

Outcomes of Pancreatic Resection for Elderly Patients With Pancreatic Cancer

Shuji Suzuki¹, Mitsugi Shimoda¹, Jiro Shimazaki¹, Yukio Oshiro¹, Kiyotaka Nishida¹, Yatsuka Sahara², Yuichi Nagakawa², Akihiko Tsuchida²

¹Department of Gastroenterological Surgery, Ibaraki Medical Center, Tokyo Medical University, Ibaraki, Japan

²Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University, Tokyo, Japan

Background: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with poor, albeit gradually improving, prognosis. We evaluated the predictive clinicophysiologic outcomes of elderly patients with PDAC.

Methods: We retrospectively examined 260 patients who underwent pancreatic resection classified into 2 groups: (A) those who were ≤ 80 years of age (B) and those who were > 80 years of age. Operative characteristics, preoperative clinicophysiologic parameters (body mass index, jaundice decompression, total bilirubin, albumin [Alb], creatinine, hemoglobin A1c, amylase, C-reactive protein [CRP], white blood cells, lymphocytes, hemoglobin, platelets, cancer antigen 19-9, carcinoembryonic antigen, neutrophil/lymphocyte ratio, prognostic nutritional index, platelet/lymphocyte ratio, and CRP/Alb ratio), disease-free survival (DFS), and overall survival (OS) were reported.

Results: There were no differences in morbidity, mortality, and preoperative clinicophysiologic parameters between the groups. Median DFS of groups A and B were 15.4 and 15.5 months, respectively. One-year/3-year OS of groups A and B were 86.7%/68% and 88.4%/69.3%, respectively. There were no differences in DFS and OS between the groups.

Conclusion: Curative resection for PDAC can be safely performed in elderly and younger patients, and elderly patients with PDAC can benefit from curative surgery without a significant decrease in survival rates.

Key words: Pancreatic cancer – Elderly patient – Clinicophysiologic parameters – Disease-free survival – Overall survival

Treatment for patients with cancer has become a major public concern as the aging population continues to grow. This is especially true in Japan, where the aging population is growing more rapidly compared with the United States and European countries.¹ From 2007 to 2011, the overall pancreatic ductal adenocarcinoma (PDAC) incidence rates were stable after slowly increasing for most of the last decade, and the death rate for PDAC increased slightly by 0.3%/yr.² As the population ages, more and more elderly patients are being diagnosed with PDAC and referred for treatment of their disease. In the Western population, two-thirds of patients with PDAC are older than 65 years.³ In Japan, the age-specific incidence of PDAC from age distribution in those <70 years old was 47.5% (<70/all ages number), and for those ≤80 years old, it was 17.9% (≤80/all ages number) based on data from 10 population-based cancer registries.⁴

On the other hand, PDAC has a bad prognosis. In global surveillance trends, age-standardized 5-year net survival estimates were generally in the range of 5% to 15% from 2000 to 2014.⁵ The 5-year survival rate after curative resection of PDAC in recent decades (2001–2007) has been reported to be 18.8% in the Japanese pancreatic cancer registry.⁶ Furthermore, surgical resection has proven to be the only effective means of curing PDAC.^{3,7} For radically resected PDAC, the 5-year survival rate is 21.3% to 44.1%, which recently improved with adjuvant chemotherapy and aggressive combined vessel resection.^{7–9} Previous studies have addressed the safety of pancreatic resection in patients aged 80 years or older with various comorbid disorders; however, the optimal therapeutic strategy for very elderly patients with PDAC remains to be determined.¹⁰

As elderly patients increase in number, treatment of older patients with PDAC is becoming more and more important. We aimed to evaluate the predictive clinicophysiologic outcomes of elderly patients with PDAC.

Methods

Between 2007 and 2015, 260 consecutive patients who underwent pancreatic resection for pancreatic cancer at the Ibaraki Medical Center and the University Hospital, Tokyo Medical University, were retrospectively examined. All patients were classified into 2 groups: (A) patients < 80 years of age and (B) patients ≥ 80 years of age. Outcomes, including operative characteristics, operative proce-

dures, postoperative pancreatic fistula, length of hospital stay, morbidity, mortality, preoperative clinicophysiologic parameters, disease-free survival (DFS), and overall survival (OS) were reported. All patients had pathologically confirmed PDAC. Data on clinicophysiologic parameters such as body mass index (BMI), jaundice decompression, total bilirubin, albumin (Alb), creatinine, hemoglobin A1c, amylase, C-reactive protein (CRP), white blood cells (WBCs), lymphocytes, hemoglobin, platelets, cancer antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), neutrophil/lymphocyte ratio (NLR), prognostic nutritional index (PNI), platelet/lymphocyte ratio (PLR), and CRP/Alb ratio (CAR), were collected.

