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18F-FDG activitiy PET/CT and CA-19.9 levels for the prediction of histopathological features and localization of peri- ampullary tumors

PANCREAS

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Original Article

ABSTRACT

Background/Aims: We sought to investigate the roles of maximum standardized uptake value (SUV_{max}) and serum carbohydrate antigen 19-9 (CA 19-9) in predicting the histopathological features of periampullary tumors.

Materials and Methods: Thirty-four patients with histologically confirmed periampullary tumors were classified into two groups, according to the localizations of their tumors (ampulla Vateri or pancreas). SUV_{max} was obtained from [(18)F]-fluorodeoxyglucose positron emission tomography computed tomography (18F-FDG PET/CT). SUV_{max} and CA 19-9 levels were measured and compared with histopathological features of the tumors. Logistic regression was used to assess the significance and independence of predictive factors.

Results: 18F-FDG PET/CT SUV_{max} (<2.5 vs. ≥2.5; p=0.031) and CA 19-9 level (normal vs. elevated; p=0.045) were significantly and independently predictive of the histopathological origin of the tumors (ampulla Vateri vs. pancreas). The ratio of CA 19-9 levels and SUV_{max} were found to be higher in cases of poorly differentiated tumors and tumors greater than 2 cm in diameter.

Conclusion: A surgical approach to treatment may be considered for patients who have both i) an established or suspected diagnosis of periampullary tumors and ii) low SUV_{max} and CA 19-9 levels.

Keywords: Neoplasm antigens, positron-emission tomograpy, diagnostic imaging

INTRODUCTION

Pancreatic cancer is one of the most aggressive malignancies and has an extremely poor prognosis. It is the fourth leading cause of cancer-related death in the Western world, with one- and five-year survival rates of approximately 19% and <5%, respectively (1). Clinically, patients who have pancreatic cancer usually present with locally advanced, unresectable, or metastatic disease.

Periampullary tumors may arise from structures near the ampulla of Vater (pancreas, common bile duct, duodenum, or the ampulla of Vater itself) (2-4). The prognosis of these tumors may vary according to their origin. Although tumors originating from the ampulla or distal choledochus are characterized by longer durations of survival, complete surgical resection has been shown to be the only means of providing cure. Early and accurate diagnosis is extremely important to both the overall survival and quality of life of patients with periampullary tumors.

Serum carbohydrate antigen 19-9 (CA 19-9) is an extensively studied and validated pancreatic cancer biomarker that has been used for the diagnosis and surveillance of periampullary tumors in non-jaundiced patients. CA 19-9 has well-known roles in predicting prognosis, overall survival, response to chemotherapy, and postoperative recurrence (5-11).

The maximum standardized uptake value (SUV_{max}) is a marker of tumor glucose metabolism detected by [18F]-

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fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT). SUV_{max} reflects tumor aggressiveness and is an independent prognostic factor in pancreatic cancer. Evaluation of SUV_{max} offers an advanced method of detecting small solid lesions, based on the focal uptake of FDG-labeled glucose in malignant tumor cell populations (12,13).

Several studies have reported the clinical utility of CA 19-9 levels and PET/CT in the diagnosis and management of periampullary tumors (14-19). Although results from these studies have been encouraging, data regarding the link between CA 19-9 levels, SUV_{max}, and confirmed histopathological features are lacking in the current literature on periampullary tumors. In this study, we aimed to investigate the role of CA 19-9 and SUV_{max} in predicting the histopathological features of periampullary tumors.

MATERIALS AND METHODS

This study included 36 patients who had a histologically confirmed or suspected diagnosis of periampullary tumor, and who underwent whole body 18-F FDG PET/CT scans at the Surgical Oncology Unit of the General Surgery Department of Cukurova University Hospital between June 2009 and February 2013. The exclusion criteria included diabetic patients and patients who were inoperable. The study was approved by our institution's ethical committee and written informed consent was obtained from each participant enrolled in the study.

The following laboratory data were recorded for all patients: bilirubin (BIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate (ALP), gamma-glutamyl transpeptidase (GGT), and CA 19-9 levels. Patients were classified according to the results of the biochemical tests that had been conducted. All of the surgical procedures and microscopic examinations of surgically resected specimens were performed by the same surgical and pathology team. The following additional data were also analyzed in this study: mean diameters of masses in histopathologic specimens, their localizations (ampulla, duodenum, head of pancreas, or distal choledochus), and the presence of lymph node metastases, lymphovascular invasion, and/or perineural invasion. Furthermore, patients were grouped according to tumor localization: group 1 included tumors originating from the ampulla, group 2 included tumors originating from the pancreas, and group 3 included tumors originating from the duodenum or distal choledocus. Because group 3 included an insufficient number of patients (n=2), these patients were excluded from the study. According to the mean diameter of the masses in histopathological specimens, we separated the patients into two groups: those with tumor sizes (diameters) less than 2 cm, and those with tumor size greater than 2 cm. Tumor differentiation was defined as well differentiated (Grade 1), intermediate (Grade 2), or poorly differentiated (Grade 3).

