Original Article

Surveillance and management for serous cystic neoplasms of the pancreas based on total hazards—a multi-center retrospective study from China

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Background: Serous cystic neoplasms (SCN) rarely have malignant potential, so accurate diagnosis of SCN is crucial for proper clinical management, especially to avoid unnecessary surgeries. However, the misdiagnosis of other pancreatic cystic neoplasm instead of SCN may highly increase the risk of malignancy in patients who receive no surgery.

Methods: Data from a total of 678 patients with pathologically confirmed to have SCN at sixteen institutions in China from January 1st, 2006 to December 31st, 2016 were retrieved to evaluate the malignancy risk of SCN.

Results: Among the 678 patients confirmed to have SCN with postoperative pathologic analysis, 649 patients (95.7%) had only one lesion and the average maximum diameter was 3.8±2.47 cm. Four patients were pathologically verified as having serous cystadenocarcinoma, so the SCN actual malignancy rate was 0.6%, while the mortality due to pancreatic surgery in these high-volume centers was nearly 0.2–2%. However, among the 99 SCN patients based on preoperative radiology, three were confirmed to have intraductal papillary mucinous

neoplasms (IPMN), nine as mucinous cystic neoplasms (MCN), and four as solid pseudopapillary tumors (SPT) after postoperative pathological analysis. Thus, the total theoretical malignancy rate resulting from preoperative misdiagnosis was elevated to approximately 2.9%, higher than the risk of perioperative mortality.

Conclusions: When SCN can't be accurately distinguished from cystic tumors of pancreas, the malignant risk of cystic tumors may be higher than perioperative risk. However, if it can be diagnosed as SCN accurately, surgery can be avoided as well.

Keywords: Serous cystic neoplasm; malignancy; surgical treatment; risk

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Introduction

Pancreatic serous cystic neoplasm (SCN) was first reported concurrently by Hodgkinson *et al.* (1) and Compagno and Oertel (2) in 1978. SCN usually appears as a great number of small agminated cysts in a honeycomb arrangement and is abundant in clear, glycogen-rich cells (3); and consists of 10–16% of pancreatic cystic tumor (PCN) cells (4). With rapid advances in cross-sectional imaging technology, SCN is frequently detected, and is commonly thought to be a benign tumor. However, the majority of SCN easily confused in clinical practice with PCN, like mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), and solid pseudopapillary tumor (SPT) that are potentially malignant (5,6). Consensus is still lacking as to whether SCN is necessary for surgical treatment or surveillance strategies.

Considering the potential risk of malignancy and mechanical complications, some centers insist that surgical treatment is necessary for SCN (7,8). Additionally, a few of these SCN patients may have turn out to have pre-malignant or malignant lesions after surgical resection. On the contrary, other medical centers only recommend resection according to guidelines on patients with SCN-relative symptoms or uncertain cyst diagnosis (9). Primary cyst size, macrocystic or oligocystic variant type, growth rate, age and history of other malignancies have been consistently proposed to predict the malignancy of SCN in recent clinical management (6,10). The ideal time point for surgical treatment hasn't yet been established which may lose the optimal opportunity for SCN resection.

In addition, SCN patients undergoing surgical resection may suffer from complications, such as severe pancreatic fistula (PF), delayed gastric emptying (DGE) and so on, the probability of surgical mortality is up to 1.0–2.7% in high-volume centers (11,12). Thus, it is critical to accurately differentiate between SCNs and other non-SCNs to provide proper treatment decisions and maintain a balance between the risk of malignancy and surgical treatment. Previous multi-center research reported that surgical treatment of SCN should be proposed in a minority of patients and only for uncertain diagnoses remaining after complete workup including computed tomography (CT) scan, magnetic resonance imaging (MRI) scan and endoscopic ultrasonography (EUS), significant and related symptoms or exceptionally when concerned that a malignancy exists (6).

