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ORIGINAL ARTICLE

Natural History and Treatment Trends in Pancreatic Cancer Subtypes

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Abstract

Background While pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer, many other histologic forms of pancreatic cancer are also recognized. These histologic variants portray unique characteristics in terms of patient demographics, tumor behavior, survival, and responsiveness to treatments.

Materials and Methods Patients who underwent surgical resection of the pancreas for non-metastatic, invasive pancreatic cancer between 2004 and 2014 were selected from the National Cancer Data Base and categorized by histologic variant according to WHO classification guidelines. Patient demographics, tumor variables, treatment characteristics, and survival were compared between histologic groups and subgroups.

Results A total of 57,804 patients met inclusion and exclusion criteria and were grouped into eight major histologic categories. Survival analysis by the histologic group showed median overall survival of 20.2 months for ductal adenocarcinoma, 20.5 months for squamous cell carcinoma, 26.8 months for mixed acinar-neuroendocrine carcinomas, 52.6 months for cystic mucinous neoplasms with an associated invasive carcinoma, 67.5 months for acinar cell carcinoma, and 69.3 months for mesenchymal tumors. Median survival was not reached for neuroendocrine tumors and solid-pseudopapillary neoplasms, with 5-year overall survival rates of 84% and 97% respectively.

Conclusions Rare subtypes of pancreatic cancer present unique clinicopathologic characteristics and display distinct tumor biologies. This study presents data on demographic, prognostic, treatment, and survival outcomes between rare forms of pancreatic neoplasms in order to aid understanding of the natural history and behavior of these neoplasms, with the hope of serving as a reference in clinical decision-making and ability to provide accurate prognostic information to patients.

Keywords Pancreatic cancer subtypes · Pancreatic adenocarcinoma · Neuroendocrine tumors · Mucinous neoplasms

Introduction

Pancreatic cancer is diagnosed in 50,000 individuals per year and is the 4th leading cause of cancer deaths among men and women in the USA,[1, 2] with 5-year survival of newly diagnosed patients dismal at 8%.[1, 3, 4] Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer; however, many other pancreatic histologic entities are also recognized.

The histology of pancreatic neoplasms is generally dichotomized into exocrine and endocrine types, depending on the cells of origin (ductal and acinar cells vs. islet of Langerhans). Exocrine pancreatic cancers comprise the majority (> 95%) of cases with ductal adenocarcinoma being the most predominate subtype at 80–85%.[5–7] The World Health Organization (WHO) also recognizes several other histologic types of pancreatic cancer, many of which display unique characteristics in terms of patient demographics, tumor behavior, and responsiveness to treatments. While pancreatic ductal adenocarcinoma has been well studied in large national analyses and multi-institutional studies,[2, 3, 6, 8–11] much less is known about rarer histologic subtypes. At present, only a few large national database studies

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have explored pancreatic neuroendocrine tumors.[12–14] Additionally, the majority of data on pancreatic acinar cell carcinoma comes from single-institution studies.[15–18] Previously known as "mucinous cystadeonomas," mucin-producing neoplasms of the pancreas have since been divided into mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN), and to date, only a few single-institution studies have explored their reported unique pathologic characteristics and biologic behavior.[19–29] Even less studied, data on squamous cell carcinoma,[30–34] malignant pancreatic mesenchymal tumors,[35–37] solid-pseudopapillary neoplasms,[38–44] and mixed acinar-neuroendocrine carcinomas[45–48] are limited entirely to case reports and single-center studies.

Consequently, many questions remain surrounding rarer pancreatic cancer histologies, including the natural history of these resected pancreatic cancer subtypes, the estimated benefit of adjuvant therapies, and predictors of improved survival within each subtype. The aim of this study was to characterize the demographic, prognostic, treatment, and survival outcomes among less common pancreatic cancer histologies.

Methods

Data Source

Patient data was obtained from the National Cancer Data Base (NCDB) Pancreas Participant User File (PUF)—a joint project of the American College of Surgeons and Commission on Cancer. The NCDB is a facility-based registry of > 1500 hospitals that captures 70% of all newly diagnosed cancers in the USA, and contains specific pathologic subtyping of pancreas cancers according to Facility Oncology Registry Data Standards (FORDS). This study was exempt from IRB review.

