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Original Article

Volumetric assessment of apparent diffusion coefficient predicts outcome following chemoradiation for cervical cancer

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ABSTRACT

Objective: To determine the utility of volumetric diffusion weighted imaging (DWI) compared to other clinical factors for predicting recurrence and survival in cervical cancer patients treated with definitive chemoradiation.

Methods and materials: We retrospectively studied cervical cancer patients treated with definitive chemoradiation between 2009–2013 at a single institution with a baseline MRI with DWI and 18F-FDG positron emission tomography/computed tomography (FDG-PET) scan. To identify clinical and imaging metrics correlated with survival and recurrence endpoints, variable importance values were calculated from random forest models. To provide clinically relevant threshold values, recursive partitioning analysis dichotomized patients into potential risk groups based on selected metrics. Cox's proportional hazard models assessed the effect of clinical and imaging factors on survival endpoints.

Results: Ninety-three patients were included in the analysis (median age 50 years). At a median follow-up of 35.6 months, 32 patients (34%) had disease recurrence. In the best multivariate model including clinical and imaging parameters, 90th percentile ADC < 1.917 was the only significantly associated factor with worse progression free survival (PFS). Overall survival, PFS, and distant metastasis free survival (DMFS) were significantly different between patient groups divided on 90th percentile ADC with threshold of 1.917×10^{-3} mm^2/s and MRI volume with threshold of 18.9 cc ($P = 0.037$, $P = 0.0002$, $P = 0.001$). High MRI volume and low ADC were associated with worse clinical outcomes.

Conclusions: Volumetric 90th percentile ADC value of the primary tumor on pretreatment MRI was a significant predictor of PFS and DMFS in cervical cancer patients, independent of established clinical factors and SUV on FDG-PET.

 Radiotherapy and Oncology 135 (2019) 58–64

Cervical cancer is the eleventh most common cancer and ninth most common cause of cancer related death in developed countries, with approximately 13,000 new cases and 4200 cancer related deaths per year in the United States [1,2]. For patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB2 to IVA disease, definitive concurrent chemoradiation is recommended based on the results of randomized trials [3–7]. Unfortunately, approximately 30% of patients develop disease recurrence after chemoradiation [3–7]. Although certain clinical factors such as stage, histology, tumor size, tumor grade, and lymph node status can help predict for patients who are at risk of worse outcomes, improved prognostication of patients with a higher risk of relapse who may benefit from treatment intensification is of paramount importance [8].

Functional magnetic resonance imaging (MRI) with diffusion weighted imaging (DWI) is a noninvasive imaging technique that measures the mobility of water, which offers a metabolic and physiologic view of the tumor microenvironment [9,10]. Apparent diffusion coefficient (ADC) is used to quantify DWI, and in general, malignant tumors have a lower ADC, reflecting the restricted motion of water molecules thought to be due to higher cellularity [10]. The prognostic value of DWI MRI has not been well defined in cervical cancer patients treated with definitive chemoradiation. Studies have reported on different ADC parameters, and the data have also been conflicting on whether a lower or higher pretreatment ADC portends a worse outcome [11–19]. In addition, several studies were limited by only using limited axial slices, rather than

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volumetric delineation, to quantify ADC, or by lack of long-term follow-up and analysis of survival and recurrence outcomes.

In this study, we sought to examine the utility of volumetric DWI MRI compared to other clinical factors for predicting recurrence and survival in cervical cancer patients treated with definitive chemoradiation.

Materials and methods

Patient selection

In this institutional review board approved study, our institution's tumor registry database was used to identify cervical cancer patients treated with definitive chemoradiation between 2009 and 2013. All patients included had an MRI with DWI sequence performed at baseline and an 18F-FDG Positron emission tomography/computed tomography (PET/CT) scan performed at baseline, and at follow-up after chemoradiation. All patients who received definitive radiation treatment with curative intent, as determined at the time of initial consultation, were included. Two patients with stage IVB disease were included who initially had suspicion of distant metastasis but a complete metabolic response to induction chemotherapy prior to definitive chemoradiation. Three patients did not receive concurrent chemotherapy secondary to comorbidities. Overall, ninety-three patients who met the above criteria were included in this retrospective analysis. Institutional records were used to extract patient, disease, imaging, and treatment characteristics as well as survival outcomes.

