Original Article

A national database analysis of acinar cell carcinoma of the pancreas, a histologically, epidemiologically, and biologically distinct entity increasing in incidence

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Background: Pancreatic acinar cell carcinoma is a rare exocrine malignancy that is distinct from pancreatic ductal adenocarcinoma. We sought to describe its changing incidence, compare its natural history to that of pancreatic ductal adenocarcinoma, and evaluate impact of treatment modalities using the National Cancer Data Base, and Surveillance Epidemiology and End Results datasets.

Methods: Patients with histologically confirmed diagnosis were identified from the National Cancer Data Base and Surveillance Epidemiology and End Results. Parametric univariate analyses were performed to compare patient characteristics, tumor types and outcomes. Incidence trends were calculated using Surveillance Epidemiology and End Results data and unadjusted Kaplan-Meier Survival analysis was performed using data from the National Cancer Data Base.

Results: Incidence of acinar cell carcinoma significantly increased by 73% over the study period compared to only 22% for ductal adenocarcinoma (P<0.01). Unadjusted and adjusted stage-specific survival was substantially superior for acinar cell carcinoma versus ductal adenocarcinoma in all stages. Pancreatic acinar cell carcinoma demonstrated lower age at diagnosis, larger and lower grade tumors, was less likely to demonstrate histopathologic lymphovascular invasion, and more likely to undergo curative-intent resection with lower positive margins compared to ductal adenocarcinoma. Amongst resected patients, ductal carcinoma histology remained the strongest independent predictor of increased mortality hazard compared to pancreatic acinar cell carcinoma.

Conclusions: Acinar cell carcinoma is a less aggressive malignancy with a significantly rising incidence of unknown etiology and better overall survival in both unadjusted analysis and after adjustment for clinically relevant predictors of mortality.

Keywords: Acinar cell carcinoma; pancreatic cancer; neoadjuvant; NCDB

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Introduction

Pancreatic acinar cell carcinoma (PACC) is a rare form of exocrine pancreatic cancer which represents only 1–2% of pancreatic cancer diagnoses (1-3). It is more common in males with a lower mean age at diagnosis compared to pancreatic ductal adenocarcinoma (PDAC) (1). Histologically it can appear as acinar cells or may be comprised of poorly differentiated cells making the morphologic diagnosis difficult. PACCs produce specific enzymes including proteases, lipases, and amylases, which can aid in diagnosis via immunohistochemical staining (4). PACC is assumed to have a better prognosis than PDAC, but is still poor with 5 year survival of only 10% (1). The preferred treatment for localized PACC tumors has been surgical resection not unlike PDAC. Resection of these cancers has been associated with increased long-term survival (4). Metastatic disease is typically not curable and is treated with systemic chemotherapy.

Due to the low incidence of disease, no studies have been able to identify the appropriate treatment regimen for patients with PACC in a randomized fashion. It is unclear what the role of chemotherapeutic agents is and what the sequence of treatment should be. Furthermore, very few studies have used large population databases to compare the characteristics, outcomes and incidence of PACC to PDAC (5,6). Reports of neoadjuvant chemotherapy (NAC) for patients with PACC are limited to case reports and small-case series, and there remains minimal data comparing the survival of patients with PACC versus PDAC treated with upfront resection versus neoadjuvant therapy (7-10). A better understanding of how patients respond to therapies is needed.

In this study, characteristics of both PACC and PDAC were compared using data from the NCDB. We evaluated the differences in stage specific survival for all stages of disease and compared them between PACC and PDAC. We then compared survival for resected PACC patients compared to resected PDAC. Additionally, since an analysis of the incidence of PACC has not been assessed in recent years, we used the SEER database to analyze the change in incidence of PACC from the years of 2005–2015. This incidence trend of PACC was compared to that of PDAC. To our knowledge, no previous studies have used two large national databases to evaluate the relationship of these two entities.

Methods

SEER data analysis

The Surveillance Epidemiology and End Results (SEER) is a population-based source of data from 9 state-based registries in the United States (US) (11). We compared incident cases of pancreatic acinar cell carcinoma and ductal adenocarcinoma for the time period available in our NCDB Participant User File (PUF – 2005-2015). ICD-O-3 topographical codes (C25.0-25.9) and histologic (8140 for PDAC and 8550 for PACC) codes were utilized to identify patients. Incidence was determined per 100,000 population adjusted to the standard population of the US in the year 2000. Percent change on an annual basis was calculated using the linear least-squares method and subsequently tested for deviation from zero using a t-distribution regression. Trends were assessed for significance using Cochran-Armitage trend analysis.

