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ORIGINAL RESEARCH

Impact of Prior Malignancy on Survival Outcomes of Stage IV Pancreatic Adenocarcinoma: SEER-Based Cohort

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Abstract

Purpose Pancreatic cancer is one of the most fatal malignancies and the fourth leading cause of cancer-related mortality in the USA. Most clinical trials involving pancreatic adenocarcinoma (PAC) patients exclude subjects with a prior malignancy because of the possible effect of prior malignancies on survival. However, no data in the medical literature support this assumption. In this paper, we aim to study the impact of having a prior malignancy on the survival outcomes of stage IV PAC.

Methods We used the surveillance, epidemiology, and end results database to review patients with stage IV PAC diagnosed between 1973 and 2014. We calculated overall and pancreatic cancer-specific survival of these patients using unadjusted Kaplan-Meier test and multivariable covariate-adjusted Cox models.

Results We reviewed 66,874 stage IV PAC patients, of which 4942 had a prior malignancy. Kaplan-Meier and Cox models showed that a history of prior malignancy did not cause significant difference in overall survival (HR = 0.938, 95%CI = 0.880–1.000, $p = .052$). However, a prior malignancy was associated with a better pancreatic cancer-specific survival (HR = 0.855, 95% CI = 0.796–0.918, $p < .001$).

Conclusion A prior malignancy before stage IV PAC was not associated with worse survival outcomes. Researchers should take these results into consideration when including/excluding patients to improve the generalizability and accuracy of their results.

Keywords Survival outcomes · Pancreatic adenocarcinoma · SEER · Clinical trials

Introduction

Pancreatic cancer is one of the most fatal malignancies and the fourth leading cause of cancer-related mortality in the USA, with a 5-year overall survival of 8% [1, 2]. Adenocarcinomas arising from exocrine glands of the pancreas constitute most of pancreatic cancer cases, most commonly arising from the head and neck [2, 3]. Although few preventive behavioral changes have been reported—such as smoking cessation, alcohol intake reduction, and healthy food maintenance—and despite recent advances in radiotherapy, surgical techniques, and chemotherapy regimens, pancreatic cancer remains a widely-prevalent and a highly lethal disease, and no definite cure exists for advanced cases. This intractable nature of pancreatic cancer necessitates ongoing trials to decrease mortality and enhance the quality of life of patients with advanced disease [4, 5].

Most clinical trials involving pancreatic adenocarcinoma (PAC) patients consider a "history of a prior malignancy" as an exclusion criterion; thus, patients of this population are generally underrepresented in clinical trials. The rationale behind this practice is mainly the possible effect of prior malignancies on the survival of patients, potentially affecting the results of these trials [6]. However, no solid evidence supports this claim, and no previous research studied the real impact of a prior malignancy on the survival of PAC. This can raise a concern about these trials' accuracy and generalizability [7, 8].

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In this study, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which is a public registry that documents recent incidence, prevalence, mortality, and survival cancer statistics, to investigate the impact of history of a prior malignancy on the overall and pancreatic cancer-specific survival of a subsequent stage IV PAC, and to assess the validity of excluding patients with prior malignancies from clinical trials on stage IV PAC [9].

Methods

Data Sources

We used SEER*Stat software (version 8.3.4) to get data from the SEER 18 registries (November 2016 submission) of the SEER database [10]. These registries cover approximately 27.8% of the US population (based on 2010 census) from 1973 to 2014 [11].

Study Population

We included stage IV PAC patients who were diagnosed during 1973–2014, and whose diagnosis did not rely only on autopsy or death certificates. Then, we excluded cases that had the following: a history of more than one primary malignancy before PAC, a history of another primary pancreatic malignancy, and/or a history of a prior malignancy diagnosed within 6 months prior to stage IV PAC (in order to eliminate the possibility of simultaneous cancers). Included patients were divided into two groups based on having a prior malignancy or not before the diagnosis of PAC.

