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The Short- and Long-Term Outcomes of Pancreatic Resection for Pancreatic Adenocarcinoma in Patients Older Than 75 Years

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The short- and long-term outcomes of pancreatic resection for pancreatic adenocarcinoma have not been fully evaluated in elderly patients. This retrospective study selected patients who underwent curative surgery for pancreatic cancer at our institution. Patients were categorized into 2 groups: nonelderly patients (age $<$ 75 years; group A) and elderly patients (age $\geq$ 75 years; group B). The surgical morbidity, surgical mortality, overall survival (OS), and recurrence-free survival (RFS) rates in the 2 groups were compared. A total of 221 patients were evaluated in the study. The overall complication rates were 44.8% in group A and 52.6% in group B. Surgical mortality was observed in 2 patients due to an abdominal abscess and cardiovascular disease in group A (1.1%) and in 1 patient due to postoperative bleeding in group B (2.6%). There were no significant differences ($P = 0.379$ and $P = 0.456$, respectively). Furthermore, the 5-year OS and RFS rates were similar between the elderly patients and nonelderly patients (18.55 versus 20.2%, $P = 0.946$ and 13.1% versus 16.0%, $P = 0.829$, respectively). The short-term outcomes and long-term survival after pancreatic resection for pancreatic adenocarcinoma were almost equal in the elderly and the

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nonelderly patients in this study. Therefore, it is unnecessary to avoid pancreatic resection for pancreatic adenocarcinoma in elderly patients simply because of their age.

Key words: Pancreatic cancer – Elderly patient – Pancreatic resection

Pancreatic cancer is one of the most lethal human cancers. It is the fifth-most common cancer and the fourth leading cause of cancer-related mortality worldwide, with a 5-year survival rate of less than 5% in all stages.[1,2] Complete resection is essential for obtaining a cure in patients with pancreatic cancer. However, the morbidity after pancreatic resection has been reported to range from 30% to 65%, and the complications are sometimes fatal.[3–7]

The number of elderly patients is rapidly growing worldwide. With people aged 75 and older representing the fastest growing subset of the population, the management of complex surgical issues promises to become even more challenging. However, previous studies excluded patients over the age of 75. Furthermore, few authors have evaluated the short- and long-term outcomes of pancreatic resection for pancreatic adenocarcinoma in patients aged 75 years and older.[8–11] Therefore, the short-term outcomes and long-term survival of pancreatic resection for pancreatic adenocarcinoma in elderly patients are still unclear. In addition, generally, elderly patients often have comorbidities and age-related physiologic problems that can lead to greater postoperative complications or poor survival than in nonelderly patients.

We retrospectively investigated the short-term outcomes and long-term survival after pancreatic resection for pancreatic adenocarcinoma in patients older than 75 years and compared them with nonelderly patients.

Patients and Methods

Patients

The study subjects were selected from the medical records of consecutive patients who underwent surgery for pancreatic cancer at the Kanagawa Cancer Center from 2005 to 2015. The inclusion criteria were as follows: (1) patients with a common pathologic type of pancreatic cancer [according to the International Union Against Cancer (UICC) TNM 7th edition][12]; (2) patients in whom curative resection was successful as the initial treatment for pancreatic cancer; and (3) patients with no synchronous or metachronous malignancies. The resected specimens were examined histopathologically and staged according to the UICC TNM 7th edition. Patients with other pancreatic and periampullary neoplasms, such as intraductal papillary mucinous neoplasms, cystadenocarcinoma, and endocrine tumors, were excluded from the present study.

Surgical procedure

All pancreatic surgeries were performed in accordance with standardized procedures that have been described elsewhere.[13–16] Briefly, in cases of distal pancreatectomy (DP), lymph node dissection was performed in the region of the celiac trunk and the superior mesenteric artery and vein, as well as behind the pancreas along the left side of the renal vein and the left adrenal gland. In each case, intraperitoneal drains were placed close to the pancreatic anastomosis and stump. In cases of pancreaticoduodenectomy (PD), subtotal stomach-preserving pancreaticoduodenectomy was performed as the standard procedure. Multiple intraperitoneal drains were placed: the first was posterior to the hepaticojejunostomy, and the second was on the anterior surface of the pancreaticojejunostomy or the closed remnant of the pancreas.

