# Prognostic Value of Metabolic and Volumetric Parameters of Preoperative FDG-PET/CT in Patients With Resectable Pancreatic Cancer

*Hyung-Jun Im, MD, PhD, Suthet Oo, MD, Woohyun Jung, MD, Jin-Young Jang, MD, PhD, Sun-Whe Kim, MD, Gi Jeong Cheon, MD, PhD, Keon Wook Kang, MD, PhD, June-Key Chung, MD, PhD, E. Edmund Kim, MD, and Dong Soo Lee, MD, PhD*

**Abstract:** In this study, we aimed to evaluate prognostic value of metabolic and volumetric parameters measured from ^{18}F fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in patients with resectable pancreatic cancer.

Fifty-one patients with resectable pancreatic cancer who underwent FDG-PET/CT and curative operation were retrospectively enrolled. The maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured from FDG-PET/CT. Association between FDG-PET/CT and clinicopathologic parameters was evaluated. The prognostic values of the FDG-PET/CT and clinicopathologic parameters for recurrence-free survival (RFS) and overall survival (OS) were assessed by univariate and multivariate analyses.

The 51 enrolled patients were followed up for a median of 21 months (mean ± SD: 23 ± 16 months, range: 1–78 months) with 33 (65%) recurrences and 30 (59%) deaths during the period. SUVmax, MTV, and TLG were associated with TNM stage and presence of lymph node metastasis. MTV and TLG were associated with presence of lymphovascular invasion, whereas SUVmax was not. On the univariate analysis, SUVmax, MTV, and TLG were associated with RFS and OS. Also, lymph node metastasis and TNM stage were associated with OS on the univariate analysis. On multivariate analysis, MTV and TLG were independent prognostic factors for RFS and OS. SUVmax was an independent prognostic factor for OS, but not for RFS.

Metabolic tumor volume and TLG were independently predictive of RFS and OS in resectable pancreatic cancer. SUVmax was an independent factor for OS, but not for RFS.

(*Medicine* 95(19):e3686)

**Abbreviations**: CA 19–9 = carbohydrate antigen 19–9, FDG-PET/CT = ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography, MTV = metabolic tumor volume, OS = overall survival, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

## INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer death in the USA and the fifth in South Korea, with a 5-year survival rate of less than 5%.[1,2] Only 20% of all diagnosed cases are resectable, and even in resectable cases, overall survival (OS) rate is around 20%.[3] Several prognostic factors have been reported in pancreatic cancer, which are carbohydrate antigen 19–9 (CA 19–9),[4] and pathologic prognostic factors, including pathologic T stage (pT stage), tumor size, lymphovascular invasion, lymph node (LN) metastasis, perineural invasion, and involvement of resection margin.[5–7] However, prognostic values of current clinicopathologic predictors are inconsistent, and most of them are available after surgical resection[8–10]; thus preoperative predictor of survival is still needed for further risk stratification in resectable pancreatic cancer.

The quantitative metabolic and volumetric parameters derived from ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) have shown prognostic value in variety of malignancies.[11–14] Recent meta-analyses revealed that maximum standardized uptake value (SUVmax) is a prognostic factor in nonsmall cell lung cancer and cervical cancer,[15,16] and volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are prognostic factors in nonsmall cell lung cancer, and head and neck cancer.[17,18] Also, in pancreatic cancer, SUVmax has been reported to be a predictor of recurrence-free survival (RFS) and OS.[19,20] However, prognostic value of SUVmax has not been well elucidated within resectable pancreatic cancer. MTV and TLG are considered to be more reliable parameters for predicting survival than SUVmax since they reflect whole tumor burden[21]; however, there are few studies that evaluated MTV and TLG as prognostic factors in patients with resectable pancreatic cancer.[22]

In the present study, we aimed to assess the association of SUVmax, MTV, and TLG from preoperative FDG-PET/CT with known clinicopathologic predictors, and to evaluate

prognostic value of SUVmax, MTV, and TLG in patients with resectable pancreatic cancer.

## METHODS

### Patients

The medical records of all patients with pancreatic cancer who underwent FDG-PET/CT scans before any treatment were reviewed retrospectively from December 2007 to July 2014. There were 59 patients who underwent curative surgical resection of pancreatic cancer for initial treatment. Among 59 patients, 8 patients with borderline resectable pancreatic cancer based on National Comprehensive Cancer Network (NCCN) guideline were excluded.[23] Finally, we enrolled 51 patients who had resectable pancreatic cancer and underwent surgery with curative intent. The patients were not treated with neoadjuvant chemotherapy. The study design and exemption of informed consent were approved by the Institutional Review Board of Seoul National University Hospital. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Inclusion criteria were patients with pathologic confirmation of pancreatic cancer, surgical resection with curative intent as an initial treatment, and FDG-PET/CT scan before treatment. Exclusion criteria were patients with borderline resectable pancreatic cancer, evidence of prior anticancer treatment before surgery, evidence of distant LN metastasis, or peritoneal seeding during surgery.

