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Original Article

Adjuvant Chemotherapy Improves Survival in Resected Early-onset Pancreatic Cancer after Neoadjuvant Therapy: A Retrospective Cohort Study Based on the SEER Database

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Abstract

Background and objectives: The incidence of early-onset pancreatic cancer (EOPC) is rising, yet optimal treatment strategies remain unclear. While adjuvant chemotherapy (ACT) has shown survival benefits in pancreatic ductal adenocarcinoma, its specific role in EOPC patients following neoadjuvant chemotherapy (NACT) and surgery remains underexplored. This study aimed to assess the clinical benefit of ACT in EOPC patients after NACT.

Methods: This retrospective cohort study analyzed pancreatic ductal adenocarcinoma patients from the SEER database (2006–2019) who received NACT followed by curative resection. Propensity score matching (1:1) was used to balance covariates such as tumor, lymph node, metastasis stage, chemotherapy, and radiotherapy. Overall survival (OS) and cancer-specific survival (CSS) were compared between patients with EOPC (<50 years) and average-onset pancreatic cancer (AOPC, ≥50 years). Multivariate Cox regression analysis was performed to identify prognostic factors.

Results: After propensity score matching (124 EOPC vs. 124 AOPC), EOPC patients had significantly longer median OS (41.0 vs. 29.0 months, P = 0.042) and CSS (48.0 vs. 30.0 months, P = 0.016). ACT was an independent prognostic factor for EOPC (OS: hazard ratio = 0.495, 95% confidence interval 0.271–0.903, P = 0.022; CSS: hazard ratio = 0.419, 95% confidence interval 0.219–0.803, P = 0.009), but not for AOPC (P > 0.05). Subgroup analysis revealed that EOPC patients with tumor, lymph node, metastasis stage II disease or those receiving ACT derived the greatest survival benefit.

Conclusions: EOPC patients exhibit superior survival following NACT and surgical resection compared to AOPC, with ACT further enhancing outcomes in this subgroup. These findings support the use of tailored ACT for EOPC and underscore the need for prospective validation.

Keywords: Pancreatic cancer; Early-onset pancreatic cancer; Average-onset pancreatic cancer; Neoadjuvant chemotherapy; Adjuvant chemotherapy; Prognosis.

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Introduction

Pancreatic cancer is one of the most lethal cancers worldwide due to its poor prognosis and is ranked as the third leading cause of cancer death.[1,2] It has been projected that pancreatic cancer will become the second leading cause of cancer death by 2030.[3–5] The risk of developing pancreatic cancer increases with age. Nearly 90% of cases are diagnosed after the age of 50.[6,7] However, the incidence is rapidly rising among younger individuals in recent years.[8]

Early-onset pancreatic cancer (EOPC) is usually defined as patients diagnosed under the age of 50, and the reported frequency varies from 4% to 18%.[9,10] Though it seems to generally share

characteristic features, EOPC has unique molecular and clinical manifestations compared to average-onset pancreatic cancer (AOPC, defined as patients ≥ 50 years old). It was reported that, compared to AOPC, EOPC appears as a more advanced disease. Patients with EOPC have fewer comorbidities and better physical fitness, making them more tolerant of aggressive treatment.[11] Moreover, specific genomic characteristics, such as wild-type *KRAS*, were more frequently observed in EOPC patients.[12] Thus, EOPC is increasingly regarded as a distinct subtype of pancreatic cancer, and specialized treatment regimens should be applied to EOPC.[13] Notably, there are still relatively few studies on the effectiveness of therapeutic strategies specifically for EOPC. Considering the lack of knowledge, more clinical research specific to EOPC is still anticipated.[14]

Recently, a comprehensive treatment approach centered around chemotherapy, including neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy (ACT), has played an important role in the management of pancreatic ductal adenocarcinoma (PDAC). Among these, NACT is increasingly being emphasized for its potential in borderline resectable and locally advanced PDAC.[15] Versteijne *et al*.[16] reported that the NACT group had a better prognosis compared to the upfront surgery group, with five-year overall survival (OS) rates of 20.5% vs. 6.5%, respectively. Ikenaga *et al*.[17] also reported that OS in patients with resected PDAC after NACT was significantly longer than in others. In addition, NACT can increase R0 resection rates by 20%.[18,19] Our previous research also suggested that ACT following NACT and surgery was associated with survival benefits in PDAC, especially in younger patients or those with aggressive tumors and a potentially good response to NACT.[20] Remarkably, there have been no studies focused specifically on the role of NACT in EOPC patients. Considering the clinical importance of EOPC, it is of great value to validate the effectiveness of ACT after systemic NACT and surgery in this special subgroup.

Our previous research has noted that younger age may affect the therapeutic efficacy of ACT after NACT and surgery.[20] However, the age boundary was not clearly defined by adopting the criteria for EOPC. Thus, the goal of this study was to further promote the application of our research among the EOPC population and to determine whether EOPC patients can benefit from the combination treatment of ACT after NACT and surgery. Since there are few large-scale retrospective studies specific to EOPC, it would be helpful to elucidate the optimal treatment regimens for EOPC patients.

