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Clinical and Prognostic Insights from 18F-FDG PET/CT in Surgically Resectable Pancreatic Cancer

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Abstract

Predicting outcomes in pancreatic cancer before surgery remains a challenge, as no reliable preoperative prognostic markers have been established. This study investigated whether 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG-PET/CT) could serve as a prognostic tool in patients eligible for pancreatic resection. We retrospectively reviewed patients who underwent preoperative PET scans followed by surgical resection from January 2007 to December 2015. The maximum standardized uptake value (SUVmax) from PET/CT was recorded, and patients were divided into high (>3.65) and low (≤3.65) SUVmax groups. These groups were compared across TNM stage, tumor differentiation, type of surgery, margin status, lymph node involvement, age, sex, diabetes, and serum CA 19-9 levels. Among 144 patients, 82 had high SUVmax tumors, and 62 had low SUVmax tumors. Survival analysis revealed that disease-free and overall survival were strongly associated with tumor stage, nodal status, grade, resection margins, and SUVmax. Patients with low SUVmax (≤3.65) experienced significantly longer survival than those with high SUVmax (>3.65, $p < 0.001$). Multivariate analysis identified these factors as independent predictors of outcome. These findings indicate that SUVmax on 18-FDG-PET/CT is a valuable prognostic marker for resectable pancreatic cancer and may assist clinicians in planning individualized treatment strategies.

Keywords: Pancreatic cancer, Fluorodeoxyglucose, Positron emission tomography, Pancreatic resection, Prognosis, SUVmax

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Introduction

Although pancreatic cancer ranks only 12th in global incidence, it is the seventh leading cause of cancer-related mortality [1]. Incidence is projected to rise due to population growth and aging. In 2018, pancreatic cancer was the second most common gastrointestinal malignancy in the United States [2], and in the European Union, it caused more deaths than breast cancer in 2017, ranking third after lung and colorectal cancers [3]. Prognosis remains poor, with five-year survival rates of 6–10% [4, 5]. At diagnosis, approximately 80% of patients present with locally advanced or metastatic disease, emphasizing the need for improved early detection, precise preoperative staging, and better therapeutic strategies. Surgery is currently the only potentially curative option [6], yet only 15–20% of patients are candidates due to advanced disease at presentation. Neoadjuvant therapy—chemotherapy and/or radiotherapy before surgery—is increasingly used in locally advanced or borderline resectable disease to reduce distant spread and facilitate tumor downstaging. However, concerns remain regarding tumor progression

during therapy, variability in protocols, and limited supporting evidence [7].

Multiple clinicopathological and molecular markers have been investigated to predict survival in pancreatic cancer, including tumor stage, histological grade [8, 9], resection margins [10], pre- and postoperative CA 19-9 levels [11, 12], and circulating tumor cells [13]. Results have been inconsistent, and patients with identical stages may exhibit markedly different outcomes.

18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) is a noninvasive imaging technique that detects increased glucose uptake in malignant tissues [14,15]. PET has been applied in diagnosis and staging of various cancers, including pancreatic carcinoma [16,17]. Higher 18-FDG uptake has been associated with tumor aggressiveness, and previous studies have suggested a prognostic role for PET in pancreatic cancer and in predicting early postoperative recurrence [18–23]. However, these studies often involved small patient cohorts, particularly for resectable (stage I–II) disease. In a prior study, we identified PET as an independent prognostic marker, including a small subset of resectable tumors (n = 16) [24].

The present study aims to determine whether 18-FDG-PET/CT-derived glucose metabolism provides additional prognostic information beyond established clinical and pathological factors in patients with resectable pancreatic adenocarcinoma.

Materials and Methods

Patient population

We retrospectively analyzed a prospectively maintained database of patients undergoing pancreatic resection from January 2007 to December 2015. Patients with intraductal papillary mucinous neoplasms, endocrine tumors, cystic neoplasms, pancreatic metastases, or periampullary cancers were excluded. The final cohort included 144 consecutive patients with histologically confirmed pancreatic ductal adenocarcinoma who underwent preoperative PET/CT within 30 days before surgery. Written informed consent was obtained from all patients.