Preoperative serum level of CA 19–9 and pathologic records of postoperative specimens were collected including tumor size, degree of differentiation (well, moderately, or poorly differentiated carcinoma), pT stage, presence of LN metastasis, microscopic perineural invasion, and lymphovascular invasion, which are reported to have prognostic value.[24–26] After the surgery, adjuvant treatment was done to all patients as following: concurrent chemo-radiotherapy (CCRT) in 41 (80.3%), chemotherapy in 9 (8.2%), radiotherapy (RT) in 1 (3.3%).

All 51 enrolled patients were regularly assessed after the surgery including contrast-enhanced CT and blood tests. Blood tests including serum CA 19–9 and contrast-enhanced CT were done every 3 to 6 months. When recurrence was suspected by contrast-enhanced CT or serum CA 19–9 level, further examinations such as FDG-PET/CT and/or magnetic resonance imaging and/or biopsy were performed to confirm recurrence. RFS was determined from the day of the surgical resection of the pancreatic cancer to the day of first evidence of recurrence was detected. OS was also assessed and determined from the day of the surgical resection of the pancreatic cancer to the day of death. Data were censored at the time of last follow-up, if patients were alive or free of recurrence.

### FDG-PET/CT Imaging and Quantification

A dedicated PET/CT scanner (Biograph 40 Truepoint, Siemens Healthcare, Knoxville, TN) was used for FDG-PET/CT imaging. The range of time interval between surgical resection and FDG-PET/CT scan was 11 to 21 days. FDG (5.18 MBq/kg body weight) was injected intravenously to the patients after they were fasted for at least 6 hours. Sixty minutes after the injection, PET/CT images were acquired. Blood glucose levels were measured immediately before administration of FDG in each patient to check the appropriateness of the blood sugar level (<180 mg/dL). PET images were acquired for 3 minutes/bed position in the 3-dimensional acquisition mode. CT images were reconstructed in a $512 \times 512$ matrix. PET images were corrected for attenuation using CT images and reconstructed in a $128 \times 128$ matrix using ordered-subsets expectation maximization. Six-millimeter full width at half maximum Gaussian filter was used for smoothing of the PET images. The FDG-PET/CT images were analyzed using a dedicated analysis software (Syngo.via, Siemens Healthcare, Knoxville, TN).

Experienced nuclear medicine physicians analyzed all of the FDG-PET/CT images. Spheric volume of interest (VOI) was drawn to include the primary pancreatic cancer lesion and not to include adjacent physiologic focal uptake. SUV was calculated as (decay-corrected activity of tissue volume)/(injected activity/body mass). Maximum value of SUV (SUVmax) within the VOI was measured. Also, MTV and mean of SUV (SUVmean) were calculated with a SUV threshold of 2.5. TLG was derived as SUVmean multiplied by MTV.

### Statistical Analysis

Statistical analyses were performed using SPSS (version 17 for Windows; SPSS Inc.). *P* values of less than 0.05 were considered statistically significant. Linear regression analysis was done to evaluate association between continuous variables. Chi-square test was done to evaluate association between categorical variables. Wilcoxon test was done to examine difference between 2 groups and to evaluate association between categorical and continuous variables. Kruskal–Wallis test was used for comparing 3 or more categories. In prognostic evaluation, all continuous variables were converted to categorical variables by grouping into 2 categories according to optimal cut-off values, which were determined by receiver-operating characteristic curve analysis. Prognostic value of each variable was evaluated using log-rank tests for univariate analysis and Cox proportional-hazard regression tests for multivariate analysis.

## RESULTS

### Patient Characteristics

Of the 51 patients, 33 patients (65%) were recurred and 30 patients (59%) were dead during the follow-up period. The average duration of clinical follow-up was $22 \pm 16$ months (mean ± SD) (median: 21 months, range: 1–78 months). The median RFS and OS were 13.4 and 26.3 months, respectively. Demographic and tumor characteristics were summarized and compared between patients with and without recurrence (Table 1). Patient classification by TNM stage was the same with LN metastasis status because all patients without LN metastasis were pT3 (stage IIA), and all patients with LN metastasis were pT2 or pT3 (stage IIB). Age, sex, diabetes mellitus (DM), types of operation, tumor size, degree of differentiation, pT stage, TNM stage, presence of LN metastasis, perineural invasion, and lymphovascular invasion were not different between patients with or without recurrence. SUVmax, MTV, and TLG were significantly higher in patients with recurrence than without recurrence (Table 1).

