Analysis of 50 cases of solid pseudopapillary tumor of pancreas: Aggressive surgical resection provides excellent outcomes

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ABSTRACT

Introduction: This study reports the clinicopathological characteristics and the perioperative and long-term treatment outcomes after aggressive surgical resection in solid pseudopapillary tumor (SPT) of the pancreas performed at a high volume center for pancreatic surgery in India.
Materials and methods: We analyzed a prospectively maintained database of the patients operated for SPT at Tata Memorial Hospital, India over a period of 11 years from February 2007 to February 2018.
Results: Fifty consecutive patients operated for SPT, during the study period were included. The median age at presentation was 24 years. Majority of the patients (43/50) were female (86%). Disease was predominantly localized in the head and uncinate process of pancreas (66%). Median tumor size was 7.7 cm (Range 1.6–15 cm). Tumor extent was radiologically defined as borderline resectable or locally advanced in 48% (n = 24) patients. Forty-six major pancreatic resections were performed, which included 10 (21%) vascular resections, 2 synchronous liver metastasectomies, 1 multi visceral resection and 5 total pancreaticosplenectomies. Five of these resections were reoperations in patients deemed inoperable on exploration at other centers. R0 resection was achieved in 47 patients (98%). Postoperative major morbidity was 19% and there was no mortality. At a median follow-up of 29 months (Range, 1–121 months), all patients were alive without any recurrence.
Conclusion: Aggressive complete surgical resection of SPT achieves excellent long-term survival. Surgery, especially for large and borderline resectable tumors, can be potentially complex and should be performed at high-volume centers to provide the best chance of cure.

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Introduction

Solid pseudopapillary tumor (SPT) of the pancreas is rare, accounting for 0.2–2.7% of exocrine pancreatic neoplasms [1]. It is usually diagnosed in young women in the third and fourth decades of life [2–6]. There has been a gradual increase in the incidence of this tumor over the last two decades, probably due to the more frequent use of cross sectional imaging in the evaluation of abdominal symptoms. However, the natural history of this disease is still not fully understood [4]. It is generally considered to be a tumor with low malignant potential, which has predominantly local effects due to gradual tumor growth [1,3]. Occasionally, tumors may exhibit florid growth and metastasis [3]. The pathogenesis of SPT is currently unknown and is thought to arise from cells of the endocrine pancreas, but origin from the exocrine pancreas cannot be ruled out [3,6]. SPT is classified according to the World Health Organization (WHO) as either an SPT with an uncertain potential for malignancy or as a solid pseudopapillary carcinoma [7,8]. Chemotherapy and radiotherapy have shown little or no benefit in the treatment of these tumors [1,3]. Surgery remains the mainstay of treatment and the only curative option [1–3]. Reported surgical procedures, however, vary from local excisions to radical resections and debulking procedures.

Tata Memorial Hospital in Mumbai is a referral, tertiary-care and high-volume center for pancreatic surgeries in India [9,10]. We had previously published our limited experience with 7 patients having SPT in 1994 and with 14 patients in 2006 and had highlighted

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certain specific radiopathological aspects of SPT in 2008 [4,5,11]. This study was undertaken to report our expanded experience in the management of 50 patients with this uncommon tumor over the last decade.

Material and methods

We analyzed a prospectively maintained database of the patients operated for SPT at Tata Memorial Hospital over a period of 11 years from February 2007 to February 2018. All 50 consecutive patients operated during the study period were included in the study. All patients underwent standard evaluation with routine blood investigations and triphasic contrast-enhanced computed tomography of the abdomen and pelvis. In cases of radiologic diagnostic uncertainty for SPT, Endoscopic Ultrasound (EUS) with or without fine-needle aspiration cytology (FNAC) was performed along with tumor markers (CEA and CA 19—9). All patients with suspected or confirmed diagnosis of SPT were offered surgery with R0 resection as the primary aim. The location and extent of the tumor determined the type of resection performed. Total pancreatectomy, vascular resections and multivisceral resections were performed whenever deemed appropriate to achieve complete resection. According to the International Study Group on Pancreatic Surgery (ISGPS) classification, postoperative complications were defined as complications occurring within 30 days of surgery [12,13]. Complications were graded as per the Clavein Dindo classification [14].

Patients were followed up every 4 months for the first 2 years, every 6 months for the next 3 years and annually thereafter. Follow-up evaluation included clinical assessment, routine blood investigations and abdominal ultrasound. Any patient complaining of significant abdominal symptoms on follow up was evaluated with additional cross sectional imaging to rule out recurrence.

