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Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis on Preoperative ^{18}F-FDG PET/CT in Patients with Pancreatic Cancer

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In this study, we aimed to assess the prognostic value of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) measured on ^{18}F-FDG PET/CT in pancreatic cancer patients who underwent resection with curative intent. **Methods:** Eighty-seven patients with pancreatic ductal adenocarcinoma who underwent ^{18}F-FDG PET/CT and subsequent surgical resection with curative intent with (30 patients) or without (57 patients) neoadjuvant therapy were retrospectively enrolled. The maximum standardized uptake value (SUVmax), MTV, and TLG were measured on ^{18}F-FDG PET/CT in all patients. The prognostic significances of PET/CT parameters and tumor factors for recurrence-free survival (RFS) and overall survival (OS) were evaluated by univariate and multivariate analyses. **Results:** Of the 87 patients, 57 (64%) experienced recurrence during the follow-up period. The tumor size, pathologic T (pT) stage, SUVmax, MTV, and TLG were significant prognostic factors for both RFS and OS ($P < 0.05$) on univariate analyses, and the presence of lymph node metastasis showed significance only for predicting RFS ($P < 0.05$). On multivariate analyses, the tumor size, MTV, and TLG were independent prognostic factors for RFS, and pT stage, MTV, and TLG were independent prognostic factors for OS. For the 57 patients who did not undergo neoadjuvant treatment, MTV and TLG remained significant predictive factors for tumor recurrence, along with tumor size and SUVmax. **Conclusion:** MTV and TLG are independent prognostic factors for predicting RFS and OS in patients with pancreatic cancer. Thus, ^{18}F-FDG PET/CT can provide useful prognostic information for patients undergoing resection of pancreatic cancer with curative intent irrespective of neoadjuvant treatment.

Key Words: pancreatic cancer; ^{18}F-FDG; PET; metabolic tumor volume; prognosis

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Pancreatic cancer is one of the most lethal carcinomas, with a 5-y survival rate of less than 15% in stage I patients and less than 1% in stage IV patients (*1–3*). Although surgical resection is the only potentially curative treatment for patients with pancreatic cancer, only 15%–20% of these patients are surgical candidates (*1,2*). Moreover, most patients who undergo resection with curative intent develop recurrence usually in the first 6–12 mo of the surgery (*4–6*). Several prognostic factors for pancreatic cancer recurrence have previously been reported including tumor size, T stage, lymph node metastasis, tumor differentiation, lymphovascular invasion, involvement of the surgical margin, and serum carbohydrate antigen 19-9 (CA19-9) level (*1,7–9*).

Currently, ^{18}F-FDG PET/CT is widely used to assess many different types of malignancy. In patients with pancreatic cancer, several studies have demonstrated an important role for ^{18}F-FDG PET/CT in staging, detecting postoperative recurrence, and evaluating the response to treatment (*6,10–13*). Other studies have shown that the standardized uptake value (SUV) of primary pancreatic cancer lesions measured on ^{18}F-FDG PET/CT can help to predict recurrence in patients with pancreatic cancer (*12,14,15*). Recently, ^{18}F-FDG PET/CT–based volumetric imaging parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have also been suggested as prognostic factors for various neoplasms (*16–18*). However, there are few studies that have evaluated volumetric parameters as prognostic factors in patients with pancreatic cancer (*19*). The objective of this study was to assess the prognostic value of these volumetric parameters on preoperative ^{18}F-FDG PET/CT and to compare their predictive values with those of conventional prognostic factors in patients with pancreatic cancer who underwent curative resection.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of all pancreatic cancer patients who underwent ^{18}F-FDG PET/CT as part of a staging work-up before treatment at our institution between January 2008 and October 2012. Of these cases, we retrospectively enrolled 87 patients with pancreatic ductal adenocarcinoma who underwent preoperative ^{18}F-FDG PET/CT before resection with curative intent with or without neoadjuvant treatment. Patients who had pancreatic cancer other than ductal adenocarcinoma, who had unresectable cancer on pretreatment imaging studies, or who had undergone palliative surgery were

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excluded from the study. All patients underwent ^{18}F-FDG PET/CT and conventional radiologic examinations including contrast-enhanced CT or MR imaging. Additionally, serum CA19-9 levels were measured before treatment. The institutional review board of our university approved this retrospective study, and the requirement to obtain informed consent was waived.

