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UROGENITAL

Prognostic value of ADC quantification for clinical outcome in uterine cervical cancer treated with concurrent chemoradiotherapy

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Abstract

Objectives To investigate the prognostic value of diffusion-weighted imaging (DWI) in predicting clinical outcome in patients with cervical cancer after concurrent chemoradiotherapy (CCRT).

Methods We enrolled 124 cervical cancer patients who received definitive CCRT and underwent 3 T-MRI before and 1 month after initiating treatment. The mean apparent diffusion coefficient (ADC) value was measured on the tumor and the changes in ADC percentage (ΔADC_{mean}) between the two time points were calculated. The Cox proportion hazard model was used to evaluate the associations between imaging or clinical variables and progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS).

Results In multivariate analysis, ΔADC_{mean} was the only independent predictor of PFS (hazard ratio [HR] = 0.2379, $p = 0.005$), CSS (HR = 0.310, $p = 0.024$), and OS (HR = 0.217, $p = 0.002$). Squamous cell carcinoma antigen, histology, and pretreatment tumor size were significantly independent predictors of PFS. Tumor size response was significantly independent predictor of CSS and OS. Using the cutoff values of ΔADC_{mean}, the PFS was significantly lower for $\Delta ADC_{mean} < 27.8\%$ ($p = 0.001$). The CSS and OS were significantly lower for $\Delta ADC_{mean} < 16.1\%$ ($p = 0.002$ and $p < 0.001$, respectively).

Conclusion The percentage change in tumor ADC may be a useful predictor of disease progression and survival in patients with cervical cancer treated with CCRT.

Key Points

- *DWI is widely used as a potential marker of tumor viability.*
- *Percentage change in tumor ADC (ΔADC_{mean}) was an independent marker of PFS, CSS, and OS.*
- *Survival was better in patients with ≥ ΔADC_{mean} cutoff value than with < the cutoff value.*

Keywords Diffusion-weighted imaging · Cervical cancer · Concurrent chemoradiotherapy · Treatment outcome · Magnetic resonance imaging

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Abbreviations

ADC	Apparent diffusion coefficient
CCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CSS	Cancer-specific survival
DWI	Diffusion-weighted imaging
EBRT	External-beam radiotherapy
FIGO	International Federation of Gynecology and Obstetrics
HR	Hazard ratio
ICC	Intraclass correlation coefficient
ICR	Intracavitary brachytherapy
LN	Lymph node
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression-free survival
ROI	Region of interest
SCC	Squamous cell carcinoma
T2WI	T2-weighted imaging
THRIVE	T1-weighted high-resolution isotropic volume examination
ΔADC_{mean}	Percentage change of mean ADC between two time points

Introduction

Concurrent chemoradiotherapy (CCRT) consisting of external-beam radiotherapy (EBRT), cisplatin-based chemotherapy, and intracavitary brachytherapy (ICR) is the recommended standard treatment for locally advanced cervical cancer for the International Federation of Gynecology and Obstetrics (FIGO) stage IB2–IVA [1]. However, a substantial number of patients experience locoregional recurrence or distant metastasis after treatment [2, 3]. Accordingly, surveillance after treatment using the appropriate modality is very important for selecting optimal adjuvant treatment strategies. Moreover, prediction of treatment outcomes such as disease progression or survival during treatment or early after initiating treatment is clinically important from the perspective of patient' counseling or improving patient' prognosis.

After treatment in locally advanced cervical cancer, the presence of residual tumor is related to poor clinical outcomes [3–5] and is a potential risk factor for the development of locoregional recurrence or distant metastasis [5]. Currently, pelvic MRI is a preferred modality to assess the extent of local disease at initial diagnosis as well as to evaluate treatment response.

