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Original Article

Peripancreatic lymphadenopathy on preoperative radiologic images predicts malignancy in pancreatic solid pseudopapillary neoplasm

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Abstract: Objective: To identify clinicopathological characters and risk factors of malignant pancreatic solid pseudopapillary neoplasm (SPN). Methods: All patients with complete clinicopathological records who underwent surgery for SPN between 2000 and 2010 were retrospective reviewed. Furthermore, we reviewed and classified the histopathology slides of all patients according to the 2010 World Health Organization criteria. Results: Of the 10 0 patients identified, 84 (84.0%) were female, and the median age was 31 (range, 13-68) years old. Median tumor size was 6.5 (range, 1.5-18) cm. Twenty-four patients (24.0%) were classified to have malignant SPN. Forty-nine patients had lymph node removed in surgery, and four (8.2%) had nodal metastases. On univariate analysis, peripancreatic lymphadenopathy on preoperative computed tomography (CT) and/or magnetic resonance (MR) images was significant risk factor of malignancy (P = 0.025). In the long-term follow up, two patients had evidence of liver metastases and underwent a second laparotomy for metastatic tumor. These two patients were followed up for 24 and 32 months respectively, and never presented with tumor recurrence again. Conclusions: Peripancreatic lymphadenopathy on preoperative radiologic images was associated with malignancy in patients with SPN. Close follow-up and review periodically were recommended for patients with malignant SPN.

Keywords: Pancreas, solid pseudopapillary neoplasm, surgery, malignant tumor

Introduction

Solid pseudopapillary neoplasm (SPN) of pancreas is a rare tumor that accounts for approximately 1-2 percent of all pancreatic neoplasms [1]. The World Health Organization (WHO) classified SPN as a potential malignant neoplasm in 2010 [2].

The incidence is increasing because of better recognition and improved radiologic imaging techniques of this neoplasm [3].

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 [4]. However, because of the rarity of the disease, the risk factors of malignancy in SPN patients are still unpredictable. Therefore, this study aims to investigate risk factors of malignant SPN and to explore the optimal surgical strategy.

Patients and methods

Patients

From January 1999 to December 2010, a total of 100 patients with complete clinicopathological records were histopathologically diagnosed with SPN at the Department of Pancreatic Tumor, Cancer Institute & Hospital of Chinese Academy of Medical Sciences (China). Patients who underwent primary operation for distant metastases in other hospitals were excluded. Demographic and clinicopathological data were collected by retrospective review of the medical records. All patients underwent enhanced computed tomography (CT) and/or magnetic resonance (MR) imaging. Other preoperative examinations included ultrasonography and endo-

scopic ultrasonography (EUS) was carried out in selected patients where there was uncertainty about the diagnosis. To assess the risk factors of malignancy, two imaging physicians independently reviewed preoperative CT/MR images of all patients. Tumor features, including solid or cystic, calcification, hemorrhage, and peripancreatic lymphadenopathy were evaluated. Levels of serum tumor makers, such as the carbohydrate antigen 19-9 (CA19-9), were examined before surgery.

All patients underwent routine CT/MR every 6 months to 1 year after surgery. Follow-up data were collected from patients' clinical records or contact with patients' relatives by telephone or fax. The date of last follow-up was April 2015. The mean follow-up time for SPN patients was 78.3 (range, 41-131) months.

Surgical management

All patients underwent curative surgery. Pancreatectomy was taken by either laparotomy or laparoscope-assisted approach. The organ-preserving surgery was applied whenever possible, especially the spleen-preserving distal pancreatectomy. If necessary, intraoperative ultrasonography was used to exclude multifocal tumor. Criterions for local resection of SPN were absence of the main pancreatic duct involvement and peripancreatic enlarged lymph nodes. The lymphadenectomy were adopted when suspicion of malignant SPN on preoperative CT/MR or lymphadenopathy found during surgery. A curative surgery was defined as en-bloc resection without positive margins (R0 resection).

Pathologic analysis

The WHO classified angioinvasion, extrapancreatic invasion, perineural invasion, or pancreatic parenchymal invasion as indicators of malignant behavior of SPN [4]. For quality control, the histopathological slides of patients diagnosed before 2010 was reviewed by pathologists to redefine the malignancy according to the 2010 WHO classification [2] and the American Joint Committee on Cancer (AJCC) seventh classification system [5]. Independent pathological assessments were made of tumor location, size, resection margin status, growth pattern, vascular invasion, perineural invasion, and cellular atypia. All patients were assessed by immunohistochemical staining to confirm the diagnosis.

