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Prognostic Value of Adjuvant Chemotherapy Following Pancreaticoduodenectomy in Elderly Patients With Pancreatic Cancer

SANG HYUN SHIN[1,2*], YEJONG PARK[1*], DAE WOOK HWANG[1], KI BYUNG SONG[1], JAE HOON LEE[1], JAEWOO KWON[1], CHANGHOON YOO[3], SHADI ALSHAMMARY[4] and SONG CHEOL KIM[1]

[1]*Division of Hepato-Biliary and Pancreatic Surgery, Department of Surgery, University of Ulsan college of Medicine and Asan Medical Center, Seoul, Republic of Korea;*
[2]*Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;*
[3]*Department of Oncology, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea;*
[4]*Department of Surgery, College of Medicine, Imam Abdcrahman Bin Faisal University, Dammam, Kingdom of Saudi Arabia*

Abstract. *Background/Aim: The aim of this study was to investigate the relationship between age and long-term survival among patients who underwent pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC). Patients and Methods: A total of 916 patients who underwent PD for curative resection of PDAC were included in this study. Patients were divided into younger (n=726, <70 years) and older (n=190, ≥70 years), and the overall survival (OS) between the two groups was compared. Results: Median OS was significantly longer in the younger group (p<0.001). However, the survival advantage among younger patients was not significant when analyzing only patients who received adjuvant chemotherapy (p=0.548). Among patients who did not receive adjuvant chemotherapy, OS was significantly longer in the younger group (p=0.003). Among patients who received neither adjuvant chemotherapy nor treatment for recurrence, survival was not significantly different between the groups (p=0.629). Conclusion: Adjuvant chemotherapy should be recommended, and additional treatment for recurrence is effective even among elderly who have not received adjuvant chemotherapy.*

*These two Authors contributed equally to this study.

Correspondence to: Song Cheol Kim, MD, Ph.D., Division of Hepato-Biliary and Pancreatic Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Republic of Korea. Tel: +82 230103936, Fax: +82 24749027, e-mail: drksc@amc.seoul.kr

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Pancreaticoduodenectomy (PD) requires highly destructive resection and complicated anastomoses, such as pancreatojejunostomy and hepaticojejunostomy. Although surgery-related mortality rates have decreased dramatically with advances in perioperative management and surgical techniques, PD is still associated with a high complication rate, with a sizeable contribution from postoperative pancreatic fistula (POPF) (1-4).

Pancreatic ductal adenocarcinoma (PDAC) is notorious for its dismal prognosis and poor clinical outcomes, and surgical resection is the only potentially curative approach. PD is the most essential step to achieve a complete cure in a patient who has resectable PDAC of the head of pancreas.

The steady growth of the elderly population has led to increasing demand for both acute and long-term healthcare services (5). In this context, various treatment modalities have been verified to be more acceptable or appropriate for older patients in acute and long-term care settings. As PDAC requires surgery to achieve complete cure, various studies have been conducted to evaluate the efficacy and safety of potentially curative procedures, especially PD, for older patients (6-13). In recent studies from large centers, PD has been demonstrated as a viable option for elderly surgical candidates, with comparable morbidity and mortality between elderly and younger patients. However, the long-term justifiability of this complicated procedure for elderly PDAC patients remains controversial (10, 14-16). PDAC has a poor postoperative prognosis, and therefore long-term results are as important as the short-term outcomes of surgery. Therefore, this study aimed to investigate the relationship between age and short-term outcomes, as well as long-term survival among patients undergoing PD for PDAC, and to contribute more definitive evidence based on a large sample size.