Imaging analysis

MRI was performed on a 1.5T GE whole body MRI system (Signa; GE Healthcare, Waukesha, Wisconsin). All studies used body coil transmission and an 8-channel phased array pelvic RF coil for signal reception. Unenhanced T1 weighted axial images, T2 weighted sagittal and axial images, and post-contrast T1 weighted axial images were obtained after intravenous gadolinium administration. Vaginal gel was consistently instilled. Three b values were used (0, 50 and 800) for the diffusion sequence. The perfusion component of the diffusion was 0–50, and 50–800 the diffusion component. Enhanced DWI was used, and the ADC map was automatically generated. ADC maps were calculated using all three B values. Three-dimensional volumetric segmentation of the primary tumor was first performed on T2 axial images and the tumor volume was extracted. Image segmentation was performed by a single physician, who was blinded to outcome. The DWI image set was then co-registered to the T2 images using a commercial image registration software, Velocity AI v.3.01 (Varian Medical Systems, Atlanta, GA). Subsequently, gross tumor volume (GTV) region of interests (ROIs) were propagated to the co-registered DWI and ADC maps. The ADC values for all voxels included in these ROIs were assessed through histogram analysis, and several parameters were extracted for analysis: mean ADC, 10th percentile ADC, 20th percentile ADC, 30th percentile ADC, 40th percentile ADC, 50th percentile ADC, 60th percentile ADC, 70th percentile ADC, 80th percentile ADC, 90th percentile ADC, and maximum ADC.

A PET/CT was obtained one hour after injection of approximately 15 mCi [555 MBq] radiolabeled FDG on an integrated PET/CT scanner (Discovery ST-8, GE Healthcare). Patients were NPO 6 hours prior to the study. Patients underwent imaging only if the baseline blood glucose level was <150 mg/dl (8.3 mmol/L) on pre-imaging measurement. Baseline maximum tumor standardized uptake value (SUV) was measured on PET/CT by the reading radiologist, documented from MIM software (MIM Software Inc. Cleveland, OH).

Treatment

All patients were treated with external beam pelvic radiation, and dose, treatment fields, and technique were at the discretion of the treating radiation oncologist. Radiation was given to a total dose of 40–45 Gy at 1.8–2 Gy per fraction. Typically, the pelvis was treated with four-field 3D-conformal technique. Patients who needed treatment of para-aortic nodes typically were treated with intensity modulated radiation fields matched to a 3D-conformal pelvic field. Within one week after completion of external beam radiation therapy, most patients received two pulsed-dose-rate intracavitary pulsed dose rate brachytherapy treatment using an after-loaded tandem and ovoid system, delivered 10–14 days apart. Each brachytherapy session lasted approximately 44–48 h, with a goal total dose delivered of 85–90 Gy. Brachytherapy treatment planning was performed using volume-based dosimetry. The high-risk clinical target volume was defined per GEC-ESTRO guidelines using a post-implant, same-day CT scan, including the cervix as well as any gross residual disease and any intrauterine or intravaginal disease with a goal total dose delivered of 85–90 Gy [20]. Patients with baseline nodal or parametrial/pelvic sidewall involvement received an external beam boost, which was given in between brachytherapy treatments, to goal total doses of 56–66 Gy for lymph nodes and 60–66 Gy for parametrial/sidewall involvement, depending on size, response to initial radiation, and adjacent critical structures. Concurrent cisplatin was delivered weekly, at a dose of 40 mg/m^2.

Follow-up

After chemoradiation, patients were followed with exam and pelvic imaging typically every 3–6 months for 2–3 years, then yearly.

Recurrence

Follow up PET/CTs were used to assess for recurrence, and any avidity above background considered concerning for recurrence and subsequently followed by biopsy, unless there was imaging evidence of widely metastatic disease. Central recurrence was defined as any recurrence in the original cervical tumor region. Nodal recurrence was defined as any recurrence within the pelvic region included within radiation fields. Locoregional recurrence included central or nodal recurrences or both.

