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Retrospective evaluation of patients diagnosed solid pseudopapillary neoplasms of the pancreas

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ABSTRACT

Purpose: Solid pseudopapillary neoplasm (SPN) is a rare, low-grade neoplasm with excellent prognosis. In this study, we evaluated clinicopathological characteristics of patients diagnosed with SPN retrospectively.

Methods: This is a retrospective study intended to characterize patients with the diagnosis of SPN between 2005 and 2015. Clinicopathological features, recurrence rate, and overall survival of 28 patients were recorded. Malignant SPN criteria were defined as the presence of distant metastasis (de-

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veloped at diagnosis or during follow up) or lymph node involvement.
Results: The mean age at diagnosis was 42 (range: 17-41). Among patients, 82% ($n = 23$) were female and 17.9% ($n = 5$) were male. The mean size of tumor was 5.81 cm (range: 2-15). The mean follow up period was 55.6 months, 1-year survival was 96.5% and 5-year survival rate was 88%. A total of 25 patients were alive at the end of follow-up period and 3 of the patients became exitus due to disease. Two patients had a metastatic presentation in livers at the diagnosis and metastasis developed in 3 patients during follow-up (liver of 1 patient, peritoneum in 1 patient and liver and peritoneum in 1 patient). The reason of admission was headache in 68% patients. The type of operation was frequently subtotal pancreatectomy ($n = 11$, 39.3%) and distal pancreatectomy ($n = 10$, 35.7%). Tumors were located frequently in body and tail regions ($n = 18$, 64.3%) and the number of patients with malignant criteria was 6 (21.4%). Although the mean age of malignant patients was significantly higher than benign patients ($P = 0.046$), there was no significant difference between 2 groups in terms of gender, tumor size, capsule invasion, perineural invasion, vascular invasion, and margin status.
Conclusion: SPN is a rarely seen tumor with low malignity potential. Surgical resection provides long-term survival rate even in local invasion or metastasis conditions.

Background

Solid pseudopapillary neoplasms (SPNs) are rare tumors accounting for 1%-2% of exocrine pancreatic tumors.[1] It is frequently seen among young women in the second and third decades of life. SPN has been defined by Franz in 1959.[2] The world health organization classified these tumors as solid pseudopapillary tumors in 1996 and reclassified them as SPNs in 2010.[3] The clinical and pathological characteristics of SPN are different than pancreatic cancer. They are histologically characterized by cystic areas and solid pseudopapillary arranged cells. They are mostly benign and most of the patients are cured after complete surgical resection (85%-95%). However, metastasis developed in 5%-15% of patients. The course of disease is generally good even in prevalent disease.[1,4-6] The most common sites of metastasis are the liver, regional lymph nodes, mesentery, omentum, and peritoneum.[7] Due to technological advances in diagnosis technologies and disease awareness, the frequency of the disease observed has been increased by 7 times when compared to 2000 years ago. The pathogenesis of the tumor is unknown. There is limited data regarding the pathogenesis, malignant potential, and optimal surgical strategy for the disease. We intended to share the results of our study on this rarely seen disease.

Materials and Methods

We retrospectively evaluated the records of 28 patients diagnosed with SPN (confirmed clinically and pathologically) between the 2005 and 2015. Age and gender of the patient, tumor size, tumor localization, and type of operation were reported as patients' clinical characteristics. We defined the malignant SPN criteria as the presence of distant metastasis (developed at diagnosis or during follow up) or lymph node involvement. Of the 28 patients, 22 benign and 6 malignant patients were identified and compared. Written consent was obtained from the patients.

Table 1
Clinicopathologic data.

		Min	-	Max	Avg	±	Std./n-%
Age		17	-	71	41.9	±	16.10
	<60				24		85.70%
	≥60				4		14.30%
Follow-up Duration (months)		9	-	126	55.6	±	29.50
Status	Died				3		10.70%
	Alive				25		89.30%
Surgical type	R0				21		75.00%
	R1				2		7.10%
	R2				5		17.90%
Gender	Female				23		82.10%
	Male				5		17.90%
Symptoms	Abdominal or back pain				19		67.90%
	Abdominal distension				2		7.10%
	Icterus				1		3.60%
	Itching				1		3.60%
	Asymptomatic				1		3.60%
	Pain and distension				4		14.30%
Localization	Head				8		28.60%
	Neck				2		7.10%
	Body and/or tail				18		64.30%
Tumor size		2	-	15	5.81	±	3.36
Capsular invasion	No				20		87.00%
	Yes				3		13.00%
Metastasis status	No				23		
	Initially				2		
	Later				3		
Lymph node involvement	Negative				12		42.90%
	Positive				2		7.10%
	Not removed				14		50.00%
Vascular invasion	No				24		92.30%
	Yes				2		7.70%
Perineural invasion	No				19		82.60%
	Yes				4		17.40%

