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Management of solid pseudopapillary neoplasms of pancreas: A single center experience of 243 consecutive patients

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ABSTRACT

Background: Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare neoplasm, which mainly affects young women. The aim of this study was to investigate the clinicopathological features and surgical management of SPNs in our institution.

Methods: Patients who underwent surgery for a pathologically confirmed SPN in our institution between January 2008 and October 2018 were collected. Their clinical characteristics and survival associations were analyzed.

Results: In total, 243 pathologically confirmed patients were analyzed in this study, including 181(74.5%) females and 62(25.5%) males. The mean age was 35.3 years old (range: 12–64 years old) with average tumor size of 4.83 cm (range: 0.8–16 cm). 239 patients underwent complete surgical resection. After median follow-up of 46 months (range: 10–118 months), four patients died due to tumor progression. All the other people were absent of local recurrence or distant metastasis.

Conclusions: SPN is a latent malignant tumor with excellent prognosis. Surgical resection is recommended even in the presence of liver metastasis. If possible, function-preserving surgery is advocated. High Ki67 index may predict the malignant potential and poor prognosis of SPNs.

Introduction

Solid pseudopapillary neoplasm (SPN) of pancreas is a rare neoplasm accounting for only 1%–2% of exocrine pancreatic tumors, which was first described by Frantz in 1959 [1]. SPN mainly affects young women and exhibits relatively indolent biological behavior with a favorable prognosis. The World Health Organization (WHO) classified these tumors as solid pseudopapillary tumors (SPTs) in 1996 and reclassified them as solid pseudopapillary neoplasms (SPNs) in 2010 [2]. Owing to its rarity, the natural history of SPN has not been clearly defined. Most available data about the diagnosis and treatment of SPN are mostly confined to case reports or small case series. However, despite generally consistent clinical and pathological characterizations, some controversies remain to be discussed.

Herein, the aim of this study was to further examine the clinicopathological features, treatment and outcome of this relatively large cohort of patients treated for SPN in our institution.

Materials and methods

Study population

From January 2008 to October 2018, 243 consecutive patients pathologically confirmed with SPN at the department of pancreatic surgery, Fudan University Shanghai Cancer Center were retrospectively reviewed. Clinical presentation, lab test, imaging details, surgical data, pathological characteristics, and follow-up

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information were collected and analyzed. Written informed consent was obtained from all the study participants. The study was approved by the Ethics Committee of our hospital. Pathological diagnosis was confirmed by two senior pathologists independently.

Statistical analysis

Statistical analysis was conducted using SPSS, version 21 (SPSS Inc., Chicago, IL). Demographic and clinical features were described as median (range) for continuous variables and as percentages for categorical variables. Means for baseline variables of interest were compared using independent sample t-tests or chi-squared tests. All tests were two-sided and tests with $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics

The 243 patients included 181 females (74.5%) and 62 (25.5%) males, the female-to-male ratio was 3:1. The mean age in all was 35.3 years (range 12–64), and for female and male was 34.7 years (range 12–60) and 37.2 years (range 15–64) respectively. Most patients were asymptomatic and diagnosed during routine physical examination (154, 63.4%). The most common clinical presentation was abdominal pain (46, 18.9%), and then abdominal discomfort (20, 8.2%), abdominal distension (15, 6.2%). The others were nonspecific and rare, including back pain (2, 0.8%), fever (1, 0.4%), weight loss (1, 0.4%), jaundice (1, 0.4%), nausea (1, 0.4%) and recurrence (2, 0.8%). The average tumor size was 4.83 cm in diameter (range 0.8–16 cm). Most tumors were located in the body and/or tail (149, 61.3%), including 2 with liver metastasis; 91 (37.4%) tumors were located in the head and neck and (2, 0.8%) were located in the retroperitoneum, including 1 primary and 1 recurrent tumor, the other recurrent patient was in the liver (1, 0.4%). Notably, one patient was diagnosed with nasopharyngeal carcinoma simultaneously, and one patient was pathologically confirmed with neuroendocrine tumor (G1) simultaneously. The clinical features of the 243 patients are listed in Table 1.

