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Original Article

Clinical characteristics, treatment patterns and survival outcomes of early-onset pancreatic adenocarcinoma: a population-based study

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Abstract: Background: Pancreatic ductal adenocarcinoma (PDAC) is a rare and refractory malignancy. Early-onset pancreatic cancer (EOPC), defined as pancreatic cancer diagnosed before the age of 50 years, is very rare. Clinical presentation and oncological outcomes of EOPC are confusing according to previous studies. Methods: We performed a retrospective, population-based study by querying the SEER database to analyze patients with PDAC from 2004 to 2018. Data on demographics, pathological characteristics, treatment patterns, and survival outcomes were compared between EOPC and pancreatic cancer in older patients. Propensity score matching (PSM) was used to minimize the potential bias of baseline characteristics between the two groups. The effect of age on changes in treatment modalities was evaluated using the Cochran-Armitage trend test. Results: The entire study enrolled 42,414 patients, including 2,916 (6.9%) patients with EOPC. Patients with EOPC were more likely to be male (56.6% vs. 51.0%, P < 0.001) and more frequently to present with a larger tumor size (40 mm vs. 37 mm, P < 0.001), vascular invasion (28.6% vs. 25.9%, P = 0.022) and distant metastasis (56.2% vs. 50.8%, P < 0.001) compared with older group. However, surgical resection rates (29.3% vs. 28.3%, P = 0.284) were fairly comparable, and most clinicopathologic characteristics were similar in the patients underwent resection. Younger patients had longer 5-year overall survival (6.9% vs. 5.5%, P < 0.001) and 5-year cancer-specific survival (8.4% vs. 7.3%, P < 0.001) among the overall cohort but had comparable prognosis among patients received surgery (both P > 0.05). Similar survival outcomes were obtained after PSM. In addition, operated patients tended to receive fewer systemic treatments at an increasing age (P_{trend} < 0.001). The survival analysis, which was stratified by age groups, suggested that younger patients only had a better prognosis than those over 70. Conclusions: Patients with EOPC exhibited an advanced stage and a male predilection at diagnosis in the overall cohort but broadly similar clinicopathologic characteristics in the operated patients. In the surgical cohort, although younger patients were more likely to receive systemic treatment, patients with EOPC presented comparable outcomes compared with elderly patients. We suggest that more research should be conducted to uncover the unique characteristics of EOPC for better clinical management.

Keywords: Early-onset pancreatic cancer, prognosis, overall survival, cancer-specific survival, treatment

Introduction

As one of the most mortiferous malignancies worldwide, pancreatic cancer remains a disease with a dismal prognosis with a 5-year overall survival (OS) rate of no more than 10% [1] and is projected to become the second most common cause of cancer-related death by 2040 [2]. Radical resection is considered to be the only potentially curative therapy for patients with pancreatic ductal adenocarcinoma (PDAC); however, less than 20% of them are eligible for surgery at diagnosis [3]. Along with advances in radiology, surgical techniques and treatment modalities, the 5-year OS rate could approach 20-30% after resection in carefully selected patients, but unfortunately, the prognosis is not encouraging [4].

The most common age of diagnosis for pancreatic cancer patients is around their seventies, and typically, a rare subgroup under the age of

50 is referred as early-onset pancreatic cancer (EOPC) according to previous studies [5-10]. The incidence of pancreatic cancer is expected to continue to rise, reaching 15.1 per 100,000 in 2030 and 18.6 in 2050, with an average annual increase of 1.1% in the upcoming three decades. Despite the proportion being merely 5-10%, EOPC contributes significantly to the total healthcare burden, with pancreatic cancer being estimated to have the longest years of life lost in 2050 [11].

Therefore, studies have been focusing on the clinicopathologic and genomic characteristics of EOPC. Nevertheless, differences between EOPC patients and the elderly ones remain to be explored, especially in terms of genetic alterations and long-term outcomes. Although EOPC shares similar risk factors with the typical patients, the currently known hereditary factors seemingly lack an association with these specific patients [12-14]. However, a recent study conducted by Bannon et al. reported that younger patients had a significantly higher prevalence of germline mutations through genetic testing for pancreatic cancer susceptibility genes [15]. Since the first report of a lower rate of KRAS mutations in EOPC by Bergmann et al., Ben-Aharon et al. also found higher SMAD4 mutations and phospho-GSK3 expression as well as increased activation of the TGF-β signaling pathway in younger patients [16, 17]. Tsang et al. compared genomic and transcriptomic data and highlighted a distinctive mutation pattern of CDKN2A and increased expression of forkhead box protein C2 (FOXC2) in EOPC [18]. Nevertheless, Raffenne et al. revealed a similar mutational landscape and global methylation profile in the two groups [19]. As for clinicopathology and survival, several retrospective studies have indicated that patients with EOPC tend to present at a more advanced stage, but with a better prognosis. On the contrary, other reports have demonstrated comparable or even worse survival in younger patients [20-23]. Given that young patients have more robust physical function and fewer comorbidities, more aggressive treatment strategies, such as surgery and (neo) adjuvant therapy, could be more likely received by EOPC patients [24].

These preceding confusing findings further suggested the heterogeneous nature of EOPC regardless of genetic discrepancies or prognostic differences, and that efforts must be directed towards discovering treatments to improve oncologic outcomes. Accordingly, we retrospectively analyzed a population-based database to identify differences in clinicopathologic parameters and long-term outcomes between EOPC patients and the elderly ones across the entire cohort and surgical group.

Materials and methods

Patient cohorts

We conducted this retrospective study by extracting data from the Surveillance, Epidemiology and End Results (SEER) cancer registry database. The SEER database released in July 2021 was used to collect information for this study through the latest SEER*Stat software (version 8.3.9.2; National Cancer Institute, Bethesda, MD, USA). The relevant variables were obtained from the SEER 18 Registries Research Plus Data, November 2020 Submission (2000-2018). The primary site codes C25.0-C25.9 and the ICD-0-3 histology codes 8140/3 and 8500/3 were used to identify patients with PDAC between 2004 and 2018, and those who met the following criteria were included: (1) the reporting source was not derived solely from autopsy or death certificate; (2) the diagnosis was pathologically confirmed through positive histology; (3) the studied disease was the only primary tumor; (4) patients had complete follow-up information and survival month > 0; (5) patients aged over 18 years and under 95 years. Exclusion criteria: (1) patients had neuroendocrine or acinar tumors; (2) patients had other pancreatic neoplasms such as endocrine tumors, intraductal papillary mucinous neoplasms, pseudopapillary or acinar cell carcinomas; (3) patients did not have complete follow-up information; (4) patients aged under 18 years or over 95 years. **Figure 1** demonstrates the detailed selection flowchart of the current study.

Data collection

Demographic variables including age at diagnosis, year of diagnosis, sex and race were extracted for each patient. Tumor-associated and follow-up variables queried were as follows: tumor location, grade, tumor size, lymph node status, summary stage, the derived AJCC

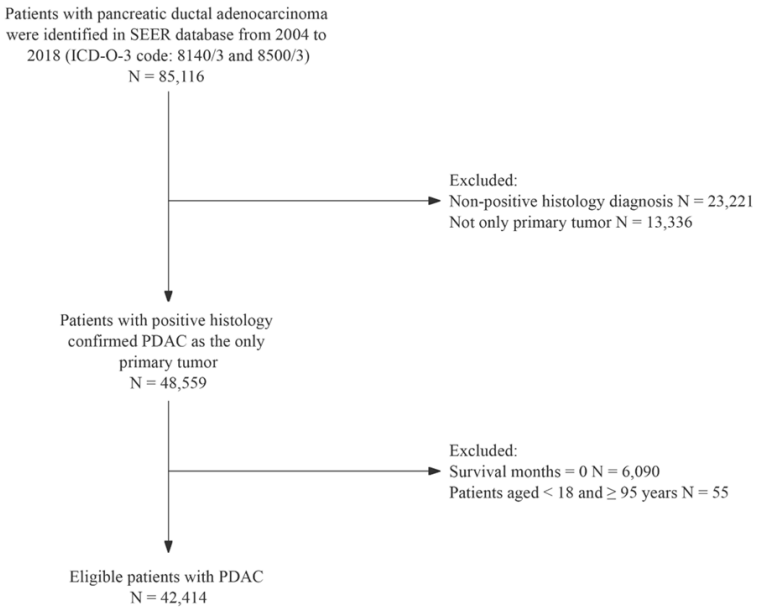

Figure 1. A flowchart of the selection of patients with pancreatic ductal adenocarcinoma in the SEER database.

stage, survival status and months of survival. Tumor size, tumor vascular invasion and lymph node status were evaluated using correlative interpretations. Based on the available data from the 7th and 6th editions of Tumor, Nodes, Metastasis (TNM) Classification, the information of tumor size, lymph node status, and the study cohort was re-staged in compliance with the definitions of the 8th AJCC staging system. Treatment information including primary surgery, chemotherapy, radiation and therapy sequence was collected. Perioperative mortality was defined as death within 90 days of surgery. OS and cancer-specific survival (CSS) were defined as the time from the date of diagnosis to the date of death attributed to all reasons and PDAC, respectively, or the date of the last follow-up. In our study, EOPC represented patients diagnosed under the age of 50 years, and the remaining group was defined as average-onset pancreatic cancer (AOPC).

Ethical statement

As the SEER database is a publicly open access, informed consent from patients and institutional ethical review were waived for this study.

Statistical analysis

The Mann-Whitney *U* test was used to analyze continuous variables that were reported as medians with interquartile range. Categorical variables were compared using the Chi-square test or Fisher's exact test and presented as frequencies with proportions, and the Bonferroni correction was applied for adjusted *P*-values when comparing two groups in a multi-group setting. Trends in treatment strategies within age groups were evaluated by the Cochran-Armitage trend test. The survival probability was analyzed using the Kaplan-Meier method, and the statistical significance was assessed with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model to identify factors with independent predictive effects on survival.

Propensity score matching (PSM) was conducted to reduce potential bias of baseline clinical characteristics between the two groups. Covariates with a standard mean difference (SMD) of more than 0.10 were considered unbalanced. Nearest neighbor matching was performed without replacement at a 1:3 ratio using a caliper width of 0.01. Baseline characteristics were matched, including sex, race, site, tumor differentiation, TNM stage and treatment patterns. To more reliably compare the differences, sensitivity analyses were performed using stabilized inverse probability of treatment weighting (IPTW), standardized mortality ratio weighting (SMRW) and overlap weighting (OW) to further assess the robustness of our findings according to the previous propensity score [25-30]. A SMD less than 0.10 indicated a good balance [31].

A two-sided *p* value less than 0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.1.2).

