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ABDOMINAL IMAGING

ORIGINAL ARTICLE

Correlation of clinical and MRI staging in cervical carcinoma treated with radiation therapy: a single-center experience

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PURPOSE
To correlate clinical and MRI findings in patients with cervical carcinoma treated with radiation therapy (RT).

MATERIALS AND METHODS
Forty-two patients with pretreatment IB–IVA cervical carcinoma were included in this retrospective study. Pre- and post-treatment MRI findings of the patients were reevaluated and compared with clinical staging. Six-month, one-year, and two-year follow-up imaging by MR was performed for 36, 20, and 7 patients, respectively. The correlation between clinical and MRI findings was assessed by a Spearman's rho (rank correlation) test. Univariate analyses were performed to identify the prognostic significance of the tumor volume and lymph node status.

RESULTS
Pre-treatment correlations between MRI and clinical findings for diagnoses without parametrial invasion, with parametrial invasion, and with pelvic sidewall invasion were 71.0%, 64.7%, and 15.8%, respectively. According to the Spearman's rho (rank correlation) test, the parametrial invasion correlation was poor ($r = 0.410$, $P < 0.01$). The correlation of clinical and MRI findings at 6 months was 88.9% ($r = 0.674$, $P < 0.0001$).

CONCLUSION
In advanced cervical cancer, the correlation of clinical and MRI staging prior to neoadjuvant RT was low despite a high correspondence in the assessment of local response after RT.

Key words: • *magnetic resonance imaging* • *neoplasm staging* • *prognosis* • *uterine cervical neoplasm*

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The most important prognostic factors for cervical cancer are tumor stage and size. Although not included in the International Federation of Gynecology and Obstetrics (FIGO) staging, the presence and extent of nodal involvement is an another important prognostic factor (1–3). The efficacy of magnetic resonance imaging (MRI) for the assessment of parametrial involvement (which is important in the primary treatment) of cervical carcinoma is widely recognized. Furthermore, the high accuracy of MRI for evaluating tumor volume and lymph node involvement is well known. In women with stage IIIB cervical tumors, the rates of recurrence, persistent disease in the pelvis, or distant metastases are very different from those of stage IIB disease (4). There are a few reports with a limited number of patients with stage IIIB cervical carcinoma that describe the accuracy of MRI for the assessment of pelvic sidewall invasion by advanced stage cervical tumors (5, 6).

The aim of the present study is to correlate clinical and MRI findings in patients with cervical carcinoma treated with radiation therapy (RT).

Materials and methods

Patient selection

This analysis was performed at a single radiation oncology department between 1996 and 2005 and included 42 previously untreated patients with cervical carcinoma who were then treated with either radiation alone or concomitant chemoradiotherapy for definitive treatment. The histopathologic diagnosis was squamous carcinoma in 37/42 patients (87.5 %) and adenocarcinoma in 5/42 patients (12.5%). Median patient age was 54.5 years (range, 27–74).

The staging workup implemented the FIGO staging system used by a team of radiation oncologists and gynecologic oncologists and was assessed with rectovaginal examinations under general anesthesia prior to RT. MRI was performed for all patients before the initiation of RT. MRI was performed at least 3 weeks after each biopsy and within 15 days before RT. At the conclusion of the external RT, just before brachytherapy, the response to treatment was once again evaluated under general anesthesia.

MRI protocol

MRI studies were performed using a 1.0-T (Magnetom Impact, Siemens, Erlangen, Germany) or 1.5-T (Magnetom Vision, Siemens) magnet system with a consistent imaging protocol. For this protocol, transverse and sagittal T1-weighted spin-echo (SE) images and transverse T1-weighted fat-saturated images of the pelvis were obtained before and after contrast enhancement with gadopentetate dimeglumine. Transverse and sagittal T2-weighted fast SE sequences of the pelvis were also obtained. Imaging parameters are summarized in Table 1.

Immediately prior to the examination, patients received parenteral butylscopolamine (20 mg) (Buscopan; Eczacibasi, Istanbul, Turkey) as an antispasmodic agent to suppress intestinal motility. Gadopentate dimeglumine (Magnevist; Schering, Berlin, Germany) was intravenously administered at a dose of 0.1 mmol per kilogram of body weight.

