

Pancreaticoduodenectomy for the treatment of pancreatic neoplasms in children: a Pediatric Surgical Oncology Research Collaborative study

Short Running Title: Pancreaticoduodenectomy in children

Sanjeev A. Vasudevan, MD<sup>1</sup>, Tu-Anh N. Ha, MD<sup>1</sup>, Huirong Zhu, PhD<sup>1</sup>, Todd E. Heaton, MD<sup>2</sup>, Michael P. LaQuaglia, MD<sup>2</sup>, Joseph T. Murphy, MD<sup>3</sup>, Wesley E. Barry, MD<sup>4</sup>; Catherine Goodhue, RN<sup>4</sup>; Eugene S. Kim, MD<sup>4</sup>, Jennifer H. Aldrink, MD<sup>5</sup>, Stephanie F. Polites, MD, MPH<sup>6</sup>, Harold J Leraas, MD<sup>7</sup>, Henry E Rice, MD<sup>7</sup>, Elisabeth T Tracy, MD<sup>7</sup>, Timothy B Lutz, MD<sup>8</sup>, Riccardo A Superina, MD<sup>8</sup>, Andrew M. Davidoff, MD<sup>9</sup>, Max R. Langham, Jr, MD<sup>9</sup>, Andrew J. Murphy, MD<sup>9</sup>, Andreana Bütter, MD<sup>10</sup> Jacob Davidson, MSc<sup>10</sup>, Richard D. Glick, MD<sup>11</sup>, James Grijalva, MD<sup>12</sup>, Kenneth W. Gow, MD<sup>12</sup>, Peter F. Ehrlich, MD, MSc<sup>13</sup>, Erika A. Newman, MD<sup>13</sup>, Dave R. Lal, MD, MPH<sup>14</sup>, Marcus M. Malek, MD<sup>15</sup>, Annie Le-Nguyen, MD<sup>16</sup>, Nelson Piché, MD<sup>16</sup>, David H. Rothstein, MD, MS<sup>17</sup>, Scott S. Short, MD<sup>18</sup>, Rebecka Meyers, MD<sup>18</sup>, Roshni Dasgupta, MD, MPH<sup>6</sup>

<sup>1</sup> Division of Pediatric Surgery, Michael E. DeBakey Department of Surgery, Texas Children's Surgical Oncology Program, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, US

<sup>2</sup> Division of Pediatric Surgery, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York City, NY, US

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/pbc.28425](https://doi.org/10.1002/pbc.28425).

This article is protected by copyright. All rights reserved.

Author Manuscript

<sup>3</sup>Division of Pediatric Surgery, UT Southwestern Medical School, Children's Medical Center, Dallas, TX, US

<sup>4</sup>Division of Pediatric Surgery, Department of Surgery, Children's Hospital Los Angeles, USC Keck School of Medicine, Los Angeles, CA, US

<sup>5</sup> Division of Pediatric Surgery, Department of Surgery, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, US

<sup>6</sup> Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, US

<sup>7</sup> Division of Pediatric Surgery, Duke University Medical Center, Durham, NC, US

<sup>8</sup> Division of Pediatric Surgery, Division of Transplant Surgery, Ann & Robert H Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, US

<sup>9</sup> Department of Surgery, St. Jude Children's Research Hospital, University of Tennessee Health Science Center, Memphis, TN, US

<sup>10</sup> Division of Pediatric Surgery, Children's Hospital, London Health Sciences Centre, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

<sup>11</sup> Division of Pediatric Surgery, Cohen Children's Medical Center, Zucker School of Medicine at Hofstra/Northwell, Queens, NY, US

<sup>12</sup> Division of Pediatric Surgery, Seattle Children's Hospital, Seattle, WA, US

<sup>13</sup> Department of Surgery, C.S. Mott Children's Hospital, The University of Michigan, Ann Arbor, MI, US

<sup>14</sup> Division of Pediatric Surgery, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, US

<sup>15</sup> Division of Pediatric General and Thoracic Surgery, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, PA, US

<sup>16</sup> Division of Pediatric Surgery, CHU Sainte-Justine, University of Montreal, Montreal, Qc, Canada

<sup>17</sup> Department of Pediatric Surgery, John R. Oishei Children's Hospital, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, US

<sup>18</sup> Division of Pediatric Surgery, Primary Children's Hospital, University of Utah School of Medicine, Salt Lake City, UT, US

Corresponding Author: Sanjeev A. Vasudevan, MD, Division of Pediatric Surgery, Michael E. DeBakey Department of Surgery, Texas Children's Surgical Oncology Program, Dan L. Duncan Cancer Center, Baylor College of Medicine, 6701 Fannin, Houston, TX, 77030, Tel- 832-824-3135, Email- sanjeevv@bcm.edu

This study was previously presented as an oral poster at the American Academy of Pediatrics 2018 Annual Meeting in Orlando, Florida from November 2-6, 2018.

All authors made substantial contributions to the design, acquisition, analysis, and interpretation of data for this study, drafted and/or revised it for important intellectual content, gave final approval of this manuscript to be published, and agreed to be accountable for all aspects of this study.

Word count: abstract - 244. Main text – 2,632.

