T2-weighted MRI findings predictive of parametrial involvement in patients with cervical cancer and histologically confirmed full thickness stromal invasion

Charis Bourgioti¹, Konstantinos Chatoupis¹, Aristeidis Antoniou¹, Evangelia Panourgias¹, Chara Tzavara², Alexandros Rodolakis³, Lia Angela Moulopoulos¹

¹Department of Radiology, Aretaieion Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece
²Department of Health, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Greece
³Department of Obstetrics and Gynaecology, Gynaecologic Oncology Unit, Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece

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ABSTRACT

Purpose: To record the T2-weighted imaging (T2WI) appearance of the cervical rim in cervical cancer patients with histologically confirmed full thickness stromal invasion and to identify any signs predictive of parametrial involvement in this particular subset of patients.

Material and Methods: During a 5-year period, 30/115 patients surgically treated for early cervical cancer (FIGO-IIB) had full thickness stromal invasion on surgicopathological examination; 15/30 patients had parametrial invasion on histology. All patients were evaluated with pelvic MRI, preoperatively. Two expert radiologists retrospectively reviewed all MRIs. The presence of the following T2WI characteristics was recorded for each side of the cervical rim: thinning (<3 mm), complete loss of normal hypointense signal, diffuse signal inhomogeneity, irregularity of inner and outer cervical border and peritumoural fat stranding. The above signs were evaluated alone and in combination in search for any correlation with parametrial involvement.
1. Introduction
Early-stage cervical carcinomas may be effectively treated with radical hysterectomy combined with pelvic lymphadenectomy or with radiation therapy alone, even though surgery is, for most gynaecologic oncology centers, the preferred therapeutic option. Reported survival rates after surgical treatment for these patients range from 72-92% [1]; differences in survival rates may be explained by the presence of unexpected adverse findings at surgery, such as bulky tumours (~4 cm), metastatic lymphadenopathy, deep cervical stromal invasion and invasion of the parametrial fat. Parametrial involvement (even microscopic) is considered a major risk factor, which may significantly compromise surgical outcome [2]. When adverse findings such as parametrial invasion are unexpectedly found at surgery, radiotherapy is recommended in order to improve prognosis for these patients; it has been reported however that adjuvant radiotherapy in surgically treated, high-risk patients, even though it reduces the risk of recurrence, is associated with an increased incidence of urologic and gastrointestinal complications often requiring treatment [3-5]. Therefore, accurate preoperative selection of surgical candidates becomes very important.

1.1 Study population
During a 5-year period (2009-2014), 115 patients (mean age: 44.7 years) FIGO stage <IIB were surgically treated for early cervical cancer; surgical decision was based predominantly on clinical information, as officially suggested by FIGO [6]. No patient had received treatment for cervical cancer before surgery. All patients underwent dedicated pelvic MRI within 30 days prior to surgery. A dedicated pathologist with experience in gynaecologic oncology (20 years of experience) examined all surgical specimens; depth of cervical invasion (superficial: tumour involves <5 mm of cervical stroma, deep: tumour involves >two thirds of total cervical stromal thickness, full thickness stromal invasion: tumour extends to serosa) and extension of tumour into parametrial tissues were recorded.

Results: Diffuse signal inhomogeneity, shaggy inner border and small focal disruptions of the normal low T2 cervical rim were the most frequent findings on T2WI. Diffuse signal inhomogeneity and peritumoural fat stranding were the only MRI features significantly associated with parametrial invasion. Complete loss of the low T2 cervical rim was observed in approximately 25% of patients with parametrial involvement. In 4/15 patients the cervical rim appeared intact.

Conclusions: Diffuse signal inhomogeneity of the cervical rim and peritumoural fat stranding were the only MRI signs significantly associated with parametrial involvement in patients with cervical cancer and full stromal invasion. An intact hypointense cervical rim does not exclude tumour extension to the parametrial fat.
Thirty/115 patients (mean age: 51.2 years) had full stromal invasion on final surgicopathological examination and formed our study group; the subset of the 30 cases evaluated in the current report was included in a previously published study [9].

Institutional review board approved and waived informed consent for this retrospective, observational study.

