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A population-based analysis of a rare oncologic entity: Malignant pancreatic tumors in children

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ABSTRACT

Purpose: To examine the clinicopathological characteristics and prognosis of pediatric patients with malignant pancreatic tumors in a population-based cohort.
Methods: The Surveillance, Epidemiology, and End Results (SEER) database was utilized to identify all pediatric patients with malignant pancreatic tumors, diagnosed between 1973 and 2013. Kaplan–Meier analysis was performed to determine median and five-year overall survival (OS) rates. Univariate survival analysis was executed using the log-rank test. Cox proportional hazards model was used to identify variables independently associated with mortality.
Results: A total of 114 patients with pancreatic malignancies were identified. Median patient age was 16 years and the majority of patients were white (64%) females (61.4%). The most prevalent histologic subtype was neuroendocrine tumors (35.1%), whereas pancreatoblastoma was more common during the first decade of life ($P < 0.001$). Distant metastases were noted in 41.7% of the patients, while 33.3% and 25% had localized and regional disease respectively. Five-year OS rates were 77%, 66.4% and 64.8% for patients with pancreatoblastoma, neuroendocrine and epithelial tumors respectively. No death was observed in the solid pseudopapillary tumor group. Only history of having cancer-directed surgery (CDS) was significantly associated with lower overall mortality (HR: 5.1, 95% CI: 2.1, 12.4).
Conclusion: Pancreatic malignancies are rare in children. Their prognosis is variable and only CDS was independently associated with superior survival.
Evidence rating/classification: Prognosis study, Level II.

Pancreatic neoplasms are extremely rare in children and account for less than 0.2% of all cancer-related childhood deaths [1]. Furthermore, pancreatic tumors are usually benign in pediatric patients; especially in the case of solid pseudopapillary tumors (SPTs) [2]. Nevertheless, malignant lesions have also been described [3,4]. Current understanding of the epidemiology and prognosis of malignant pancreatic tumors in pediatric patients is largely based on case reports and small single institutional case series [3–8]. Pancreatoblastoma is considered the most common malignancy during the first decade of life, while SPTs are the most common during the second decade of life [9,10]. Tumors of variable histologic subtypes have also been described in children, including pancreatic neuroendocrine tumors (pNETs), lymphomas, pancreatic epithelial carcinomas and sarcomas [8,11,12].

The heterogeneity of surgical approaches and lack of standardized chemotherapy protocols confounds our understanding regarding the outcomes of pancreatic malignancies in children [7]. The present study aims to provide an up-to-date review of the epidemiology, clinicopathological characteristics and prognosis of malignant pancreatic tumors in pediatric and adolescent patients by utilizing a population-based registry, which enables the follow-up of a large number of patients diagnosed with this rare oncologic entity.

1. Material and methods

1.1. Data source and subjects

The cohort of patients was abstracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database

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[13], which incorporates high quality data deriving from 18 cancer registries and covers approximately 27.8% of the total US population based on the 2010 census [14]. The SEER database is a public dataset; all patient data are de-identified and available to the public for research purposes. This study did not require an institutional review board approval.

1.2. Data collection and coding

The following criteria were applied to identify all pediatric and adolescent patients with malignant pancreatic tumors diagnosed between 1973 and 2013; (i) histologically confirmed tumor located at the pancreas (ICD-O-3 site code C.25) [15], (ii) patient age ≤ 19 years, (iii) diagnosis not obtained from autopsy or death certificate allowing for collection of follow-up data. Only a single patient was excluded on this criterion.

Demographic and clinicopathological parameters were extracted using the "case listing" option. Staging information was based on the SEER historic stage; localized cancer is limited to the primary organ without evidence of spread, regional cancer has spread beyond the primary site to nearby lymph nodes or tissues while distant cancer has spread from the primary site to distant organs or distant lymph nodes. Tumor grade when available was re-coded into a three-tier grading system; grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (including both poorly differentiated and undifferentiated tumors). Cancer-directed surgery (CDS) was defined in the SEER database as any procedure that is performed to modify, control, remove, or destroy primary or metastatic cancer tissue. Site-specific surgery codes were employed to identify patients who underwent CDS and to determine the nature of the procedure performed. Information deriving from the histopathology report was used to determine whether lymph node (LN) sampling/dissection was performed and the status of examined LNs.

1.3. Statistical analysis

Frequency distribution of categorical variables was compared using the chi-square test while that of continuous with the Mann–Whitney U or Kruskall Wallis test as applicable. Five-year and median overall survival (OS) was estimated following generation of Kaplan–Meier curves. The log-rank test was employed to perform comparisons of survival between different groups. Cox proportional hazards model was used to identify variables independently associated with mortality. Statistical analysis was performed with the SPSS v.24 statistical package. The alpha level of statistical significance was set at 0.05, and all P values were two-sided.

Table 1
Histologic subtypes and frequency encountered.

