Original Article

Early Metabolic Response Assessed Using ^{18}F-FDG-PET/CT for Image-Guided Intracavitary Brachytherapy Can Better Predict Treatment Outcomes in Patients with Cervical Cancer

Nalee Kim[1], Won Park[1], Won Kyung Cho[1], Duk-Soo Bae[2], Byoung-Gie Kim[2], Jeong-Won Lee[2], Tae-Joong Kim[2], Chel Hun Choi[2], Yoo-Young Lee[2], Young Seok Cho[3]

Departments of [1]Radiation Oncology, [2]Obstetrics and Gynecology, and [3]Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose This study aimed to identify the prognostic value of early metabolic response assessed using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) during radiation therapy (RT) for cervical cancer.

Materials and Methods We identified 116 patients treated with definitive RT, including FDG-PET/CT–guided intracavitary brachytherapy, between 2009 and 2018. We calculated parameters including maximum (SUV_{max}) and mean standardized uptake values (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) for baseline FDG-PET/CT (PET_{base}) and image-guided brachytherapy planning FDG-PET/CT (PET_{IGBT}). Multivariable analyses of disease-free survival (DFS) and overall survival (OS) were performed.

Results We observed a time-dependent decrease in PET parameters between PET_{base} and PET_{IGBT}; ΔSUV_{max}, ΔSUV_{mean}, ΔMTV, and ΔTLG were 65%, 61%, 78%, and 93%, respectively. With a median follow-up of 59.5 months, the 5-year DFS and OS rates were 66% and 79%, respectively. Multivariable analysis demonstrated that $\Delta SUV_{max} \geq 50\%$ was associated with favorable DFS (hazard ratio [HR], 2.56; 95% confidence interval [CI], 1.14 to 5.77) and OS (HR, 5.14; 95% CI, 1.55 to 17.01). Patients with $\Delta SUV_{max} \geq 50\%$ (n=87) showed better DFS and OS than those with $\Delta SUV_{max} < 50\%$ (n=29) (DFS, 76% vs. 35%, p < 0.001; OS, 90% vs. 41%, p < 0.001, respectively). Adenocarcinoma was frequently observed in $\Delta SUV_{max} < 50\%$ compared to $\Delta SUV_{max} \geq 50\%$ (27.6% vs. 10.3%, p=0.003). In addition, models incorporating metabolic parameters showed improved accuracy for predicting DFS (p=0.012) and OS (p=0.004) than models with clinicopathologic factors.

Conclusion Changes in metabolic parameters, especially those in SUV_{max} by > 50%, can help improve survival outcome predictions for patients with cervical cancer treated with definitive RT.

Key words Uterine cervical neoplasms, Fluorodeoxyglucose F18, Radiotherapy, Image-guided brachytherapy

Introduction

[18]F-fluorodeoxyglucose–positron emission tomography (FDG-PET) imaging plays a key role in determining disease stages at diagnosis in patients with cervical cancer. With the revised Fédération Internationale de Gynécologie et d'Obstétrique staging, precise evaluation of lymph nodes and distant metastasis with FDG-PET has become important. In addition to its use for diagnostic purposes, FDG-PET can be used for prognoses prediction and radiation therapy (RT) planning [1]. However, magnetic resonance imaging (MRI) is most frequently used for image-guided brachytherapy (IGBT) in clinical practice. We have previously reported the feasibility of PET-based IGBT [2,3]. Biological information on FDG-PET could help visualize metabolic active region that could complement the poor contrast resolution of computed tomography (CT)–guided IGBT. The traditional response criteria—response evaluation criteria in solid tumors—is often limited due to cystic or necrotic changes of tumors, obscured margins, and post-inflammatory changes in the cervix [4]. In this context, tumor metabolic response assessed using FDG-PET can be valuable for treatment response evaluations [1,5].

Several studies have also suggested the potential role of FDG-PET in the early detection of treatment response during RT in other solid tumor [6-9]. Herein, we aimed to determine the predictive value of metabolic parameters obtained using pretreatment FDG-PET and IGBT planning FDG-PET.

Materials and Methods

1. Patient population

Data or medical records of patients with cervical cancer

who received definitive RT with PET-based IGBT between 2009 and 2018 were retrospectively reviewed. Patients were excluded if the baseline PET (PET$_{base}$) was performed at another institution or not available (n=48), if planning data for IGBT was not available (n=42), and if follow-up details were missing (n=6). After implementing the inclusion and exclusion criteria, data on 116 patients were analyzed (S1 Fig.). This study was approved by the institutional review board (SMC. 2020-10-052), which waived the need for informed consent due to the retrospective nature of the study. All patients underwent complete clinical staging, including physical examination, abdominopelvic CT, pelvic MRI, and FDG-PET.

2. Treatment

All patients were treated with external beam RT (EBRT) using three-dimensional conformal RT and high-dose-rate IGBT. Eighty-seven patients (75.0%) were treated with whole pelvic EBRT with an upper field border of the L4-L5 interspace. For 28 patients with retroperitoneal lymph node involvement at diagnosis, extended-field EBRT was delivered with an upper field border of the T12-L1 interspace. After administering 45 Gy in 25 fractions, a parametrial boost of 5.4 Gy was performed using a midline block with 4-cm central shielding. The median total dose of EBRT was 50.4 Gy (interquartile range [IQR], 50.4 to 50.4). PET-based IGBT with an Iridium-192 source started with a parametrial boost with a total dose of 24 Gy in six fractions. The median overall treatment time and the interval between EBRT and IGBT were 51 days (IQR, 49.0 to 54.5) and 33 days (IQR, 30.0 to 39.0), respectively. The detailed procedure of PET-based IGBT has been described previously [2,3].