To evaluate liver or retroperitoneal LN metastasis and hydronephrosis, transverse T1- (pre- and post-contrast enhanced) and T2-weighted SE MRI of the upper abdomen was also performed.

Radiotherapy (RT) protocol

All patients were treated with two or four doses of opposing pelvic field radiation to 50.4 Gy in 28 fractions using 15 MV photons. RT is summarized in detail in Table 2. Concomitant chemotherapy with cisplatin 40 mg/m^2 per week for four weeks was administered to 13 patients after 2000.

Follow-up

Patients were followed by a radiation oncologist at 3-month intervals for the first two years and 6-month intervals thereafter. Follow-up MRI was performed at the 6-month, first-year, and second-year visits. MR images were compared with clinical staging. The last follow-up was completed in December 2006. Follow-up details are summarized in Tables 3 and 4.

Analysis of MR images

Acquired images were interpreted by the same radiologist, who had more than five years of experience in reading pelvic MR images. The radiologist was provided with no retrospective knowledge of detailed clinical findings or treatment outcomes. The MR images of each case were evaluated with respect to the following: (a) tumor volume, (b) status of the parametrium, pelvic sidewall, sacrouterine ligament, upper vagina, urinary bladder, and rectum, and (c) LN metastasis (7, 8). Maximal tumor diameter was measured three-dimensionally based on T2-weighted images in the anteroposterior (D_{ap}), lateral (D_l), and craniocaudal (D_{cc}) dimensions. The MRI-derived tumor volume was calculated by the following equation: $V = D_{ap} \times D_l \times D_{cc} \times \pi/6$. The criterion for sacrouterine ligament involvement was based on thickening of the ligament (7). The terms "complete" and "partial" invasion of the sacrouterine ligaments (SUL) were used to define whether or not, respectively, the pelvic sidewall was involved (8). Paraaortocaval and pelvic LN with a transverse diameter greater than 10 mm were considered positive nodes (2).

On MR images obtained after the initiation of RT, the following features were recorded according to previously published guidelines: (a) The appearance of the cervix on unenhanced T1- and T2-weighted images and on contrast-enhanced T1-weighted images. The cervix was considered normal when, on T2-weighted images or on contrast-enhanced T1-weighted images, there was (a) reconstitution of zonal anatomy, or (b) demonstration of homogenously low signal intensity in the cervix. A significant early decrease in the signal intensity and volume of the tumor were considered to represent a good response to RT (9). Tumor recurrence was diagnosed when (a) an irregular or widened endocervical canal was found, (b) the cervical stroma was of high signal intensity, or (c) a measurable tumor mass with medium or

Table 1. Pelvic MRI protocol

	FOV	Matrix	TR/TE (ms)	Slice thickness (mm)
Transverse/sagittal T1-weighted				
1.5 T	20–28	256 x 512	580/15	≤5
1.0 T	20–28	154 x 512	680–780/15–30	≤5
Transverse/sagittal T2-weighted				
1.5 T	20–28	256 x 512	4900/103	≤5
1.0 T	20–28	154 x 512	3500–4000/90–100	≤5

Table 2. Radiotherapy protocol

Radiation field	Number of patients (percentage)
Pelvis EBRT + ICBT	32 (76.2%)
Pelvis EBRT + ICBT + PA EBRT	6 (14.3%)
Pelvis EBRT + external boost	4 (9.5%)
Whole pelvis + boost dose	Radiation dose
	70.4 (64–83) Gy

EBRT, external beam radiation therapy; ICBT, intracavitary brachytherapy; PA, paraaortic

Table 3. The number of patients followed up by MRI

MRI follow-up	n
6th month	36
1st year	20
2nd year	7

Table 4. The last clinical outcome and follow-up period results

The last clinical outcome	n	Median follow-up period (months)
Alive without disease	24	69 (range, 36–108)
Alive with disease	2	
Died from disease	14	29 (range, 17–116)
Died from an intercurrent disease	2	

high signal intensity was present (9, 10). Also recorded was demonstration of any tumor mass within the parametria, pelvic sidewall, or any other side in the pelvis. In addition, any changes thought to be due to post-RT fibrosis within previous tumor infiltration areas such as the parametrium and SUL were recorded (10).