Diffusion-weighted imaging (DWI) is a functional imaging technique that analyzes differences in extracellular water proton movement, allowing discrimination between tissues with varying cellularity. In addition to evaluating morphological changes, it can quantify diffusion by calculating an apparent diffusion coefficient (ADC). Owing to diffusion restriction in malignant tumors caused by increased cellular density, DWI provides useful information for tumor aggressiveness, subtype characterization, and treatment responses. Currently, DWI is widely used as a potential marker of tumor viability in oncologic imaging [6]. For cervical cancer, a few studies have reported the usefulness of DWI in predicting an immediate or clinical response to CCRT; however, these results may be limited due to small patient populations and short-term follow-up periods of less than 2 years [7–12]. To date, no studies with a cohort of mid-term or long-term follow-up and a relatively large number of patients have reported regarding the utility of DWI as a prognostic factor for clinical outcome in patients with locally advanced cervical cancer. Thus, the purpose of the present study was to retrospectively investigate the prognostic value of DWI in predicting clinical outcome in patients with cervical cancer after CCRT, with mid-term follow-up and a relatively larger population.

Materials and methods

Patients

Our local institutional review board approved the study and waived the need for informed consent because of the retrospective study design. Between April 2009 and December 2015, 139 biopsy-proven cervical cancer patients treated with CCRT underwent 3 T-MRI including DWI before and 1 month after treatment in our institution. Of these, 15 patients were excluded for the following reasons: history of prior treatment ($n = 12$), no DWI ($n = 1$), severe artifacts due to hip arthroplasty ($n = 1$), and no visible tumor on MRI ($n = 1$). Finally, 124 consecutive patients (mean age, 56.9 years; range, 28–85 years) were included (Fig. 1).

MRI protocols

All MRI scans were obtained with a 3.0 T system (Intera Achieva TX, Philips Healthcare) equipped with a phased-array body coil. Pelvic routine MRI was performed before treatment (mean, 14.6 days; range, 2–21 days), 1 month after CCRT initiation (mean, 28.7 days; range, 19–40 days) and 1 month after completion of CCRT. In our institution, MRI at 1 month after CCRT initiation was performed because the patient management strategy may be changed; for example, subsequent ICR can be omitted if the therapeutic response is poor or the residual tumor is outside the clinical target volume of ICR, and because tumor volume reduction during CCRT or RT is associated with prognostic significance [13]. The protocol included T1-weighted imaging, T2-weighted imaging (T2WI), DWI with background body signal suppression, and postcontrast fat-saturated T1-weighted high-resolution

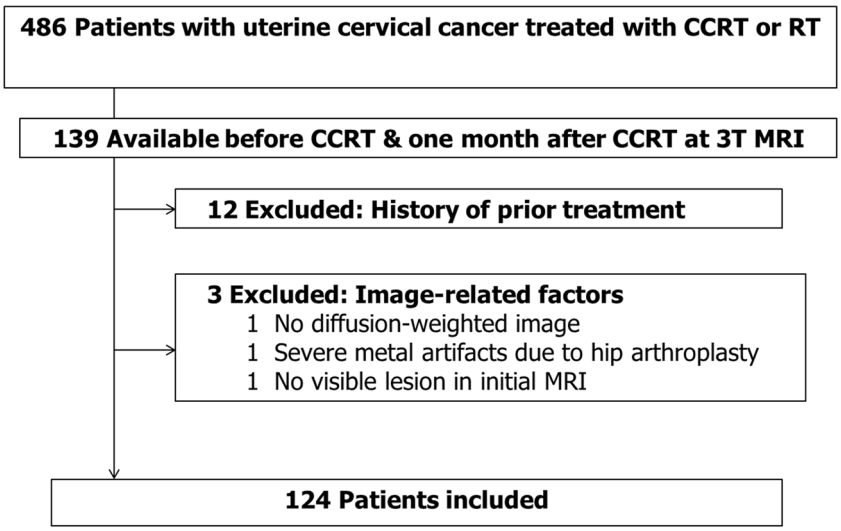

Fig. 1 Flowchart of patient enrollment

isotropic volume examination (THRIVE). Diffusion encoding gradients were applied at *b*-values of 0–1000 s/mm^2 in the three orthogonal directions of the motion-probing gradients. An apparent diffusion coefficient (ADC) map was automatically constructed using manufacturer-provided software.