Statistical analysis

Unless indicated otherwise, continuous data are presented as median (IQR, interquartile range) and analyzed by the Mann-Whitney *U* test or independent *t* test, as appropriate. The χ^2 test, Fisher's exact tests and Cochran-Mantel-Haenszel test were used to perform comparisons of categorical data. Statistical significance was accepted at $P < 0.05$. All statistical analysis was done using SAS 9.3 (SAS Institute Inc., Kerry, NC, USA).

Results

Clinicopathological outcomes

The cohort contained 16 men and 84 women, a male-to-female ratio of 1:5.25. The median age of patients was 31 (range, 13-68) years old at the time of SPN diagnosis. Fifty-three patients (53%) of the SPN were asymptomatic and were detected incidentally. Eighty-six patients (81.1%) were correctly diagnosed by preoperative imaging and eight neoplasms (9.3%) were suspected to be malignant. Among these lesions, 35, 15, and 50 were located in the head, neck, body and tail of the pancreas, respectively.

All patients underwent resection with curative intent. The surgical procedure performed depended on the location of tumors: 24 patients underwent pancreaticoduodenectomy (the Whipple procedure); 33 subjects had distal pancreatectomy with splenectomy and 43 patients underwent other procedures, including local resection, duodenum-preserving pancreatic head resection, central pancreatectomy, spleen-preserving distal pancreatectomy, and combined organs resection. Two patients with liver metastases received synchronous resection of primary tumor and metastatic liver tumor. Three patients received en-bloc resection of adjacent structures with suspicion of local tumor invasion, including one superior mesenteric vein resection, one segmental transverse colonic resection, and one left adrenalectomy. Forty-nine patients (49.0%) received lymphadenectomy and the median number of dissected lymph nodes was 8 (2-21). A total of 50 patients (50%) underwent lymphadenectomy, whereas only 3 individuals (6%) had metastatic lymph nodes.

A total of 24 patients (24.0%) had SPNs with histological findings of malignancy based on

Table 1. Demographic and clinical features of the entire cohort and patients with malignant SPN

	No. of the entire cohort (n = 100)	No. of patients with malignant SPN (n = 24)	%
Age (years, median, range)	31 (13-68)	32 (14-66)	
Sex			
Male	16	2	8.3
Female	84	22	91.7
Symptoms			
With	47	14	58.3
Without	53	10	41.7
Tumor location			
Head and uncinate	35	11	45.8
Neck	15	2	8.4
Body and tail	50	11	45.8
Tumor diameter (cm, average, range)	6.5 (1.5-18)	6.5 (1.5-15)	
pT*			
T1	3	1	4.2
T2	66	10	41.6
T3	31	13	54.2
Distant metastases			
Yes	2	2	8.3
No	98	22	91.7
Tumor feature			
Solid and cystic	86	21	87.5
Solid	14	3	12.5
Surgical treatment			
Pancreaticoduodenectomy (Whipple)	24	8	33.3
Duodenum-preserving pancreatic head resection	5	1	4.2
Central pancreatectomy	8	1	4.2
Distal pancreatectomy with splenectomy	33	7	29.2
Spleen-preserving distal pancreatectomy	10	2	8.3
Local resection	15	0	0
Combined organs resection	5	5	20.8
Outcome			
Alive	98	22	91.7
Dead	2	2	8.3
Follow-up (months, median, range)	78 (41-131)	87 (52-131)	

*Tumor stage was defined according to the 7th AJCC TNM staging system.

the 2010 WHO histological criteria [2]. Demographic and clinical characteristics of the whole cohort and patients with malignant SPN are summarized in **Table 1**.

Analysis of risk factors in patients with malignant SPN

Of the 24 patients with malignant SPN, 22 patients had peripancreatic tissue invasion (91.7%), followed by vascular invasion with tumor thrombus (9 patients, 37.5%), perineural invasion (7 patients, 29.2%), adjacent organs invasion (1 patient, 4.2%), and liver metastasis (1 patients, 4.2%). Thirteen of the 24 patients with malignant SPN were T3 according to the AJCC tumor node metastasis (TNM) staging system [5]. All four patients with lymph node metastases were identified in malignant SPN group.

