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Long-Term Effect of Pancreaticoduodenectomy Combined with Revascularization for Resectable Pancreatic Carcinoma in Elderly Patients

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Background: Pancreaticoduodenectomy combined with revascularization (PDR) is the main surgical procedure for resectable pancreatic ductal adenocarcinoma (PDAC) with venous system invasion, but this procedure is discouraged in elderly patients because of physical complexity. Our aim was to explore the differences of perioperative and survival in patients of different ages who underwent PDR.

Material/Methods: We reviewed data from PDAC patients undergoing PDR from 2007 to 2018. Patients were subdivided into 3 groups according to age: <60 years, 60-70 years, and ≥70 years. Postoperative complications and long-term survival were compared among the 3 groups.

Results: From 626 patients, 185 had en bloc venous resection who underwent PDR (103, 55, and 27 patients from young to elderly). Increasing age was linked to a higher prevalence of ICU management (P=0.035) and more serious complications (grade ≥III, P=0.043); overall mortality was 8.1% and did not significantly differ among age-matched groups. Further, there was no difference in overall survival (OS) or progression-free survival (PFS) based on age (<60, 60-70, ≥70, median OS were 9.7, 8.4 vs 9.1 months, respectively, P=0.787; median PFS were 6.9, 6.1 vs 8.4 months, respectively, P=0.603). However, patients <60 years whose tumors invaded the superior mesenteric vascular had better survival outcomes when compared with the other 2 groups (11.5 vs 8.4, 9.1 months, P=0.049).

Conclusions: The results show that age should not be considered an absolute contraindication for PDR, as elderly patients can achieve the same surgical efficacy and long-term survival prognosis.

Keywords: Pancreatic Adenocarcinoma • Revascularization • The Elderly • Complications • Survival Prognosis

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Background

Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease that is predicted to become the second leading cause of cancer-related death in the United States by 2030, and the 5-year survival rate remains low, at 0-10.8% [1]. The Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review states that pancreatic carcinoma is predominantly a disease of the older population, rarely occurring before the age of 40 years [2]. Indeed, the risk of developing pancreatic cancer has been shown to increase with age, with the highest peak occurring between 60 and 80 years of age [3]. In China, both the incidence (ASR: 5.02/105 in 2017) and mortality (ASR: 5.67/105 in 2017) of pancreatic cancer were the highest in the population aged 85-90 years [4]. Therefore, age should not be ignored in the diagnosis and treatment of pancreatic cancer.

Major pancreatic surgery for PDAC is justified in elderly patients [5]. Previous studies have shown that a higher rate of preoperative comorbidities in elderly patients (>75 years) tended to increase the rate of nonsurgical postoperative complications (P=0.002). However, surgical complications and tumor-specific survival were not found to differ between the elderly and the younger patients with pancreaticoduodenectomy (PD) for PDAC of the pancreatic head [6]. Despite the perception that surgical resection is the only known potentially curative treatment, less than 20% of patients are candidates for resection owing to the high incidence of distant metastases or loco-regional spread at the time of diagnosis [7,8]. In addition, more disheartenigly, a limited subset of patients have different degrees of invasion of the portal vein (PV) and/or superior mesenteric vascular (SMV), including bilateral narrowing or occlusion. Typically, pancreaticoduodenectomy combined with revascularization (PDR) surgery is the universally accepted priority for clinically resectable PDAC. As the population is aging rapidly, it is likely that more elderly patients with PDAC with regional vascular invasion will be diagnosed.

Nevertheless, there are few reports on the influence of age over 60 years on the safety and survival benefits of PDAC after PDR. This highlights the need for both multidisciplinary treatments for patients of an advanced age as well as suitable approaches for stratifying patients according to the most effective treatment regimen. Due to the perceived frailty of elderly individuals, we retrospectively compared the outcomes of the late elderly (≥70), young elderly (60-70) and younger (<60) patients who had undergone PDR for PDAC at our medical center during the past 12 years to determine whether it is safe, feasible, and worthwhile for the elderly patient population.

Material and Methods

Study Design

This was a retrospective review of all consecutive patients with PDAC who had undergone curative PDR at our medical center between January 1, 2007, and October 31, 2018. Preoperative, intraoperative, and postoperative data are continuously documented for intra- and extra-clinical benchmarking. The series of patients was divided into 3 groups according age: group A, <60 years; group B, 60-70 years; and group C, ≥70 years. None of the patients had received radiotherapy or chemotherapy before surgery. The inclusion criteria were assessed for resectable pancreatic head adenocarcinoma by the surgery and radiological specialist according to the National Comprehensive Cancer Network (NCCN) definitions and no other concomitant cancer. Patients with pancreatic body/tail tumors, periampullary carcinoma, cholangiocarcinoma, duodenal adenocarcinoma, neuroendocrine tumors, or other histology were excluded. This study was approved and supervised by the Ethics Committee of Southwest Hospital, Third Military Medical University, Chongqing, China.

