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Primary malignant pancreatic neoplasms in children and adolescents: A 20 year experience ☆

Yesenia Rojas [a], Carla L. Warneke [b], Chetan A. Dhamne [c], Kuojen Tsao [d], Jed G. Nuchtern [a], Kevin P. Lally [c,d,e], Sanjeev A. Vasudevan [a], Andrea A. Hayes-Jordan [c,d,e], Darrell L. Cass [a], Cynthia E. Herzog [c], M. John Hicks [f], Eugene S. Kim [a,1], Mary T. Austin [c,d,e,*,1]

[a] *Department of Pediatric Surgery, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA*
[b] *Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*
[c] *Department of Pediatrics, Children's Cancer Hospital, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*
[d] *Department of Pediatric Surgery, Children's Memorial Hermann Hospital, The University of Texas Health Science Center at Houston Medical School, Houston, TX, USA*
[e] *Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*
[f] *Department of Pathology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA*

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Abstract

Background: Malignant pancreatic neoplasms in children and adolescents are rare. The clinical presentation, pathologic characteristics, management, and outcomes at two institutions are discussed.

Methods: We retrospectively reviewed all pediatric patients (age < = 18 years) treated for malignant pancreatic neoplasms at two institutions between 1991 and 2011.

Results: Thirty-one patients were identified with median age of 14.7 years (4–18 years). The most common histology was solid pseudopapillary tumor (SPT) (n = 22, 71%) followed by neuroendocrine tumors (n = 4, 13%), pancreatoblastoma (n = 4, 13%), and one unclassified spindle cell neoplasm (3%). Most patients presented with abdominal pain (n = 22, 71%). Complications included pancreatic leak, pseudocyst formation, pancreatitis, pancreatic insufficiency, and small bowel obstruction. The overall 1- and 5-year survival was 96% (95% CI 74%–99%) and 78% (95% CI 43%–93%). Median follow-up among patients alive at the end of follow-up was 20 months (< 1 month–16.2 years). Patients with SPT had better overall survival compared to patients with neuroendocrine tumors or pancreatoblastomas (Log-rank; p = 0.0143).

Conclusion: The majority of pediatric and adolescent patients present with SPTs which are usually resectable and associated with an excellent prognosis. Other histologic subtypes more often present with distant metastases and portend a worse prognosis.

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* Corresponding author. 1400 Pressler, Unit 1406, Houston, TX 77030–1439. Tel.: +1 713 794 4408; fax: +1 713 794 5720.
E-mail address: Maustin@mdanderson.org (M.T. Austin).

[1] Eugene S. Kim, MD and Mary T. Austin, MD, MPH are co-senior authors on this manuscript.

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Pancreatic neoplasms in children and adolescents are exceedingly rare and consist of a heterogeneous group of tumors which represent a spectrum of disease, from benign to malignant. Reported malignant pancreatic tumors in pediatric patients include pancreatoblastomas (PB), acinar cell carcinomas, ductal adenocarcinomas, solid pseudopapillary tumors (SPT), pancreatic neuroendocrine tumors (NET), sarcomas, lymphomas and cystadenocarcinomas [1-10]. Due to the varied histopathology of pancreatic malignant neoplasms, the clinical characteristics and outcomes of each type of tumor are also very diverse.

Given the rarity of the disease, only a few single institution series and case reports with limited numbers of patients have been published in the pediatric literature [5-7]. The recent release of large population-based cancer registries, such as the Surveillance, Epidemiology and End Results (SEER) registry, has allowed the review, although limited, of a large number of pediatric pancreatic neoplasms. In 2008, using SEER registry data, Perez et al. [4], reported an overall incidence of malignant pancreatic tumors in children, ages 0–19 years, of 0.18 case per million people in the United States. Similarly, Dall'Igna et al. [5] reported 21 malignant pancreatic tumors prospectively registered in the Italian TREP (Tumor Rari in Eta Pediatrica [Rare Tumors in Pediatric Age]) project over 8 years, which accounted for only 4% of all the rare tumors registered. The annual incidence was estimated to be 0.20 case per million in the 0–19 year old group [5].