However, in some low-income cities or low-volume centers, CT and MRI scans are used instead of EUS due to institutional inexperience with EUS technology so that precise preoperative diagnosis is highly difficult. There is a remarkable trend for other types of PCN to be misdiagnosed with SCN, which may significantly increase the risk of malignancy. Therefore, in our study, two cohorts of SCN patients from multi-centers were analyzed to compare the total risk of malignancy due to radiological misdiagnosis with risk of surgical mortality. This analysis indicated that preoperative radiological diagnosed SCN with limited examinations still has the potential to be administered with surgical treatment.

Methods

Patient population and data source

SCN patients who underwent curative resection in 16 Chinese institutions between January 2006 and December 2016 were retrospectively enrolled in this study. Enhanced abdominal CT or MRI scans were routinely performed before operation. According to their radiological data, number of lesions and tumor characteristics of maximum

diameter, mural nodule, oligocystic or polycystic, enhancing cyst wall, separation, calcification and solid mass were all included in our analysis. The intraoperative situation, postoperative pathology and complications were recorded as well. However, owing to a retrospective essence and total usage of EUS biopsy was less than 20% among all institutes at that time, patients with EUS biopsy before surgery were excluded in this study. Additionally, patients were divided into two cohorts. One cohort included all patients confirmed to have SCN with postoperative pathological analysis, and the other cohort contained all patients diagnosed as SCN with preoperative MRI or CT scan. All SCN patients preoperatively diagnosed with radiology were done in accordance with its radiological characteristics, and all indications for surgery were considered by the attending doctors according to the current domestic guideline at the time and hospital protocol. The ethics committee of Zhongshan Hospital, Fudan University approved this study (B2014-019).

CT and MRI

CT and MRI scans were individually read by radiologists with over 10 years of experience and by pancreatic surgeons with over 5 years of experience to enhance the reliability of imaging diagnosis. The final report was determined after both the radiologist and pancreatic surgeon had separately analyzed the images and then come to an agreement.

Definition of postoperative complications

PF was defined in accordance with criteria published in 2005 by the International Study Group on Pancreatic Fistulas (ISGPF). DGE can be divided into grade A, B, and C according to the definition of the International Study Group on Pancreatic Surgery and sometimes needed to be confirmed by endoscopy or an upper gastrointestinal gastrografin series.

Statistical analysis

All statistical analyses were performed with SPSS 21.0 statistical package (SPSS Inc., Chicago, IL, USA) for Windows. Correlations and differences between categorical or continuous variables were analyzed with Pearson Chi-squared test, Fisher's Exact test or Student's *t*-test. A P value <0.05 was considered as a statistically significant difference.

Results

Clinical characteristics of SCN patients with postoperative pathological diagnosis

From our multi-center data, 678 patients were finally pathologically confirmed as having SCN after resection. As revealed in their preoperative MRI or CT scan (*Table 1*), 649 patients (95.7%) had only one lesion and the average of maximum diameter was 3.80±2.47 cm. Among the whole patients, 27 patients (5.5%) manifested mural nodule, while 15 patients showed enhancing mural nodule. Then 336 patients (68.2%) had oligocystic variant, while 31.8% of patients had polycystic variant. The wall enhancement of cyst existed in 170 patients (33.1%), cystic separation in 227 patients (43.7%), calcification in 72 patients (14.4%) and solid mass in 147 patients (28.9%).

The average of operative time was 243.01±95.64 hours and the average of intraoperative hemorrhage volume was 192.52±204.84 mL. In addition, the optimal surgical procedure was chosen to excise the tumor lesion and 529 patients (84.9%) underwent open surgery. After pathologic analysis, we found that no patients had nerve bundle infiltration or liver metastasis, while 15 patients (2.8%) had peripancreatic fat infiltration, three patients (0.6%) had vascular invasion and two patients (0.4%) had lymph node metastasis (*Table 2*). The average hospital stay was 17.06±12.89 days and the percentage of patients with DGE was 11.8% and five of those patients suffered from DGE of grade C after surgery. PF occurred in 262 patients (44.0%) and four patients had grade C PF, as shown in *Table 3*. Of 678 patients, only four patients had serous cystic carcinoma (SCC), so the actual malignancy rate of SCN was approximately 0.6%.

