



Outcome and prognosis after pancreatectomy in patients with solid pseudopapillary neoplasms

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ABSTRACT

Background: Solid pseudopapillary neoplasms (SPN) are rare and represent approximately 4% of all cystic pancreatic tumors. The prognosis is excellent, although 10–15% of SPN patients show metastasis at the time of surgery or tumor recurrence during follow-up after pancreatectomy. Aim of the study was to analyze surgical management, risk factors for malignancy as well as long-term outcome and prognosis of this distinct tumor entity.

Method: All patients with pancreatic resection for SPN between 10/2001 and 07/2018 in the authors' institution were identified from a prospective database. Clinicopathologic details, perioperative data and long-term follow-up results were retrospectively analyzed.

Results: Fifty-two patients were identified, 44 (85%) of them were female and the median age was 29 years (IQR 9–71). Seven (13%) patients showed a malignant behaviour of SPN with N1 (n = 2) or M1 (n = 1) disease at resection; 5 patients developed tumor recurrence, after a median of 21 months. During follow-up time (median 54 months) all patients were alive, the 5- and 10-year rates for disease-free survival were 89.0% and 81.6%, respectively. Significant risk factors for recurrence were age <18 years (p = 0.0087) and parenchyma-preserving surgical approaches (p = 0.0006). The postoperative long-term outcome showed ECOG = 0–1 in all patients, with resection related exocrine insufficiency in 20 (41%) and diabetes mellitus in 2 (4%) patients.

Conclusions: Age < 18 years is a significant risk factor for malignancy in SPN, and parenchyma preserving resections harbor a significant risk for tumor recurrence. As recurrence may occur late, a systematic life-long follow-up should be performed.

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Introduction

Solid pseudopapillary neoplasms of the pancreas (SPN) were initially described in 1959 by Frantz [1]. In 1996, the World Health Organization (WHO) classified them as borderline tumors of the exocrine pancreas with respect to their potential of recurrence and metastatic dissemination [2]. After initial case reports, over the last decade an increasing number of case series were published revealing that SPN account for 3–4% of all pancreatic cystic lesions, affecting predominantly (>80%) young women and being located mainly in the body or tail of the pancreas [3,4]. Symptoms, if

present, are unspecific, and at least one third of all SPN are found incidentally by imaging for other indications. The typical CT or MRI finding is a mass composed of both – cystic and solid – components surrounded by a well-defined capsule, however, by the radiologic appearance these tumors might also be misdiagnosed as ductal adenocarcinoma of the pancreas (PDAC), neuroendocrine tumor (NET) or unspecified inhomogenous cystic neoplasm of the pancreas [5,6]. In contrast to other pancreatic cysts, for which surveillance might be considered, surgery is basically recommended by the time of diagnosis as the therapy of choice for SPN [7]. Long-term follow-up after SPN resection reveals a recurrence rate of 0–14% [3,8–10,19–31]. To date, several aspects are not consistent in the current literature. There is no uniform definition of malignancy of the primary tumor as the microscopic WHO features [2] are not consequently assessed in the available literature and are reported in only 16–40% of all SPN [8–10] (Table 1). In

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Abbreviations.

DP	distal pancreatectomy
SPN	solid pseudopapillary neoplasm
PD	pancreaticoduodenectomy
PE	pancreatectomy
WHO	World health organisation
GIST	gastrointestinal stroma tumor
NET	neuroendocrine tumor
PDAC	pancreatic ductal adenocarcinoma
ASA	American Society of Anesthesiologists
BMI	body mass index

contrast, malignancy in terms of lymph node involvement or distant metastases is reported regularly and is observed in 0–16% of patients (Table 1). Most importantly, the extension of resection is under debate: some authors have explicitly advocated parenchyma-sparing surgical approaches (i.e. enucleation or central pancreatectomy) to minimize the risk of endocrine and exocrine pancreatic dysfunction in the mostly young patients with a long life expectancy [11,12]. In contrast, the European evidence based guidelines on the management of pancreatic cystic neoplasms recommend an oncological surgical approach for SPN with respect to their malignant potential [7]. However, all surgical series on SPN include patients treated by local approaches and data on risk factors for malignancy that could allow a tailored approach are rare.

Our study aimed to compare clinicopathological aspects in patients with versus without malignant behavior, as well as recurrence after distal pancreatectomy (DP), partial pancreaticoduodenectomy (PD) or total pancreatectomy (PE) versus parenchyma-sparing resection for SPN. Moreover, the long-term postoperative outcome was assessed.

Methods*Study design and patients*

Data of all patients treated for SPN at the Department of Surgery, University of Heidelberg, Germany, between October 2001 and July 2018 were extracted from a prospectively maintained database, that includes all pancreatic resections. Data were retrospectively analyzed with regard to surgical procedures, malignancy at the time of the initial operation and the long-term prognosis and outcome. Malignancy is defined as either synchronous metastasis (M1 for SPN in any extrapancreatic organ), lymph node spread (N1 for any resected lymph nodes) or tumor recurrence (local or metastatic, pathologically confirmed). The study was approved by the local ethics committee (approval no.: S 011/15).

Data collection and outcome parameters

Baseline data acquisition included patients' gender and age, body mass index (BMI), history of diabetes and preceding carcinoma, history of smoking (yes/no), disease-related symptoms, American Society of Anesthesiologists (ASA) score and tumor characteristics in the pre-operative cross-sectional diagnostic imaging. Outcome parameters included operative procedure, operation time, blood loss, postoperative complications within 30 days after surgery (postpancreatectomy hemorrhage (PPH), postoperative pancreatic fistula (POPF), lymphatic fistula, delayed gastric emptying (DGE), re-operation) as well as length of hospital stay and

mortality. Pathological work-up included tumor size, TNM stage and R status. Tumor staging was based on the American Joint Committee on Cancer (AJCC) Staging Manual, 7th edition [13]. Also tumor necrosis, malignant microscopic features according to the WHO definition (infiltration of pancreatic tissue surrounding the SPN or of the peripancreatic fat tissue, lymphangio invasion, vessel invasion, neural invasion) [2] and the proliferation activity were considered [14]. PPH, POPF, DGE and lymphatic fistula were defined according to the current ISGPS definitions [15–17]. The severity of complications was graded according to the Clavien-Dindo system [18].

