboratory evaluation includes a complete blood count, liver and renal function tests, blood sugar, serum electrolytes, serum electrolytes, viral marker and viral marker and urinalysis. In selected patients with extraperitoneal spread of disease (especially nodal involvement in high-risk tumors), serum levels of CA 125 maybe elevated and can be used to monitor response to therapy. The serum human epididymis protein (HE4) levels are elevated in aggressive types of disease and are useful for detecting early disease recurrence.

Genetic evaluation is suggested for younger patients (< 50 years), family history of uterine and colorectal malignancies and those with known related genetic syndrome.

Imaging Guidelines

Screening

Routine screening is not recommended for endometrial carcinoma because majority of the patients with endometrial cancer present with abnormal uterine bleeding and at a stage with disease confined to the uterus. In addition, there is no non-invasive test available with sufficiently high specificity and sensitivity for screening. However, in patients with Lynch syndrome, endometrial biopsy is recommended every 1 to 2 years beginning at the age of 30 to 35 years as a screening procedure.

Diagnosis and Staging

Staging of endometrial carcinoma is primarily surgical and typically performed with laparoscopy. The diagnosis is established by histopathological evaluation and MRI maybe done in equivocal cases to distinguish between cancers of endometrial and cervical origin. Preoperative disease assessment requires depth of myometrial invasion (MRI) and histologic type and grade (endometrial biopsy).

Transabdominal and transvaginal ultrasound are used as baseline screening modalities in patients presenting with abnormal uterine bleeding or postmenopausal bleeding. Transvaginal US has accuracies ranging from 73% to 84% in assessing myometrial invasion with high sensitivity (71% to 100%), and specificity (72% to 100%).

Computed tomography (CT) has a limited role in evaluating myometrial invasion and cervical extension in endometrial cancer. In comparative studies of CT with US or MRI for myometrial invasion, the accuracy of CT is reported to be 58% to 61% versus 68% to 69% for US and 88% to 89% for MRI. In select cases, CT chest and abdomen is indicated as a part of metastatic workup.

Dynamic contrast-enhanced MRI is the preferred imaging modality to evaluate myometrial invasion with high accuracy (59% to 100%), sensitivity (71% to 100%), and specificity (72% to 100%). The staging accuracy ranges from 83% to 92%.

PET CT is considered to be better in the evaluation of lymph node metastases and metabolically active nodes of any size are considered to metastatic. It is also superior in the assessment of extrapelvic disease and bone metastases.

MRI Sequences and Imaging Protocols

Scanner: There is improved signal-to-noise ratio (SNR), spatial resolution, anatomic detail and faster scanning techniques with the use of 3 Tesla (T) scanners. The use of phase-array surface abdominopelvic coil is recommended for both 1.5 T and 3.0 T scanners.

Patient preparation: Fasting is advised for 4 hours, but water intake is encouraged before the scan. A moderately full bladder is required during the scan and the patient should be asked to void ~30 to 45 minutes before the examination.
Antispasmodic drugs such as butylscopolamine (40 mg) IM/IV or glucagon IV/IM (0.5–1.0 mg) are recommended to reduce bowel motion. Vaginal opacification with ~10 mL of lignocaine 2% jelly gives optimal contrast resolution. MRI Technique and Sequences: In the pelvis, T2W FSE sequences are the mainstay of evaluation. Sequences are oriented in relation to the pelvis or dedicated to the uterine axis. T2-weighted images include a small FOV (512 × 256 matrix, 24 cm FOV) sagittal T2WI of the pelvis and a small FOV T2W sequences of pelvis in the axial oblique plane perpendicular to the uterine corpus. T1W sequence of the pelvis in the axial plane is followed by diffusion-weighted imaging (DWI) in axial oblique (in sync with the axial oblique T2WI). Large FOV (256 × 256 matrix, 32 cm FOV) T1- or T2-weighted image of upper abdomen is obtained to evaluate for lymph nodes and hydronephrosis. DWI in the axial plane (large FOV) is also acquired in sync with the large FOV T2 sequence. The dynamic contrast-enhanced sequences are acquired for the assessment of preservation of endometrial halo and differential enhancement of the endometrial soft tissue and the myometrium. Dynamic acquisition can be done in the sagittal plane using a three-dimensional gradient echo T1WI, fat-saturated sequence following the administration of 0.1 mmol/kg of gadolinium at 2 mL/s. Images are acquired before contrast injection and then at 25 seconds, 1 minute and 2 minutes after injection followed by a delayed sequence in the axial oblique plane 4 minutes after injection.