Materials and Methods

Patient database. Between January 2000 and December 2014, PD with curative intent was conducted on 1655 PDAC patients at Asan Medical Center in Seoul, South Korea. Because this study aimed to compare the short- and long-term outcomes of PD for resectable PDAC without major arterial invasion according to age group, the patients who underwent total pancreatectomy, distal pancreatectomy, major arterial resection, or neoadjuvant therapies were excluded. Finally, 916 patients were included in this study, and the medical records of these patients were retrospectively reviewed. Clinical, pathological, and surgical data were collected using our institute's electronic medical records. Follow-up data were also obtained from these records, and the follow-up duration was measured from the time of surgery until death or the last follow-up examination. Postoperative pancreatic fistula (POPF) and overall complications were assessed and graded based on the criteria of the International Study Group of Pancreatic Fistula (17) and the Clavien-Dindo complication classification (18), respectively. Tumor, node, and metastasis (TNM) staging was applied according to the eighth edition of the American Joint Committee on Cancer (AJCC) manual (19).

Preoperatively, all patients were assessed using computed tomography (CT) with a pancreatic protocol and magnetic resonance cholangiopancreatography (MRCP). In accordance with the diagnostic strategy at our institute, most patients with PDAC underwent 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) for initial cancer staging to identify hidden metastasis. Once diagnosed, potential candidates for surgical resection were assessed for comorbidities, such as diabetes, hypertension, cardiovascular disease, neurologic disease, and pulmonary disease. After pancreatectomy, all patients underwent CT to assess surgical complications, including POPF, on the fifth postoperative day. All patients who underwent pancreatectomy and were diagnosed with PDAC by surgical biopsy were recommended to receive adjuvant chemotherapy based on 5-fluorouracil or gemcitabine. However, adjuvant chemotherapy was actually administered to selected candidates according to performance status or patient preference. For postoperative surveillance, CT was performed and CA19-9 levels were examined every 3 months during the first 2 postoperative years and every 6 months thereafter. If necessary, FDG-PET, chest CT, or biopsy was performed to confirm recurrence. Locoregional recurrence was defined as cancer recurrence at the pancreatic resection site. Cancer recurrence in the liver, lungs or any other distant site was classified as distant metastasis. The peritoneal dissemination was classified as peritoneal carcinomatosis. We defined patients who had recurred but did not visit hospital for >1 year or who did not visit for >1 year within 5 years after surgery, as lost-to-follow-up.

For comparative analyses, patients were divided into two age groups. The younger group included patients younger than 70 years of age, and the older group consisted of patients 70 years of age or older. A third age group – with patients 80 years of age and older – was added for survival analysis. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board.

Statistical analysis. Categorical variables were expressed as frequencies and percentages, and continuous variables were reported as means, medians, and range. The chi-square or linear by linear association tests were used to compare categorical variables, and Student's *t*-test was used to compare continuous variables. Actuarial survival analysis and comparisons were performed using the Kaplan–Meier method and the log-rank test. *p*-Values <0.005 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, USA) version 21.0.

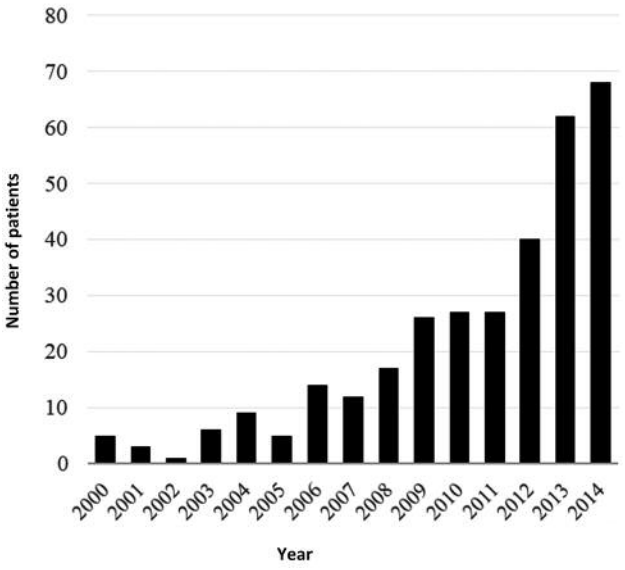

Figure 1. *The number of elderly patients (age ≥70, n=322) who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma between January 2000 and December 2014.*