Materials and methods

Patient selection and data source

All enrolled PDAC patients who received NACT and surgical resection in this study were from the same population as our previous study, following the inclusion and exclusion criteria,[20] and were obtained from the SEER*Stat Database (https://seer.cancer.gov/). In detail, a subset of resected PDAC patients who received systemic chemotherapy either before surgery or both before and after surgery were enrolled in this retrospective study. Patients with C25.3–C25.9, clinical or pathological stage IV disease, missing lymph node metastasis or tumor size information, or unspecific or inconsistent radiotherapy information were excluded. Patients with a survival time of less than one month were also excluded because they were more likely to die or be censored due to perioperative complications. The SEER*Stat Database: Incidence – SEER Research Plus Data, 17 Registries, Nov 2021 Sub (2000–2019) was used.

This study was conducted in compliance with the Helsinki Declaration and reported in accordance with the STROCSS (Strengthening The Reporting of Cohort Studies in Surgery) criteria.[21] For each patient, all the collected information from the database was the same as in our previous study.[20] In this study, EOPC was defined as age < 50 years at the time of PDAC diagnosis, while AOPC was defined as age ≥ 50 years, according to previously published research.[22,23] Additionally, tumor, lymph node, metastasis (TNM) stage of the 8th edition of the American Joint Committee on Cancer was evaluated. OS was defined as the time from surgery to the date of death, and cancer-specific survival (CSS) was defined as the time from surgery to the date of cancer-related death or last follow-up. As it used public and de-identified data from secondary research, and all data were freely available in the SEER database for research after access was granted, this study was not considered human participant research and did not require institutional review board approval according to the Ethics Committee of our institute.

Statistical analysis

The R and SPSS 21.0 software were used for statistical analyses in this study. The relationships between EOPC and categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. The EOPC cohort was matched to the AOPC group using a 1:1 nearest-neighbor propensity score matching (PSM) algorithm that accounted for all potential confounders (caliper width = 0.1 standard deviation) using the MatchIt package in the R project. Specifically, sex, tumor grade, race, tumor site, radiotherapy, adjuvant chemotherapy, T classification, N classification, TNM stage, and marital status were included in the PSM analysis. Standardized mean difference was used for balance assessment. After PSM, a standardized mean difference less than 0.1 indicated excellent balance. In addition, as our previous publication mentioned, regimen types were not identified in the model due to a lack of precise data on systemic NACT and ACT in the database. However, we divided the time into three periods, as previously reported: 2006–2011, 2012–2014, and 2015–2019, as a covariate in the Cox proportional hazards models,[20] since FOLFIRINOX (combined leucovorin calcium [folinic acid], fluorouracil, irinotecan hydrochloride, and oxaliplatin) and gemcitabine with nab-paclitaxel were used in the neoadjuvant setting beginning in 2011 and 2013 in the USA, respectively.

The unadjusted OS and CSS were analyzed using Kaplan–Meier curves with log-rank tests and plotted using GraphPad Prism 8 software. Independent prognostic indicators were identified using univariate and multivariate Cox proportional hazards regression models. Additionally, the interactions between EOPC and each significant prognostic variable were examined using a single multivariable Cox regression model adjusted for all factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each interaction coefficient in the EOPC group. *P*-values < 0.05 were considered statistically significant.

Results

Demographic and clinicopathological characteristics

There were 1,589 PDAC patients who received NACT re-analyzed—the same cohort as in our previous study, following the published criteria.[20,24] Among the entire cohort, 124 (7.8%) patients were defined as EOPC, while 1,465 (92.2%) were classified as AOPC. Correlation analysis showed that marital status ($P < 0.001$) was significantly associated with EOPC, and Asian or Pacific Islander race ($P = 0.050$) was potentially correlated with EOPC (Table 1).

Table 1. Demographic and clinicopathological characteristics of patients with EOPC and AOPC after neoadjuvant chemotherapy and surgery

