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Different Prognostic Implications of ^{18}F-FDG PET Between Histological Subtypes in Patients With Cervical Cancer

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Abstract: This study aimed to investigate whether the predictive values of intensity- and volume-based PET parameters are different between histological subtypes in patients with cervical cancer.

Ninety patients, 65 with squamous cell carcinoma (SCC) and 25 with non-SCC (NSCC), who underwent pretreatment ^{18}F-FDG PET/CT and pelvic MRI, were studied retrospectively. In addition to SUV_{max} and SUV_{mean}, metabolic-tumor-volume (MTV) was determined by thresholding of 40% SUV_{max} and total-lesion-glycolysis (TLG) was calculated. Clinical factors and PET metabolic indices were compared between SCC and NSCC. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method with cutoffs determined by ROC analyses to stratify SCC and NSCC patients separately. Factors associated with survival were assessed with univariate and multivariate analyses using the Cox regression model.

No significant differences were observed in clinical factors other than tumor size or ^{18}F-FDG PET metabolic indices between SCC and NSCC. The Kaplan–Meier estimates of 2-year PFS and OS rates were 60% and 70% for SCC and 40% and 76% for NSCC, respectively. Multivariate analyses showed that MTV and TLG were the independent prognostic factors for PFS and OS in SCC; in contrast, SUV_{max} was the independent prognostic factor for PFS and OS in NSCC.

Metabolic burden (MTV and TLG) could be beneficial for the prognostic prediction of cervical SCC patients; in contrast, metabolic intensity (SUV_{max}) could be beneficial for the prognostic prediction of NSCC patients. The different prognostic implications might be based on the differences of tissue integrity and histological heterogeneity between SCC and NSCC.

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Abbreviations: ^{18}F-FDG = 2-[^{18}F]-fluoro-2-deoxy-D-glucose, AC = adenocarcinoma, ASC = adenosquamous carcinoma, AUC = area under the curve, CCRT = concurrent chemoradiation therapy, CI = confidence interval, CT = computed tomography, DFS = disease-free survival, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, LNs = lymph nodes, MRI = magnetic resonance imaging, MTV = metabolic-tumor-volume, NAC = neoadjuvant chemotherapy, NSCC = nonsquamous cell carcinoma, OS = overall survival, PET = positron emission tomography, PFS = progression-free survival, RH = radical hysterectomy, ROC analysis = receiver-operating-characteristic analysis, SCC = squamous cell carcinoma, SUV = standardized uptake value, TLG = total-lesion-glycolysis, VOI = volume of interest.

INTRODUCTION

Invasive cervical cancer is one of the most common cancers in women worldwide. Cervical cancer has been classified into 2 major histological types: squamous cell carcinoma (SCC) and non-SCC (NSCC), such as adenocarcinoma (AC) and adenosquamous carcinoma (ASC). SCC accounts for 75% of cervical cancer while AC accounts for 20% to 25% of cervical cancer.[1,2] Although AC comprises a minority of cervical cancers, its relative and absolute frequency has increased over the last 4 decades despite the wider application of cervical cancer screening.[3–5] The difficulties associated with accessibility to glandular lesions in screening and histological variability have been implicated in the increased incidence of AC. NSCC differs from SCC regarding anatomical origin, risk factors, dissemination, recurrence sites, and metastasis rates. A recent large population-based analysis showed that AC was associated more with a poorer prognosis in the early and advanced stages than SCC.[5]

Positron emission tomography (PET) with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is of significant value for the evaluation of cervical cancer patients because it has the capacity to identify lymph node involvement, distant disease, and recurrence.[6,7] It also provides prognostic information by quantifying intensity-based metabolic parameters such as standardized uptake value (SUV) and volume-based metabolic parameters such as metabolic-tumor-volume (MTV) and total-lesion-glycolysis (TLG).