Tables: 4. Supplementary tables: 3

Figures: 2

Keywords: pancreaticoduodenectomy, Whipple, pancreatic neoplasms, children, solid pseudopapillary tumor of the pancreas, pancreatoblastoma

PD	pancreaticoduodenectomy
PSORC	Pediatric Surgical Oncology Collaborative
SPN	Solid pseudopapillary tumor of the pancreas
EUS	Endoscopic ultrasound

## Abstract

Background: To better characterize short and long-term outcomes in children with pancreatic tumors treated with pancreaticoduodenectomy (PD).

Methods: Patients 21 years of age or younger who underwent PD at Pediatric Surgical Oncology Collaborative (PSORC) hospitals between 1990-2017 were identified. Demographic, clinical information and outcomes (operative complications, long-term pancreatic function, recurrence, and survival) were collected.

Results: Sixty-five patients from 18 institutions with a median age of 13 years (4 months – 22 years) and a median (IQR) follow up of 2.8 (4.3) years were analyzed. Solid pseudopapillary tumor of the pancreas (SPN) was the most common histology. Postoperative complications included pancreatic leak in 14% (n=9), delayed gastric emptying in 9% (n=6), marginal ulcer in 1 patient, and perioperative (30-day) death due to hepatic failure in 1 patient. Pancreatic insufficiency was observed in 32% (n=21) of patients, with 23%, 3%, and 6% with exocrine, or endocrine insufficiencies, or both, respectively. Children with SPN and benign neoplasms all survived. Overall, there were 14 (22%) recurrences and 11 deaths (17%). Univariate analysis revealed non-SPN malignant tumor diagnosis, preoperative vascular involvement, intraoperative transfusion requirement, pathologic vascular invasion, positive margins, and need for neoadjuvant chemotherapy as risk factors for recurrence and poor survival. Multivariate analysis only revealed pathologic vascular invasion as a risk factor for recurrence and poor survival.

Conclusion: This is the largest series of pediatric PD patients. PD is curative for SPN and benign neoplasms. Pancreatic insufficiency is the most common postoperative complication. Outcome is primarily associated with histology.

## **Introduction**

Pancreatic tumors are an uncommon diagnosis amongst children, with an incidence of pancreatic malignancies in children of only 0.018 per 100,000 in the US, compared to 12.6 per 100,000 adults<sup>1,2</sup>. Pancreatic neoplasms requiring pancreaticoduodenectomy (PD) in children are even more rare<sup>3</sup>. Literature on short and long-term outcomes after PD in children is very limited<sup>4</sup>. Due to the low incidence of PD being performed at any one institution, a multi-institutional retrospective review of children undergoing PD was initiated through the Pediatric Surgical Oncology Research Collaborative (PSORC), a multi-institutional collaborative with the aim of furthering research in pediatric surgical oncology. The purpose of this study was to perform a comprehensive analysis of children with pancreatic tumors undergoing PD with a focus on preoperative evaluation, operative technique, perioperative care, and short- and long-term complications to better understand the perioperative problems, and to ultimately improve the surgical care of these patients.

## **Methods**

Patients 21 years of age or younger who underwent PD for pancreatic tumors at PSORC member institutions between 1990-2017 were identified. Demographic, clinical information and outcomes (operative complications, long-term pancreatic function, recurrence, and survival) were retrospectively extracted from medical records.

Operative complications were all defined and diagnosed by each member institution's surgeon and treatment team. Short-term complications (pancreatic leak, marginal ulcer,

perioperative death, gastroduodenal artery bleed, and biliary stricture) were all defined clinically. Long-term complications (exocrine, endocrine pancreatic insufficiency, and delayed gastric emptying) were defined as requiring medical or surgical intervention. Specifically, exocrine insufficiency was defined as requiring prolonged pancreatic enzymes. Endocrine insufficiency was defined as requiring anti-hyperglycemics or insulin. Vitamin deficiency was defined as requiring fat soluble vitamin (A, D, E, or K) supplementation. Statistical analyses, performed by an outcomes statistician at Texas Children's Hospital who is the third author of this study, included Fisher's exact and Mann Whitney tests when appropriate. Univariate log rank/cox modeling and multivariate cox modeling were used to analyze correlations with recurrence and survival. Results were considered significant at a  $P$  value of  $<0.05$ . This study was approved by each participating PSORC member institution's review board. Data use agreements between all participating PSORC member institutions and the lead institution for this study were established.

## Results

### Demographics and clinical characteristics

Sixty-five children from 18 institutions who underwent PD for treatment of pancreatic tumors were identified. Within the 27-year period, each hospital reported a median of 2.5 cases (range 1- 15 cases). The demographic, diagnostic, and treatment characteristics are summarized in Table 1. The median age at diagnosis was 13 years (range 4 months – 21 years) and the majority of patients were Caucasian. Underlying genetic abnormalities identified in the cohort include Beckwith-Wiedemann syndrome

and Lynch syndrome, each in two patients. The most common diagnosis was solid pseudopapillary tumor of the pancreas (SPN) (n=34, 52%) (Table 2). Preoperative diagnostic evaluation included endoscopic ultrasound (EUS) biopsy (n=18, 28%), cross-sectional imaging alone (n=15, 23%), open biopsy (n=10, 15%), percutaneous biopsy (n=7, 11%), with the remainder (n=15, 23%) being unspecified. Of the patients later found to have SPN after surgical resection, 19 (56%) underwent a pre-operative biopsy. Data regarding whether percutaneous biopsy was FNA at the time of EUS versus core needle biopsy was not recorded. All patients underwent advanced imaging. The presence or absence of preoperative biopsy (including EUS biopsy, open biopsy, and percutaneous biopsy) had no significant association with postoperative complications, recurrence, or death ( $p>0.5$ ). Twenty-three percent (n=15) of patients showed tumor involvement of either the superior mesenteric artery (SMA), superior mesenteric vein (SMV), portal vein, and/or middle colic artery on preoperative workup, of whom 67% (n=10) had non-SPN malignant tumors.

