Recurrence of Solid Pseudopapillary Neoplasms of the Pancreas: Results of a Nationwide Study of Risk Factors and Treatment Modalities

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Abstract word count: 249

Text word count: 2404

Brief running title: Risk factors for SPPN recurrence.

Keywords: solid pseudopapillary tumor, pancreas, recurrence, survival, pediatric.

Figures: 2

Tables: 3

Supplemental files: 2

Abbreviations	
SPPN	Solid pseudopapillary neoplasms of the pancreas
GCPOT	Group of Pediatric Surgeons Operating on Tumors
WHO	World Health Organization
HIPEC	hyperthermic intraperitoneal chemotherapy

Conflict of interest Statement

Dr S Irtan, Dr L. Galmiche-Rolland, Dr C. Elie, Dr D. Orbach, MD, Pr A. Sauvanet, Dr D. Elias, Dr F. Guérin, Dr C. Coze, Dr C. Faure-Conter, Pr F. Becmeur, Dr M. Demarche, Pr R.B.Galifer, Dr M.A. Galloy, Pr G. Podevin, Pr D. Aubert, Pr C. Piolat, Pr P. De Lagausie and Pr S. Sarnacki have no conflicts of interest or financial ties to disclose.

Abstract

Background: Solid pseudopapillary neoplasms of the pancreas (SPPN) can relapse very late, but little is known of risk factors for recurrence and of optimal treatment. We aimed to identify risk factors for recurrence and to analyze treatment modalities in all French pediatric cases of SPPN over the past 20 years.

Material and methods: Data were collected from pediatric oncologists and surgeons, and also from adult pancreatic surgeons in order to identify late recurrences.

Results: Fifty-one patients (41 girls) were identified. Median age at diagnosis was 13.1 years [8.7-17.9]. Abdominal pain was the commonest presenting symptom (32/49, 65%). The tumor was located in the pancreatic head in 24 patients (47%). Preoperative biopsy or cytology was performed in 14 cases (28%). All patients were operated on, a median of 23 days [0-163] after diagnosis. The rate of postoperative morbidity was 29%. With a median follow-up of 65 months [0.3-221], the overall and event-free survival was 100% and 71% respectively. Seven patients (13.7%) relapsed, a median of 43 months [33-94] after initial surgery. Six were treated surgically, either alone (n=3), or with perioperative chemotherapy (n=2) or hyperthermic intraperitoneal chemotherapy (n=1). One patient in whom further treatment was not feasible was still alive at last news. Risk factors for recurrence were positive surgical margins (p=0.03) and age less than 13.5 years at diagnosis (p=0.03).

Conclusion: SPPN recurrence in this pediatric series was a rare and late event that did not undermine overall survival. Complete surgical removal of recurrent tumors appears to be the best option.

Introduction

Originally described by Frantz in 1959 [1], solid pseudopapillary neoplasms of the pancreas (SPPN) took their definitive name from the last World Health Organization histologic classification of pancreatic tumors in 1996 [2]. Representing up to 1-2% of all exocrine pancreatic tumors in adults and 8-17% of pancreatic tumors in children, SPPN occurs mainly in females at an average age of 22 years, and is symptomatic in up to 80% cases [3]. The pathogenetic mechanisms are unknown. An origin from quiescent pancreatic stem cells (deregulation of the βcatenin signaling pathway with overexpression of Sox 9 and PDX1) [4] or from ovarian tissue [5] has been suggested. Abnormal nuclear accumulation of βcatenin (shown by immunohistochemistry) and associated point mutations within exon 3 of the *CTNNB1* gene, suggest a role of the Wnt signaling pathway [6,7]. The treatment of choice is complete surgical resection alone, as SPPN is considered to have low malignant potential (estimated doubling time 765 days) [8,9]. Recurrences have been reported up to 19 years after initial surgical resection [10], and there is no consensus on their management. In this French nationwide study, we collected pediatric cases of SPPN diagnosed over the past 20 years in order to study risk factors for recurrence and its treatment.

Patients and methods

In an attempt to identify all pediatric cases of SPPN diagnosed in France over the past 20 years and because no registry existed, we e-mailed all members of the Group of Pediatric Surgeons Operating on Tumors (GCPOT), which comprises all French surgeons involved in the treatment of pediatric tumors, including pancreatic tumors. Eighteen (66%) of the 27 centers contacted responded, of which 12 declared at least one patient (range 1 to 11) corresponding to our search criteria, for a total of 42 patients.

