Clinicopathological features and prognostic factors of solid pseudopapillary neoplasms of pancreas

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Abstract: To explore the clinicopathological features of solid pseudopapillary neoplasm (SPN) of pancreas and to analyze the related factors of SPNs with aggressive behavior. Clinical data of SPN patients admitted in the Single Center of Peking University Cancer Hospital from January 2007 to September 2017 were retrospectively analyzed. The correlations of clinicopathological features with aggressive SPNs and distant metastasis after curative resection were analyzed using univariate analysis. Twelve of the total 54 SPN patients were diagnosed as aggressive SPNs. Univariate analysis suggested clinical features had no correlations with aggressive SPNs. Patients were followed up for an average of 5.0 years, four of them developed distant metastases. Univariate analysis indicated that distant metastasis of SPNs was correlated with the aggressive behaviors (P=0.031). Moreover, vessels invasion (VI) and Ki-67>4% (P=0.012) were the independent risk factors of distant metastasis of SPNs. The aggressive SPNs, especially VI and Ki-67>4% are the independent factors correlated with distant metastases after SPNs surgery.

Keywords: Pancreatic tumor, solid pseudopapillary neoplasm, metastasis, treatment, risk factor.

INTRODUCTION

Solid pseudopapillary neoplasm (SPN) of pancreas is a relatively rare pancreatic disease frequently occurring in young women, which accounts for 0.13%-2.7% of all pancreatic tumors (Lam *et al*., 1999; Mao *et al*., 1995). In 1996, WHO Pathological Classification officially named such solid and cyst tumors as solid pseudopapillary tumor with undefined biological behavior. While in 2010, the WHO Pathological Classification of Digestive System changed the definition of SPN into a malignant tumor from the previously borderline tumor. However, the classification also stressed SPN to be a low-grade malignant tumor (Fléjou 2011). About 10%-15% of SPN cases have aggressive behavior, such as lymphovascular and perineural invasion, adjacent organs invasion, or even distant metastases (Sperti *et al*., 2008). Radical surgical resection remains the major treatment for SPN, but not much research of treatment related with SPNs' prognosis and long-term survival is available. Thus, we performed a retrospective study of SPN of pancreas. The objectives of this study were to describe the clinicopathologic characteristics, surgical treatment, and long-term outcome. The incidence of SPTP is low, accounting for 0.15-3.2% of all pancreatic tumors, 1-2% of pancreatic exocrine tumors and 6% of pancreatic cystic tumors. In recent years, with the deepening understanding of this tumor, its incidence has increased significantly. Currently, it is reported that the proportion of this tumor in all exocrine pancreatic tumors has reached 8%. Data show that 90% of SPTP patients are young women, the average age is 25 years old, the male-to-female ratio is 1: 9.5. The tumors are rare in children, and the incidence of these tumors is low in males and elderly females. The disease occurs in all ethnic groups, but most of them are black and young women in East Asia.

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METHODS

The study has been approved by patients. Clinical data of 54 SPN cases were collected from January 2007 to September 2017 in Hepato-Pancreato-Biliary Surgery Department of Peking University Cancer Hospital. All cases underwent surgical resection. The diagnosis of SPN was based on microscopic appearance of the tumor and results of immunohistochemical staining. Clinical presentation, surgical data, pathological features, and follow-up data were documented according to specific groups. Aggressive SPN was defined as the presence of tumor invasion to the peripancreatic tissues, pancreatic parenchyma or adjacent organs, vessels invasion, perineural invasion, lymph node metastasis or distant metastasis.

The statistical analyses were performed using SPSS software, version 13.0 (SPSS, Chicago, IL, USA). Wilcoxon Rank Sum test was used to compute the age difference between low-grade malignant SPNs and aggressive SPNs. Two-tailed chi-squared test ($\chi 2$) or Fisher's exact test was used to evaluate the correlation

between SPN distant metastases and aggressive pathological features. A two-sided P-value less than 0.05 was considered statistically significant.

RESULTS

Clinical features (table 1)

Data from a total of 54 cases were collected, including 9 males and 45 females, with the male-to-female ratio of 1:5. The age of all patients ranged from 12 to 69 years, with an average age of onset of 32.6 years. Specifically, the average age of onset in males and females was 37.6 and 31.6 years, respectively.