#### Treatment

All patients underwent open PD. An adult hepatobiliary surgeon assisted with or performed the PD in 34% of the cases (n=22). A pylorus-preserving PD (63%) with a perianastomotic drain (68%) was the most common procedure performed. Two patients underwent vascular reconstruction. Both of these patients had pancreaticoblastoma. One patient underwent a portal vein reconstruction because a tumor thrombus was found in the portal vein. The other patient underwent portal vein and hepatic artery reconstruction because tumor was encasing the portal vein, hepatic artery, and superior mesenteric vein. None of the patients with SPN underwent neoadjuvant or adjuvant chemotherapy. Data regarding the specific neoadjuvant and



adjuvant chemotherapy regimens were not recorded in this study. Twenty-nine percent (n=19) and 12% (n=8) of patients received an intraoperative or postoperative packed red blood cell (PRBC) transfusion, respectively. Sixty-nine percent (n=45) of patients required ICU care postoperatively. The median hospital length of stay was 12 days (3-56 days). Positive margins and vascular invasion on histology were found in 9 (14%) and 14 (22%) patients, respectively.

### Complications

Short-term postoperative complications (Table 3) were defined as complications persisting less than 30 days after PD and included pancreatic leak in 14% of patients (n=9), marginal ulcer in 1 patient (2%), and perioperative death due to hepatic failure in 2% of patients (n=1). No patient suffered from gastroduodenal bleeding or biliary stricture postoperatively. For short-term postoperative complications, Clavien-Dindo grades I (n=1), II (n=2), III (n=2), and V (n=1) were present<sup>5</sup>. Long-term postoperative complications (Table 4) were defined as complications at 1 year or greater after PD and included pancreatic insufficiency in 21 patients (32%), delayed gastric emptying in 6 patients (9%), and vitamin deficiencies in 3 patients (5%). For long-term postoperative complications, Clavien-Dindo grades II (n=4) and III (n=1) were present<sup>5</sup>. No risk factors for pancreatic leak were identified while longer operative times and ICU length of stays were associated with long-term complications (Supplementary table 1).

### Outcomes

The median (IQR) follow-up was 2.8 years (4.3 years). Overall, 28% of patients (n=18) had over 5 years of follow-up. Five percent of patients (n=2) developed a second malignancy. One patient with Lynch syndrome who underwent PD for duodenal

adenocarcinoma later developed both colon and breast adenocarcinoma, and another patient who underwent PD for pancreatic neuroblastoma later developed dermatofibrosarcoma protuberans. Children with SPN and benign neoplasms all survived. Out of the patients with SPN, positive margins and vascular invasion on histology were both found 2 patients (6%). The remainder of the patients with SPN had negative margins and no vascular invasion on pathology. Of the patients with SPN, only 1 patient (3%) had recurrence. The patient with SPN who had recurrence had positive margins and vascular invasion on pathology. Overall, there were 14 (22%) recurrences (Figure 1) with 11 deaths (17%) (Figure 2). The median time to recurrence from date of PD was 1.5 years (46 days – 4.4 years). Significant risk factors for recurrence on univariate analyses included need for neoadjuvant chemotherapy, preoperative vascular involvement, non-SPN malignant tumor, intraoperative transfusion requirement, pathologic vascular invasion, and positive margins (Supplementary table 2). Similarly, significant risk factors for death on univariate analyses also included need for neoadjuvant chemotherapy, preoperative vascular involvement, non-SPN malignant tumor, intraoperative transfusion requirement, pathologic vascular invasion, and positive margins (Supplementary table 2). Vascular invasion on pathology (HR=8.293, CI=1.101- 62.460, p=0.0400; HR=11.235, CI=1.052 -120.025, p=0.0453) was found to be an independent predictor of both recurrence and death on multivariate analyses (Supplementary table 3). Neither recurrence nor survival was impacted by age, race, operative time, insurance status, preoperative comorbidities, presence of an hepatobiliary surgeon specializing in care of adults, type of PD, type of pancreaticojejunostomy, use of stents or use of drains.

## Discussion

Pancreaticoduodenectomy, also known as the Whipple procedure, is the gold standard for surgical treatment of pancreatic malignancies involving the head of the pancreas in adults<sup>6,7</sup>. However, due to the rarity of pancreatic neoplasms in children, reports on outcomes of PD in children are limited. We utilized the PSORC to identify and examine 65 patients at 18 different institutions to enrich the literature on outcomes and complications of PD in children.

Cross-sectional imaging alone, including CT and/or magnetic resonance imaging (MRI), was used for preoperative diagnostic evaluation in 15 children in our study. MRI is often used in children due to the risks of radiation exposure with high resolution CT and better tissue characterization to detect occult lesions.<sup>8,9,10</sup> Endoscopic ultrasound (EUS) biopsy (n=18) was most commonly used for preoperative diagnostic evaluation in our study. Overall, EUS was utilized during preoperative workup in 20 children. A study performed by Law et al showed an increase in diagnostic accuracy from 24% with CT alone to 82% with the addition of EUS with fine needle aspiration (FNA) for the diagnosis of SPN<sup>11</sup>. We did not collect data on the diagnostic accuracy of FNA versus core needle biopsy. However, a study showed that FNA could be 100% diagnostic for SPN with detection of the *CTNNB1* ( $\beta$ -catenin) mutation<sup>12</sup>. This study was not performed in children specifically but could be a viable approach to diagnosing SPN.