Patient Cohort

Patients who underwent surgical resection of the pancreas for invasive cancer between 2004 and 2014 were considered for inclusion. Patients with pancreatic intraepithelial neoplasia 3 (PanIN-3) or metastatic disease (TNM stage IV) were excluded. Additional exclusion criteria included patients with missing histology data or non-specific histology data (e.g., neoplasm, malignant; tumor cell, malignant) or cases with histology consistent with a non-pancreas primary cancer. From the remaining cohort (n = 57,804), patients were assigned into one of eight overarching histologic groups according to the WHO pancreatic tumor classification scheme.[49] These groupings were confirmed by a pathologist specializing in pancreatic cancer (KAM). For the purpose of this manuscript, previously reported neuroendocrine tumor variants such as "carcinoid, glucagonoma, gastrinoma, and insulinoma" among others are represented as "well-differentiated neuroendocrine tumors." Small-cell and large-cell neuroendocrine carcinoma comprise the "poorly differentiated neuroendocrine carcinoma" group. According to more recent literature incorporating 2000 WHO or 2006–2012 IAP inclusion criteria, 4–13% of patients with MCN, along with 17.7% of patients with branch duct IPMN, and 43.1% with main duct IPMN will have invasive carcinoma.[19, 22, 25–27] For the purposes of this manuscript, the carcinomas arising from MCN/IPMN are referred to as cystic mucinous neoplasms with an associated invasive carcinoma. Within the three most common groups (1. ductal adenocarcinoma; 2. neuroendocrine tumors; and 3. cystic mucinous neoplasms (MCN or IPMN) with an associated invasive carcinoma), patients were further categorized by histologic variant for additional analysis. Only those variants with a minimum threshold of 20 patients were included.

Covariates included age, gender, race, Charlson-Deyo comorbidity score, tumor size, tumor grade, American Joint Committee on Cancer (AJCC) clinical stage, and presence of positive lymph nodes. Treatment-specific independent variables included surgical resection, radiation therapy, chemotherapy, and sequence of these modes of therapy.

Statistical Analysis

The primary endpoint was overall survival calculated from date of diagnosis. Kaplan-Meier survival curves were generated for each of the eight major histologic groups. For the three most common histologic groups (ductal adenocarcinoma, neuroendocrine tumors, and cystic mucinous neoplasms with an associated invasive carcinoma), patients were further split into subgroups based on histologic variant and Kaplan-Meier survival analysis of these variants was performed. Univariate statistical analysis was performed using chi-square, Fisher's exact (categorical variables), or Kruskal-Wallis (continuous variables) to compare the eight histologic groups of interest with regard to patient demographics, comorbidity, tumor characteristics, treatment modalities, and survival outcomes. Factors associated with overall survival were determined using a multivariate Cox proportional hazards model. Model covariates included age, race, gender, CDCC score, clinical stage, tumor size, node positivity, margin status, treatment group, chemotherapy treatment, radiation therapy, and histological type. Patients with missing vital status or last contact were excluded from survival analysis (n = 7165).

Results

Patient and Tumor Characteristics

A total of 57,804 patients met inclusion and exclusion criteria and were grouped into eight major histologic categories

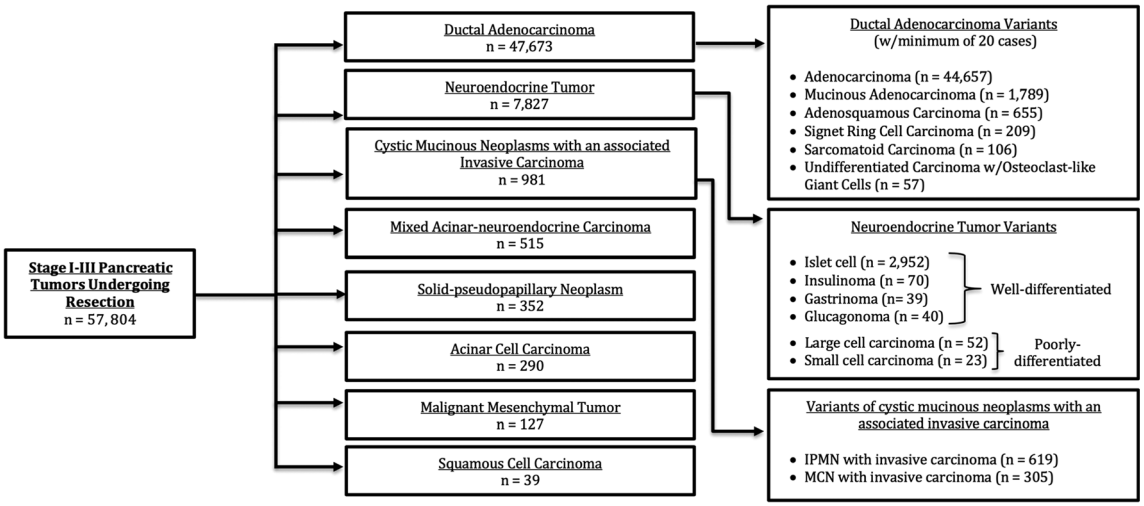

Fig. 1 Frequency of pancreatic neoplasms According to WHO Classification. IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm

(Fig. 1). The most common pancreatic tumor was ductal adenocarcinoma, comprising 82% of all patients undergoing resection for pancreatic neoplasms. Of all patients with ductal adenocarcinoma ($n = 47{,}673$), 6% of patients had a variant such as mucinous adenocarcinoma ($n = 1785$), adenosquamous carcinoma ($n = 655$), or signet ring cell carcinoma ($n = 209$). Neuroendocrine tumors ($n = 7827$, 14% of all tumors) and cystic mucinous neoplasms with an associated invasive carcinoma ($n = 981$, 2% of all tumors) were the next most common histologic groups, and variants within these two groups are displayed in Fig. 1.