Data Acquisition

All patients who underwent contrast-enhanced CT and/or MRI were performed on an individual basis preoperatively, and then en bloc resection of PDR with associated lymphadenectomies was performed by experienced pancreatic surgeons. Clinical data were extracted from the medical records, including preoperative examination data (epidemiological information and laboratory values, as shown in **Table 1**) [9], intraoperative features (location of vascular invasion, modes of reconstruction, duration of operation, and blood loss, as shown in **Table 2**), and postoperative complications (pancreatic fistula [10], biliary fistula, delayed gastric emptying [11] and others [12]). Furthermore, we focused on the resection margin status, lymph node status, presence of perineural invasion and vascular infiltration, extent of distant metastasis, and degree of differentiation in the histopathologic analysis, and then these patients were staged according to the 8th edition of the American Joint Committee on Cancer [13].

The preoperative CT/MRI imaging examinations and the features observed during intraoperative exploration were the determining factors for the selection of segmental vascular resection. Reconstruction of PV, SMV, or confluence of PV-SMV included primary closure, end-to-end anastomosis, and an interposition graft dictated by anatomical necessity. Vital status was collected based on the last follow-up visit or telephone consultation, and the follow-up period ended in May 2021.

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Statistical Analysis

Statistical analysis was performed using univariate analysis in combination with multivariate analysis. Categorical variables are presented as percentages and were compared using the chi-squared test. Continuous variables are presented as medians (ranges) and were analyzed using the one-way ANOVA or Kruskal-Wallis test according to normally distributed or non-normally distributed data. OS of those who had PDR was estimated by Kaplan-Meier survival curves and compared using the log-rank test. Multivariable analyses used Cox proportional hazards regression models. All statistical tests were two-tailed, and $P<0.05$ was considered statistically significant. Data analyses were performed using SPSS software version 22.0 (IBM, Armonk, New York, USA), and survival curves were generated using GraphPad Prism software version 8.0 (San Diego, USA).

Results

Population Characteristics

Over the past 12 years, a total of 626 patients with pancreatic head adenocarcinomas have undergone open pancreaticoduodenectomy at our center, and 185 patients (29.6%) who underwent en bloc PDR and best supportive care were included in this study. The median age was 58 years (interquartile range, IQR 33-80): 103 patients (55.7%, median 50, IQR 33-59) were <60 years, 55 patients (30%, median 63, IQR 60-69) were between 60 and 70 years, and 27 patients (14.6%, median 71, IQR 70-80) were aged ≥70 years. **Table 1** outlines the demographic and clinical presentations of the 3 groups. Among them, there were statistically significant differences in NRS 2002 score, ASA classification, and concomitant comorbidity, which is reflected in a higher NRS 2002 score and ASA stage and the presence of previous hypertension, coronary artery disease, and COPD in the elderly patients (group C). However, tobacco and alcohol use, history of abdominal surgery, preoperative jaundice and biliary drainage, and preoperative laboratory values were not significantly different among the 3 groups.

Perioperative Hospitalization and Pathologic Diagnosis

The type of PD includes the classic Whipple procedure or PPPD combined with vein resection and reconstruction. The surgical outcomes of the different age groups are shown in **Table 2**. The intraoperative values of multiple parameters, such as vascular invasion site, types of venous reconstruction, ligation of splenic vein, combined organ resection, operation duration, blood loss, transfusion and postoperative hospital stay, did not increase with age. Additionally, comparing group A with group B (41.7% and 40%, respectively), tumor invasion into the SMV was more commonly observed in elderly patients (group C: aged ≥70 years, 51.9%). Regardless of the site of vascular invasion, the most common form of vascular reconstruction used during surgery was end-to-end anastomosis, which was performed in 51 patients (49.5%) who were <60 years (group A), 30 patients (54.5%) who were between 60 and 70 years (group B), and 70 patients (74.1%) who were ≥70 years (group C). However, elderly patients were more likely to require intensive care unit (ICU) management ($P=0.035$, **Table 2**).

All the enrolled patients in this study had a proven histological diagnosis of pancreatic head ductal adenocarcinoma. Statistical analysis of 185 patients revealed that there was no difference among the 3 age groups in terms of tumor size, differentiation, pathological invasion of PV-SMV, neurological invasion, resection margin, or TNM staging (**Table 2**).

Postoperative Complications

A total of 114 patients (61.6%) experienced postoperative complications of different grades, of whom 15 patients (8.1%) died within 90 days; namely, 6 patients (5.8%) in group A, 4 patients (7.3%) in group B and 5 patients (18.5%) in group C, with no significant difference observed among the groups. With regard to surgery-related death, the top 2 most common causes were intra-abdominal hemorrhage (9, 60%) and pulmonary infection (5, 35.7%).