Descriptive statistics such as mean, standard deviation, median lowest value, median highest value, frequency and rates were calculated. Independent samples *t* test and the Mann-Whitney *U* test were used to compare the variables between 2 groups. Categorical variables were compared with Pearson chi-square test and Fisher's exact test. Overall survival was performed utilizing Kaplan-Meier method.

Results

The mean age of 28 patients was 42. Among patients, 82% ($n = 23$) were female and 17.9% ($n = 5$) were male. The mean size of tumor was 5.81 cm (range: 2-15). The mean follow-up period was 55.6 months, 1-year survival was 96.5% and 5-year survival rate was 88%. A total of 25 patients were alive at the end of follow-up period and 3 of them became exitus due to disease. Metastasis was detected in livers of 2 patients during diagnosis; it developed in total of 3 patients during follow-up. Of these 3 patients, liver metastasis developed in 1 patient after 54 months, peritoneal metastasis developed in 1 patient after 40 months and both liver and peritoneal metastasis developed in 1 patient after 10 months. The most frequent reason of admission was headache in 68% of patients ($n = 19$). Tumor developed frequently in body and tail regions ($n = 18$, 64.3%) (Table 1). The type of operation was frequently subtotal pancreatectomy ($n = 11$, 39.3%) and distal pancreatectomy ($n = 10$, 35.7%). The number of patients with malignant criteria (presence of metastasis at diagnosis and during follow up, involvement of lymph node) was 6 (21.4%). While the mean age of malignant patients was significantly higher than benign

Table 2
Effect of gender and age on survival.

	Mean survival time (months)	95% CI		
		Lower bound	Upper bound	*P*
Age (≤60)	118.9	105.6	132.1	*0.032*
Age (>60)	75	35.7	123	
Gender (woman)	118.9	43.9	70.8	*0.014*
Gender (man)	79.4	60.7	122.3	
Kaplan-Meier (Log-rank)				

CI, confidence interval.

Table 3
Predictive factors of malignant SPNs.

		Malignant	Benign	All	*P*
Margin	Negative	3	18	21	0.144
	Positive	3	4	7	
Capsule invasion	No	5	15	20	1
	Yes	0	3	3	
Perineural invasion	No	4	15	19	1
	Yes	1	3	4	
Vascular invasion	No	5	19	24	0.415
	Yes	1	1	2	
Gender	Female	4	19	23	0.285
	Male	2	3	5	
Total		**6**	**22**	**28**	
Mean tumor size		5.58	5.87	5.81	0.856
Mean age (years)		53.5	38.82	41.9	*0.046*

patients ($P = 0.046$), there was no significant difference between 2 groups in terms of gender, tumor size, capsule invasion, perineural invasion, vascular invasion, and margin status (Table 2). Of the 28 patients operated, 21 patients underwent R0 resection, 2 patients underwent R1 resection, and 5 patients underwent R2 resection. The ratio of vascular invasion, perineural invasion, and capsule invasion was 7.1% (2/24), 14.3 (4/19), and 13.6% (3/20), respectively. Dissection was performed in 14 patients; 12 were negative and 2 were positive. A total of 5 patients received adjuvant therapy (2 patients chemotherapy, 2 patients radiotherapy, 1 patient both chemotherapy, and radiotherapy). One patient had higher level of CEA (>5 ng/mL) and 1 patient had higher level of Ca 19-9 (>39 U/mL) before the operation. Age of the patient which was ≥60 and male gender was negatively correlated with survival rate (Table 3).

Discussion

SPNs are rare tumors of the pancreas and account for approximately 1%-2% of exocrine pancreatic tumors and 5% of pancreatic cystic tumors.[8] They are frequently seen in the second and third decades of life.[9] The median age of patients in the study was 42 years, which is significantly older than in the literature.[6,10] The incidence was greater in females than males (female-to-male ratio was 4.6:1).