Demographic and tumor-specific features differed between the 8 major histologic groups (Table 1). Patients with solid-pseudopapillary tumors were much younger, with a median age of 36 years compared to median ages of 59–67 for all other histologic groups. While Caucasian patients comprised the majority of the study population, there was a higher proportion of African-American patients within the solid-pseudopapillary neoplasm cohort (24%, $p < 0.001$) compared to other histologic groups (9–16% African-American). Most groups displayed a roughly equal male-female ratio, with the exception of squamous cell carcinoma and acinar cell carcinoma histologies, which more strongly favored males (62% and 68%, respectively; $p < 0.001$), and solid-pseudopapillary neoplasms which favored females (87%, $p < 0.001$) (Table 1).

Subgroup analysis evaluating ductal adenocarcinoma and neuroendocrine tumor variants are shown in Supplementary Tables 4 and 5. Patients with poorly differentiated neuroendocrine carcinomas were older (median age 64 vs 59, $p = 0.015$) and had larger tumors (35 mm vs. 27 mm, $p < 0.001$) (Supplementary Table 4) compared to patients with well-differentiated neuroendocrine tumors. Compared to other variants of pancreatic ductal adenocarcinoma, the sarcomatoid cohort was comprised of a higher proportion of African-American patients (12%, $p = 0.028$). All variants were slightly male predominant with the exception of sarcomatoid histology which was primary female predominant (44%, male, $p < 0.001$). Median tumor size among pancreatic ductal adenocarcinoma variants ranged from 31 to 50 mm, with osteoclast-like giant cell tumors being the largest (50 mm, $p < 0.001$), and pure ductal adenocarcinomas the smallest (31 mm, $p < 0.001$) (Supplementary Table 5).

Treatment Characteristics

Table 1 summarizes treatment characteristics of the eight histologic groups. R0 resections predominated across all groupings but were most commonly achieved in neuroendocrine tumors and solid-pseudopapillary neoplasms (89% and 88%, respectively; $p < 0.001$); patients with malignant mesenchymal tumors (spindle cell, giant cell, sarcomas, fibromas, myxofibromas, liposarcoma, myoliposarcoma, leiomyosarcoma, angiosarcoma, gastrointestinal stromal tumors, peripheral neuroectodermal tumors) were least likely to achieve an R0 resection (73%, $p < 0.001$). Patients with ductal adenocarcinoma more often received neoadjuvant or adjuvant radiation therapy (7% and 31%, respectively; $p < 0.001$) and chemotherapy (11% and 47%, respectively; $p < 0.001$), while neuroendocrine tumors and solid-pseudopapillary neoplasm had adjuvant treatments least often (Table 1).

Within the neuroendocrine cohort, patients with poorly differentiated neuroendocrine carcinomas more often received radiation (4% neoadjuvant, 17% adjuvant) and chemotherapy (6% neoadjuvant, 29% adjuvant) compared to those with well-differentiated neuroendocrine tumors (Supplementary Table 4). For variants of ductal adenocarcinoma, neoadjuvant therapies were most commonly utilized in patients with pure adenocarcinoma (7% neoadjuvant radiation, 12% neoadjuvant chemotherapy), and were least often utilized in those with

Table 1 Comparison of demographics, pathologic tumor variables, and treatment characteristics according to World Health Organization histologic classification

	Ductal adenocarcinoma ($N = 47,673$)	Neuroendocrine ($N = 7827$)	Cystic mucinous neoplasm (IPMN/MCN) with invasive carcinoma ($N = 981$)	Mixed acinar-neuroendocrine carcinoma ($N = 515$)	Solid-pseudopapillary neoplasm ($N = 352$)	Acinar cell carcinoma ($N = 290$)	Malignant mesenchymal tumors ($N = 154$)	Squamous cell carcinoma ($N = 39$)	*P* value
Age-median years (IQR)	67 (15)	59 (18)	67 (15)	66 (16)	36 (20)	64 (18)	60 (21)	66 (20)	< 0.001
Race									
Caucasian	86%	82%	85%	84%	69%	89%	82%	82%	< 0.001
African-American	10%	12%	10%	10%	24%	9%	16%	13%	
Other/unknown	4%	6%	6%	6%	8%	4%	2%	5%	
Male	51%	51%	46%	53%	13%	68%	52%	62%	< 0.001
Comorbidity score 0–1*	93%	94%	92%	92%	98%	96%	98%	90%	< 0.001
Tumor size, mm (IQR)	32 (18)	27 (29)	40 (45)	38 (28)	46 (50.75)	47.5 (45)	50 (42)	50 (35)	< 0.001
Lymph node positive	63%	29%	24%	57%	8%	34%	18%	49%	< 0.001
Tumor grade									
Well differentiated	9%	65%	22%	16%	22%	9%	11%	3%	< 0.001
Moderately differentiated	47%	13%	32%	28%	5%	26%	9%	31%	
Poorly differentiated	33%	4%	13%	35%	1%	17%	13%	41%	
Undifferentiated	1%	1%	1%	2%	0%	2%	35%	5%	
Unknown or NA	9%	18%	32%	19%	72%	46%	32%	21%	
R0 resection margin	75%	89%	85%	75%	88%	81%	73%	77%	< 0.001
Radiation timing									
Neoadjuvant	7%	0%	2%	3%	0%	5%	6%	5%	< 0.001
Adjuvant	31%	3%	18%	19%	3%	26%	21%	26%	
None/unknown	62%	97%	80%	78%	97%	70%	74%	69%	
Chemotherapy timing									
Neoadjuvant	11%	1%	2%	8%	0%	7%	6%	8%	< 0.001
Adjuvant	47%	4%	30%	41%	3%	45%	28%	36%	
None/unknown	42%	95%	67%	51%	97%	48%	66%	56%	
Chemotherapy modality									
Single agent	39%	2%	27%	29%	3%	33%	17%	21%	< 0.001
Multiagent	22%	3%	9%	19%	1%	20%	15%	23%	
None/unknown	40%	95%	64%	52%	96%	48%	68%	56%	

