Elderly Pancreatic Adenocarcinoma Cancer Patients Could Benefit From Postoperative Chemotherapy

Bin Xu, MD,* Jinbo Shi, MD,† Wenjie Lu, MD,* Yulian Wu, PhD,* and Xin Dong, PhD*

Objectives: The study aim to investigate whether elderly patients with resectable pancreatic ductal adenocarcinoma (PDAC) could benefit from postoperative chemotherapy.

Methods: This study selects the data of PDAC patients who were diagnosed between 2004 and 2014 from the Surveillance, Epidemiology, and End Results program. Median overall survival (mOS) is determined by Kaplan-Meier survival curves. Multivariate logistic regression analysis and hazard ratio are employed to assess the association among potential prognostic factors. Propensity score matching evaluation is used to reduce bias.

Results: In total, there are 11,865 PDAC patients selected from the Surveillance, Epidemiology, and End Results database. Elderly PDAC patients have poor prognoses compared with younger (mOS, 15 vs 21 months). The possible reason might be that the elderly patients are less likely to receive postoperative chemotherapy. After propensity score matching, it is found that, for those who receive postoperative chemotherapy, although the mOS of older group is not as good as that of the younger group (mOS, 20 vs 23 months; 18-month survival rate: 53.4% vs 61.3%), the mOS of older group prolonged by postoperative chemotherapy is similar to that of younger group (9 vs 9 months).

Conclusions: Elderly PDAC patients (≥70 years) might benefit from the currently used postoperative chemotherapy regimens.

Key Words: resectable pancreatic ductal adenocarcinoma, postoperative chemotherapy, SEER, cancer survival

Although surgical techniques and systemic therapies for treating malignant tumors have made remarkable progress during the past decades, pancreatic ductal adenocarcinoma (PDAC) remains one of the most challenging malignant diseases to be overcome in the world.[1] Relevant studies have predicted that pancreatic cancer will become the second leading cause of cancer related death in the United States in the next 20 years. Approximately 85% of PDAC patients are in the position of either unresectable or metastatic when being diagnosed, and only 10% of them survived longer than 5 years in the United States. For those who have the opportunity to obtain surgical resection, the prognosis remains poor, with only 20% of the 5-year survival rate.[2,3] The poor prognosis of pancreatic cancer is still a major problem that plagues humans.

Compared with younger counterparts, older patients are more likely to suffer from pancreatic cancer.[4] The onset is most commonly observed from 60 to 80 years old.[5] Because of poor health status or comorbidities, elderly patients with PDAC generally have a worse prognostic survival than younger patients.[6] Even for the elderly patients who are in good physical condition and have few complications, factors, such as age and cancer-induced cachexia, might prevent them from receiving more active treatments.[6] What is more, whether elderly PDAC patients should receive postoperative chemotherapy has not been specifically mentioned in the latest National Comprehensive Cancer Network guidelines yet.[7] Clinicians usually use the Eastern Cooperative Oncology Group as standard to assess patients' physical conditions to determine whether postoperative chemotherapy is needed or not.[8–11] Generally speaking, the best postoperative treatment regimen for elderly PDAC patients remains controversial.

The Surveillance, Epidemiology, and End Results (SEER) program is a long-established and publicly-available resource that allows for population-based surveillance and analysis of all cancers in the United States,[12] and the statistical data is of large scale and good quality, which reveals the risk model and trend of tumor.[13] This study explores whether elderly patients with PDAC could benefit from the currently used postoperative chemotherapy regimens based on SEER.

MATERIALS AND METHODS

Ethics Statement

Patients from the SEER database had previously consented to participate in any scientific research worldwide. This clinical research was approved by the Institutional Review Board of The Second Affiliated Hospital of Zhejiang University School of Medicine.