Comparison of post-RT clinical and MRI findings

The existence of post-RT parametrial heterogeneity and SUL thickening concordant with fibrosis on MRI and clinical examination findings was compared and correlated with pretreatment parametrial and sacrouterine ligament findings.

Statistical analysis

The correlation between the MRI and clinical findings was assessed by Spearman's rho (rank correlation) test. "r" values of ≥ 0.75, 0.74–0.50, and < 0.50 were considered to represent a very good correlation, good correlation, and poor correlation, respectively.

Univariate analysis was performed to identify the prognostic significance of the tumor volume and LN status. The differences between the two groups were tested for statistical significance using an unpaired t test or chi-square test. $P < 0.05$ was considered to represent a statistically significant difference.

Results

Clinical-radiologic correlation in cervical cancers before treatment

The mean tumor volume was found to be 29.3 ± 23 mL (range, 1.6–108.93 mL) with MR imaging. Patients were staged clinically as IB (n = 1), IIA (n = 2), IIB (n = 19), IIIB (n = 19), and IVA (n = 1) (FIGO classification) prior to RT. For the 42 patients, the agreement between MRI and clinical findings in the staging of IIB and IIIB was 73.6% (14/19) and 36.8% (7/19), respectively. Twenty-one (50%) patients were staged equally by MRI and clinical findings, 14 patients (33.3%) were understaged (Figs. 1 and 2), and seven patients (16.7%) were overstaged (Table 5).

When 84 parametrial areas in 42 patients were evaluated, the agreement between MRI and clinical findings for the diagnosis of zero, partial, and complete parametrial invasion was 71.0 % (22/31), 64.7% (22/34), and 15.8% (3/19), respectively (Table 6). According to the Spearman's rho test, the parametrial invasion correlation was poor (r = 0.410, $P < 0.01$).

The agreement between clinical and MR findings for pre-RT SUL involvement was 93.4% (57/61), 12.5% (1/8), and 26.7% (4/15) for zero, partial, and complete SUL invasion, respectively (Table 6). The total discordance in SUL findings between MRI and clinical examination was 26% (22/84). According to the Spearman's rho test, the SUL invasion correlation was considered good (r = 0.532, $P < 0.01$).

The agreement between clinical and MRI findings for pre-RT vaginal invasion was 43.5% (10/23), 58.8% (10/17), and 100% (2/2) for no invasion, 2/3 proximal invasion, and 1/3 distal invasion, respectively (Table 7). According to the Spearman's rho test, the pre-RT vaginal invasion correlation was considered poor (r = 0.196, $P < 0.11$).

Pelvic and paraaortic LN positivity in patients staged as ≤ IIB and ≥ IIIB were found to be 40.9% and 65.0% for clinical staging and 45.2% and 72.7% for MR imaging, respectively (Table 8). Because biopsy and PET-CT could not be feasibly obtained, LN positivity was determined according to MRI findings.

The incidence of LN metastases in patients with tumor volumes of <30 mL and ≥30 mL was found to be 42.9% and 71.4%, respectively (Table 9).

No statistically significant differences were found when correlating LN metastasis ratios with tumor volume or clinical and MR staging ($P = 0.08$ and $P = 0.11$, respectively).

Clinical-radiologic correlation in cervical cancer after treatment

The post-treatment 6-month clinical exam and MRI results of 36 patients are summarized in Table 10. In the assessment of a local response to treatment, the correlation between the clinical and MRI findings was 88.9% (32/36).

The existence of post-RT parametrial heterogeneity concordant with fibrosis on MRI and clinical findings was evaluated. The agreement of clinical and MRI findings was 75.8%. Similarly, the agreement of clinical and MRI findings with respect to sacrouterine thickening and tension was 75.0%.

