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Title

Pretreatment Mean Apparent Diffusion Coefficient is Significantly Correlated with Event-free Survival in Patients with FIGO Stages Ib to IIb Cervical Cancer

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Abstract

Objectives: To assess the prognostic impact of the pretreatment mean apparent diffusion coefficient (ADC_{mean}) values of tumors obtained by diffusion-weighted magnetic resonance imaging (MRI). We evaluated the prognostic value of the ADC_{mean} for event-free survival (EFS) and overall survival (OS) among patients with uterine cervical cancer.

Methods/Materials: We included 171 patients diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage Ib–IIIb cervical cancer by pretreatment MRI scans, regardless of therapeutic methods. In all patients, and in patients with squamous cell carcinoma (SCC, $n = 123$), the optimal cutoff values of the tumor ADC_{mean} for EFS and for OS were determined, respectively. The prognostic significance of the ADC_{mean} was evaluated using univariate and multivariate Cox regression analyses.

Results: In the univariate analyses, the ADC_{mean} values were significantly associated with negative effects on EFS both in all patients and in patients with SCC, while not being significantly associated with OS in both groups. In the multivariate analysis, ADC_{mean} was an independent biomarker for EFS ($P < 0.05$) in patients with SCC along with lymph node metastasis and definitive surgery, whereas ADC_{mean} was not independently significant in EFS in all patients.

Conclusions: The pretreatment ADC_{mean} value of the tumor was an independent prognostic factor for EFS in FIGO stage Ib to III squamous cell carcinoma of the uterine cervix.

Introduction

Uterine cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide ⁽¹⁾. The most common histopathology subtypes are squamous cell carcinoma (SCC) and adenocarcinoma, accounting for 75% and 20%, respectively ⁽²⁾. Poor prognostic factors for cervical cancers include the International Federation of Gynecology and Obstetrics (FIGO) stage, lymph node metastasis, histopathology subtypes of the disease ⁽²⁻⁴⁾, parametrial invasion ⁽⁵⁾, and tumor diameter ⁽⁶⁾.

Magnetic resonance imaging (MRI) is now considered important for the precise pretreatment evaluation of cervical cancer: for example, the tumor size, its location, parametrial invasion and any lymph node metastasis ⁽⁷⁾. Moreover, recent advances in MRI techniques enable measurements of quantitative parameters, which reflect more than morphology ^(7, 8). The apparent diffusion coefficient (ADC) value obtained from a series of diffusion-weighted images (DWI) is one of these parameters attracting increasing attention in oncology ^(7, 9). The ADC is considered to reflect the diffusivity of protons in the tissue of interest ⁽⁹⁾. Though controversial, ADC values are thought to be inversely correlated with tumor cellularity and with the aggressiveness of the tumor ⁽⁹⁾. Several studies have shown that the ADC value of a tumor serves as a predictive biomarker for treatment response and for clinical prognosis in different types of cancers ⁽¹⁰⁻¹⁴⁾. For cervical cancer, Nakamura et al. showed that the pretreatment mean ADC value (ADC_{mean}) was an independent biomarker for predicting disease recurrence in patients with FIGO stage Ib1 to IIb cervical tumors treated by primary radical surgery ⁽¹⁵⁾. However, to the best of our knowledge, there have been no reports about the predictive value of ADC including patients with stage III tumors, regardless of treatment selections.

The aim of the study was to evaluate the prognostic importance of ADC values in patients with FIGO stage Ib1 to IIIb cervical cancer, given any type of treatment, in comparison with other known prognostic factors. Since the propensity of adenocarcinoma to have a higher ADC than SCC is known⁽¹⁶⁾, we also assessed the ADC values exclusively in patients with SCC.