We also contacted adult surgeons involved in pancreatic surgery in all French University hospitals to determine if they had managed patients operated on for a SPPN in childhood or adolescence and who had relapsed in adulthood: 13 of the 25 surgeons contacted by email responded, of whom two declared relevant cases. In addition, one center had operated on seven adolescents (<18 y), who were added to the pediatric series.

In total, we collected data on 51 patients, of whom 16 have already been described in case reports or short series [11-15]. The data collected included demographic features (age at diagnosis, presenting signs and symptoms such as abdominal pain/trauma/mass, pancreatitis, and other incidental findings), biological and radiological characteristics (tumor size and location, homogeneity or heterogeneity, dilatation of the main pancreatic duct or common bile duct, invasion of adjacent organs, venous thrombosis), preoperative biopsy (percutaneous fine-needle aspiration or surgical biopsy), treatment modalities, postoperative morbidity, pathologic analysis of the specimen (presence of a capsule, resection margins, neural or vascular invasion, necrosis or lymphadenopathy, signs of tumor rupture) and survival. All the pathology reports were reviewed by a senior pathologist (LGR). If a recurrence was identified, we collected data on its diagnosis, treatment and outcome.

Statistical Analysis

R software (http://cran.r-project.org/) was used for all analyses. Quantitative data are expressed as mean (± SD) or median (range) and qualitative data as numbers or percentages. Follow-up was calculated from the date of surgery to the date of relapse or last follow-up. Survival was analyzed with the Kaplan-Meier method. Risk factors for recurrence were identified using the log-rank test for categorical variables and a Cox model for continuous variables.

Results

General features

The clinical features of the entire cohort are listed in Table I. Males and females were equally distributed according to age at diagnosis (Figure 1). The main presenting symptom was abdominal pain (n=32/49, 65%), associated with an abdominal mass (n=3) or abdominal trauma (n=3); other diagnostic circumstances included isolated abdominal trauma (n=4, 8%), isolated pancreatitis (n=3, 6%), or an isolated painless abdominal mass (n=2, 4%). The diagnostic circumstances were fortuitous in 5 patients (10%), unknown in 2 patients, and unusual in 3 patients (6%: jaundice and pruritus; hemorrhagic ulcer; or upper gastrointestinal bleeding revealing esophageal and gastric varices related to portal hypertension secondary to biliary cirrhosis due to common bile duct compression by the tumor) [12]. None of the patients had metastases or local tumor dissemination at initial diagnosis.

The tumors were mainly heterogeneous and located in the head of the pancreas (Table I). The median tumor size (longest axis) was 70 mm [20-180]. Extension to adjacent organs was observed in 3 patients (pancreato-splenic ligament in one case, and transverse mesocolon in two cases). Five patients had peritoneal effusion at diagnosis; one patient with hemoperitoneum had no malignant cells on cytology. No tumor rupture was seen on imaging studies.

Preoperative biopsy was performed by percutaneous fine needle aspiration in 10 patients (20%) and by laparoscopy in 2 patients. Per surgical frozen section was performed in 14 cases.

Treatment modalities and histologic characteristics of the resected specimen

All the patients underwent surgery, a median of 23 days [0-163] after diagnosis based on imaging or biopsy (Table II). Tumor resection was combined with cholecystectomy (n = 6), appendectomy (n = 4), colectomy (n=2), vascular suture (n=2), splenectomy (n=1), partial gastrectomy (n = 1) or jejunostomy (n = 1). The tumor was resected by laparoscopy in two cases.

Postoperative morbidity occurred in 29% of patients, a median of 13 days [4-83] after surgery (Table II). The main postoperative complication was pancreatic fistula (n=4), that resolved spontaneously in two cases and necessitated re-operation in one case (because of associated biliary leakage) and per-endoscopic drainage in another case.