The rarity of malignant pancreatic neoplasms in children, limited experience at individual institutions, and incomplete large population-based cancer registries have limited our understanding of these tumors. In this study, we report one of the largest malignant pancreatic tumor series obtained from two tertiary referral centers. Our purpose is to delineate the clinical and pathological characteristics of malignant pancreatic neoplasms in children and describe the management approaches and outcomes for these rare tumors.

1. Material and methods

1.1. Patients and study design

This was a retrospective, observational study of all primary malignant pancreatic tumors in patients ≤ 18 years of age who were treated at the University of Texas MD Anderson Cancer Center (MDACC) or Texas Children's Hospital (TCH) in Houston, Texas between 1991 and 2011. Patients were included if they were ≤ 18 years of age and had a primary malignant pancreatic tumor. No eligible patients were excluded from the study.

1.2. Data collection and statistical analysis

All clinical data were obtained from electronic medical records and paper charts. Collected variables include patient demographics, age at the time of diagnosis, date of diagnosis, significant past medical history, clinical presentation, final diagnosis and tumor type, tumor size, grade, stage of disease, metastasis if present, tumor markers, type of surgery, complications, length of follow-up and status at the end of follow-up. Patient demographics and clinical characteristics were summarized using means, standard deviations, medians, minimum and maximum values for continuous variables, and counts and percentages for categorical variables. To examine associations between variables, we used the Kruskal–Wallis test or Fisher's exact test as appropriate.

Survival curves were constructed using the Kaplan–Meier method and strata were compared with the log rank test. Associations between independent variables and survival were further investigated using univariate Cox proportional hazards regression models. Survival was defined as time from cancer diagnosis until death or last follow-up. Patients alive at the end of follow-up were censored. No adjustments were made for multiple comparisons. All *P*-values were 2-tailed and considered significant at alpha < 0.05. Analyses were conducted using SAS® for Windows (release 9.2, SAS Institute, Cary, North Carolina).

1.3. Ethics and policy

This study was approved by the Institutional Review Board at both institutions (MDACC Protocol DR10-0460, BCM IRB H-28726).

2. Results

2.1. Demographics and clinical characteristics

The study population included 31 children, median age 14.7 years (range 4–18 years), who were diagnosed with pancreatic cancer and treated at one of the two study institutions. Patients were diagnosed between May 1, 1993, and July 31, 2010. Most patients were referred from an outside institution (71%). Patient demographics and clinical characteristics are summarized in Table 1. The study population is comprised of 26 females (84%) and 5 males (16%). The average BMI of the patients was 20.8 (12.0–36.4). Five patients (16%) had comorbidities including MEN syndrome, gastroschisis, and prematurity.

Of the resected pancreatic specimens, tumor type was most commonly SPT (n = 22, 71%). Other types included 4 neuroendocrine tumors (13%), 4 pancreatoblastomas (13%), and 1 unclassified spindle cell tumor (3%). Most tumors (52%) were found in the tail of the pancreas, and 4 patients had tumors in multiple sites. Seven of the 31 patients (23%) presented with metastatic disease, including 3 patients with pancreatoblastomas, 2 patients with neuroendocrine tumors, 1 patient with SPT, and the single patient with unclassified spindle cell tumor. Of the patients with liver metastases, the

Table 1 Study population demographics and clinical presentation.

	n (%)
Race	
Hispanic	13 (42)
White	9 (29)
Black	4 (13)
Asian/Other	5 (16)
Presenting symptoms	
Abdominal pain	22 (71)
Nausea/emesis	8 (26)
Abdominal mass	4 (13)
Weight loss	2 (6)
Other	10 (32)
Co-morbidities	5 (16)

primary tumor was located in the head of the pancreas in 2 patients, the tail of the pancreas in 4 patients and was multifocal in one patient.

