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Research article

Diffusion weighted MRI for the detection of myometrial invasion in carcinoma endometrium

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ABSTRACT

Depth of myometrial invasion (<50% vs. >50%) is a critical prognostic factor in endometrial carcinoma, influencing the need for lymphadenectomy. MRI, particularly diffusion-weighted imaging (DWI), is increasingly playing a role in preoperative assessment. To determine the diagnostic accuracy of DWI in detecting myometrial invasion compared to dynamic contrast-enhanced (DCE) and T2-weighted (T2W) sequences, and to assess interobserver agreement. This retrospective study included 40 patients with surgically confirmed grade 1–2 endometroid adenocarcinoma who underwent preoperative MRI (T2W, DCE, and DWI). Two blinded radiologists independently assessed myometrial invasion. Sensitivity, specificity, accuracy, predictive values, and interobserver agreement (kappa statistics) were calculated using histopathology as the reference standard. DWI demonstrated the highest diagnostic accuracy for both observers (92.5% and 90%), followed by DCE (90% and 82.5%) and T2W (72.5% and 70%). DWI showed the highest sensitivity (100% and 94.7%) and negative predictive value (100% and 94.7%). Accuracy of DWI was significantly better than T2W for both observers (p=0.004). In the subset with coexisting fibroids/adenomyosis (n=10), DWI maintained high accuracy (90%) and sensitivity (100%). Interobserver agreement was near-perfect for DWI (κ=0.849) versus moderate for DCE (κ=0.554) and T2W (κ=0.529). DWI outperforms T2W and is at least equivalent to DCE in assessing myometrial invasion, with excellent interobserver agreement. Given its advantages—no contrast requirement, shorter scan time, and utility in renal failure or contrast allergy—DWI has the potential to replace DCE in routine MRI protocols for endometrial carcinoma staging.

Keywords: Endometrial carcinoma, Diffusion-weighted imaging (DWI), Myometrial invasion, MRI staging.

INTRODUCTION

Endometrial carcinoma is an important gynaecological malignancy worldwide. The extent of the primary tumor and nodal disease can be assessed on MRI, which plays an important role in staging and planning treatment.

Myometrial invasion is one of the most important prognostic factors, which correlates with tumor grade, lymph node metastasis, and overall patient survival [1, 2]. According to the Revised FIGO 2023 staging of Carcinoma Endometrium, stage IA is where the tumor invades less than 50% of the myometrium, and stage IB is where the tumor invades more than 50% of the myometrium [1]. It is important to differentiate between stages IA and IB, as stage IB has a higher likelihood of lymph node metastases and requires a more aggressive surgical approach [2]. Management of Stages I and II of Carcinoma endometrium is primarily surgical (hysterectomy with bilateral salpingo-oophorectomy) [3]. The role and benefit of lymph node dissection have been controversial and may be done in patients with stage IB and II tumors [3]. Lymphadenectomy allows complete and accurate surgical staging, which helps in assessing the need for adjuvant treatment, and can prevent radiation therapy from being given unnecessarily [4]. However, it comes with its own associated morbidity, such as the risk of lymphocele formation (7-10%) and the risk of lymphedema of the lower limbs (up to 23%) [4, 5]. Multiple studies have shown no significant improvement in survival after lymphadenectomy in patients with early-stage disease and grade 1 or 2 endometroid adenocarcinoma on histology [5–9]. Thus, the need for lymphadenectomy in patients with stage I disease needs assessment based on factors that increase the risk for lymph node metastases and recurrence [10–12]. The European Society of Medical Oncology (ESMO) recommends avoiding lymphadenectomy in low-risk patients (grade 1 or 2 endometroid adenocarcinoma with <50%

myometrial invasion), while it is recommended in high-risk patients (high-grade tumours/ deep myometrial invasion).

The standard MR protocol includes high-resolution T2-weighted (T2W) images in various planes, T1-weighted images, dynamic contrast-enhanced sequences, and diffusion-weighted sequences. The endometrium appears as a high signal-intensity structure, followed by the low-intensity junctional zone and the intermediate-intensity myometrium. In carcinoma endometrium, the tumor is usually intermediate on T2W images and hypoenhancing on contrast-enhanced images. Tumors show restricted diffusion, i.e high signal on diffusion-weighted images and low signal on corresponding ADC (apparent diffusion coefficient) images [15]. Endometrial carcinoma reaches its peak enhancement on DCE MRI at 1 minute, and shows gradual washout, appearing hypointense relative to the myometrium in the later phases [16]. Figure 1 shows the typical appearance of endometrial carcinoma on different MRI sequences, and Figure 2 demonstrates the assessment of depth of myometrial invasion on MRI.