The cohort had a mean age of 66.3 years (range 48–82), including 70 men and 74 women. Surgical procedures were performed by a single team and included pylorus-preserving pancreaticoduodenectomy for head tumors, distal pancreatectomy with splenectomy for body/tail tumors, and total pancreatectomy in cases with extensive pancreatic involvement or high-risk anastomoses. Limited involvement of the superior mesenteric-portal axis (<2 cm) or arterial involvement without extrapancreatic disease did not preclude surgery. Standard lymph node dissection was performed according to tumor location, and para-aortic nodes were sampled when appropriate. Resection margins were classified as R0 (negative) or R1 (tumor ≤1 mm from margin) per Leeds criteria [25]. Tumors were staged using the UICC TNM classification [26].

Clinical and pathological variables analyzed included age, sex, diabetes, type of surgery, preoperative CA 19-9 levels, TNM stage, lymph node status, tumor grade, resection status, disease-free survival (DFS), and overall survival (OS). DFS was calculated from surgery to radiologic recurrence or last follow-up, and OS from surgery to death or last follow-up. Patients were followed with physical exams, imaging, and tumor marker assessments every 3 months for the first 2 years and every 6 months thereafter. Adjuvant gemcitabine-based chemotherapy was administered when indicated. Ethical approval was obtained in accordance with institutional guidelines and the Declaration of Helsinki.

18-FDG-PET/CT imaging

PET/CT scans were acquired using Biograph-16™ (Siemens) from 2007–2012 and Discovery™ (GE Healthcare) from 2013–2015. Patients fasted for ~6 hours, with pre-scan glucose <110 mg/dL for nondiabetics and <200 mg/dL for diabetics. Scans were performed 50–70 minutes after injection of 150–400 MBq of 18-FDG, covering the base of the skull to the proximal legs. Additional focused scans were obtained for the hepato-pancreatic region at 90–100 minutes when needed. Images were reconstructed using standard algorithms, and the maximum standardized uptake value (SUVmax) was calculated by placing a circular region of interest over the tumor area with the highest FDG uptake. Scans were interpreted by an experienced nuclear medicine physician.

Statistical analyses

All analyses were conducted using STATA version 14.1 (College Station, Texas, USA). Receiver operating characteristic (ROC) curves were used to determine the SUVmax threshold that best predicted disease-free survival (DFS) and overall survival (OS) after pancreatic surgery. The optimal cut-off point was defined as the value closest to the top-left corner of the ROC plot, representing the best balance between sensitivity and specificity. Patients were then divided into two groups based on SUVmax (≤ 3.65 vs. > 3.65) for univariate comparisons. Differences between groups were assessed using appropriate statistical tests, including Mann–Whitney U, chi-square, Fisher's exact, or Student's t-test. The impact of variables such as age, sex, tumor stage, histological grade, lymph node involvement, margin status, diabetes, and preoperative CA 19-9 levels on survival was evaluated using both univariate and multivariate analyses. Kaplan–Meier curves were generated to estimate survival, with differences tested by the log-rank method. Multivariate survival analyses were performed using Cox proportional

hazards models. A p-value < 0.05 was considered statistically significant.

Results and Discussion

The study included 144 patients, with a median age of 66.3 years (range 48–82), comprising 70 men and 74 women. Fifty-three patients had diabetes, and 93 had elevated preoperative CA 19-9 levels. Surgical procedures included pylorus-preserving pancreaticoduodenectomy (n = 106), distal pancreatectomy with splenectomy (n = 34), and total pancreatectomy (n = 4). Segmental portal-mesenteric vein resection was performed in 21 cases. Pathology revealed positive resection margins (R1) in 38 patients (26.4%), lymph node metastases in 103 patients, and 95 tumors (66%) classified as well- or moderately differentiated. Adjuvant gemcitabine-based chemotherapy was given to 132 patients (92%).

The median SUVmax for the cohort was 4.0 (range 1.0–12.0). ROC analysis determined 3.65 as the optimal cut-off for predicting survival outcomes, with an area under the curve (AUC) of 0.66 (95% CI: 0.542–0.77) **(Figure 1)**. Patients with SUVmax > 3.65 had significantly higher CA 19-9 levels, more lymph node involvement, and a greater proportion of poorly differentiated tumors compared with patients with SUVmax ≤ 3.65. No significant differences were observed between the groups in terms of age, sex, diabetes, tumor stage, type of surgery, or receipt of adjuvant therapy. Complete follow-up was available for all patients, ranging from 6 to 152 months.