Patients

The data of patients with PDAC was selected from the SEER (2004–2014) database. All cases in SEER are identified by the topographical code of "pancreas" (International Classification of Disease for Oncology, third edition) using SEER*Stat software (version 8.3.8, NCI, Bethesda, Md). The histology codes 8140/3 and 8500 were used to identify the specific patients with PDAC. Participants were uniformly restaged according to the eighth edition of the American Joint Committee on Cancer Staging Manual. After the following exclusions, a total of 11,856 PDAC patients who have no distal metastasis and underwent surgical resection were collected for further analysis. Follow-up time ranged from 0 to 81 months. The principles for inclusion are as follows: (1) 18 years or older; (2) PDAC as the first malignant tumor with histology diagnosis; (3) without distant metastasis at the time when diagnosed; (4) received surgical resection; (5) specific number

TABLE 1. Log-Rank Tests for OS of All Nonmetastatic Operated PDAC Patients (n = 11,856)

Characteristics	No. Patients	mOS, mo	18-Month Survival Rate, %	P
Overall	11,856	19.0	51.1	
Age, y				<0.01
<50	743	21.0	56.0	
50–59	2280	22.0	57.5	
60–69	3921	20.0	53.4	
70–79	3680	17.0	46.5	
≥80	1232	15.0	42.9	
Race				0.22
White	9772	19.0	51.3	
Black	1186	18.0	47.9	
Other	898	20.0	53.3	
Sex				<0.01
Male	5955	18.0	49.8	
Female	5901	20.0	52.4	
Insurance status				<0.01
Insured or any Medicaid	9197	20.0	52.4	
Uninsured	201	20.0	54.3	
Unknown	2458	17.0	45.9	
Marital status				<0.01
Married	7472	20.0	52.5	
Divorced/widowed	4384	18.0	48.7	
Tumor site				<0.01
Head of pancreas	8901	19.0	51.0	
Body of pancreas	788	21.0	55.2	
Tail of pancreas	1074	19.0	50.5	
Other	1093	18.0	49.1	
Grade				<0.01
Well-differentiated	1133	27.0	64.8	
Moderately differentiated	5889	21.0	55.2	
Poorly or undifferentiated	4167	15.0	40.3	
Unknown	667	24.0	59.3	
Stage				<0.01
IA	954	38.0	73.5	
IB	2209	26.0	61.8	
IIA	784	18.0	49.7	
IIB	4678	18.0	49.3	
III	3231	15.0	40.0	
Chemotherapy				<0.01
No chemotherapy	3798	11.0	35.0	
Yes	8058	22.0	58.6	
Radiotherapy				<0.01
No radiotherapy	7442	17.0	46.4	
Yes, postoperative	3934	22.0	58.9	
Yes, preoperative	480	24.0	59.9	

OS, overall survival.

of positive regional lymph nodes; (6) specific size of tumor; (7) specific information about whether received chemotherapy or not; (8) died of PDAC or still alive.

Definition of Variables

Demographic characteristics include age, sex, race, insurance status, marital status at diagnosis. Age is treated as an ordinal variable: young (<50, 50–59, 60–69 years) and elderly (70–79, ≥80 years). Race is classified as White, Black, and others (including Asian/Pacific Islander and others). Insurance status is categorized as uninsured, insured, or Medicaid and unknown. Insured or Medicaid patients have lower financial burden, therefore they are able to get timely treatment, which might lead to a better survival.[14] Marital status is classified as married, unmarried or widowed. Compared with those who are unmarried, married patients could receive more support from their partners and might have a healthier lifestyle, which could impact the survival.[15,16]

TABLE 2. Multivariate Analysis for OS of All Patients
(n = 11,856)