One patient developed a seroma 4 years after surgery and underwent further surgery because of suspected recurrence. Two patients developed pseudocysts, 6 and 18 months after surgery, which resolved spontaneously in one case and was surgically drained in the other case. One patient developed left hepatic artery thrombosis after initial resection and underwent multiple surgeries for severe postoperative complications [11]. The patient with biliary cirrhosis underwent liver transplantation 7 years 8 months after tumor surgery [12]. Histologic analysis revealed a capsule in more than 80% of cases, and capsule invasion in half these cases. Signs of malignancy, as defined by the 2010 World Health Organization (WHO) classification, including vascular, perineural or peripancreatic tissue invasion, were present in 22 patients (43.1%): 16 patients had one criterion, five 2 criteria and one all 3 criteria (Table I).

Risk factors for relapse and treatment modalities

The overall and event-free survival rates at 15 years were respectively 100% and 71% [53-94] (Figure 2A). Seven patients (13.7%) relapsed, a median of 41.8 months after initial surgery [33-94]. One patient experienced two relapses at a 10.6-month interval. During a median follow-up of 65 months [0.3-221], recurrences were found in 5 patients by routine follow-up imaging (CT or MRI), by the occurrence of hypogastric pain in one patient, and by self-examination (mass) in one patient. The relapse was localized to the pancreas in two patients and disseminated to the whole peritoneum in the other five patients. One patient had chest nodules. The patients who relapsed had been diagnosed at a maximum age of 13.1 years, and all three patients diagnosed before the age of 10 years relapsed. Age at diagnosis was unknown in one patient who relapsed. The only significant risk factors for relapse were age under 13.5 years at diagnosis (p=0.03) (Figure 2B) and positive surgical margins at initial tumor resection (p=0.03) (Figure 2C). No significant influence of tumor size, tumor location, tumor rupture, percutaneous or surgical preoperative biopsy, vascular or peripancreatic tissue invasion was found (Table III).

At relapse, six patients underwent cytoreductive surgery, either alone (n=3) or with hyperthermic intraperitoneal chemotherapy (HIPEC) (n=1), pre-operative chemotherapy (four cycles of 5-FU - oxaliplatin – irinotecan, n=1) or postoperative chemotherapy (six cycles of 5-FU - oxaliplatin – irinotecan, n=1). The patient who received preoperative chemotherapy had stable disease at time of surgery and persistent chest nodules at the end of chemotherapy; these were carefully monitored and remained stable. In the last patient, the tumor recurred 3 years after initial surgery (subtotal resection) and invaded the head of the pancreas and the hepatic pedicle up to the gallbladder. Radical surgery with extensive pancreatic resection and liver transplantation was considered too risky and no treatment was delivered, but the patient was alive 20 months later.

Discussion

Published pediatric series of SPPN tumors are rare and small [8, 16-32], the largest including 45 patients aged from 9 to 20 years [32]. As no registry exists for this specific tumor in our country, we conducted the survey by emailing our colleagues, pediatric surgeons but also adult ones to retrieve late recurrences of patients operating during childhood. Although only 66% of French pediatric centers responded to our survey, we were able to collect data on 51 patients. Because of the specificities of pancreatic surgery, some adolescents were managed by adult surgeons, as in the majority of published series. Few previous studies of SPPN have separately analyzed adults and children [19]. The main features of SPPN in children are a higher frequency of abdominal pain [8,18,25,30,32] and fewer incidental diagnoses (22%) [19,33]. An exhaustive review of the literature shows that SPPN are equally distributed in the head, body and tail of the pancreas, and have a mean size of 7 cm (Supplemental Table I). Outcome is reported to be excellent, with an estimated recurrence rate of about 5.5%, comparing favorably with that in adults [3].

Clinical and pathological factors found to be predictive of recurrence in adult series or combined adult and pediatric series include male gender [34], younger age [19,35], abdominal injury or rupture [13,36,37], large tumor size [33,38] and microscopic features of malignancy such as vascular, perineural and peripancreatic tissue invasion [33,39,40]. Patients with metastases at diagnosis tend to be older [35,36,41] and are at a higher risk of recurrence and death [39,40].

In our series, the only two significant risk factors for relapse were age under 13.5 years at diagnosis and positive surgical margins after initial tumor resection. No significant influence of tumor size, tumor location, tumor rupture, percutaneous or surgical preoperative biopsy, and vascular or peripancreatic tissue invasion was noted.