*Charlson-Deyo Comorbidity Score

undifferentiated carcinoma with osteoclast-like giant cells (2% neoadjuvant radiation, 2% neoadjuvant chemotherapy, $p < 0.001$) (Supplementary Table 5). Patients with undifferentiated carcinoma with osteoclast-like giant cells were again the least likely to receive adjuvant radiation (19%), however were the most likely to receive adjuvant chemotherapy (56%, $p < 0.001$) (Supplementary Table 5).

Survival Analysis

Kaplan-Meier survival curves for the eight main histologic groups are shown in Fig. 2. Median follow-up time for all patients, as measured by the time spanning from date of diagnosis to last contact or death, was 24.4 months. Survival by histologic group showed median OS of 20.2 months for ductal adenocarcinoma (22% 5-year OS), 20.5 months for squamous cell carcinoma (27% 5-year OS), 26.8 months for mixed acinar-neuroendocrine carcinomas (37% 5-year OS), 52.6 months for cystic mucinous neoplasms with an associated invasive carcinoma (51% 5-year OS), 67.5 months for acinar cell carcinoma (51% 5-year OS), and 69.3 months for mesenchymal tumors (55% 5-year OS) (Table 2). Median survival was not reached for neuroendocrine tumors and solid-pseudopapillary neoplasms, with 5-year overall survival rates of 84% and 97% respectively (Table 2).

Kaplan-Meier survival curves for histologic variants within ductal adenocarcinoma, neuroendocrine tumors, and cystic mucinous neoplasms with associated invasive carcinomas are shown in Figs. 3, 4, and 5. Among all patients with adenocarcinoma, those with undifferentiated carcinoma with osteoclast-like giant cells had the most favorable survival, while those with signet ring cell carcinoma had the least (Fig. 3) (HR 0.5; $p = 0.005$ vs. HR 1.4; $p = 0.016$) (Table 3). Well-differentiated neuroendocrine tumors displayed the best survival, while poorly differentiated neuroendocrine carcinomas displayed the worst (Fig. 4). Roughly equivalent survival curves were observed for cystic mucinous neoplasms with an associated invasive carcinoma (Fig. 5).

When evaluating predictors of survival across histologic groups, not achieving an R0 resection was a significant predictor of mortality within each of the three groups (Table 3). For those with ductal adenocarcinoma, receipt of neoadjuvant chemotherapy (HR 0.8; $p = 0.005$), adjuvant chemotherapy (HR 0.9; $p < 0.001$), or adjuvant radiation (HR 0.9; $p < 0.001$) was associated with improved survival (Table 3). Receipt of neoadjuvant (HR 0.4; $p = 0.029$) radiation, on the other hand, was associated with less favorable survival (HR 1.2; $p < 0.001$) (Table 3). Similarly, when evaluating histologic variants of pancreatic ductal adenocarcinoma, R0 resection remained a significant predictor of survival (HR 1.6–2.4, $p < 0.001$) (Supplementary Table 5). Additionally, neoadjuvant and adjuvant chemotherapy, along with adjuvant radiation, all trended toward improved survival, while neoadjuvant radiation trended toward worse outcomes (Supplementary Table 6). Receipt of chemotherapy or radiation therapy did not significantly impact survival for variants of neuroendocrine tumors or those with cystic mucinous neoplasms with associated invasive carcinomas (Supplementary Table 7, Table 3).