Table 1. Standardized Uptake Values and Patients' Clinical and Pathological Details

	All Patients	SUVmax ≤ 3.65	SUVmax > 3.65	*p* Value
Patients, *n* (%)	144	62 (43.1%)	82 (56.9%)	
Age, yrs (mean ± SD)	66.32 ± 11.40	66.48 ± 09.32.	67.55 ± 10.31	
Sex M	70	32	38	
F	74	30	44	
UICC				0.158
I–II, *n* (%)	114 (79.2%)	52 (45.6%)	62 (54.4%)	
III–IV, *n* (%)	30 (20.8%)	10 (33.3%)	20 (66.7%)	
Grade, *n* (%)				0.023
Well- or moderately differentiated (G1–G2)	95 (66%)	47 (49.5%)	48 (50.5%)	
Poorly-differentiated (G3)	49 (34%)	15 (30.6%)	34 (69.4%)	
Resection margins				0.232
R0, *n* (%)	106 (73.6%)	48 (45.3%)	58 (54.7%)	
R1, *n* (%)	38 (26.4%)	14 (36.8%)	24 (63.2%)	
Lymph nodes				0.036
Negative, *n* (%)	41 (28.5%)	23 (56.1%)	18 (43.9%)	
Positive, *n* (%)	103 (71.5%)	39 (37.9%)	64 (62.1%)	
Diabetes				0.170
No, *n* (%)	90 (62.5%)	42(46.7%)	48(53.3%)	
Yes, *n* (%)	54 (37.5%)	20 (37%)	34 (63%)	
SUVmax, mean (±SD)	5 (±3.2)	2.6 (±1.2)	6.9 (±3.1)	
Serum CA 19-9, mean (±SD)	524.5 (±1123)	392.9 (±1051.9)	623.9 (±1172.1)	0.88
Serum CA 19-9, median (IQR), range	114 (IQR 23–382) range 1–6637	52.9 (IQR 18–256) range 1–6637	154.35 (IQR 27–470) range 1–5460	0.032
CA 19-9 < 114 kU/L	81 (56.3%)	41 (50.6%)	40 (49.4%)	0.028
CA 19-9 > 114 kU/L	63 (43.7%)	21 (33.3%)	42 (66.7%)	
OS, median (95%CI)	22 (19–27)	28 (24–37)	19 (16–22)	0.002
DFS, median (95%CI)	12 (10–14)	20 (14–23)	9 (8–11)	0.001

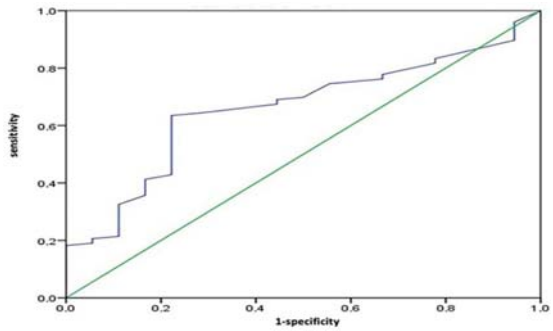

Figure 1. Receiver operator characteristic (ROC) curve for maximum standardized uptake value (SUVmax) cut-off, showing that the most effective cut-off was 3.65 (AUC 0.659, 95%CI 0.542–0.77)

Disease-free survival

During a median follow-up period of 56.7 months (range 2–70 months), disease recurrence occurred in 126 of the 144 patients (87.5%). The overall median disease-free survival (DFS) for the cohort was 11.6 months.

In univariate Cox regression analysis **(Table 2)**, lymph node involvement, histological grade, resection margin status, tumor stage, and preoperative SUVmax were significantly associated with DFS, whereas diabetes and serum CA 19-9 levels showed no significant correlation. Multivariate analysis confirmed that these same factors remained independent predictors of DFS **(Table 2)**. Patients with a preoperative SUVmax above 3.65 experienced a markedly shorter DFS compared with those with SUVmax ≤ 3.65 (p = 0.001) **(Figure 2)**. When stratified by tumor stage, elevated SUVmax continued to predict poorer DFS even among patients with stage I–II disease, with those having SUVmax ≤ 3.65 showing significantly longer DFS (p = 0.0004) **(Figure 3)**.