The influence of young age at diagnosis in SPPN recurrence is in keeping with previous reports on patients treated for localized SPPN during childhood (Supplemental Table I). The explanation for this remains unclear. This may be due to a specific tumor biology according to age. In a previous analysis, we identified PDX1 and Sox9 proteins expression in the cytoplasmic compartment of SPPN, favoring the hypothesis that SPPN originated from transformation of quiescent pancreatic stem cells [4]. Analysis of genetic alterations by array comparative genomic hybridization reported several chromosomal abnormalities, such as 13q, 17q, 1q and 8q gains that positively correlated with more aggressive histologic feature of the tumor [42]. On the contrary, immunohistochemistry failed to demonstrate a link between the expression of MMP-7, cyclin-D1, c-myc, and Ki-67 and the potential malignancy of SPPN [43]. Central review of all specimen and analysis of molecular markers that could correlate with the aggressive behaviour was unfortunatly not possible in the present series because of its retrospective, multicentric and long-term nature.

Despite this limitation, we studied the presence of signs of malignancy, as perineural, peripancreatic or vascular invasion [26,30,44], which were recently reported to be a major risk factor for relapse in adults. These features were found to be an independent predictor of tumor relapse in multivariable analysis of a large multicenter cohort [33]. We found no histologic features predictive of recurrence, except for microscopically positive margins, which were found ten times more often in patients who relapsed.

There are few published data on the influence of positive margins [25], although complete surgical excision has always been recommended [3]. Different types of pancreatic resection are used according to the tumor location. In order to preserve long-term pancreatic exocrine and endocrine functions, enucleation was used in 13.7% of our patients, as compared to 8.2% overall in pediatric series (Supplemental Table II) and 4.7% in adults [3]. The high rate of conservative surgery could not be related to a younger age at surgery but might explain the

high frequency of microscopically positive margins in our patients who relapsed (60%). Postoperative complications, mainly related to pancreaticoduodenectomy and spleen-preserving distal pancreatectomy, occurred in 25% of our patients but are reported in up to 50% of cases after minimally invasive surgery [30]. Interestingly, none of our patients with postoperative complications relapsed.

Abdominal blunt injury has been incriminated in tumor spread at initial diagnosis [36,37], and laparoscopic biopsy was held responsible for peritoneal recurrence in the first report of laparoscopic management of SPPN [13]. Later studies supported the safety both of percutaneous needle aspiration [15,18] and of laparoscopy for the diagnosis and treatment of SPPN [29,30]. In our series, we found no significant influence of laparoscopy or tumor rupture, either pre- or peri-operatively, on the risk of relapse.

SPPN recurrences tended to occur late, up to 95 months after initial diagnosis in our series and 14 years in the literature, calling for very long-term follow-up [10]. Contrary to initial treatment, there is no consensus on the treatment of recurrences. Repeat resection of peritoneal seeding has been widely used, with good outcomes, even in case of incomplete removal (Supplemental Table I) [45,46]. Radiofrequency ablation seems the best option if liver metastases are not easily resectable (Supplemental Table I) [10,32,35]. The use of hyperthermic intraperitoneal chemotherapy has only been reported once in this setting [47]. The rationale for using this demanding surgical technique was that the tumor recurrences were often confined to the peritoneum and that systemic chemotherapy is ineffective, despite reported relapsed tumor shrinkage with etoposide-ifosfamide-cisplatinum [16] or 5FU-cisplatinum [48]. It remains to be seen whether this innovative technology has a place in the treatment of recurrent SPPN [49].

Conclusion

This large pediatric series confirmed that resection of SPPN in the pediatric population should be complete, even if it implies heavy surgery and reconstruction procedures. Microscopic malignant features were not associated with recurrence but should certainly be taken in account in individual patient management. Contrary to previous reports, tumor rupture did not seem to be deleterious, and laparoscopy did not appear to be contraindicated, when it allowed microscopically complete resection.

The complexity of this rare surgery in children and the need for long-term postoperative follow-up necessitate close collaboration between pediatric and adult teams. The high risk of recurrence observed in younger children is still not understood and underlines the need for further molecular analysis taking into account the potential developmental aspect of this pancreatic tumor.

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Figure Legends

Figure 1: Age distribution according to gender.