Discussion

Approximately 30 percent of women with invasive cervical cancer die from recurrent or persistent disease after initial therapy (11, 12). The majority

Table 5. Correlation between clinical staging and MRI staging

	MRI staging								
Clinical staging	IA	IB	IIA	IIB	IIIB	IVA	IVB	Total (%)	Spearman's rho test
IA	-	-	-	-	-	-	-	-	
IB	-	-	-	1	-	-	-	1 (2.4)	
IIA	-	-	-	2	-	-	-	2 (4.8)	
IIB	1	1	2	14	1	-	-	19 (45.2)	
IIIB	-	-	-	10	7	2	-	19 (45.2)	
IVA	-	-	-	-	-	-	1[a]	1 (2.4)	
IVB	-	-	-	-	-	-	-	-	
Total (%)	1 (2.4)	1 (2.4)	2 (4.8)	27 (64.3)	8 (19)	2 (4.8)	1 (2.4)	42	r = 0.553[b], $P < 0.01$

[a]In MRI staging, liver metastasis
[b]"r"values of ≥0.75, 0.74–0.50, and <0.50 show very good correlation, good correlation, and poor correlation, respectively

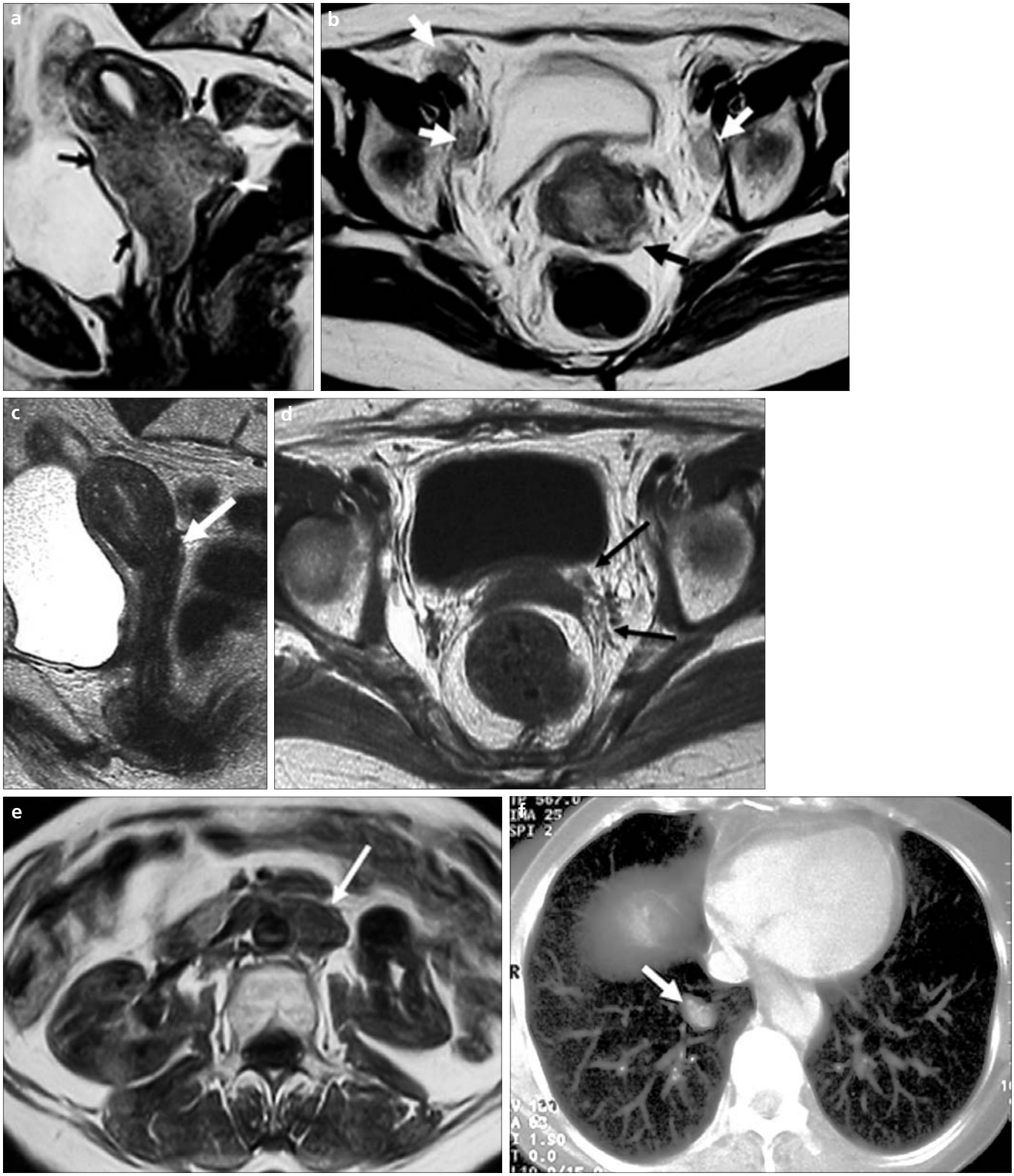

Figure 1. a–f. A 52-year-old woman with cervical carcinoma staged as IIIB clinically and staged as IIB with MRI before treatment. Sagittal T2-weighted MR image **(a)** shows a bulky cervical tumor *(arrows)* before radiation therapy. Axial T2-weighted axial MR image **(b)** shows a cervical mass with left parametrial invasion *(black arrow).* Bilateral external iliac lymph node enlargements are also seen *(white arrows)* before therapy. Sagittal T2-weighted **(c),** and axial T1-weighted **(d)** MR images show complete tumor *(arrow)* and lymph node regression at the sixth month after therapy. An axial T1-weighted MR image **(e)** shows left paraaortic lymph node enlargement at the first year after therapy *(arrow).* Thoracic computed tomographic image **(f)** shows a metastatic nodule in the right lung *(arrow)* and progression of paraaortic lymph node enlargements (not shown) in the second year after therapy. However, there was no pelvic recurrence in the first and second years after radiation therapy (not shown).