Staging
Endometrial Carcinoma
Carcinomas are usually isointense on T1WI and hyperintense (relative to the myometrium) on T2WI. The lesion shows...
diffusion restriction with low mean ADC values. Post-contrast administration, tumor enhances slowly and less avidly than the myometrium.

Assessment of myometrial invasion is crucial in the staging of endometrial carcinoma. Deep myometrial invasion is excluded in the presence of an intact junctional zone (JZ) along with smooth early subendometrial enhancement (25–60 seconds). Disruption of the JZ with the tumor within the outer myometrium is suggestive of myometrial invasion (> 50%). The presence of leiomyomas or adenomyosis can result in an overestimation of the depth of myometrial invasion. Deep myometrial invasion is best assessed during the equilibrium phase (2–3 minutes after contrast injection). An imaging delay of ~90 seconds is considered optimal timing for best tumor-myometrium contrast. Delayed-phase images (4–5 minutes after contrast) are useful for detecting cervical stromal invasion.

For extraperitoneal extension, T2WI should be interpreted in conjunction with the DWI. The presence of intermediate to high signal intensity tumor causing disruption of the normal low signal intensity cervical stroma is suggestive of cervical stromal invasion on T2WI.

Serosal involvement is suggested by an irregular uterine contour/disrupted low signal intensity of the uterine serosa on T2WI, and a loss of the normal edge of enhancing myometrium on DCE sequences. Tumor abutting or indenting the bladder/rectum over a significant area; tumor interrupting the low signal intensity of the bladder/rectal muscular layer or tumor invading the bladder/rectal muscular wall on T2WI is suggestive of bladder/rectal involvement. The presence of bullous edema alone is not sufficient to label it as stage IVA disease. Adnexal deposits can be well picked up on DWI and T2WI. Lymph node involvement can be well picked up on T1WI and DWI. Morphological features such as short-axis diameter of more than 10 mm, rounded shape, loss of fatty hilum are features that help to identify suspicious lymph nodes. However, there is a degree of overlap in the sizes and ADC values of benign and malignant pelvic lymph nodes.

For treatment response, the role of CEMRI and ADC values is still evolving. The commonest site for recurrence is the vagina followed by pelvic and paraaortic lymph nodes. The presence of a T2 hyperintense mass with disruption of the normal low signal intensity linear configuration of the vault is suggestive of vault recurrence.

**Uterine Sarcomas**

The primary uterine sarcomas are leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and adenosarcoma. Usually, the diagnosis of sarcomas is made after hysterectomy or myomectomy. The staging of LMS and ESS is different and that of adenosarcoma is the same as endometrial carcinoma. Size is an important criterion in staging though myometrial invasion in LMS and ESS is definitional.

T2WI and contrast enhanced T1WI (Fig. 5) are useful in assessing the size, spread into adnexa, abdominal tissues, bladder or rectum (key T descriptors). LMS are usually solid.

