Original paper

Changes in magnetic resonance T2-weighted imaging signal intensity correlate with concurrent chemoradiotherapy response in cervical cancer

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Abstract

Purpose: This study is aimed to compare magnetic resonance imaging (MRI) parameters and clinical pathological factors (CPF) of residual tumor group with non-residual tumor group in cervical cancer (CC) patients during concurrent chemoradiotherapy (CCRT), and thus to establish a biomarker for individualized treatment strategy.

Material and methods: From May 2014 to November 2015, 164 CC patients were included in this retrospective study. T2-weighted MRI was performed at pre-treatment (week-0), the completion of external radiotherapy (RT) (week-4), and one month after the completion of CCRT, using 3.0T MR scanner with regular pelvic coil. Mean signal intensity and tumor size on T_2WI images were measured and calculated for each tumor, and lumbar 4-5 intervertebral disc at week-0 and week-4. All patients subsequently underwent routine follow-up, including periodic clinical and imaging examinations when necessary. Receiver operator characteristics (ROC) analysis were conducted to determine cut-off values.

Results: The residual tumor group showed a higher Δ tumor-to-disc signal intensity ratio (ΔTDR) than non-residual tumor group (0.78 ± 0.30 vs. 0.48 ± 0.19, $t = 3.42$, $p < 0.05$). The biomarker of combined MRI parameter and CPF showed the highest diagnostic performance than single MRI parameter or CPF alone.

Conclusions: MRI parameter ΔTDR may be an independent prognostic factor for predicting residual tumor occurrence in CC after CCRT treatment. The combination of MRI parameter and CPF can serve as a valuable biomarker to distinguish CC with higher possibility of residual tumor occurrence.

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Key words: cervical cancer, magnetic resonance imaging, signal intensity, concurrent chemoradiotherapy, treatment response.

Purpose

Despite the introduction of effective screening and therapy strategies, cervical cancer (CC) is still the second most common gynecologic cancer among women worldwide [1]. Women with advanced CC (International Federation of Gynecology and Obstetrics stage IB2-IVA) consider concurrent chemoradiotherapy (CCRT) as their primary choice to achieve complete cure. However, further treatment options are severely limited if initial treatment fails [2]. Many well-known prognostic factors including cancer stage, lymph node status, histology, and parametrial invasion are used to guide therapy selection; however, no factor is specialized to detect treatment failure. A reliable biomarker is therefore needed to identify patients at great risk for treatment failure in order to timely modify treatment strategies.

As magnetic resonance (MR) technology advances recently, more attention has been drawn to new MR sequences like diffusion-weighted imaging (DWI), MRI spectroscopy (MRS), and dynamic contrast-enhanced MRI (DCE-MRI) [3]. However, these advanced sequences increase scan time and elevate equipment requirements compared to conventional MRI examination. Thus, T_2WI is still the most adopted scan sequence in CC [4]. High signal intensity (SI) on T_2WI represents changes in tumor

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permeability, perfusion, and surrounding inflammation [5]. Because of high cellularity and cellular water content, pre-treatment tumors have prolonged transverse relaxation times with correspondingly high SI in T2-weighted sequence. Radiotherapy leads to progressive replacement of tumor tissue by scar tissue, resulting in shortened transverse relaxation times and reduced SI on T_2WI [6]. Therefore, tumors with persistent high SI on T_2WI, despite several weeks of chemoradiation therapy, may represent a treatment-resistant tumor subtype [7]. The adoption of 3.0 T MRI shortens scan time, enhances signal-to-noise ratio (SNR), and allows for the identification of small lesion with higher accuracy.

In this study, we analyzed the changes of T_2WI SI together with patients' clinical pathological characteristics in CC during CCRT in order to explore a reliable biomarker to assess and predict treatment response in CC.

Material and methods

Patient population

Our hospital ethics committee has approved the study and informed consent was obtained from every participant included. From May 2014 to November 2015, 174 women with biopsy-proven CC staged IB1-IV treated with standard CCRT were retrospectively considered for inclusion. All patients underwent pre-treatment MRI, CCRT, and clinical follow-up. Inclusion criteria were as follows: 1. Uterine CC confirmed by biopsy, and time interval between biopsy and baseline MRI no longer than two weeks; 2. Tumor maximal diameter > 1.0 cm; 3. No previous radiation or chemotherapy; and 4. No contraindications for CCRT or MRI examination. Ten patients were excluded because of incomplete MRI examination, owing to personal reason. Finally, 164 patients were enrolled in the study.