Variables	Groups, No. (%)					
	Crude data set			Matched data set		
	EOPC (n = 124)	AOPC (n = 1,465)	*P*-value	EOPC (n = 124)	AOPC (n = 124)	*P*-value
Sex			0.740			1.000
Female	58 (46.8)	708 (48.3)		58 (46.8)	58 (46.8)	
Male	66 (53.2)	757 (51.7)		66 (53.2)	66 (53.2)	
Grade			0.997			0.989
Well	6 (4.8)	65 (4.5)		6 (4.8)	5 (4.0)	
Moderate	23 (18.5)	276 (18.8)		23 (18.5)	78 (62.9)	
Poor/Undifferentiated	17 (13.7)	218 (13.7)		17 (13.7)	23 (18.5)	
Unknown	78 (62.9)	1,001 (63.0)		78 (62.9)	18 (14.5)	
Race			0.050			1.000
Black	12 (9.7)	141 (9.6)1		12 (9.7)	12 (9.7)	
White	96 (77.4)	230 (84.0)		96 (77.4)	96 (77.4)	
Asian or Pacific Islander	14 (11.3)	84 (5.7)		14 (11.3)	14 (11.3)	
Others	2 (1.6)	10 (0.7)		2 (1.6)	2 (1.6)	
Tumor site			0.981		1	0.723
Head	106 (85.5)	1,256 (85.7)		106 (85.5)	02 (82.3)	
Body	12 (9.7)	135 (9.2)		12 (9.7)	16 (12.9)	
Tail	6 (4.8)	74 (5.1)		6 (4.8)	6 (4.8)	
Radiotherapy			0.954			0.310
No	68 (54.8)	786 (53.7)		68 (54.8)	56 (45.2)	
ART	10 (8.1)	143 (9.8)		10 (8.1)	17 (13.7)	
ART and NART	1 (0.8)	14 (1.0)		1 (0.8)	1 (0.8)	
NART	45 (36.3)	522 (35.6)		45 (36.3)	50 (40.3)	
Adjuvant chemotherapy			0.648			0.897
No	73 (58.9)	893 (61.0)		73 (58.9)	74 (59.7)	
Yes	51 (41.1)	572 (39.0)		51 (41.1)	50 (40.3)	
T classification			0.437			0.426
T1	14 (11.3)	152 (10.4)		14 (11.3)	10 (8.1)	
T2	64 (51.6)	836 (57.1)		64 (51.6)	74 (59.7)	
T3	29 (23.4)	261 (17.8)		29 (23.4)	21 (16.9)	
T4	17 (13.7)	216 (14.7)		17 (13.7)	19 (15.3)	
N classification			0.969			0.871
N0	63 (50.8)	756 (51.6)		63 (50.8)	62 (50.0)	
N1	42 (33.9)	480 (32.8)		42 (33.9)	40 (32.3)	
N2	19 (15.3)	229 (15.6)		19 (15.3)	22 (17.7)	
TNM staging system			0.117			0.510
I	33 (26.6)	504 (34.4)		33 (26.6)	37 (29.8)	
II	56 (45.2)	537 (36.7)		56 (45.2)	47 (37.9)	
III	35 (28.2)	424 (28.9)		35 (28.2)	40 (32.3)	
Marital status			<0.001			1.000
Married	79 (63.7)	890 (66.9)		79 (63.7)	79 (63.7)	
Single (never married)	32 (25.8)	159 (10.9)		32 (25.8)	32 (25.8)	
Others	13 (10.5)	326 (22.3)		13 (10.5)	13 (10.5)	

AOPC, average-onset pancreatic cancer; ART, adjuvant radiotherapy; EOPC, early-onset pancreatic cancer; NART, neoadjuvant radiotherapy; TNM, tumor, lymph node, metastasis.

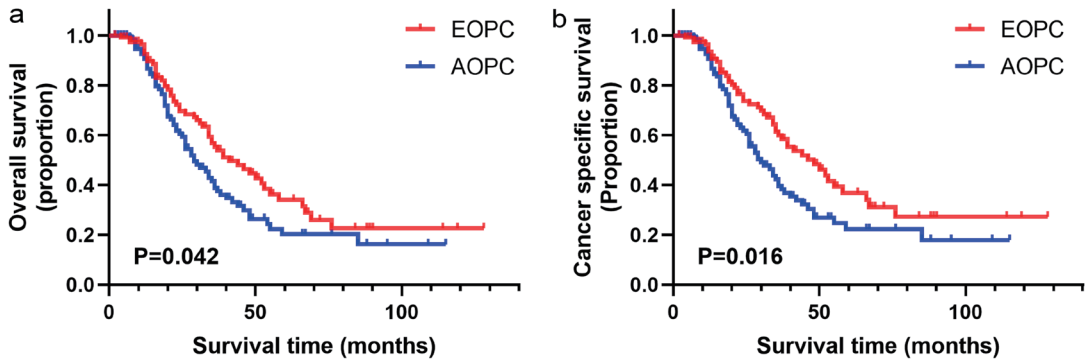

Fig. 1. Overall survival (a) and cancer-specific survival (b) stratified by early-onset pancreatic cancer and average-onset pancreatic cancer in the total matched patient cohort. AOPC, average-onset pancreatic cancer; EOPC, early-onset pancreatic cancer.

A PSM model was then utilized between the EOPC and AOPC groups to reduce confounders. After 1:1 PSM adjusted for all potential confounders, the distribution of all included variables was adequately balanced. Finally, 124 EOPC patients and 124 AOPC patients were perfectly matched (Table 1). Histograms of propensity scores before and after matching are shown in Figure S1.

Prognosis of EOPC patients after NACT

The median OS and CSS of the matched cohorts were 35.0 (interquartile range (IQR): 20.0–67.0) and 36.0 (IQR: 20.0–76.0) months, respectively. The OS rates at one, three, and five years were 91.6%, 47.0%, and 27.1%, respectively, and the CSS rates were 92.1%, 49.5%, and 29.5%, respectively. The median OS in the EOPC group was significantly longer than in the AOPC group [41.0 (IQR: 22.0–76.0) vs. 29.0 (IQR: 19.0–54.0) months, P = 0.042; Fig. 1a]. In the EOPC group, the one-, three-, and five-year OS rates were 92.6%, 55.4%, and 34.0%, respectively, while in the AOPC group, they were 90.6%, 38.8%, and 20.2%, respectively. Similarly, the median CSS in the EOPC group was also significantly longer [48.0 (IQR: 24.0–not reached) vs. 30.0 (IQR: 19.0–55.0) months, P = 0.016; Fig. 1b]. The cumulative one-, three-, and five-year CSS rates in the EOPC group were 93.5%, 59.9%, and 36.8%, respectively, compared to 90.6%, 39.6%, and 22.3% in the AOPC group.

