Diffusion weighted imaging in endometrial cancer

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Learning objectives

- Review the revised 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system for endometrial cancer.
- Consider current MRI protocols utilised for preoperative staging of endometrial cancer.
- Explore the potential role of diffusion weighted MRI in the staging of endometrial cancer.
Background

Endometrial carcinoma is the most commonly diagnosed gynaecological malignancy in the United Kingdom\(^1\). It occurs most commonly in Caucasian women, with peak incidence between age 70 and 74\(^1\). Risk factors for developing endometrial cancer include unopposed oestrogen intake, tamoxifen use, nulliparity, obesity and diabetes\(^1\). Increasing population age, obesity and decreasing fertility rates are causing the incidence of endometrial cancer to continue to rise\(^1\).

Prognosis varies greatly and depends on the histological grade of the tumour, the depth of myometrial invasion, lymphovascular invasion (LVSI) and lymph node status\(^2\). Depth of myometrial invasion is the single most important morphological prognostic factor; it correlates with tumour grade, lymph node status and overall survival\(^3\). Endometrial cancer is usually diagnosed and histologically graded by pipelle biopsy. It is surgically staged with the International Federation of Gynaecology and Obstetrics (FIGO) staging system, last revised in 2009\(^2\). As FIGO stage correlates with prognosis, preoperative staging is essential to allow tailoring of treatment\(^2\).

Magnetic resonance imaging (MRI) is the most valuable imaging tool for preoperative staging of endometrial cancer\(^4\). The combination of T2WI and contrast enhanced T1WI is superior to unenhanced MRI, ultrasonography and computed tomography\(^4\). More recently it has been suggested that the addition of diffusion weighted MRI imaging (DWI) to MRI protocols could increase the accuracy of staging.

This review will recap the revised 2009 FIGO staging system and explore MRI protocols currently used to preoperatively stage endometrial cancer. Brief consideration of the impact of staging on treatment strategies shall be made. The potential role of DWI in the staging of endometrial cancer shall then be discussed with reference to recent published literature.
FIGO Staging

Endometrial cancer is staged with the FIGO staging system. This system was first devised in 1988, and following new evidence about prognostic factors underwent major revision in 2009\(^2\). FIGO stage correlates with prognosis and preoperative staging is therefore essential to allow tailoring of the overall treatment and of the surgical approach\(^2\). Table 1 summarises the 2009 FIGO staging system.

**Treatment of Endometrial Cancer**

Standard therapy for endometrial cancer includes total hysterectomy and bilateral salpingo-oophorectomy with peritoneal washings\(^5\). Patients who have stage II disease will usually undergo radical hysterectomy with removal of the uterus, cervix, upper vagina, parametrium, ovaries and fallopian tubes\(^6\).

Systematic pelvic and para-aortic lymphadenectomy is part of the FIGO surgical staging system however performing systematic lymphadenectomy in all patients is controversial\(^6,7\). The incidence of lymph node metastases increases from 3% in stage IA disease to 46% in IB disease\(^8\). Systemic lymphadenectomy is recommended for patients with endometrial cancer of intermediate or high risk of recurrence however there is evidence that patients with grade 1 or 2 endometrial adenocarcinoma with FIGO stage IA and no LVSI will gain no survival benefit\(^9\). The disadvantage of systemic lymphadenectomy is an approximately 7% risk of lymphocele formation after surgery, increased anaesthesia and operating time, and the need for a specialised oncological surgeon\(^10\).

Stage III or IV tumours, which have spread out of the uterus, have more varied treatment depending on patient age, tumour histology and pattern of spread. Typically treatment will involve debulking surgery followed by chemotherapy and radiotherapy\(^6\).

Fertility sparing treatment is a possibility for some of the 8-14% of women who develop the disease whilst of childbearing age\(^5\). Hormonal treatments may be offered for grade 1 tumours which express progesterone receptors and which show no evidence of LVSI, myometrial invasion, distant metastatic disease or concurrent ovarian tumour\(^5\).
**Current MRI Staging**

MRI can assist in preoperative assessment and treatment planning by predicting the depth of myometrial invasion, cervical stromal invasion and lymph node involvement. Contrast enhanced MRI is superior to ultrasonography, CT and unenhanced MRI.