### Association Between FDG-PET/CT and Clinicopathologic Parameters

Age, sex, DM, CA 19–9, tumor size, degree of differentiation, and presence of perineural invasion were not associated with SUVmax, MTV, and TLG. TNM stage and presence of LN metastasis were significantly associated with SUVmax, MTV, and TLG. Also, presence of lymphovascular invasion was

**TABLE 1.** Patient Characteristics According to Recurrence Status

| Characteristics | All Patients (N = 51) | Recurrence (n = 33) | Nonrecurrence (n = 18) | P |
|---|---|---|---|---|
| Age, yrs | | | | 0.822 |
|   Mean (range) | 63 (29−84) | 63 (29−84) | 62 (48−75) | |
| Sex | | | | 0.387 |
|   Male | 31 | 22 | 9 | |
|   Female | 20 | 11 | 9 | |
| Diabetes mellitus | | | | 0.08 |
|   Yes | 27 | 16 | 11 | |
|   No | 24 | 17 | 7 | |
| Tumor size, cm | | | | 0.819 |
|   Mean (range) | 3.2 (1.5−5.8) | 3.3 (2.2−5.5) | 3.1 (1.5−5.8) | |
| Differentiation | | | | 0.376 |
|   Well | 2 | 2 | 0 | |
|   Moderate | 42 | 27 | 15 | |
|   Poor | 7 | 4 | 3 | |
| pT stage | | | | 0.756 |
|   T2 | 1 | 1 | 0 | |
|   T3 | 50 | 32 | 18 | |
| Lymph node metastasis | | | | 0.986 |
|   N0 | 24 | 15 | 9 | |
|   N1 | 27 | 18 | 9 | |
| TNM stage | | | | 0.986 |
|   IIA | 24 | 15 | 9 | |
|   IIB | 27 | 18 | 9 | |
| Perineural invasion | | | | 0.309 |
|   Yes | 9 | 4 | 5 | |
|   No | 42 | 29 | 13 | |
| Lymphovascular invasion | | | | 0.587 |
|   Yes | 21 | 15 | 6 | |
|   No | 30 | 18 | 12 | |
| CA 19−9, U/mL | | | | 0.509 |
|   Mean (range) | 728.9 (1 − 10581) | 826.6 (1.4−10581) | 550.1 (1−3280) | |
| SUVmax | | | | 0.037 |
|   Mean (range) | 6.58 (1.25−13.96) | 7.18 (2.38−13.96) | 5.5 (1.25−9.35) | |
| MTV, mL | | | | 0.038 |
|   Mean (range) | 13.52 (0−57.66) | 15.84 (0.0−57.66) | 9.40 (0.0−26.54) | |
| TLG | | | | 0.031 |
|   Mean (range) | 52.30 (0−278.5) | 64.4 (0−278.5) | 34.04 (0−83.87) | |
| Operation type | | | | 0.9 |
|   Whipple | 6 | 4 | 2 | |
|   PPPD | 19 | 12 | 7 | |
|   Distal pancreatectomy | 22 | 15 | 7 | |
|   Total pancreatectomy | 4 | 2 | 2 | |

CA 19−9 = carbohydrate antigen 19−9, MTV = metabolic tumor volume, PPPD = pylorus preserving pancreatoduodectomy, pT stage = pathologic T stage, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

significantly associated with MTV and TLG, but not with SUVmax (Table 2).

## Evaluation of Prognostic Factors for Recurrence-Free Survival

Tumor size, LN metastasis, TNM staging, lymphovascular invasion, perineural invasion, SUVmax, MTV, TLG, and CA 19−9 were evaluated for RFS. The cut-off values for tumor size, SUV max, MTV, TLG, and CA 19−9 level were determined as 2.7 cm, 4.2, 7.38 $cm^3$, 18.6, and 203.6 μ/mL, respectively, by receiver-operating characteristics curve analysis. In univariate analysis, only SUVmax, MTV, and TLG were significantly associated with RFS (Table 3, Figure 1). Since all factors are reported to have prognostic value in previous reports, all variables were used in multivariate analysis. FDG-PET/CT parameters were assessed separately because they are closely correlated each other (SUVmax vs MTV, $r = 0.658, P < 0.0001$; SUVmax vs TLG, $r = 0.746$, $P < 0.0001$; MTV vs TLG, $r = 0.968$, $P < 0.0001$). On multivariate analyses, MTV and TLG were significant for RFS, but SUVmax was not significant (Table 4). There was no significant parameter if all PET parameters were analyzed in the same model.

