Primary tumor SUV_{max} on preoperative FDG-PET/CT is a prognostic indicator in stage IA2-IIB cervical cancer patients treated with radical hysterectomy

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Abstract. The objective of the present study was to investigate the prognostic value of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) uptake by primary tumors on positron emission tomography/computed tomography (PET/CT) in surgically resectable cervical cancer. A total of 59 patients with stage IA2-IIB cervical cancer who underwent preoperative FDG-PET/CT, followed by radical hysterectomy and lymphadenectomy, were included in the study. The maximum standardized uptake value (SUV_{max}) of the primary tumor was measured, and the association between the SUV_{max} and clinicopathological factors or patient outcomes was analyzed. The SUV_{max} was significantly higher in patients with an advanced stage, lymph node metastasis, lymph-vascular space involvement and large tumors. The overall survival (OS) and progression-free survival (PFS) of patients with a high SUV_{max} were significantly lower compared with patients with a low SUV_{max}, using an optimal cut-off value of 7.36 for OS and 5.59 for PFS obtained from receiver operating characteristic curve analysis. Similarly, OS and PFS in patients with a high SUV_{max} were significantly lower in 39 patients with stage IB using a cut-off value of 7.90 and 6.69 for OS and PFS, respectively. Finally, multivariate analyses showed that the SUV_{max} of the primary tumor was an independent prognostic factor for impaired PFS in all patients and those with stage IB alone. These findings demonstrated that a high SUV_{max} on preoperative PET/CT was correlated with unfavorable clinical outcomes in patients receiving radical hysterectomy, suggesting that the SUV_{max} of the primary tumor may be a prognostic indicator for surgically-treated, early-stage invasive cervical cancer.

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Introduction

The second most prominent cancer in women worldwide is cervical cancer. The general treatment for cervical cancer is surgery, radiotherapy or both, with or without chemotherapy. Primary concurrent chemoradiotherapy has recently been used for advanced disease, and additionally, for early-stage locally advanced disease (1,2). In Japan, the majority of stage IB through to IIB disease patients are treated with radical hysterectomy (3,4). There is a good prognosis associated with stage IB-IIB cervical cancer; however, following surgery a significant number of patients develop recurrence. Several clinicopathological parameters have been used to assess the risk of relapse, including the histological subtype, lymph node status, lymph-vascular space involvement (LVSI), parametrial invasion and tumor size (5-8). For patients in the high-risk groups, postoperative radiotherapy with or without chemotherapy has been performed previously (3,4,9,10). However, due to its impact on survival and the quality of life, the selection of patients for adjuvant therapy remains controversial (4,9). Therefore, in addition to the conventional clinicopathological parameters, the identification of more reliable and convenient markers that are closely associated with the biological behavior of cervical cancer and the individualization of adjuvant therapy based on these indicators is required to improve the survival of patients with stage I-II disease, as well as for preventing the unnecessary use of adjuvant therapy.

The use of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) with computed tomography (CT) has been introduced over the past decade, and is now a well-established imaging modality for the diagnosis, staging and treatment monitoring of numerous types of cancer. Previous studies have shown that the maximum standardized uptake value (SUV_{max}), a semiquantitative simplified measurement of the tissue deoxyglucose metabolic rate measured on FDG-PET/CT, could be a parameter for evaluating malignancy and for assessing the prognosis of patients with ovarian cancer (11,12) and endometrial cancer (13-15). Therefore, the use of SUV_{max} as a new biomarker that is easily measureable on PET/CT prior to the start of treatment in patients with gynecological malignancies has received considerable attention.

In cervical cancer, previous studies have demonstrated the usefulness of PET/CT for the staging or assessment of lymph node metastasis (16,17). However, the correlation between the FDG uptake and clinicopathological outcome of the primary tumor has not yet been sufficiently studied and its prognostic impact remains controversial (18-21). Furthermore, there have been few studies regarding the clinical impact of the preoperative SUV_{max} in patients with early-stage (I-II) disease treated with radical hysterectomy (19,20,22). The present study investigated the SUV_{max} of primary tumors measured by preoperative FDG-PET/CT in stage IA2-IIB invasive cervical cancer patients undergoing radical hysterectomy, and aimed to clarify whether the SUV_{max} could be a prognostic indicator for these patients.