NCDB data analysis

Histopathologic, demographic, and outcome comparisons were performed as a cohort study of the NCDB participant user file (PUF) of patients presenting for curative-intent surgery of pancreatic acinar cell carcinoma and ductal adenocarcinoma during the time period outlined above. The NCDB contains records from over 30 million cancer cases treated at more than 1500 Commission on Cancer (CoC) approved hospitals in the US and is expected to capture roughly 70% of newly diagnosed cases of cancer in the US (12).

Patients with acinar cell carcinoma and ductal adenocarcinoma were sought using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography (25.0–25.9) and histology codes (8140 for PDAC, 8550 for PACC). Curative-intent surgery was defined as surgery of primary site codes 20–90. Patients with surgical codes 0 (no surgery) and 99 (Unknown) were considered to have had no curative intent surgery. Patients not treated at the reporting hospital were excluded. TNM staging is recorded in the NCDB using American Joint Commission on Cancer (AJCC) 6th/7th edition staging classification dependent on year of diagnosis, and the 'analytic stage group' variable was used for staging. This variable is based on pathologic staging where available and clinical staging where pathologic staging information is

missing. Patients with missing follow-up or final pathologic staging data were excluded as were those who developed cancer at more than one site.

Statistical analysis

Normally distributed continuous data were treated with mean/standard deviation (SD) and significance was tested with a student's t-test (two-tailed). Continuous data with non-normal distributionwere expressed as median and inter-quartile range (IQR) with significance testing performed using the Mann-Whitney U-test. Categorical variables with uniform distribution were assessed for significance with Pearson's chi-square tests while categorical variables with non-uniform distribution were tested with the Fisher's exact test. Missing data were tracked with indicator variables as shown in the tables.

The Kaplan-Meier method was used for survival estimation with the definition of survival being time from diagnosis to death or censor. Significance testing comparison of survival curves was performed with the log-rank test. Overall survival is reported due to the fact that the NCDB does not provide data on recurrence or cause of death. To estimate independent impact of covariates on survival, the method of Cox proportional hazards was developed in resected patients which included tumor subtype, clinical stage, tumor grade, node status, margins, and receipt of radiation and/or chemotherapy. Statistical significance was set at a P<0.05. Analysis of data was performed using R version 3.5.2 "Eggshell Igloo" (R Foundation for Statistical Computing – Vienna, Austria www.r-project.org). The Mayo Clinic Institutional Review Board has deemed this study exempt from review. The study was conducted in compliance with the Helsinki Declaration (revision from 2013).

Results

We identified 137,962 patients with PDAC and 589 with PACC in the NCDB. There were several features which were significantly different between the two tumor types which is detailed in *Table 1*. Patients with PACC were more likely to be male (72.8% *vs.* 51.7%) and were younger at the time of diagnosis (64.0 *vs.* 68.0 years old). Patients with PACC had significantly larger tumors (5.4 *vs.* 4.2 cm) at the time of diagnosis. Patients with PACC were more likely to have nodal involvement (49.3% *vs.* 28.2%) and were less often located in the head of the pancreas (44.5% *vs.* 51.7 %).

A minority of patients treated with systemic chemotherapy were sequenced in neoadjuvant fashion (2.8% PDAC and 4.4% PACC). Patients with PACC more often underwent curative-intent surgery (43.8% *vs.* 16.4%) and were less likely to have positive resection margins (20.4% *vs.* 24.2%). There was no statistically significant difference between PACC and PDAC amongst the entire cohort of patients diagnosed during the study period in regards to number of patients receiving chemotherapy or radiation therapy, race, Charlson Deyo score, or year of diagnosis. The interval survival for patients with PACC was better at 1, 2, and 3 years compared to PDAC.

Cox proportional hazard model for resected patients revealed several statistically significant predictors of mortality hazard and can be seen in *Table 2*. Among resected patients, predictors of mortality included stage three and four tumors; stage 3 (HR: 1.26; 1.16–1.36) and stage 4 (HR: 1.85; 1.70–2.01). Additional predictors included high tumor grade (HR: 1.32, 1.27–1.36), positive resection margin (HR: 1.62, 1.56–1.68), omission of radiation (HR: 1.12; 1.08–1.16). After adjustment for stage, grade, nodal status, margins, chemotherapy and radiation, PDAC histology remained the strongest independent predictor of mortality (HR 2.33, 95% CI: 1.95–2.78).