Image analysis

All images were analyzed in consensus by two radiologists (C.K.K. and K.G., who have 13 and 2 years of experience in pelvic MRI, respectively) on our picture archiving and communication system (Centricity Enterprise version 3.0, GE Healthcare). The radiologists were only aware that patients had biopsy-proven cervical cancer. The location and boundary of the tumor were determined on T2WI, DWI, and postcontrast fat-saturated THRIVE for both pretreatment and posttreatment MRI. First, to measure the mean ADC (ADC_{mean}) value in the tumor at each time point, a region of interest (ROI) was manually drawn by an experienced radiologist (C.K.K.) on the single axial ADC map image that showed its maximal dimension of the tumor. The ROIs were drawn to include as much of the tumor as possible, but cystic or necrotic portion within the tumor was excluded from the ROI measurements on the basis of postcontrast THRIVE findings. Second, to evaluate interreader agreement and variability, a less-experienced radiologist (K.G.) independently measured the ADC_{mean} value of tumors in 42 patients using the same method as the experienced radiologist. These analyses were performed on different days. The diameter of the tumor and presence of pelvic lymph node (LN) metastasis and parametrial invasion were also determined. Any LNs with short-axis diameter greater than 5 mm as observed on MRI were considered to be positive [14]. Percentage changes in tumor ADC_{mean} (ΔADC_{mean}) between pretreatment and posttreatment were calculated using the following equation: (posttreatment ADC_{mean} − pretreatment ADC_{mean}) / pretreatment ADC_{mean} × 100 (%). Tumor size response between pretreatment and posttreatment was calculated according to the following equation: (pretreatment size − posttreatment size) / pretreatment size × 100 (%).

Treatment

All patients underwent EBRT and high-dose-rate ICR with an iridium-192 source. EBRT was performed on the whole pelvis with 10 or 15 MV photon beams at a daily dose of 1.8–2.0 Gy, for a median dose of 50.4 Gy over the total course of treatment. High-dose-rate ICR was initiated to deliver a total dose of 24 Gy with 4 Gy per insertion three times per week in six fractions. Concurrent chemotherapy was conducted as follows: cisplatin 60 mg/m^2 and 5-fluorouracil 1000 mg/m^2/day were administered every 3 weeks in 37 patients, and 87 patients received cisplatin 40 mg/m^2 weekly. The schedule of CCRT is shown in Fig. 2. The median overall treatment time was 47 days (41–57 days).

Clinical and histopathologic factors

After the completion of CCRT, clinical responses were evaluated 1 month later by physical examination, PET/CT, and abdominopelvic MRI. Patients were clinically and radiologically followed approximately every 3 to 4 months for the first 2 years, every 6 months for the next 3 years and once annually thereafter. Physical examination, Papanicolaou smear, and serum tumor markers were checked at each visit. Routine annual imaging surveillance was performed using abdominopelvic computed tomography (CT) or MRI and chest radiography. If there was suspicion for tumor recurrence based on the clinical examination or imaging studies, PET/CT or imaging-

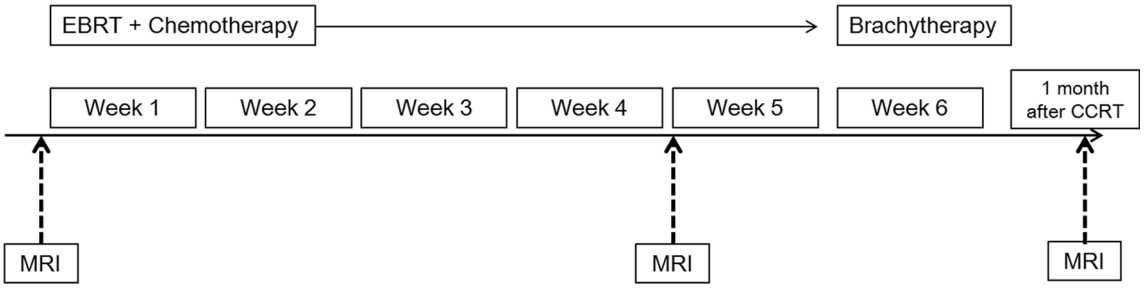

Fig. 2 Treatment schedule and MRI examination

guided biopsy was performed. Disease progression was categorized as locoregional recurrence or distant metastasis.

Statistical analysis

The duration of progression-free survival (PFS) was calculated from the date of the start of treatment to the date of any disease progression or last follow-up. The duration of cancer-specific survival (CSS) and overall survival (OS) were calculated from the date of the start of treatment to the date of cervical cancer-specific death or last follow-up and to the date of death or last follow-up, respectively.