Patients with a performance status of 3 or 4 were ineligible for surgical intervention in all generations. If they had an American Society of Anesthesiologists' physical status system score of 1, 2, or 3 under general operative conditions, pancreaticoduodenectomy (PD) was performed in all ages. Postoperative main complications of this study were classified as grades 3 to 5 by the Clavien-Dindo's classification.¹¹ Delayed gastric emptying in this study was defined as grade B/C of the International Study Group of Pancreatic Surgery.¹² Postoperative pancreatic fistula was defined based on the International Study Group on Pancreatic Fistula definition.¹³

Statistical analysis

Continuous variables were compared using the Student *t* test and χ^2 test. Kaplan-Meier survival curves were generated and compared using log-rank tests. Cox proportional hazard models were used to perform multivariate analyses. $P < 0.05$ was considered statistically significant. The SPSS statistical software package, version 22.0 (IBM Corp, Chicago, Illinois) was used for statistical analyses.

Ethical conduct

This study was approved by the Research Ethics Committee of Ibaraki Medical Center, Tokyo Medical University (acceptance number 16-26). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration. This article does not contain any study performed on animals by any of the authors. The requirement for obtaining written informed consent from each patient was waived because of the study's retrospective design.

Table 1 Analyses of operative background relationship between groups A and B

Variable	Group A (≤80 years of age)	Group B (>80 years of age)	P
Number	220	40	
Age (yr)	65.55 ± 0.62	82.50 ± 0.35	<0.001
Sex			
Male	142	18	0.022
Female	78	22	
Location			
Total	8	1	0.35
Head	149	23	
Body/tail	63	16	
Operative procedure			
Pancreaticoduodenectomy	149	23	0.35
Distal pancreatectomy	63	16	
Total pancreatectomy	8	1	
Jaundice decompression			
(−)	124	27	0.224
(+)	96	13	
mGPS			
0,1	194	33	0.287
2	24	7	
Stage			
0	1	0	0.444
Ia	7	2	
Ib	5	0	
IIa	48	13	
IIb	154	23	
III	0	0	
IV	5	2	
R			
0	183	28	0.119
1	33	10	
2	4	2	

mGPS, modified Glasgow prognostic score; R, resectability.

We provided the patients with the opportunity to opt out.

Results

The mean patient age was 68.15 years (range, 36–88 years), and the cohort included 160 men and 100 women. Surgical methods included primary distal pancreatectomy in 79 patients (including en bloc celiac axis resection in 10), PD in 172 patients (pylorus preserving in 10, subtotal stomach preserving in 149, and conventional in 13), and total pancreatectomy in 9 patients. The analyses of the operative background relationship between groups A and B are shown in Table 1. Groups A and B consisted of 220 and 40 patients, respectively. The average age was 65.55 ± 0.62 years in group A and 82.50 ± 0.35 years in group B. There were 142 males and 78 females in group A and 18 males and 22

females in group B. There were significant differences in age and sex. Operative procedures in both groups (pancreaticoduodenectomy/distal pancreatectomy/total pancreatectomy) were 149/63/8 in group A and 23/16/1 in group B ($P = 0.35$). The stages in both groups (0/Ia/Ib/IIa/IIb/III/IV) were 7/5/48/154/0/5 in group A and 2/0/12/23/0/2 in group B ($P = 0.444$). The preoperative background in these groups did not differ in terms of location, biliary decompression, modified Glasgow Prognostic Score (mGPS), stage, and resectability (R). There were no differences in any of the preoperative clinicophysiological parameters, as shown in Table 2. Preoperative inflammation and immunologic findings such as CRP, WBCs, NLR, PLR, and CAR were not significantly different, and nutritional findings such as Alb and PNI were not significantly different. In this study, neoadjuvant therapies were administered in 39 cases (15%) as follows: 25 with radiation+gemcitabine+S-1, 8 with gemcitabine+S-1, 3 with gemcitabine+nab-paclitaxel, 2 with radiation+gemcitabine, and 1 with gemcitabine. Adjuvant chemotherapies were administered in 179 cases (68.8%) as follows: 97 cases with S-1, 75 with gemcitabine+S-1, 62 with gemcitabine, 4 with gemcitabine+cisplatin, 2 with gemcitabine+nab-paclitaxel, and 1 with tegafur/uracil. Neoadjuvant therapies in group A were significantly more than those in group B. As shown in Table 3, there was no significant difference between groups A and B in postoperative variables such as adjuvant chemotherapies, morbidity, mortality, postoperative pancreatic fistula, and length of hospital stay. The median DFS of groups A and B was 15.4 and 15.5 months ($P = 0.764$), respectively (Fig. 1). One-year/3-year OS of groups A and B was 86.7%/68% and 88.4%/69.3% ($P = 0.412$), respectively (Fig. 2). There were no differences between these groups in terms of DFS and OS.