Surgery-related overall complications were similar across all 3 age groups according to the Clavien-Dindo classification (61.2%, 61.8%, and 63%, respectively), but more serious complications (grade ≥III) occurred mainly in the late elderly group (≥70 years, 33.3%) than in the other groups (12.6% and 12.7%, $P=0.043$), and these results may be related to the incidence of postoperative organ dysfunction and pulmonary infection in the late elderly group. However, the rates of relevant postoperative grade V complications were similar in different age groups. Further subdivision of the patients based on the type of complication (pancreatic fistula, non-pancreatic anastomotic leakage, lymphatic leakage, DGE, hemorrhage, blood transfusion for non-hemorrhagic anaemia, thoracic or abdominal puncture and drainage, thoracic or abdominal puncture and drainage, intraperitoneal infection, and re-laparotomy) revealed that there were no significant differences across the different age groups. In addition, we noted a statistically significant difference in the rate of pulmonary infection ($P=0.002$) but not the rate of overall infections ($P=0.239$), which may be because 4 patients had both pulmonary infection and intraperitoneal infection. Interestingly, the patients aged ≥70 years had a lower incidence of non-pancreatic anastomotic leakage, DEG grade B/C, and post-pancreatectomy hemorrhage grade A/B (**Table 3**).

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Table 1. Comparison the demographic and clinical characteristics of the PDAC patients who underwent PDR according to age.

Variables	Total (n=185)	Age <60 y (n=103)	60 y ≤ Age <70 y (n=55)	Age ≥70 y (n=27)	*P* value
Male*	121 (65.4)	70 (68.0)	33 (60.0)	18 (66.7)	0.599
Tobacco*	79 (42.7)	44 (42.7)	22 (40.0)	13 (48.1)	0.782
Alcohol*	63 (34.1)	33 (32.0)	19 (34.5)	11 (40.7)	0.694
NRS 2002 ≥3*	64 (34.6)	26 (25.2)	12 (21.8)	26 (96.3)	0.000
ASA classification*					0.000
I	115 (62.2)	77 (74.8)	29 (52.7)	9 (33.3)	
II	70 (37.8)	26 (25.2)	26 (47.3)	18 (66.7)	
Comorbidity*	52 (28.1)	18 (17.5)	17 (30.9)	17 (63.0)	0.000
Hypertension	28 (15.1)	10 (9.7)	8 (14.5)	10 (37.0)	0.004
Coronary artery disease	5 (2.7)	2 (1.9)	0 (0)	3 (11.1)	0.026
Diabetes mellitus	26 (14.1)	11 (10.7)	10 (18.2)	5 (18.5)	0.306
COPD	8 (4.3)	2 (1.9)	2 (3.6)	4 (14.8)	0.023
History of abdominal surgery*	8 (4.3)	3 (2.9)	5 (9.1)	0 (0)	0.139
Preoperative jaundice*	123 (55.5)	72 (70.0)	35 (63.6)	16 (59.3)	0.503
Preoperative biliary drainage*	19 (10.3)	11 (10.7)	5 (9.1)	3 (11.1)	1.000
Total bilirubin (μM/L)**	138.4 (6.1-566.0)	141.9 (6.1-476.5)	135.0 (7.2-451.2)	135.2 (7.8-566.0)	0.682
Haemoglobin (g/L)**	124.0 (74.0-161.0)	125.0 (81.0-161.0)	121.0 (74.0-151.0)	125.0 (81.0-161.0)	0.259
Albumin (g/L)**	40.5 (26.9-55.1)	41.0 (32.3-49.1)	38.9 (28.0-55.1)	40.4 (26.9-55.0)	0.068
White cell (10^9/L)**	5.6 (1.4-13.8)	5.7 (1.4-13.8)	5.4 (3.0-10.2)	5.4 (3.4-10.9)	0.431
Creatinine (μM/L)**	61.0 (3.5-135.0)	62.2 (3.5-135.0)	59.0 (4.1-90.0)	63 (36.3-106.0)	0.326
Prothrombin time (sec)**	11.2 (3.5-59.0)	11.3 (3.5-16.6)	11.3 (9.5-59.0)	11.4 (10.0-18.0)	0.519
CA19-9 (U/ml)**	150.6 (1.7-1200.0)	150.6 (1.7-900.0)	123.0 (2.0-1000.0)	170.2 (2.0-1200.0)	0.540

NRS 2002 – Nutritional risk screening 2002; ASA classification – American Society of Anaesthesiology classification; COPD – Chronic Obstructive Pulmonary Disease. * Results are presented as number (percentages); ** results are presented as median (range).

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Table 2. Perioperative and pathologic characteristics of the PDAC patients who underwent PDR according to age.