In our study, 10 patients underwent open biopsy and 7 patients underwent percutaneous biopsy. The utility in obtaining a preoperative biopsy in children would be to distinguish between SPN and other malignant pathologies. In the Nasher *et al* study, children with pancreatic tumors (n=14) all had preoperative transabdominal ultrasound and CT scans and only 1 patient underwent a pre-excisional biopsy<sup>13</sup>. All

children had complete surgical resection of the pancreatic mass and the authors concluded that the majority of children with pancreatic tumors are good surgical candidates since they present with isolated lesions<sup>13</sup>.

The most common overall histologic diagnosis was SPN. Similar to previous studies, the most common pancreatic malignancy in younger children (10 years, range 4 – 18 years) was pancreatoblastoma while that in older children (14 years, range 8 – 19 years) was SPN<sup>2,14-17</sup>. SPN does have a typical appearance on MRI and does not require sampling to confirm; however, differentiating the diagnosis of pancreatoblastoma from SPN can be challenging without an elevation in alpha fetoprotein (AFP)<sup>18</sup>. The pathognomonic squamoid corpuscles of pancreatoblastoma would only be visible on histology; therefore, sampling of the tumor may be of value when this diagnosis is suspected so that neoadjuvant chemotherapy can be used to reduce the tumor size prior to surgery<sup>19</sup>. SPN is a low-grade malignancy with minimal metastatic potential, and multiple other studies have likewise reported excellent prognosis after resection<sup>14,16,20,21</sup>.

While a diagnosis of non-SPN malignant tumor was found to be a risk factor for both recurrence and death, children with SPN all survived and only one child with SPN had recurrence in this study. The patient with recurrence originally underwent enucleation of a pancreatic head SPN at an outside hospital. The enucleated mass had positive margins. This patient then presented with recurrent pancreatic head SPN and underwent a PD at a PSORC institution and had no recurrence after PD. Enucleation is a technique that can be used for SPN pathology in a subgroup of patients with the proper anatomic relations<sup>22-26</sup>. A head of the pancreas mass is usually very close to the portal vein/SMV, bile duct, and pancreatic duct; therefore successful enucleation with a negative margin may not be possible. A few studies have reported enucleation in

children with SPN where positive margins seem to be associated with recurrence<sup>20,21,27</sup>.

These results collectively suggest that negative margin resection should be the goal of surgical resection for SPN since adjuvant therapy is currently not recommended.

The majority of our patients underwent pylorus-preserving PD. We found that there was no significant difference in short- or long-term complications, recurrence, or death between patients who underwent pylorus-preserving PD versus non-pylorus-preserving PD similar to what is seen in adults<sup>28</sup>. Duct-to-mucosa and sock-type pancreaticojejunostomies were performed at equal rates in our study. The type of pancreaticojejunostomy had no significant difference in short- or long-term complications or death which was again consistent with adult literature<sup>29</sup>. Most of our patients had a perianastomotic drain placed. The presence or absence of a drain had no significant effect on the short- or long-term complications or death. The majority of patients with SPN in our study did not undergo chemotherapy.

Twenty-nine percent (n=19) of patients received an intra-operative PRBC transfusion, with a median of 2 PRBC units (0.5 - 8 PRBC units). Intraoperative PRBC transfusion was found to be a significant risk factor for both death and recurrence on univariate analysis. Although an association between PRBC transfusion and outcomes in children after PD has not been established, this association has been shown in adults. Yeh *et al* and Kneuert *et al* both found perioperative PRBC transfusion to be an independent predictor of recurrence and death after PD in adults<sup>30,31</sup>. However, our study differs from these studies in that intraoperative, but not postoperative, transfusion of PRBC was found to be significantly associated with recurrence (p=0.045) and survival (p=0.0017). While the definitive mechanism behind the impact of PRBC transfusion on disease recurrence and death is currently unknown, intraoperative transfusion

requirement may be a proxy for the proximity of the tumor to major vessels, thus rendering the achievement of negative margins more technically challenging. This may explain why PRBC transfusion was not an independent risk factor for recurrence or death.

The most common short-term postoperative complication was pancreatic leak, found in 14% (n=9) of our patients. Lindholm *et al* and Choi *et al* reported pancreatic leak rates at 8% (n=1) and 9% (n=2) in children after PD, respectively<sup>14,17</sup>. The mean and standard deviation operative times for patients in this study with and without pancreatic leak were  $476 \pm 201$  and  $374 \pm 188$  minutes, respectively, although this was not statistically significant (p=0.14). We found that preoperative comorbidities, need for neoadjuvant chemotherapy, assistance by an adult hepatobiliary surgeon, type of pancreaticojejunostomy anastomosis, peri-anastomotic drain, postoperative chemotherapy, and postoperative radiation were not associated with pancreatic leak. Additionally, non-SPN malignant diagnoses had a similar rate of short-term postoperative complications compared to the SPN and benign group.