After the gross tumor volume was delineated based on IGBT planning FDG-PET (PET$_{IGBT}$), high-risk clinical target volume (HRCTV) was defined according to the GEC-ESTRO guidelines [10]. Briefly, the HRCTV included the gross tumor volume with a 1-cm margin, clinically suspected lesion, and entire cervix. Planning for EBRT and PET-based IGBT was calculated using the Pinnacle (V6.5, Philips, Madison, WI) and PLATO (V14.3, Nucletron, Veenendaal, Netherlands), respectively. From CT and FDG-PET/CT obtained during planning, we could retrospectively calculate a dose of 90% HRCTV (D90). The biologically equivalent dose in 2 Gy fractions (EQD2) at D90 HRCTV were calculated using EBRT and IGBT.

Concurrent chemotherapy was administered to 108 patients (93.1%) as follows: cisplatin 40 mg/m^2 weekly (n=77, 66.4%) or cisplatin 60 mg/m^2 (day 1) and 5-fluorouracil 1,000 mg/m^2/day (days 1-5) every 3 weeks (n=31, 26.7%).

3. ^{18}F-FDG-PET/CT

Both PET$_{base}$ and PET$_{IGBT}$ were obtained 45 minutes after injecting FDG (370 MBq) using a Discovery Ste scanner (GE Healthcare, Milwaukee, WI). Prior to each scan, patients fasted for 6 hours before FDG administration with a glucose level of < 200 mg/dL. After a tracer uptake time of 45 minutes, a low-dose, non-contrast, whole-body CT was performed using a continuous spiral technique with a 16-slice helical CT (140 keV, 30-170 mAs with an AutomA mode, section width of 3.75 mm). PET images with a voxel size of 4.29×4.29×4.25 mm were reconstructed using an iterative ordered-subsets expectation-maximization algorithm (28 subsets, two iterations).

4. PET metrics

All primary cervical tumors, defined as the region of interest, were delineated on PET$_{base}$ and PET$_{IGBT}$ consistently by a single radiation oncologist (N.K.) with the PET Edge algorithm in MIM software (Mim Software Inc., Cleveland, OH), which sets the contour boundary at the location where the signal gradient is highest. Images of each cervical tumor were evaluated semi-quantitatively by measuring and calculating the maximum activity concentration in the tumor (SUV$_{max}$) and mean concentration of FDG in the tumor (SUV$_{mean}$) normalized to patient body weight. The average SUV plus two standardized deviations of the metabolic tumor volume (MTV) was calculated from the sum of the areas with two-dimensional tumor contours by multiplying the corresponding slice thickness. Total lesion glycolysis (TLG) was calculated by multiplying the SUV$_{mean}$ with the MTV. The relative change in each parameter between PET$_{base}$ and PET$_{IGBT}$ was calculated using the following equation:

$$\Delta[Parameter]\%=\{[Parameter_{base}-Parameter_{IGBT}]/Parameter_{base}\}\times100$$

5. Follow-up

After the completion of the planned treatment, all patients were followed up for 1 month after treatment, every 3 months during the first 2 years, and every 6-12 months thereafter. Local failure was defined as progressive disease at the cervix, vagina, or parametrium based on either radiological evaluation or histological confirmation. Regional and distant failures were defined as regional lymph node recurrence within the RT field and metastases to lymph nodes or other organs outside the RT field, respectively.

6. Statistical analysis

Disease-free survival (DFS) and overall survival (OS) were the primary study endpoints. DFS and OS rates were measured from the date of RT commencement to the date of any failure or death from any cause. Survival curves were estimated using the Kaplan-Meier method and compared using

the log-rank test. Since there was a significant variation in the optimal cutoff value for PET parameters, receiver operating characteristics curve analyses for DFS were performed to identify the cutoff thresholds for parameters (S2 Fig.). Multivariable analysis was performed using the Cox proportional hazards model with variables that were significant in univariable analysis. In addition, Delong's test was performed to compare the predictive value of the final selected model for DFS and OS. Differences between metabolic responders and non-responders were compared using Pearson's chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. All statistical analyses were performed using R (ver. 3.6.4, R Foundation for Statistical Computing, Vienna, Austria). A p-value of < 0.05 was considered statistically significant.

Results

1. Patients

With a median age of 55 years (IQR, 48 to 64), most patients (n=99, 85.3%) were diagnosed with squamous cell carcinoma (Table 1). The median tumor size was 5.1 cm (IQR, 4.0 to 6.3), and more than half of the patients (n=86, 74.1%) had a tumor measuring > 4 cm; 31 patients (26.7%) had tumors measuring > 6 cm. According to the 2018 revised staging, 89 patients (76.7%) were diagnosed with stage III-IV disease. The median total EQD2 to D90 HRCTV was 77.9 Gy (IQR, 75.5 to 81.2).