To assess the clinical factors predictive of malignant SPN, clinicopathological characteristics were compared between patients with

Table 2. Analysis of risk factors in patients with malignant SPN according to the 2010 WHO classification

	No. of Benign SPN (n = 76)	No. of Malignant SPN (n = 24)	P*
Sex			0.345#
Male	14	2	
Female	62	22	
Age (years)			0.726#
≤ 50	66	22	
> 50	10	2	
Symptoms			0.202
Yes	33	14	
No	43	10	
Tumor location			0.349
Head and uncinate	24	11	
Neck	13	2	
Body and tail	39	11	
Tumor calcification			0.824
Yes	24	7	
No	52	17	
Tumor diameter (cm)			0.561
≤ 5	40	11	
> 5	36	13	
pT			0.016†
T1	2	1	
T2	56	10	
T3	18	13	
Tumor feature			1.000
Solid and cystic	65	21	
Solid	11	3	
Tumor hemorrhage			0.430
Yes	54	15	
No	22	9	
Peripancreatic lymphadenopathy			0.025
Yes	14	21	
No	62	2	
CA19-9			0.616
≤ 37.0	73	22	
> 37.0	3	2	

*χ^2 test, except #Fisher's exact test, †Cochran-Mantel-Haenszel test.

benign lesions and those with malignant neoplasms. On univariate analysis, peripancreatic lymphadenopathy on preoperative CT/MR images was significant risk factor of malignancy (P = 0.025). However, none of the other clinicopathological factors, including age, sex, tumor location, tumor diameter, increased CA19-9 or tumor features (solid or cystic, calcification, and hemorrhage) was significant predictive factors of malignancy (All P > 0.05). The comparison of clinicopathological characteristics between malignant and benign SPN are summarized in **Table 2**.

Long-term survival of patients

The follow-up data showed a median survival time of 78 months, ranging from 41-131 months after the time of surgery; the actual 3- and 5-year survival rates were 99% and 98%, respectively. One patient underwent distal pancreatectomy with splenectomy and died of multiple organs function failure 28 months after surgery. Another patient occurred tumor recurrence 4 years after surgery and died of tumor hemorrhage 3 months later. Both of these two patients were diagnosed with malignant SPN. There was statistically significant difference between the benign and malignant groups (P = 0.0138). The survival curves of patients with malignant or benign SPN are shown in **Figure 1**.

Two patients (2%) suffered from distant metastases after surgery. One patient who underwent distal pancreatectomy and splenectomy developed liver metastases 36 months after surgery. The other patient who underwent pancreaticoduodenectomy developed isolated liver metastases 28 months after the first surgery. These two patients underwent a second laparotomy for metastatic tumor. They werefollowed up for 24 and 32 months respectively, and never presented with tumor recurrence again. In the long-term following-up, 9 patients presented post-surgical dyspepsia and 5 patients suffered from insulin-dependent diabetes.

Discussion

SPN is a rare neoplasm of the pancreas, only accounting for 1%-2% of all pancreatic tumors

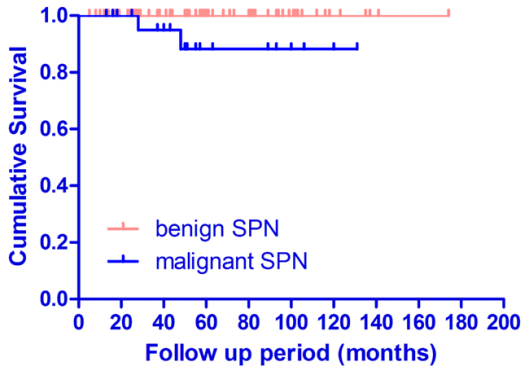

Figure 1. Survival curves, and comparison of cumulative survival rates after surgery, according to benign or malignancy of SPN. There was statistically significant difference between these two groups (P = 0.0138).

and 6% to 12% of pancreatic cystic tumors [1]. Most patients of SPN are young female [6], with a male-to-female ratio of 1:5.25 and median age of 31 in our cohort. The molecular events associated with the development of SPN have recently been discovered. SPN is characterized by activating β-catenin gene mutations, which interfere with protein phosphorylation [7]. Translocation of β-catenin into the nucleus regulates the transcription of the growth regulatory genes cyclin D1 and c-myc. Furthermore, β-catenin interacts with E-cadherin, preventing normal cell- to-cell interactions [8].