Some of the previous studies showed tumor ^{18}F-FDG uptake (SUV) as a predictive biomarker, whereas others showed volume-based indices (MTV and TLG) were significant prognostic factors for treatment responses or long-term prognoses in cervical cancer patients.[8–13] Despite accuracy and wide utility of PET parameters, still there are controversies about which metabolic parameters are genuinely predictive indicators for the prognosis of cervical cancer patients. Most of the previous studies were conducted with SCC patients as a major group

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TR participated in data analysis and writing the paper. TeT participated in ^{18}F-FDG PET scans, data analysis, and paper writing. MY, YC, AS, TK, YY participated in patient recruitment and treatment (surgery and/or chemotherapy). TaT participated in ^{18}F-FDG PET scans and provided radiation therapy. HK was involved in supervision and participated in ^{18}F-FDG PET scans. HO was involved in supervision and reviewing the paper.
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and other histological subtype, NSCC patients were very few in number. Only 1 research was conducted until now to evaluate prognostic value of ^{18}F-FDG PET in cervical NSCC (AC/ASC) patients.[14] The significance of ^{18}F-FDG PET as a prognostic predictor for each subtype of cervical cancer is not understood in detail. Discrepancies found in previous research findings might be caused by analyzing data irrespective of different histological subtypes of cervical cancer which could show different trends for the prognostic predictability of ^{18}F-FDG PET. Therefore, the aim of the present study was to investigate the predictive performance of intensity- and volume-based metabolic parameters of ^{18}F-FDG PET in cervical cancer patients according to the histological subtype which could be beneficial for individualized patient care and treatment planning.

METHODS

Patients

We retrospectively reviewed the medical records of all patients with cervical cancer who underwent ^{18}F-FDG PET/CT and pelvic MRI as part of a staging workup prior to treatment at the University of Fukui Hospital from June 2006 to December 2013. Enrollment required: histologically confirmed cervical cancer; stage IB–IVA determined by the 2009 International Federation of Gynecology and Obstetrics (FIGO) classifications; clinical features of interest for multivariate Cox regression analysis; and availability of follow-up information regarding survival status for a maximum period of 36 months. Patients with distant metastases (FIGO stage IVB) were excluded. Finally, 90 patients (65 SCCs and 25 NSCCs, mean age = 55.2 years) were enrolled in this study. For this type of retrospective study formal consent was not required. This study was approved by the Institutional Review Board for human investigations.

PET/CT Imaging

The PET/CT imaging protocol was described previously.[15] Whole-body PET scans with ^{18}F-FDG were performed with a combined PET/CT scanner (Discovery LS; GE Medical Systems, Milwaukee, WI), which permitted the simultaneous acquisition of 35 image slices in a 3-dimensional acquisition mode with interslice spacing of 4.25 mm. The PET/CT scanner incorporated an integrated 4-slice multidetector CT scanner, which was used for attenuation correction. CT scanning parameters were as follows: Auto mA (upper limit, 40 mA; noise index, 20), 140 kV, 5-mm section thickness, 15-mm table feed, and pitch of 4. After at least 4 hours of fasting, patients received an intravenous injection of 185MBq ^{18}F-FDG and image acquisition began 50 minutes after the injection. A whole-body emission scan was performed from the head to the inguinal region with 2 minutes per bed position (7–8 bed positions). PET data were reconstructed by the iterative reconstruction method selecting 14 subsets and 2 iterations, a 128×128 matrix, and postsmoothing with an 8-mm Gaussian filter. The reconstructed images were then converted to a semiquantitative image corrected by the injection dose and subject's body weight (= SUV).

Image Analysis

^{18}F-FDG PET/CT images were retrospectively interpreted by the consensus of 2 experienced radiologists (TaT and HO with 19 and 16 years of experience in oncologic PET, respectively) who had no knowledge of the other imaging results or the clinical data. Lymph nodes (LNs) with increased ^{18}F-FDG uptake, even if they were smaller than 1 cm in short-axis diameter on CT images, were defined as PET positive LNs (LN metastasis).

Tumor size was measured on MR images as a maximum diameter of the primary tumor. Subsequently, ^{18}F-FDG PET images were coregistered to individual MR images using automatic registration software (AW VS4; GE Medical Systems). Volume of interest (VOI) was placed on the primary site and the tumor contour was delineated to include voxels presenting SUV values greater than 40% of maximum SUV (SUV_{max}) (Figure 1).[16] The extracted tumor volume was defined as metabolic-tumor-volume (MTV), and total-lesion-glycolysis (TLG) was calculated as the product of the mean SUV (SUV_{mean}) and MTV. SUV_{max} and SUV_{mean} were used as intensity-based metabolic parameters; MTV and TLG were used as volume-based parameters for further analyses.

