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Pancreaticoduodenectomy for Pediatric and Adolescent Pancreatic Malignancy: A Single-Center Retrospective Analysis

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Abstract

Purpose—While pancreaticoduodenectomy (PD) has been extensively studied in adults, there are few data pertaining specifically to pediatric patients. We retrospectively analyzed PD-associated morbidity and mortality in pediatric patients.

Methods—Our analytic cohort included all consecutive patients ≥ 18 years of age treated at our institution from 1993-2015 who underwent PD. Patient data (demographics, disease characteristics, surgical and adjuvant treatment, length of hospital stay, and postoperative course) were extracted from the medical records.

Results—We identified 12 children with a median age of 9 years (7 female, 5 male). Final diagnoses were pancreatoblastoma (n=3), solid pseudopapillary tumor (n=3), neuroblastoma (n=2), rhabdomyosarcoma (n=2), and neuroendocrine carcinoma (n=2). Four patients underwent PD for resection of recurrent disease. 75% (9/12 patients) received neoadjuvant therapy. The median operative time was approximately 7 hours with a mean blood loss of 590cc. The distal pancreas was invaginated into the posterior stomach (n=3), into the jejunum (n=5) or directly sewn to the jejunal mucosa (n=4). There were no operative deaths. There were 4 patients (34%) with Grade II complications, 1 with a Grade IIIb complication (chest tube), and 1 with a Grade IV complication (re-exploration). The most common long-term morbidity was pancreas exocrine supplementation (n=10; 83%). Five patients (42%) diagnosed with either solid pseudopapillary tumor or rhabdomyosarcoma are currently alive with a mean survival of 77.4 months.

Conclusion—Pancreaticoduodenectomy is a feasible management strategy for pediatric pancreatic malignancies and is associated with acceptable morbidity and overall survival. Long-term outcome is most dependent on histology of the tumor.

Level of Evidence—IV

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Keywords

Pancreaticoduodenectomy; Whipple procedure; pancreatic tumor; pancreatoblastoma; solid pseudopapillary tumor

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Introduction

Pancreatic and biliary pathology are very rare among the pediatric population[1-3]. Even rarer is the small patient subset that requires a pancreaticoduodenectomy (PD) to treat the disease process. The majority of patients are diagnosed with malignancy of the head of the pancreas, either a primary tumor or a metastatic lesion. Other less common lesions include benign pancreatic lesions or distal biliary abnormalities. In either case, the only option for treatment in these patients is a PD.

The overall morbidity and mortality rates associated with PD in adults have been extensively studied[4-6]. Reported rates have decreased over the years with improved surgical techniques and have now seemingly stabilized at a rate of 30-40% for morbidity and 1%-3% for mortality[7-9]. Common complications include pancreatic, gastric or jejunal fistula, anastomotic stricture, delayed gastric emptying, and loop syndromes. In the adult population, some investigators have developed algorithms to stratify complications and the risk of complications, according to patient and tumor characteristics[9-11]. The infrequent use of PD in pediatric patients hampers accurate prediction of short- and long-term morbidity in this population[12, 13], and also precludes prediction of which patients are at increased risk for complications.

We analyzed our experience with PD in pediatric patients treated at our tertiary referral center to identify the morbidity and mortality associated with this procedure. We hypothesized that our pediatric patients have decreased morbidity and mortality compared to the adult population; such a finding would be consistent with previous speculations that reduced morbidity and mortality are due to the generally better health status of the patients, the consistency of pediatric pancreatic tissue, and differences in adult and pediatric disease processes[12]. Our secondary endpoint was to assess any differences in outcome among patients with primary vs. metastatic disease who are managed with PD, in order to shed light on whether extensive surgery is appropriate for the treatment of metastatic disease.