In the matched data, AOPC type, ACT, advanced N stage, and advanced TNM stage were all considered risk indicators for OS and CSS. After multivariate analysis, EOPC type was independently correlated with longer survival (P = 0.030, HR = 0.666; 95% CI, 0.462–0.960 for OS; P = 0.012, HR = 0.615; 95% CI, 0.420–0.899 for CSS) compared to AOPC. Longer OS and CSS were also significantly related to the administration of ACT (Table 2).

Subgroup interaction analysis

As EOPC is considered an extremely distinct cohort, interaction analysis was performed to identify subgroups that may benefit differently from EOPC. When analyzing the unadjusted subgroups of ACT, we discovered a significant correlation with EOPC only in patients receiving ACT (P = 0.089, HR = 0.592; 95% CI, 0.320–1.097 for OS; P = 0.026, HR = 0.488; 95% CI, 0.255–0.936 for CSS; Fig. 2a, b). In analysis of the unadjusted adjuvant radiotherapy (ART) subgroups, we found that patients receiving ART were potentially correlated with EOPC in terms of overall and cancer-specific mortality (P = 0.050, HR = 0.368; 95% CI, 0.129–1.050 for OS; P = 0.050, HR = 0.368; 95% CI, 0.129–1.050 for CSS; Fig. 2c, d). In addition, those only in TNM stage II were significantly correlated with EOPC (P = 0.009, HR = 0.505; 95% CI, 0.297–0.859 for OS; P = 0.002, HR = 0.424; 95% CI, 0.244–0.737 for CSS; Fig. 2e, f). However, patients not receiving ACT (Fig. S2a, b), without ART (Fig. S2c, d), in TNM stage I (Fig. S3a, b) or III (Fig. S3c, d), or with pathological N category showed no significant correlation with EOPC in the unadjusted subgroup analysis.

An HR for each category of every variable within EOPC compared to AOPC was obtained when each interaction term was adjusted for ACT, ART, N classification, and TNM stage. Among these interactions, EOPC was significantly correlated with lower cancer-specific mortality in patients receiving ACT and those in TNM stage II (Table S1).

Therapeutic advantage of ACT in EOPC and AOPC patients after NACT

As ACT was identified as another significant prognostic indicator in the matched cohort, an interaction analysis was conducted, and a significant correlation was found between ACT and EOPC (P-interaction = 0.014 for OS and P-interaction = 0.009 for CSS). The median CSS was significantly longer in EOPC patients receiving ACT compared to those without ACT [55.0 (IQR: 37.0–not reached) vs. 36.0 (IQR: 21.0–67.0) months, P = 0.045; five-year CSS rate: 51.7% vs. 26.3%, respectively; Fig. 3a], and a similar trend was observed in OS, though not statistically significant [55.0 (IQR: 31.0–not reached) vs. 35.0 (IQR: 16.0–67.0) months, P = 0.074; five-year OS rate: 44.2% vs. 24.1%, respectively; Fig. 3b]. However, no significant difference was found between ACT and non-ACT cohorts in AOPC patients [30.0 (IQR: 19.0–85.0) vs. 28.0 (IQR: 18.0–48.0) months, P = 0.372 for CSS; five-year CSS rate: 36.3% vs. 17.5%, respectively; Fig. 3c; 30.0 (IQR: 19.0–85.0) vs. 26.0 (IQR: 18.0–48.0) months, P = 0.275 for OS; five-year OS rate: 35.4% vs. 15.8%, respectively; Fig. 3d]. In EOPC patients, ACT was significantly identified as an independent prognostic factor for both OS (P = 0.022, HR = 0.495; 95% CI, 0.271–0.903) and CSS (P = 0.009, HR = 0.419; 95% CI, 0.219–0.803) after adjusted analysis (Table 3), while no obvious benefit of ACT was found in AOPC patients (Table 4). Thus, EOPC—unlike AOPC—patients might significantly benefit from ACT after NACT and surgical resection.

Discussion

Using the SEER database, we have demonstrated that EOPC patients had a better prognosis after NACT and surgery compared to AOPC patients. After adjusted analysis, EOPC exhibited a significant correlation with reduced cancer-specific mortality in pa-

Table 2. Univariate and multivariate Cox regression analyses for overall survival and cancer-specific survival in the matched cohort

Variables	Overall survival			Cancer-specific survival		
	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)
Type						
AOPC	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
EOPC	0.045	0.030	0.666 (0.462–0.960)	0.018	0.012	0.615 (0.420–0.899)
Sex						
Female	Ref.			Ref.		
Male	0.311			0.326		
Grade						
Well	Ref.			Ref.		
Moderate	0.780			0.838		
Poor/Undifferentiated	0.234			0.313		
Unknown	0.714			0.861		
Race						
Black	Ref.			Ref.		
White	0.904			0.575		
Asian or Pacific Islander	0.169			0.142		
Others	0.986			0.792		
Tumor site						
Head	Ref.			Ref.		
Body	0.358			0.506		
Tail	0.583			0.639		
Year of diagnosis						
2006–2011	Ref.			Ref.		
2012–2014	0.473			0.651		
2015–2019	0.353			0.253		
Neoadjuvant radiotherapy No Yes	Ref. 0.964			Ref. 0.883		
Adjuvant radiotherapy						
No	Ref.			Ref.		
Yes	0.186			0.104		
Adjuvant chemotherapy						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.040	0.016	0.618 (0.417–0.916)	0.043	0.015	0.603 (0.401–0.908)
T classification						
T1	Ref.			Ref.		
T2	0.440			0.516		
T3	0.757			0.690		
T4	0.760			0.802		
N classification						
N0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
N1	0.007	0.141	1.466 (0.881–2.442)	0.004	0.088	1.595 (0.933–2.725)
N2	0.003	0.049	1.983 (1.004–3.916)	0.002	0.035	2.139 (1.056–4.334)
TNM staging system						
I	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