A total of 26 cases discovered the tumors in physical examination, and 2 discovered the tumors by themselves through palpation. Other 26 patients discovered their tumors in examination due to abdominal discomfort or abdominal pain, including 2 developing obvious vomiting symptom who had the tumors in the pancreatic head. Additionally, two patients had serious abdominal pain due to tumor rupture and hemorrhage.

All patients underwent Computed Tomography and/or MRI examination preoperatively. Among them, seventeen cases had the tumors in the pancreatic head (31.4%), five in the pancreatic neck (9.2%), and 32 in the pancreatic body and tail (59.2%). Dotted or flake calcification could be observed within tumors in 15 cases (27.8%), and slight dilation of pancreatic duct was seen in 3 cases with no cholangiectasis or jaundice. A sum of 39 cases was confirmed with SPN preoperatively (72.2%), while the remaining 15 cases were misdiagnosed of cystadenoma, pancreatic neuroendocrine neoplasm or pancreatic cancer preoperatively. In addition, eleven cases received Positron Emission Computed Tomography/CT examination, all these SPNs showed 18F-FDG uptake, with the SUVmax ranging from 4.33-44.8.

In total, 19 cases underwent distal pancreatectomy plus splenectomy; among them, two cases had synchronous peritoneal metastases, which were treated with total peritonectomy with organs combined resection. Nine cases underwent spleen-preserving distal pancreatectomy. Ten cases underwent central pancreatectomy. Eight had pancreaticoduodenectomy, including 1 underwent synchronous right trisectionectomy of liver due to multiple liver metastases and 1 patient altered to total pancreaticoduodenectomy due to the brittle quality of pancreas. Eight cases underwent enucleation to preserve pancreatic parenchyma, among them, seven cases had the tumors in pancreatic head and 1 in the pancreatic body. No surgery-related death was reported postoperatively. One patient had lymphatic fistula. Additional 21 patients had pancreatic fistulas, including 11 of grade A, nine of grade B and one of grade C, who had splenic artery hemorrhage and cured by interventional hemostasis.

Pathological features

The diameter of the 54 SPNs ranged from 1.0cm to 17.0cm, with the average diameter of 5.8cm. A total of 12 (22.2%) cases were diagnosed as aggressive SPNs according to the malignant features, including 9 with peripancreatic fat tissue invasion, three with pancreatic parenchyma invasion, three with adjacent gastric or duodenal wall invasion, three with VI, three with perineural invasion and 1 with multiple liver metastases. Only the patient with multiple liver metastases had 2 lymph node metastases and the remaining 53 cases had 156 lymph nodes detected, all of which were reactive hyperplasia.

Prognosis and statistical analysis

All the 54 patients were followed up for an average of 5.0 years (0.3-10.0). Among the 42 (77.8%) patients of low-grade malignant SPN, one patient was discovered extensive abdominal and pelvic metastases 6 years after her primary SPN resection. She then developed lung metastases 3 months after debulking surgery of peritoneal metastases. Meanwhile, the average follow-up period for the 12 aggressive SPNs patients was 4.3 years (0.3-8.6); among them, two patients developed liver metastases 1.2 and 1.4 years respectively after surgery, one died of progressed liver metastases at 5.2 years, and another patient still survived 5.5 years till now. In addition, another 1 case had pelvic metastasis 1.9 years after surgery. Moreover, no abnormalities were found in the remaining 50 patients until the last follow-up.

Correlation analysis of tumor clinical features with aggressive SPN suggested that, patient age, sex, symptoms at visit, tumor site and size, calcification in tumor and dilated pancreatic duct in imaging had no statistically differences compared with the aggressive behavior of SPNs (table 2). However, aggressive SPNs was significantly correlated with the distant metastases after surgery (P=0.031). Subsequently, all pathological factors for diagnosing aggressive SPNs were analyzed, the results of which suggested that only VI was correlated with the distant metastases after SPNs surgery (P = 0.012). In addition, ki-67 expression in the primary tumors of all patients were also retrospectively analyzed in this study, the results of which indicated that ki-67 > 4% was markedly correlated with the distant metastases of SPNs (P = 0.012) (table 3).