Demographic, radiological and pathological characteristics and perioperative outcome variables (operative time, blood loss, hospital stay, morbidity and mortality, etc.) were recorded in the database. Follow-up information was updated through review of hospital electronic medical records and by directly contacting the patients. Statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) software, version 20.0 for Windows (SPSS Inc., Chicago, IL). Continuous variables were reported as median with range. Categorical variables were described using frequency distributions. Overall survival (OS) was defined as the time from surgical resection to the last follow-up or death of the patient. Disease-free survival (DFS) was defined as the time between surgical resection and clinical evidence of recurrent or metastatic disease.

Compliance with ethical standards

The data of the present study were collected in the course of common clinical practice, and accordingly, the signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol was in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and is later amendments. Since this was a retrospective study, formal consent for this study was not required and no approval of the institutional research committee was needed.

Results

Fifty patients underwent surgery for SPT during the study period. There were 43 (86%) females and 7 males, with a ratio of 6:1 suggesting a significant female preponderance. Demographic

characteristics are described in Table 1. The median age at presentation was 24 years. The majority of the patients presented with abdominal pain or discomfort (60%). Diagnosis was incidental in as many as 22% patients. Most of the tumors were located in the head and uncinate region of the pancreas (66%) and were large in size (Median tumor size was 7.7 cm). In spite of this, even large SPTs did not present with obstructive jaundice. Only one patient presented with obstructive jaundice secondary to tumor compression of the biliary system.

Tumor extent was radiologically defined as borderline resectable or locally advanced in 24 patients (48%) and resectable in 52% patients. Two patients presented with synchronous liver metastases. Most of the patients had a preoperative clinico-radiological diagnosis or suspicion of SPT. Eleven patients had already undergone EUS at other centers and only two patients were subjected to EUS guided FNAC at our center in view of diagnostic uncertainty.

Forty-eight patients underwent complete surgical resection in our study. Two patients were deemed unresectable after sufficient trial dissection, due to the complete encasement of the superior mesenteric artery and the presence of collaterals with portal cavernoma formation along with severe portal hypertension. The perioperative details are mentioned in Table 2. Ten patients (20%) required superior mesenteric vein/portal vein (SMV/PV) resection, which was reconstructed primarily (type I vein resection) in two patients, by end-to-end anastomosis (type III vein resection) in six patients and by synthetic venous prosthesis (type IV vein resection) in two patients as per the ISGPS classification of porto-mesenteric resections [15]. Two patients required synchronous liver metastatectomy, one underwent left hemicolectomy with left nephrectomy and five underwent total pancreaticosplenectomy in order to achieve R0 resection. Five of these resections were reoperations in patients deemed inoperable on exploration at other centers, mostly due to the large tumor size and adjacent organ or vascular invasion.

R0 resection was achieved in 47 patients (98%), whereas one underwent R1 resection following enucleation. Histopathological characteristics are described in Table 2. All patients were pathologically confirmed to have SPT. Postoperative major morbidity (Clavein-Dindo grade III/IV) was 19% and the rate of grade II complications was 14.6% (Table 2). There was no perioperative mortality. One patient required re-exploration for postpancreatectomy hemorrhage (PPH) and eight patients with clinically relevant postoperative pancreatic fistula (CR-POPF B) were managed with radiologically placed drains. The perioperative morbidity was comparable to the standard pancreatic surgeries performed at our center in the same time span ($n = 1114$) with a major postoperative morbidity of 21.90% and mortality of 3.70%.

Table 1
Demographic characteristics.

Variable	$n = 50$
Median age, years (range)	24 (10—59)
Gender	
Male	07 (14%)
Female	43 (86%)
Presentation	
Symptomatic	39 (78%)
Incidentally detected	11 (22%)
Abdominal discomfort and/or pain	30 (60%)
Obstructive jaundice	01 (2.0%)
Prior exploration elsewhere	05 (10%)
Palpable abdominal mass	06 (12%)
Median tumor size (cm)	7.7 (1.6—15)
Location	
Head and uncinate part of pancreas	33 (66%)
Body and tail of pancreas	17 (34%)
Liver metastasis	02 (4.0%)

Table 2
Perioperative and histopathology details.