Statistical analysis

Endpoints assessed included overall survival, progression free survival, freedom from local failure, freedom from locoregional failure, freedom from distant metastasis, and freedom from recurrence. All survival rates were calculated from the end date of radiation. For progression free survival, local failure, locoregional failure, distant metastases, and death were scored as events.

To identify possible clinical and DWI derived metrics correlated to each endpoint, we calculated variable importance values from random forest models [21]. For each endpoint, we use the Gini importance measure, which incorporates a weighted mean for each individual trees' improvement at each split (or branch) produced for each variable in the model. One-thousand random forests models were ran for each endpoint in R using the randomForest package [22], and the features with the highest cumulative Gini importance scores were selected as potential features for further modeling. To provide clinically relevant threshold values, the selected features were then used as inputs in a

recursive partitioning analysis (RPA) to dichotomize patients into potential risk groups on a per endpoint basis.

Data analysis was performed using Stata/MP 13.0 statistical software. Fisher's exact test assessed measures of association in frequency tables. The equality of group medians was assessed with the Wilcoxon rank-sum (Mann–Whitney) test. The survival function was carried out using Kaplan–Meier estimates. The log rank test assessed the equality of the survivor function across groups. A *p*-value of 0.05 or less was considered to be statistically significant. Statistical tests were based on a two-sided significance level.

The Cox's proportional hazard model assessed the effect of factors of significance on the survival end points for univariate and multivariate analysis. The estimated hazard ratio is reported. Variables such as age, baseline SUV, baseline mean ADC, and MRI volume were analyzed both continuously as well as by categorizing above and below the median. Multivariate analysis was performed on all factors found to have a p-value of 0.25 or less on univariate analysis. Backward elimination was performed with the least significant factor eliminated in a step-wise manner until the most significant variables were identified.

Results

Patient, tumor and treatment characteristics

Baseline patient, imaging, and treatment characteristics are listed in Table 1. Sixty-six patients (71%) had squamous cell carcinoma. The remaining 27 patients (29%) had adenocarcinoma ($n = 19$), adenosquamous ($n = 4$), clear cell ($n = 2$), small cell ($n = 1$), or carcinoma not otherwise specified ($n = 1$). Fifty-nine patients (63%) had positive lymph nodes at diagnosis: 49 patients (83%) with pelvic lymph node involvement and 10 (17%) with para-aortic lymph node involvement. The median maximum SUV of the primary tumor on baseline PET/CT was 15.1 (range, 4.6–43.4). The median mean ADC of the primary tumor on baseline DWI MRI was 1.25×10^{-3} mm^2/s (range, 0.12–3.92 $\times 10^{-3}$ mm^2/s). The median 90th percentile ADC of the primary tumor was 1.87×10^{-3} mm^2/s (range, 0.76–5.76 $\times 10^{-3}$ mm^2/s).

Table 1
Baseline patient, tumor, and treatment characteristics.

Characteristic	No. of Pts (%) ($n = 93$)
Median age at diagnosis, years (range)	50 (26–94)
Tumor Histology, n (%)	
Squamous	66 (71%)
Adenocarcinoma/Other	27 (29%)
Tumor differentiation, n (%)	
Well	1 (1%)
Moderate	40 (43%)
Poor	37 (40%)
Unknown	15 (16%)
FIGO stage, n (%)	
IB1	6 (6%)
IB2	23 (25%)
IIA	7 (8%)
IIB	30 (32%)
III	21 (23%)
IV	6 (6%)
Lymph node involvement	
Positive	59 (63%)
Para-aortic	10 (17%)
Pelvic	49 (83%)
None	34 (37%)
Baseline PET SUV max	
Median (range)	15.1 (4.6–43.4)
MRI tumor volume (cm^3)	
Median (range)	43.5 (2.6–994.3)
90th percentile ADC	
Median (range)	1.87 (0.76–5.76)
Mean ADC	
Median (range)	1.25 (0.12–3.92)

Abbreviations: 3D = 3-dimensional; ADC = apparent diffusion coefficient; FIGO = International Federation of Gynecology and Obstetrics; MRI = magnetic resonance imaging; PET SUV = positron emission tomography standardized uptake value.