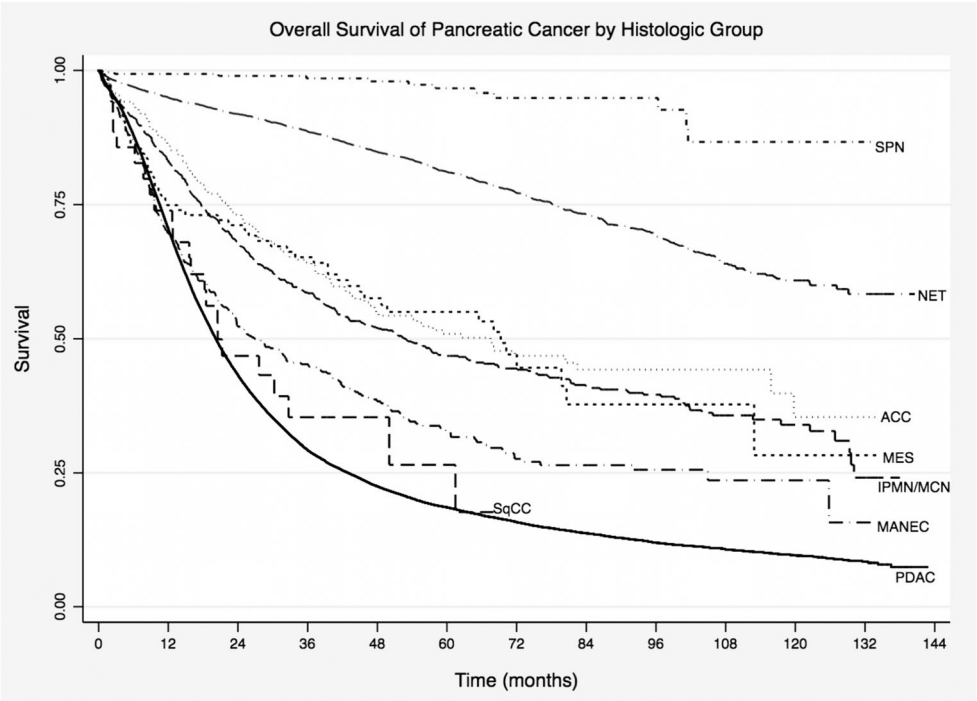

Fig. 2 Kaplan-Meier curves representing overall survival of patients with the pancreatic cancer histologic group. Kaplan-Meier representing overall survival of patients diagnosed with pancreatic cancer by histologic group. SPN, solid-pseudopapillary neoplasm; NET, neuroendocrine tumor (well and poorly differentiated); ACC, acinar cell carcinoma; MES, malignant mesenchymal tumors; IPMN/MCN, invasive carcinomas arising from cystic mucinous neoplasms; MANEC, mixed acinar-neuroendocrine carcinoma; SqCC, squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma

Table 2 Comparison of median survival and 5-year overall survival by histologic group

Histologic type	Median survival (months)	5-year overall survival (%)
Ductal adenocarcinoma (all)	20.2	22
Adenocarcinoma	13.7	18
Undifferentiated carcinoma with osteoclast-like giant cells	48.2	44
Sarcomatoid carcinoma	20.1	27
Mucinous adenocarcinoma	30.3	33
Signet ring cell carcinoma	13.7	10
Adenosquamous carcinoma	14.3	18
Squamous cell carcinoma	20.5	27
Mixed acinar-neuroendocrine carcinoma	26.8	37
Cystic mucinous neoplasms (IPMN/MCN) with an associated invasive carcinoma	52.6	51
Acinar cell carcinoma	67.5	51
Malignant mesenchymal tumors	69.3	55
Neuroendocrine tumors	–	84
Well differentiated	–	84
Poorly differentiated	27.4	20
Solid-pseudopapillary neoplasms	–	97
Overall	24.4	27

Discussion

Because there are few small studies addressing outcomes following resection for rarer pancreatic cancer subtypes, this study sought to better characterize the demographic, prognostic, treatment, and survival outcomes between recognized variants of pancreatic cancer. This represents a large national database study evaluating the clinicopathologic characteristics, treatment, and survival outcomes in both common and rare forms of pancreatic cancer. Ultimately, this information can serve as a reference that can aid in the decision-making and counseling of patients diagnosed with these rare pancreatic neoplasms.

Ductal adenocarcinoma is the most predominant form of pancreatic cancer in the USA and has been well studied using large national datasets.[2, 3, 6, 8–11] The clinicopathologic characteristics of this ductal adenocarcinoma cohort are similar to those previously described with a slight male predominance, increasing incidence with age, and significant lymph node positivity.[50–52] The median survival of this cohort was 20.2 months, which falls within the range of 1–2 years described by several others.[8, 10, 11, 50–62] When broken down by histologic variants of adenocarcinoma, signet ring cell carcinoma was associated with significantly worse survival (HR 1.4) which was comparable to the effect of a non-R0 resection (HR 1.5), while undifferentiated carcinomas with osteoclast-like giant cells (HR 0.5) and mucinous adenocarcinomas (HR 0.6) were associated with more favorable survival. Knowledge of overall survival outcomes for these rare variants of ductal adenocarcinoma may help guide decisions regarding multidisciplinary approaches to treatment.

