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Research article

Evaluation of various apparent diffusion coefficient measurement techniques in pre-operative staging of early cervical carcinoma

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A R T I C L E I N F O

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A B S T R A C T

Purpose: DW-MRI parameters such as ADC hold the potential for more reliable staging of cervical cancer. We compared 2D region of interest (ROI) measurement techniques to 3D tumor analysis in the evaluation of ADC for cervical cancer. Secondly, we evaluated the utility of ADC for assessing parametrial and/or lymph node involvement.
Method: This prospective patient cohort registered cervical cancer patients who underwent pre-operative MRI with T1, T2W, and axial DWI. Retrospectively, two observers independently and blindly scored mean, minimum, and maximum ADC using three methods: a) 3D-Tumor analysis, b) single freehand ROI (2D-Slice), and c) single circular ROI (2D-Circle). Another observer scored parametrial and lymph node involvement on T1/T2W sequences. Parametrial and/or lymph node involvement were determined by surgical-pathologic results. The diagnostic performance of ADC for predicting the latter was evaluated by ROC curve, uni and multivariate analyses.
Results: Of 58 included patients, parametrial and/or lymph node involvement was found in 9 and 11 patients, respectively. Mean ADC (ADC_{Mean}) was least dependent on ROI technique, with interobserver variability (ICC: 0.88–0.90) and linear correlation (Pearson's *r*: 0.95–0.96). To the contrary, minimal and maximal ADC were significantly influenced by 2D-ROI techniques. ADC_{Mean} was shown to be an independent predictor of parametrial (AUC: 0.80–0.86; OR: 16, 1.4–178) and/or lymph node involvement (AUC: 0.74–0.79; OR: 5.1, 1.1–24).
Conclusions: Single ROI measurements are a reliable method for determining ADC_{Mean} in cervical cancer. Second, ADC_{Mean} serves as a potential parameter for prediction of parametrial involvement prior to radical hysterectomy.

1. Introduction

Cervical carcinoma of stage Ib1-IIA on the 2014 International Federation of Gynaecology and Obstetrics (FIGO) staging system is generally treated by radical hysterectomy combined with pelvic lymphadenectomy. [1] However, approximately 20% of parametrial involvement (FIGO stage ≥ IIB) or lymph node metastases are missed at the clinical staging [2,3]. As a consequence, these patients may need additional chemo-radiation treatment after surgery, resulting in further complications and higher costs [4]. Recently, the European Society of Gynaecologic Oncology (ESGO) incorporated pelvic T2W-MRI as a mandatory workup tool for cervical cancer staging [5]; however, the role of DWI sequences for pre-operative staging is not clear [6,7]. Studies assessing T2W-MRI parameters for parametrial involvement, found a high negative but a rather low positive predictive value [7–10]. DWI studies on cervical cancer have focused on evaluating the ADC parameter that quantifies diffusion restriction [11]. Low mean ADC (ADC_{Mean}) values are associated with an increased incidence of parametrial invasion. [12,13] Although assessments of other risk factors for disease recurrence such as lymph node metastases may be conflicting [13,14], ADC_{Mean} values were associated with survival and risk of recurrence in three retrospective studies. [13,15,16]

The optimization of ADC measurements is of great importance. [12,13] In most studies, ADC is measured from the slice with the largest tumor diameter, using either a single circle-like Region of Interest (ROI), [12,17] multiple small circle-like ROIs [13], or a single freehand