Concurrent chemoradiotherapy therapeutic regimen

All patients were treated with a combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). EBRT was delivered to the whole pelvis, with a total dose of 50 Gy (daily dose of 2 Gy, 5 times per week) and accompanied by concurrent chemotherapy: six cycles of weekly cisplatin (40 mg/m^2) or three cycles of cisplatin (75 mg/m^2) at 3-week intervals. ICBT was initiated after an EBRT dose of 46-50 Gy. ICBT was delivered once or twice a week in 4-5 fractions, with a fractional dose of 6-7 Gy at point A. The median dose of ICBT was 28 Gy and the median biological effective dose (BED) was 47.8 Gy (range, 23.3-64.7 Gy) to point A.

MRI protocol

Each patient underwent serial MR examinations at 3 time points: before the start of RT (week-0), at the completion of external RT (week-4), and one month after the completion of CCRT. All patients underwent pelvic MR scanning on a clinical 3.0T whole-body MR scanner (Magnetom Trio Tim, Siemens Medical, Erlangen, Germany) by using the 18-channel surface phased-array body coil to cover the entire pelvis. Routine female pelvic MR images were acquired as follows: axial T1-weighted spin-echo (SE) images (TR/TE, 741/11 m/sec; slice thickness/gap, 4/1 mm, acquisition time, 92 sec), and axial and sagittal T2-weighted turbo spin-echo (TSE) images (TR/TE, 4732/95 m/sec for axial plane and 3000/86 m/sec for sagittal plane; slice thickness/gap, 4/1 mm; matrix, 320 × 320, total acquisition time, 157 sec).

Image analysis

Two radiologists (with 20- and 12-years' experience in gynecological MR imaging) independently assessed cervical tissues on MRI images. Both radiologists were blinded to the clinical and pathological patients' information. Discrepancies were resolved by consensus. All patients underwent clinical evaluation and histological biopsy. Thus, the FIGO (International Federation of Gynecology and Obstetrics) stage and lymph nodes status of CC were determined according to the clinical and MRI evaluation.

Tumor size was determined by the longest diameter measured in three axes [8]. Average T2 SI was measured for the tumor and for the lumbar 4-5 intervertebral disc. A tumor-to-disc SI ratio (TDR) was defined as follows:

$$TDR = \text{mean tumor SI} / \text{mean intervertebral disc SI}$$

Since the SI of the intervertebral disc remained stable during CCRT [9], a comparison between the week-0 and week-4 TDR yielded a self-normalized method to counter interpatient differences. The change in SI between week-4 and week-0 was defined as follows:

$$\Delta TDR = TDR_{week\text{-}4} / TDR_{week\text{-}0}$$

Pre-treatment clinical classification and treatment evaluation

Combined clinical pathological factors (CCPF) were dichotomized into unfavorable (stage III or IV or positive lymph nodes) versus favorable (stage I or II and negative lymph nodes) categories. Each CPF was weighted equally.

Treatment response was classified into non-residual and residual tumor groups. Non-residual tumor was defined as no tumor found on T_2WI at one month after completion of the therapy. Residual tumor was defined as a visible residual tumor on T_2WI.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (version 17.0, SPSS Inc., Chicago, IL, USA). All continuous variables were recorded as means ± standard deviations (SD). The intra-class correlation coefficient (ICC) was used to evaluate the interobserver agreement between the 2 radiologists for measurements of tumor size and SI. Comparison of MRI parameters and clinical pathological characteristics between non-residual and residual tumor groups was performed using independent sample *t* test or the Pearson χ^2 test, as appropriate. Uni- and multivariate logistic regression were used to analyze prognostic factors of CC patients. Receiver operating characteristic (ROC) analysis were conducted to determine cut-off values. Diagnostic performances of parameters in predicting

the post-treatment residual tumors occurrence were evaluated and compared using maximum Youden index (the sum of sensitivity and specificity). A two-tailed p value less than 0.05 was considered statistically significant.