Squamous cell carcinoma of the pancreas, although exceedingly rare, was associated with median survival of only 20.5 months, which is roughly equivalent to that observed in ductal adenocarcinoma. Therefore, treatment considerations

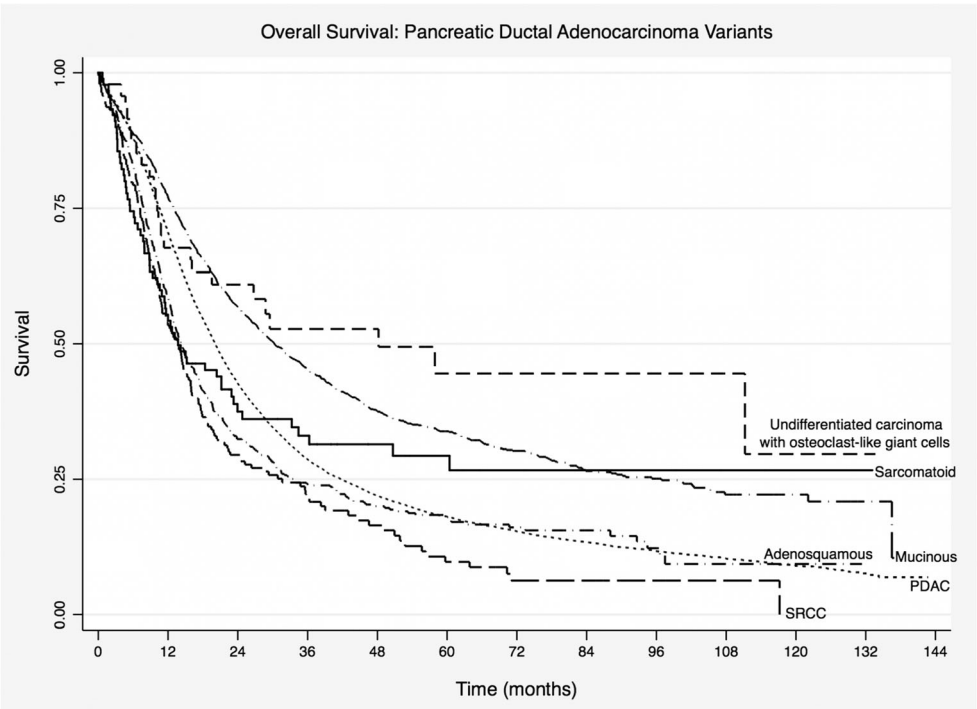

Fig. 3 Kaplan-Meier curves representing overall survival of patients with pancreatic ductal adenocarcinoma by histologic variant. PDAC, pancreatic ductal adenocarcinoma; SRCC, signet ring cell carcinoma

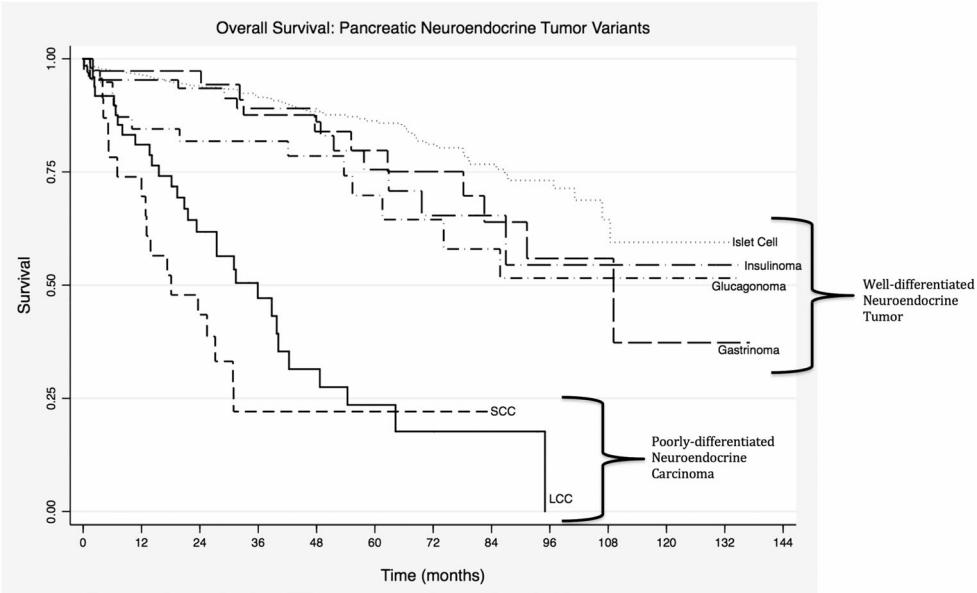

Fig. 4 Kaplan-Meier curves representing overall survival of patients diagnosed with pancreatic neuroendocrine tumors by histologic variant. SCC, small-cell carcinoma; LCC, large-cell carcinoma

and patient counseling should take into account the aggressive biology of these tumors.

