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 Kim1, Won Park1, Won Kyung Cho1, Duk-Soo Bae2, Byoung-Gie Kim2, Jeong-Won Lee2, Tae-Joong Kim2, Cheol Hun Choi2, Jeong-Won Lee2, Young Seok Cho2

Departments of 1Radiation Oncology, 2Obstetrics and Gynecology, and 3Nuclear 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 ΔSUV$_{max}$ ≥ 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 ΔSUV$_{max}$ ≥ 50% (n=87) showed better DFS and OS than those with ΔSUV$_{max}$ < 50% (n=29) (DFS, 76% vs. 35%, p < 0.001; OS, 90% vs. 41%, p < 0.001, respectively). Adenocarcinoma was frequently observed in ΔSUV$_{max}$ < 50% compared to ΔSUV$_{max}$ ≥ 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<sub>base</sub>) 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 parametrical 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 parametrical 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<sub>IBGT</sub>), 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<sup>2</sup> weekly (n=77, 66.4%) or cisplatin 60 mg/m<sup>2</sup> (day 1) and 5-fluorouracil 1,000 mg/m<sup>2</sup>/day (days 1-5) every 3 weeks (n=31, 26.7%).

3. <sup>18</sup>F-FDG-PET/CT

Both PET<sub>base</sub> and PET<sub>IGBT</sub> were obtained 45 minutes after injecting FGD (370 MBq) using a Discovery Ste scanner (GE Healthcare, Milwaukee, WI). Prior to each scan, patients fasted for 6 hours before FGD 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<sub>base</sub> and PET<sub>IGBT</sub> 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 the highest. Images of each cervical tumor were evaluated semi-quantitatively by measuring and calculating the maximum activity concentration in the tumor (SUV<sub>max</sub>) and mean concentration of FGD in the tumor (SUV<sub>mean</sub>) normalized to patient body weight. The average SUV plus two standard 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<sub>mean</sub> with the MTV. The relative change in each parameter between PET<sub>base</sub> and PET<sub>IGBT</sub> was calculated using the following equation:

\[ \Delta[Parameter]\% = \left( \frac{[Parameter_{base} - Parameter_{IGBT}]}{Parameter_{base}} \right) \times 100 \]

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.). Multivariate analysis was performed using the Cox proportional hazards model with variables that were significant in univariate 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 ΔSUV was 50.3 (IQR, 47.2 to 64.7), and ΔMTV was 64.9 (IQR, 54.4 to 78.8), respectively (Table 1, Fig. 1). Except for three patients who showed an increased SUV after treatment, all parameters generally decreased on PET from baseline to the follow-up scan (Fig. 2). The median total EQD2 to D90 HRCTV was 77.9 Gy (IQR, 75.5 to 81.2).

2. PET metrics

The median SUVmax, SUVmean, MTV, and TLG of PETbase 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). Except for three patients who showed an increased SUV after treatment, all parameters generally decreased on PET from baseline to the follow-up scan (Fig. 2). The median ΔSUV was 50.3 (IQR, 47.2 to 64.7), and ΔMTV was 64.9 (IQR, 54.4 to 78.8), respectively (Table 1, Fig. 1). Except for three patients who showed an increased SUV after treatment, all parameters generally decreased on PET from baseline to the follow-up scan (Fig. 2). The median total EQD2 to D90 HRCTV was 77.9 Gy (IQR, 75.5 to 81.2).

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, ΔSUVmax < 50% was significantly associated with 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