DISCUSSION

SPN is a relatively rare exocrine pancreatic neoplasm, which frequently occurs in the adolescent and young women. According to literature reports, the male-to-female morbidity ratio is about 1:10 (Mao *et al*., 1995; Papavramidis and Papavramidis 2005). In this study, male patients account for a higher proportion, with the male-to-female ratio of 1:5. SPN has no specific clinical

Table 1: Clinical features of 54 patients with SPNs

Parameter	Patient number (n=54)	%
Age (years, mean(range))	32.7 (12-69)	
Sex		
Male	9	16.7%
Female	45	83.3%
Symptom		0.0%
Abdominal discomfort	26	48.2%
Vomiting	2	3.7%
Palpable lesion	2	3.7%
Routing examination	26	48.2%
Size (cm, mean(range))	5.8 (1.0-17.0)	
Location		
Head	17	31.5%
Neck	5	9.3%
Body or tail	32	59.3%
Surgical treatment		
Enucleation	8	14.8%
Pancreaticoduodenectomy	7	13.0%
Central pancreatectomy	10	18.5%
Total pancreaticoduodenectomy	1	1.9%
Distal pancreatectomy	9	16.7%
Distal pancreatectomy+splenectomy	19	35.2%
Total peritonectomy	2	3.7%
Follow-up (years, mean(range))	5.0 (0.3-10)	
Outcome		
Alive	53	98.2%
Dead	1	1.9%

symptoms, which are mostly abdominal pain to various degrees and abdominal mass, accompanying with or without vomiting and nausea. Notably, an increasing number of patients without any symptoms are discovered in routine physical examination. Large tumors may rupture, leading to hemorrhage and severe abdominal pain. Meanwhile, minority patients may develop symptoms of biliary obstruction or digestive tract obstruction (Hao *et al*., 2006). According to literature, five of the 186 patients developed obstructive jaundice and 2 had duodenal obstruction. The obstructive symptoms in patients are not related to tumor size, it depends on tumor site instead.

The preoperative diagnosis of SPN counts largely on CT or MRI examinations. Typical imaging manifestations are a large well-encapsulated mass with varying solid and cystic components caused by hemorrhagic degeneration, which present with a mix of high and low signal intensity on T1- and T2-weighted images of MRI. Of them, the cystic part may show hemorrhage signal, while the solid part may show peripheral heterogeneous enhancement and progressive fill-in, with the enhancement lower than that in the pancreatic parenchyma (Cantisani *et al*., 2003). In addition, the capsule enhancement occurs early and obviously. Calcification can be seen in about 30% tumors. Specifically, eggshell-like calcification concentrating on tumor periphery is the characteristic feature of SPN (Choi *et al*., 2006). In contrast, the atypical imaging manifestations are mainly dilation of pancreatic duct or cholangiectasis, extra capsular invasion or liver metastases (Palmucci *et al*., 2012). F-18 FDG PET/CT showed limited diagnostic value for SPNs. In our study, eleven patients received PET/CT examination, and all tumors had high FDG uptake, with the maximum SUVmax of 44.8. Therefore, the small SPN lacking the typical features is frequently misdiagnosed as neuroendocrine neoplasm or pancreatic adenocarcinoma. F-18 FDG PET/CT has limited value in identifying suspected SPN, but it can evaluate tumor loads for SPN with distant metastases.

Preoperative biopsy is not the routine examination for SPN, even though fine needle biopsy is recommended in some retrospective studies for cases with undefined diagnosis that may affect treatment selection, but controversy existed (Levy *et al*., 2008). Most SPNs are composed of cystic and solid parts with certain tension; therefore, transabdominal needle biopsy may induce content outflow and even abdominal implantations. Virgilio reported four recurrences of SPN cases all because of biopsy (Virgilio *et al*., 2014). Therefore,

Table 2: Predictive factors for aggressive SPNs

Clinicopathologic factors	Low-grade SPNs (n=42)	Aggressive SPNs (n=12)	*p* value
Mean age (years)	31.9 (12-69)	34.9 (24-53)	0.274
Gender			
Male	6	3	0.399
Female	36	9	
Symptoms			
Present	21	5	0.747
Absent	21	7	
Tumor location			
Head	11	6	0.236
Neck	5	0	
Body or tail	26	6	
Tumor size (cm)			
<5	15	3	0.730
>5	27	9	
Radiological features			
Calcification	13	2	0.474
Dilated pancreatic duct	2	1	0.537

preoperative needle biopsy should be conducted with caution. Tumors involving controversial surgical procedures frequently locate in head of pancreas; as a result, endoscopic needle biopsy is recommended if necessary, which is associated with relatively higher accurate diagnosis rate and fewer complications (Bardales *et al*., 2004).