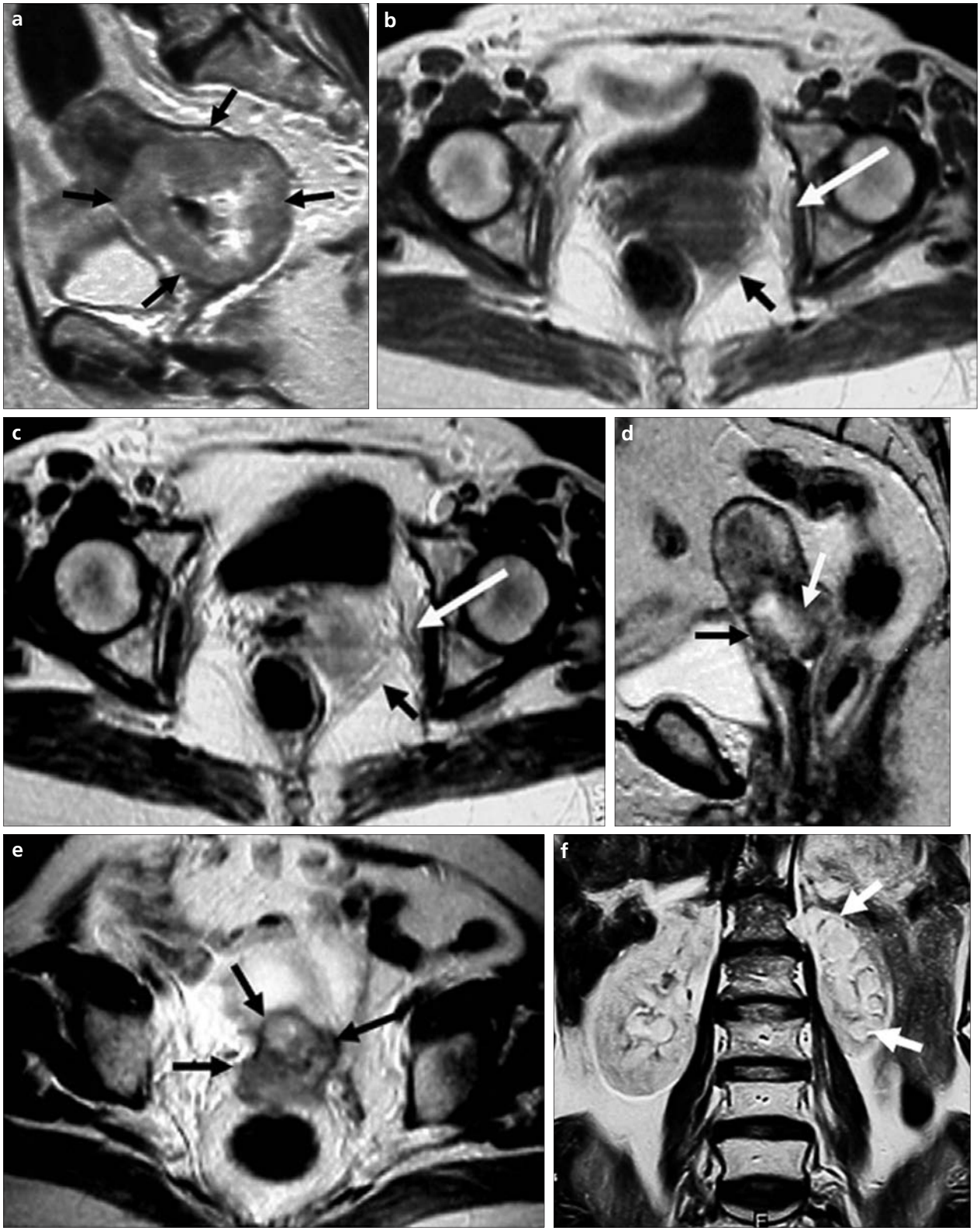

Figure 2. a–f. A 50-year-old woman with cervical carcinoma staged as IIIB clinically and staged as IIB with MRI before treatment. Sagittal T2-weighted MR image **(a)** shows a bulky, necrotic cervical tumor *(arrows)* before therapy. Axial T1-weighted pre- **(b)** and post-contrast **(c)** MR images show diffuse parametrial heterogeneity and contrast enhancement at the left the obturator fossa *(white arrows)* and left sacrouterine ligament thickening *(black arrows)* before therapy. At the sixth month after radiation therapy, partial tumor regression was seen (not shown). Sagittal **(d)** and axial **(e)** T2-weighted MR images show progression of the cervical tumor *(arrows)* at the first year after radiation therapy. Coronal T2-weighted MR image **(f)** shows left hydronephrosis *(arrow)* at the first year after radiation therapy.

Table 6. Correlation between clinical staging and MRI-based staging with respect to parametrial and sacrouterine ligament invasion findings for 84 regions pre-RT