Figure 1: Sagittal T2W image (a) shows a T2 intermediate tumour (*) within the endometrial cavity, which appears hypoenhancing compared to the myometrium on DCE image (b). The lesion appears hyperintense on DWI (c) and hypointense on ADC map (d), suggestive of restricted diffusion

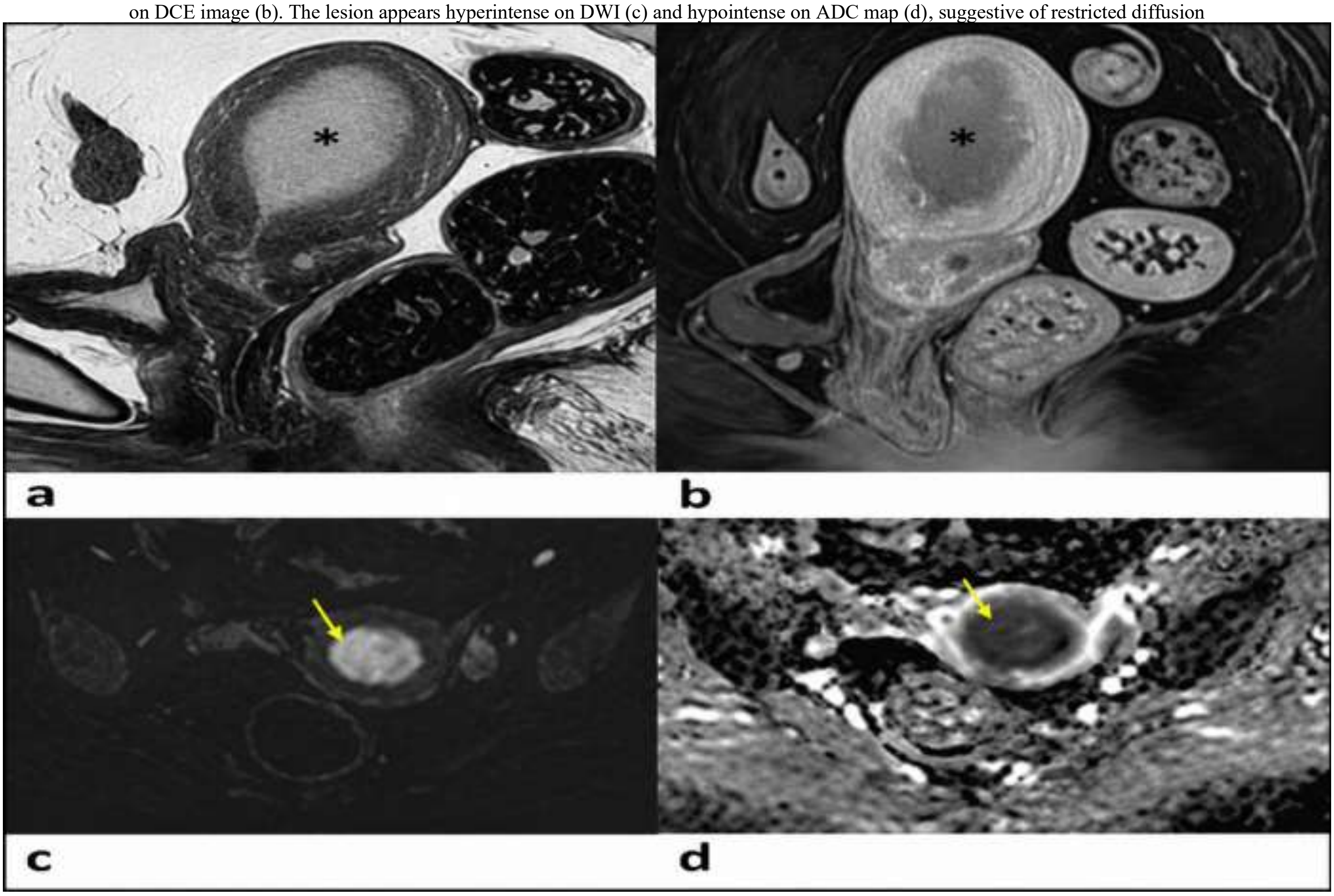
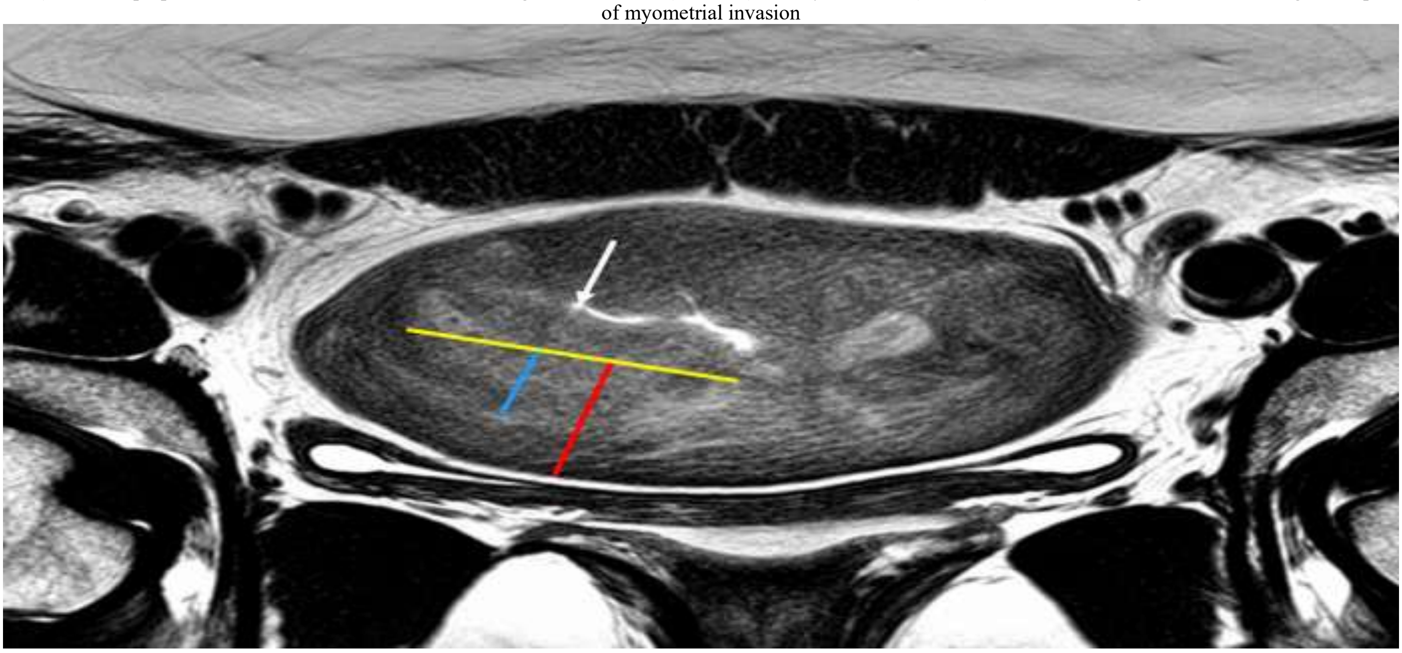


