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The optimal surgical approach for solid pseudopapillary neoplasm of the pancreas: A retrospective study

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Abstract

The most effective surgical approach for solid pseudopapillary neoplasms (SPNs) remains unclear. We conducted a retrospective study of 14 patients diagnosed with SPN between September 2013 and October 2021. Thirteen patients were female, and the median age was 39.5 (18–63) years. The mean tumour diameter was 5.2 ± 2.2 (range, 2–10) cm. The type of surgery was decided based on the tumour location and the extrapancreatic invasion status. The conservative (organ-preserving) surgical procedure was spleen-preserving distal pancreatectomy (n=3). The radical surgical procedures included pancreaticoduodenectomy, with either venous reconstruction (n=2) or without (n=4), and distal pancreatectomy + splenectomy (n=5); similar to performed for pancreatic cancer regional lymphadenectomy was not performed. Tumour resection margins were free in all patients. There were no cases of lymph node metastasis, but the number of examined lymph nodes was significantly higher in the radical surgery group (p=0.03). A female patient developed multiple liver metastases one year after distal pancreatectomy + splenectomy. Her number of examined lymph nodes was the highest of the cohort (n=24). The mean follow-up time was 40 ± 23.5 months. All patients were alive at the end of the study. In conclusıon; necessity for radical surgery may be associated with malignant behaviour. Therefore, the extent of the surgical operation may be expanded during radical procedures for SPNs.

Keywords: conservative surgery, optimal surgical approach, radical surgery, solid pseudopapillary neoplasm

1. Introduction

Solid pseudopapillary neoplasms (SPNs) are rare, cystic exocrine tumours that account for 1–2% of all pancreatic neoplasms (1). SPNs occur most often in young women and with no notable symptoms (2, 3). These tumours are generally large, well-circumscribed, and consist of solid and cystic components (4). Although most SPNs have stable characteristics, malignant behaviour has been identified in 10–15% of patients (5-7). Surgical resection is the mainstay and only curative treatment strategy whether the disease shows a malignant behaviour or not (1-13). Many authors recommend conservative surgery because of the low malignancy potency of these tumours (1-6, 8-10, 13). However, in the case of pancreatic parenchymal infiltration and involvement of adjacent structures, radical surgical approaches are required (7). In this study, we aimed to present the outcomes of our cohort of 14 patients with SPN in whom 11 radical surgical procedures were performed.

2. Materials and Methods

The study was approved by the ethics committee (2021/462). We searched our database and found records of 14 patients with a confirmed pathological diagnosis of SPN from September 2013 to October 2021. We conducted a retrospective study to analyse the patient variables, such as their demographics, clinical presentation, radiological findings, tumour size and location, strategy of the surgery, pathological and immunohistochemical analyses, as well as short and long-term outcomes. Informed consent was obtained from all the study participants.

The radical surgical procedures included pancreaticoduodenectomy (with or without venous reconstruction) and distal pancreatectomy + splenectomy, and the conservative surgical procedure was spleen-preserving distal pancreatectomy (7). Whenever feasible, we performed conservative surgery. Regional lymphadenectomy recommended by The International Study Group on Pancreatic Surgery for pancreatic adenocarcinoma was not routinely performed (14). Postoperative pancreatic fistulas were evaluated considering The International Study Group of Pancreatic Surgery consensus recommendations (15). Postoperative complications were evaluated according to Clavien-Dindo classifications (16), and those ≥ 3A were defined as severe. R0 resection was considered tumour-free surgical margin whereas R1 was considered the microscopic presence of tumour cells at the surgical margin. Univariate analyses of clinicopathological features were performed to compare the conservative and radical procedures. All statistical analyses were performed using IBM SPSS 26.0 (IBM Corp., Armonk, New York, USA).

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3. Results

3.1. Clinical features

The clinicopathological features are listed in Table 1. Thirteen of the 14 patients were female, and the median age was 39.5 (18–63) years. The most common clinical presentation was abdominal pain: it was found in half of the patients. One patient was referred with jaundice. No patient had weight loss, a history of trauma, or pancreatitis. The tumours were located on the head/neck in six and body/tail in eight patients. The mean tumour diameter was 5.2 ± 2.2 (range, 2–10) cm.

