Original Article

Prognostic Strength of CA 19-9, Demographic Parameters, and Maximum Standardized Uptake Value of Baseline 18F-FDG PET/CT in Treatment-naïve Patients with Pancreatic Carcinoma

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Abstract

Aim and Background: The aim of this study was to evaluate the prognostic value of imaging-based variables and tumor marker in predicting the progression-free survival (PFS) in treatment-naïve pancreatic cancer (PC) using baseline 18-fluorodeoxyglucose (^{18}FDG) positron emission tomography/computed tomography (PET/CT). **Materials and Methods:** This retro-prospective study was conducted at PET/CT imaging facility of JCIA health-care facility of Pakistan. Total 68 patients with PCs were retrospectively included who had ^{18}FDG PET/CT for staging from March 2017 to December 2020. Thirty-two patients had unresectable Stage IV disease on baseline imaging while the remaining 36 underwent Whipple's procedure and both categories were followed by chemotherapy with/without immunotherapy. These patients were followed for a median period of 18 months (1–62 months) for PFS. Logistic regression analysis and receiver operating characteristic (ROC) analysis were used for independent predictors of patients' demographics, tumor characteristics, CA 19-9, and maximum standardized uptake value (SUVmax) in PFS. Kaplan–Meier's survival curves were analyzed to measure PFS using ROC-derived significant cutoff values of CA 19-9 and SUVmax. **Results:** Median PFS was 18 months (11-45) with 60% (41/68) patients were either died or labelled having metabolic progressive disease (MPD. Using logistic regression analysis, significant correlations were found for Stage IV disease and pancreatic body/tail tumor with disease progression (odd ratio: 7.535 and 4.803, respectively; $P < 0.05$). Gender, obesity, histological tumor type, and ^{18}FDG-avid regional nodes did not show a significant impact on PFS. On ROC analysis, SUVmax >5.3 of primary tumor and baseline CA 19-9 >197 U/ml were found to have a significant negative correlation with PFS (area under the curve: 0.827 and 0.911, respectively; $P < 0.0001$) and no association of age and primary tumor size in PFS. Significantly, shorter PFS was found using ROC-derived cutoff values of SUVmax >5.3 versus ≤5.3 of primary tumor (mean and 95% confidence interval [CI]: 16.7 vs. 48.5 and 10–23 vs. 41–56; log-rank = 25.014; $P < 0.0001$) and baseline CA 19-9 >197 versus ≤197 U/ml (mean and 95% CI: 11.8 vs. 46.9 and 7–16 vs. 39–55; log-rank = 38.217; $P < 0.0001$). **Conclusion:** SUVmax >5.3 of primary tumor and baseline CA 19-9 >197 U/ml were found to have a significant negative correlation with PFS in treatment-naïve PC patients. Among demographics, only Stage IV disease and pancreatic tail and body tumors were found to have a negative association with disease progression.

Keywords: *18-Fluorodeoxyglucose positron emission tomography/computed tomography, CA 19-9, maximum standardized uptake value, pancreatic cancer, progression-free survival*

Introduction

Pancreatic Cancer (PC) is one of the most notorious cancers with dismal prognosis. According to the American Cancer Society's statistics published in 2022, about 62,210 Americans (32,970 men and 29,240 women) will be diagnosed with PC and about 49,830 (25,970 men and 23,860 women) will die due to the same.[1] It is well known that PC has a poor prognosis because of the difficulty of detecting the primary tumor in early stage and the aggressive characteristics of the disease. The five-year survival rate of patients with localized PC is 37%, but for patients with regional and distant metastasis, it is 12% and 3%, respectively.[2] To improve the prognosis of patients with PC, an early diagnosis is crucial and imaging plays an important role in detection,

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staging, and respectability of disease.[3] Commonly used imaging modalities are ultrasound (US), endoscopic US, computed tomography (CT), magnetic resonance imaging, and positron emission tomography/CT (PET/CT) using 18-fluorodeoxyglucose (^{18}FDG) as radiotracer.[4] ^{18}FDG PET/CT has superior diagnostic accuracy for distant metastasis which could avoid unjustified surgery in 10%–27% of cases.[5,6] Various studies have been conducted to estimate the prognostic value of ^{18}FDG PET/CT using various cutoff values of maximum standardized uptake value (SUVmax).[7-9] Cancer antigen 19-9 (CA 19-9) is an important diagnostic and prognostic serum biomarker for PC. Higher pretreatment CA 19-9 levels are usually associated with poor prognosis and changes in its titer after treatment also provide prognostic information.[9] The aim of this study was to determine the prognostic strength of imaging-based parameters and CA 19-9 on progression-free survival (PFS) in treatment-naïve PC patients using baseline ^{18}FDG PET/CT scan.

