Received:
10 January 2017

Revised:
29 April 2017

Accepted:
4 May 2017

<https://doi.org/10.1259/bjr.20170035>

Cite this article as:

Ueno Y, Lisbona R, Tamada T, Alaref A, Sugimura K, Reinhold C. Comparison of FDG PET metabolic tumour volume *versus* ADC histogram: prognostic value of tumour treatment response and survival in patients with locally advanced uterine cervical cancer. *Br J Radiol* 2017; **90**: 20170035.

FULL PAPER

Comparison of FDG PET metabolic tumour volume *versus* ADC histogram: prognostic value of tumour treatment response and survival in patients with locally advanced uterine cervical cancer

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Objective: To evaluate the prognostic utility of volume-based parameters of fluorine-18 fludeoxyglucose positron emission tomography (¹⁸F-FDG PET) and apparent diffusion coefficient (ADC) histogram analysis for tumour response to therapy and event-free survival (EFS) in patients with uterine cervical cancer receiving chemoradiotherapy.

Methods: The study included 21 patients diagnosed with locally advanced uterine cervical cancer who underwent pre-treatment MRI and ¹⁸F-FDG PET and were treated with concurrent chemoradiotherapy. ¹⁸F-FDG parameters: maximum and mean standardized uptake value; metabolic tumour volume (MTV); total lesion glycolysis (TLG); ADC parameters: maximum, mean and minimum values; percentile ADC values (10–90%); skewness and kurtosis of ADC were measured and compared between the responder and non-responder groups using a Wilcoxon rank-sum test. The Cox regression analysis and Kaplan–Meier survival curves were performed for EFS analysis.

Results: MTV and TLG of the primary tumour were significantly higher in the non-responder group than in the responder group ($p = 0.04$ and $p = 0.01$). Applying Cox regression multivariate analysis, MTV [hazard ratio (HR), 4.725; $p = 0.036$], TLG (HR, 4.725; $p = 0.036$) and 10-percentile ADC (HR, 5.207; $p = 0.048$) showed a statistically significant association with EFS. With the optimal cut-off value, the EFS rates above the cut-off value for MTV and TLG were significantly lower than that below the cut-off value ($p = 0.002$ and $p = 0.002$).

Conclusion: Pre-treatment volume-based quantitative parameters of ¹⁸F-FDG PET may have better potential than ADC histogram for predicting treatment response and EFS in patients with locally advanced cervical cancer.

Advances in knowledge: In this study, pre-treatment volume-based quantitative parameters of ¹⁸F-FDG PET had better potential than ADC histogram for predicting treatment response and survival in patients with locally advanced cervical cancer.

INTRODUCTION

Uterine cervical cancer is the fourth most common cancer in females worldwide and has the fourth highest mortality rate among all cancers in females.¹ Concurrent radiation therapy with cisplatin-based chemotherapy (CRT) has been widely accepted as first-line therapy for patients with advanced cervical cancer.^{2,3} If pre-treatment imaging was able to identify patients at high risk for disease recurrence before the start of CRT, a personalized treatment plan could be devised by conducting more intensive follow-up and/or considering alternate treatment options.

In recent years, the role of fluorine-18 fludeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/CT in the staging and management of gynaecological cancers has been increasing.^{4–6} The maximum standardized uptake value (SUV_{max}) is currently the most commonly used parameter in ¹⁸F-FDG PET/CT. However, the SUV_{max} only shows the highest intensity of ¹⁸F-FDG uptake, as measured by the highest pixels within a region of interest (ROI), and cannot reflect the metabolic activity of the whole tumour. Recently, metabolic tumour volume (MTV), which is a volumetric or quantitative measurement of tumour cells with high glycolytic

activity, has been shown to be a better predictor of prognosis than the SUV_{max} in several cancers including cervical uterine cancer.^{7–11}

Apparent diffusion coefficient (ADC), derived from diffusion-weighted imaging (DWI), is an additional quantitative imaging parameter now being widely used in oncology for disease detection, characterization and assessment of treatment response in several cancers.^{12–15} Although the mean ADC value within an ROI is a convenient quantitative measure that is widely used, the predictive value of the pre-CRT mean ADC as a reliable biomarker for treatment response in patients with cervical carcinoma remains controversial.^{13–15} Recent studies have suggested that volume-based ADC parameters using histogram analysis can interrogate the biological heterogeneity of tumours by classifying domains of different diffusivity, which may have prognostic and predictive implications.^{15–19}

These volume-based approaches may provide additional metrics of tumour properties that cannot be evaluated by ROI-based measurements alone. To our best knowledge, no studies have directly evaluated the prognostic ability with potential threshold value of volume-based parameters of ^{18}F -FDG PET/CT and ADC for predicting treatment outcomes in patients with cervical cancer. The objective of this study was to investigate the

capability of volumetric quantitative parameters measured on pre-treatment ^{18}F -FDG PET/CT and on ADC maps for predicting treatment response and survival rates in cervical cancer patients treated with concurrent CRT.

