Early Alteration in Apparent Diffusion Coefficient and Tumor Volume in Cervical Cancer Treated with Chemoradiotherapy or Radiotherapy: Incremental Prognostic Value over Pretreatment Assessments

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Running title:

Incremental value of early change of ADC

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Abstract

<Purpose>

Our study aimed to evaluate a prognostic value of early changes in apparent diffusion coefficients (ADC) and tumor volume during treatment in patients with cervical cancer treated with chemoradiotherapy or radiotherapy, and to assess whether the early changes provided an incremental value to pre-treatment ADC and tumor volume in predicting disease recurrences.

<Methods and Materials>

A total of 103 patients with stage IB–IVA cervical cancer including 76 (74%) patients with stage ≥ IIIA who underwent magnetic resonance imaging before and during (25±4.6 days after start) the treatment were enrolled. Eighty-one patients received chemoradiotherapy and the remaining 22 had radiotherapy. Both a volumetric ADC and volume of a tumor before and during treatment were measured. %ADC increase and %Volume reduction were defined as changes in the ADCs and tumor volume before and during treatment, respectively.

<Results>

During a median follow-up of 2.7 years, 42 (41%) patients had disease recurrences. Univariate Cox regression analysis revealed that pre-treatment ADC (Hazard ratio [HR]=2.8; p=0.002), %ADC increase (HR=6.8; p<0.001), and %Volume reduction (HR=2.7; p=0.003) were significant predictors for disease recurrences. On multivariate analysis, %ADC increase was the only independent predictor (adjusted HR=5.2; p<0.001) for disease recurrences when adjusted for %Volume reduction and pre-treatment ADC. Global chi-square analysis demonstrated that %ADC increase and %Volume reduction had an additional prognostic value over pre-treatment ADC and tumor volume (p<0.05). Kaplan–Meier curve analysis showed that both smaller %ADC increase and %Volume reduction were associated with worse prognosis in disease-free survival (log-rank, p<0.001 and p=0.002, respectively).

<Conclusions>

Among patients with cervical cancer treated with chemoradiotherapy or radiotherapy, early changes

in tumor ADCs and tumor volume during treatment are associated with better prognosis. %ADC increase and %Volume reduction during the treatment have an additional prognostic value for predicting tumor recurrence to pre-treatment ADC and tumor volume.

List of all abbreviations:

FIGO = International Federation of Gynecology and Obstetrics

ADC = apparent diffusion coefficient

DWI = diffusion weighted imaging

T2WI = T2 weighted image

CCRT = concurrent chemoradiotherapy

CDDP = cisplatin

PTX = paclitaxel

SD = standard deviation

SCC = squamous cell carcinoma antigen (ng/ml)

CI = confidence interval

Introduction

Concurrent chemoradiotherapy (CCRT) is the established recommended treatment for patients with locally advanced uterine cervical cancer (1-4). However, approximately 30% of cervical cancer patients receiving CCRT will develop local recurrence or distant metastasis (5). Therefore, early identification of patients at higher risk of disease recurrences might be important for optimizing therapeutic strategies. There are several known prognostic factors, including nodal status and tumor size (6,7).

Recently, the role of imaging biomarkers in predicting prognosis after CCRT in cervical cancer patients has acquired greater interest (8-10). Diffusion-weighted imaging (DWI) provides noninvasive measurement of the apparent diffusion coefficient (ADC), which reflects water proton mobility quantified and has been shown to be associated with tumor cellularity. Several studies have indicated the value of ADC in the prediction of patients' outcome after CCRT (5,11,12). Gladwish et al. (5) showed that volumetrically derived ADC before treatment was associated with disease recurrence in cervical cancer patients treated with CCRT. However, these previous studies investigated the prognostic value of ADCs measured before the treatment. The assessment of early alteration of ADC in response to treatment may provide more accurate risk stratification of patients with cervical cancer.

Therefore, the aim of our study was to evaluate whether early changes in ADCs and tumor volume during treatment were associated with disease recurrence in patients with cervical cancer treated with CCRT or radiotherapy and to assess whether the early changes provided an incremental value to pre-treatment ADC and tumor volume in predicting disease recurrences.

Methods and Materials

Using our institution’s radiation therapy database, we identified 153 cervical cancer patients treated with definitive CCRT or radiotherapy between September 2007 and January 2018 (Supplementary Figure 1). Patients were included if they had International Federation of Gynecology and Obstetrics (FIGO) stage IB to IVA cervical cancer, had no distant metastasis before treatment and underwent MRI studies with DWI sequence before and during the treatment. One hundred eight patients met the inclusion criteria. Forty-five patients were excluded because 3 patients had cervical

cancer with stage IVB, 4 had metastases and 38 patients had no MRI before or during the treatment. Five of the 108 patients were lost to follow-up (n=5). Therefore, in this study, 103 patients who met these criteria were analyzed. Medical records were used to obtain data regarding patient characteristics, pathology, imaging parameters, radiation treatment plans, recurrences, and survival. The study was performed in accordance with the Declaration of Helsinki statement (13). The institutional review board approved this retrospective study and waived the written informed consent requirement.

