VOLUME 4 | ISSUE 3

Women's Imaging ORIGINAL ARTICLE

# Proposed MRI sequences for local staging of endometrial cancer: a single center experience

Charis Bourgioti[1], Konstantinos Chatoupis[1], Aristeidis Antoniou[1], Evangelia Panourgias[1], Chara Tzavara[2], Lia Angela Moulopoulos[1]

[1]*Department of Radiology, Aretaieion Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece*

[2]*Department of Health, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Greece*

SUBMISSION: 7/5/2019 | ACCEPTANCE: 15/9/2019

## ABSTRACT

**Purpose:** To present our experience with preoperative staging of endometrial cancer (EC) using dedicated MRI protocol at a tertiary referral center for female pelvic imaging.

**Material and Methods:** Between April 2013 and June 2018, 117 women (mean age: 59.9 years ± SD: 12.7) with newly diagnosed, biopsy-confirmed EC, underwent pelvic MRI for staging. In all patients, T2-weighted (T2W), T1- weighted (T1W), dynamic T1W gradient echo contrast-enhanced images (DCE) and diffusion weighted (DWI) images were obtained. Two expert radiologists prospectively recorded the following tumour prognostic factors: size, depth (< or ≥50%) of myometrial involvement, cervical extension, extrauterine spread and metastatic nodes; MRI predictive ability for each of the above characteristics was statistically tested with ROC curve analysis, using surgicopathological results as the standard of reference. Chi square and Student's t-test were used for possible association of maximal tumour/myometrial contrast on DCE with prognostic tumour histological features including type, grade, size and depth of myometrial invasion. Qualitative assessment regard-

CORRESPONDING AUTHOR, GUARANTOR

**Corresponding author:** Charis Bourgioti, MD: Department of Radiology, Aretaieion Hospital, School of Medicine, National and Kapodistrian University of Athens, 76 Vassilisis Sofias Ave, 11528, Athens, Greece, E-mail: charisbourgioti@yahoo.com

**Guarantor:** Lia Angela Moulopoulos, MD, Professor of Radiology, Department of Radiology, Aretaieion Hospital, School of Medicine, National and Kapodistrian University of Athens, 76 Vassilisis Sofias Ave, 11528, Athens, Greece, E-mail: lia.angela1312@gmail.com

ing usefulness of applied MRI sequences for tumour local staging was also addressed.
**Results:** MRI exhibited high diagnostic accuracy for prediction of myometrial invasion (AUC=0.86, 95% CI: 0.78-0.93, p<0.001), cervical invasion (AUC=0.86, 95% CI: 0.70-1.00, p<0.001) and pelvic nodal involvement (AUC=0.90, 95% CI: 0.69-1.00, p=0.003). No association was found between maximal tumour/myometrial contrast on DCE and known histologic prognostic factors. For evaluation of myometrial invasion, DCE received significantly better rating compared to T2W or DWI alone; the combination of T2W and DCE (T2W+DCE) exhibited significantly better results for assessment of myometrial invasion compared to T2W+DWI and it was equally effective compared to T2W+DWI+DCE. For tumour cervical extension, DCE received significantly better rating compared to T2W or DWI alone; T2W+DCE and T2W+DCE+DWI significantly improved diagnosis of cervical invasion. For evaluation of metastatic lymphadenopathy, T2W was significantly more helpful than DWI; T2W+DWI were not superior to T2W alone for the evaluation of nodal metastases.
**Conclusions:** MRI is accurate for preoperative local staging of EC. DCE-MRI optimises assessment of myometrial and cervical invasion.

KEY WORDS
Endometrial cancer/Staging; MR imaging/diagnosis; MR imaging/Dynamic Contrast Enhanced; MR imaging/Diffusion Weighted Imaging

## *Introduction*

Endometrial cancer (EC) is the sixth most common malignancy worldwide, with approximately 320,000 new cases diagnosed annually [1]. It represents the most frequent cancer of the female genital tract, with increased incidence in high-income countries, including North America and Europe; mortality rate, however, is higher in the low-income populations possibly because of limited access to health care programs [2]. The increased prevalence of physical inactivity and subsequent obesity in the developed world is the major predisposing factor for endometrioid-type adenocarcinoma, which accounts for over 90% of endometrial cancers [3]; genetic mutations seem to be responsible for the other, less common (10%) but more aggressive histologies, such as serous and clear cell carcinomas [4].

Endometrial cancer is a curable disease, especially in the early stages, with surgery being the most appropriate treatment. Current International Federation of Gynaecology and Obstetrics (FIGO) guidelines recommend the use of imaging preoperatively to identify important prognostic tumour characteristics, including depth of myometrial invasion, cervical stromal involvement, extrauterine spread and lymph node metastases. Accurate assessment of these tumour features enables better prediction of risk for recurrence and, therefore, planning of the surgical approach to include, if required, resection of lymph nodes [1, 5].

Due to its high contrast resolution and reproducibility, Magnetic Resonance Imaging (MRI) is currently the imaging modality of choice for local preoperative staging of endometrial carcinoma [6, 7]. Dedicated MRI protocols for endometrial cancer staging typically include high-resolution T2-weighted (T2W) sequences along with dynamic contrast-enhanced T1-weighted (DCE) sequences [8-10]. During the last years, Diffusion-Weighted Imaging (DWI) has been incorporated as an adjunct to T2W and DCE in routine MRI protocols for EC staging [11]; however, it still remains to be determined whether the combination of T2W and DWI is actually superior to DCE-MRI for the pre-operative evaluation of important prognostic endometrial tumour features [8].

In this study, we present our experience with preoperative staging of endometrial cancer using dedicated MRI at an academic tertiary referral center for female pelvic disorders; we address the contribution of individual MRI sequences and their combinations for local tumour staging.

## *Material and Methods*

### *Study population*

Our Institutional Review Board approved this prospective study; informed consent was obtained from all individuals participating in the study. Between April 2013 and June 2018, 123 patients with newly diagnosed, bi-

opsy-confirmed endometrial cancer underwent pelvic MRI for staging purposes. Six/123 patients were precluded from surgery, due to presence of high perioperative risk factors (n=4) or patient's denial (n=2); these patients were excluded from further analysis. The remaining 117 patients (mean age: 59.9 years ± *SD*:12.7) received surgical treatment and formed our study group. Most of the study patients (n=92, 78.6%) were postmenopausal. None of our patients had any prior treatment for endometrial cancer.Time interval between pelvic MRI and surgical treatment did not exceed 30 days (mean time: 10 ± 2days).

All 117 patients underwent radical hysterectomy, bilateral oophorectomy and peritoneal washing. Eighty-seven patients were also treated with systemic pelvic lymphadenectomy, 2 had selective lymphadenectomy and in 16 patients omental resection was also performed; in 19 patients with macroscopically large (>2 cm) tumours, para-aortic nodal sampling was performed as well.

***MRI protocol***

All MRI studies were performed with a 1.5-T unit (Philips Medical Systems, Best, The Netherlands). A phased-array dedicated body coil was used. All patients received instructions to fast for at least 6 hours prior to the MRI exam; all patients received hyoscine butyl bromide orally (40 mg) or intramuscularly (20 mg) before the MRI exam, to limit bowel motion. All patients received a bolus injection of 0.1 mmol/kg body weight gadolinium-based contrast agent intravenously, followed by 20 ml of 0.9% saline flush.