Adjuvant chemotherapy

Treatment with gemcitabine was initiated within 8 weeks after surgery. The patients received a weekly dose of 1000 mg/m^2 for 3 weeks, followed by 1 week of rest. S-1 chemotherapy was started within 10 weeks after surgery.[17] The patients received 40 mg S-1 per square meter of body surface area twice a day for 4 weeks, followed by 2 weeks of rest as 1 course (6-week schedule) or 2 weeks followed by 1 week of rest as 1 course (3-week schedule).[18] All of the patients in the present study received either gemcitabine or S-1 treatment for 6 months.

Definition of postoperative complications

The grade 2 to 5 postoperative complications (according to the Clavien-Dindo classification) that occurred during hospitalization and/or within 30 days after surgery were retrospectively determined from the patient's records.[19] Grade 1 complications

Table 1 Baseline characteristics of the study patients

Characteristics	Group A (<75 years) [number of patients (%)] (n = 183)	Group B (≥75 years) [number of patients (%)] (n = 38)	*P* value
Age (years)			
Median	66	77	
(Range)	(30–74)	(75–86)	
Sex			0.056
Male	108 (59.0%)	16 (42.1%)	
Female	75 (41.0%)	22 (57.9%)	
Body mass index			0.737
Median	21.7	22.0	
(Range)	(15.6–33.7)	(15.8–28.1)	
ASA-PS			0.017
1	32 (17.5%)	0 (0%)	
2	144 (78.7%)	37 (97.4%)	
3	7 (3.8%)	1 (2.6%)	
Comorbidity			
Hypertension	40 (21.9%)	13 (34.2%)	0.038
COPD	9 (4.9%)	7 (18.4%)	0.001
Diabetes mellitus	44 (24.0%)	6 (15.8%)	0.347
Preoperative laboratory data			
Albumin (g/dL)	4.0 (2.3–4.8)	3.9 (3.0–5.0)	0.172
Hemoglobin (g/dL)	12.7 (8.4–17.9)	12.4 (8.6–15.8)	0.222
White blood cells	5300 (2800–15,500)	5200 (3300–9400)	0.405

were not evaluated, to exclude the possibility of a description bias in the patient's records.

Follow-up

Patients were followed up at outpatient clinics. Hematologic tests and physical examinations were performed at least every 3 months for 5 years. In the patients who received adjuvant chemotherapy, hematologic tests and physical examinations were performed at least every 2 weeks during adjuvant chemotherapy and at least every 3 months for 5 years after the patients finished adjuvant chemotherapy. The carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) tumor marker levels were checked at least every 3 months for 5 years. Patients underwent a computed tomography examination every 3 months during the first 3 years after surgery and then every 6 months until 5 years after surgery.

Evaluations and statistical analysis

Overall survival (OS) was defined as the period between surgery and death. Recurrence-free survival (RFS) was defined as the period between surgery and recurrence or death, whichever came first. The data of the patients who did not experience an event were censored on the date of the final observation. OS and RFS curves were calculated using the Kaplan-Meier method and compared by the log-rank test. Comparisons of the 2 groups were performed using the unpaired χ^2 method or Student's *t*-test. $P < 0.05$ was considered statistically significant. The data are expressed as the median (range). The SPSS software package (v11.0J Win; SPSS, Chicago, Illinois) was used for all statistical analyses. This study was approved by the institutional review board of the Kanagawa Cancer Center.