Materials and Methods

This retro-prospective study was conducted at PET/CT imaging facility of JCIA health-care facility of Pakistan. The study was duly approved by the Ethical Review Committee of the university (ERC: 2021-6292-17887). Total 68 patients with PCs were included who had ^{18}FDG PET/CT for staging from March 2017 to December 2020. Patients with a history of surgical intervention and/or treatment were excluded from the study. The clinical and pathologic records of all patients were reviewed, and the following were analyzed: age, sex, Tumor nodes metastasis stage, SUVmax, tumor size and location, type of treatment (surgery, CyberKnife, chemotherapy, or radiation therapy), and baseline CA 19-9 serum levels (chemiluminescent: serum reference: nondetectable to 39 U/ml). All patients (with unresectable disease or post-Whipple's surgery) underwent chemotherapy with/without immunotherapy. Patients were followed for a median period of 18 months (1–62 months) for PFS. Logistic regression analysis and receiver operating characteristic (ROC) analysis were used in the prediction of prognostic strength of patients and tumor demographics, CA 19-9, and imaging-derived parameters in PFS. Kaplan–Meier's survival curves were analyzed to measure PFS using ROC-derived significant cutoff values of CA 19-9 and SUVmax.

18-Fluorodeoxyglucose positron emission tomography/computed tomography imaging

^{18}FDG PET/CT was performed as per the institutional protocol adopted from EANM guidelines.[10] All patients had 4–6 h fasting (only plain water was allowed) and a fasting blood sugar <200 mg% before receiving an intravenous ^{18}FDG dose of 3 mbq/kg in the uptake room. During uptake period (55–75 min), patients were requested to lie comfortably and allowed to take about 500–1000 ml of plain water. No oral or intravenous iodinated contrast was used. Urinary bladder was emptied prior to calling the patient for PET/CT imaging suite. A low-dose CT examination (mid-brain to mid-thigh) starting from head to toe followed by acquisition of PET images using 3 min/bed position from toe to head in all patients.

Image analysis

All PET/CT scans were examined retrospectively by three observers (two nuclear physicians and a radiologist – all having more than 10 years' experience) on an interactive computer display using fusion software (Mirada; Mirada Medical Ltd., Oxford, UK). This software allows the review of PET, CT, and fused data using transaxial, sagittal, and coronal displays. To perform quantitative analysis, the SUVmax was calculated in primary pancreatic tumor. For SUV analysis, a circular region of interest was placed over the area of maximal focal ^{18}FDG uptake suspected to be a tumorous focus, and the maximal values were obtained.

Statistical analysis

Commercially available Packages Microsoft Excel 2016, Medcalc® Version 20.2., MedCalc Software Ltd, Belgium and the Statistical package for social sciences (IBM SPSS 19®), USA) were used for statistical analysis. All values are expressed as means ± standard deviations. Patients were stratified and analyzed by univariate analysis with respect to age, sex, body mass index (BMI), primary tumor type, cancer antigen (CA) 19-9 level, tumor size, tumor location, presence of nodal and nonnodal metastases (staging), and the SUVmax of the primary tumor. Logistic regression and receiver operating characteristic (ROC) analysis were applied for categorical and numerical predictors having significant cut off values. PFS was defined as time from the baseline ^{18}FDG-PET study to disease progression or death. Overall cumulative survival was analyzed using the Kaplan–Meier method, and differences in survival between subgroups based on ROC-derived cutoff values were compared using the log-rank test.

Results

Patient characteristics

Table 1 depicts patients' demographics, primary tumor sizes (PTSs) and location, histopathology, extent of disease, and metabolic and biochemical parameters.