Discussion

The safety of pancreatic resection has improved in recent years because of improvements in surgical techniques, perioperative care, and postoperative management. Resection has become a feasible procedure even for elderly patients.^{14–16} Contrary to previous studies that suggest that age is not an independent risk factor for patients undergoing PD,^{17–19} postoperative morbidity and mortality of elderly patients were significantly higher than that of younger patients in several previous reports.^{19–21} Turrini *et al*²² reported that elderly patients might

Table 2 Analyses of preoperative clinicophysiologic background factors between groups A and B

Variable	Group A (≤ 80 years of age) \pm SD	Group B (> 80 years of age) \pm SD	P
BMI (kg/m ²)	21.82 \pm 0.21	21.75 \pm 0.55	0.073
Total bilirubin (mg/dL)	1.34 \pm 0.11	1.16 \pm 0.27	0.553
Albumin (mg/dL)	3.74 \pm 0.03	3.74 \pm 0.08	0.97
Creatine(mg/dL)	0.83 \pm 0.07	0.81 \pm 0.07	0.85
Hemoglobin A1C (%)	6.64 \pm 0.13	6.25 \pm 0.22	0.144
Amylase (IU/L)	100.77 \pm 8.01	97.50 \pm 10.55	0.806
CRP (mg/dL)	1.03 \pm 0.17	1.08 \pm 0.49	0.932
WBC (/ μ L)	5614.55 \pm 125.17	5690.00 \pm 284.65	0.809
Lymphocytes (/ μ L)	1473.11 \pm 37.24	1355.58 \pm 80.89	0.192
Hemoglobin (g/dL)	12.15 \pm 0.11	12.07 \pm 0.23	0.758
Platelets ($\times 10^4$ / μ L)	21.55 \pm 0.53	20.48 \pm 1.10	0.385
CA19-9 (U/mL)	444.18 \pm 76.21	531.53 \pm 150.24	0.606
CEA (ng/mL)	4.93 \pm 0.45	4.26 \pm 0.67	0.408
NLR	2.78 \pm 0.13	3.34 \pm 0.39	0.181
PNI	44.70 \pm 0.38	44.13 \pm 1.01	0.601
PLR	163.06 \pm 5.53	178.78 \pm 17.79	0.403
CAR	0.32 \pm 0.05	0.35 \pm 0.17	0.849

BMI, body mass index; CA19-9, cancer antigen 19-9; CAR, CRP/albumin ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutritional index; WBC, white blood cell.

obtain comparable advantages from pancreatectomies for PDAC than did younger patients, and healthy elderly patients with resectable PDAC should not be excluded from surgical resection of PDAC solely because of their age. In previous reports, several diseases involved periampullary lesions. Outcomes for pancreatectomies of PDAC

with dissection of extended lymph nodes were different than those of pancreatectomies for other diseases such as distal bile duct cancer, ampulla of Vater cancer, and duodenal cancer. Therefore, we aimed to evaluate the predictive clinicophysiologic outcomes for only PDAC in elderly patients.