Methods

We queried our institutional pediatric surgery database for all consecutive patients 18 years old or younger who underwent PD between October 1, 1993, and December 31, 2014. No eligible patients were excluded from this study. Demographic information, preoperative assessment, operative details, hospital stay, pathology, and outcomes were extracted from electronic medical records and analyzed using descriptive statistics. Specific outcomes of interest included short-term postoperative complications that occurred during the initial hospital stay, as well as any evidence of long-term sequelae noted during follow-up clinic visits. This retrospective study was approved by our center's Institutional Review Board (#WA0539-14), which granted a waiver of patient informed consent requirements.

Results

Seven girls and 5 boys were identified who met study inclusion criteria and were treated during the 21-year study period (Table 2). The mean age was 9 years (range: 2-18 years). Diagnoses included pancreatoblastoma (n=3), solid pseudopapillary tumor (SPT; n=3), neuroblastoma (n=2), rhabdomyosarcoma (n=2), and pancreatic neuroendocrine tumor (PNET) (n=2). All patients underwent planned PD procedures on the recommendation of a multidisciplinary pediatric tumor board, whose consensus was based on the ability to achieve an R0 resection. These recommendations were made after review of multiple sequential imaging studies that found isolated disease within the pancreas that was controlled or stable with adjuvant therapy.

In 8 of 12 patients, PD was performed as part of treatment for a new diagnosis of malignancy confirmed either by open biopsy or classic radiologic imaging. The remaining 4 patients had PD performed as a secondary operation to treat metastatic disease located in the head of the pancreas with diagnosis of either rhabdomyosarcoma (n=1), PNET (n=2), or neuroblastoma (n=1). All patients undergoing treatment of recurrent disease had undergone previous debulking surgery. In addition, 75% (n=9 of 12) underwent chemotherapy or radiation therapy prior to PD.

The most common presenting symptom in our cohort was abdominal pain (67%, 8/12), which was reported in 3 of 5 patients with new malignancy and in 5 of 7 patients with recurrent disease. The second most common presenting symptom was jaundice (34%, 4/12), which developed in only 1 patient with newly diagnosed malignancy vs. 3 patients with recurrent disease. Additional symptoms included nausea/emesis (34%, 4/12), increased abdominal girth (25%, 3/12), fever (17%, 2/12), decreased oral intake (17%, 2/12), diarrhea (8%, 1/12), and failure to thrive (8%, 1/12). Preoperatively, one patient underwent biliary drainage with open cholecystojejunostomy and biopsy of pancreatic lesion (patient had previous resection of left adrenal neuroblastoma and concern for recurrence versus new PNET, pathology was new PNET).

A pylorus-sparing procedure was performed in all patients. The distal pancreas was invaginated into the posterior stomach (3/12), end jejunum (5/12), or jejunal mucosa (4/12). The mean length of the procedure was 6 hours, 49 minutes, with a range of 3-14 hours (median length: 7 hours). Depending on the patient, the reported operative time included any necessary liver resection or biopsy (n=4), central line insertion (n=3), gastrostomy insertion (n=2), colon resection (n=1), or intraoperative radiation therapy (n=1). Intraoperative blood loss was a mean 593cc (range: 200cc – 1200cc; median: 600cc) and transfusion was required in 6 of 12 patients. During the procedure, 0/12 patients underwent vascular reconstruction, 5/12 patients underwent lymph node dissection, and 5/12 patients had peritoneal drains placed. There were no intra-operative complications in these patients.

Postoperatively, patients spent a mean of 10.6 days in the hospital (range: 5-28 days, median: 8.5 days), with a mean of 5.2 days in the intensive care unit (range: 0-25 days; median, 3 days). The 30-day mortality in this study was 0%, and all patients were discharged in stable condition.

In concordance with the Clavien-Dindo classification of postoperative events (Table 2), Grade II complications, which require medical intervention only, occurred in 4 of 12 (33%) of patients. Two patients developed postoperative fevers that required antibiotic treatment of bacteremia (n=1) and *Clostridium difficile* (n=1), and 2 patients experienced a prolonged return of normal bowel function. One patient developed a Grade III event that required interventional radiology placement of pleural and peritoneal drains for an intra-abdominal abscess. In addition, a single patient experienced a Grade IV event in which large pleural and peritoneal fluid collections developed secondary to pancreatic leak. These fluid collections subsequently became infected with Enterococcus and yeast, requiring reoperation after abdominal wound dehiscence. This patient was the only one who experienced a pancreatic leak in our series.