Results

Background of the patients

Two-hundred twenty-one patients were eligible for the present study. The median age was 68 years (range, 30–86 years). One-hundred twenty-four patients were male, and 97 were female. The median follow-up period was 58.2 months (range, 3.6–132.9 months). One hundred eighty-three patients were classified as nonelderly patients (group A) and 38 as elderly patients (group B). The background of the patients is summarized Table 1. The American Society of Anesthesiology (ASA) score was significantly worse, and the incidence of the hypertension (HT) and chronic obstructive pulmonary disease (COPD) was significantly higher in group B than in group A ($P = 0.017$, $P = 0.038$, and $P = 0.001$, respectively). Furthermore, there was a slight difference in the sex composition between the groups ($P = 0.056$). However, similar values were

Table 2 Surgical and pathologic findings

Characteristics	Group A (<75 years) [number of patients (%)] (n = 183)	Group B (≥75 years) [number of patients (%)] (n = 38)	*P* value
Type of surgery			0.030
DP	50 (27.3%)	4 (10.5%)	
PD or TP	133 (72.7%)	34 (89.5%)	
Operation time (min)			0.679
Median	482	512	
(Range)	(140–1995)	(188–817)	
Blood loss (ml)			0.566
Median	1065	1167	
(Range)	(30–10,175)	(230–8730)	
Intraoperative transfusion			0.071
Yes	91 (49.7%)	25 (65.8%)	
No	92 (50.3%)	13 (34.2%)	
Pathologic stage			0.378
Stage I	8 (4.4%)	0 (0%)	
Stage IIA	32 (17.5%)	10 (26.3%)	
Stage IIB	121 (66.1%)	24 (63.2%)	
Stage III	0 (0%)	0 (0%)	
Stage IV	22 (12.0%)	4 (10.5%)	
Number of harvested lymph nodes			0.120
Median	28	23.5	
(Range)	(1–92)	(4–67)	
Tumor diameter (mm)			0.411
Median	36	35	
(Range)	(5–105)	(17–85)	
Peritoneal wash cytology status			0.795
Positive	22 (12.0%)	4 (10.5%)	
Negative	161 (88.0%)	34 (89.5%)	

TP, total pancreatomy.

observed in body mass index and preoperative laboratory data findings.

Surgical and pathologic findings

The operative details and pathological findings are shown in Table 2. Among the intraoperative outcomes, although the type of surgery was significantly different between the groups ($P = 0.030$), the length of surgery, blood loss, and incidence of intraoperative transfusion were similar ($P = 0.679$, $P = 0.566$, and $P = 0.071$, respectively). Among the pathologic findings, the pathologic stage was stage IIA and IIB in most patients, with no significant differences between the 2 groups. Furthermore, the number of harvested lymph nodes, tumor diameter, and the incidence of peritoneal wash cytology status were similar between the groups.

Postoperative complications

The postoperative outcomes and associated details are shown in Tables 3 and 4. The overall complication rates were 44.8% in group A and 52.6% in group B. There were no statistically significant differences ($P = 0.379$). Pancreatic fistula and delayed gastric emptying were the most frequently diagnosed complications in group A, followed by abdominal abscess. In contrast, delayed gastric emptying was the most frequently diagnosed complication in group B, followed by pancreatic fistula and abdominal abscess. Surgical mortality was observed in 2 patients due to an abdominal abscess and cardiovascular disease in group A (1.1%) and in 1 patient due to postoperative bleeding in group B (2.6%). There were no significant differences between the groups ($P = 0.456$)

Survival analysis

The OS rates at 3 and 5 years after surgery were 28.2% and 18.5% in group A and 20.2% and 20.2% in group B, respectively. The difference was not statistically significant ($P = 0.946$). The OS curves are shown in Fig. 1.