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**Fig. 4** Dynamic contrast-enhanced MRI pelvis in carcinoma endometrium (stage IB). T1 axial oblique (A) and T2 sagittal (B) show an ill-defined polypoidal mass lesion (‘’) in the endometrial cavity. DCE MRI (C) shows mild contrast enhancement of tumor and disruption of subendometrial zone of enhancement (arrow in C) with myometrial invasion of > 50%. DWI (D) shows diffusion restriction (‘’) with low ADC value in the ADC map (E). Post contrast T1 axial oblique (F) shows myometrial invasion of >50% with intact serosal margin (arrow in F).
masses with irregular margins, hemorrhagic T1 hyperintense areas, and intermediate to high signal on T2WI with heterogeneous post contrast enhancement and diffusion restriction. ADC values in LMS range from $0.791 \pm 0.145 \times 10^{-3}$ to $1.17 \pm 0.15 \times 10^{-3}$ mm$^2$/s.$^{35}$

PET CT is considered superior in evaluation of lymph nodes and extra pelvic metastases. Table 1 summarizes the TNM and FIGO staging of uterine cancers including carcinoma and sarcoma.

Follow-up/Surveillance

Endometrial Carcinoma
In cases of non-fertility-sparing treatment for endometrial carcinoma, imaging is to be guided by the symptoms of the patient, risk assessment, and clinical signs of recurrent or metastatic disease (palpable mass; lymphadenopathy; vaginal tumor; and any new pulmonary, abdominal or pelvic symptoms).$^{36,37}$ Based on these symptoms, CT abdomen and/or chest CT maybe performed. Whole body PET/CT and/or CEMRI abdomen can be performed as clinically indicated in selected patients.$^{10,38}$

In cases of fertility-sparing treatment, repeat CEMRI pelvis is preferred for patients with persistent endometrial carcinoma (6–9 months of failed medical therapy), especially if further fertility-sparing approaches are being considered.$^{10}$ Additional imaging can be considered based on the clinical concern for metastases.

In case of suspected recurrence or metastases, CT abdomen and/or chest CT is recommended with whole body PET/CT and MRI abdomen indicated in select patients.

Uterine Sarcoma
In cases of uterine sarcoma, CECT of the chest/abdomen/pelvis (or CEMRI abdomen with NCCT chest) is recommended every 3 to 6 months for the first 3 years and then every 6 to 12 months for the next 2 years. Subsequently, annual to biannual imaging can be considered for up to an additional 5 years (varies according to the stage and histology grade and can be done every 3 months). Additional imaging, including PET/CT, is based on the clinical concern for metastases.$^{10,39}$

Principles of Management

Treatment planning should be done in multidisciplinary tumor board.$^{40}$ For the management of early-stage including high-risk cases, minimally invasive approach is preferred.$^{41}$ The steps include peritoneal wash cytology, exploration of intra-abdominal structures, type-I extra fascial hysterectomy, bilateral salpingo-oophorectomy + lymphadenectomy. More extensive procedures including radical hysterectomy are needed to take negative margins in advanced disease.$^{40}$ Decision of systematic lymphadenectomy is based on the risk of nodal involvement. In patients with low-grade endometrioid adenocarcinoma with tumor size $\leq 2$ cm and with none or superficial myometrial invasion, the risk of nodal
involvement is < 1% and hence, lymph node dissection can be safely omitted. While systematic pelvic and para aortic nodal dissection is done for the purpose of staging in those with intermediate-risk factors, nodal dissection is recommended for therapeutic benefit too. Sentinel node biopsy should be considered for staging if facilities are available. Infra colic omentectomy should be done for serous variants and carcinosarcoma. Younger women with uterus confirmed well-differentiated endometrioid adenocarcinoma and no myometrial invasion may be offered fertility preserving treatment. Decision for adjuvant therapy is decided using prognostic risk stratification based on predictive factors and molecular profile (< Table 2>).

### Management of Recurrent Disease

Recurrent disease is difficult to treat and evidence on efficacy of available modalities is limited. The most common site is vaginal vault and for radiation naïve cases radiotherapy is preferred. Advanced radiation techniques including SBRT and IMRT have shown better patient tolerance. For previously irradiated cases either surgery or systemic therapy are preferred. Pelvic recurrence is associated with relatively poor outcome and management depends on disease distribution and nature of prior therapy. For distant recurrence systemic chemotherapy is used. Several targeted therapeutic agents are investigated with promising potential. Immunotherapy has shown promising results and pembrolizumab is

