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EDITORIAL

Advances in magnetic resonance imaging of endometrial cancer

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Endometrial cancer is the most commonly diagnosed gynaecological malignancy in affluent societies [1]. It occurs most frequently in white women, with peak incidence between ages 55 and 65. Risk factors include unopposed oestrogen intake, use of tamoxifen, nulliparity, obesity, and diabetes. The incidence of endometrial cancer in the United Kingdom has increased by more than 40% between 1993 and 2007. This significant rise is predominantly due to a large increase in incidence in women aged 60–79 [1]. These trends are very similar for most European countries [2]. The increase in prevalence of obesity and decreases in fertility may partly account for the observed rapid increase in incidence and imply that endometrial cancer in postmenopausal women will become a more substantial public health problem in the future.

Prognosis depends on a number of factors, including stage, depth of myometrial invasion, lymphovascular invasion, nodal status and histological grade. Depth of myometrial invasion is the single most important morphologic prognostic factor, correlating with tumour grade, lymph node metastases and overall patient survival. Incidence of lymph node metastases increases from 3% with superficial myometrial invasion (stage IA) to 46% with deep myometrial invasion (stage IB) [3]. Preoperative knowledge of these factors is crucial in tailoring the surgical approach. The histological grade can be determined at endometrial sampling, whereas depth of myometrial invasion can only be assessed preoperatively by MRI. Therefore, MRI can assist in preoperative assessment and treatment planning by accurately predicting depth of myometrial invasion, cervical stromal invasion and lymph node involvement. This information allows selection of patients for pelvic or para-aortic lymph node sampling whilst obviating the need for surgery in patients with low risk disease. MRI can also provide additional useful information such as uterine size, tumour volume, ascites and adnexal pathology which in turn may determine whether the surgical approach is transabdominal, transvaginal or laparoscopic.

Lymphadenectomy in early (stage I) endometrial cancer remains a controversial issue. Two large prospective multicentre studies investigated whether pelvic lymphadenectomy could improve survival of women with endometrial cancer [4, 5]. Both studies reported no benefit in overall or recurrence free survival in the patients randomized to lymphadenectomy. Conversely, the SEPAL study [6] showed that in patients with intermediate or high risk of endometrial cancer recurrence, combined pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy alone. The authors acknowledged that MRI is an important factor for predicting lymph node metastasis, and in combination with tumour grade and histology could be helpful to discriminate patients with very low risk of recurrence. Therefore,

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preoperative accurate assessment of depth of myometrial invasion by MRI remains an important factor in surgical planning [7].

Functional imaging by means of dynamic multiphase contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion weighted magnetic resonance imaging (DW-MRI) are becoming part of the standard imaging protocols for staging patients with endometrial cancer. This is mainly due to the limitations of morphologic imaging, particularly in the accurate assessment of the depth of myometrial invasion especially in the presence of pitfalls such as loss of junctional zone definition (very common in post-menopausal patients), poor tumour to myometrium contrast, myometrial compression by polypoid tumour, leiomyomas, and adenomyosis. To date, it has been accepted that the combination of DCE-MRI and T2W images offers a 'one-stop' examination with the highest efficacy for staging of patients with endometrial cancer [8, 9] and this protocol has been implemented by most European cancer centres as well as recommended in the ESUR Endometrial Cancer Staging Guidelines [10]. Nevertheless, there is no consensus in the literature regarding the added value of DCE-MRI in staging of endometrial cancer. Although the majority of the published studies demonstrate that the addition of multiphase DCE-MRI to T2W imaging leads to a significant improvement in the accuracy of assessment of the deep myometrial invasion [8, 9, 11–15], some authors have found no significant difference [16, 17].

In a recent prospective study published in European Radiology in 2010, Rechichi et al. found that DW-MRI was very accurate in assessing myometrial invasion with a sensitivity, specificity, positive and negative predictive value of 84.6%, 70.6%, 52.4% and 92.3%. The corresponding values for dynamic gadolinium-enhanced imaging and T2W imaging were 69.2%, 61.8%, 40.9%, 84.0% and 92.3%, 76.5%, 60.0%, 96.3% respectively. The interobserver agreement in assessing the depth of myometrial invasion was substantial for both T2W and DW imaging (k = 0.91 and 0.74 respectively) and moderate for dynamic imaging (k = 0.45). They suggested that DWI could potentially replace dynamic imaging as an adjunct to routine T2WI for preoperative evaluation of endometrial cancer [18].