Mixed acinar-neuroendocrine carcinoma showed survival outcomes intermediate between acinar cell carcinoma and classical ductal adenocarcinoma. While the overall survival in our study (26.8 months) was higher than that reported in the literature secondary to our exclusion of stage IV patients, our findings nevertheless suggest that the biology of these tumors more closely resembles the aggressive nature of adenocarcinoma than the rather indolent course observed for many neuroendocrine tumors.[46, 63] Cystic mucinous neoplasms with associated invasive carcinomas, acinar cell carcinomas, and malignant mesenchymal tumors showed much longer survival rates compared to adenocarcinoma, with 5-year survival at 51–55% after resection.

Solid-pseudopapillary neoplasms were found to be most common among young women in their thirties and affected a great proportion of African-Americans. These tumors had excellent survival following resection with 5-year survival of 97%. Likewise, patients with well-differentiated neuroendocrine tumors had excellent chance of lasting survival with 5-year survival rates of 84%. The subset of neuroendocrine

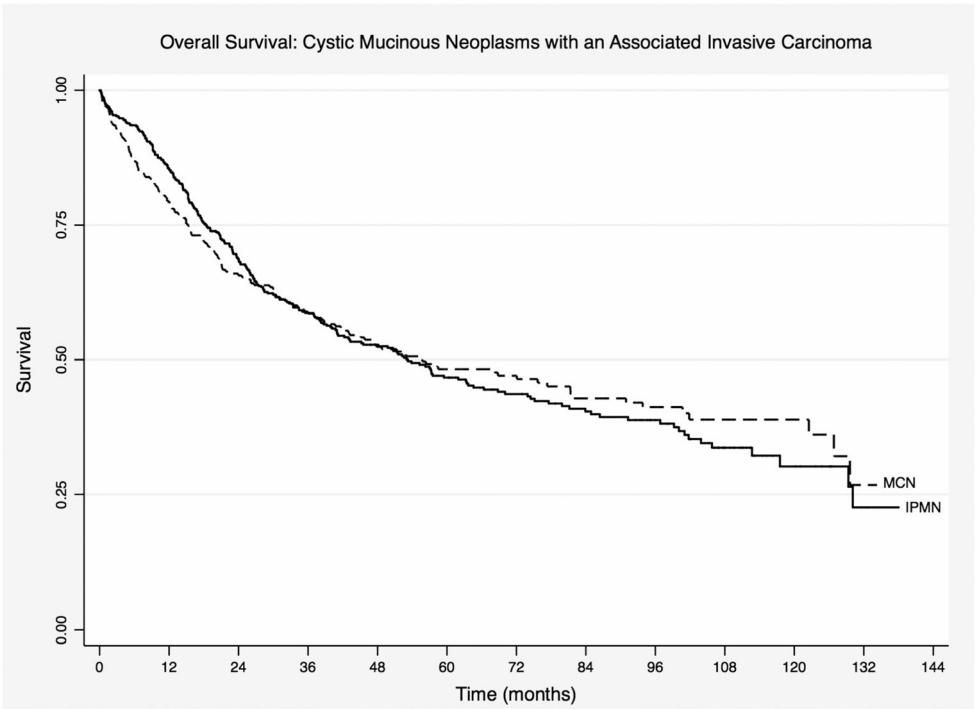

Fig. 5 Kaplan-Meier representing overall survival of patients diagnosed with cystic mucinous neoplasms with associated invasive carcinomas by histologic variant. IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm

Table 3 Cox proportional hazards analysis for factors associated with survival in patients with pancreatic ductal adenocarcinoma, cystic mucinous neoplasms with invasive carcinoma, and neuroendocrine tumors

	Hazard ratio for mortality	95% CI	*P* value
Ductal adenocarcinoma			
Subtypes			
Adenocarcinoma	1.0	Reference	
Undifferentiated carcinoma with osteoclast-like giant cells	*0.5*	*(0.3–0.8)*	*< 0.001*
Sarcomatoid carcinoma	1.0	(0.8–1.3)	0.994
Mucinous adenocarcinoma	*0.6*	*(0.6–0.7)*	*< 0.001*
Signet ring cell carcinoma	*1.4*	*(1.3–2.0)*	*< 0.001*
Adenosquamous carcinoma	*1.2*	*(1.1–1.3)*	*< 0.001*
Non R0 resection	*1.5*	*(1.5–1.5)*	*< 0.001*
Chemotherapy			
None/unknown	1.0	Reference	
Neoadjuvant	*0.8*	*(0.7–1.0)*	*0.005*
Adjuvant	*0.9*	*(0.8–0.9)*	*< 0.001*
Radiation			
None/unknown	1.0	Reference	
Neoadjuvant	*1.2*	*(1.1–1.3)*	*< 0.001*
Adjuvant	*0.9*	*(0.9–0.9)*	*< 0.001*
Cystic mucinous neoplasms (IPMN/MCN) with an associated invasive carcinoma			
Non R0 resection	*1.6*	*(1.3–1.8)*	*< 0.001*
Chemotherapy			
None/unknown	1.0	Reference	
Neoadjuvant	0.4	(0.8–1.5)	0.157
Adjuvant	0.9	(0.6–1.4)	0.713
Radiation			
None/unknown	1.0	Reference	
Neoadjuvant	0.7	(0.2–2.4)	0.585
Adjuvant	1.1	(0.8–1.6)	0.483
Neuroendocrine			
Subtypes			
Well differentiated	*1.0*	*Reference*	
Poorly differentiated	*3.5*	*(2.2–5.6)*	*< 0.001*
Non R0 resection	*1.5*	*(1.3–1.8)*	*< 0.001*
Chemotherapy			
None/unknown	1.0	Reference	
Neoadjuvant	–	–	–
Adjuvant	1.5	(0.6–3.8)	0.393
Radiation			
None/unknown	1.0	Reference	
Neoadjuvant	0.2	(0.2–1.6)	0.132
Adjuvant	1.2	(0.5–2.6)	0.718