There is some agreement regarding MRI protocols between recent guidelines from the European Society of Urogenital Imaging and a paper by Beddy et al. Both suggest that patients should void approximately 1 hour before the examination as a full bladder may degrade T2 weighted images, and that an antiperistaltic, buscopan or glucagon, should be administered or alternatively the patient can fast for 4 hours prior to MRI.

For non-contrast sequences there is agreement that MRI should include at least two T2WI sequences in sagittal, axial oblique, or coronal oblique orientations. Beddy also suggests the addition of an axial T1WI sequence. Imaging of the upper abdomen and retroperitoneum is considered optional given the limited sensitivity of MRI to detect lymph node metastases without lymph node specific contrast agents. If the upper abdomen and retroperitoneum are to be imaged then axial T2WI or coronal T1WI sequences are recommended.

There is controversy regarding the most appropriate contrast enhanced imaging to perform. Beddy et al recommend sagittal dynamic contrast enhanced (DCE) MRI prior to contrast and then post 0.1mmol/kg gadolinium at 25s, 60s and 120s. The European Society of Urogenital Imaging guidelines favour single pre and post gadolinium 3D T1WI sequences, with the post gadolinium images acquired at 120 +/- 30s after contrast injection. DCE-MR offers superior temporal resolution but lacks spatial resolution compared to a single T1WI 3D sequence. The reduced spatial resolution of DCE-MRI may lead to false negative findings in deep myometrial invasion in small uteri. DCE-MRI may be of value when looking for subtle disruption of the junctional zone by early subendometrial contrast enhancement however. This has been described as a characteristic for endometrial invasion and may be important if fertility sparing treatment is considered. It should be noted that this finding is typically not seen during menstruation and during the first part of the cycle.

Both papers suggest that an additional axial oblique post contrast sequence should be obtained 3-4 minutes post contrast if there is suspicion of cervical invasion.
Functional imaging by means of DWI is increasingly becoming part of routine protocols. As with most applications of DWI there is no standard set of optimised b-values used for staging endometrial cancer. The European guidelines from 2009 do not include DWI in their protocol, however Beddy et al suggest performing sagittal (b=0 smm$^{-2}$ & b=500 smm$^{-2}$) and axial oblique (b=0 smm$^{-2}$ & b=800 smm$^{-2}$) diffusion weighted sequences.

**Diffusion Weighted Imaging**

DWI involves probing the motion of water in tissues. Signal returned is influenced by the microscopic structure of the tissue, with pathological tissues often demonstrating restricted diffusion. DWI provides intrinsic contrast and may be particularly useful in patients with contraindications to intravenous gadolinium. In endometrial cancer the increased cellularity of the tumour causes restricted diffusion leading to increased signal on the diffusion weighted images and a reduced apparent diffusion coefficient (ADC).

DWI could not initially be applied to body imaging because images become distorted resulting in misregistration artefacts attributable to chemical shift artefacts. More recently parallel imaging techniques and echo planar sequences have reduced image distortion and increased signal to noise ratio, making body DWI possible.

Low to medium b value sequences (50 - 800 smm$^{-2}$) can be used to create ADC maps, and there is some evidence that quantitative measurements of ADC may be useful in distinguishing malignant from benign tissues. DWI is not used widely as a quantitative tool however; a lack of standard protocols and differences between scanners hampers its adoption as such. It should be noted that regions of interest for calculating ADC must not be placed on necrotic tissue as this may increase the ADC value and so mimic benign pathology.

High b values (> 1000 smm$^{-2}$) make images more sensitive to water diffusion, so there is increased contrast between normal and cancerous tissue, but with the drawback of decreased anatomical detail of adjacent structures. High b value sequences can be fused with standard T2 sequences to create false-colour fused images which help with anatomical localisation, see figure 2.

**Diagnosing Endometrial Cancer**

DWI may be useful for primary diagnosis of endometrial cancer, although this is unlikely to be necessary due to the ease of pipelle sampling. It could be utilised in patients...
who refuse hysteroscopy or patients with vaginal or cervical stenosis in whom it can be difficult to perform biopsy\textsuperscript{22}. ADC values have been found to differ significantly between malignant and benign endometrial lesions\textsuperscript{15-17,19,21-24} and in some instances there was no overlap between the ADC of normal endometrium and that of endometrial cancer\textsuperscript{19}.