Incidence of PACC increased by 73% over the twelve year study period, while the incidence of PDAC increased by only 22%. This difference was statistically significant with P<0.01. The ratio of incidence change between PACC *vs.* PDAC was also significant at 59% increase over the study period (*Figure 1*). Stage-specific survival was found to be significantly better for all stages of PACC when compared to PDAC (*Figure 2*). Stage I disease showed the greatest difference in survival probability. Kaplan-Meier analysis for all stages combined and in resected patients also demonstrated improved survival for patients with PACC compared to PDAC and can be seen in *Figure 3*. Kaplan-Meier analysis was performed over a 60-month period and survival was found to be higher for patients with PACC for the duration of this period of time in all analyses performed.

Discussion

In the present study, we investigated the increased incidence of PACC and identified improved overall survival for patients with PACC as compared to PDAC. Despite PACC presentation with larger tumor size, there is a lower likelihood of lymph node involvement and patients with PACC are less likely to have positive margins at the time of

Table 1 Cohort demographic and surgical characteristics and overall outcomes

Variable	PACC, n=589	PDAC, n=137,962	P value
Median age [IQR]	64.0 [54.0, 73.0]	68.0 [59.0, 76.0]	<0.001
Female Sex	28.2%	49.3%	<0.001
Race			0.311
Caucasian	84.6%	82.4%	
African American	10.7%	10.7%	
Other	4.8%	4.8%	
Charlson Deyo Score			0.188
0	72.5%	69.0%	
1	22.1%	25.1%	
2+	5.4%	5.4%	
Facility type			<0.001
Non-Academic	48.2%	55.4%	
Academic/Research	46.9%	43.8%	
Missing	4.9%	0.9%	
Year of diagnosis			0.904
2004	6.6	7.6	
2005	8.0	7.9	
2006	7.0	8.1	
2007	8.8	8.5	
2008	8.8	9.1	
2009	8.8	9.3	
2010	9.5	9.2	
2011	9.0	9.6	
2012	11.7	9.9	
2013	10.2	10.2	
2014	11.5	10.6	
Clinical Stage (%)			<0.001
Stage I	16.1%	8.2%	
Stage II	20.2%	16.4%	
Stage III	6.3%	12.2%	
Stage IV	37.7%	46.8%	
Missing	19.7%	16.4%	
Median tumor size (cm) [IQR]	5.4 [3.4, 12.0]	4.2 [3.0, 8.0]	<0.001
N1+ Status	49.3%	28.2%	<0.001
CA 19-9 Elevated (% of available)	37.8%	75.9%	<0.001

Table 1 (*continued*)

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Variable	PACC, n=589	PDAC, n=137,962	P value
Tumor location (head)	44.5%	51.7%	<0.001
Positive margin (% of available)	20.4%	24.2%	<0.001
Curative surgery	43.8%	16.4%	<0.001
Radiation	20.2%	20.3%	0.994
Chemotherapy	58.4%	56.9%	0.247
Neoadjuvant	4.4%	2.8%	<0.001
Median OS (months)			
Interval survival (all patients)			
1 year	65.3%	30.1%	<0.001
2 year	48.0%	13.3%	<0.001
3 year	38.6%	8.0%	<0.001

PDAC, pancreatic ductal adenocarcinoma; PACC, pancreatic acinar cell carcinoma;

surgical resection. These findings, along with the improved overall survival at all stages, suggests that PACC is a less aggressive malignancy than PDAC. The 73% increase in incidence over a 12 year study period is of significant interest. The study demonstrated that the incidence is increasing at a much faster rate than PDAC. The reason for the increasing incidence is unknown and is a subject for further investigation which should be followed with interval studies. Possible explanations for this increased incidence is improvements in the ability to identify this histologic subtype, increased incidental identification during abdominal imaging for other purposes, or due to genetic factors.

Due to its rarity, there is a lack of information in the current literature describing epidemiologic or modifiable risk factors for PACC. However, elucidating genetic risk factors and associations may aid investigators in identification of pathways involved in the development of PACC and, subsequently, development of specific targeted therapies for the disease. Studies investigating the molecular characterization of PACC have identified a number of associated genetic mutations (4,13,14). Genes which have been identified as mutant in select tumors include *TP53*, *BRAF*, *SMAD4*, *CDK2NA*, *MMR/MSI*, *RB1*, *APC*, *JAK1*, *MEN1*, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *MSH2*, several of which are targetable action genes (4,13,14). One particularly interesting gene of those identified is *MMR/MSI* which has therapeutic implications. Pembrolizumab