(continued)

Table 2. *(continued)*

Variables	Overall survival			Cancer-specific survival		
	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)
II	0.011	0.220	1.468 (0.795–2.712)	0.013	0.291	1.417 (0.742–2.708)
III	0.005	0.297	1.437 (0.727–2.838)	0.005	0.340	1.414 (0.694–2.879)
Marital status						
Married	Ref.			Ref.		
Single (never married)	0.780			0.900		
Others	0.997			0.928		

AOPC, average-onset pancreatic cancer; CI, confidence interval; EOPC, early-onset pancreatic cancer; Ref., reference group; TNM, tumor, lymph node, metastasis.

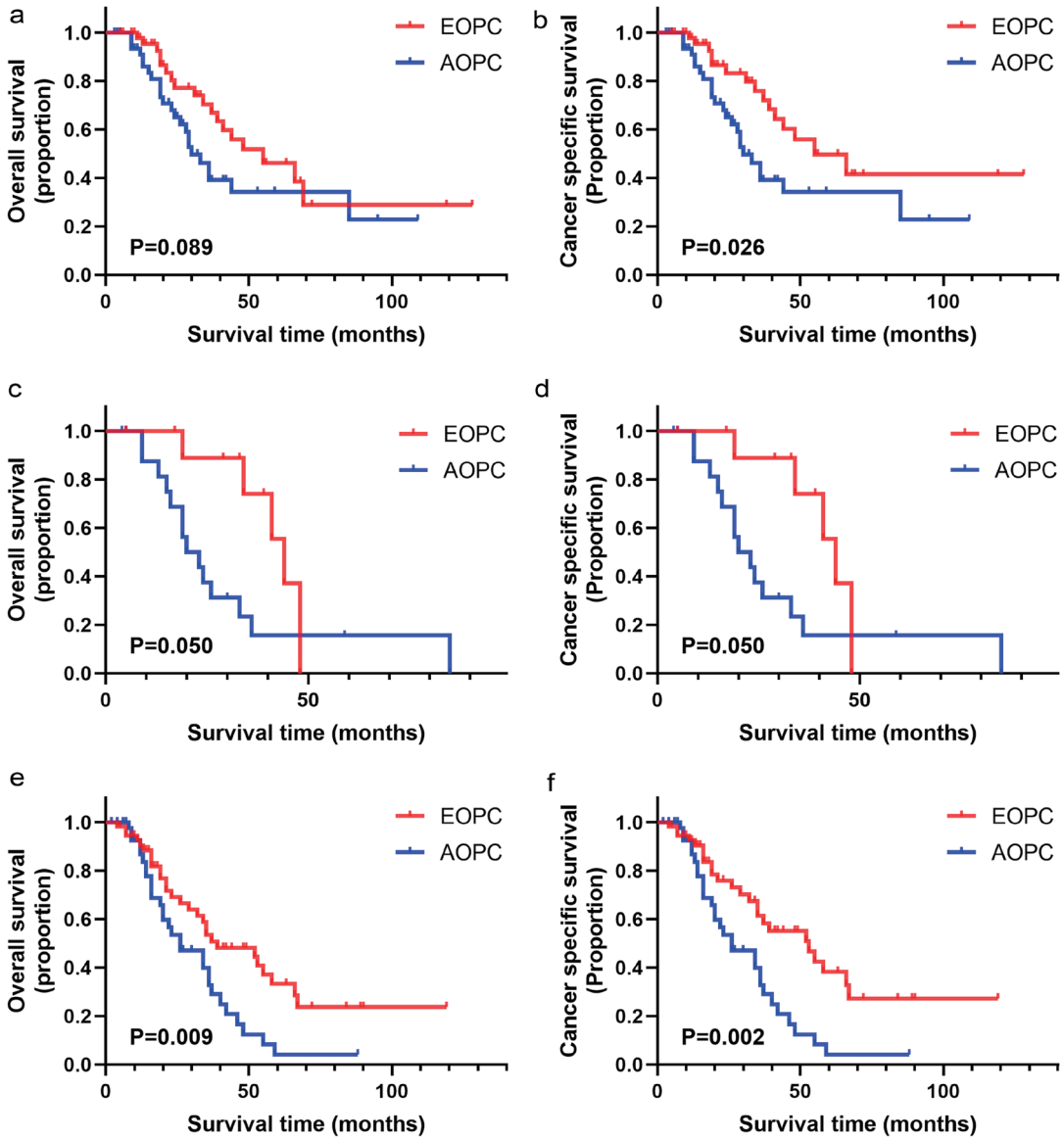

Fig. 2. Overall survival and cancer-specific survival stratified by early-onset pancreatic cancer and average-onset pancreatic cancer in subgroup patients receiving adjuvant chemotherapy (a, b), adjuvant radiotherapy (c, d), or with TNM stage II (e, f). AOPC, average-onset pancreatic cancer; EOPC, early-onset pancreatic cancer; TNM, tumor, lymph node, metastasis.