Long-term postoperative complications included delayed gastric emptying, vitamin, and pancreatic deficiencies. Notably, 42% of patients in our study had some form of long-term postoperative complication. The pancreatic insufficiency rate of 32% (n=21) is less than the reported rates of 60%-83% in the literature for children undergoing PD<sup>17,32</sup>. Additionally, of the patients with pancreatic insufficiency, 71% had exocrine insufficiency which were all successfully treated with pancreatic enzyme supplementation. The finding of delayed gastric emptying in 9% (n=6) of patients is less than the 17% reported by Lindholm *et al* (n=2)<sup>17</sup>. Of the 6 patients with delayed gastric emptying, only 1 underwent a pylorus preserving PD while the other 5 did not have a

pylorus preserving PD. Non-SPN malignant diagnoses also had a similar rate of long-term postoperative complications compared to patients with SPN. The association between presence of long-term complications and ICU length of stay is difficult to explain. We can only speculate that ICU length of stay is a proxy for more complex surgery and more extensive pancreatic resection leading to the eventual development of these complications.

The recurrence and mortality rates in this series were 22% and 17%, respectively, during a median (IQR) follow up of 2.8 (4.3) years. Other studies of children who have undergone PD for pancreatic tumors reported a recurrence rate of 43% and mortality rates of 13% - 58%<sup>15,17,32</sup>. Perez *et al* concluded that survival for children with malignant pancreatic tumors is significantly greater for patients who have surgery compared to those who do not undergo surgical resection ( $p=0.001$ )<sup>2</sup>. The effect of PD volume at a single institution on the complication, recurrence, and survival rates could not be determined given that the median number of cases per institution was relatively low at 2.5 cases, with the number of total cases ranging from 1-15 (IQR 3) with 5 institutions having only 1 case.

There are several limitations to this study. The retrospective nature of this study invariably results in some missing data. Additionally, since this was a retrospective study, uniform criteria for postoperative complications were not defined in advance. The inclusion criteria for this study was broad and not disease specific by necessity. Weaknesses include a lengthy study period of 27 years and the inclusion of a breadth of ages of children with varying pathologies in the head of the pancreas requiring PD. Regardless of these limitations, a prospective study of PD in children will be unlikely due to the low number of cases in any one institution; however, we feel that this multi-

center consortium approach has provided guidance on operative methods, expected complication rates, and outcomes of children undergoing PD for neoplasm.

### **Conclusion**

PD can be performed safely in children for the treatment of pancreatic neoplasms.

Pylorus-preserving PD with a peri-anastomotic drain is the most common procedure.

Pancreatic leak and pancreatic exocrine insufficiency are the most common short-term and long-term postoperative complications, respectively. Outcomes in this study were primarily associated with histology.

### **Conflicts of Interest**

No financial disclosures or conflicts of interest to report.

### **Acknowledgements**

The consortium would like to acknowledge Misty Troutt for organizing all of the member institutions, managing the central IRB approval and data use agreements.

### **References**

1. Browse the Tables and Figures - SEER Cancer Statistics Review (CSR) 1975-2015. *SEER* Available at: [https://seer.cancer.gov/archive/csr/1975\\_2015/browse\\_csr.php?sectionSEL=22&pageSEL=sect\\_22\\_table.05](https://seer.cancer.gov/archive/csr/1975_2015/browse_csr.php?sectionSEL=22&pageSEL=sect_22_table.05). Accessed: 16th June 2019.



2. Perez EA, Gutierrez JC, Koniaris LG, Neville HL, Thompson WR, Sola JE. Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. *J. Pediatr. Surg.* 2009; 44: 197–203.
3. Jaksic T, Yaman M, Thorner P, Wesson DK, Filler RM, Shandling B. A 20-year review of pediatric pancreatic tumors. *Journal of Pediatric Surgery.* 1992; 27(10): 1315–1317.
4. Shamberger R, Hendren W, Leichtner A. Long-term nutritional metabolic consequences of pancreaticoduodenectomy in children. *Surgery.* 1994; 115: 382–388.
5. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications. A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Annals of Surgery.* 2004; 240 (2): 205–213.
6. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: Early misconceptions, initial milestones and the pioneers. *Hpb.* 2011; 13: 377–384.
7. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg.* 2015; 220 (4): 530–536.
8. Chu LC, Goggins MG, Fishman EK. Diagnosis and detection of pancreatic cancer. *Cancer J.* 2017; 23: 333–342.
9. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2017: Clinical practice guidelines in Oncology. *JNCCN.* 2017; 15(8):1028–1061.
10. Brenner DJ, Hall EJ, Phil D. Computed Tomography – An Increasing Source of Radiation Exposure. *N Eng J Med.* 2007; 352 (22): 2277–2284.