Survival

At a median follow-up of 35.6 months (range, 7.8–64.4 months), 32 patients (34%) had disease recurrence. Eleven patients (12%) had a central recurrence, 16 patients (17%) had a locoregional recurrence either centrally or in regional nodes, and 22 patients (24%) had a distant metastasis. Fifty-five patients were alive and free of disease, 15 alive with disease, and 23 had died of their disease. The 1-year and 2-year overall survival rates were 91% and 82%, respectively. The 1-year and 2-year locoregional recurrence-free survival rates were 86% and 82%, respectively. The 1-year and 2-year central recurrence-free survival rates were 89% and 87%. The 1-year and 2-year progression-free survival rates were 74% and 63%.

ADC analysis

Clinical factors including age, FIGO stage, tumor histology and differentiation, and lymph node positivity and type as well as DWI MRI parameters including ADC mean, max, 10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, 90th percentiles, and MRI volume were included in the random forest variable importance and RPA analysis. RPA analysis identified the 90th percentile ADC (ADC90) as well as MRI volume as significant parameters for discriminating progression-free survival and identified thresholds of 1.917×10^{-3} mm^2/s and 18.9 cc, respectively. These variables were then included in the regression models for survival.

Univariate and multivariate analyses

In univariate analysis for overall survival, para-aortic lymph node positivity and 90th percentile ADC < 1.917 were significant factors associated with worse survival, and FIGO clinical stage III-IV was borderline significant ($P = 0.06$) (Table 2). In the best multivariate model, para-aortic lymph node positivity ($P = 0.051$) and 90th percentile ADC with a cut-off of 1.917 ($P = 0.054$) were borderline significantly associated with overall survival (Table 2).

In univariate analysis for progression-free survival, FIGO stage III–IV, para-aortic lymph node positivity and 90th percentile ADC < 1.917 were significant factors associated with worse PFS (Table 3). In the best multivariate model, 90th percentile ADC < 1.917 was the only significantly associated factor with worse PFS. Patients with lower 90th percentile ADC (<1.917, compared with ≥1.917) had a worse progression-free survival (HR 2.55, 95% CI 1.18–5.49, $P = 0.017$).

In univariate analysis for distant metastasis free survival, lymph node positivity, para-aortic lymph node positivity and 90th percentile ADC < 1.917 were significantly associated with worse DMFS (Table 4). In the best multivariate model, lymph node positivity and 90th percentile ADC < 1.917 were associated with DMFS (Table 4). Patients with lower 90th percentile ADC (<1.917, compared with ≥1.917) had worse DMFS (HR 3.57, 95% CI 1.20–10.63, $P = 0.02$) as did patients with positive lymph nodes (HR 3.03, 95% CI 1.00–9.18, $P = 0.05$).

There were no significant associations found between age, tumor histology, differentiation, and baseline PET SUV maximum value and OS, PFS, or DMFS on univariate or multivariate analysis. There were no significant associations found between ADC, or any other factor, and locoregional recurrence.

Table 2
Univariate/multivariate Cox regression analysis of factors associated with mortality.

	Univariate			Multivariate		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
ADC 90th percentile						
<1.917	2.72	1.01–7.35	**0.048**	2.69	0.98–7.34	0.054
≥1.917	1.00	–	–	1.00	–	–
MRI volume	1.00	0.996–1.004	0.84			
PET SUV max (baseline)	0.99	0.93–1.05	0.72			
Age						
<50	1.00	–	–			
≥50	0.74	0.32–1.70	0.48			
Histology						
Squamous	1.00	–	–			
Adenocarcinoma/Other	0.80	0.32–2.05	0.65			
FIGO Stage						
I	1.00	–	–			
II	0.98	0.31–3.11	0.97			
III–IV	2.77	0.96–8.01	0.06			
Tumor differentiation						
Well-moderate	1.00	–	–			
Poor	1.15	0.46–2.84	0.77			
Lymph Node Positive						
No	1.00	–	–			
Yes	1.74	0.68–4.41	0.25			
Lymph Node Type						
No lymph nodes	1.00	–	–	1.00	–	–
Pelvic	1.44	0.54–3.83	0.47	1.20	0.45–3.23	0.72
Para-aortic	3.58	1.08–11.82	**0.037**	3.29	0.99–10.89	0.051

Bold values indicates statistically significant with $P < 0.05$.