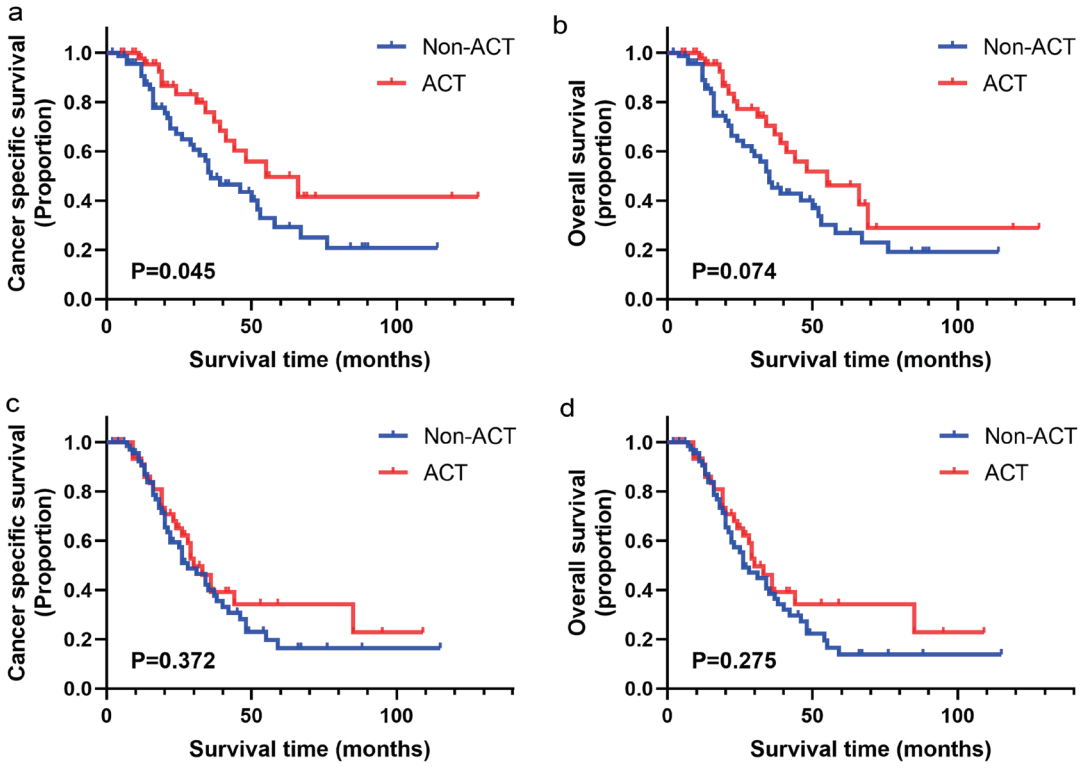

Fig. 3. Overall survival and cancer-specific survival stratified by adjuvant chemotherapy in subgroup patients with early-onset pancreatic cancer (a, b) or average-onset pancreatic cancer (c, d). ACT, adjuvant chemotherapy.

tients undergoing ACT and those classified with TNM stage II. Further analysis of the therapeutic advantage of ACT showed that patients with EOPC, rather than AOPC, benefited from ACT following NACT and surgery. Our study provides a fresh perspective on understanding the association between treatment and prognosis in EOPC.

Recently, NACT has been validated to improve OS outcomes and is recommended to downstage patients with primary or borderline resectable PDAC.[25] The pathological outcomes might also be improved after NACT with a higher R0 resection rate and negative lymph node metastasis.[26] Moreover, NACT could identify PDAC patients who are tolerant to surgery combined with ACT and might significantly benefit from it.[27] It has been reported that patients who respond to NACT could obviously benefit from it with longer survival compared to those who did not respond or who progressed.[28] Meanwhile, the response rate to NACT in younger PDAC patients was considered to be higher than that of their older counterparts, which might lead to distinct prognoses in different age groups.[29] Our current study also mentioned that patients with EOPC were correlated with better survival after NACT and surgery compared to AOPC. Also, EOPC, rather than AOPC, could experience significant advantages from ACT following NACT and surgical resection. Additionally, the rapid development of targeted therapies has provided NACT with more options. Castet *et al*.[12] reported that PDAC patients who underwent targeted therapies demonstrated extended OS in contrast to those who did not. Currently, there are various targeted therapies specific to distinct genomic characteristics, such as epidermal growth factor receptor inhibitors for *KRAS* wild-type tumors, poly (ADP-ribose) polymerase inhibitors (PARPi) for *BRCA*1/2 mutations, and CDK4/6 inhibitors for CDKN2A-deficient tumors.[30–33] Notably, several previous studies have mentioned that EOPC might have a special genomic landscape. Compared to AOPC, young patients with PDAC are more likely to present with tumors that are *KRAS* wild-type or harbor *BRCA* mutations.[13,34,35] In consideration of the distinct phenotypes, NACT combined with targeted treatments may potentially yield greater benefits in patients with EOPC. In the future, it is imperative to expand the scope of clinical research toward targeted therapies tailored to the specific genetic characteristics found in EOPC.