Neoplasm	Frequency	Relative rate (%)
Neuroendocrine	40	35.1
Small cell carcinoma, NOS	1	0.9
Pancreatic endocrine tumor, malignant	14	12.3
Insulinoma, malignant	1	0.9
Gastrinoma, malignant	2	1.8
Mixed pancreatic endocrine and exocrine tumor, malignant	1	0.9
Carcinoid tumor, NOS	1	0.9
Neuroendocrine carcinoma, NOS	20	17.5
Solid pseudopapillary tumor	16	14
Pancreatoblastoma	18	15.8
Epithelial	29	25.5
Carcinoma, NOS	4	3.6
Papillary carcinoma, NOS	6	5.3
Adenocarcinoma, NOS	7	6.1
Solid carcinoma, NOS	1	0.9
Papillary adenocarcinoma, NOS	2	1.8
Papillary cystadenocarcinoma, NOS	1	0.9
Mucinous adenocarcinoma	1	0.9
Signet ring cell carcinoma	1	0.9
Acinar cell carcinoma	6	5.3
Non-epithelial or unknown	11	9.6
Neoplasm, malignant	3	2.6
Leiomyosarcoma, NOS	1	0.9
Rhabdomyosarcoma, NOS	1	0.9
Alveolar rhabdomyosarcoma	1	0.9
Peripheral neuroectodermal tumor	3	2.6
Neuroblastoma, NOS	2	1.8

Table 2
Demographic, clinicopathological characteristics and management of pediatric and adolescent patients with malignant pancreatic tumors.

	NET	PB	SPT	EC	p-Value
Age (median)	18 y	5.5 y	17 y	15 y	<0.001
Age					<0.001
<10	2 (5%)	13 (72.2%)	1 (6.3%)	5 (17.2%)	
10–16	12 (30%)	4 (22.2%)	5 (31.3%)	11 (37.9%)	
17–19	26 (65%)	1 (5.6%)	10 (62.5%)	13 (44.8%)	
Gender					0.018
Male	20 (50%)	9 (50%)	1 (6.3%)	11 (37.9%)	
Female	20 (50%)	9 (50%)	15 (93.8%)	18 (62.1%)	
YOD					0.021
1988–2000	14 (35%)	8 (44.4%)	1 (6.3%)	15 (51.7%)	
2001–2013	26 (65%)	10 (55.6%)	15 (93.8%)	14 (48.3%)	
Race					n.s.
White	30 (75%)	13 (72.2%)	11 (73.3%)	19 (65.5%)	
Non-White	10 (25%)	5 (27.8%)	4 (26.7%)	10 (34.5%)	
Stage*					0.002
Localized	10 (26.3%)	5 (27.8%)	11 (68.8%)	6 (22.2%)	
Regional	5 (13.2%)	5 (27.8%)	4 (25%)	11 (40.7%)	
Distant	23 (60.5%)	8 (44.4%)	1 (6.3%)	10 (37%)	
Location*					n.s.
Head	9 (39.1%)	8 (66.7%)	5 (38.5%)	16 (69.6%)	
Body/Tail/Other	14 (60.9%)	4 (33.3%)	8 (61.5%)	7 (30.4%)	
Size*					0.01
Median cm	4.25 (n = 24)	10.6 (n = 11)	5.8 (n = 12)	3.5 (n = 19)	
Grade*					0.023
Grade I	8 (53.3%)	-	6 (85.7%)	2 (18.2%)	
Grade II	3 (20%)	-	1 (14.3%)	7 (63.6%)	
Grade III/IV	4 (26.7%)	1 (100%)	-	2 (18.2%)	
CDS					0.018
No	21 (52.5%)	5 (27.8%)$^{\alpha}$	2 (12.5%)	8 (27.6%)	
Yes	19 (47.5%)	13 (72.2%)	14 (87.5%)	21 (72.4%)	
LND*^					n.s.
No	2 (12.5%)	5 (38.5%)	2 (14.3%)	2 (11.8%)	
Yes	14 (87.5%)	8 (61.5%)	12 (85.7%)	15 (88.2%)	
LN status*					0.027
Positive	7 (41.2%)	4 (50%)	-	4 (26.7%)	
Negative	10 (58.8%)	4 (50%)	12 (100%)	11 (73.3%)	
Radiotherapy					n.s.
No/unknown	37 (92.5%)	16 (88.9%)	16 (100%)	26 (89.7%)	
Yes	3 (7.5%)	2 (11.1%)	-	3 (10.3%)	

NET: neuroendocrine tumor; PB: pancreatoblastoma; SPT: solid pseudopapillary tumor; EC: other epithelial carcinoma; YOD: year of diagnosis; CDS: cancer-directed surgery; LND: lymphadenectomy; LN: lymph node; n.s.: not significant. *Based on available information; $^{\alpha}$Includes one case with unknown information; ^If CDS was performed.

2. Results

2.1. Cohort characteristics

A total of 114 eligible cases of histologically confirmed malignant pancreatic tumors in pediatric or adolescent patients were identified. Median patient age was 16 years (range < 1–19 years). Twenty-five patients (21.9%) were <10 years old, while 37 (32.5%) and 52 (45.6%) were 10–16 and >16 years old, respectively. Most patients were white (64%, N = 73/114) females (61.4%, N = 70/114). The majority of cases (60.5%) available in the SEER database were diagnosed in or after 2001.

Most tumors (51.8%, 44/85) originated from the head of the pancreas, while 36.5% (31/85) from the body or tail; 10 tumors (11.7%) had overlapping lesions or had other origin. Information on tumor grade was available only for 38 cases; 44.7% were grade 1, while 28.9% were