The authors are to be commended for the prospective design and detailed histopathological analysis in this study. In addition to the evaluation of the depth of myometrial invasion, the authors estimated the myometrial thickness in all cases. Incorrect evaluation of depth of myometrial invasion was mainly due to over-calling deep invasion. This was found to be the result of a combination of overestimation of tumour invasion into the myometrium and underestimation of myometrial thickness in all three

Fig. 1 Stage IB endometrial cancer. **a** Sagittal T2W image, (**b**) axial T2W image, (**c**) DW image (b = 800), (**d**) ADC map, (**e**) fusion image of sagittal T2W and DWI, and dynamic contrast-enhanced (**f**) early and (**g**) equilibrium phase T1W demonstrate a distended endometrial cavity by presence of a large tumour (T in **a**–**f**). A Nabothian cyst (N) is seen in the cervix uteri. The tumour shows restricted diffusion in the ADC map (**e**), whereas the high signal intensity of the Nabothian cyst on the b800 DW image (**c**) can be attributed to a T2-shine-through effect. While the arterial phase (**f**) does not provide any additional information, the image acquired in the equilibrium phase (2 min.) allows a good delineation of the tumour which enhances less than the adjacent myometrium (**f**). While histologically confirmed myometrial invasion of the ventral uterine wall was correctly diagnosed on T2W (*arrows*), tumor extent would have been underestimated by DWI alone

pulse sequences. It is perhaps interesting to note that this group previously reported a sensitivity of 87.5% for contrast enhanced MRI compared with 71.4% for T2WI. The authors do not comment on this change in their local results. It may be that technical advances have resulted in improvements in T2W sequences.

There are a few methodological limitations that the reader must take in account when evaluating the results of this article. Firstly, the DW and dynamic images were acquired in a single plane (axial) whereas the T2W images were acquired in three orthogonal planes (sagittal, axial oblique and coronal oblique). This may explain the higher accuracy of T2W images as optimal assessment of depth of myometrial invasion requires evaluation of at least two orthogonal planes.

Secondly, the only dynamic images used for evaluation of the depth of myometrial invasion were those obtained in the portal venous phase whereas the maximum tumour to myometrium contrast is achieved in the equilibrium phase (2 min post injection) which is the most optimal phase of enhancement for assessment of the depth of myometrial invasion. This may have resulted in the lower accuracy of dynamic imaging compare to other sequences. One could even argue that since the distinction between tumours confined to the endometrium and those who invade the inner myometrium is no longer of clinical importance, as both categories are classified as stage IA in the revised FIGO staging system [19], the early phases of enhancement (arterial and portal phase) may no longer be needed for staging of endometrial cancer (Fig. 1). Therefore, "static", spin-echo contrast-enhanced imaging may be a suitable alternative to "dynamic" imaging [10].

Thirdly, single b-value DW images (b = 500) were reviewed in isolation, with no comparison with respective ADC maps. The DW images should always be evaluated together with ADC maps and other anatomical sequences (e.g. T1W and T2W images) in order to avoid potential pitfalls in image interpretation such as T2 shine-through, water restriction in normal and non-malignant tissues and lesions with low cellularity (Figs. 1 and 2). Erroneous

