ANTICANCER RESEARCH *37*: 5309-5316 (2017)
doi:10.21873/anticanres.11957

Study on the Validity of Pancreaticoduodenectomy in the Elderly

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Abstract. *Aim: Pancreaticoduodenectomy (PD) is still the only curative treatment for periampullary cancer. Confirming the outcomes of PD in elderly patients is important as the aging population continues to grow. Patients and Methods: We analyzed 340 patients with periampullary cancer who underwent PD, dividing them into three groups by age: group A: aged 64 years or younger, n=115; group B: 65-74 years, n=144; and group C: 75 years or older, n=81. Results: Group C had a significantly higher 60-day mortality of 6.3% (p=0.04), the lowest 5-year overall survival rate of 9.9% (p=0.02), and there was no impact of staging of the Union for International Cancer Control classification on overall survival of patients with pancreatic cancer. Independent prognostic factors of group C in the multivariate analysis were pancreatic cancer and reoperation. Conclusion: For elderly patients aged 75 years or over, caution should be exercised in selecting PD for patients with pancreatic cancer.*

The elderly population aged 65 years and over is now increasing in developed countries. In 2014, there were 46 million people aged 65 years and over living in the United States alone, accounting for 15% of the total population. In 2030, the number of older Americans is expected to grow to 74 million, representing nearly 21% of the total U.S. population (1). In Japan, the number and proportion of the elderly people aged 65 years and over reached 34.6 million in 2016, accounting for the highest proportion of 27% (2). Advanced age of 60 years and over is noted as a risk factor for periampullary cancer; therefore, the number of elderly patients who require pancreaticoduodenectomy (PD) as a curative treatment is expected to further increase (3).

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Key Words: Geriatric surgery, pancreaticoduodenectomy, survival.

The validity of performing PD for older patients remains controversial. Nowadays, the applicability of PD in elderly patients is determined on a case-to-case basis, considering various factors such as comorbidity, cancer staging, frailty, life expectancy, and postoperative quality of life. Although the evaluation of the grade of frailty for surgery remains to be established, approximately 20-30% of those over 75 years would be considered frail, and this figure tends to increase with age (4).

Knowing the surgical outcomes of PD in older patients is important to assist for decision making, because PD is still the only curative treatment for periampullary cancer, even in the elderly. This study aimed to confirm the validity of PD for elderly patients compared with their non-elderly counterparts.

Patients and Methods

This study was approved by the Institutional Review Board of the Jikei University School of Medicine in October, 2015. Among the 436 patients who underwent PD for various indications between January 2003 and December 2010 at four affiliated hospitals of the Jikei University School of Medicine, Tokyo, Japan, 340 patients with an operative indication of pancreatic cancer (n=178), bile duct cancer (n=96), or ampullary cancer (n=66) were evaluated in this retrospective study. All four hospitals are currently certified by the Japanese Society of Hepato- Biliary-Pancreatic Surgery as high-volume centers. The patients who had a performance status of 3 or more, an American society of anesthesiologists (ASA) physical status of grade 5 or more, or dementia were considered as contraindicated for PD regardless of age. In our affiliated hospitals, consultation with each patient's cardiologist or pulmonologist for those with a medical history of cardiac or pulmonary disease is routinely performed to evaluate operability. The final decision for the indication of PD was made by the team conference with the attending surgeon, taking into consideration the consultants and anesthesiologists' evaluations, preoperative testing, and patient's performance status. None of the patients in this study received neoadjuvant chemotherapy or radiotherapy. The 340 patients were divided into three groups according to their chronological age: group A, the non-elderly (aged 64 years or younger; n=115; 33.8%); group B, the early elderly (65-74 years; n=144; 42.3%); and group C, the late elderly (75 years or older; n=81; 23.8%). The patients' preoperative and intraoperative clinicopathologic characteristics are shown in Table I.

