Features and Treatment of Peritoneal Metastases from Solid Pseudopapillary Neoplasms of the Pancreas

ABCF Jianhui Wu
BDE Xiuyun Tian
DEF Bonan Liu
CE Chengpeng Li
ACDG Chunyi Hao

Background: Solid pseudopapillary neoplasms (SPNs) of the pancreas may present widespread peritoneal metastases, but the treatment of this malignancy has not been well described and requires further investigation.

Material/Methods: Four cases of SPN with significant peritoneal metastases in our department were operated and retrospectively summarized after long-term follow-up. Eight more cases of peritoneal metastatic SPN from the PubMed database were also included in the analysis.

Results: Peritoneal metastases of SPNs have different gross features. The benign nodules were tenacious and well encapsulated, while the malignant nodules were soft and prone to slow bleeding. However, neither of these nodules invaded the small intestines or mesentery. Of the 12 disseminated cases, 7 had history of primary tumor rupture, whereas the others had tumors malignant in nature. A total of 14 surgical events were documented, including 3 complete cytoreductive surgeries (CCRS), 9 cytoreductive surgeries (CRS), and 2 debulking surgeries. After follow-up ranging from 0.3 to 6.1 years, the results of the Fisher's exact test showed no difference between CCRS and CRS in treating either low-grade or high-grade malignant SPNs (P=0.257 and P=0.203, respectively). For all cases of SPN with peritoneal metastases, the CCRS procedure could significantly improve tumor-free survival (TFS) compared to the CRS procedure (P=0.046).

Conclusions: SPN rupture could cause significant peritoneal metastases, and either disruption or biopsy of these lesions should be avoided. Peritoneal metastases from SPNs vary both in gross features and biological mechanisms. CCRS may offer optimal therapeutic outcomes and longer TFS for individuals with significant peritoneal metastases of SPNs.

MeSH Keywords: Decompression, Surgical • Peritoneal Neoplasms • Peritoneum

Abbreviations: CRS – cytoreductive surgery; CCRS – complete cytoreductive surgery; PM – peritoneal metastases; SPNs – solid pseudopapillary neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/909363
Background

The incidence of solid pseudopapillary neoplasm (SPN) of the pancreas comprises 0.13% to 2.7% of all pancreatic tumors. It occurs primarily in young women with a male-to-female incidence ratio of approximately 1: 8 [1–3]. In 2010, the WHO Classification of Tumors of the Digestive System redefined SPN as a malignant tumor from its previous definition as a borderline tumor. However, the classification also stressed that SPN should be a low-grade malignant tumor [4]. Surgical resection is the only effective method for treating SPN. To achieve favorable prognosis, surgeons should ensure that the tumor is entirely resected while preserving the functions of the adjacent organs as much as possible [5,6].

SPNs primarily affect adolescents who do not undergo routine medical examinations. Some tumors can grow undetected, and in some cases, accidental trauma can cause the tumors to rupture and result in acute abdominal and peritoneal metastases [7–9]. However, some SPNs do not rupture, especially more aggressive lesions, and could produce peritoneal metastases as well [10,11]. Such cases are rarely reported and summarized. A consensus on the therapeutic management for such conditions has not been established. In this study, 4 patients with SPNs with widespread peritoneal metastases who were treated by our department were detailed and analyzed. The clinicopathological characteristics of the metastases in these cases are unique, with some differences among them. We also analyzed 8 more cases from previously published articles to determine the optimal therapeutic strategies to cure SPNs with widespread peritoneal metastases.

Material and Methods

Clinical data

The clinical records of 4 patients with peritoneal metastases originating from SPNs who were treated between January 2007 and January 2017 at Peking University Cancer Hospital were retrospectively reviewed. The peritoneal metastases were confirmed via exploratory surgery followed by pathological diagnosis of the specimens. A diagnosis of SPN was based on the microscopic appearance of the tumor and immunohistochemical staining results. Clinical presentation, surgical details, pathological features, and follow-up data were documented according to specific groups.