Furthermore, regular follow-up visits in the outpatient department for pancreatic diseases were documented and analyzed, which were conducted every 6–12 months. Follow-up visits include MRI, physical examination, routine blood analysis, anamnesis regarding any complains, medication and quality of life (via EORTC Q 30). Follow-up data were obtained through routine follow-up visit, through telephone contact or by email. Recurrence and general health status according to the performance status of the Eastern Cooperative Oncology Group (ECOG) [19] were recorded between 1 January and 1 August, 2018.

Statistical analysis

Data management and statistical analysis were carried out by SAS® software release 9.4 (SAS Institute, Cary, North Carolina, USA). The quantitative variables age, BMI, serum levels of CA 19-9 and CEA, tumor size, duration of operation, blood loss, and hospital stay were presented as median and interquartile range (IQR), if not otherwise stated. The nonparametric Mann-Whitney u test was used to compare continuous parameters between the two groups. For categorical parameters absolute and relative frequencies were computed and compared between the two groups using the Fisher's exact test. Overall survival was defined as the time from the date of primary pancreatic resection to either death from any cause or last follow-up. Disease-free survival was defined as the time from the date of the operation to disease recurrence or last follow-up. Patients lost to follow-up were excluded from survival analyses. Survival was estimated using the Kaplan-Meier method. Patients alive at the last follow-up were censored and marked in the figures (∅). The 5- and 10-year disease-free survival rates are presented. The log-rank test was used to compare survival curves. Two-sided P values were computed and a difference was considered statistically significant at $P < 0.05$. Multivariable logistic regression analysis was performed to identify factors associated with malignant behaviour of SPN. Odds ratios with its corresponding p-values were calculated.

Results*Patient characteristics*

During the observation period, a total of 52 patients were included in the study. 44 of the SPN patients were female (85%), four of them were <18y. Overall, the patients were between 8 and 71 years old with a median age of 29 years (IQR 9–71). Upon presentation, 31 patients (67%) were symptomatic with jaundice (n = 3), nausea and vomiting (n = 5), weight loss (n = 9) or abdominal pain (n = 22). Pancreatic body and tail were the location of 57% of all tumors (n = 29/52), the median size was 4.4 cm (range 2.6–6.3). An elevation of preoperative serum CA 19-9 was found in 12% of the patients (n = 6/44), and ranged from 40.9 to 370.6 U/ml (Table 2).

In the preoperative cross-sectional imaging (i.e. MRI and/or CT scan), the diagnosis of SPN was correctly made in 37/52 patients

(70%). The remaining lesions were preoperatively characterized as follows:

- duodenal GIST (gastrointestinal stroma tumor, $n = 1$) in a 72-year old man,
- NET (neuroendocrine tumor, $n = 2$) in a 33-year old woman, postoperative histology: synchronous SPN and NET, and in a 52-year old woman with preoperative histology suspicious for NET,
- MCN (mucinous cystic neoplasm, $n = 1$) in an 18-year old female patient
- PDAC (pancreatic ductal adenocarcinoma, $n = 5$),
- other unspecified solid tumor ($n = 5$).

In one patient, SPN was accidentally found during an emergency operation.

Two male patients showed preceding extrapancreatic malignancies (melanoma $n = 1$, Hodgkin's disease and renal cell cancer $n = 1$). No extrapancreatic malignancies were observed in female patients.

Surgical procedures

The initial surgical procedures included 44 standard oncological resections and 8 parenchyma-preserving approaches, three of them including local lymph node dissection (Table 2). The most common initial procedure was distal pancreatectomy (DP) ($n = 25$, 49%), in four patients performed laparoscopically. The spleen was preserved in 11 patients. Partial pancreaticoduodenectomy (PD) was performed in 16 (35%) and a total pancreatectomy (PE) was conducted in two patients due to preexisting insulin dependent diabetes mellitus and a centrally located tumor with complete atrophy of the pancreatic remnant ($n = 1$) or due to a soft high-risk pancreatic remnant to avoid POPF ($n = 1$). In terms of parenchyma-preserving procedures, segmental resection and enucleation was conducted in 5 resp. 4 patients (10 resp. 8%). Enucleation was performed for two SPNs located in the pancreatic head with a tumor size of 4.5 cm and 5.5 cm, respectively, one SPN located in the pancreatic body with a tumor size of 1.7 cm, and for one SPN located in the pancreatic tail with a tumor size of 1.5 cm. During one of the enucleations, the tumor perforated (Table 5). There was another iatrogenic tumor rupture during an exploration, with a partial PD conducted 4 days later (mentioned as primary resection). In one patient an initial R2 resection during emergency laparotomy following blunt abdominal trauma with tumor rupture was performed, followed by a formal PD and consecutive metastases resection.

Histopathological findings

Table 2 summarizes the histopathological findings including tumor size, TNM stage, R status, tumor necrosis and malignant microscopic features. The Ki-67 index was determined in 36 patients: <1%: $n = 15$; <2%: $n = 17$; <3%: $n = 1$; <5%: $n = 3$. None of the SPNs with malignant behavior was associated with a Ki-67 index >4%, which is discussed as a cut-off value for malignancy in the literature [14]. On the other hand, those SPN with a Ki-67 index >4% ($n = 3$) did not show malignant behavior in our series. In addition, the mitosis rate was not elevated in SPN tumors in this study.

Multivariable logistic regression analysis including age at operation, tumor cell infiltration of the peripancreatic fat tissue, lymphangio invasion, and neural invasion confirmed age at operation under 18 years ($p = 0.0156$, odds ratio = 16.46) and tumor cell infiltration of the peripancreatic fat tissue ($p = 0.0608$, odds ratio = 6.27) as factors associated independently with malignant behaviour of SPN.

Postoperative morbidity and survival

The most common postoperative complications were POPF B and DGE (each $n = 6$, 12%) (Table 3). Six patients (12%) underwent re-laparotomy for the following complications: PPH at the site of pancreaticojejunostomy, POPF grade C as well as insufficiency of the biliodigestive anastomosis.

Sex specific differences were found in overall SPN incidence (85% female) and median age which was 10 years younger in women than men ($p = 0.0451$). Tumor location differed without statistical significance (female: 60% of SPNs located in the pancreatic body and/or tail, male: 63% located in the head). No signs of malignancy, i.e. no lymph node involvement or M1 disease at primary resection and no tumor recurrence, were found in any male patient.