Table I. *Clinical characteristics of patients who underwent pancreaticodudenectomy by age.*

Factor	Group A Age <65 years (n=115)	Group B Age (65-74) years (n=144)	Group C Age (≥75) years (n=81)	*p*-Value
Pre-operative				
Age, years, median (IQR)	58 (53-61)	70 (67-72)	77 (76-79)	<0.001
Gender: male/female	76/39	89/55	43/38	0.18
Diabetes mellitus	26 (23.4%)	40 (28.4%)	20 (25.3%)	0.68
Indication				0.94
Pancreatic cancer	60 (52.2%)	75 (52.1%)	43 (53.1%)	
Bile duct cancer	30 (26.1%)	43 (29.9%)	23 (28.4%)	
Ampullary cancer	25 (21.7%)	26 (18.1%)	15 (18.5%)	
Stage				0.98
0	1 (0.9%)	2 (1.4%)	0	
IA + IB	24 (20.9%)	35 (24.3%)	18 (22.2%)	
IIA + IIB	64 (55.7%)	81 (56.3%)	46 (56.8%)	
III	26 (22.6%)	26 (18.1%)	17 (21.0%)	
Cholangitis	18 (15.9%)	18 (12.7%)	13 (16.5%)	0.67
Total bilirubin (mg/ dl), mean±SD	1.9±1.4	2.3±2.4	1.9±1.7	0.21
Operative				
Operative time (min), median (IQR)	485 (395-600)	478 (390-560)	445 (374-533)	0.02
Blood loss (ml), median (IQR)	1,040 (335-4,280)	950 (240-3,500)	940 (318-2,410)	0.12
Procedure, n (%)				0.52
Classical Whipple	59 (51.3%)	80 (55.6%)	48 (59.3%)	
SSPPD	28 (24.3%)	25 (17.4%)	17 (21.0%)	
PPPD	28 (24.3%)	39 (27.1%)	16 (19.8%)	
Concomitant portal vein resection (n, %)	9 (7.8%)	15 (10.4%)	1 (1.2%)	0.02

IQR: Interquartile range; SD: standard deviation; PD: pancreaticoduodenectomy, *i.e.*; classical Whipple; SSPPD: substomach-preserving pancreaticoduodenectomy; PPPD: pylorus-preserving pancreatoduodenectomy.

Preoperative factors such as the indication for surgery, disease stage, and prevalence of diabetes mellitus were not significantly different among the three groups.

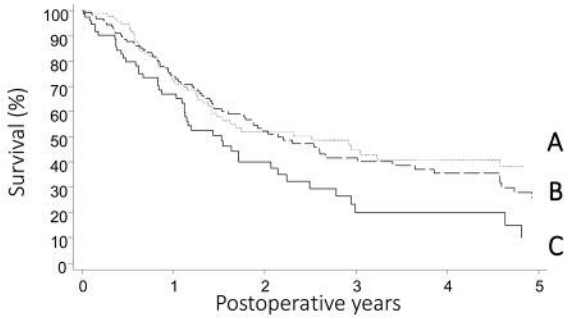
In terms of the operative factors, the median operative time was 445 minutes for group C, which was shorter than that in the other two groups, and was significantly shorter than that for group A. Concomitant resection of the portal vein was significantly low in group C as compared to the other groups (p=0.02).

Surgical procedures. All patients underwent laparotomy through a midline incision. Classic PD, subtotal stomach-preserving pancreaticoduodenectomy (SSPPD), or pylorus-preserving pancreaticoduodenectomy (PPPD) was performed after assessing resectability by excluding liver, peritoneal, or any other distant metastases. The extent of gastric resection (PD, SSPPD, or PPPD) was chosen according to the tumor extension or the preference of the attending surgeon. Reconstruction was conducted using a modified Child method. Basically, the pancreaticojejunostomy (PJ) procedure was performed in two-layer, end-to-side, duct-to-mucosa style with an external transabdominal pancreatic duct stent.

Definition of outcome measures. Postoperative pancreatic fistula (POPF) was defined according to the definitions proposed by the International Study Group on Pancreatic Fistulas (5). Delayed gastric emptying (DGE) was graded based on the International Study Group of Pancreatic Surgery consensus definition (6). Perioperative mortality in the present study was defined as death within 60 days of PD. The overall survival was determined as the period from the date of the surgery until the end of follow-up or the date of death from any cause. For pathological staging, the Union for International Cancer Control (UICC) classification was utilized (7).