### 2.2 MRI protocol

All MRI studies were performed with a 1.5-Tesla unit (Philips Healthcare, Best, The Netherlands) using a phased-array dedicated body coil. All patients were instructed to fast for at least 6 h prior to the MRI examination, and all received hyoscine butyl bromide (40 mg) orally, 30 min before the MRI scan, to limit bowel motion. MRI was performed at least 10 days after tumour biopsy to avoid false-positive findings associated with post-biopsy inflammatory changes. None of the patients had absolute or relative contraindications for the MRI examination. All patients received a bolus injection of 0.1 mmol/kg gadolinium contrast medium intravenously, followed by 20 ml of 0.9% saline flush.

MRI protocol included T2-weighted (T2-W) Turbo Spin Echo (TSE) sequences in the sagittal [Time Repetition/Time Echo (TR/TE), 3,500/90 ms; number of signals acquired (NSA), 2; slice thickness/gap, 3.5/1.2 mm; Field of View (FOV), 25 cm], and axial oblique (TR/TE, 3,900/125 ms; NSA, 6; slice thickness/gap, 4.0/0.4 mm; FOV, 18 cm) planes. Axial T1-weighted (T1-W) (TR/TE, 400/13 ms; NSA, 1; slice thickness/gap, 6/2 mm; FOV, 36 cm), and T2-W (TR/TE, 3,500/90 ms; NSA, 2; slice thickness/gap, 4.5/1 mm; FOV, 38 cm) images were obtained through the pelvis and up to the level of the renal hilum to evaluate nodal status. Axial T2-W fat-suppressed TSE (TR/TE, 2,000/70 ms; NSA, 2; slice thickness/gap, 4.5/1 mm; FOV, 35 cm), and diffusion-weighted images (DWI) (TR/TE, 3,000/70 ms; NSA, 12; slice thickness/gap, 6/1 mm; FOV, 35 cm; b-values 0, 1,000 s/mm2) were obtained in 10/30 patients, since these sequences were added to the MRI protocol after initiation of the study. Sagittal dynamic T1-W contrast-enhanced images (Dynamic Contrast Enhanced MRI - DCE-MRI, TR/TE, 15/4.2 mm; flip angle, 45°; NSA, 2; FOV, 17 cm) were acquired every 17 s for a total of 3 min, followed by an axial T1-W fat-suppressed sequence (TR/TE, 400/20 ms; NSA, 2; slice thickness/gap, 4.5/1 mm; FOV, 35 cm).

### 2.3 MRI interpretation

Data for the subset of patients with histologically proven full thickness stromal invasion (n=30) regarding the predictive ability of MRI for tumour parametrial extension were extracted from the previously studied original population of 115 patients [9].

Typically, normal cervical stroma is seen as a thick homogeneous low signal intensity rim on T2-W MR images; cervical tumour was defined as a lesion with higher T2 signal compared to the surrounding cervical stroma. Parametrial infiltration was recorded when there was nodularity of cervical contour with tumour bulge into the parametrial space, irregularity of the interface between tumour and parametrial fat or evidence of a soft-tissue mass within the parametrial fat.

All 30 MRIs were retrospectively reviewed by two radiologists with experience in female imaging (reader 1: 20 years of experience, reader 2: 7 years of experience) in consensus, after completion of the initial study.

Each side of the cervical rim was evaluated separately on T2WI (right: RT, left: LT) and the following imaging characteristics were recorded in a total of 60 cervical rim sides (RT/LT): signal homogeneity (homogeneous, inhomogeneous), internal contour (smooth, irregular), low T2 rim disruption (complete, focal) and rim thickness (>3 mm, ≤3 mm); peritumoural stranding and previously established MRI signs of parametrial invasion (i.e. tumour bulge into the parametrial fat, irregularity of the interface between tumour and parametrial fat and presence of soft-tissue mass within the parametrial fat) were also recorded for each side of the cervical rim.