Patients and methods

Patient selection. A total of 59 patients with stage IA2-IIB invasive cervical cancer who underwent radical hysterectomy and pelvic lymphadenectomy at Wakayama Medical University Hospital (Wakayama, Japan) between December 2008 and June 2013 were included in this retrospective study. All patients underwent preoperative FDG-PET/CT scans at Wakayama Minami Radiology Clinic subsequent to providing informed consent. No patient underwent paraaortic node biopsy/dissection as those suspected of having paraaortic node metastasis on preoperative PET/CT were excluded from the study. The median age of patients was 46 years, ranging 30-68 years. The patients were staged preoperatively according to the International Federation of Gynecology and Obstetrics (FIGO) criteria: 6 were stage IA2, 36 were IB1, 3 were IB2, 4 were IIA and 10 were IIB. The postoperative pathological diagnosis and evaluation of clinicopathological parameters, including lymph node metastasis, LVSI and tumor size, were performed by pathologists. The histological subtype was classified: 35 cases were squamous cell carcinoma (SCC), 19 were adenocarcinoma (AC) and 5 were adenosquamous carcinoma (ASC). Patients with a specific histology other than SCC and AC/ASC were not included. The FIGO stage IB patients with positive lymph nodes, LVSI or a larger tumor size (≥4 cm) and all FIGO stage II patients received postoperative adjuvant therapy involving either whole pelvic irradiation with/without chemotherapy [three courses of cisplatin (70 mg/m^2) on day 1 plus 5-fluorouracil (700 mg/m^2) on days 1-4; every 4 weeks] or chemotherapy alone [three courses of paclitaxel (175 mg/m^2) on day 1 plus carboplatin AUC5 on day 1; every 3 weeks]. Patients receiving primary radiotherapy/concurrent chemoradiation therapy without surgery or receiving any form of preoperative treatment were excluded from this study. The study was approved by the ethics committee of Wakayama Medical University.

FDG-PET/CT and imaging analysis. Positron emission tomography studies were performed with a PET scanner (SET-3000BCT/L; Shimadzu, Kyoto, Japan) with an axial resolution of 3.9 mm and a 20-cm field of view, as described in our previous study (12). At the time of the tracer injection, all the patients had fasted for ≥5 h and had blood glucose levels <150 mg/dl. Images were acquired from the top of the head to the mid-thigh 50 min after the intravenous injection of ^{18}F-FDG (2.6 MBq/kg body weight). Following completion of the PET scan, CT images were obtained with a multidetector row CT scanner (Brilliance 64; Philips Medical Systems, Best, The Netherlands). Fusion images of PET and CT were made using a Workstation (EV Insite; PSP Corp., Tokyo, Japan). FDG-PET/CT images were evaluated by a nuclear medicine physician or radiologist. For each study, the SUV_{max} of the primary tumor was measured. SUV is a semiquantitatively analyzed value of radiotracer uptake and is defined as the ratio of radiotracer activity per milliliter of tissue to the activity in the injected dose corrected for decay and the body weight of the patient.

Data analysis. The association between the SUV_{max} of the primary tumor and clinicopathological or prognostic factors was investigated. The SUV_{max} was compared among groups using the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed in order to determine the cut-off values of the SUV_{max}. Overall survival (OS) was calculated from the date of surgery to that of fatality, and progression-free survival (PFS) was calculated from the date of surgery to that of recurrence. The median follow-up period was 28.1 months, ranging 3.3-63 months. Survival analyses were performed according to the Kaplan-Meier method. A comparison of the survival between groups was performed with the log-rank test. The Cox proportional-hazard regression model was used for multivariate analyses to explore the impact of individual variables on survival. $P<0.05$ was was considered to indicate a statistically significant difference.