Results

Clinicopathological characteristics and postoperative outcomes. Figure 1 shows the increasing trend of the number of elderly patients (age ≥70) at Asan Medical Center, Seoul, South Korea. Table I shows the demographic and clinicopathological characteristics of both age groups. Of 916 patients who underwent PD (with or without pylorus preservation) for PDAC, 716 were younger than 70 years, and 190 were at least 70 years old. Male patients were predominant in the younger age group (62.5%), but the proportions of males and females were relatively equal in the older age group (52.1% male *vs.* 47.9% female). Older patients tended to have more comorbidities, including diabetes, hypertension, and other cardiovascular, neurologic, and pulmonary diseases.

Between the two groups, there were no significant differences in clinicopathological features, including tumor markers (CA19-9 and CEA), operative technique (venous resection), and pathology results (tumor size, differentiation, staging, lymphovascular invasion, perineural invasion, and resection margin status). Mean postoperative hospital stay, POPF incidence, and overall complication rates were similar between the two groups.

Table I. *Clinicopathological characteristics and postoperative outcomes by age group.*

Factors		Age <70 years, n=726 n (%)	Age ≥70 years, n=190 n (%)	p-Value
Gender	Female	272 (37.5)	91 (47.9)	0.010
	Male	454 (62.5)	99 (52.1)	
Body Mass Index (kg/m^2)	Mean	22.7	22.7	0.973
	Median	22.6	22.5	
	Range	14.2-31.6	15.3-33.1	
Comorbidity				
Diabetes	Yes	195 (26.9)	73 (38.4)	0.002
Hypertension	Yes	199 (27.4)	93 (48.9)	<0.001
Cardiovascular	Yes	20 (2.8)	18 (9.5)	<0.001
Neurology	Yes	3 (0.4)	4 (2.1)	0.037
Pulmonary	Yes	8 (1.1)	8 (4.2)	0.008
Clinicopathologic features				
CA19-9	≤37 U/ml	224 (30.9)	56 (29.5)	0.789
	>37 U/ml	480 (66.1)	128 (67.3)	
	NA	22 (3.0)	6 (3.2)	
CEA	≤5 ng/ml	542 (74.7)	153 (80.5)	0.166
	>5 ng/ml	112 (15.4)	22 (11.6)	
	NA	72 (9.9)	15 (7.9)	
Venous resection	Yes	206 (28.4)	52 (27.4)	0.856
Tumor size (cm)	Mean	3.1	3.0	0.773
	Median	3.0	3.0	
	Range	0.8-9.0	1.2-6.0	
Tumor differentiation	WD	75 (10.3)	20 (10.5)	0.876
	MD	544 (74.9)	136 (71.6)	
	PD	94 (12.9)	26 (13.7)	
	NA	13 (1.9)	8 (4.2)	
T stage*	T1	111 (15.3)	16 (8.4)	0.256
	T2	530 (73.0)	156 (82.1)	
	T3	85 (11.7)	18 (9.5	
N stage*	N0	289 (31.6)	83 (43.7)	0.243
	N1	390 (53.7)	98 (51.6)	
	N2	47 (6.5)	9 (4.7)	
Lymphovascular invasion	Presence	381 (52.5)	111 (58.4)	0.165
Perineural invasion	Presence	605 (83.3)	159 (83.7)	> 0.99
Resection margin†	R0	574 (79.1)	142 (74.7)	0.201
	R1	152 (20.9)	48 (25.3)	
Postoperative outcomes				
Hospital stay	Mean	20.1	18.8	0.139
	Median	18.0	16.0	
	Range	6-94	6-150	
POPF	No	602 (82.9)	160 (84.2)	0.892
	Grade A	92 (12.7)	17 (8.9)	
	Grade B	28 (3.9)	13 (6.8)	
	Grade C	4 (0.6)	0 (0.0)	
Complications‡	No	438 (60.3)	121 (64.0)	0.547
	Grade I-II	243 (33.5)	55 (29.1)	
	Grade III-V	45 (6.2)	14 (6.9)	

*T and N stage were based on AJCC (American Joint Committee on Cancer) 8th edition. †R1 was defined as a distance of the tumor from the resection margin ≤1 mm. ‡Complications were graded using the Clavien-Dindo complication classification. CA19-9: Carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; POPF: postoperative pancreatic fistula.