Follow-up data were available for 49/52 patients (94%) with a median follow-up time of 54 months (range 2–230 months) (Table 5). Loss of exocrine pancreas function was observed in 40% ($n = 19$). New-onset diabetes mellitus occurred only in the 2 patients who had undergone a total pancreatectomy. 14 patients (29%) suffered from long-term complaints like unspecific abdominal pain or recurrent pancreatitis. Three patients had to undergo re-operation with resection and re-anastomosis of the pancreaticojejunostomy for recurrent pancreatitis 4, 15 and 24 months after the initial operation. In terms of oncological follow-up, no sign of recurrent SPN were found in 44/49 patients (90%). Five female patients (10%) showed metastatic or local recurrence. Distinct features in these patients were tumor size, intraoperative tumor perforation as well as the type of surgical management. Detailed features are summarized in Table 4. No tumor-related mortality occurred during the follow-up period (Fig. 1A). The 5- and 10-year rates for disease-free survival were 89.0% and 81.6%, respectively (Fig. 1B). Significant risk factors for tumor recurrence were age <18 years ($p = 0.0006$, Fig. 2A), parenchyma-sparing surgical procedure ($p = 0.071$, Fig. 2B) and tumor necrosis ($p = 0.052$, Fig. 2C).

Discussion

The present study provides a large single-center collective of patients resected for SPN as a rare pancreatic tumor entity. SPN shows a favorable prognosis, but is not yet fully understood regarding its biological behaviour and factors that are associated with tumor spread or recurrence. To our knowledge, it is the largest single institute case series on children and adults in Europe, and the second largest in Europe/North America. Our data show that malignancy in SPN is a relevant aspect and indicate that the surgical management has an important impact on the patients' prognosis, namely that parenchyma-preserving resections or tumor perforation – regardless if caused accidentally by trauma or by surgical manipulation – are decisive factors for recurrence or metastatic seeding.

In the past decade, worldwide experience with SPN has steadily increased, comparable to all pancreatic cystic tumors. This is reflected by the current literature, as shown in Table 1. Small European reports included five to 18 patients in England, Sweden, Greece and Italy [20–24]. Fifty-one patients, all of them children <18 years, were analyzed in a French multi center study [25]. US publications from MD Anderson ($n = 64$, 2014), Memorial Sloan Kettering ($n = 45$, 2010) and Johns Hopkins ($n = 37$, 2009) included a comparable number of patients [26–28]. Further single center studies came from Canada and Israel (each $n = 32$) [29,30]. Larger patient collectives were analyzed in some single and multi-institutional reports from China and South Korea, whereas there are only a few multicenter studies respective database analyses in the western countries [9,25,31,32]. In our study the preoperative

Table 1
Publications of SPN series >4 patients.

Parameter	Author (date of publication) country/ observation period	SPN Resections n (f/m)	Malignancy in initial op n N1/M1 (location)	Patterns of Recurrence n (f/m) Local/ Metast/	TTR, mean (months)	Death, disease related	Survival	Risk factors for recurrence
single center studies								
1	McCluney S [20] (2018) England 2006–2016	11 (10f/1 m)	0/11	24 mo: 0/11	–	0	DFS 100%	–
3	Scandavini [21] (2018) Sweden/Karolinska 2004–2017	9 (7f/2 m) <16y	0/9	80 mo: 0/9	–	0	DFS 100%	–
4	Ansari [22] (2011) Sweden/Lund 1980–2011	16 (13f/3 m)	2/16 (13%) • 1 N1 • 1 M1 (gallbladder)	1/16 (7%) • M+ (liver)	4 mo	1	15/16 DFS	literature review on risk factors: • male • extrapancreatic invasion • incomplete resection
5	Antoniou [24] (2017) Greece Time period not assessed	5 (all f)	0	46 mo: 0/5	–	0	OS 100%	–
6	Beltrame [23] (2016) Padua/Italy 1997–2013	18 (16f/2 m)	1/18 • M1 (liver)	1/18 (6%) • M+ (liver)	32 mo	1	median DFS: 82 mo	n.a
7	Serrano [29] (2014) Canada/Toronto 1999–2013	32 (26f/6 m)	3/32 (9%) • 1 M1 (liver) • 1 M1 (liver and colon infiltration) • 1 N1	43 mo: 3/32 (9%) • 1 M+ (liver) • 1 M+ (liver, 3x recurrent) • 1 M+ (liver and retroperit.)	72 mo	1 (11years after initial operation)	median DFS: 88 mo	• Synchronous liver met • Lymphovascular invasion • Tumor capsule invasion
8	Reddy [28] (2009) Baltimore/USA (Johns Hopkins) 1970–2008	37 (33f/4 m)	4/37 (10%) • 1 R2 resection • 2 N1 • 1 not resectable with distant metastases	55 mo: 1/37 (4%) • 1x pc	89	1	35/36 patients disease free	n.a.
9	Butte [27] (2010) New York/USA (SloanKettering) 1987–2009	45 (38f/7 m)	7/45 (16%) • 4 locally unresectable • 4 M1 (liver)	44 mo: 2/45 (4%) • 1x local • 1x local & M+ (liver)	n.a.	3	median DFS: 44 mo	• Large tumor size
11	Lubezky [30] (2017) Israel 1995–2016	32 (29f/3 m)	2/32 (7%) • 1x M1 (liver) • 1x infiltration(duoden) • 13x WHO pos (40%)	49 mo: 3/32 (9%) • 2x M+ (liver) • 1x M+ (peritoneal & lymph nodes)	52 (12–84)	0	5/10 y DFS: 97/90%	• Large tumor size
12	Song H [36] (2017) China 2005–2017	53 (46f/7 m)	1/53 • Locally not resectable	48 mo: 1/48 (2%) • local, after enucleation	96	2	5/10y DFS 96%/96%	• Capsule incomplete
13	Xu [8] (2017) China 2008–2015	121 (93f/28 m)	4/121 (3%) • 3x M1 (liver) • 1x N1 • 35x WHO pos (mf) (29%)	43 mo: 3/103 (3%) • 3x M+ (liver)	n.a.	1		• Synchron liver met • Peripancreatic fat infiltration • Lymphovascular invasion
14	Cai [12] (2014) China (2003–2013)	115 (100f/15 m)	6/115 (5%) • 5x M1 (liver) • 1x locally irresectable	58 mo: 2/115 (2%) • 1 local • 1 x M+ (liver)	7 mo	1	OS 98.3%, DFS 97%	Not assessed
Multi center studies								
15	Irtan [25] (2016) France (1996–2016)	51 (41f/10 m) all < 18y	1/51 (2%) • 1x N1	65 mo: 7/51(14%) • 2x local • 5x M+ (peritoneal)	43 mo		OS 100%	• positive surgical margins • young age (<13.5 y)
16	Marchegiani [9](2016) Verona/Italy and Boston/USA (1986–2014)	131 (113f/18 m)	2/131 (1%) • 1x M1 (liver), • 1x N1 • + 16x WHO pos. (16%)	62 mo: 2/105(1.5%) • 1x local and M+(peritoneal) • 1x M+ (liver&peritoneal)	64 mo	1	5y DFS: 98.4%	• capsular invasion • infiltrative growth
17	Kang [10](2014) Korea (1990–2008)	351 (317f/34 m)	6/351 (2%) • 4x M1 (liver) • 1x M1(peritoneal) • 1x N1 • 98x WHO pos.(28%)	9/317(3%): • 1x local • 8x M+	18,6 mo	1(0.2%)	5y DFS: 95.4%; 10y DFS 93.7%	• tumor size > 8 cm • stage IV
18		340 (279f/61 m)	28 (8%)	n.a.	n.a.	7 (2%)	median survival:	• no surgical resection