The RFS rates at 3 and 5 years after surgery were 21.4% and 13.1% in group A and 16.0% and 16.0% in group B, respectively. The difference was not

Table 3 Postoperative outcomes

Characteristics	Group A (<75 years) [number of patients (%)] (n = 183)	Group B (≥75 years) [number of patients (%)] (n = 38)	*P* value
Surgical complications			0.379
Yes	82 (44.8%)	20 (52.6%)	
No	101 (55.2%)	18 (47.3%)	
Mortality			0.456
Yes	2 (1.1%)	1 (2.6%)	
No	181 (98.9%)	37 (97.4%)	
Length of postoperative hospital stay			0.396
Median	23	23	
(Range)	(7–269)	(14–90)	
Adjuvant chemotherapy			0.001
Yes	164 (89.6%)	26 (68.4%)	
No	19 (10.4%)	12 (31.6%)	
Median OS (months)			0.946
Median	23.1	22.2	
(Range)	(18.8–27.4)	(17.0–27.4)	
Median RFS (months)			0.829
Median	11.2	11.0	
(Range)	(9.1–13.3)	(5.5–16.4)	
First recurrence site			
Liver	37 (20.2%)	8 (21.1%)	0.908
Lymph node	43 (23.5%)	10 (26.3%)	0.711
Peritoneal	34 (18.6%)	4 (10.5%)	0.231
Local	19 (10.4%)	3 (7.9%)	0.641

statistically significant ($P = 0.829$). The RFS curves are shown in Fig. 2.

Discussion

The present study showed that the short- and long-term outcomes of pancreatic resection for pancreatic adenocarcinoma in patients older than 75 years of age were similar to those in nonelderly patients. Therefore, our results suggest that pancreatic resection for pancreatic adenocarcinoma is a safe option with similar survival benefits regardless of the age of the patient and may still be performed in elderly patients who are deemed candidates in all other respects.

The short-term outcomes, including overall postoperative complication rates, mortality rates, and length of hospital stay, were similar between elderly and nonelderly patients. Furthermore, the details of the postoperative complications were similar between the groups. Similar results were observed in previous reports. Oliveira-Cunha *et al* reviewed the

Table 4 Details of surgical complications

Characteristics	Group A (<75 years) [number of patients (%)]	Group B (≥75 years) [number of patients (%)]
Pancreatic fistula (grade 2/3a/3b/4a/4b/5)	18 (9.8%) 16/1/1/0/0/0	4 (10.5%) 2/2/0/0/0/0
Abdominal abscess (grade 2/3a/3b/4a/4b/5)	14 (7.7%) 6/6/1/0/1/0	3 (7.8%) 1/1/0/1/0/0
Anastomotic leakage (grade 2/3a/3b/4a/4b/5)	3 (1.6%) 1/2/0/0/0/0	0 (0%) 0/0/0/0/0/0
Pneumonia (grade 2/3a/3b/4a/4b/5)	5 (2.7%) 4/0/0/1/0/0	1 (2.6%) 0/0/0/1/0/0
Postoperative bleeding (grade 2/3a/3b/4a/4b/5)	2 (1.1%) 0/2/0/0/0/0	3 (7.8%) 1/0/1/0/0/1
Delayed gastric empty (grade 2/3a/3b/4a/4b/5)	18 (9.8%) 18/0/0/0/0/0	5 (13.2%) 5/0/0/0/0/0
Portal vein thrombosis (grade 2/3a/3b/4a/4b/5)	1 (0.5%) 1/0/0/0/0/0	1 (2.6%) 1/0/0/0/0/0
Cardiovascular disease (grade 2/3a/3b/4a/4b/5)	2 (1.1%) 1/0/0/0/0/1	0 (0%) 0/0/0/0/0/0
Cholangitis (grade 2/3a/3b/4a/4b/5)	3 (1.6%) 0/1/0/2/0/0	2 (5.3%) 2/0/0/0/0/0
Chylous ascite (grade 2/3a/3b/4a/4b/5)	10 (5.5%) 7/2/0/1/0/0	1 (2.6%) 1/0/0/0/0/0
Gastrointestinal bleeding (grade 2/3a/3b/4a/4b/5)	4 (2.2%) 4/0/0/0/0/0	1 (2.6%) 1/0/0/0/0/0
Delirium (grade 2/3a/3b/4a/4b/5)	5 (2.7%) 5/0/0/0/0/0	3 (7.8%) 3/0/0/0/0/0
Surgical site infection (grade 2/3a/3b/4a/4b/5)	9 (4.9%) 9/0/0/0/0/0	1 (2.6%) 1/0/0/0/0/0
Ileus (grade 2/3a/3b/4a/4b/5)	2 (1.1%) 2/0/0/0/0/0	1 (2.6%) 1/0/0/0/0/0