Significant values in italics

tumor patients classified as poorly differentiated neuroendocrine carcinoma (small cell and large cell) had significantly worse survival compared to well-differentiated tumors, and thus these patients may be more likely to benefit from neoadjuvant or adjuvant treatment pathways; however, certainly, further studies would be needed to explore these possibilities.

At present, surgery remains the mainstay of treatment for the majority of patients with resectable disease regardless of histological types, with curative resection reported as one of the most important factors associated with increased median survival.[13, 14, 30, 31, 33–37, 64–67] The findings in our study highlight this, as we found non-R0 resection to be significantly associated with worse mortality in all three of the major histologic subgroups we examined, along with many of the histologic variants within those groups.

For the majority of these rare pancreatic cancers, the role of chemotherapy and radiation treatments remains poorly understood. Cisplatin and 5-FU have been used in patients with pancreatic squamous cell carcinoma,[30, 34] doxorubicin-based chemotherapy for those with pancreatic sarcomas,[35] cisplatin and etoposide-based therapy for poorly differentiated neuroendocrine carcinomas,[43, 67] and gemcitabine ± oxaliplatin for invasive carcinomas arising from cystic mucinous neoplasms (MCN/IPMN).[22, 28] In patients with acinar cell carcinoma, some reports describe improved survival in the setting of chemotherapy, whether given in neoadjuvant setting to improve surgical candidacy or in general terms of overall survival, while others have not noted superior outcomes in patients that received adjuvant chemotherapy.[17, 18, 68–70] In our study, a significant association with improved survival was only observed in patients with ductal adenocarcinoma who received neoadjuvant or adjuvant chemotherapy. Neoadjuvant radiation was associated with worse survival, possibly reflecting selection bias for patients with more advanced disease. There were no significant survival associations based on receipt of neoadjuvant or adjuvant therapies for patients with neuroendocrine tumors or cystic mucinous neoplasms with associated invasive carcinomas. These findings again highlight the implications of tumor biology, propensity to use these adjuvant/neoadjuvant treatments in patients with more advanced disease, practitioner practice preferences, and small sample sizes associated with rare histologic diagnoses. Additionally, these findings highlight the uncertain role for chemotherapy and radiation outside of ductal adenocarcinoma.

While there are many strengths of a large, diverse, national population, there are several limitations that must be acknowledged. First, there is risk of incomplete data and recording errors inherent in any registry, which has been addressed in the literature for the NCDB.[71, 72] Second, while critical to draw data from a large population when dealing with very rare histologic entities, doing so often precludes the ability to confirm the specifics of the pathological workup. Moreover, current pathological classifications may not represent or directly correspond to those previously used at time of data collection. Third, in-depth information regarding comorbidities and other

specific treatment variables (e.g., type of chemotherapy administered) that have the ability to significantly affect outcomes is not available. Finally, information regarding treatment decision-making is not available in the NCDB, creating selection bias for those receiving neoadjuvant and adjuvant therapies in the multivariable analysis.

Conclusions

Rare subtypes of pancreatic cancer present unique clinicopathologic characteristics and display distinct tumor biologies. This study presents data on demographic, prognostic, treatment, and survival outcomes between rare forms of pancreatic neoplasms in order to aid understanding of the natural history and behavior of these neoplasms, with the hope of serving as a reference in clinical decision-making and ability to provide accurate prognostic information to patients.

Authors' Contributions Courtney J. Pokrzywa made substantial contribution to the study conception and design, data analysis and interpretation, and manuscript drafting and revision. Daniel E. Abbott made substantial contribution to the study conception and design, data analysis and interpretation, and manuscript drafting and revision. Kristina A. Matkowskyj made substantial contribution to the study conception and design, data analysis and interpretation, and manuscript drafting and revision. Sean Ronnekleiv-Kelly made substantial contribution to the study design, data interpretation, and manuscript revision. Emily R. Winslow made substantial contribution to the study design, data interpretation, and manuscript revision. Sharon M. Weber made substantial contribution to the study design, data interpretation, and manuscript revision. Alexander V. Fisher made substantial contribution to the study conception and design, data analysis and interpretation, and manuscript drafting and revision. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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