The clinical presentation of the tumor is usually nonspecific. Abdominal discomfort or vague pain is the most common symptom, followed by a gradually enlarging mass and compression signs induced by the tumor. Some patients are completely asymptomatic, with the tumor detected incidentally by imaging studies or routine physical examination. In our study, the most common reason for admission to the hospital was stomach ache and/or abdominal distension (89.3%). Usually there is no evidence of pancreatic insufficiency, abnormal liver function tests, cholestasis, elevated pancreatic enzymes, or an endocrine syndrome. Tumor markers are also generally unremarkable.[9,11] In our study, the level of CEA was higher in 1 patient and the level of Ca 19-9 was higher in another patient.

These neoplasms are reported to more commonly arise from the tail,[8] but can also arise from any other portion of the pancreas. In our series, body and/or tail were the most common site for the tumor (64.3%), followed by head (28.6%), and neck (7.1%). In a 2010 study from China, head was the most common site (39.8%) followed by the tail (24.1%).[9] In another study performed in Pakistan in 2014, the most common site was found as tail (40%).[12] However, a study from Korea by Lee et al[13] reported 80.9% of SPNs to be located in the body or tail of the pancreas.

The malignancy potential of these neoplasms is low, and metastasis developed in approximately 10%-15% of the patients.[14] In patients with SPN that is limited to pancreas, more than 95% of the patients are cured following the complete surgical resection.[15] Long survival rate has been observed in patients with malignant SPN.[16] In British medical literature, 5-year survival rate has been found to be 95% in 718 patients.[11] In our study, the 5-year survival rate was found to be 88%. Due to the favorable prognosis and excellent long-term survival, predictive factors of survival are difficult to identify. Therefore, all SPN patients need long-term follow-up, which is as important as the evaluation of benign and malignant tumors. Several studies have evaluated the clinicopathologic parameters predicting malign behavior, but showed conflicting results.

Butte et al[17] analyzed a total of 45 patients with SPN, and defined malignant SPN as the presence of regional or distant metastasis, relapse or locally advanced unresectable tumor. They classified and compared the patients as malignant ($n = 36$) and nonmalignant ($n = 9$) patients and found that malignant SPNs were significantly associated with large tumor size ($P < 0.005$) but not with age, sex, margin status, tumor location, type of surgery, invasion into normal parenchyma, perineural invasion, vascular invasion, and presence of lymph node metastasis. Kang et al have analyzed a total of 33 patients with SPN. They defined SPNs with malignant potential as those with pancreatic parenchymal invasion, capsular invasion, perineural invasion, lymph node metastasis, cellular atypical, or liver metastasis.[18] They found that SPNs with malignant potential were significantly associated with tumor size >5 cm ($P = 0.022$) but not associated with mean tumor size, sex, age, tumor location, presence and duration of symptoms, and presence of calcifications. In the present study, malignant SPN was defined as patients with distant metastasis (developed at diagnosis or during follow up) or lymph node involvement. Of the 28 patients, 22 patients with nonmalignant SPN and 6 with malignant SPN were compared to each other. While the mean age of patients with malignant SPN was significantly higher than patients with benign SPN, there was no significant difference between 2 groups in terms of gender, tumor size, capsule invasion, perineural invasion, vascular invasion, and margin status.

Complete aggressive surgical resection should be performed for these neoplasms even in the presence of invasion into adjacent organs and distant metastases based on the prolonged survival after complete surgical resection.[19,20]

Adjuvant therapy is used only in a small number of patients because of the high resectability of SPN. The role of chemotherapy or chemoradiotherapy in the treatment of SPN is also unclear. In some studies, adjuvant chemotherapy and radiotherapy are reported in some unresectable cases with good results.[21,22] In our study, 4 of the patients received adjuvant therapy [$n = 2$ radiotherapy; $n = 2$ chemotherapy (gemcitabine)]. Of the patients receiving adjuvant radiotherapy, peritoneal metastasis developed in 1 patient after 4 years and patient became exitus.

Conclusion

The prognosis of SPNs is good, even with invasion as well as metastases or local recurrence. In this study, we reported clinicopathologic features of SPN in our population. The tumor affected young females and followed a favorable prognosis in most cases.

References

1. Martin RC, Klimstra DS, Brennan MF, Conlon KC. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? *Ann. Surg. Oncol.*. 2002;9:35–40.
2. Frantz VK. Papillary tumors of the pancreas: benign or malignant? *Tumors Pancreas*. 1959:32–33.