Variables	Total (n=185)	Age <60 y (n=103)	60 y ≤ Age <70 y (n=55)	Age ≥70 y (n=27)	*P* value
Type of PD*					0.851
PPPD	29 (15.7)	15 (14.6)	10 (18.2)	4 (14.8)	
Whipple	156 (83.3)	88 (85.4)	45 (81.8)	23 (85.2)	
Vascular invasion site*					0.755
PV	23 (12.4)	12 (11.7)	7 (12.7)	4 (14.8)	
Confluence of SMV and PV	83 (44.9)	48 (46.6)	26 (47.3)	9 (33.3)	
SMV	79 (42.7)	43 (41.7)	22 (40.0)	14 (51.9)	
Types of venous reconstruction*					0.073
Interposition graft	70 (37.8)	44 (42.7)	22 (40.0)	4 (14.8)	
End-to-end anastomosis	101 (54.6)	51 (49.5)	30 (54.5)	20 (74.1)	
Primary closure	14 (7.6)	8 (7.8)	3 (5.5)	3 (11.1)	
Ligation of splenic vein*	26 (14.1)	16 (15.5)	6 (10.9)	4 (14.8)	0.764
Combined organ resection*	11 (5.9)	6 (5.8)	2 (3.6)	3 (11.1)	0.386
Operation duration (min)**	460 (178-960)	470 (245-960)	458 (277-814)	410 (178-640)	0.063
Operative blood loss (ml)**	600 (200-7200)	600 (200-7200)	600 (200-4000)	600 (200-1700)	0.566
Operative blood transfusion (ml)**	400 (0-3500)	400 (0-3500)	300 (0-2550)	400 (0-1200)	0.689
Postoperative hospital stay (days)**	20 (5-164)	21 (5-164)	19 (8-36)	19 (6-42)	0.246
ICU stay (days)**	3 (1-90)	3 (1-90)	3 (1-25)	3 (2-13)	0.035
Tumor size (cm)**	3 (2.1-4.0)	3 (2.1-4.0)	3 (3.0-3.5)	3.5 (2.5-4.0)	0.588
Degree of differentiation*					0.783
Well	14 (7.6)	5 (4.9)	3 (5.5)	13 (48.1)	
Moderate	130 (70.3)	78 (75.7)	39 (70.9)	13 (48.1)	
Poor	41 (22.2)	20 (19.4)	13 (23.6)	8 (29.6)	
Pathological invasion of PV-SMV*	38 (20.5)	17 (16.5)	12 (21.8)	9 (33.3)	0.150
Neurological invasion*	90 (48.6)	55 (53.4)	22 (40.0)	13 (48.1)	0.275
Resection margin*					0.505
R0	176 (95.1)	98 (95.1)	51 (92.7)	51 (92.7)	
R1	9 (4.9)	5 (4.9)	4 (7.3)	0	
TNM staging*					0.837
I	105 (56.8)	55 (53.3)	34 (61.8)	16 (59.3)	
II	57 (30.8)	34 (33.0)	15 (27.3)	8 (29.6)	
III	13 (7.0)	9 (8.7)	2 (3.6)	2 (7.4)	
IV	10 (5.4)	5 (4.9)	4 (7.3)	1 (3.7)	

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Table 2 continued. Perioperative and pathologic characteristics of the PDAC patients who underwent PDR according to age.

Variables	Total (n=185)	Age <60 y (n=103)	60 y ≤ Age <70 y (n=55)	Age ≥70 y (n=27)	*P* value
T staging*					0.346
T1	41 (22.1)	22 (21.3)	14 (25.5)	5 (18.5)	
T2	109 (58.9)	56 (54.3)	33 (60.0)	20 (74.0)	
T3	30 (16.2)	22 (21.3)	6 (10.9)	2 (7.4)	
T4	5 (2.7)	3 (2.9)	2 (3.6)	0	
N staging*					0.267
N0	131 (70.8)	72 (59.9)	42 (76.4)	17 (63.0)	
N1	44 (23.8)	23 (22.3)	13 (23.6)	8 (29.6)	
N2	10 (5.4)	8 (7.8)	0	2 (7.4)	
Distant metastasis*	10 (5.4)	5 (4.9)	4 (7.3)	1 (3.7)	0.900

* Results are presented as a number (percentage); ** results are presented as the median (range).

Table 3. Postoperative complications of stays the PDAC patients who underwent PDR according to age.

Variables	Total (n=185)	Age <60 y (n=103)	60 y ≤ Age <70 y (n=55)	Age ≥70 y (n=27)	*P* value
Clavien-Dindo classification	114 (61.6)	63 (61.2)	34 (61.8)	17 (63.0)	0.985
I	29 (15.7)	15 (14.6)	11 (20.0)	3 (11.1)	
II	56 (30.3)	35 (34.0)	16 (29.1)	5 (18.5)	
III	12 (6.5)	7 (6.8)	4 (7.3)	1 (3.7)	
IV	13 (7.0)	5 (4.9)	1 (1.8)	7 (25.9)	
V	4 (2.2)	1 (1.0)	2 (3.6)	1 (3.7)	
Grade of complication ≥III	29 (15.8)	13 (12.6)	7 (12.7)	9 (33.3)	0.043
Pancreatic fistula	15 (8.1)	9 (8.7)	4 (7.3)	2 (7.4)	1.000
Grade A	7 (3.9)	4 (3.9)	2 (3.6)	1 (3.7)	
Grade B	3 (1.6)	2 (1.9)	1 (1.8)	0	
Grade C	4 (2.2)	3 (2.9)	1 (1.8)	1 (3.7)	
Non-pancreatic anastomotic leakage	11 (5.9)	9 (8.7)	2 (3.6)	0	0.227
Biliary anastomotic leakage	7 (3.8)	6 (5.8)	1 (1.8)	0	
Gastrointestinal anastomotic leakage	4 (2.2)	3 (2.9)	1 (1.8)	0	
Lymphatic leakage	6 (3.2)	5 (4.8)	0	1 (3.7)	0.229
Delayed gastric emptying	21 (11.4)	13 (12.6)	7 (12.7)	1 (3.7)	0.495
Grade A	7 (3.9)	3 (2.9)	3 (5.5)	1 (3.7)	
Grade B	9 (4.9)	8 (7.8)	1 (1.8)	0	
Grade C	5 (2.7)	2 (1.9)	3 (5.5)	0	

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Table 3 continued. Postoperative complications of stays the PDAC patients who underwent PDR according to age.