is a PD-L1 inhibitor that is FDA approved as of October 2020 for use in all *MMR/MSI* unresectable solid tumors which have progressed following treatment with no alternative viable options (15). The rate of microsatellite instability in PACC tumors has been reported to range from 8–15%, which is much higher than that reported in PDAC (1–2%) (2,4,16). There is no data recommending a change in therapy based on tumor instability, however, given the availability and potential benefit of these targeting therapies, it would be prudent to obtain MSI information in cases of PACC as it may broaden systemic therapy options. Another intriguing genetic finding is that *KRAS* mutations are found less frequently PACC when compared to PDAC. This may provide a molecular basis for the improved survival as patients with *KRAS* wildtype PDAC have a better prognosis than those with *KRAS* mutations (16).

Since tumor biology portends a significant variation in response to treatment modalities, it will become increasingly important to determine histologic subtype when formulating a treatment plan. Determining histologic subtypes can be difficult. The presentation of PACC can be non-specific although there are some distinct differences unique to that of ductal carcinoma. For example, the finding of elevated lipids is seen in 50% of patients, with up to 10% of patients having lipase hypersecretion syndrome, which presents as subcutaneous fat necrosis, polyarthralgia, occasional eosinophilia and nonbacterial thrombotic endocarditis (1). These are often absent and may create

Table 2 Cox proportional hazard model for resected patients

Variable	Items	N	Hazard Ratio Plot	HR (95% CI)	P value
Type	PDAC	22,573		Reference	
	PACC	258		0.43 (0.36, 0.51)	<0.001
Clinical stage		8,794		Reference	
	1	4,911		0.85 (0.81, 0.88)	<0.001
	2	7,499		0.99 (0.96, 1.03)	0.636
	3	888		1.26 (1.16, 1.36)	<0.001
	4	739		1.85 (1.70, 2.01)	<0.001
Tumor grade		8,794		Reference	
	High	7,789		1.32 (1.27, 1.36)	<0.001
	Missing	3,082		0.95 (0.91, 1.00)	0.044
Node status	N0	6,916		Reference	
	N1+	13,389		0.93 (0.88, 0.98)	0.011
	Missing	2,526		1.56 (1.50, 1.61)	<0.001
Margins	Negative	16,831		Reference	
	Positive	5,099		1.47 (1.36, 1.59)	<0.001
	Missing	901		1.62 (1.56, 1.68)	<0.001
Radiation	Radiation	8,910		Reference	
	No Radiation	13,779		1.12 (1.08, 1.16)	<0.001
	Missing	142		0.91 (0.74, 1.10)	0.327
Chemotherapy	Chemotherapy	15,165		Reference	
	No Chemotherapy	6,618		1.05 (0.98, 1.14)	0.177
	Missing	1,048		1.65 (1.59, 1.71)	<0.001

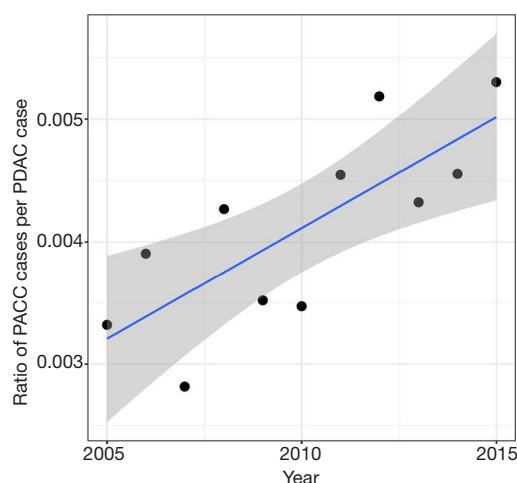PDAC, pancreatic ductal adenocarcinoma; PACC, pancreatic acinar cell carcinoma.

Figure 1 Rate change of PACC cases per PDAC cases over the course of the study. PDAC, pancreatic ductal adenocarcinoma; PACC, pancreatic acinar cell carcinoma.

difficulties in the diagnosis of PACC (2).

Despite being clinically absent in many patients these unique features can aid in diagnosis (1,16). Serum lipase is a tumor marker for PACC and should be checked (17). Distinct imaging findings also can help to differentiate PACC from PDAC, although they are less helpful at differentiating from other tumors of the pancreas. Computed tomography (CT) is considered the standard diagnostic modality for PACC (18). On CT, PACC has central hypodensity, a well-defined enhancing capsule and internal calcifications (19,20). In order to achieve the correct diagnosis, pathology, tumor presentation and imaging findings should be carefully reviewed. Once histology is identified, the treatment can be tailored to tumor subtype and response to treatment can be studied for application to future patient treatment planning.