Results

Interobserver agreement in imaging analysis

The measurements of tumor size and SI had excellent interobserver reproducibility. Of all the tumor size in the non-residual tumor group and the residual tumor group, the interobserver agreement showed an ICC of 0.91 (95% confidence interval [CI], 0.85-0.93). In addition, the agreement between the 2 observers was obtained in the SI measurements with an ICC of 0.86 (95% CI, 0.79-0.91).

Clinical pathological characteristics between non-residual tumor group and residual tumor group

Patients' clinical pathological characteristics were presented in Tables 1 and 2. One month after the CCRT completion, 118 out of 164 patients had no residual tumor, and the remaining 46 patients had residual tumors shown on MRI. Pre-treatment patients with FIGO stage III-IV tumor and positive lymph node metastasis tended to have residual tumors than those in patients with I-II tumor and negative lymph node status ($\chi^2 = 25.85$, $p < 0.01$; $\chi^2 = 15.13$, $p < 0.01$, respectively). No significant differences in age and histological type were found between the two groups ($\chi^2 = 0.14$, $p = 0.72$; $\chi^2 = 0.49$, $p = 0.48$, respectively).

MRI parameters between non-residual tumor group and residual tumor group

As presented in Table 2, pre-treatment tumor size was 4.19 ± 1.34 cm and 4.82 ± 1.26 cm ($t = 1.56$, $p = 0.13$), and week-4 tumor size was 1.85 ± 0.77 cm and 1.95 ± 0.69 cm ($t = 0.03$, $p = 0.98$) in non-residual and residual tumor group, respectively. Change in tumor size was 2.34 ± 1.23 cm in non-residual group and 2.96 ± 1.30 cm in residual tumor group. There was no significant difference between the two groups ($t = 1.34$, $p = 0.19$).

Pre-treatment, week-4, and Δ tumor SI in non-residual tumor group were 413.06 ± 126.12, 202.41 ± 104.17, and 210.65 ± 206.58, while in residual tumor group were 378.5 ± 134.14, 207.35 ± 121.75, 182.00 ± 128.89, respectively. Parameters mentioned above showed no significant difference between the two groups ($t = 0.71$, $p = 0.48$; $t = 0.32$, $p = 0.75$; $t = 0.68$, $p = 0.50$, respectively). Pre-treatment TDR were 1.00 ± 0.44, 0.75 ± 0.31 and week-4 TDR were 0.53 ± 0.35, 0.73 ± 0.38 in non-residual tumor group and residual tumor group, the differences between two groups showed no significance ($t = 1.78$, $p = 0.09$; $t = 1.41$, $p = 0.17$, respectively). ΔTDR was significantly higher in residual tumor group than non-residual tumor group (0.78 ± 0.30 vs. 0.48 ± 0.19, $t = 3.42$, $p = 0.03$). Figure 1 compared tumor size and SI of non-residual tumor group with those of residual tumor group.

Multivariate logistic regression showed that FIGO stage, lymph node status, and ΔTDR were significantly correlated with the occurrence of residual tumor. Patients with higher ΔTDR had higher risk ratios for residual tumor occurrence. Details are presented in Table 3.

ROC analysis of MRI parameters and clinical pathological factors

ROC curve analysis yielded a cutoff ΔTDR value of 0.65 for distinguishing post-treatment residual tumor occurrence from the non-residual tumor, as presented in Figure 2. The area under the curve (AUC) of ΔTDR was 0.81.

Diagnostic performances of ΔTDR, CPF, CCPF, and combined MRI-CCPF parameters for predicting post-treatment residual tumor occurrence are shown in Table 4. For single CPF (FIGO stage or lymph node status), sensitivities and specificities were inferior in predicting treatment outcomes. CCPF also displayed poor prediction, with a low sensitivity of 75.29%, specificity of 54.35%, positive predictive values (PPV) of 73.06%, and negative predictive values (NPV) of 62.50%, compared with ΔTDR. MRI parameter ΔTDR demonstrated higher diagnostic performance in predicting post-treatment residual tumor occurrence, with sensitivity of 80.65%, specificity of 83.87%, PPV of 69.20%, and NPV of 92.30%, compared with single CPF and CCPF. The combination of ΔTDR and CCPF exhibited the highest predictive performance, with a sensitivity of 93.22%, specificity of 91.96%, PPV of 94.83%, and NPV of 87.33%, compared with a single MRI parameter ΔTDR or CCPF alone.