Variables	Total (n=185)	Age <60 y (n=103)	60 y ≤ Age <70 y (n=55)	Age ≥70 y (n=27)	*P* value
Post-pancreatectomy hemorrhage	30 (16.2)	17 (16.5)	10 (18.2)	3 (11.1)	0.787
Grade A	10 (5.4)	6 (5.8)	4 (7.3)	0	
Grade B	3 (1.6)	1 (1.0)	2 (3.6)	0	
Grade C	17 (9.2)	10 (9.7)	4 (7.3)	3 (11.1)	
Gastrointestinal hemorrhage	22 (11.9)	13 (12.6)	8 (14.5)	1 (3.7)	0.352
Intraperitoneal hemorrhage	15 (8.1)	9 (8.7)	3 (5.5)	3 (11.1)	0.562
Hepatic ischemia–reperfusion injury	26 (14.1)	18 (17.5)	5 (9.1)	3 (11.1)	0.369
Blood transfusion for non-hemorrhagic anemia	25 (13.5)	14 (13.6)	7 (12.7)	4 (14.8)	1.000
Thoracic or abdominal puncture and drainage	13 (7.0)	10 (9.7)	2 (3.6)	1 (3.7)	0.402
Organ dysfunction	17 (9.2)	6 (5.8)	3 (5.5)	8 (29.6)	0.002
MODS	7 (3.8)	3 (2.9)	3 (5.5)	1 (3.7)	
Single-organ dysfunction	10 (5.4)	3 (2.9)	0	7 (25.9)	
Infections	51 (27.6)	27 (26.2)	13 (23.6)	11 (40.7)	0.239
Pulmonary infection	25 (13.5)	9 (8.7)	6 (10.9)	10 (37.0)	0.002
Intraperitoneal infection	28 (15.1)	19 (18.4)	6 (10.9)	3 (11.1)	0.410
Re-laparotomy	19 (10.3)	11 (0.7)	5 (9.1)	3 (11.1)	1.000
Mortality (90 d)	15 (8.1)	6 (5.8)	4 (7.3)	5 (18.5)	0.095

Results are presented as a number (percentage); MODS – multiple organ dysfunction syndromes.

Survival Analysis

At follow-up, a total of 170 patients (91.9%) in the study group who underwent PDR for PDAC achieved the expected postoperative recovery. By the follow-up date of May 2021, 151 patients had died due to cancer-specific causes, 156 had developed tumor recurrence, and 19 patients (11.2%) were censored for nearly 14 years (14 patients survived, and 5 patients were lost to follow-up). The overall median follow-up time was 51.9 months (IQR: 30.4-157.1, 95% CI: 46.786-57.014). The median OS time was 9.2 months (IQR: 5.9-17.9, 95% CI: 8.169-10.231), and the 0.5-, 1-, 2-, 3-, 4-, and 5-year OS rates were 74.1%, 35.3%, 17.1%, 9.8%, 8.0%, and 6.6%, respectively. The median PFS time was 6.7 months (IQR: 3.8-11.2, 95% CI: 5.573-7.827), and the 0.5-, 1-, 2-, 3-, 4-, and 5-year PFS rates were 55.8%, 22.0%, 11.02%, 7.1%, 4.1%, and 2.4%, respectively. We further plotted the K-M curves of the OS and PFS of patients at different age stages, and the results showed that age was not related to these factors (**Figure 1**). The median OS was 9.7 months, 8.4 months, and 9.1 months for patients aged <60 years, 60 years ≤ age <70 years to ≥70 years, respectively, with a *P* value of 0.787. The median PFS was 6.9 months, 6.1 months, and 8.4 months, with a *P* value of 0.603 (**Figure 1A, 1B**).

In contrast, significantly longer OS was associated with postoperative adjuvant antineoplastic therapy (12.9 vs 7.9 mo. HR=0.470, 95% CI: 0.329-0.670, *P*=0.000) in all age groups. To assess the influence of these prognostic factors, we assessed OS and PFS for patients in the different age groups (**Table 4**). In our series, compared to older patients preoperatively diagnosed with PDAC and SMV invasion, younger patients had better OS outcomes (11.5 vs 8.4 and 9.1 months, **Figure 1C**), but there was no difference in PFS among the 3 patient groups (7.2 vs 6.2 and 8.4 months, **Figure 1D**). Other independent risk factors affecting long-term outcomes were not related to age.