Figure 2: Axial T2W image shows a T2 intermediate tumour (arrow) invading the myometrium. A line is drawn along the inner margin of myometrium (yellow line), and two perpendicular lines are drawn, to the outer edge of the tumour (blue line) and myometrium (red line). The ratio of lengths of these lines gives depth of myometrial invasion



There has been increasing interest in the role of diffusion-weighted imaging in the detection of myometrial invasion. Diffusion-weighted imaging (DWI) uses the difference in mobility of water molecules in tissues to characterise them. Apparent diffusion coefficient (ADC) is a measure of diffusion. It is calculated mathematically from different b-values (representing the strength of the diffusion gradient). Areas of restricted diffusion appear bright on DWI and dark on the corresponding ADC map. The ADC value is expressed in mm2/sec [17]. Endometrial cancers have been found to have a lower ADC value (~0.88 x 10^-3 mm^2/sec) compared to normal endometrium (~1.53 x 10^-3 mm^2/sec). Lower ADC values also correlate with a higher-grade tumor [15]. Thus, diffusion-weighted imaging is a helpful tool in detecting myometrial invasion and determining the grade of the tumor.

Although most endometrial tumors are hypoenhancing, a few tumours can be iso or hyperenhancing, in which case the accuracy of DCE is reduced. The presence of peritumoral inflammatory enhancement can cause error in staging. The presence of adenomyosis or a thickened junctional zone also limits the accuracy of DCE [2].

DWI is helpful in such cases and can be used in patients with contrast allergy or renal failure as well. These factors show the advantages of DWI over DCE and justify the need for studies comparing the diagnostic accuracy of both.

Aims and objectives

A retrospective study to determine the accuracy and value of DWI in detecting the extent of myometrial invasion, as compared to DCE and T2W.

To compare the diagnostic accuracy of DWI, DCE and T2W in determining depth of myometrial invasion in cases with co-existing uterine fibroids and/or adenomyosis.

To assess interobserver agreement.

MATERIALS AND METHOD

Study design and type of study

Retrospective descriptive analytical study.

Eligibility criteria

Inclusion criteria: Patients with surgically confirmed primary endometrial cancer (Grade 1 and 2 endometroid adenocarcinoma on histology) who underwent pre-operative MRI at our institute (including T2W, DCE and DWI).

Exclusion criteria

Patients who underwent pre-operative MRI at a different institute.

Patients who were not operated on subsequently or operated on outside.

Patients whose MRI exam is incomplete or missing any of the required sequences.

Patients who were operated on more than 8 weeks after the MRI was performed.

Post-chemotherapy/post-radiation therapy patients.

Sample size and duration of study

This is a retrospective study with a sample size of 40 patients, presenting between February 2019 and October 2020.

Budget: Nil

Ethical considerations

The study was conducted after clearance from the Institutional Review Board

Ethics Committee. The study was also conducted in accordance with the ICMR Revised National Ethical Guidelines for biomedical and health research involving human participants, 2017.

Consent

Waiver of consent was requested as this is a retrospective descriptive analytical study.

Methodology

Identify patients with carcinoma endometrium who have undergone pre-operative MRI followed by surgery (TAH+BSO) presenting between January 2019 to January 2021.

Two radiologists with >10 years and 3 years of experience respectively, blinded to the histopathology report, interpreted the images and assessed myometrial invasion using three sets of sequences: T2W, DCE, and DWI. The presence of uterine fibroids and/or adenomyosis on imaging was recorded and confirmed on histopathology.

The imaging and histopathological data were tabulated and analysed. Sensitivity, specificity, negative and positive predictive value, and diagnostic accuracy for each sequence were calculated. Interobserver variability was also assessed.

All the details of the patients were obtained from institutional electronic medical records (EMR), and all images were obtained from the institutional picture archiving and communication system (PACS).

Equipment

Scans were performed on a Philips Ingenia 1.5T MRI system and a General Electric (GE) Signa HDxT 1.5T MRI system using a phased array body coil.

Patients were asked to fast for four hours prior to the scan, and Inj Buscopan (hyoscine butylbromide) 20mg i.m was administered to reduce bowel movement artefacts.

Imaging was done with the patient in the supine position.

Sequences

Dedicated Small field of view (FOV) high resolution T2W sequence in oblique axial and coronal planes angled along the endometrial cavity.

Dedicated oblique sagittal small field of view (FOV) Small FOV 24 cm high resolution T2W sequence.

Axial T1W and T2W large FOV images of the pelvis.

Large FOV T2W image of the abdomen in the coronal plane to include the kidneys for hydronephrosis

Axial T1W sequence for screening the upper abdomen for retroperitoneal lymph nodes and visceral/skeletal metastases.

Diffusion weighted sequences performed in the axial plane with echo planar technique with b values of 0, 500 and 800s/mm2. Corresponding ADC maps were generated.

Dynamic post-contrast sequences taken in the sagittal plane with Multihance (Gadobenate dimeglumine) or Omniscan (Gadodiamide DTPA) injected intravenously at a dose of 0.1mmol/kg at a rate of 2ml/sec, with images acquired at 0, 25, 60, 150 and 240 seconds.