	MRI findings				
	Without parametrial invasion	Parametrial invasion	Extension to the pelvic wall	Total (%)	Spearman's rho test
Clinical findings					
Without parametrial invasion	22 (71.0%)	9 (29%)	-	31 (36.9%)	
Parametrial invasion	10 (29.4%)	22 (64.7%)	2 (5.9%)	34 (40.5%)	
Extension to the pelvic wall	5 (26.3%)	11 (57.9%)	3 (15.8%)	19 (22.6%)	
Total		42 (50%)	5 (6%)	84	r = 0.410[a], $P < 0.01$
	Without SUL invasion	SUL invasion	Extension to the pelvic wall	Total (%)	
Without SUL invasion	57 (93.4%)	3 (4.9%)	1 (1.6%)	61 (72.6%)	
SUL invasion	7 (87.5%)	1 (12.5%)	-	8 (9.5%)	
Extension to the pelvic wall	5 (33.3%)	6 (40%)	4 (26.7%)	15 (17.9%)	
Total	69 (82.1%)	10 (11.9%)	5 (6%)	84	r = 0.532[a], $P < 0.01$

SUL, sacrouterine ligament
[a]"r"values of ≥0.75, 0.74–0.50, and <0.50 show very good correlation, good correlation, and poor correlation, respectively

Table 7. Correlation between clinical staging and MRI staging for pre-RT vaginal invasion