According to guidelines of the National Comprehensive Cancer Network, all patients were classified as either resectable (72 patients, 83%) or borderline resectable (15 patients, 17%). All borderline resectable patients had undergone neoadjuvant chemoradiation therapy before surgery, and 15 resectable patients had also undergone neoadjuvant treatment as per the results of pretreatment imaging studies. All patients underwent surgical resection with curative intent with or without neoadjuvant treatment; 58 patients (67%) underwent pylorus-preserving pancreaticoduodenectomy, 18 (21%) underwent distal pancreatectomy, 8 (9%) underwent classic pancreaticoduodenectomy, and 3 (3%) underwent total pancreatectomy. The tumor pathology for each patient was carefully evaluated to obtain histopathologic information with respect to tumor size, differentiation, pathologic T (pT) stage, presence of lymph node metastasis, microscopic perineural invasion, and lymphovascular invasion. On the basis of these histopathologic results and the clinical condition of the patients, 65 patients (75%) underwent postoperative adjuvant chemotherapy with or without radiotherapy.

All 87 enrolled patients had clinical follow-up after treatment that included diagnostic imaging studies and blood tests. The mean duration of clinical follow-up was 19 ± 12 mo (median, 16 mo; range, 4–60 mo). During the follow-up period, patients were clinically assessed every month. Blood tests including serum CA19-9 and contrast-enhanced abdominopelvic CT were performed every 4–6 mo. If the clinical assessment or follow-up studies showed an abnormal finding, additional diagnostic studies and biopsy with histopathologic confirmation were performed to evaluate for recurrence.

^{18}F-FDG PET/CT Scan

All ^{18}F-FDG PET/CT scans were obtained with a dedicated PET/CT scanner (Discovery Ste [GE Healthcare] or Biograph TruePoint 40 [Siemens Healthcare]). In patients who had undergone neoadjuvant treatment, the mean time period between ^{18}F-FDG PET/CT scan and surgical resection was 108 ± 31 d. In patients who did not undergo neoadjuvant treatment, this time period was 15 ± 20 d. All patients fasted for at least 6 h before the PET/CT scan. The median blood glucose level was 110.0 mg/dL, with a range of 67.0–340.0 mg/dL. Of 87 patients, 13 patients (15%) exceeded the blood glucose level of 150.0 mg/dL. A dose of approximately 5.5 MBq/kg of ^{18}F-FDG was intravenously injected 60 min before imaging. After the initial low-dose CT (Discovery Ste, 30 mA, 130 kVp; Biograph TruePoint, 36 mA, 120 kVp), a PET scan was obtained, extending from the neck to the proximal thighs, with an acquisition time of 3 min per bed position in 3-dimensional mode. PET images were reconstructed using ordered-subset expectation maximization with attenuation correction.

Data Analysis

^{18}F-FDG PET/CT images were reviewed by 2 nuclear medicine physicians using an Advantage Workstation 4.5 (GE Healthcare). Maximum SUV (SUVmax), mean SUV, and MTV on PET images were measured using the volume viewer software. Each tumor was examined with a spheric-shaped volume of interest (VOI) that included the entire lesion in the axial, sagittal, and coronal planes. With the use of CT images, ^{18}F-FDG uptake of normal organs such as the bowel, stomach, and liver was not included in the VOI. SUVmax of the VOI was calculated as (decay-corrected activity/tissue volume)/(injected dose/body weight). MTV was defined as total tumor volume with an SUV of 2.5 or greater, and the MTV and mean SUV of the VOI were automatically calculated. TLG was calculated as (mean SUV) × (MTV). In addition, SUVmax corrected for the blood glucose level (glucose-corrected SUVmax) was calculated as (SUVmax) × (blood glucose level)/100 (*14*), and then glucose-corrected TLG was also calculated using glucose-corrected SUVmax,