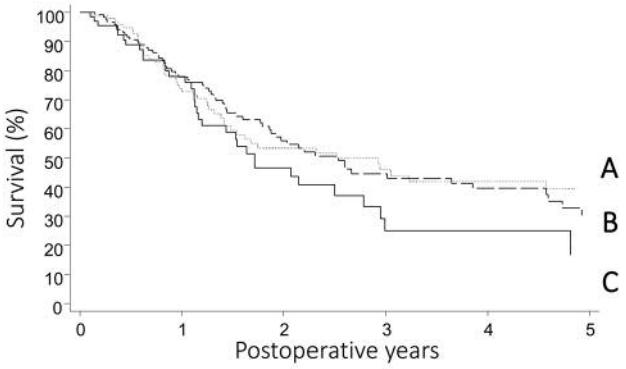
Assessments. The primary endpoint was to investigate the impact of age on short-term outcomes after PD, and the secondary endpoint was to evaluate long-term survival rates of the patients.

Statistical analysis. Results are presented as the mean±standard deviation or the median with interquartile ranges depending on data distribution. Continuous variables were compared between the study groups using the independent samples *t*-test or the Mann–Whitney *U*-test. Categorical data were compared using the chi-squared test and Fisher's exact test, as appropriate. Kaplan–Meier survival curve estimates and log-rank tests were used to compare survival rates. Significant prognostic factors depicted in the univariate analysis were entered into Cox proportional hazards analyses to determine the prognostic value for overall survival. Patients who died within 60 days of PD were excluded from analyses of prognostic factors. All p-values were two-sided, and a value of $p<0.05$ was considered significant. All analyses were performed using Stata Version 12.0 (StataCorp LP, College Station, TX, USA).



	5-year survival (%)	Median survival (months)
Group A (n=115)	38.3	30.6
Group B (n=144)	25.7	26.1
Group C (n=81)	9.9	18.6

Figure 1. *Five-Year overall survival according to age group: Group A, the non-elderly (aged 64 years or younger); group B, the early elderly (65-74 years); and group C, the late elderly (75 years or older). The rate for group C was the lowest and significantly lower than those for the other groups ($p<0.01$ compared with group A; $p<0.02$ compared to group B.*



	5-year cancer-specific survival (%)
Group A (n=115)	39.3
Group B (n=144)	30.3
Group C (n=81)	16.7

Figure 2. *Five-Year cancer-specific survival rate according to age group: Group A, the non-elderly (aged 64 years or younger); group B, the early elderly (65-74 years); and group C, the late elderly (75 years or older). The rate for group C was the lowest although no significant difference was observed among the three groups ($p=0.17$ C compared with group A; $p=0.12$ compared to group B).*

Results

Perioperative outcomes. There were no differences in the median duration of postoperative hospital stay, the incidence of postoperative major complications such as POPF, DGE, and total intra-abdominal complications among the three groups (Table II). Groups B and C experienced significantly higher rates of reoperation than group A. Group C had the highest mortality rate of 6.3% ($p=0.04$). Among the five deaths in group C, three were due to infection, such as pneumonia and catheter infection, whereas no infection-related death was observed in groups A and B.

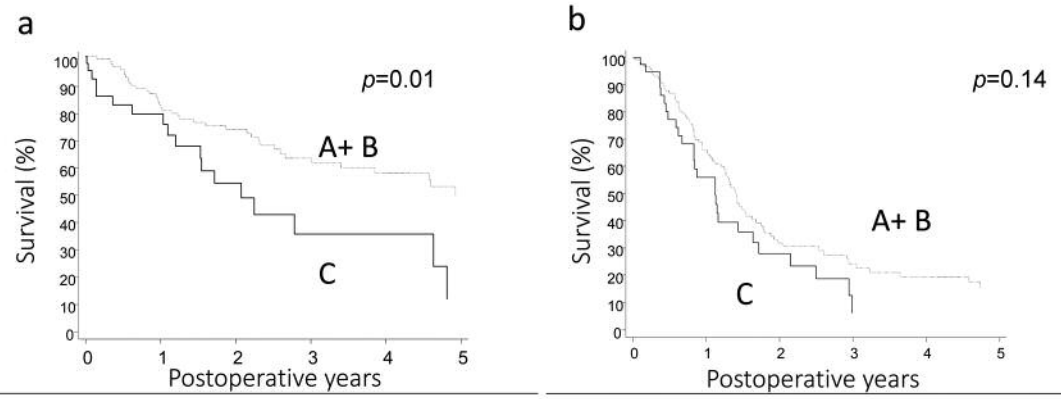
Long-term survival. Group C yielded a significantly lower 5-year overall survival as compared to the other two groups. The difference between group A and B was not significant (Figure 1). The 5-year cancer-specific survival rate of 16.7% in group C was the lowest, although there was no significant difference observed among the three groups (Figure 2).