Within each of the included cases, we reviewed the following variables: age, sex, marital status, grade of PAC, specific site of malignancy in the pancreas, treatment modalities (surgery, radiation, and chemotherapy), survival months, vital state, and the cause of death. Additionally, in cases with prior malignancies, we reviewed the site of the prior malignancy, and calculated the latency period between the two diagnoses.

Outcomes

Our main outcome was the difference in survival between the two previously mentioned groups; we calculated both overall survival and pancreatic cancer-specific survival to study the impact of the presence of a prior malignancy. Survival was measured as the interval in months between date of diagnosis and date of death provided by SEER. Patients were followed until respective dates of death or censored at the end of 2014 (last date of death in 2016 SEER submission). In case of pancreatic cancer-specific survival, patients were additionally censored if they died because of any cause other than the pancreatic cancer.

Statistical Analysis

We used chi-square test to study the characteristics of the sample, and compare them according to the presence or absence of a prior malignancy. We used unadjusted Kaplan-Meier test to calculate overall and pancreatic cancer-specific survival and construct survival curves. We also used multivariable adjusted Cox models to calculate the survival and adjust for the following factors: the presence of a prior malignancy, age at diagnosis of pancreatic cancer, sex, race, marital status, grade of pancreatic cancer, and surgery as a treatment option for pancreatic cancer. We used SEER*Stat software (version 8.3.4) to access the data, and SPSS software (version 23, IBM, NY) to analyze it [10]. All statistical tests were two sided, and a p value of less than .05 was considered significant.

Results

Patient's Characteristics

We reviewed the records of 66,874 patients with stage IV PAC, of which 4942 (7.4%) had a history of a prior malignancy. Table 1 describes baseline characteristics. The most common malignancy before stage IV PAC was prostate cancer and constituted about (31%) of cases. Less common malignancies were breast cancer (18%), colorectal cancer (11%), urinary bladder cancer (6%), endometrial cancer (4%), lung cancer (4%), melanoma (4%), kidney cancers (3%), and non-Hodgkin lymphomas (3%). About half cases with prior malignancies (55%) had their PAC diagnosis after more than 5 years of the first malignancy.

Effect of Prior Malignancy on Overall and Pancreatic Cancer-Specific Survival of Stage IV Pancreatic Adenocarcinoma

Kaplan-Meier test did not show any difference in overall survival in patients with a history of a prior malignancy compared to those without a history of prior malignancy. However, pancreatic cancer-specific survival was better among patients with a prior malignancy (Fig. 1).

After adjusting for multiple factors (the presence of a prior malignancy, age at diagnosis of pancreatic cancer, sex, race, marital status, grade of pancreatic cancer, and surgery as a treatment option for pancreatic cancer), multivariable covariate-adjusted Cox models also showed that the overall survival did not differ in patients with a prior malignancy (HR = 0.938, 95%CI = 0.880–1.000, p = .052) compared to

Table 1 Baseline characteristics of stage IV pancreatic adenocarcinoma cohort ($N = 66,874$)

Patient characteristics	All patients No.	Patients with a prior malignancy No. (%)+	*P* value*
Age at diagnosis			< .001
40–65	29,026	1144 (3.9%)	
> 65	37,848	3798 (10.0%)	
Sex			< .001
Male	36,083	2913 (8.1%)	
Female	30,791	2029 (6.6%)	
Race			.003
White	53,757	4057 (7.5%)	
Black	8390	596 (7.1%)	
Others#	4600	288 (6.3%)	
Marital status			< .001
Single	7601	430 (5.7%)	
Married	38,650	2978 (7.7%)	
Separated	840	35 (4.2%)	
Divorced	6092	409 (6.7%)	
Widowed	11,412	922 (8.1%)	
Site			.874
Head of pancreas	25,342	1901 (7.5%)	
Body of pancreas	8655	652 (7.5%)	
Tail of pancreas	11,078	829 (7.5%)	
Other parts of pancreas	892	60 (6.7%)	
Overlapping pancreas lesions	5947	431 (7.2%)	
Grade			.638
Well differentiated	2596	193 (7.4%)	
Moderately differentiated	7323	497 (6.8%)	
Poorly differentiated	10,664	744 (7.0%)	
Undifferentiated, anaplastic	681	52 (7.6%)	
Radiation			.039
Yes	5951	400 (6.7%)	
No/unknown	60,923	4542 (7.5%)	
Surgery			.131
Yes	3242	237 (7.3%)	
No	54,861	4417 (8.1%)	
CHEMO			.009
yes	30,086	2135 (7.1%)	
No/unknown	36,788	2807 (7.6%)	
Vital status			< .001
Alive	3542	310 (8.8%)	
Dead	63,332	4632 (7.3%)	