On follow-up, all patients were assessed and grouped according to whether they experienced recurrence of their cancer. The SUVmax, MTV, and TLG on ^{18}F-FDG PET/CT and other tumor factors were compared between the 2 subgroups using Mann–Whitney U tests, χ^2 tests, and Fisher exact tests. Survival curves were estimated using the Kaplan–Meier method to calculate cumulative recurrence-free survival (RFS) rates and overall survival (OS) rates. Survival time was defined as the time from surgical resection to recurrence (or death) or last follow-up visit at our medical center. Variables for survival analyses included ^{18}F-FDG PET parameters and tumor factors that showed significant differences between patients with and without evidence of recurrence. For statistical analyses, all variables for survival analysis were grouped into 2 categories according to specific cutoff values. The optimal cutoff values were determined using receiver-operating-characteristic curve analysis. The significance of the predictive value of each variable was evaluated using log-rank tests on univariate analysis and using Cox proportional hazards regression tests on multivariate analysis. The multicollinearity between MTV and TLG was evaluated by calculating Spearman rank correlation coefficient before multivariate analysis. Afterward, all the patients were reclassified into neoadjuvant-treatment or no-neoadjuvant-treatment subgroups, and survival analysis was performed. Because the neoadjuvant-treatment subgroup included patients with resectable disease and borderline resectable disease and the number of patients in the subgroup was small, subgroup analysis was performed only in the subgroup of patients without neoadjuvant treatment. Statistical analyses were performed using SPSS (version 20.0 for Windows; SPSS Inc.). P values of less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 87 patients enrolled in this study, 57 (64%) experienced recurrence during the clinical follow-up period after surgical resection. The median RFS and OS times were 12.7 and 29.4 mo, respectively. The most common site of recurrence was the liver, followed by local recurrence, the peritoneum, lung, and lymph nodes. The characteristics of the enrolled patients are shown in Table 1. Of the 30 [Table 1] patients who underwent neoadjuvant treatment, 4 showed no evidence of residual tumor on histopathologic evaluation of the resected specimen and were classified as stage pTx. These patients were excluded from the TNM stage classification. Moreover, for 10 of 30 patients who underwent neoadjuvant treatment, tumor differentiation could not be accurately defined because of post-treatment change; thus, differentiation was assessed only in the remaining 77 patients. In 1 patient, a solitary metastatic lesion was found in the liver during the operation, without any abnormal findings on preoperative ^{18}F-FDG PET/CT or MR imaging, and the patient was subsequently classified as stage IV. On ^{18}F-FDG PET/CT, 3 patients had pancreatic cancer lesions with an SUVmax less than 2.5, and MTV and TLG values were assigned as 0.0.

In comparing patients with and without recurrence, tumor size, pT stage, TNM stage, MTV, TLG, and glucose-corrected TLG showed significant differences ($P < 0.05$); meanwhile, the presence of lymph node metastasis, SUVmax, and glucose-corrected SUVmax were of marginal significance ($P = 0.07$, 0.06, and 0.05, respectively). Serum CA19-9 levels in patients with recurrence tended to be higher than those of patients without recurrence, though this was not statistically significant ($P > 0.05$).

