The Role of Imaging in Advanced Endometrial Carcinoma

Helen Addley[1] and Evis Sala[2]

1. Registrar; 2. Lecturer, and Honorary Consultant, Department of Radiology, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust

Abstract

Imaging in endometrial carcinoma has many roles. It is used in the initial assessment of symptomatic patients for demonstration of abnormal endometrial thickness. Once the histological diagnosis of endometrial carcinoma is confirmed, imaging can accurately stage the tumour, facilitating surgical and oncological treatment planning. This article will review the different imaging techniques available and their roles in staging, treatment selection and follow-up of patients with endometrial carcinoma.

Endometrial carcinoma is the fourth most common female cancer and the most common malignancy of the female reproductive tract.[1] Adenocarcinomas arise from the uterine epithelium and constitute 90% of endometrial cancers. The remaining histological types of endometrial carcinoma include adenocarcinoma with squamous differentiation, adenosquamous carcinoma, clear cell carcinoma and papillary serous carcinoma. Serous papillary carcinoma behaves like ovarian cancer and hence has a worse prognosis compared with grade 1 and 2 endometrial adenocarcinoma. Endometrial cancer primarily presents at stage I (80% of cases) and the standard treatment is either laparoscopic hysterectomy or total abdominal hysterectomy and bilateral salpingo-oophorectomy. The prognosis for endometrial carcinoma depends on a number of factors, including stage, depth of myometrial invasion, lymphovascular invasion, nodal status and histological grade. Determination of the depth of myometrial invasion is important, since it correlates with the incidence of lymph node metastases. Pre-operative evaluation of prognostic factors helps in sub-specialist treatment planning. Although endometrial carcinomas are typically diagnosed at endometrial biopsy, imaging fulfils an important role in both the assessment and staging of these patients.

Role of Ultrasound

The main role of transvaginal ultrasound (TVS) is the accurate assessment of endometrial thickness in patients presenting with post-menopausal bleeding. Ultrasound is widely available, does not involve the use of ionising radiation and has a high negative predictive value, facilitating the assessment of post-menopausal patients into high- and low-risk groups. Ultrasound has a high sensitivity in assessing whether the endometrium is abnormal but a low specificity because benign conditions can also cause a thickened endometrium.[2] Usually, a normal post-menopausal endometrium is atrophic, measuring less than 5mm in thickness and appearing as a thin echogenic line. Endometrial thickness must be assessed on TVS by measuring the two opposing endometrial

layers in the sagittal plane, excluding endometrial fluid in the measurement. Endometrial cancer appears as non-specific thickening of the endometrium that is difficult to distinguish from hyperplasia or a polyp, unless myometrial invasion is present. The diagnosis of endometrial cancer is then usually established on the basis of endometrial biopsy or curettage, often undertaken at the time of hysteroscopy. Colour and pulsed Doppler improves diagnostic accuracy as most endometrial carcinomas have abnormal blood flow with intratumoural or peritumoural blood vessels. Endometrial carcinoma can be associated with low impedance flow, both in the intramyometrial arteries and in the uterine arteries. Hysterosonography is a rarely used technique that has been shown to improve the sensitivity[3] and specificity[4] of ultrasound examination. It involves the instillation of normal saline via a small catheter under TVS and therefore distends the endometrial cavity with fluid. This helps in identifying whether there is an intracavitary lesion, such as endometrial polyp, causing thickening or whether there is a subendometrial cause, such as leiomyoma. In patients with endometrial carcinoma, the endometrial cavity cannot be easily distended and there is irregular thickening of the endometrium.[4] Although ultrasound is excellent at assessing the thickness of the endometrium, staging of endometrial carcinoma once histological diagnosis has been made is better served by other imaging modalities, especially magnetic resonance imaging (MRI). The main role of ultrasound is to gain an accurate assessment of endometrial thickness with TVS in patients presenting with post-menopausal bleeding.