*Two-sided *P* value was calculated from chi-square

+This number represents the percentage of patients with a prior malignancy within each characteristic. #Represents (American Indian/AK Native, Asian/Pacific Islander)

those without a history of prior malignancy. However, pancreatic cancer-specific survival was better in patients with a prior malignancy (HR = 0.855, 95% CI = 0.796–0.918, $p < .001$) compared to those without a prior malignancy. Table 2 summarizes the multivariable covariate-adjusted Cox models for overall and pancreatic cancer-specific survival of stage IV PAC patients.

Effect of Latency Between the Two Diagnoses, and the Site of the Prior Malignancy on Overall Survival of Stage IV Pancreatic Adenocarcinoma

Neither Kaplan-Meier test nor multivariable covariate-adjusted Cox models showed a difference in overall survival among patients with a prior malignancy in all latency groups

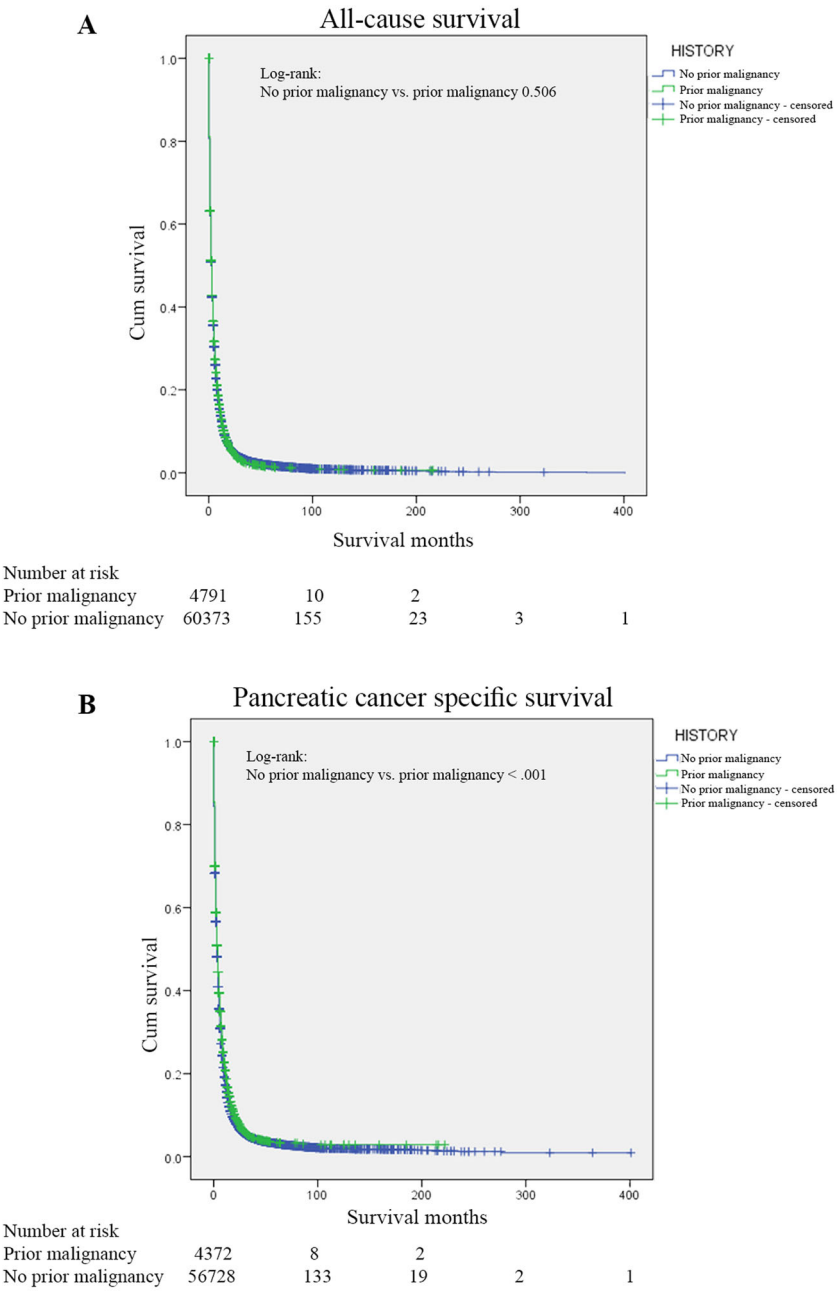

Fig. 1 All-cause (**a**) and pancreatic cancer-specific (**b**) survival of stage IV PAC with and without prior malignancy

(data not shown). Furthermore, when overall survival was calculated according to the site of the prior malignancy, none of the sites was associated with different overall survival than patients with no prior malignancy (data not shown).

Discussion

Clinical trials are a cornerstone in enhancing patient-centered healthcare [12]. It is crucial to design these trials properly, and cautiously assess their internal and external validity in order to increase their impact and reduce scientific waste. The recruitment process and selection criteria are important aspects of the methodology of clinical trials [13]. Shortfalls in recruiting patients can result in lower yield results and invalid representation of a certain population [14, 15]. In the field of cancer research, reports have demonstrated that researchers commonly exclude patients with a previous history of malignancy in their clinical trials with no hard evidence supporting this practice [9]. In our study, and using the SEER database (which is a large population-based cancer database), we found that 7.4% of 66,874 patients with stage IV PAC had prior malignancies. We also found that such

