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Standardized uptake value on positron emission tomography/computed tomography predicts prognosis in patients with locally advanced pancreatic cancer

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Abstract

Background: The aim of the present study was to investigate the use and value of maximum standardized uptake value (SUVmax) on positron emission tomography/computed tomography (PET/CT) images as a prognostic marker for patients with locally advanced pancreatic cancer (LAPC).

Materials and methods: The medical records of all consecutive patients who underwent PET/CT examination in our institution were retrospectively reviewed. Inclusion criteria were histologically or cytologically proven LAPC. Patients with distant metastasis were excluded. For statistical analysis, the SUVmax of primary pancreatic cancer was measured. Survival rates were calculated using the Kaplan–Meier method, and multivariable analysis was performed to determine the association of SUVmax with overall survival (OS) and progression-free survival (PFS) using a Cox proportional hazards model.

Results: Between July 2006 and June 2013, 69 patients were enrolled in the present study. OS and PFS were 14.9 months [95% confidence interval (CI) 13.1–16.7] and 8.3 months (95% CI 7.1–9.5), respectively. A high SUVmax (>5.5) was observed in 35 patients, who had significantly worse OS and PFS than the remaining patients with a low SUVmax ($P = 0.025$ and $P = 0.003$). Univariate analysis showed that SUVmax and tumor size were prognostic factors for OS, with a hazard ratio of 1.90 and 1.81, respectively. A high SUVmax was an independent prognostic factor, with a hazard ratio of 1.89 (95% CI 1.015–3.519, $P = 0.045$).

Conclusion: The present study suggests that increased SUVmax is a predictor of poor prognosis in patients with LAPC.

Key words: Locally advanced pancreatic carcinoma—Standardized uptake value—Positron emission tomography/computed tomography—Chemoradiotherapy—Prognosis

Pancreatic ductal adenocarcinoma, also known as pancreatic cancer, is the fourth most common cause of cancer-related death in the United States [1]. Pancreatic carcinoma has a very poor prognosis, with a 1-year survival rate of 25%, and less than 20% of patients present with localized, potentially curable tumors [2, 3]. Current evidence supports the use of gemcitabine or fluoropyrimidine-based chemoradiation in a subset of patients without early metastatic disease [4–7]. Therefore, chemoradiotherapy is the standard regimen for the treatment of locally advanced pancreatic cancer (LAPC) and has contributed to improve survival [8, 9]. However, in some patients, disease progression occurs within a few months of chemoradiotherapy. Therefore, the identification of prognostic factors is important for the design of effective, individualized therapeutic strategies, and tailored follow-up schemes for patients with LAPC.

Positron emission tomography/computed tomography (PET/CT) is a widely used diagnostic tool that combines anatomic imaging with functional imaging using 18F-fluorodeoxyglucose (18F-FDG), a biomarker of cellular metabolism [10]. Standardized uptake value (SUV) has been increasingly recognized as a predictor of treatment response and is associated with poor survival

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in various malignancies [11–13]. The aim of the present study was to examine the use and value of maximum SUV (SUVmax) levels on the prognosis of patients with locally advanced pancreatic carcinoma.

Patients and methods

Patients

All consecutive patients who underwent PET/CT examination at Shengjing Hospital between July 2006 and June 2013 were retrospectively reviewed. Patients with pancreatic cancer from this retrospective database who met the following inclusion criteria were included in the study: (1) patients with pre-therapy baseline PET/CT scan data; (2) a diagnosis of ductal adenocarcinoma by histology or cytology; (3) incurable, locally advanced or unresectable disease on clinical or surgical staging examination; (4) no distant metastatic disease; and (5) no history or concurrent diagnosis of another type of cancer. Finally, 69 patients with LAPC who underwent 18F-FDG PET/CT examination were enrolled in this retrospective study. Chemoradiotherapy comprised external beam radiotherapy (median radiation dose: 50.4 Gy). Forty-seven patients had received chemoradiotherapy, 13 patients received radiotherapy alone, and 9 patients had been treated with chemotherapy alone.