### 2.4 Statistical analysis

Quantitative variables are expressed as mean values (SD). Qualitative variables are expressed as absolute and relative frequencies. The prognostic ability of MRI for parameters concerning parametrial involvement was evaluated with the receiver operating characteristic (ROC) curve. The overall performance of the ROC analysis was quantified by computing the area under the curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was not different from chance. The accuracy of MRI was evaluated with calculation of sensitivity, specificity, positive (PPV) and negative (NPV) predictive values. Chi square and Fisher’s exact tests were used for the comparison of proportions.
All \( p \) values reported were two-tailed. Statistical significance was set at 0.05 and analyses were conducted using STATA statistical software (version 11.0).

### Results

#### 3.1 Patient characteristics

For the 30 study patients (mean age: 51.2 years, SD=13.7 years) tumour histology was squamous cell carcinoma in 20/30 (66.7%), adenocarcinoma in 8/30 (26.7%) and adenosquamous carcinoma in 2/30 (6.7%); most of the patients (\( n=16, 53.3\% \)) had grade II tumours, while grade I and grade III carcinomas were diagnosed in 3/30 (10%) and 11/30 (36.7%) of our study patients, respectively. All patients were treated with radical hysterectomy (Wertheim procedure) and 13/30 (43.3%) received adjuvant therapy due to histological findings of more advanced disease.

Fifteen/30 patients had parametrial infiltration on fi-
nal histology. In 5/30 patients, the tumour relapsed six months after surgery; in most of these patients (3/5) the tumour recurred within the pelvis. All five patients had adverse surgicopathologic findings including tumour size >4 cm (n=2), parametrial involvement (n=3) and lymph node metastases (n=4). Patient demographics are presented in detail in Table 1.

3.2 Predictive ability of MRI for parametrial involvement
In our group of patients with histologically proven full thickness stromal invasion from cervical cancer (n=30), the percent agreement between MRI assessment and histology for parametrial invasion was 80%. The predictive ability of MRI for parametrial invasion gave an AUC equal to 0.72 and sensitivity, specificity, NPV and PPV values equal to 73.3%, 86.7%, 76.5% and 84.6%, respectively (Table 2). Compared to the original study group (n=115), MRI sensitivity for assessment of parametrial status in the subset of patients with full stromal invasion was equally moderate (73.3%) while specificity was also high (86.7% vs. 97%). In the subset of patients with full stromal invasion, MRI NPV for parametrial invasion was moderate compared to the original study population (76.4% vs. 96%) while PPV remained high (84.6% vs. 78.5%) (Fig. 1).

3.3 T2WI features of full thickness stromal invasion with parametrial extension
Retrospective per parametrium analysis showed that, in cases with true parametrial involvement (final histology), the most frequent T2WI findings of the fully invaded cervical rim per side were: Signal inhomogeneity (RT side: 92.3%, LT side: 83.3%), shaggy inner border (RT side: 68.2%, LT side: 75%) and focal disruptions (RT side: 53.8%, LT side: 58.3%). Complete loss of the low T2 cervical rim was observed in approximately 25% of cases with parametrial invasion (RT side: 23.1%, LT side: 25%) (Fig. 2). Only diffuse signal inhomogeneity of the cervical rim showed significant correlation (p<0.05) with the presence of parametrial disease in patients with full cervical stromal invasion. The above results are fully presented in Table 3.

Peritumoural stranding was observed in 18/30 invaded parametria and in 9/30 intact parametria; the presence of peritumoural stranding was significantly associated with parametrial involvement (p=0.007). Previously established signs of parametrial involvement (i.e. tumour protrusion into the parametrium, irregular borders between tumour and parametrial fat, soft-tissue mass within the parametrial fat) were also found to be significantly (p=0.045) associated with the presence of parametrial involvement (Table 3).

4. Discussion
Our results -derived from a previously studied population of 115 patients surgically treated for early cervical cancer- showed that MRI was moderately accurate (AUC=0.72,
Table 2. Accuracy of MRI assessment for the prediction of parametrial invasion in women with full stromal invasion.