Univariate and multivariate Cox proportional hazard analyses were used to evaluate the associations between clinical or imaging variables and PFS, CSS, or OS. Clinical variables included age, FIGO stage, serum squamous cell carcinoma (SCC) antigen level, and histology. MRI variables included pretreatment tumor size, tumor size response, presence of parametrial invasion, presence of pelvic LN metastasis, pretreatment ADC_{mean}, and ΔADC_{mean}. Variables with p values < 0.2 in the univariate analysis were further analyzed in the multivariate analysis. p values and 95% confidence intervals (CIs) for hazard ratio (HR) were corrected by Bonferroni's method. Similar analyses were performed including the optimal cutoff value of ΔADC_{mean} which was determined as the point at which the log-rank p value is at a minimum. The actuarial PFS, CSS, and OS rates were calculated by the Kaplan-Meier method and the results were compared using the log-rank test. The ADC value between SCC and adenocarcinoma was evaluated using the independent t test.

Inter-reader reliability and variability were evaluated using the intraclass correlation coefficient (ICC) and the coefficient of variation [15], respectively. The ICC value was judged to provide poor reliability (0.00–0.20), fair reliability (0.21–0.40), moderate reliability (0.41–0.60), good reliability (0.61–0.80), or excellent reliability (0.81–1.00). A two-sided p value < 0.05 was considered statistically significant for all statistical tests. Statistical analyses were performed using SAS software (Version 9.4, SAS Institute) and R (R 3.3.2; http://www.R-project.org).

Results

Baseline characteristics

During a median follow-up period of 43.5 months (range, 2.5–82.8 months), 20 patients (16.1%) deceased and of these, cervical cancer-specific deaths occurred in 18 patients (14.5%). Disease progression occurred in 40 (32.3%) patients: locoregional recurrence ($n = 19$), distant metastasis ($n = 25$), or both ($n = 4$).

Patient characteristics are summarized in Table 1. The mean SCC antigen levels were 13.1 mg/dL. On histopathological findings, SCC was found in 103 (83.1%) patients. Other subtypes were found in 21 (16.9%) patients: adenocarcinoma ($n = 17$), adenosquamous cell carcinoma ($n = 3$), and lymphoepithelial-like carcinoma ($n = 1$). The mean tumor ADC values of pretreatment and posttreatment were 0.933×10^{-3} mm^2/s and 1.308×10^{-3} mm^2/s, respectively, and there was a significant difference between them ($p < 0.001$). The mean ΔADC_{mean} value was 42.1%. The mean ADC values of SCC and adenocarcinoma were $0.919 \pm 0.113 \times 10^{-3}$ mm^2/s and $0.999 \pm 0.184 \times 10^{-3}$ mm^2/s, respectively, and they were significantly different ($p = 0.009$). The mean tumor size of pretreatment and posttreatment were 55.4 mm and 25.2 mm, respectively, and they were significantly different ($p < 0.001$). The mean tumor size response was 55.2%. Parametrial invasion on MRI was found in 106 (85.5%) patients.

Risk factors associated with treatment outcome

The results of univariate and multivariate analyses for clinical outcome are presented in Tables 2, 3, and 4. In univariate analysis, histology ($p = 0.020$), pretreatment tumor size ($p = 0.001$), and ΔADC_{mean} ($p = 0.002$) were significantly associated with PFS. However, other variables including age, FIGO stage, SCC antigen, pelvic LN metastasis, parametrial invasion, and pretreatment ADC_{mean} were not associated with PFS (all $p > 0.05$). ΔADC_{mean} and tumor size response were the only factors associated with CSS ($p < 0.001$ and $p = 0.001$, respectively) and with OS ($p < 0.001$ and $p = 0.001$, respectively). In multivariate analysis, ΔADC_{mean} was the only independent predictor for PFS (HR = 0.379, $p = 0.005$), CSS

Table 1 Patient characteristics ($n = 124$)