2. PET metrics

The median SUV_{max}, SUV_{mean}, MTV, and TLG of PET_{base} were 13.4 (IQR, 10.4 to 17.6), 6.4 (IQR, 5.1 to 8.5), 40.4 mL (IQR, 18.9 to 64.7), and 264.9 (IQR, 110.0 to 544.6), respectively (Table 1, Fig. 1). Except for three patients who showed an increased SUV_{max}, all parameters generally decreased on PET_{IGBT}: the median ΔSUV_{max}, ΔSUV_{mean}, ΔMTV, and ΔTLG were 65.4% (IQR, 50.3 to 73.0), 60.5% (IQR, 48.1 to 66.9), 78.3% (IQR, 64.5 to 88.5), and 92.9% (IQR, 84.2 to 96.0), respectively. In addition to each cutoff value for PET parameters of PET_{base} and PET_{IGBT}, a threshold of 50%, 60%, 85%, and 95% was calculated as the optimal cutoff value for ΔSUV_{max} (area under curve [AUC], 0.702), ΔSUV_{mean} (AUC, 0.711), ΔMTV (AUC, 0.568), and ΔTLG (AUC, 0.621), respectively (S3 Fig.).

3. Treatment outcomes

During the median follow-up of 59.5 months (IQR, 24.3 to 87.0), the 5-year DFS and OS rates for the entire cohort were 66.4% and 78.5%, respectively (Fig. 2). Twenty-two and 31 patients experienced locoregional and distant failures, respectively. After adjusting for multiple clinical and PET parameters, $\Delta SUV_{max} < 50\%$ was significantly associated with

Table 1. Baseline characteristics

	Total (n=116)
Patient and tumor characteristic	
Age (yr)	55 (48-64)
Pathology	
Squamous cell carcinoma	99 (85.3)
Adenocarcinoma	16 (13.8)
Adenosquamous carcinoma	1 (0.9)
Tumor size (cm)	5.1 (4.0-6.3)
≤ 4	30 (25.9)
> 4, ≤ 6	55 (47.4)
> 6	31 (26.7)
Pelvic lymph node involvement	86 (74.1)
Retroperitoneal lymph node involvement	28 (24.1)
FIGO stage[a)]	
I	2 (1.7)
II	25 (21.6)
III	81 (69.8)
IV	8 (6.9)
Treatment characteristics	
HRCTV (cm³)	51.7 (34.0-81.1)
Total (EBRT+IGBT) D90 HRCTV (Gy)	77.9 (75.5-81.2)
Metabolic parameter	
$PET_{base}SUV_{max}$	13.4 (10.4-17.6)
$PET_{base}SUV_{mean}$	6.4 (5.1-8.5)
$PET_{base}MTV$ (mL)	40.4 (18.9-64.7)
$PET_{base}TLG$	264.9 (110.0-544.6)
$PET_{IGBT}SUV_{max}$	5.0 (3.5-6.6)
$PET_{IGBT}SUV_{mean}$	2.7 (2.2-3.3)
$PET_{IGBT}MTV$ (mL)	7.8 (3.4-14.2)
$PET_{IGBT}TLG$	20.2 (7.6-43.2)
ΔSUV_{max} (%)	65.4 (50.3-73.0)
ΔSUV_{mean} (%)	60.5 (48.1-66.9)
ΔMTV (%)	78.3 (64.5-88.5)
ΔTLG (%)	92.9 (84.2-96.0)

Values are presented as number (%) or median (interquartile range). D90 HRCTV, biologically equivalent dose in 2Gy fractions to 90% of HRCTV (α/β of 10); EBRT, external beam radiation therapy; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRCTV, high-risk clinical target volume; IGBT, image-guided brachy-therapy; MTV, metabolic tumor volume; PET_{base}, baseline FDG-PET/CT; PET_{IGBT}, image-guided brachytherapy planning FDGPET/CT; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; TLG, total lesion glycolysis. [a)]FIGO stage refers to the revised 2018 FIGO staging.