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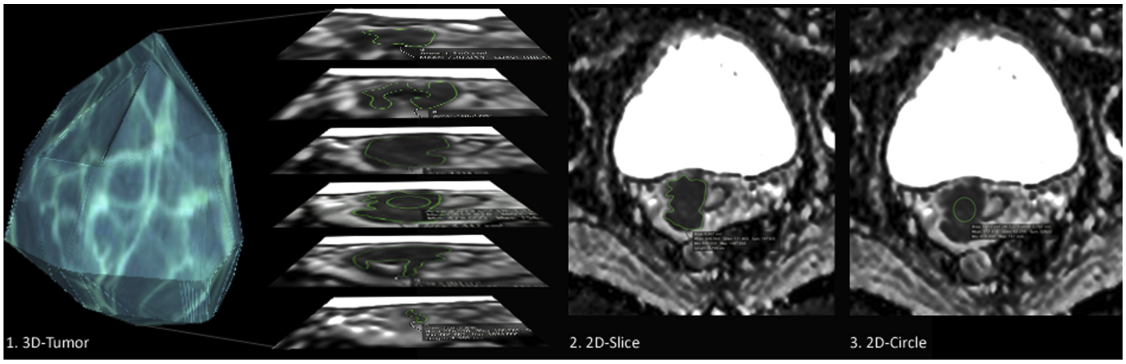

Fig. 1. ADC measurement techniques for cervical cancer.

ROI containing all visible tumor on that slice [16]. In addition to two-dimensional (2D) methods, a three-dimensional (3D) method has been used, in which a freehand ROI containing all visible tumor is drawn on all subsequent slices. It has been hypothesized that 3D analysis is superior to 2D methods, with a reduction in variability due to the absence of having to select the appropriate 2D-ROI, especially in heterogenic tumors [18,19]. However, research in other tumor types has revealed conflicting results regarding observer variability with usage of different ROI techniques [20–23]. To date, it remains unclear whether 3D-ROI are superior to 2D-ROI in the evaluation of cervical cancer, and as 3D-ROIs are more time consuming, a single representative 2D-ROI may be preferable in clinical practice [19].

Besides the variation in ROI techniques, DWI evaluation was performed by a single observer in most cervical cancer studies, [12,13,16–19] and a variety of ADC parameters (ADC_{Mean}, minimum ADC_{Min}, and maximum ADC_{Max}) have been assessed. The clinical value of ADC_{Min}, ADC_{Max} and whether these ADC parameters are reproducible and sufficiently stable to support their use in clinical practice remains to be determined. [13]

The primary aim of this study was to compare three ADC measurement techniques: a) 3D whole tumor analysis (3D-Tumor), b) a 2D single ROI at the largest diameter (2D-Slice), and c) a 2D single circular ROI at the largest diameter (2D-Circle). Secondly, we aimed to evaluate the predictive value of the ADC parameters for parametrial and/or lymph node involvement.

2. Methods and materials

2.1. Patients

This cohort study performed between April 2011 and July 2016 prospectively registered patients diagnosed with histologically proven primary cervical cancer and eligible for radical hysterectomy with pelvic lymphadenectomy. The diagnostic workup of patients consisted of a gynaecological examination, chest X-ray, and MRI of the pelvis. As our centre expected to have a new 3 T MRI and 3 T PET-MRI scanner installed in the near future, the study design accounted for changes in scan protocols by allowing state of the art MRI with updated protocols. All patients were discussed by a multi-disciplinary team consisting of a nuclear physician, radiologist, pathologist, gynaecologic oncologists, medical oncologist, and radiation oncologist. Patients with a history of previous treatment (e.g., radiation and/or chemotherapy) and/or failure to visualize the cervical cancer on T2 and/or DWI were excluded from this study. Ethical approval for the study was given and the requirement for informed consent for the use of (coded) images was waived by the local ethical committee as the data were retrospectively analysed anonymously in accordance with the Institutional Review Board guidelines (IRB:16-4-023).

2.2. MRI

MRI was performed within 8 weeks prior to surgery. The majority of the MRI examinations (n = 33, 57%) were performed on a 1.5 T MRI unit with a phased array surface coil. Patients were placed in a feet-first supine position. The imaging protocol consisted of standard 2D T2W fast spin echo images in three orthogonal directions. The axial and coronal images were angled perpendicular and parallel to the cervical axis, respectively. The remaining MR examinations (n = 25, 43%) were performed on a 3 T MRI unit using a similar T2W protocol. A single-shot echo planar protocol was used for the axial DWI, with b-values of 0 and 1000s/mm^2 (b-values of 0 and 800 s/mm^2 were used in four patients), and ADC maps were automatically generated. In all patients, additional T1W sequences were acquired to facilitate the assessment of pelvic lymph nodes. Patients received neither bowel preparation nor anti-spasmodic agents during the MRI examinations. (Appendix, scan protocol.) All examinations were made on an Intera Achieve; Philips Medical Systems, Best, The Netherlands; or Siemens Magnetom Avanto / Biograph mMR PET-MR, Siemens Healthineers, Erlangen, Germany.