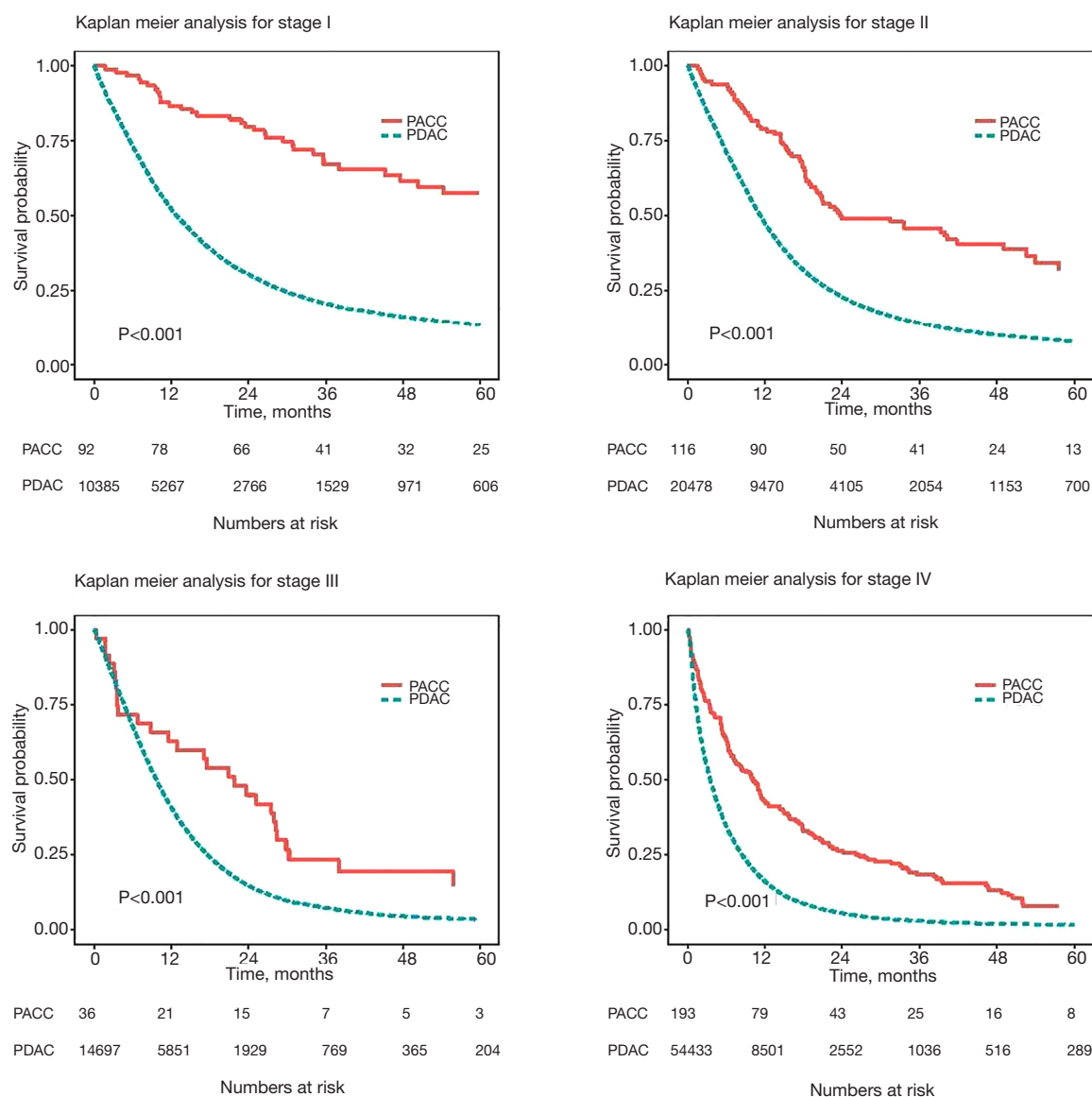In conclusion, it is important to recognize that,

Figure 2 Stage specific survival (all patients) (Reprinted with permission from Elsevier. HPB Journal). PDAC, pancreatic ductal adenocarcinoma; PACC, pancreatic acinar cell carcinoma.

although it has a more favorable prognosis than its ductal counterpart, PACC is an aggressive cancer that requires aggressive treatment. When surgical resection is pursued an R0 resection should be the goal (18). The role of NAC in increasing the likelihood of an R0 resection is another subject of interest which can be examined in future studies. Patients with Stage IV disease and patients with positive margins after surgical resection should be highly considered for multimodal therapy to attempt to treat residual disease as best possible. Although this tumor is rare and the increased incidence may not be immediately clinically significant, this could change over time and this rare cancer may be seen more often in coming decades.