inferior DFS (hazard ratio [HR], 2.56; 95% confidence interval [CI], 1.14 to 5.77; p=0.023) and OS (HR, 5.14; 95% CI, 1.55 to 17.01; p=0.007) (Table 2). In addition, the adenocarcinoma
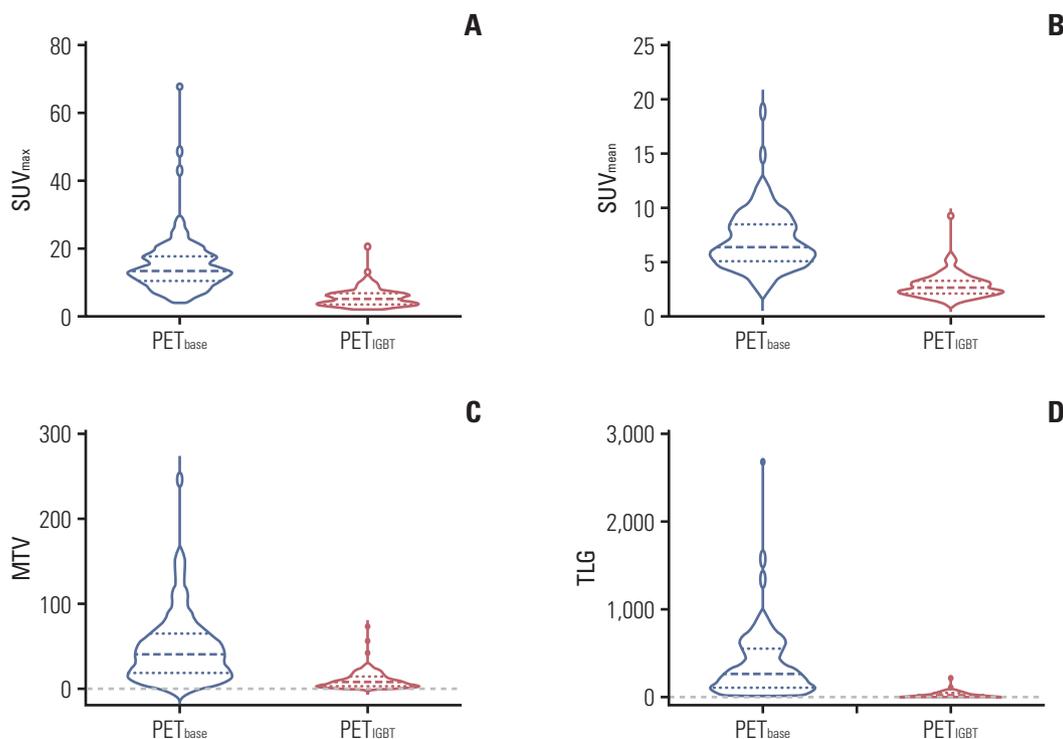
Fig. 1. Metabolic parameters of the primary tumor in PET$_{base}$ and PET$_{IGBT}$: SUV$_{max}$ (A), SUV$_{mean}$ (B), MTV (C), and TLG (D). FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; MTV, metabolic tumor volume; PET$_{base}$, baseline FDG-PET/CT; PET$_{IGBT}$, image-guided brachytherapy planning FDG-PET/CT; SUV$_{max}$, maximum standardized uptake value; SUV$_{mean}$, mean standardized uptake value; TLG, total lesion glycolysis.
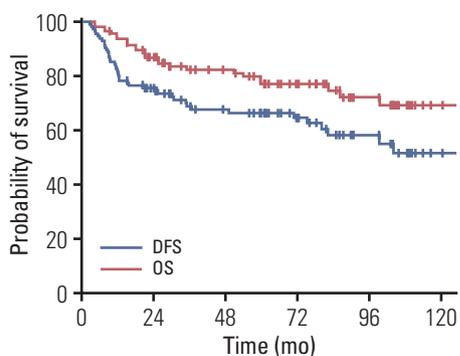

Fig. 2. Kaplan-Meier curves of disease-free survival (DFS) and overall survival (OS) outcomes for all patients.

component remained significant prognostic factor in the multivariable analysis for DFS (HR, 2.98; 95% CI, 1.38 to 6.48; p=0.006) and OS (HR, 2.65; 95% CI, 1.14 to 6.16; p=0.024).

The 5-year DFS rates of 87 patients with ΔSUV$_{max} \geq 50\%$ and 29 patients with ΔSUV$_{max} < 50\%$ were 76.0% and 35.2%, respectively (p < 0.001) (Fig. 3A). The corresponding 5-year OS rates were 89.7% and 40.7%, respectively (p < 0.001) (Fig. 3B). In the subgroup analysis based on an ΔSUV$_{max}$

of 50%, more patients with ΔSUV$_{max} < 50\%$ presented with adenocarcinoma or adenosquamous carcinoma compared to those with ΔSUV$_{max} \geq 50\%$ (27.6% vs. 10.3%, p=0.003) (Table 3). Patients with ΔSUV$_{max} \geq 50\%$ had higher PET$_{base}$ SUV$_{max}$ (p < 0.001) (Fig. 4A), SUV$_{mean}$ (p < 0.001) (Fig. 4B), MTV (p=0.048) (Fig. 4C), and TLG (p=0.003) (Fig. 4D) than those with ΔSUV$_{max} < 50\%$. The SUV$_{max}$ (p < 0.001) (Fig. 4A) and SUV$_{mean}$ (p < 0.001) (Fig. 4B) were significantly lower in patients with ΔSUV$_{max} \geq 50\%$ than in those with ΔSUV$_{max} < 50\%$ (Table 3). In addition to SUV$_{max}$, relative changes in SUV$_{mean}$, MTV, and TLG of patients with ΔSUV$_{max} \geq 50\%$ were larger than those of patients with ΔSUV$_{max} < 50\%$ (Table 3).

We observed a statistically significant improvement in predicting DFS when incorporating PET parameters (AUC, 0.755 vs. 0.690; p=0.012) (S4A Fig.) compared with the prediction model of clinicopathologic factors. The prediction model with PET parameters showed improved performance for OS (AUC, 0.782 vs. 0.629; p=0.004) (S4B Fig.).