Small FOV oblique multiplanar post-contrast fat-saturated sequences

Large FOV post-contrast axial fat-saturated sequence of the pelvis and axial and coronal post-contrast fat-saturated sequences of the upper abdomen.

Statistical analysis plan

Categorical data is presented as counts (percentages) and

Continuous data is presented as mean (SD) or median (IQR).

The following parameters for the extent of myometrial invasion were compared for the 3 sequences, i.e DWI, T2W and DCE, keeping the histopathological report as the standard: accuracy, sensitivity, specificity, positive and negative predictive value.

>50% myometrial invasion was considered positive, and <50% myometrial invasion was considered negative.

The accuracy of the different sequences in the evaluation of the extent of myometrial invasion was compared with the Chi-square test and p-value adjustment by the Benjamini- Hochberg procedure for controlling the false discovery rate in multiple comparisons.

For the interobserver agreement between two readers, the kappa statistic will be used to measure the agreement, where a kappa of 0 means no agreement and 1 means perfect agreement.

Values of $p < 0.05$ were considered statistically significant.

All data were analysed using SPSS software.

RESULTS

Age at diagnosis

The median age at diagnosis was 58 years (52-63).

Depth of myometrial invasion on histopathology

Out of the total sample of 40 patients, 21 patients (52.5%) had <50% myometrial invasion on histopathology, while 19 patients (47.5%) had >50% myometrial invasion on histopathology.

Co-existing uterine fibroids and/or adenomyosis

Out of 40 patients, a total of 10 patients had co-existing uterine fibroids and/or adenomyosis, out of which 9 patients had uterine fibroids only, one patient had adenomyosis only, and one patient had both uterine fibroids and adenomyosis.

Diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of T2W, DWI and DCE for determining depth of myometrial invasion

These values for all three sequences and both observers are summed up in Table 1. DWI had the highest accuracy, sensitivity, and negative predictive value for both observers, while DCE had a higher or nearly equal specificity and positive predictive value.

The results for the subset of patients with co-existing uterine fibroids and/or adenomyosis are summed up in Table 2.

Table 1: Summary of the comparison of diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of T2W, DWI and DCE.

Observer 1	**Diagnostic accuracy**	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**
T2W	72.5%	89.4%	57.1%	65.3%	85.7%
DWI	92.5%	100%	85.7%	86.3%	100%
DCE	90%	94.7%	85.7%	85.7%	94.7%
Observer 2					
T2W	70%	78.9%	61.9%	65.2%	76.4%
DWI	90%	94.7%	85.7%	85.7%	94.7%
DCE	82.5%	73.6%	90.4%	87.5%	79.1%

Table 2: Summary of the comparison of diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of T2W, DWI and DCE in the subset of patients with co-existing uterine fibroids and/or adenomyosis.

Observer 1	**Diagnostic accuracy**	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**
T2W	60%	66.67%	57.14%	40%	80%
DWI	90%	100%	85.71%	75%	100%
DCE	80%	66.67%	85.71%	66.67%	85.71%
Observer 2					
T2W	80%	100%	71.43%	60%	100%
DWI	90%	100%	85.71%	75%	100%
DCE	90%	66.67 %	100%	100%	87.5%

Table 3: Pairwise comparison of accuracy, sensitivity, and specificity of T2W, DWI and DCE with p values (significant p values have been highlighted).

Sequence pair	**Observer 1**			**Observer 2**		
	p value			**p value**		
	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity
T2W vs DWI	0.004	0.15	0.08	0.0046	0.08	0.025
T2W vs DCE	0.008	0.31	1	0.17	0.31	0.014
DWI vs DCE	0.31	0.31	0.08	0.08	0.045	0.31

Inter-observer agreement

Kappa values were computed to measure inter-observer agreement for each sequence, where kappa of 0 means no agreement and 1 means perfect agreement.

There was near perfect agreement with DWI, and moderate agreement was recorded with T2W and DCE. Kappa values for inter-observer agreement are shown in Table 4.