Surgery procedures

Cytoreductive surgery (CRS) comprises peritonectomy procedures and visceral resections to remove all macroscopic disease and leave no residual disease [12]. Because the peritoneal metastases were not widespread in some cases, visceral resections either alone or with partial peritonectomy appeared adequate. Thus, we define complete cytoreductive surgery (CCRS) as operations consisting of total peritonectomy procedures plus extended visceral resections. In addition, total peritonectomy procedures comprised the resection of 6 sections as first described by PH Sugarbaker [13]. Debulking surgery was used as a palliative option to remove most gross residual tumor loads.

According to the literature, high-grade malignant SPNs have either microscopic or gross malignant features, which include cellular atypia, capsule invasion, peripancreatic fat invasion, perineural invasion, lymphovascular invasion and distant metastases [4,6].

A literature search in PubMed was conducted with the following terms of solid pseudopapillary tumor, solid and cyst tumor, rupture, trauma, peritoneal metastasis, and peritoneal carcinomatosis. Only patients who underwent surgical treatment were included.

Statistical analysis

The statistical analyses were performed using SPSS software, version 13.0 (SPSS, Chicago, IL, USA). Either a two-tailed chi-squared test ($\chi^2$) or Fisher’s exact test was used to evaluate the correlation between surgical strategy and tumor-free survival (TFS). Kaplan-Meier survival analysis was used to evaluate the patients’ TFS, and $P$ values were calculated by the log rank test. A two-sided $P$ value less than 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of SPNs in our series

The 4 patients (3 women and one man) were on average 28.5 years old when they were first diagnosed. Three patients had acute abdominal pain, and 2 (patients A and B) had abdominal trauma that caused tumor rupture, which was confirmed via laparotomy. Patient C had spontaneous but moderate abdominal pain 6 months before peritoneal metastases were detected. Patient D had routine follow-up during which the peritoneal metastases were discovered.

The size of the 4 primary SPNs ranged from 7 cm to 15 cm and were all located in the body or tail of the pancreas. The metastatic lesions varied in size and shape. The primary tumor in patients A and B had similar biological characteristics and the same incipient peritoneal metastases. The metastatic nodules were mostly spherical or hemispherical in shape, firm to the
touch, and well encapsulated. Tumor invasion was not so aggressive such that small nodules were easily removed from the peritoneal surfaces (Figure 1A), but the larger nodules had invasive behavior, especially the tumors in patient B (Figure 1B). The metastatic lesions of patients C and D showed more aggressive behavior in appearance. The tumors were soft to the touch and prone to slow bleeding. They were large and irregular in shape, with the largest metastatic masses measuring 12.0 cm and 8.0 cm, respectively. Even the small nodules infiltrated into the serosa and blood vessels (Figure 1C). However, neither the small intestine nor mesentery were affected in all 4 cases (Figure 1D).

In the microscopic findings, both metastatic tumors from patients B and C had vascular thrombi. In addition to metastatic tumor, patient C had 2/8 positive lymph nodes, but her lymph nodes were all negative (0/7) during explored in her first primary tumor resection. The 4 metastatic tumors had different infiltration abilities to adjacent structures. The tumor from patient A infiltrated to only parts of the peritoneum. Tumors from patients B and D invaded the gastrointestinal serosa. However, the tumor from patient C invaded the deepest, as it penetrated the submucosa of the gastric wall and muscularis propria of the colon.

Immunochemistry of Ki-67 expression was 20% in metastatic tumors from patient C but was 5% in her primary tumor. In all other cases, Ki-67 expression was 1–2%.

Analysis of reports in the medical literature combined with our cases

A total of 8 patients (all female; mean age 28.3 years) with SPNs with peritoneal metastases who underwent surgery has been reported. Upon inclusion of these patients with our series, the mean primary tumor size was 12.5 cm. Two (16.7%)
tumors were in the head of the pancreas, and 10 (83.3%) were in the body or tail.

Six (50.0%) patients had trauma that caused the primary tumors to rupture; 1 (8.3%) experienced iatrogenic injury. For the remaining 5 patients, the causes of peritoneal metastasis are likely the malignant characteristics of the primary tumor. The mean duration time from primary tumor resection to peritoneal metastasis detection was 6.1 years (range 1.2–13.0 years), while the mean duration was 5.7 years in cases where the tumor ruptured.