The MRI protocol included T2-weighted (T2W) TSE images in the sagittal [(Repetition Time/Echo Time (TR/TE), 3500/90 msec; number of signals acquired (NSA), 3; Slice/Gap, 3.5/1.2 mm; field of view (FOV), 25 cm] and axial oblique, parallel to the long axis of the endometrial cavity (true coronal) (TR/TE, 3900/125 msec; NSA, 6; Slice/Gap, 4/0.4 mm; FOV, 18 cm), planes. Axial T1-weighted (T1W) (TR/TE, 400/13 msec; NSA, 1; Slice/Gap, 6/2 mm; FOV, 36 cm) and T2W (TR/TE, 3500/90 msec; NSA, 2; Slice/Gap, 4.5/1 mm; FOV, 38 cm) TSE images were obtained through the pelvis and up to the level of the renal hilum to evaluate presence of haemorrhage or nodal status, respectively. Axial T2W fat-suppressed TSE images (T2W-FS) (TR/TE, 2000/70 msec; NSA, 2; Slice/Gap, 4.5/1 mm; FOV, 35 cm) were obtained to look for fluid collections or bone marrow changes. In all patients, sagittal, dynamic T1W gradient echo contrast-enhanced images (DCE, TR/TE, 15/4.2 msec; flip angle, 45°; NSA, 2; FOV, 17 cm) were acquired every 17 sec for a total of 3 min, followed by a T1W fat-suppressed sequence (T1W-FS) (TR/TE, 400/20 msec; NSA, 2; Slice/Gap, 4.5/1 mm; FOV, 35 cm) in the axial or sagittal plane. Axial DWI with *b* values 0, 600, 1000 sec/mm$^2$ (TR/TE, 3000/70 msec; NSA, 12; Slice/Gap, 6/1 mm; FOV, 35 cm) were also included; axial oblique DWI was additionally obtained in a selected number of patients with ambiguous findings of deep myometrial invasion (n=20).

***MRI interpretation***

All MRIs were independently reviewed by two radiologists with experience in female pelvic imaging (reader 1: 10 years of experience, reader 2: 25 years of experience), blinded to initial tumour histological type and grade.

Both radiologists were asked to record the presence of endometrial tumour, depth of myometrial invasion (<50%, ≥50%) and tumour extension to the cervical stroma parametrial tissues, ovaries and adjacent organs (bladder, bowel). Nodal status (location, size, morphology) was recorded as well. Before the beginning of the study, both readers agreed to the following diagnostic characteristics of endometrial tumour: low to intermediate signal intensity on T2W images, hypovascularity relative to the normal myometrium on DCE MRI and restricted diffusivity on high *b* value DWI **(Figs. 1-3)**.

Myometrial invasion was recorded when there was loss of the low T2 signal of the junctional zone and inhomogeneity of the adjacent myometrium, interruption of the normal subendometrial enhancement on arterial DCE images and irregularity of the tumour-myometrial interface on any sequence (T2W, DCE, DWI). When tumour involved ≥50% of the myometrial wall (i.e. minimum distance from tumour to uterine serosa/total myometrium thickness, both measured in the sagittal plane), deep myometrial invasion was diagnosed **(Fig. 1)**.

When there was extension of the tumour to the cervical canal and inhomogeneity of the adjacent cervical stroma or loss of the hypointense stromal rim on T2W images, cervical stromal invasion was diagnosed **(Fig. 2)**. Positive signs for parametrial extension included irregularity of the interface between tumour and parametrium or soft-tissue mass within the adipose tissue encasing

the parametrial vascular plexus.

The presence of an extrauterine soft-tissue mass attached to or invading the ovary (-ies) or within the peritoneum or interrupting the low T2 signal of the bladder/bowel wall was required for the diagnosis of ovarian or bladder/bowel involvement **(Fig. 4)**.

A short-axis >1 cm for para-aortic nodes and >7 mm for pelvic lymph nodes and the internal nodal necrosis, spiculated nodal borders and extranodal soft-tissue mass were recorded as positive signs for metastatic nodal involvement.

***MRI sequence evaluation***

Individual MRI sequences were independently reviewed by both radiologists after completion of the study with knowledge of the surgicopathological results and were rated as no/less helpful or helpful/very helpful for assessing depth of myometrial involvement, cervical stromal invasion and metastatic lymphadenopathy.

Maximal contrast between the hypovascular endometrial tumour and the hypervascular normal myometrium was visually assessed on DCE images and optimal times were recorded; possible association with tumour histological characteristics including type, grade, size and depth of myometrial invasion was also tested.

In cases of disagreement, consensus was reached after discussion between the two readers.

***Standard of Reference***

A dedicated pathologist in gynaecologic oncology (25 years of experience) examined all surgical specimens and tumour surgicopathological staging was based on FIGO guidelines. The following tumour characteristics were recorded on the histopathological report: histological type, differentiation/grade (well differentiated/1, moderately differentiated/2, poorly differentiated/3), size (all three maximal diameters), depth of tumour extension into myometrium (limited to endometrial cavity, <50%, ≥50%), cervical stromal involvement, extrauterine extension to the fallopian tubes/ovaries, parametrial fatty tissues, bladder/bowel or omentum, and nodal metastases.

***Statistical analysis***

Quantitative variables are expressed as mean values (SD). Qualitative variables are expressed as absolute and relative frequencies. The concordance of MRI with surgery relative to tumour size was evaluated with the computation of intraclass correlation coefficients (ICC). ICCs equal to or lower than 0.40 indicate poor to fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement and over 0.80 excellent agreement. Kappa coefficients were computed as a measure of agreement between the readers. Large Kappa values indicate small disagreement, in comparison with chance levels. The maximum value of 1 indicates perfect agreement, values ≥0.75 are considered as excellent agreement and values >0.4 indicate acceptable reliability. The prognostic ability of the surgical assessment and MRI for staging parameters was evaluated with the receiver operating characteristic (ROC) curve. The overall performance of the ROC analysis was quantified by computing area under the curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was not different than chance. MRI accuracy was evaluated with calculation of sensitivity, specificity, positive and negative predictive values. Chi square and Fisher's exact tests were used for the comparison of proportions. Student's t-test was used for the comparison of mean values between two groups. All p values reported are

**Table 1. Sample's characteristics**

| | *N (%)* |
|---|---|
| Age, mean (SD) | 59.9 (12.7) |
| Menopausal | 92 (78.6) |
| Histology | |
| Endometrioid | 100 (85.5) |
| Non-Endometrioid | 17 (14.5) |
| Grade | |
| 1 | 45 (38.5) |
| 2 | 45 (38.5) |
| 3 | 27 (23.0) |
| Post-operative Radiotherapy/ Chemotherapy | 51 (43.6) |
| Tumour size (surgery), median (IQR) | 2.5 (1.05-4.00) |
| Tumour size (MRI), median (IQR) | 2.5 (1.00-3.75) |