Data availability

All the data in the current study are publicly available in the Surveillance, Epidemiology and End Results database (https://seer.cancer.gov/). The authors obtained authorization to

Table 1. Baseline characteristics of the overall cohort before and after PSM

Characteristics	Before PSM		*p* Value	After PSM		*p* Value
	EOPC N = 2916	AOPC N = 39498		EOPC N = 2914	AOPC N = 8717	
Age, years*			< 0.001			< 0.001
Median [IQR]	46 [42, 48]	67 [60, 75]		46 [42, 48]	62 [60, 65]	
Sex, n (%)			< 0.001			0.711
Female	1651 (56.6)	20136 (51.0)		1650 (56.6)	4972 (57.0)	
Male	1265 (43.4)	19362 (49.0)		1264 (43.4)	3745 (43.0)	
Race, n (%)			< 0.001			0.093
White	2079 (71.3)	30568 (77.4)		2079 (71.3)	6264 (71.9)	
Black	540 (18.5)	5607 (14.2)		539 (18.5)	1570 (18.0)	
Others	282 (9.7)	3243 (8.2)		281 (9.6)	863 (9.9)	
Unknown	15 (0.5)	80 (0.2)		15 (0.5)	20 (0.2)	
Site, n (%)			0.981			0.88
Head	1512 (51.9)	20541 (52.0)		1510 (51.8)	4542 (52.1)	
Body/Tail	774 (26.5)	10481 (26.5)		774 (26.6)	2329 (26.7)	
Other	630 (21.6)	8476 (21.5)		630 (21.6)	1846 (21.2)	
Tumor Differentiation, n (%)			0.235			0.326
Well	149 (5.1)	1726 (4.4)		147 (5.0)	381 (4.4)	
Moderate	632 (21.7)	8502 (21.5)		632 (21.7)	1900 (21.8)	
Poor	541 (18.6)	7200 (18.2)		541 (18.6)	1556 (17.9)	
Unknown	1594 (54.7)	22070 (55.9)		1594 (54.7)	4880 (56.0)	
T stage, n (%)			< 0.001			0.927
T1	206 (7.1)	2811 (7.1)		205 (7.0)	598 (6.9)	
T2	915 (31.4)	14030 (35.5)		915 (31.4)	2791 (32.0)	
T3	736 (25.2)	9005 (22.8)		736 (25.3)	2234 (25.6)	
T4	600 (20.6)	7310 (18.5)		600 (20.6)	1755 (20.1)	
Unknown	459 (15.7)	6342 (16.1)		458 (15.7)	1339 (15.4)	
Size, mm*			< 0.001			0.674
Median [IQR]	40 [29, 50]	37 [28, 49]		40 [29, 50]	39 [29, 50]	
Vascular Invasion, n (%)			0.022			0.765
None	1646 (56.4)	23139 (58.6)		1645 (56.5)	5015 (57.5)	
Vein	232 (8.0)	2942 (7.4)		232 (8.0)	662 (7.6)	
Artery	600 (20.6)	7310 (18.5)		600 (20.6)	1755 (20.1)	
Unknown	438 (15.0)	6107 (15.5)		437 (15.0)	1285 (14.7)	
N stage, n (%)			0.687			0.872
N0	2224 (76.3)	30466 (77.1)		2223 (76.3)	6716 (77.0)	
N1	375 (12.9)	4912 (12.4)		374 (12.8)	1082 (12.4)	
N2	213 (7.3)	2705 (6.8)		213 (7.3)	618 (7.1)	
Unknown	104 (3.6)	1415 (3.6)		104 (3.6)	301 (3.5)	
M stage, n (%)			< 0.001			0.582
M0	1252 (42.9)	18813 (47.6)		1252 (43.0)	3667 (42.1)	
M1	1639 (56.2)	20062 (50.8)		1637 (56.2)	4984 (57.2)	
Unknown	25 (0.9)	623 (1.6)		25 (0.9)	66 (0.8)	
AJCC stage, 8th, n (%)			< 0.001			0.761
IA	77 (2.6)	1151 (2.9)		77 (2.6)	215 (2.5)	
IB	216 (7.4)	4249 (10.8)		216 (7.4)	668 (7.7)	
IIA	139 (4.8)	1978 (5.0)		139 (4.8)	393 (4.5)	

IIB	287 (9.8)	3976 (10.1)		287 (9.8)	873 (10.0)	
III	432 (14.8)	5825 (14.7)		432 (14.8)	1258 (14.4)	
IV	1639 (56.2)	20062 (50.8)		1637 (56.2)	4984 (57.2)	
Unknown	126 (4.3)	2257 (5.7)		126 (4.3)	326 (3.7)	
Surgery, n (%)			0.284			0.188
No	2063 (70.7)	28317 (71.7)		2062 (70.8)	6281 (72.1)	
Yes	853 (29.3)	11181 (28.3)		852 (29.2)	2436 (27.9)	
Systemic treatment, n (%)			< 0.001			0.551
No	562 (19.3)	13148 (33.3)		562 (19.3)	1664 (19.1)	
Neoadjuvant therapy	82 (2.8)	1028 (2.6)		82 (2.8)	222 (2.5)	
Adjuvant therapy	2185 (74.9)	24543 (62.1)		2183 (74.9)	6605 (75.8)	
Both	87 (3.0)	779 (2.0)		87 (3.0)	226 (2.6)	

*Continuous variables were reported as medians (interquartile ranges). EOPC: Early-Onset Pancreatic Cancer; AOPC: Average-Onset Pancreatic Cancer; PSM: Propensity Score Matching; IQR: Interquartile Range.

access the SEER database supported by the National Cancer Institute (Reference Number 11122-Nov2020).

Results

Baseline characteristics and survival differences in the whole cohort

After screening according to the selection criteria, a total of 41,414 patients with confirmed PDAC were enrolled in this study, including 2,916 (6.9%) with EOPC. See **Table 1** for detailed comparisons between EOPC and AOPC. In the entire cohort, the mean age at diagnosis was 66 years, and that of the EOPC and AOPC groups was 46 and 67 years, respectively. Apparently, males accounted for a larger proportion in the EOPC group (56.6% vs. 51.0%, $P < 0.001$). In the overall cohort, white patients were the majority, but there were more younger black patients (18.5% vs. 14.2%, $P < 0.001$). Although tumor site and differentiation had comparable distribution in both groups, the EOPC patients tended to present with a larger median size of tumor and more invasion behavior toward peripheral vessels (40 mm vs. 37 mm, $P < 0.001$; 28.6% vs. 25.9%, $P = 0.022$). No significant difference was found between EOPC and AOPC regarding lymph node involvement (23.7% vs. 22.9%, $P = 0.678$), but the rate of distant metastasis was higher in the EOPC group, with a statistical significance when comparing with the AOPC group (56.2% vs. 50.8%, $P < 0.001$). Notably, surgery was performed in a similar proportion in EOPC and AOPC groups (29.3% vs. 28.3%, $P = 0.284$), and patients with EOPC were more likely to receive more systemic treatment in comparison with those with AOPC (80.7% vs. 66.7%, $P < 0.001$). In the EOPC group, the median OS and CSS were 9 months and 10 months, respectively, which were longer than 7 months and 8 months in the AOPC group (both $P < 0.001$). Compared to the elderly patients, younger patients were associated with longer 5-year OS (6.9% vs. 5.5%, $P < 0.001$) and 5-year CSS rates (8.4% vs. 7.3%, $P < 0.001$, **Figure 2A** and **2B**).

Comparison of clinical characteristics and survival in the surgical cohort

In the surgical cohort, there were still more black patients in the EOPC group than in the AOPC group (15.4% vs. 11.4%, $P < 0.001$). Sex distribution didn't reach a statistical significance between them. There were no significant differences between the EOPC and AOPC groups in the following characteristics: tumor location, differentiation, median tumor size, vascular invasion, lymph node metastasis rate and clinical stage. Despite a higher proportion of a higher T stage (T3&T4: 31.4% vs. 27.1%, $P = 0.014$) and more harvested lymph nodes of EOPC patients versus AOPC patients (median: 16 vs. 15, $P = 0.002$), the other tumor-related features were fairly comparable between the two groups. The proportion of patients with systemic treatment administered was much higher in the EOPC group (86.5% vs. 74.5%, $P < 0.001$), either in terms of neoadjuvant therapy (18.8% vs. 15.1%, $P = 0.03$) or adjuvant therapy (77.6% vs. 66.1%, $P < 0.001$). The perioperative mortality rate was higher in the elderly group (5.0%

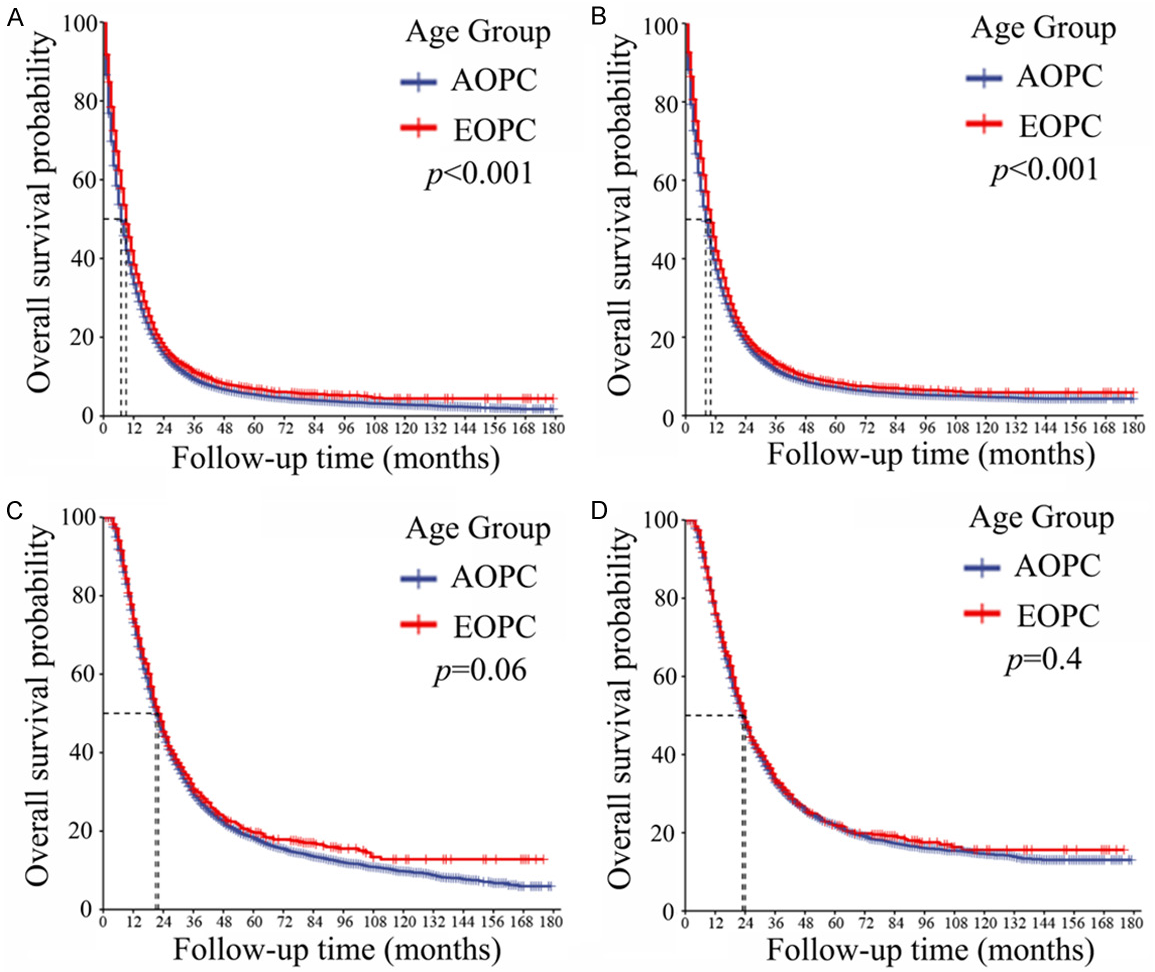

Figure 2. Comparison of overall survival (A) and cancer-specific survival (B) in the whole cohort and the surgical cohort (C, D) between patients with EOPC and those with AOPC. EOPC: Early-Onset Pancreatic Cancer; AOPC: Average-Onset Pancreatic Cancer.

vs. 2.9%, *P* = 0.009), but the reason for death was similar between the two groups (caused by pancreas: 81.5% vs. 86.4%, *P* = 0.78). The detailed clinical characteristics are presented in **Table 2**. The median OS was 22 months and 21 months for the EOPC and AOPC groups, respectively (*P* = 0.06, **Figure 2C**). Similarly, the median CSS had no significant difference between young and elderly patients (24 vs. 23 months; *P* = 0.38, **Figure 2D**). The 5-year OS rate and CSS rate were also comparable (OS: 19.6% vs. 18.4%; CSS: 21.8% vs. 22.0%; both *P* > 0.05).

Survival analysis after PSM

All baseline characteristics were well-balanced for subsequent survival analyses after PSM of the whole cohort (**Table 1**) and the surgical cohort (**Table 2**). After PSM, those with EOPC still had a higher 5-year OS (6.9% vs. 5.8, *P* = 0.002; **Figure 3A**) and CSS (8.4% vs. 7.7%, *P* = 0.007; **Figure 3B**) in the overall patients. However, there were no significant differences in the OS and CSS curves in operated patients between the two groups (both *P* > 0.05, **Figure 3C** and **3D**).