Long-term outcomes were assessed with respect to chronic medication use and chronic disability. The most commonly administered medications were pancreatic enzyme supplements (n=10 of 12 patients). Additional chronic medications included loperamide (2/12 patients) and metoclopramide (1/12 patients). Long-term disability was limited to 5/12 patients who reported diarrhea (n=2), delayed gastric emptying (n=2), and abdominal pain (n=1) at outpatient follow-up.

At the time of our analysis, 5 patients (42%) were alive without evidence of disease with a mean survival of 77.4 months (range: 3-168 months; median: 50 months), and 7 patients (58%) succumbed to progressive disease after a mean of 42.3 months (range: 5-136 months; median: 19 months) following PD (Figure 1). All surviving patients had either solid pseudopapillary tumor (n=3) or rhabdomyosarcoma (n=2), and two of these patients had undergone PD for recurrent disease. Consequently, we concluded that there was no apparent adverse effect on survival among patients who underwent PD for resection of recurrent disease.

Discussion

Pancreaticoduodenectomy is an exceedingly rare procedure performed in the pediatric population[3, 8, 14]. We present our series of 12 patients who underwent PD at our institution over the last 21 years. The gold standard for pancreatic malignancy, regardless of tumor type, is surgical resection. The extent of surgical resection required for complete debulking is dictated by tumor location[15]. Whenever possible, less extensive resection is advocated; however, a minority of patients will still require resection of the pancreatic head and hepatobiliary reconstruction.

Proper discussion of risks and benefits is of particular difficulty due to the lack of literature. Counseling both the patients and caregivers is of particular concern given the extensiveness of the procedure, as well as the overall prognosis of their malignancy. The goal of this paper was to provide a starting point for this conversation and review the current literature to determine the safety of PD in this population.

In published retrospective reviews of pancreatic tumors, the reported incidence of pediatric pancreatic malignancy is 0.018 cases per 100,000 people[16], and the most common

histologies are pancreaticoblastoma in younger patients and SPT in adolescents[15-18]. In the surgical management of these patients, PD is usually not required for complete tumor extirpation; the overwhelming majority of surgical resections are distal pancreatectomies. For the few cases of patients undergoing PD, the existing literature on does not focus on the associated complications and expected outcome.

For example, in a retrospective study of pediatric patients treated for pancreatic tumors at the Hospital for Sick Children in Toronto, van den Akker et al. found that out of 27 patients, only 8 (29.6%) required a PD, most of whom (n=5 of 8) were diagnosed with SPT [19]. There were, however, no reported complications and the survival was not stratified according to surgical procedure.

In a retrospective review of SPT from Children's Hospital Los Angeles, Speer et al. reported their 20-year history with 11 cases and included data on surgical outcomes for all pancreatic resections[20]. Of their 11 cases, 4 patients required a PD. The median length of stay for all patients was 8 days (range 5-19 days) and complications occurred in 36% patients. Complications were pancreatic leak, delayed gastric emptying, and fat malabsorption requiring medical management, but the authors did not state which complications were associated with each type of surgical procedure or whether there were differences in complication rates for specific types of surgeries. Similarly, a multi-institutional study also reviewed data on 31 patients with pancreatic malignancy[18]. Of all pancreatic tumors, 29 were amenable to surgical treatment and 9 patients underwent PD. Eight of 9 patients were diagnosed with SPT. The entire series had a complication rate of 38% due to malabsorption, pancreatic insufficiency, pancreatitis, dumping syndrome, pseudocyst formation, and small bowel obstruction; however, there was no information linking surgical procedure to complication type.

We were able to identify a relatively low rate of complications within our high-risk patient population. Our overall rate of complication was 50%, or 6 out of 12 patients. Of the complications, only 2 (16%) were Clavien-Dindo grade greater than or equal to 3 requiring surgical, endoscopic or radiologic intervention. The Grade IV complication was the only patient who required an addition procedure in the operating room. The remaining four Grade II complications required only pharmacological treatment and had a minimal impact on overall hospitalization.