**Table 2. Sensitivity, specificity, negative (NPV) and positive predictive values (PPV) for the MRI evaluation of tumour characteristics in patients with endometrial cancer**

| | *Histology* | | *MRI* | | *Sensitivity (%)* | *Specificity (%)* | *PPV (%)* | *NPV (%)* |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | | |
| **Myometrial invasion** | | | | | | | | |
| <50% | 63 | 53.8 | 71 | 60.7 | 77.8 | 93.7 | 91.3 | 83.1 |
| ≥50% | 54 | 46.2 | 46 | 39.3 | | | | |
| **Cervical invasion** | | | | | | | | |
| No | 106 | 90.6 | 109 | 93.2 | 72.7 | 100.0 | 100.0 | 97.2 |
| Yes | 11 | 9.4 | 8 | 6.8 | | | | |
| **Adnexa/Ovarian metastasis** | | | | | | | | |
| No | 112 | 95.7 | 113 | 96.6 | 80.0 | 100.0 | 100.0 | 99.1 |
| Yes | 5 | 4.3 | 4 | 3.4 | | | | |
| **Parametrial invasion** | | | | | | | | |
| No | 115 | 98.3 | 117 | 100.0 | 0.0 | 100.0 | - | 98.3 |
| Yes | 2 | 1.7 | 0 | 0.0 | | | | |
| **Vaginal invasion** | | | | | | | | |
| No | 117 | 100.0 | 117 | 100.0 | - | 100.0 | - | 100.0 |
| Yes | 0 | 0.0 | 0 | 0.0 | | | | |
| **Adjacent organ invasion** | | | | | | | | |
| No | 116 | 99.1 | 117 | 100.0 | 0.0 | 100.0 | - | 99.1 |
| Yes | 1 | 0.9 | 0 | 0.0 | | | | |
| **Metastatic pelvic lymph nodes** | | | | | | | | |
| No | 107 | 91.5 | 100 | 85.5 | 60.0 | 89.7 | 35.3 | 96.0 |
| Yes | 10 | 8.5 | 17 | 14.5 | | | | |
| **Metastatic para-aortic lymph nodes** | | | | | | | | |
| No | 116 | 99.1 | 117 | 100.0 | 0.0 | 100.0 | - | 99.1 |
| Yes | 1 | 0.9 | 0 | 0.0 | | | | |

two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 22.0).

## Results

### *Sample characteristics*

Sample consisted of 117 women, mean age 59.9 years (SD ± 12.7 years). Mean tumour size on surgical specimen was 2.5 cm (median interquartile range (IQR): 1.05-4.00). Tumour was in the majority of cases of endometrioid histology (n=100, 85.5%); non-endometrioid types included serous-papillary (n=9), clear cell (n=6) and undifferentiated (n=2) tumours. Forty-five/117 (38.5%) patients had grade 1 tumours, 45/117 (38.5%) grade 2, and 27/117 (23.0%) patients grade 3 tumours.

According to final surgicopathological examination deep myometrial invasion (≥50%) was detected in 54/117 (46.7%) patients; tumour extension to cervical stroma, parametrial tissue or adnexa was recorded in 11 (9.4%), 2 (1.7%) and 5 (4.3%) patients, respectively. Pelvic metastatic lymphadenopathy was present in 10 (8.5%) of the study patients, while metastatic para-aortic nodes were detected in 1/117 patients (0.9%). None of our patients had vaginal wall invasion; bowel invasion was detected in one case.

In 51/117 patients (43.6%) adjuvant chemoradiation was required, due to adverse prognostic factors on final histology. Sample's full demographic and clinical characteristics are presented in **Tables 1** and **2**.

*Diagnostic accuracy of preoperative MRI for tumour characteristics*

The ICC between MRI and surgicopathological results

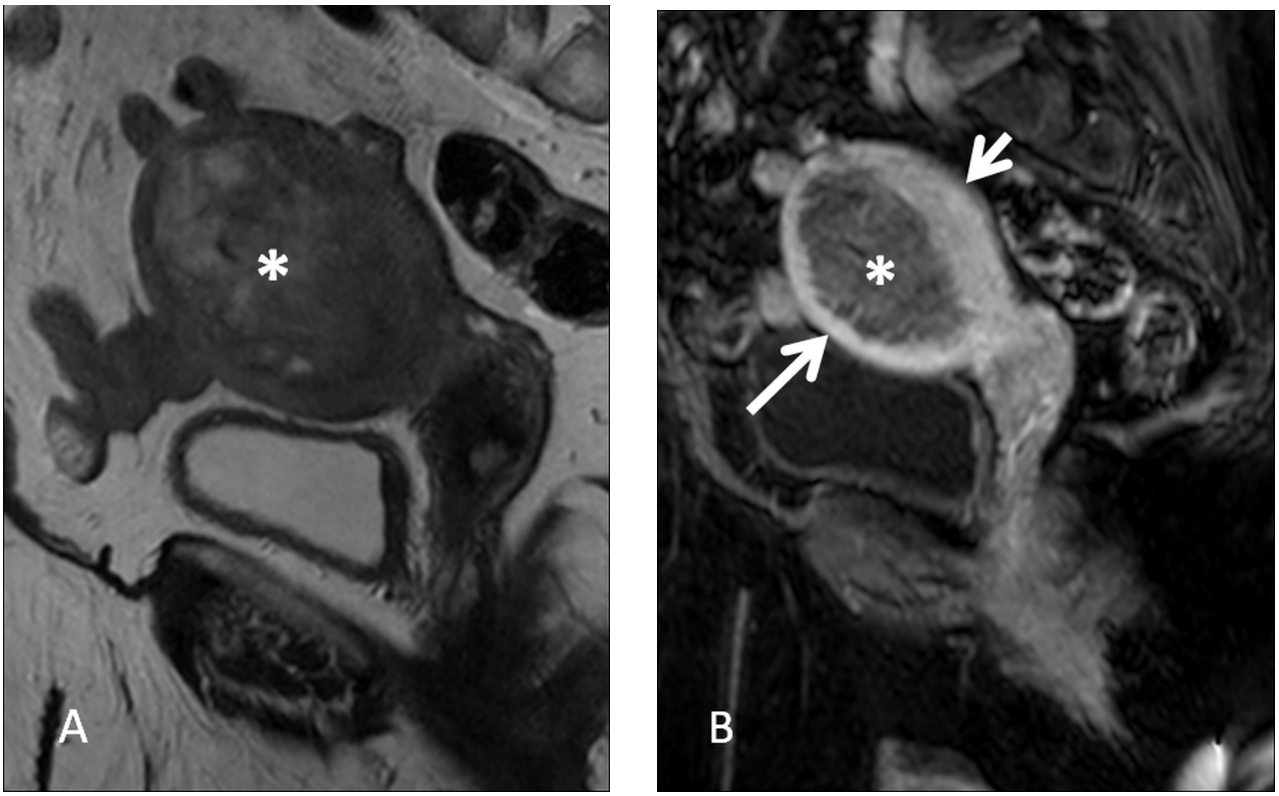


***Fig. 1.*** *56-year-old woman with biopsy confirmed endometrioid endometrial cancer, grade 1.* ***A.*** *T2-weighted image in the sagittal plane shows a large heterogeneous soft-tissue mass occupying the endometrial cavity (*).* ***B.*** *Corresponding early DCE image in the sagittal plane demonstrates deep (>50%) extension of the tumour within the anterior myometrial wall (long arrow). Short arrow points to the normal posterior myometrium. Endometrial cancer exhibits a typical hypovascular enhancement pattern on DCE images. DCE: Dynamic Contrast-Enhanced.*

for tumour size was high and equal to 0.997 (95% CI: 0.995-0.998, p<0.001). Sensitivity (SE), specificity (SP), negative (NPV) and positive predictive values (PPV) for MRI regarding the evaluation of tumour characteristics compared to surgicopathological findings are presented in detail in **Table 2**. MRI exhibited high accuracy values for prediction of myometrial invasion (AUC=0.86, 95% CI: 0.78-0.93, p<0.001), with 77.8% SE, 93.7% SP, 91.3% PPV and 83.1% NPV. MRI diagnostic indices of cervical invasion were also quite accurate with an AUC equal to 0.86 (95% CI: 0.70-1.00, p<0.001) and, SE, SP, PP and NP values equal to 72.7%, 100.0%, 100.0% and 97.2%, respectively. MRI performance for identification of ovarian involvement was excellent (AUC=0.90, 95% CI: 0.69-1.00, p<0.001); reported SE, SP, PPV and NPV values were 80.0%, 100.0%, 100.0% and 99.1%, respectively. MRI exhibited low SE (60.0%) and PPV (35.3%), albeit high SP (89.7%) and NPV (96.0%) values for the detection of metastatic pelvic lymphadenopathy; however, overall diagnostic performance for nodal assessment was high with an AUC equal to 0.90 (95% CI: 0.69-1.00, p=0.003).