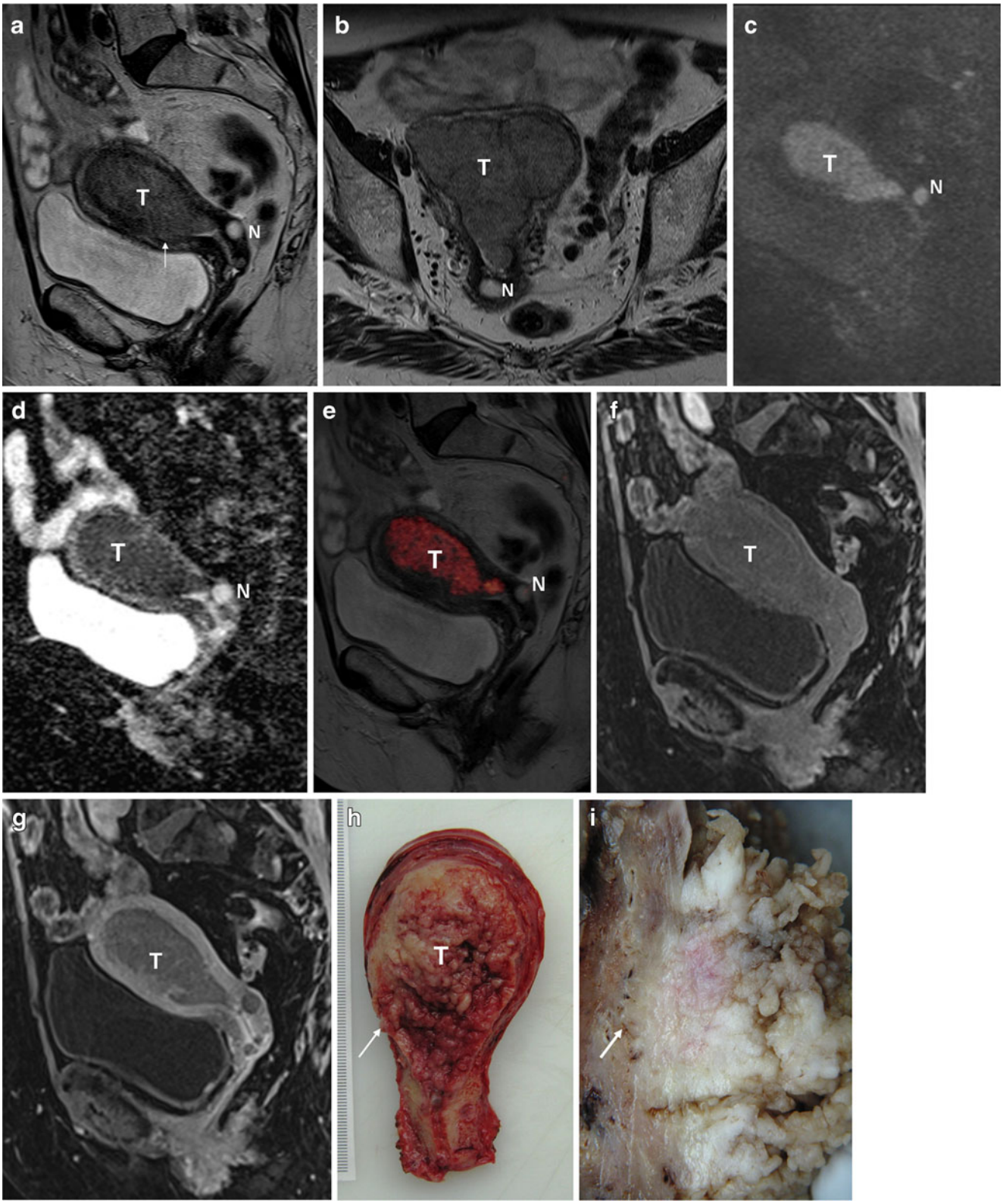

image interpretation may occur if high *b*-value images are viewed in isolation without cross-referencing them to the corresponding ADC maps. High signal intensity on DW images and low signal intensity on the corresponding ADC maps due to restricted diffusion may also occur in areas of retained mucus in an obstructed endometrial cavity, coagulative necrosis and abscesses. In such cases, the anatomic images are very helpful. Some malignant tumours