METHODS AND MATERIALS

Subjects

This retrospective study included 21 patients treated with definitive concurrent CRT for cervical cancer between July 2008 and January 2015. The patients' mean age was 50.0 years (range 39–67 years). The inclusion criteria were as following: (1) histologically proven cervical cancer with locally advanced stage (Stages IB2–IVA); (2) undergoing both MRI and ^{18}F -FDG PET/CT within 3 weeks before treatment; (3) receiving CRT in our institute. Exclusion criteria were as following: (1) previous treatment before undergoing MRI or ^{18}F -FDG PET/CT; (2) a history of primary treatment other than CRT; (3) previous diagnosis of another malignant disease; (4) pre-treatment MRI without DWI; or (5) discontinued follow-up within 2 years after completing treatment. The clinical stage was determined according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO).²⁰ The diagnosis of primary cervical cancer is made by pathological examination from specimens obtained by trans-vaginal cervical cone biopsies and pre-treatment staging was

Figure 1. A 57-year-old patient with International Federation of Gynecology and Obstetrics Stage IIB squamous-cell carcinoma. Oblique short axial T_2 weighted image (a) and apparent diffusion coefficient (ADC) map (b) of the largest section of tumour. Fluorine-18 fludeoxyglucose positron emission tomography/CT images depict metabolic tumour volume (MTV) in (c) axial and (d) sagittal planes. The results of each parameter are shown (e). This patient showed complete response to concurrent chemoradiotherapy. SUV, standardized uptake value; TLG, total lesion glycolysis.

based on the results of pelvic MRI, whole-body CT and/or ^{18}F -FDG PET/CT. Lymph nodes (LNs) $>1\text{ cm}$ in short-axis diameter on MRI and/or CT accompanied by focal ^{18}F -FDG uptake higher than that of the surrounding tissue on ^{18}F -FDG PET/CT were considered to be abnormal.²¹ This retrospective study was approved by the institutional review board of the McGill University Health Center, Montreal, QC, Canada (IRB number # 15-366-MUHC), and the need for patient-informed consent was waived.

Concurrent chemoradiotherapy

Therapy comprised of standard radiotherapy (RT) in combination with concurrent weekly cisplatin-containing chemotherapy. RT consisted of external-beam RT and intracavitary brachytherapy. External pelvic irradiation was administered with a daily fraction of 1.8 Gy, 5 days a week, with a total dose of 45 Gy. Brachytherapy was given with a total dose of 24 Gy with a fraction size of 8 Gy. Patients with pelvic LN metastasis received a booster dose ranging from 0 and 10 Gy at 1.8–2 Gy per fraction to the lateral pelvic side wall. All patients received six courses of cisplatin-based chemotherapy (40 mg m^{-2}) combined with RT.

Integrated fluorine-18 fludeoxyglucose positron emission tomography/CT examination

All ^{18}F -FDG PET/CT studies were performed using Discovery ST scanner (GE Healthcare, Montreal, QC), according to standard institutional clinical protocol. The patients were required to fast for at least 6 h before the time of their appointment. If the serum glucose level was $>11.1\text{ mmol l}^{-1}$ (200 mg dl^{-1}), then the study was rescheduled. A volume of 400 ml of barium sulfate oral

contrast was administered and 0.22 mCi kg^{-1} (8.14 MBq kg^{-1}) of ^{18}F -FDG was injected intravenously. An ^{18}F -FDG emission scan extending from the base of the skull to the mid thighs was obtained 60 min after intravenous injection of ^{18}F -FDG. Emission scans were acquired for 4–5 min per field of view depending on the body weight, each covering 15 cm, at an axial sampling thickness of 3.75 mm/slice. The 16-slice helical CT acquisition was performed prior to a full-ring dedicated PET scan of the same axial image. The CT component was operated with an X-ray tube voltage peak of 140 kVp, 90 mA, a 1.75:1 pitch, a slice thickness of 3.75 mm, a rotational speed of 0.8 s/rotation and a detector row configuration of $6 \times 0.625\text{ mm}$. The patient was allowed to breathe normally during the PET and CT acquisitions. The PET images were reconstructed using CT-derived attenuation correction using ordered subset expectation maximization software.