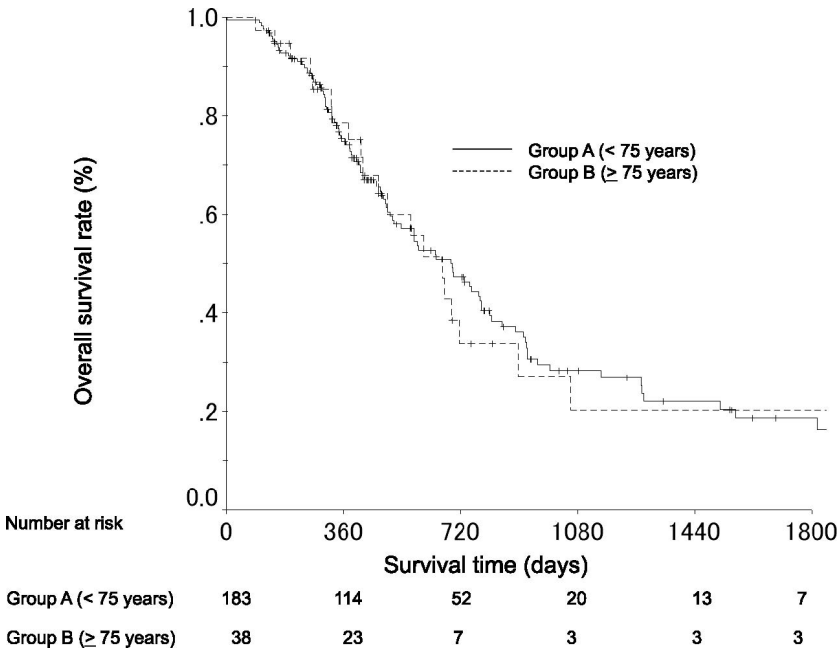

Fig. 1 Overall survival in patients ≥75 years and those <75 years old.

records of 428 patients undergoing pancreatic resection for malignancy between 2000 and 2009.[11] They reported on 119 patients 70 years of age or older and 309 patients less than 70 years of age, and showed a similar morbidity and mortality in both groups (12.6% versus 21.0%, $P = 0.059$ and 3.4% versus 2.6%, $P = 0.75$, respectively). Moreover, Hatzaras *et al* reviewed the records of 517 patients undergoing pancreatic resection for malignancy between 1990 and 2007.[8] They reported on 27 patients 80 years of age or older (range, 80–91 years) and 490 patients less than 80 years of age (range, 20–79 years) and showed a similar morbidity and mortality in both groups (52% versus 59%, $P = 0.4$ and 3.7% versus 3.7%, $P = 1.0$, respectively). In their report, infectious complications were the most frequently diagnosed complication, followed by pancreatic fistula in the patients less than 80 years of age. Similarly, infectious complications and cardiovascular disease were the most frequently