Based on the data from these reviews with our institution's findings, we recommend that parents and caregivers be advised that there is a 40-50% short-term morbidity. Our morbidity rate was higher than reported by other institutions, most likely because our institution as a tertiary referral center and because the investigators at other institutions included all pancreatic resections in their analysis. Even though our morbidity rate is relatively high, the severity of those complications was relatively low overall.

The most severe complications were noted in a report from the Children's Hospital of Boston, in which 18 cases of pancreatic malignancy, treated over a 90-year period, were analyzed[21]. There were 5 patients who underwent PD, among whom 2 complications occurred: subphrenic abscess and aortoenteric fistula. The latter complication, which

developed in a patient with pancreatic acinar cell carcinoma who had received preoperative chemotherapy and iodine-131 radiation seeds, eventually led to aortic rupture and death.

Comparing our data to similarly high-risk patients who underwent PD, a recent retrospective review from Italy in 2014 described the records of 5 pediatric patients[3]. These patients presented with SPT (n=1), rhabdomyosarcoma (n=2), and pancreatic endocrine neoplasia (n=2). Two patients in the cohort required portal vein reconstruction. The investigators reported no short-term complications, but 2 patients developed stricture of the pancreaticojejunal anastomosis, a long-term complication that required reoperation.

At this time, we have not been able to identify any long-term complications. Of our series, the 5 survivors have a mean of 77 months follow-up. We are unable to draw conclusions regarding which type of anastomosis is best in these patients over the long term, but it should be a goal of surgery to provide long-term drainage of the biliary and pancreatic systems.

In our cohort, we noted that a large proportion of patients were taking pancreatic enzymes on long-term follow-up. Shamberger et al. analyzed the long-term metabolic and nutritional consequences of PD in a series of 5 pediatric patients[22] and found that, following resection, patients had very low levels of pancreatic function. They concluded that normal development was dependent on supplementation of pancreatic enzymes. Supplementation of fat-soluble vitamins was also recommended. In addition to exocrine function, endocrine pancreatic deficiencies were retrospectively analyzed by Sugito et al. in 6 patients with pancreatic tumors[23]. Two patients in this study underwent PD and both were found to have increasing HbA1c levels and decreased pancreatic parenchyma on computed tomography over time.

These reports by Shamberger et al. and Sugito et al. highlight concerns over pancreatic endocrine and/or exocrine insufficiency following PD[22, 23]. In the adult population, reported rates are 56-73% for exocrine insufficiency and 20-25% for endocrine insufficiency. In our series, none of the patients required treatment for endocrine failure. The rates for the adult population also vary according to pylorus preservation, with higher failure rates for both exocrine and endocrine function when such a procedure is undertaken. One proposed mechanism leading to insufficiency is that pylorus contractions cause frequent stasis within the pancreatic duct, ultimately leading to parenchyma destruction[24, 25].

A 2008 analysis of pediatric pancreatic malignancies extracted from the Surveillance, Epidemiology, and End Results (SEER) registry found surgery to be an independent predictor of survival with $p=0.001$ [16]. Of the 58 patients included in the analysis, only 60% (n=33) underwent resection; the remaining patients (n=17) did not undergo resection because of distant metastatic disease. Mortality of patients not receiving surgical debulking was 15-fold higher than patients who underwent surgery. Not surprisingly, survival of pancreatic malignancy is closely associated with the extent of surgical resection.

The overall efficacy of surgical treatment for patients with pancreatic malignancy combined with the relatively low severity of complications leads us to recommend resection wherever R0 resection is feasible. In more aggressive tumors, there was less benefit and we were

unable to ascertain the overall benefit of radical resection. There was clearly a benefit in the more indolent malignancies such as SPT.