Comparison of progression-free survival by patients' characteristics

We analyzed the relation between PFS and patients' characteristics (categorical data) using logistic regression [Table 2]. No significant difference in PFS was found for gender (male vs. female), BMI (obese and nonobese), tumor type (adenocarcinoma vs. mucinous type; SUVmax 7.3 ± 4.4 vs. 2.3 ± 1.1; $P < 0.002$), and presence or

Table 1: Demographics of pancreatic cancer patients on baseline fluorodeoxyglucose positron emission tomography/computed tomography (*n*=68)

Variables	Values
Age (years), mean±SD	60±11 (30–83)
Male, *n* (%)	48 (71)
Female, *n* (%)	20 (29)
BMI (kg/m^2), mean±SD	25.481±4.496
CA 19-9 (U/mL), median and range	184.44 (<1.2–100,000)
PTS (mm), median and range	36 (12–113)
SUVmax, median and range	5.8 (1.2–24.0)
Tumor type, *n* (%)	
Ductal adenocarcinoma	60 (88)
Mucinous	8 (12)
Anatomical distribution of primary tumor, *n* (%)	
Head/uncinate	45 (66)
Body and tail	23 (34)
Nodal/distant metastasis, *n* (%)	
No nodal/distant metastasis	8 (12)
Regional/retroperitoneal nodes	26 (38)
Extra abdominal nodes	4 (6)
Stage IV disease	30 (44)
Follow-up (months), median, and range	18 (1–62)
Numbers of progression/death	41 (60)
PFS (mean 95% CI; median 95% CI; SE)	30.9 (24.6–37.2); 18 (11–45); 3.19

SD: Standard deviation, BMI: Body mass index, PTS: Primary tumor size, SUVmax: Maximum standardized uptake value, PFS: Progression-free survival, CI: Confidence interval, SE: Standard error, CA: Cancer antigen

absence of ^{18}FDG-avid nodal metastasis ($P < 0.05$). However, pancreatic tail and body tumors were found to have significantly shorter PFS with higher odd ratio (4.803; confidence interval [CI]: 1.077–21.419). Similarly, Stage IV disease was found to have significantly shorter PFS with higher odd ratio (7.535; CI: 1.876–30.259).

Comparison of progression-free survival according to maximum standardized uptake value and CA 19-9

Using ROC analysis for measurable predictors, we could not find a significant association between PFS with age, BMI, and PTS (mm) [Figure 1 and Table 3]. However, a significant association was found for SUVmax and CA 19-9. The cutoff value of SUVmax >5.3 was found to have a shorter survival than those having ≤5.3 (sensitivity: 78.05%; specificity: 77.78%; $P < 0.0001$). For CA 19-9, cutoff >197 U/ml was found to have shorter survival than ≤197 U/ml (sensitivity: 73.17%; specificity: 96.0%; $P < 0.0001$).

Survival analysis

Kaplan–Meier's plots were drawn for SUVmax [Figure 2] and CA 19-9 [Figure 3]. Significant shorter PFS was found using ROC-derived cutoff values of SUVmax >5.3 versus ≤5.3 of primary tumor (mean and 95% CI: 16.7 vs. 48.5 and 10–23 vs. 41–56; log-rank = 25.014; $P < 0.0001$), while shorter PFS was found for CA 19-9 > 197 versus ≤197 U/ml (mean and 95% CI: 11.8 vs. 46.9 and 7–16 vs. 39–55; log-rank = 38.217; $P < 0.0001$).

Table 2: Logistic regression analysis for correlation between disease progression and independent variables on baseline fluorodeoxyglucose positron emission tomography/computed tomography in patients with pancreatic cancer

Variables	Coefficient	SE	Wald	OR	95% CI		*P*
					Upper	Lower	
Gender							
Female (*n*=20)	−1.410	0.789	3.191	0.244	0.052	1.147	0.074
Male (*n*=48)							
Obesity; BMI >30 kg/m^2							
Obese (*n*=8)	−0.683	1.055	0.419	0.505	0.064	3.996	0.517
Nonobese (*n*=60)							
Histological tumor type							
Mucinous (*n*=8)	−1.944	1.333	2.126	0.143	0.011	1.953	0.145
Adeno-CA (*n*=60)							
Anatomical tumor site							
Head/uncinate=45	1.569	0.762	4.233	4.803	1.077	21.419	0.039*
Body/tail (*n*=23)							
18FDG-avid nodal metastasis							
Present (*n*=26)	1.1129	0.779	2.0412	3.043	0.661	14.011	0.153
Absent (*n*=42)							
Stage IV on 18FDG PET/CT							
Present (*n*=30)	2.019	0.709	8.106	7.535	1.876	30.259	0.004*
Absent (*n*=38)							

*P<0.05. BMI: Body mass index, CI: Confidence interval, SE: Standard error, CA: Cancer antigen, ^{18}FDG PET/CT: ^{18}Fluorodeoxyglucose positron emission tomography/computed tomography