Variable	$n = 50$
Type of Pancreatic resection	
Classical pancreaticoduodenectomy	06 (12%)
Pylorus-preserving pancreaticoduodenectomy	17 (34%)
Total pancreatectomy	05 (10%)
Distal pancreaticosplenectomy	16 (32%)
Median pancreatectomy	02 (04%)
Enucleation	02 (04%)
Inoperable	02 (04%)
Extended Resections	
Vascular resection (PV/SMV) [15]	10 (20%)
Type I	02
Type III	06
Type IV	02
Liver metastasectomy	02 (04%)
Multi Visceral Resection	01
Median blood loss (mL)	700 (range, 100–8000)
Median duration of surgery (min)	390 (range, 70–800)
Median hospital stay (days)	11 (range, 5–69)
Complications	
Clavein-Dindo grade	
II	7 (14.6%)
IIIa	8 (17%)
IIIb	1 (02%)
Major and Minor complications	
CR-POPF B [12]	08 (17%)
PPH	01 (02%)
DGE B [13]	02 (04%)
Chyle leak	03 (06%)
Intra-abdominal collections	02 (04%)
Final histopathology (SPT)	50
LVI	3 (06%)
PNI	2 (04%)
Margin status	
Uninvolved (R0)	47 (98%)
Involved (R1)	01
Lymph node metastasis ($n = 48$)	2 (04%)
Median lymph node yield	11(5–63)
(In Pancreaticoduodenectomy and Total Pancreatectomy, $n = 28$)	
Liver metastasis	2 (04%)

PV/SMV = portal vein/superior mesenteric vein, CR-POPF = clinically relevant postoperative pancreatic fistula, PPH = postpancreatectomy hemorrhage, DGE = delayed gastric emptying, LVI = lymphovascular invasion, PNI = perineural invasion.

At a median follow-up of 29 months (mean 37 months; range 1–121 months), all patients who had undergone resection were alive without disease recurrence. One of the two inoperable patients had received radiotherapy followed by chemotherapy along with radiofrequency ablation (RFA) of the liver metastasis and is currently on follow up with us with progression of disease. The other patient with inoperable disease is lost to follow-up.

Discussion

Our study demonstrates excellent prognosis and long-term outcomes for SPT after aggressive surgical resection. Complete surgical resection is the treatment of choice even in the presence of extensive local disease and distant metastases [16–18].

SPTs are usually bulky tumors and may occur anywhere within the pancreas [1,2,16]. A systematic review of 2744 SPTs by Law et al. [2] reported a mean tumor size of 8.6 cm. In this study, majority of the SPTs were located in the body and tail of the pancreas (59.3%; $n = 1626$) followed by 36% ($n = 988$) in the head or uncinate process. In contrast, we noted more SPTs (66%) arising from the head and uncinate part of the pancreas. This difference is most likely a result of referral bias, as patients with pancreatic head tumors who needed pancreaticoduodenectomy were often referred to tertiary centers as compared to distal pancreatic tumors.

The median tumor size in our series was 7.7 cm. Nearly half of the patients (48%) were radiologically defined as borderline resectable or locally advanced. This may be due to their low malignant potential and their tendency to invade locally rather than spread systemically. Quite often they remain asymptomatic for a long duration before attaining a large size and starting to produce a dull aching pain.

A total of 13 patients had undergone EUS evaluation with or without FNAC. EUS evaluation and tissue diagnosis is not mandatory in all cases, especially when there is a clear indication for surgery such as radiological suspicion of SPT/malignancy or presence of symptoms [4,19]. In cases with diagnostic uncertainty on cross sectional imaging, EUS with or without FNAC can be performed [20–22].

The accurate assessment of resectability and vascular involvement was facilitated by multidetector CT with angiography [23]. SMV/PV resection was planned when there was an evidence of vessel wall involvement by the tumor [16]. In our series, forty-six patients required major pancreatic resections in order to achieve R0 resection. 20% ($n = 10$) of the patients required SMV/PV resection and reconstruction and one patient required multivisceral resection. Cheng et al. [24] demonstrated excellent long-term survival after en bloc synchronous SMV/PV or multivisceral resection in SPTs. In a review, Sperti et al. [25] also justified the benefits of

Table 3
Outcomes after aggressive surgical resection of SPT in a single center.