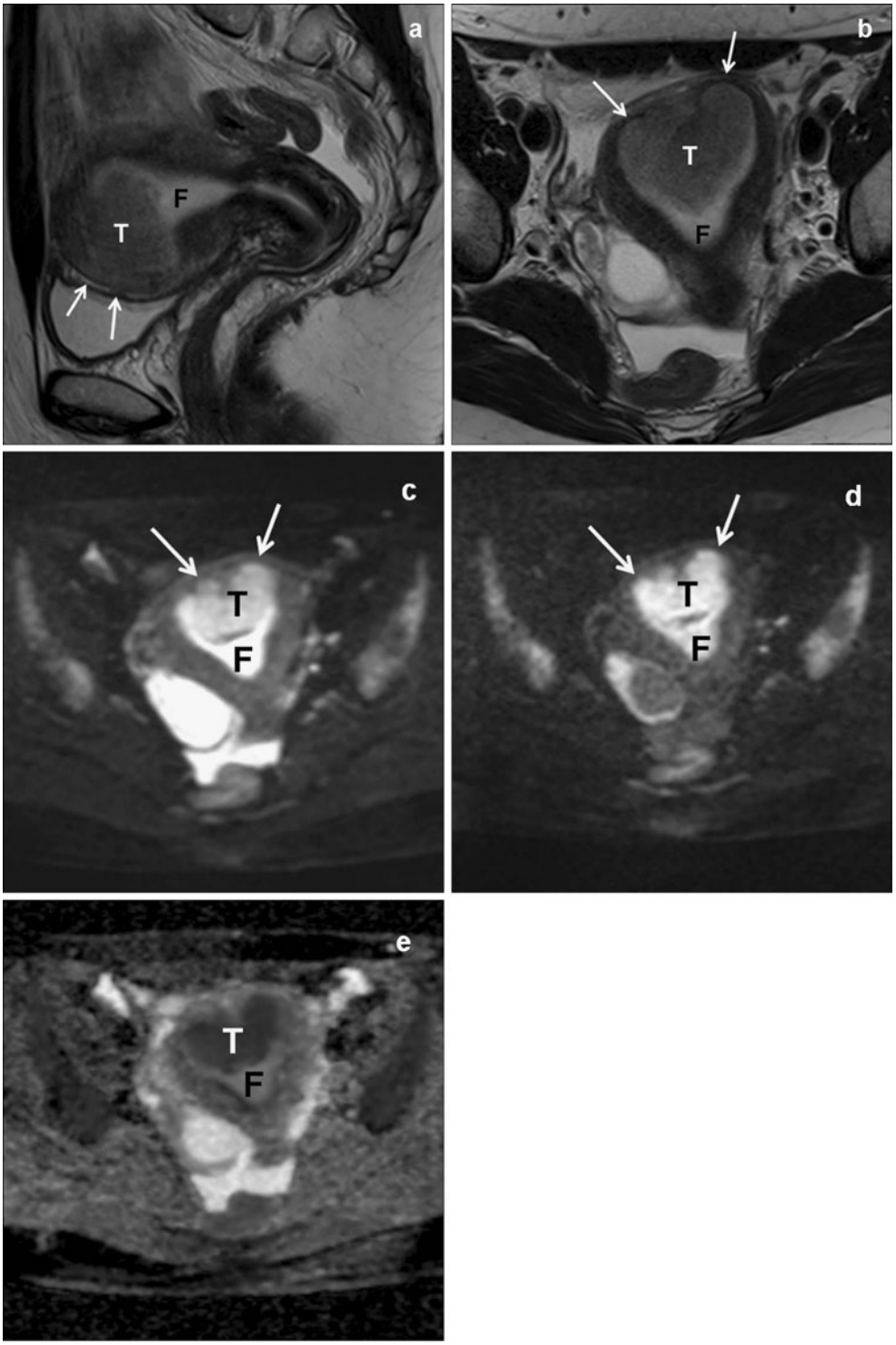

Fig. 2 Stage IB endometrial cancer. **a** Sagittal T2W image, (**b**) axial T2W image, (**c**) DW image (b = 400), (**d**) DW image (b = 1000), and (**e**) ADC map demonstrate a distended endometrial cavity by presence of tumour (T in **a–e**) and fluid (F in **a–e**). The tumour shows restricted diffusion in the ADC map (**e**). The low b-value DW image (**c**) and the ADC map (**e**) allow better differentiation between tumour and fluid within the endometrial cavity. The deep myometrial invasion is perhaps easier to appreciate on DW images (*arrows* in **c**, **d**) compared to T2W images (*arrows* in **a**, **b**)

such as well differentiated adenocarcinomas may have little restricted diffusion due to their low cellularity. These may not be visible on DW images and appear bright on ADC maps due to the high ADC value. Correlation with anatomical sequences and potential use of post-processing software for image fusion (T2W and DW images) are therefore very useful in these cases (Fig. 1).