The complications classified as Clavien-Dindo grade III–V are presented in Table II. Intraabdominal fluid collection, such as with POPF, was the most common complication in both groups. In both groups, the most severe complications were associated with the procedure itself and not with preoperative comorbidities.

Following PD for PDAC, there was a significant between-group difference in the proportion of patients who received

adjuvant chemotherapy (Table III); 74.5% of patients in the younger age group received adjuvant chemotherapy, compared with 31.6% in the older age group ($p<0.001$). Recurrence rate was similar between two groups ($p=0.747$), but there was a significant difference in the proportion of patients who received treatment for recurrence: 73.0% in younger group *vs*. 37.1% in the older group ($p<0.001$).

Survival analysis. Disease-free survival (DFS) and overall survival (OS) for all patients are shown in Figure 2. There was no significant difference in DFS between the two groups ($p=0.186$), but OS was significantly longer in the younger group ($p<0.001$). Among patients under 70 years old, the median OS was 23.5 months, and the 1-, 3-, and 5-year survival rates were 78.8%, 35.1%, and 25.2%, respectively. Among patients 70 years of age or older, the median OS was 16.7 months, and the 1-, 3-, and 5-year survival rates were 66.8%, 23.4%, and 16.3%, respectively. When the older age group was subdivided into patients ≥70 years of age but <80 years (n=176) *vs*. those ≥80 (n=14) (Figure 3), survival curves showed that there were significant differences between the younger (<70 years) group and the other groups ($p<0.001$ for younger versus older and $p<0.001$ for younger versus octogenarian group), but there was no difference between the 70- to 79-year group and the ≥80 group ($p=0.303$). Median survival was 23.5 months in the <70 group, 16.5 months in the 70- to 79-year age group, and 17.3 months in the ≥80 group.

Although survival analysis revealed a significant survival advantage among younger patients, this survival benefit was not significant when a subgroup analysis that included only those patients who received adjuvant chemotherapy was applied (Figure 4A, $p=0.548$). However, in the analysis of only the patients who did not receive adjuvant chemotherapy, there was again a significant survival advantage for the younger age group (Figure 4B, $p=0.003$). Among patients who received neither adjuvant chemotherapy nor treatment for recurrence, survival was not significantly different between the two age groups (Figure 4C, $p=0.629$).

Discussion

Many studies have demonstrated that PD can be safely performed in elderly patients, with acceptable hospital stay durations, as well as acceptable POPF, complication, and mortality rates (6-9, 12-16). In the present study, there were no significant differences in morbidity between patients older and younger than 70 years old. Additionally, there was only one death (representing 0.10% of patients) that occurred within 30 postoperative days, due to postoperative sepsis. This finding was comparable to a previous report on mortality after pancreatic resection in a high-volume center (20). Other studies have reported higher mortality rates, ranging from 17.8% to 25.0% for PD among elderly patients (21-23), but most reports have advanced the conclusion that PD can be safely performed in patients with good clinical performance status.

Table II. *Detailed descriptions of grade III-V Clavien-Dindo complications*.

Complications	Age <70 years n	Age ≥70 years n
Surgical wound problem	4	0
Intraabdominal fluid collection	20	6
Arterial pseudoaneurysm	3	0
Postoperative bleeding	5	1
Postoperative sepsis*	2	1
SMV-PV stenosis	5	2
Pulmonary embolism	0	1
Gastric-Jejunal ulceration	2	0
Intestinal obstruction	4	3

*One patient with postoperative sepsis died of septic shock within 30 postoperative days.