Survival data from our limited series of patients does not give insight into the overall survival of patients following PD due to their diverse and extensive disease processes. Of 7 patients who died, 3 had recurrent metastatic disease to the pancreas, 1 had primary neuroblastoma, and 3 had pancreaticoblastoma. Of the 5 surviving patients, 3 had SPT and 2 had rhabdomyosarcoma. The disease processes affecting the deceased patients are typically associated with lower survival rates, but we were unable to infer if survival was prolonged by PD. We do note, however, that despite more advanced disease, those patients had acceptable surgical morbidity and no 30-day mortality following PD.

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Abbreviations

PD	pancreaticoduodenectomy
SPT	Solid Pseudopapillary Tumor
PNET	Pancreatic Neuroendocrine Tumor

Figure 1. Kaplan Meier analysis of overall survival for all patients ($n = 12$). The 95% confidence intervals are indicated by the dotted lines.

Table 1

Demographics, tumor histology, surgical data, and complications for patients who underwent pancreaticoduodenectomy (N=12).

Pt	Age (yr)	Sex	Pre-op Diagnosis	Prior Surgery	Neoadj. RT or Chemo	Status	Survival (months)	Additional Procedures	Lymph Node Dissection	Length of Procedure (hours)	Est. Blood Loss	Trans-fusion	Hospital Days	ICU Days	Post-op Complications	Chronic Medications	Chronic Disability
1	2	F	Recurrent neuroblastoma	Yes	Yes	DOD	5	CVC, liver biopsy	Yes	3.06	750	Yes	10	10	None	Pancrealipase	None
2	1	M	Neuroblastoma	No	Yes	DOD	6	CVC, liver biopsy, colon resection, Mediport	Yes	6.59	800	Yes	7	6	None	Pancrealipase, loperamide	Diarrhea
3	9	M	Pancreato-blastoma	Yes	Yes	DOD	19	CVC	No	7.23	1200	Yes	6	3	None	Pancrealipase	None
4	11	F	Recurrent islet cell tumor	Yes	Yes	DOD	136	None	No	8.05	300	No	7	0	None	Pancrealipase	Delayed gastric emptying
5	7	M	Pancreato-blastoma	No	Yes	DOD	12	Liver biopsy, IORT, Gtube	Yes	10.07	700	No	6	2	None	None	None
6	10	F	Pancreato-blastoma	Yes	Yes	DOD	70	None	No	-	500	No	7	3	Ileus	Pancrealipase	None
7	10	M	Recurrent PNET	Yes	Yes	DOD	48	None	Yes	-	-	-	13	3	Bacteremia	None	None
8	6	M	RMS	No	Yes	Alive	22	Liver resection	Yes	5.59	550	Yes	14	4	C difficile	Pancrealipase	None
9	18	F	SPT	No	No	NED	50	None	No	5.53	675	No	28	25	Large pleural effusions, abdominal wall abscess, wound dehiscence, pancreatic leak	Pancrealipase	Diarrhea
10	2	F	Recurrent RMS	Yes	Yes	Alive	144	Gtube	No	7.02	200	No	5	3	None	Pancrealipase	None
11	15	F	SPT	Yes	No	NED	168	None	No	7.4	600	Yes	12	0	Bilateral pleural effusion, abdominal abscess	Pancrealipase, loperamide	Abdominal pain
12	13	F	SPT	No	No	NED	3	None	No	6	250	No	13	3	Delayed gastric emptying, pancreatitis	Pancrealipase, Metoclopramide	Delayed gastric emptying

CVC=central venous catheter placement; DOD=died of disease; ICU=intensive care unit; IORT=intraoperative radiation therapy; NED=no evidence of disease; PNET=pancreatic neuroendocrine tumor; RMS=rhabdomyosarcoma; RT=radiation therapy; SPT=solid pseudopapillary tumor.

Table 2

Clavien–Dindo classification of surgical complications.

Grade	Description
I	Deviation for normal postoperative course without need for intervention
II	Requiring pharmacological treatment
III	Requiring surgical, endoscopic or radiologic intervention
IV	Life-threatening complication
V	Death of patient