




# Solid pseudopapillary neoplasms of the pancreas: Case series with a review of the literature

Alper Uğuz<sup>1</sup> , Ömer Vedat Ünalp<sup>1</sup> , Göksever Akpınar<sup>2</sup> , Can Avni Karaca<sup>3</sup> , Nevin Oruç<sup>4</sup> , Deniz Nart<sup>5</sup> , Funda Yılmaz<sup>5</sup> , Ahmet Aydın<sup>4</sup> , Ahmet Çoker<sup>1</sup> 

<sup>1</sup>Department of General Surgery, Ege University School of Medicine, İzmir, Turkey

<sup>2</sup>Department of General Surgery, University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Turkey

<sup>3</sup>Department of General Surgery, Izmir University of Economics School of Medicine, İzmir, Turkey

<sup>4</sup>Department of Gastroenterology, Ege University School of Medicine, İzmir, Turkey

<sup>5</sup>Department of Pathology, Ege University School of Medicine, İzmir, Turkey

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## ABSTRACT

**Background/Aims:** The solid pseudopapillary neoplasms are quite rare tumors of the pancreas, comprising roughly 1-2% of all pancreatic neoplasms. It has a low malignant potential and usually affects young females. Despite increasing number of articles in the last decade, there is still debate on the pathogenesis, malignant potential and optimal surgical strategy for the solid pseudopapillary neoplasms.

**Materials and Methods:** Medical recordings of 326 patients who were operated due to pancreatic mass were retrospectively analyzed. Patient demographics, presenting symptoms, surgical and pathologic characteristics of the tumor, postsurgical course, long-term survival, and other relevant data were extracted from patients' charts.

**Results:** Majority of the patients were female in consistency with the classic data in the literature. All the patients underwent curative intent resections. Tumors were commonly localized in the tail of the pancreas making distal pancreatectomy the most commonly performed surgical procedure. Mean tumor diameter was 5.8 centimeters with tumor sizes ranging from 1 to 19 cm.

**Conclusion:** The solid pseudopapillary neoplasms of the pancreas is a rare tumor with low malignant potential, which is more common in females of reproductive age, with abdominal pain being their most common presentation. The short-term outcomes in patients following surgical R0 resection are excellent. However, proximal placement of the tumor and female gender may have slightly worse prognosis. We hope that our findings from a series of patients represent a contribution to the existing literature on SPN, and authors declare their willingness to provide further details for future meta-analyses.

**Keywords:** Pancreas, solid pseudopapillary neoplasms, surgery

## INTRODUCTION

Solid pseudo-papillary neoplasms (SPNs) of the pancreas were first described in 1959 by Frantz who defined these lesions as a new type of pancreatic tumor. These rare lesions harboring solid and cystic components comprise nearly 1%-2% of all the pancreatic neoplasms and were previously misclassified as non-functioning islet cell tumors (1). SPNs have low malignant potential and usually affect young women. The prognosis is generally good owing to the rarity of metastasis and high rates of long-term survival achieved through surgical resection of the primary tumor and of the malignant tumor (2, 3). Although we have witnessed an increasing number of publications on this disease in the past decade, several issues remain unresolved, including the exact pathogenesis, malignant potential, and optimal surgical management strategies (1, 3). We believe

that better management of this indolent disease may lead to a dramatic improvement in the treatment outcome. Therefore, in this study, we share our experience and findings in our patients with SPN, with the objectives of better characterization of the disease as well as providing data for future meta-analyses.

## MATERIALS AND METHODS

Medical records of 326 patients who underwent surgery in our unit owing to a pancreatic mass between January 2000 and December 2013 were retrospectively analyzed. During this period, 24 patients who had a pathologically confirmed diagnosis of SPN were included in the study. All the relevant data, including patient demographics, presenting symptoms, surgical and pathologic characteristics of the tumor, post-surgical course, and long-term

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Corresponding Author: Alper Uğuz; dralperuguz@yahoo.com

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survival, were retrieved from hospital records. Informed consent for the surgery was provided by all patients. Out-patient records and phone calls were used for patient follow-up. No approval for the study protocol was obtained from the local ethics committee owing to the retrospective nature of the study. Informed consent was also not provided.

### Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine normal distribution of variables. Continuous variables with normal distribution were presented as mean±standard deviation. Median value was used for variables without normal distribution. Statistical comparison of the parametric variables between 2 groups was carried out using the Student's t-test. The Mann-Whitney U test was used to compare non-parametric variables between 2 groups. Qualitative variables were presented as percentages, and the correlation between categorical variables was investigated using the Chi-square test and Fisher's exact test. Overall survival rates were estimated using the Kaplan-Meier method, and the log-rank test was used for the comparison of outcomes. A  $p < 0.05$  was considered statistically significant.