Materials and Methods

Patient selection

Ethics approval for this retrospective study was granted by our institutional review board in June, 2013, and the need for informed consent was waived. Between January 2006 and December 2012, 220 patients with FIGO stage Ib1 to IIIb cervical

carcinomas were treated in our institution. All biopsy specimens were diagnosed by experienced pathologists. All patients were staged clinically by experienced gynecological oncologists based on the FIGO system, and those clinical stages determined were not reassessed in the study. Among them, patients for whom pretreatment DWI studies were performed in our institution were included in this study. Patients were excluded based on the following criteria: no pretreatment MRI study in our institution (n=14); no definitive detection of cervical cancer by MRI (n=23 at stage 1b1); difficulty in measuring ADC values because of a tumor size smaller than 25mm² (n=2 at stage 1b1, and n=1 at stage IIA1); poor image quality due to metal or motion artifacts (n=4). We limited the MRI scanners to those manufactured by Siemens, to avoid possible variability in ADC values, and five patients were excluded. The remaining 171 patients were included. Clinical data were collected regarding patient age, tumor histopathology according to World Health Organization (WHO) classification, parametrial invasion, maximum tumor size measured by MRI, FIGO stage, lymph node metastasis, and the type of treatment. Patients and tumor characteristics are listed in Table 1.

Event-free survival (EFS) and overall survival (OS) were chosen as clinical outcomes. EFS was defined as the time from the pretreatment MRI to the date of any events including recurrence, progression, or death. OS was defined as the time from the pretreatment MRI to the date of death.

Treatments

In our institution, radical hysterectomy and adjuvant chemotherapy (with or without neoadjuvant chemotherapy, NACT) has been performed for the majority of patients with FIGO stage Ib1–IIb tumors. Thus, concurrent chemoradiation therapy (CCRT) as the primary treatment for patients with stage IIb tumors is rather uncommon. Hence, most patients with FIGO stage Ib1–IIb cervical cancers had been treated with radical surgery (128/147). Among them, NACT was performed for 49/128 patients (three with stage Ib1, 14 with Ib2, and 32 with IIb). Adjuvant chemotherapy was performed for 95 patients (28 with stage Ib1, 22 with Ib2, five with IIA, and 40 with IIb). Postoperative CCRT was performed for nine patients (one with stage Ib1, one with Ib2, and seven with IIb), and RT for one patient with stage Ib1. As a primary treatment, CCRT was performed for seven patients (one with stage Ib1, one with Ib2, one with IIA, and four with IIb), and RT for 12 patients (five with stage Ib1, two with Ib2, one with IIA, and four with IIb).

Patients with FIGO stage III cervical cancer (n=24) were mainly treated with CCRT (n=14 with stage IIb) or radiotherapy (RT) alone (n=6, two with stage IIIa, four

with stage IIIb). NACT, surgery, and adjuvant chemotherapy were performed for two patients (one with stage IIIa and one with IIIb), and chemotherapy alone for two patients (one with stage IIIa and one with IIIb).

Follow-up examinations were generally performed every 4 months for the first 2 years, every 6 months for the 3rd and 4th years, and every 12 months from the 5th year on. The observation period was over in August, 2013, which was after eight months from the final enrollment. The mean follow-up was 39 months, with a range of one to 91 months.

DWI protocols

MRI studies were performed with 1.5T (Avanto or Symphony: Siemens, Erlangen, Germany) or 3.0T MRI scanners (Skyra or Trio: Siemens, Erlangen, Germany). For all examinations, patients were placed in the supine position and had a partially filled bladder. Prior to examinations, 20mg of hyoscine butylbromide (Buscopan®; Boehringer Ingelheim, Ingelheim am Rhein, Germany) was administered to reduce bowel motion unless there was a contraindication.

A sagittal DWI was acquired in all patients. The parameters for DWI were as follows: repetition time and echo time (TR/TE; msec/msec), 5000/70 (3.0T) or 3000/70 (1.5T); field-of-view in mm/mm, 260×200–240; band width in Hz/pixel, 2000–2200 (3.0T) or 1700 (1.5T); section thickness/intersection gap, 4mm/1mm; fat suppression technique, spectral attenuated inversion recovery (SPAIR) for 3.0T and chemically selective suppression (CHESS) for 1.5T. The b values (s/mm^2) were 0, 500, and 1000 (until February 2009) or 0, 100, 500, and 1000 (from March 2009). Other sequences included in our routine pelvic MRIs were sagittal and axial T2-weighted images, sagittal T1-weighted images, and coronal half-Fourier acquisition single-shot turbo spin-echo (HASTE) images.