MRI

All pre-CRT pelvic MRI was performed on a 1.5-T MR scanner unit (Signa Excite; GE Healthcare, Waukesha, WI) by using an eight-element pelvic phased-array surface coil. For all MRI examinations, patients were placed in the supine position with an empty urinary bladder. Fast-recovery, fast spin-echo T_2 weighted images were obtained in the sagittal and transverse planes with the following parameters: repetition time ms/echo time ms, 4575/100; matrix, 512×256 ; number of signals acquired, 4; field of view, 24 cm; section thickness, 4 mm; and bandwidth, 31.25 kHz. Transverse oblique fast recovery fast spin-echo T_2 weighted imaging was subsequently performed with the following parameters: repetition time ms/echo time ms, 4000/100; matrix, 512×256 ; number of signals acquired, 4; field

Figure 2. A 40-year-old patient with International Federation of Gynecology and Obstetrics Stage IIIB squamous-cell carcinoma. Oblique short axial T_2 weighted image (a) and apparent diffusion coefficient (ADC) map (b) of the largest section of tumour. Fluorine-18 fludeoxyglucose positron emission tomography/CT images depict metabolic tumour volume (MTV) in (c) axial and (d) sagittal planes. The results of each parameter are shown (e). This patient showed no response to concurrent chemoradiotherapy. SUV, standardized uptake value; TLG, total lesion glycolysis.

of view, 24 cm; section thickness, 4 mm; and bandwidth, 31.25 kHz. The transverse oblique plane was perpendicular to the endocervical cavity, resulting in a short-axis view. Transverse oblique and sagittal DWI of the pelvis was performed using the following parameters: repetition time ms/echo time ms, 5000/69; matrix, 128×256 ; number of signals acquired, eight; field of view, 32 cm; section thickness, 6 mm; b -values, 0 and 1000 s mm^{-2} . Dynamic contrast-enhancement imaging of the pelvis was performed following the administration of 0.1 mmol kg^{-1} of body weight of gadolinium chelate (Gadovist®; Bayer, Montreal, QC) by using a three-dimensional gradient-echo T_1 weighted volume acquisition with the following parameters: repetition time ms/echo time ms, 3.6/1.75; number of signals acquired, one; matrix, 320×192 ; field of view, 26 cm; section thickness, 4 mm; and bandwidth, 62.50 kHz. Images were acquired at multiple phases of contrast medium enhancement in both the sagittal and transverse oblique planes at 25, 60, 120 and 180 s. Patients were given 40 mg of hyoscine butyl bromide (Buscopan; Boehringer, Ingelheim, Germany) intramuscularly before image acquisition to reduce bowel and uterine peristalsis.

Positron emission tomography/CT image analysis

All PET/CT studies were electronically retrieved and analyzed using commercially available software (FusionViewer v. 2.1; Nihon Medi-Physics Co., Japan) on a personal computer (Intel® Core™2 Quad; CPU Q8400 @ 1322.66 GHz, 3-GB random access memory) by a board-certified PET physician with 5 years' experiences (YU).

PET, CT and fused PET/CT images were displayed in axial, coronal and sagittal planes. A volume of interest (VOI) was placed over each suspicious cervical carcinoma in every patient (Figure 1). Care was taken to avoid inclusion of physiological ^{18}F -FDG uptake (e.g. excreted tracer in the bladder and/or rectum) within the tumour VOIs.

The following quantitative metrics were recorded: the highest SUV within any voxel included in the tumour VOI (SUV_{max}); the MTV defined as the sum of all voxels with a $\text{SUV} > 42\%$ of SUV_{max} ; and the total lesion glycolysis (TLG) defined as the MTV multiplied by the average SUV (SUV_{mean}) of all voxels with a $\text{SUV} > 42\%$ of SUV_{max} . The threshold of 42% of SUV_{max}

Table 1. Characteristics of patients in the responder and non-responder groups

Characteristics	Group		<i>p</i> -value
	Responder (<i>n</i> = 15)	Non-responder (<i>n</i> = 6)	
Age (years) ^a	47.00 ± 10.52	51.26 ± 7.70	0.36
Max tumour diameter ^a	56.00 ± 25.18	46.93 ± 9.85	0.39
FIGO stage ^b			
IB2	0	1	0.10
IIA2	1	0	
IIB	11	2	
IIIA	0	1	
IIIB	3	2	
Pelvic LN metastasis ^b			
Yes	7	6	0.04
No	8	0	
Para-aortic LN metastasis ^b			
Yes	0	0	1.00
No	15	6	
Distant metastasis ^b			
Yes	0	0	1.00
No	15	6	
Histology ^b			
SCC	15	5	0.28
Non-SCC	0	1	
Event-free survival (months) ^a	34.83 ± 18.32	15.53 ± 24.06	0.01

FIGO, International Federation of Gynecology and Obstetrics, LN, lymph node, max, maximum; SCC, squamous-cell carcinoma.