Table 2 Multivariable covariate-adjusted Cox models for overall and pancreatic cancer-specific survival for stage IV pancreatic adenocarcinoma, with adjustment for the following factors; the presence of a prior malignancy, age at diagnosis of pancreatic cancer, sex, race, marital status, grade of pancreatic cancer, and surgery as a treatment option for pancreatic cancer

Patient characteristics	All-cause HR* (95% CI)†	All-cause *P value*‡	pancreatic cancer-specific HR* (95% CI)†	Cancer-specific *P* value‡
Prior cancer diagnosis (vs none)				
Prior malignancy	0.938 (0.880–1.000)	.052	0.855 (0.796–0.918)	< .001
Age (vs 40–65), year				
> 65	1.369 (1.320–1.420)	< .001	1.366 (1.314–1.420)	< .001
Sex (vs male)				
Female	0.914 (0.881–0.948)	< .001	.919 (0.885–0.956)	< .001
Race (vs white)				
Black	1.112 (1.056–1.172)	< .001	1.090 (1.031–1.152)	.003
Others#	.970 (0.908–1.036)	.368	0.952 (0.888–1.022)	.173
Marital status (vs married)				
Single	1.184 (1.120–1.252)	< .001	1.139 (1.074–1.209)	< .001
Widowed	1.298 (1.234–1.366)	< .001	1.269 (1.202–1.340)	< .001
Divorced	1.207 (1.135–1.282)	< .001	1.176 (1.102–1.254)	< .001
Separated	1.351 (1.143–1.597)	< .001	1.265 (1.054–1.518)	.011
Site (vs head of pancreas)				
Body of pancreas	0.915 (0.870–0.962)	.001	0.929 (0.881–.979)	.006
Tail of pancreas	1.000 (0.956–1.046)	.995	1.002 (0.955–1.051)	.940
Other parts of pancreas	0.976 (0.851–1.120)	.732	0.971 (0.839–1.122)	.687
Overlapping pancreas lesions	1.074 (1.013–1.138)	.017	1.088 (1.023–1.157)	.007
Grade (vs well differentiated)				
Moderately differentiated	1.572 (1.479–1.671)	< .001	1.607 (1.506–1.715)	< .001
Poorly differentiated	2.050 (1.932–2.176)	< .001	2.081 (1.953–2.217)	< .001
Undifferentiated, anaplastic	1.841 (1.640–2.068)	< .001	1.769 (1.561–2.005)	< .001
Surgery (vs no)				
Yes	0.453 (0.428–0.478)	< .001	0.430 (0.405–0.456)	< .001