Statistical Analysis

The χ^2 test and unpaired t test were used to assess differences in clinical factors (age, tumor size, FIGO stage, PET positive LNs, and treatment method) and ^{18}F-FDG PET metabolic parameters (SUV_{max}, SUV_{mean}, MTV, and TLG) between SCC and NSCC.

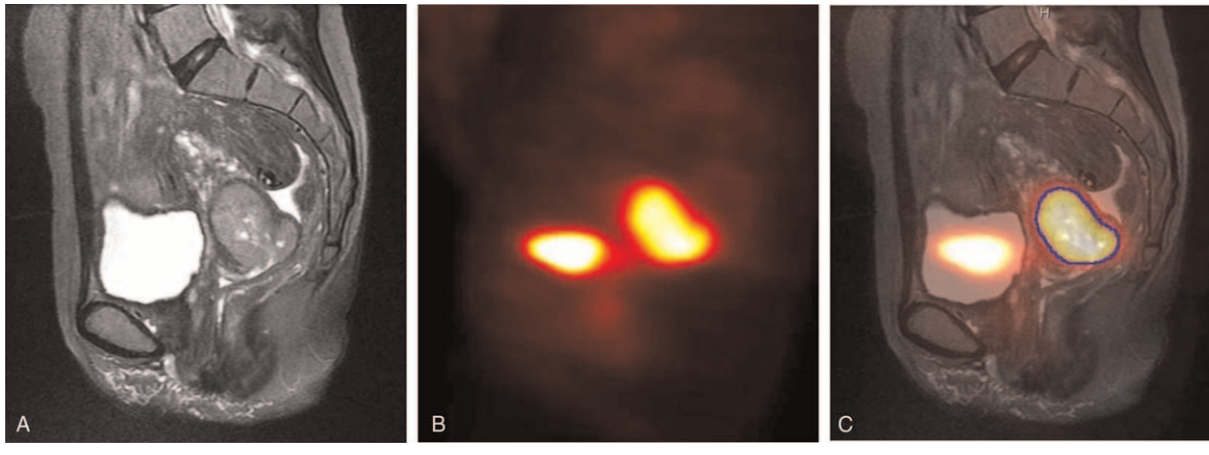

FIGURE 1. T2-weighted MR (A), ^{18}F-FDG PET (B), and coregistered (C) images of a 46-year-old woman with stage IIB cervical ASC. Tumor contour (blue line) was delineated to include voxels presenting SUV values greater than 40% of SUV_{max} on the coregistered image (C).

Receiver-operating-characteristic (ROC) analyses were performed separately in SCC and NSCC to determine optimal cut-off values for tumor size, SUV_{max}, SUV_{mean}, MTV, and TLG and divide patients with or without events (disease progression and overall death) at the time of the last follow-up after treatment. The significance of the difference between the area under the ROC curves (AUCs) was then tested using the method of DeLong et al.[17]

In the survival analysis, clinical factors and PET parameters were categorized into 2 groups each. Potential factors associated with progression-free survival (PFS) and overall survival (OS) were analyzed in univariate and multivariate analyses using a Cox proportional hazard regression model. Variables with $P < 0.05$ in the univariate analysis were selected for the multivariate analysis. PFS and OS were estimated using the Kaplan–Meier method, and their comparison was based on the log-rank test.

All statistical analyses were performed using MedCalc (version 14) and IBM SPSS Statistics (version 22). A probability of less than 0.05 was considered significant.

RESULTS

Patient Characteristics

The characteristics of all 90 patients are summarized in Table 1. Tumor size (maximum diameter) of SCC was significantly larger than that of NSCC ($P = 0.02$). None of the other clinical factors or ^{18}F-FDG PET metabolic indices showed significant differences between SCC and NSCC. The median follow-up periods for surviving patients were 27 months (range, 2–36 months) and 28 months (range, 2–36) in SCC and NSCC, respectively. During the follow-up, 40 SCC patients (61%) were alive without recurrent disease while 6 (9%) developed locoregional recurrence or metastasis. Eighteen SCC patients (28%) died from disease progression and 1 (2%) died from another disease. On the other hand, 11 NSCC patients (44%) were alive without recurrent disease while 7 (28%) developed recurrence. Seven NSCC patients (28%) died from disease progression. The Kaplan–Meier estimates of 2-year PFS and OS rates were 60% and 70% for SCC and 40% and 76% for NSCC, respectively.