Tumor histology was significantly associated with patient age, gender, tumor stage, positive lymph node status, liver metastasis, and having a complete resection (Table 2). Children with pancreatoblastomas were younger (median 4.5, range 4.0–10.7 years) compared to other histological groups (median 15.5, range 8.0–18.7 years) ($P = 0.0027$). Patients with SPT were more commonly female ($P = 0.0124$). Presence of metastasis was more frequent among the neuroendocrine tumors and pancreatoblastomas than SPT ($P = 0.0011$). None of the patients with SPT had positive lymph nodes, but 1 patient in each of the other tumor histology groups had positive lymph nodes ($P = 0.0094$). Liver metastases were detected in 1 patient with neuroendocrine tumor (25%), 3 patients with pancreatoblastomas (75%), and one patient with SPT (5%) ($P = 0.0062$). Complete resection of tumor was more frequently accomplished in patients with SPT (82%) versus those with other tumor types ($P = 0.0019$).

Table 2 Univariate analysis by tumor histology.

	Tumor Type				Total n (%)
	NE n (%)	PB n (%)	SPT n (%)	SC n (%)	
Age					
≤ 10 years	0 (0)	3 (75)	3 (13.6)	0 (0)	7 (22.6)
> 10 years	4 (100)	1 (25)	19 (86.4)	1 (100)	24 (77.4)
Gender					
Female	3 (75)	2 (50)	21 (95)	0 (0)	26 (83.9)
Male	1 (25)	2 (50)	1 (5.0)	1 (100)	5 (16.1)
Stage at presentation					
Focal	2 (50)	1 (25)	20 (95)	0 (0)	23 (76.7)
Metastatic	2 (50)	3 (75)	1 (4.8)	1 (100)	7 (23.3)
Lymph node involvement					
No	2 (66.7)	3 (75)	22 (100)	0 (0)	27 (90)
Yes	1 (33.3)	1 (25)	0 (0)	1 (100)	3 (10)
Liver metastases					
No	3 (75)	1 (25)	21 (95.5)	1 (100)	26 (83)
Yes	1 (25)	3 (75)	1 (4.5)	0 (0)	5 (16.1)
Complete resection					
No	4 (100)	2 (50)	4 (18.2)	1 (100)	11 (35.5)
Yes	0 (0)	2 (50)	18 (81.8)	0 (0)	20 (64.5)

PB: pancreatoblastoma, NET: pancreatic neuroendocrine tumor, SPT: solid pseudopapillary tumor, SC: unclassified spindle cell tumor.

2.2. Treatment

Twenty-nine of the 31 patients had operative therapy (94%). The two patients that did not undergo resection were patients with neuroendocrine tumors that presented with unresectable metastatic disease and carcinomatosis. Complete surgical resection was achieved in 65% (n = 20) of the patients. Eight of the 9 pancreato-duodenectomies performed were for SPTs located at the head of the pancreas. Only 6 patients (19%) received chemotherapy: 4 patients with pancreatoblastoma and 2 with neuroendocrine tumors. Surgical complications occurred in 8 of 29 patients (28%). Complications included malabsorption/malnutrition, diabetes, pancreatic insufficiency, pancreatitis, dumping syndrome, pseudocyst formation, and small bowel obstruction. Surgical complications were not significantly associated with surgical procedure, tumor type, site, or size.

2.3. Survival analysis

In our study period, there were 4 deaths during follow-up. All of these patients had metastatic disease including 2 patients with pancreatoblastoma and 2 patients with neuroendocrine tumors. Moreover, two patients were alive with disease at the end of follow-up. The median follow-up for the 27 patients who were alive at the end of follow-up was 20 months and ranged from < 1 month to 16.2 years. The estimated rate of overall 1-year and 5-year survival after diagnosis was 96% (95% CI 74% to 99%) and 78% (95% CI 43% to 93%), respectively.

Overall survival from date of diagnosis did not appear to be significantly associated with patient age, race, tumor location, stage, tumor size, or complete resection. However, female gender was significantly associated with improved overall survival compared to males ($P = 0.0133$). In addition, patients with liver metastasis had a poorer prognosis ($P = 0.0407$).