The MR images were retrospectively independently analysed by two experienced observers (CM 8 and JEM 4 years of experience) who were blinded to the patient information and outcomes. Both observers measured ADC_{Mean}, ADC_{Min} and ADC_{Max} values within ROIs created using the following three methods (Fig. 1):

a) (3D-Tumor) by placing freehand ROIs along the border of the suspected tumor (diffusion restricted area) on all slices of the axial ADC maps;
b) (2D-Slice) by placing one freehand ROI incorporating all visible tumor at the suspected largest tumor diameter on the axial ADC maps;
c) (2D-Circle) by placing a circular ROI with a surface area of 1 cm^2 at the suspected largest tumor diameter, or in the case of a smaller tumor, an ROI as large as possible.

No cystic or necrotic tumor areas were included in the ROIs. All measurements were scored with morphological confirmation of the location of the tumor on axial, coronal, and sagittal T2W images, as well as DWI sequences. The maximum diameter of the cervical tumor was measured on the axial and coronal T2W images. The 3D-Tumor ADC measurements were assessed in consensus by both reviewers as they were used as a reference standard. A third observer (FB, 12 years of experience) scored the likelihood of parametrial involvement on T2W images and lymph node metastases on T2W and T1W images. The imaging criteria for the assessment of parametrial involvement are shown in the Appendix. This observer was blinded to the DWI, ADC, and clinical outcomes. Measurements were performed on a dedicated Osirix v5.9 DICOM system (Pixmeo SARL, Bernex Geneva, Switzerland).

2.3. Reference standard, data management and statistical analysis

The reference standard was histological results obtained by the pathologist. Baseline characteristics are described as mean ± SD, or median (IQR) for non-normally distributed parameters. Proportions (%) are used for categorical values. The mean values of the ADC measurement methods were compared with a paired sample *t*-test, and correlations were assessed with Pearson's correlation coefficient.

For all analyses, the results of observer 1 (CM; experienced abdominal radiologist) were used. Interobserver variability was quantified with the intraclass correlation coefficient (ICC). ROC curves were constructed to determine the corresponding AUCs for ADC_{Mean} values obtained from the ADC measurement methods (3D-Tumor, 2D-Slice, and 2D-Circle), and for determination of parametrial and/or lymph node involvement. The AUCs were compared according to the method described by De Long et al. [24] The optimal ADC cut-off value was determined according to the point nearest to the upper left corner in the ROC curve. Univariable and multivariable logistic regression analyses were performed to calculate odds ratios (OR) for the use of ADC for predicting parametrial and lymph node involvement. Regression analysis was performed to determine the association between ADC measurements, tumor diameter on MRI, and subjective MRI analysis of parametrial invasion and lymph node metastases.

Statistical analyses were performed using SPSS Statistics v20.0 (IBM SPSS Inc., Chicago, Ill) and Stata v11.0 (StataCorp LP, Texas). P-values less than 0.05 were considered statistically significant.

3. Results

3.1. Patients

Seventy-two consecutive patients were eligible for this study. Fourteen patients were excluded from the cohort because of claustrophobia or pacemaker (n = 2, no MRI), insufficient MRI image quality (n = 4, artefacts, no reliable ADC map), lack of DWI sequences (n = 4, MRI performed in referral centre), or failure to visualize cancer on the MRI (n = 4). A final total of 58 patients were included in this cohort study (Fig. 2, Flowchart). Baseline characteristics of the patients are listed in Table 1.