Table 1. Baseline characteristics

| Patient and tumor characteristic | Total (n=116) |
|----------------------------------|--------------|
| **Age (yr)**                     | 55 (48-64)   |
| **Pathology**                    |              |
| Squamous cell carcinoma          | 99 (85.3)    |
| Adenocarcinoma                   | 16 (13.8)    |
| Adenosquamous carcinoma          | 1 (0.9)      |
| **Tumor size (cm)**              |              |
| ≤ 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**                   |              |
| 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              |              |
|----------------------------------|--------------|
| PETbaseSUVmax                    | 13.4 (10.4-17.6) |
| PETbaseSUVmean                   | 6.4 (5.1-8.5) |
| PETbaseMTV (mL)                  | 40.4 (18.9-64.7) |
| PETbaseTLG                       | 264.9 (110.0-544.6) |
| PETcorrectSUVmax                 | 5.0 (3.5-6.6) |
| PETcorrectSUVmean                | 2.7 (2.2-3.3) |
| PETcorrectMTV (mL)               | 7.8 (5.4-14.2) |
| PETcorrectTLG                    | 20.2 (7.6-43.2) |
| ΔSUVmax (%)                      | 65.4 (50.3-73.0) |
| ΔSUVmean (%)                     | 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, 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; PETcorrect, baseline FDG-PET/CT; PETcorrect, image-guided brachytherapy planning FDG-PET/CT; SUVmax, maximum standardized uptake value; SUVcorrect, mean standardized uptake value; TLG, total lesion glycolysis. *FIGO stage refers to the revised 2018 FIGO staging.
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 Δ\( \text{SUV}_{\text{max}} \geq 50\% \) and 29 patients with Δ\( \text{SUV}_{\text{max}} < 50\% \) 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 Δ\( \text{SUV}_{\text{max}} \) of 50%, more patients with Δ\( \text{SUV}_{\text{max}} < 50\% \) presented with adenocarcinoma or adenosquamous carcinoma compared to those with Δ\( \text{SUV}_{\text{max}} \geq 50\% \) (27.6% vs. 10.3%, \( p = 0.003 \)) (Table 3). Patients with Δ\( \text{SUV}_{\text{max}} \geq 50\% \) had higher PET\( \text{base} \) \( \text{SUV}_{\text{max}} \) (\( p < 0.001 \)) (Fig. 4A), SUV\( \text{mean} \) (\( p < 0.001 \)) (Fig. 4B), MTV (\( p = 0.048 \)) (Fig. 4C), and TLG (\( p = 0.003 \)) (Fig. 4D) than those with Δ\( \text{SUV}_{\text{max}} < 50\% \). The SUV\( \text{max} \) (\( p < 0.001 \)) (Fig. 4A) and SUV\( \text{mean} \) (\( p < 0.001 \)) (Fig. 4B) were significantly lower in patients with Δ\( \text{SUV}_{\text{max}} \geq 50\% \) than in those with Δ\( \text{SUV}_{\text{max}} < 50\% \) (Table 3). In addition to SUV\( \text{max} \), relative changes in SUV\( \text{mean} \), MTV, and TLG of patients with Δ\( \text{SUV}_{\text{max}} \geq 50\% \) were larger than those of patients with Δ\( \text{SUV}_{\text{max}} < 50\% \) (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.).
Discussion

We found that the early metabolic response of relative changes in PET parameters, especially an ΔSUV\(_{\text{max}}\) 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.
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$\text{max}$ 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 $\Delta$SUV$\text{max}$ 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$\text{max}$ 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$\text{max}$ 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$\text{max}$ ≥ 50%) than in non-responders ($\Delta$SUV$\text{max}$ < 50%) in our study (all p < 0.05). Therefore, we could postulate

### Table 2. Continued

| Variable | Univariable analysis |          |          |          |          |
|----------|----------------------|----------|----------|----------|----------|
|          | HR 95% CI p-value    | HR 95% CI p-value |
| $\Delta$SUV$\text{max}$ (≥ 50% vs. < 50%) | 7.57 3.39-16.90 < 0.001 | 5.14 1.55-17.01 0.007 |
| $\Delta$SUV$\text{mean}$ (≥ 60% vs. < 60%) | 3.75 1.50-9.35 0.005 | 1.03 0.28-3.73 0.965 |
| $\Delta$MTV (≥ 85% vs. < 85%) | 1.54 0.65-3.66 0.331 | - - - - |
| $\Delta$TLG (≥ 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 ($\alpha/\beta$ 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$\text{max}$, maximum standardized uptake value; SUV$\text{mean}$, mean standardized uptake value; TLG, total lesion glycolysis. *FIGO stage refers to the revised 2018 FIGO staging.