All 12 patients underwent surgical resection with different initial procedures. One patient underwent CCRS treatment. Eight patients initially underwent CRS, and 2 required a follow-up CCRS surgery due to tumor recurrence. Three of the remaining 6 patients had tumor recurrence and were treated with CRS, debulking surgery, or conservative treatment (1 each). Among the remaining 3 patients, 1 is patient C from our series in whom the peritoneal metastases could not be curatively resected due to the malignant infiltration into vital or organ and vessels; she was still alive at her 1.0-year follow-up, but lung metastases were detected within 3 months postoperatively. The other 2 patients underwent observation for the peritoneal metastases; as their diseases progressed, one patient underwent debulking surgery 2 years later to treat multiple metastases and the other patient underwent CRS 1.4 years later [11,14–20] (Table 1).

Because all patients survived and have limited follow-up data, our study mainly analyzed the correlation of surgical procedures and TFS. The data regarding debulking surgery and patients

| No. | Treatment/Publishyear | Sex/Age | Primary location | Primary size (cm) | Primary malignancy | Time to PM (yr) | PM cause | PM size (cm) | Treatment | Follow-up (yr) | Outcome |
|-----|----------------------|---------|------------------|-------------------|-------------------|----------------|----------|-------------|-----------|--------------|---------|
| A   | 2011                 | F/12    | Body             | 8.0               | Low-grade         | 2.0           | Trauma   | 0.3–1.5     | CRS       | 6.1          | Tumor free |
| B   | 2013                 | M/23    | Tail             | 15.0              | High-grade        | 8.0           | Trauma   | 0.2–6.0     | CCRS      | 4.5          | Tumor free |
| C   | 2010                 | F/51    | Tail             | 7.0               | High-grade        | 6.0           | Malignant| 0.5–1.2     | Debulking | 1.2          | Lung mets |
| D   | 2016                 | F/28    | Tail             | 17.0              | High-grade        | 5.0           | Malignant| 0.2–8.0     | CRS       | 1.0          | Tumor free |
| 1   | Ogawa T 1993 [14]    | F/50    | Body-Tail        | NA                | High-grade        | 0             | Malignant| NA          | CRS       | 1.2          | Tumor free |
| 2   | Lévy P 1997 [15]     | F/NA    | Body-Tail        | NA                | Low-grade         | 1.2           | Trauma   | NA          | CRS       | NA          |
| 3   | Andronikou S 2003 [16]| F/9  | Tail             | 10.0              | Low-grade         | 4.0           | Trauma   | 3.0         | Observation| NA          |
| 4   | Park SE 2006 [11]    | F/16    | Tail             | 20.0              | High-grade        | 6.0           | Malignant| 15.0        | CRS       | NA          |
| 5   | Kyokane T 2008 [17]  | F/51    | Body             | 12.0              | Low-grade         | 6.5           | Trauma   | 0.3–9.5     | CRS       | 1.3          | NA        |
| 6   | Tajima Y 2012 [18]   | F/12    | Head             | 14.0              | Low-grade         | 6.1           | Trauma   | 1.0         | Observation| CRS        | 0.3       |
| 7   | Honore C 2012 [19]   | F/22    | Tail             | NA                | High-grade        | 13.0          | Surgery  | NA          | CRS       | 2.6          | Tumor free |
| 8   | Lee HS 2017 [20]     | F/37    | Head             | 9.9               | High-grade        | 8.9–22.7      | Malignant| 1.3–4.3     | CRS*      | NA          |

CRS – cytoreductive surgery; CCRS – complete cytoreductive surgery; HIPEC – hyperthermic intraperitoneal chemotherapy; PM – peritoneal metastases; NA – not available. * Patient underwent 8 surgeries; the CRS was her first operation for PM.
Table 2. Statistical results of surgically treated SPNs with peritoneal metastases.

| SPNs with PM       | CCRS | CRS | \(P\) value |
|-------------------|------|-----|-------------|
|                   | Recur| No recur | Recur | No recur |
| Low-grade         | 0    | 1    | 2          | 2       | 0.257 |
| TFS (years)       | /    | 6.1  | 1.15±0.78  | 0.80±0.71|
| High-grade        | 0    | 2    | 3          | 2       | 0.203 |
| TFS (years)       | /    | 3.55±1.34 | 0.57±0.23 | 1.10±0.14|
| Total             | 0    | 3    | 5          | 4       | 0.046 |
| TFS (years)       | /    | 4.40±1.75 | 0.80±0.53 | 0.87±0.51|

CRS – cytoreductive surgery; CCRS – complete cytoreductive surgery; PM – peritoneal metastases; SPNs – solid pseudopapillary neoplasms; TFS – tumor-free survival.