Our study demonstrated that the type of tumor was significantly associated with overall survival ($P = 0.0143$). Patients with neuroendocrine tumors or pancreatoblastomas had a worse prognosis than patients with SPT. Paired comparisons of tumor type demonstrated that overall survival of patients with SPT was significantly better than patients with pancreatoblastomas ($P = 0.0269$) or neuroendocrine tumors ($P = 0.0028$). There was no statistically significant evidence that overall survival of patients with neuroendocrine tumors and pancreatoblastomas differed from each other ($P = 0.4328$). Estimated 3-year survival

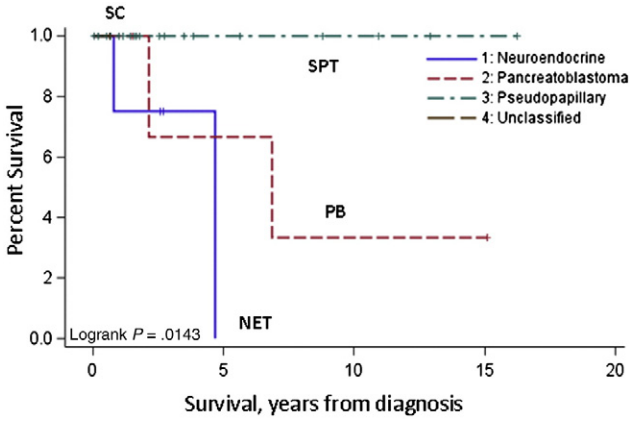

Fig. 1 Overall survival curve by histology. SPT: solid pseudopapillary tumor, PB: pancreatoblastoma, NET: neuroendocrine tumor, SC: unclassified spindle cell tumor.

rate was 75% (95% CI 13% to 96%) for patients with neuroendocrine tumors, 67% (95% CI 5% to 95%) for those with pancreatoblastomas, and 100% for patients with SPT (Fig. 1).

3. Discussion

Primary malignant pancreatic neoplasms in children are exceedingly rare. Large referral centers have reported less than 10 cases of malignant pancreatic tumors in children over a 20-year period [6,7]. Most recently, the Memorial Sloan-Kettering Cancer Center reported 17 malignant pancreatic tumors treated over a 35-year period, from 1967 to 2002 [8]. In this study, we present one of the largest institutional series of malignant pancreatic neoplasms in children, with 31 cases treated over a 20-year period.

Based on our review, and similar to most recently published series [5-7], the majority of pediatric and adolescents present with solid pseudopapillary tumors (SPT). This histologic subtype accounted for 71% (n = 22) of all tumors in our series. Previously believed to be rare, SPT accounts for 1% to 3% of pancreatic tumors overall [8,11,12]. Although we did not find a statistically significant association between SPT and race in our series, review of the literature suggests that SPT is more common in non-Caucasians, especially Asians [8,11,13]. Solid pseudopapillary tumors (SPTs), also known as solid and cystic tumor of the pancreas, or Frantz's tumor, were first described by Frantz in 1959 [12,14]. These tumors commonly present with abdominal pain or mass, predominantly affect young women, have a low malignant potential, and are usually resectable and associated with excellent prognosis.

The current recommended treatment for solid pseudopapillary tumors (SPTs) is complete surgical resection, including debulking of metastatic lesions [12,15-17]. SPT can develop in any part of the pancreas, which will dictate the surgical procedure needed to completely resect the tumor. Minimally invasive distal pancreatectomies for SPTs have been safely performed in children, including one patient in this series [18]. Although complete resection was more frequently performed on patients with SPT versus other tumor types, 18% of SPT patients had positive margins but remained alive at the end of follow-up including one patient who underwent a pancreaticoduodenectomy. In our study, positive margins did not affect the outcome of patients with SPT, suggesting that enucleation when feasible, rather than radical resection is likely sufficient to achieve long-term survival [10,15,19,20,13]. Furthermore, we found that no patients who underwent surgical resection for SPT had evidence of lymph node involvement. As such, we feel that a dedicated lymphadenectomy may not be necessary when resecting SPT tumors of the pancreas.