Characteristics	HR (95% CI)	P
Age, y		
<50	Reference	
50–59	0.927 (0.845–1.016)	0.105
60–69	1.039 (0.953–1.134)	0.384
70–79	1.190 (1.091–1.299)	<0.001
≥80	1.206 (1.089–1.334)	<0.001
Sex		
Male	Reference	
Female	0.893 (0.858–0.93)	<0.001
Insurance status		
Insured or any Medicaid	Reference	
Uninsured	0.925 (0.784–1.090)	0.351
Unknown	1.126 (1.073–1.182)	<0.001
Marital status		
Married	Reference	
Divorced/widowed	1.077 (1.032–1.123)	0.001
Tumor site		
Head of pancreas	Reference	
Body of pancreas	0.971 (0.894–1.055)	0.488
Tail of pancreas	0.984 (0.916–1.056)	0.647
Other	0.988 (0.922–1.060)	0.739
Grade		
Well-differentiated	Reference	
Moderately differentiated	1.291 (1.199–1.390)	<0.001
Poorly or undifferentiated	1.706 (1.582–1.841)	<0.001
Unknown	1.288 (1.152–1.439)	<0.001
Stage		
IA	Reference	
IB	1.540 (1.402–1.691)	<0.001
IIA	1.929 (1.724–2.158)	<0.001
IIB	2.320 (2.127–2.530)	<0.001
III	3.058 (2.796–3.345)	<0.001
Chemotherapy		
No chemotherapy	Reference	
Yes	0.585 (0.558–0.614)	<0.001
Radiotherapy		
No radiotherapy	Reference	
Yes, postoperative	0.912 (0.869–0.956)	<0.001
Yes, preoperative	0.918 (0.825–1.023)	0.121

CI indicates confidence interval.

Tumor characteristics include the position of tumor (located at head, body, or tail of pancreas), differentiation grade and American Joint Committee on Cancer stage. Treatment characteristics include chemotherapy and radiotherapy.

Statistical Analysis

All data are analyzed by IBM (Armonk, NY) SPSS 26.0 software. Frequency of demographic and clinic categorical variables is calculated. An 18-month survival rate and median overall survival (mOS) months are estimated by log-rank tests. Multivariate analysis is performed by means of cox-regression to calculate hazard ratios (HRs) and 95% confidence interval so as to find independent prognostic factors. The oncological outcomes of different ages are analyzed by propensity score matching (PSM) analysis. Here, $P < 0.05$ is considered statistically significant.

RESULTS

Clinical Features and Univariate Analysis Calculated by Log-Rank Test

In this study, there are 11,856 PDAC and pancreatic adenocarcinoma patients (all received surgical resection) gathered from SEER. After the log-rank tests, it is found that age, sex, insurance status, marital status, tumor position, differentiation grade, stage, chemotherapy, radiotherapy are prognostic factors (Table 1). As for age, elderly patients (≥70 years) have an evidently worse prognosis. Apparent drop of mOS and 18-month survival rate for elderly patients are observed when compared with the younger (mOS: 15–17 vs 20–22 months; 18-month survival rate: 42.9%–46.5% vs 53.4%–57.5%; $P < 0.01$). Details of other clinical features and results of log-rank tests are also shown in Table 1.

Multivariate OS Cox Regression Analysis

The statistically significant parameters in log-rank tests are further analyzed in the Cox regression. As shown in Table 2, the results of multivariate Cox regression analysis prove that age, marital status, differentiation grade, stage, chemotherapy, radiotherapy are significantly associated with mOS in PDAC patients ($P < 0.05$) and are independent factors affecting the mOS of PDAC patients. Older PDAC patients have higher HRs than younger patients.

No Chemotherapy Rates of PDAC Patients Among Different Ages

The PDAC patients are divided into five groups by age and the no chemotherapy rates of different groups are computed. We discover that the no chemotherapy rates continue to rise by the age (from 19.0% to 60.5%). In addition, the 18-month survival rates got worse (from 56.0% to 42.9%). The results are presented in Table 3 and Figure 1. Overall, according to Table 2 and Table 3, the survival of the first 3 age groups (<50, 50–59, 60–69 years) are similar. Thus, in the further analysis, the first 3 age groups are merged into one group (age, <70 years).

mOS of PDAC Patients Among Different Age Groups Treated With or Without Chemotherapy Before PSM

According to the results in the previous section, a question arises. Do the lower chemotherapy rates among elderly PDAC patients lead to worse overall survival? To solve this question, a subgroup analysis is designed. As shown in Table 4 and Figure 2, PDAC patients are divided into three groups according to their

TABLE 3. No Chemotherapy Rates and Postoperative Survival Rates in Different Ages