^aNumbers are average ± standard deviation.

^bNumbers are patient numbers.

Bold values indicate a statistically significant difference.

Table 2. Imaging parameters in the responder and non-responder groups

Variables	Group		<i>p</i> -value
	Responder (<i>n</i> = 15)	Non-responder (<i>n</i> = 6)	
PET parameter			
SUV _{mean}	8.20 ± 3.40	9.42 ± 1.80	0.55
SUV _{max}	13.04 ± 4.51	17.14 ± 4.20	0.14
MTV (ml)	34.81 ± 39.82	78.53 ± 47.40	0.04
TLG (g)	24.22 ± 19.62	68.81 ± 37.20	0.01
ADC parameter			
ADC _{mean} (×10 ^{−3} mm ² s ^{−1})	0.99 ± 0.18	1.06 ± 0.12	0.45
ADC _{min} (×10 ^{−3} mm ² s ^{−1})	0.45 ± 0.23	0.40 ± 0.21	0.55
ADC _{max} (×10 ^{−3} mm ² s ^{−1})	2.06 ± 0.70	2.18 ± 0.29	0.29
ADC _{90%} (×10 ^{−3} mm ² s ^{−1})	1.30 ± 0.28	1.34 ± 0.17	0.45
ADC _{75%} (×10 ^{−3} mm ² s ^{−1})	1.11 ± 0.20	1.17 ± 0.14	0.55
ADC _{50%} (×10 ^{−3} mm ² s ^{−1})	0.94 ± 0.16	1.01 ± 0.11	0.41
ADC _{25%} (×10 ^{−3} mm ² s ^{−1})	0.84 ± 0.10	0.91 ± 0.10	0.25
ADC _{10%} (×10 ^{−3} mm ² s ^{−1})	0.77 ± 0.15	0.84 ± 0.09	0.33
Skewness	0.82 ± 0.69	0.98 ± 0.16	0.72
Kurtosis	1.51 ± 0.92	1.42 ± 0.46	0.93

ADC, apparent diffusion coefficient; MTV, metabolic tumour volume; PET, positron emission tomography; SUV, standardized uptake value; TLG, total lesion glycolysis.

Numbers are average ± standard deviation.

Bold values indicate a statistically significant difference.

was chosen for defining MTV on the basis of the research by Erdi et al,²² as the optimal cut-off for delineating the volume of lesions in PET.

MR image analysis

All MR studies were electronically retrieved and analyzed with commercially available software (ImageJ v. 1.49; National Institutes of Health, Bethesda, MD) using a macro program on a personal computer (Intel Core2 Quad; CPU Q8400 @ 1322.66 GHz, 3-GB random access memory). The ADC value of each tumour was measured by two radiologists experienced in pelvic imaging (YU and AA, with 5 and 10 years' experience, respectively) in consensus, who were aware of the diagnosis of cervical cancer but fully blinded to clinical outcome of patients. A voxel-based analysis of each VOI was performed in each patient. The ROIs were manually drawn around the entire lesion on each consecutive tumour-containing slice of ADC maps, with reference to corresponding *T*₂ weighted images and contrast-enhanced *T*₁ weighted images for accurate border delineation (Figures 1 and 2). If the tumour was present on more than one slice, the ROIs pertaining to the tumour were added to a VOI.

The ADC of each voxel was automatically calculated using the following formula: $ADC = (\ln SI_0 - \ln SI) / b$, where *SI*₀ corresponds to the signal intensity without diffusion weighting (*b* = 0 s/mm²), *SI* is the signal intensity obtained at *b* = 1000 s/mm². ADC_{mean} was the

average value of all the ADC values within any voxel included in the tumour VOI. ADC_{min} was the lowest ADC of one voxel within tumour VOI, and ADC_{max} was the highest ADC of one voxel within tumour VOI. ADC_{*n*%} was the point at which *n*% of the voxel values that constituted the histogram are found to the left.^{15–19} In addition, the maximal diameter of each tumour was measured on the *T*₂ weighted images and used for the analysis of this study.