Table 4: Kappa values for inter-observer agreement for T2W, DWI and DCE

	Kappa Value	**p value**
T2W	0.529	0.001
DWI	0.849	0.000
DCE	0.554	0.000

DISCUSSION

Carcinoma of the endometrium is an important gynaecological malignancy and MRI is the standard imaging modality used for staging and pre-operative assessment. The depth of myometrial invasion (<50% or>50%) is one of the most important factors for prognosis and deciding the next step of management. Our study attempts to compare the performance of three MRI sequences, i.e T2W, DWI and DCE in the assessment of myometrial invasion in carcinoma endometrium.

Our study is a retrospective study of a sample of 40 patients with surgically confirmed carcinoma endometrium, who underwent pre-operative MRI at our institute, and the imaging of these patients was interpreted by two independent observers.

DWI had the highest diagnostic accuracy with both observers (92.5% and 90% respectively), followed by DCE (90% and 82.5% respectively), and T2W had the least accuracy (72.5% and 70%). Similar results have been shown by Gil et al, Beddy et al and Takeuchi et al [19]. The accuracy of DWI was significantly higher than T2W for both observers, (p value 0.004) with no significant difference between DWI and DCE. The accuracy of DCE was also significantly higher than that of T2W for the first observer (p value 0.008). Rechichi et al obtained the highest accuracy with T2W followed by DWI, and the least accuracy with DCE [20].

Both observers obtained the highest sensitivity for deep myometrial invasion with DWI (100% for the first observer and 94.7 for the second observer). DCE had a higher sensitivity than T2W with the first observer (94.7% and 89% respectively). Gil et al also observed similar results. The sensitivity of DWI was significantly higher than that of DCE for the second observer (p value 0.045). T2W had a higher sensitivity than DCE for the second observer (78.9% and 73.6% respectively), as also observed by Rechichi et al. Deng et al and Seo et al observed a higher sensitivity with DCE than DWI, while the meta-analysis by Andreano et al reported no significant difference between the sensitivity of DWI and DCE [21-23].

For the first observer, DWI and DCE had an equal specificity of 85.7%, while T2W had a lower specificity (57%). Deng et al also recorded an equal specificity with DWI and DCE [23]. The second observer obtained the highest specificity with DCE (90.4%) followed by DWI (85.7%) and the least with T2W (61.9%). The specificity of DWI and DCE were significantly higher than that of T2W for the second observer (p values 0.025 and 0.014 respectively) Higher specificity with DWI than DCE was observed by multiple studies.

DWI had the highest positive predictive value (PPV) with the first observer (86.3%), followed by DCE (85.7%) and T2W (65.3%). Similar results were reported by other studies as well. The second observer obtained the highest PPV with DCE (87.5%) followed by DWI (85.7%), and least with T2W (65.2%). Rechichi et al found the highest PPV with T2W, however, the PPV of DWI was higher than that of DCE [20].

Our study showed the highest negative predictive value (NPV) with DWI for both observers (100% and 94.7% respectively) than DCE (94.7% and 79.1% respectively) and T2W (85.7% and 76.4% respectively), which is in accordance with the findings of Gil et al and Beddy et al. However, Seo et al reported a higher NPV with DCE than with DWI [22].

In the subset of patients with co-existing uterine fibroids and/or adenomyosis, DWI had high accuracy (90%) and high sensitivity and NPV (100%) for both observers. However, an equal specificity of 87.7% was obtained with DCE for the first observer, and an equal accuracy of 90% was obtained with DCE for the second observer. The second observer also obtained higher specificity and PPV (100%) with DCE than DWI; and an equally high sensitivity and NPV (100%) with T2W as DWI. These values could mean that although DWI has a good diagnostic performance in cases with co-existing pathologies, the role of T2W and DCE in improving accurate diagnosis of deep myometrial invasion cannot be ignored. However; these need further validation with larger studies, as we had a relatively small sample (10) of patients with co-existing uterine fibroids and/or adenomyosis.

Our study also assessed inter-observer agreement for each of the sequences. We obtained the highest inter-observer agreement with DWI, with a kappa value of 0.849, suggestive of near-perfect agreement. Moderate agreement was obtained with DCE (kappa value 0.554) and T2W (kappa value 0.529). Beddy et al also found DWI to have the highest inter-observer agreement. Rechichi et al found better inter-observer agreement with DWI than with DCE, however, T2W had the highest inter-observer agreement. Seo et al also found the highest inter-observer agreement with T2W, and nearly equal agreement with DWI and DCE.