TABLE 1
Patient Characteristics According to Recurrence

Characteristic	Total (n = 87)	Recurrence (n = 57)	No recurrence (n = 30)	P
Age (y)	61 ± 10	61 ± 11	63 ± 8	0.6
Sex				0.8
Male	52	23	12	
Female	35	34	18	
Diabetes mellitus	44	30 (68)	14 (32)	0.7
Neoadjuvant treatment				0.9
Yes	30	20 (67)	10 (33)	
No	57	37 (65)	20 (35)	
Adjuvant treatment				0.3
Yes	65	45 (69)	20 (31)	
No	22	12 (55)	10 (45)	
Tumor location				0.4
Head	65	40 (62)	25 (38)	
Body	16	13 (81)	4 (19)	
Tail	6	4 (67)	1 (33)	
Operation type				0.4
Classic pancreaticoduodenectomy	8	6 (75)	2 (25)	
Pylorus-preserving pancreaticoduodenectomy	58	35 (60)	23 (40)	
Total pancreatectomy	3	3 (100)	0 (0)	
Distal pancreatectomy	18	13 (72)	5 (28)	
Serum CA19-9 level (U/mL)	536.6 ± 1,379.7	644.9 ± 1,679.1	330.9 ± 366.6	0.2
Tumor size (cm)	2.1 ± 0.9	2.3 ± 0.8	1.8 ± 1.0	0.01
pT stage				0.002
Tx	4	1 (25)	3 (75)	
T1	13	5 (38)	8 (62)	
T2	4	2 (50)	2 (50)	
T3	66	49 (74)	17 (26)	
Lymph node metastasis				0.07
Yes	48	27 (56)	21 (44)	
No	39	30 (77)	9 (23)	
TNM stage (n = 83)				0.01
IA–IB	13	5 (38)	8 (62)	
IIA	31	21 (68)	10 (32)	
IIB	38	30 (79)	8 (21)	
IV	1	0 (0)	1 (100)	
Differentiation (n = 77)				0.2
Well	10	9 (90)	1 (10)	
Moderate	59	38 (64)	21 (36)	
Poor	8	5 (63)	3 (37)	
Perineural invasion				0.3
Yes	51	36 (71)	15 (29)	
No	36	21 (58)	15 (42)	
Lymphovascular invasion				0.6
Yes	25	18 (72)	7 (28)	
No	62	39 (63)	23 (37)	
SUVmax				0.06
Median	4.4	4.5	3.9	
Range	2.1–17.3	2.2–17.3	2.1–13.7	
Glucose-corrected SUVmax				0.05
Median	5.4	5.9	4.9	
Range	2.4–16.9	2.6–16.9	2.4–15.4	
MTV (cm^3)				0.02
Median	3.9	4.1	2.0	
Range	0.0–28.1	0.0–28.1	0.0–18.9	
TLG (g)				0.02
Median	13.6	15.4	7.6	
Range	0.0–102.9	0.0–102.9	0.0–89.7	
Glucose-corrected TLG (g)				0.02
Median	14.7	16.5	8.4	
Range	0.0–156.9	0.0–135.9	0.0–156.9	

Data in parentheses are percentages.

Prognostic Factors

The tumor size, serum CA19-9 level, pT stage, presence of lymph node metastasis, SUVmax, MTV, and TLG were evaluated as variables in the survival analysis. The optimal cutoff values for tumor size, serum CA19-9 level, SUVmax, MTV, TLG, glucose-corrected SUVmax, and glucose-corrected TLG were 2.0 cm, 180 U/mL, 4.7, 3.0 cm^3, 10.0 g, 3.7, and 15.0 g, respectively, as determined by receiver-operating-characteristic curve analysis. The significance of variables for predicting RFS and OS on univariate analysis is shown in Table 2. The tumor size, pT stage, presence of lymph node metastasis, SUVmax, MTV (Fig. 1A), and TLG (Fig. 1B) were significant prognostic factors on univariate analysis for RFS, and the tumor size, pT stage, SUVmax, MTV (Fig. 1C), and TLG (Fig. 1D) were significant prognostic factors for OS. Furthermore, glucose-corrected SUVmax and TLG were also evaluated as prognostic factors and showed statistical significance on univariate analysis. Although glucose-corrected SUVmax showed better results than SUVmax for both RFS and OS, TLG had a higher predictive value than glucose-corrected TLG for predicting OS.

[Table 2] [Fig. 1]

Of the variables included in the univariate analysis, those with a P value of less than 0.05 were selected for multivariate analysis. Because TLG is calculated by multiplication of the mean SUV and MTV, there was a significant correlation between MTV and TLG ($r = 0.959$, $P < 0.0001$). Hence, MTV and TLG were assessed separately. On multivariate analysis, only tumor size, MTV, and TLG were determined to be statistically significant for RFS and pT stage showed marginal significance (Table 3), and for OS, pT stage, MTV, and TLG were determined to be significant (Table 4).

[Table 3] [Table 4]

Prognostic Factors in Subgroup Analysis

Subgroup survival analysis was performed for 57 patients (mean age, 63 ± 9 y; 31 men and 26 women) who underwent resection with curative intent without neoadjuvant treatment. Tumor size, serum CA19-9 level, T stage, presence of lymph node metastasis, SUVmax, MTV, and TLG were evaluated on univariate analysis. Of these variables, size, SUVmax, MTV, and TLG were significant predictive factors ($P = 0.04$, 0.03, 0.0006, and 0.0001, respectively) for RFS, and pT stage showed marginal significance ($P = 0.07$).