Sensitive analysis

To further validate the robustness of the results, IPTW, SMRW and OW adjusted survival analyses were performed based on the propensity score. The baseline characteristics of the two groups were found to be better balanced in the overall and surgical cohorts (Tables S1 and S2; Figure S1). In the overall cohort, younger patients demonstrated statistically significant

Table 2. Baseline characteristics of the overall cohort before and after PSM

Characteristics	Before PSM		*p* Value	After PSM		*p* Value
	EOPC N = 771	AOPC N = 10452		EOPC N = 763	AOPC N = 2278	
Age, years*			< 0.001			< 0.001
Median [IQR]	46 [42, 48]	67 [60, 74]		46 [42, 48]	63 [60, 67]	
Sex, n (%)			0.421			0.465
Female	401 (52.0)	5272 (50.4)		398 (52.2)	1225 (53.8)	
Male	370 (48.0)	5180 (49.6)		365 (47.8)	1053 (46.2)	
Race, n (%)			< 0.001			0.754
White	572 (74.2)	8387 (80.2)		571 (74.8)	1729 (75.9)	
Black	119 (15.4)	1196 (11.4)		118 (15.5)	328 (14.4)	
Others	73 (9.5)	854 (8.2)		73 (9.6)	220 (9.7)	
Unknown	7 (0.9)	15 (0.1)		1 (0.1)	1 (0.0)	
Perioperative Morbidity, n (%)	22 (2.9)	524 (5.0)	0.009	22 (2.9)	64 (2.8)	1
Pancreas-related Death, n (%)	19 (86.4)	427 (81.5)	0.78	3 (13.6)	14 (21.9)	0.541
Site, n (%)			0.058			0.345
Head	569 (73.8)	7830 (74.9)		564 (73.9)	1739 (76.3)	
Body/Tail	114 (14.8)	1686 (16.1)		113 (14.8)	318 (14.0)	
Other	88 (11.4)	936 (9.0)		86 (11.3)	221 (9.7)	
Tumor Differentiation, n (%)			0.244			0.966
Well	73 (9.5)	913 (8.7)		72 (9.4)	201 (8.8)	
Moderate	364 (47.2)	4928 (47.1)		362 (47.4)	1090 (47.8)	
Poor	231 (30.0)	3410 (32.6)		227 (29.8)	682 (29.9)	
Unknown	103 (13.4)	1201 (11.5)		102 (13.4)	305 (13.4)	
T stage, n (%)			0.014			0.926
T1	129 (16.7)	1542 (14.8)		127 (16.6)	387 (17.0)	
T2	377 (48.9)	5786 (55.4)		374 (49.0)	1128 (49.5)	
T3	186 (24.1)	2206 (21.1)		183 (24.0)	553 (24.3)	
T4	56 (7.3)	626 (6.0)		56 (7.3)	147 (6.5)	
Unknown	23 (3.0)	292 (2.8)		23 (3.0)	63 (2.8)	
Size, mm*			0.29			0.598
Median [IQR]	31 [24, 45]	32 [25, 40]		31 [24, 45]	32 [24, 43]	
Vascular Invasion, n (%)			0.529			0.868
None	642 (83.3)	8868 (84.8)		634 (83.1)	1912 (83.9)	
Vein	53 (6.9)	689 (6.6)		53 (6.9)	159 (7.0)	
Artery	56 (7.3)	626 (6.0)		56 (7.3)	147 (6.5)	
Unknown	20 (2.6)	269 (2.6)		20 (2.6)	60 (2.6)	
N stage, n (%)			0.872			0.655
N0	265 (34.4)	3702 (35.4)		263 (34.5)	764 (33.5)	
N1	305 (39.6)	4144 (39.6)		302 (39.6)	914 (40.1)	
N2	195 (25.3)	2517 (24.1)		192 (25.2)	590 (25.9)	
Unknown	6 (0.8)	89 (0.9)		6 (0.8)	10 (0.4)	
Lymph nodes examined*			0.002			0.057
Median [IQR]	16 [10, 23]	15 [9, 22]		16 [10, 23]	16 [9, 23]	
Lymph nodes examined, n (%)			0.095			0.663
< 15	332 (43.1)	4895 (46.8)		327 (42.9)	1008 (44.2)	
≥ 15	433 (56.2)	5453 (52.2)		430 (56.4)	1257 (55.2)	
Unknown	6 (0.8)	104 (1.0)		6 (0.8)	13 (0.6)	

Positive Lymph Nodes*			0.404			0.731
Median [IQR]	1 [0, 4]	1 [0, 3]		1 [0, 4]	1 [0, 4]	
AJCC stage, 8th, n (%)			0.382			0.913
IA	64 (8.3)	788 (7.5)		62 (8.1)	186 (8.2)	
IB	114 (14.8)	1855 (17.7)		114 (14.9)	346 (15.2)	
IIA	51 (6.6)	662 (6.3)		51 (6.7)	130 (5.7)	
IIB	281 (36.4)	3823 (36.6)		278 (36.4)	854 (37.5)	
III	234 (30.4)	2959 (28.3)		231 (30.3)	692 (30.4)	
Unknown	27 (3.5)	365 (3.5)		27 (3.5)	70 (3.1)	
Surgery Type, n (%)			0.832			0.446
Whipple	568 (73.7)	7714 (73.8)		562 (73.7)	1729 (75.9)	
Total Pancreatoectomy	108 (14.0)	1516 (14.5)		107 (14.0)	298 (13.1)	
Partial Pancreatoectomy	95 (12.3)	1222 (11.7)		94 (12.3)	251 (11.0)	
Systemic treatment, n (%)			< 0.001			0.816
No	104 (13.5)	2668 (25.5)		103 (13.5)	285 (12.5)	
Neoadjuvant therapy	69 (8.9)	880 (8.4)		69 (9.0)	195 (8.6)	
Adjuvant therapy	522 (67.7)	6210 (59.4)		518 (67.9)	1588 (69.7)	
Both	76 (9.9)	694 (6.6)		73 (9.6)	210 (9.2)	

*Continuous variables were reported as medians (interquartile ranges). EOPC: Early-Onset Pancreatic Cancer; AOPC: Average-Onset Pancreatic Cancer; PSM: Propensity Score Matching; IQR: Interquartile Range.

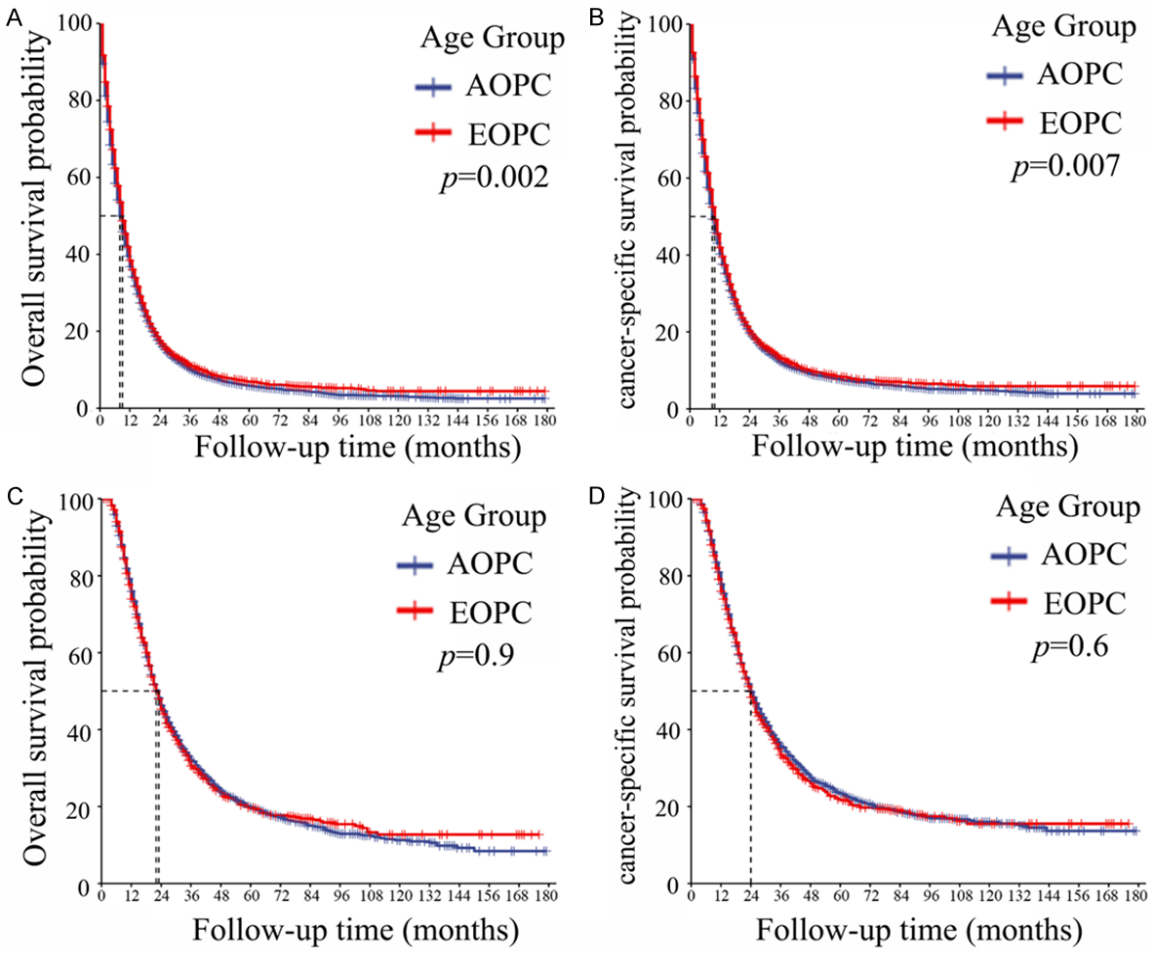

Figure 3. Comparison of overall survival (A) and cancer-specific survival (B) in the whole cohort and the surgical cohort (C, D) between patients with EOPC and those with AOPC after PSM. EOPC: Early-Onset Pancreatic Cancer; AOPC: Average-Onset Pancreatic Cancer; PSM: Propensity Score Matching.

Table 3. Systematic treatment distribution by age groups among operated patients

Treatment Strategy	Age Group, years	No. (%)		*P*	P_{trend}
Systemic treatment	All	8451 (75.3%)		< 0.001	< 0.001
	< 50	667 (86.5%)			
	50-59	1966 (83.3%)	< 50 vs. 50-59	0.208*	
	60-69	3176 (80.2%)	< 50 vs. 60-69	< 0.001*	
	≥ 70	2642 (63.9%)	< 50 vs. ≥ 70	< 0.001*	
Neoadjuvant therapy	All	949 (8.5%)		< 0.001	< 0.001
	< 50	69 (8.9%)			
	50-59	227 (9.6%)	< 50 vs. 50-59	1*	
	60-69	385 (9.7%)	< 50 vs. 60-69	1*	
	≥ 70	268 (6.5%)	< 50 vs. ≥ 70	0.078*	
Adjuvant therapy	All	6732 (60.0%)		< 0.001	< 0.001
	< 50	522 (67.7%)			
	50-59	1538 (65.2%)	< 50 vs. 50-59	1*	
	60-69	2482 (62.7%)	< 50 vs. 60-69	0.049*	
	≥ 70	2190 (53.0%)	< 50 vs. ≥ 70	< 0.001*	
Both therapy	All	770 (6.9%)		< 0.001	< 0.001
	< 50	76 (9.9%)			
	50-59	201 (8.5%)	< 50 vs. 50-59	1*	
	60-69	309 (7.8%)	< 50 vs. 60-69	0.340*	
	≥ 70	184 (4.5%)	< 50 vs. ≥ 70	< 0.001*	

p_{trend} from Cochran-Armitage trend test; * from Chi-square test adjusted by Bonferroni methods.

survival advantages in OS and CSS after IPTM (median OS: 9 vs. 7 months; median CSS: 10 vs. 8 months; both $P < 0.001$, Figure S2A and S2B), and similar results were obtained after SMRW and OW (Table S3). The Kaplan-Meier survival curves of OS and CSS are illustrated in Figures S3A, S3B and S4A, S4B. Likewise, EOPC had a comparable prognosis compared with AOPC in operated patients (Table S4; Figures S2C, S2D, S3C, S3D, S4C, S4D).