TABLE 1. Patient Characteristics According to Histological Subtypes

Characteristics	SCC (n = 65)	NSCC (n = 25)	*P*
Age	55.4 ± 14.0	54.6 ± 15.2	0.81
Tumor size (cm)	4.8 ± 2.1	3.6 ± 1.7	0.02
FIGO stage			0.96
IB	17 (26%)	8 (32%)	
IIA-B	22 (34%)	8 (32%)	
IIIA-B	20 (31%)	7 (28%)	
IVA	6 (9%)	2 (8%)	
PET positive LNs			0.71
None	41 (63%)	18 (72%)	
Pelvic alone	15 (23%)	4 (16%)	
Para-aortic	9 (14%)	3 (12%)	
Treatment			0.34
Surgery included	37 (57%)	17 (68%)	
Other than surgery	28 (43%)	8 (32%)	
SUV_{max}	11.9 ± 6.3	12.4 ± 8.8	0.74
SUV_{mean}	7.1 ± 4.1	7.4 ± 5.9	0.79
MTV	31.1 ± 28.1	20.9 ± 17.5	0.09
TLG	262.6 ± 373.3	190.9 ± 311.3	0.40

Continuous variables were expressed as the mean ± standard deviation and categorical variables were presented as a frequency and percentage.

ROC Analysis

Optimal cut-off values and AUCs determined by the ROC analyses in SCC and NSCC are shown in Table 2. The AUCs of tumor size and 4 PET parameters were taken as approximate indicators of the prediction of event occurrence because the ROC analysis had no information on survival periods. Volume-based parameters in SCC showed greater AUCs, indicating greater accuracy in the prediction of event occurrence than that of intensity-based parameters. Based on pairwise comparisons of AUCs, TLG showed significantly greater accuracy for predicting disease progression than SUV_{max} and SUV_{mean} ($P = 0.01$ and $P = 0.005$, respectively), and TLG showed significantly greater accuracy for predicting overall death than SUV_{max} and SUV_{mean} ($P = 0.01$ and $P = 0.005$, respectively). In contrast, intensity-based parameters showed greater AUCs, indicating greater accuracy in the prediction of event occurrence than that of volume-based parameters in NSCC. No significant differences were observed among tumor size and 4 AUCs in NSCC. Each cut-off value was used for subsequent survival analyses.

Survival Analysis

In SCC, univariate analyses showed that tumor size, FIGO stage, PET positive LNs, treatment method, SUV_{max}, SUV_{mean}, MTV, and TLG correlated with decreased PFS ($P < 0.05$), and the same factors other than PET positive LNs, correlated with decreased OS ($P < 0.05$) (Table 3). In NSCC, univariate analyses revealed that FIGO stage, PET positive LNs, treatment method, SUV_{max}, and SUV_{mean} correlated with decreased PFS ($P < 0.05$), while the FIGO stage, PET positive LNs, SUV_{max}, and SUV_{mean} correlated with decreased OS ($P < 0.05$) (Table 3).

Since SUV_{max} and SUV_{mean} were strongly correlated, only SUV_{max} was used for subsequent multivariate analyses in SCC and NSCC. Furthermore, since tumor size, MTV, and TLG were related variables regarding volume, 3 different models including size, MTV, and TLG separately were used for multivariate analyses in SCC. In SCC (Table 4), SUV_{max} (HR = 2.87, 95% CI 1.04–7.90, $P = 0.04$), MTV (HR = 7.58, 95% CI 1.84–31.2, $P = 0.01$), and TLG (HR = 4.54, 95% CI 1.57–13.1, $P = 0.01$) were independent prognostic factors for PFS, while MTV (HR = 10.6, 95% CI 2.54–44.2, $P = 0.001$) and TLG (HR = 11.6, 95% CI 2.62–51.6, $P = 0.001$) were independent prognostic factors for OS. In NSCC (Table 5), SUV_{max} was the only independent prognostic factor for PFS (HR = 12.9, 95% CI 1.69–99.5, $P = 0.01$) and for OS (HR = 6.98, 95% CI 1.17–41.6, $P = 0.03$). Kaplan–Meier survival curves of each PET index for PFS and OS in SCC and NSCC are shown in Figures 2 and 3, respectively.