Finally and most importantly, the most useful evaluation would have been comparison of T2W imaging versus T2W imaging + dynamic imaging versus T2W imaging + DW-MRI to determine the added value of dynamic imaging and DW-MRI as none of these techniques can be used in isolation. The T2W images remain crucial for anatomical reference due to their high spatial resolution which both

dynamic and DW-MRI sequences lack. This is analogous to co-location of FDG-PET images with CT.

Other studies have also evaluated the accuracy of DW-MRI in assessment of myometrial invasion [20–22] and have shown similar results. Shen at al. [20] compared the use of DW-MRI and DCE-MRI in the evaluation of depth of myometrial invasion and found that the diagnostic accuracy was 62% for DW-MRI compared to 71% for DCE-MRI. However, both DW-MRI and DCE-MRI images were acquired in the sagittal plane only. This may have contributed to a relatively low accuracy in the evaluation of myometrial invasion as the presence of two orthogonal planes is mandatory for an accurate assessment. DW-MRI was also useful in detection of drop metastases in the cervix or metastatic foci outside the uterus, such as adnexa or peritoneum [20]. Lin et al. [22] demonstrated an accuracy of 88% in determining the depth of myometrial invasion using fused T2W and DW images at 3.0 T.

Detection of nodal metastases remains elusive. Improvements in sensitivity have been reported at 3 T by Lin et al. [22]. In patients with cervical or uterine cancer, they found that a combination of nodal size and the relative tumour to node ADC resulted in an increase in sensitivity compared with size criteria from 25 to 83%, whilst maintaining very high specificities. However, Nakai et al. reported no difference in diagnostic performance between size criteria and DWI in differentiating benign from malignant nodes in 18 patients with gynaecologic cancer [23]. A more recent study of 259 patients with various pelvic tumours also reported no improvement in sensitivity [24]. Rechichi et al. did not report their findings in relation to nodal appearances.

DW-MRI may also help to differentiate endometrial cancer from normal endometrium. This has limited clinical utility as the diagnosis of endometrial cancer is made at endometrial biopsy, however, pipelle sampling has an error rate and up-staging of the tumour grade may occur in up to 15% of patients. In these cases, DW-MRI may influence surgical planning by improving pre-operative detection of high grade tumours. The ADC value of endometrial cancer is significantly lower than of endometrial polyps and of normal endometrium [25, 26]. ADC values can provide useful information in differentiating malignant from benign endometrial lesions with a sensitivity, specificity and accuracy of 85%, 100% and 92% respectively [25]. High grade endometrial carcinomas have high cellular density and are expected to have lower ADC values (Fig. 1) compare to low-grade ones. Tamai et al. [26] found a trend towards lower ADC values in high grade endometrial cancers. However, one should be aware that there is no reliable cut-off ADC value that is diagnostic of presence of malignancy. Also, tumour necrosis associated with poorly differentiated tumours can have increased ADC values.

In conclusion, DW-MRI is an important imaging technique which may enable accurate staging of endometrial cancer compared to conventional T2W images alone (Fig. 1) and obviate the need for dynamic contrast enhanced images. This may be particularly helpful in cases of tumours that are either iso- or hyper-intense relative to the myometrium or when the use of intravenous contrast medium is contra-indicated. This would also result in shorter examination time which leads to a reduction in the cost of MRI. However, the reader must be aware that well-designed studies are required to directly compare the accuracy of combined T2W & DW-MRI with combined T2W & DCE-MRI before one decides to replace dynamic imaging with DW-MRI. DW-MRI cannot replace T2W sequences as it lacks anatomical details that are crucial for accurate assessment of depth of myometrial invasion. Furthermore, the DWI should always be evaluated together with ADC maps and other anatomical sequences (e.g. T1W and T2W images) in order to avoid potential pitfalls in image interpretation.

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