**TABLE 2.** Association of FDG-PET/CT Parameters With Clinicopathologic Parameters

| Parameters | SUVmax | | MTV | | TLG | |
|---|---|---|---|---|---|---|
| | $R^2$ or Mean $\pm$ SD | $P$ | $R^2$ or Mean $\pm$ SD | $P$ | $R^2$ or Mean $\pm$ SD | $P$ |
| Age | 0.034 | 0.195 | 0.035 | 0.191 | 0.027 | 0.248 |
| Tumor size | 0.0001 | 0.944 | 0.028 | 0.237 | 0.017 | 0.360 |
| CA 19–9 | 0.004 | 0.638 | 0.01 | 0.429 | 0.009 | 0.514 |
| Sex | | 0.183 | | 0.402 | | 0.882 |
|   Male | 6.1 ± 2.2 | | 14.6 ± 11.7 | | 55.6 ± 53.1 | |
|   Female | 7.5 ± 3.5 | | 11.7 ± 8.3 | | 50.3 ± 40.5 | |
| DM | | 0.955 | | 0.385 | | 0.509 |
|   Yes | 6.7 ± 3.0 | | 11.7 ± 8.6 | | 47.8 ± 40.1 | |
|   No | 6.5 ± 2.6 | | 15.3 ± 12.1 | | 58.9 ± 55.4 | |
| Differentiation | | | | | | |
|   Well | 5.9 ± 2.1 | 0.350 | 9.4 ± 4.3 | 0.054 | 33.8 ± 19.6 | 0.07 |
|   Moderate | 6.8 ± 2.8 | | 15.0 ± 11.3 | | 59.4 ± 51.8 | |
|   Poor | 5.0 ± 2.4 | | 5.8 ± 5.2 | | 21.8 ± 23.0 | |
| LN metastasis | | 0.04 | | 0.025 | | 0.02 |
|   Yes | 7.2 ± 2.6 | | 16.8 ± 11.9 | | 68.2 ± 56.3 | |
|   No | 5.9 ± 2.9 | | 9.9 ± 7.8 | | 37.4 ± 32.2 | |
| TNM stage | | 0.048 | | 0.025 | | 0.02 |
|   IIA | 7.2 ± 2.6 | | 16.8 ± 11.9 | | 68.2 ± 56.3 | |
|   IIB | 5.9 ± 2.9 | | 9.9 ± 7.8 | | 37.4 ± 32.2 | |
| Perineural invasion | | 0.497 | | 0.367 | | 0.305 |
|   Yes | 6.7 ± 2.7 | | 14.2 ± 10.7 | | 56.2 ± 49.6 | |
|   No | 6.1 ± 3.3 | | 10.5 ± 10.4 | | 42.0 ± 44.8 | |
| Lymphovascular invasion | | 0.096 | | 0.047 | | 0.039 |
|   Yes | 7.3 ± 2.6 | | 17.7 ± 12.9 | | 72.6 ± 62.1 | |
|   No | 6.1 ± 2.8 | | 10.7 ± 7.8 | | 40.4 ± 31.2 | |

DM = diabetes mellitus, R = correlation coefficient, SD = standard deviation.

## Evaluation of Prognostic Factors for Overall Survival

In univariate analysis, presence of LN metastasis, SUV-max, MTV, and TLG were significantly associated with OS (Table 3, Figure 2). All variables were used in multivariate analysis because all factors are reported to have prognostic value in previous studies. FDG-PET/CT parameters were assessed separately. On multivariate analyses, SUVmax, MTV, and TLG were significant for OS (Table 5). There was no significant parameter if all PET parameters were analyzed in the same model.

## DISCUSSION

In the present study, we demonstrated that MTV and TLG were independent prognostic factors for RFS in patients with resectable pancreatic cancer. Also, SUVmax, MTV, and TLG were independent prognostic factors for OS.

Prognostic value of FDG-PET/CT for pancreatic cancer has been reported. SUVmax has been shown to be a significant prognostic factor for RFS and OS in multiple studies.[8,19,27] In a meta-analysis, SUVmax was a significant prognostic factor for OS with hazard ratio of 2.39 [confidence interval (CI) 1.57–3.63].[28] However, prognostic value of SUVmax in resectable pancreatic cancer has been inconsistent in the previous studies. SUVmax was not independently predictive of RFS and OS in the study by Xu et al[22]; however, Choi et al reported that SUVmax was an independent prognostic factor of RFS and

OS.[19] In the present study, SUVmax was an independent predictor of OS, but not of RFS. Meanwhile, MTV and TLG are considered to be more comprehensive parameters to reflect metabolic tumor burden than SUVmax.[29–31] Recently, several studies have shown that volumetric parameters are associated with the prognosis in patients with pancreatic cancer. MTV and TLG were found to be independent prognostic factors in patients with locally advanced pancreatic cancer treated with chemoradiation therapy,[32] with resectable or borderline resectable pancreatic cancer,[31] and also, with resectable pancreatic cancer.[22] There has been only 1 study to evaluate prognostic value of MTV and TLG in resectable pancreatic cancer. Xu et al reported that MTV and TLG were independent risk predictors for RFS and OS in resectable pancreatic cancer and the same result was reproduced by the present study. Also, in the present study, MTV and TLG were more useful than SUVmax for predicting RFS, which is in accordance to the previous study by Xu et al.[22] Also, MTV and TLG were more strongly associated with lymphovascular invasion than SUVmax. Thus, MTV and TLG could be more reliable parameters for prediction of survival in patients with resectable pancreatic cancer.