## RESULTS

### Demographic Data and Clinical Symptoms

Consistent with the previously published data, most patients were females (male patients,  $n=5$ ; 20.8%). Their mean age was 47.2 years, with no significant age differences between male and female patients ( $p=0.28$ ).

All the patients underwent resection with curative intent, with a 100% of R0 resection rate.

The most common presenting symptom was blunt abdominal pain alone, which was observed in 54.2% ( $n=13$ ) of the patients, followed by dyspeptic complaints (25%,

$n=6$ ) and other gastrointestinal symptoms accompanying abdominal pain (21.8%,  $n=5$ ).

Endoscopic ultrasonography (EUS) and fine-needle aspiration biopsy (FNAB) were used to establish a preoperative diagnosis in 91.7% ( $n=21$ ) of the patients. However, EUS was used for diagnosis at another institute except for 4 patients.

### Tumor Characteristics

Distal pancreatectomy was the most common surgical procedure because most tumors were located in the tail of the pancreas (45.8%,  $n=11$ ). Other tumor locations included the pancreatic head (37.5%,  $n=9$ ) and body (16.7%,  $n=4$ ).

Tumor size ranged between 1 and 19 cm, and the average tumor diameter was 5.8 cm.

Although vascular invasion was very rare (4.2%,  $n=1$ ), capsular invasion was present in half of the tumors (50%,  $n=12$ ). The most common microscopic feature was perineural invasion, which was found in 18 (75%) patients.

$\beta$ -cadherin was positive in 22 (91.7%) patients, followed by CD56 (87.5%,  $n=21$ ), CD10 (79.2%,  $n=19$ ), alpha-1 antitrypsin ( $\alpha$ -1 AT) (75%,  $n=18$ ), neuron-specific enolase (NSE) (75%,  $n=18$ ), synaptophysin (70.8%,  $n=17$ ), and vimentin (70.8%,  $n=17$ ) positivity. Chromogranin and cytokeratin were tested positive in only 25% and 20.8% of the patients, respectively.

Nuclear atypia was present in 66.7% ( $n=16$ ) of the tumors, and the mean Ki-67 index was 4.5%, ranging between 0 and 15%.

The demographics and pathological data are summarized in Table 1.

There were no significant differences in tumor characteristics between female and male patients.  $p$  values for the differences between the tumor characteristics are shown in Table 2.

### Outcomes

The average follow-up duration was 60 months, and 85% ( $n=21$ ) of the patients were alive at the time of the last follow-up. There were 3 recorded mortalities. The mean estimated overall survival was 144.5 months, and the median overall survival was 149.6 months. There were no perioperative mortalities, and R0 resection rate was

### MAIN POINTS

- SPN is a rare tumor with a low malignant potential therefore sharing more experience and findings will provide more data for future meta-analyses.
- Results after surgical excision are excellent, and resection is feasible even in the presence of local invasion or metastasis.

**Table 1.** Demographic and tumor characteristics in 24 patients with SPN.

Data	Number of patients
Age (years)	47.3±19.2
Female/Male (%)	19 (79.2)/5 (20.8)
Symptoms (%)	
Abdominal pain	13 (54.2)
Dyspeptic complaints	6 (25.0)
Abdominal pain+dyspeptic complaints	2 (8.3)
Weight loss+dyspeptic complaints	1 (4.2)
Abdominal pain+diarrhea	1 (4.2)
Abdominal pain+back pain	1 (4.2)
Tumor localization (%)	
Head	9 (37.5)
Body	4 (16.7)
Tail	11 (45.8)
Tumor diameter (cm)	5.8 (1.0-19.0)
Perineural invasion	18 (75.0)
Capsular invasion	12 (50.0)
Vascular invasion	1 (4.2)
β-cadherin	22 (91.7)
Cytokeratin	5 (20.8)
Synaptophysin	17 (70.8)
Vimentin	17 (70.8)
Chromogranin	6 (25.0)
NSE	18 (75.0)
α-1 AT	18 (75.0)
CD10	19 (79.2)
CD56	21 (87.5)

NSE: neuron-specific enolase; AT: antitrypsin; SPN: solid pseudo-papillary neoplasm; CD: cluster of differentiation

100%. However, 6 patients had surgical complications; 5 of them had Clavien-Dindo grade I and 1 of them had Clavien-Dindo grade III complications.

## DISCUSSION

SPNs are uncommon neoplasms of the pancreas with a low malignant potential for which surgical resection remains the main therapeutic strategy (4). SPNs have pre-

**Table 2.** Comparison of overall survival rates according to demographic and tumor characteristics. Tumor localization was the characteristic that significantly influenced the overall survival (p=0.044).