Characteristic	
Age (years)	56.9 ± 12.6
FIGO stage	
Ib	11 (8.9)
IIa	12 (9.7)
IIb	62 (50.0)
IIIa	11 (8.9)
IIIb	12 (9.7)
IV	16 (12.9)
SCC antigen (ng/mL)	13.1 ± 22.6
Histology	
SCC	103 (83.1)
Adenocarcinoma/others	21 (16.9)
MRI findings	
Pretreatment ADC	0.933 ± 0.130
SCC	0.919 ± 0.113
Adenocarcinoma	0.999 ± 0.184
Posttreatment ADC	1.308 ± 0.207
ΔADC_{mean} (%)	42.1 ± 24.8
Pretreatment tumor size (mm)	55.4 ± 19.7
Posttreatment tumor size (mm)	25.2 ± 15.9
Tumor size response (%)	55.2 ± 23.4
Parametrial invasion (+)	106 (85.5)
Pelvic lymph node metastasis (+)	95 (76.6)

Date presented as mean ± standard deviation or *n* (%). *ADC* ($\times 10^{-3}$ mm^2/s), apparent diffusion coefficient; *FIGO*, International Federation of Gynecology and Obstetrics; *SCC*, squamous cell carcinoma

(HR = 0.310, $p = 0.024$), and OS (HR = 0.217, $p = 0.002$) (Supplementary Figure 1). The SCC antigen ($p = 0.024$), histology ($p = 0.045$), and pretreatment tumor size ($p = 0.015$) were independent predictors for PFS. Tumor size response was an independent predictor for CSS (HR = 0.022, $p = 0.004$) and OS (HR = 0.027, $p = 0.004$). Pretreatment tumor size was an independent predictor for OS ($p = 0.039$).

The Kaplan-Meier curves for PFS, CSS, and OS are presented in Fig. 3. The 3-year PFS, CSS, and OS were 70% (95% CI, 62–79%), 85% (95% CI, 78–92%), and 84% (95% CI, 77–91%), respectively. The optimal cutoff values of ΔADC_{mean} were 27.8% for PFS and 16.1% for CSS and OS, respectively. The actuarial PFS was worse in patients with $\Delta ADC_{mean} < 27.8\%$ than in those with $\Delta ADC_{mean} \geq 27.8\%$, with a 3-year survival rate of 50% (95% CI, 36–70%) compared with 79% (95% CI, 71–89%). Patients with $\Delta ADC_{mean} < 16.1\%$ were worse than those with $\Delta ADC_{mean} \geq 16.1\%$, with a 3-year CSS of 51% (95% CI, 29–90%) compared with 89% (95% CI, 83–95%) ($p < 0.001$) and a 3-year OS of 45% (95% CI, 24–83%) compared with 89% (95% CI, 83–95%) ($p < 0.001$).

Inter-reader reliability and variability

For the inter-reader reliability and variability of tumor ADC_{mean} measurements, ICC and CV were 0.915 (95% CI, 0.848–0.953) and 3.9% for pretreatment, and 0.814 (95% CI, 0.681–0.895) and 5.6% for posttreatment, respectively.

Discussion

A few previous studies have reported that DWI has the potential for predicting disease control or survival in cervical cancer patients treated with CCRT or RT, but these had a relatively short-term follow-up of less than 2 years and/or small patient populations [11, 12, 16]. No studies addressing the utility of DWI have been reported for mid-term or long-term follow-up

Table 2 Cox regression analysis of clinical and MRI variables for progression-free survival

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.000	0.976–1.025	0.998			
FIGO (≥ IIb)	1.591	0.623–4.064	0.332			
SCC antigen	1.012	0.999–1.026	0.084	1.017	1.002–1.031	0.024
Histology	2.293	1.145–4.591	0.020	2.278	1.017–5.101	0.045
Pretreatment tumor size	1.023	1.009–1.038	0.001	1.020	1.004–1.037	0.015
Tumor size response	0.334	0.079–1.417	0.137	0.611	0.126–2.970	0.541
Pelvic LN metastasis	1.827	0.765–4.360	0.175	1.736	0.722–4.171	0.218
Parametrial invasion	0.978	0.412–2.321	0.965			
Pretreatment ADC_{mean}	1.000	0.998–1.003	0.588			
ΔADC_{mean} (≥ 27.8%)	0.378	0.203–0.705	0.002	0.379	0.191–0.751	0.005