![Fig. 3. Clinical outcomes according to the reduction in maximum standardized uptake value (SUV$\text{max}$); disease-free survival (A) and overall survival (B).](image-url)
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-

| Patient and tumor characteristic | ΔSUV_{max} ≥ 50% (n=87) | ΔSUV_{max} < 50% (n=29) | p-value |
|---------------------------------|--------------------------|--------------------------|---------|
| **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**                  |                          |                          |         |
| 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)**             |                          |                          |         |
| ≤ 4                             | 5.2 (4.2-6.4)            | 5.0 (3.7-6.0)            | 0.177   |
| > 4, ≤ 6                        | 20 (23.0)                | 10 (34.5)                | 0.429   |
| > 6                             | 42 (48.3)                | 13 (44.8)                |         |
| **Pelvic lymph node involvement**| 25 (28.7)               | 6 (20.7)                 |         |
| **Retroperitoneal lymph node involvement** | 62 (71.3) | 24 (82.8) | 0.327 |

| **Treatment characteristic** | **PET parameter** | **PET base** | **PET IGBT** |
|-------------------------------|-------------------|-------------|-------------|
| **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_{IGBT}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 (5.9-8.9)   | < 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 |
| **ΔSUV_{max}**                | 17.4 (7.3-35.4)   | 35.2 (11.6-61.2) | 0.073 |
| **ΔSUV_{mean}**               | 68.2 (61.9-75.2)  | 33.7 (12.8-44.7) | < 0.001 |
| **ΔMTV**                      | 93.1 (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, 18F-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. FIGO stage refers to the revised 2018 FIGO staging.
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 ΔSUV max < 50% could be more clinically accessible and cost-effective. 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 ΔSUV 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 PETbase and PETIGBT. 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.

Electronic Supplementary Material
Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement
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.

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.

Conflicts of Interest
Conflict of interest relevant to this article was not reported.

References
1. Herrera FG, Prior JO. The role of PET/CT in cervical cancer. Front Oncol. 2013;3:34.
2. Nam H, Huh SJ, Ju SG, Park W, Lee JE, Choi JY, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography guided conformal brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2012;84:e29-34.
3. Oh D, Huh SJ, Park W, Ju SG, Nam H, Lee JE. Clinical outcomes in cervical cancer patients treated by FDG-PET/CT-based 3-dimensional planning for the first brachytherapy session. Medicine (Baltimore). 2016;95:e3895.
4. Engin G. Cervical cancer: MR imaging findings before, during, and after radiation therapy. Eur Radiol. 2016;16:313-24.
5. Yoon JW, Kim S, Kim SW, Kim YT, Kang WJ, Nam EJ. PET/CT response criteria (European Organization for Research and Treatment of Cancer) predict survival better than response evaluation criteria in solid tumors in locally advanced cervical cancer treated with chemoradiation. Clin Nucl Med. 2016;41:677-82.
6. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8:797-805.
7. Kim N, Cho H, Yun M, Park KR, Lee CG. Prognostic values of mid-radiotherapy (18)F-FDG PET/CT in patients with esophageal cancer. Radiat Oncol. 2019;14:27.
8. Kim N, Kim JS, Geol Lee C. Predictive value of interim 18F-FDG-PET in patients with non-small cell lung cancer treated with definitive radiation therapy. PLoS One. 2020;15:e0236350.
9. Kim S, Oh S, Kim JS, Kim YK, Kim KH, Oh DH, et al. Prognostic value of FDG PET/CT during radiotherapy in head and neck cancer patients. Radiat Oncol J. 2018;36:95-102.
10. Haie-Meder C, Potter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol. 2005;74:235-45.
11. Kidd EA, Thomas M, Siegel BA, Dehdashti F, Grigsby PW. Changes in cervical cancer FDG uptake during chemoradiation and association with response. Int J Radiat Oncol Biol Phys. 2013;85:116-22.
12. Lin LL, Yang Z, Mutic S, Miller TR, Grigsby PW. FDG-PET imaging for the assessment of physiologic volume response during radiotherapy in cervix cancer. Int J Radiat Oncol Biol Phys. 2006;65:177-81.
13. Schwarz JK, Lin LL, Siegel BA, Miller TR, Grigsby PW. 18-
F-Fluorodeoxyglucose-positron emission tomography evaluation of early metabolic response during radiation therapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2008;72:1502-7.