Table 2. Association Between Preoperative Variables and Disease-Free Survival on Univariate [a] and Multivariate [b] Cox Regression Model. HR = hazard ratio

Variables	HR [a]	95%CI [a]	*P* Value [a]	HR [b]	95%CI [b]	*P* Value [b]
Lymph node metastases	2.33	1.511–3.596	<0.0001	1.779	1.130–2.800	0.013
Pathological grade	1.581	1.090–2.293	0.016	1.661	1.137–2.426	0.009
Radicality	2.047	1.377–3.044	<0.0001	1.840	1.223–2.769	0.003
Stage	2.181	1.429–3.330	<0.0001	1.787	1.144–2.794	0.011
Diabetes	1.352	0.942–1.941	0.102	-	-	-
SUVmax	1.106	1.051–1.165	<0.0001	1.085	1.025–1.148	0.004
CA 19-9	1.001	0.999–1.001	0.312	-	-	-

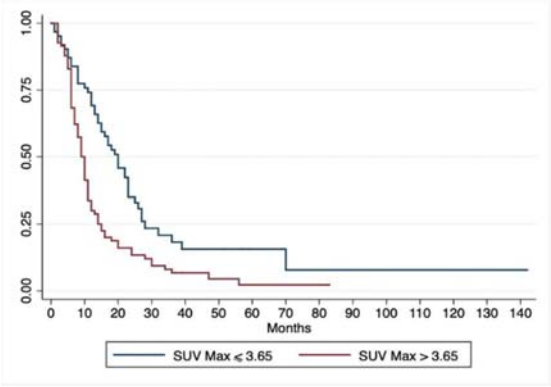

Figure 2. Kaplan–Meier curve for disease-free survival estimated for patients with preoperative SUVmax > 3.65 and those with SUVmax ≤ 3.65

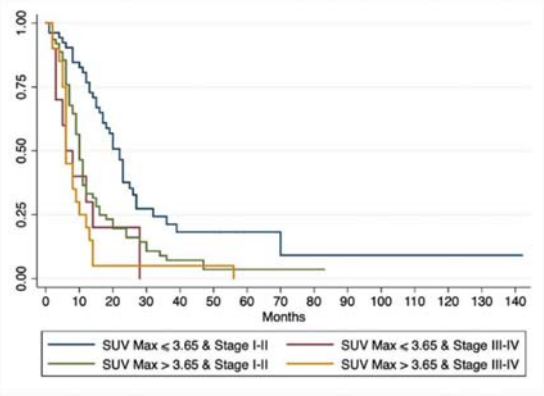

Figure 3. Kaplan–Meyer estimates for disease-free survival based on preoperative tumor stage and high or low SUVmax

Overall survival

During a median follow-up of 100.8 months (range 6–152), 125 of 144 patients (87%) died due to pancreatic cancer, with two additional deaths from causes unrelated to the disease. The median overall survival (OS) for the cohort was 22.4 months (range 19–27 months).

Univariate Cox regression analysis **(Table 3)** demonstrated that lymph node metastases, tumor grade, resection margin status, tumor stage, and preoperative SUVmax were significantly associated with OS, while diabetes and serum CA 19-9 levels were not. Multivariate analysis confirmed these same factors as independent predictors of OS **(Table 3)**.

Kaplan–Meier survival curves showed that patients with a preoperative SUVmax > 3.65 had significantly shorter OS compared with those with SUVmax ≤ 3.65 (p < 0.001) **(Figure 4)**. Stratification by tumor stage revealed that elevated SUVmax predicted poorer OS in stage I–II patients (p = 0.0002), whereas no significant difference was observed in stage III–IV disease (p = 0.71). Notably, stage I–II patients with SUVmax > 3.65 had survival outcomes comparable to stage III–IV patients with SUVmax ≤ 3.65 **(Figure 5)**. At the last follow-up, 17 patients remained alive (16 disease-free), including 13 in the low SUVmax group and four in the high SUVmax group (one with recurrent disease).

Table 3. Association Between Preoperative Variables and Overall Survival on Univariate [a] and Multivariate [b] Cox Regression Model

Variables	HR [a]	95%CI [a]	*P* Value [a]	HR [b]	95%CI [b]	*P* Value [b]
Lymph node metastases	2.433	1.588–3.721	<0.0001	1.730	1.101–2.719	0.017
Pathological grade	1.493	1.030–2.165	0.034	1.484	1.017–2.163	0.040
Radicality	2.352	1.583–3.495	<0.0001	2.079	1.374–3.147	0.001
Tumor stage	2.489	1.637–3.784	<0.0001	2.127	1.369–3.305	0.001
Diabetes	1.222	0.851–1.756	0.278	-	-	-
SUVmax	1.074	1.025–1.124	0.002	1.055	1.001–1.111	0.044
CA 19-9	1.001	0.999–1.001	0.196	-	-	-