MR imaging was performed in a 1.5 T whole-body MR system with 16-channel receiver coils. DWI images were obtained using single-shot, echo-planar imaging with b values of 0 and 800, 0 and 1,000, or 0 and 2000 s/mm^2 in the axial plane to generate ADC maps. The b values of 0 and 1000, 0 and 2000, or 0 and 800 in DWIs were used in 93.7% (n=193), 3.4% (n=7), or 2.9% (n=6) of the patients, respectively. T2-weighted images (T2WI) using turbo spin-echo (TSE) techniques were obtained in axial and sagittal planes with the following parameters: repetition time (TR)/echo time (TE), 3000–5000/85 ms; slice thickness, 5 mm; inter-slice gap, 1 mm; number of slices, 19-25; FOV, 22 cm; number of signals acquired (NSA), 1; TSE factor, 8. Oblique coronal T2WI with TSE perpendicular to the long axis of the uterus was acquired with the following parameters: TR/TE, 3000–4000/85 ms; slice thickness, 4 mm; inter-slice gap, 1 mm; number of slices, 15-19; FOV, 22 cm; number of signals acquired (NSA), 1; TSE factor, 8.

ADCs before and during (25±4.6 days after start) the treatment were measured independently by two observers (S.N., a radiologist with 5 years of experience and Y.W., a radiation oncologist with 5 years of experience). The mean ADC value of the tumor was determined by tracing the tumor border in all slices that comprised the tumor. A pre-ADC and mid-ADC were defined as the ADCs measured before and during the treatment. A %ADC increase was defined as the percent increase in the tumor ADC measured during the treatment as compared with that before the treatment [(mid-ADC – pre-ADC) / pre-ADC x 100].

The T2WI images were transferred to a radiation treatment planning system (Eclipse version 13.6, Varian Medical Systems, Inc., Palo Alto, CA, USA) in order to measure the gross tumor volume. Two observers (S.N. and Y.W.) independently measured the tumor volume by tracing the tumor contour on the T2WI images with the aid of the radiation treatment planning system to

complement the MR image inter-slice gaps.

A pre-Volume and mid-Volume were defined as the tumor volume measured on pre- and mid-treatment MRI, respectively. A %Volume reduction was defined as the percent decrease in the tumor volume measured during the treatment as compared with that before the treatment [(pre-Volume – mid-Volume / pre-Volume x 100)]. The pre-ADC, mid-ADC, %ADC increase, pre-Volume, mid-Volume, and %Volume reduction measured by the two observers were averaged to be used as parameters for statistical analysis.

All patients underwent standard external beam radiation therapy and intracavitary brachytherapy with or without concurrent chemotherapy, excluding five patients who had an external beam boost to the primary lesion instead of intracavitary brachytherapy (Supplementary Figure 2). With external beam radiation therapy, a dose of 50–50.4 Gy in 25–28 fractions (5 days/week) was delivered to the pelvis with or without the para-aortic region by using 6 or 10 MV photons. After receiving 30.6–50.4 Gy of external radiation, patients were treated with high-dose-rate brachytherapy to a dose of 12–24 Gy (1 day/week). Mid-treatment MRI in all patients preceded brachytherapy. After the start of brachytherapy, a central shield was inserted to an external beam radiation field to reduce the dose to rectum. Brachytherapy treatment planning was performed using either volume-based dosimetry or point-based dosimetry. Twenty patients received an external beam boost to areas of initial nodal or parametrial involvement to a dose of 5.4–10.8 Gy in 3–6 fractions, which was usually given in between brachytherapy treatments.

Eighty-one patients received concurrent chemotherapy. Cisplatin was typically delivered weekly at a dose of 35–40 mg/m^2 (maximum dose, 70 mg) during the treatment as prescribed by gynecologic oncologists.

Follow-up information was collected through a review of clinical records. The primary endpoint was disease recurrence-free survival. Disease recurrences includes locoregional recurrences and distant metastases. The secondary endpoint was overall survival. Follow-up duration was calculated from the first day of radiation therapy to the date of death or the last follow-up visit. Patients received general physical and pelvic examinations and imaging tests every 3-6 months. Disease recurrence was evaluated using computed tomography (CT), MRI, or biopsy. Locoregional recurrences included either recurrences in the original primary cervical tumor region and/or nodal

recurrences within the pelvic or para-aortic region in the external beam radiation fields. Distant metastases were any recurrences outside the external beam radiation fields. Patients with persistent disease were considered as those that relapsed on the first day of radiation therapy.

Continuous variables are expressed as the mean ± standard deviation or the median (range), as appropriate, and were analyzed using Mann–Whitney U tests. Categorical variables are shown as numbers (percentages) and were compared using the Fisher exact test. Cox analysis was carried out to assess the association of parameters with disease-free survival, and the results are expressed as hazard ratio (HR) with 95% confidence interval (CI). Multivariate analysis was performed using the "enter" method for variables with p value <0.05 in univariate analysis. The prognostic values of parameters were assessed by calculating the global chi-square test. Kaplan–Meier curve analysis was performed to estimate disease-free survival and overall survival. Receiver operating characteristics (ROC) curve analysis was performed to assess the diagnostic performance of variables in the prediction of disease recurrence. The areas under the ROC curves (AUCs) were calculated, and the optimal cutoff value was determined as the threshold maximizing the Youden index. Intraclass correlation coefficients were calculated to assess the interobserver reproducibility of %ADC increase and %Volume reduction. A two-sided p value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 23.0 (SPSS, Inc., Chicago, Illinois) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population, including age, FIGO stage, pathology, nodal involvement, chemotherapy, radiotherapy, tumor marker, b value measured on DWI are listed in Table 1. The mean age of the patients was 61 ± 13 years. The proportions of patients with FIGO stage ≥IIIA were 74% (n=76).