Preoperative diagnoses

Diagnosis of SPNs is often made incidentally during regular physical examination, or at other imaging studies. Laboratory values usually are not contributory. Tumor markers, such as CA 19–9, CA 125, CEA were almost in the normal range. Only 9 (3.7%) patients in our series presented with a slight elevation of CA19-9. However, the value of CA 72–4 was higher than normal range in 21 (8.6%) patients. On radiological examination, SPNs usually demonstrate a solid and cystic tumor with well-circumscribed capsule. Typically, solid components enhance with pancreatic parenchyma on arterial and venous phases. Intratumoral calcification was present in 71 (29.2%) patients. Additionally, only 25 (10.3%) cases presented with dilatation of the upstream pancreatic main duct. PET/CT scan was performed in 24 patients in our series. 15 of them demonstrated elevated SUV_{max} and 9 were normal. EUS was also performed in 22 patients. The findings of EUS were relatively nonspecific. Among them, 4 patients received EUS-FNA. Two patients were diagnosed to be SPNs with pathological confirmation, the other two were suggested unlikely to be a typical adenocarcinoma. At initial presentation, local invasion was rare. Only two patients were found to be presented with synchronous liver metastasis.

Surgical data

All 243 patients underwent surgical resection, among which 239 patients underwent complete surgical resection. The patient diagnosed with double tumor received treatment of nasopharyngeal carcinoma first. The surgical procedures included pancreaticoduodenectomy (Whipple, 50, 20.6%), pylorus-preserving pancreaticoduodenectomy (11, 4.5%), distal pancreatectomy with spleenectomy (127, 52.3%), spleen-preserving distal pancreatectomy (22, 9.1%), central pancreatectomy (16, 6.6%), tumor enucleation (9, 3.7%), total pancreatectomy resection (3, 1.2%), resection of retroperitoneum tumor (1, 0.4%). Simultaneous metastasectomy of the liver were performed in the two patients with liver metastasis. The other 2 patients who were recurrent in the liver and retroperitoneum received partial hepatectomy and resection of retroperitoneum tumor. Laparoscopic operations were performed in 30

Table 1
Clinicopathological characteristics of patients with SPNs(n = 243).

Clinical characteristics		n	%
Age	1–18	12	4.9
	19–50	203	83.5
	≥50	28	11.5
Gender	Male	62	25.5
	Female	181	74.5
Symptoms	Asymptomatic	154	63.4
	Abdominal pain	46	18.9
	Abdominal distension	15	6.2
	Discomfort	20	8.2
	Recurrence	2	0.8
	Others	6	2.4
Localization	Head	64	26.3
	Neck	27	11.1
	Body	70	28.8
	Tail	79	32.5
	Retroperitoneum	2	0.8
	liver	1	0.4
Pancreatic duct dilation		25	10.3
Calcification		71	29.2
Peripheral aggression		14	5.8
Nerve invasion		23	9.5
Vascular invasion		8	3.3
LN metastasis		2	0.8

cases, including 28 laparoscopic distal pancreatectomy (LDP) and 2 laparoscopic pancreaticoduodenectomy (LPD). There were no surgical residuals in all patients. Postoperative recovery was uneventful. The surgical procedures of the 243 patients are listed in Table 2.

Pathological and immunohistochemistry features

Grossly, most SPNs are well circumscribed. The mean size of the tumor was 4.83 cm. The cut surface usually shows large spongy areas of hemorrhage alternating with both solid and cystic degeneration. Microscopically, no tumor residuals were detected in the margin. Vascular invasion was detected in 8 (3.3%) patients and perineural invasion was detected in 23 (9.5%) patients. All dissected enlarged lymph nodes were confirmed to be benign or reactive hyperplasia pathologically, except in the two patients with synchronous liver metastasis (Table 1).