The probability of residual tumor occurrence in patient with unfavorable MRI parameter was significantly

Table 1. Patients' clinical pathological characteristics

Patients' characteristics	
No. of patients	164
Median age (range)	53.7 (30-77) years
FIGO stage	
IB1-IIA	53
IIB	73
III-IV	38
Lymph node	
Negative	112
Positive	
Pelvic LN	41
Para-aortic LN	11
Histology	
Squamous cell carcinoma	148
Adenocarcinoma	11
Adenosquamous carcinoma	5
Interval between MRI and initial of the therapy (range)	8 (1-13) days

FIGO – International Federation of Gynecology and Obstetrics; LN – lymph node

Table 2. Univariate analysis of clinicopathological variables and MRI parameters between non-residual and residual tumor groups in patients with cervical cancer

	Non-residual (n = 118)	Residual (n = 46)	χ^2 or t value	p value
CPF				
Age (years)			0.14	0.72
< 50	73	27		
≥ 50	45	19		
Histologic type			0.49	0.48
Squamous cell carcinoma	107	40		
Other	11	6		
FIGO stage*			25.85	< 0.01
I-II	103	23		
III-IV	15	23		
Lymph node status*			15.13	< 0.01
Positive	27	25		
Negative	91	21		
MRI parameters				
Week-0 tumor size (cm)	4.19 ± 1.34	4.82 ± 1.26	1.56	0.13
Week-4 tumor size (cm)	1.85 ± 0.77	1.95 ± 0.69	0.03	0.98
Δ Tumor size (cm)	2.34 ± 1.23	2.96 ± 1.30	1.34	0.19
Week-0 tumor SI	413.06 ± 126.12	378.5 ± 134.14	0.71	0.48
Week-4 tumor SI	202.41 ± 104.17	207.35 ± 121.75	0.32	0.75
Δ Tumor SI	210.65 ± 206.58	182.00 ± 128.89	0.68	0.50
Week-0 TDR	1.00 ± 0.44	0.75 ± 0.31	1.78	0.09
Week-4 TDR	0.53 ± 0.35	0.73 ± 0.38	1.41	0.17
ΔTDR*	0.48 ± 0.19	0.78 ± 0.30	3.42	0.03

*CPF – clinical pathological factors; FIGO – International Federation of Gynecology and Obstetrics; TDR – tumor-to-disc SI ratio *represents statistically significant difference ($p < 0.05$)*

higher than that in patient with favorable MRI parameter (90.91% vs. 5.00%). When Δ TDR was equal to or greater than 0.65, the probability of residual tumor occurrence increased significantly compared with that in ΔTDR < 0.65 regardless of in patients with favorable CCPF (from 4.60% to 83.33%) or in patients with unfavorable CCPF (from 6.06% to 96.15%) (Tables 5 and 6).

Discussion

The present study is the first research to combine T_2WI SI with CPF as biomarkers to predict the occurrence of residual tumor in CC. The results of this study showed that CC with higher ΔTDR, FIGO staging, and positive lymph node metastasis responded poorly to CCRT. By adopting these biomarkers, we can identify patients who tend to have residual tumor early during CCRT in order to timely modify the treatment regime.

Several researches similar to our study had been published. Kuang *et al*. [10] reported that the ADC increased percentage was higher in complete response patient group than those in partial response and stable disease patient group after two weeks therapy and four weeks therapy. Yang *et al*. [11] exhibited that DCE-MRI parameters maximum slope of increase (MSI) and signal enhancement ratio (SER) were lower in residual tumor patient group, and the combined imaging biomarker showed excellent predictive value in CCRT treatment response assessment. However, DWI and DCE-MRI are not prevalent in developing country. Biomarker T_2WI SI combined with CPF in our study is simple and easy to put into practice, which can be widely applied in clinical daily work.