Results

Association between the SUV_{max} of the primary tumor and the clinicopathological factors. The clinicopathological characteristics and the median SUV_{max} of the primary tumor in each group are shown in Table I. The median of the SUV_{max} values for all 59 patients was 4.31, with a range of 0.00-20.29. As shown in Fig. 1A, the SUV_{max} for stage IB1 was significantly higher compared to that for stage IA2 (P=0.046), and the SUV_{max} for stage IB2 was significantly higher than those for stage IA2 and IB1 (P=0.018 and P=0.023, respectively). In addition, the SUV_{max} for stage IIB was significantly higher than those for stage IA2 (P=0.005) and IB1 (P=0.003); however, not for stage IB2 or IIA. Similarly, the SUV_{max} was significantly higher in patients with a pathologically positive pelvic lymph node (P=0.002) (Fig. 1C) and with a positive LVSI (P=0.044) (Fig. 1D), while no significant correlation was observed between the SUV_{max} and histological subtype (Fig. 1B). In addition, the SUV_{max} in patients with a pathologically measured tumor size of ≥20 mm (n=28) was significantly higher compared to in patients with a tumor size of <20 mm (n=31) (data not shown).

Determination of cut-off values of the SUV_{max} for predicting the presence of risk factors. As shown in Table II, ROC curve analysis demonstrated that the optimal cut-off value of the SUV_{max} for predicting a pathologically positive lymph node status was 6.03, with a sensitivity of 80%, specificity of 73%, and area under the curve (AUC)=0.764, while the cut-off value of the SUV_{max} for predicting a positive LVSI was 4.42, with a sensitivity of 67%, specificity of 63%, and AUC=0.655. There was a significant correlation between the SUV_{max} and lymph

node status (P=0.002) or LVSI (P=0.044). Similarly, ROC curve analysis revealed that the optimal cut-off values of the SUV_{max} for predicting tumor sizes of ≥20 and ≥40 mm were 4.71 and 9.66, respectively, with relatively high sensitivity and specificity, and there was a significant correlation between the SUV_{max} and tumor size.

Correlation of the SUV_{max} of the primary tumor with patient survival. Based on the ROC curve analysis, the optimal cut-off values of the SUV_{max} for predicting OS and PFS in all 59 patients were 7.36 and 5.59, respectively (Fig. 2A and B). Using these cut-off values, the OS rate of patients with a high SUV_{max} (SUV ≥7.36) was significantly lower compared with patients with a low SUV_{max}(SUV_{max}<7.36) (P=0.04) (Fig. 2C). Similarly, the PFS rate of patients with a high SUV_{max}(SUV ≥5.59) was significantly lower compared with patients with a low SUV_{max}(SUV_{max}<5.59) (P=0.006) (Fig. 2D).

Subsequently, the impact of the preoperative SUV_{max} on the prognosis of 39 patients with stage IB disease alone was analyzed. Based on the ROC curve analysis, the optimal cut-off values of the SUV_{max} for predicting OS and PFS in stage IB patients were 7.90 and 6.69, respectively (Fig. 3A and B). The OS and PFS rates in patients with high SUV_{max} values (SUV ≥7.90 and ≥6.69) were significantly lower compared to those of patients with low SUV_{max} values (P=0.001 and P=0.014, respectively) (Fig. 3C and D).

To clarify whether the SUV_{max} could be an independent prognostic factor in cervical cancer patients, multivariate analyses were performed. As shown in Table III, multivariate analysis demonstrated that a high SUV_{max} in the primary tumor was an independent prognostic factor for impaired PFS (hazard ratio=3.947, P=0.011) among the variables including FIGO stage, lymph node metastasis, LVSI, tumor size and histological subtype. Similarly, a high SUV_{max} was an independent factor for predicting impaired PFS when analyzed in stage IB patients alone (hazard ratio=4.851, P=0.026) (Table IV).

Table I. Clinicopathological characteristics of 59 cervical cancer patients.