Age, y	No Chemotherapy Rate, %	18-mo Survival Rate, %	mOs, mo
<50	19.10	56.00	21.0
50–59	21.40	57.50	22.0
60–69	26.00	53.40	20.0
70–79	38.20	46.50	17.0
≥80	60.50	42.90	15.0
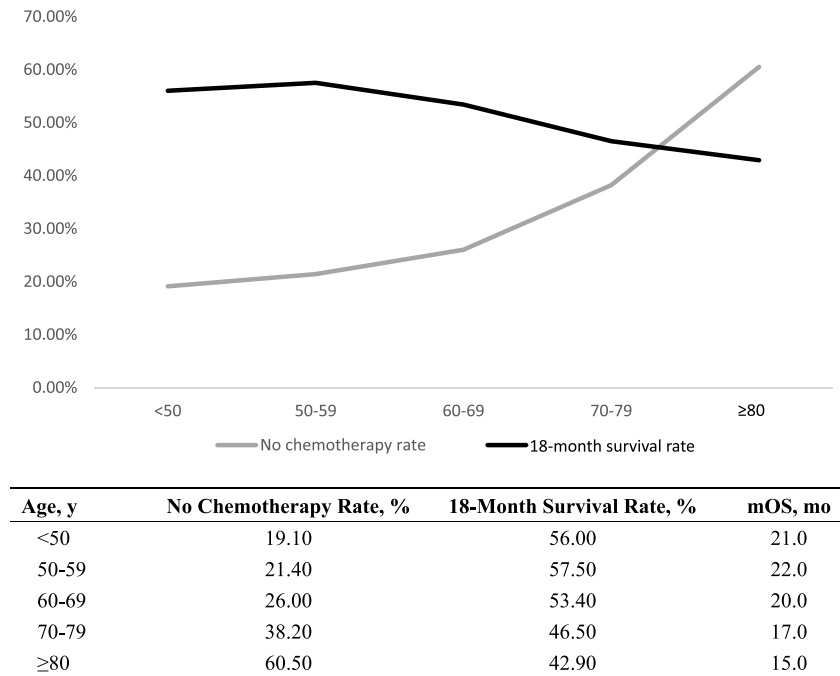
FIGURE 1. No chemotherapy rates and postoperation survival rates in different ages.

Age, y	No Chemotherapy Rate, %	18-Month Survival Rate, %	mOS, mo
<50	19.10	56.00	21.0
50-59	21.40	57.50	22.0
60-69	26.00	53.40	20.0
70-79	38.20	46.50	17.0
≥80	60.50	42.90	15.0

ages (<70, 70–79, ≥80 years). Compared with younger patients, although the elderly patients have worse survival whether they received postoperative chemotherapy or not (chemotherapy: mOS, 23.0, 21.0, 20.0 months, respectively, $P < 0.01$; no chemotherapy: mOS: 13.0, 10.0, 11.0 months, respectively, $P < 0.01$), the mOS improved by chemotherapy are almost the same (10.0, 11.0, 9.0 months, respectively). In other words, postoperative chemotherapy can improve the survival for PDAC patients regardless of age differences. The results in Figure 3 also demonstrate this point.

Intergroup Differences of All Independent Prognosis Factors Among Age Groups

The previous analysis has preliminarily shown that older patients could benefit from postoperative chemotherapy, but some other factors still need to be considered. In other words, the intergroup differences of other independent prognosis factors are neglected. Thus, the intergroup differences of all independent

prognosis factors among age groups should be calculated (Table 5). It is found that the rates of divorced and widowed have an obvious increase with age (from 34.9% to 47.2%, $P < 0.01$). Similar results could be observed in the no-radiotherapy rate (from 56.0% to 82.3%, $P < 0.01$). These intergroup differences may affect the accuracy of the conclusion, so a further PSM analysis is carried out to reduce these biases.

mOS of PDAC Patients Among Different Age Groups Treated With or Without Chemotherapy After PSM