Role of Magnetic Resonance Imaging

Endometrial carcinomas are typically diagnosed at endometrial biopsy or dilatation and curettage, with MRI being reserved to evaluate the extent of disease. Clinical staging may understage endometrial carcinoma by up to 22% and therefore in 1998 the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgicopathological staging system instead. The depth of myometrial

Figure 1: TVS Image Demonstrating Sagittal Section of the Uterus
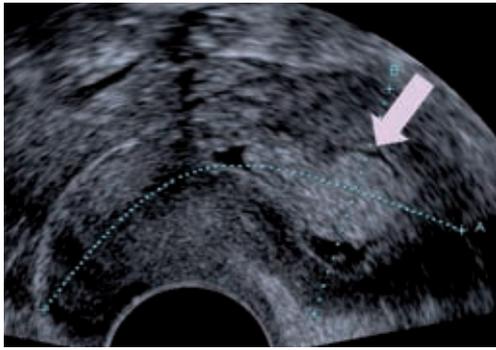
Thickened endometrium (pink arrow) surrounded by rim of fluid in the endometrial cavity.

Figure 2: Sagittal MRI Following Administration of Intravenous Gadolinium
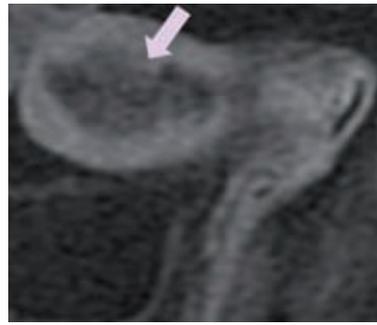
Demonstrating the low-signal endometrial tumour filling the endometrial cavity and seen separately to the high-signal enhancing myometrium.

Figure 3: Axial MRI of the Same Patient
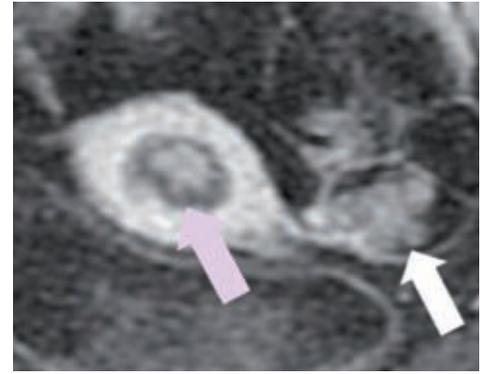
Demonstrating the endometrial tumour (pink arrow) and involvement of the left fallopian tube (white arrow) consistent with stage 3A disease.

invasion is probably the single most important morphological prognostic factor as it correlates with tumour grade, tumour extension into the cervix, and incidence of pelvic and para-aortic lymph node metastases. MRI is better than clinical assessment, computed tomography (CT) and ultrasound in staging endometrial carcinoma, with a staging accuracy of 85–93%.[5–8] Imaging criteria for staging of endometrial cancer are based on the tumour nodes metastasis (TNM)/FIGO classification. MRI can assist in treatment planning as it determines which patients would benefit from pelvic or para-aortic lymph node sampling or lymphadenectomy in the case of enlarged lymph nodes and which patients may benefit from pre-operative radiotherapy when more advanced disease is suspected. The MR protocol is important for accurate staging of endometrial carcinoma and ideally the patient should have an empty urinary bladder prior to the examination. Artefacts from bowel peristalsis can degrade image quality; administration of an antispasmodic, such as buscopan, may be helpful. On unenhanced T_1-weighted images, endometrial carcinoma is isointense compared with the normal endometrium. Although endometrial cancer may demonstrate high signal intensity on T_2-weighted sequences, it is more typically heterogeneous. Routine use of dynamic intravenous contrast enhancement is necessary for state-of-the-art MR evaluation of endometrial carcinoma.[5,6,9] Following the delivery of intravenous contrast medium, there is early enhancement of endometrial cancer relative to the normal endometrium, allowing identification of small tumours, even those contained by the endometrium. In the later phases of enhancement, i.e. the equilibrium phase, the tumour appears hypointense relative to the myometrium.