Limitations

This study is limited by its retrospective nature. Furthermore, the use of large databases creates additional limitations. First, re-review of pathologic specimens or cross-sectional imaging is not possible with NCDB data.
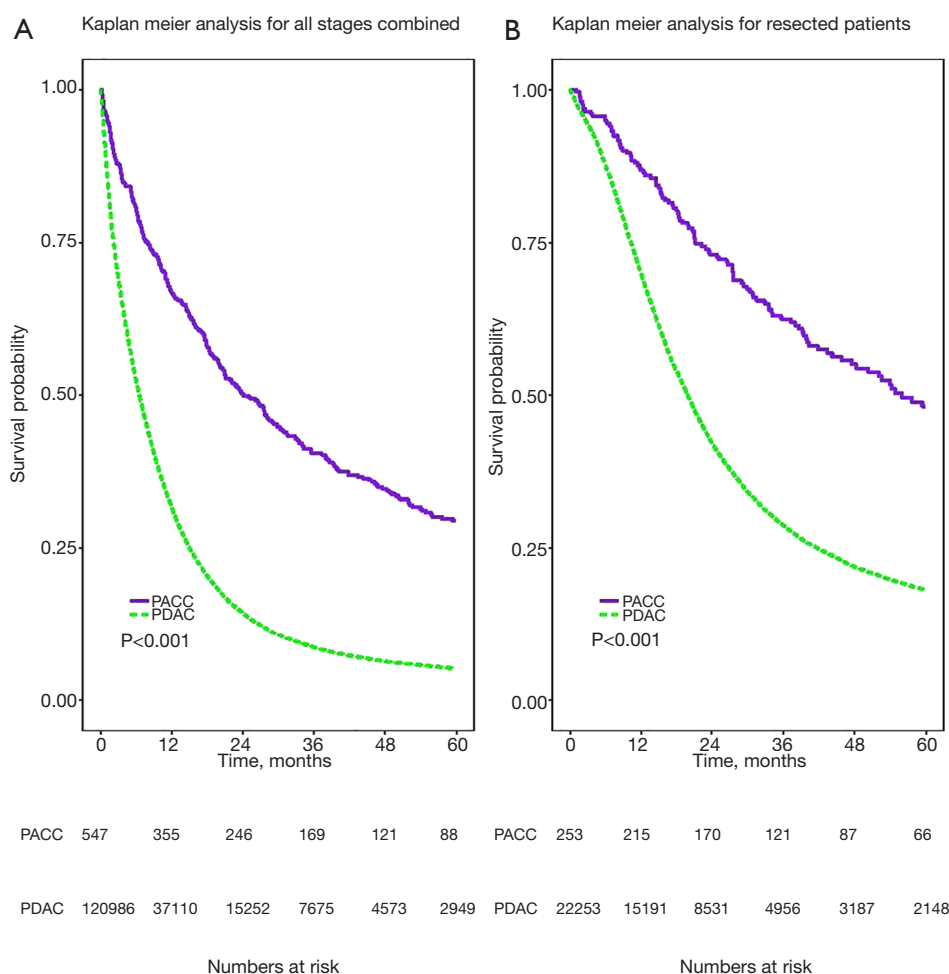
Figure 3 Kaplan-Meier analysis for all stages combined in (A) all patients and (B) resected patients. PDAC, pancreatic ductal adenocarcinoma; PACC, pancreatic acinar cell carcinoma.

Additionally, while we examined the chemotherapy pattern between PACC and PDAC using NCBD data, we could not provide comparable results using the SEER database as SEER does not have chemotherapy sequencing data (with respect to surgery) before 2019. Furthermore, the NCDB and SEER databases do not provide granular details on the chemotherapy (i.e., chemotherapy types, dose, cycles, and duration). The NCDB database is also limited to CoC approved facilities, leaving approximately 30% of cancer diagnosis uncaptured in our analysis. Another limitation of this study is determining the clinical significance of the increasing incidence. PACC is a very rare malignancy; therefore, the increase in incidence may be statistically significant but not clinically relevant for a period of time.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apc-21-1). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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