Table 1. Clinicopathological features of 14 patients with SPNs

	Patients (n=14)	%
Age years, mean (range)	39.5 (18-63)	
Gender		
Female	13	92.9
Symptoms		
Abdominal pain	5	35.7
Abdominal pain and jaundice	1	7.1
Abdominal pain and diarrhea	1	7.1
Nausea and vomiting	1	7.1
Radiographic appearence		
Solid-cystic	8	57.1
Solid	4	28.6
Cystic	2	14.3
Calcification on imaging, yes	8	57.1
Location		
Head or neck	6	42.9
Body or tail	8	57.1
Radical surgery		
Pancreaticoduodenectomy	6	42.9
Distal pancreatectomy + splenectomy	5	35.7
Conservative surgery		
Splen preserving distal pancreatectomy	3	21.4
Size cm, mean (range)	5.2 (2-10)	
Resection margin status		
R0	14	100
Lenf node status		
Number of metastasis	0	0
Follow-up months, mean±sd	40.0 ± 23.5	
Recurrence		
Hepatic metastasis	1	7.1
Outcome		
Alive	14	100

3.2. Preoperative investigations

Preoperative tumour markers (carbohydrate antigen 19-9 [CA 19-9] and carcinoembryonic antigen [CEA]) were tested in eight cases, and they were within normal limits.

Radiological scans were performed preoperatively, including computed tomography (CT) in 11 patients and magnetic resonance imaging (MRI) in 5 patients. On imaging, the tumours were described as well-encapsulated in all cases, solid and cystic in eight cases, and solid in four cases. Eight patients had calcifications, while seven had haemorrhage and necrosis. SPN was being referred in the imaging reports of eight patients.

Endoscopic ultrasonography (EUS) with fine-needle aspiration biopsy (FNA) was performed in five patients. A definitive preoperative pathological diagnosis was obtained in only one patient whose tumour was at the pancreatic head. Two patients were misdiagnosed with pancreatic neuroendocrine tumours and two others with unidentified benign lesions.

3.3. Surgical management and postoperative outcomes

In Table 2, we evaluate the clinicopathological features according to surgical approach. The type of surgery was decided based on the tumour location and involvement of adjacent structures, such as the portal and splenic veins. Eleven patients underwent radical surgery, including pancreaticoduodenectomy in six (concomitant end-to-end portal vein reconstruction in one and primary venorraphy in one) and distal pancreatectomy + splenectomy in five. The remaining three patients underwent spleen-preserving distal pancreatectomy. The total mean operation time was 3.9 hours; it ranged from 1.8 to 6.8 hours. Intraoperative blood transfusion was required in eight patients. The length of stay, intraoperative blood transfusion, and operation time were significantly higher in the radical surgery group ($p<0.05$).

Table 2. Comparison of surgical approaches

Clinicopathologic factors	Radical (n = 11)	Conservative (n = 3)	p value
Gender, famele	11 (100)	2 (66.7)	0.21
Age, years (mean± SD)	41 ± 14.7	34 ± 6.2	0.44
Symptoms, yes, n (%)	8 (72.7)	1 (33.3)	0.50
Tumor location, n (%)			0.20
Head or neck	6 (54.5)	0	
Body or tail	5 (45.5)	3 (100)	
Tumor size, cm (%)			1.0
<5	5 (45.5)	1 (33.3)	
>5	6 (54.5)	2 (66.7)	
Intraoperative blood transfusion, unit (median, range)	2 (0-3)	1 (0-1)	0.03+
Operation time, hour (mean ± SD)	4.2± 1.8	2.6 ± 0.3	0.01+
Postoperative complications, yes, n (%)	6 (54.5)	0	0.20
Lengt of stay, day (median, range)	9 (5-21)	5 (4-5)	0.02+
Hemorrhage or necrosis, n (%)			1.0
No	1 (9.1)	0	
Hemorrhage	2 (18.2)	1(33.3)	
Hemorrhage + necrosis	8 (72.7)	2(66.7)	
Tumor capsul formation, n (%)			1.0
Intact	4 (36.4)	1 (33.3)	
Perforation	3 (27.3)	1 (33.3)	
Invasion	4 (36.4)	1 (33.3)	
Evaluated lymph node number (median, range)	12 (0-24)	0 (0-6)	0.03+
Recurrence, yes, n (%)	1 (9.1)	0	0.58
Tumor feature, n (%)			1.0
Solid and cystic	7 (63.6)	3 (100)	
Solid	2 (14.3)	0	
Cystic	2 (14.3)	0	
Follow-up time month (mean ± SD)	39.2 ± 7.3	43 ± 14.7	0.81

+: statistically significant

No patient in the cohort had any severe postoperative complications. Nine patients developed postoperative

complications, including pancreatic fistula (n=2), wound infection (n=3), both of these (n=2), and delayed gastric emptying (n=2).