Discussion

Identifying and preventing tumor rupture is critical for any type of malignant tumor, even for SPNs, which are considered low-grade malignant neoplasms. SPNs can grow unnoticed into large tumors and rupture by accident. The incidence of SPN rupture among 292 cases was reported at 2.7% [21]. Blunt abdominal trauma was the most common reason according to review articles [22,23]; other reasons include spontaneous rupture and iatrogenic injury. Kim reported that tumor rupture is a risk factor for SPN recurrence [24]. However, only 2 of the 12 patients with ruptured SPN had peritoneal metastasis with 27 months of follow-up data as described on the report by Kyokane [17]. Thus, whether the rupture is the real reason for peritoneal carcinomatosis is debatable [8]. We speculate that the causes of SPN rupture without metastatic spread may be as follows. (1) The SPN arises from a region in the pancreas that is deep within the abdomen. Minor bleeding sites may be wrapped by the greater omentum; thus, dissemination into the abdominal cavity is prevented, such as the case described by Kyokane, in which the tumors had all implanted around the ruptured area. (2) Because of the low malignancy of SPN, a median follow-up time of 27 months is not enough to detect small nodules. Our study showed that the mean duration for peritoneal metastasis detection was 5.7 years in individuals with ruptures.

Because a minor rupture can cause disseminations of SPNs, the safety and necessity of tumor biopsy must be carefully evaluated. SPNs are a cyst and solid tumor with surface tension, especially in larger masses. Any needle puncture can cause content outflow. Furthermore, Virgilio reported 4 individuals with SPN recurrence due to biopsy [25]. Currently, most pancreatic surgeons believe that the diagnosis of SPNs should be based predominately on radiological assessments. Biopsy is suggested only in critical situations, and the puncture path should be well designed to minimize the risk of leakage [26,27].

Tumor injury is a crucial factor that can result in the peritoneal metastasis of SPNs, yet rupture is only a physical activator. Whether the biological nature of SPNs can cause peritoneal metastases has rarely been discussed. Some pathological features associated with aggressive tumor behavior, such as lymphovascular invasion, perineural invasion, local invasion of the tumor capsule, and surrounding tissue invasion, have been used to define high-grade malignant SPNs. However, due to limited follow-up interval or erroneous theory, neither clinical recurrence nor metastases had been correlated with these malignant features [6]. For example, the pathological results of patient C revealed that her primary tumor did not exhibit any predictive features for her metastases that were discovered 6.0 years later. However, Ki-67 expression in her primary tumor was 5%, predicting an adverse outcome according...
to some authors [28]. Accurate risk and predictive factors for SPNs are still under investigation.

We noticed that metastatic tumors derived from low-grade and high-grade malignant SPNs have some differences regarding the gross manifestation and biological behavior. Most SPNs are low-grade malignant with benign behavior and good prognosis, and tumor rupture is the primary cause for peritoneal metastases. The low-grade tumors are firm and well-defined, which is in accordance with the description in the study by Tajima [18]. However, high-grade malignant SPNs can infiltrate and metastasize into related and distant organs. The metastatic tumors are soft to the touch and can spontaneously rupture into cells that can detach and spread, resulting in dissemination. There are some commonalities between the 2 distinct classes of SPNs, the most important of which is that none of the metastatic tumors in our cohort infiltrated the small intestinal serosa or mesentery. Within all cases assessed, mesentery seed involvement was reported but was described as only scattered nodules [18]. In addition, there was no evidence of ascites in any of these reported cases, even in those with extensive peritoneal metastases. The unique characteristics of peritoneal metastases from SPNs are suitable for radical surgical resection.