If the safety of PD for elderly patients with resectable PDAC is well established, a more important question is whether curative PD can achieve long-term survival. Since the 2000s, chemotherapy regimens based on 5-fluorouracil or gemcitabine have been recognized as effective for adjuvant therapy in patients undergoing PD for resectable PDAC (24-27), including at our institution (28). However, there are few studies on the efficacy of established adjuvant therapy regimens for PDAC in elderly patients undergoing PD, and previous randomized control trials on the subject included few elderly patients aged over 70 years (24-27).

Several studies have reported a lack of association between age and OS among elderly patients who had undergone PD for resectable PDAC (7, 8, 13, 14, 16). Di Carlo *et al*. reported that there was no significant difference in median survival in 98 PDAC patients who underwent pancreatic resection (<70 group: 16 months, ≥70 group: 14 months, $p=0.09$) (9). Khan *et al*. also reported that age was not related to DFS and OS ($p=0.30$ and $p=0.14$, respectively) (10). However, in the present study, the OS of elderly patients who underwent PD for resectable PDAC was not favorable, and the younger age group had a significantly longer median OS ($p<0.001$). On the other hand, there were no differences in recurrence rate and DFS between the two groups ($p=0.747$ and 0.186, respectively).

The first likely contributing factor towards poorer survival among elderly patients was that the proportion receiving adjuvant chemotherapy was lower (74.5% in the younger age group *vs*. 31.6% in the older age group, $p<0.001$ in Table III).