DISCUSSION

In the present study, we assessed the predictive value of pretreatment ^{18}F-FDG PET on the basis of metabolic intensity and metabolic tumor burden according to the histological subtype in cervical cancer patients. Our results demonstrated the different prognostic implications of ^{18}F-FDG PET between

TABLE 2. ROC Analyses for Cut-Off Determination and Comparison of Event Prediction in SCC and NSCC

	SCC (n = 65)					NSCC (n = 25)				
Event	**Size**	**SUV_{max}**	**SUV_{mean}**	**MTV**	**TLG**	**Size**	**SUV_{max}**	**SUV_{mean}**	**MTV**	**TLG**
Recurrence										
Cutoff	4.2	10.7	6.0	26.5	231	2.7	13.4	7.4	13.8	160
AUC	0.73	0.70*	0.69#	0.83	0.84*,#	0.63	0.72	0.70	0.52	0.58
Death										
Cutoff	4.2	12.5	7.0	30.4	231	3.5	14.1	7.4	13.8	160
AUC	0.78	0.72**	0.71***	0.88	0.89**,***	0.69	0.78	0.77	0.56	0.64

Pairwise comparison.
* $P = 0.01$.
# $P = 0.005$.
** $P = 0.01$.
*** $P = 0.005$.

cervical SCC and NSCC. The volume-based parameters, MTV and TLG, were independent prognostic factors, irrespective of FIGO stages, PET positive LNs, treatment method, and SUV_{max} for PFS and OS in SCC patients. On the other hand, intensity-based parameter, SUV_{max}›, was the independent prognostic factor, irrespective of FIGO stages, PET positive LNs,, and treatment method for PFS and OS in NSCC patients. Therefore, discrimination of histological subtypes is important for prognostic prediction of cervical cancer patients by ^{18}F-FDG PET. Our results are consistent with a previous investigation with lung cancer patients which reported SUV_{max} of primary tumor as a significant prognostic determinant for patients with AC but not with SCC.[18]

The only previous study to evaluate the prognostic significance of preoperative ^{18}F-FDG PET in cervical NSCC (AC and ASC) was conducted by Chou et al.[14] They enrolled stage IB/IIB cervical AC/ASC patients, and univariate analyses revealed that SUV_{max} of the primary tumor >5.3, stage IIB, deep cervical stromal invasion, tumor size measured by MRI ≥40 mm, and pelvic lymph node metastasis correlated with decreased OS. Due to the small number of events (9 overall deaths) relative to all patient populations (n = 83), a multivariate analysis was not performed in their study. Although the sample size of NSCC (n = 25) in our study was smaller than that in their study, a multivariate analysis was possible and revealed that SUV_{max} was an independent prognostic factor for PFS and OS in NSCC patients.

Most of the previous studies that evaluated the predictive value of ^{18}F-FDG PET focused on the major histological subtype of cancer or mixed minorities with it. However, the incidence of SCC, a predominant subtype of cervical cancer, has progressively declined since the introduction of the

TABLE 3. Univariate Analyses of Factors Associated With PFS and OS in SCC and NSCC

	SCC (n = 65)				NSCC (n = 25			
	PFS		**OS**		**PFS**		**OS**	
Variables	**HR 95% CI**	***P***	**HR 95% CI**	***P***	**HR 95% CI**	***P***	**HR 95% CI**	***P***
Age								
≤ or > 50	1.21 (0.53–2.76)	0.66	1.33 (0.52–3.38)	0.55	2.59 (0.89–7.52)	0.08	4.25 (0.82–21.9)	0.085
Tumor size								
≤ or >cutoff	4.15 (1.55–11.2)	0.005	9.12 (2.10–39.6)	0.003	1.50 (0.42–5.40)	0.53	3.55 (0.69–18.3)	0.13
FIGO stage								
I/II or III/IV	4.61 (1.96–10.9)	0.001	6.57 (2.35–18.4)	0.001	3.27 (1.13–9.49)	0.03	6.17 (1.19–32.0)	0.030
PET positive LN								
− or +	2.75 (1.22–6.19)	0.015	2.24 (0.91–5.53)	0.081	3.44 (1.16–10.1)	0.025	4.52 (1.00–20.4)	0.049
Treatment								
Surgery + or −	3.63 (1.54–8.51)	0.003	5.90 (2.10–16.6)	0.001	2.99 (1.02–8.71)	0.045	4.18 (0.93–18.84)	0.063
SUV_{max}								
≤ or >cutoff	3.65 (1.36–9.78)	0.010	3.08 (1.21–7.85)	0.018	14.1 (2.84–69.6)	0.001	8.27 (1.59–43.1)	0.012
SUV_{mean}								
≤ or >cutoff	4.07 (1.39–11.9)	0.010	3.63 (1.30–10.1)	0.014	13.7 (2.74–68.0)	0.001	5.74 (1.11–29.8)	0.038
MTV								
≤ or >cutoff	9.70 (3.29–28.6)	0.001	16.9 (4.82–59.1)	0.001	1.12 (0.31–4.07)	0.86	3.09 (0.60–15.9)	0.18
TLG								
≤ or >cutoff	7.48 (2.94–19.0)	0.001	12.5 (3.62–43.2)	0.001	1.69 (0.58–4.89)	0.33	2.94 (0.65–13.2)	0.16