*Association of maximal tumour/myometrial contrast on DCE with prognostic tumour histological features*

In 5/117 (4.3%) patients optimal tumour/myometrial contrast on DCE images was recorded within the first 60 sec after contrast injection; in most of the study patients (n=54, 46.2%), it was recorded at the time interval 60-120 sec after intravenous contrast administration. In 50 (42.7%) patients, optimal tumour/myometrial contrast was achieved between 120 and 180 sec after injection and, in only in 8 (6.8%) patients, it was recorded after 180 sec from the initial administration of the gadolinium-based contrast agent.

In order to facilitate statistical analysis, we grouped the cases in those patients who had optimal tumour/myometrial contrast within 120 sec from contrast injection (n=59/117, 50.43%) patients and those who had optimal tumour/myo-

| Table 3. Maximal tumour/myometrial contrast resolution in association with tumour's histological prognostic factors | | | |
|---|---|---|---|
| | Maximal tumour/myometrium contrast on DCE (sec) | | |
| | ≤120 | >120 | |
| | N (%) | N (%) | P |
| **Histological type** | | | |
| Non-Endometrioid | 13 (22.0) | 4 (6.9) | 0.057+ |
| Endometrioid | 46 (78.0) | 54 (93.1) | |
| **Histological grade** | | | |
| 1 | 22 (37.3) | 23 (39.7) | 0.456+ |
| 2 | 20 (33.9) | 25 (43.1) | |
| 3 | 17 (28.8) | 10 (17.2) | |
| **Tumour size (surgery), median (IQR)** | | | |
| | 2.5 (2.0 - 4.0) | 3.0 (2.2 - 4.5) | 0.302++ |
| **Myometrial invasion (histology)** | | | |
| <50% | 33 (55.9) | 30 (51.7) | 0.648+ |
| >50% | 26 (44.1) | 28 (48.3) | |

*+Pearson's chi-square test; ++Student's t-test*

| Table 4. Qualitative assessment of the applied MRI sequences and their combination for important prognostic tumour characteristics | | | | | | |
|---|---|---|---|---|---|---|
| | T2WI | DCE | DWI/ADC | T2WI+DCE | T2WI+DWI/ADC | T2WI+DCE+DWI/ADC |
| | A | B | C | D | E | F |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| **Myometrial involvement** | | | | | | |
| No/less helpful | 58 (49.6) | 15 (12.8) | 43 (36.8) | 17 (14.5) | 50 (42.7) | 17 (14.5) |
| Helpful/very helpful | 59 (50.4)[B] | 102 (87.2) | 74 (63.2)[B] | 100 (85.5)[A] | 67 (57.3) | 100 (85.5)[A,C] |
| **Cervical involvement** | | | | | | |
| No/less helpful | 38 (32.5) | 5 (4.3) | 70 (59.8) | 7 (6.0) | 37 (31.6) | 7 (6.0) |
| Helpful/very helpful | 79 (67.5)[B] | 112 (95.7) | 47 (40.2)[B] | 110 (94.0)[A] | 80 (68.4)[C] | 110 (94.0) [A,C] |
| **Metastatic lymph nodes** | | | | | | |
| No/less helpful | 0 (0.0) | - | 23 (19.7) | - | 0 (0.0) | - |
| Helpful/very helpful | 117 (100.0)[C] | - | 94 (80.3) | - | 117 (100.0)[C] | - |