Measurement of ADC values

Post-processing to calculate the ADC value from the DWI was performed automatically on each scanner. Polygonal regions of interest (ROIs) were placed manually on the maximum sagittal section of the tumor on the ADC map, and the mean value (ADC_{mean}) of all whole pixels within the ROI was obtained. All ROIs were drawn by one radiologist specialized in gynecological imaging with 6 years of experience, by referencing the sagittal DWI and T2-weighted images and by avoiding the cystic and necrotic areas carefully (Figure 1).

The ADC value of each pixel was calculated according to the following formula:

$\text{SI}_b = \text{SI}_{b0} \times \exp(-b \times \text{ADC})$, where SI_b and SI_{b0} corresponded to the signal intensities of

specific b value and b0 images, respectively.

As already stated, we used two different methods in calculating ADC values at different periods: three b values from January 2006 to February 2009, and four b values from March 2009 to December 2012. There was a tendency for the ADC_{mean} measured from three b values to be higher than those from four b values, and this was statistically significant by Student's *t* test ($P = 0.01$). The mean values of ADC_{mean} of the former and the latter were $0.901 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.834 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. Thus, in addition to the assessment of original ADC_{mean} , we also assessed corrected ADC_{mean} : ADC_{mean} obtained from four b values were corrected by adding $0.067 \times 10^{-3} \text{ mm}^2/\text{s}$, which corresponds to the difference in the mean values of $0.901 - 0.834 = 0.067$.

Statistical analysis

As mentioned above, we obtained two types of ADC_{mean} : original and corrected ADC_{mean} . The associations between patient outcomes (EFS and OS) and the two types of ADC_{mean} as well as clinical factors were explored using univariate Cox proportional hazards regression analysis, in the whole group ($n=171$) and in patients with SCC (the SCC group, $n=123$). The clinical factors included age, definitive surgery, FIGO stage, parametrial invasion, lymph node metastasis, and maximum tumor size. In the whole group, the histopathology type (i.e. SCC or others) was also included. Cox proportional hazards regression analyses were performed for a range of ADC values with $0.005 \times 10^{-3} \text{ mm}^2/\text{s}$ increments using the in-house script written for MATLAB® (R2013b, The MathWorks, Natick, MA, USA), and the optimal cutoff values for tumor ADC_{mean} were determined respectively for EFS and OS in the whole group, and in the SCC group. Statistical differences between two groups (i.e. above and below the cutoff value) were analyzed by the Kaplan–Meier method and the log-rank test by MedCalc Statistical Software® (Version 12.4.0.0 MedCalc Software, Ostend, Belgium).

To assess the independency of ADC_{mean} , multivariate analyses were performed using the Cox proportional hazard model with multiple variables, by including variables statistically significant in the univariate analyses. For all statistical analyses, $P < 0.05$ was considered significant and all p-values were two-sided.

Results

Patient outcome: EFS

In total ($n=171$), 57 events occurred within the observation period: 27 recurrences or progressions, and 30 deaths. In the SCC group ($n=123$), 38 events occurred within the observation interval: 19 recurrences or progressions, and 19 deaths.

Patient outcome: OS

In total, 30 events occurred within the observation interval and 26 were diagnosed as a cancer-related death. In the SCC group, 19 events occurred and 15 were diagnosed as a cancer-related death.

Univariate analyses

For EFS, the original ADC_{mean} cutoff values were determined as $0.920 \times 10^{-3} \text{ mm}^2/\text{s}$, in both the whole group and the SCC group. Based on the cutoff values, patients were divided into the higher and lower ADC_{mean} groups. In the whole group ($n=171$), 44 patients were in the higher group and 127 were in the lower group. In the SCC group ($n=123$), 28 patients were in the higher group and 95 were in the lower group. The corrected ADC_{mean} cutoff values for EFS were determined as $0.960 \times 10^{-3} \text{ mm}^2/\text{s}$ in the whole group and $0.945 \times 10^{-3} \text{ mm}^2/\text{s}$ in the SCC group. In the whole group, 43 patients were in the higher group and 128 were in the lower group. In the SCC group ($n=123$), 32 patients were in the higher group and 91 were in the lower group. Univariate analyses showed that both the original and corrected ADC_{mean} were prognostic factors for EFS in both groups (Table 2).