Several meta-analyses and systematic reviews have evaluated the clinicophysiologic outcomes of elderly patients who underwent PDAC. Sukharamwala *et al*²³ found that patients ≥ 80 years of age had a higher rate of postoperative mortality and incidence of pneumonia compared with younger patients after PD. Casadei *et al*²⁴ suggested that

Table 3 Analyses of postoperative factors between groups A and B

Variable	Group A (≤ 80 years of age)	Group B (> 80 years of age)	P
Number	220	40	
Neoadjuvant therapies			
(-)	182	39	0.016
(+)	38	1	
Adjuvant therapies			
(-)	65	16	0.189
(+)	155	24	
Morbidity (%)	29.1	22.5	0.449
Mortality (%)	0.45	2.5	0.285
Postoperative main severe complication			
Cardiac complication	0	0	
Respiratory complication	0	2	
Infectious complication	9	0	
Brain infarction	1	0	
Cholangitis	3	1	
Bleeding	10	0	
Delayed gastric emptying	7	0	
Postoperative pancreatic fistula			
(-), Biochemical leak	203	36	0.542
grade B/C	17	4	
Length of stay in hospital (days)	25.48 \pm 1.29	26.05 \pm 4.00	0.869

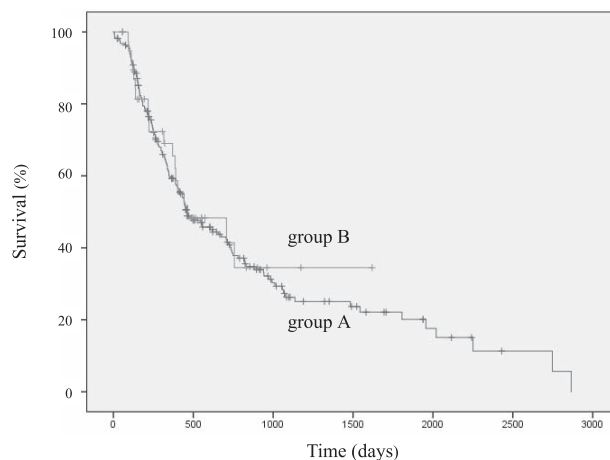


Fig. 1 Kaplan-Meier curves for DFS of patients with PDAC between group A (≤ 80 years of age) and group B (> 80 years of age); there were no significant differences ($P = 0.764$).

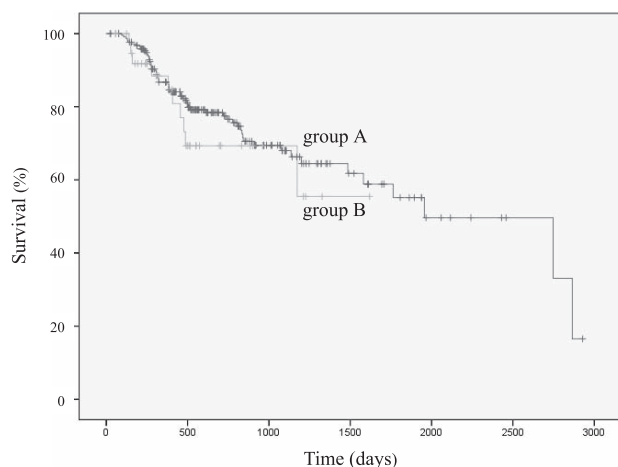


Fig. 2 Kaplan-Meier curves for OS of patients with PDAC between group A (≤ 80 years of age) and group B (> 80 years of age); there were no significant differences ($P = 0.412$).

patients ≥ 80 years of age have increased postoperative mortality and morbidity rates, as well as the incidence of cardiac complications and longer length of hospital stays than younger patients. They also suggested that pancreatic resection could be recommended only in a selected group of patients ≥ 80 years of age. Oguro *et al*²⁵ studied 561 patients, including 22 patients ≥ 80 years of age who underwent PD for pancreatic cancer, and found that

patients in this age range should be carefully selected because these patients had a higher incidence of severe postoperative complications but only a slightly better long-term survival. These researchers revealed that elderly patients had a higher risk of mortality, morbidity, and some complications than did younger patients, and therefore, an appropriate selection of elderly patients was important.

We investigated recent reports evaluating the outcomes in patients ≥ 80 years of age who underwent pancreatic resection after 2010 (Table 4).^{10,16,21,22,25–28} The results of these 8 studies showed that the difference in morbidity between elderly patients and younger patients has gradually decreased over time and that overall mortality rates of elderly patients undergoing this procedure have decreased.