Clinical characteristics of radiologically diagnosed SCN

Considering to its low malignancy rate, we further analyzed 99 patients diagnosed with SCN after preoperative MRI or CT scan. We found 93.9% of patients had only one lesion and its average maximum diameter was 3.81±1.84 cm. Other radiological characteristics are listed in *Table 1*. Among the whole group, 72 patients (80.0%) accepted open surgery. Only one patient had a positive lymph node exam after pathological examination (*Table 2*); their average hospital stay was 15.02±9.49 days. The percentage of patients with DGE was up to 6.7%, but none had DGE of grade C after surgery. A total of 41 patients had postoperative PF, as

Table 1 Characteristics of preoperative MRI or CT manifestation in SCN patients diagnosed pathologically or radiologically

Variables	Pathologically diagnosed as SCN (n=678)	Radiologically diagnosed as SCN (n=99)
Number of lesions		
1	560	93
2	7	5
3	3	1
>3	15	0
Unknown	93	0
Maximum diameter (cm)	3.80±2.47	3.81±1.84
Mural nodule		
Yes	27	8
No	462	91
Unknown	189	0
Enhancing mural nodule		
Yes	15	5
No	450	94
Unknown	213	0
Oligocystic or polycystic		
Oligocystic variant	336	57
Polycystic variant	157	42
Unknown	185	0
Enhancing cyst wall		
Yes	170	47
No	343	52
Unknown	165	0
Separation		
Yes	227	67
No	293	32
Unknown	158	0
Calcification		
Yes	72	20
No	428	79
Unknown	178	0
Sites of calcification		
Margin	22	4
Centre	48	16
None	10	79
Unknown	598	0
Solid mass		
Yes	147	23
No	362	76
Unknown	169	0

SCN, serous cystic neoplasm.

Table 2 Characteristics of intraoperative observation in SCN patients diagnosed pathologically or radiologically

Variables	Pathologically diagnosed as SCN (n=678)	Radiologically diagnosed as SCN (n=99)
Operative time (h)	243.01±95.64	NA
Intraoperative hemorrhage (mL)	192.52±204.84	NA
Surgical procedures		
PD	92	9
PPPD	59	14
Segmental resection	66	9
Exploratory laparotomy	2	0
Total pancreatectomy	3	0
Distal pancreatectomy	75	7
Distal pancreatosplenectomy	223	37
Medial pancreatectomy	26	0
Tumor exenteration	39	14
Unknown	93	9
Surgical approach		
Laparoscope	94	18
Open	529	72
Unknown	55	9
Nerve bundle infiltration		
Yes	0	0
No	532	90
Unknown	146	9
Peripancreatic fat infiltration		
Yes	15	1
No	517	89
Unknown	146	9
Vascular invasion		
Yes	3	0
No	529	90
Unknown	146	9
Total lymph node examined	2.25±4.37	2.14±3.58
Positive lymph node	0.005±0.095	0.022±0.207
0	553	92
1	1	0
2	1	1
Unknown	123	6
Liver metastasis		
Yes	0	1
No	678	92
Unknown	0	6

SCN, serous cystic neoplasm.

Table 3 Characteristics of postoperative complications in SCN patients diagnosed pathologically or radiologically

Variables	Pathologically diagnosed as SCN (n=678)	Radiologically diagnosed as SCN (n=99)
Hospital stay (Days)	17.06±12.89	15.02±9.49
Blood glucose (POD1)	8.34±3.03	8.24±3.64
Delayed gastric emptying		
Grade A	53	5
Grade B	14	1
Grade C	5	0
None	537	49
Unknown	69	9
Pancreatic fistula		
Grade A	206	36
Grade B	52	5
Grade C	4	0
None	334	49
Unknown	82	9
Pancreatic fistula with infection		
Yes	50	1
No	533	89
Unknown	95	9
Pancreatic fistula with puncture drain		
Yes	10	3
No	573	87
Unknown	95	9
Pancreatic fistula with reoperation		
Yes	4	0
No	579	90
Unknown	95	9
Pancreatic fistula with death		
Yes	1	0
No	582	90
Unknown	95	9
Biliary fistula		
Yes	5	1
No	600	89
Unknown	73	9
VTE		
Yes	2	0
No	604	90
Unknown	72	9

SCN, serous cystic neoplasm.

shown in *Table 3*. However, among these patients, three patients were diagnosed with IPMN, nine with MCN and four with SPT after postoperative pathological examination. The radiological characteristics of these sixteen non-SCN patients showed that enhancing cyst wall was found in five patients, oligocystic variant in eleven patients, separation of cyst in ten patients, calcification in three patients and solid mass in three patients.