Quantitative measurement of ADC values has the potential to help to grade tumours\textsuperscript{8}. The ADC values of endometrial cancers of higher grade show tendency to decrease compared to those of lower grade, although estimation of histologic grade based on ADC values seems difficult because of considerable overlap\textsuperscript{19,25}. Other investigators have found that ADC values do not correlate with histologic tumour grade, depth of myometrial invasion or the presence of lymph node metastases\textsuperscript{23}.

**Myometrial Invasion**

Depth of myometrial invasion correlates with tumour grade, lymph node metastases and overall patient survival\textsuperscript{26}. Patients with greater than 50% myometrial invasion have a greater than 6 fold higher risk of having nodal metastases than those with less than 50% invasion\textsuperscript{3}. Identification of the absence of myometrial involvement is critical for young patients with grade 1 endometrial adenocarcinoma, since fertility sparing treatment may still be an option\textsuperscript{18}.

Beddy et al found that more patients were staged correctly with DWI than with DCE-MRI\textsuperscript{26}. Known pitfalls in the assessment of myometrial invasion on MRI (leiomyoma, adenomyosis, poor tumour-myometrium contrast and loss of the junctional zone) did not affect the ability of readers to assess the degree of myometrial invasion with DWI\textsuperscript{26}.

Shen et al demonstrated similar sensitivities for the detection of myometrial invasion for T2WI + DCE-MRI and T2WI + sagittal and axial oblique DWI MRI\textsuperscript{22}. In 5 of their 31 patients DWI provided information which changed preoperative staging. Differing b values were utilised for the first 5 patients, before it was decided that a b value of 1000 was best to depict tumour extent\textsuperscript{22}.

Retchini found DWI alone to be more sensitive than DCE-MRI alone in the assessment of myometrial invasion, although numbers of patients were low and findings were not statistically significant\textsuperscript{27}. Takeuchi also demonstrated improved accuracy of staging myometrial invasion with DWI versus DCE-MR, although again this difference was not statistically significant\textsuperscript{17}.
Figure 1 shows an example of diffusion weighted imaging versus post contrast sequences in a patient with stage IA endometrial carcinoma from our institution.

Lin et al found that fused T2WI and DWI sequences could improve assessment of myometrial invasion. They found that the addition of fused T2/DWI sequences to standard T2WI and DCE-MRI improved pathological correlation significantly and also that T2WI combined with fused T2WI/DWI imaging was significantly more accurate than T2WI with DCE-MRI\textsuperscript{18}. Figure 2 shows an example of fused T2/DWI sequences from our institution.

Although results from these initial studies are encouraging it should be noted that all of these early studies have included fewer than 50 patients\textsuperscript{17,18,22,26,27}.

**Cervical Stromal Invasion**

There is very little literature on the usefulness of DWI in detecting cervical stromal invasion in endometrial cancer. Beddy et al compared the accuracy DWI and DCE-MR in overall staging accuracy in endometrial cancer\textsuperscript{26}. Their patient cohort included four patients with stage II disease. Both readers correctly identified cervical stromal invasion more often on the DWI than the DCE-MR images (3/4 vs 2/4 for reader 1; 2/4 vs 1/4 for reader 2), however numbers are too small to draw any conclusions\textsuperscript{26}.

**Lymph Node Involvement**

Although systemic lymphadenectomy is part of the FIGO staging system\textsuperscript{2} it carries significant risk of complications\textsuperscript{10}. Identification of the presence of nodal metastases would allow better selection of patients for lymphadenectomy and potentially avoid unnecessarily aggressive surgery\textsuperscript{20}. Using size criteria to differentiate benign from malignant nodes MRI has a sensitivity of between 24-73\%\textsuperscript{14}.

Lymph node specific contrast agents composed of ultra-small particles of iron oxide have been shown to increase MRI sensitivity to 82-93\%\textsuperscript{29}. However these agents are required to be administered 24 hours prior to MRI and the product used in these studies has since been withdrawn.