3.4. Pathological findings

All tumour specimens had a fibrous pseudocapsule, multiple solid and cystic components, and areas of haemorrhage and necrosis, and the observed fibrous capsule was thin, the tumours pseudopapillary, and there were uniform, poorly cohesive neoplastic cells. There was capsule perforation and capsule involvement in four and five patients, respectively. There was infiltration of the splenic veins, portal veins, and pancreatic parenchyma in four, two, and eight patients, respectively. There were no lymph node metastases, but the examined lymph node number was significantly higher in the radical surgery group (p=0.03). The resection margins were free in all patients. There was no lymphovascular or perineural invasion. The mitotic activity was low or undetectable in all patients. Immunohistochemical examinations included ß-catenin, vimentin, CD-10, CD-56, alfa-1-antitrypsin, neuroendocrine markers (chromogranin A, synaptophysin), progesterone receptors, cytokeratin (AE1/AE3), and Ki-67. The immunohistochemical features of the cohort are listed in Table 3.

Table 3. Immunohistochemical features of 14 patients with SPNs

Antigen	Test number n,(%)	Positive (%)
Beta-catenin	13 (92.9)	13 (100)
CD-10	13 (92.9)	12 (92.3)
CD-56	7 (50)	6 (85.7)
Alfa-1-antitripsin	6 (42.8)	5 (83.3)
Vimentine	11(78.6)	11 (100)
Progesteron receptor	8 (57.1)	8 (100)
Neuroendocrine markers		
Chromogranin A	11 (78.6)	3 (27.3)
Synaptophysin	12 (85.7)	5 (41.7)
Ki-67 (≤ 3 %)	7 (50)	7 (100)
Cytokeratin (AE1/AE3)	2 (14.3)	1 (50)

3.5. Follow-up and survival

After discharge, the patients were followed up every 3 or 6 months by cross-sectional imaging (CT or MRI) and routine laboratory investigations. The mean follow-up time was 40.0 ± 23.5 months.

A 46-year-old female patient developed multiple liver metastases at the end of the first year. She had undergone distal pancreatectomy + splenectomy because of a solid, calcified lesion on preoperative imaging, and splenic vein invasion was observed intraoperatively. On pathological investigation, the tumour was 8.5 cm, had areas of haemorrhage and necrosis, was solid, and had an intact capsule but was invaded by tumour cells, and splenic vein involvement was observed. Twenty-four non-metastatic lymph nodes were detected, and this was the highest number in the cohort.

4. Discussion

The current cohort included 14 patients with SPN who underwent radical or conservative surgery (n=11 and 3, respectively). The length of stay, intraoperative blood transfusion, operation time, and examined lymph node number were found to be significantly higher in the radical surgery group, as expected.

Surgical resection is a unique treatment for SPNs. The surgical strategy should be decided based on the tumour location and involvement of adjacent structures (11). Complete resection should be the primary strategy irrespective of whether the adjacent structures are involved or not (10). Although SPNs have a low malignant potential (17), the association between pancreatic parenchymal infiltration , extrapancreatic invasion , R1 resection , lymph node metastasis , and likely recurrence is known (2, 13). Although regional lymphadenectomy was not recommended in most studies, because lymph node metastasis is rare (1, 9, 10, 12), there may be recurrence in lymph nodes (8) or locally (7, 12, 13). The number of the lymph nodes that are surgically removed is essential for staging of pancreatic ductal adenocarcinoma: patients with higher than 12 lymph nodes have been found to have longer survival (18). The evaluated highest number of lymph nodes (n=24) in this series was in a patient with liver metastasis, and invasion of the splenic vein was observed both in the intraoperative and pathological examination. For these reasons, regional lymphadenectomy and confirmation of R0 resection margin may be necessary during radical surgery. On the other hand, we think that conservative surgery should be performed both when there is no suspicion of structure involvement on imaging and when the diagnosis of SPN is confirmed pathologically before surgery.

Unfortunately, serum tumour markers are not helpful in preoperative diagnosis (4, 9, 10, 12, 19). In a multicenter study (9) in which 97 cases were examined, the CEA levels were elevated in two patients and the CA19-9 levels in three patients. Similarly, Goh et al. found elevated levels only in 2 of 23 patients (19). Reddy et al. (4), Butte et al. (12), and Bostancı et al. (10) did not observe any elevated tumour marker levels in their cohorts. In this study, we examined eight cases preoperatively, and there were no elevated tumour marker levels.