11. Law JK, Stoita A, Weaver W, et al. Endoscopic ultrasound-guided fine needle aspiration improves the pre-operative diagnostic yield of solid-pseudopapillary neoplasm of the pancreas: an international multicenter case series (with video). *Surg Endosc.* 2014; 28: 2592-2598.
12. Springer S, Wang Y, Molin MD, et al. A Combination of Molecular Markers and Clinical Features Improve the Classification of Pancreatic Cysts. *Gastroenterology.* 2015; 149: 1501-1510.
13. Nasher O, Hall NJ, Sebire NJ, de Coppi P, Pierro A. Pancreatic tumours in children: diagnosis, treatment and outcome. *Pediatr Surg Int.* 2015; 31: 831–835.
14. Choi SH, Kim SM, Oh JT, Park JY, Seo JM, Lee SK. Solid pseudopapillary tumor of the pancreas: a multicenter study of 23 pediatric cases. *Journal of Pediatric Surgery.* 2006; 41:1992–1995.
15. Shorter NA, Glick RD, Klimstra DS, Brennan MF, LaQuaglia MP. Malignant pancreatic tumors in childhood and adolescence: The Memorial Sloan-Kettering experience, 1967 to present. *Journal of Pediatric Surgery.* 2002; 37(6): 887–892.
16. Rojas Y, Warneke CL, Dhamne CA, et al. Primary malignant pancreatic neoplasms in children and adolescents: A 20 year experience. *Journal of Pediatric Surgery.* 2012; 47: 2199–2204.
17. Lindholm EB, Alkattan AK, Abramson SJ, et al. Pancreaticoduodenectomy for pediatric and adolescent pancreatic malignancy: A single-center retrospective analysis. *Journal of Pediatric Surgery.* 2017; 52: 299–303.

18. ChungEM, TravisMD, ConranRM. Pancreatic Tumors in Children: Radiologic-Pathologic Correlation. *RadioGraphics*. 2006;26: 1211–1238.
19. Glick RD, Pashankar FD, Pappo A,LaQuagliaMP. Management of Pancreatoblastoma in Children and Young Adults: *J PediatrHematolOncol*. 2012; 34:S47–S50.
20. SpeerAL, BarthelER, PatelMM,GrikscheitTC. Solid pseudopapillary tumor of the pancreas: A single-institution 20-year series of pediatric patients. *Journal of Pediatric Surgery*. 2012; 47: 1217–1222.
21. van den AkkerM, Angelini P, Taylor G, Chami R, Gerstle JT, Gupta A. Malignant pancreatic tumors in children: A single-institution series. *Journal of Pediatric Surgery*. 2012;47: 681–687.
22. Yu P, Cheng X, Du Y, et al. Solid Pseudopapillary Neoplasms of the Pancreas: a 19-Year Multicenter Experience in China. *J Gastrointest Surg*. 2015; 19: 1433-1440.
23. Kim MJ, Choi DW, Choi SH, et al. Surgical treatment of solid pseudopapillary neoplasms of the pancreas and risk factors for malignancy. *BJS*. 2014; 101: 1266-1271.
24. Cai Y, Ran X, Xie S, et al. Surgical Management and Long-Term Follow-Up of Solid Pseudopapillary Tumor of Pancreas: A Large Series from a Single Institution. *J Gastrointest Surg*. 2014; 18: 1935-1940.
25. Estrella JS, Rashid A, Wang H, et al. Solid Pseudopapillary Neoplasm of the Pancreas- Clinicopathologic and Survival Analyses of 64 Cases From A Single Institution. *Am J Surg Path*. 2014; 38(2): 147-157.

26. Song KB, Kim SC, Hwang DW, et al. Enucleation for benign or low-grade malignant lesions of the pancreas: Single-center experience with 65 consecutive patients. *Surgery*. 2015; 158(5): 1203-1209.
27. Hwang J, Kim DY, Kim SC, et al. Solid-pseudopapillary neoplasm of the pancreas in children: Can we predict malignancy? *Journal of Pediatric Surgery*. 2014; 49: 1730-1733.
28. Hüttner FJ, Fitzmaurice C, Schwarzer G, et al. Pylorus-preserving pancreaticoduodenectomy (ppWhipple) versus pancreaticoduodenectomy (classicWhipple) for surgical treatment of periampullary and pancreatic carcinoma (Review). *Cochrane Database of Systematic Reviews*. 2016; 2: 1-47.
29. Singh AN, Pal S, Mangla V, et al. Pancreaticojejunostomy: Does the technique matter? A randomized trial. *J Surg Oncol*. 2018;117: 389–396.
30. Yeh JJ, Gonen M, Tomlinson JS, Idrees K, Brennan MF, Fong Y. Effect of blood transfusion on outcome after pancreaticoduodenectomy for exocrine tumour of the pancreas. *British Journal of Surgery*. 2007; 94: 466–472.
31. Kneuert PJ, Patel SH, Chu CK, et al. Effects of Perioperative Red Blood Cell Transfusion on Disease Recurrence and Survival After Pancreaticoduodenectomy for Ductal Adenocarcinoma. *Ann Surg Oncol*. 2011;18: 1327–1334.
32. D'Ambrosio G, del Prete L, Grimaldi C, et al. Pancreaticoduodenectomy for malignancies in children. *Journal of Pediatric Surgery*. 2014;49: 534–538.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figures Legend:

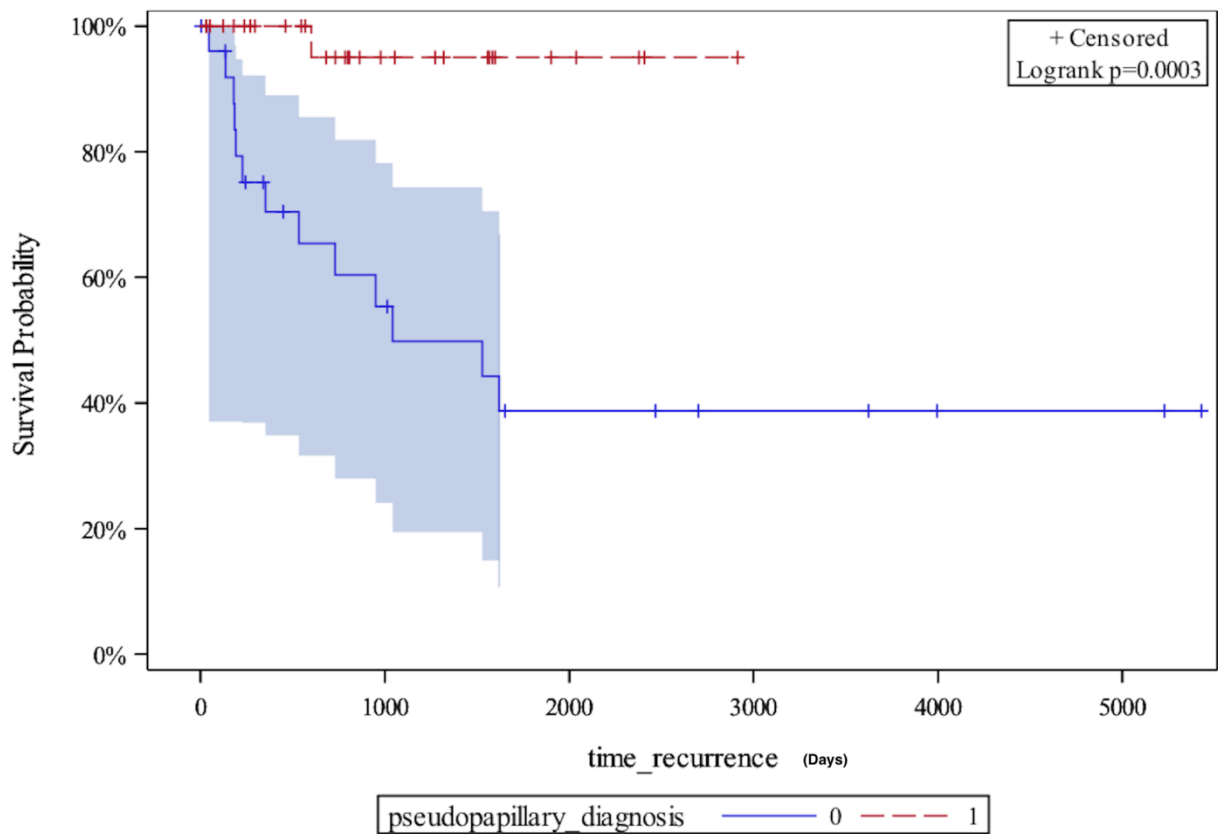


Figure 1: Kaplan Meier curve for recurrence with 95% Hall-Wellner bands

Red line = solid pseudopapillary tumor of the pancreas (SPN) diagnosis

Blue line = malignant non-SPN diagnosis

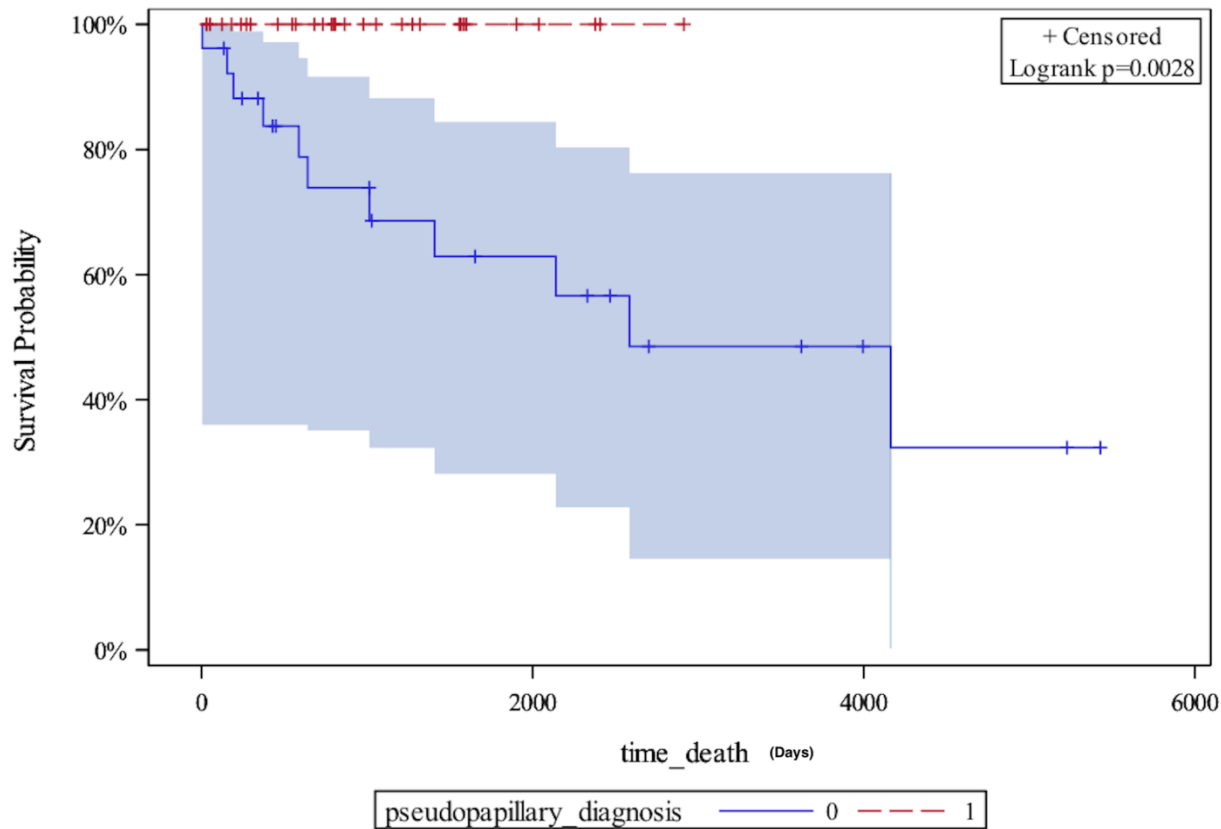


Figure 2: Kaplan Meier curve for death with 95% Hall-Wellner bands

Red line = solid pseudopapillary tumor of the pancreas (SPN) diagnosis

Blue line = malignant non-SPN diagnosis

**Tables and Figures**

Table 1. Demographic, diagnostic, and treatment characteristics

<b>Characteristic</b>	<b>Number of patients (%)</b>
Race	
Caucasian	37 (60)
African-American	7 (11)
Asian	2 (3)
Other	19 (29)
Age – median [range]	13 [0.33 – 22] y
Preoperative comorbidities	22 (34)
Obesity	4 (6)
Beckwith-Wiedemann syndrome	2 (3)
Lynch syndrome	2 (3)
Von Willebrand disease	1 (2)
Mixed connective tissue disease	1 (2)
Sickle cell trait	1 (2)
Pancreatic divisum	1 (2)
Inflammatory bowel disease	1 (2)
Chronic pancreatitis	1 (2)
Von Hippel Lindau disease	1 (2)
Jaundice	1 (2)
Anxiety	1 (2)
Hepatitis C	1 (2)
Hyper IgM syndrome	1 (2)
Other	3 (5)
Insurance	

Private	33 (51)
Uninsured	7 (11)
Government	19 (29)
Preoperative diagnostic method	
Endoscopic ultrasound biopsy	18 (28)
Imaging only	15 (23)
Open biopsy	10 (15)
Percutaneous biopsy	7 (11)
Unspecified	15 (23)
Vascular involvement on preoperative diagnosis	15 (23)
Clear of vessels	50 (77)
SMV only	6 (9)
SMV and SMA	5 (8)
Portal vein	2 (3)
Portal vein, hepatic artery, SMV	1 (2)
Middle colic artery	1 (2)
Neoadjuvant chemotherapy	16 (25)
Neoadjuvant radiation	7 (11)
Adult hepatobiliary surgeon involved	22 (34)
Open PD	65 (100)
Pylorus-preserving PD	41 (63)
Perianastomotic drain	44 (68)
Pancreaticojejunostomy	
Duct-to-mucosa	31 (48)
Sock-type	31 (48)
Unspecified	3 (5)
Pancreaticojejunostomy stent	9 (14)
Hepaticojejunostomy stent	5 (8)