Table 2. Prognostic factors for disease-free survival and overall survival

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Disease-free survival						
Age (continuous)	0.99	0.97-1.02	0.507	-	-	-
Pathology (SCC vs. ADC/AD-SC)	3.56	1.81-6.98	< 0.001	2.98	1.38-6.48	0.006
FIGO stage[a)] (I-II vs. III-IV)	3.25	1.16-9.11	0.025	4.16	1.31-13.19	0.016
Overall treatment time (≤ 56 days vs. > 56 days)	1.26	0.58-2.73	0.566	-	-	-
Chemotherapy regimen (cisplatin vs. cisplatin/5-FU)	1.11	0.64-1.93	0.701	-	-	-
HRCTV (< 50 cm³ vs. ≥ 50 cm³)	2.17	1.13-4.19	0.021	1.00	0.99-1.01	0.657
D90 HRCTV (≥ 78 Gy vs. < 78 Gy)	1.39	0.76-2.54	0.293	-	-	-
Tumor size (cm)						
≤ 4 vs. 4-6	1.17	0.51-2.69	0.709	-	-	-
≤ 4 vs. > 6	2.07	0.88-4.90	0.096	-	-	-
$PET_{base}SUV_{max}$ (< 9 vs. ≥ 9)	2.11	0.75-5.92	0.155	-	-	-
$PET_{base}SUV_{mean}$ (< 7 vs. ≥ 7)	0.57	0.30-1.08	0.084	-	-	-
$PET_{base}MTV$ (< 40 mL vs. ≥ 40 mL)	2.23	1.18-4.23	0.014	1.81	0.86-3.79	0.118
$PET_{base}TLG$ (< 144 vs. ≥ 144)	1.03	1.00-1.07	0.073	-	-	-
$PET_{IGBT}SUV_{max}$ (< 5 vs. ≥ 5)	2.16	1.15-4.06	0.016	0.60	0.21-1.71	0.342
$PET_{IGBT}SUV_{mean}$ (< 3 vs. ≥ 3)	1.98	1.08-3.61	0.026	1.57	0.61-4.10	0.351
$PET_{IGBT}MTV$ (< 9 mL vs. ≥ 9 mL)	2.19	1.19-4.03	0.012	1.38	0.67-2.83	0.386
$PET_{IGBT}TLG$ (< 30 vs. ≥ 30)	1.44	1.13-1.83	0.004	0.99	0.93-1.05	0.762
ΔSUV_{max} (≥ 50% vs. < 50%)	4.10	2.21-7.60	< 0.001	2.56	1.14-5.77	0.023
ΔSUV_{mean} (≥ 60% vs. < 60%)	3.30	1.69-6.44	< 0.001	2.16	0.95-4.87	0.065
ΔMTV (≥ 85% vs. < 85%)	1.51	0.77-2.95	0.231	-	-	-
ΔTLG (≥ 95% vs. < 95%)	1.02	0.88-1.16	0.937	-	-	-
Overall survival						
Age (continuous)	1.01	0.98-1.04	0.467	-	-	-
Pathology (SCC vs. ADC/AD-SC)	3.82	1.69-8.61	0.001	2.65	1.14-6.16	0.024
FIGO stage[a)] (I-II vs. III-IV)	1.69	0.58-4.90	0.337	-	-	-
Overall treatment time (≤ 56 days vs. > 56 days)	2.33	0.97-5.60	0.060	-	-	-
Chemotherapy regimen (cisplatin vs. cisplatin/5-FU)	0.86	0.42-1.74	0.665	-	-	-
HRCTV (< 50 cm³ vs. ≥ 50 cm³)	2.02	0.88-4.65	0.100	-	-	-
D90 HRCTV (≥ 78 Gy vs. < 78 Gy)	1.33	0.61-2.90	0.473	-	-	-
Tumor size (cm)						
≤ 4 vs. 4-6	0.84	0.31-2.27	0.724	-	-	-
≤ 4 vs. > 6	1.40	0.50-3.96	0.520	-	-	-
$PET_{base}SUV_{max}$ (< 9 vs. ≥ 9)	1.13	0.39-3.30	0.816	-	-	-
$PET_{base}SUV_{mean}$ (< 7 vs. ≥ 7)	0.54	0.23-1.23	0.143	-	-	-
$PET_{base}MTV$ (< 40 mL vs. ≥ 40 mL)	1.56	0.71-3.45	0.268	-	-	-
$PET_{base}TLG$ (< 144 vs. ≥ 144)	1.05	0.96-1.04	0.964	-	-	-
$PET_{IGBT}SUV_{max}$ (< 5 vs. ≥ 5)	3.65	1.46-9.09	0.005	1.86	0.68-5.05	0.226
$PET_{IGBT}SUV_{mean}$ (< 3 vs. ≥ 3)	2.45	1.11-5.41	0.026	1.26	0.44-3.25	0.378
$PET_{IGBT}MTV$ (< 9 mL vs. ≥ 9 mL)	1.61	0.74-3.49	0.227	-	-	-
$PET_{IGBT}TLG$ (< 30 vs. ≥ 30)	1.65	0.86-3.16	0.130	-	-	-

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Discussion

We found that the early metabolic response of relative changes in PET parameters, especially an ΔSUV_{max} of 50%, can be deemed an important predictive factor for patients treated with definitive RT. Metabolic parameters are better than clinicopathologic factors for predicting survival outcomes.