Kim et al found significant differences in ADC value between metastatic and non-metastatic lymph nodes in patients with endometrial cancer. Although there was some overlap in ADC values they reported the sensitivity of ADC for differentiating metastatic
from non-metastatic nodes as 87%\textsuperscript{30}. Other studies have found that although DWI may help with the identification of lymph nodes compared with T2WI images, the ADC cannot reliably distinguish between metastatic and non-metastatic nodes\textsuperscript{31,32}. Figure 3 compares T2WI, DWI and fused T2/DWI images to illustrate how DWI can increase conspicuity of lymph nodes.

Although the usefulness of absolute ADC values for differentiating benign and metastatic lymph nodes remains in doubt, calculating relative ADC (rADC) values using renal cortex or primary tumour as a reference tissue may be valuable\textsuperscript{33,34}. By measuring primary tumour ADC, lymph node ADC and lymph node long and short axis diameter Lin et al were able to increase their sensitivity for the detection of metastatic lymph nodes from 25\% to 83\%\textsuperscript{33}. Specificity remained high, at 99\%. The smallest metastatic node identified was only 5mm in short axis diameter\textsuperscript{33}.

**Extrauterine Spread**

No papers discussing the usefulness of DWI in detecting parametrial, bowel, bladder or distant metastatic spread in endometrial cancer could be identified.
**Table 1**: Summary of the 2009 FIGO staging system for endometrial cancer adapted from Beddy et al (2012).2

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**Fig. 1:** a) T2WI, b) 3D T1 post gadolinium sequence, c) DWI (b=800 s/mm2), and d) ADC. Images show a stage IA endometrial cancer involving the right lateral wall of the uterus (arrow) to a myometrial depth of less than 50%. Post contrast image (b) and DWI image (c) provide similar images for assessing the depth of myometrial invasion.

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Fig. 2: a) T2WI, b) DWI (b=800 s/mm²), c) ADC, and d) fused T2/DWI. Uterine anatomy is most clearly depicted on T2WI (in this case the endometrial cavity is displaced anteriorly by a large fibroid). Tumour extent is clearer as high signal on the DWI image however. ADC illustrates corresponding low signal indicative of restricted diffusion. Fused T2/DWI image allows more accurate assessment of myometrial invasion by combining sensitivity of DWI with anatomical detail of T2WI.

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**Fig. 3:** a) T2WI, b) DWI (b=800 s/mm²), and c) fused T2/DWI. Images demonstrate a right external iliac node (arrow) and smaller left sided nodes. These nodes are more conspicuous on DWI images, and fusion of T2/DWI helps with anatomical localisation.

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Conclusion

Endometrial cancer is the most common gynaecological malignancy in the United Kingdom. It is staged using the FIGO surgical staging guidelines. FIGO stage correlates with prognosis and preoperative staging is essential to tailor treatment. MRI is the most accurate staging modality currently used and protocols should include small field of view T2WI in at least two orthogonal planes plus some form of post contrast T1WI and perhaps larger field of view sequences to detect retroperitoneal lymphadenopathy.

Body DWI is a relatively novel imaging technique which allows detection of pathological tissues by measuring the diffusion of water within them. It offers the possibility to diagnose endometrial cancer in patients who cannot undergo hysteroscopic biopsy, to more accurately stage those patients diagnosed with endometrial cancer prior to treatment and may be especially useful in patients who cannot receive gadolinium contrast.

Several studies have shown that the ADC value of endometrial cancer is significantly lower than that of normal endometrium or benign endometrial pathologies. DWI has also been found to be as sensitive, or more sensitive, than DCE-MRI in the staging of myometrial invasion. However studies have been small and some results have not been statistically significant. There is little evidence for the usefulness of DWI in detecting cervical infiltration or local or distant spread so far. DWI can be used to increase the conspicuity of lymph nodes at MRI staging. Although absolute ADC values may not be able to differentiate benign from metastatic lymph nodes, there have been promising results from early studies of the rADC of lymph nodes.

Despite obvious promise, a lack of standard protocols limits the comparability of current studies, and in particular the use of the quantitative ADC values.

In conclusion, there is growing evidence to support the routine use of DWI sequences in MRI staging of endometrial cancer, in particular in patients who cannot receive gadolinium contrast. However further research is required to determine the exact sensitivity of DWI and what protocols will maximise its usefulness. In future it may become a suitable alternative to contrast enhanced T1WI meaning no injection will be required and money will be saved on the cost of contrast.
References


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