EOPC is more likely to appear as a more advanced disease. Patients with EOPC are reported to have a higher rate of unresectable and distant metastatic disease (usually liver).[13] Even with resectable PDAC, EOPC demonstrates a higher likelihood of postoperative recurrence.[36] Given its high degree of malignancy, EOPC is best managed by multidisciplinary treatments including surgery, adjuvant, and neoadjuvant therapies. Fortunately, due to their younger age, patients with EOPC have better physical fitness and fewer comorbidities, which enable them to tolerate more toxic therapy and benefit from aggressive regimens.[11] In fact, combination chemotherapy is more commonly used for EOPC.[37] FOLFIRINOX and gemcitabine combinations are recommended as first-line systemic treatment options.[38,39] Compared to gemcitabine combinations, FOLFIRINOX can prolong the survival of patients undergoing pancreatic resection at the cost of more side effects.[40] A phase III Unicancer GI PRODIGE 24/CCTG PA.6 trial reported that the median disease-free survival and OS were 21.6 months and 54.4 months in the modified-FOLFIRINOX group versus 12.8 months (HR = 0.58; 95% CI, 0.46–0.73; $P < 0.001$) and 35.0 months (HR = 0.64; 95% CI, 0.48–0.86; $P = 0.003$) in

Table 3. Univariate and multivariate Cox regression analyses for overall survival and cancer-specific survival in early-onset pancreatic cancer patients

Variables	Overall survival			Cancer-specific survival		
	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)
Sex						
Female	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Male	0.084	0.048	1.792 (1.004–3.198)	0.138	0.075	1.747 (0.944–3.232)
Grade						
Well	Ref.			Ref.		
Moderate	0.466			0.396		
Poor/Undifferentiated	0.777			0.960		
Unknown	0.395			0.286		
Race						
Black	Ref.			Ref.		
White	0.525			0.414		
Asian or Pacific Islander	0.400			0.383		
Others	0.923			0.905		
Tumor site						
Head	Ref.			Ref.		
Body	0.977			0.532		
Tail	0.975			0.976		
Year of diagnosis						
2006–2011	Ref.			Ref.		
2012–2014	0.514			0.694		
2015–2019	0.265			0.193		
Neoadjuvant radiotherapy						
No	Ref.			Ref.		
Yes	0.730			0.631		
Adjuvant radiotherapy						
No	Ref.			Ref.		
Yes	0.875			0.895		
Adjuvant chemotherapy						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.080	0.022	0.495 (0.271–0.903)	0.050	0.009	0.419 (0.219–0.803)
T classification						
T1	Ref.			Ref.		
T2	0.732			0.605		
T3	0.516			0.262		
T4	0.801			0.600		
N classification						
N0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
N1	0.075	0.088	1.936 (0.907–4.131)	0.067	0.036	2.483 (1.063–5.799)
N2	0.024	0.080	2.579 (0.893–7.451)	0.020	0.056	3.104 (0.973–9.902)
TNM staging system						
I	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
II	0.211	0.996	1.003 (0.395–2.543)	0.419	0.488	0.701 (0.257–1.913)
III	0.069	0.762	1.182 (0.401–3.487)	0.136	0.884	0.917 (0.288–2.923)
Marital status						
Married	Ref.			Ref.		
Single (never married)	0.591			0.639		
Others	0.588			0.462		

CI, confidence interval; Ref., reference group; TNM, tumor, lymph node, metastasis.

Table 4. Univariate and multivariate Cox regression analyses for overall survival and cancer-specific survival in average-onset pancreatic cancer patients

Variables	Overall survival			Cancer-specific survival		
	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)	Univariate *P*-value	Multivariate *P*-value	Hazard ratio (95% CI)
Sex						
Female	Ref.			Ref.		
Male	0.895			0.916		
Grade						
Well	Ref.			Ref.		
Moderate	0.336			0.340		
Poor/Undifferentiated	0.196			0.197		
Unknown	0.277			0.317		
Race						
Black	Ref.			Ref.		
White	0.527			0.849		
Asian or Pacific Islander	0.336			0.295		
Others	0.944			0.816		
Tumor site						
Head	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Body	0.326	0.646	1.178 (0.585–2.374)	0.269	0.599	1.207 (0.598–2.434)
Tail	0.049	0.012	5.137 (1.432–18.422)	0.047	0.009	5.574 (1.539–10.185)
Year of diagnosis						
2006–2011	Ref.			Ref.		
2012–2014	0.700			0.809		
2015–2019	0.654			0.535		
Neoadjuvant radiotherapy						
No	Ref.			Ref.		
Yes	0.639			0.642		
Adjuvant radiotherapy						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.073	0.297	1.418 (0.735–2.735)	0.054	0.254	1.469 (0.758–2.847)
Adjuvant chemotherapy						
No	Ref.			Ref.		
Yes	0.282			0.378		
T classification						
T1	Ref.			Ref.		
T2	0.346			0.599		
T3	0.502			0.320		
T4	0.714			0.999		
N classification						
N0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
N1	0.041	0.780	1.118 (0.512–2.438)	0.025	0.785	1.115 (0.511–2.434)
N2	0.049	0.450	1.459 (0.547–3.890)	0.033	0.465	1.444 (0.540–3.862)
TNM staging system						
I	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
II	0.007	0.055	2.415 (0.981–5.949)	0.003	0.029	2.807 (1.111–7.090)
III	0.028	0.229	1.736 (0.707–4.267)	0.013	0.135	2.020 (0.804–5.078)
Marital status						
Married	Ref.			Ref.		
Single (never married)	0.804			0.711		
Others	0.430			0.403		