Table 2. Continued

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
ΔSUV_{max} ($\geq 50\%$ vs. $< 50\%$)	7.57	3.39-16.90	< 0.001	5.14	1.55-17.01	0.007
ΔSUV_{mean} ($\geq 60\%$ vs. $< 60\%$)	3.75	1.50-9.35	0.005	1.03	0.28-3.73	0.965
ΔMTV ($\geq 85\%$ vs. $< 85\%$)	1.54	0.65-3.66	0.331	-	-	-
ΔTLG ($\geq 95\%$ vs. $< 95\%$)	2.72	1.42-5.22	0.003	2.55	1.00-6.54	0.051

The foreparts of the parentheses were set as the reference group. 5-FU, 5-fluorouracil; ADC, adenocarcinoma; AD-SC, adenosquamous carcinoma; CI, confidence interval; D90 HRCTV, biologically equivalent dose in 2 Gy fractions to HRCTV (α/β of 10); FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HR, hazard ratio; HRCTV, high-risk clinical target volume; MTV, metabolic tumor volume; PET$_{base}$, baseline FDG-PET/CT; PET$_{IGBT}$, image-guided brachytherapy planning FDG-PET/CT; SCC, squamous cell carcinoma; SUV$_{max}$, maximum standardized uptake value; SUV$_{mean}$, mean standardized uptake value; TLG, total lesion glycolysis. [a)]FIGO stage refers to the revised 2018 FIGO staging.
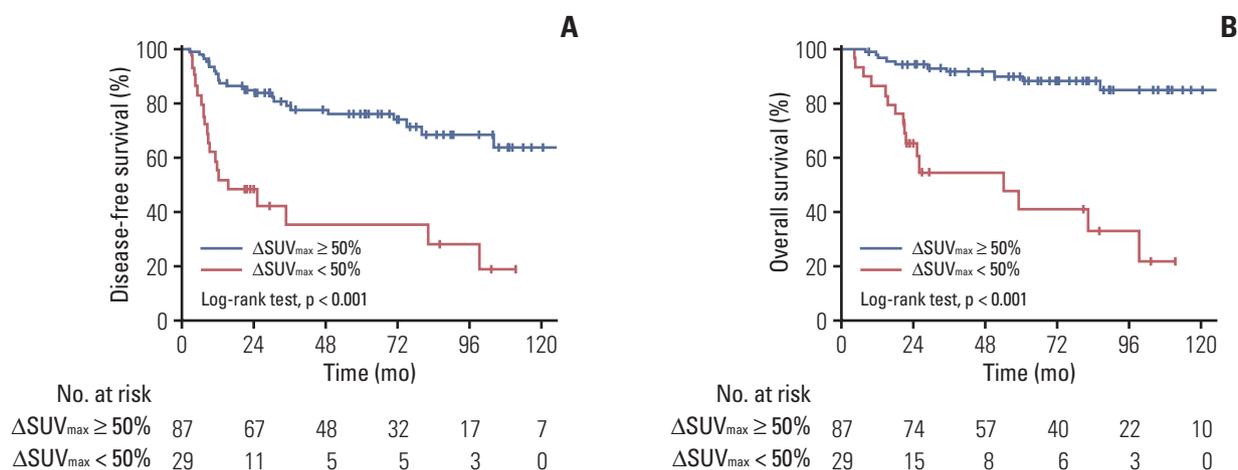

Fig. 3. Clinical outcomes according to the reduction in maximum standardized uptake value (SUV$_{max}$): disease-free survival (A) and overall survival (B).

Several previous studies have been investigated using a limited number of patients with cervical cancer treated with RT [11-15]. Kidd et al. [11] observed a time-dependent change during and after RT and found a correlation between MTV or SUV$_{max}$ at week 4 and treatment response. Visual assessment based on residual FDG uptake in the primary tumor also showed its diagnostic ability in predicting outcomes [12,13,15]. A recent study by Leseur et al. [14] suggested different cutoff values of MTV and TLG for PET$_{base}$ and PET$_{IGBT}$. In agreement with the findings of previous reports, our findings showed a time-dependent change in the metabolic parameters. Moreover, we could suggest clinically useful cutoff criteria based on the dynamics of these metabolic parameters. In addition, we found that incorporating PET parameters, such as an ΔSUV_{max} of 50%, into well-known prognostic factors, can potentially lead to a more accurate

prediction of treatment outcomes.

The degree of PET avidity in the primary tumor or lymph node has been deemed as a predictive biomarker in cervical cancer [1,16-19]. A recent study using a deep learning model for PET$_{base}$ in 142 patients suggested the feasibility of PET$_{base}$ in predicting outcomes in cervical cancer [16]. In addition, Kidd et al. [17] reported that the SUV$_{max}$ of the primary tumor might be an independent and important predictor of tumor aggressiveness, treatment response, and OS based on the PET$_{base}$ findings of 287 patients. They also demonstrated that PET-avid nodes can stratify patients into distinct groups, and the SUV$_{max}$ of the lymph node itself could be a predictive marker for recurrence, DFS, and OS [18,19]. However, PET$_{base}$ parameters were higher in metabolic responders ($\Delta SUV_{max} \geq 50\%$) than in non-responders ($\Delta SUV_{max} < 50\%$) in our study (all p < 0.05). Therefore, we could postulate