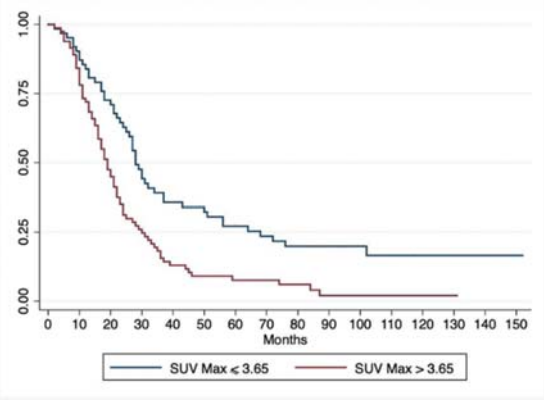

Figure 4. Kaplan–Meier curves for overall survival of patients with preoperative SUVmax > 3.65 and those with SUVmax ≤ 3.65

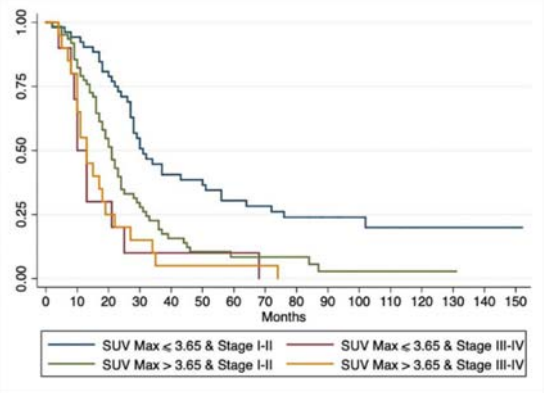

Figure 5. Kaplan-Meyer curves for overall patient survival by preoperative stage and SUVmax category

Providing an accurate preoperative prognosis for patients with pancreatic cancer is essential for tailoring treatment strategies, whether surgical or multimodal. This is particularly relevant for patients with seemingly localized, resectable pancreatic carcinoma, as some authors advocate neoadjuvant therapy over immediate surgery, although definitive benefits remain uncertain. The rationale for employing PET/CT preoperatively in this context lies in the characteristic metabolic features of malignant pancreatic cells, notably accelerated glucose transport and enhanced glycolysis. Overexpression of glucose transporter 1 (Glut-1) and key glycolytic enzymes has been well-documented in pancreatic adenocarcinoma [27, 28].

18-FDG, a glucose analog, is actively transported into tumor cells via Glut-1 and phosphorylated by hexokinase, reflecting both carbohydrate metabolism and tumor activity. The standardized uptake value (SUV) offers a semi-quantitative assessment of 18-FDG accumulation and can be easily obtained on preoperative PET/CT scans. Accordingly, 18-FDG-PET/CT is valuable not only for differentiating benign from malignant lesions but also for detecting recurrence and evaluating response to neoadjuvant therapy [19, 29, 30]. Early studies have suggested a link between 18-FDG uptake and prognosis in pancreatic cancer, though they involved small patient cohorts [20, 24, 31]. Nakata *et al.* [31] first proposed SUV as a metabolic prognostic factor, reporting significantly shorter survival in patients with SUV > 3.0 compared with those with SUV < 3.0. In a later, larger cohort, however, SUV predicted survival only in unresectable cases, not in resectable tumors [18].

In our study of 144 patients with histologically confirmed pancreatic adenocarcinoma, high SUVmax (>3.65) and low SUVmax (≤3.65) groups were comparable in terms of age, sex, tumor stage, grade, serum CA 19-9, diabetes status, and type of surgery. Despite this, both DFS and OS were significantly impacted by SUVmax, with low SUVmax patients experiencing median DFS and OS of 20 and 28 months, respectively, versus 9 and 19 months for high SUVmax patients ($p = 0.001$). Univariate analysis confirmed that tumor stage, grade, lymph node involvement, and margin status were also significantly associated with survival, while multivariate analysis identified SUVmax, stage, grade, margins, and nodal status as independent predictors of DFS and OS.