Immunohistochemical studies were performed in most cases. Results were typically positive for vimentin (Vim, 71/72, 98.6%), β-catenin (214/219, 97.7%), progesterone receptor (PR, 190/199, 95.5%), synaptophysin (Syn, 163/200, 81.5%), CD56 (92/98, 93.9%), neuronspecific enolase (NSE, 19/20, 95.0%), CD10 (155/162, 95.7%). In addition, AE1/AE3 was detected positive in 159/205 (77.6%), CD99 in 129/167 (77.2%), α-ACT in 17/18 (94.4%), CAM5.2 in 11/11 (100%), α-AT in 20/20 (100%). On the opposite, results were typically negative for chromaffin granule protein A (CgA, 182/200, 91.0%), estrogen receptor (ER, 10/11, 90.9), insulin (15/15, 100%), Trypsin (64/64, 100%), SSTR2 (38/44, 86.4%), Chymotrypsin (28/28, 100%), Chromogranin A (15/15, 100%), Synaptophysin (11/11, 100%). Ki-67 was detected in 213 patients, 107 (50.2%) with index ≤1%, 38(17.8%)with index 1–2%, 54(25.4%) with index 2–5%, 6(2.8%)with index 5–10%. Ki67 of 30% was detected in two patients,one with synchronous liver metastasis and the other with retroperitoneum recurrence. The immunohistochemical features of the tumors were listed in Table 3.

Follow-up

The median follow-up period was 46 months (range: 10–118 months). Routine laboratory tests, abdominal US and CT/MRI were performed every 3–6 months. In total four patients developed recurrence including the two patients with synchronous liver metastasis. After imaging evaluation, two received re-operation. The other two rejected further surgery. They died of tumor progression with overall survival time of 52, 43, 38 and 21 months separately. The 1-, 3-, 5-year survival rate was 100%, 99.6% and 98.4% respectively in our institution. All the other patients were absent of local recurrence or distant metastasis.

Discussion

According to previous reports, solid pseudopapillary neoplasms (SPNs) consist 0.3–2.7% of all pancreatic tumors, and their diagnosis have recently been increasing steadily with more than 60% of total cases reported in the last decade [3–5]. Therefore the clinicopathological features of the disease and its management becomes more and more important. Clinically, most studies reported that SPNs predominantly affected young female patients [4,6]. However, in our relatively larger patient cohort, the female-to-male ratio was 3:1, indicating the difference of incidence rates between different races and the incidence rate of male patients is rising. Machado and colleagues showed that age at the time of diagnosis was older among male than female patients [7]. Although, the average age was also older among male (37.2) than female (34.7) in our study, no statistical difference ($P = 0.119$) was found between them. SPNs occur more frequently in the body and tail of the pancreas. Extrapancreatic location is extremely rare and is related mainly to the ectopic pancreatic tissue in the omentum or the mesocolon [8]. Hibi and colleagues described a very unusual case of SPT, which developed in the greater omentum and metastasized initially to the liver, followed by repetitive intraabdominal recurrence [9]. In our cohort, two patients developed in the retroperitoneum. During the follow-up, one young female developed similar repetitive intraabodominal recurrence and followed by repetitive surgery. Therefore, SPNs arising outside the pancreas might indicate a more lethal subgroup [9].

Preoperatively, most patients are asymptomatic and diagnosis was often made incidentally during regular abdominal examination. The value of preoperative tumor markers is limited. Tumor markers, such as CA19-9 and carcinoembryonic antigen (CEA), are almost normal, however the value of CA 72–4 was more frequently higher than normal range in 21 (8.6%) patients. Imaging evaluation like multiphasic enhanced computed tomography (CT) or magnetic resonance imaging (MRI) could differentiate most typical SPNs from other pancreatic tumors [10]. Due to its asymptomatic feature, the tumors were usually large when diagnosed, and brought extensive psychological stress to patients. However, although the average tumor size was 4.83 cm, tumors less than 2 cm still accounted for 10.3% in our study. This may be contributed to the more frequently regular examination of people in recent years. Such small SPNs can sometimes mimic pancreatic adenocarcinoma. Besides, SPNs often resemble pancreatic neuroendocrine tumor both in histomorphology and immunophenotype, and should be identified carefully, but sometimes they can exist simultaneously.