Correlation between preoperative radiological characteristics and SCN diagnosis

A total of 99 patients diagnosed with SCN before surgery had diverse radiological characteristics. For example, 16.16% of patients were diagnosed with non-SCN post-operatively via pathological test. To improve diagnostic accuracy preoperatively, we further analyzed the preoperative radiological characteristics between SCN and non-SCN. However, no significant difference in characteristics were found between SCN and non-SCN, including lesion numbers, maximum diameter, mural nodule, oligocystic or polycystic variant, cyst wall, separation, calcification, solid mass, pancreatic atrophy, pancreatitis, MPD connection and MPD dilation (*Table 4*). Therefore, the exact differential diagnosis of SCN by traditional radiological methods before surgery remains difficult.

Development of risk prediction formula

Through a recent survey in China, it showed the malignancy rate of IPMN was nearly 32.1%, MCN was about 10.4% and SPT was approximately 12.3% (13). Thus, we constructed a novel formula, total theoretical risk of malignancy of SCN diagnosis = [32.1%X + 10.4%Y + 12.3%Z + 0.6% (n – X – Y – Z)]/n (X, number of pathological IPMN diagnosis; Y, number of pathological MCN diagnosis; Z, number of pathological SPT diagnosis; n, total patients with preoperative SCN diagnosis). Within the imaging diagnosis of SCN before surgery, the tumors were confirmed by the finial pathological examination as IPMN, MCN, SPT and SCN after surgical resection. However, the different risks of malignancy in these cystic tumors were stated in our previous study (13). So based on risk weight of final pathological diagnosis, this formula was established to calculate the theoretical malignant risk. Through this formula, we calculated a theoretical malignant risk index of 2.9%, which was higher than the surgical

Table 4 The correlation of radiological characteristics between SCN and non-SCN

Variables	SCN (n=83)	Non-SCN (n=16)	P value
Number of lesions			0.249
1	79	14	
≥2	4	2	
Maximum diameter (cm)	3.90±1.83	3.30±1.85	0.259
Mural nodule			1.000
Yes	7	1	
No	76	15	
Enhancing mural nodule			1.000
Yes	4	1	
No	79	15	
Oligocystic or polycystic			0.323
Oligocystic variant	46	11	
Polycystic variant	37	5	
Enhancing cyst wall			0.156
Yes	42	5	
No	41	11	
Separation			0.629
Yes	57	10	
No	26	6	
Calcification			1.000
Yes	17	3	
No	66	13	
Solid mass			0.888
Yes	20	3	
No	63	13	
Pancreatic atrophy			0.701
Yes	5	0	
No	78	16	
Pancreatitis			1.000
Yes	2	0	
No	81	16	
MPD connection			0.414
Yes	2	1	
No	81	15	
MPD dilation			0.365
Yes	9	0	
No	74	16	

SCN, serous cystic neoplasm.

mortality of nearly 0.2–2% in these high-volume centers.. Taken together, our results show that surgical resection should be undertaken depending on limited radiological diagnosis and detailed surgical plan in SCN.

Discussion

Pancreatic cancer deserves more attention as a precancerous lesion that is remarkably malignant with a limited 5-year overall survival (14,15). Pancreatic cysts are differentiated based on their malignant potential, and SCN virtually never progresses to an invasive lesion (16). Currently, however, the management of SCN remains controversial. In our study, the actual malignancy rate of SCN with postoperative pathological diagnosis was just 0.6%, which was lower than the mortality rate of pancreatic surgery. However, SCN diagnosis was inaccurate before surgery as 16 out of 99 SCN patients were finally pathologically diagnosed as non-SCNs. According to their separate malignant potential, the total theoretical malignancy rate of radiological SCN diagnosis was up to 2.9% which was higher than pancreatic surgical mortality. Thus, considering the malignancy rate and surgical mortality, the management of SCN deserves a more careful diagnostic check.