Table 3
Univariate/multivariate Cox regression analysis of factors associated with progression free survival.

	Univariate			Multivariate		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
ADC 90th percentile						
<1.917	2.83	1.34–5.98	**0.007**	2.55	1.18–5.49	**0.017**
≥1.917	1.00	–	-	1.00	–	–
MRI volume	1.00	0.998–1.003	0.96			
PET SUV max (baseline)	1.02	0.97–1.06	0.45			
Age						
<50	1.00	–	–			
≥50	0.84	0.44–1.58	0.58			
Histology						
Squamous	1.00	–	–			
Adenocarcinoma/Other	0.62	0.28–1.35	0.23			
FIGO Stage						
I	1.00	–	–	1.00	–	–
II	1.12	0.47–2.67	0.79	0.93	0.39–2.23	0.87
III–IV	2.55	1.13–5.73	**0.02**	1.98	0.86–4.54	0.11
Tumor differentiation						
Well-moderate	1.00	–	–			
Poor	1.59	0.76–3.32	0.22			
Lymph Node Positive						
No	1.00	–	–			
Yes	1.26	0.64–2.51	0.50			
Lymph Node Type						
No lymph nodes	1.00	–	–			
Pelvic	1.04	0.51–2.15	0.91			
Para-aortic	2.94	1.15–7.49	**0.024**			

Bold values indicates statistically significant with $P < 0.05$.

Clinical and ADC threshold analysis

OS, PFS, and DMFS were significantly different between patient groups with 90th percentile ADC < 1.917, compared with ≥1.917 on log rank analysis ($P = 0.039$, $P = 0.004$, $P = 0.007$, respectively) (Fig. 1). OS, PFS, and DMFS were also significantly different between patient groups divided based on 90th percentile ADC with a threshold of 1.917 and MRI volume with a threshold of 18.9 cm^3 ($P = 0.037$, $P = 0.0002$, $P = 0.001$, respectively) (Fig. 2). The group with low MRI volume and high ADC had the best clinical outcomes and the group with high volume and low ADC had the worse clinical outcomes.

Discussion

Our results show that the volumetric 90th percentile ADC of the primary tumor on pretreatment MRI was a significant predictor of

Table 4
Univariate/multivariate Cox regression analysis of factors associated with distant metastasis free survival.

	Univariate			Multivariate		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
ADC 90th percentile						
<1.917	3.98	1.35–11.77	**0.01**	3.57	1.20–10.63	**0.02**
≥1.917	1	–	–	1	–	–
MRI volume	0.99	0.995–1.004	0.76			
PET SUV max (baseline)	1.04	0.99–1.09	0.12	1.05	0.998–1.10	0.059
Age						
<50	1	–	–			
≥50	0.59	0.25–1.38	0.22			
Histology						
Squamous	1	–	–			
Adenocarcinoma/Other	0.34	0.10–1.16	0.08			
FIGO Stage						
I	1	–	–			
II	1.19	0.39–3.63	0.77			
III–IV	2.22	0.74–6.64	0.15			
Tumor differentiation						
Well-moderate	1	–	–			
Poor	1.21	0.48–3.06	0.68			
Lymph Node Positive						
No	1	–	–	1	–	–
Yes	3.16	1.07–9.35	**0.04**	3.03	1.00–9.18	**0.05**
Lymph Node Type						
No lymph nodes	1	–	–			
Pelvic	2.78	0.91–8.45	0.07			
Para-aortic	6.28	1.55–25.41	**0.01**			

Bold values indicates statistically significant with $P < 0.05$.