An analysis of short-term outcomes revealed that elderly patients developed more postoperative anorexia and cachexia, thus compromising their nutritional and functional status more frequently than did younger patients.¹⁷

There were no differences in postoperative complications such as pancreatic fistula and delayed gastric empty between older patients and younger patients.^{29,30} Postoperative cardiac complications in several studies were significantly more frequent in patients 80 years or older than

Table 4 Recent reports evaluating the outcomes in patients aged 80 years and older undergoing pancreatic resection after 2010

Reference	Indication	Operation	Age (yr)	N	Morbidity (%)	Mortality (%)	Five-year DFS (%)	DFS (median, mo)	Five-year OS (%)	OS (median, mo)	OS: P
Hatzaras <i>et al</i> ¹⁶	Pancreatic malignancy	PD and DP	< 80	490	59	3.7	—	—	34.8	21.9	0.18
			≥ 80	27	53	3.7	—	—	33.1	33.3	
de la Fuente <i>et al</i> ²¹	Periampullary neoplasms	PD	< 80	5700	35.8	2.7	—	—	—	—	—
			≥ 80	593	45.2	6.2	—	—	—	—	—
Stauffer <i>et al</i> ²⁶	Periampullary neoplasms	PD	< 80	434	—	—	—	—	—	—	—
			≥ 80	32	50	0	—	—	—	25.8	—
Belyaev <i>et al</i> ²⁷	Benign and malignant	PD, DP, and TP	< 80	1705	42	2.5	—	—	—	—	—
			≥ 80	76	72.4	11.8	—	—	18.8	28.2	—
Oguro <i>et al</i> ²⁵	Peripancreatic malignancy	PD	< 80	539	9.6	0.9	—	—	51	65	0.277
			≥ 80	22	27.3	4.5	—	—	46	43	
Turrini <i>et al</i> ²²	PDAC	PD, DP, and TP	< 80	868	—	3.1	—	—	33.2	35.3	0.16
			≥ 80	64	—	4.2	—	—	0	30	
Frakes <i>et al</i> ²⁸	PDAC	PD	< 70	106	—	—	17.2	15.6	26.7	23	0.62
			≥ 80	26	—	—	16	17.1	15.4	18.7	
Sho <i>et al</i> ¹⁰	PDAC	PD, DP, and TP	< 80	1302	23	2	—	—	—	16.6	0.006
			≥ 80	99	18	1	—	—	—	23.2	
Our study	PDAC	PD, DP, and TP	< 80	220	29.1	0.45	20.1	15.4	55.2	65.2	0.412
			≥ 80	40	22.5	2.5	34.5	15.5	55.5	Not reached	

DFS, disease-free survival; DP, distal pancreatectomy; OS, overall survival; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; TP, total pancreatectomy.

in younger patients.²⁴ However, the incidences of cardiopulmonary complications, reintervention rate, and readmission rate in another meta-analysis were similar in these groups.²² In this study, there was no significant difference between variables, including hospital stay ($P = 0.869$), morbidity ($P = 0.449$), and mortality ($P = 0.285$). Sho *et al*¹⁰ reported that the postoperative prognosis in older patients was not as good as that in younger patients, possibly because of less frequent completion of adjuvant chemotherapy. As our report revealed, similar to younger patients, older patients could have received adjuvant chemotherapies; there were no differences between older and younger patients in terms of DFS and OS in our study. Our study also indicated no difference in complications between younger and elderly patients (Table 4).

The 5-year survival rate after curative resection of PDAC in recent decades (2001–2007) has been reported to be 18.8%.⁵ The results in Table 3 show that there was no difference in OS among patients included in the study; however, the OS of elderly patients and younger patients was prolonged. Patients also need to be aware that surgical resection is the only curative option for PDAC.¹⁹ Moreover, the main cause of death in elderly patients who underwent pancreatectomy was PDAC recurrence, similar to younger patients.¹⁷ In reasonably healthy patients, the benefit of surgical resection for PDAC does not decrease with age, and these patients can experience long-term survival and good quality of life.^{19,31} Therefore, the life-limiting factor in these elderly patients with resected PDAC has more to do with their cancer than their age.^{15,16,22}

There are several limitations associated with our study. First, the criteria for selecting elderly patients were not standardized among the hospitals. Hence, additional multicenter investigations involving larger patient populations are needed before definitive conclusions can be drawn. Although the research design was retrospective, our PDAC cases were consecutive.

Conclusions

Pancreatic curative resection for PDAC can be safely performed in both elderly and younger patients. Furthermore, the benefits that elderly patients receive from curative surgery for PDAC and OS rates are comparable to those received by younger patients.

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