After surgery, histologic examination identified parametrial involvement in 9 patients (7 patients with parametrial invasion and 2 with pathologic parametrial lymph nodes) and pelvic lymph node metastases in 11 patients. In one patient, the surgical procedure was discontinued because of bulky histologically-positive lymph nodes and obvious parametrial involvement, and the patient was therefore included as positive for parametrial involvement.

Table 1
Baseline characteristics (n: 58).

Age years (range)	47	(27–82)
FIGO stage (clinical)*	IA2	1 (2%)
	IB1	49 (84%)
	IB2	5 (9%)
	IIA	2 (3%)
	IIB	1 (2%)
Pathology		
Tumor subtype	SCC	45 (78%)
	ADC	9 (15%)
	ASC	3 (5%)
	CCC	1 (2%)
Parametrial involvement	9	(15%)
Lymph node metastases	11	(18%)
Time from scan to operation weeks (range)	2.7	(0–8)

All variables are described as mean ± SD or median (IQR) for non-normally distributed parameters. Proportions (%) were used for categorical values. *FIGO 2014 classification, SCC: squamous cell carcinoma; ADC: adenocarcinoma; ASC: adenosquamous carcinoma; CCC: clear-cell carcinoma.

3.2. ADC measurement techniques

The ADC_{Mean} values differed significantly between all three ROI methods ($p < 0.01$). Despite absolute differences, the Pearson's correlation coefficients showed near perfect correlations between all three ROI methods for the ADC_{Mean} values (Table 2). The regression analysis indicates a linear relationship for ADC_{Mean}, with a regression coefficient of 0.92 between 3D-Tumor and 2D-Circle measurements (Fig. 3). The 2D-Tumor techniques for ADC_{Min} and ADC_{Max} showed only moderate and poor correlations, respectively, with 3D-Tumor (Table 2). Interobserver variability (Table 2) was excellent for ADC_{Mean} and average to good for ADC_{Min} and ADC_{Max} (ICCs = 0.88–0.90, 0.67–0.70, and 0.63–0.75, respectively). Additional analyses showed no significant differences in ADC_{Mean} between the 1.5 and 3 T groups ($p = 0.18$).

3.3. ADC as a predictor of parametrial involvement or lymph node metastasis in cervical cancer

The ADC_{Mean} parameter showed the highest potential (highest AUCs), which was combined with the lowest interobserver variability (Table 2), and this parameter was therefore evaluated in the univariable

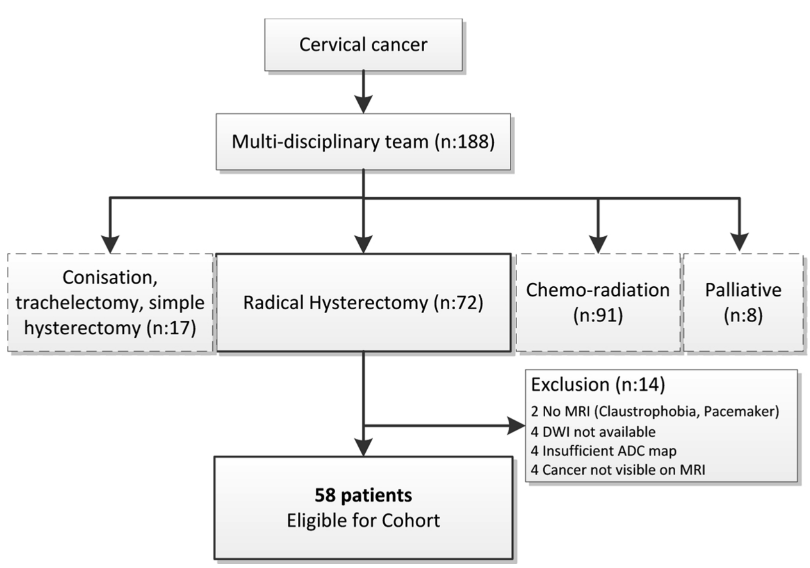

Fig. 2. Flowchart.

Table 2
ADC_{Mean}, ADC_{Min}, and ADC_{Max} values for all three measurement techniques. Interobserver variability (ICC) and Pearson's correlation coefficient (r) between 3D-Tumor and 2D ROI techniques.