Table 3. Patient and tumor characteristics according to metabolic response

	$\Delta SUV_{max} \geq 50\%$ (n=87)	$\Delta SUV_{max} < 50\%$ (n=29)	p-value
Patient and tumor characteristic			
Age (yr)	54 (48-63)	56 (46-65)	0.678
Pathology			
SCC	78 (89.7)	21 (72.4)	0.033
ADC/AD-SC	9 (10.3)	8 (27.6)	
FIGO stage[a)]			
I	2 (2.3)	0	0.491
II	21 (24.1)	4 (13.8)	
III	59 (67.8)	22 (75.9)	
IV	5 (5.7)	3 (10.3)	
Tumor size (cm)	5.2 (4.2-6.4)	5.0 (3.7-6.0)	0.177
≤ 4	20 (23.0)	10 (34.5)	0.429
> 4, ≤ 6	42 (48.3)	13 (44.8)	
> 6	25 (28.7)	6 (20.7)	
Pelvic lymph node involvement	62 (71.3)	24 (82.8)	0.327
Retroperitoneal lymph node involvement	20 (23.0)	8 (27.6)	0.802
Treatment characteristic			
Total EBRT dose (Gy)	50.4 (50.4-50.4)	50.4 (50.4-50.4)	0.745
Total IGBT dose (Gy)	24.0 (24.0-24.0)	24.0 (24.0-24.0)	0.420
HRCTV (cm³)	51.0 (33.6-74.2)	60.3 (35.9-92.6)	0.637
Total (EBRT+IGBT) D90 HRCTV (Gy)	78.3 (75.9-81.5)	76.5 (75.0-79.4)	0.092
PET parameter			
$PET_{base}SUV_{max}$	15.4 (11.1-18.8)	11.0 (7.2-12.6)	< 0.001
$PET_{base}SUV_{mean}$	7.2 (5.6-9.0)	5.6 (4.2-6.4)	< 0.001
$PET_{base}MTV$ (mL)	46.0 (20.3-68.3)	35.1 (14.8-43.9)	0.048
$PET_{base}TLG$	311.7 (113.3-628.1)	150.8 (90.2-240.3)	0.003
$PET_{IGBT}SUV_{max}$	4.2 (3.3-5.9)	6.8 (5.9-8.8)	< 0.001
$PET_{IGBT}SUV_{mean}$	2.4 (2.1-3.1)	3.3 (2.8-4.1)	< 0.001
$PET_{IGBT}MTV$ (mL)	7.1 (3.3-13.1)	9.6 (4.7-18.3)	0.259
$PET_{IGBT}TLG$	17.4 (7.5-35.4)	35.2 (11.6-61.2)	0.073
ΔSUV_{max}	68.2 (61.9-75.2)	33.7 (12.8-44.7)	< 0.001
ΔSUV_{mean}	62.4 (56.8-70.9)	41.6 (25.8-47.9)	< 0.001
ΔMTV	83.1 (70.8-89.1)	58.4 (47.6-83.3)	0.004
ΔTLG	93.6 (87.8-86.5)	77.2 (61.2-93.0)	< 0.001

Values are presented as number (%) or median (interquartile range). ADC, adenocarcinoma; AD-SC, adenosquamous carcinoma; D90 HRCTV, biologically equivalent dose in 2 Gy fractions to 90% of HRCTV (α/β of 10); EBRT, external beam radiation therapy; FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRCTV, high-risk clinical target volume; IGBT, image-guided brachytherapy; MTV, metabolic tumor volume; PET_{base}, baseline FDG-PET/CT; PET_{IGBT}, image-guided brachytherapy planning FDG-PET/CT; SCC, squamous cell carcinoma; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; TLG, total lesion glycolysis. [a)]FIGO stage refers to the revised 2018 FIGO staging.

that relative changes in PET parameters are more feasible in predicting outcomes than pretreatment parameters. Further investigation using deep learning that incorporates PET_{base} and PET_{IGBT} can provide a more robust prediction model.

Advances in imaging analysis have facilitated ways to integrate MRI in treatment prediction [20-23]. A recent multi-center study of 275 patients demonstrated that radiomic features in MRI could potentially identify patients expected to have a favorable response before neoadjuvant chemotherapy [22]. Additionally, Wormald et al. [23] analyzed 378 patients with stage I-II disease and reported that combining textural into clinical factors can improve recurrence predictions. Fur-
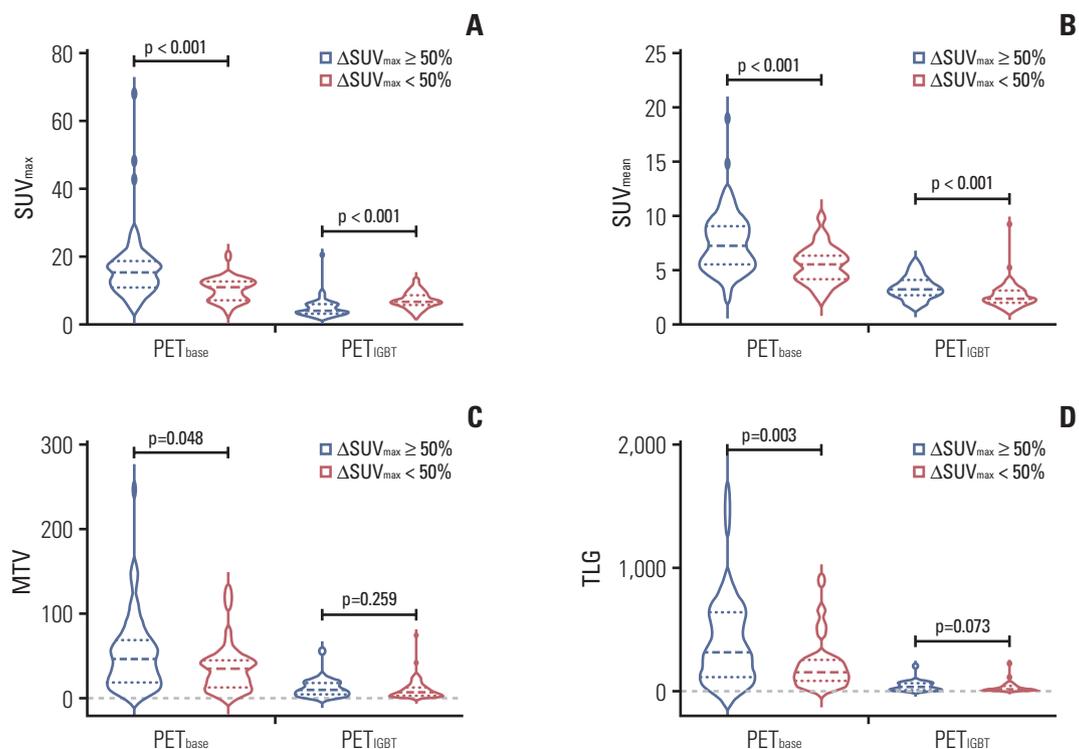
Fig. 4. Metabolic parameters of primary tumor in PET_{base} and PET_{IGBT} according to ΔSUV_{max} of 50%: SUV_{max} (A), SUV_{mean} (B), MTV (C), and TLG (D). FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; MTV, metabolic tumor volume; PET_{base}, baseline FDG-PET/CT; PET_{IGBT}, image-guided brachytherapy planning FDG-PET/CT; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; TLG, total lesion glycolysis.