DISCUSSION

In the present study, we evaluated the significance of volumetric parameters measured on preoperative ^{18}F-FDG PET/CT for predicting prognosis in patients with pancreatic cancer. Our results demonstrate that MTV and TLG of pancreatic cancer lesions are independent prognostic factors for predicting RFS and OS after surgical resection with curative intent, with predictive values comparable to those of tumor size and pT stage. Additionally, in the subgroup of patients who underwent surgical resection without neoadjuvant treatment, MTV and TLG were again determined to be statistically significant predictors of recurrence.

To date, there has been only 1 study that has evaluated the use of volumetric parameters on ^{18}F-FDG PET/CT for predicting clinical outcomes in patients with pancreatic cancer (*19*). Parlak et al. (*19*) performed ^{18}F-FDG PET/CT before definite concurrent chemoradiotherapy in 30 patients with locally advanced pancreatic cancer. They used gross tumor volume (GTV) measured during

TABLE 2
Significance of Prognostic Factors on Univariate Analysis

Variable	RFS		OS	
	Median (mo)	*P*	Median (mo)	*P*
Tumor size		0.0001		0.0008
≤2 cm	42.0		—	
>2 cm	9.9		21.4	
pT stage		0.0002		0.004
Tx, T1	46.9		—	
T2–T3	11.0		23.0	
Lymph node metastasis		0.03		0.07
No	17.5		37.2	
Yes	10.3		22.0	
Serum CA19-9 level		0.2		0.1
≤180 U/mL	12.2		34.4	
>180 U/mL	12.7		21.4	
SUVmax		0.03		0.03
≤4.7	12.9		34.4	
>4.7	9.9		20.6	
MTV		0.0004		0.001
≤3.0 cm^3	42.0		—	
>3.0 cm^3	10.3		21.4	
TLG		0.001		0.001
≤10.0 g	25.6		—	
>10.0 g	9.9		21.4	
Glucose-corrected SUVmax		0.002		0.003
≤3.7	42.0		—	
>3.7	11.1		22.0	
Glucose-corrected TLG		0.006		0.05
≤15.0 g	47.7		37.2	
>15.0 g	20.9		21.4	

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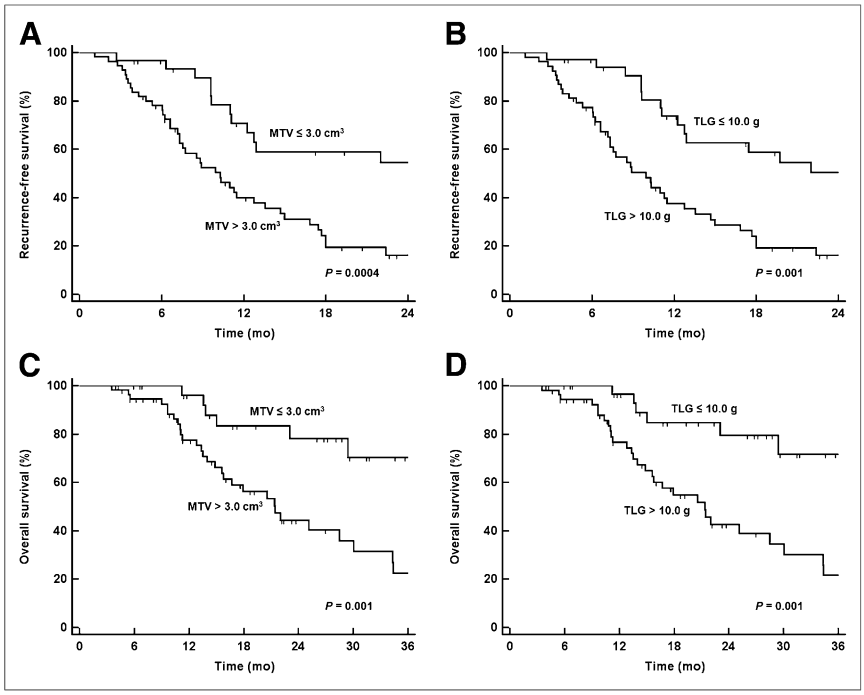

FIGURE 1. Cumulative RFS curves according to MTV (A) and TLG (B) and cumulative OS curves according to MTV (C) and TLG (D) of pancreatic cancer lesions in enrolled patients (n = 87).