ADC, apparent diffusion coefficient; *FIGO*, International Federation of Gynecology and Obstetrics; *LN*, lymph node; *SCC*, squamous cell carcinoma

Table 3 Cox regression analysis of clinical and MRI variables for cancer-specific survival

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.002	0.966–1.039	0.920			
FIGO (≥ IIb)	0.577	0.206–1.619	0.296			
SCC antigen	1.007	0.998–1.027	0.462			
Histology	1.156	0.334–4.005	0.819			
Pretreatment tumor size	1.016	0.994–1.038	0.151	1.020	0.999–1.042	0.056
Tumor size response	0.019	0.002–0.200	0.001	0.022	0.002–0.288	0.004
Pelvic LN metastasis	0.837	0.298–2.347	0.735			
Parametrial invasion	0.427	0.152–1.199	0.106	0.456	0.148–1.409	0.173
Pretreatment ADC_{mean}	1.002	0.998–1.005	0.339			
ΔADC_{mean} (≥ 16.1%)	0.181	0.070–0.469	< 0.001	0.310	0.112–0.856	0.024

ADC, apparent diffusion coefficient; *FIGO*, International Federation of Gynecology and Obstetrics; *LN*, lymph node; *SCC*, squamous cell carcinoma

in a larger patient population. In this study, which had a mid-term median follow-up period of 43.5 months in 124 patients treated with CCRT, we found that ΔADC_{mean} (percentage change ADC_{mean}) in cervical cancer was the only independent prognostic factor for PFS, CSS, and OS. In particular, with cutoff values of 27.8% ΔADC_{mean} for PFS and 16.1% for CSS and OS, patients with lower ΔADC_{mean} values revealed significantly worse survivals than those with the cutoff values or greater. These findings indicate that ΔADC_{mean} may be a useful marker for treatment outcome in cervical cancer patients treated with CCRT, which can help clinicians with patient counseling, selecting optimal adjuvant treatment strategies, or designing a clinical study.

A few studies have reported that percent ADC changes between before and after CCRT in cervical cancer were predictive of clinical or immediate response [8, 11, 12, 17, 18]. Onal et al [11] evaluated treatment responses using ADC in 46 cervical cancer patients treated with CCRT, with a median follow-up of 28 months. In their study, percent ADC change in tumors was a prognostic marker for OS but was not associated with disease-free survival. Park et al [12] investigated the prognostic value of DWI and PET/CT in 67 cervical cancer patients treated with CCRT, with a median follow-up of 2.7 years. They found that percentage changes in ADC mean and maximum standardized uptake value before and 1 month after CCRT had similar values in predicting disease progression after treatment. However, they did not assess CSS or OS. Consistent with previous studies, our results demonstrated that percentage change in tumor ADC_{mean} was the only prognostic factor for PFS, CSS, and OS.

In our study, the 3-year PFS, CSS, and OS were significantly better in patients with a ΔADC_{mean} value at or above the cutoff than in patents with lower ΔADC_{mean}. These findings were in accordance with previously reported results [11,

Table 4 Cox regression analysis of clinical and MRI variables for overall survival

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.013	0.978–1.048	0.470			
FIGO (≥ IIb)	0.667	0.242–1.835	0.433			
SCC antigen	1.009	0.991–1.026	0.327			
Histology	1.495	0.498–4.490	0.474			
Pretreatment tumor size	1.018	0.998–1.040	0.082	1.021	1.001–1.041	0.039
Tumor size response	0.021	0.002–0.195	0.001	0.027	0.002–0.315	0.004
Pelvic LN metastasis	0.745	0.286–1.94	0.547			
Parametrial invasion	0.493	0.179–1.356	0.171	0.590	0.197–1.765	0.345
Pretreatment ADC_{mean}	1.003	1.000–1.006	0.361			
ΔADC_{mean} (≥ 16.1%)	0.137	0.057–0.332	< 0.001	0.217	0.084–0.559	0.002

ADC, apparent diffusion coefficient; *FIGO*, International Federation of Gynecology and Obstetrics; *LN*, lymph node; *SCC*, squamous cell carcinoma

12]. Effective treatment may substantially decrease the viable tumor burden, resulting in a change in water diffusion properties. Therefore, greater changes in tumor ADC before and after treatment potentially suggest that the tumors are more sensitive to treatment.