Differences in treatment strategies by age stratification

In light of the disparities in systemic treatment utilization between the two age groups, we further stratified the AOPC group by every ten years using the Cochran-Armitage trend statistic and Chi-square test adjusted by Bonferroni correction (age groups: < 50, 50-59, 60-69, ≥ 70), so as to determine the influence of age on systemic treatment. In the operated cohort, 75.3% of patients with PDAC had been treated with systemic treatment. Young patients were more likely to receive systemic treatment than old ones, and the rate of systemic treatment administrated to patients decreased as they aged (86.5% for EOPC patients and 63.9% for patients older than 70 years; $p_{trend} < 0.001$). Less than 10% of patients had neoadjuvant therapy, and the rate was similar among the three younger groups (8.9%, 9.6% and 9.7%, respectively); however, the rate declined to 6.5% in patients over 70 years ($p_{trend} < 0.001$). The combination of neoadjuvant and adjuvant therapy was also underutilized, with a rate under 10% in each age group (9.9%, 8.5%, 7.8% and 4.5%, respectively; $p_{trend} < 0.001$). While most participants received adjuvant therapy after resection, the proportion presented a downward trend with increasing age (67.7%, 65.2%, 62.7% and 53.0%, respectively; $p_{trend} < 0.001$, **Table 3**; **Figure 4**). We further analyzed treatment patterns in different clinical stages and found similar decreasing trends regarding the rate of receiving systemic treatment as age increased (Table S5; Figure S5).

Survival analysis between EOPC and other age groups

EOPC patients didn't show a survival advantage in the operated cohort. Further analyses were performed to evaluate whether younger

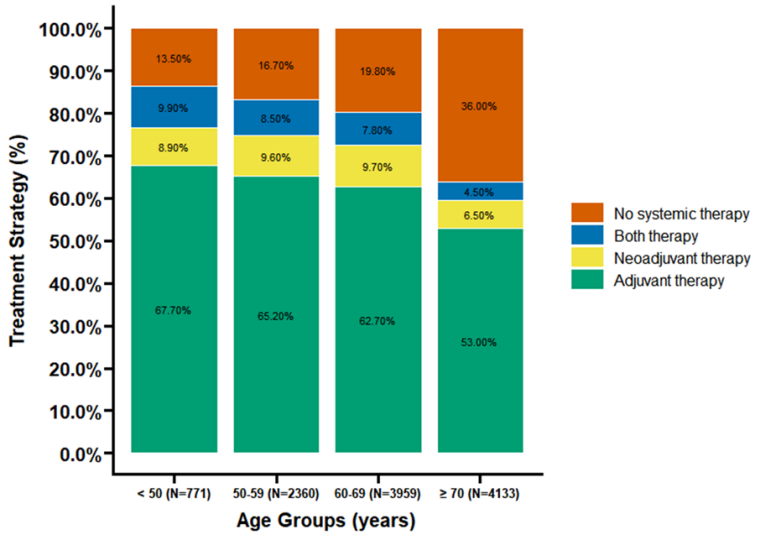

Figure 4. Systematic treatment distribution by age groups among operated patients.

patients survived a similar period to all the age groups beyond 50 years. It was found that EOPC patients only had better 5-year OS and CSS than the oldest age group (OS: 19.6% vs. 15.4%, $P < 0.001$; CSS: 21.8% vs. 20.0%; $P = 0.0047$; **Figure 5**). Cox proportional hazards regression analyses were performed to investigate prognostic factors of OS and CSS and explore whether age affected survival after adjusting for potential confounding factors in the surgical cohort. As presented in Tables S6 and S7, patients over 70 years still had worse survival compared with EOPC patients (OS, HR: 1.179, 95% CI 1.073-1.295, $P = 0.001$; CSS, HR: 1.1, 95% CI 1.005-1.223, $P = 0.04$). However, there was no significant difference in survival between EOPC and the other two older groups after covariate adjustments.

Discussion

EOPC is defined as patients who are diagnosed with pancreatic cancer before the age of 45, 50 or 55 years, according to previous studies, while the cut-off age hasn't come to an agreement among different researchers [32]. Recently, increasing studies tend to use the age of 50 as the partition age [24, 32, 33]. EOPC accounted for 6.9% of the total PDAC population in our study, which is generally similar to the 5.7-10.3% range reported from former single-center and population-based studies [20-22]. As far as sex and race differences are concerned, males and blacks accounted for a large proportion in the overall cohort of EOPC patients, which is in accordance with previous reports [20, 21]. Smoking is one of the explanations for the difference in sex distribution, as men are more likely to start smoking at an earlier age. Our findings of tumor characteristics were also widely similar to another analysis based on the National Cancer Database [20]. In this study, EOPC patients appeared to have larger tumor sizes, more advanced T staging and more distant metastases. However, a study conducted by Ansari et al., also based on the SEER database, suggested there was no significant difference with regards to tumor size [23]. This inconsistent finding may partly be due to the fact that instead of comparing the median tumor size of the two groups, they separated tumor sizes into categorical variables using 2 cm as a cut-off value. In agreement with several studies, tumor site, lymph node involvement and tumor differentiation displayed insignificant differences in our study. A study by Ordonez et al. demonstrated that younger patients with PDAC had a slightly higher predilection for blacks, private insurance and multimodality therapy than the older ones. Furthermore, EOPC patients were less likely to develop a tumor in the head, poor differentiation, small tumor, lymphovascular invasion, lymph node involvement and late tumor stage in the surgical cohort [20]. Our findings are in broad agreement with their results, except for lymphovascular invasion, although no statistical significance has been observed in some characteristics. Similarly, Ntala et al. also identified no statistically significant difference in these pathological characteristics [21].

Radical surgical resection has always been deemed the only cure for potentially resectable patients. Due to the relative rarity of EOPC, the proportion of patients who received surgery ranged from 16% to 100% in single-center research [10, 20, 21]. Beeghly-Fadiel et al. performed a relatively large sample size research with 118 EOPC patients included, reporting

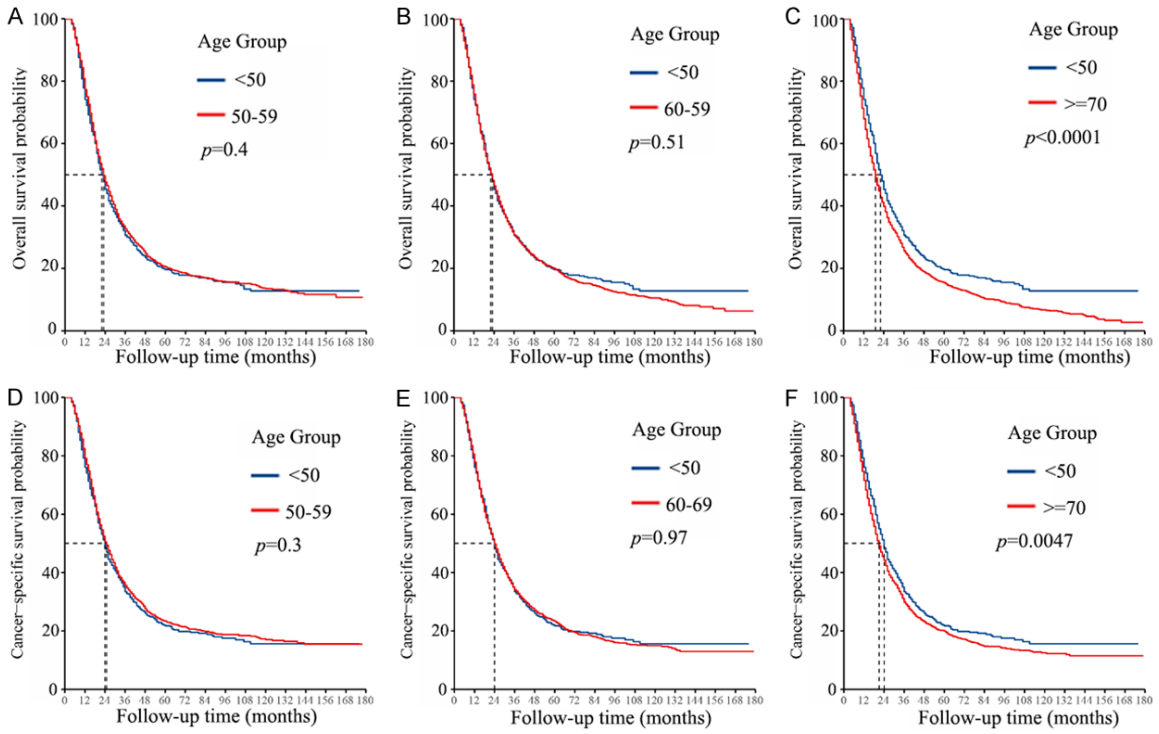

Figure 5. Kaplan-Meier analysis of overall survival and cancer-specific survival in the EOPC group versus the 50-59 age group (A, D), 60-69 age group (B, E), and over 70 age group (C, F), respectively. EOPC: Early-onset pancreatic cancer.

that 23.3% and 22.5% of patients underwent surgery in the EOPC and AOPC groups, respectively [22]. However, Ansari et al. and Ordonez et al. found a significant difference between the two age groups in resection rates based on two large national-wide databases, with the resection rates of the younger and older patients being 25.5% and 20.0% in Ordonez's study, and 23.2% and 19.9% in Ansari's study, respectively [20, 23]. Nonetheless, in contrast to the results, our findings demonstrated that 29.3% and 28.3% of patients received surgery in EOPC and AOPC groups, respectively, with no significant difference between the two groups. Additionally, our study indicated that up to 75% of patients chose multimodality treatment in the surgical cohort, and about 60% received postoperative adjuvant therapy, both of which were slightly higher than those of the previous reports [24, 34]. These differences may partly be explained because we included patients with PDAC as the only primary malignant tumor and the cautious selection of eligible participants. Furthermore, when further stratified for age, our study first uncovered that in the surgical cohort, the trend for systemic therapy decreased as patients aged. In the present study, we found an obviously reduced percentage of patients who received multimodal treatment in the oldest age group; however, the rate was mostly comparable between EOPC and the other two age groups. Similar trends were found after further analyses stratified by clinical staging. This suggests that age may have an important effect on the treatment strategies received in current clinical management. Likewise, Saadat et al. found that younger patients had nearly 4-fold higher odds of receiving multimodal treatment after adjusting for measured confounders [24]. Miksad et al. considered age as a prominent source of confounding factor [35]. Younger patients may be healthier, which leads to fewer patients seeking medical evaluations and consequently a higher possibility of diagnosis of EOPC at an advanced stage. However, in turn, a better physical condition may allow patients to undergo more systemic treatment than the older ones. Besides, some sociodemographic characteristics such as income, insurance status and transportation resources may also influence patients' choice

of treatment patterns no matter how old they are.

Survival outcomes varied across different studies. A small sample size may be an interpretation for the inconsistency of results. However, results from two large population-based studies were also confusing, which makes it more difficult to understand the biological differences between the two groups. Ansari et al. reported that younger patients had a worse oncological outcome either in the overall cohort or in the operated cohort [23]. Ordonez et al. reported contrary results, arguing that EOPC patients had a survival benefit both in the whole and surgical cohorts [20]. Our findings remain different from previous reports, and we suggested that younger patients had a better survival in the overall cohort but a similar survival probability after surgical resection. Besides, we used PSM, IPTW, SMRW and OW methods to minimize the effect of confounders, thus validating the reliability of the results. One of the putative explanations for the seemingly contradictory findings is the different inclusion criteria in the study cohort. Both the other two large studies did not exclude patients with other malignancies that can increase selection bias to survival analyses. Ordonez et al. also included patients such as those with mucinous adenocarcinoma and intraductal papillary-mucinous carcinoma, which were younger at diagnosis and more suitable for surgery compared with PDAC. All of these may add a benefit to survival. In addition, our study found that patients with EOPC had lower perioperative mortality than older patients, but no significant difference was identified regarding the cause of death. However, most previous studies did not compare perioperative mortality, and only a few single-centers with a small sample size found no difference. But this finding should be cautiously interpreted. Elderly patients may have relatively worse performance and more comorbidities, so that radical resection may hit them harder and cause more deaths in the perioperative period.