PET/CT protocol and SUV

The PET/CT protocol of Shengjing hospital was used. Scans were performed on a Discovery ST 16 PET/CT scanner (GE, US, 2005), a 16-slice multi-detector row CT scanner, with a voltage of 120–140 kV, at 160–240 mA, without any intravenous contrast agents; the 18F-FDG was synthesized at our hospital; the pH value ranged between 4.5 and 8.5, and radiochemical purity was >98%. Patients fasted for more than 4 h; 10 patients with diabetes, before the scan, were drawn blood to verify that the glucose level ranged 4.5–6.5 mmol/L, and 18F-FDG was injected into the cubital vein at 5.55 MBq/kg. Fasting pelvis to neck PET/CT imaging (including CT imaging scan and PET emission scan) was performed after 60 ± 10 min of rest; the patient was instructed to breathe slowly; 6 ± 1 beds were scanned (each bed for 3 min at 25 ± 5 min intervals), and a pre-prepared mixture of milk and Diatrizoate Meglumine (10 mL/kg, diatrizoate meglumine titrated to a final concentration of approximately 1 g/100 mL) was consumed within 5 min. Immediately following, the local stomach area PET/CT scan (scanning two beds below the top of the diaphragm with 3D, each bed for 3 min) was performed. A Xeleris Functional Imaging Workstation (General Electric, Milwaukee, WI, USA) was used. The cross-sectional, sagittal, coronal, and fused images were obtained by the iterative reconstruction method after attenuation correction, with a slice thickness of 5 mm.

FDG PET images were interpreted by two experienced nuclear medicine physicians blinded to the clinical outcomes. FDG uptake was calculated as SUV (radioactivity concentration in tissue in becquerels per cm^3/injected dose in becquerels/patient body weight in grams). In this study, the initial scanning SUVmax was defined as the maximum activity concentration in the tumor/(injected dose/body weight). The SUVmax of pancreatic cancer was used for further analysis.

Statistical analysis

For survival analysis, patients were divided into two groups (high and low SUV) based on the median value of SUVmax. Patients with a SUVmax > 5.5 were assigned to the high SUVmax group. Associations between baseline characteristics and SUVmax level were analyzed using the Chi-square test. Survival time was calculated and analyzed using of Kaplan–Meier method and log-rank test. Interactions between factors including age, sex, tumor size, tumor location, performance status, CA19-9 level, and SUVmax level were tested using univariate and multivariate analyses with a Cox proportional hazards model. In all statistical tests, $P \leq 0.05$ indicated statistical significance.

Results

A total of 69 patients were included in the present study, and none of the patients withdrew from the study during the follow-up period. The patients' clinical characteristics are described in Table 1. At a median follow-up of 36 months (range 3–64 months), 52 patients had died from disease progression. The predominant cause of treatment failure was the development of distant metastases, with the liver as the most common site of metastasis (22/69 patients, 31.9%).

As shown in Fig. 1A, B, median progression-free survival (PFS) and median overall survival (OS) were 8.3 months and 14.9 months, respectively. As shown in Fig. 2, OS was significantly worse in the high SUVmax group than in the low SUVmax group (12.6 months vs. 16.6 months, $P = 0.025$). PFS was also significantly shorter in the high SUVmax group (6.6 vs. 9.6 months, $P = 0.003$).

Univariate analysis showed that SUVmax level and tumor size were predictors of OS (Table 2). Multivariate analysis using the Cox regression model showed that SUVmax was an independent prognostic indicator for OS, with a hazard ratio (HR) of 1.890 (95% confidence interval (CI) 1.015–3.519, $P = 0.045$). High CA19-9 levels did not show significant statistical power in multivariate analysis ($P = 0.175$).