Supplementary Table 1 shows the mean values of pre-ADC, mid-ADC, %ADC increase, pre-Volume, mid-Volume, and %Volume reduction in all subjects. The mean %ADC increase was 35 ± 18% and the mean %Volume reduction was 69 ± 19%.

During a median follow-up of 2.7 years (range, 0.7–10.1 years), 42 (41%) patients had a disease

recurrence. Locoregional recurrences and distant metastasis were observed in 13 and 19 patients, respectively, and the remaining ten patients had both. Disease recurrences were confirmed by imaging only (n=28), biopsy only (n=5), or both imaging and biopsy (n=9). Of the 42 patients with a disease recurrence, death occurred in eleven patients, who were censored at the time of death. There was no death due to other causes.

In Figure 1, box plots summarized (A) %ADC increase and (B) %Volume reduction in patients with and without disease recurrences. %ADC increases in patients with disease recurrences were significantly higher than those in patients without disease recurrences ($p<0.001$). The median values of %ADC increase in patients with and without disease recurrences were 18% (quartile range, 13-28%) and 44% (quartile range, 33-55%), respectively. Similarly, %Volume reductions in patients with disease recurrences were significantly higher than those in patients without disease recurrences ($p=0.001$). The median values of %Volume reduction in patients with and without disease recurrences were 66% (quartile range, 51-77) and 77 (quartile range, 68-83%), respectively.

Table 2 shows univariate and multivariate predictors of disease recurrence. The univariate analysis revealed that pre-ADC, %ADC increase, %Volume reduction was significantly associated with disease recurrence. Lower %ADC increase (<median (33%)) was the strongest predictor of all (Hazard ratio (HR), 6.8; 95% confidence interval (CI), 2.3–15.3; $p<0.001$). The presence of nodal involvement, tumor maker (squamous cell carcinoma antigen), and the absence of chemotherapy did not show statistically significant difference in predicting disease recurrence. In the multivariate analysis, only %ADC increase remained an independent predictor (adjusted HR of %ADC increase, 5.2; 95% CI, 2.1-12.6; $p<0.001$) for disease recurrence when adjusted for pre-ADC and %Volume reduction.

Kaplan–Meier curve analysis (Figure 2) demonstrated that patients with %ADC increase <median (33%) had significantly lower rates for disease-free survival (3-year rate, 38% vs. 90%; $p<0.001$; Figure 2-A) and overall survival (82% vs. 100%; $p=0.005$; Figure 2-B) than those with %ADC increase ≥median. %Volume reduction <median (72%) was associated with worse prognosis in disease-free survival (3-year rate, 47% vs. 79%; $p=0.002$; Figure 2-C) and overall survival (84% vs. 98%; $p=0.083$; Figure 2-D) compared with %Volume reduction ≥median.

Figure 3 showed the additive value of assessing early changes in tumor ADCs and volume

compared to pre-treatment MRI only. A global chi-square value of combined pre-ADC and pre-Volume was 12.1. By adding %Volume reduction to combined pre-ADC and pre-Volume, the global chi-square increased to 18.5 (p=0.011), and, furthermore, the addition of %ADC increase to these resulted in the significant increase of a global chi-square (32.0, p<0.001).

AUCs of pre-ADC, %ADC increase, pre-Volume, and %Volume reduction for predicting disease recurrences were 0.71, 0.88, 0.58, and 0.69, respectively. The optimal cutoff values were 1.02 mm^2/sec (57% sensitivity, 87% specificity, 75% positive predictive value [PPV], and 75% negative predictive value [NPV]) for pre-ADC, 30.1% (83% sensitivity, 80% specificity, 75% PPV, and 88% NPV) for %ADC increase, 112ml (24% sensitivity, 92% specificity, 67% PPV, and 64% NPV) for pre-Volume, and 66.7% (62% sensitivity, 77% specificity, 65% PPV, and 75% NPV) for %Volume reduction, respectively.

Intraclass correlation coefficients of %ADC increase and %Volume reduction from two observers were 0.86 (95%CI, 0.80-0.90) and 0.85 (95%CI, 0.79-0.90), respectively.

Discussion

The main finding of our study was that, among patients with cervical cancer treated with CCRT or radiotherapy, smaller changes in ADCs and tumor volume observed during treatment were associated with unfavorable disease-free survival and overall survival, and had an additional prognostic value over pre-treatment ADC and tumor volume.

Previous studies have indicated that the pre-treatment ADC may be useful for predicting adverse outcomes after CCRT in cervical cancer patients (5,11,12). Marconi et al. (11) studied 66 patients including 44 patients with stage I–II cancer, and found that higher ADCs were significantly associated with worse disease-free survival (HR = 3.632; p = 0.035) and disease-specific survival (HR = 4.401; p = 0.043). Ho et al. (12) demonstrated that in 69 patients including 48 patients with stage I–II cancer, the mean ADC value before treatment was the only imaging feature that was an independent predictor of disease-free survival in cervical cancer treated with CCRT. Importantly, populations in these studies mostly included patients with earlier stage cervical cancer, which was potentially operable. In addition, these previous studies did not investigate the prognostic value of ADC change before and during treatment. Recently, Das et al. (14) studied 24 patients with cervical

cancer and reported that early ADC change in absolute value was significantly higher in good responders than in poor responders ($p = 0.003$). Similarly, a study by Smoye et al. (15) showed that, among 20 patients treated for cervical cancer, survivors had higher early ADC changes compared to non-survivors. Although the results by Das and Smoye was consistent with our results, the present study investigated a substantially larger population, and demonstrated the incremental value of early ADC change to pre-treatment ADC or tumor volume change for the risk stratification of patients with cervical cancer.