Study number of patients (n)	Median tumor size (cm)	SMV/PVR	Liver metastasectomy	MVR	PD/TP	Major morbidity (%)	Median follow-up (months)	Recurrence	Death due to SPT
Present study, n = 48	7.7 (1.6–15)	10	2	1	23/5	19	29 (1–121)	Nil	Nil
Cheng et al. [24], n = 10	12 (4–20)	8	–	2	–	50	68 (12–110)	1	1
Cai et al. [41], n = 115	6.3 (1–25)	2	5	3	33/0	19.1	58 (6–121)	2	Nil
Kim et al. [31], n = 114	4.2 (1.2–15)	2	3	6	39/0	22	57 (1–177)	4	Nil
Dai et al. [42], n = 45	6.3 (1.5–16)	2	Nil	Nil	9/0	20	52 (10–179)	1	Nil
Goh et al. [27], n = 16	9.5 (5–24)	1	Nil	2	3/0	25	43 (3–186)	Nil	Nil
Bostanci et al. [43], n = 16	5.6 (2–11)	1	3	Nil	7/1	19	49 (6–99)	Nil	Nil
Martin et al. [30], n = 18	8 (1–20)	Nil	4	Nil	7/0	–	96	3	1
Song et al. [44], n = 52	6.4 (2–14)	Nil	Nil	4	9/0	27	48 (3–123)	3	2
Reddy et al. [45], n = 36	4.5 (0.3–12)	Nil	Nil	3	14/1	30	56 (1–330)	1	Nil
Patil et al. [4], n = 13	6.8 (3–18)	Nil	Nil	2	4/0	8	36 (6–96)	Nil	Nil
Morikawa et al. [46], n = 17	5.2	Nil	1	Nil	4/0	47	51 (1–206)	1	Nil

SMV/PVR = superior mesenteric vein/portal vein resection; MVR = multivisceral resection; PD/TP = pancreaticoduodenectomy/total pancreatectomy.

vascular resection and reconstruction in locally aggressive SPT.

Extensive lymphadenectomy is not performed regularly in SPTs, because of the very rare incidence of lymph node metastases [16,26,27]. Only two patients in our study were found to have lymph node metastases on final pathology. However, regional lymph nodes in the resection template would usually be removed particularly while resecting large tumors.

SPT may present with distant metastases in 10–15% patients at the time of diagnosis [28,29]. The most common sites for metastases are liver, regional lymph nodes, mesentery, omentum and peritoneum [6]. Several retrospective studies have reported that long-term survival improves with complete surgical resection for synchronous or metachronous metastases [6,30,31]. Surgical resection or debulking is also recommended, even in the presence of distant metastases in contrast to other pancreatic malignancies. In our series, two patients had undergone non-anatomical liver resection for synchronous metastases with good long-term outcomes. Patients with liver and lymph node metastases were clinico-pathologically not different from other SPTs.

Five patients, who were deemed inoperable on exploration elsewhere, underwent R0 resection at our center. Three patients out of these five, required vein (SMV/PV) resection and total pancreaticosplenectomy was performed in two patients. The reason for inoperability at the initial surgery was suspected vascular involvement or large/bulky tumor. Previous exploration increases the complexity of re-operative pancreatic surgery. Re-exploration can be safely performed only in a center with adequate experience [32–34]. To avoid such re-explorations, patients with large tumors with vascular invasion should be referred to high-volume centers with adequate experience in pancreatic resections [35,36].

The role of neo-adjuvant or adjuvant chemotherapy and radiotherapy in the treatment of SPT is limited [3,37–40]. Common indications are candidates unfit for surgery and patients with recurrence. 5-Fluorouracil and gemcitabine are the two most commonly used chemotherapeutic agents [2]. No adjuvant therapy was offered to our patients after complete resection. One patient with unresectable SPT and liver metastases, who received radiotherapy followed by chemotherapy (gemcitabine) along with RFA of the liver lesion, is still surviving with progression of disease.

The overall five-year survival rate after resection is 95–97% [1,30]. Yu et al. [16] found that the estimated 1-, 3-, and 5-year survival rates were 99.4%, 97.5%, and 96.9% respectively. Tumor recurrence rate was <10% [1,25], and recurrences usually occurred within 4 years after surgery [16,25,31]. In our series, at a median follow-up of 29 months with 80% of the patients following up for more than a year, all patients were alive without any recurrence, which is comparable to data reported in the literature. These excellent long term as well as peri-operative outcomes are also

possibly due to the fact that these surgeries were performed in a high volume center by experienced pancreatic surgeons [10,35,36].

When compared to our previous reports, a gradual increase was observed in the number of patients treated annually and in the complexity of resections performed [5,6]. The data on extended resections for SPT (SMV/PV resections, liver metastasectomies, multivisceral resections) performed in a single center is limited (Table 3). Our study demonstrated excellent long-term outcomes after aggressive surgery for SPT, which is perhaps the largest Indian experience.

Conclusion

Aggressive complete surgical resection of SPT achieves excellent long-term survival. Surgery, especially for large and borderline resectable tumors, can be potentially complex and should be performed at high-volume centers to provide the best chance of cure.

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Conflict of interest

None to declare.

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