3. Klöppel G, Hruban RH, Klimstra DS, et al.. Solid-pseudopapillary tumor of pancreas. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *World Health Organization Classification of Tumours of the Digestive System*. Lyon: IARC; 2010:327–330.
4. Klöppel G, Lüttges J, Klimstra DS, Hruban RH, Kern SE, Adler G. Solid-pseudopapillary neoplasm. In: Hamilton SR, Aaltonen LA, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System*. Lyon: IARC Press; 2000:246–248.
5. Raffel A, Cupisti K, Krausch M, et al. Therapeutic strategy of papillary cystic and solid neoplasm (PCSN): a rare non-endocrine tumor of the pancreas in children. *Surg Oncol*. 2004;13:1–6.
6. Lam KY, Lo CY, Fan ST. Pancreatic solid-cystic-papillary tumor: clinicopathologic features in eight patients from Hong Kong and review of the literature. *World J Surg*. 1999;23:1045–1050.
7. Yagci A, Yakan S, Coskun A, et al. Diagnosis and treatment of solid pseudopapillary tumor of the pancreas: experience of one single institution from Turkey. *World J Surg Oncol*. 2013;11:308.
8. Klimstra DS, Wenig BM, Heffess CS. Solid-pseudopapillary tumor of the pancreas: a typically cystic carcinoma of low malignant potential. *Semin Diagn Pathol*. 2000;17:66–80.
9. Yu PF, Hu ZH, Wang XB, et al. Solid pseudopapillary tumor of the pancreas: a review of 553 cases in Chinese literature. *World J Gastroenterol*. 2010;16:1209–1214. doi:10.3748/wjg.v16.i10.1209.
10. Nishihara K, Nagoshi M, Tsuneyoshi M, Yamaguchi K, Hayashi I. Papillary cystic tumors of the pancreas: assessment of their malignant potential. *Cancer*. 1993;71:82–92.
11. Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. *J Am Coll Surg*. 2005;200:965–972.
12. Ud Din N, Arshad H, Ahmad Z. Solid pseudopapilllary neoplasm of the pancreas. A clinicopathologic study of 25 cases from Pakistan and review of literature. *Ann Diagn Pathol*. 2014;18:358–362.
13. S L, J J, D H, K P, S K. Clinical features and outcome of solid pseudopapillary neoplasm: differences between adults and children. *Arch Surg*. 2008;143:1218–1221.
14. Tang LH, Aydin H, Brennan MF, Klinstra DS. Clinically aggressive solid pseudopapillary tumor of pancreas: a report of cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. *Am J Surg Pathol*. 2005;29:512–519.
15. Geers C, Moulin P, Gigot JF, et al. Solid and pseudopapillary tumor of the pancreas-review and new insights into pathogenesis. *Am J Surg Pathol*. 2006;30:1243–1249.
16. Kim CW, Han DJ, Kim J, et al. Solid pseudopapillary tumor of the pancreas: can malignancy be predicted? *Surgery*. 2011;149:625–634.
17. Butte JM, Brennan MF, Gonen M, et al. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. *J Gastrointest Surg*.. 2011;15:350–357.
18. Kang CM, Kim KS, Sub Choi J, Kim H, Jung Lee W, Ro Kim B. Solid pseudopapillary tumor of the pancreas suggesting malignant potential. *Pancreas*. 2006;32(3):276–280.
19. Lee JS, Han HJ, Choi SB, Jung CW, Song TJ, Choi SY. Surgical outcomes of solid pseudopapillary neoplasm of the pancreas: a single institution's experience for the last ten years. *Am Surg*. 2012;78:216–219.
20. Cai Y, Ran X, Xie S, et al. Surgical management and long-term follow-up of solid pseudopapillary tumor of pancreas: a large series from a single institution. *J Gastrointest Surg*. 2014;18:935–940.
21. Fried P, Cooper J, Balthazar E, Fazzini E, Newall J. A role for radiotherapy in the treatment of solid and papillary neoplasms of the pancreas. *Cancer*. 1985;56:2783–2785.
22. Matsuda Y, Imai Y, Kawata S, et al. Papillary-cystic neoplasm of the pancreas with multiple hepatic metastases: a case report. *Gastroenterol Jpn*. 1987;22:379–384.