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
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<tbody>
<tr>
<td>Invasion of parametria (right)</td>
<td></td>
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<tr>
<td>MRI</td>
<td>0.82 (0.67-0.96)*</td>
<td>69.2 (38.6-90.9)</td>
<td>94.1 (71.3-99.9)</td>
<td>90.0 (55.5-99.8)</td>
<td>80.0 (56.3-94.3)</td>
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<tr>
<td>Invasion of parametria (left)</td>
<td></td>
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<tr>
<td>MRI</td>
<td>0.79 (0.60-0.99)*</td>
<td>83.3 (51.6-97.9)</td>
<td>88.9 (65.3-98.6)</td>
<td>83.3 (51.6-97.9)</td>
<td>88.9 (65.3-98.6)</td>
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<tr>
<td>Invasion of parametria (left and/or right)</td>
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<tr>
<td>MRI</td>
<td>0.72 (0.53-0.91)*</td>
<td>73.3 (44.9-92.2)</td>
<td>86.7 (59.5-98.3)</td>
<td>84.6 (54.5-98.1)</td>
<td>76.5 (50.1-93.2)</td>
</tr>
</tbody>
</table>

‡ Area under the curve (95% Confidence Interval); *p<0.05

Table 3. Correlation of T2WI features with parametrial involvement.

<table>
<thead>
<tr>
<th>Parametrial invasion (histology) (Right)</th>
<th>Negative</th>
<th>Positive</th>
<th>p</th>
<th>Parametrial invasion (histology) (Left)</th>
<th>Negative</th>
<th>Positive</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Total loss of low T2 cervical rim</td>
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<td></td>
</tr>
<tr>
<td>Negative</td>
<td>10 (58.8)</td>
<td>10 (76.9)</td>
<td>0.440**</td>
<td>13 (72.2)</td>
<td>9 (75.0)</td>
<td>1.000**</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7 (41.2)</td>
<td>3 (23.1)</td>
<td></td>
<td>5 (27.8)</td>
<td>3 (25.0)</td>
<td></td>
<td></td>
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<tr>
<td>Thin (&lt;3 mm) but overall preserved cervical rim</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>14 (82.3)</td>
<td>8 (61.5)</td>
<td>0.242**</td>
<td>14 (77.8)</td>
<td>7 (58.3)</td>
<td>0.418**</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3 (17.7)</td>
<td>5 (38.5)</td>
<td></td>
<td>4 (22.2)</td>
<td>5 (41.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiny focal disruptions</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Negative</td>
<td>11 (64.7)</td>
<td>6 (46.2)</td>
<td>0.310*</td>
<td>12 (66.7)</td>
<td>5 (41.7)</td>
<td>0.176*</td>
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<tr>
<td>Positive</td>
<td>6 (35.3)</td>
<td>7 (53.8)</td>
<td></td>
<td>6 (33.3)</td>
<td>7 (58.3)</td>
<td></td>
<td></td>
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<tr>
<td>Shaggy inner border of cervical rim</td>
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<tr>
<td>Negative</td>
<td>9 (52.9)</td>
<td>4 (30.8)</td>
<td>0.225*</td>
<td>11 (61.1)</td>
<td>3 (25.0)</td>
<td>0.052*</td>
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<tr>
<td>Positive</td>
<td>8 (47.1)</td>
<td>9 (68.2)</td>
<td></td>
<td>7 (38.9)</td>
<td>9 (75.0)</td>
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<tr>
<td>Signal inhomogeneity of cervical rim</td>
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<tr>
<td>Negative</td>
<td>12 (70.6)</td>
<td>1 (7.7)</td>
<td>0.001*</td>
<td>11 (61.1)</td>
<td>2 (16.7)</td>
<td>0.026*</td>
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<tr>
<td>Positive</td>
<td>5 (29.4)</td>
<td>12 (92.3)</td>
<td></td>
<td>7 (38.9)</td>
<td>10 (83.3)</td>
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<tr>
<td>Peritumoural stranding</td>
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<tr>
<td>Negative</td>
<td>14 (82.3)</td>
<td>5 (38.5)</td>
<td>0.023**</td>
<td>12 (66.7)</td>
<td>2 (16.7)</td>
<td>0.007*</td>
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<tr>
<td>Positive</td>
<td>3 (17.7)</td>
<td>8 (61.5)</td>
<td></td>
<td>6 (33.3)</td>
<td>10 (83.3)</td>
<td></td>
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<tr>
<td>Obvious parametrial involvement signs</td>
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<tr>
<td>Negative</td>
<td>14 (82.3)</td>
<td>9 (69.2)</td>
<td>0.667**</td>
<td>15 (83.3)</td>
<td>5 (41.7)</td>
<td>0.045**</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3 (17.7)</td>
<td>4 (30.8)</td>
<td></td>
<td>3 (16.7)</td>
<td>7 (58.3)</td>
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*Pearson’s chi square test; **Fisher’s exact test
p<0.05) in predicting parametrial extension in the subset of cervical cancer patients with full thickness stromal invasion. Furthermore, the predictive ability of MRI for excluding parametrial involvement in this subgroup of patients was relatively high (NPV 76.4%), albeit lower compared to the 96% NPV of the original study population. This observation prompted us to retrospectively analyse T2WI of those patients from the original study group who had histologically proven full thickness stromal invasion, in search of findings predictive of tumour extension to parametrial tissues, aiming to increase MRI staging accuracy.