Discussion

In this retrospective analysis, data on 185 PDAC patients who underwent PDR from our center were analyzed. The patients were divided into 3 groups according to age: the late elderly

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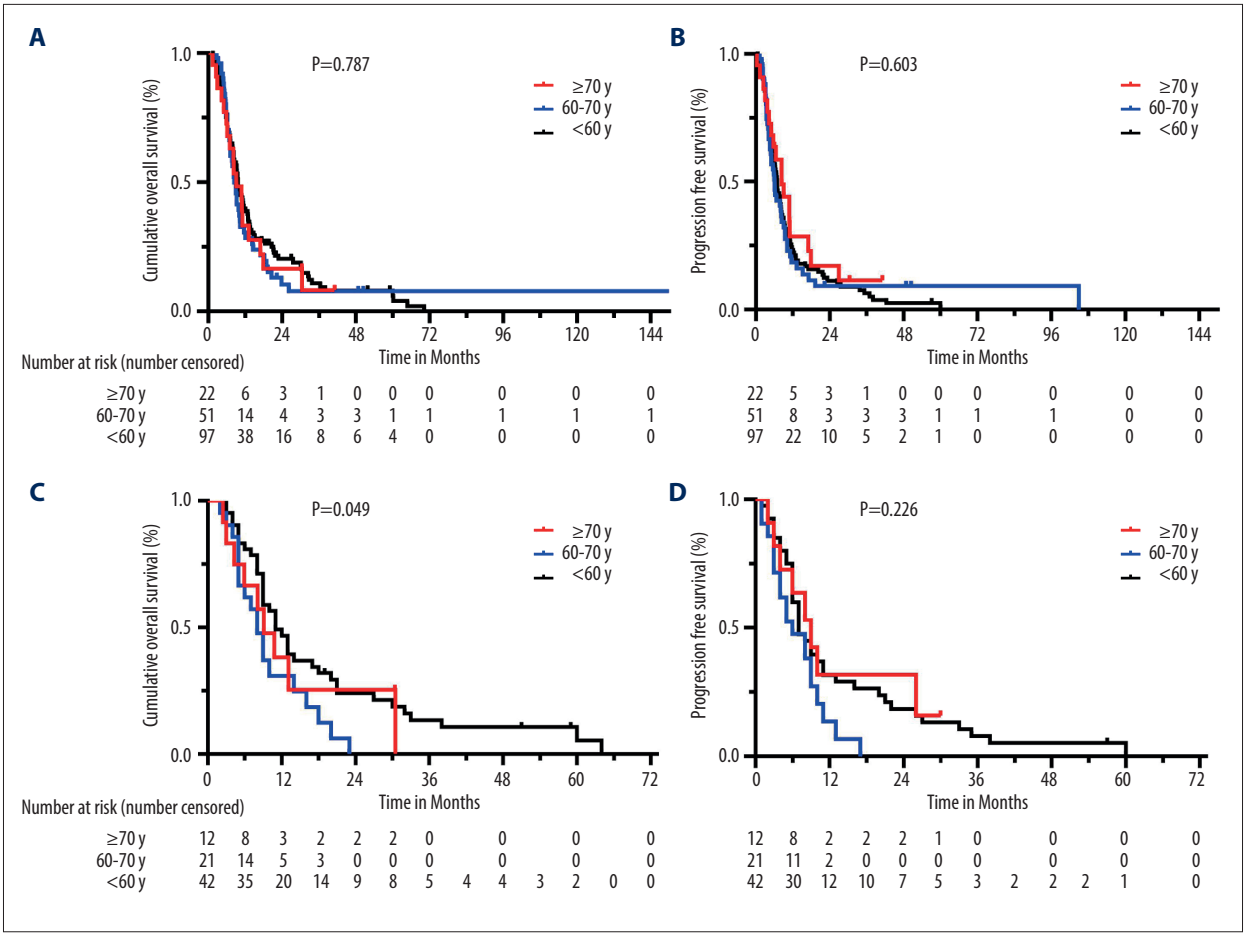

Figure 1. Kaplan-Meier estimates of OS and PFS for the 3 age group patients of PDAC treated with PDR: (**A, B**) shows the age-related OS and PFS for all patients, (**C, D**) shows the age-related OS and PFS for patients of PDAC with SMV invasion.

group (≥70), the young elderly group (60-70), and the younger group (<60). Then, we explored the difference and prognosis after PDR in different age groups. The analysis suggested that late elderly patients had a higher NRS 2002, more comorbidities, and an increased risk of anesthesia than their younger counterparts. However, these preferences did not affect the incidence of postoperative complications and mortality in patients of different ages, nor did they affect OS and PFS.