Since PDAC patients are mainly over 50 years old, random comparisons of EOPC with the entire elderly group may result in a bias in survival outcomes. Therefore, we further divided the elderly group into three subgroups and compared the survival of EOPC with each of them. Tsang et al. combined four individual studies to explore the potential genomic and prognostic differences between patients younger than 55 years and those older than 70 years and performed an independent survival analysis using a provincial population dataset. No differences in OS were noted across the onset age groups except in a small study from the PanGen cohort [18]. Ben-Aharon et al. also reported comparable survival outcomes from the TCGA cohort and the Australian cohort using the same age-onset definition [17]. However, our further analyses suggested that even after adjusting for potential confounding factors, patients with EOPC had a better outcome than those older than 70 years. We should be discreet in considering EOPC as a distinct entity, as a slight benefit in survival may be magnified by poorer performance and fewer systemic treatments administered in older patients.

Differences in clinical presentation and outcomes suggest that EOPC may have a distinct genetic etiology, so there have been several in-depth studies of genomic alterations research based on relatively large datasets. Ben-Aharon et al. found that younger patients had higher SMAD4 and PI3KCA mutation rates, increased activation of the TGF-β pathway and higher expression of GSK3 [17]. Tsang et al. found that EOPC tumors showed a lower mutation rate, together with a distinct mutation pattern in CDKN2A and a significantly upregulated FOXC2, which is related to epithelial-to-mesenchymal [18]. However, Raffenne et al. found no differences in the mutational landscape of key driver genes and global methylation profile [19]. Furthermore, Varghese et al. analyzed 138 patients for germline testing and found 31.9% of them had a pathogenic germline variant and 27.5% had harbored alterations in cancer susceptibility genes [33]. These genetic differences suggest that at least a small proportion of EOPC patients may be genetically different from the older patients, highlighting the importance of implementing genomic testing in younger patients to discover potential alternatives that could be used in future precision medicine.

This study still has several critical limitations. First, our study was based on a large, national, retrospective cancer registry with a long period. These features may be advantages for the rari-

ty of EOPC; however, there can also be potential biases in the selection criteria for surgery and clinical management, especially in a retrospective national-wide database. Moreover, while we selected pancreatic adenocarcinoma patients with more restrictive conditions, there are still several non-specified pathological types included that may influence either clinicopathologic characteristics or oncologic outcomes. Second, there was a dearth of important information available regarding detailed systemic treatment regimens and changes in treatment modalities over time. Additionally, data on performance status, smoking history, family history, tumor markers, resection margin status, complications and recurrence are not registered in the SEER database. Most importantly, there is no genetic information in the database, which leads to the inability to discover potential unique genomic profiles that could characterize younger patients.

Conclusion

In conclusion, EOPC displays a later stage and a male predilection at diagnosis in the overall cohort but broadly similar clinicopathologic characteristics in operated patients. Although patients with EOPC had inferior OS and CSS in the whole cohort, the oncologic outcomes were fairly comparable after surgical resection. Besides, younger patients were more likely to receive systemic treatment. Further research is warranted to direct towards molecular alterations occurring in EOPC and, more importantly, to better understand and elucidate the enigma of early-onset PDAC that may be useful to exploit more precise personalized therapeutic strategies to improve clinical outcomes.

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Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics of the overall cohort after different propensity weighted methods

Characteristics	IPTW		*p* Value	SMRW		*p* Value	OW		*p* Value
	EOPC N = 3111.7	AOPC N = 39284.2		EOPC N = 2916	AOPC N = 2917.6		EOPC N = 2863.3	AOPC N = 2863.3	
Age, years*			< 0.001	46 [42, 48]	66 [59, 74]	< 0.001			< 0.001
Median [IQR]	46 [42, 48]	67 [60, 75]					46 [42, 48]	66 [60, 74]	
Sex, n (%)			0.107			0.919			1
Female	1650.8 (53.1)	20182.0 (51.4)		1651.0 (56.6)	1654.7 (56.7)		1510.6 (56.3)	1510.6 (56.3)	
Male	1460.8 (46.9)	19102.2 (48.6)		1265.0 (43.4)	1262.9 (43.3)		1172.7 (43.7)	1172.7 (43.7)	
Race, n (%)			0.992			1			1
White	2395.6 (77.0)	30237.2 (77.0)		2079.0 (71.3)	2079.5 (71.3)		1928.1 (71.9)	1928.1 (71.9)	
Black	453.7 (14.6)	5694.1 (14.5)		540.0 (18.5)	541.0 (18.5)		486.8 (18.1)	486.8 (18.1)	
Others	255.1 (8.2)	3264.7 (8.3)		282.0 (9.7)	281.9 (9.7)		256.0 (9.5)	256.0 (9.5)	
Unknown	7.3 (0.2)	88.2 (0.2)		15.0 (0.5)	15.3 (0.5)		12.4 (0.5)	12.4 (0.5)	
Site, n (%)			0.859			0.999			1
Head	1600.5 (51.4)	20424.4 (52.0)		1512.0 (51.9)	1511.4 (51.8)		1389.6 (51.8)	1389.6 (51.8)	
Body/Tail	832.4 (26.7)	10425.0 (26.5)		774.0 (26.5)	775.0 (26.6)		713.7 (26.6)	713.7 (26.6)	
Other	678.8 (21.8)	8434.8 (21.5)		630.0 (21.6)	631.1 (21.6)		580.0 (21.6)	580.0 (21.6)	
Tumor Differentiation, n (%)			0.934			1			1
Well	144.2 (4.6)	1736.7 (4.4)		149.0 (5.1)	149.2 (5.1)		135.2 (5.0)	135.2 (5.0)	
Moderate	677.9 (21.8)	8461.1 (21.5)		632.0 (21.7)	633.5 (21.7)		582.0 (21.7)	582.0 (21.7)	
Poor	569.6 (18.3)	7169.6 (18.3)		541.0 (18.6)	541.1 (18.5)		497.0 (18.5)	497.0 (18.5)	
Unknown	1720.0 (55.3)	21916.8 (55.8)		1594.0 (54.7)	1593.8 (54.6)		1469.0 (54.7)	1469.0 (54.7)	
T stage, n (%)			0.969			1			1
T1	224.9 (7.2)	2794.4 (7.1)		206.0 (7.1)	206.2 (7.1)		189.7 (7.1)	189.7 (7.1)	
T2	1079.7 (34.7)	13840.9 (35.2)		915.0 (31.4)	914.2 (31.3)		849.2 (31.6)	849.2 (31.6)	
T3	729.7 (23.5)	9023.5 (23.0)		736.0 (25.2)	737.8 (25.3)		673.8 (25.1)	673.8 (25.1)	
T4	584.5 (18.8)	7326.7 (18.7)		600.0 (20.6)	600.7 (20.6)		548.4 (20.4)	548.4 (20.4)	
Unknown	492.9 (15.8)	6298.7 (16.0)		459.0 (15.7)	458.8 (15.7)		422.1 (15.7)	422.1 (15.7)	
Size, mm*			0.621			0.684			0.674
Median [IQR]	37 [28, 50]	37 [28, 49]		40 [29, 50]	39 [29, 50]		39 [28, 50]	38 [29, 50]	
Vascular Invasion, n (%)			0.61			0.366			0.384
None	1807.2 (58.1)	22976.1 (58.5)		1646.0 (56.4)	1668.5 (57.2)		1518.4 (56.6)	1537.6 (57.3)	
Vein	252.3 (8.1)	2915.7 (7.4)		232.0 (8.0)	206.1 (7.1)		213.9 (8.0)	190.4 (7.1)	
Artery	584.5 (18.8)	7326.7 (18.7)		600.0 (20.6)	600.7 (20.6)		548.4 (20.4)	548.4 (20.4)	
Unknown	467.7 (15.0)	6065.8 (15.4)		438.0 (15.0)	442.3 (15.2)		402.6 (15.0)	406.9 (15.2)	

N stage, n (%)			0.965			1		1
N0	2386.3 (76.7)	30276.5 (77.1)		2224.0 (76.3)	2223.9 (76.2)		2047.8 (76.3)	2047.8 (76.3)
N1	392.5 (12.6)	4897.6 (12.5)		375.0 (12.9)	376.0 (12.9)		344.7 (12.8)	344.7 (12.8)
N2	221.5 (7.1)	2702.9 (6.9)		213.0 (7.3)	213.4 (7.3)		195.3 (7.3)	195.3 (7.3)
Unknown	111.5 (3.6)	1407.1 (3.6)		104.0 (3.6)	104.3 (3.6)		95.5 (3.6)	95.5 (3.6)
M stage, n (%)			0.957			1		1
M0	1468.7 (47.2)	18583.7 (47.3)		1252.0 (42.9)	1252.0 (42.9)		1159.6 (43.2)	1159.6 (43.2)
M1	1597.7 (51.3)	20100.4 (51.2)		1639.0 (56.2)	1640.6 (56.2)		1499.9 (55.9)	1499.9 (55.9)
Unknown	45.3 (1.5)	600.1 (1.5)					23.8 (0.9)	23.8 (0.9)
AJCC stage, 8th, n (%)			0.276			0.738		0.711
IA	99.9 (3.2)	1133.5 (2.9)		77.0 (2.6)	72.9 (2.5)		71.6 (2.7)	67.7 (2.5)
IB	279.5 (9.0)	4156.3 (10.6)		216.0 (7.4)	238.6 (8.2)		201.6 (7.5)	223.4 (8.3)
IIA	171.9 (5.5)	1951.5 (5.0)		139.0 (4.8)	129.0 (4.4)		129.3 (4.8)	119.7 (4.5)
IIB	308.3 (9.9)	3953.4 (10.1)		287.0 (9.8)	292.6 (10.0)		264.3 (9.9)	269.4 (10.0)
III	477.0 (15.3)	5788.2 (14.7)		432.0 (14.8)	424.6 (14.6)		398.6 (14.9)	391.3 (14.6)
IV	1597.7 (51.3)	20100.4 (51.2)		1639.0 (56.2)	1640.6 (56.2)		1499.9 (55.9)	1499.9 (55.9)
Unknown	177.4 (5.7)	2201.0 (5.6)		126.0 (4.3)	119.4 (4.1)		117.9 (4.4)	111.9 (4.2)
Surgery, n (%)			0.547			0.961		1
No	2211.3 (71.1)	28137.0 (71.6)		2063.0 (70.7)	2062.9 (70.7)		1899.6 (70.8)	1899.6 (70.8)
Yes	900.4 (28.9)	11147.2 (28.4)		853.0 (29.3)	854.7 (29.3)		783.6 (29.2)	783.6 (29.2)
Systemic treatment, n (%)			0.214			0.231		0.239
No	979.3 (31.5)	12709.4 (32.4)		562.0 (19.3)	574.5 (19.7)		536.1 (20.0)	548.2 (20.4)
Neoadjuvant therapy	99.0 (3.2)	1016.1 (2.6)		82.0 (2.8)	69.1 (2.4)		76.6 (2.9)	64.5 (2.4)
Adjuvant therapy	1975.5 (63.5)	24743.4 (63.0)		2185.0 (74.9)	2172.7 (74.5)		1994.1 (74.3)	1982.0 (73.9)
Both	57.9 (1.9)	815.2 (2.1)		87.0 (3.0)	101.2 (3.5)		76.4 (2.8)	88.6 (3.3)

*Continuous variables were reported as medians [interquartile ranges]. PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMRW, standardized mortality ratio weighting; OW, overlap weighting.