Characteristics	Patients, n (%)	Median SUV_{max}
Total	59 (100.0)	4.31
Stage		
IA2	6 (10.2)	1.29
IB1	36 (61.0)	3.73
IB2	3 (5.1)	11.03
IIA	4 (6.8)	5.27
IIB	10 (16.9)	8.05
Histology		
SCC	35 (59.3)	3.80
AC/ASC	24 (40.7)	4.89
LN metastasis		
Negative	44 (74.6)	3.79
Positive	15 (25.4)	8.56
LVSI		
Negative	35 (59.3)	3.81
Positive	24 (40.7)	7.70

SCC, squamaous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; LN, lymph node; LVSI, lymph-vascular space involvement; SUV_{max}, maximum standardized uptake value.

Discussion

There have been several studies showing the association between the FDG uptake within tumors evaluated by the SUV_{max} and clinical outcome in cervical cancer patients, although its impact on disease recurrence or survival remains controversial. Kidd *et al* (18) reported that the SUV_{max} was a sensitive biomarker of the prognosis in patients with cervical cancer including stage IA2-IVB treated with surgery, chemoradiation, or palliation. Xue *et al* (23) also reported that the SUV_{max} is predictive of the disease-free survival in stage IB1-IVB cervical cancer patients treated with radiation therapy. By contrast, Cho *et al* (20) demonstrated that a high pretreatment SUV_{max} was not predictive of recurrence in 81 patients with IB1-IVB disease treated with surgery or concurrent chemoradiation. These different results may be due to treatment bias as disease stages and treatment modalities were diverse. When focusing on surgically-treated early-stage (FIGO stage IA or IB1 to IIA) cervical cancer, there have been controversial studies on the role of the SUV_{max} (19,21,24). Lee *et al* (19) and Yun *et al* (24) showed that a high SUV_{max} was correlated with impaired disease-free survival, while Crivellaro *et al* (21) showed that the SUV_{max} was not associated with recurrence. To clarify the prognostic impact of the SUV_{max} on preoperative PET/CT, the present study focused on FIGO stage IA2 to IIB patients who had undergone the standardized surgical procedure (radical hysterectomy and pelvic lymphadenectomy) in a single institution.

The present results showed that a high SUV_{max} of the primary tumor was significantly correlated with the presence of conventional clinicopathological risk factors, such as positive lymph node metastasis, LVSI and a large tumor size. In addition, the OS and PFS in patients with a higher SUV_{max} were significantly lower compared with those with a lower SUV_{max}. Furthermore, a high SUV_{max} was an independent prognostic factor for impaired PFS on multivariate analysis. These findings suggest that the SUV_{max} of the primary tumor could be a prognostic indicator for surgically-resected early-stage invasive cervical cancer. Notably, the OS and PFS in patients with a higher SUV_{max} were also lower when analyzed in the stage IB group alone. As the SUV_{max} can be easily measured on a preoperative FDG-PET/CT, it may be a promising non-invasive biomarker to evaluate the risk of recurrence/fatality and to select patients who should receive adjuvant therapy following radical hysterectomy, particularly in stage IB patients.

In the present study, the optimal cut-off values of the SUV_{max} for predicting individual risk factors and assessing the prognosis using ROC curve analyses were determined. The cut-off value for predicting lymph node metastasis was 6.03. Furthermore, the cut-off levels for poor OS and PFS were 7.36 and 5.59, respectively, in all IA2-IIB patients, while those for OS and PFS in stage IB alone were 7.90 and 6.69, respectively. These values may

Table II. Receiver operating characteristic curve analyses of SUV_{max} cut-off values for predicting risk factors.

Variables	Sensitivity, %	Specificity, %	AUC	Optimal cut-off SUV_{max} value	95% CI	P-value
Positive LN status	80	73	0.764	6.03	0.624-0.904	0.002
Positive LVSI	67	63	0.655	4.42	0.512-0.799	0.044
Tumor size, mm						
≥20	71	74	0.793	4.71	0.678-0.907	<0.001
≥40	80	85	0.919	9.66	0.838-0.999	0.02

LN, lymph node; LVSI, lymph-vascular space involvement; AUC, area under the curve; CI, confidence interval; SUV_{max}, maximum standardized uptake value.