Outcome data

Post-treatment surveillance consisted of follow-up visits every 3 months for the first 2 years and every 6 months after 2 years. At 3 months after completion of CRT, patients were followed up with physical examination, chest radiography, tumour marker measurements, Papanicolaou tests and imaging studies using pelvic MRI or whole-body PET/CT.

The treatment response and prognosis were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors 1.1²³ or PET Response Criteria in Solid Tumors 1.²⁴ Patients with complete (metabolic) response and partial (metabolic) response were considered the responders whereas patients with stable (metabolic) disease and progressive (metabolic) disease were classified as non-responders. Recurrent disease was defined as evidence of local, regional or distant disease 6 months after the completion of therapy, determined by biopsy and/or follow-up imaging. The event-free survival (EFS) period was defined as the time between assignment and disease recurrence or death.

Table 3. Optimal cut-off values and diagnostic abilities of each imaging parameter for treatment response

Variables	Optimal cut-off value	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	Az [95% CI]
PET parameter							
SUV _{mean}	7.91	100 (6/6)	40.0 (6/15)	57.1 (12/21)	40.0 (6/15)	100 (6/6)	0.58 [0.33–0.80]
SUV _{max}	13.75	100 (6/6)	53.3 (8/15)	66.7 (14/21)	46.1 (7/13)	100 (7/7)	0.71 [0.44–0.89]
MTV (ml)	71.47	66.7 (4/6)	93.3 (14/15)	85.7 (18/21)	80.0 (4/5)	87.5 (14/16)	0.78 [0.46–0.93]
TLG (g)	679.69	66.7 (4/6)	93.3 (14/15)	85.7 (18/21)	80.0 (4/5)	87.5 (14/16)	0.84 [0.54–0.96]
ADC parameter							
ADC _{mean} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	1.15	50.0 (3/6)	86.7 (13/15)	76.1 (16/21)	60.0 (3/5)	81.2 (13/16)	0.61 [0.31–0.84]
ADC _{min} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.28	50.0 (3/6)	86.7 (13/15)	76.1 (16/21)	60.0 (3/5)	81.2 (13/16)	0.58 [0.32–0.82]
ADC _{max} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	2.06	83.3 (5/6)	47.7 (8/15)	57.1 (13/21)	38.5 (5/12)	87.9 (8/9)	0.65 [0.39–0.85]
ADC _{90%} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	1.47	50.0 (3/6)	86.7 (13/15)	76.2 (16/21)	60.0 (3/5)	81.3 (13/16)	0.61 [0.32–0.84]
ADC _{75%} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	1.28	50.0 (3/6)	86.7 (13/15)	76.2 (16/21)	60.0 (3/5)	81.3 (13/16)	0.59 [0.29–0.83]
ADC _{50%} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.94	83.3 (5/6)	46.7 (7/15)	57.1 (12/21)	38.5 (5/13)	87.5 (7/8)	0.62 [0.33–0.84]
ADC _{25%} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.85	83.3 (5/6)	60.0 (9/15)	66.7 (14/21)	45.4 (5/11)	90.0 (9/10)	0.66 [0.36–0.87]
ADC _{10%} ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.86	66.7 (4/6)	73.3 (11/15)	71.4 (15/21)	50.0 (4/8)	84.6 (11/13)	0.64 [0.35–0.86]
Skewness	0.80	100 (6/6)	26.7 (4/15)	47.6 (10/15)	36.2 (6/17)	100 (4/4)	0.44 (0.23–0.68)
Kurtosis	1.99	100 (6/6)	33.3 (5/15)	52.3 (11/15)	37.5 (6/16)	100 (5/5)	0.51 [0.26–0.75]

ADC, apparent diffusion coefficient; Az, area under the curve; CI, confidence interval; MTV, metabolic tumour volume; NPV, negative-predictive value; PET, positron emission tomography; PPV, positive-predictive value; SUV, standardized uptake value; TLG, total lesion glycolysis.

Figures in parentheses show actual numbers.

Figures in brackets show 95% CIs.