Table S2. Baseline characteristics of the surgery cohort after different propensity weighted methods

Characteristics	IPTW			SMRW			OW		
	EOPC N = 822.2	AOPC N = 10395.5	*p* Value	EOPC N = 771	AOPC N = 771.4	*p* Value	EOPC N = 710.3	AOPC N = 710.3	*p* Value
Age, years*			< 0.001			< 0.001			< 0.001
Median [IQR]	46 [42, 48]	67 [60, 74]		46 [42, 48]	66 [60, 73]		46 [42, 48]	66 [60, 73]	
Sex, n (%)			0.188			0.886			1
Female	437.2 (53.2)	5256.6 (50.6)		401.0 (52.0)	403.3 (52.3)		370.0 (52.1)	370.0 (52.1)	
Male	385.0 (46.8)	5138.9 (49.4)		370.0 (48.0)	368.1 (47.7)		340.2 (47.9)	340.2 (47.9)	
Race, n (%)			0.991			1			1
White	655.3 (79.7)	8298.2 (79.8)		572.0 (74.2)	572.1 (74.2)		531.7 (74.9)	531.7 (74.9)	
Black	95.7 (11.6)	1217.9 (11.7)		119.0 (15.4)	118.9 (15.4)		107.1 (15.1)	107.1 (15.1)	
Others	69.4 (8.4)	858.8 (8.3)		73.0 (9.5)	73.2 (9.5)		66.8 (9.4)	66.8 (9.4)	
Unknown	1.8 (0.2)	20.6 (0.2)		7.0 (0.9)	7.2 (0.9)		4.7 (0.7)	4.7 (0.7)	
Perioperative Morbility, n (%)	37.6 (4.6)	507.9 (4.9)	0.758	22.0 (2.9)	24.3 (3.2)	0.642	20.9 (2.9)	22.9 (3.2)	0.672
Pancreas-related Death, n (%)	5.6 (15.0)	93.8 (18.5)	0.694	3.0 (13.6)	4.3 (17.6)	0.633	2.9 (13.7)	4.1 (17.7)	0.632
Site, n (%)			0.094			0.152			0.143
Head	623.6 (75.8)	7771.2 (74.8)		569.0 (73.8)	560.1 (72.6)		525.8 (74.0)	517.0 (72.8)	
Body/Tail	111.6 (13.6)	1684.7 (16.2)		114.0 (14.8)	132.9 (17.2)		104.3 (14.7)	121.9 (17.2)	
Other	87.0 (10.6)	939.5 (9.0)		88.0 (11.4)	78.4 (10.2)		80.2 (11.3)	71.4 (10.1)	
Tumor Differentiation, n (%)			0.894			1			1
Well	69.4 (8.4)	913.1 (8.8)		73.0 (9.5)	72.9 (9.4)		66.7 (9.4)	66.7 (9.4)	
Moderate	387.0 (47.1)	4902.1 (47.2)		364.0 (47.2)	364.5 (47.3)		335.4 (47.2)	335.4 (47.2)	
Poor	262.7 (32.0)	3371.5 (32.4)		231.0 (30.0)	230.0 (29.8)		213.5 (30.1)	213.5 (30.1)	
Unknown	103.1 (12.5)	1208.7 (11.6)		103.0 (13.4)	104.0 (13.5)		94.6 (13.3)	94.6 (13.3)	
T stage, n (%)			0.997			1			1
T1	122.0 (14.8)	1547.3 (14.9)		129.0 (16.7)	128.6 (16.7)		117.5 (16.5)	117.5 (16.5)	
T2	449.9 (54.7)	5708.8 (54.9)		377.0 (48.9)	377.5 (48.9)		350.7 (49.4)	350.7 (49.4)	
T3	174.6 (21.2)	2215.3 (21.3)		186.0 (24.1)	185.8 (24.1)		169.8 (23.9)	169.8 (23.9)	
T4	52.9 (6.4)	631.9 (6.1)		56.0 (7.3)	56.2 (7.3)		51.2 (7.2)	51.2 (7.2)	
Unknown	22.8 (2.8)	292.1 (2.8)		23.0 (3.0)	23.4 (3.0)		21.1 (3.0)	21.1 (3.0)	
Size, mm*			0.895			0.639			0.649
Median [IQR]	30 [25, 41]	32 [25, 40]		31 [24, 45]	32 [25, 43]		31 [24, 45]	32 [25, 42]	
Vascular Invasion, n (%)			0.914			0.955			0.961
None	690.9 (84.0)	8810.5 (84.8)		642.0 (83.3)	644.2 (83.5)		591.6 (83.3)	593.9 (83.6)	
Vein	58.4 (7.1)	684.0 (6.6)		53.0 (6.9)	49.5 (6.4)		49.1 (6.9)	45.8 (6.5)	
Artery	52.9 (6.4)	631.9 (6.1)		56.0 (7.3)	56.2 (7.3)		51.2 (7.2)	51.2 (7.2)	
Unknown	20.0 (2.4)	269.1 (2.6)					18.3 (2.6)	19.4 (2.7)	

N stage, n (%)			0.801			1		1
N0	280.6 (34.1)	3673.9 (35.3)		265.0 (34.4)	264.5 (34.3)		244.0 (34.4)	244.0 (34.4)	
N1	330.9 (40.2)	4121.5 (39.6)		305.0 (39.6)	305.8 (39.6)		281.6 (39.6)	281.6 (39.6)	
N2	205.6 (25.0)	2512.1 (24.2)		195.0 (25.3)	195.2 (25.3)		179.2 (25.2)	179.2 (25.2)	
Unknown	5.1 (0.6)	87.9 (0.8)		6.0 (0.8)	5.9 (0.8)		5.5 (0.8)	5.5 (0.8)	
Lymph nodess examined*			0.073			0.244			0.219
Median [IQR]	16 [10, 22]	15 [9, 22]		16 [10, 23]	16 [10, 23]		16 [10, 23]	16 [10, 23]	
Lymph nodess examined, n (%)			0.565			0.997			1
< 15	373.0 (45.4)	4841.0 (46.6)		332.0 (43.1)	331.5 (43.0)		307.2 (43.2)	307.2 (43.2)	
≥ 15	443.6 (54.0)	5452.7 (52.5)		433.0 (56.2)	434.0 (56.3)		397.6 (56.0)	397.6 (56.0)	
Unknown	5.6 (0.7)	101.8 (1.0)		6.0 (0.8)	5.9 (0.8)		5.5 (0.8)	5.5 (0.8)	
Positive Lymph Nodes*			0.486			0.92			0.895
Median [IQR]	1 [0, 3.74]	1 [0, 3]		1 [0, 4]	1 [0, 4]		1 [0, 4]	1 [0, 4]	
AJCC stage, 8th, n (%)			0.94			0.997			0.998
IA	63.5 (7.7)	787.0 (7.6)		64.0 (8.3)	61.6 (8.0)		58.2 (8.2)	56.6 (8.0)	
IB	133.8 (16.3)	1827.0 (17.6)		114.0 (14.8)	117.5 (15.2)		106.2 (14.9)	109.2 (15.4)	
IIA	49.6 (6.0)	662.1 (6.4)		51.0 (6.6)	52.9 (6.9)		46.7 (6.6)	48.5 (6.8)	
IIB	307.3 (37.4)	3797.2 (36.5)		281.0 (36.4)	276.6 (35.9)		259.6 (36.5)	255.4 (36.0)	
III	241.6 (29.4)	2958.0 (28.5)		234.0 (30.4)	234.6 (30.4)		214.8 (30.2)	215.1 (30.3)	
Unknown	26.4 (3.2)	364.2 (3.5)		27.0 (3.5)	28.2 (3.7)		24.8 (3.5)	25.5 (3.6)	
Surgery Type, n (%)			0.503			0.599			0.58
Whipple	608.6 (74.0)	7668.7 (73.8)		568.0 (73.7)	565.4 (73.3)		523.8 (73.8)	520.6 (73.3)	
Total Pancreatoectomy	108.8 (13.2)	1512.5 (14.5)		108.0 (14.0)	117.0 (15.2)		98.9 (13.9)	107.5 (15.1)	
Partial Pancreatoectomy	104.8 (12.7)	1214.3 (11.7)		95.0 (12.3)	89.0 (11.5)		87.5 (12.3)	82.1 (11.6)	
Systemic treatment, n (%)			0.897			1			1
No	193.6 (23.5)	2567.3 (24.7)		104.0 (13.5)	103.7 (13.4)		99.5 (14.0)	99.5 (14.0)	
Neoadjuvant therapy	73.0 (8.9)	879.2 (8.5)		69.0 (8.9)	69.2 (9.0)		64.0 (9.0)	64.0 (9.0)	
Adjuvant therapy	499.2 (60.7)	6235.7 (60.0)		522.0 (67.7)	522.3 (67.7)		478.9 (67.4)	478.9 (67.4)	
Both	56.5 (6.9)	713.3 (6.9)		76.0 (9.9)	76.1 (9.9)		67.9 (9.6)	67.9 (9.6)	

*Continuous variables were reported as medians [interquartile ranges]. Abbreviation: PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMRW, standardized mortality ratio weighting; OW, overlap weighting.

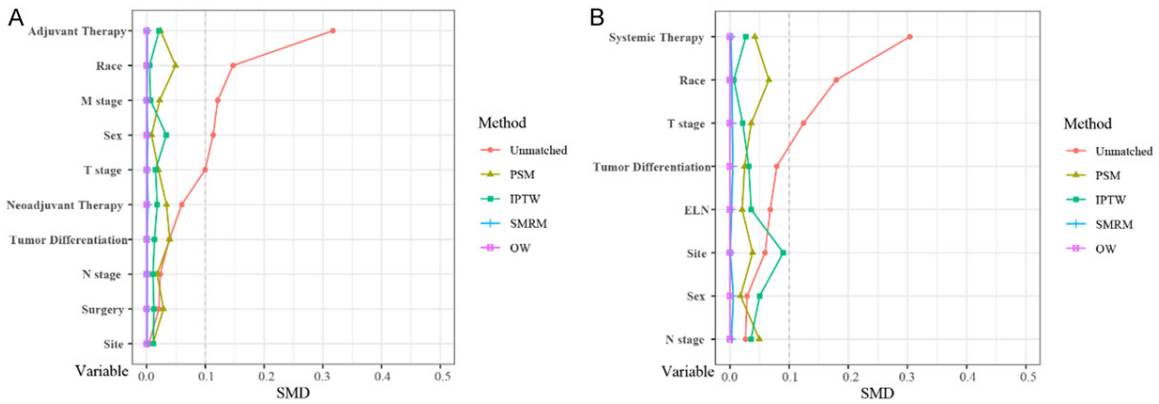

Figure S1. Standard mean differences of matching covariates in the overall cohort (A) and the surgery cohort (B) after different propensity score methods.

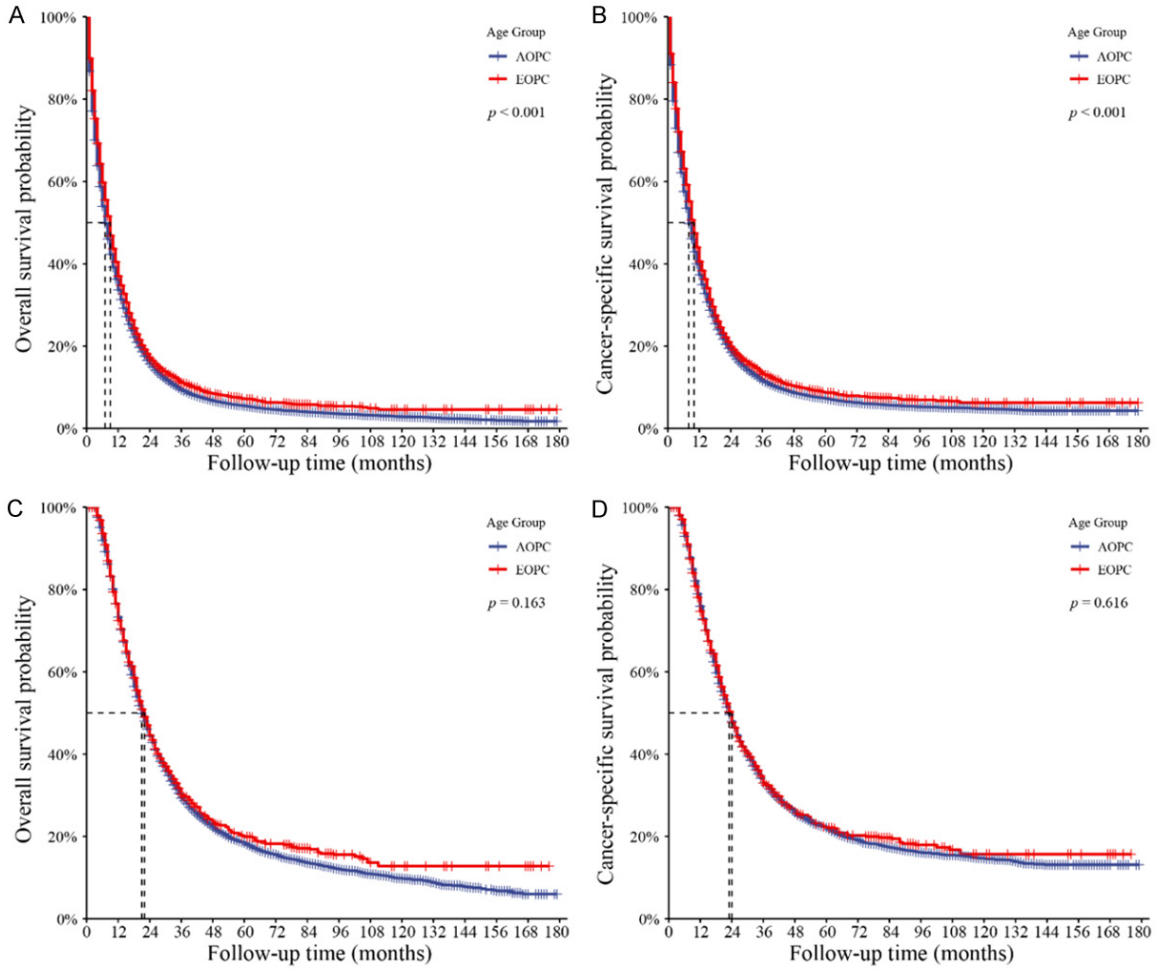

Figure S2. Comparison of overall survival (A) and cancer-specific survival (B) in the whole cohort and the surgery cohort (C, D) between patients with EOPC and patients with AOPC after IPTW.