Table III. Univariate and multivariate analyses of progression-free survival in 59 cervical cancer patients.

	Univariate	Multivariate		
Variables	P-value	Hazard ratio	95% CI	P-value
FIGO stage				
IA2-1B2	0.026	1.429	0.431-4.740	0.560
IIA-IIB				
Histology				
SCC	0.413	0.917	0.298-2.825	0.881
AC/ASC				
LN metastasis				
Negative	0.007	1.503	0.407-5.549	0.541
Positive				
LVSI				
Negative	0.030	1.555	0.470-5.143	0.469
Positive				
Tumor size, mm				
<20	0.047	1.343	0.410-4.395	0.626
≥20				
SUV_{max}				
<5.59	0.006	3.947	1.366-11.407	0.011
≥5.59				

SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; LN, lymph node; LVSI, lymph-vascular space involvement; CI, confidence interval; SUV_{max}, maximum standardized uptake value.

be easy to use and aid the preoperative risk stratification in each patient as an index. Consistent with the present results, the study by Yun *et al* (24) showed that the cut-off value of an SUV_{max} >6 was predictive of disease-free survival in stage IA-IIA cervical cancer. By contrast, Lee *et al* (19) reported that a much higher cut-off value (SUV_{max} ≥13.4) was predictive of disease recurrence in stage IB1-IIA. The study by Kidd *et al* (18) showed three subgroups according to the SUV_{max} cut-off values: Low (<5.2), middle (5.2-13.3) and high risk (>13.3). The variation in the optimal cut-off values of the SUV_{max} among the studies may be dependent on the setting of PET scanning conditions and its imaging analysis in each institution or on the targeted patient conditions, such as disease stage.

In addition to the SUV_{max}, several other metabolic parameters of FDG-PET/CT have been measured in gynecological cancers. Kitajima *et al* (25) demonstrated that the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of the primary tumors were correlated with clinicopathological features and are more useful for differentiating high risk from low risk compared to the SUV_{max} alone in endometrial cancer. In cervical cancer, their usefulness remains controversial. Kim *et al* (22) and Chung *et al* (26) reported that MTV was an independent prognostic factor for disease recurrence in patients with stage IA-IIB and IB-IIA, respectively. By contrast, the study by Crivellaro *et al* (21) showed that MTV and TLG were not predictors of recurrence in IB1-IIA