There has been an increase in the diagnosis of SPNs in the last decade with more using in the use of abdominal imaging techniques (2). Although different imaging methods have been used to diagnose SPNs (1), CT is the most commonly used abdominal imaging technique (2, 9, 12). On CT, these tumours typically appear as well-circumscribed masses with varying degrees of solid components, haemorrhage in cystic degeneration, and sometimes calcification (2, 12). Solid components frequently get contrasted in a similar way to the pancreatic parenchyma on arterial and venous phases, which is unlike the case in adenocarcinomas and neuroendocrine tumours (4). MRI can detect cystic degeneration, haemorrhage, and the integrity of the tumour capsule better than CT (3, 10). Eleven of the patients in our series were assessed with CT and 5 with MRI, and 8 of the 14 were diagnosed or suspected of

having SPN. From our experience, evaluation with MRI is required when CT provides insufficient results.

Notably, some studies have recently reported the EUS-FNA findings for the preoperative diagnosis of SPN (2, 4, 12, 20). However, these reports differ in the rate of using EUS-FNA and its diagnostic accuracy. As per the meta-analysis of Law et al, the diagnostic rate was 69.5% (2). According to a multicenter study (20), the diagnosis of SPN was made in 21 of 28 patients. In the study by Butte et al., 40% of the patients underwent FNA, and the diagnostic rate was 56% (12). A definitive diagnosis was obtained in one of five patients before surgery in the current study. In our opinion, the differential diagnosis of SPN affects the choice of surgical procedure. If there is no suspicion of parenchymal or extrapancreatic invasion on preoperative imaging, EUS-FNA and standardised pathological examination are required.

In some studies, malignant behaviour was associated with male sex (7), younger age (4), tumours larger than 5 cm (8, 11, 12), and capsular invasion on pathological assessment (13). Lubezky et al. detected liver recurrence in 4 out of 32 patients, and they presented tumour diameter as the only significant factor for recurrence (mean 8 vs. 5.2 cm) (8). Butte et al. also underlined the prognostic importance of tumour diameter (mean 7.8 vs. 4.2 cm) with regard to recurrence (12). Similar to the literature, our patient with recurrence had a tumour larger than 5 cm in diameter and pathological capsular invasion. Remarkably, her age (46 years) and sex were not risk factors for recurrence in the current literature.

Recent studies highlight beta-catenin, e-cadherin, and CD10 as important in the diagnosis of SPN (13, 17). However, immunohistochemical studies are not sufficient to determine the prognosis of these tumours (13). In contrast, advanced nuclear grade, perineural-lymphovascular invasion, high mitotic activity, and extensive necrosis may be related to poor prognosis (11, 13). There is promising research on the prognostic significance of the Ki-67 immunoreactivity ratio (3, 9, 13). In a study by Yepuri et al., more than 4% Ki-67 immunoreactivity was associated with early recurrence, but the results were not significant (13). In the current study, we did not observe perineural-lymphovascular invasion, and mitotic activity was low; additionally, Ki-67 immunoreactivity was lower than 4%.

SPNs show 2–15% malignant behaviour following surgery (2, 5, 6, 8). The most common recurrence areas of SPNs are the liver and the peritoneum (5, 8, 13), and the median recurrence times were 41 (13) and 50.5 months (2) in recent meta-analyses. Metastasis may be present at the time of diagnosis or develop in the years following surgery (8). Fortunately, patients have been reported to have a long life expectancy despite having developed recurrence (5). Surgery has not been determined to be of value in metastatic disease (8). However, some authors (5, 9) recommend surgery in case of resectable metastasis, whether determined perioperatively or during follow-up. Adjuvant treatment with 5-FU or gemcitabine and/or radiotherapy may be helpful for the treatment of unresectable metastatic SPNs (2). One of our patients developed multiple metastases in the liver one year after surgery, and adjuvant chemotherapy was planned followıng a decision by a multidisciplinary team.

Some meta-analyses (2, 13) have recommended a follow-up time of at least 5 years. However, long-term follow-up (up to 15 years) is essential for those with poor prognostic factors (13). The mean follow-up time in the current cohort was 40 ± 23.5 months; it was similar to those of the previous series (49.2 (8), 44 (12), and 36.1 (2) months). A critical question for follow-up is which imaging method to use. The contribution of positron emission tomography in determining recurrence remains undefined, but some SPNs markedly uptake 2-deoxy-2-fluoro-D-glucose during preoperative diagnosis (21). We think that, in addition to CT and/or MRI, positron emission tomography should be utilised in patients with potentially poor prognostic factors. The main limitations of this study were its retrospective nature and the small number of patients.

In conclusion, necessity for radical surgery may be associated with malignant behaviour. Therefore, the extent of the surgical operation and lymphadenectomy may be expanded during radical procedures for SPNs. In contrast, whenever feasible, conservative surgical procedures should be performed.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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