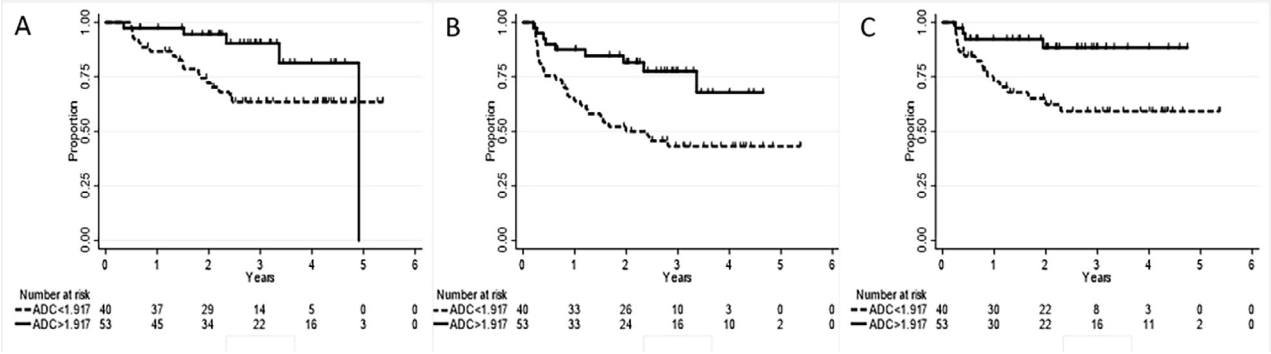

Fig. 1. Overall survival (A), progression-free survival (B), and distant metastasis free survival (C) were significantly different between patient groups with 90th percentile ADC < 1.917, compared with ≥1.917 on log rank analysis ($P = 0.039$, $P = 0.004$, $P = 0.007$, respectively).

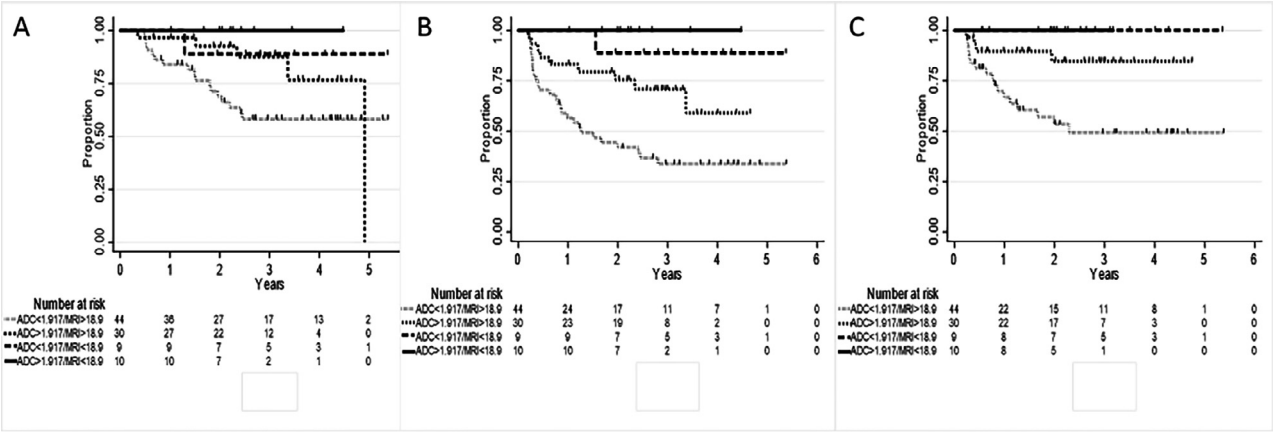

Fig. 2. Overall survival (A), progression-free survival (B), and distant metastasis free survival (C) were significantly different between 4 patient groups divided based on 90th percentile ADC with a threshold of 1.917 and MRI volume with a threshold of 18.9 ($P = 0.037$, $P = 0.0002$, $P = 0.001$, respectively).

progression-free survival and distant-metastasis free survival in cervical cancer patients, independent of established clinical factors and SUV on FDG-PET. We identified a 90th percentile ADC threshold of $<1.917 \times 10^{-3}$ mm^2/s that, either alone or in combination with an MRI volume threshold of >18.9 cm^3 distinguishes patients with significantly worse clinical outcomes including overall survival, progression-free survival, and distant metastasis free survival.