Table 1 (continued)

Parameter	Author (date of publication) country/ observation period	SPN Resections n (f/m)	Malignancy in initial op n N1/M1 (location)	Patterns of Recurrence n (f/m) Local/ Metast/	TTR, mean (months)	Death, disease related	Survival	Risk factors for recurrence
	Jutric [31] (2017) Portland (USA) 1998–2011	44: no surgery due to reasons not specified	• 25x M1 (liver, lung, distal LN) • 3x unknown site				• overall 11.8y • no surgery 3.8 y	• stage IV • type of treatment facility
19	Hanada [35] (2018) Japan (1990–2015)	288 (214f/74 m) 10 inoperable	4/278 (1%) • 1x N1 • 3x M1 (2x liver, 1x lung)	51 mo: 6/256 (2%) 4x local 2x M+ (liver)	32 mo	3	5y DFS 97.1%	• Invasion (extrapancreatic and extracapsular) • Limited resection NO risk factor
20	Huffmann [32] (2018) Mayo clinic: national cancer database Minnesota/USA (2004–2012)	304 (259f/45 m) 22: not resected	15x M1 23x N1 No of patients with combined N1 and M1 is not assessed	60 mo	n.a.	n.a.	5y OS after resection 98% (5y OS of M1 pats: 41%)	• Male • M1 • N1
Literature review								
21	Law [3] (2014) Literature review (1961–2012)	2744 (2408f/336 m)	124/1532 (8%) 24x N1 118x M1 (location n.a.)	36 mo: 86/1952 (4%)	50,5 mo	29/1952 (2%)	n.a.	n.a.
22	Gao [39] (2018) Metaanalysis of 10 publications prior to 2018, incl 6 of this table	1091 (all before 2017)	n.a.	n.a.	n.a.	n.a.	n.a.	• larger tumors (diameter > 5 cm) • M1 • N1 • R1

f: female, m: male, n.a.: not assessed, M1: synchronous metastasis, M+: metachronic metastasis, mo: month, DFS: disease free survival, OS: overall survival, WHO: world health organisation.

diagnosis of SPN was correctly made in only 70% of resected SPN patients. Most of the preoperative misdiagnoses occurred in the first period of this study, namely between 2001 and 2008. This might be referred to shortcomings in diagnostic tools and pathways at that time. Today cross-sectional imaging studies, preferably MRI, and endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) biopsy are the diagnostic tools of choice in patients with suspicious SPN. Modern MRI scans provide sufficient diagnostic accuracy without radiation exposure and should therefore be preferably used, especially in young patients. In addition, EUS-FNA may be performed to increase correct diagnosis before planning pancreatic surgery.

With regard to the most important outcome parameters, a recent review summarized 292 case reports and 191 patient series and included 2285 patients with SPN resection that were analyzed [3]. The results of the studies confirm the recent findings in our study regarding SPN distribution in sex and tumor location, mean tumor size, primary metastasis patterns and recurrence as well as the perioperative surgical outcomes. The predominant occurrence of SPN in females is not completely understood yet, a hormone dependency has not been described and specific sex hormone receptors are not expressed by SPN [33]. Furthermore, malignancy in SPN is not uniformly defined to date. Pathologic tumor staging including lymph node status has not been assessed in many studies in the past as lymph node dissection has been carried out infrequently.

In contrast, synchronous metastasis (mostly hepatic, rarely peritoneal or in resected distant lymph nodes) was consistently described in the literature in 0–16% of patients. The microscopic WHO criteria for malignancy include lymphovascular and capsular invasion as well as peripancreatic infiltration [2]. If assessed, the microscopic features were reported in 16–40% of the primary pathologic findings [8–10]. McCluney et al. performed a literature

review in attempt to describe the immunohistochemical staining of SPN. The authors retrieved 38 out of 297 articles from their database search that described this topic [20]. This underlines the heterogeneity of pathological workup for SPN. In the literature, primary malignancy is consistently reported for the initial resection and is observed in 0–16% whereas tumor recurrence in post-operative long-term follow-up is found in up to 14% of the patients (Table 1). This is in accordance with the primary malignancy rate of 6% and an additional recurrence rate of 10% in the present patient collective.

In our study no patient with complete follow-up showed SPN-specific mortality underlining the overall low malignant potential of this entity which is in accordance with the literature reporting only few patients with aggressive SPN behavior and SPN-related mortality (1.3%–4.4% [3,9,34]). The comprehensive review by Law et al. [3] reported that 8% of the patients showed malignancy in the primary pathology, 4% developed SPN recurrence and 2% died from the tumor, however, risk factors for malignancy were not analyzed.

Most of the studies lack in analyzing an association of recurrence and initial surgical procedure, or negotiate any relation [9,35]. If assessed, risk factors for SPN recurrence are widely different: incomplete capsule, lymphovascular invasion, incomplete resection, large tumor size, male gender, metastasis in the initial pathology and treatment facility without specialized experience were reported (Table 1).