		MRI findings				
		Without invasion	2/3 proximal invasion	1/3 distal invasion	Total	Spearman's rho test
Clinical findings	Without invasion	10 (43.5%)	13 (56.5%)	-	23 (54.8%)	
	Invasion	7 (41.2%)	10 (58.8%)	2 (100%)	19 (45.2%)	
Total		17	23	2	42	r = 0.196[a], $P = 0.11$

[a]"r"values of ≥0.75, 0.74–0.50, and <0.50 show very good correlation, good correlation, and poor correlation, respectively

Table 8. Correlations between clinical and MRI stage with lymph node status

Factor	LN positivity[a] (%)	*P* value
Clinical stage		
≤IIB	9/22 (40.9)	0.118
≥IIIB	13/20 (65.0)	
MRI stage		
≤IIB	14/31 (45.2)	0.116
≥IIIB	8/11 (72.7)	

LN, lymph node
[a]Verified by MRI findings because biopsy was not feasible

Table 9. Correlation between tumor volume and lymph node status

Factor	LN positivity (%)	*P* value
Tumor volume		
<30 mL	12/28 (42.9)	0.08
≥30 mL	10/14 (71.4)	

LN, lymph node

Table 10. Assessment of local response to the treatment, 6-month post-treatment clinical and MRI results

		MRI findings					
		Without response	Partial response	Complete response	Recurrence	Total	Spearman's rho test
Clinical findings	Without response	-	1	-	-	1	
	Partial response		-	1	-	1	
	Complete response	-	2	30	-	32	
	Recurrence	-	-	-	2	2	
Total		-	3	31	2	36	r = 0.674[a] $P = 0.0001$

[a]"r" values of ≥0.75, 0.74–0.50, and <0.50 show very good correlation, good correlation, and poor correlation, respectively

of recurrences occur within 2 years of diagnosis, and the prognosis is poor with most patients dying as a result of uncontrolled disease (12). The total pelvic failure rate and 10-year actuarial incidence of distant metastasis in stage III disease is approximately two times higher than in stage IIB (13, 14). These data indicate the importance of stage IIIB diagnosis in helping to determine prognosis prior to treatment.

MRI findings that are suggestive of pelvic sidewall involvement have been defined (8, 15). Although there is increased availability of MRI in clinical settings, the accuracy of MRI criteria to differentiate between stage IIB and stage IIIB cannot be determined due to an insufficient number of IIIB patients in MRI-related articles. A study by Bipat et al. reviewed 49 articles published between 1985–2002 and demonstrated that stage IIIB MRI accuracy has not been reported (15). In the American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183 study, only 18 of 208 patients were stage IIIB, and no stage IIIB MRI accuracy was reported (16). The sensitivity for the detection of advanced stage (≥ IIB) disease with the FIGO clinical staging, CT imaging, and MRI was 29%, 42%, and 53%, respectively; the specificity was 99%, 82%, and 74%, respectively; and the negative predictive value was 84%, 84%, and 85%, respectively (6). Kodaira et al. reported that only 18 (24.3%) of 74 patients with stage IIIB disease were diagnosed as having hydronephrosis (3). In a recent study, the accuracy, sensitivity, and specificity for clinical staging were found to be higher than for MRI-based staging (for clinical staging: 75%, 66% and 81%; for MRI staging: 58%, 52%, and 63%, respectively) in the evaluation of parametrial involvement in patients with ≥IIB cervical carcinoma. However, only five of 84 patients had stage III cancer in that study (7).

Similarly to the aforementioned study, the present study included 19 patients with clinically staged IIIB cancer, and clinical and MRI-based staging correlation for the diagnosis of pelvic sidewall invasion was found to be poor (15.8%), while for the diagnosis of parametrial invasion, the correlation was 64.7%. Because surgery was not an option for stage IIB and IIIB patients, histopathological confirmation was not possible. However, MRI findings for the patients staged both clinically and with MRI as stage IIIB and IIB before treatment were re-evaluated. In six of 11 patients clinically diagnosed with pelvic sidewall invasion, parametrial heterogeneity and contrast enhancement were detected in the area between the tumor and pelvic sidewall. These findings were seen in slices at the level passing through the obturator fossa; these slices were outside the maximal tumor diameter and were determined to be overlooked by the radiologist. Although tumor invasion and edema or inflammation cannot be differentiated using MR findings, considering that tumor lymphatic drainage is mainly from the obturator fossa (17), such findings can be suggestive of a stage IIIB diagnosis seen on MR imaging. However, histopathologic corroboration of these results in a larger series is still needed.