	3D-Tumor mean (SD)	2D-Slice mean (SD)	2D-Circle mean (SD)		2D-Slice ICC	2D-Circle ICC	2D-Slice r	2D-Circle r
ADC_{Mean}	1.05 (0.21)	1.02 (0.23)*	0.98 (0.23)*	3D-Tumor ADC_{Mean}	0.90^	0.88^	0.95^	0.96^
ADC_{Min}	0.64 (0.24)	0.67 (0.25)*	0.73 (0.23)*	3D-Tumor ADC_{Min}	0.67^	0.70^	0.60^	0.54^
ADC_{Max}	1.64 (0.25)	1.44 (0.26)*	1.24 (0.28)*	3D-Tumor ADC_{Max}	0.63^	0.75^	0.53^	0.23

*$p < 0.01$ compared with 3D-Tumor ADC. ^$p < 0.01$. SD: standard deviation; ICC: interclass correlation coefficient, r: Pearson's correlation coefficient.

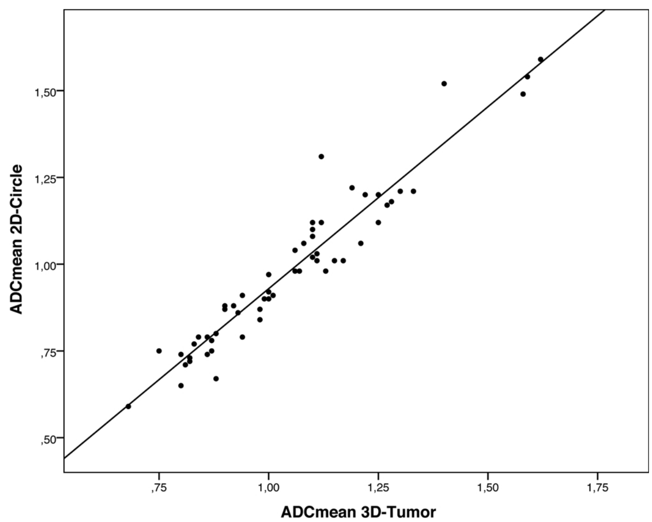

Fig. 3. Scatterplot of ADC_{Mean} values from 3D-Tumor and 2D-Circle ROIs, including regression analysis.

and multivariable analyses. For ADC_{Mean}, comparable results were found for all ROI techniques. The AUCs of ADC_{Mean}, ADC_{Min}, and ADC_{Max} for predicting parametrial involvement, lymph node metastasis, and the combination of parametrial or lymph node involvement are shown in Table 3.

The univariable analyses showed subjective assessment of the parametrium on T2W-MRI to be a significant risk factor for parametrial involvement (Table 4). The univariable and multivariable analyses showed 3D-Tumor ADC_{Mean} to be a independent predictor of parametrial involvement compared to tumor diameter and subjective assessment of the parametrium on T2W-MRI (OR:16, 1.4–178); Table 4). For either parametrial or lymph node metastasis the ORs of an ADC_{Mean} value < 0.94 was also statistically significant (OR 5.1, 1.1–24; $p < 0.05$; Table 5).

4. Discussion

Our results support the use of a 2D-ROI drawn at the slice of the largest tumor diameter for the measurement of ADC_{Mean}. Moreover, our results suggest ADC_{Mean} as an independent predictor for parametrial involvement and/or lymph node metastases in early stage cervical carcinoma.

Of the three ADC parameters evaluated, the ADC_{Mean} value showed the lowest interobserver variability. As the linear associations between 3D and 2D techniques were high; the 2D measurements were able to represent whole tumor ADC_{Mean}. To allow for comparisons between studies using different ROI techniques, correction factors to adjust for the linear correlation should be used, which should help justify the use of the less time-consuming options.