Discussion

Most patients with LAPC have a poor prognosis. A broad variety of potential biomarkers are currently un-

der investigation, such as tissue biomarkers, epigenetic markers, and blood markers including circulating tumor cells [14–16]. Early evidence suggests that tumor KRAS mutational status or VEGF pathway genetic variants may serve as such predictive markers [17–19]. However, these novel biomarkers require further validation. In the present study, we tested SUVmax on PET CT as a potential biomarker for LAPC.

Table 1. Baseline characteristics of evaluable patients ($N = 69$)

Characteristics	Value
Gender, *n* (%)	
Men	40 (58.0)
Women	29 (42.0)
Age (years)	
<60	28 (40.6)
≥60	41 (59.4)
Location, *n* (%)	
Head	35 (50.7)
Body	19 (27.5)
Tail	15 (21.8)
Tumor size (cm)	
<3	26 (37.7)
≥3	43 (62.3)
Performance status (ECOG)	
0	22 (31.9)
1	31 (44.9)
2	16 (23.2)
CA19-9 U/mL (%)	
<300	30 (43.5)
≥300	39 (56.5)
Treatment	
Chemoradiotherapy	47 (68.1)
Radiotherapy	13 (18.8)
Chemothetapy	9 (13.0)

To the best of our knowledge, this retrospective study is a large scale study to show the prognostic role of SUVmax level in patients with LAPC. Our study showed that pre-treatment SUVmax was strongly correlated with OS and PFS, and survival time was significantly longer in patients with low SUVmax than in those with high SUVmax. Univariate and multivariate analyses confirmed that SUVmax level is an independent prognostic factor. In addition, we showed that tumor size was a predictor of poor prognosis in these patients.

SUV has been widely used since the late 1980s and shown to be a robust indicator that can easily be calculated for the evaluation of PET data [20]. A high SUVmax at diagnosis has been associated with inferior survival in a variety of malignancies [11, 13]. In pancreatic cancer, the clinical usefulness of FDG PET in monitoring treatment efficacy and predicting treatment responses and prognosis was reported previously [21–25]. In our previous research, ROC curve showed that the best cutoff value of SUVmax for distinguishing benign from malignant tumors was 5.49. Therefore, in the present study, we chose the SUVmax cutoff of 5.5 based on the median value of SUVmax [26]. Patients in the high SUVmax tertile had inferior survival compared with patients in the low tertile (HR 1.909; $P = 0.032$). This predictive power was confirmed by multivariate analyses (HR 1.890; $P = 0.045$) after correcting for known prognostic variables. This result is consistent with the report by Moon et al. who showed that SUVmax can predict prognosis in patients with LAPC, beyond the conventional role of PET/CT as a diagnostic modality [27]. Pedersen et al. reported that ^{18}F-FDG-up-