The treatment strategies of SPN with peritoneal metastases reported in review articles include conservative treatment, debunking surgery, CRS, CCRS, and HIPEC. Although CCRS showed no difference with CRS procedures in treating either low-grade or high-grade SPNs in our analysis, CCRS significantly improved TFS in all SPNs with peritoneal metastases. In fact, the essential purpose for treating peritoneal metastases is to remove all the lesions. Some authors chose CRS because the disseminations were not serious; however, the CRS operation does not include a total peritonectomy procedure, resulting in an increased risk of tumor recurrence. Patient A was our first case.
of SPNs with widespread metastasis. We lacked the experience to conduct a total peritoneectomy at that time, although we believed the metastases were completely resected. The residual tumor was found deep inside the gap between the ligament teres hepatitis and left lateral lobe 1.8 years later and the lesions were misdiagnosed as liver metastases. We performed a second hepatectomy to remove the recurrences, as well as membranes around the hepatoduodenal ligament and other around the peritoneum, to achieve a total peritoneectomy; currently, the patient’s TFS is 6.1 years. Similarly, patient B initially underwent CCRS with total peritoneectomy; although this patient was diagnosed with high-grade malignant SPNs, his TFS is currently 4.5 years.

Although there is increased risk for recurrence in SPNs treated with CRS, it should be noted that more surgeries can result in an increased risk of complications that can reduce the quality of life or even cause death. Furthermore, low-grade malignant SPNs, which in peritoneal metastatic cases predominately caused by accidently rupture, accounted for most SPNs cases. However, our study indicated at least 2 cases (patient B and Case No. 7) in only 7 that presented rupture and had aggressive features such as tumor thrombus and vessel invasion; these were classified as high-grade malignant SPNs. We speculated that high-grade malignant SPNs are more susceptible to rupture under the same external forces. Thus, every ruptured SPN encountered may have a higher likelihood of being a high-grade malignancy. Moreover, Lee reported 1 patient who underwent 8 surgical resections for SPN peritoneal implantation and distant metastases [20]. Although the patient was diagnosed with high-grade malignant SPN due to liver metastases, the Ki-67 expression of the resected tumors increased over time. We speculate that SPN gains more aggressive characteristics when it recurs and metastasizes. Thus, conducting more radical surgical treatment during the first encounter is particularly important.

Conclusions

For patients of SPNs with significant peritoneal metastases, CCRS should be the primary treatment to achieve the longest TFS. The characteristics of SPNs, particularly implantation modes, also enabled the possibility of R0 resection. For some SPNs with regional disseminations, it appeared that CRS was more adequate than CCRS, but it should be noted that there is still a high possibility of tumor recurrence with this procedure. Because our retrospective study describes a small number of cases and limited survival information, its conclusions should be interpreted with caution. However, SPNs have unique oncologic features and slow progression. The CCRS has a more radical intention and may theoretically result in a better prognosis.

Conflicts of interest

None.

References:

1. Hao CY, Lu AP, Xing BC et al: Solid pseudopapillary tumor of the pancreas: Report of 8 cases in a single institution and review of the Chinese literature. Pancreatology, 2006; 6: 291–96
2. Papavramidis T, Papavramidis S: Solid pseudopapillary tumors of the pancreas: Review of 718 patients reported in English literature. J Am Coll Surg, 2005; 200: 965–72
3. 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: 1209–14
4. Flejou JF: [WHO Classification of digestive tumors: The fourth edition]. Ann Pathol, 2011, 31: 527–31 [in French]
5. Martin RC, Klimstra DS, Brennan MF, Conlon KC: Solid pseudopapillary tumor of the pancreas: A surgical enigma? Ann Surg Oncol, 2002; 9: 35–40
6. Lubesky N, Popoulas M, Lessing Y et al: Solid pseudopapillary neoplasm of the pancreas: Management and long-term outcome. Eur J Surg Oncol, 2017; 43: 1056–60
7. Potc S, Kavalar R, Horvat M, Gadjiev EM: Urgent whipple resection for solid pseudopapillary tumor of the pancreas. J Hepatobiliary Pancreat Surg, 2003; 10: 386–89
8. Takamatsu S, Nagano H, Ohtsukasa S et al: A case of spontaneous ruptured solid pseudopapillary tumor of the pancreas treated by laparoscopic surgery. Case Rep Med, 2013; 2013: 953240
9. Huang SC, Wu TH, Chen CC, Chen TC: Spontaneous rupture of solid pseudopapillary neoplasm of the pancreas during pregnancy. Obstet Gynecol, 2013; 121: 486–88
10. Wang WB, Zhang TP, Sun MQ et al: Solid pseudopapillary tumor of the pancreas with liver metastasis: Clinical features and management. Eur J Surg Oncol, 2014; 40: 1572–77
11. Park SE, Park NS, Chun JM et al: A case of recurrent solid pseudopapillary tumor of the pancreas with involvement of the spleen and kidney. Cancer Res Treat, 2006; 38: 118–20
12. Mehta SS, Bhatt A, Glehen O: Cytoreductive surgery and peritonectomy procedures. Indian J Surg Oncol, 2016; 7: 139–51
13. Sugarbaker PH: Peritonectomy procedures. Cancer Treat Rev, 2007; 33: 247–64
14. Ogawa T, Isaji S, Okamura K et al: A case of radical resection for solid cystic tumor of the pancreas with widespread metastases in the liver and greater omentum. Am J Gastroenterol, 1993; 88: 1436–39
15. Levy P, Bougarian J, Gayet B: Diffuse peritoneal carcinoma of pseudo-papillary and solid tumor of the pancreas. Role of abdominal injury. Gastroenterol Clin Biol, 1997; 21: 789–93 [in French]
16. Andronikou S, Moon A, Ussher R: Peritoneal metastatic disease in a child after excision of a solid pseudopapillary tumour of the pancreas: A unique case. Pediatr Radiol, 2003; 33: 269–71
17. Kyokane T, Iyomasa S, Sawaiaki N et al: A Case of successful resection for peritoneal recurrence of solid pseudopapillary tumor of the pancreas occurred in 6.5 years after rupture of the tumor. Nippon Shokaki Geka Zasshi, 2008; 41: 1815–20
18. Tajima Y, Kihara N, Maeda J et al: Peritoneal and nodal recurrence 7 years after the excision of a ruptured solid pseudopapillary neoplasm of the pancreas: Report of a case. Surg Today, 2012; 42: 776–80
19. Honore C, Goede D, Dartigues P et al: Peritoneal carcinomatosis from solid pseudopapillary neoplasm (Frantz’s tumour) of the pancreas treated with HIPEC. Anticancer Res, 2012; 32: 1069–73
20. Lee HS, Kim HK, Shin BK et al: A rare case of recurrent metastatic solid pseudopapillary neoplasm of the pancreas. J Pathol Transl Med, 2017; 51: 87–91
21. Mao C, Guvendi M, Domenico DR et al: Papillary cystic and solid tumors of the pancreas: A pancreatic embryonic tumor? Studies of 3 cases and cumulative review of the world's literature. Surgery, 1995; 118: 821–28

22. Potrc S, Kavalar R, Ivanecz A, Gadzijev EM: Acute presentation of a solid pseudopapillary tumor of the pancreas. Wien Klin Wochenschr, 2004; 116(Suppl. 2): 100–3

23. Huang HL, Shih SC, Chang WH et al: Solid pseudopapillary tumor of the pancreas: Clinical experience and literature review. World J Gastroenterol, 2005; 11: 1403–9

24. Kim CW, Han DJ, Kim J et al: Solid pseudopapillary tumor of the pancreas: Can malignancy be predicted? Surgery, 2011; 149: 625–34

25. Virgilio E, Mercantini P, Ferri M et al: Is EUS-FNA of solid pseudopapillary neoplasms of the pancreas as a preoperative procedure really necessary and free of acceptable risks? Pancreatology, 2014; 14: 536–38

26. Lévy P, Auber A, Ruszniewski P: Do not biopsy solid pseudopapillary tumors of the pancreas! Endoscopy, 2008; 40: 959

27. Bardales RH, Centeno B, Mallery JS et al: Endoscopic ultrasound-guided fine-needle aspiration cytology diagnosis of solid pseudopapillary tumor of the pancreas: A rare neoplasm of elusive origin but characteristic cytomorphic features. Am J Clin Pathol, 2004; 121: 654–62

28. Yang F, Yu X, Bao Y et al: Prognostic value of Ki-67 in solid pseudopapillary tumor of the pancreas: Huashan experience and systematic review of the literature. Surgery, 2016; 159: 1023–31