The incidence and overall mortality of PDAC correlate with increasing age and are slightly higher in men than in women [14]. It is occasionally difficult to make treatment decisions for elderly patients because physicians base their treatment decisions on physical function, the comorbidity of the patient, the progression of the tumor, and their personal willingness to receive treatment. Growing evidence has demonstrated that PDR is as safe and effective as PD for patients with PDAC [15,16]. Median survival was found to be significantly longer among patients undergoing PD or PDR than in those undergoing palliative operation (surgical bypass, *P*=0.0001) [17]. Clearly, regardless of age, surgical resection is always the best strategy for patients who have tumors that can be removed, even if lymph node metastases or vascular invasion is present. This study only focused on elderly patients who underwent PDR. Among the 185 patients with PDAC who had local progression of vascular invasion at our center over the past decade, 82 were ≥60 years (44.3%), and 27 were ≥70 years (14.6%). Our results generally demonstrated that the survival prognosis of elderly patients is comparable to that of young patients.

Predictably, patients aged 70 and older had a higher NRS 2002 score, higher anesthesia risk, and more preoperative complications than other age groups. But, considering overall postoperative complications, our data do not confirm the previously reported findings of an overall higher incidence of complications in the elderly population [18,19]. However, there was a significant difference in the incidence of grade III or higher complications according to age. Compared with patients in the 2 relatively young groups, the late elderly group was more likely to experience advanced complications (n=9, 33.3%), organ dysfunction (n=8, 29.6%), and pulmonary infection (n=10, 37%). This may be associated with organ degeneration and the level

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of vulnerability of the elderly. A study of immunonutritional and physical indices in elderly individuals suggested that individuals >80 years old who underwent PD had a significantly higher neutrophil-lymphocyte ratio and a lower prognostic nutritional index, reduced muscle strength, and impaired walking ability [20]. Pancreatic leakage is the most concerning complication after pancreatic surgery [21]. Our study did not conclude that elderly patients with PDAC had a higher risk of pancreatic fistula, which is consistent with results from other large-cohort studies [22,23].

Previous scholars have observed that elderly patients with surgically resected pancreatic carcinoma have a significant decrease in overall survival with increasing age [24,25]. Li and Liu's study reported that the age limit was 60 years [2]. In our retrospective study, the median OS and PFS were not significantly different at 60 and 70 years old, respectively, and age was not found to be a contraindication for PDR. In addition to assessing the effect of TNM staging, the degree of differentiation, and postoperative adjuvant antineoplastic therapy, we

Table 4. Analysis of the OS and PFS of PDAC patients who underwent PDR according to age.

Variables	OS			
	Age <60 y (n=97)	60 y ≤ Age <70 y (n=51)	Age ≥70 y (n=22)	*P* value
Preoperative CA19-9 ≥200 IU/L	9.2 (7.638-10.762)	7.1 (3.892-10.308)	8.1 (3.587-12.613)	0.474
Vascular invasion site				
PV	14.7 (0.000-33.238)	–	17.9 (6.858-28.942)	0.436
Confluence of PV-SMV	7.2 (5.343-9.057)	8.9 (6.401-11.399)	7.0 (4.690-9.310)	0.673
SMV	11.5 (8.386-14.614)	8.4 (5.619-11.181)	9.1 (4.941-13.259)	0.049
Venous reconstruction				
Interposition graft	9.7 (8.771-10.629)	7.1 (5.566-8.634)	6.1 (0.220-11.980)	0.628
End-to-end anastomosis	9.6 (7.717-11.283)	9.2 (7.048-11.352)	8.3 (6.469-10.131)	0.693
Primary closure	14.7 (0.000-40.063)	–	–	0.293
T stage 1/2	11.2 (8.595-13.805)	8.9 (7.783-9.927)	9.1 (5.253-12.947)	0.509
N stage 1/2	9.2 (5.764-12.636)	8.4 (6.051-10.749)	5.9 (0.000-12.968)	0.833
TNM stage				
I/II	9.7 (7.718-11.682)	8.9 (7.845-9.955)	10.8 (7.267-14.333)	0.736
III/IV	7.1 (1.329-12.871)	6.7 (3.580-9.820)	3.0 (0.439-5.561)	0.479
Degree of differentiation				
Well	12.1 (8.278-15.922)	6.1 (5.620-6.580)	10.9 (0.000-34.329)	0.345
Moderate	9.9 (8.036-11.735)	10.1 (8.395-11.805)	8.3 (6.750-9.850)	0.451
Poor	5.8 (5.143-6.457)	6.9 (5.256-8.544)	4.3 (0.000-11.982)	0.977
Postoperative adjuvant antineoplastic therapy	14.7 (9.175-20.225)	9.2 (5.973-12.427)	13.1 (8.591-17.609)	0.184

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Table 4 continued. Analysis of the OS and PFS of PDAC patients who underwent PDR according to age.