Operative time - median [range]	7.2 [1.5 - 21.5] h



EBL - median [range]	250 [50 - 5,000] cc
PRBC transfusion	
Intraoperative	19 (29)
Median [range]	2 [0.5 - 8] PRBC u
Postoperative	8 (12)
Median [range]	1 [1 -7] PRBC u
Postoperative antibiotics	49 (75)
Postoperative mechanical ventilation	14 (22)
Median [range]	1.5 [1-7] d
Postoperative ICU	45 (69)
Median [range]	2 [1-27] d
Hospital LOS - median [range]	12 [3 - 56] d
Positive margins on histology	9 (14)
Vascular invasion on histology	14 (22)
Adjuvant chemotherapy	17 (26)
Adjuvant radiation	4 (6)

Table 2. Histological diagnoses

<b>Histologic diagnosis</b>	<b>Number of patients (%)</b>
SPN	34 (52)
Benign neoplasm	3 (5)
Malignant neoplasms	28 (43)
Pancreatoblastoma	8 (12)
Carcinoma	5 (8)
Rhabdomyosarcoma	3 (5)
Neuroblastoma	3 (5)
Neuroendocrine	4 (6)
Ewing sarcoma	2 (3)
Anaplastic large cell lymphoma	1 (2)
Pancreatic islet cell tumor	1 (2)

Table 3. Short-term postoperative complications &lt; 30 days after PD

<b>Short-term complication</b>	<b>Number of patients (%)</b>	<b>Treatment (n)</b>	<b>Clavien-Dindo Classification</b>
Pancreatic leak	9 (14)	Surgical drain placement (6)	III
		Percutaneous drainage (1)	III
		Octreotide (1)	II
		Observation (1)	I
Marginal ulcer	1 (2)	PPI and PRBC transfusion (1)	II

Perioperative death	1 (2)	-----	V
Gastroduodenal artery bleed	0	-----	-----
Biliary stricture	0	-----	-----

Table 4. Long-term postoperative complications  $\geq$  1 year after PD

Long-term complication	Number of patients (%)	Treatment (n)	Clavien-Dindo Classification
Pancreatic Insufficiency	21 (32)		
Exocrine	15 (23)	Pancrealipase (13)	II
Endocrine	2 ( )	Insulin (2)	II
Both	4 (6)	Pancrealipase and insulin (4)	II
Delayed gastric emptying	6 (9)	Medical management (3)	II
		Surgical management (Gastrotomy, gastrojejunostomy, or jejunostomy tube) (3)	III
Vitamin deficiency	3 (5)	-----	-----