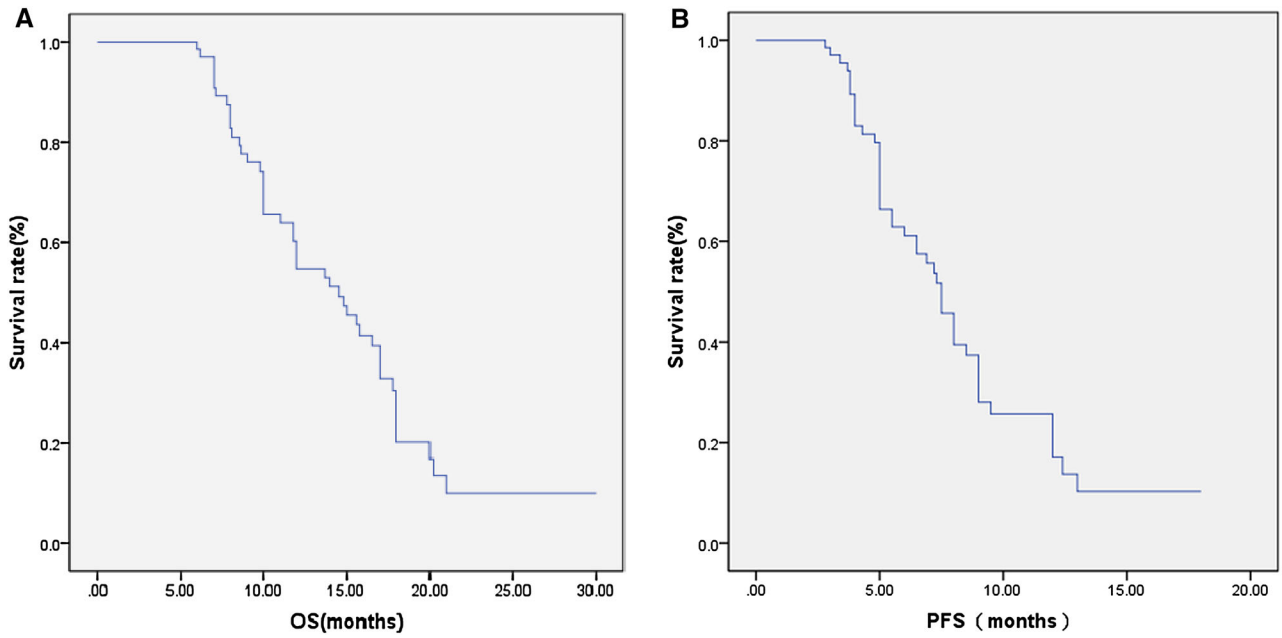

Fig. 1. **A** Overall survival of 69 patients with locally advanced pancreatic cancer. **B** Progression-free survival of 69 patients with locally advanced pancreatic cancer.

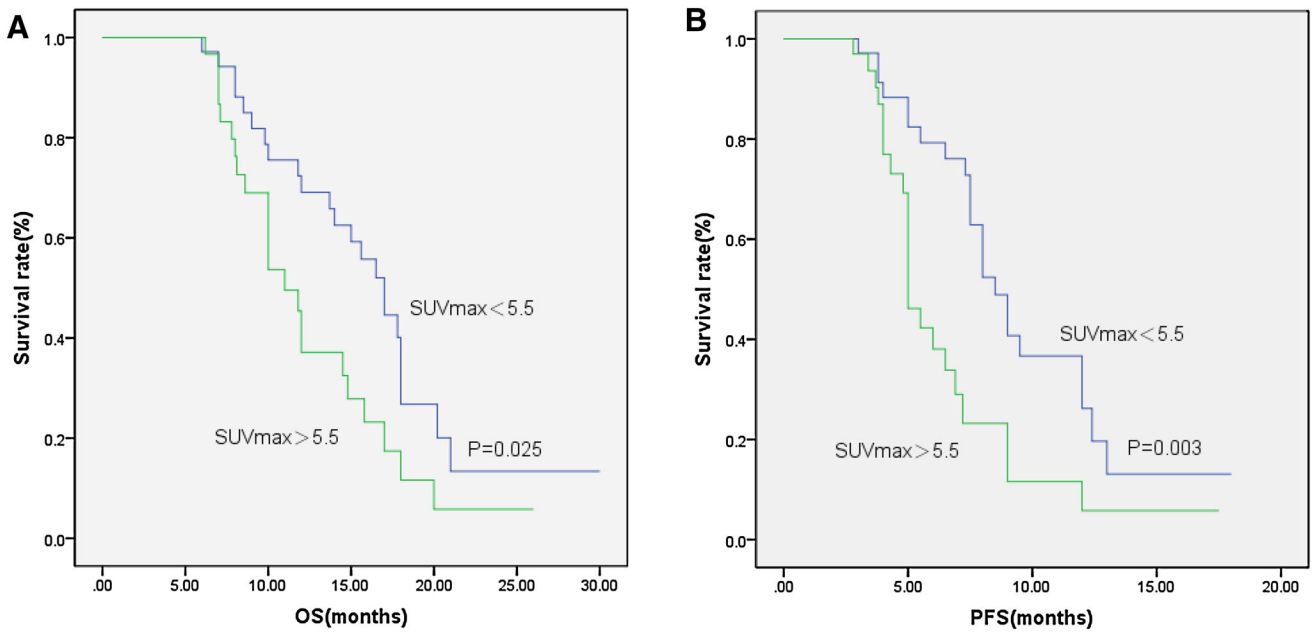

Fig. 2. **A** Overall survival of the low SUVmax group and the high SUVmax group. **B** Progression-free survival of the low SUVmax group and the high SUVmax group.