^{18}F-fluorodeoxyglucose-positron emission tomography (PET)/CT can be used to predict the prognosis of cervical cancer patients. Park et al. (16) showed that changes of ADC and standardized uptake value (SUV) during CCRT had a similar prognostic value for predicting disease recurrence after CCRT in cervical cancer. According to the study by Ho and colleagues (17), there was an inverse correlation between ADC and SUV in cervical tumor. DWI and PET/CT might have a complementary role for assessment of cervical cancer. However, DWI is less expensive when compared to PET/CT, and does not require contrast administration.

Our results imply that, among patients with advanced cervical cancer, early response to CCRT determined by ADC change was useful for identifying patients at high risk of disease recurrence. Lower %ADC increase may be an important factor for optimizing therapeutic strategies after mid-treatment MRI. Such therapeutic strategies may include the prescription of brachytherapy focused on potentially viable areas where ADC values only slightly increased between pre- and mid-treatment MRI and the use of a more intensive chemotherapy regimen.

Our study has several limitations. First, it was a retrospective study at a single institution. Therefore, our results should be confirmed by a prospective multicenter trial. Second, five patients received an external beam boost to the primary lesion instead of brachytherapy. Third, 22 (21%) patients had no chemotherapy. Although the absence of chemotherapy was not associated with disease recurrences in the Cox regression analysis in the current study subjects, further rigorous evaluation may be necessary to determine the influence of the chemotherapy.

In conclusion, among patients with cervical cancer treated with chemoradiotherapy or radiotherapy, early increase in ADCs and reduction of tumor volume during treatment were useful indicators in predicting the risk of disease recurrences and had an additional prognostic value over

pre-treatment ADC and tumor volume.

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Figures

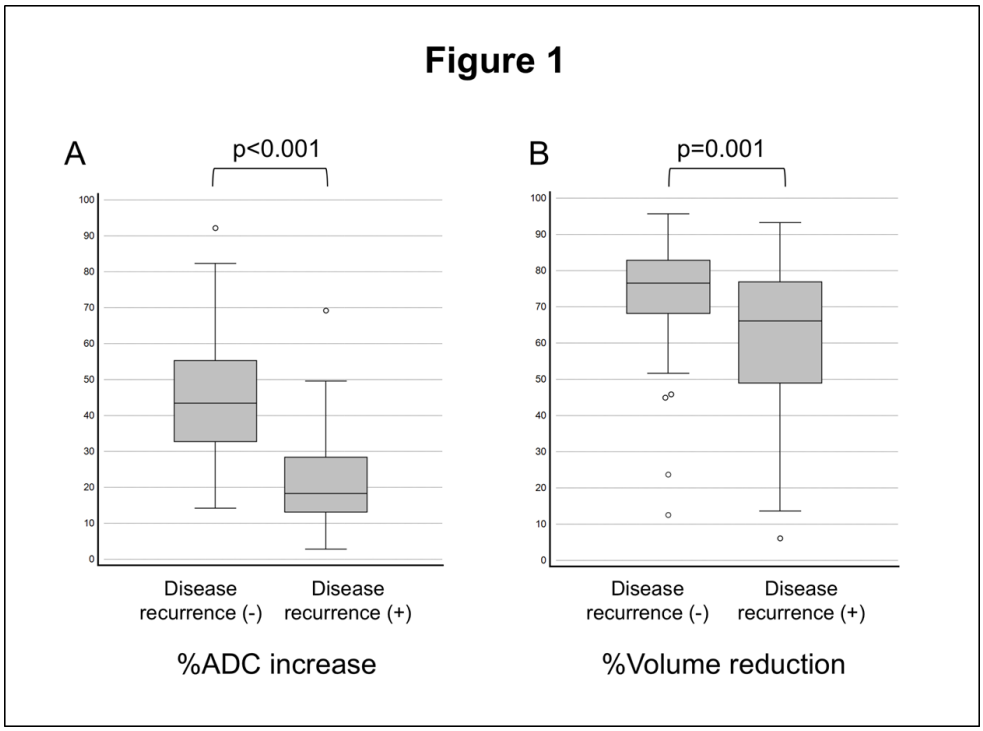


Figure 1: Box plots of %ADC increase and %Volume reduction in patients with and without disease recurrences

Box plots summarize (A) %ADC increase and (B) %Volume reduction in patients with and without disease recurrences. ADC = apparent diffusion coefficient.