Most of the patients, especially patients without symptoms, are diagnosed by radiologic imaging. In general, SPN is diagnosed by CT or MR, which shows the presence of a heterogeneously enhanced solid and cystic mass with relatively clear margin [9]. Other preoperative examinations, such as the EUS or endoscopic retrograde cholangiopancreatography (ERCP) can be helpful to exclude multi-foci neoplasm or possible invasion of the main pancreatic duct [10]. Because of limited data and the possibility of peritoneal seeding, the use of endoscopic ultrasonography with fine-needle aspiration (EUS-FNA) on SPN is still contraindicated [11].

The WHO defined angioinvasion, extrapancreatic invasion, perineural invasion, or pancreatic parenchymal invasion as malignant behavior of SPN on postoperative pathological tissues [4]. However, because of the rarity of the disease, the risk factors of malignancy in SPN patients are still unpredictable. In this study, we defined preoperative lymphadenopathy on CT/MR was significant risk factor of malignancy (P = 0.025). Furthermore, none of the clinicopathological factors, including age, sex, tumor location, tumor diameter, increased CA19-9 or tumor features (solid or cystic, calcification, and hemorrhage) was significant predictive factors of malignancy (All P > 0.05). Tumor markers, such as CA19-9 and carcinoembryonic antigen (CEA), were always normal [12]. Only five patients in our series presented a slight elevation of CA19-9. On univariate analysis, increased level of serum CA19-9 was not significant predictive factor of malignant SPN (P = 0.616).

To achieve a radical resection, synchronous combined adjacent organs resection or en-bloc resection of superior mesenteric vein-portal vein could be performed [13]. Our series included three patients who received resection of adjacent structures, including one synchronous superior mesenteric vein resection, one case of transverse colon involvement, and one case of left adrenal invasion. At the time of our follow-up, the patient who underwent synchronous en-bloc resection of superior mesenteric vein remains alive without tumor recurrence. For the two patients with liver metastases, we performed synchronous resection of primary tumor plus wedge resection of the metastatic liver tumor, resulting in good survival. Due to low-grade malignancy and the surrounding dense fibrous capsule, local resection is indicated for smaller tumors distant from the main pancreatic duct, without affecting long-term survival [14].

In general, routine lymphadenectomy is not recommended because the incidence of metastatic lymph node is rare [15]. However, there is still no consensus on the necessity of lymphadenectomy for SPN. Other reports have also notified that lymph node recurrence may occur in patients with SPN even several years after first surgery [16]. Thus, these studies recommended radical resection with routine lymphadenectomy [17]. In our cohort, we found that peripancreatic lymphadenopathy on preoperative radiologic images was associated with malignancy in SPN. Moreover, four of our postoperative pathology specimens showed metastatic lymph nodes, and all of these patients had malignant SPN. So we still think that routine

lymphadenectomy should be adopted when lymphadenopathy found or suspicion of malignant SPN on preoperative CT/MR imaging.

Tumor recurrence or distant metastases may happen in 5% of SPN patients after radical resection [18], whereas only two patients (1.7%) suffered from distant metastases in our series. Some other studies reported that metastasis of SPN typically occurs in liver, lung and peritoneum [19]. We support the view that patients with local recurrence or distant metastases could still be treated by second surgery. Patients with SPN undergoing surgical resection achieved good long-term survival. In our cohort, the two patients who suffered from liver metastases all underwent second resection and achieved a 24 and 32 months disease-free period during the follow-up, respectively. In patients with inoperable liver metastases, liver transplantation or radiofrequency ablation (RFA) could be performed [20]. Although the use of chemotherapy or radiotherapy on patients with unresectable SPN has been reported, the value of these treatments is still controversial [21].

In conclusion, adequate operative resection is the mainstay of SPN treatment. The peripancreatic lymphadenopathy on preoperative radiologic images was associated with malignancy in patients with SPN. Thus, routine lymphadenectomy is recommended when lymphadenopathy found or suspicion of malignant SPN on preoperative CT/MR imaging. If active operative resection or interventional treatment is performed, long-term survival can be achieved even after recurrence or distant metastases.

Disclosure of Conflict of Interest

None.

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