For ADC_{Min} and ADC_{Max}, the differences between the ROI techniques were significant, without a strong linear agreement. Therefore, these parameters should be interpreted with caution. The discrepancies between the techniques could be explained by single ADC hotspots within the tumor, which were shown by 3D-tumor analysis but missed in the single ROI methods. An alternative method to potentially overcome this problem is histogram analysis to further characterize the diffusion properties of cervical cancer. Moreover, with the exclusion of outlying values, more reliable and reproducible measurements should be obtainable. [18] While histogram analysis is an evolving method for analysing DWI, 3D delineation of the whole tumor, as performed in a limited number of studies, remains time consuming [25–27].

In our study, 3D-tumor analyses were performed by two readers in consensus because interobserver variability was suggested to be the biggest source of error concerning ADC measurements in other cancer types. Gladwish et al. evaluated ADC prior to radiation treatment and found a difference of 10% between 2D and 3D techniques, with good interobserver variability. [28] The size of a circle-like ROI is important in this respect [29], with breast and rectal carcinoma studies suggesting that a small ROI contributes to greater variability in ADC in comparison with a freehand ROI delineating as much as possible of the visible tumor. [19,22,30]

To date, the correlation between lymph node metastases and ADC_{Mean} shows a substantial variety in different retrospective studies [14]; however, the majority of studies found a correlation [13,16]. The correlation of ADC_{Mean} is stronger and more uniform for parametrial involvement albeit in retrospective trials [13]; another research group showed that a combination of ADC_{Mean} and subjective analysis of the parametrium on T2W-MRI increased AUC for predicting parametrial invasion. They used circle-like ROIs and recognized this to be a potential limitation of their retrospective study. In addition to this they did not assess interobserver variability. [12] The relatively large proportion of IIB carcinoma in most studies hampers extrapolation to clinical practice, as these patients are generally treated with chemoradiation therapy. Moreover, this patient selection could have increased the sensitivity of the test, whereas in our opinion, ADC would be of particular additional value in patients without clear parametrial invasion on T2W-MRI and/or clinical examination. Woo et al. recently questioned the additional value of ADC_{Mean} for the assessment of

Table 3
AUC values for ADC_{Mean}, ADC_{Max}, and ADC_{Min} for predicting parametrial, lymph node, and the combination of parametrial and lymph node metastasis.

ROI Technique	ADC	Cut-off$^{\times 10^{-3}}$ mm/s	AUC (SD)	Parametrial Involvement (n = 9)	Lymph Node Involvement (n = 11)	Parametrial or Lymph Node Involvement (n = 14)
3D-Tumor	ADC_{Mean}	0.94		0.81 (0.70–0.92) *	0.67 (0.51–0.82)	0.74 (0.60–0.88) *
	ADC_{Max}	1.55		0.52 (0.30–0.74)	0.63 (0.47–0.80)	0.59 (0.41–0.77)
	ADC_{Min}	0.57		0.82 (0.71–0.94) *	0.60 (0.40–0.80)	0.72 (0.57–0.87) **
2D-Slice	ADC_{Mean}	0.89		0.80 (0.79–0.91) *	0.68 (0.52–0.83)	0.74 (0.60–0.87) *
2D-Circle	ADC_{Mean}	0.88		0.86 (0.76–0.95) *	0.72 (0.57–0.87) **	0.79 (0.67–0.92) *

*$p < 0.01$. **$p < 0.05$.

Table 4
Uni- and multivariate analysis: 3D-Tumor ADC_{Mean} as an independent parameter for predicting parametrial involvement.

	AUC (SD)	Odds ratio (univariate)	Odds ratio (multivariate)^
$ADC_{Mean} < 0.94 \times 10^{-3}$ mm/s	0.81 (0.70–0.92)*	18.1 (2.1–158)*	16.0 (1.4–178)**
FIGO stage < 1B	0.47 (0.26–0.68)	0.35 (0.03–4.3)	–
PA type (SCC vs. other)	0.57 (0.36–0.79)	2.0 (0.4–9.1)	–
DM tumor T2W-MRI	0.68 (0.50–0.85)	1.4 (0.8–2.4)	0.8 (0.3–1.8)
Suspicion of PMI on T2W-MRI	0.77 (0.60–0.93)	1.8 (1.1–2.9)*	1.6 (0.9–2.7)

*$p < 0.01$. **$p < 0.05$, ^Multivariate corrected for other MRI parameters: suspicion of parametrial invasion and DM tumor, SCC: squamous cell carcinoma, PA: pathology, DM: diameter, PMI: parametrial invasion.