*Note: A, B, C, D, E, F indicate significant differences between groups*

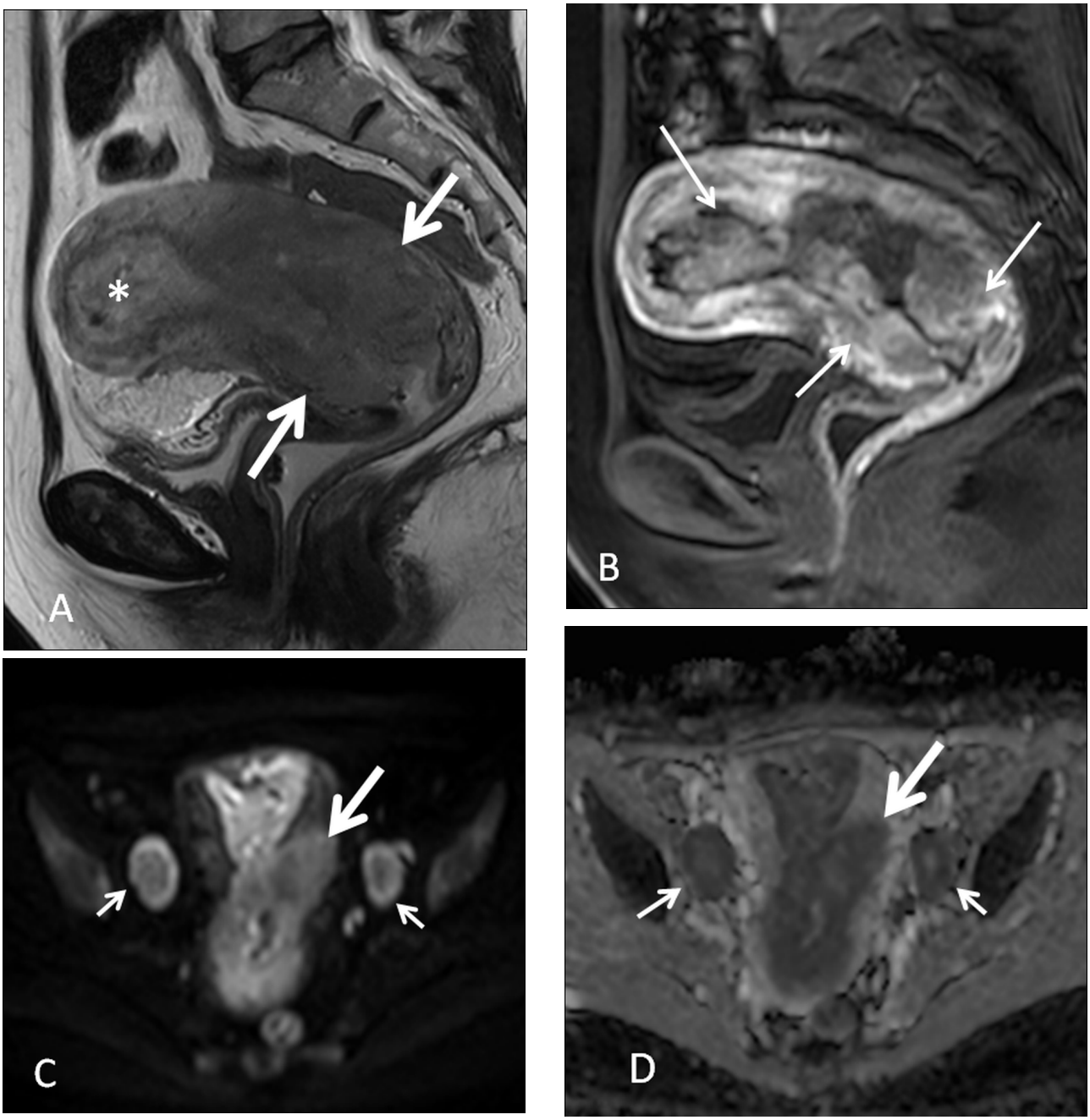


***Fig. 2.*** *52-year-old woman presenting with persistent vaginal bleeding.* ***A.*** *Sagittal T2-weighted image shows a large mass filling the endometrial cavity (*) and extending to the cervical canal (arrows).* ***B.*** *Corresponding sagittal DCE image in early arterial phase (30 sec) shows a predominantly hypovascular mass with several hypervascular areas within the mass (thin arrows). The mass demonstrates high signal intensity on high b value DWI and low signal intensity on corresponding ADC map (**C, D**). There is deep invasion of the left myometrial wall (long arrows in **C** and **D**). Note bilateral enlarged obturator lymph nodes (short arrows in **C** and **D**). Biopsy was positive for poorly differentiated endometrioid cancer with sarcomatous elements (carcinosarcoma). DCE: Dynamic Contrast-Enhanced, DWI: Diffusion-Weighted Image.*

metrial contrast >120 sec after injection (n=58/117, 49.57%) patients. No association was found between maximal tumour/myometrial contrast on DCE ≤120 sec versus >120 sec and known histologic prognostic factors including type, grade, size and depth of myometrial invasion (**Table 3**).

*Analysis of usefulness of individual MRI sequences and their*

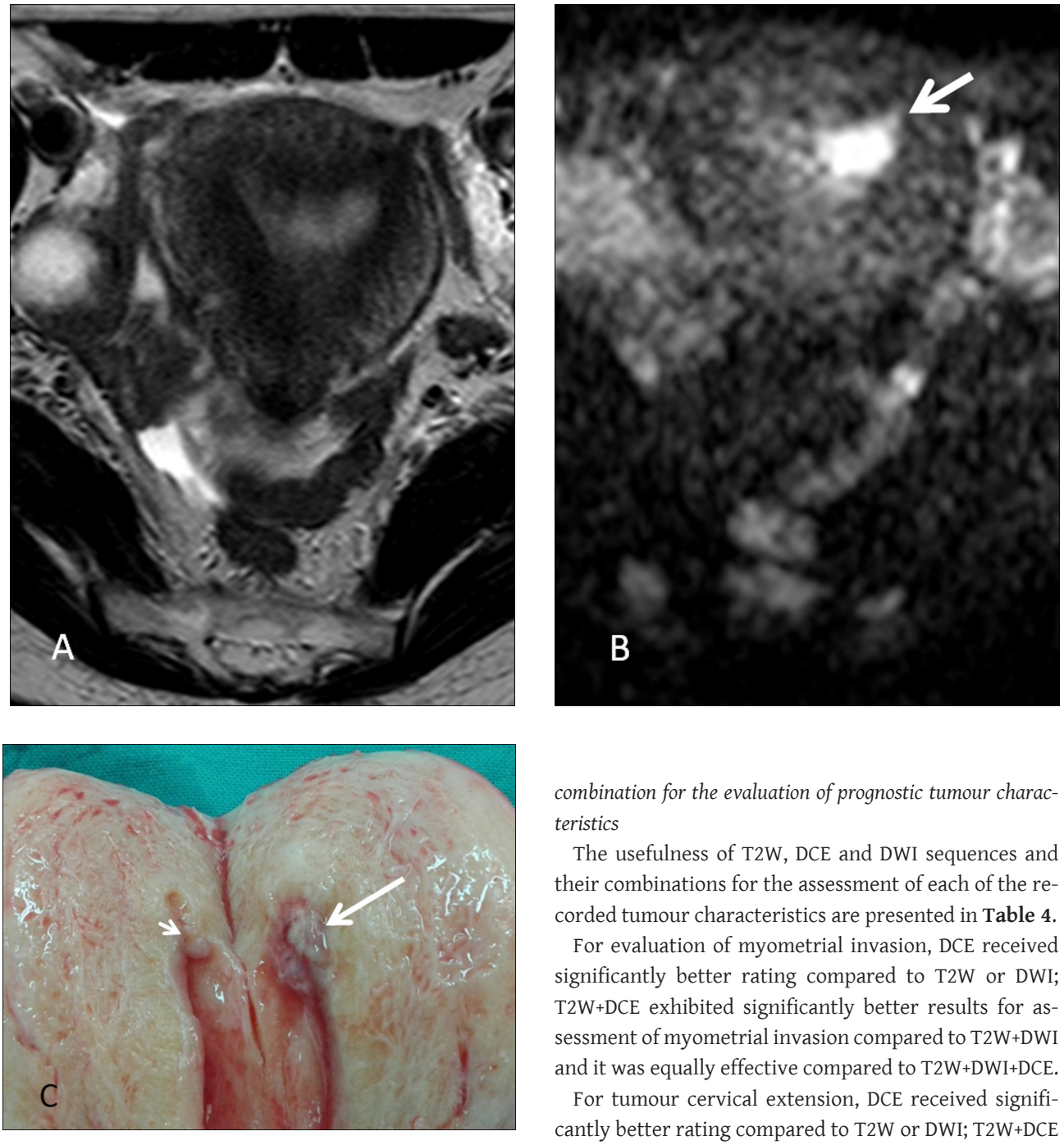


***Fig. 3.*** *44-year-old woman with abnormal vaginal bleeding and hysteroscopic biopsy positive for grade 1 endometrioid cancer.* ***A.*** *There is no clear evidence of an endometrial tumour on the axial T2-weighted image.* ***B.*** *Corresponding high b value axial diffusion-weighted image shows a high signal intensity focus within the left uterine cornu (arrow). Cancerous tissue was confirmed on hysterectomy specimen (long arrow in* ***C****). Also shown is a small benign endometrial polyp within the right uterine cornu (short arrow in* ***C****).*

*combination for the evaluation of prognostic tumour characteristics*

The usefulness of T2W, DCE and DWI sequences and their combinations for the assessment of each of the recorded tumour characteristics are presented in **Table 4**.

For evaluation of myometrial invasion, DCE received significantly better rating compared to T2W or DWI; T2W+DCE exhibited significantly better results for assessment of myometrial invasion compared to T2W+DWI and it was equally effective compared to T2W+DWI+DCE.

For tumour cervical extension, DCE received significantly better rating compared to T2W or DWI; T2W+DCE and T2W+DCE+DWI significantly improved diagnosis of cervical invasion.

Relative to the evaluation of metastatic lymphadenopathy, T2W was significantly more helpful than DWI; T2W+DWI were not superior to T2W alone for the evaluation of nodal metastases. Since DCE was obtained only for uterine evaluation in the sagittal plane, it was not used for nodal detection.