Difficulties in obtaining a precise radiological diagnosis preoperatively, symptoms resulting from SCN involvement, and risk of malignant transformation are considered to be the main arguments for surgical resection (7,8). In contrast, the severe morbidity and mortality of surgery and tumor indolence are powerful arguments supporting a more conservative approach. There is still no consensus on the ideal treatment approach for diagnosed SCN.

Some medical centers selected patients for surgery according to tumor size and growth rates. In a small single center study, tumors less than 4 cm had a slower growth rate than tumors greater than or equal to 4 cm (17). Growth rate was confirmed to be significantly higher for tumors no less than 4 cm in a recent study (6). According to the Japan Pancreas Society, SCN larger than 4 cm was an indication for surgical resection, and pathological findings including papillary proliferation, nuclear atypia, venous invasion, peripancreatic fat tissue infiltration, and lymph vessel invasion were indicative of malignant SCN (3). In addition, some studies reported that symptomatic SCN was also a suitable indicator for surgery, a tumor which was responsible for the symptoms (18).

Some surgeons have advocated for an active, early

surgical strategy for the improvement of pancreatic surgery and risk of complications of an asymptomatic SCN (7). This strategy hinted at the essentiality of evaluating the risk-benefit balance between surgery and follow-up. In some high-volume centers, mortality of surgical strategy was much lower than reported. Furthermore, long-term and short-term morbidity of pancreatic surgery remained high with PF, DGE, diabetes mellitus and/or exocrine pancreatic insufficiency (11,19-21). Therefore, all treatment options should be carefully considered.

Among our data, only 13.7% of SCN patients were diagnosed correctly before surgery at that time, and 55.8% were given only a suggested PCN diagnosis. One reason for the low accuracy was preoperative diagnosis in China employed only MRI or CT scan for routine examination far more than EUS. However, once casually increased preoperative SCN diagnosis at such level, the misdiagnosis rate of other PCNs may severely increase. So only we absolutely make sure the SCN diagnosis, then the misdiagnosis rate may decrease. Clinicians should keep in mind that increased misdiagnosis rate is usually accompanied by increased rough diagnosis of SCN in common volume hospital.

Accurate diagnosis before surgery seemed to be much more significant. If SCN patients can be accurately diagnosed with radiological tests, many of them can avoid pancreatic surgery. On CT scan, SCNs are generally polycystic, and although a sunburst calcification is pathognomonic, only 11% to 30% of tumors are apparent (22,23). MRI scanning can reveal accurate visualizations of the lesions' structure, in particular the presence of septa; but this method lacks sensitivity to calcifications. Magnetic resonance cholangiopancreatography (MRCP) is more popular that gives a better evaluation of spatial relationship between the pancreatic or biliary duct and the lesions to discriminate the differential diagnosis. The absence of communication with the Wirsung duct allows a certain diagnosis of SCN (24). EUS was preliminarily reported to have 82.93% accuracy when used to determine the differential diagnosis between SCN and MCN (5). In addition, previous researches have reported on clinical features and molecular marker panels that showed promise for the accurate classification of PCN and identification of cysts that required surgical treatment in the future (16,25).

Conclusions

We described the specific mortality and natural history of SCNs using a large Chinese cohort from multiple expert centers. Our findings suggested that SCN was almost a completely benign lesion with a malignancy rate was just 0.6%. However, considering its potential misdiagnosis, the total malignancy rate went up to 2.9%, which was higher than the risk of surgical mortality. Thus, a surgical strategy should be considered in a minority of patients based on the patient volume at the institution, surgical skills available and patient conditions. When SCN can't be accurately distinguished from cystic tumors of pancreas, the risk of malignance of cystic tumors may be higher than surgical risk. However, if it can be diagnosed as SCN correctly like using EUS, SCN should not be performed with surgery as well. Only when we pay more attention to such a benign tumor can risk balance between malignancy and surgical mortality be achieved.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The ethics committee of Zhongshan Hospital, Fudan University approved this study (B2014-019).

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