radiotherapy planning as a metabolic parameter on ^{18}F-FDG PET/CT and showed that patients with a GTV of less than 100.0 cm^3 had significantly longer OS and progression-free survival than patients with a GTV of more than 100.0 cm^3. GTV is a parameter that is typically used in radiotherapy, however. MTV and TLG, on the other hand, are typical^{18}F-FDG PET/CT volumetric parameters used for survival analysis (*16–18*). In this study, we examined the prognostic value of MTV and TLG measured on preoperative ^{18}F-FDG PET/CT. The results of our study demonstrated that MTV and TLG are independent prognostic factors and had a stronger association with RFS and OS than SUVmax, which was used as the primary parameter in previous PET/CT studies (*12–15*). MTV is defined as the volume of tumor tissue that shows increased ^{18}F-FDG uptake over a set threshold, which was an SUV of 2.5 in our study. TLG is representative of the metabolic activity throughout the entire cancer lesion, and a large TLG may reflect a small volume of tissue with high ^{18}F-FDG uptake or a large volume of tissue with lower ^{18}F-FDG uptake (*17*). Hence, volumetric parameters such as MTV and TLG can more accurately reflect the metabolic burden of cancer lesions and predict prognosis, compared with SUVmax (*16–18,20*). The results of our study also showed that there were greater significant differences in MTV and TLG than in SUVmax between patients with and without recurrence and that only MTV and TLG were independent prognostic factors for both RFS and OS among the ^{18}F-FDG PET/CT parameters analyzed.

Several prognostic factors for predicting recurrence of pancreatic cancer have been suggested, and tumor size, pT stage, lymph node metastasis, tumor differentiation, lymphovascular invasion, and serum CA19-9 level have been shown to be significant predictors (*1,7–9*). Because exact tumor size, pT stage, presence of lymph node metastasis, tumor differentiation, and lymphovascular invasion of the tumor can be assessed only by examining the surgical specimen, they cannot be used to predict clinical outcomes before surgery. In contrast, ^{18}F-FDG PET/CT is a noninvasive imaging tool that has been widely used to stage patients with pancreatic cancer before treatment (*6,21*). In addition to its original function of detecting metastatic lesions, the metabolic parameters of ^{18}F-FDG PET/CT in the primary lesion can be used to predict prognosis before surgical resection with curative intent and are comparable to conventional prognostic factors such as pT stage and tumor size. Therefore, patients with high MTV and TLG on preoperative ^{18}F-FDG PET/CT can be assumed to be at high risk for cancer recurrence, and intensive adjuvant treatment or close follow-up is needed after surgical resection. When considering postoperative recurrence is associated with poor survival outcomes, neoadjuvant treatment followed by radical surgery can be considered for those high-risk patients.

In this study, we included patients who underwent surgical resection of pancreatic cancer with curative intent irrespective of neoadjuvant treatment. Therefore, patients with heterogeneous clinical conditions were included in the study: patients with borderline resectable lesions who underwent neoadjuvant treatment, patients with resectable cancer who underwent neoadjuvant treatment, and patients with resectable cancer who did not undergo neoadjuvant treatment. This setup may have influenced the results of our study because recurrence rates were not different according to

TABLE 3
Multivariate Analysis of Prognostic Factors for RFS

Variable	Model with MTV		Model with TLG	
	P	Hazard ratio	*P*	Hazard ratio
Tumor size	0.003	2.81 (1.42–5.56)	0.03	3.16 (1.05–9.49)
pT stage	0.09	2.52 (0.84–7.55)	0.05	3.01 (0.99–9.12)
Lymph node metastasis	0.3	1.36 (0.77–2.40)	0.6	1.12 (0.68–2.04)
SUVmax	0.8	1.00 (0.51–1.79)	0.7	0.90 (0.48–1.71)
MTV	0.001	2.34 (1.23–4.44)		
TLG			0.003	2.59 (1.39–4.83)

Data in parentheses are 95% confidence intervals.