The pathological diagnosis of SPN mainly depends on its histologic and cytological appearance, and no specific molecular biomarkers are available at present. Generally, SPN is diagnosed based on the microscopic findings of papillary-like structure which is formed by neoplastic cells arranging radially around the minute fibrovascular stalks, as well as the exclusion of some known pancreatic tumors (Hao *et al*., 2006). Moreover, intratumoral hemorrhage, necrosis, cystic degeneration, foam cell aggregation and cholesterol granulation, as well as positive AAT, AACT, NSE and Vimentin staining under immunohistochemistry can support such diagnosis (Adams *et al*., 2008). E-cadherin, β-catenin and CD10 are mostly used in the differential diagnosis of SPN (Burford *et al*., 2009). Almost all SPNs harbor somatic point mutations in exon 3 of CTNNB1; therefore, β-catenin shows positive nuclear expression, whereas E-cadherin displays negative expression (Zhu *et al*., 2014; Chetty *et al*., 2008).

Surgical resection is the preferred method for treating SPN, the common surgical procedures include tumor enucleation, pancreaticoduodenectomy, central and distal pancreatectomy. Difference in prognosis among different surgical procedures is not statistically significant (Yu *et al*., 2010). SPN is a low grade malignant neoplasm; therefore, complete tumor resection and negative incisal margin should be guaranteed first; then to preserve peripheral organ's structure and function as much as possible. The long-term prognosis of patients following complete resection is excellent with 10-year disease free survival rates approaching 94% (Lubezky *et al*., 2017). Aggressive surgical treatment should be carried out even though in the presence of liver metastases and abdominal implantations (Wang *et al*., 2014). Our data suggest that one case has pancreatic head SPN accompanying with liver metastases, and pancreaticoduodenectomy and right trisectionectomy of liver are performed. Although multiple metastases are discovered in the residual liver 1.2 years postoperatively, the patient survived 5.5 years till now. Additionally, one patient dead for multiple liver metastases 1.4 years after surgery, but her overall survival time was 5.2 years.

The different manifestation of SPNs had promoted series research on the malignant behaviors. Some studies have shown a correlation between tumor size above 5 cm, tumor necrosis, the male patients were associated with aggressive SPNs (Tipton *et al*., 2006; Hu *et al*., 2013). However, no correlation of clinical or imaging features with aggressive SPNs is found in the current study. Therefore, large sample data are required in further study for predicting the aggressive behavior.

SPNs could have malignant features had been widely recognized. However, most studies did not confirm the correlation between aggressive SPNs and postoperative recurrence or metastases because of the limited metastatic cases, or the insufficient follow-up period. However, our review data suggests that the aggressive behaviors of SPNs are remarkably correlated with distant metastases, which can predict the risk of distant metastases after

Table 3: Predictive factors for distant metastases of resected SPNs

Parameters	SPNs without distant metastases	SPNs with distant metastases	*p* value
Cases No.	n=50	n=4	
Aggressive SPN cases	9	3	0.031
Malignant features			
Pancreatic parenchyma invasion	3	0	1.0
Gastroduodenum invasion	2	1	0.210
Peripancreatic fat invasion	7	2	0.125
Vessels invasion	1	2	0.012
Perineural invasion	2	1	0.210
LN metastases	0	1	0.074
Ki-67 expression			
>4%	6	3	0.012
<4%	44	1	

SPNs be curatively resected. Nevertheless, pancreas and adjacent organs invasion, as well as perineural invasion of SPNs are not correlated with distant metastases; instead, only VI is significantly associated with the distant metastasis after SPN surgery. The metastatic mechanisms of SPN is surmised to be similar with some gastrointestinal malignancies. In addition, Ki-67 >4% showed a significant association with distant metastases of SPNs in this study with statistical significance, consistent with the conclusions of Yang's report (Yang *et al*., 2016). However, it should also be noted that there is no absolute correlation between the aggressive SPN and Ki-67 >4%. Due to the long course of SPNs progression, closely long-term follow-up is required for SPN patients with either aggressive behavior or elevated Ki-67 expression.

CONCLUSION

SPNs of pancreas frequently arise in young women, most of which are low-grade malignant tumors with favorable prognosis. No clinical imaging features are available for predicting aggressive SPNs currently. Therefore, aggressive surgical resection and preservation of peripheral organs' function remain the preferred treatment. In addition, aggressive SPNs, especially vessels invasion and Ki-67 >4% are the independent factors correlated with distant metastases after SPNs surgery. Such patients require closer follow-up postoperatively.

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