TABLE 4. Multivariate Analyses of Factors Associated With PFS and OS in SCC

	PFS						OS					
	Model A		Model B		Model C		Model A		Model B		Model C	
Variables	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*	HR 95% CI	*P*
Tumor size												
< or >cutoff	1.05 (0.24–4.51)	0.95					2.51 (0.40–15.9)	0.33				
FIGO stage												
I/II or III/IV	3.26 (0.86–12.3)	0.08	3.19 (0.91–11.2)	0.07	3.35 (0.96–11.7)	0.06	2.23 (0.56–8.85)	0.25	2.74 (0.81–9.25)	0.11	2.50 (0.72–8.69)	0.15
PET positive LN												
− or +	1.67 (0.69–4.02)	0.25	1.54 (0.65–3.66)	0.33	1.7 (0.72–4.04)	0.23						
Treatment												
Surgery + or −	1.10 (0.31–3.89)	0.88	0.42 (0.11–1.66)	0.22	0.67 (0.18–2.46)	0.54	2.15 (0.57–8.14)	0.26	1.00 (0.28–3.59)	1.00	1.78 (0.50–6.31)	0.37
SUV_{max}												
≤ or >cutoff	2.87 (1.04–7.90)	0.04	1.33 (0.44–4.04)	0.61	1.76 (0.61–5.04)	0.30	1.89 (0.71–5.06)	0.21	1.22 (0.45–3.26)	0.69	0.56 (0.18–1.71)	0.31
MTV												
≤ or >cutoff			7.58 (1.84–31.2)	0.01					10.6 (2.54–44.2)	0.001		
TLG												
≤ or >cutoff					4.54 (1.57–13.1)	0.01					11.6 (2.62–51.6)	0.001

TABLE 5. Multivariate Analyses of Factors Associated With PFS and OS in NSCC

	PFS			OS		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
FIGO stage						
I/II or III/IV	0.86	(0.06–11.7)	0.91	6.24	(0.98–39.7)	0.052
PET positive LNs						
− or +	1.12	(0.23–5.35)	0.89	5.51	(0.91–33.3)	0.063
Treatment						
Surgery + or −	2.90	(0.23–37.0)	0.41			
SUV_{max}						
≤ or >cutoff	12.9	(1.69–99.5)	0.014	6.98	(1.17–41.6)	0.033

Papanicolaou test, whereas that of NSCC, such as AC, has increased.[3,4] Cervical AC shows different features from SCC in epidemiological, histological, and clinical aspects. The latest comprehensive review by Fujiwara and Monk[19] focused on the issue: ''Why is it different?''. They emphasized the need to make a different treatment strategy and stressed the importance of intensifying research into the molecular profile of AC.

