

**American College of Radiology
ACR Appropriateness Criteria®**

Clinical Condition: Endometrial Cancer of the Uterus

Variant 1: Newly diagnosed endometrial cancer; diagnostic work-up and staging.

| Radiologic Procedure | Rating | Comments | RRL* |
|---|--------|---|----------------------------------|
| MRI pelvis with contrast | 8 | See comments regarding contrast in text under "Anticipated Exceptions." | None |
| X-ray chest | 6 | | Min |
| MRI abdomen with contrast | 4 | See comments regarding contrast in text under "Anticipated Exceptions." | None |
| CT abdomen with contrast | 4 | | Med |
| CT pelvis with contrast | 4 | | Med |
| US pelvis transvaginal | 4 | | None |
| <u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate | | | *Relative Radiation Level |

Variant 2: Assessing the depth of myometrial invasion.

| Radiologic Procedure | Rating | Comments | RRL* |
|---|--------|---|----------------------------------|
| MRI pelvis with contrast | 9 | See comments regarding contrast in text under "Anticipated Exceptions." | None |
| MRI pelvis without contrast | 6 | | None |
| CT pelvis with contrast | 4 | | Med |
| US pelvis transvaginal | 4 | | None |
| US hysterosonogram | 1 | Very low risk of malignant cell dissemination into peritoneal cavity. | None |
| <u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate | | | *Relative Radiation Level |

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Clinical Condition: Endometrial Cancer of the Uterus

Variant 3: Lymph node evaluation.

| Radiologic Procedure | Rating | Comments | RRL* |
|--|---------------|--|----------------------------------|
| CT pelvis with contrast | 8 | Either CT or MRI is appropriate. | Med |
| MRI pelvis with contrast | 8 | Either CT or MRI is appropriate. See comments regarding contrast in text under "Anticipated Exceptions." | None |
| FDG-PET whole body | 5 | Applies to stand-alone PET without CT or MRI on all endometrial cancer including grade I. Fusion PET/CT under investigation. | High |
| US pelvis transvaginal | 2 | | None |
| Rating Scale: 1=Least appropriate, 9=Most appropriate | | | *Relative Radiation Level |

Variant 4: Assessing endocervical tumor extent.

| Radiologic Procedure | Rating | Comments | RRL* |
|--|---------------|---|----------------------------------|
| MRI pelvis with or without contrast | 8 | See comments regarding contrast in text under "Anticipated Exceptions." | None |
| US pelvis transvaginal | 4 | | None |
| CT pelvis with contrast | 4 | | Med |
| Rating Scale: 1=Least appropriate, 9=Most appropriate | | | *Relative Radiation Level |

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ENDOMETRIAL CANCER OF THE UTERUS

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Summary of Literature Review

Cross-sectional imaging in the pretreatment evaluation of gynecologic cancer patients can play an important role. In cancer of the uterus, it offers an assessment of morphologic prognostic factors, including tumor size, depth of penetration, stage of disease, and lymph node status. Imaging should be viewed as a complementary tool rather than competitive with the other methods of tumor evaluation (eg, clinical or surgical assessment).

Clinical Background and Prognostic Factors

Endometrial carcinoma is the fourth most common cancer in women and the leading invasive malignancy in the female genital tract. About 39,080 new cases and 7,400 deaths were expected in the United States in 2007 [1]. Endometrial cancer primarily presents at stage I (80% of cases), and the recommended treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Depending on prognostic factors such as depth of myometrial invasion and tumor grade, lymphadenectomy may also be indicated. The major diagnostic factors necessary for the preoperative evaluation of endometrial cancer are:

1. Determination of the risk of lymph node metastasis in order to have subspecialist surgical consultation available.
2. Diagnosis of gross cervical invasion, which requires preoperative radiation therapy or a different treatment plan, (ie, radical hysterectomy instead of total abdominal hysterectomy).
3. Detection of advanced disease.

The most important prognostic variables for carcinoma of the uterus are the histologic grade and the stage of tumor (Appendix 1), including depth of myometrial invasion and lymph node metastasis [2,3]. In a study of 1,566 patients with adenocarcinoma of the uterus, the depth of myometrial invasion was found to be the single most important prognostic factor. In stage IA and IB disease,

when the tumor is confined to the endometrium or to the superficial myometrium, the incidence of para-aortic lymph node metastases is <2.5%. Conversely, in stage IC disease, when there is deep myometrial invasion, para-aortic lymph node metastases occur in 15%-45% [3,4].