In contrast, gender, location of tumors, calcification and capsular invasion were not found to be risk factors for malignancy by Song et al. [36]. Irtan et al. described R1 resection and young age <13.5 years as relevant risk factors for tumor recurrence [25]. This is partly in accordance with our results, showing an age <18 years and parenchyma sparing operation procedures – potentially leading to R1/R2 resections – as significant risk factors for recurrence. Moreover, our study observed accidental iatrogenic or traumatic

Table 2
Demographic and clinicopathological characteristics (at primary tumor operation).
Data are presented as total number and percent (n (%)) if not otherwise stated.

Parameter	Total	No signs of malignancy	Signs of malignancy	P value
Total number	52 (100)	45 (100)	7 (100)	
Female: male	44 (84.6): 8 (15.4)	37 (82.2): 8 (17.8)	7 (100): 0 (0.0)	0.578
Age [years]				0.0087
< 18	5 (9.6)	2 (4.4)	3 (42.9)	
18 - <40	34 (66.4)	32 (71.1)	2 (28.6)	
≥ 40	13 (25.0)	11 (24.4)	2 (28.6)	
Age* (range)	29 (9 - 71)	29 (14 - 71)	26 (9 - 64)	0.429
BMI [kg/m²]				0.319
<18.5	5 (10.4)	4 (9.3)	1 (20.0)	
18.5 - <25	25 (52.1)	21 (48.8)	4 (80.0)	
25 - <30	10 (20.8)	10 (23.3)	0 (0.0)	
≥ 30	8 (16.7)	8 (18.6)	0 (0.0)	
Missing values	4	2	2	
BMI* (IQR)	22.5 (20.2–26.7)	22.6 (20.3–27.0)	21.3 (19.6–21.6)	0.138
Alcohol yes: no	26 (56.5): 20 (43.5)	24 (57.1): 18 (42.9)	2 (50.0): 2 (50.0)	1.0
Smoking yes: no	16 (36.4): 28 (63.6)	15 (37.5): 25 (62.5)	1 (25.0): 3 (75.0)	1.0
Symptoms yes: no	31 (67.4): 15 (32.6)	28 (66.7): 14 (33.3)	3 (75.0): 1 (25.0)	1.0
Diabetes mellitus yes: no	3 (6.1): 46 (93.9)	2 (4.7): 41 (95.3)	1 (16.7): 5 (83.3)	0.330
ASA				0.230
I	5 (11.1)	4 (10.3)	1 (16.7)	
II	38 (84.4)	34 (87.2)	4 (66.7)	
III	2 (4.4)	1 (2.6)	1 (16.7)	
Missing values	7	6	1	
Preoperative CA 19-9* (IQR) [U/mL]	10.3 (6.3–19.7)	10.1 (6.2–19.7)	17.8 (13.3–43.0)	0.182
Missing values	7	4	3	
Preoperative CEA* (IQR) [g/L]	0.6 (0.2–1.2)	0.6 (0.2–1.2)	0.7 (0.2–1.7)	0.980
Missing values	11	7	4	
Surgical procedure				0.192
Distal pancreatectomy (DP)	25 (48.1)	22 (47.7)	3 (42.9)	
Pancreaticoduodenectomy (PD)	16 (30.8)	15 (33.3)	1 (14.3)	
Central pancreatectomy	5 (9.6)	4 (8.9)	1 (14.3)	
Enucleation	4 (7.7)	2 (4.4)	2 (28.6)	
Total pancreatectomy	2 (3.8)	2 (4.4)	0 (0.0)	
R-classification				0.0372
R0	41 (89.1)	38 (92.7)	3 (60.0)	
R1	4 (8.7)	3 (7.3)	1 (20.0)	
R2	1 (2.2)	0 (0.0)	1 (20.0)	
RX	1	1		
Missing values	5	3	2	
Tumor size [cm]				0.476
≤ 2	8 (15.4)	7 (15.6)	1 (14.3)	
>2 - 4	17 (32.7)	16 (35.6)	1 (14.3)	
>4 - 8	20 (38.5)	17 (37.8)	3 (42.9)	
> 8	7 (13.5)	5 (11.1)	2 (28.6)	
Size* (IQR)	4.4 (2.6–6.3)	4.0 (2.4–6.0)	5.2 (4.0–9.0)	0.222
Necrosis yes: no	5 (9.6): 47 (90.4)	3 (6.7): 42 (93.3)	2 (28.6): 5 (71.4)	0.129
Infiltration of tumor capsule/surrounding pancreatic tissue yes: no	15 (28.8): 37 (71.2)	13 (28.9): 32 (71.1)	2 (28.6): 5 (71.4)	1.0
Lymphangio invasion yes: no	2 (3.8): 50 (96.2)	0 (0.0): 45 (100.0)	2 (28.6): 5 (71.4)	0.0158
Tumor cell infiltration of peripancreatic fat tissue yes: no	12 (23.1): 40 (76.9)	8 (17.8): 37 (82.2)	4 (57.1): 3 (42.9)	0.0415
Angioinvasion yes: no	3 (5.8): 49 (94.2)	2 (4.4): 43 (95.6)	1 (14.3): 6 (85.7)	0.358

*median values presented. IQR, interquartile range.

tumor injury as an important risk factor for recurrence. This may be explained by either systemic tumor cell spilling or a local non-radical resection leading to late tumor recurrence. This aspect of recurrence risk raises the question of the optimal management strategy from a surgical point of view, as intraoperative mechanical tumor cell spilling should urgently be avoided. Although there is no doubt that surgery is the therapy of choice for SPN, there is controversy regarding the extent of resection. In larger series, the rate of local approaches (enucleation and central pancreatectomies) ranges between 4% and 19% [3,9,30,36,37]. Despite the fact that these local approaches are preferable in terms of operative trauma as well as functional outcome due to the preservation of pancreatic tissue, it remains unclear if they are feasible for SPN treatment from an oncological point of view. The European guidelines for the management of cystic pancreatic tumors consequently recommend a standard resection [7], however, this has obviously not been

accepted in general in the past and local approaches have been described as the preferable option in children [11,12]. Law et al. reported 202 enucleations (8.8% of all reported pancreas resections 1961–2012) - but no data are given on a potential relationship between the documented recurrences and the initial type of operative procedure [3]. Another recent report in 45 Korean children and young adults <21 years showed 8 enucleations (19%) and a considerable recurrence rate of 33% in primary malignant SPNs [38]. However, the event of recurrence is not analyzed with regard to the performed surgical procedure in that report either but a correlation between local approaches and non-radical resection with a high risk for residual tumor or local recurrence risk seems to be reasonable.