There were some researches of using T2 SI to predict treatment response. Kim *et al*. [12] proved that post-chemoradiation therapy (CRT) SI on T2-weighted MRI could help to predict partial complete response after preoperative CRT patients with rectal cancer. King *et al*. [13] reported that the change pattern of tumor SI on T2-weighted image was associated with chemoradiotherapy treatment outcome in primary head and neck squamous cell carcinoma patients. Our research demonstrated

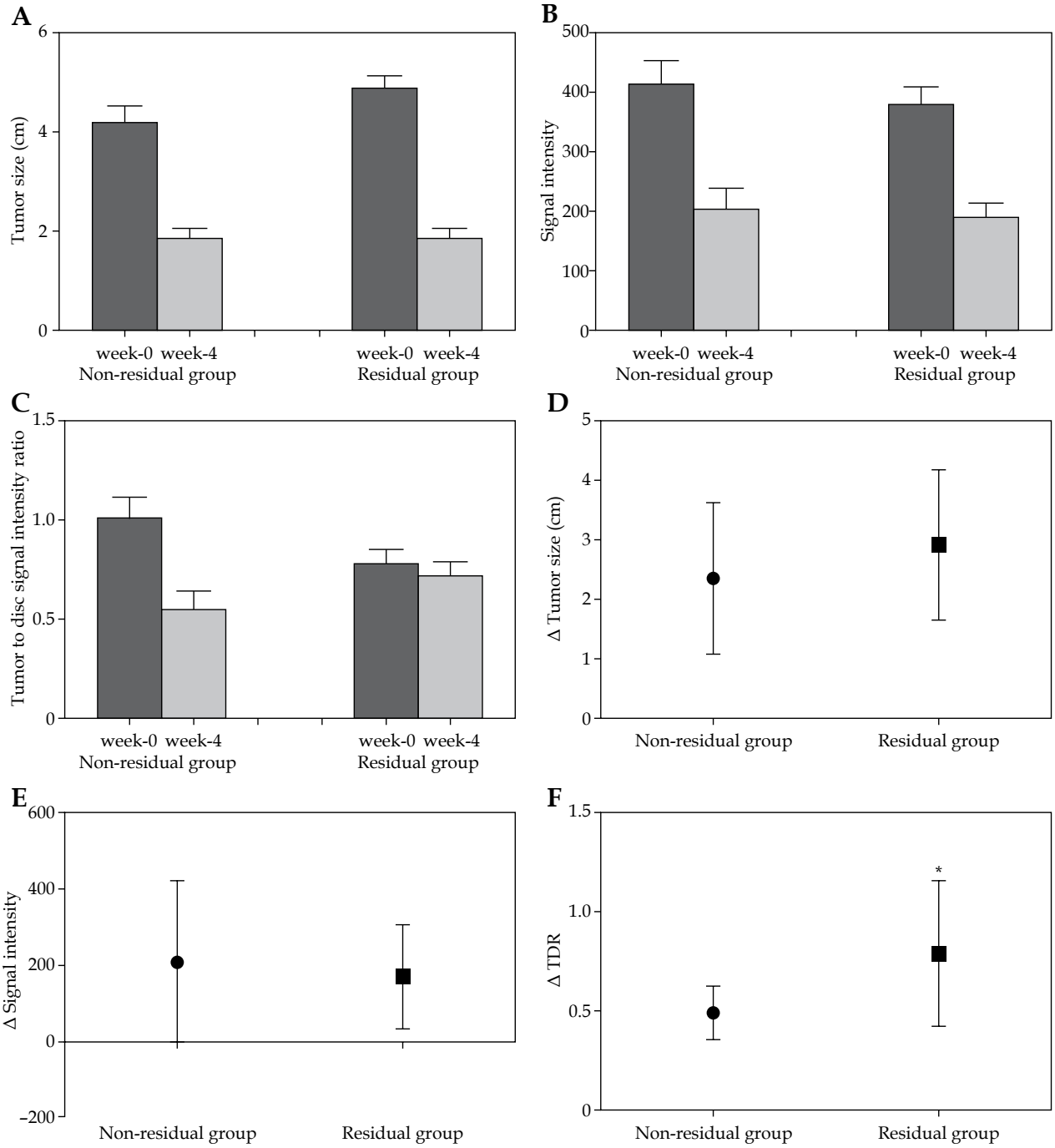

Fig. 1. The change of tumor size, tumor signal intensity (SI), and tumor-to-disc SI ratio (TDR) values in non-residual and residual tumor groups, *represents statistically significant difference ($p < 0.05$)

Table 3. Multivariate analyses for MRI parameters and clinical pathological factors (CPF)