Despite the improvement of MRI protocols for cervical cancer staging with the implementation of new functional techniques like diffusion-weighted imaging (DWI), T2WI remains the basic MRI sequence for the detection of parametrial invasion in cervical cancer, mostly because it provides excellent anatomic detail and contrast resolution. According to the literature, MRI accuracy for identification of cervical cancer extension to parametrial tissues is very high, ranging from 88-97%, while, in a recent meta-analysis, the reported sensitivity and specificity values were 0.76 (95% CI 0.67-0.84) and 0.94 (95% CI 0.91-0.95), respectively [12]. In the case of small tumours, totally confined to the cervix, or in the presence of quite large cervical cancers obviously occupying parametrial fat, diagnosis is usually easy for both clinical examination and MRI. However, in patients with full thickness (focal or diffuse) replacement of normal cervical stroma by cancerous tissue, it may be difficult, even for an experienced gynaecologic oncologist and a dedicated radiologist, to determine early extension of the tumour to the parametrial fat [13].

Even though patients with full thickness stromal invasion form a group requiring particular management [8, 13], there are only few studies focusing on the diagnostic performance of MRI for the evaluation of this subgroup of patients. In studies published in the mid-90s, reported MRI sensitivity and specificity values for assessing the presence of full thickness stromal invasion, ranged from 56-94% and 62-91%, respectively [10, 14-16]. More
recently, Park et al. reported an 85% accuracy of T2-W imaging regarding parametrial invasion in patients with full thickness stromal invasion [17]. Our study showed MRI sensitivity and specificity values equal to 73.3% and 86.7%, respectively, with only moderate NPV for parametrial involvement in this subset of patients with complete invasion of the cervical stroma (76.4%).

In most studies, complete loss of the T2 hypointense cervical rim is considered as the most helpful MRI feature for identifying full thickness invasion of the cervical stroma from cancerous tissue and for predicting tumour parametrical extension [8, 13, 18]; however, this sign was observed in only 25% of our study patients with true positive parametrial involvement and this may account for the lower MRI NPV regarding parametrical involvement in our study group. In fact, we noted that other imaging features, such as diffuse signal inhomogeneity of the cervical stroma, tiny focal disruptions of the cervical rim and a “shaggy” appearance of the inner cervical contour were more frequent than complete loss of the low T2 cervical rim in patients with full stromal invasion. Furthermore, in four of our patients with proven parametrial invasion, the low T2 cervical rim appeared intact and MRI failed to identify extension of tumour to the outer cervical margin; this may be explained by the low T2 signal of the tumour resembling the normal fibrous cervical stroma, or by the presence of microscopic full stromal invasion.

According to our research, there are no previous reports focusing on the T2-W MRI appearance of the cervical rim in cervical cancer patients with full thickness stromal invasion. Knowledge of the different T2 features of the invaded cervical rim may potentially help readers better estimate the depth of tumour extension to the cervical stroma and, therefore, to better evaluate the adjacent parametrical fat. In our study, diffuse T2 signal inhomogeneity of the cervical rim and peritumoural fat stranding were the only imaging features significantly correlated with parametrial invasion, although our findings need to be tested in larger populations.