In the present study, enucleation was performed in four patients, resulting in 2 local recurrences, 21 and 48 months post-operatively (see patients 6 and 7, Table 3). Despite the small

Table 3

Perioperative data and morbidity at initial operation of 50 SPN patients. Two patients were excluded because of missing perioperative data.

Parameter	N	%	Median	IQR
Duration of operation [min]			183	130–299
missing values	4	7.8		
Blood loss [ml]			350	100–600
missing values	7	13.7		
Non-surgical complications	9	18.0		
Pulmonal	4	8.0		
urinary tract infection	2	4.0		
Surgical complications	25	50.0		
DGE	6	12.0		
DGE A	5	10.0		
DGE B	1	2.0		
POPF B,C	8	16.0		
POPF B	6	12.0		
POPF C	2	4.0		
Abscess	1	2.0		
Bleeding	2	4.0		
wound healing disorder	3	6.0		
chylus leak	2	4.0		
Cholangitis	2	4.0		
Classification of surgical complications (Clavien-Dindo)				
1	7	14.0		
2	12	24.0		
3a	1	2.0		
3b	5	10.0		
Relaparotomy	6	12.0		
Hospital mortality	0	0.0		
Hospital stay [days]			10	8–17

*IQR, interquartile range. DGE, Delayed gastric emptying.

Table 4

Characteristics of seven patients with primary metastatic or recurrent SPNs.

	Initial resection	Tumour characteristic	TTR	Kind of treatment (xth month after initial operation)	Current status (x months after initial operation)
Patient 1 ♀ 65y	DP and liver resection for Ø7,5 cm pancreatic tumour and liver metastasis	T3N0M1R0 Synchronous solitary liver metastasis			Lost to follow up
Patient 2 ♀ 27y	DP and Splenectomy	T3N1R1 Ø5,2 cm			Disease free 6 mo postop, regular FU
Patient 3 ♀ 47y	Exploration, tumor rupture, PD 4 days later	T3N0R0, intra-OP tumour perforation	96, 102, 108, 115, 157	Recurrent surgery for liver-, nodal and peritoneal metastases (96., 102., 108. mo)	Progressive liver metastases since 45 months without treatment Metastasis in the pelvis (157 mo) "watch & wait" (patients' decision) (160 mo)
Patient 4 ♀ 38y	DP	T2N1M0, R0 Ø9cm	15, 64, 77	<ul style="list-style-type: none"> Local and systemic chemotherapy for liver metastases (17.-54. mo) Segmental liver resection of metastasis (49. and 64. mo) RFA and IRE of liver metastasis (69. and 77. mo) 	Recurrent livermetastasis, Under observation (80 mo)
Patient 5 ♀ 13y	R2 resection	Initial tumour rupture with extensive bleeding for abdominal trauma	12, 84, 77	<ul style="list-style-type: none"> PD, R1 (ext.) (12. mo) Completion pancreatectomy (65. mo) Chemotherapy peritoneal for carcinosis and liver metastases (66.-77.mo) left hemihepatectomy (79. mo) 	No sign for recurrence Regular FU (132 mo)
Patient 6 ♀ 10y	Enucleation	not assessed	21	DP for local recurrence (21. mo)	No sign for recurrence Regular FU (88 mo)
Patient 7 ♀ 8y	Enucleation, tumor rupture	not assessed	48	PD and liver resection for local and hepatic recurrence (48. mo)	No sign for recurrence Regular FU (221 mo)

Table 5

Follow-up: recurrence and long-term outcome in 49/52 patients (85%).

Outcome	10/2001-07/2018 n = 49
Postop follow up visits (n),median (range)	6 (1–20)
Median Follow up time, (months) after op, median (range)	54 (2–230)
Recurrence (n)	5/48 (10%)
Time to 1st recurrence, months, median (range)	21 (12–102)
Loss of function (in n patients)	n = 19 (39%)
• postop diabetes	2 (4%)
• exocrine insufficiency	19 (39%)
Postop. long-term complaints (in n patients)	n = 14 (29%)
• incisional hernia	3
• recurrent pancreatitis	5
• dumping syndrome	1
• reduced productivity	3
• abdominal pressure/nausea	2
• revision of the pancreaticojejunostomy	3

number, this observation supports an oncological approach in accordance with the European Guidelines for pancreatic cystic tumors [7]. Furthermore, the current experience for SPN shows that even almost 100 years after their first analysis by Frantz [1], entitled "Papillary tumors of the pancreas: benign or malignant", this question cannot finally be answered.