18F-FDG PET/CT: All patients were asked to fast for at least 4 hours before the procedure. Blood glucose concentrations were measured to ensure that all serum glucose levels were below 144 mg/dL before intravenous injection of 18-FDG. Approximately 370 MBq (10 mCi) of FDG was administered to each patient via the antecubital vein. Patients over 70 kg in weight received a dose of 444 MBq (12 mCi) 18-FDG. After the patients had been placed in a resting position in a closed room, a whole-body image was acquired in approximately 60 minutes, following the administration of 18-FDG. PET scans were acquired on an integrated PET-CT system (Biograph LSO DUO PET-CT Scanner, Siemens, Hoffman Estates, IL, USA), which combines a high-resolution PET scanner for 3-dimensional image acquisition with a dual-detector spiral CT scanner. SUV_{max} was recorded and patients were grouped having either $SUV_{max} < 2.5$ or $SUV_{max} \geq 2.5$.

Statistical analysis

Continuous variables that followed normal distributions are expressed as mean ± standard deviation (SD). Variables that did not follow normal distributions are summarized in terms of their medians and ranges. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Comparisons of normally distributed continuous variables were performed using Student's t-test or one-way analysis of variance (ANOVA). The Mann-Whitney U-test or the Kruskal-Wallis test was used when a variables was not normally distributed. The Cohen's kappa test was used to analyze intra-group correlations. Logistic regression analyses were performed to evaluate the independent risk factors related to tumor origin. All data were entered and analyzed using the Statistical Package for Social Sciences, version 19.0 (SPSS Inc., Chicago, IL, USA). P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 36 patients were enrolled in the study, 34 of whom were included in our analyses. Figures 1 and 2 present PET-CT

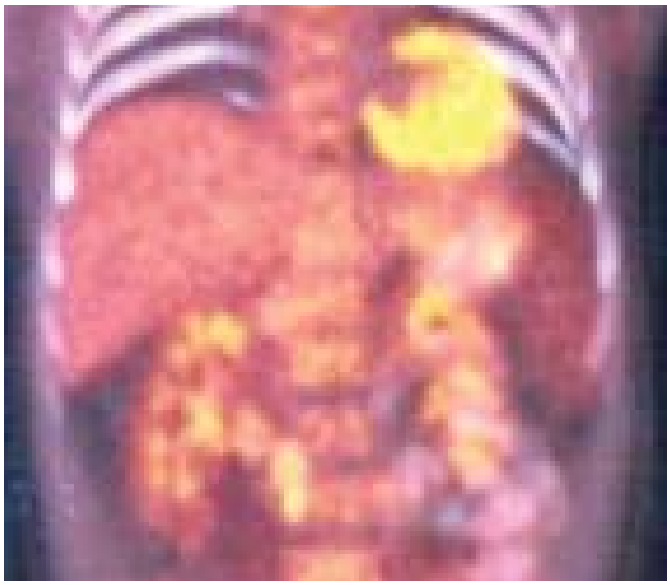

Figure 1. PET-CT scan showing lower uptake for the ampullary tumor.

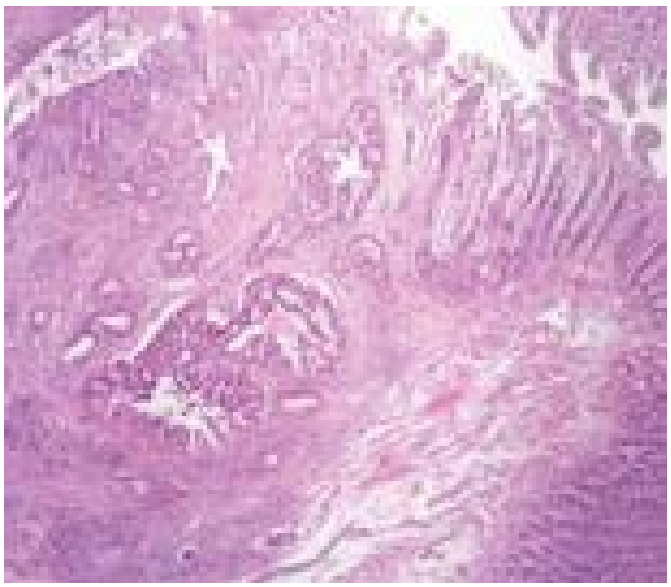

Figure 2. Histopathological investigation of the ampullary tumor.