Although there is no consensus for the most optimal threshold to measure MTV; MTV using threshold of SUV 2.5 has shown significant prognostic value in multiple types of malignancies. In the meta-analyses of nonsmall cell lung cancer and head and neck cancer, MTV using threshold of SUV 2.5 was found to be predictive of prognosis.[33,34] Also MTV using threshold of SUV 2.5 predicted outcome in pancreatic

**TABLE 3.** Prognostic Factors on Univariate Analysis

| Parameters | RFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of Patients | Number of Recurrence | Median, Months | *P* | Number of Patients | Number of Death | Median, Mos | *P* |
| Tumor size, cm | | | | | | | | |
| ≤2.7 | 15 | 7 | 37.8 | 0.122 | 15 | 7 | 43.5 | 0.375 |
| >2.7 | 36 | 26 | 15.2 | | 36 | 23 | 29.7 | |
| TNM staging | | | | | | | | |
| IIA | 24 | 15 | 21.2 | 0.185 | 24 | 12 | 41.8 | 0.016 |
| IIB | 27 | 18 | 15.2 | | 27 | 18 | 26.3 | |
| Lymphovascular invasion | | | | | | | | |
| No | 30 | 18 | 16.7 | 0.636 | 30 | 17 | 29.7 | 0.941 |
| Yes | 21 | 15 | 16.1 | | 21 | 13 | 32.3 | |
| Lymph node metastasis | | | | | | | | |
| No | 24 | 15 | 21.2 | 0.185 | 24 | 12 | 41.8 | 0.016 |
| Yes | 27 | 18 | 15.2 | | 27 | 18 | 26.3 | |
| Perineural invasion | | | | | | | | |
| No | 9 | 4 | 15.4 | 0.709 | 9 | 4 | 43.9 | 0.248 |
| Yes | 42 | 29 | 16.1 | | 42 | 26 | 29.7 | |
| CA 19−9, U/mL | | | | | | | | |
| ≤831 | 32 | 22 | 16.1 | 0.622 | 32 | 20 | 29.9 | 0.819 |
| >831 | 19 | 11 | 16.7 | | 19 | 10 | 43.5 | |
| SUVmax | | | | | | | | |
| ≤4.2 | 10 | 3 | 24.3 | 0.047 | 10 | 2 | — | 0.018 |
| >4.2 | 41 | 30 | 15.2 | | 41 | 28 | 29.7 | |
| MTV, mL | | | | | | | | |
| ≤7.38 | 17 | 7 | 24.3 | 0.008 | 17 | 6 | 41.7 | 0.006 |
| >7.38 | 34 | 26 | 13.4 | | 34 | 24 | 22.6 | |
| TLG | | | | | | | | |
| ≤18.6 | 13 | 4 | — | 0.011 | 13 | 4 | — | 0.025 |
| >18.6 | 38 | 29 | 13.4 | | 38 | 26 | 26.5 | |

CA 19−9 = carbohydrate antigen 19−9, MTV = metabolic tumor volume, OS = overall survival, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

cancer.[32,35] Thus, we choose SUV 2.5 for the threshold to segment the tumor. Xu et al used mediastinal blood pool for the threshold to measure MTV,[22] although mediastinal blood pool uptake is less commonly used for a threshold because the variance is slightly higher than the liver uptake in test−retest examination.[36] However, regardless of different methods to measure MTV, prognostic values of MTV and TLG were similar between the study by Xu et al and the present study.

Threshold of SUV 2.5 has limitation in assessing tumor with lower SUVmax than 2.5. In the present study, there were 2 patients who had tumors with lower SUVmax than 2.5 (1.25 and 2.38). Among the 2 patients, the one with SUVmax of 2.38 had recurrence and died by the disease 36 months after the surgery, and the other survived free of the disease until the last follow-up (78 months).

Known prognostic factors such as tumor size, CA 19−9, TNM staging, pT stage, LN metastasis, and perineural
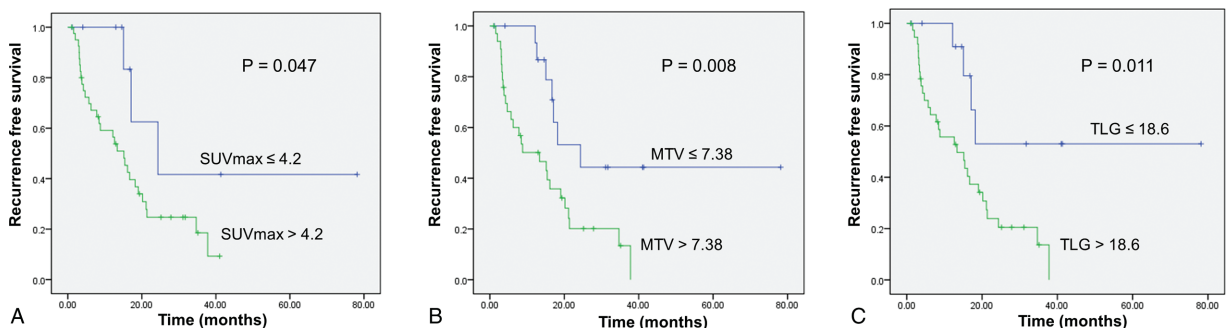


**FIGURE 1.** Kaplan–Meier survival curve for RFS according to SUVmax (A), MTV (B), and TLG (C). MTV = metabolic tumor volume, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