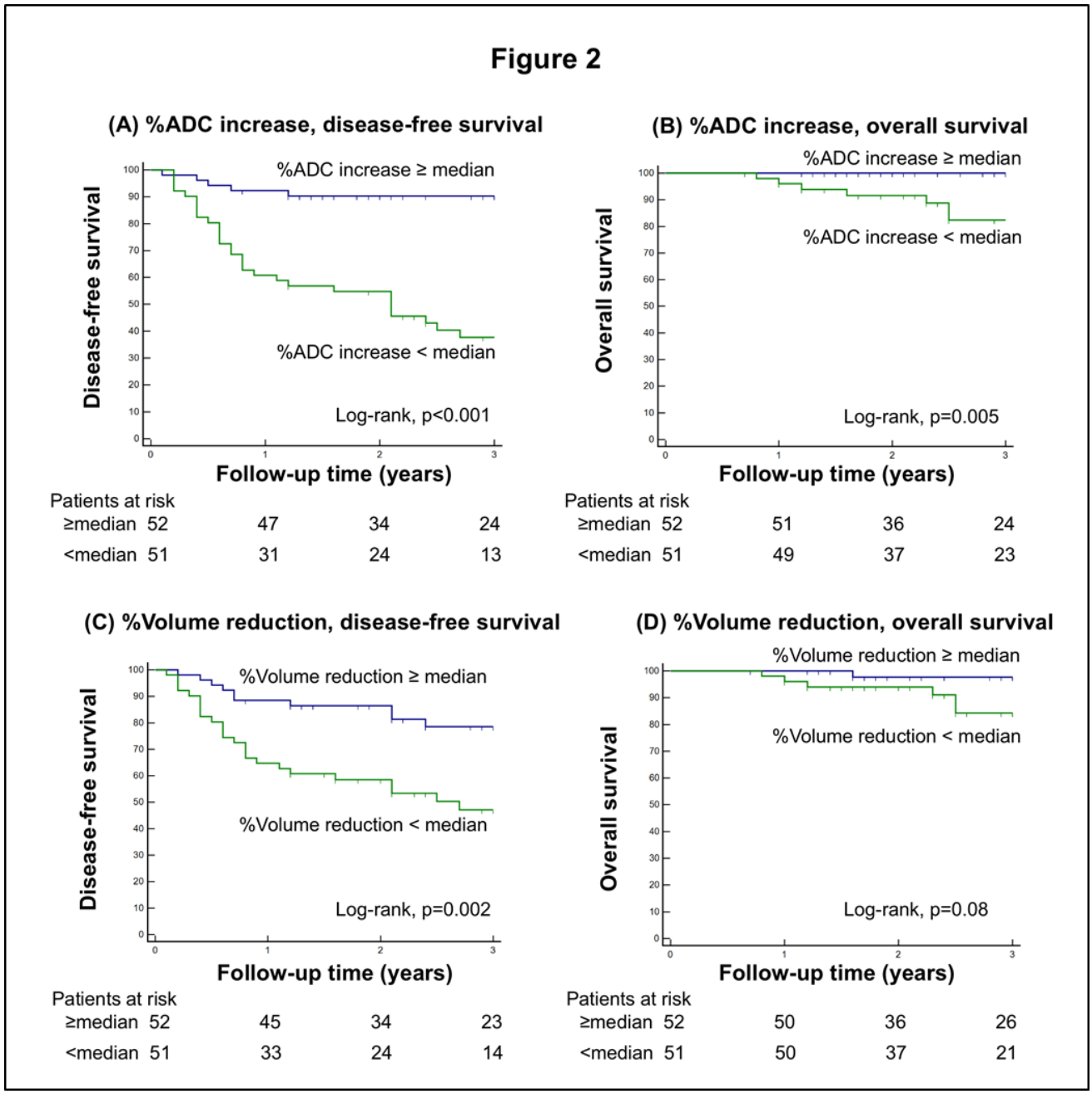


Figure 2: Kaplan-Meier curve analysis by %ADC increase and %Volume reduction

The figures (A) and (B) show Kaplan-Meier curves in patients stratified by the median (33%) of %ADC increase for prediction of disease-free survival and overall survival, respectively. The figures (C) and (D) show Kaplan-Meier curves in patients stratified by the median (72%) of %Volume reduction for prediction of disease-free survival and overall survival, respectively.

ADC = apparent diffusion coefficient.