The Kaplan–Meier plots were performed respectively, and showed that the patients in the lower ADC_{mean} group demonstrated shorter EFS, compared with the patients in the higher ADC_{mean} group in all analyses. P values by log-rank tests in the SCC group and in the whole group were 0.0084 and 0.0057 in the corrected ADC_{mean} (Figure 2), while 0.0034 and 0.02 in the original ADC_{mean} .

The OS rates were not statistically significant between two subgroups at any original/ corrected ADC_{mean} cutoff value, both in the whole group and in the SCC group. Thus, multivariate analyses were not performed.

Among clinical factors, the presence of lymph node metastasis, FIGO stage, tumor size, parametrial invasion, and definitive surgery was statistically significant for EFS both in the whole group and in the SCC group (Table 2). These factors were included in the following multivariate analyses.

Multivariate analyses

Multivariate analyses showed that both the original and corrected ADC_{mean} were independent prognostic factors for EFS in SCC group ($P = 0.02$, and 0.03 , respectively) along with lymph node metastasis and definitive surgery. Neither the original nor corrected ADC_{mean} for EFS in the whole group were an independent prognostic factor. Detailed results of multivariate analyses are shown in Table 3.

Discussion

In this study, we evaluated the prognostic importance of ADC_{mean} in patients with stage Ib–IIIb cervical carcinomas. We excluded patients with FIGO stage IV tumors, because metastasis and the involvement of other pelvic organs would have had a greater influence on the prognosis.

As we mentioned in the part of *Measurement of ADC values*, we made a minor change of the number of b values, from three to four b values, at March 2009. In terms of the validity of ADC measurements, three or more b value techniques are generally recommended⁽⁹⁾. Both methods we used might be robust enough. The latter method would be less sensitive to perfusion bias⁽⁹⁾, while it theoretically needs a little longer scan time.

We made analyses not only in the whole group, but also in the SCC group to exclude the influence of adenocarcinoma. A higher ADC value of adenocarcinomas compared with that of SCC was reported in patients with cervical cancers⁽¹⁶⁾. The weaker correlations between the ADC values and tumor cellularity in patients with adenocarcinomas was also reported⁽⁹⁾. These characteristic of adenocarcinoma would affect the prognostic power of ADC values.

Known prognostic factors were all significant by our univariate analyses, consistent with previous reports. These included lymph node metastases, FIGO stages, tumor size, parametrial invasion, and a history of definitive surgery. However, FIGO stages, tumor size, and parametrial invasion were not found to be independent by the multivariate analyses. These factors are normally taken into consideration to decide the treatment therapy and might be integrated into a decision for definitive surgery. Both the original and corrected ADC_{mean} were prognostic factors for EFS in the whole group and also in the SCC group by univariate analyses. Furthermore, in the multivariate analysis of the SCC group, the both ADC_{mean} were independent prognostic factors for EFS in the SCC group. These results indicate that ADC_{mean} might be a new useful biomarker in patients with cervical cancer, reflecting the tumor's characteristics such as aggressiveness.

In our study, ADC_{mean} was not significant in the multivariate analysis for EFS in the whole group, while Nakamura et al. reported that ADC_{mean} was an independent factor for Disease Free Survival (DFS) in patients with FIGO stage Ib1–IIb treated by primary radical hysterectomy, regardless of histopathology type⁽¹⁵⁾. The difference between their results and ours might be explained by the patient groups, with more cases of advanced carcinomas in our study, such as patients with FIGO stage III, extensive lymph node metastases, or bulky tumor treated by CCRT or NACT followed