Our results raised the same question; ''Why is it different?'' Histopathology regarding tissue integrity and histological heterogeneity may explain the differences observed in the predictive value of ^{18}F-FDG PET between SCC and NSCC. SCC is composed of polygonal and spindle cells, which form into masses with central keratin and necrosis.[19] Keratins are the main structural proteins in epithelial cells, which assemble from heterodimers into intermediate filaments, thereby contributing to cell stiffness and tissue integrity.[20,21] Due to the presence of central keratin, SCC may have the high structural integrity of cancer tissues. On the other hand, AC is composed of glands of varying sizes and papillae lined by columnar cells with an eosinophilic cytoplasm and brisk mitotic activity, resulting in lower tissue integrity compared with SCC. In addition, AC is histologically more heterogeneous than SCC. Although SCC has several subtypes, most of them (more than 90%) are keratinizing or nonkeratinizing. In contrast, the distribution of subtypes of cervical AC varies. Due to these histopathological differences, AC may have lower tissue integrity and a higher frequency of distant metastasis in a cell-dependent manner than SCC. ASC with squamous and glandular elements was found to have mixed features. As a result, the volume-based parameters (MTV and TLG) that reflect metabolic tumor burden may be independent prognostic factors for PFS and OS in SCC having higher tissue integrity and lower histological heterogeneity, whereas the intensity-based parameter, SUV_{max}, which reflects the metabolic (mitotic) activity of each cancer cell, may be an independent prognostic factor for PFS and OS in NSCC due to lower tissue integrity and greater histological heterogeneity. One of the recent studies evaluated the associations of quantitative parameters derived from MRI and ^{18}F-FDG PET/CT with clinical and histopathological prognostic factors, disease-free survival (DFS), and OS in cervical cancer patients[22] and emphasized on the need of a head-to-head comparison between SUV_{max} and MTV or TLG to assess whether a volumetric approach to ^{18}F-FDG uptake quantification would yield better results than the use of SUV_{max}. From this point of view, our results showing implication of intensity- and volume-based parameters between histological subtypes of cervical cancer were noteworthy.

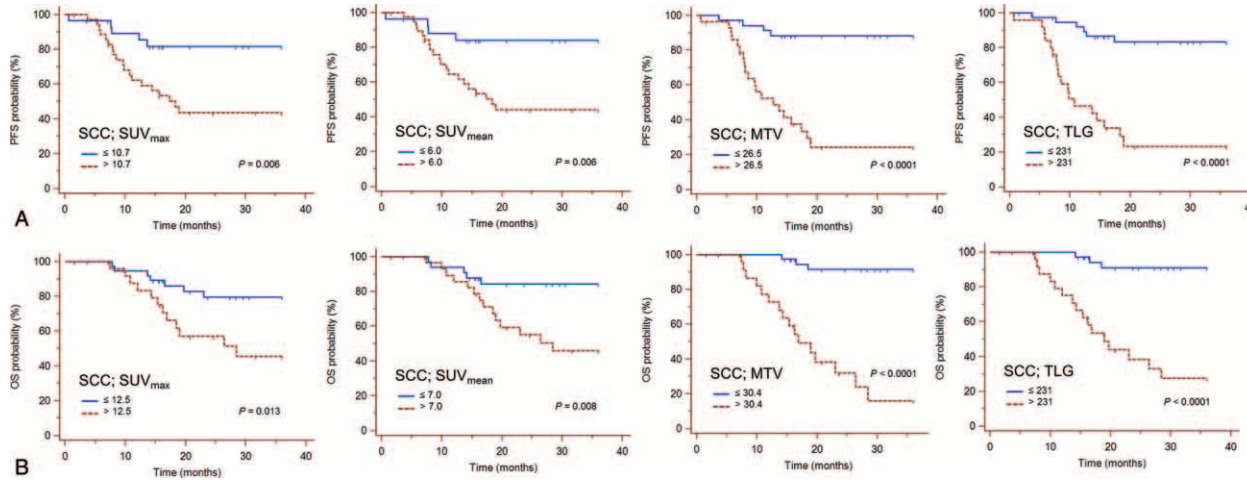

FIGURE 2. Kaplan–Meier estimates for PFS (A) and OS (B) of 65 patients with cervical SCC stratified by SUV_{max}, SUV_{mean}, MTV, and TLG.

Clinical implications of our results could be beneficial for cervical cancer patients in which the incidence of each subtype has changed over the last 4 decades. Patient prognosis widely differs between SCC and NSCC. Non-invasively, using these volume- and intensity-based ^{18}F-FDG PET parameters, physicians can evaluate patient prognosis and accordingly they can plan separate as well as effective treatment strategy for each histological subtype. Patients having same cancer stage could have different prognosis which could be evaluated properly using MTV and TLG in SCC and SUV_{max} in NSCC.

Presently, physicians are providing treatment to cervical cancer patients according to cancer stages. Despite histological differences, current treatment algorithms do not distinguish between SCC and AC. Current treatment strategy has not shown equal effectiveness for SCC and AC patients.[23] Specially, AC patients from stages IB2 to IIB are not showing optimal prognosis when treated by current standard, concurrent chemoradiation therapy (CCRT), or radical hysterectomy (RH). It may be necessary to make different treatment strategy for cervical AC which needs to be integrated into international guidelines to change practice patterns.