Figure 2: Disease-free survival (A) of the entire cohort with the confidence interval; (B) according to age at diagnosis; and (C) according to surgical margin status.

Table legends

Table I. Clinical, radiological and histological characteristics.

Table II. Type of surgery and related morbidity for the management of primary tumor.

Table III. Differences between disease-free and recurrent SPPN.

Supplemental Table I. Details of treatment for recurrent SPPN in the literature.

Supplemental Table II. Specific pediatric series of primary SPPN highlighting the clinical features, treatment modalities and outcome.

Fig. 1

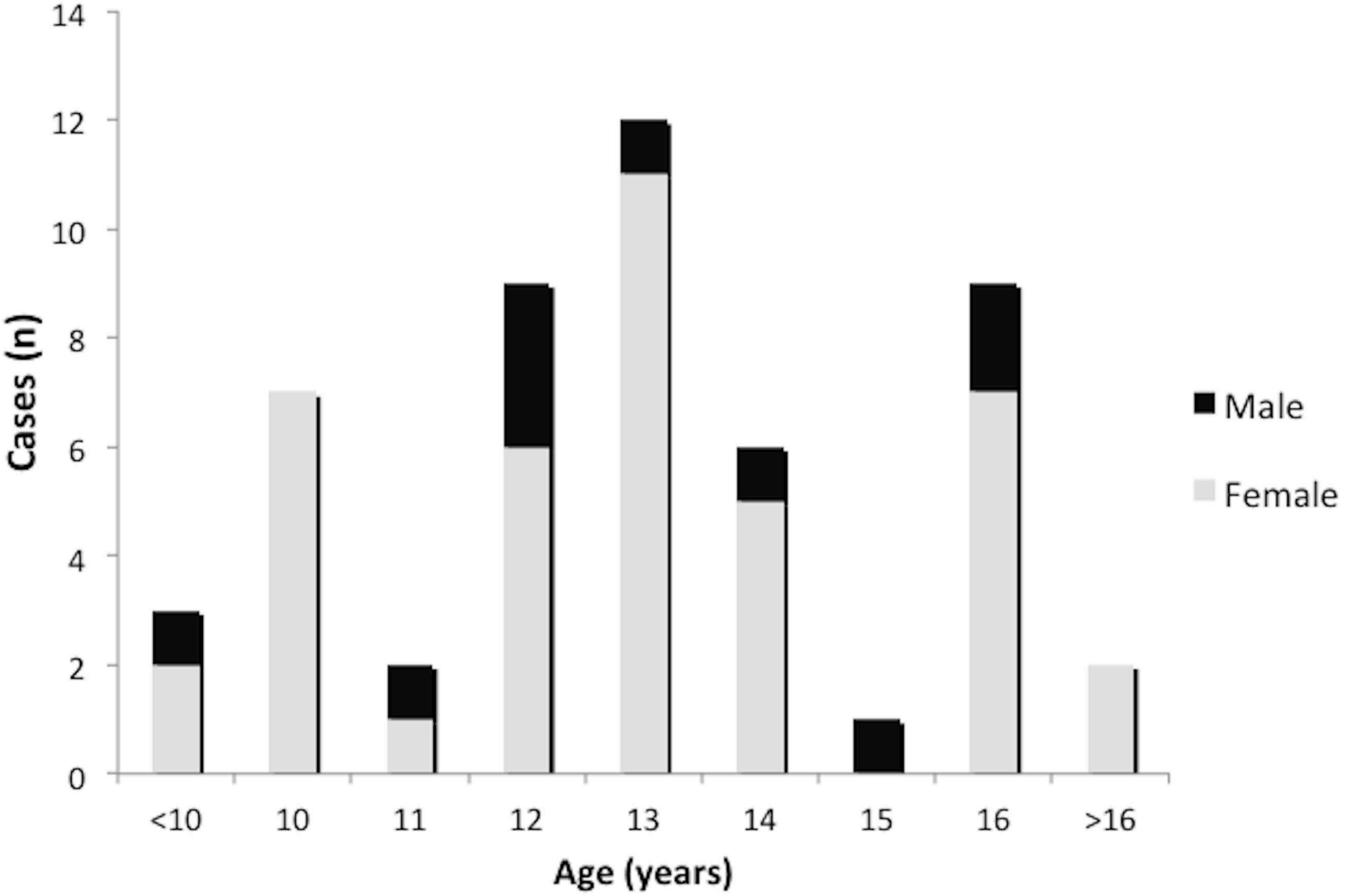
14
12
10
8
6
4
2
0
Cases (n)
<10
10
11
12
13
14
15
16
>16
Age (years)
Male
Female