thermore, Lucia et al. [24,25] developed a multiparametric radiomics model using PET_{base} and MRI and demonstrated its power in predicting recurrence or local control after external validation. However, a radiomics model is not routinely available in clinical practice. Therefore, the assessment of relative changes in metabolic parameters based on PET_{IGBT} could be more clinically accessible and cost-effective. Additionally, both volumetric assessment and tumor marker (i.e., squamous cell carcinoma antigen) are suggested as predictors for treatment outcomes, there remains the issue of interobserver variability in tumor delineation, under-or over-estimated tumor volume assessment, and optimal cutoff values for tumor markers [26]. In this context, metabolic parameters of $\Delta SUV_{max} < 50\%$ reduce interobserver variability and could provide an additional information reflecting tumor biology.

In the current study, a consistent adverse prognostic impact of adenocarcinoma histology was observed in multivariable analysis, including metabolic parameters. In addition, adeno/adenosquamous carcinoma was more frequently observed in patients with $\Delta SUV_{max} < 50\%$. The impact of adeno/adenosquamous carcinoma on outcomes has been noted in several studies [27,28]. However, a revised classification

of adenocarcinoma histology has provoked a new issue due to its heterogeneity [29]. We found that several patients with adenocarcinoma showed a favorable metabolic response, but some patients did not, resulting in different outcomes among patients with adeno/adenosquamous carcinoma. Due to its rarity, the number of patients with adeno/adenosquamous carcinoma was limited in previous mid-RT PET studies and in the current study (17 patients) [3,11-14]. Therefore, further subgroup analysis of metabolic parameters based on subtypes of adenocarcinoma could not be conducted. Further analyses incorporating new classification of adenocarcinoma histology and metabolic parameters can further our understanding of heterogeneity of this pathology type.

Detection of early response appears to be a predictor of the likelihood of treatment failure, which makes it easier to stratify poor responders with current treatment strategies. Further intensification with adjuvant chemotherapy as the OUTBACK trial (clinicaltrials.gov, NCT 01414608), RT dose escalation as in non-small cell lung cancer (NCT 01507428), or early administration of immune-checkpoint blockade (NCT 02760225, NCT 03829007, and NCT 03853187) can be beneficial for these patients. Further investigations are needed

to determine whether early salvage surgery can be effective in metabolic non-responders with cervical cancer who are expected to respond in the late phase or have early progression.

There are several limitations in the current study. First, the results should be interpreted with caution since this is a retrospective analysis without external validation. Since the cutoff values were derived using Youden's index in the current study, different optimal thresholds can be calculated in further studies with a larger sample size. However, our analysis was strengthened because of using consistent and modern FDG-PET/CT and practically applicable PET-based IGBT. Additionally, the criteria for relative changes in metabolic parameters can be easily accessible in further clinical implementation. Possible inflammatory changes during RT might mimic changes in tumor metabolism [30]. However, previous studies have proved that PET at week 4 can be reliable in predicting treatment outcomes [11], which is consistent with the current study findings.

To the best of our knowledge, the current study is the largest analysis to incorporate metabolic parameters of PET_{base} and PET_{IGBT}. We expect that the current criteria based on the dynamics of metabolic parameters will help develop personalized treatment plans for patients with cervical cancer during RT.

Author Contributions

Conceived and designed the analysis: Kim N, Park W, Cho WK, Cho YS.

Collected the data: Kim N, Cho WK.

Contributed data or analysis tools: Kim N, Park W, Cho WK, Bae DS, Kim BG, Lee JW, Kim TJ, Choi CH, Lee YY, Cho YS.

Performed the analysis: Kim N, Park W.

Wrote the paper: Kim N, Park W, Cho YS.

Review the paper: Park W, Cho WK, Bae DS, Kim BG, Lee JW, Kim TJ, Choi CH, Lee YY, Cho YS.

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