While baseline diffusion-weighted imaging and association with outcomes has been studied in cervical cancer patients, previous studies have reported on different ADC parameters with conflicting conclusions on whether lower pretreatment ADC portends a better or worse outcome [11–19]. The mixed results in the literature may be due to limitations in ADC evaluation methods. Of note, several studies only used single or limited axial slice ROIs to quantify ADC, which has previously been shown to have significantly less interobserver reproducibility than volumetric analysis in other solid malignancies [23–25]. Several studies have previously shown that early change in ADC during chemoradiation is associated with clinical response [16,17,26,27]. However, there have only been a few studies in cervical cancer that have examined the prognostic value of pretreatment ADC in survival and disease recurrence [13,15,18,28]. Nakamura et al and Himoto et al demonstrated that lower baseline ADC mean was associated with disease recurrence in patients treated with primarily radical hysterectomy [13,28]. In another study, Nakamura et al found that in 69 patients treated with radiation with or without chemotherapy, lower pretreatment and posttreatment ADC mean extracted from 2D ROIs were associated with worse DFS and OS on univariate analysis, and posttreatment ADC mean associated with worse DFS and OS on multivariate analysis [15]. Gladwish et al [11] examined 85 locally advanced cervical cancer patients treated with definitive chemoradiation and found that lower baseline 95 percentile ADC was associated with worse disease-free survival. However, this study did not include baseline PET parameters or MRI tumor volume, both of which were included in our study.

Additionally, in our study, we used random forest variable importance measures to identify clinical factors and volumetric DWI parameters that would add to existing clinical models of disease prognosis. Through our analysis, we identified that ADC and MRI volume were more highly ranked variables in terms of association with clinical outcomes than even other known important clinical factors including stage, histology, and lymph node status. We found pretreatment ADC to be the most significant predictor of progression-free survival on multivariate analysis, more significant than stage or any other clinical factors including histology or lymph node involvement. Moreover, we identified ADC and MRI volume threshold cut-offs that divided patients into groups with significantly different OS, PFS, and DMFS. Eventually, the goal would be to incorporate DWI into predictive models for identifying cervical cancer patients who have more aggressive tumors and may benefit from treatment escalation. In order to do so, we attempted in our study to identify threshold ADC and MRI volume cut-offs that can be used as a starting point for validation in future studies.

In this study, we did not find any significant association with baseline tumor maximum SUV on PET scan and clinical outcomes. In other studies, total metabolic tumor volume and total lesion glycolysis have been associated with more advanced disease at diagnosis, as well as increased risk of recurrence [29–32]. Higher tumor avidity on PET has been reported to correlate with survival in some studies, whereas others have demonstrated no correlation of baseline SUV and disease recurrence [31,33–37]. Volumetric quantification of SUV may be a more robust prognostic factor, which we did not assess in this study.

Our study also has limitations, including its retrospective design and relatively limited patient size. The optimal threshold values of baseline ADC and MRI volume in predicting outcome may need to be further refined in a larger group of patients. Additionally, we did not have mid- or posttreatment DWI MRI scans available and therefore could not report on the significance of the change in ADC or of posttreatment ADC.

In conclusion, the volumetric 90th percentile ADC value of the primary tumor on pretreatment MRI was a significant predictor of progression free and distant metastasis free survival in cervical cancer patients, independent of established clinical factors and SUV on FDG-PET, and seems to be a useful biomarker that should be further studied and confirmed in future prospective studies.

Author contributions

Study concept: J.C.H, P.F., C.E.C, A.S.R.M., C.D.F, A.H.K. Data collection and analysis: J.C.H., P.F., C.E.C, A.S.R.M, C.D.F, P.R.B, P.K.A, A.H.K. Manuscript writing: J.C.H, P.F., C.E.C, A.S.R.M, P.R.B, M.M.F., A.J, A.H.K

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