Table 2
Surgical procedures of SPNs (n = 243).

Procedures	Number of patients
Whipple	50 (20.6%)
PPPD	11 (4.5%)
Distal pancreatectomy	129 (53.1%)
Spleen preserving distal pancreatectomy	22 (9.1%)
Central pancreatectomy	16 (6.6%)
Enucleation	9 (3.7%)
Total pancreatectomy	3 (1.2%)
Other	3 (1.2%)

Table 3
Immunohistochemical profile of SPNs.

Antigen	Total number	Positive(%)	Negative(%)
β-catenin	219	214 (97.7)	5 (2.1)
CgA	200	18 (9.0)	182 (91.0)
PR	199	190 (95.5)	9 (4.7)
Vim	72	71 (98.6)	1 (1.4)
NSE	20	19 (95.0)	1 (5.0)
Syn	200	163 (81.5)	37 (18.5)
CD56	98	92 (93.9)	6 (6.1)
CD10	162	155 (95.7)	7 (4.3)
AE1/AE3	205	159 (77.6)	46 (22.4)
CD99	167	129 (77.2)	38 (22.8)
ER	11	1 (9.1)	10 (90.9)
insulin	15	0 (0)	15 (100)
a-AT	20	20 (100)	0 (0)
α-ACT	18	17 (94.4)	1 (5.6)
CAM5.2	11	11(100)	0(0)
Trypsin	64	0(0)	64 (100)
SSTR2	44	6 (13.6)	38 (86.4)
Chymotrypsin	28	0(0)	28(100)
Chromogranin A	15	0 (0)	15 (100)
Synaptophysin	11	11 (100)	0 (0)

Fine-needle aspiration cytology therefore may be useful in obtaining the diagnosis. Due to the limited specimen of EUS-FNA, the preoperative accuracy was not consistent among different reports. Butte et al. reported on 45 patients, 18 of whom had preoperative biopsy, with a diagnostic accuracy of only 56% [11], while Lubezky et al. reported the sensitivity and specificity of the EUS-FNA was 90.9% and 100% respectively [12]. In our cohort, only 4 patients underwent EUS-FNA, and 2 (50%) was pathologically confirmed. Therefore, preoperative biopsy of the tumor is not recommended to perform routinely, and EUS-FNA will only be recommended for those unresectable cases.

Surgically, more than 95% patients can be resected completely. As the tumor is usually diagnosed in young adults and exhibits relatively indolent behavior, postoperative quality of life should be taken into consideration. Therefore, function-preserving surgery is advocated to maintain the function of pancreas, as well as the adjacent organs. For example, PPPD can be performed in patients with a tumor in the head of the pancreas, and tumors in the tail can be treated with spleen-preserving distal pancreatectomy, and tumors in the neck or body of the pancreas can be managed by enucleation or central pancreatectomy to reserve as more pancreatic parenchyma as possible, as there are reports that the insufficient resident volume of pancreas was associated with endocrine and exocrine insufficiency [13]. Besides, laparoscopic surgery is recommended. However, function-preserving surgeries, especially central pancreatectomy and laparoscopic surgeries should be restricted to specialized high-volume pancreatic centers, as the higher risks of postoperative complications and the importance of experience based on center volume to perform such complex operations [13–15]. Extensive lymphatic dissection is not necessary, as lymph node metastasis of SPN is extremely rare [12]. For the minority patients with local invasion or even liver metastasis, aggressive surgery is supported. As showed in our previous report, complete resection of both the primary tumor and the metastases are advocated whenever possible. In the cases of local recurrence or distant metastases, second surgery is justified [16]. There are reports of liver transplantation for unresectable metastatic SPNs, however all the reports are case report and the experience in this area is quite limited [17,18].