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TABLE 4
Multivariate Analysis of Prognostic Factors for OS

Variable	Model with MTV		Model with TLG	
	P	Hazard ratio	*P*	Hazard ratio
Tumor size	0.5	1.32 (0.51–3.37)	0.4	1.49 (0.59–3.75)
pT stage	0.02	6.30 (1.30–30.62)	0.01	7.83 (1.55–39.54)
SUVmax	0.8	1.1 (0.52–2.29)	0.7	0.85 (0.40–1.82)
MTV	0.02	3.69 (1.28–10.62)		
TLG			0.003	4.85 (1.75–13.49)

Data in parentheses are 95% confidence intervals.

whether neoadjuvant or adjuvant treatment was performed, which is contradictory to results reported in previous studies (*22,23*). In addition, histopathologic variables including pT stage, presence of lymph node metastasis, and differentiation of the cancer lesion can be significantly affected by neoadjuvant treatment, which could have biased our results. The main purpose of this study, however, was to examine the prognostic value of volumetric parameters on ^{18}F-FDG PET/CT in pancreatic cancer patients, whereas the other variables were mainly used for comparison. Moreover, postneoadjuvant pT stage and lymph node metastasis have been shown to be significant prognostic factors for predicting cancer recurrence (*24*).

In patients with pancreatic cancer, the prevalence of diabetes mellitus is reportedly as high as 68%, which is significantly higher than in patients with other types of cancer or in healthy individuals (*25,26*). Because ^{18}F-FDG uptake of tumor lesions is dependent on blood glucose levels,^{18}F-FDG uptake in pancreatic cancer is reduced in patients with elevated blood glucose levels or a history of diabetes mellitus (*27*). Furthermore, a previous study by Lee et al. (*14*) demonstrated that glucose-corrected SUVmax was a better prognostic factor than uncorrected SUVmax for predicting pancreatic cancer recurrence after curative surgical resection. In our study, the incidence of diabetes mellitus was 51%, which was comparable to that reported in previous studies (*14,25,26*). Further, 15% of enrolled patients in the study had blood glucose levels of more than 150 mg/dL before injection of ^{18}F-FDG despite sufficient fasting time and delay of examination. We calculated the glucose-corrected SUVmax and mean SUV, and survival analysis using glucose-corrected SUVmax and TLG was further performed. However, although the glucose-corrected SUVmax showed better results than SUVmax, there was no significant difference between TLG and glucose-corrected TLG for predicting RFS, and, for predicting OS, TLG had a higher predictive value than glucose-corrected TLG. Therefore, multivariate analyses were performed using only MTV and TLG instead of using glucose-corrected TLG. Unlike SUVmax, volumetric parameters such as MTV and TLG can be used as prognostic factors without correction for blood glucose levels in pancreatic cancer patients.

There were several limitations to our study. First, because we enrolled patients who underwent radical surgical resection with curative intent, only the patients with favorable responses to neoadjuvant chemoradiation treatment were enrolled among the borderline resectable cancer patients, potentially skewing the sample toward those cases that may have a better prognosis. Second, we used a threshold SUV of 2.5 for measuring MTV of pancreatic cancer lesions. Some of the enrolled patients showed diffuse ^{18}F-FDG uptake in the pancreatic parenchyma distal to the cancer lesion, mainly because of obstructive pancreatitis. In those patients, it was difficult to differentiate tumor uptake from uptake due to pancreatitis, which may have affected the measurement of MTV. Third, in patients with tumor sizes of less than 2.0 cm, partial-volume effects could affect the ^{18}F-FDG uptake of the tumor, underestimating the values of MTV and TLG. Finally, this was a retrospective single-center study, and thus the results might be subject to selection bias. Further studies are needed to elucidate the prognostic values of volumetric PET/CT parameters.

CONCLUSION

In the present study, MTV and TLG measured on preoperative ^{18}F-FDG PET/CT are independent and significant prognostic factors for predicting RFS and OS after surgical resection with curative intent in patients with pancreatic cancer. Patients with low MTV or TLG have significantly better clinical outcomes than patients with high MTV or TLG. Further, MTV and TLG showed a more significant association with RFS and OS than SUVmax.

DISCLOSURE

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REFERENCES

1. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th ed. AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer.* 2007;110:738–744.
2. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet.* 2004;363:1049–1057.
3. Grassetto G, Rubello D. Role of FDG-PET/CT in diagnosis, staging, response to treatment, and prognosis of pancreatic cancer. *Am J Clin Oncol.* 2011;34:111–114.
4. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol.* 2007;14:2088–2096.
5. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg.* 2007;246:734–740.
6. Heinrich S, Goerres GW, Schäfer M, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. *Ann Surg.* 2005;242:235–243.
7. Hata S, Sakamoto Y, Yamamoto Y, et al. Prognostic impact of postoperative serum CA 19-9 levels in patients with resectable pancreatic cancer. *Ann Surg Oncol.* 2012;19:636–641.