**TABLE 4.** Multivariate Analysis for RFS

| Parameters | Model With SUVmax | | Model With MTV | | Model With TLG | |
| | P | Hazard Ratio (Confidence Interval) | P | Hazard Ratio (Confidence Interval) | P | Hazard Ratio (Confidence Interval) |
| --- | --- | --- | --- | --- | --- | --- |
| Tumor size | 0.19 | 1.89 (0.72−4.99) | 0.17 | 1.98 (0.75−5.24) | 0.14 | 2.0 (0.79−5.12) |
| Lymphovascular invasion | 0.59 | 0.81 (0.38−1.75) | 0.97 | 1.02 (0.49−2.08) | 0.92 | 1.04 (0.50−2.14) |
| TNM staging | 0.82 | 1.09 (0.51−2.37) | 0.97 | 0.98 (0.44−2.19) | 0.95 | 0.97 (0.46−2.07) |
| Perineural invasion | 0.43 | 0.62 (0.19−2.04) | 0.7 | 0.80 (0.26−2.47) | 0.36 | 0.58 (0.18−1.86) |
| CA 19−9 | 0.99 | 1.00 (0.42−2.42) | 0.99 | 1.00 (0.44−2.29) | 0.49 | 0.74 (0.32−1.75) |
| SUVmax | 0.06 | 3.85 (0.94−15.81) | | | | |
| MTV | | | 0.02 | 3.09 (1.21−7.89) | | |
| TLG | | | | | 0.04 | 3.04 (1.07−8.70) |

CA 19−9 = carbohydrate antigen 19−9, MTV = metabolic tumor volume, OS = overall survival, RFS = recurrence-free survival, SUV-max = maximum standardized uptake value, TLG = total lesion glycolysis.

invasion[19,37,38] were not found to be significant prognostic factors in the present study. The discrepancy of the present study with previous studies could be caused by a relatively homogenous patient group regarding histopathologic result in the present study. The difference in RFS according to TNM staging was not found to be significant probably because the present study only included patients with stage IIA and IIB which was not widely varied. Prognostic significance of tumor size, CA 19−9, lymphovascular invasion, and perineural invasion were not consistent thoughout the previous studies. In several studies, tumor size, CA 19−9, lymphovascular invasion, and perineural invasion were not significant prognostic factors as in the present study.[8,9] Moreover, FDG-PET parameters could be better prognostic factors than conventional pathologic predictors such as tumor size, pT stage, presence of lymph node metastasis, tumor differentiation, and lymphovascular invasion of the tumor because the pathologic parameters can only be assessed after surgical resection.

Although curative resection is the current standard treatment for resectable pancreatic cancer, still we are facing frequent recurrence and short life expectancy after curative resection. In the present study, 65% of the patients developed recurrence. Recently, neoadjuvant chemotherapy in resectable pancreatic cancer has been proposed to reduce local recurrence and improve survival. No adequately powered prospective trial has been done yet to prove advantage of neoadjuvant chemotherapy in resectable pancreatic cancer. One retrospective study reported that neoadjuvant chemotherapy group showed longer OS than surgery-first group.[39] However, there is still a concern to loose chance for complete resection by delaying surgery. Thus, further prognostic stratification of resectable pancreatic cancer would be beneficial to select candidate for neoadjuvant chemotherapy. The present study showed that SUVmax, MTV, and TLG can further stratify prognosis in resectable pancreatic cancer; thus FDG-PET/CT image can be utilized in selection of patients who can be able to have benefit from neoadjuvant chemotherapy in the future clinical trial.

The retrospective design is a limitation of the present study. Because of limited spatial resolution of PET/CT, patients with small tumor sizes could be affected by partial-volume effects. Relatively homogenous patient group of the present study can be a limitation because less generalizability, however, could show prognostic significance of FDG-PET/CT parameters even in the limited patient group, whereas other factors were not significant. Further larger-size prospective studies are warranted to elucidate the prognostic values of FDG-PET/CT parameters.

## CONCLUSIONS

Metabolic tumor volume and TLG are independent prognostic factors for both RFS and OS in patients with resectable
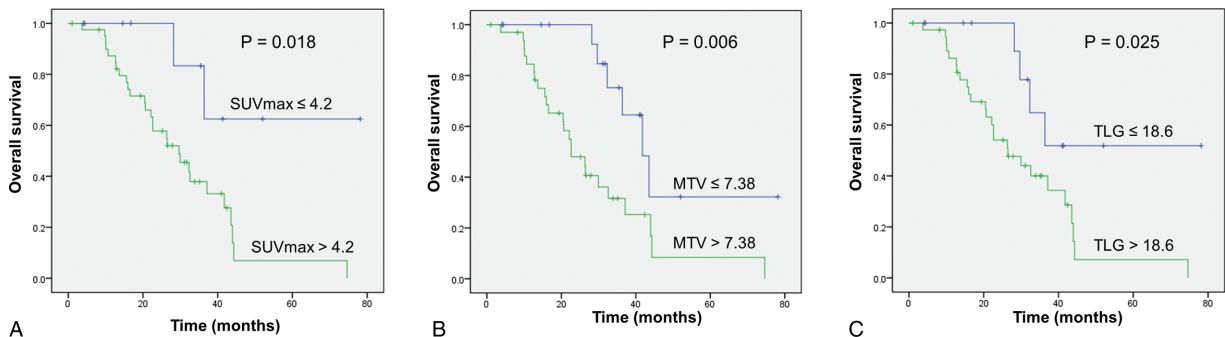