Although not included in the FIGO staging system, nodal disease also has a great impact on survival, and the presence of metastatic nodes indicates a poorer prognosis within each stage. Poor prognostic factors such as FIGO stage ≥IIB, large tumor diameter (≥4–5 cm) either clinically or with MRI, and large tumor volume (≥30 mL) are significantly related to pelvic nodal involvement (1–3, 18). However, in the current study, the differences between LN positivity according to tumor volume and clinical or MRI-based staging were not found to be statistically significant. Similarly, Kodaira et al. reported that for patients with stage III disease, size/volume and lymph node status derived from MRI showed a significant correlation with the development of distant metastasis but failed to predict local advancement. In addition, size/volume analysis showed no apparent relationship with disease-free survival. For patients with stage III disease, MRI may provide beneficial information for predicting distant metastasis but not local advancement (4).

It is important to note that for patients with cervical cancer, previous studies showed that as much as 30%–50% of malignant cases are associated with normal-sized lymph nodes (19, 20). Although the limited spatial resolution of PET scans makes the identification of small metastases (0.5 cm or less in short-axis diameter) and LNs difficult, the accuracy of PET/CT has been reported to be as high as 99.6% for the diagnosis of LNs larger than 0.5 cm in diameter (21). PET-CT is superior to MRI and CT because PET-CT does not rely on the size of a LN to determine its invasive status, allowing much earlier detection of metastases. In a systematic review and meta-analysis, Selman et al. stated that the imaging methods currently used to detect LN status may be inaccurate, that PET may have a potential role for diagnosis, and that sentinel node biopsy may provide a minimally invasive and accurate assessment of lymph node status (22). Because an accurate assessment of LN status in the staging of cervical cancer is important for directing treatment and reducing morbidity, further research is needed to assess the effect of implementing such tests on patient outcomes and health service costs.

In the evaluation of local response, MRI allows both an assessment of the response to RT and a distinction between residual or recurrent tumor and radiation-induced fibrosis on the basis of volume and signal intensity (7–9). In an initial study and consistent with our results, MRI demonstrated a good correlation with clinical examination and transvaginal biopsy, and it correctly predicted residual tumor or recurrence in 27 of 28 patients with cervical cancer who were treated with primary RT (7). Similarly, in another study, MRI had a 90.4% accuracy rate in assessing tumor and parametrial spread regression after neoadjuvant chemoradiotherapy (23). However, benign conditions such as edema, inflammation, bleeding, and/or necrosis may also generate false positive results, especially within 3 months of RT. Manfredi et al. reported that MRI was 78% accurate for evaluating the tumor response; however, in 22% of patients, benign conditions were not distinguishable from the residual tumor. In this study, four of 18 patients had false positive MRI findings due to focal hyperplasia of the endocervical glands caused by inflammation in three cases and necrosis in one case (24). Although dynamic MRI can improve specificity, early radiation change continues to pose a problem because it may show early enhancement (25). For this reason, MRI should be performed at least 6 months after the completion of radiation therapy. In the case of a discordance between clinical and MRI findings, transvaginal or computed tomography-guided biopsy should be performed.

The principal limitation of this study was the use of a 1.0-T and a 1.5-T system with different parameters and slice thicknesses (3–5 mm). Moreover, because surgery is not an option for advanced cervical carcinoma, the lack of pathologic correlation is an additional important limitation. Lastly, this is a retrospective study with a small series and it lacks multiple observers (interobserver variation).

In conclusion, although the correlation between clinical and MRI findings was high for the assessment of local response to the treatment, it was low when correlating the clinical and MR staging results in patients with advanced cervical cancer. For this reason, future randomized clinical trials supported by histopathologic and/or PET-CT findings are needed, not only to validate our findings but also to shed more light on the potential utility of MRI-based staging in advanced cervical carcinoma.

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