The PDAC patients younger than 70 years are set as cohort 1, 70 to 79 years old as cohort 2, and older than 80 years as cohort 3. The PSM evaluation is performed between cohort 1 and cohort 2 (2275 pairs), cohort 1 and cohort 3 (487 pairs), respectively. After PSM, compared with the younger group, the elderly patients aged 70 to 79 years have a worse survival whether they received postoperative chemotherapy or not (chemotherapy: mOS, 21.0 vs 25.0 months; 18 months survival rate: 55.4% vs 63.2%, respectively, $P < 0.01$ and no chemotherapy: mOS: 10.0 vs 13.0 months; 18-month survival rate: 31.9% vs 37.0%; respectively, $P < 0.01$). However, the mOS prolonged by chemotherapy are virtually the same (12.0 vs 11.0 months). Similar results could be observed between cohort 1 (age, <70 years) and cohort 3 (age, ≥80 years) (Table 6, Figs. 4 and 5).

DISCUSSION

Pancreatic cancer, with a 5-year survival rate of 7.2%, is considered one of the most deadly cancers in China's cancer registry.[17] At the time of diagnosis, less than 20% of PDAC patients have the opportunity to receive radical operation. Also, more than 60% of the patients suffer from tumor recurrence after surgery.[2,3] Therefore, to prolong postoperative survival, perioperative chemotherapy is of vital importance for PDAC patients. As the National Comprehensive Cancer Network guideline proposes, postoperative chemotherapy is regarded as the main adjuvant treatment modality for PDAC patients.[7]
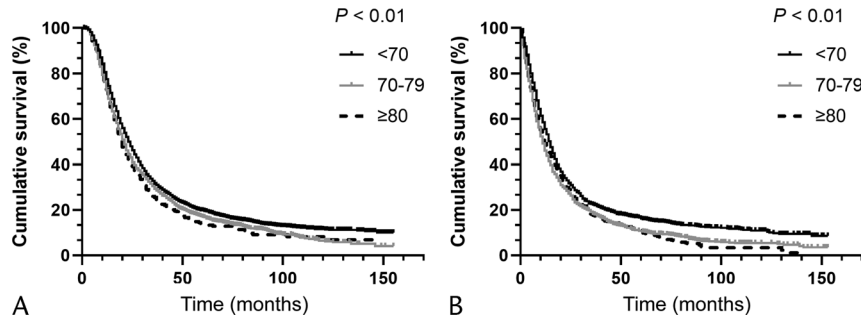
TABLE 4. mOS and 18-Month Survival Rates of PDAC Patients Treated With or Without Chemotherapy Before PSM

Treatment	Age Group			P
	<70 y	70–79 y	≥80 y	
Treated with chemotherapy				<0.01
No. patients	5296	2275	487	
mOS, mo	23.0	21.0	20.0	
18-mo survival rate, %	60.50	55.40	53.40	
No chemotherapy				<0.01
No. patients	1648	1405	745	
mOS, mo	13.0	10.0	11.0	
18-mo survival rate, %	37.30	31.90	36.00	
mOS increased, mo	10.0	11.0	9.0	

FIGURE 2. A, OS analysis for PDAC patients who received chemotherapy before PSM. B, OS analysis for PDAC patients who did not receive chemotherapy before PSM.

Because of its features, such as rapid progression and late detection, pancreatic cancer frequently assaults the elderly.[18] Because of the high morbidity of the elderly, the number of elderly PDAC patients will continue to increase with the aging trend of the population. Dr. Smith and his fellows[19] concluded that approximately 70% of PDAC patients will have been diagnosed in older adults by 2030. Despite recent advances in PDAC therapy, PDAC is still a challenge for aged patients. The reason might be the lack of information about the safety and efficiency of chemotherapy in recent clinical trials in which few elderly patients participated.[6] Clinicians usually use Eastern Cooperative Oncology Group standards to assess a patient's competence to decide whether or not postoperative chemotherapy is needed.[8–11] However, it is still not clear whether elderly patients can benefit from it. Therefore, it is difficult to locate a balance between appropriate age and the adjuvant postoperative chemotherapy for elderly PDAC patients.