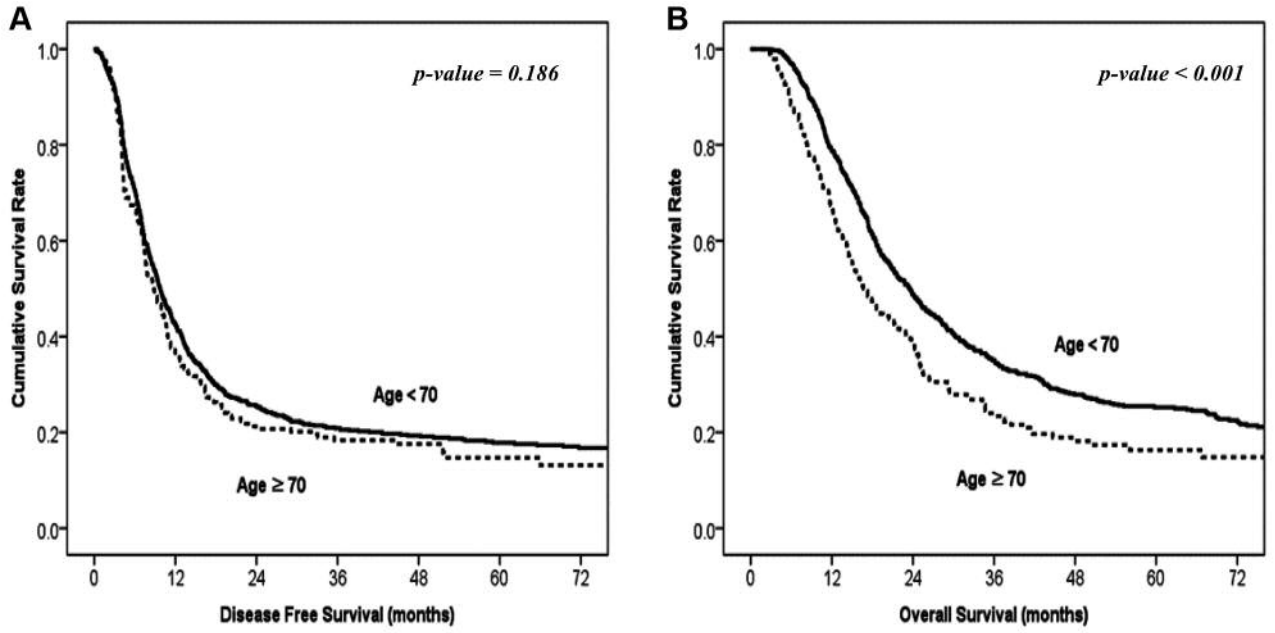

Figure 2. *Kaplan–Meier survival curves. (A) Disease-free survival (DFS) in the younger (age <70 years, n=726) and older (age ≥70 years, n=190) age groups (p=0.186). In the younger group, the median DFS was 9.8 months, and the 1-, 3-, and 5-year DFS rates were 42.5%, 20.9%, and 17.8%, respectively. In the older group, the median DFS was 8.8 months, and the 1-, 3-, and 5-year DFS rates were 36.1%, 18.3%, and 14.7%, respectively. (B) Overall survival (OS) between the younger and older groups (p<0.001). The median follow-up period for the 916 patient was 22.0 months. In the younger group, the median OS was 23.5 months, and the 1-, 3-, and 5-year survival rates were 78.8%, 35.1%, and 25.2%, respectively. In the older group, the median OS was 16.7 months, and the 1-, 3-, and 5-year survival rates were 66.8%, 23.4%, and 16.3%, respectively.*

Table III. *Additional treatment following pancreaticoduodenectomy.*

Factors	Age <70 years, n=726 n (%)	Age ≥70 years, n=190 n (%)	*p*-Value
Adjuvant chemotherapy			
No	185 (25.5)	130 (68.4)	<0.001
Yes	541 (74.5)	60 (31.6)	
Recurrence			
No	128 (17.6)	31 (16.3)	0.747
Yes	598 (82.4)	159 (83.7)	
Treatment for recurrence (n=757)			
No	161 (27.0)	100 (62.9)	<0.001
Yes	436 (73.0)	59 (37.1)	

This was demonstrated through subgroup analysis wherein OS was not significantly different between older and younger patients who received adjuvant chemotherapy (Figure 4A, p=0.548). Various reports have emphasized that adjuvant therapy is beneficial for prognosis in resected PDAC, and this applies equally to elderly patients (24-27, 29, 30).

There were no differences in recurrence rate and DFS between the two age groups, but the administration rate of treatment for recurrence was higher among patients younger than 70 years of age (73.0%) than among patients 70 years old and above (37.1%, p<0.001). This is the second likely contributor to the survival difference between the age groups. There was a significant difference in OS between the groups among patients who did not receive adjuvant chemotherapy (Figure 4B, p=0.003), but no significant difference among patients who received neither adjuvant chemotherapy nor treatment for recurrence (Figure 4C, p=0.629). These findings suggest that the additional treatment for recurrence is effective even if the patient did not receive adjuvant chemotherapy.