In the present study, there was no significant disagreement between the two readers concerning the rating of

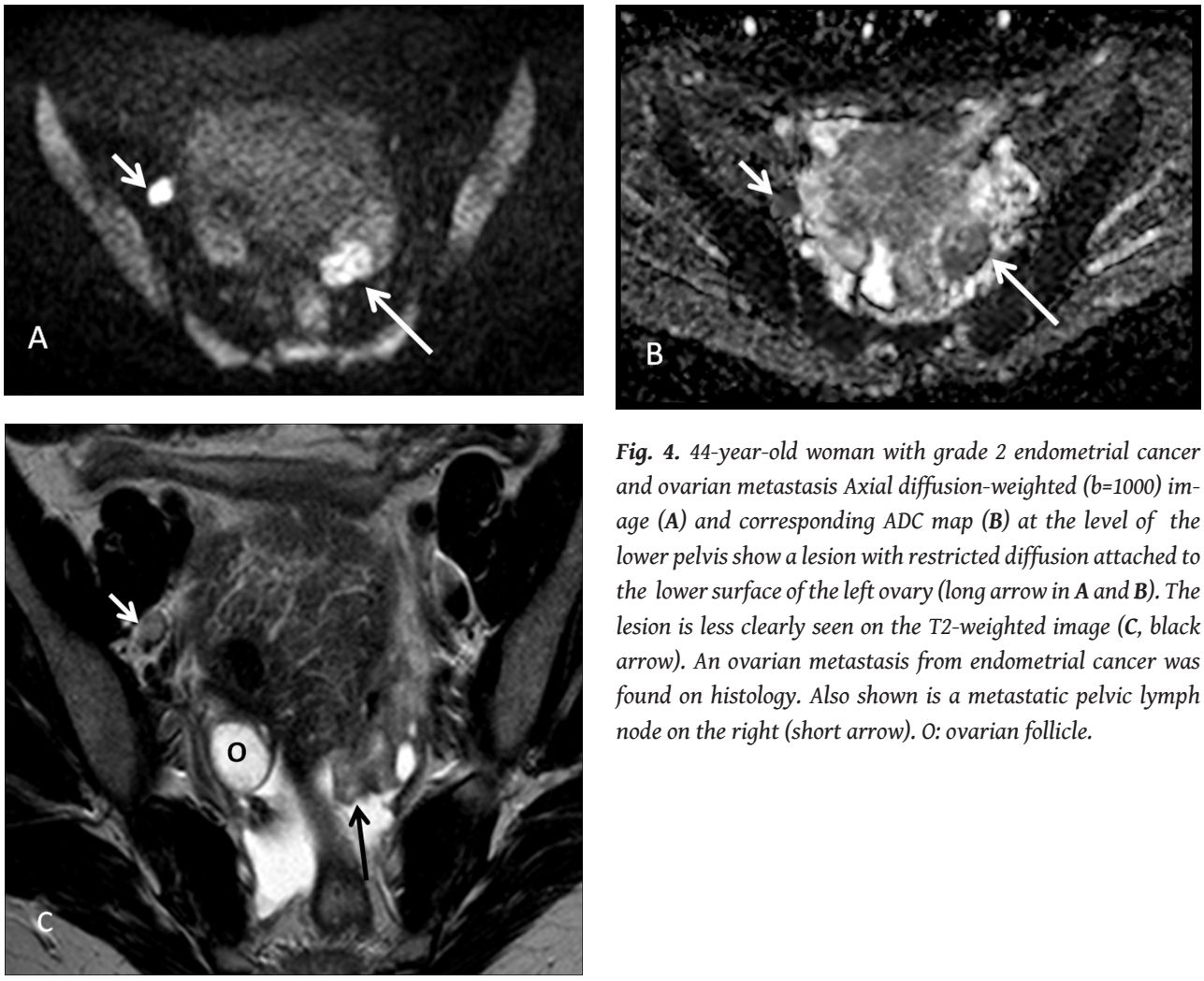


***Fig. 4.*** *44-year-old woman with grade 2 endometrial cancer and ovarian metastasis Axial diffusion-weighted (b=1000) image (**A**) and corresponding ADC map (**B**) at the level of the lower pelvis show a lesion with restricted diffusion attached to the lower surface of the left ovary (long arrow in **A** and **B**). The lesion is less clearly seen on the T2-weighted image (**C**, black arrow). An ovarian metastasis from endometrial cancer was found on histology. Also shown is a metastatic pelvic lymph node on the right (short arrow). O: ovarian follicle.*

each sequence; agreement between the two readers was excellent with mean kappa values 0.91 for T2W, 0.97 for DCE and 0.93 for DWI.

## *Discussion*

Our results support prior reports on the increased accuracy of staging EC and assessing important tumour characteristics including myometrial and cervical invasion and nodal status using dedicated MRI [1-11]. Interestingly, in our study DCE images received the highest rating for evaluation of myometrial and cervical involvement, while T2-weighted images were the most useful for the characterisation of metastatic nodes.

Metastatic nodal involvement is the strongest predictor for tumour recurrence and its incidence is strongly associated with high grade tumours and deep (≥50%) myometrial invasion (18% vs. 5% for patients with <50% myometrial invasion) [12]. Surgical staging is the gold standard for nodal evaluation, however extensive pelvic lymphadenectomy is associated with increased morbidity rates, more so if combined with radiotherapy, which may be required if there is evidence of more advanced disease on final histology [13]; moreover, the therapeutic benefits of total lymphadenectomy remain controversial [1]. Therefore, preoperative identification of tumour characteristics predictive of nodal metastases, such as deep myometrial invasion, help surgeons avoid unnecessary nodal dissection and plan appropriate adjuvant radiotherapy treatment [5]. Current data support adjuvant radiation therapy in high-risk patients, especially those with grade 3 histology, deep myometrial invasion and/or LVSI or unfavourable histologies; in women with node-positive (Stage IIIC) disease, the combination of adjuvant chemotherapy and radiation therapy is associated

with higher disease control and better survival rates [1].

Another important prognostic factor for EC is tumour extension to the cervical stroma (FIGO stage II). Preoperative identification of stage II disease is critical because it requires radical rather than total hysterectomy (including resection of the broad ligament) and bilateral salpingo-oophorectomy; if extra fascial total abdominal hysterectomy is performed in these patients, there is a significantly higher likelihood for need of postoperative radiotherapy and tumour recurrence [14]. Adjuvant radiotherapy in stage II disease is usually reserved for those patients with positive nodes and/or involved surgical margins. Interestingly, neoadjuvant therapy followed by simple hysterectomy may also be an alternative option for women with clinically overt stage II disease; in cases of extensive cervical disease with parametrial involvement, full external pelvic radiotherapy and intracavitary brachytherapy may be employed either preoperatively or as definitive therapy with successful outcomes [1].

Several studies have shown that preoperative MRI and intraoperative frozen sections are both accurate means of assessing depth of myometrial invasion and cervical involvement in patients with EC [15-17]. Our data support the high accuracy of MRI for assessing deep myometrial invasion (77.8% SE and 93.7% SP) and cervical stromal invasion (72.7% SE and 100.0% SP). Although, in most cases myometrial or cervical invasion is readily identified on MRI, there are challenges in the estimation of the actual depth of myometrial invasion; these include large tumours (causing enlargement of the endometrial cavity or cervix and thinning of the adjacent stroma), concurrent corpus or cervical pathology such as adenomyosis, leiomyomas, Nabothian cysts or polyps, microscopic tumour extension (inherently not detectable) and tumour arising in the cornua uteri (where the myometrium is normally thinner).