8. Lewis R, Drebin JA, Callery MP, et al. A contemporary analysis of survival for resected pancreatic ductal adenocarcinoma. *HPB (Oxford).* 2013;15: 49–60.
9. Kato K, Yamada S, Sugimoto H, et al. Prognostic factors for survival after extended pancreatectomy for pancreatic head cancer: influence of resection margin status on survival. *Pancreas.* 2009;38:605–612.
10. Asagi A, Ohta K, Nasu J, et al. Utility of contrast-enhanced FDG-PET/CT in the clinical management of pancreatic cancer: impact on diagnosis, staging, evaluation of treatment response, and detection of recurrence. *Pancreas.* 2013; 42:11–19.
11. Kauhanen SP, Komar G, Seppänen MP, et al. A prospective diagnostic accuracy study of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg.* 2009; 250:957–963.
12. Okamoto K, Koyama I, Miyazawa M, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography/computed tomography predicts early recurrence after pancreatic cancer resection. *Int J Clin Oncol.* 2011;16: 39–44.
13. Topkan E, Parlak C, Kotek A, Yapar AF, Pehlivan B. Predictive value of metabolic ^{18}FDG-PET response on outcomes in patients with locally advanced pancreatic carcinoma treated with definitive concurrent chemoradiotherapy. *BMC Gastroenterol.* 2011;11:123.
14. Lee SM, Kim TS, Lee JW, Kim SK, Park SJ, Han SS. Improved prognostic value of standardized uptake value corrected for blood glucose level in pancreatic cancer using F-18 FDG PET. *Clin Nucl Med.* 2011;36:331–336.
15. Hwang JP, Lim I, Chang KJ, Kim BI, Choi CW, Lim SM. Prognostic value of SUVmax measured by fluorine-18 fluorodeoxyglucose positron emission tomography with computed tomography in patients with pancreatic cancer. *Nucl Med Mol Imaging.* 2012;46:207–214.
16. Oh JR, Seo JH, Chong A, et al. Whole-body metabolic tumour volume of ^{18}F-FDG PET/CT improves the prediction of prognosis in small cell lung cancer. *Eur J Nucl Med Mol Imaging.* 2012;39:925–935.
17. Ryu IS, Kim JS, Roh JI, et al. Prognostic value of preoperative metabolic tumor volume and total lesion glycolysis measured by ^{18}F-FDG PET/CT in salivary gland carcinomas. *J Nucl Med.* 2013;54:1032–1038.
18. Fendler WP, Philippe Tiega DB, Ilhan H, et al. Validation of several SUV-based parameters derived from ^{18}F-FDG PET for prediction of survival after SIRT of hepatic metastases from colorectal cancer. *J Nucl Med.* 2013;54:1202–1208.
19. Parlak C, Topkan E, Onal C, Reyhan M, Selek U. Prognostic value of gross tumor volume delineated by FDG-PET-CT based radiotherapy treatment planning in patients with locally advanced pancreatic cancer treated with chemoradiotherapy [abstract]. *Radiat Oncol.* 2012;7:37.
20. Davison J, Mercier G, Russo G, Subramaniam RM. PET-based primary tumor volumetric parameters and survival of patients with non-small cell lung carcinoma. *AJR.* 2013;200:635–640.
21. Delbeke D, Rose DM, Chapman WC, et al. Optimal interpretation of FDG PET in the diagnosis, staging and management of pancreatic carcinoma. *J Nucl Med.* 1999;40:1784–1791.
22. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer.* 2013;119:2692–2700.
23. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA.* 2007;297:267–277.
24. Estrella JS, Rashid A, Fleming JB, et al. Post-therapy pathologic stage and survival in patients with pancreatic ductal adenocarcinoma treated with neoadjuvant chemoradiation. *Cancer.* 2012;118:268–277.
25. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas.* 2013;42:198–201.
26. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology.* 2008;134:95–101.
27. Diederichs CG, Staib L, Glatting G, Beger HG, Reske SN. FDG PET: elevated plasma glucose reduces both uptake and detection rate of pancreatic malignancies. *J Nucl Med.* 1998;39:1030–1033.

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