Although solid pseudopapillary tumors (SPTs) can present as large invasive tumors with metastases, they are remarkably indolent when compared to other malignant pancreatic tumors [11]. In SPT, metastases are uncommon with only 10%–15% of patients with advanced disease at diagnosis [8,11]. In 2002, Martin et al. [21] reported 24 cases of SPT in children and adults, of which 4 of the patients presented with synchronous liver metastases. After resection of primary tumor and liver lesions, one patient was alive and disease-free at 11 years [21]. There are additional reports of patients living more than 10 years with stable metastatic disease [8]. These studies indicate that complete excision of metastatic lesions can provide benefit in patients with metastatic SPT. In our study, only one of 22 SPT patients (5%) had metastatic disease at presentation and was alive and disease-free at 30 months of follow-up after resection of the primary tumor and metastatic liver lesions. The use of chemotherapy and radiation has been reported in some cases of aggressive disease; however, their role in the treatment of SPT remains unclear [22]. Tamoxifen use in a positive estrogen receptor tumor has been anecdotally reported with uncertain benefits [23].

Solid pseudopapillary tumors (SPTs) are associated with excellent prognosis, even in patients with metastatic disease [8,15]. In our review, the overall survival of patients with SPT was significantly better than that of patients with other histologic tumors. Our estimated 5-year survival rate was 100% for patients with SPT. This is comparable to previously reported 5-year survival rates of 90% to 95% [18]. In most studies of clinical outcomes of SPT, no pathologic or clinical factors predictive of prognosis have been identified [21,22]. However, based on case reports of recurrent metastatic disease years after primary resection, long term follow-up is warranted [12].

Neuroendocrine tumors (NET) are rare and can arise from any organ that has endocrine cells, including the thyroid, breast, testes, ovary, thymus, lung, small and large intestine, and the pancreas. If not completely resected, these tumors often recur locally or metastasize. In children, approximately 10% to 20% of these tumors will present with metastases

[24]. In our group, 50% of the patients with pancreatic neuroendocrine tumors had metastatic disease at presentation. In the pancreas, neuroendocrine tumors can be functional or non-functional and are commonly associated with genetic syndromes, such as MEN [5]. In our study, one patient had NET associated with MEN1 syndrome and was previously diagnosed with hyperparathyroidism as well as a pituitary adenoma. Current treatment of pancreatic neuroendocrine tumors includes a combination of surgery and chemotherapy [24]. These tumors do not respond well to conventional chemotherapeutic agents, however due to high level expression of somatostatin receptor, response to PRRNT (peptide receptor radionuclide therapy) has been demonstrated in children and young adults [25]. All of the patients in our series that presented with metastatic disease subsequently died of disease by the end of follow-up.

Pancreatoblastoma (PB) is reported to be one of the most common pancreatic tumors in childhood and adolescence [4,8,26]. Consistent with previous literature, we found that children with pancreatoblastomas had a younger median age, usually presenting during the first decade of life, as compared to patients with SPT and pancreatic NET [4]. However, one patient in our study population presented at nearly 11 years of age. Approximately one third of pancreatoblastomas are metastatic at the time of diagnosis [8,27]. If disease is limited to the pancreas, pancreatoblastoma patients often have a favorable prognosis. More than 95% of these patients are cured by complete surgical resection. Conversely, prognosis is poor if the tumor is unresectable [26]. Adjuvant chemotherapy and radiation are recommended for unresectable tumors [26,28]. A variety of chemotherapeutic agents have been used with variable success; however, cisplatin and doxorubicin are most often used for treatment of pancreatoblastoma [29].

According to the SEER database, the overall incidence of malignant pancreatic tumors in children is 0.18 case per million people in the United States [4]. Incidence rates by race reveal that Asians have the highest incidence of pancreatic tumors in children. The incidence in the US Asian population was 0.038 case per 100,000 at risk with Asians comprising 19% of the total SEER population group [4]. Unlike the SEER database, our study population was unique, given that 42% of our patients were self-identified Latino. We did not find a statistically significant association between race or ethnicity and the type of tumor; however, further evaluation is limited due to paucity of this information in previous pediatric studies [5-7,9,10].

The overall survival and outcomes of primary malignant pancreatic tumors in children vary by tumor histology. The majority of the children with a pancreatic tumor will present with solid-pseudopapillary tumors which are usually resectable and associated with excellent prognosis. Other tumor types, including pancreatoblastomas and pancreatic neuroendocrine tumors, more often present with distant metastases and portend a worse prognosis. Regardless of the tumor type, complete surgical resection is the main treatment modality for primary malignant neoplasms in children, and the type of surgery performed is dependent on the location of the tumor and extent of the disease.

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