Stage IA tumours (limited to the endometrium) appear as a normal or widened endometrium. An intact junctional zone (JZ) and a band of early subendometrial enhancement exclude deep myometrial invasion.[10] In stage IB disease, the tumour extends less than 50% into the myometrium, with associated disruption or irregularity of the JZ and subendometrial enhancement. The presence of a low-signal-intensity tumour (later phases of enhancement) within the outer myometrium or beyond indicates deep myometrial invasion – stage IC disease. Erroneous MRI assessment of the depth of myometrial invasion may occur due to an indistinct zonal anatomy, the presence of co-existent benign pathology (leiomyomas, adenomyosis), tumour extension into the uterine cornu and presence of a polypoid tumour that distends the uterus so that a thin rim of myometrium is stretched over it rather than deeply infiltrated.[11] In stage IIA, invasion of the endocervix appears as a

widening of the internal os and endocervical canal, with preservation of the normal low-signal-intensity fibrocervical stroma on T_2-weighted images. Disruption of the fibrocervical stroma by a high-signal-intensity tumour on T_2-weighted images together with disruption of normal enhancement of the cervical mucosa by a low-signal-intensity tumour on late dynamic contrast-enhanced MRI indicate cervical stroma invasion – stage IIB disease. In stage III disease, the tumour extends outside the uterus but not outside the true pelvis. Parametrial involvement – stage IIIA – appears as disruption of the serosa with direct extension into the surrounding parametrial fat.[12] In stage IIIB disease the tumour extends into the upper vagina and there is segmental loss of the low-signal-intensity vaginal wall. In stage IIIC disease lymphadenopathy is present. Assessing whether there is nodal disease can be difficult and size and signal characteristics of the node are routinely used. There are other techniques, such as ultra-small-particle iron oxide (USPIO) MRI, that have been shown to increase the sensitivity of detection of involved nodes that have normal size and signal characteristics on standard MRI. This technique uses USPIO as a negative contrast medium. Involved nodes are demonstrated following USPIO administration on T_2 and T_2-weighted images. Although this technique has demonstrated an increase in sensitivity without a decrease in specificity for detection of lymph-node metastases, the technique is limited to research applications only and is not currently used in routine clinical practice.[13] A tumour that extends beyond the true pelvis or invades the bladder or rectum constitutes stage IV disease. Loss of low signal intensity of the bladder or rectal wall indicates stage IVA disease. In stage IVB disease, distant metastasis, malignant ascites or peritoneal deposits are present. The main role of MRI is in the staging and treatment selection of patients with endometrial carcinoma following positive histological diagnosis.

Role of Computed Tomography

CT with both intravenous and oral contrast medium may be used to stage endometrial carcinoma when MRI is contraindicated. Endometrial tumours appear as low-attenuation lesions relative to a normally enhancing myometrium. CT has limited value in the accurate assessment of myometrial invasion due to its low contrast resolution and hence the inability to visualise the JZ. CT is most useful in confirming the presence of enlarged lymph nodes, which indicate stage III disease. There is a tendency to understage bladder and bowel involvement. Cervical extension is difficult to evaluate as the cervix is poorly delineated on CT. There is a reported sensitivity of 83% and specificity of 42% for the detection of stage IC disease and a sensitivity of 25% and
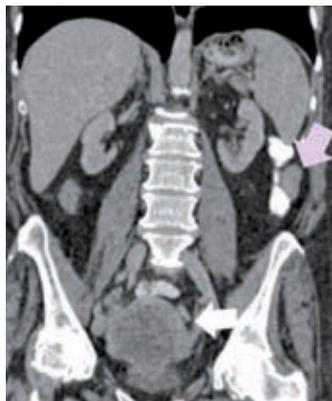
Coronal image demonstrating the soft-tissue tumour and distension of the uterus (white arrow) and a serosal deposit of the descending colon (pink arrow).
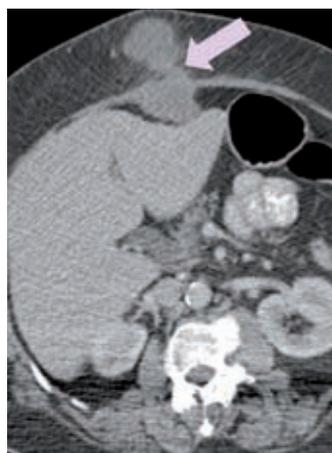
Demonstrating metastatic serosal deposit and extension anterior to the liver into the abdominal wall.

specificity of 70% for detection of cervical involvement (stage II).[8] CT has a role in evaluation of advanced endometrial carcinoma, as distant metastatic disease as well as nodal disease can be clearly assessed. Distant metastases most commonly occur in the liver, lung and peritoneum. CT is routinely used to assess the chest and upper abdomen for the presence of metastatic disease in patients with papillary serous, clear cell and sarcoma histological subtypes. CT examination is also used before and after chemo/radiotherapy for the assessment of disease response. The main role of CT is in the assessment of metastatic and distant nodal disease in patients with advanced endometrial carcinoma and those with papillary serous, clear cell and sarcoma histological subtypes, as well as for assessment of disease response following treatment with chemotherapy.