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**Table 1** TNM and FIGO staging of malignancies of the uterine corpus (carcinoma endometrium, carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma) (Adapted from reference ^10^)

<table>
<thead>
<tr>
<th>FIGO</th>
<th>Carcinoma Endometrium &amp; Carcinosarcoma</th>
<th>Sarcoma (Leiomyosarcoma &amp; Endometrial stromal sarcoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary lesion cannot be assessed</td>
<td>Primary lesion cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary lesion.</td>
<td>No evidence of primary lesion</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>Growth limited to the uterus</td>
</tr>
<tr>
<td>T1a</td>
<td>IA</td>
<td>Size of the lesion ≤ 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Lesion &gt; 5 cm</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Lesion seen beyond the uterus, within the pelvis</td>
</tr>
<tr>
<td>T2a</td>
<td>II A</td>
<td>Lesion involves adnexa</td>
</tr>
<tr>
<td>T2b</td>
<td>II B</td>
<td>Lesion involves other pelvic tissues</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Lesion infiltrates abdominal tissues</td>
</tr>
<tr>
<td>T3a</td>
<td>III A</td>
<td>One site</td>
</tr>
<tr>
<td>T3b</td>
<td>III B</td>
<td>More than one site</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Lesion invades bladder or rectum</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N0(+)</td>
<td>Isolated cancer cells in regional lymph node(s), not &gt; 0.2 mm</td>
<td>Isolated cancer cells in regional lymph node(s) not &gt; 0.2 mm</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis in pelvic lymph nodes</td>
<td>Regional lymph node metastasis (FIGO IIIC)</td>
</tr>
<tr>
<td>N1mi</td>
<td>III C1</td>
<td>Regional lymph node metastasis in pelvic lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>III C1</td>
<td>Regional lymph node metastasis in pelvic lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Regional lymph node metastasis to para-aortic lymph nodes</td>
<td>Lesion invades bladder or rectum</td>
</tr>
<tr>
<td>N2mi</td>
<td>III C2</td>
<td>Lesion invades bladder or rectum</td>
</tr>
<tr>
<td>N2a</td>
<td>III C2</td>
<td>Lesion invades bladder or rectum</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)</td>
</tr>
</tbody>
</table>

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Table 2 Selection criteria of adjuvant therapy. Adapted from Concin et al.40

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Common treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>No adjuvant treatment</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Vaginal brachytherapy Consider observation if age &lt; 60 years</td>
</tr>
<tr>
<td>High-intermediate risk</td>
<td>Vaginal brachytherapy Consider EBRT, if LVSI un-equivocally positive, especially if no lymph node dissection or sentinel nodes have been performed.</td>
</tr>
<tr>
<td>High-risk</td>
<td>I. EBRT, Consider VBT, if no LVSI II. Vaginal brachytherapy if grade 1–2 disease (e.g., stage II disease) III. Pelvic radiotherapy if Stage I, grade 3 LVSI un equivocally positive, Stage II IV. Stage III-combined radiotherapy and chemotherapy Non-endometrioid I. Stage IA-vaginal brachytherapy after full surgical staging, II. LVSI negative Stage IB-II: combined external beam RT and chemotherapy</td>
</tr>
</tbody>
</table>

Summary of Recommendations

- The FIGO staging system for endometrial carcinoma is primarily surgical and based on histopathology.
- Imaging, though not mandatory, is useful in the preoperative evaluation of tumor stage, especially assessment of myometrial invasion and cervical stromal extension.
- Dynamic contrast-enhanced MRI with DWI has high staging accuracy and is the preferred imaging modality.
- In cases of clinically suspected recurrence post treatment, PET/CT is the preferred imaging modality for the evaluation of recurrent disease.

Synoptic Reporting Formats

The reporting formats for MRI pelvis (for primary disease) and CECT abdomen (for follow-up evaluation) have been provided.

Funding

None.

Conflicts of Interest

None declared.

References

1. Female Genital Tumours. WHO Classification of Tumors, 5th ed. Vol. 4. Lyon, France. International Agency for Research on Cancer; 2020