CI, confidence interval; Ref., reference group; TNM, tumor, lymph node, metastasis.

the gemcitabine group.[41] However, adverse events of grade 3 or 4 occurred in 75.9% of the patients in the modified-FOLFIRINOX group and in 52.9% of those in the gemcitabine group. Therefore, FOLFIRINOX is currently recommended only for patients with good performance status. Patients with EOPC typically have fewer comorbidities than those with AOPC and are consequently more suitable for a FOLFIRINOX strategy. Regrettably, due to the lack of chemotherapeutic regimen details in the SEER database, we failed to explore the preference for different regimens in EOPC. Research on FOLFIRINOX compared to gemcitabine combinations will be of great value for patients with EOPC.

The incidence of node metastasis in EOPC remains uncertain compared to AOPC. Tingstedt *et al.*[10] and Takeda *et al*.[37] reported that EOPC tended to have a higher N stage, while He *et al*.[42] reported that no significant difference of node positivity was observed between EOPC and AOPC. In our current study, although we failed to find significance in the rate of node metastasis, we observed that EOPC was significantly associated with lower cancer-specific mortality in patients with TNM stage II category (mainly T3 or N1 disease) after NACT, rather than those with TNM stage I or III category. Thus, we speculated that PDAC patients with stage I may have potential for a radical response to NACT in both EOPC and AOPC groups. For those with stage III PDAC, both subgroups may fail to respond to NACT. It is likely that only patients with aggressive tumors and potential response (stage II) to NACT may gain greater benefit from EOPC. This was consistent with Mendis *et al*.,[43] who reported that the more favorable outcomes in EOPC were overall derived from increased treatment in the curative setting and increased therapy in the palliative setting. Several studies also support our hypothesis.[44–46] Above all, this is the first study to incorporate the TNM staging system in such an analysis, including ACT for EOPC patients after NACT and surgery.

The prognosis of EOPC remains controversial compared to AOPC among all clinical studies so far. Several studies argued that EOPC had a worse prognosis because of its advanced and aggressive tumor biology.[10,47] Other studies suggested that patients with EOPC might benefit from active treatment, resulting in their survival not being inferior to that of AOPC. The prognosis of EOPC did not show a significant difference compared to the control group due to better performance status and the ability to tolerate more aggressive therapy.[7,23,48] A previous extensive retrospective study, encompassing 72,906 pancreatic cancer patients, was conducted utilizing data from the SEER database spanning the period from 2004 to 2016, performed by Ansari *et al*.[9] The matched analysis showed that EOPC was associated with poorer five-year OS and five-year CSS in the overall analysis and subgroup analysis regarding surgery, which seemed contrary to our findings. The above study included all patients diagnosed with PDAC and only took surgical status into consideration for further subgroup analysis, which was fundamentally different from the focus of our study. Notably, Ansari *et al*.[9] also acknowledged that EOPC patients tended to receive more treatments. Based on the current trend of more EOPC patients undergoing NACT, we designed our study with the anticipation that this subgroup might exhibit distinct prognoses. The results also corroborated our speculation and showed that younger PDAC patients might benefit from ACT after NACT and surgery. We believe that our analysis is more representative of the real-world situation and may provide greater confidence in undergoing ACT following NACT for EOPC patients.

However, several limitations remain in our study. First, many important indicators are lacking in the SEER database, such as CA19-9 levels, margin status, pathological response, performance status, and detailed regimens and durations. Our previous research has discussed the interactive effect of CA19-9 variations on ACT efficacy,[20] which in general is that CA19-9 variations reflecting therapeutic response and tumor biology may have an interactive effect on ACT efficacy. Notably, it was recently reported that EOPC was associated with higher CA19-9 levels compared to AOPC.[36] Second, the definition of EOPC and AOPC was not uniform in most studies, which may affect the application of our results. Third, this study had a retrospective nature, so a multicenter, large-scale, and prospective study is required to confirm our results and eliminate the above biases.

Conclusions

This is the first retrospective study focusing on cohorts of EOPC patients receiving NACT and suggests possible survival benefits for resected EOPC patients after NACT compared to AOPC patients. Moreover, EOPC patients may further obtain therapeutic advantage from ACT after NACT and surgery. Additional RCTs are necessary to ascertain the potential benefits of ACT and its impact on patients with EOPC, aiming to formulate improved treatment strategies and guidelines specific to this clinically significant subgroup.

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Conflict of interest

The authors have no conflict of interest.

Author contributions

Data analysis (TH, WW), statistical analysis, manuscript writing (TH, WW, NP, WL, LL), data acquisition (JH), manuscript review (TH, WW, HY, JH, QC, ZX, ZJ, YJ, NP, WL, LL), funding acquisition, guarantor (NP, WL, LL). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study was conducted in compliance with the Helsinki Declaration and reported in accordance with the STROCSS criteria.

The data used in the study are derived from a de-identified SEER database. As this study utilized secondary research involving de-identified data, it was not considered human participant research and did not require institutional review board approval. The individual consent for this retrospective analysis was waived.

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author.

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