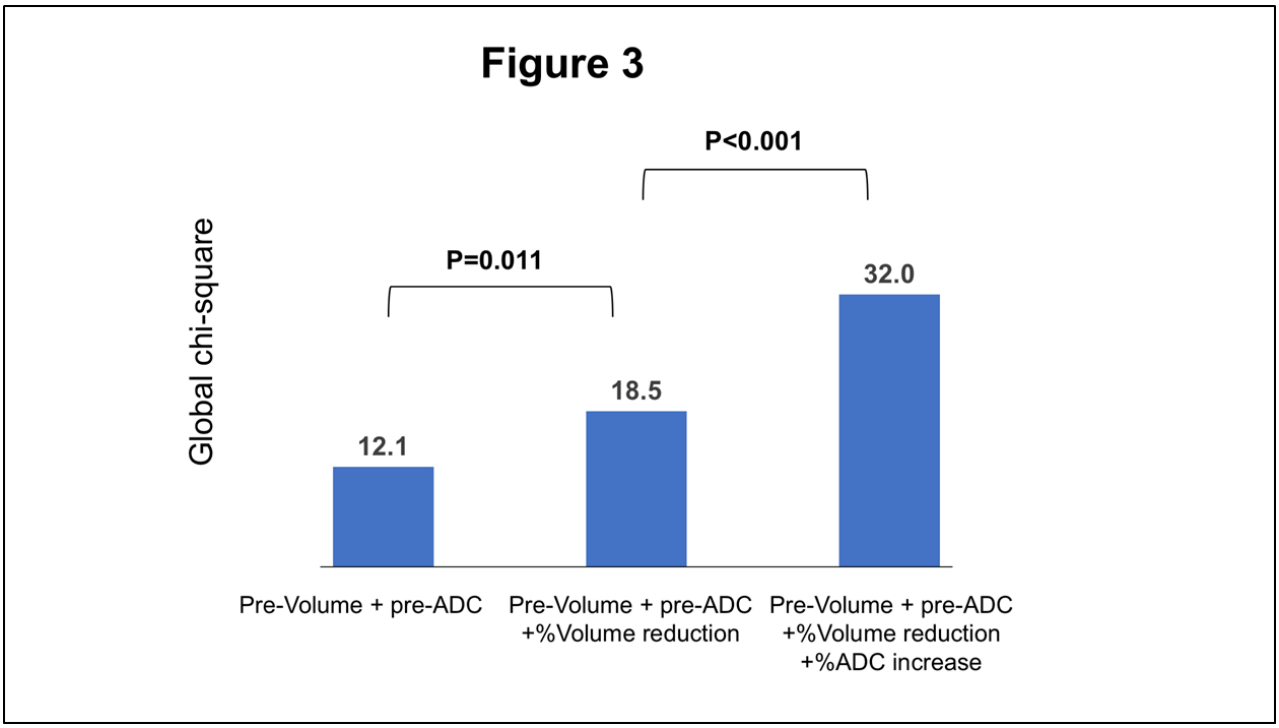


Figure 3: Global chi-square analysis

The figure shows a global chi-square analysis which puts focus on the incremental value of %Volume reduction and %ADC increase.

ADC = apparent diffusion coefficient.