In this study, it is identified that age, marital status, differentiation grade, stage, chemotherapy, and radiotherapy are independent prognostic factors for PDAC patients. Elderly patients have a conspicuously poor prognosis after surgical resection when compared with the younger patients (mOS, 15.0–17.0 vs 20.0–22.0 months, respectively). Further subgroup analysis reveals that, with age, the rate of divorce has an evident increase (from 34.9% to 47.2%, $P < 0.01$). Separated patients may receive less support from their families and have unhealthy lifestyles, which may affect their survival. Similar results could be observed in the no chemotherapy rate and the no-radiotherapy rate (from 19.1% to 60.5%, $P < 0.01$; from 56.0% to 82.3%, $P < 0.01$; respectively). All of the factors mentioned above can lead to poor prognosis in elderly PDAC patients. Therefore, whether the low rate of postoperative chemotherapy is responsible for the poor prognosis of elderly

PDAC patients is still contentious. Hence, a PSM analysis is carried out to reduce the biases of marital status and radiotherapy. After that, a subgroup analysis reveals that elderly patients have relatively poor prognosis, but the prolongation of postoperative survival months in elderly patients who received postoperative chemotherapy is similar to younger patients. This means that older PDAC patients could benefit from postoperative chemotherapy.

The results of some clinical trials also support this conclusion. The CONKO-001 clinical trial confirmed that gemcitabine could improve OS compared with surgery alone for resectable PDAC patients.[20] The JASPAC-01 trial showed the superiority of the fluoropyrimidine prodrug S1 over gemcitabine in the Asian population.[21] The ESPAC-4 trials indicated that the gemcitabine plus capecitabine may offer more survival benefits when compared with single gemcitabine regimen (median OS, 28 vs 25.5 months).[22] In those studies, PDAC patients older than 65 years have similar survival when compared with younger patients, but no detailed information for elderly patients (age, >80 years) was provided.

Although elderly PDAC patients could benefit from postoperative chemotherapy, the low chemotherapy rate leads to poor overall survival. What factors lead to a lower rate of postoperative chemotherapy in elderly PDAC patients? First, aged patients have a higher rate of getting postoperative complications. Chen et al[23] showed in their retrospective analysis that elderly patients had more severe postoperative complications after pancreatic resection. They found that aging is an independent risk factor for severe postoperative complications after pancreatic resection. Merkow et al[24] revealed that postoperative complications are associated with adjuvant chemotherapy omission and treatment delays. Another study also showed that avoiding postoperative complications after
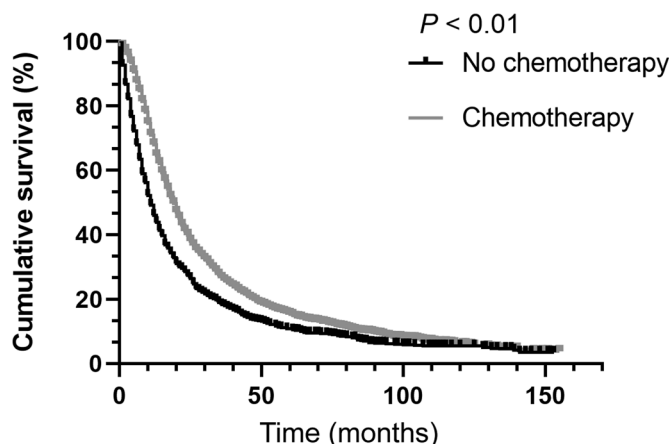

FIGURE 3. OS Analysis for elderly PDAC patients (≥70 years).