In our study, DCE was rated as the single most useful sequence for the evaluation of deep myometrial involvement. The significant role of DCE for the assessment of the depth of myometrial invasion has been shown, with meta-analysis data supporting that DCE-MRI is not only equally sensitive, but even more specific than T2W for the detection of deep tumour extension within the myometrium [18]. The additive value of DWI has also been extensively evaluated and currently, DWI is part of the MRI protocol for EC staging recommended by the European Society of Urogenital Radiology (ESUR) [8]. Several studies have compared DCE and DWI for the evaluation of myometrial invasion, but results are inconsistent; some authors demonstrated superiority of DWI over DCE for myometrial assessment in patients with EC [10, 19, 20], while other studies report equal performance of both techniques [11, 21]. In our study population, DCE alone as well as T2W+DCE images exhibited significantly better results for the assessment of myometrial invasion compared to DWI alone or T2W+DWI. In a recent meta-analysis by Deng et al, although diagnostic performance of DWI and DCE-MRI for myometrial invasion was similar, the combination of T2W and DWI was found superior to either DWI or DCE alone [22]. Technical differences may be responsible for the inconsistency of their results with those of our study; we performed DWI with a 1.5 T unit, and images were routinely acquired in the axial plane with a large FOV to allow for pelvic lymph node assessment; axial oblique DWI was additionally obtained only in a selected number (n=20) of patients with suspected deep myometrial invasion. All of the above may have further compromised the inherently low resolution of DWI sequences.

According to published data, MRI accuracy for cervical stromal infiltration by EC was equally high (>90%) for all three MRI sequences (T2W, DCE and DWI) [7]. In our cohort, DCE MRI received significantly better rating compared to either T2W or DWI for evaluation of cervical involvement; furthermore, T2W+DCE was equally helpful as the combination of all three sequences (T2W+DWI+DCE) questioning the value of replacing DCE images with the non-invasive DWI. Recently however, Lin et al. reported that DWI MRI had superior diagnostic performance compared to DCE for the detection of cervical stromal invasion in patients with EC, but their studies were performed with a 3T unit [23].

Our results support the routine administration of gadolinium chelates intravenously in patients with EC, because contrast-enhanced sequences provide higher spatial resolution images compared to DWI, enabling better delineation of the interface between the hypovascular tumour and the hypervascular myometrium and facilitating assessment of myometrial and cervical involvement. DWI is of particular value in those patients who cannot receive gadolinium-based contrast agents, in the less common endometrial tumours which may be iso- or hyperintense to the myometrium on contrast-enhanced images (i.e. carcinosarcomas), in cases of concurrent uterine adenomyosis

or other pathology and to assist detection of extrauterine/peritoneal disease. However, the lower intrinsic spatial resolution of DWI, susceptibility artefacts due to bowel gas and the need for direct comparison of this sequence with anatomic T2W images may explain the lower ratings for this sequence regarding myometrial and cervical assessment, in our study population. Higher resolution images, with use of 3T units [24, 25], smaller FOV [26], and acquisition of DWI in the same axial oblique plane as T2W images [8] may potentially increase diagnostic confidence regarding DWI for the assessment of tumour invasion of the myometrium or cervix.

According to previous reports, myometrial invasion is best depicted during the equilibrium phase (2 min 30 sec after the injection) of DCE scans [27, 28], while cervical stromal invasion is best evaluated on delayed images (4-5 min after injection) [8]. Based on this information, the ESUR panel discussed replacement of DCE-MRI with a single phase high spatial resolution contrast-enhanced sequence obtained at 2 min 30sec after injection; DCE images may be limited to specific diagnostic challenges (i.e. assessing the integrity of the subendometrial zone of enhancement in EC patients desiring preservation of fertility) [8]. Interestingly, in almost half of the patients in our study, optimal contrast between the endometrial tumour and adjacent myometrium on DCE images was achieved within 120 sec from gadolinium injection. It should also be noted that early (<45 sec) DCE images are helpful for the discrimination between the hypovascular endometrial carcinoma and cervical cancer in cases of uterine tumours of indeterminate histology, since the latter typically presents with early contrast uptake and rapid contrast washout [29]. For these reasons, we believe that DCE-MRI is an essential part of an MRI protocol for EC staging.

Preoperative, metastatic lymph node detection rates with MRI are similar to those of high-quality CT scans with reported sensitivity and specificity values ranging from 38% to 89% and 78% to 99%, respectively [30]. In accordance, in our cohort MRI SE was moderate (60.0%) but SP was quite high (89.7%) for the detection of metastatic pelvic lymphadenopathy. We found T2W images significantly more helpful than DWI for the identification of metastatic lymph nodes; additionally, the combination of T2WI+DWI was not found superior to T2W alone for the detection of nodal metastases. DWI is excellent for identifying lymph nodes in the order of a few mm; however, it has no additive value in the differential diagnosis of malignant versus benign nodes [31]. Despite encouraging initial reports that 3T DWI-MRI may significantly increase the sensitivity for metastatic lymph node detection by combining the size criterion and nodal ADC values [32], no concrete conclusions have been reached as there is need for larger, better-structured studies with strict standardisation of DWI protocols to evaluate its diagnostic performance for the discrimination between benign and metastatic lymph nodes [33]. We believe that the observation of other morphologic features of metastatic nodal involvement besides size in our study (central necrosis, spiculation, etc), best seen on high-resolution T2W images may account for the better rating of T2W sequences compared to DWI.

Our study has several limitations. First, it was conducted at a single institution, although the study sample (n=117) allowed adequate statistical analysis. All data were collected during a 5-year time interval; several technical upgrades were performed within this period and may have positively affected image interpretation. Also, we are aware that there were differences regarding technical details of applied DWI sequences compared to other studies. We routinely performed DWI in the axial plane, with large FOV to also evaluate nodal status; axial oblique DWI images were only obtained when there was suspicion of deep myometrial involvement. Both readers who participated in the study were experienced in the field of female pelvic imaging; results from general radiologists regarding MRI accuracy for EC staging and for evaluation of important prognostic tumour characteristics remain to be seen. Finally, an important limitation of our study is that only a small number (n=13) of our study patients had evidence of ≥stage II disease; even though this potentially limits the applicability of our results, similar numbers have been reported in other studies, since EC is more frequently detected at an early stage (stage I).