Many studies have reported that pretreatment DWI may be a useful prognostic factor for survival and recurrence outcomes in cervical cancer [16, 19, 20]. Lower pretreatment ADC values were associated with worse disease-free survival in early-stage cervical cancer patients treated mostly with surgery [19]. Regarding patients treated with CCRT, a previous study demonstrated that a lower pretreatment 95th percentile ADC was associated with worse DFS [20]. Ho et al [16] found that pretreatment ADC was an independent predictor of disease-free survival in cervical cancer patients treated with CCRT. Onal et al [11] demonstrated that pretreatment ADC in cervical cancer patients treated with CCRT was an independent prognostic factor for disease-free survival and OS. However, our study demonstrated no significant associations with treatment outcomes. These discrepancies may be explained by different patient populations with different follow-up durations, variations in ADC measurements, and different DWI parameters affecting ADC values. Therefore, further investigations are warranted.

Various variables, such as age, FIGO stage, tumor size, tumor size or volume response, presence of pelvic LN

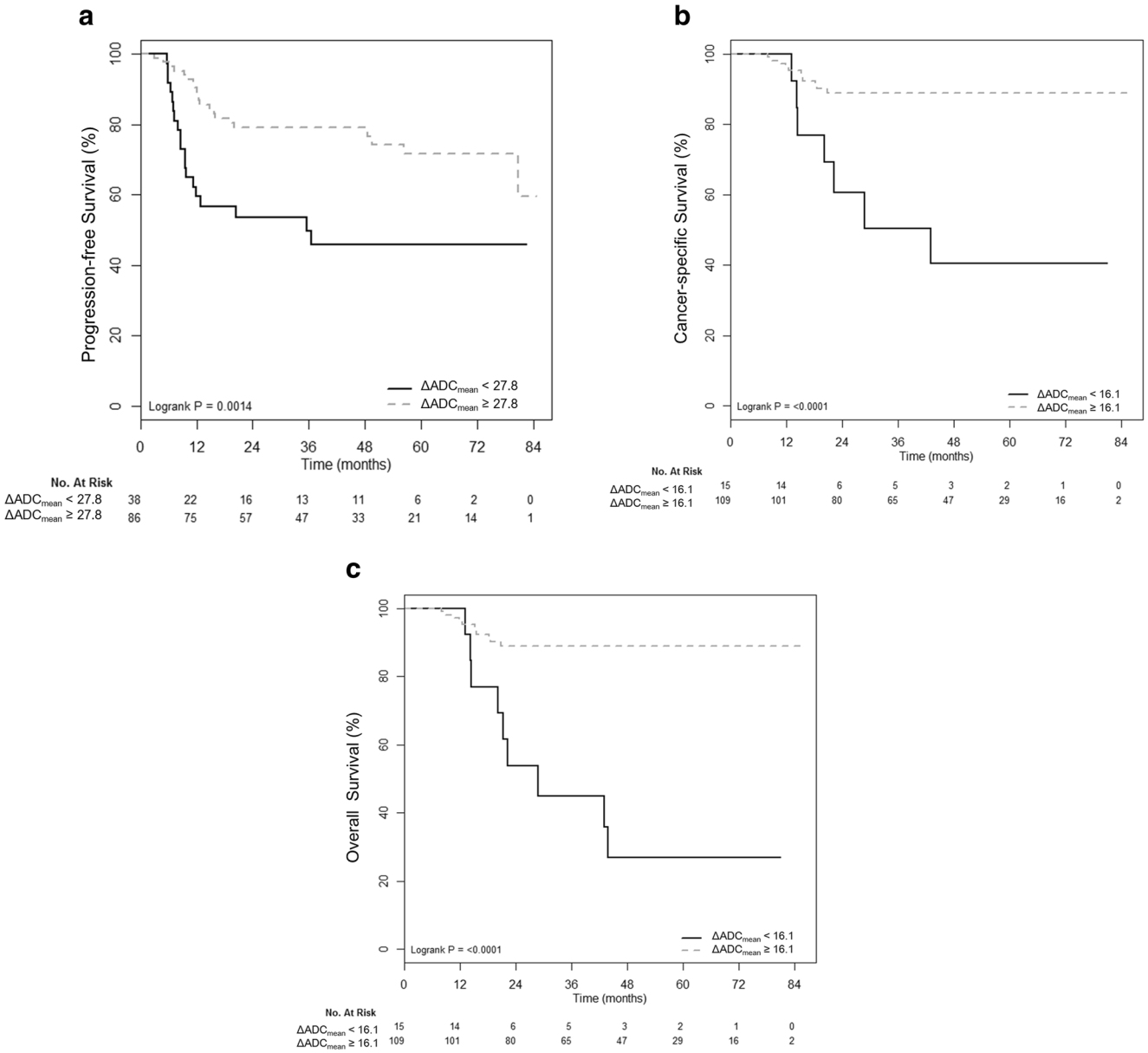

Fig. 3 Kaplan-Meier analyses of progression-free survival (PFS, **a**), cancer-specific survival (CSS, **b**) and overall survival (OS, **c**), comparing patients with < cutoff value of ΔADC_{mean} versus ≥ cutoff value of ΔADC_{mean}. Cutoff values of ΔADC_{mean} are 27.8% for PFS, and 16.1% for CSS and OS

metastasis, or cancer histology (SCC versus non-SCC), have been suggested as prognostic factors for treatment outcome [13, 21–24]. In our study, SCC antigen and histology (SCC versus non-SCC) were significant independent prognostic factors for PFS. Pretreatment tumor size was a significant independent prognostic factor for OS. Also, tumor size response was a significant independent predictor for CSS and OS. However, no other factors demonstrated significant associations with PFS, CSS, or OS. These discrepancies are partly explained by different patient populations with different follow-up periods.

Conflicting results have been shown for the utility of DWI in evaluating histological subtypes in cervical cancer [25, 26]. Xue et al [25] reported that the ADC value of SCC was significantly lower than that of adenocarcinoma in cervical cancer. However, Winfield et al [26] reported that no significant difference was found between the subtypes. In our study, the ADC value of SCC was significantly lower than that of adenocarcinoma, which was in line with a previous study [25]. In our multivariate analysis, histologic subtype was an independent predictor of PFS, while it was not associated with CSS or OS. A further study with larger populations is needed.