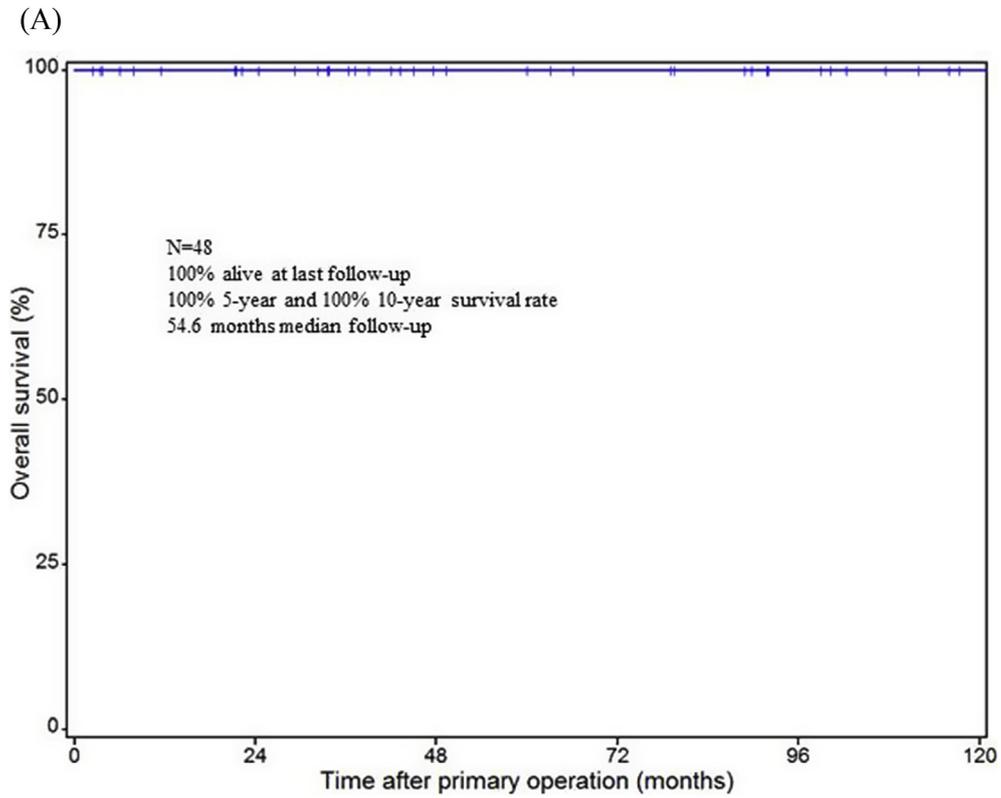


Fig. 1A. Overall survival.

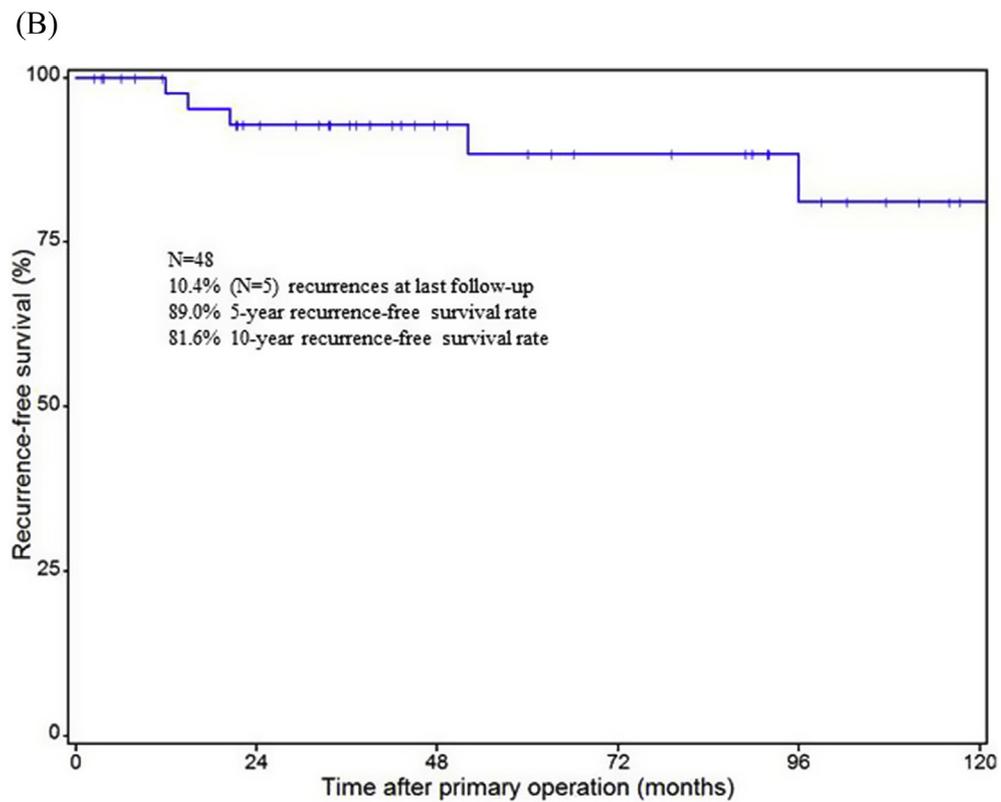


Fig. 1B. Recurrence free survival.

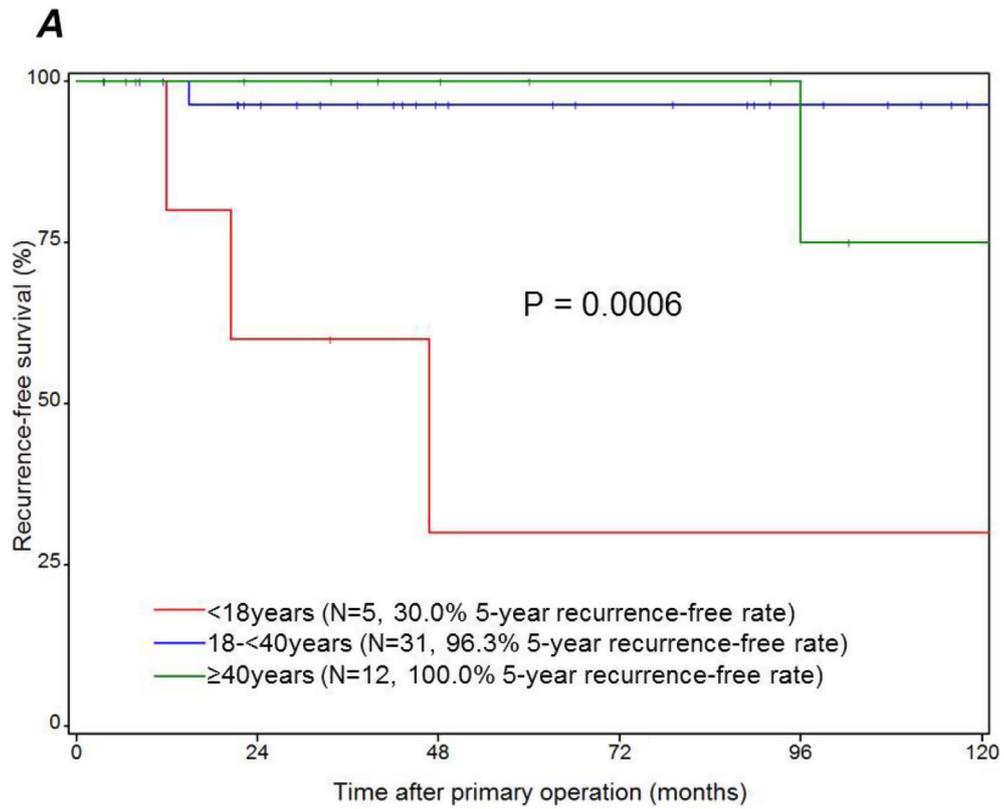


Fig. 2A. Recurrence-free survival according to age at primary resection.