	OR	OR (95% CI)	*p* value
CPF			
FIGO stage (I-II vs. III-IV)	6.87	3.11 to 15.16	< 0.01
LN status (positive vs. negative)	0.25	0.12 to 0.51	< 0.01
MRI parameter			
Δ TDR	0.01	0.003113 to 0.03222	< 0.01

OR – odds ratio; CI – confidence interval; CPF – clinical pathological factors; FIGO – International Federation of Gynecology and Obstetrics; LN – lymph node; TDR – tumor-to-disc SI ratio

Table 4. Diagnostic performance of MRI, clinical pathological factors (CPF), combined CPF (CCPF), and combined MRI/CPF parameter for predicting post-treatment residual tumor occurrence

	Cut-off value	AUC	*p*	Sensitivity	Specificity	PPV	NPV
MRI parameter							
ΔTDR	0.65	0.81	< 0.001	80.65%	83.87%	69.20%	92.30%
CPF							
FIGO stage	–	–	–	87.29%	50.00%	81.75%	60.53%
LN status	–	–	–	22.88%	45.65%	51.92%	18.75%
CCPF	–	–	–	75.29%	54.35%	73.06%	62.50%
Combined MRI-CCPF	–	–	–	93.22%	91.96%	94.83%	87.33%

AUC – area under the curve; PPV – positive predictive value; NPV – negative predictive value; TDR – tumor-to-disc SI ratio; CPF – clinical pathological factors; LN – lymph node; CCPF – combined CPF

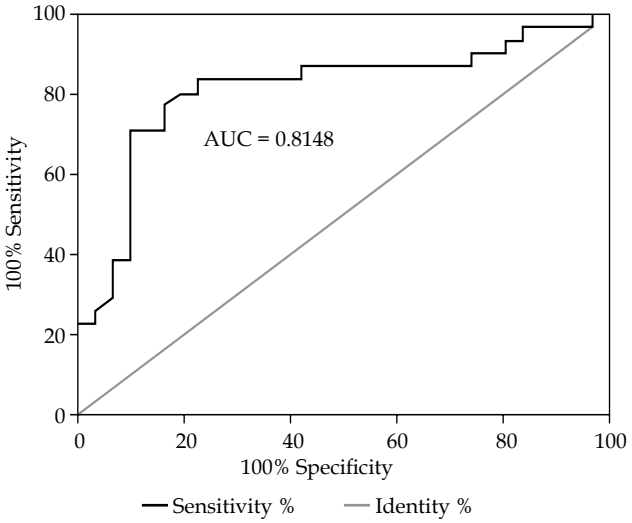

Fig. 2. ROC curve of Δ tumor-to-disc SI ratio (ΔTDR) for distinguishing post-treatment residual tumor occurrence from non-residual tumor

Table 5. ΔTDR for estimating the probability of post-treatment residual tumor occurrence

	No. of patients	No. of residual tumor	Percentage
ΔTDR < 0.65	120	6	5.00
ΔTDR ≥ 0.65	44	40	90.91

TDR – tumor-to-disc SI ratio

that treatment response was better in CC patients, with significant decrease of SI on T2-weighted images than those with slight decrease.

Tumor heterogeneity mainly accounts for treatment response variability in the same chemoradiotherapy [14]. Because MRI parameters only exhibited part of tumor properties to predict CCRT treatment response in CC, we added CPF to intensify the difference between non-residual tumor and residual tumor groups. By combining MRI parameters with CCPF, the diagnostic ability of combined biomarker increased significantly. The sensitivity and specificity of combined biomarker were 93.22% and 91.96%, which were significantly higher than MRI parameters or CCPF alone. By adding unfavorable MRI parameter, the probability of residual tumor occurrence rose strikingly whether in patient with favorable CCPF or in patient with unfavorable CCPF.

Our research has some limitations. First, this was a retrospective study with inherited limitations [15]; therefore, a randomized prospective study is required. Secondly, the follow-up period was short and survival analysis was absent in this article. The further follow-up is continued, and results will be revealed in our coming article.

In conclusion, CC patients with ΔTDR ≥ 0.65 show higher possibility of residual tumor occurrence. MRI parameter ΔTDR may be an independent prognostic factor for predicting post-treatment residual tumor occurrence in CC. By combining ΔTDR with CCPF, the new biomarker exhibits the highest diagnostic ability and predictive value for evaluating CCRT treatment response in CC patients.