Statistical analysis

To determine differences in the PET parameters (SUV_{mean}, SUV_{max}, MTV and TLG); ADC parameters (ADC_{mean}, ADC_{min}, ADC_{max}, ADC_{90%}, ADC_{75%}, ADC_{50%}, ADC_{25%}, ADC_{10%}, skewness and kurtosis); other variables, including age, maximum tumour diameter, FIGO stage, pelvic LN status, para-aortic LN status, distant metastasis and histology, which can be prognostic factors;^{25–27} and EFS among the responder and non-responder groups, all parameters were compared by means of analysis of variance with Wilcoxon rank-sum test.

To determine the optimal cut-off values of PET and ADC parameters, as markers for distinguishing the responder groups from the non-responder groups, receiver operating characteristic (ROC) analyses were performed. Univariate and multivariate analyses of potential prognostic factors were performed using the Cox proportional hazards regression model. Variables that showed statistical significance ($p < 0.05$) in the univariate analysis were included in the multivariate

analysis. To determine the usefulness of PET and ADC parameters for prediction of prognosis after CRT, EFS for the two groups divided by each of the adapted cut-off values were compared by using the Kaplan–Meier method followed by the log-rank test. Commercially available software (JMP v. 10; SAS Institute Japan Ltd, Tokyo, Japan) was used for all statistical analyses. A p -value of <0.05 was considered significant in all analyses.

RESULTS

21 patients with local advanced cervical cancer (age range, 39–67 years; mean age, 50 years), 1 of whom was diagnosed as Stage IB2, 1 as Stage IIA2, 13 of whom were diagnosed as Stage IIB, 1 as Stage IIIA and 8 as Stage IIIB, were enrolled in this study. On pathological examination, 20 were diagnosed with squamous-cell carcinoma and 1 with adenocarcinoma. 13 patients had pelvic node metastasis. No patients had para-aortic LN metastasis or other distant metastasis pre-treatment. The follow-up period ranged from 11 to 82 months (mean 19.6 months). Eight patients had disease progression, and two patients passed away during the

Table 4. Univariate Cox analyses for predicting event-free survival rate

Variables	HR (95% CI)	<i>p</i> -value
PET parameter		
SUV _{mean}		
≥7.91	2.908 (0.495–54.995)	0.266
<7.91	0.343 (0.025–0.571)	
SUV _{max}		
≥13.75	9.663 × 10 ¹⁰ (1.608–1.608)	0.016
<13.75	1.034 × 10 ^{−9} (0.621–0.621)	
MTV (ml)		
≥71.47	7.631 (1.745–39.225)	0.007
<71.47	0.131 (0.025–0.571)	
TLG (g)		
≥679.69	7.631 (1.748–39.225)	0.007
<679.69	0.131 (0.025–0.571)	
ADC parameter		
ADC _{mean} (×10 ^{−3} mm ² s ^{−1})		
≥1.15	3.474 (0.669–16.156)	0.128
<1.15	0.288 (0.062–1.474)	
ADC _{min} (×10 ^{−3} mm ² s ^{−1})		
≥0.28	0.650 (0.139–4.779)	0.629
<0.28	1.563 (0.209–7.197)	
ADC _{max} (×10 ^{−3} mm ² s ^{−1})		
≥2.06	5.040 (0.085–95.475)	0.077
<2.06	0.190 (0.010–1.168)	
ADC _{90%} (×10 ^{−3} mm ² s ^{−1})		
≥1.47	3.473 (0.669–16.159)	0.128
<1.47	0.287 (0.061–1.494)	
ADC _{75%} (×10 ^{−3} mm ² s ^{−1})		
≥1.28	3.473 (0.669–16.159)	0.128
<1.28	0.287 (0.061–1.494)	
ADC _{50%} (×10 ^{−3} mm ² s ^{−1})		
≥0.94	2.478 (0.569–16.950)	0.237
<0.94	0.403 (0.589–1.750)	
ADC _{25%} (×10 ^{−3} mm ² s ^{−1})		
≥0.85	3.019 (0.692–20.651)	0.146
<0.85	0.331 (0.048–1.443)	
ADC _{10%} (×10 ^{−3} mm ² s ^{−1})		
≥0.86	5.167 (1.099–36.373)	0.037
<0.86	0.193 (0.027–0.907)	

(Continued)

Table 4. (Continued)

Variables	HR (95% CI)	<i>p</i> -value
Skewness		
≥0.80	6.540 × 10 ¹⁰ (0.638–0.638)	0.108
<0.80	1.527 × 10 ^{−9} (1.566–1.566)	
Kurtosis		
≥1.99	0.597 (0.080–2.631)	0.516
<1.99	1.623 (0.379–11.521)	

ADC, apparent diffusion coefficient; CI, confidence interval; HR, hazard ratio; MTV, metabolic tumour volume; PET, positron emission tomography; SUV, standardized uptake value; TLG, total lesion glycolysis. Bold values indicate a statistically significant difference.

follow-up period. The results comparing patient characteristics and EFS among responder and non-responder groups are shown in Table 1. Pelvic LN status and EFS of the responder group were significantly different from those of the non-responder groups (pelvic LN status; $p = 0.04$, EFS; $p = 0.01$).