Table S3. Comparison of OS and CSS between EOPC and AOPC patients in the overall cohort

	PSM		*P* Value	IPTW		*P* Value	SMRW		*P* Value	OW		*P* Value
	EOPC	AOPC		EOPC	AOPC		EOPC	AOPC		EOPC	AOPC	
OS			0.002			< 0.001			< 0.001			< 0.001
1 year	38.4%	36.8%		37.0%	33.7%		38.4%	36.1%		38.3%	35.9%	
3 year	11.1%	10.1%		11.1%	9.4%		11.1%	10.0%		11.1%	10.0%	
5 year	6.9%	5.8%		7.2%	5.5%		6.9%	5.8%		6.9%	5.8%	
median, months	9	8		9	7		9	8		9	8	
CSS			0.007			< 0.001			< 0.001			< 0.001
1 year	41.9%	40.2%		40.5%	37.3%		41.9%	39.6%		41.8%	39.5%	
3 year	13.3%	12.3%		13.3%	11.6%		13.3%	12.2%		13.2%	12.1%	
5 year	8.4%	7.7%		8.8%	7.3%		8.4%	7.6%		8.4%	7.6%	
median, months	10	9		10	8		10	9		10	9	

Abbreviation: PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMRW, standardized mortality ratio weighting; OW, overlap weighting.

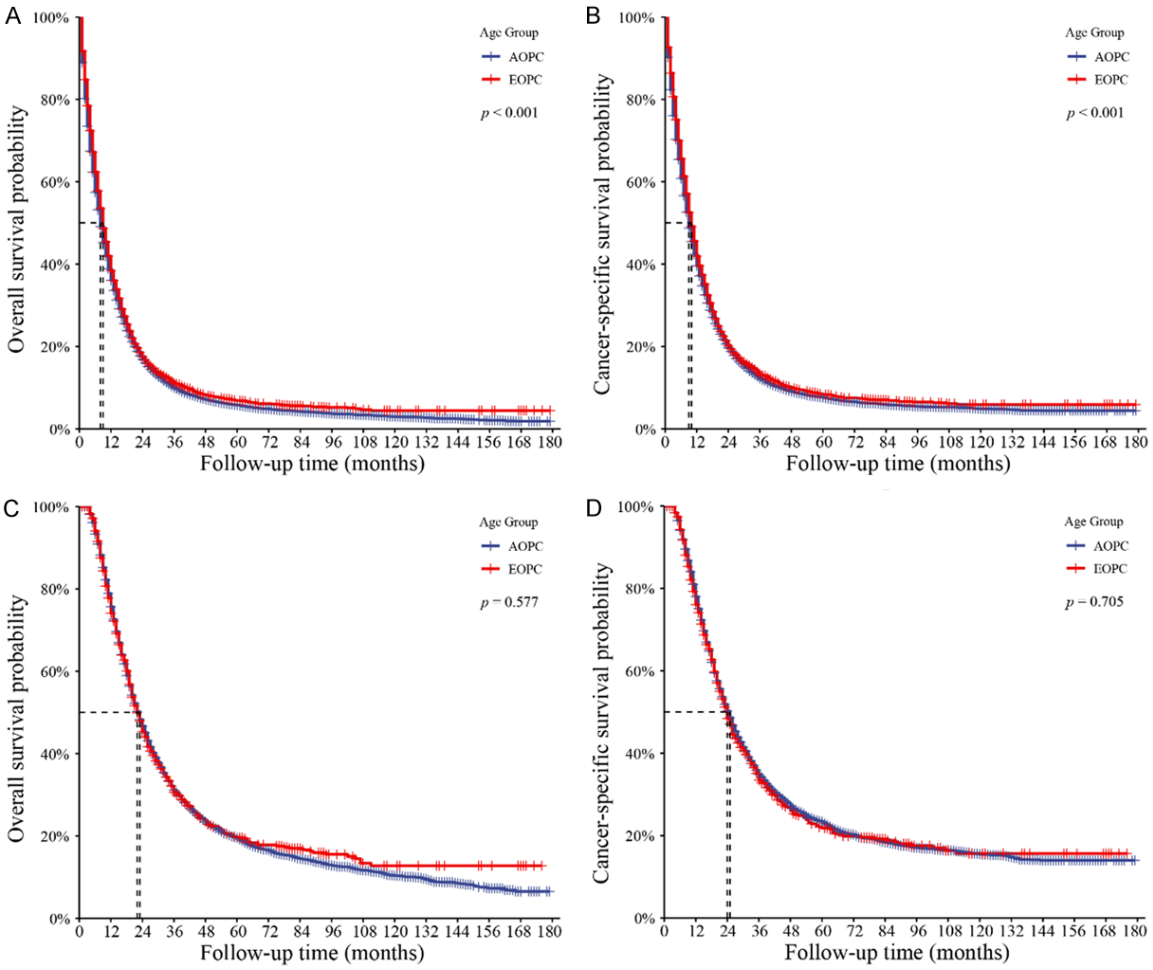

Figure S3. Comparison of overall survival (A) and cancer-specific survival (B) in the whole cohort and the surgery cohort (C, D) between patients with EOPC and patients with AOPC after SMRW.

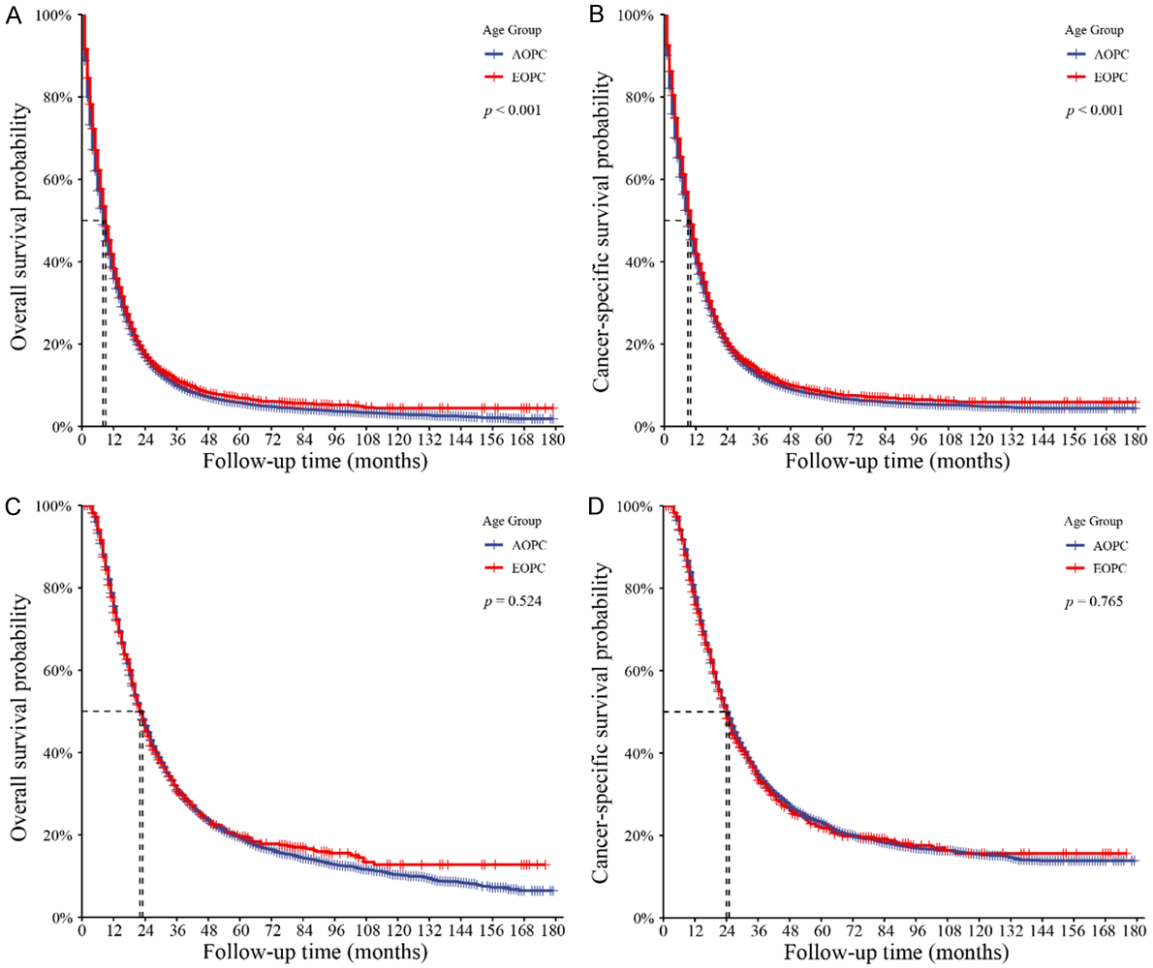

Figure S4. Comparison of overall survival (A) and cancer-specific survival (B) in the whole cohort and the surgery cohort (C, D) between patients with EOPC and patients with AOPC after OW.

Table S4. Comparison of OS and CSS between EOPC and AOPC patients in the surgery cohort

	PSM		*P*	IPTW		*P*	SMRW		*P*	OW		*P*
	EOPC	AOPC	Value	EOPC	AOPC	Value	EOPC	AOPC	Value	EOPC	AOPC	Value
OS			0.9			0.163			0.577			0.524
1 year	71.8%	73.2%		69.2%	69.7%		72.0%	73.2%		71.8%	73.0%	
3 year	29.7%	31.2%		28.8%	27.9%		29.7%	30.0%		29.6%	29.9%	
5 year	19.0%	19.4%		19.0%	17.5%		19.1%	18.8%		19.0%	18.7%	
median, months	22	22		21	20		22	22		22	22	
CSS			0.6			0.616			0.705			0.765
1 year	74.0%	75.5%		71.8%	72.8%		74.2%	75.9%		74.0%	75.7%	
3 year	32.4%	35.1%		31.7%	31.7%		32.6%	33.8%		32.5%	33.6%	
5 year	21.1%	23.2%		21.3%	21.2%		21.3%	22.6%		21.2%	22.5%	
median, months	23	24		23	22		23	24		23	24	

Abbreviation: PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMRW, standardized mortality ratio weighting; OW, overlap weighting.