by radical hysterectomy. In these patients, other risk factors might have had a stronger weight on the prognosis, compared with patients with early stage cancers. Cervical adenocarcinoma is known as an aggressive histopathology subtype in advanced stages⁽²⁾. Therefore, the increased risk of adenocarcinomas in patients with advanced stage tumors might have affected the result. Despite their aggressiveness, the higher ADC values in adenocarcinomas compared with SCC might have had a negative influence on the analyses. From the results of our study, we suggest that ADC_{mean} may contribute to screen high-risk patients, especially in those with SCC. Whether ADC_{mean} could be a risk factor for the prognosis of cervical adenocarcinoma should be assessed further. It might be optimal to obtain ADC cutoffs for respective histological subtypes, taking histological features into consideration. The difference in methods used to obtain ROIs of ADC_{mean} might be another cause of the discrepancy between our results and those of Nakamura et al. We placed ROIs on the maximum sectional diameter of the tumor, while they placed ROIs on sections of the whole tumor. Our method would be easy to use clinically, although ROIs can represent limited fractions of tumors. Further studies for the validation of methods used to obtain ROIs are needed.

ADC_{mean} was a significant biomarker for EFS, but not for OS. Even in the univariate analysis of OS in the SCC group, it was not statistically significant. The negative result might be due to the small number of events in OS. Therefore, further studies to investigate the influence of ADC_{mean} on OS with a larger number of patients are needed to assess the prognostic power of ADC values for OS.

There were several limitations in this study. The first was the reproducibility of ADC as a biomarker. ADC_{mean} were obtained from MRI scanners with different magnetic field strengths (1.5 and 3.0T), although we limited machines to those manufactured by Siemens. Theoretically, ADC is independent of the strength of the static magnetic field^(9, 17). The minor change in the methods of calculation since March 2009 should also be noted. This is why we performed the bias correction for ADC_{mean} based on the difference of averaged values. DWI is a relatively novel technique, thus the consensus for the imaging protocol was not yet fully obtained. In future, ADC calculations with more robust repeatability and reproducibility might lead to a better evaluation of the advantage of ADC. Second, the number of patients was relatively small, especially in terms of OS. In the SCC group, there were only 19 events included. As mentioned above, studies with a larger number of patients would enable a more precise evaluation of ADC_{mean} for predicting OS. Third, there might have been a bias for treatment selection. In our institution, the majority of patients with FIGO stage IIb cervical cancer were treated by radical hysterectomy with or without NACT. Thus, to be

widely used, our results should be verified in institutions where CCRT or RT is the major treatment for those patients. Previous reports suggested the correlation of ADC values at 2 weeks after the start of CCRT and the change in ADC values in 2 weeks with the eventual response, or the correlation of the posttreatment ADC_{mean} with patient prognosis^(14, 18, 19). These parameters could be preferable for the prognosis of patients treated by CCRT, even though they are obtained after the initiation of treatment. To evaluate the utilities of these ADC parameters, further studies on the relationship between ADC values and treatment outcome of patients treated by CCRT or RT are necessary.

Conclusions

We have shown that the pretreatment ADC_{mean} could be an independent prognostic biomarker for EFS in patients with FIGO stage Ib to IIb squamous cell cervical cancers. Taking histological subtypes into consideration is useful in using ADC values as a prognostic factor.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Table legends

TABLE 1. Patients and tumor characteristics

TABLE 2. Results of univariate Cox regression analyses for event-free survival in the whole group, and in the SCC group.

TABLE 3. Results of multivariate Cox regression analyses for event-free survival in the whole group, and in the SCC group.

Figure legends

FIGURE 1.

Referencing the sagittal T2-weighted images (A) and diffusion-weighted images, the region of interest was placed manually on the apparent diffusion coefficient (ADC) map (B), and the pretreatment mean ADC value (ADC_{mean}) was obtained.

FIGURE 2. The Kaplan–Meier curves for the event-free survival (EFS) rates of the whole group (A) and the squamous cell carcinoma (SCC) group (B), using the corrected mean ADC values (ADC_{mean}). The cutoff values of the whole group and the SCC group were $0.960 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.945 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. The *P* values were calculated using the log-rank test.