When assessing tumor response to treatment, reliability in any quantitative parameters is a prerequisite. Our results showed that the inter-reader reliability of ADC_{mean} in tumors was excellent on pretreatment and posttreatment, with less than 5.6% variation. These results are consistent with a previous study [18].

There were several limitations in our study. First, our study was a retrospective study in a single center, with a relatively small patient population and mid-term follow-up period. However, compared with previous studies with follow-up under 2 years [11, 12, 16], our study had a relatively long-term median follow-up period of 43.5 months and a larger number of patients ($n = 124$). Further validations with a larger number of patients and long-term follow-up greater than 5 years may be necessary for clinical application. Second, our study could not be free of measurement errors because ADC values were derived from manually drawn ROIs. Third, the mean ADC change within the ROI of the tumor on a single ADC map image has limited utility in assessing posttreatment response regarding tumor heterogeneity. Further studies will be needed to be conducted with histogram analyses or three-dimensional ROI measurements. Fourth, our study performed follow-up DWI at 1 month after initiating treatment. As an early marker of therapeutic response prediction, there is an issue of determining the optimal time window for performing DWI. A recent study has reported that 2 weeks after CCRT initiation can be the optimal time window in evaluating the therapeutic response in cervical cancer patients treated with CCRT, but it had the limitation of using morphological response as the therapeutic outcome, instead of clinical outcome [27]. Further studies are needed to determine the optimal time window for DWI examination for early prediction of clinical outcome. Finally, although the presence of para-aortic lymph node metastasis is an important prognostic factor [28], this was not analyzed in our study. A further study including the presence of para-aortic lymph node metastasis will enhance our results.

In conclusion, our results demonstrated that the percentage change in tumor ADC may be a useful predictor of disease progression and survival in patients with cervical cancer treated with CCRT. Furthermore, ADC measurements in cervical cancer revealed excellent inter-reader reliability. A further study with a larger population and long-term follow-up period greater than 5 years may be required for personalized medicine.

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Compliance with ethical standards

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Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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