14. Leseur J, Roman-Jimenez G, Devillers A, Ospina-Arango JD, Willaume D, Castelli J, et al. Pre- and per-treatment 18F-FDG PET/CT parameters to predict recurrence and survival in cervical cancer. Radiother Oncol. 2016;120:512-8.

15. Oh D, Lee JE, Huh SJ, Park W, Nam H, Choi JY, et al. Prognostic significance of tumor response as assessed by sequential 18F-fluorodeoxyglucose positron emission tomography/computed tomography during concurrent chemoradiation therapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2013;87:549-54.

16. Shen WC, Chen SW, Wu KC, Hsieh TC, Liang JA, Hung YC, et al. Prediction of local relapse and distant metastasis in patients with definitive chemoradiotherapy-treated cervical cancer by deep learning from [(18)F]-fluorodeoxyglucose positron emission tomography/computed tomography. Eur Radiol. 2019;29:6741-9.

17. Kidd EA, Siegel BA, Dehdashti F, Grigsby PW. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. Cancer. 2007;110:1738-44.

18. Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutch DG, Powell MA, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. J Clin Oncol. 2010;28:2108-13.

19. Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutch S, Mutch DG, et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2010;77:1085-91.

20. Nam H, Park W, Huh SJ, Bae DS, Kim BG, Lee JH, et al. The prognostic significance of tumor volume regression during radiotherapy and concurrent chemoradiotherapy for cervical cancer using MRI. Gynecol Oncol. 2007;107:320-5.

21. Fields EC, Weiss E. A practical review of magnetic resonance imaging for the evaluation and management of cervical cancer. Radiat Oncol. 2016;11:15.

22. Sun C, Tian X, Liu Z, Li W, Li P, Chen J, et al. Radiomic analysis for pretreatment prediction of response to neoadjuvant chemotherapy in locally advanced cervical cancer: a multi-centre study. EBioMedicine. 2019;46:160-9.

23. Wormald BW, Doran SJ, Ind TE, D’Arcy J, Petts J, deSouza NM. Radiomic features of cervical cancer on T2-and diffusion-weighted MRI: prognostic value in low-volume tumors suitable for trachelectomy. Gynecol Oncol. 2020;156:107-14.

24. Lucia F, Visvikis D, Desseroit MC, Miranda O, Malhaire JP, Robin P, et al. Prediction of outcome using pretreatment (18)F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2018;45:768-86.

25. Lucia F, Visvikis D, Vallieres M, Desseroit MC, Miranda O, Robin P, et al. External validation of a combined PET and MRI radiomics model for prediction of recurrence in cervical cancer patients treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2019;46:864-77.

26. Lee JH, Lee SW, Kim JR, Kim YS, Yoon MS, Jeong S, et al. Tumor size, volume, and marker expression during radiation therapy can predict survival of cervical cancer patients: a multi-institutional retrospective analysis of KROG 16-01. Gynecol Oncol. 2017;147:577-84.

27. Yang K, Park W, Huh SJ, Bae DS, Kim BG, Lee JW. Clinical outcomes in patients treated with radiotherapy after surgery for cervical cancer. Radiat Oncol J. 2017;35:39-47.

28. Noh JM, Park W, Kim YS, Kim JY, Kim HJ, Kim J, et al. Comparison of clinical outcomes of adenocarcinoma and adenosquamous carcinoma in uterine cervical cancer patients receiving surgical resection followed by radiotherapy: a multicenter retrospective study (KROG 13-10). Gynecol Oncol. 2014;132:618-23.

29. Hodgson A, Park KJ. Cervical adenocarcinomas: a heterogeneous group of tumors with variable etiologies and clinical outcomes. Arch Pathol Lab Med. 2019;143:34-46.

30. Hautzel H, Muller-Gartner HW. Early changes in fluorine-18-FDG uptake during radiotherapy. J Nucl Med. 1997;38:1384-6.