Parameter	Survival months (95% confidence interval)	p
Sex		0.26
Male	150	
Female	100	
Tumor localization		0.044
Head	100	
Body	56.7±15.5 <sup>a</sup>	
Tail	150	
Tumor diameter		0.940
<5 cm	150	
≥5 cm	150 (79.1-220.1)	
Perineural invasion		0.302
Absent	150	
Present	102.6±6.1 <sup>a</sup>	
Capsular invasion		0.323
Absent	150	
Present	104.3±10.2	
Vascular invasion		0.623
Absent	150.1±12.0 <sup>a</sup>	
Present	150	
β-cadherin		0.857
Negative	150	
Positive	148.0±13.5 <sup>a</sup>	
Cytokeratin		0.320
Negative	109.3±7.1 <sup>a</sup>	
Positive	150	
Synaptophysin		0.931
Negative	150	
Positive	148.1±13.2 <sup>a</sup>	
Vimentin		0.924
Negative	150	
Positive	146.0±14.5 <sup>a</sup>	
Chromogranin		0.212
Negative	107.3±7.9 <sup>a</sup>	
Positive	150	
NSE		0.829
Negative	150	
Positive	143.2±16.2 <sup>a</sup>	
CD10		0.866
Negative	150	
Positive	143.7±16.0 <sup>a</sup>	
CD56		0.293
Negative	100	
Positive	150	
Nuclear Atypia		0.757
Negative	150	
Positive	142.2±16.6 <sup>a</sup>	

NSE=: neuron-specific enolase; CD: cluster of differentiation

<sup>a</sup>Mean value.

**Table 3.** Comparison of demographic and tumor characteristics by sex. There were no significant differences between females and males in any of the variables ( $p>0.05$ ).

Parameter	Female (n: 19)	Male (n: 5)	p
Age (year)	44.8±18.6	56.6±20.2	0.230
Tumor localization			0.055
Head (%)	6 (31.6)	3 (60.0)	
Body (%)	2 (10.5)	2 (40.0)	
Tail (%)	11 (57.9)	None	
Tumor diameter (cm)	6.0 (2.0-19.0)	3.5 (1.0-17.0)	0.265
Tumor diameter group			0.075
<5 cm (%)	6 (31.6)	4 (80.0)	
≥5 cm (%)	13 (68.4)	1 (20.0)	
Perineural invasion (%)	13 (68.4)	5 (100.0)	0.202
Capsular invasion (%)	9 (47.4)	3 (60.0)	0.500
Vascular invasion (%)	1 (5.3)	None	0.792
β-cadherin (%)	17 (89.5)	5 (100.0)	0.620
Cytokeratin (%)	4 (21.1)	1 (20.0)	0.730
Synaptophysin (%)	14 (73.7)	3 (60.0)	0.462
Vimentin (%)	13 (68.4)	4 (80.0)	0.538
Chromogranin (%)	6 (31.6)	None	0.202
NSE (%)	13 (68.4)	5 (100.0)	0.202
α-1 AT (%)	13 (68.4)	5 (100.0)	0.202
CD10 (%)	14 (73.7)	5 (100.0)	0.274
CD56 (%)	17 (89.5)	4 (80.0)	0.521
Nuclear atypia (%)	12 (63.2)	4 (80.0)	0.445
Ki-67 index (%)	4.0 (0-15.0)	5.0 (0-11.0)	0.836

NSE: neuron-specific enolase; AT: antitrypsin; CD: cluster of differentiation

viously classified as borderline malignant tumors by the World Health Organization in 2006 owing to their relatively indolent nature. In 2010, these tumors were re-classified as low-grade malignant neoplasms (5). During the continuing controversy over the classification of SPNs, there are currently no preoperative criteria for the diagnosis of malignant SPNs. Some studies have reported certain tumor characteristics predictive of malignancy, such as the pancreatic duct dilatation, vessel encasement, and an incomplete capsule, with or without metastases (6). How-

ever, because of the rarity of the condition and limited number of reported cases, the exact role of these criteria has been obscure (1, 7).

Blunt abdominal pain alone or along with gastrointestinal discomfort were the most common symptoms in our patients. As radiological imaging studies using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) generally show a well-defined large mass, mostly in the form of a thick-walled cystic structure or a solid mass with some cystic components. Because the cytological features of SPNs are highly characteristic, a fine-needle biopsy of the cystic wall can provide valuable information for preoperative diagnosis (8). In this regard, EUS-FNAB is becoming increasingly popular and can be useful in identifying the tumor (9, 10). A new meta-analysis has indicated that EUS-FNAB in pancreatic tumors has become much more sensitive (91 %) and specific (96.5 %) (11). There is a characteristic appearance on EUS for SPN, but it is difficult to obtain diagnostic information with EUS-FNAB for distal and small lesions. EUS-FNAB is diagnostic in most of the patients and especially helpful to differentiate SPN from a neuroendocrine tumor (12, 13). Our institute did not have EUS before 2009. However, after 2009, it could not be performed routinely. Therefore, EUS and FNAB data were both extracted from the study. Moreover, 4 of our patients who underwent EUS-FNAB at our institute showed presence of a blood-containing cystic material. Along with radiological imaging with CT and MRI, endoscopic FNAB was utilized for all but 2 of our patients (91.7%).