Postoperatively, recurrence after radical resection of a SPN can occur in 2%–10% of cases [2,4]. Only 4 patients (4/243, 1.6%) developed recurrence after surgery in our cohort, including the two cases with synchronous liver metastasis at initial presentation. Many studies have tried to predict its malignant potential with clinicopathological factors. Lee and colleagues suggested that calcification was more frequently observed in malignant SPN [19]. Kang et al. reported in a multicenter analysis in Korea that a tumor size larger than 8 cm, microscopic malignant features and stage IV were significant prognostic factors for tumor recurrence [4]. Huffman et al. reported that female sex, resection of primary tumor, and absence of metastasis were correlated with improved survival [2]. However, all these associations were not observed in our study. Our findings indicate that high Ki-67 index may correlate with the malignancy and poor outcome of SPNs, which is in consistent with previous study [20,21]. The accumulation of large-scale clinical data is still required to support this view. Although, according to the WHO criteria, angioinvasion, extrapancreatic invasion, perineural invasion, or pancreatic parenchymal invasion are indicators of malignant behavior of SPN on postoperative pathological tissues. In spite of this, many studies failed to identify patients who may develop local recurrence or distant metastasis following primary surgery with clinicopathological features [22]. Actually, asynchronous metastatic disease after surgery is rare. Metastatic disease was mostly identified synchronously at the time of initial presentation. In cases of unresectable tumour or recurrent disease, adjuvant radio- or chemotherapy should be considered [16,23]. Although a few individual attempts have been reported, there is no consensus of standard chemotherapy regimens for the unresectable or recurrent SPNs. In considering any of these treatments, it is important to bear in mind that patients may have a good quality of life for many years without any treatment at all. Patients with unresectable tumors who survived more than 10 years after surgery have been reported, since the doubling time of this tumor appears to be slow (765 days) [24]. The prognosis of SPN patients was good with a 5-year survival rate of 96.9%. The estimated 1-, 3- and 5-year survival rate was 99.4%, 97.5%, and 96.9% respectively [25].

Biologically, most SPNs are indolent. SPNs generally exhibit a benign course and a low malignant potential. The origin of SPNs is still unclear. Ductal, exocrine [26], genital ridge/ovarian anlage-related cells [27], as well as stem cells [28] have been hypothesized as the origin of the tumor. Some studies report that sex hormone may play a role in the development of SPNs, because SPNs predominantly affect women at the beginning of their reproductive period. Progesterone receptors are present in more than 80% of cases, whereas oestrogen receptors are absent, indicating that abnormal activation of the progesterone pathway may contribute to the disease [29]. Indeed, during pregnancy, progesterone levels elevated dramatically. Spontaneous rupture of a pancreatic SPN in a pregnant woman has been reported [30]. Therefore, some surgeons recommend immediate surgical resection during pregnancy. However, Yee reported a case where close monitoring for tumor growth was done during pregnancy and a successful pancreaticoduodenectomy was performed after term delivery [31]. Besides, no differences in immunohistochemical stains for sex hormone receptors had been found attributable to gender alone [32]. Therefore, link between elevated progesterone levels and tumor growth has not been established. The effect of tamoxifen for patients with positive oestrogen receptor is limited. Only isolated case has been reported to be successful [33]. Further investigations into the role of progesterone or other sex hormones in the development of SPN are needed.

Genetically, in contrast to pancreatic ductal adenocarcinoma, SPN is not associated with changes in KRAS, p53, CNKN2A/p16 or SMAD4 genes [34]. A recent report summarized several pathways involved in the pathophysiology of SPN, including Wnt/β-catenin pathway, Hedgehog, Notch and Androgen receptor signaling pathways. However, no implications have been extensively explored, maybe because of the satisfying prognosis in almost all patients. So far, no familial occurrence of SPN has been reported.

In conclusion, our report is the first large enough single center study to demonstrate that most SPNs are biologically indolent and can be resected completely. Given the excellent prognosis and indolent behavior, function-preserving surgery is advocated. Aggressive surgery is justified as long as the metastatic disease involvement is limited.

Conflicts of interest

No potential conflicts of interest were disclosed.

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