Table 2. Standardized uptake value as a prognostic variable: Cox model for overall survival

Variable	Number (total = 69)	Univariate analysis			Multivariate analysis	
		Median (month) [95% CI]	HR [95% CI]	*P*	HR [95% CI]	*P*
Gender						
Men	40	13.6 [11.4–15.9]				
Women	29	15.5 [13.0–18.0]	0.794 [0.439–1.433]	0.443	1.124 [0.580–2.178]	0.730
Age						
<60	28	14.9 [12.2–17.6]				
≥60	41	14.7 [12.6–16.7]	1.067 [0.592–1.925]	0.829	0.911 [0.471–1.762]	0.782
Location						
Head	35	14.6 [12.1–17.0]				
Body	19	15.1 [11.5–18.8]				
Tail	15	14.3 [12.0–16.7]	1.035 [0.724–1.478]	0.852	1.155 [0.803–1.662]	0.436
Tumor size (cm)						
<3	26	16.5 [14.0–18.9]				
≥3	43	13.0 [10.8–15.2]	1.811 [1.007–3.257]	0.047	1.597 [0.807–3.160]	0.179
PS (ECOG)						
0	22	14.6 [11.4–17.8]				
1	31	16.2 [13.6–18.8]				
2	16	12.5 [10.4–14.6]	1.156 [0.789–1.694]	0.458	1.065 [0.700–1.621]	0.767
CA19-9 U/mL (%)						
<300	30	16.2 [13.6–18.8]				
≥300	39	13.2 [11.2–15.2]	1.742 [0.964–3.148]	0.066	1.653 [0.799–3.421]	0.175
SUVmax						
≤5.5	34	16.6 [14.0–19.2]				
>5.5	35	12.6 [10.5–14.6]	1.909 [1.059–3.441]	0.032	1.890 [1.015–3.519]	0.045

take (SUVmax) in atherosclerotic lesions of patients is associated with the key molecular marker of hypoxia HIF-1α [28]. Overexpression of HIF-1α has been reported in pancreatic adenocarcinomas and is associated with survival [29]. Hypoxia could explain the correlation between SUVmax differences and survival in patients with LAPC.

Our results showed that tumor size was significantly correlated with survival in univariate analysis, although it was not an independent factor in multivariate analysis. CA19-9 levels are elevated in patients with carcinoma such as gastric, bile duct, and pancreatic as well as colorectal cancers [30, 31]. Baseline-elevated CA19-9 in pancreatic cancer is associated with a poor prognosis [32, 33].Contrary to previous reports, CA19-9 level was not significantly associated with survival in our present study. However, the possibility that a cut-off value of 300 U/mL might affect the survival analysis cannot be excluded.

The present study had several limitations. First, this is a retrospective study. Because of the small number of these chemotherapy only or radiation only patients, the adjustment was not made and the relationship between treatment strategies and survival could not be assessed. Second, we were unable to evaluate the prognostic value of whole metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Third, treatment responses to chemotherapy and/or radiotherapy could not be predicted because some of the patients in the study were not assessed effectively. Despite these limitations, our results suggested that SUVmax is a potent prognostic factor associated with OS and PFS in patients with LAPC. Our findings suggest the potential of PET/CT imaging for the identification of novel targets for individualized therapy for this challenging disease.

In conclusion, the present large retrospective study of newly diagnosed LAPC patients showed that a high pretreatment SUVmax on PET/CT is correlated with inferior survival. Similar predictive effects were noted for tumor size. These findings suggest that PET/CT imaging is a potential prognostic tool for patients with LAPC.

Conflict of interest None.

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