Thus, overall, DWI had the best diagnostic performance out of the three sequences in our study for both observers. The sensitivity and specificity of DWI were significantly better than T2W, and sensitivity significantly better than DCE for the second observer, as also observed by Gil et al. However, the differences were not statistically significant for the first observer.

The better diagnostic performance of DWI is likely due to its superiority in assessment of myometrial invasion in cases with adenomyosis, leiomyomas, indistinct junctional zone, and hypoenhancing or isoenhancing tumours. Figure 3 demonstrates a case of carcinoma endometrium with adenomyosis.

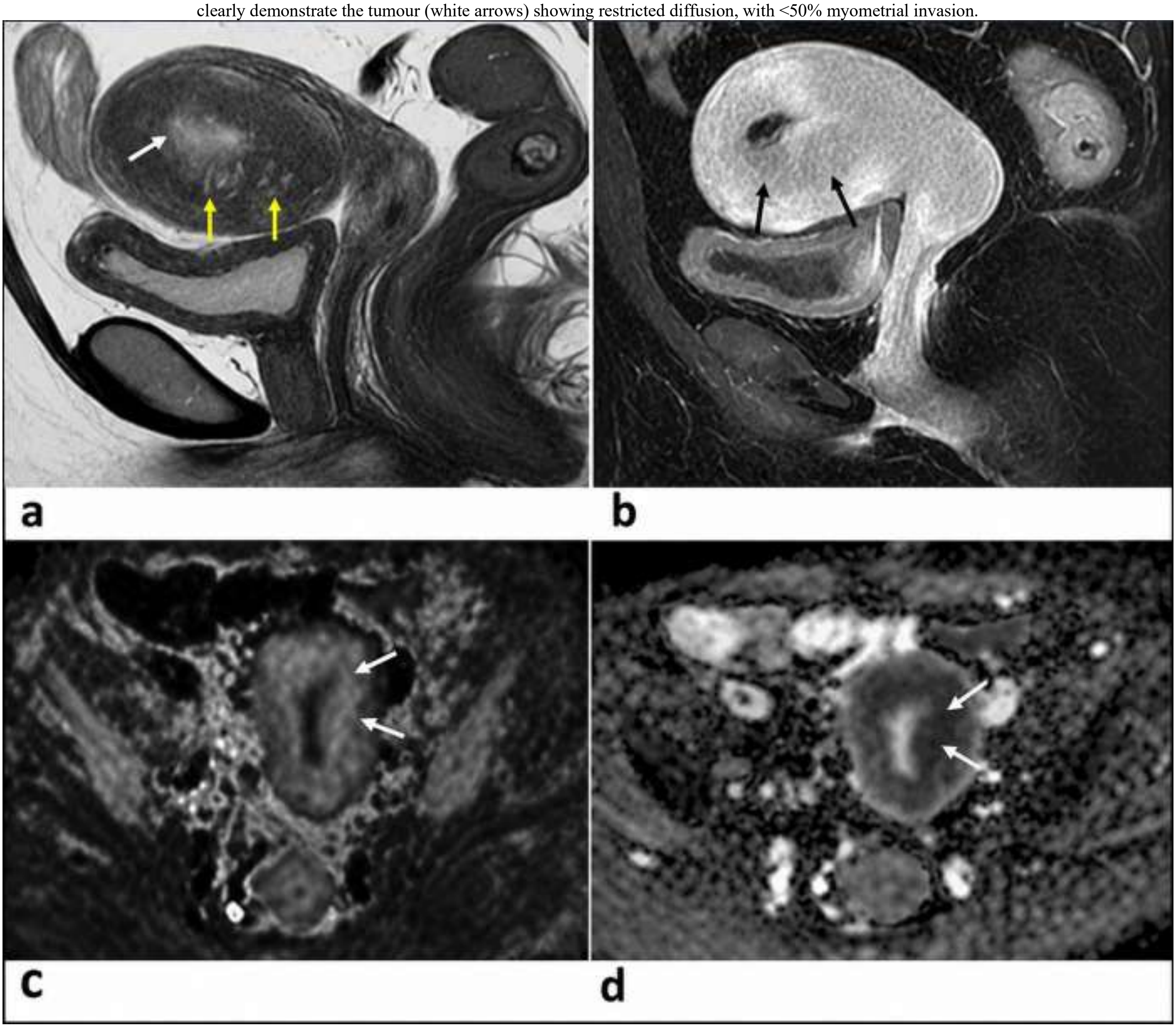
The high sensitivity and negative predictive value of DWI help in the accurate staging of patients with deep myometrial invasion, and in deciding their further management in terms of requiring pelvic lymphadenectomy.