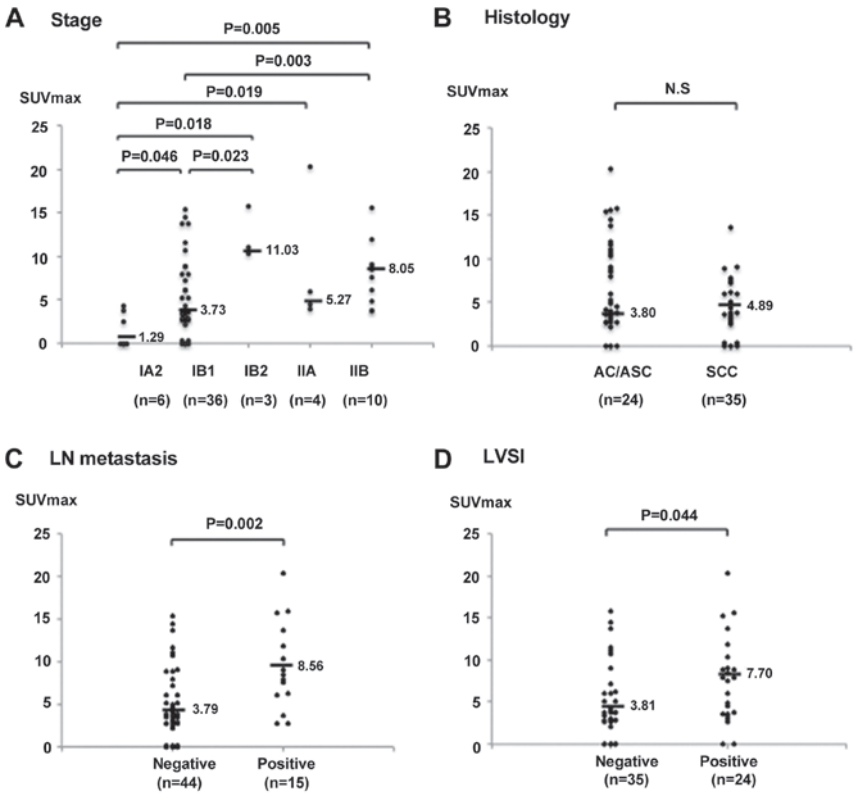

Figure 1. Association between the SUV_{max} and clinicopathological factors in 59 cervical cancer patients. (A) Stage, (B) histology, (C) LN metastasis and (D) LVSI. SUV_{max}, maximum standardized uptake value; LN, lymph node; LVSI, lymph-vascular space involvement; AC, adenocarcinoma; ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; N.S., not significant.

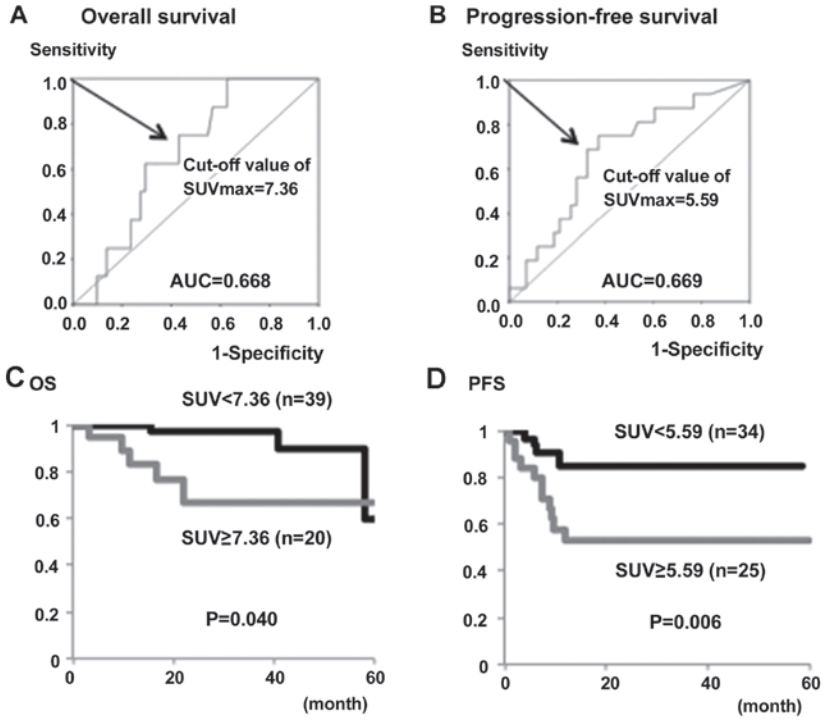

Figure 2. Receiver operating characteristic curve analysis and Kaplan-Meier plots for OS and PFS in 59 cervical cancer patients. OS, overall survival; PFS, progression-free survival; SUV, standardized uptake value; AUC, area under the curve.

disease. Yoo *et al* (27) reported that TLG and the lymph node status, but not MTV, were independent prognostic factors for survival in stage IB-IVB. Considering the importance of intratumoral FDG metabolic heterogeneity (28), the present study focusing on the SUV_{max} alone is simple, but may have limitations. Further studies using multimetabolic parameters

Table IV. Univariate and multivariate analyses of progression-free survival in 39 stage IB patients.