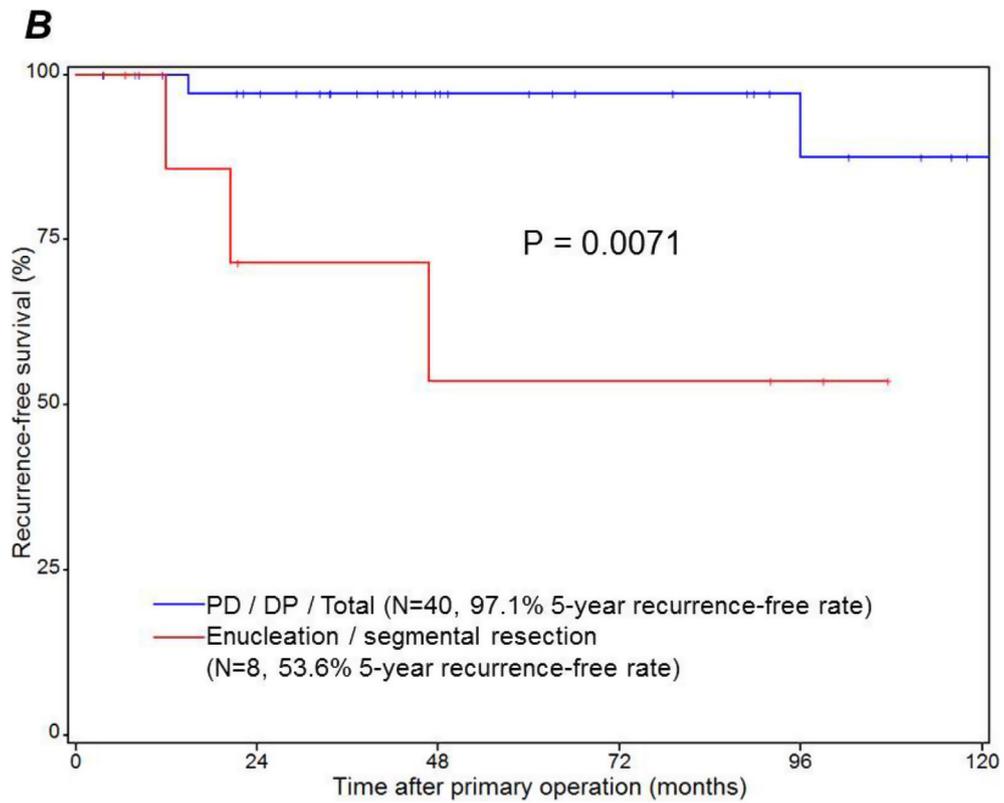


Fig. 2B. recurrence free survival according to type of resection.

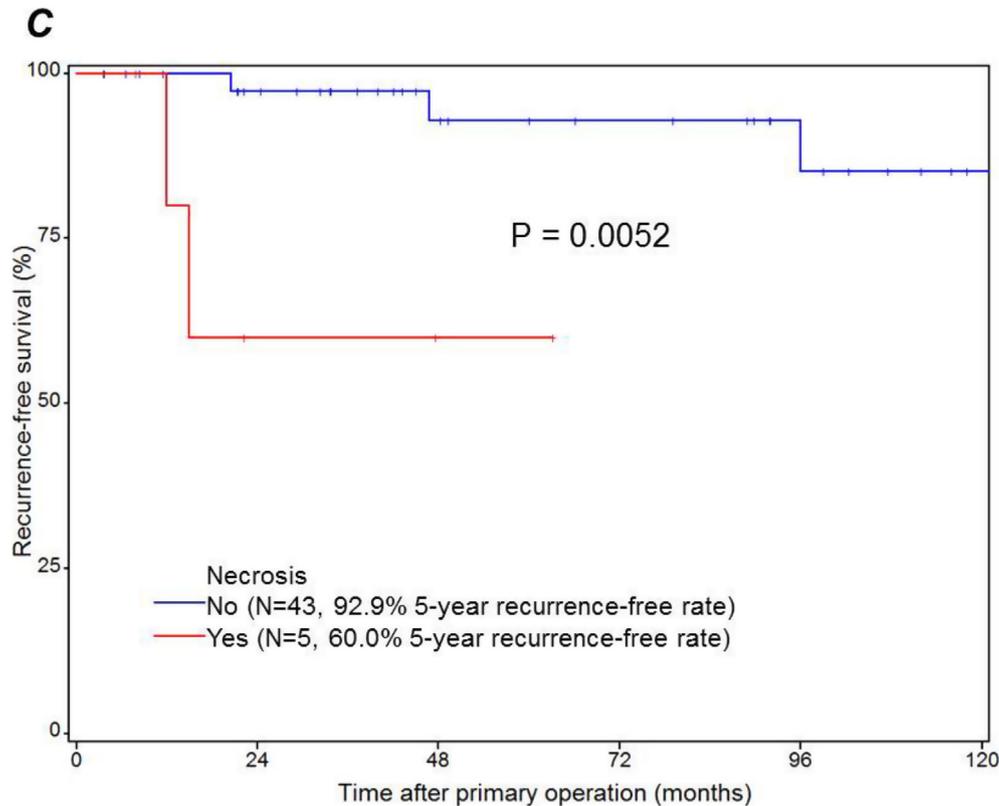


Fig. 2C. Recurrence-free survival according to tumor necrosis. 48 patients were considered (3 patients were lost to follow up, 1 patient underwent surgery < 6 months before data recording).

Conclusion

The present single-center study represents the largest experience in the surgical management of SPN in Europe. From the results, SPN can be characterized as a rare pancreatic tumor entity with an excellent prognosis independently from its relevant malignant potential. As this risk of malignancy can hardly be predicted at the time of diagnosis in most patients, an oncological resection should be chosen as the standard of care as limited approaches may be associated with an increased risk of recurrence and metastatic spread of the disease, significantly impairing patients' long-term prognosis. Furthermore, the observation of disease recurrence even more than 10 years after resection underlines the importance of a life-long follow-up for SPN patients postoperatively.

Disclosure of conflicts of interest

All authors declare no conflicts of interest.

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