Notably, stratification by tumor stage revealed that SUVmax strongly influenced survival in stage I–II disease, whereas this effect was not observed in stage III–IV tumors. Serum CA 19-9 and diabetes status did not significantly affect outcomes. The differential survival may reflect the intrinsic biological aggressiveness indicated by SUVmax, even when conventional prognostic factors are similar. 18-FDG-PET/CT may be less reliable in diabetic patients, potentially reducing its prognostic accuracy in this subgroup. Recent studies have suggested that SUVmax and CA 19-9 can independently predict pathological stage and OS, though CA 19-9 has limitations due to non-expression in a subset of the

population and variability influenced by hepatic or renal dysfunction [32–34].

Overall, our findings support previous evidence that SUVmax, as measured by 18-FDG uptake, is a straightforward and reliable preoperative prognostic marker in pancreatic cancer, consistent with observations in other malignancies [21, 22, 35–40]. **Table 4** summarizes other studies evaluating SUVmax as a prognostic indicator in resectable pancreatic cancer.

Table 4. The Literature Reporting Differences in Overall Survival and Disease-Free Survival by SUVmax

Author	Year	Design	*n*	SUVmax	OS (mo)	*p*	DFS (mo)	*p*
Okamoto *et al.* [21]	2011	R	56	<5.5 >5.5	NA	-	NA	0.025
Choi *et al.* [36]	2013	R	64	≤3.5 >3.5	45.4 vs. 23.5	0.011	26.1 vs. 9.2	0.002
Lee *et al.* [38]	2014	R	87	≤4.7 >4.7	34.4 vs. 20.6	0.03	12.9 vs. 9.9	0.03
Kitasato *et al.* [37]	2014	R	41	≤3.4 >3.4	NR	-	610 vs. 354 days	0.04
Yamamoto *et al.* [22]	2015	R	128	<6.0 ≥6.0	37 vs. 18	<0.001	23 vs. 6	<0.001
Ariake *et al.* [39]	2018	R	138	<4.85 ≥4.85	50.4 vs. 21.5	<0.001	24.3 vs. 10.3	<0.001
Present series	2020	R	144	≤3.65 >3.65		<0.001		<0.001

R = retrospective; OS = overall survival; DFS = disease-free survival; NR = not reported; NA =not applicable; mo = months.

Including our study, seven retrospective analyses [21, 22, 36–39] have evaluated a total of 658 patients. Although the SUVmax cut-off values differed across studies, all reported significantly longer DFS in patients with low SUVmax, and four studies also demonstrated improved OS [22, 36, 38, 39]. Because SUVmax reflects only peak metabolic activity rather than the overall tumor burden, some investigators have assessed metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as potential prognostic indicators [38, 41, 42]. Xu *et al.* [42] found that both MTV and TLG independently predicted DFS and OS, outperforming CA 19-9 levels, SUVmax, and tumor size. These results were corroborated by Lee *et al.* [38] in 87 patients with resectable pancreatic carcinoma, including 30 who received neoadjuvant therapy, showing that MTV and TLG remained independent prognostic factors regardless of preoperative treatment. Nevertheless, SUVmax is simpler, faster to calculate, and, in our experience and that of others, provides equally valuable prognostic information.

While previous studies have highlighted the importance of tumor histopathology in predicting outcomes [8–13, 43], such information is typically only available postoperatively. The major advantage of SUVmax measured on preoperative 18-FDG-PET/CT is that it can be obtained before any intervention. Its prognostic value appears comparable to tumor staging, suggesting that combining SUVmax with imaging-based disease extent may enhance the stratification of patients and better inform treatment planning.

There is growing evidence that elevated glycolytic activity, as reflected by 18-FDG uptake, correlates with tumor aggressiveness and clinical outcomes, allowing prediction of DFS and OS. Consequently, 18-FDG-PET/CT could help identify patients with resectable pancreatic cancer at higher risk of early recurrence or shorter survival, who might benefit from neoadjuvant therapy. Future studies could explore the prognostic value of SUVmax measured before and after neoadjuvant chemotherapy to guide treatment decisions.

This study has some limitations. It was retrospective and conducted at a single institution, and variations in adjuvant therapy during the study period could have influenced outcomes. Nevertheless, the substantial cohort and PET data were sufficient to demonstrate statistically significant and clinically meaningful differences.

Conclusions

Preoperative SUVmax measured on 18-FDG-PET/CT provides valuable prognostic information in patients with pancreatic cancer and can assist in stratifying patients for clinical trials or guiding therapeutic decisions, including the choice between surgery and systemic therapy.

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