Variables	PFS			
	Age <60 y (n=97)	60 y ≤ Age <70 y (n=51)	Age ≥70 y (n=22)	*P* value
Preoperative CA19-9 ≥200 IU/L	6.3 (4.389-8.211)	5.0 (2.805-7.195)	6.5 (0.000-13.679)	0.957
Vascular invasion site				
PV	7.1 (2.353-11.847)	–	17.9 (6.858-28.942)	0.095
Confluence of PV-SMV	5.0 (3.793-6.207)	6.0 (4.736-7.264)	5.7 (3.904-7.496)	0.998
SMV	7.6 (6.362-8.838)	6.2 (1.586-10.814)	8.4 (4.395-9.057)	0.226
Venous reconstruction				
Interposition graft	5.9 (2.491-9.309)	4.6 (3.723-5.477)	5.7 (0.000-11.580)	0.397
End-to-end anastomosis	6.9 (6.444-7.356)	7.8 (4.997-10.603)	8.3 (4.870-11.730)	0.740
Primary closure	12.4 (0.000-34.020)	–	–	0.303
T stage 1/2	7.8 (6.549-9.051)	6.1 (3.303-8.897)	8.4 (4.747-12.053)	0.854
N stage 1/2	5.3 (3.287-7.313)	5.8 (3.804-7.796)	3.0 (0.000-8.544)	0.879
TNM stage				
I/II	7.0 (5.808-8.192)	6.0 (4.671-7.329)	9.1 (5.744-12.456)	0.472
III/IV	4.0 (0.945-7.055)	6.7 (2.021-11.379)	3.0 (0.439-5.561)	0.711
Degree of differentiation				
Well	6.7 (0.624-12.776)	6.1 (5.620-6.580)	10.9 (0.000-36.345)	0.416
Moderate	7.0 (5.622-8.378)	8.2 (5.818-10.582)	8.3 (4.271-12.329)	0.918
Poor	5.0 (3.028-6.972)	4.0 (2.708-5.292)	4.3 (0.000-9.485)	0.225
Postoperative adjuvant antineoplastic therapy	7.9 (6.230-9.570)	6.0 (3.849-8.151)	11.0 (6.921-15.079)	0.281

Postoperative adjuvant therapy includes chemotherapy, radiotherapy, biological therapy, traditional Chinese medicine therapy, etc.

further explored whether different vascular invasion sites on the PV-SMV axis have a different influence on prognosis and survival. Patients aged <60 years who had invasion into the SMV trunk had a longer survival time (11.5 mo.) than with the 60-70 age group and ≥70 age group (8.4 months and 9.1 months), and *P* value was 0.049. Additionally, patients with macroscopic invasion of the PV trunk had a better prognosis (OS was 14.7 months in <60 years and 17.9 months in ≥60 years), while those with invaded PV-SMV confluence had a worst prognosis (OS was 7.2 months in <60 years and 8.3 months in another group). The *P* values for overall OS were 0.022 (<60 years) and 0.019 (≥60 years) (data not shown). In addition, primary closure was significantly better than end-to-end anastomosis and interposition grafting in our univariate survival analysis results (OS was 27.5 vs 9.1, 9.2 months, *P*=0.022; PFS was 22.0 vs 7.0, 5.7 months, *P*=0.004, data not listed). Our results

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are similar to those reported by Ravikumar's group [26]. As discussed above, according to the preoperative imaging and intraoperative exploration of the invasion site of the PV-SMV system, primary closure vascular reconstruction is preferred when conditions permit, regardless of age.

To prolong long-term survival, adjuvant therapy is indispensable. Considerable controversy remains over whether patients should undergo preoperative neoadjuvant therapy for borderline resectable PDAC [27]. This retrospective study was also conducted in accordance with the principle of early surgery, and the results showed that adjuvant therapy after PDR had no effect on long-term survival, regardless of age. Nevertheless, as age increased, the number of patients receiving adjuvant therapy gradually decreased: 43 (44.3%), 17 (33.3%), and 5 (22.7%), respectively. Elderly patients are often discouraged from receiving adjuvant therapy because of adverse events, and most of them fail to finish the whole chemotherapy regimen. In fact, other researchers have shown that elderly patients suffer a higher incidence of severe adverse events (50% vs 28.3%, P=0.001) [28] and completion of planned adjuvant chemotherapy (AC) is a significant independent factor for PFS and OS [29]. Overall, although severe adverse events were more frequently observed in the elderly, the toxicity profile was acceptable when considered together with the survival benefits. The postoperative adjuvant anti-tumor therapy used in our study was mainly chemotherapy (50 cases, 76.9%). In addition, patients who received adjuvant chemoradiotherapy had significantly survival benefit than those who did not [30,31]. Therefore, regardless of age, the advantages of complete postoperative comprehensive treatment should not be underestimated.

Several limitations of our study should be acknowledged. First, there is inevitably a patient selection bias because our center treats patients who are seriously ill, as well as those who are transferred from other hospitals due to comorbidities and their overall level of fitness. Second, this was a single-center review with a small sample size, which in turn may limit the applicability of our results to other populations. Third, we did not assess the role of neoadjuvant therapy. Future studies, preferably larger patient cohorts from multiple centers, are needed to further confirm our preliminary conclusions.

Conclusions

In summary, the current study demonstrated that advanced age is not an independent contraindication to PDR. Regardless of the age of the patient undergoing PDR, there was no difference in postoperative complications or long-term survival benefits (OS and PFS), but the severity of complications (grade ≥III) was higher for patients older than 70 years than for younger patients. Importantly, it is necessary for late elderly patients with PDAC to be evaluated by a multidisciplinary team of physicians before undergoing PDR.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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