At presentation, SPNs are generally larger than other pancreatic malignancies, with a size ranging between 2 and 25 cm (4, 14). In our patient group, the mean diameter of the tumor was 7.25 cm (range: 1-19 cm). Despite being bulky tumors, resection of these tumors is relatively easy owing to their slow growth. Our R0 resection rate of 100% reflects this behavior of the tumor.

Pathogenesis of SPNs remains unclear, and their cellular origins are yet to be defined. Although several authors have investigated the role of sex-specific hormonal receptors in the occurrence of SPNs on the basis of the preponderance of younger women in the patient population, no supporting evidence could be derived from these studies (9, 15, 16). Tanaka et al. (17) have shown the significance of Wnt signaling with β-cadherin mutations using diffuse cytoplasmic and nuclear positivity for β-cadherin. β-cadherin mutations were present in 91.7% of our patients, consistent with these data. However, no

statistically significant correlations were found between  $\beta$ -cadherin and survival or prognosis.

Acinar cell carcinomas and islet cell neoplasms should be included in the differential diagnosis of SPNs. As SPNs test positive for CD56,  $\alpha$ -1 AT, CD10, NSE, and vimentin, immunohistochemistry should provide adequate differential diagnostic information (16). Accordingly, our patient group also showed high positivity rates for these markers as can be seen Table 1.

In some patients with SPN, focal synaptophysin expression can be found, which is often accompanied by a cellular morphology of rounded nuclei with a coarser chromatin pattern (18). However, positivity for synaptophysin was present in 70.8% of our patients, which was higher than previously reported. This latter finding may reflect certain ethnic differences. However, it should be borne in mind that CD56 and synaptophysin are both present in SPNs and endocrine tumors of the pancreas.

SPN is associated with a favorable prognosis, even in the presence of metastases or invasion. According to a study by Kato et al. (19), the estimated tumor doubling time is 765 days. When the disease is limited to the pancreas, complete surgical excision provides curative treatment for more than 95% of patients with SPN. Local invasions, recurrences, or limited metastases do not pose contraindications for resection (9, 20). Consistent with these data, excellent outcomes have been observed in our patient group, with estimated median survival times of up to 150 months. The reported overall mortality was up to 2%, and recurrence was up to 10% to 15% (21). There were no patients with metastases among our group. In our patient group, there were 3 mortalities, corresponding to a mortality rate that is higher than previously reported. However, it should be noted that 2 of these patients were over the age of 70 years, and all of the mortality etiologies are not related with SPN.

Although SPNs mostly occur in younger female patients, cases of male and elderly patients have also been described (22-24). The reported median age at the time of diagnosis is 26 years (9, 25). Consistent with these data, the majority of our patients were young females, and there were fewer male and elderly patients in our series. The oldest patient was 81 years old. The average age for female patients was 44 years. Some recent findings have suggested that there could be sex-related differences in the prognosis of patients with SPN (5). Our statistical analyses, taking all the possible of prognostic param-

eters into account, failed to detect such a sex-related difference. However, our results should be interpreted cautiously owing to the small size of our study population in general and male patient population in particular. The relevant data are summarized in Table 3. Most of the SPNs occur in the tail and body of the pancreas. Among our patients, the most common lesion site was the tail of the pancreas, and 62.5% (n=15) of our patients had their lesion in the pancreatic tail or body. Interestingly, female sex and proximal location of the tumor have slightly shown worse prognosis in our group, but there was no significant statistical difference (p=0.044). Median pancreatic placement of the tumor has shown slightly worse prognosis without sex-related difference owing to the proximity of the tumor to the celiac and superior mesenteric artery and the complexity of lymph drainage.

In conclusion, SPN is a rare tumor with a low malignant potential, mostly affecting females in the reproductive age and presenting with abdominal pain. SPN is associated with certain distinctive radiological and histological characteristics, and any patient with probable SPN should undergo surgical resection with adequate follow-up. Short-term results after surgical excision are excellent, and resection is feasible even in the presence of local invasion or metastasis, which could require metastasectomy. Although laparoscopic and parenchyma-sparing surgery of the pancreas may play a role in the treatment of this disease in future, these approaches warrant further investigation. Female patients with proximal tumor placement may need careful follow-up. We hope that our findings from a series of patients contribute to the existing literature on SPN, and authors declare their willingness to provide further details for future meta-analyses.

Female patients with proximal tumor placement may need careful follow-up.

**Ethics Committee Approval:** N/A.

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