**FIGURE 2.** Kaplan–Meier survival curve for OS according to SUVmax (A), MTV (B), and TLG (C). MTV = metabolic tumor volume, OS = overall survival, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

**TABLE 5.** Multivariate Analysis for OS

| Parameters | Model With SUVmax | | Model With MTV | | Model With TLG | |
|---|---|---|---|---|---|---|
| | *P* | Hazard Ratio (Confidence Interval) | *P* | Hazard Ratio (Confidence Interval) | *P* | Hazard Ratio (Confidence Interval) |
| Tumor size | 0.39 | 1.61 (0.54–4.78) | 0.72 | 1.22 (0.42–3.58) | 0.43 | 1.52 (0.54–4.26) |
| Lymphovascular invasion | 0.08 | 0.48 (0.21–1.09) | 0.18 | 0.57 (0.25–1.30) | 0.27 | 0.64 (0.29–1.41) |
| TNM staging | 0.17 | 1.87 (0.76–4.59) | 0.17 | 1.94 (0.75–5.02) | 0.16 | 1.9 (0.79–4.60) |
| Perineural invasion | 0.83 | 1.14 (0.35–3.76) | 0.41 | 1.63 (0.51–5.17) | 0.65 | 1.32 (0.41–4.22) |
| CA 19–9 | 0.44 | 0.67 (0.21–1.09) | 0.59 | 0.78 (0.32–1.93) | 0.36 | 0.64 (0.25–1.65) |
| SUVmax | 0.02 | 8.11 (1.42–46.24) | | | | |
| MTV | | | 0.01 | 3.55 (1.32–9.53) | | |
| TLG | | | | | 0.04 | 3.77 (1.07–13.33) |

CA 19–9 = carbohydrate antigen 19–9, MTV = metabolic tumor volume, OS = overall survival, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

pancreatic cancer. SUVmax is not independently predictive for RFS, but for OS. These parameters could be utilized to identify patients at high risk who might need aggressive adjuvant and neoadjuvant chemoradiotherapy after further validation in larger prospective studies.

## REFERENCES

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64:9–29.

2. Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. *Cancer Res Treat.* 2013;45:1–14.

3. Li D, Xie K, Wolff R, et al. Pancreatic cancer. *Lancet.* 2004;363:1049–1057.

4. Dong Q, Yang XH, Zhang Y, et al. Elevated serum CA 19-9 level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma: a pilot study *World J Surg Oncol.* 2014;12:171.

5. 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.

6. Lewis R, Drebin JA, Callery MP, et al. A contemporary analysis of survival for resected pancreatic ductal adenocarcinoma. *HPB (Oxford).* 2013;15:49–60.

7. 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.

8. Yamamoto T, Sugiura T, Mizuno T, et al. Preoperative FDG-PET predicts early recurrence and a poor prognosis after resection of pancreatic adenocarcinoma. *Ann Surg Oncol.* 2015;22:677–684.

9. Moon SY, Joo KR, So YR, et al. Predictive value of maximum standardized uptake value (SUVmax) on 18F-FDG PET/CT in patients with locally advanced or metastatic pancreatic cancer. *Clin Nucl Med.* 2013;38:778–783.

10. Oshima M, Okano K, Muraki S, et al. Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectable pancreatic cancer. *Ann Surg.* 2013;258:336–346.

11. O JH, Choi WH, Han EJ, et al. The prognostic value of (18)F-FDG PET/CT for early recurrence in operable breast cancer: comparison with TNM stage. *Nucl Med Molec Imaging.* 2013;47:263–267.

12. Costelloe CM, Macapinlac HA, Madewell JE, et al. 18F-FDG PET/CT as an indicator of progression-free and overall survival in osteosarcoma. *J Nucl Med.* 2009;50:340–347.

13. Hyun SH, Choi JY, Shim YM, et al. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. *Ann Surg Oncol.* 2009;17:115–122.

14. Yoo J, Choi JY, Moon SH, et al. Prognostic significance of volume-based metabolic parameters in uterine cervical cancer determined using 18F-fluorodeoxyglucose positron emission tomography. *Int J Gynecol Cancer.* 2012;22:1226–1233.

15. Na F, Wang J, Li C, et al. Primary tumor standardized uptake value measured on F18-fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non–small-cell lung cancer receiving radiotherapy: meta-analysis. *J Thorac Oncol.* 2014;9:834–842.

16. Sarker A, Im HJ, Cheon GJ, et al. Prognostic implications of the SUVmax of primary tumors and metastatic lymph node measured by 18F-FDG PET in patients with uterine cervical cancer: a meta-analysis. *Clin Nucl Med.* 2016;41:34–40.