It has been reported that, when the thickness of the low T2 cervical rim is more than 3 mm, parametrial invasion may be excluded with an extremely high accuracy (specificity: 96-99%, NPV: 94-100%) [8, 17]. In our study, the presence of a thin (<3 mm) or totally absent low T2 cervical rim was observed in only a small number of cases and this may account for the poor statistical significance of this finding; on the contrary, diffuse T2 signal inhomogeneity of the cervical rim and peritumoural fat stranding was the only feature significantly associated with parametrial invasion in patients with full thickness cervical stromal replacement by cancerous tissue. This observation suggests that the cervical rim should not only be thick (>3 mm) but it should also be homogeneous, in order to more accurately diagnose absence of parametrical involvement.

As expected, previously reported MRI signs of parametrial involvement, such as nodularity of cervical margin, irregular tumour-to-parametrium interface and obvious soft-tissue mass within the parametria with/or without pe-
uterine vessel encasement, showed significant correlation with tumour extension to parametrial fat. The presence of any of the above signs significantly increases the certainty of a true-positive diagnosis for parametrial invasion.

In our study, peritumoural fat stranding was another imaging feature significantly associated with parametrial invasion. Even though we found that peritumoural stranding was strongly suggestive of extracervical extension of tumour, it is well known that non-neoplastic conditions like post-biopsy/conisation bleeding or peritumoural inflammation observed with larger tumours, may also cause stranding and complicate imaging findings [19, 20]. DW images may potentially discriminate between inflammation and tumour, since only the latter shows restricted diffusivity [18, 21] (Fig. 3).

Park et al. reported that the positive predictive value for parametrial invasion increased when fusion of T2-weighted and diffusion-weighted images with background body signal suppression (DWIBS) was performed [17]. In our study, DW images were obtained in only a small number of patients (n=10); they did not significantly improve the predictive ability of MRI for tumour extension to the parametrial tissue. DW images, even though they better delineate tumour borders, have inherently low spatial resolution and therefore, result in poor quality anatomic images. However, recent meta-analysis data support the use of DWI as a complementary technique to T2WI in order to improve the diagnostic performance of MRI in detecting parametrial involvement in cervical cancer [12].

Our study has several limitations. Firstly, we retrospectively evaluated a small population (n=30) accumulated over a 5-year period and, therefore, the statistical significance of our results may be weak. Data for this subset of patients were derived from a previously studied population of 115 patients who were surgically treated for early cervical cancer; this may have introduced a selection bias. It should be noted that surgical decision for all patients was predominantly based on clinical staging and patients’ will for surgical therapy; all patients who received surgical treatment in our study had no clinical evidence of advanced cervical disease before surgery. In our study, MRI results regarding parametrial assessment were based on interpretation of T2WI only. DW images were added later to our MRI protocol and did not seem to affect MRI diagnostic accuracy for parametrial evaluation in the selected study group; however, they were available in only 10/30 patients, so statistically significant data could not be obtained. The radiologists who participated in our study were experienced in imaging of the female pelvis. MRI interpretation was performed in consensus and no interobserver agreement was calculated. Results could have been different, if general radiologists interpreted the findings. We believe however that recognition of subtle MRI signs of cervical stromal invasion requires expertise. Finally, our study was conducted with a 1.5 T unit; higher magnetic fields (3T) may potentially augment reader diagnostic performance.

In conclusion, our results show that MRI exhibits only moderate NPV for parametrial involvement in the subset of patients with early cervical cancer and full stromal invasion. Complete loss of the low T2 cervical stroma was observed in less than 25% of patients with parametrial involvement; signal inhomogeneity, tiny focal disruptions and irregular inner border of the cervical rim were more frequently observed in patients with parametrial invasion. Cervical rim inhomogeneity and peritumoural fat stranding were significantly associated with extension of tumour to the parametrial fat in patients with full thickness stromal invasion; search for these signs may potentially increase diagnostic confidence for accurate parametrial assessment in patients with cervical cancer.

Conflict of interest
The authors declared no conflicts of interest.

REFERENCES