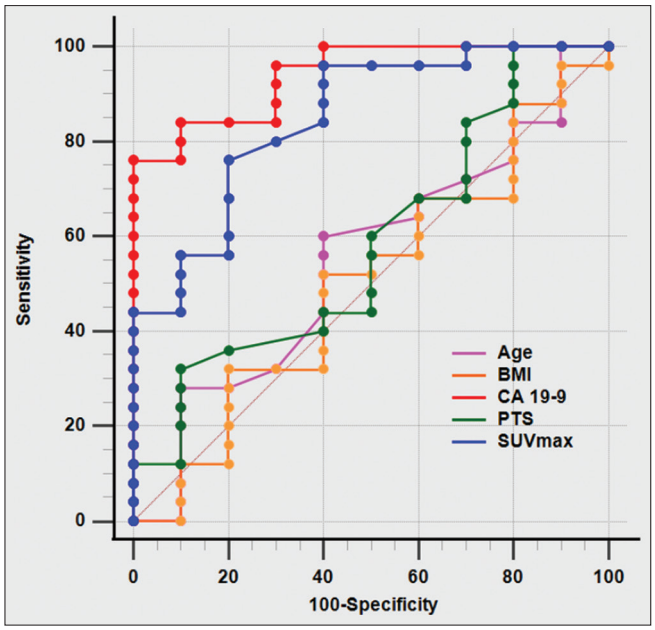

Figure 1: Receiver operating characteristic curves of measurable variables on baseline ^{18}fluorodeoxyglucose positron emission tomography/computed tomography in patients with pancreatic cancer in the prediction of disease progression on 5-year follow-up. BMI: Body mass index, CA 19-9: Cancer antigen, PTS: Primary tumor size, SUVmax: Maximum standardized uptake value

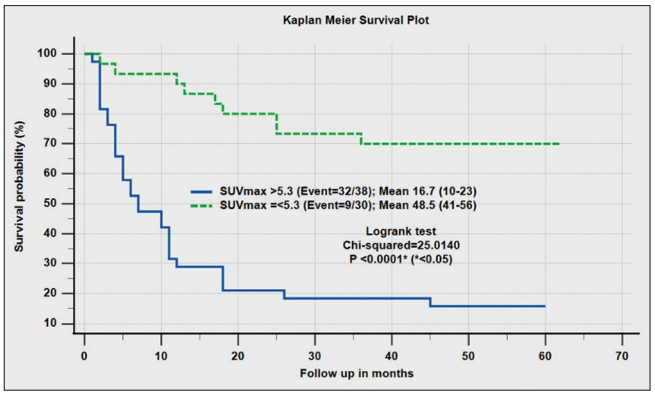

Figure 2: Kaplan–Meier survival plots of progression-free survival on 5-year follow-up in pancreatic cancer patients with maximum standardized uptake value at cutoff 5.3 of primary tumor on baseline 18-fluorodeoxyglucose positron emission tomography/computed tomography. SUVmax: Maximum standardized uptake value

Discussion

The aim of this study was to determine the impact of demographic factors, SUVmax, and CA 19-9 upon PFS in treatment-naïve patients with pancreatic cancer. In this study, age, gender, and BMI did not show a significant association with PFS. It is generally considered that old age and BMI are associated with higher incidence and poor outcome in PC likely due to age-related impaired organ function and reduced tolerance to treatment.[11] However, there are published studies showing no significant relation between these factors and PFS as we found in our study.[12] We also did not find a significant impact of mucinous carcinoma and ductal adenocarcinoma upon PFS despite having significantly higher SUVmax in the later group. Our findings are in contradiction with published data revealing that invasive mucinous carcinoma has better survival rates than ductal adenocarcinoma.[13] However, a published study also not revealed a significant survival difference in stage-matched analysis between invasive mucinous and ductal adenocarcinoma.[14] PC is characterized by early lymphatic invasion and involvement of regional nodes in resectable cases is reported in about 70%–80% with decreased survival.[15] In our study, we did not find a significant impact of nodal metastasis on PFS and plausible explanation could be a small number of N0 disease in study population (08/68). We found significantly shorter PFS in patients with pancreatic tail and body tumors than those involving head or uncinate process. According to published data, PC involving head or uncinate process has a 5% reduced mortality risk as compared with tumors arising in the body/tail. Major reasons for such different prognoses probably rely on the lack of early symptoms and presence of locally advanced or metastatic disease at initial presentation in tail/body tumors.[16] In our study, the incidence of Stage IV disease was 50% with significantly shorter PFS which is in accordance with published data with dismal prognosis.[17]