Several clinical studies were performed to provide effective treatment to AC patients. A retrospective review of neoadjuvant chemotherapy (NAC) followed by RH versus RH alone found that NAC plus RH improved median OS in patients with AC.[24] CCRT with paclitaxel plus cisplatin was potentially more effective than single-agent cisplatin for AC patients.[25] Another approach would be CCRT with neoadjuvant and adjuvant chemotherapy. A recent study in AC patients, randomized to CCRT alone versus NAC followed by CCRT followed by 2 further cycles of chemotherapy using cisplatin plus paclitaxel showed improved DFS and OS in later group who received additional cycles of therapy.[26] On the other hand, in SCC patients, NAC showed higher efficacy compared with NSCC patients and the combination of bevacizumab and chemotherapy also showed positive treatment response.[27,28]

In our study, NSCC patients with higher SUV_{max} showed significantly lower PFS and OS, thereby leading to worse prognosis. This finding demonstrates the potential value of SUV_{max} as a prognostic predictor in NSCC patients. Therefore, NSCC patients with higher SUV_{max} could be considered high-risk patients and might be provided with NAC followed by RH, or CCRT with double-agents instead of traditional stage-specific treatment. On the other hand, SCC patients with greater MTV and TLG had significantly worse PFS and OS. Considering MTV and TLG as prognostic indicators, SCC patients

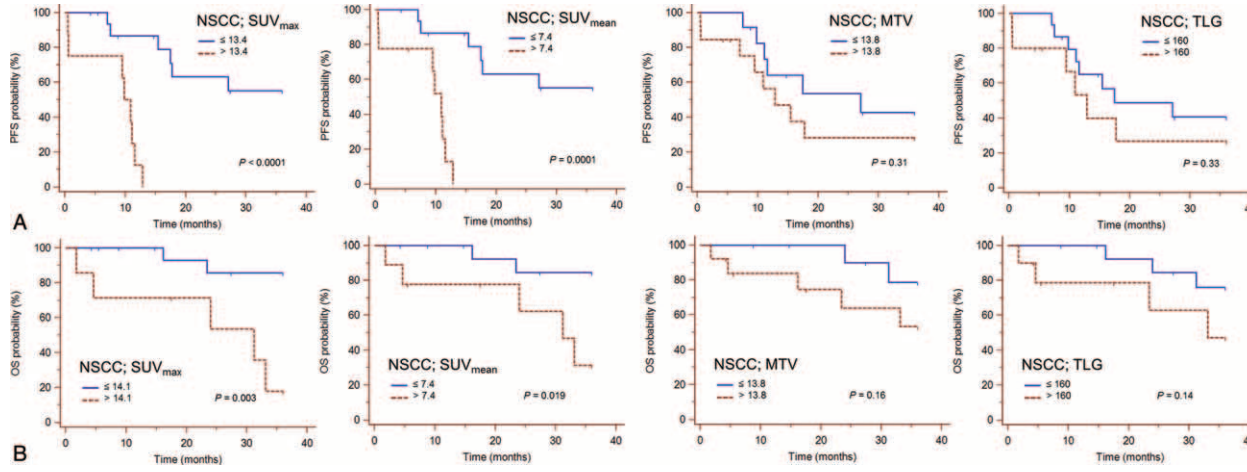

FIGURE 3. Kaplan–Meier estimates for PFS (A) and OS (B) of 25 patients with cervical NSCC stratified by SUV_{max}, SUV_{mean}, MTV, and TLG.

having greater MTV and TLG could be regarded as high-risk patients and might be treated with advanced approaches instead of conventional ones.

Potential limitations of the present study were small sample size as well as inclusion of patients with different clinical stages with heterogeneous treatment methods. These results require future validation with a larger patient population.

CONCLUSIONS

Pretreatment ^{18}F-FDG PET provided different prognostic implications between histological subtypes in patients with cervical cancer. Metabolic tumor burden (MTV and TLG) could be beneficial for the prognostic prediction of patients with SCC, whereas metabolic intensity (SUV_{max}) could be beneficial for NSCC. These results may be attributed to the differences in cancer tissue integrity and histological heterogeneity between SCC and NSCC.

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