17. Im HJ, Pak K, Cheon GJ, et al. Prognostic value of volumetric parameters of F-FDG PET in non-small-cell lung cancer: a meta-analysis. *Eur J Nucl Med Mol Imaging.* 2015;42:241–251.

18. Pak K, Cheon GJ, Nam HY, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. *J Nucl Med.* 2014;55:884–890.

19. Choi HJ, Kang CM, Lee WJ, et al. Prognostic value of 18F-fluorodeoxyglucose positron emission tomography in patients with resectable pancreatic cancer. *Yonsei Med J.* 2013;54:1377–1383.

20. Shinoto. M, Yamada##S, Yoshikawa K, et al. Usefulness of 18F-fluorodeoxyglucose positron emission tomography as predictor of distant metastasis in preoperative carbon-ion radiotherapy for pancreatic cancer. *Anticancer Res.* 2013;33:5579–5584.

21. Malek E, Sendilnathan A, Yellu M, et al. Metabolic tumor volume on interim PET is a better predictor of outcome in diffuse large B-cell lymphoma than semiquantitative methods. *Blood Cancer J.* 2015;5:e326.

22. Xu H-X, Chen T, Wang W-Q, et al. Metabolic tumour burden assessed by 18F-FDG PET/CT associated with serum CA 19-9

predicts pancreatic cancer outcome after resection. *Eur J Nucl Med Molec Imaging.* 2014;41:1093–1102.

23. Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. *World J Gastroenterol.* 2014;20:10740–10751.

24. Humphris JL, Chang DK, Johns AL, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol.* 2012.

25. Cameron JL, Crist DW, Sitzmann JV, et al. Factors influencing survival after pancreaticoduodenectomy for pancreatic cancer. *Am J Surg.* 1991;161:120–125.

26. Ozaki H, Hiraoka T, Mizumoto R, et al. The prognostic significance of lymph node metastasis and intrapancreatic perineural invasion in pancreatic cancer after curative resection. *Surg Today.* 1999;29:16–22.

27. Kitasato Y, Yasunaga M, Okuda K, et al. Maximum standardized uptake value on 18F-fluoro-2-deoxy-glucose positron emission tomography/computed tomography and glucose transporter-1 expression correlates with survival in invasive ductal carcinoma of the pancreas. *Pancreas.* 2014;43:1060–1065.

28. Dong A, Wang Y, Dong H, et al. FDG PET/CT findings of solid pseudopapillary tumor of the pancreas with CT and MRI correlation. *Clin Nucl Med.* 2013;38:e118–e124.

29. Im HJ, Kim TS, Park SY, et al. Prediction of tumour necrosis fractions using metabolic and volumetric 18F-FDG PET/CT indices, after one course and at the completion of neoadjuvant chemotherapy, in children and young adults with osteosarcoma. *Eur J Nucl Med Mol Imaging.* 2012;39:39–49.

30. Im HJ, Kim YK, Kim YI, et al. Usefulness of combined metabolic-volumetric indices of (18)F-FDG PET/CT for the early prediction of neoadjuvant chemotherapy outcomes in breast cancer. *Nucl Med Mol Imaging.* 2013;47:36–43.

31. Kim YI, Kim SK, Paeng JC, et al. Comparison of F-18-FDG PET/CT findings between pancreatic solid pseudopapillary tumor and pancreatic ductal adenocarcinoma. *Eur J Radiol.* 2014;83:231–235.

32. Choi HJ, Lee JW, Kang B, et al. Prognostic significance of volume-based FDG PET/CT parameters in patients with locally advanced pancreatic cancer treated with chemoradiation therapy. *Yonsei Med J.* 2014;55:1498–1506.

33. Im HJ, Pak K, Cheon GJ, et al. Prognostic value of volumetric parameters of (18)F-FDG PET in non-small-cell lung cancer: a meta-analysis. *Eur J Nucl Med Mol Imaging.* 2015;42:241–251.

34. Pak K, Cheon GJ, Nam HY, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. *J Nucl Med.* 2014;55:884–890.

35. Lee JW, Kang CM, Choi HJ, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis on preoperative (1)(8)F-FDG PET/CT in patients with pancreatic cancer. *J Nucl Med.* 2014;55:898–904.

36. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50(Suppl 1):122S–150S.

37. Lee SM, Bae SK, Kim TH, et al. Value of 18F-FDG PET/CT for early prediction of pathologic response (by residual cancer burden criteria) of locally advanced breast cancer to neoadjuvant chemotherapy. *Clin Nucl Med.* 2014;39:882–886.

38. Rahim MK, Kim SE, So H, et al. Recent trends in PET image interpretations using volumetric and texture-based quantification methods in nuclear oncology. *Nucl Med Molec Imaging.* 2014;48:1–15.

39. Papalezova KT, Tyler DS, Blazer DG 3rd et al. Does preoperative therapy optimize outcomes in patients with resectable pancreatic cancer? *J Surg Oncol.* 2012;106:111–118.