Table 6. ΔTDR and combined clinical pathological factors (CCPF) for estimating the probability of post-treatment residual tumor occurrence

MRI parameter	Favorable CCPF			Unfavorable CCPF		
	No. of patients	No. of residual tumors	Percentage	No. of patients	No. of residual tumors	Percentage
ΔTDR < 0.65	87	4	4.60	33	2	6.06
ΔTDR ≥ 0.65	18	15	83.33	26	25	96.15

Favorable CCPF: stage I-II and negative lymph node; Unfavorable CCPF: stage III-IV or positive lymph node

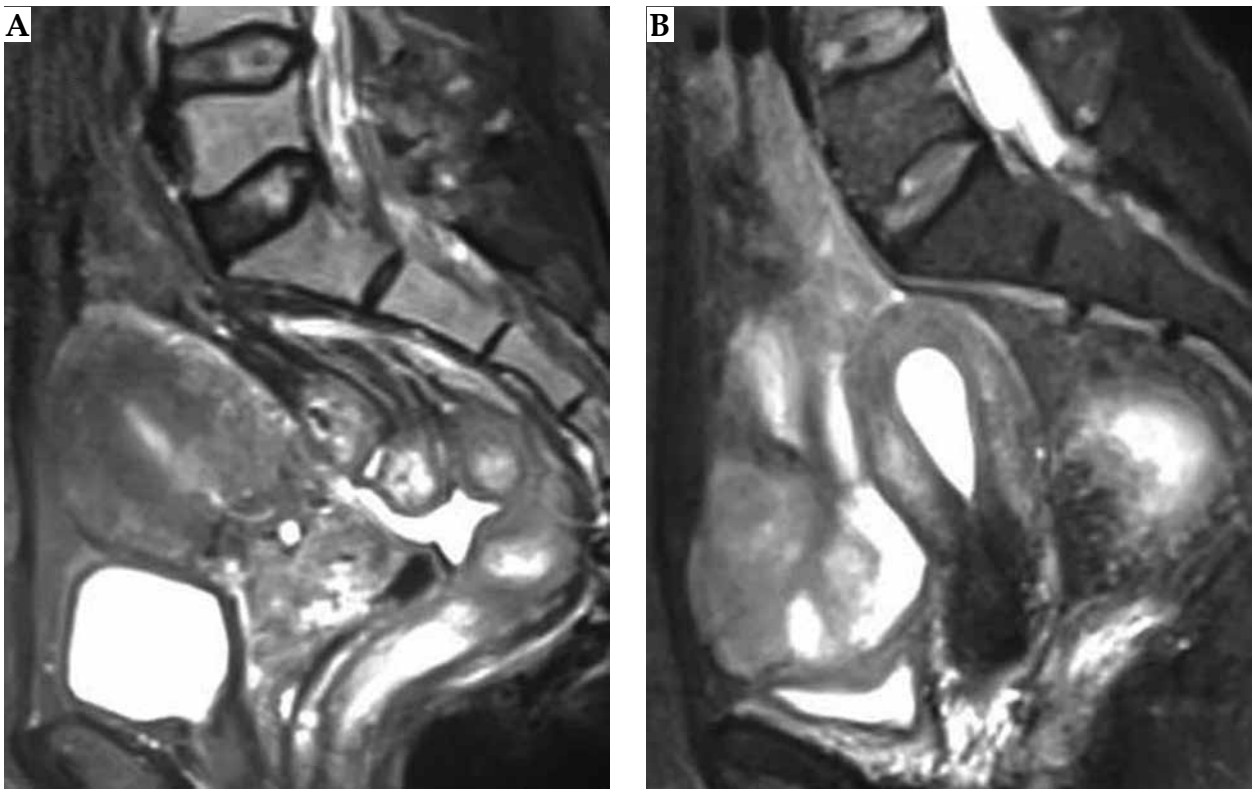

Fig. 3. MR T2-weighted images of a 47-year-old woman with cervical squamous cell carcinoma exhibited tumor signal intensity (SI) change at week-0 (**A**) and week-4 (**B**)

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Disclosure

Authors report no conflict of interest.

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