Table S5. Systemic treatment administered stratified by age group in different clinical stage in the surgery cohort

Treatment Strategy	Age Group, years	AJCC Stage I			P_{trend}	AJCC Stage II			P_{trend}	AJCC Stage III			P_{trend}
		No. (%)		*P*		No. (%)		*P*		No. (%)		*P*	
Systemic treatment	All	2005 (71.1%)		< 0.001	< 0.001	2493 (78.1%)		< 0.001	< 0.001	3682 (76.4%)		< 0.001	< 0.001
	< 50	153 (86.0%)				198 (84.6%)				293 (88.3%)			
	50-59	440 (80.3%)	< 50 vs. 50-59	0.538*		606 (85.0%)	< 50 vs. 50-59	1*		847 (84.2%)	< 50 vs. 50-59	0.426*	
	60-69	759 (76.6%)	< 50 vs. 60-69	0.033*		958 (72.9%)	< 50 vs. 60-69	1*		1355 (71.1%)	< 50 vs. 60-69	0.012*	
	≥ 70	653 (59.1%)	< 50 vs. ≥ 70	< 0.001*		731 (67.0%)	< 50 vs. ≥ 70	< 0.001*		1187 (65.6%)	< 50 vs. ≥ 70	< 0.001*	
Neoadjuvant therapy	All	310 (11.0%)		0.001	0.021	263 (8.2%)		0.007	0.028	319 (6.6%)		0.018	0.002
	< 50	19 (10.7%)				19 (8.1%)				29 (8.7%)			
	50-59	66 (12.1%)	< 50 vs. 50-59	1*		66 (9.3%)	< 50 vs. 50-59	1*		79 (7.9%)	< 50 vs. 50-59	1*	
	60-69	134 (13.5%)	< 50 vs. 60-69	1*		113 (9.8%)	< 50 vs. 60-69	1*		115 (6.9%)	< 50 vs. 60-69	1*	
	≥ 70	91 (8.2%)	< 50 vs. ≥ 70	1*		65 (6.0%)	< 50 vs. ≥ 70	1*		96 (5.3%)	< 50 vs. ≥ 70	0.086*	
Adjuvant therapy	All	1467 (52.0%)		< 0.001	< 0.001	2004 (62.8%)		< 0.001	< 0.001	4817 (64.1%)		< 0.001	< 0.001
	< 50	111 (62.4%)				153 (65.4%)				241 (72.6%)			
	50-59	314 (57.3%)	< 50 vs. 50-59	1*		483 (67.7%)	< 50 vs. 50-59	1*		691 (68.7%)	< 50 vs. 50-59	1*	
	60-69	528 (55.3%)	< 50 vs. 60-69	0.151*		760 (65.8%)	< 50 vs. 60-69	1*		1130 (67.7%)	< 50 vs. 60-69	0.466*	
	≥ 70	514 (46.6%)	< 50 vs. ≥ 70	< 0.001*		608 (55.7%)	< 50 vs. ≥ 70	0.040*		1026 (56.7%)	< 50 vs. ≥ 70	< 0.001*	
Both therapy	All	228 (8.1%)		< 0.001	< 0.001	226 (7.1%)		0.007	< 0.001	275 (5.7%)		< 0.001	< 0.001
	< 50	23 (12.9%)				26 (11.1%)				23 (6.9%)			
	50-59	60 (10.9%)	< 50 vs. 50-59	1*		57 (8.0%)	< 50 vs. 50-59	0.858*		77 (7.7%)	< 50 vs. 50-59	1*	
	60-69	97 (9.8%)	< 50 vs. 60-69	1*		85 (7.4%)	< 50 vs. 60-69	0.322*		110 (6.6%)	< 50 vs. 60-69	1*	
	≥ 70	48 (4.3%)	< 50 vs. ≥ 70	< 0.001*		58 (5.3%)	< 50 vs. ≥ 70	0.006*		65 (3.6%)	< 50 vs. ≥ 70	0.030*	

P_{trend} from Cohran-Armitage trend test; * from Chi-squared test adjusted by Bonferroni methods.

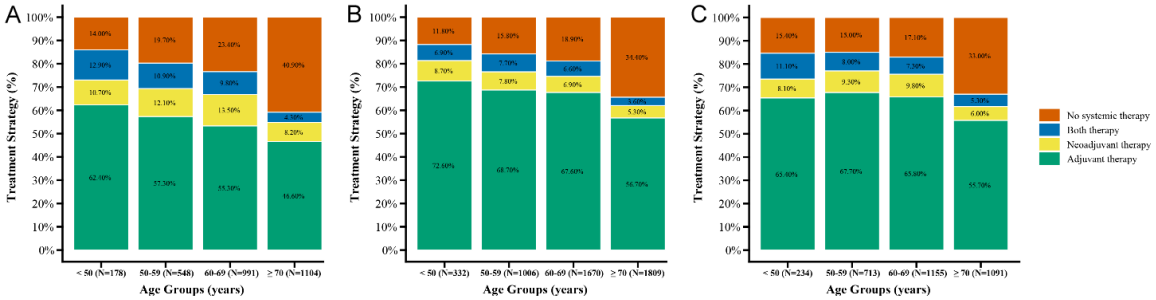

Figure S5. Systematic treatment distribution by age group among operated patients in Stage I (A), Stage II (B), and Stage III (C).

Table S6. Univariate and multivariate cox regression analyses of overall survival in the surgery cohort

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	*P*-Value	HR	(95% CI)	*P*-Value
Age Group			< 0.001			< 0.001
> 50	Ref	-		Ref	-	
50-59	0.962	0.871-1.062	0.439	0.937	0.849-1.035	0.2
60-69	1.032	0.940-1.134	0.508	1.021	0.929-1.121	0.671
≥70	1.241	1.130-1.362	0.022	1.179	1.073-1.295	0.001
Sex			0.1			
Male	Ref	-				
Female	0.963	0.921-1.007	0.1			
Race			0.082			
White	Ref	-				
Black	1.016	0.947-1.090	0.664			
Others	0.915	0.841-0.994	0.037			
Unknown	0.658	0.342-1.265	0.209			
Site			< 0.001			0.002
Head	Ref	-		Ref	-	
Body/Tail	0.862	0.809-0.919	< 0.001	0.889	0.832-0.949	< 0.001
Other	0.992	0.917-1.072	0.834	0.997	0.921-1.080	0.951
Tumor Differentiation			< 0.001			< 0.001
Well	Ref	-		Ref	-	
Moderate	1.428	1.310-1.558	< 0.001	1.375	1.244-1.480	< 0.001
Poor	1.830	1.674-2.000	< 0.001	1.698	1.552-1.857	< 0.001
Unknown	1.186	1.063-1.324	0.002	1.296	1.153-1.458	< 0.001
T stage			< 0.001			< 0.001
T1	Ref	-		Ref	-	
T2	1.530	1.429-1.638	< 0.001	1.313	1.20-1.436	< 0.001
T3	1.797	1.662-1.943	< 0.001	1.474	1.333-1.629	< 0.001
T4	1.956	1.754-2.182	< 0.001	1.935	1.601-2.339	< 0.001
Unknown	1.531	1.321-1.774	< 0.001	2.013	0.923-4.392	0.079
Vascular Invasion			< 0.001			< 0.001
None	Ref	-		Ref	-	
Vein	1.229	1.131-1.335	< 0.001	1.259	1.155-1.372	< 0.001
Artery	1.348	1.228-1.480	< 0.001	1.474	1.333-1.629	< 0.001
Unknown	1.026	0.889-1.184	0.724	0.585	0.368-0.931	0.024

N stage			< 0.001			< 0.001
N0	Ref	-		Ref	-	
N1	1.469	1.393-1.549	< 0.001	1.369	1.151-1.628	< 0.001
N2	1.937	1.824-2.057	< 0.001	1.596	1.299-1.960	< 0.001
Unknown	1.642	1.301-2.072	< 0.001	1.382	0.762-2.506	0.287
AJCC stage, 8th			< 0.001			0.004
IA	Ref	-		Ref		-
IB	1.528	1.371-1.703	< 0.001	1.223	1.063-1.409	0.005
IIA	1.912	1.679-2.178	< 0.001	1.394	1.183-1.643	< 0.001
IIB	2.147	1.942-2.374	< 0.001	1.267	1.024-1.569	0.029
III	2.803	2.803-2.530	< 0.001	1.404	1.102-1.788	0.006
Unknown	2.154	1.853-2.505	< 0.001	1.408	0.727-2.729	0.31
Systemic treatment			< 0.001			< 0.001
No	Ref	-		Ref	-	
Neoadjuvanat therapy	0.658	0.597-0.724	< 0.001	0.602	0.541-0.671	< 0.001
Adjuvant therapy	0.769	0.729-0.812	< 0.001	0.670	0.634-0.709	< 0.001
Both therapy	0.554	0.496-0.618	< 0.001	0.488	0.434-0.548	< 0.001

Table S7. Univariate and multivariate cox regression analyses of cancer-specific survival in the surgery cohort

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	P	HR	(95% CI)	P
Age Group			< 0.001			< 0.001
> 50	Ref	-		Ref	-	
50-59	0.950	0.857-1.053	0.327	0.925	0.834-1.025	0.138
60-69	1.001	0.907-1.104	0.988	0.989	0.896-1.090	0.818
≥70	1.153	1.046-1.272	0.004	1.100	0.997-1.214	0.058
Sex			0.206			
Male	Ref	-				
Female	0.970	0.925-1.017	0.206			
Race			0.012			
White	Ref	-				
Black	0.989	0.917-1.066	0.773			
Others	0.901	0.824-0.985	0.022			
Unknown	0.404	0.168-0.970	0.043			
Site			< 0.001			0.002
Head	Ref	-		Ref	-	
Body/Tail	0.850	0.794-0.910	< 0.001	0.886	1.826-0.951	< 0.001
Other	0.988	0.910-1.073	0.778	1.001	0.920-1.090	0.973
Tumor Differentiation			< 0.001			< 0.001
Well	Ref	-		Ref	-	
Moderate	1.475	1.344-1.620	< 0.001	1.394	1.269-1.531	< 0.001
Poor	1.931	1.755-2.125	< 0.001	1.777	1.614-1.957	< 0.001
Unknown	1.217	1.081-1.369	0.001	1.320	1.164-1.497	< 0.001
T stage			< 0.001			< 0.001
T1	Ref	-		Ref	-	
T2	1.618	1.502-1.743	< 0.001	1.351	1.228-1.486	< 0.001
T3	1.901	1.748-2.067	< 0.001	1.514	1.361-1.685	< 0.001
T4	2.055	1.829-2.309	< 0.001	1.933	1.581-2.363	< 0.001
Unknown	1.527	1.342-1.841	< 0.001	1.846	0.803-4.245	0.149

Vascular Invasion			< 0.001			< 0.001
None	Ref	-		Ref	-	
Vein	1.229	1.127-1.342	< 0.001	1.254	1.145-1.373	< 0.001
Artery	1.349	1.222-1.489	< 0.001	1.514	1.361-1.685	< 0.001
Unknown	1.013	0.870-1.180	0.867	0.651	0.390-1.087	0.101
N stage			< 0.001			< 0.001
N0	Ref	-		Ref	-	
N1	1.526	1.442-1.615	< 0.001	1.402	1.167-1.685	< 0.001
N2	2.036	1.910-2.169	< 0.001	1.610	1.295-2.002	< 0.001
Unknown	1.717	1.343-2.193	< 0.001	1.442	0.773-2.688	0.25
AJCC stage, 8th			< 0.001			0.002
IA	Ref	-		Ref		-
IB	1.651	1.464-1.861	< 0.001	1.273	1.092-1.485	0.002
IIA	2.065	1.791-2.382	< 0.001	1.451	1.214-1.733	< 0.001
IIB	2.378	2.128-2.658	< 0.001	1.319	1.049-1.657	0.018
III	3.133	2.798-3.509	< 0.001	1.500	1.158-1.943	0.002
Unknown	2.336	1.983-2.751	< 0.001	1.469	0.734-2.941	0.278
Systemic treatment			< 0.001			< 0.001
No	Ref	-		Ref	-	
Neoadjuvanat therapy	0.687	0.620-0.761	< 0.001	0.625	0.558-0.701	< 0.001
Adjuvant therapy	0.804	0.759-0.851	< 0.001	0.687	0.647-0.729	< 0.001
Both therapy	0.578	0.514-0.649	< 0.001	0.501	0.443-0.566	< 0.001