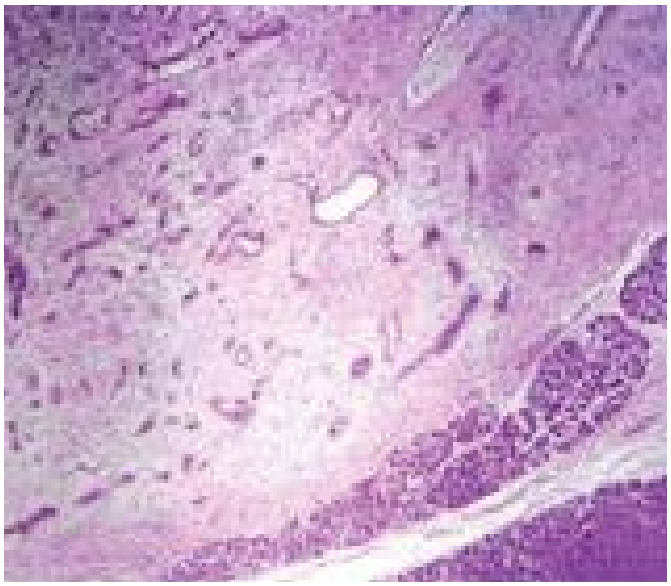

Figure 4. Histopathological investigation of the pancreatic tumor.

and histological results for cases of ampullary and pancreatic tumor, respectively. The biochemical features of the groups are summarized in Table 1. Group 1 (tumors originating from the ampulla) included 22 patients and group 2 (tumors originating from the pancreas) included 12 patients. We did not find any statistically significant differences between the groups in terms of preoperative biochemical values (ALT, AST, ALP, and GGT; p>0.05).

The clinical features of the groups are presented in Table 2. Differentiation was poorer in patients belonging to group 2 than in their counterparts in group 1. Lymph node metastasis (LNM) and perineural invasion (PI) were more common in group 2 than in group 1 (p=0.016 and p=0.027, respectively). The frequency of lymphovascular invasion (LI) did not differ significantly between the two groups. However, higher levels

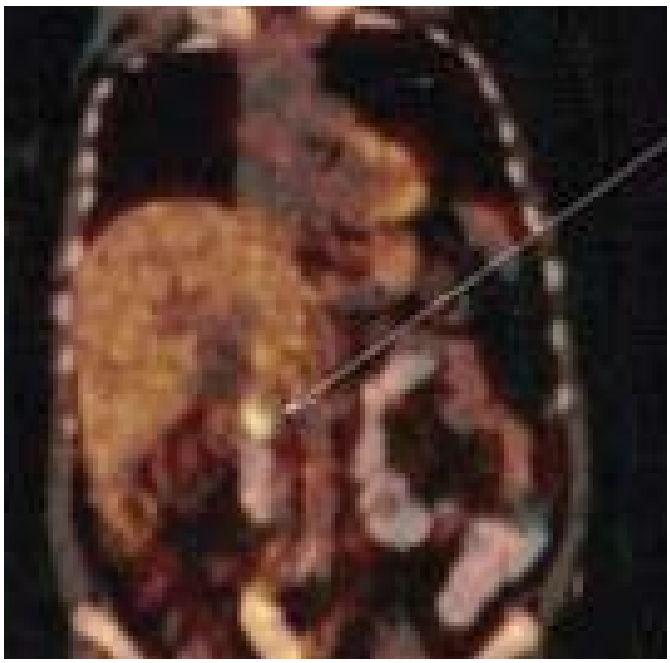

Figure 3. PET-CT scan showing higher uptake for the pancreatic tumor.

Table 1. Demographic and biochemical features of the groups

		Group 1 Ampulla		Group 2 Pancreas		
		n	%	n	%	p
BIL	Normal	9	40.9	8	66.7	0.151
	High	13	59.1	4	33.3	
ALT	Normal	7	31.8	3	25.0	0.677
	High	15	68.2	9	75.0	
AST	Normal	6	27.3	4	33.3	0.711
	High	16	72.7	8	66.7	
ALP	Normal	8	36.4	6	50.0	0.440
	High	14	63.6	6	50.0	
GGT	Normal	5	22.7	3	25.0	0.881
	High	17	77.3	9	75.0	

BIL: Bilirubin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphate; GGT: Gamma-glutamyl Transpeptidase .

of CA 19-9 and SUV_{max} were observed in group 2 (p=0.002 and p=0.002, respectively) (Table 2).