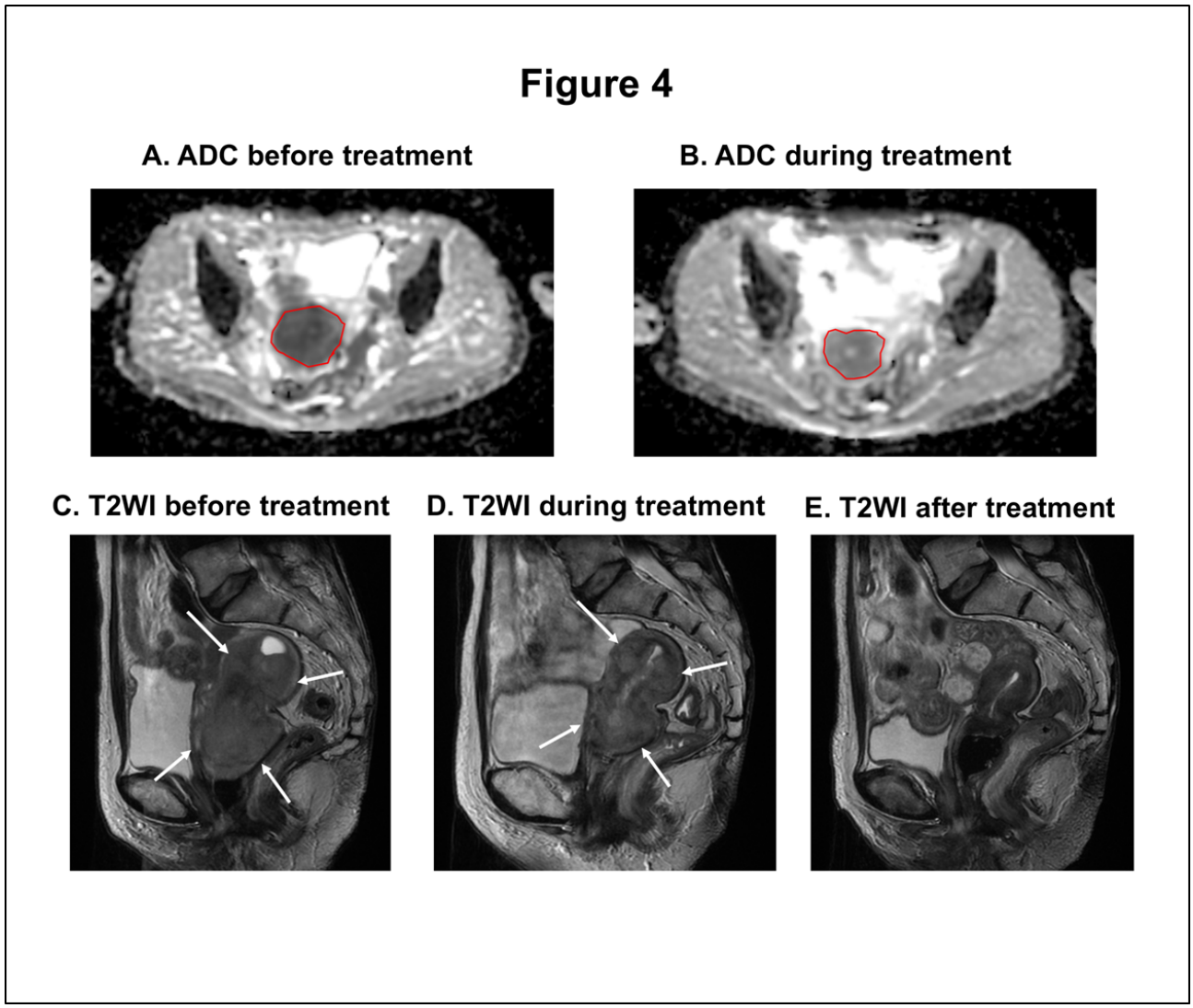


Figure 4: A case of a patient who had no disease recurrences

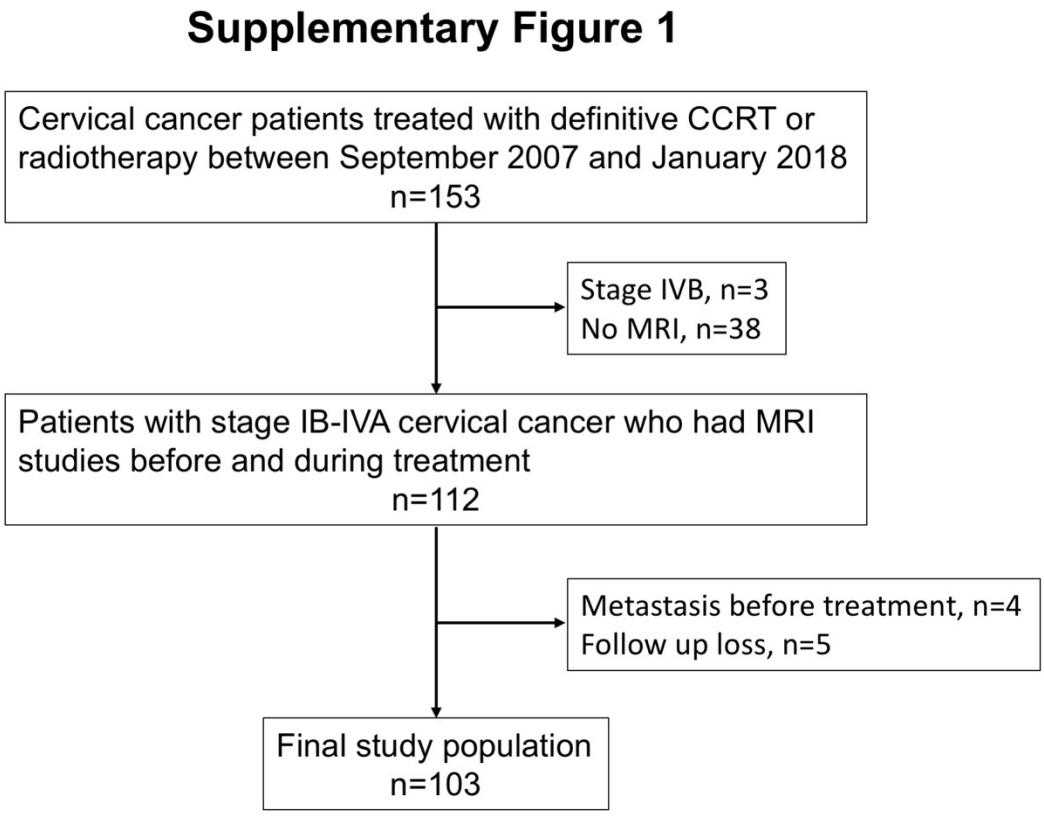
The figures show images of a patient with FIGO stage IIIB who had no disease recurrences. The figures (A) and (B) show ADCs of a tumor (red region of interest) before (0.89 mm^2/sec) and during (1.26 mm^2/sec) treatment, respectively. Therefore, a %ADC increase was 42%, which was higher than the median of %ADC increases. T2WIs before (Figure C) and during (Figure D) treatment demonstrated decrease (%Volume reduction = 57%) of the tumor volume (white arrow). In a T2WI after treatment (Figure E), a complete response to treatment was confirmed. During a follow up of 7 years, the patient had no disease recurrences.

ADC = apparent diffusion coefficient; T2WI = T2 weighted image; FIGO = International Federation of Gynecology and Obstetrics

Supplementary Table 1. Imaging results

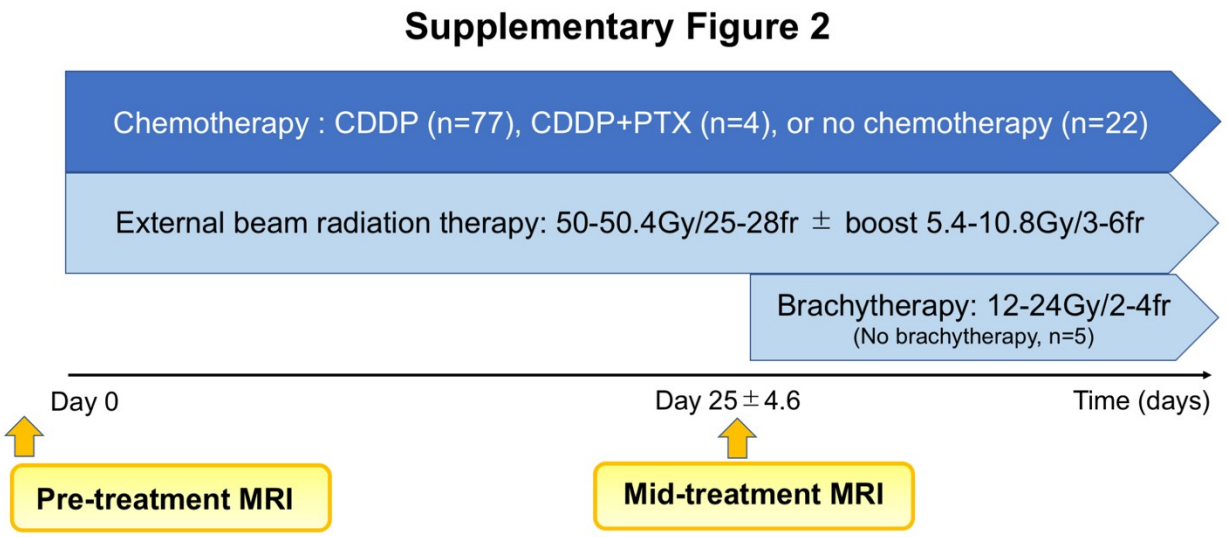
Parameter	Value
ADC	
Pre-ADC (mm^2/sec)	0.95±0.12
Mid-ADC (mm^2/sec)	1.27±0.13
%ADC increase (%)	35±18
Tumor volume	
Pre-Volume (ml)	63±57
Mid-Volume (ml)	19±20
%Volume reduction (%)	69±19

ADC = apparent diffusion coefficient.