Table 2 shows the comparison of PET parameters and ADC parameters in responder and non-responder groups. The primary-tumour MTV and TLG in non-responders was significantly higher than the corresponding value of lesions in responders (MTV, $p = 0.04$; TLG, $p = 0.01$). All other volumetric imaging parameters demonstrated no significant differences between these two groups.

The optimal cut-off value and predictive ability of each imaging parameter analyzed are shown in Table 3. Although statistical significance was not achieved, the ROC analyses showed that the area under the curve of TLG (0.84) was larger than that of every

Table 5. Multivariate Cox analyses for predicting event-free survival rate

Variables	HR (95% CI)	<i>p</i> -value
SUV _{max}		
≥13.75	1.047×10^9 (0.710–6.020)	0.084
<13.75	9.543×10^{-10} (0.167–1.395)	
MTV (ml)		
≥71.47	4.725 (1.107–23.983)	0.036
<71.47	0.211 (0.041–0.902)	
TLG (g)		
≥679.69	4.725 (1.107–23.983)	0.036
<679.69	0.211 (0.041–0.902)	
ADC _{10%} ($\times 10^{-3}$ mm ² s ⁻¹)		
≥0.86	5.207 (1.000–41.105)	0.048
<0.86	0.192 (0.024–0.990)	

ADC, apparent diffusion coefficient; CI, confidence interval; HR, hazard ratio; MTV, metabolic tumour volume; SUV, standardized uptake value; TLG, total lesion glycolysis. Bold values indicate a statistically significant difference.

other imaging parameter; the accuracy of MTV (85.7%) and TLG (85.7%) were the highest among all the imaging parameters evaluated.

The results of univariate Cox regression analyses for prediction of EFS are shown in Table 4. The univariate Cox regression model analysis indicated that SUV_{max} (≥ 13.75), MTV (≥ 71.47 ml), TLG (≥ 679.69 g) and $ADC_{10\%}$ ($\geq 0.86 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) of the tumour were significantly associated with EFS rate ($p = 0.044$, $p = 0.016$, $p = 0.007$ and $p = 0.037$, respectively). The multivariate Cox regression model analysis indicated that MTV, TLG and $ADC_{10\%}$ were significantly and independently associated with the EFS rate ($p = 0.036$, $p = 0.036$ and $p = 0.048$, respectively) (Table 5).

The Kaplan–Meier curves of EFS are shown in Figure 3. The differences in EFS between the two groups divided by MTV threshold at 71.4 ml and TLG threshold at 679.7 g were significant ($p = 0.002$, and $p = 0.002$, respectively). The differences in EFS between the two groups divided by SUV_{max} threshold at 13.75 was marginal significant ($p = 0.05$). There were no significant differences in EFS between the two groups divided by other factors (SUV_{mean} , $p = 0.29$; SUV_{max} , $p = 0.36$; ADC_{mean} , $p = 0.42$; ADC_{min} , $p = 0.48$; ADC_{max} , $p = 0.80$; $ADC_{90\%}$, $p = 0.42$; $ADC_{75\%}$, $p = 0.42$; $ADC_{50\%}$, $p = 0.25$; $ADC_{25\%}$, $p = 0.16$; $ADC_{10\%}$, $p = 0.75$; skewness, $p = 0.45$; and kurtosis, $p = 0.52$).

DISCUSSION

In this study, MTV and TLG achieved statistically significant differences between the responder and non-responder groups. Pelvic LN status and EFS of the non-responder group were significantly different from those of the responder group, but other clinical characteristics showed no significant differences between responder and non-responder groups. Multivariate Cox regression analysis indicated that MTV, TLG and $ADC_{10\%}$ were statistically significant prognostic factors for EFS. In a comparison of EFS using two different quantitative parameters and their respective optimal cut-off values for distinguishing one group

from the others, MTV and TLG responders showed better prognosis than MTV and TLG non-responders. The results of this study thus indicated that MTV and TLG were better predictors of tumour response and EFS than other imaging parameters.