TABLE 5. Differences in Number of Patients in Different Age Groups Before PSM

Characteristics	Age Group, n (%)			Overall, n (%)	P
	<70 y	70–79 y	≥80 y		
Marital status					<0.01
Married	4519 (65.1)	2302 (62.6)	651 (52.8)	7472 (63.0)	
Divorced/widowed	2425 (34.9)	1378 (37.4)	581 (47.2)	4384 (37.0)	
Grade					
Well-differentiated	644 (9.3)	360 (9.8)	129 (10.5)	1133 (9.6)	
Moderately differentiated	3474 (50.0)	1819 (49.4)	596 (48.4)	5889 (49.7)	
Poorly or undifferentiated	2394 (34.5)	1310 (35.6)	463 (37.6)	4167 (35.1)	
Unknown	432 (6.2)	191 (5.2)	44 (3.6)	667 (5.6)	
Stage					
IA	557 (8.0)	283 (7.7)	114 (9.3)	954 (8.0)	
IB	1207 (17.4)	758 (20.6)	244 (19.8)	2209 (18.6)	
IIA	451 (6.5)	244 (6.6)	89 (7.2)	784 (6.6)	
IIB	2742 (39.5)	1426 (38.8)	510 (41.4)	4678 (39.5)	
III	1987 (28.6)	969 (26.3)	275 (22.3)	3231 (27.3)	
Chemotherapy					<0.01
No chemotherapy	1648 (23.7)	1405 (38.2)	745 (60.5)	3798 (32.0)	
Yes	5296 (76.3)	2275 (61.8)	487 (39.5)	8058 (68.0)	
Radiotherapy					<0.01
No radiotherapy	3886 (56.0)	2542 (69.1)	1014 (82.3)	7442 (62.8)	
Yes, postoperative	2705 (39.0)	1025 (27.9)	204 (16.6)	3934 (33.2)	
Yes, preoperative	353 (5.1)	113 (3.1)	14 (1.1)	480 (4.0)	

pancreatectomy can contribute to the long-term survival of PDAC patients after pancreatectomy.[25] Second, the physical conditions of elderly patients may be relatively poor. Weight loss and changes in body composition are common in PDAC patients, especially in the elderly.[26] A Japanese retrospective study demonstrated that low body mass index was associated with an increased risk of death (normal weight: HR, 0.58; $P = 0.038$; overweight/obese: HR, 0.54; $P = 0.059$) in Japanese PDAC patients who received surgical resection.[27] Another study also demonstrated that aging is a risk factor for increased toxicity and decreased tolerance to chemotherapy because of poor physical conditions.[28] Third, because of conservative attitudes, older PDAC patients themselves tend to refuse postoperative chemotherapy. This study indicates that elderly PDAC patients do benefit from postoperative chemotherapy, which makes chemotherapy a reasonable option for elderly PDAC patients.

The highlights of this research are follows. First, 11,856 PDAC participants are selected from SEER between the years of 2004 to 2014. With such a large number of samples, the accuracy and reliability of the results can be guaranteed. Second, the relationship between age and chemotherapy is systematically analyzed. It has been shown that elderly PDAC patients might benefit from postoperative chemotherapy, which provides reference basis for postoperative adjuvant treatments for elderly PDAC patients.

However, there are some inevitable limitations. Although the data from SEER has an overwhelming advantage in quantity, the details of surgical margins, radiation dose, chemotherapy regimens, and chemotherapy sequence are not recorded. In addition, SEER lacks some key clinical information such as carbohydrate antigen 19–9 levels and body mass index, which might be vital for prognostic analysis.[29,30] What is more, PSM analysis cannot balance unobservable confounding factors, and therefore residual

TABLE 6. mOS and 18-Month Survival Rates of PDAC Patients Treated With or Without Chemotherapy After PSM