Fig. 2

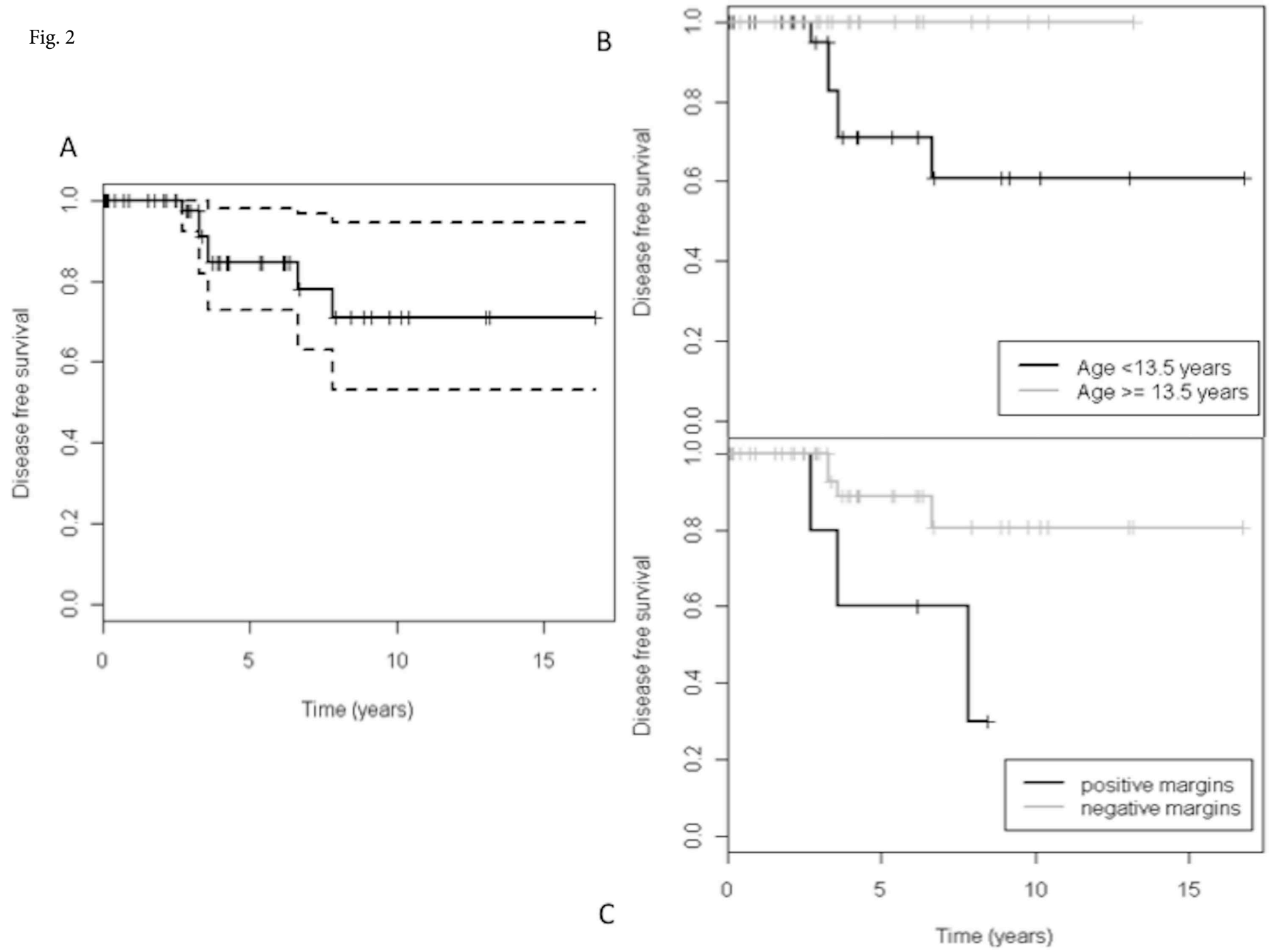
A
Disease free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
Time (years)
B
Disease free survival
Age <13.5 years
Age >= 13.5 years
C
Disease free survival
positive margins
negative margins
Time (years)