The International Federation of Gynecology and Obstetrics (FIGO) staging is not accurate to assess the depth of myometrial invasion or the presence of lymphadenopathy. Because clinical staging carries an overall error in understaging of about 13%-22%, FIGO has recommended routine surgical staging since 1988 [2]. Preoperative imaging of endometrial carcinoma can define the extent of disease in order to tailor treatment and indicate referral to a subspecialist if deep myometrial invasion, cervical extension, or lymphadenopathy is suspected. Diagnostic imaging may also be helpful in a primarily obese, elderly population in which radiation therapy rather than surgery might be advocated as a primary treatment or as a preoperative adjuvant to surgery.

Use of Imaging in Clinical Guidelines

Transabdominal and Transvaginal Ultrasound

Transabdominal ultrasound (US) is considered unreliable in staging endometrial cancer. The use of transvaginal US has shown some promise in the evaluation of myometrial invasion. Reported accuracies for myometrial invasion in stage I range from 69%-93% in differentiating deep invasion (stage IC) from absent or superficial invasion (stages IA and IB) [5-10], and from 68%-69% in differentiating stage IA from stage IB from stage IC [11,12]. A study using high-frequency transvaginal US showed a similar accuracy of 73% in assessing myometrial invasion [13]. However, studies directly comparing the accuracy of transvaginal US to that of contrast-enhanced magnetic resonance imaging (MRI) for staging have consistently demonstrated that the latter performs with greater accuracy [6,12].

In addition, there are insufficient reports about the value of transvaginal US in predicting cervical extension, parametrial invasion, or lymphadenopathy. In one study, transvaginal US showed cervical involvement in only 7 of 10 patients with cervical extension [14].

Hysterosonography, (ie, transvaginal US evaluation of the uterus after intracavitary saline infusion), has been considered as a imaging modality for evaluating deep myometrial invasion with accuracy of 89% (17/19) in one series [15]. However, recent reports indicate that the procedure disseminates malignant cells into the peritoneal cavity in 6%-7% of patients with an established diagnosis of endometrial cancer [16,17]. Although there is no evidence that this dissemination increases rates of intraperitoneal metastases, these results imply that

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hysterosonograms have the potential to upstage a patient from disease confined to the uterus (stage I or II) to stage III thereby altering postsurgical treatment and follow-up algorithms. While use of hypertonic saline has been proposed to induce cell lysis and potentially decrease or eliminate the risk of peritoneal spread, this has not yet been practically demonstrated in the literature.

Computed Tomography

Computed tomography (CT) has been used for evaluating endometrial carcinoma, with emphasis on evaluating the depth of myometrial invasion and assessing lymph node status. In studies comparing CT with US or MRI, the accuracy of CT for myometrial invasion is reported to be from 58%-61% versus 68%-69% in US and 88%-89% in MRI [6,10]. One study found no significant difference between helical CT and US for diagnosing deep myometrial invasion [6]. The value of CT in diagnosing cervical extension is not evident, because an easy identification of the margin between the cervix and the uterine corpus is difficult on axial imaging planes. Moreover, most reports suffer from having a few patients with stage II, which may prevent valid conclusions to be drawn. Preoperative evaluation of multidetector CT (MDCT) for staging endometrial carcinoma has not as yet been evaluated in randomized prospective controlled trials.

Magnetic Resonance Imaging

MRI is significantly superior to US in the evaluation of both tumor extension into the cervix and myometrial invasion [6,11-13]. A meta-analysis study showed that the efficacy of contrast-enhanced MRI is significantly better than that of US, CT, or noncontrast MRI in evaluating the depths of myometrial invasion in patients with endometrial cancer [18]. Contrast-enhanced MRI performs significantly better than unenhanced MRI for evaluation of the depth of myometrial invasion [18]. The superiority of MRI compared to CT and clinical staging has also been documented [6,10]. MRI provides the most accurate and consistent evaluation of patients with endometrial cancer. The overall staging accuracy of MRI has been reported to be between 85%-93% [6,10,12,19,20]. The efficacy of MRI is improved with the use of dynamic contrast-enhanced imaging. The assessment of the depth of myometrial invasion shows significant improvement with the use of dynamic scanning (accuracy of 55%-77% for noncontrast images versus 85%-91% for contrast-enhanced images) [21-25]. Compared with T2-weighted images, the use of contrast media will reduce both overestimation as well as underestimation of depth of myometrial invasion. An erroneous MRI assessment of the depth of myometrial invasion can sometimes be ascribed to as large polypoid endometrial cancer, which distends the uterus so that the thin rim of myometrium is stretched over it rather than deeply infiltrated [12]. Cervical extension can be

diagnosed reliably with accuracy ranging from 86%-95% [22,26,27]. One study comparing MRI with fractional curettage and hysteroscopy showed that MR imaging had the highest sensitivity (91%) and specificity (96%) for diagnosing cervical involvement in endometrial cancer [26]. A recent meta-analysis showed that use of contrast-enhanced MRI significantly affects the post-test probability of deep myometrial invasion in patients with all grades of endometrial cancer and could be used to select patients for specialist referral [28].