In this study, we used SUVmax which is the most widely used semiquantitative parameter to find its predictive value for survival. Furthermore, SUVmax was found to significantly affect PFS in the SUVmax ≤ and >5.3 groups by univariate and multivariate analysis (48.5 months vs. 16.7 months, respectively). Previously published studies have also found the same findings with different cutoff values of SUVmax like 6.1 and 4 (better PFS with lower SUVmax).[8,18]

CA 19-9 is an important serum biomarker and higher pretreatment levels are usually associated with a poor prognosis while postoperative levels are related to disease burden. In this study, the median level of CA 19-9 was 184.44 U/ml and patients with cutoff >197 U/ml were found to have a shorter PFS (mean: 11.8 months) than those with ≤197 U/ml (mean: 46.9 months). Our findings are in accordance with a recently published meta-analysis of 41 studies.[19] This meta-analysis found that cutoff-defined lower pretreatment or posttreatment CA 19-9 levels in PC patients predict longer survival. Furthermore, different cutoff values to differentiate between lower and higher CA 19-9 levels or the changes in CA 19-9 levels after treatment had generally similar survival outcomes.[18]

Our study has certain limitations. First is retrospective nature based on collection of data from hospital registry, but we have followed these patients prospectively for outcome. The second limitation is significant variation in PTSs (12–113 mm) which could influence the results.

Table 3: Receiver operating characteristics analysis of measurable variables on baseline 18-fluorodeoxyglucose positron emission tomography/computed tomography in patients with pancreatic cancer in the prediction of disease progression

Test variables	AUC	Criterion	Sensitivity	Specificity	SE	95% CI		*Z* statistics	*P*
						Lower limits	Upper limits		
Age (years)	0.577	>62	48.78	74.07	0.071	0.451	0.696	1.078	0.2810
BMI (kg/m^2)	0.530	>27.392	31.71	85.19	0.073	0.405	0.652	0.416	0.6777
CA 19-9 (U/mL)	0.911	>197	73.17	96.00	0.033	0.815	0.967	12.355	<0.0001*
PTS (mm)	0.527	>10	100.00	16.67	0.108	0.356	0.693	0.248	0.8042
SUVmax	0.827	>5.3	78.05	77.78	0.051	0.717	0.908	6.371	<0.0001*

*P<0.05. BMI: Body mass index, PTS: Primary tumor size, SUVmax: Maximum standardized uptake value, SE: Standard error, CI: Confidence interval, CA: Cancer antigen, AUC: Area under the curve

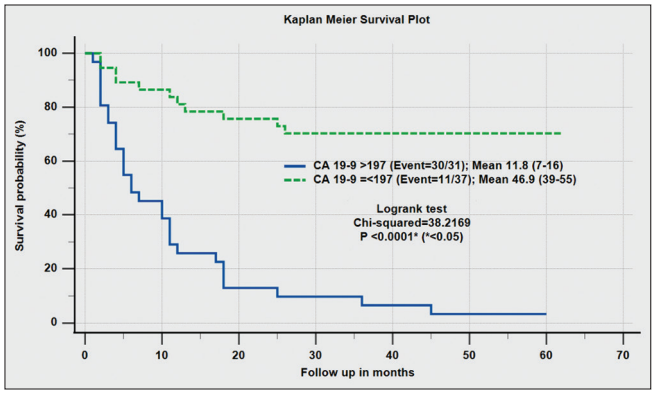

Figure 3: Kaplan–Meier survival plots of progression-free survival on 5-year follow-up in pancreatic cancer patients with baseline CA 19-9 value at cutoff 197. CA 19-9: Cancer antigen

Smaller tumors are amenable to underestimation of ^{18}FDG uptake and SUVmax and overestimation of survival due to partial volume effect.[19] To address this limitation, a large prospective study with selected tumor size criteria is warranted.

Conclusion

We conclude that in treatment-naïve PC, primary tumor SUVmax >5.3 in baseline ^{18}FDG PET/CT and baseline CA 19-9 >197 U/ml were found to have a significant negative correlation with PFS. Among demographics, only Stage IV disease and pancreatic tail/body tumors were found to have a significant negative correlation with disease progression.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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