The efficacy of CRT and the pattern of disease progression have been shown to be dependent on the biological heterogeneity of the tumour.^{28,32} Consequently, various functional imaging techniques have been investigated for the purpose of assessing and monitoring tumour response before treatment. ^{18}F -FDG PET/CT has been reported as a useful biomarker for predicting treatment response in cervical cancers.^{5,28,30} Although SUV_{max} is a convenient quantitative measure and widely used, it is a measurement of a single pixel with the highest radiotracer concentration within the ROI and, as such, may not reflect the heterogeneous nature of the primary tumour. Furthermore, SUV_{max} is easily affected by statistical noise and pixel size while SUV_{mean} is derived from the whole tumour and is considered to be less influenced by statistical noise than SUV_{max} . However, previous studies indicated that SUV_{mean} does not sufficiently reflect the heterogeneous nature and volume of the primary tumour.^{8,10} Our results are consistent with these hypotheses. In recent years, several studies have suggested an advantage of MTV and TLG over SUV parameters^{7–11} for prediction of prognosis with specific tumours, including uterine cervical cancer. Chung et al⁸ demonstrated that MTV was a better predictor of recurrence, LN metastasis, parametrial invasion and FIGO stage than SUV_{max} . Miccò et al¹¹ reported that MTV and TLG were stronger independent prognostic factor for disease-free survival and performed better in this regard than other ^{18}F -FDG PET/CT parameters. The results of our study strongly support these previous reports.

Several studies revealed that cellular tumours with low baseline pre-treatment ADC values respond better to chemotherapy or radiation treatment than tumours with high pre-treatment ADC values because the latter are likely to be more necrotic.^{16,31,34} This is based on the theory that necrotic tumours are frequently

Figure 3. Event-free survival of patients with uterine cervical cancer assessed by metabolic tumour volume (MTV) and total lesion glycolysis (TLG). (a) The median event-free survival period of patients with MTV <71.47 ml was significantly longer than with MTV ≥ 71.47 ml ($p = 0.002$). (b) The median event-free survival period of patients with TLG <679.69 g was significantly longer than with TLG ≥ 679.69 g ($p = 0.002$).

hypoxic, acidotic and poorly perfused, leading to diminished sensitivity to chemotherapy and RT.^{31,33} To more precisely evaluate the necrotic component within a heterogeneous tumour, histogram-based analysis has been suggested to assess early therapeutic response and predict survival in patients with specific cancers.^{14–19} In uterine cervical cancer patients treated with CRT, McVeigh et al¹⁵ demonstrated that the ADC_{90%} was lower in responders than in non-responders. Heo et al¹⁷ reported the pre-CRT ADC_{75%} served as a biomarker for predicting tumour recurrence in patients with uterine cervical cancer treated with CRT. In contrast to those studies, our study showed the all ADC parameters had no significant differences between the responder and non-responder groups, and only ADC_{10%} among the ADC parameters had a significant association for EFS in Cox regression analysis. The difference between our study and previous ones may reflect differences in the patient population characteristics. The patients enrolled in our study were diagnosed with locally advanced cancer, whereas previous studies^{15,17} enrolled patients with earlier stage disease. Our study suggests that MTV and TLG can reflect the heterogeneity of advanced cervical cancer more precisely than ADC histogram parameters. As the number of previous studies dealing with ADC histogram analysis for evaluation of uterine cervical cancer prognosis is limited, further prospective studies are needed. There is also a possibility that change of the ADC histogram parameters during CRT is a better predictor of treatment response and survival

in patients with uterine cervical cancer than the pre-treatment parameters, and this will be the objective of a future study.

Our study has the several limitations. First, it was performed with a small number of patients. Nevertheless, the advantages of MTV and TLG were proved in every statistical analysis in this study. Second, this was a retrospective study. ¹⁸F-FDG PET/CT was not performed in every case of cervical cancer in our institution before primary treatment. This may have introduced a selection bias in performing surveillance ¹⁸F-FDG PET/CT according to physicians' preference and may have influenced the study results.

Despite these limitations, our study clearly showed that MTV and TLG can be used to identify patients with advanced uterine cervical cancer treated with CRT at high risk for recurrence. Although ADC_{10%} was deemed to be the best of the ADC parameters for predicting EFS, our results also suggest that volume-based ¹⁸F-FDG PET/CT analysis could provide more effective information than volume-based ADC histogram analysis for predicting treatment outcome for patients with advanced uterine cervical cancer.

ACKNOWLEDGMENTS

The authors thank Teruki Sone, MD, PhD, for technical support in data analyzing.

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