Role of Fluorodeoxyglucose-positron Emission Tomography/Computed Tomography

Currently, there is little literature on the use of fluorodeoxyglucose positron emission tomography (FDG-PET)/CT in endometrial cancer. Sensitivities and specificities of 96–100% and 78–88%, respectively, have been reported in detecting recurrence.[14] One study has evaluated the impact of FDG-PET on the management of patients with advanced (stage III/IV) endometrial carcinoma or recurrent carcinoma and shown that FDG-PET or FDG-PET combined with MRI and CT has a higher sensitivity in overall lesion detection than MRI and CT alone.[15] FDG-PET had a positive clinical impact in up to 50% of patients. The main role of FDG-PET/CT is expanding and in the future may be combined with MRI to increase sensitivity in both staging and follow-up assessments.

Role of Imaging in Treatment Follow-up of Endometrial Carcinoma

The vagina is the sole site of recurrence in 30–50% of patients with endometrial carcinoma. The remainder develop pelvic or para-aortic lymph node involvement or systemic spread, manifesting as hepatic, pulmonary or osseous metastasis, or peritoneal carcinomatosis.

Magnetic Resonance Imaging

MR examination following treatment is an excellent way to assess local disease recurrence. Tumour extension into the bladder or rectal wall is suggested by abnormally high signal intensity on MR T_2-weighted imaging. Vaginal vault recurrence after radical surgery for endometrial carcinoma is indicated by loss of low-signal-intensity linear configuration of the vaginal vault and associated soft-tissue mass of high signal intensity on T_2-weighted images, similar to that of the primary tumour.[16] Dynamic post contrast-enhanced MRI has been shown to be helpful in improving specificity and accuracy of detection of tumour recurrence, with maximum tumour enhancement between 45 and 90 seconds.[17] However, serial imaging – imaging-guided biopsy or PET/CT – may be required to further clarify the situation.

Computed Tomography

CT examination is excellent in the follow-up of distant metastatic disease and nodal disease. The volume of metastatic pulmonary nodules or liver or bony metastatic disease can be accurately assessed by CT following the administration of both intravenous and oral contrast medium. In the future, the sensitivity of disease recurrence in imaging follow-up may be increased by the use of combined PET/CT examination.

Conclusion

The recommended imaging algorithm for endometrial cancer is TVS as the primary imaging approach for assessment of endometrial thickness, with MRI reserved for cases where hysteroscopy is unsuccessful or repeated biopsy results are inconclusive. MRI is the imaging modality of choice for staging, treatment selection and follow-up of patients with endometrial cancer. CT is used for evaluating distant peritoneal or nodal metastases in patients with advanced-stage disease and those with clear cell or serous papillary carcinoma. FDG-PET/CT may have a role in the future in post-treatment surveillance of these patients and also in assessing distant disease. ■

Helen Addley is a third-year Resident in Clinical Radiology at Addenbrooke's Hospital in Cambridge. She is particularly interested in abdominal and pelvic oncologic imaging. She is a member of the Royal College of Radiologists (RCR), the European Society of Radiology (ESR) and the Radiological Society of North America (RSNA). Dr Addley completed her medical training at Oxford University (Exeter and Green Colleges).
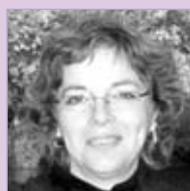
Evis Sala is a Lecturer in Radiology at the University of Cambridge and an Honorary Consultant Radiologist at Addenbrooke's Hospital in Cambridge. Dr Sala is Lead Radiologist for imaging of gynaecological malignancies for West Anglia Cancer Network and Lead for gynaecology imaging at Addenbrooke's Hospital.

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