	Univariate	Multivariate		
Variables	P-value	Hazard ratio	95% CI	P-value
Histology				
SCC	0.475	1.054	0.222-5.001	0.948
AC/ASC				
LN metastasis				
Negative	0.150	1.932	0.412-9.069	0.404
Positive				
LVSI				
Negative	0.380	1.097	0.276-4.363	0.895
Positive				
Tumor size, mm				
<20	0.134	1.171	0.216-6.352	0.854
≥20				
SUV_{max}				
<6.69	0.014	4.851	1.206-19.513	0.026
≥6.69				

SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; LN, lymph node; LVSI, lymph-vascular space involvement; CI, confidence interval; SUV_{max}, maximum standardized uptake value.

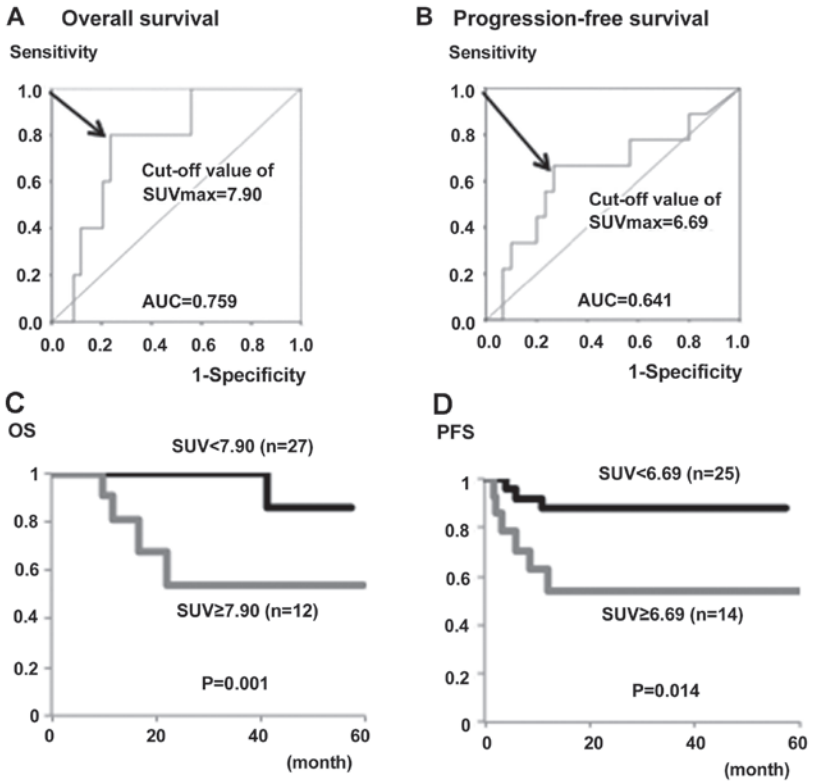

Figure 3. Receiver operating characteristic curve analysis and Kaplan-Meier plots for OS and PFS in 39 stage IB patients. OS, overall survival; PFS, progression-free survival; SUV, standardized uptake value; AUC, area under the curve.

of FDG-PET/CT, including the SUV_{max}, MTV and TLG, are required to clarify the optimal prognostic parameter for stage IA2-IIB invasive cancer patients undergoing radical hysterectomy. Furthermore, in combination with these metabolic parameters of FDG-PET analysis, immunohistochemical expression of glucose-metabolism-related proteins, such as

glucose transporter 1 and cytoplasmic hexokinase II (29,30), serum SCC antigens (31,32) and the mean apparent diffusion coefficient on MRI (33) have also been reported to be prognostic biomarkers. The most appropriate combination of PET parameters with other optimal non-invasive biomarkers remains to be determined.

In conclusion, the present study demonstrated that a high SUV_{max} on preoperative PET/CT correlates with an unfavorable clinical outcome in FIGO stage IA2-IIB patients who have undergone radical hysterectomy. These findings suggest that the SUV_{max} of the primary tumor may be a promising prognostic indicator for risk stratification in surgically-treated, early-stage invasive cervical cancer patients.

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