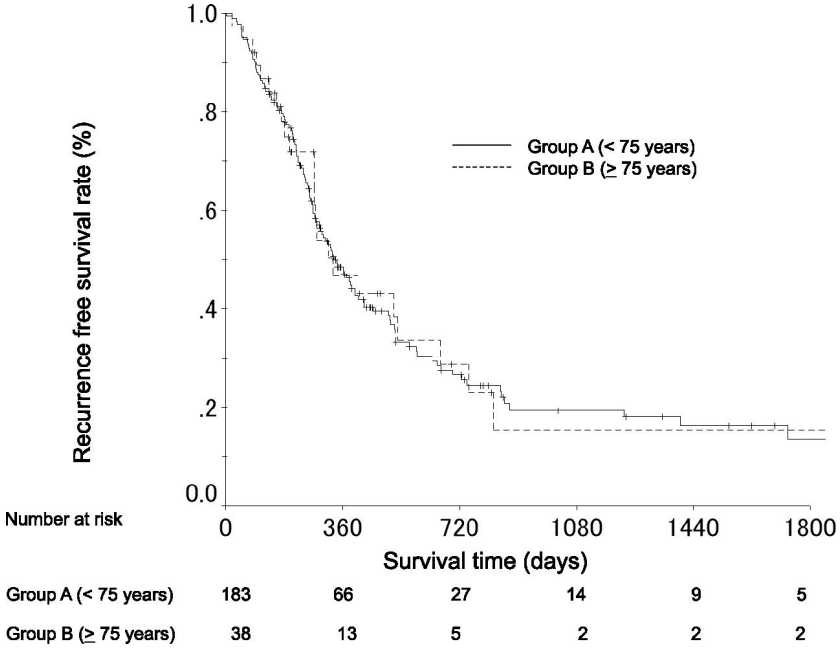

Fig. 2 RFS in the patients ≥75 years and those <75 years old.

diagnosed complication, followed by pancreatic fistula in the patients 80 years of age or older. Lee *et al* also reported similar results.[20] In contrast, Melis *et al* evaluated the short-term outcomes and long-term survival after PD for pancreatic adenocarcinoma in 200 patients and divided them into 2 groups using a cutoff value of 80 years old.[9] They reported that overall morbidity and length of postoperative stay were increased in elderly patients compared with younger ones (44.0% versus 68.0%, $P = 0.03$ and 13.7 versus 20 days, $P = 0.01$, respectively). These data suggest that when complications occur in elderly patients, they rapidly increase in severity.

In the present study, the 5-year OS rates and RFS rates were similar between the elderly and nonelderly patients (18.55 versus 20.2%, $P = 0.946$ and 13.1% versus 16.0%, $P = 0.829$, respectively). Furthermore, the median OS and RFS were similar between the 2 groups. Similar results were observed in the previous studies. Hatzaras *et al* reported that the OS was 21.9 months in the patients who were less than 80 years of age and 33.3 months in the patients who were 80 years of age or older.[8] Melis *et al* also reported that the OS was 13.1 months in the patients who were less than 80 years of age and 17.3 months in the patients who were 80 years of age or older after a median follow-up of 35 months.[9] On the contrary, Oliveira-Cunha *et al* reported that the OS was 57.3 months in the patients who were less than 70 years of age and 78.7 months in the patients who were 70 years of age or older ($P < 0.001$).[11] Further study should be focused on this issue.

When interpreting our results, special attention is required, because the present study was carried out on a case series from a single center. Morbidity may have been affected by surgical indication, and this selection bias is its major limitation. In these cases, the surgical indication was determined by 6 physicians, including an anesthesiologist, who took into consideration the activities of daily living, performance status, medical history, physical examinations, and organ function, as is done in general community hospitals. However, there is a possibility that only patients with good status were selected because our hospital is a regional cancer center that treats only cancer patients. Elderly patients who have comorbidities and visit general hospitals often undergo surgery at the same hospital where they were diagnosed with pancreatic cancer. Indeed, the ASA physical status (ASA-PS), the incidence of comorbidity, and preoperative laboratory data were similar between the 2 groups. Therefore, the elderly people in the present study were selected and fit for surgery in the present study, and it is difficult to generalize. Considering these limitations of the present study, further studies should focus on which patients are candidates for surgery and will do well after pancreatic resection for pancreatic adenocarcinoma.

In summary, both the short-term outcomes and long-term survival after pancreatic resection for pancreatic adenocarcinoma were almost equal in the elderly and nonelderly patients in this study. Therefore, it is unnecessary to avoid pancreatic resection for pancreatic adenocarcinoma in elderly patients, who may be good candidates for surgery, simply because of their age.

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