PET/CT SUV_{max} was significantly higher for tumors with intermediate and poor differentiation than for well-differentiated tumors. In addition, SUV_{max} was found to be significantly higher in tumors with perineural invasion than in tumors without perineural invasion (p<0.05). Elevated CA 19-9 and high SUV_{max} were significantly more common in cases of poorly differentiated tumors and tumors with diameters greater than 2 cm (p<0.05)., and kappa levels over 0.50 indicated a good correlation between groups (Table 3).

Logistic regression analysis showed that SUV_{max} and CA 19-9 levels were significantly and independently associated with tumor localization. Particularly, elevated CA 19-9 and SUV_{max} were associated with an increased probability of the tumor having originated in the pancreas (Table 4).

Table 2. Clinical features of the groups

		Group 1 Ampulla		Group 2 Pancreas		p
		n	%	n	%	
Lymph node metastasis	No	15	68.2	3	25.0	0.016
	Yes	7	31.8	9	75.0	
Lymphovascular invasion	No	6	27.3	1	8.3	0.192
	Yes	16	72.7	11	91.7	
Perineural invasion	No	10	45.5	1	8.3	0.027
	Yes	12	54.5	11	91.7	
Tumor differentiation	Good	11	50.0	2	16.7	0.050
	Mid-poor	11	50.0	10	83.3	
Tumor diameter	<2	14	63.6	3	25.0	0.031
	>2	8	36.4	9	75.0	
CA 19-9	Normal	16	72.7	2	16.7	0.002
	High	6	27.3	10	83.3	
SUVmax	<2.5	14	63.6	1	8.3	0.002
	>2.5	8	36.4	11	91.7	

SUV_{max}: maximum standardized uptake; CA 19-9: Carbohydrate Antigen 19.9

DISCUSSION

Periampullary tumors can originate from the ampulla, duodenum, head of the pancreas, or distal choledochus. Notably, tumors originating from ampulla or distal choledochus demonstrate better prognosis. In contrast, pancreatic is usually locally advanced, unresectable, or metastatic at the time of diagnosis. Early and accurate diagnosis is extremely important to the overall survival and quality of life of patients with periampullary tumors (1-4).

Carbohydrate antigen 19-9 is a gold-standard serum marker for the diagnosis of pancreatic cancer in symptomatic patients (5-7). Pre-operative CA 19-9 serum levels may provide important prognostic information in patients with pancreatic cancer. Indeed, they correlate with tumor stage and independently predict overall survival (8-10). Unfortunately, non-specific expression in several benign and malignant diseases, false-negative results in the Lewis-negative genotype, and increased false-positive results in the presence of obstructive jaundice severely limit the clinical utility of serum CA 19-9 levels in the manage-

Table 4. Results of the logistic regression analyses

Variables	B	OR	95% CI	p
CA 19-9 (Positive)	3.074	21.6	1.3-352.6	0.031
SUVmax (>2.5)	4.838	126.1	1.1-14397.7	0.045
Tumor diameter (>2 cm)	2.418	11.2	0.3-426.6	0.193
Tumor differentiation (Mid-poor)	1.433	4.2	0.1-130.1	0.414
Constant	-7.142	0.001		0.033

SUVmax: maximum standardized uptake; CA 19-9: Carbohydrate Antigen 19-9; B: model coefficient; OR: odds ratio; CI: confidence interval.

The dependent variable is the origin of the tumor (0= Ampulla, 1= Pancreas).

Table 3. Tumor diameter, differentiation, and clinical features

		Tumor diameter n (%)			Tumor differentiation n (%)		
		<2 cm	>2 cm	p Kappa	Good	Mid-poor	p Kappa
CA 19-9	Normal	14 (82.4)	4 (23.5)	0.59	11 (84.6)	7 (33.3)	0.49
	High	3 (17.6)	13 (76.5)	0.001	2 (15.4)	14 (66.7)	0.004
SUVmax	<2.5	14 (82.4)	1 (5.9)	0.76	11 (84.6)	4 (19.0)	0.64
	>2.5	3 (17.6)	16 (94.1)	0.000	2 (15.4)	17 (81.0)	<0.001
Lymph node metastasis	No	12 (70.6)	6 (35.3)	0.35	10 (76.9)	8 (38.1)	0.36
	Yes	5 (29.4)	11 (64.7)	0.039	3 (23.1)	13 (61.9)	0.028
Lymphovascular invasion	No	7 (41.2)	0 (.0)	0.41	7 (53.8)	0 (0.0)	0.59
	Yes	10 (58.8)	17 (100.0)	0.003	6 (46.2)	21 (100.0)	0.000
Perineural invasion	No	10 (58.8)	1 (5.9)	0.53	10 (76.9)	1 (4.8)	0.74
	Yes	7 (41.2)	16 (94.1)	0.001	3 (23.1)	20 (95.2)	0.000
Tumor differentiation	Good	11 (61.1)	2 (12.5)	0.48			
	Mid-poor	7 (38.9)	14 (87.5)	0.004			