Table 5
Uni- and multivariate analysis: 3D-Tumor ADC_{Mean} as an independent parameter for parametrial or lymph node involvement.

	AUC (SD)	Odds ratio (univariate)	Odds ratio (multivariate)^
$ADC_{MeanTotal} < 0.94 \times 10^{-3}$ mm/s	0.74 (0.60–0.88)*	6.0 (1.6–22)*	5.1 (1.1–24)**
FIGO stage < 1B	0.49 (0.31–0.66)	0.6 (0.1–7.4)	–
PA type (PCC vs. other)	0.59 (0.41–0.77)	2.5 (0.7–9.5)	–
DM tumor MRI	0.62 (0.47–0.77)	1.3 (0.8–2.1)	1.0 (0.5–1.9)
Suspicion of PMI T2W-MRI	0.74 (0.59–0.88)*	2.4 (1.3–4.3)*	1.5 (0.9–2.4)
Suspicion of lymph node MRI	0.47 (0.30–0.64)	0.9 (0.5–1.5)	0.7 (0.4–1.3)

*$p < 0.01$. **$p < 0.05$. ^Multivariate corrected for other MRI parameters: suspicion of parametrial invasion, lymph node metastases, and DM, SCC: squamous cell carcinoma, PA: pathology, DM: diameter, PMI: parametrial invasion.

parametrial invasion when it was used as an adjunct to subjective T2W-MRI of the parametrium. However, because of the retrospective nature of their study, it might not have had sufficient power to justify subgroup analysis. [31] They hypothesized that the correlation between ADC_{Mean} and parametrial invasion was predominantly caused by MRI invisible tumors. We recognise that this might have influenced ADC_{Mean} and therefore excluded MRI invisible tumors prior to analysis.

Our study has some limitations. DWI was performed on both 1.5 and 3 T. Theoretically, major differences in ADC caused by differences in field strength are not expected. Ex vivo phantom models have indicated some small differences; however, in vivo literature indicates no significant differences in the ADC values of cervical cancer nor abdominal organs between 1.5 and 3 T. [32] Our analyses showed no significant differences in ADC_{Mean} between the 1.5 and 3 T groups, as supported by other research groups. [31] Moreover, our study represents common general practice, where introduction of more advanced techniques and scanners is inevitable. Second, due to the introduction of new scanning protocols, imaging parameters varied to some extent. Current recommendations for DWI to optimize signal-to-noise ratio and decrease artefacts were followed. [33] The changes in our protocol and the possible subsequent effect on ADC values were previously evaluated by other research groups [34–36]. These protocol changes had a small effect on the ADC value comparable with ADC variability as seen between vendors and single-system day-day repeatability (2,3–6,3%) [35]. However, as we assessed ROI measurement techniques within the same patient and protocol, it is implausible that these differences have affected these results. For the clinical data, the differences in field strength, scan protocol and B-value could have had some effect on the ADC values. However, these differences most likely have not have hampered our interpretation of the results. As there is little existing evidence for an optimal cut-off value, a predefined cut-off value was not defined prior to analysis of the dataset. However, for circle-like ROIs, the cut-off values mentioned in all prior studies are comparable with our suggested cut-off: $0.85–0.90 \times 10^{-3}$ mm/s. For values within this band of suggested cut-offs, the effects on the results of this study are negligible.

5. Conclusion

This study shows that ADC_{Mean} is an independent predictor of parametrial involvement. Single ROI measurements are a reliable method for determining ADC_{Mean} in cervical cancer. Combining ADC_{Mean} with T2W-MRI and clinical risk factors could result in more reliable pre-treatment staging, less adjuvant treatments, and therefore reduced patient burden and cost.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.06.021.

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