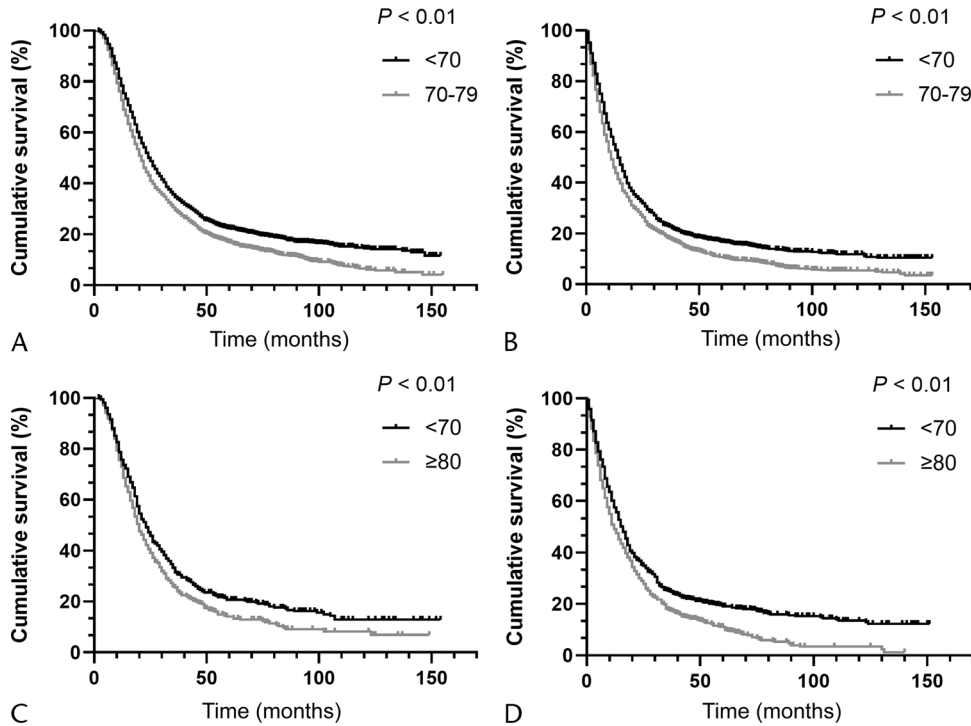|	Age Group			Age Group		
	<70 y	70–79, y	P	<70 y	≥80 y	P
Chemotherapy						<0.01
No. patients	2275	2275		487	487	
mOS, mo	25	21	<0.01	23	20	
18-mo survival rate, %	63.20	55.40		61.30	53.40	
No chemotherapy						<0.01
No. patients	1405	1405		745	745	
mOS, mo	13	10	<0.01	14	11	
18-month survival rate, %	37.00	31.90		40.30	36.00	
mOS increased, mo	12	11		9	9	

FIGURE 4. A, OS analysis for PDAC patients (age, <70 vs 70–79 years) who received chemotherapy after PSM. B, OS analysis for PDAC patients (age, <70 vs 70–79 years) who did not receive chemotherapy after PSM. C, OS analysis for PDAC patients (age, <70 vs ≥80 years) who received chemotherapy after PSM. D, OS analysis for PDAC patients (age, <70 vs ≥80 years) who did not receive chemotherapy after PSM.
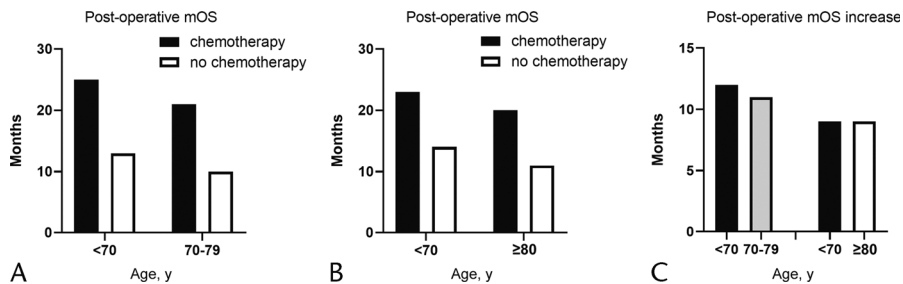
FIGURE 5. A, Postoperation mOS for PDAC patients (age, <70 vs 70–79 years). B, Postoperation mOS for PDAC patients (age, <70 vs ≥80 years). C, Postoperation mOS increased by chemotherapy (the first and second columns in panel C are from OS analysis after the first PSM, as shown in panel A. The third and fourth columns in panel C are from OS analysis after the second PSM, as shown in panel B).

deviation still exists. Finally, because of the lack of detailed chemotherapy information, the effects of specific chemotherapy regimens on the survival of elderly PDAC patients cannot be analyzed. More prospective studies are required for further exploration and verification in the future.

CONCLUSION

Elderly PDAC patients (≥70 years) could benefit from the currently used postoperative chemotherapy regimens. More prospective studies are required to verify the conclusion of this study.

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