Lymphangiography

Lymphangiography is not recommended for evaluating cancer of the endometrium. Not only because it is invasive (and very few imaging centers offer this service) but also, because of the difficulties in the evaluation of pelvic nodes, its performance is not reproducible and, even performed optimally, slightly inferior to that of CT and MRI.

Positron Emission Tomography

The role of positron emission tomography (PET) in endometrial cancer imaging is still under investigation. In detecting lymph node involvement by tumor, PET performs with accuracy (95%) comparable to that of CT or MRI [29,30]. However, because 45% of endometrial cancer is stage I and not FDG-avid, the reported improved sensitivity of PET (60%-86%) is only true for nodes >1 cm. This limitation, coupled with the limitations of PET in assessing intraperitoneal tumor implants and parenchymal metastases makes CT and MRI preferable in detecting extrauterine disease. PET was reported to be useful in the post-therapy surveillance, both for localizing suspected recurrences and for detecting asymptomatic recurrent disease [31]. A study showed that in the detection of recurrence and the evaluation of treatment response, FDG-PET, with help by CT and/or MRI, performed better (sensitivity 100%, specificity 88.2%, and accuracy 93.3%) compared with CT and/or MRI (sensitivity 84.6%, specificity 85.7%, and accuracy 85%) and tumor markers, ie CA125, CA19-9, CEA, and sialyl TN antigen, (sensitivity 100%, specificity 70.6%, and accuracy 83.3%). The results of FDG-PET correlated well with the clinical outcome of the patients, with patients having negative PET results tending to show disease-free courses [32].

Recommended Imaging Approach

Because contrast-enhanced MRI demonstrates the highest accuracy for overall staging of endometrial cancer, it should be used, when available, as the preferred modality for treatment planning. Transvaginal US can be used to assess the depth of myometrial invasion and cervical involvement, albeit with less accuracy than MRI. CT and MRI perform equivalently for assessing nodal involvement. PET is promising in the post-treatment surveillance of endometrial cancer patients. However,

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there are no outcome studies or cost-effectiveness analyses on imaging evaluation of endometrial cancer.

Summary

Patients with endometrial carcinoma should undergo diagnostic imaging only in cases of clinical staging difficulties, including those with medical comorbidities that preclude surgery, large tumors, high histologic tumor grade, or possible cervical involvement. If imaging is needed, MRI is the most accurate technique and should be the preferred modality.

Anticipated Exceptions

Nephrogenic systemic fibrosis (NSF), also known as nephrogenic fibrosing dermopathy) was first identified in 1997 and has recently generated substantial concern among radiologists, referring doctors and lay people. Until the last few years, gadolinium-based MR contrast agents were widely believed to be almost universally well tolerated, extremely safe and non-nephrotoxic, even when used in patients with impaired renal function. All available experience suggests that these agents remain generally very safe, but recently some patients with renal failure who have been exposed to gadolinium contrast agents (the percentage is unclear) have developed NSF [33-35], a syndrome that can be fatal. Further studies are necessary to determine what the exact relationships are between gadolinium-containing contrast agents, their specific components and stoichiometry, patient renal function and NSF. Current theory links the development of NSF to the administration of relatively high doses (eg, >0.2mM/kg) and to agents in which the gadolinium is least strongly chelated. The FDA has recently issued a “black box” warning concerning these contrast agents (http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705HCP.pdf).

This warning recommends that, until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated GFR <30 mL/min/1.73m²), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s) [34].

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Additional information regarding

radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

| Relative Radiation Level Designations | |
|---------------------------------------|-------------------------------|
| Relative Radiation Level | Effective Dose Estimate Range |
| None | 0 |
| Minimal | < 0.1 mSv |
| Low | 0.1-1 mSv |
| Medium | 1-10 mSv |
| High | 10-100 mSv |

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Appendix 1. Revised Surgical FIGO Staging of Endometrial Carcinoma [2]

| Stage | Definition |
|-------|---|
| 0 | Carcinoma in situ |
| I | Tumor confined to corpus |
| | IA tumor limited to endometrium |
| | IB invasion smaller than 50% of myometrium |
| | IC invasion equal to or greater than 50% of myometrium |
| II | Tumor invades cervix but does not extend beyond uterus |
| | IIA invasion of endocervix |
| | IIB cervical stromal invasion |
| III | Tumor extends beyond uterus but not outside pelvis. |
| | IIIA invasion of serosa, adnexa, or positive peritoneal cytology |
| | IIIB invasion of vagina |
| | IIIC pelvic and/or para-aortic lymphadenopathy |
| IV | Tumor extends outside pelvis and/or invades bladder or rectal mucosa |
| | IVA invasion of bladder or rectal mucosa |
| | IVB distant metastasis (includes intra-abdominal or inguinal lymphadenopathy) |

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