Good inter-observer agreement with DWI indicates that DWI is a reliable sequence, and that different radiologists with varied experience can achieve accurate results with DWI.

With the diagnostic performance of DWI being better than T2W and at least equal to or slightly superior to DCE, and its advantages over DCE including lesser scan time and usability in patients with renal failure and allergy to Gadolinium-based contrast agents, DWI has the potential to replace DCE in the MRI protocol for carcinoma endometrium. However, owing to equal or better specificity and positive predictive value, DCE still plays a role in confidently ruling out myometrial invasion, which is particularly important in patients planned for fertility-sparing treatment [24]. In addition to DWI, DCE can be helpful in cases where the extent of myometrial invasion is doubtful, to avoid over-staging and the morbidity associated with unnecessary lymphadenectomy.

One of the drawbacks of DWI is its poor anatomical resolution. This can be overcome by using fused images of T2W and DWI, or modified Diffusion-weighted sequences such as FOCUS-DWI (field of view (FOV) optimized and constrained undistorted single-shot DWI) and DWIBS (Diffusion weighted whole-body imaging with background body signal suppression) [25].

Figure 3: (a) Sagittal T2W image shows a T2 intermediate tumour (white arrow), with thickened junctional zone and myometrial cysts (yellow arrows), suggesting adenomyosis. (b) Sagittal delayed DCE image shows hypoenhancing areas in myometrium (black arrows). Axial DWI image (c) and ADC map (d) clearly demonstrate the tumour (white arrows) showing restricted diffusion, with <50% myometrial invasion.



CONCLUSION

The primary aim of our study was to assess the accuracy and added value of DWI in the assessment of myometrial invasion in carcinoma endometrium, as compared to T2W and DCE. Myometrial invasion is one of the most important prognostic factors in carcinoma endometrium, and MRI plays an important role in its pre-operative assessment. We obtained a higher accuracy with DWI as compared to T2W and DCE. We also observed higher sensitivity and negative predictive values with DWI than with T2W and DCE.

The specificity of DWI was equal to that of DCE with a higher positive predictive value for the first observer, however, the second observer obtained a higher specificity and positive predictive value with DCE than DWI. In cases with co-existing uterine fibroids and/or adenomyosis, DWI had high accuracy, sensitivity and NPV for both observers; although specificity with DCE was equal for the first observer, and specificity and PPV were higher with DCE for the second observer. The sensitivity and negative predictive value of T2W also matched that of DWI for the second observer.

The secondary aim of our study was to assess the interobserver agreement for these sequences. We found near-perfect agreement with DWI, and moderate agreement with DCE and T2W.

Thus, overall, DWI had a better diagnostic performance than DCE and T2W in assessing the depth of myometrial invasion, with significantly higher accuracy than T2W. Its high accuracy, sensitivity and negative predictive value make it an invaluable sequence in pre-operative evaluation of myometrial invasion. Owing to its advantages such as accurate staging in cases with adenomyosis or fibroids, shorter scanning time and usability in patients with renal failure or MRI contrast allergy, it has the potential to replace DCE in the MRI protocol for carcinoma endometrium.

However, in view of varying results in different studies, further studies on larger samples and prospective studies which account for the effect of pre-operative MRI staging on patient outcomes are required to validate the results of this study.

The use of newer and upcoming techniques such as DWI and T2W fusion images, FOCUS DWI, artificial intelligence and PET-MRI can further increase the accuracy of MRI in the assessment of myometrial invasion. These newer avenues are worth exploring to help radiologists make a difference in selecting the appropriate treatment in patients with carcinoma endometrium and improve their survival and quality of life.

Conflicts of Interest: No conflict of interest

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