Table I. Clinical, radiological and histological characteristics

Clinical Features	**Frequency, %, median [range]**
Sex	
Male	10/50 (22%)
Female	41/50 (78%)
Age, year	13.1 [8.7-17.9]
Symptoms	
Yes	45/49 (88%)
No	6/49 (12%)
Radiological Features	
Location	
Head	24 (47%)
Isthmus	2 (4%)
Body	8 (16%)
Tail	17 (33%)
Radiological appearance	
Heterogeneity	44 (86%)
Solid	5 (10%)
Homogeneity	1 (2%)
Hypodensity	1 (2%)
Tumor size, mm	70 [20-120]
Abdominal effusion	5/50 (10%)
Dilatation of main pancreatic duct	9/50 (18%)
Dilatation of common bile duct	3/50 (6%)
Pathological features	
Presence of capsule	42/50 (84%)
Capsule invasion	21 (50%)
Vascular invasion	8/50 (16%)
Perineural invasion	12 (24%)
Peripancreatic tissue invasion	7 (14%)
Positive margins	5 (10%)
Lymph nodes metastasis	1 (2%)
Tumor rupture	2 (4%)
Tumor necrosis	11/50 (22%)

Table II. Type of surgery and related morbidity for the management of primary tumor.

Type of Surgery	Nb of patients	Morbidity
Pancreaticoduodenectomy	18 (35%)	Pancreatic fistula (n=1) Pleural effusion (n=1) Delayed gastric emptying (n=1) Stenosis of the pancreatojejunal anastomosis (n=1) Twist of the biliodigestive anastomosis (n=1) Thrombosis of the hepatic artery (n=1)
Central pancreatectomy	6 (12%)	Pancreatic and biliary fistula (n=1)
Distal pancreatectomy + splenectomy	8 (16%)	None
Spleen preserving distal pancreatectomy	12 (23%)	Pancreatic fistula (n=1) Left gastric artery bleeding (n=1) Seroma (n=2)
Tumor enucleation	7 (14%)	Pancreatic fistula (n=1)

Nb Number

Table III. Differences between disease-free and recurrent SPPN.

	Number of subjects	Number of recurrences (%*)	p-value (Log Rank test)
Age, yr**			0.03
<13.5 y	29	6 (39%)	
≥ 13.5 y	20	0 (0%)	
Sex			0.92
Male	10	1 (25%)	
Female	41	6 (29%)	
Clinical features			
Abdominal pain**			0.38
No	17	4 (33%)	
Yes	32	3 (14)	
Abdominal trauma**			0.19
No	42	4 (15%)	
Yes	7	2 (63%)	
Tumor size, mm			0.10
<80	21	3 (19%)	
≥80	13	4 (52%)	
Tumor location			0.33
Head	24	2 (21%)	
Isthmus	2	1 (50%)	
Body	8	0 (0%)	
Tail	17	4 (40%)	
Morbidity			0.07
No	36	7 (39%)	
Yes	15	0 (0%)	
Pathological features			
Presence of capsule***			0.55
No	8	1 (14%)	
Yes	42	6 (34%)	
Capsule invasion***			0.65
No	20	2 (31%)	
Yes	21	3 (35%)	
Vascular invasion***			0.18
No	42	4 (16%)	
Yes	8	2 (0%)	
Perineural invasion			0.74
No	39	5 (30%)	
Yes	12	2 (21%)	
Peripancreatic tissue invasion			0.78

No	44	6 (32%)	
Yes	7	1 (17%)	
Positive margins			0.03
No	46	4 (19%)	
Yes	5	3 (70%)	
Lymph nodes metastasis			0.55
No	50	7 (31%)	
Yes	1	0 (0%)	
Tumor rupture			0.61
No	49	7 (30%)	
Yes	2	0 (0%)	
Tumor necrosis			0.20
No	40	7 (34%)	
Yes	11	0 (0%)	

*percentage of recurrence is calculated from Kaplan-Meyer estimation for each subgroups (i.e. taking into account censored patients)
** two missing data
*** one missing data