*This number represents the hazard ratio for all cause and pancreatic-cancer specific death for the above covariables. All statistical tests were two sided

†This represents confidence interval. ‡Two-sided *P* value was calculated from multivariable covariate-adjusted Cox models. #Represents (American Indian/AK Native, Asian/Pacific Islander)

medical history did not have a significant effect on the overall or cancer-specific survival of patients. Contrariwise, prior malignancies were associated with an increase in cancer-specific survival. This can be attributed to patients with a significant medical history being more cautious about their health or receiving a more strict screening and care. However, more investigations are required to confirm this result and objectively explain it.

PAC is a highly fatal malignancy. In 2017, an estimate of 43,090 pancreatic cancer-related deaths is expected to take place in the USA [6]. The intractable nature of pancreatic cancer, along with the lack of definite cure for advanced diseases, necessitates ongoing trials to enhance the quality of life especially in patients with advanced disease [6]. In our study, we focused on stage IV as most pancreatic cancer trials are on systemic chemotherapy and targeting stage IV patients. Our data suggest that patients with stage IV PAC and a prior history of malignancy have higher odds of this malignancy being in the prostate, breast, or colorectal area. This can be attributed to the high worldwide prevalence of these cancers and might not have direct association with pancreatic cancer itself.

Prior malignancies can represent a barrier to patients' enrollment in these trials and, consequently, reduce the external validity and applicability of the drawn conclusions [15, 16]. Several potential rationales stand behind excluding this specific population. The most commonly raised concern is the expected lower survival rate in these patients compared to others who have no significant history of malignancy [17]. For PAC, the findings of our study completely opposed this

claim and revealed no significant decrease in the survival for patients with prior cancers. This is consistent with studies on other tumors such as lymphomas, lung cancer, and tumors of the gastrointestinal tract [6, 16, 18–20]. Other researchers argue those patients with multiple or preceding malignancies might not tolerate newly developed drugs well [7]. However, presumptions of patients' tolerability can induce performance bias, and it is better to investigate it as a separate outcome with stratification of the trial's sample if needed. This allows for a more objective approach and assessment of the drug's safety and the effect of medical history. The past treatments that patients may have received while treating their first cancer are also reported as a playmaker, when it comes to deciding eligibility criteria in clinical trials [6]. It is thought that these prior therapies might interfere and possibly affect the effectiveness of the investigated treatment. This is a valid concern that can be tackled by excluding patients who received prior therapy with high risk of interference, or preferably, stratifying the groups and report any noted interactions. A more in-depth understanding of these issues is required to balance the benefits and harms of excluding a valuable group of patients, jeopardizing the generalizability of the trial, and precluding a potential benefit that such patients can gain by joining a research project.

This study, like other SEER-based studies, is limited by the availability of data in the registries. For instance, systemic therapies and treatment regimens are not well covered in the database, and they do not recommend using the available treatment data for comparison due to its low sensitivity [21]. Another limitation is the possibility of missing follow-up data of patients if they move from SEER areas, causing underreporting in second malignancies. Another limitation is the absence of sufficient information to know whether previous malignancies were treated, untreated, or incompletely treated before the pancreatic malignancy. Further details related to SEER-related limitations are demonstrated in separate reports [22, 23].

In summary, it is recommended to avoid excluding patients with prior malignancies in clinical trials that investigate new therapies and potentially beneficial approaches in PAC. There is no evidence to support such practice especially when it comes to survival, on the contrary, it may negatively impact the generalizability and accrual of the study.

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Compliance with Ethical Standards

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

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