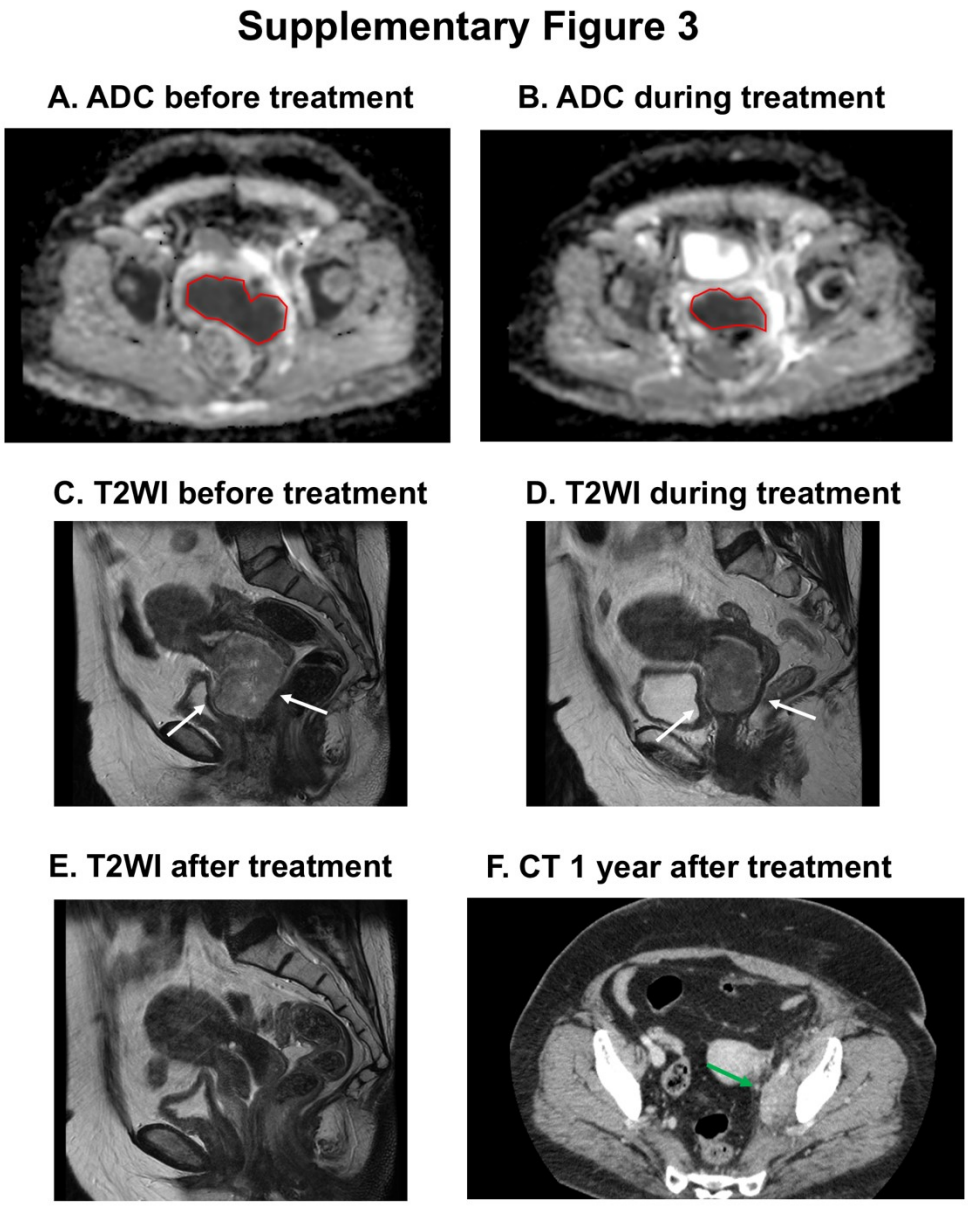
Supplementary Figure 1: Study flow chart

CCRT = concurrent chemoradiotherapy; MRI = magnetic resonance imaging.



Supplementary Figure 2: Treatment regimen

CDDP = cisplatin; PTX = paclitaxel; MRI = magnetic resonance imaging.



Supplementary Figure 3: A case of a patient who had a disease recurrence

The figures show images of a patient with FIGO stage IIIB who had a disease recurrence. The figures (A) and (B) show ADCs of a tumor (red region of interest) before (0.92 mm2/sec) and during (1.07 mm2/sec) treatment, respectively. Therefore, a %ADC increase was 16%, which was lower than the median of %ADC increases. T2WIs before (Figure C) and during (Figure D) treatment demonstrated decrease (%Volume reduction = 53%) of the tumor volume (white arrow). A T2WI after treatment (figure E) shows a complete response to treatment. In the figure (F), a CT image one year after treatment reveals a disease recurrence (green arrow).

ADC = apparent diffusion coefficient; T2WI = T2 weighted image; FIGO = International Federation of Gynecology and Obstetrics