SUVmax: maximum standardized uptake; CA 19-9: Carbohydrate Antigen 19-9.

ment of pancreatic cancer (6,7). In our study, lower CA 19-9 levels were observed in patients who belonged to the ampulla group and did not have cholangitis. However, patients belonging to the pancreatic cancer group had higher CA 19-9 levels, a finding that has also been demonstrated in previous studies (5-7,11). On the other hand, we detected a correlation between CA 19-9 levels and SUV_{max} or tumor size As has been shown repeatedly in previous studies, SUV_{max}, tumor differentiation, and tumor size are independently predictive of prognosis. Hence, our study supports the hypothesis that CA 19-9 levels may be useful as a prognostic indicator.

The PET/CT technique is an advanced method of detecting small solid lesions, and is assisted by the focal uptake of FDG-labeled glucose in malignant tumor cell populations (12-15). The current literature includes relatively little data regarding the diagnostic role of PET/CT in patients with periampullary tumors (16-19). Although the FDG-sensitivity of tumors originating from the pancreas has been reported to be between 88% and 92% (17, 19-25), there are limited findings for tumors that originate from the ampulla or distal choledochus (16-18). The pancreatic malignancy has variously been reported to be 2.2, 2.5, 2.8, and 3.0 (20, 22, 26-28). In the present study, we used an SUV_{max} threshold of 2.5 in our comparisons of SUV_{max} with the histopathological features of periampullary tumors. In our study, 14 of the 22 ampullary tumors and 1 of the 12 pancreatic tumor did not exhibit SUV_{max} >2.5, and we found that the mean SUV_{max} was significantly higher in the pancreas group than in the ampulla group. Therefore, PET/CT is not a useful tool for the diagnosis of tumors originating from the ampullary region. In fact, low or normal SUV_{max} may be suggestive of ampullary localization of a periampullary mass.

Although combined advanced diagnostics are currently available, these methods have limited abilities to detect periampullary lesions smaller than 2 cm In our study, SUV_{max} was significantly lower for tumors smaller than 2 cm, as compared with tumors larger than 2 cm. Some researchers have emphasized that ampullary tumors less than 1 cm in diameter may not have any SUV_{max} on PET/CT (15,16,18,21). In the ampulla group, PET/CT observable SUV_{max} was higher for tumors with diameters greater than 2 cm (15, 22, 25* In several studies of ampullary tumors, PET/CT SUV_{max} was higher for tumors with diameters greater than 2 cm (15,22,25) In the present study, we also found an association between tumor size and differentiation.

In our study, tumors in the ampullary group were well or intermediately differentiated. In contrast, the pancreas group only included two patients who had well or intermediately differentiated tumors. There is limited data regarding the correlation between SUV_{max} and tumor differentiation. Interestingly, we were able to demonstrate a direct correlation between SUV_{max} and tumor differentiation. In addition, all of the cases of perineural invasion had poor differentiation, and the presence of perineural invasion was associated with increased SUV_{max} in our data. Although it has been suggested that perineural invasion is prognostic of poor survival (29), there are no previous data regarding the correlation between perineural invasion and PET/CT SUV_{max}.

Many studies have reported that tumor origin, tumor size, tumor differentiation, CA 19-9 level, and perineural invasion are prognostic factors (25, 29). The results of our study demonstrate an important association between FDG activity and all of these parameters. We suggest that FDG activity is not only important during diagnosis, but might also be considered to be a new prognostic factor (25,30).

In conclusion, preoperative PET/CT and CA 19-9 evaluations of patients with periampullary tumors may contribute to data on the tumor's origin, perineural invasion, and/or differentiation. Thus, a surgical approach should be considered for patients who are known or suspected to have periampullary tumors, and who have low SUV_{max} and CA 19-9 levels. However, larger prospective randomized studies are needed to support our findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee.

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