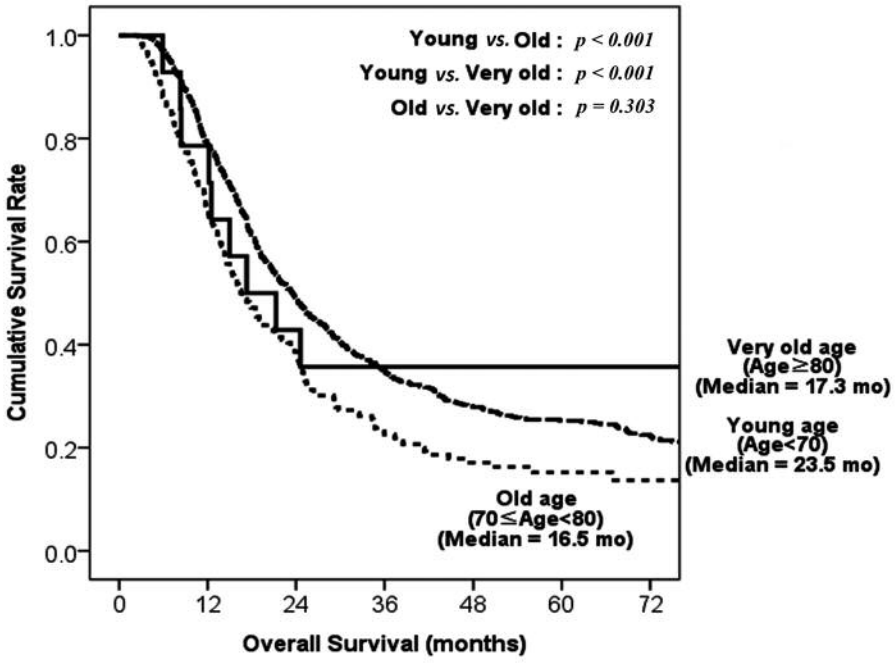

Figure 3. *Kaplan–Meier survival curve. When the analysis considered a third age group (age ≥80, n=14) , there were significant differences between the younger (age <70, n=726) and the other groups (p<0.001 for younger vs. older [≤70age <80, n=176] and p<0.001 for young vs. oldest [age ≥80]), but there was no significant difference between the older group and the oldest group (p=0.303). Median survival was 23.5 months in the younger group, 16.5 months in the older group, and 17.3 months in the oldest group.*

The administration rate of adjuvant chemotherapy and the rate of additional treatment in recurrence were both lower in the older age group, and both of these observations help explain why overall survival was worse among patients 70 years of age and older. Older patients are prescribed less chemotherapy because they generally have more comorbidities (Table I), and their physicians often project that recovery will be slower among older patients. However, although there are no well-established standard criteria for PD for resectable PDAC in elderly patients, most surgical candidates have an American Society of Anesthesiologists (ASA) physical status score less than 2 or an Eastern Cooperative Oncology Group (ECOG) performance status score between 0 and 2. Therefore, if postoperative clinical performance status is adequate, adjuvant chemotherapy should be prescribed to potentially improve OS in patients over 70 years old.

The present study has limitations related to its retrospective design and highly selected population from a single tertiary institution. Because there were few patients over 80 years, there was a limitation in confirming survival effects in this subgroup. The regimen of adjuvant chemotherapy was not consistent in all patients in the cohort, and it has been changed according to the change of time flow and guidelines. There were no prescribing criteria for adjuvant chemotherapy for elderly patients; prescriptions were primarily based on physician preferences. In terms of treatment for recurrence, it was also inconsistent, and different treatment options have been performed for each individual. Nevertheless, to our knowledge, this was a study with the largest sample size of elderly patients undergoing PD for resectable PDAC, and we were able to demonstrate the role of adjuvant therapy in elderly patients over 70 years through subgroup analysis.

In conclusion, PD can be performed safely in elderly patients diagnosed with an initially resectable PDAC who have good clinical performance status. Additionally, adjuvant chemotherapy should be recommended, and additional treatment for recurrence is effective even among elderly patients who have not received adjuvant chemotherapy.

Authors' Contributions

Substantial contributions to the conception or design of the work: Sang Hyun Shin, Yejong Park, Dae Wook Hwang, Ki Byung Song, Jae Hoon Lee, Jaewoo Kwon, Changhoon Yoo, Song Cheol Kim; Acquisition of data: Sang Hyun Shin, Yejong Park, Dae Wook Hwang, Jae Hoon Lee, Jaewoo Kwon, Shadi Alshammary; Analysis and interpretation of data: Sang Hyun Shin, Yejong Park, Song Cheol Kim, Ki Byung Song, Changhoon Yoo, Shadi Alshammary; Statistical Analysis: Sang Hyun Shin, Yejong Park, Dae Wook Hwang, Jae Hoon Lee; Drafting of manuscript: Sang Hyun Shin, Yejong Park; Critical revision: Sang Hyun Shin, Yejong Park, Dae Wook Hwang, Ki Byung Song, Jae Hoon Lee. Thereafter, in the final revising process of this manuscript, all Authors discussed the interpretation of the data and intellectual contents.