MRI is a useful tool for local staging of endometrial carcinoma. It accurately identifies adverse tumour characteristics such as deep myometrial or cervical invasion, extrauterine disease and metastatic lymphadenopathy. DCE MRI is an important tool for the assessment of myometrial and cervical integrity and we believe that it should still be routinely performed for EC staging, particularly with 1.5T units. R

## *Conflict of interest*

*The authors declared no conflicts of interest.*

# References

1. Amant F, Mirza MR, Koskas M, et al. Cancer of the corpus uteri. *Int J Gynecol Obstet* 2018; 143(Suppl. 2): 37-50.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; 68(1): 7-30.
3. Nevadunsky NS, Van Arsdale A, Strickler HD, et al. Obesity and age at diagnosis of endometrial cancer. *Obstet Gynecol* 2014; 124(2 Pt 1): 300-306.
4. Edmondson RJ, Crosbie EJ, Nickkho-Amiry M, et al. Markers of the p53 pathway further refine molecular profiling in high-risk endometrial cancer: A TransPORTEC initiative. *Gynecol Oncol* 2017; 146(2): 327-333.
5. Lin MY, Dobrotwir A, McNally O, et al. Role of imaging in the routine management of endometrial cancer. *Int J Gynecol Obstet* 2018; 143(Suppl. 2): 109-117.
6. Haldorsen IS, Salvesen HB. Staging of endometrial carcinomas with MRI using traditional and novel MRI techniques. *Clin Radiol* 2012; 67(1): 2-12.
7. Bonatti M. Stuefer J, Oberhofer N, et al. MRI for local staging of endometrial carcinoma: Is endovenous contrast medium administration still needed? *Eur J Radiol* 2015; 84(2): 208-214.
8. Nougaret S, Horta M, Sala E, et al. Endometrial cancer MRI staging: Updated guidelines of the European society of urogenital radiology. *Eur Radiol* 2019; 29(2): 792-805.
9. Hori M, Kim T, Onishi H, et al. Endometrial cancer: preoperative staging using three-dimensional T2-weighted turbo spin-echo and diffusion-weighted MR imaging at 3.0 T: a prospective comparative study. *Eur Radiol* 2013; 23(8): 2296-2305.
10. Beddy P, Moyle P, Kataoka M, et al. Evaluation of depth of myometrial invasion and overall staging in endometrial cancer: comparison of diffusion-weighted and dynamic contrast-enhanced MR imaging. *Radiology* 2012; 262(2): 530-537.
11. Andreano A, Rechichi G, Rebora P, et al. MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. *Eur Radiol* 2014; 24(6): 1327-1338.
12. Chi DS, Barakat RR, Palayekar MJ, et al. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. *Int J Gynecol Cancer* 2008; 18(2): 269-273.
13. Lewandowski G, Torrisi J, Potkul RK, et al. Hysterectomy with extended surgical staging and radiotherapy versus hysterectomy alone and radiotherapy in stage I endometrial cancer: a comparison of complication rates. *Gynecol Oncol* 1990; 36(3): 401-404.
14. Xu G, Wang D, Ling X, et al. Diagnostic value of assessment of cervical involvement in early-stage endometrial adenocarcinoma: Comparison of magnetic resonance imaging (MRI) versus hysteroscopy. *Med Sci Monit* 2018; 24: 7952-7957.
15. Ugaki H, Kimura T, Miyatake T, et al. Intraoperative frozen section assessment of myometrial invasion and histology of endometrial cancer using the revised FIGO staging system. *Int J Gynecol Cancer* 2011; 21(7): 1180-1184.
16. Cade TJ, Quinn MA, McNally OM, et al. Predictive value of magnetic resonance imaging in assessing myometrial invasion in endometrial cancer: is radiological staging sufficient for planning conservative treatment? *Int J Gynecol Cancer* 2010; 20(7): 1166-1169.
17. Ozturk E, Dikensoy E, Balat O, et al. Intraoperative frozen section is essential for assessment of myometrial invasion but not for histologic grade confirmation in endometrial cancer: a ten-year experience. *Arch Gynecol Obstet* 2012; 285(5): 1415-1419.
18. Wu LM, Xu JR, Gu HY, et al. Predictive value of T2-weighted imaging and contrast-enhanced MR imaging in assessing myometrial invasion in endometrial cancer: a pooled analysis of prospective studies. *Eur Radiol* 2013; 23(2): 435-449.
19. Rechichi G, Galimberti S, Signorelli M, et al. Myometrial invasion in endometrial cancer: diagnostic performance of diffusion-weighted MR imaging at 1.5-T. *Eur Radiol* 2010; 20(3): 754-762.
20. Sala E, Rockall A, Rangarajan D, et al. The role of dynamic contrast-enhanced and diffusion weighted magnetic resonance imaging in the female pelvis. *Eur J Radiol* 2010; 76(3): 367-385.
21. Seo JM, Kim CK, Choi D, et al. Endometrial cancer: utility of diffusion-weighted magnetic resonance imaging with background body signal suppression at 3T. *J Magn Reson Imaging* 2013; 37(5): 1151-1159.
22. Deng L, Wang QP, Chen X, et al. The combination of

Diffusion- and T2-Weighted Imaging in predicting deep myometrial invasion of endometrial cancer: A systematic review and meta-analysis. *J Comput Assist Tomogr* 2015; 39(5): 661-673.
23. Lin G, Huang YT, Chao A, et al. Endometrial cancer with cervical stromal invasion: diagnostic accuracy of diffusion-weighted and dynamic contrast enhanced MR imaging at 3T. *Eur Radiol* 2017; 27(5): 1867-1876.
24. Lin G, Ng KK, Chang CJ, et al. Myometrial invasion in endometrial cancer: diagnostic accuracy of diffusion-weighted 3.0-T MR imaging--initial experience. *Radiology* 2009; 250(3): 784-792.
25. Rizzo S, Femia M, Buscarino V, et al. Endometrial cancer: an overview of novelties in treatment and related imaging keypoints for local staging. *Cancer Imaging* 2018; 18(1): 45.
26. Takeuchi M, Matsuzaki K, Harada M. Evaluating myometrial invasion in endometrial cancer: Comparison of reduced field-of-view diffusion-weighted Imaging and dynamic contrast-enhanced MR Imaging. *Magn Reson Med Sci* 2018; 17(1): 28-34.
27. Park SB, Moon MH, Sung CK, et al. Dynamic contrast-enhanced MR imaging of endometrial cancer: optimizing the imaging delay for tumour-myometrium contrast. *Eur Radiol* 2014; 24(11): 2795-2799.
28. Manfredi R, Mirk P, Maresca G, et al. Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. *Radiology* 2004; 231(2): 372-378.
29. Bourgioti C, Chatoupis K, Panourgias E, et al. Endometrial vs. cervical cancer: development and pilot testing of a magnetic resonance imaging (MRI) scoring system for predicting tumor origin of uterine carcinomas of indeterminate histology. *Abdom Imaging* 2015; 40(7): 2529-2540.
30. Rauch GM, Kaur H, Choi H, et al. Optimization of MR imaging for pretreatment evaluation of patients with endometrial and cervical cancer. *Radiographics* 2014; 34(4): 1082-1098.
31. Nougaret S, Tirumani SH, Addley H, et al. Pearls and pitfalls in MRI of gynecologic malignancy with diffusion-weighted technique. *AJR Am J Roentgenol* 2013; 200(2): 261-276.
32. Lin G, Ho KC, Wang JJ, et al. Detection of lymph node metastasis in cervical and uterine cancers by diffusion-weighted magnetic resonance imaging at 3T. *J Magn Reson Imaging* 2008; 28(1): 128-135.
33. Shen G, Zhou H, Jia Z, et al. Diagnostic performance of diffusion-weighted MRI for detection of pelvic metastatic lymph nodes in patients with cervical cancer: a systematic review and meta-analysis. *Br J Radiol* 2015; 88(1052): 20150063.

READY - MADE CITATION

Bourgioti C, Chatoupis K, Antoniou A, Panourgias E, Tzavara C, Moulopoulos LA. Proposed MRI sequences for local staging of endometrial cancer: a single center experience. Hell J Radiol 2019; 4(3): 3-16.