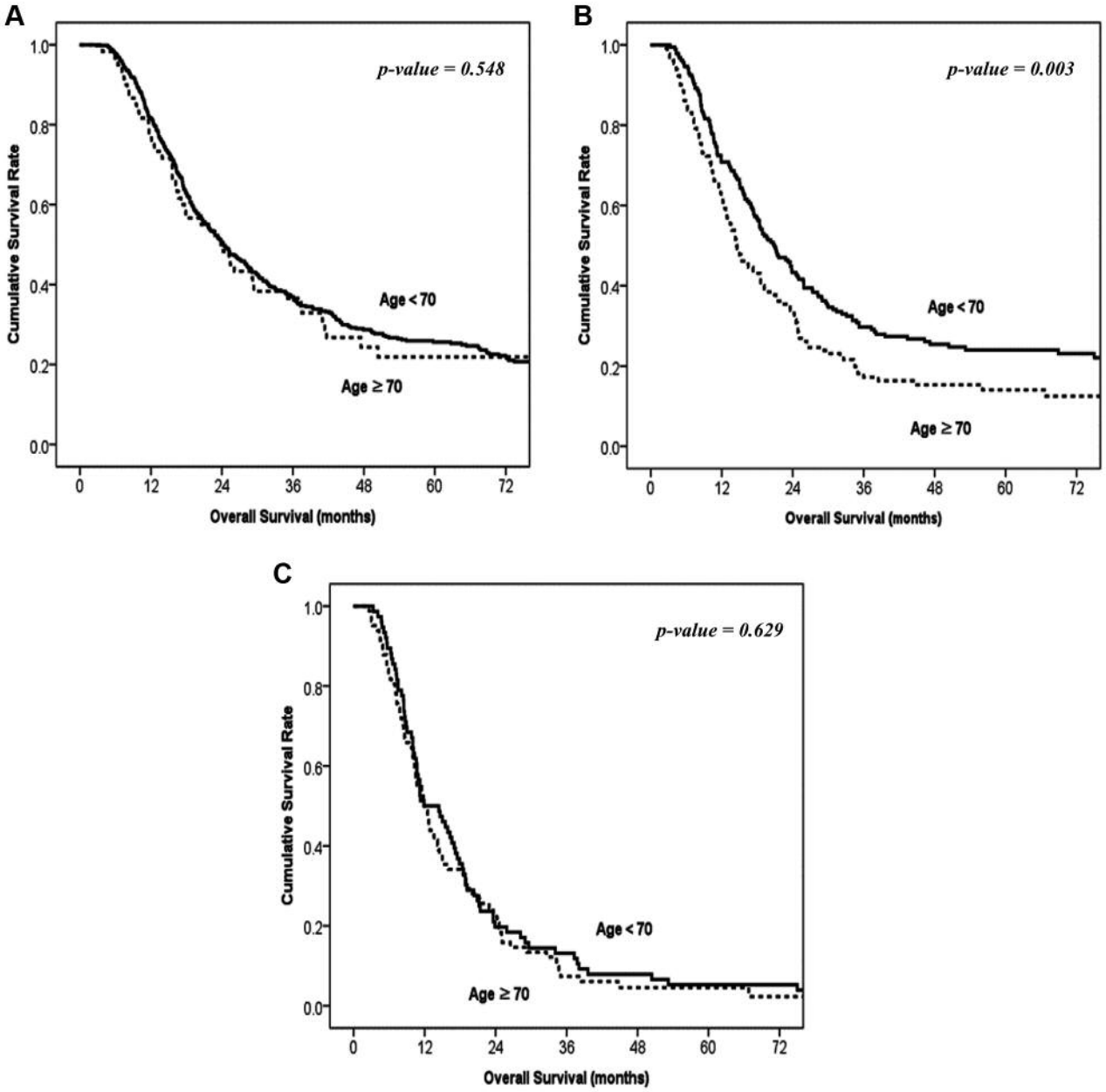

Figure 4. *Kaplan–Meier survival curves for the younger (age <70 years) and older (age ≥70 years) age groups. Overall survival (OS) (A) among the patients who received adjuvant therapy (n=601) and (B) among the patients who did not receive adjuvant therapy (n=315). (C) OS among patients who received neither adjuvant therapy nor treatment for recurrence (n=158).*

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Conflicts of Interest

The Authors have no conflicts of interest regarding this study.

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