Figure 3 shows the Kaplan–Meier curves for 5-year overall survival according to the pathological diagnosis for operative indication. For those with non-pancreatic cancer, the overall survival rate in group C was significantly lower than that in their counterparts (groups A and group B), with a median survival time of 25.2 months (Figure 3a). For those with pancreatic cancer, the median survival time in group C was only 13.7 months; however, the survival rate of group C was not significantly lower than that of groups A and B (Figure 3b).

Prognostic factors. Table III provides the results of univariate and multivariate analyses of prognostic factors for the three groups. In the univariate analysis, the diagnosis of pancreatic cancer, its stage, intraoperative blood loss, concomitant resection of the portal vein, and intra-abdominal complications were identified as risk factors for poorer survival rate in group A or B. In group C, reoperation was identified as a risk factor in addition to the disease and its stage.

In the multivariate analysis, pancreatic cancer was noted as an independent prognostic factor in groups B and C. UICC stage was noted as an independent prognostic factor in groups A and B but not in group C. Concomitant resection of the portal vein was noted as an independent prognostic factor in group A. Reoperation was noted as an independent prognostic factor in group C.

Figure 4 shows the Kaplan–Meier curves for 5-year overall survival of patients with pancreatic cancer according to the UICC stage in groups A and B *versus* group C. In groups A and B, a significant difference in survival rates by stage was observed (Figure 4a); however, in group C, no difference in survival rates by stage was observed (Figure 4b). The median survival duration in groups A and B depended on disease stage. However, this trend was not noted for group C patients.



	5-year survival (%)	Median survival (months)
Group A + B (n=124)	49.3	59.9
Group C (n=38)	11.8	25.2

	5-year survival (%)	Median survival (months)
Group A + B (n=135)	15.6	17.0
Group C (n=43)	6.2	13.7

Figure 3. *Five-Year overall survival according to the indication for surgery by age group: Group A, the non-elderly (aged 64 years or younger); group B, the early elderly (65-74 years); and group C, the late elderly (75 years or older). a: Non-pancreatic cancer. The survival rate for group C (median survival time of 25.2 months) was significantly lower than that for groups A and B (p=0.01). b: Pancreatic cancer. The median survival time for group C was only 13.7 months, although the survival rate for group C was not significantly lower than that of groups A and B (p=0.14).*

Discussion

Previous studies in past fast two decades have compared the mortality and morbidity among younger and elderly patients who underwent PD (3, 8-11). In the majority of these studies, postoperative mortality and morbidity of older patients were slightly higher, but comparable to those of younger patients; however, the differences were significant in several large series (3, 8-11). In the present study, compared to patients younger than 75 years, patients aged 75 years and over had a significantly higher mortality rate, with half of the deaths being infection-related, such as pneumonia and sepsis due to catheter infection. Recently, a statistically significant increase in postoperative pneumonia in elderly patients (odds ratio in those aged 75 years or older as compared to their younger counterparts: 5.03; 95% confidence interval (CI)=2.45-10.34; $p<0.0001$) (12) and postoperative pneumonia following PD as a high risk factor of mortality have been reported (13). Faraj *et al*. noted that septic shock has a significantly higher incidence (6.5%) in patients over the age of 65 years, and was an independent risk factor for mortality (14). Aging of the immune system is observed because the capacity of the immune system to properly handle foreign microorganisms decreases with advanced age (15).

As to the significantly shorter operative time and the lowest rate of concomitant resection of the portal vein in group C, shorter operative times in elderly groups has been reported in other series (16), that may be linked to the surgeon's willingness to shorten the operative time for the older patients considering that they are at greater risk. The lowest rate of concomitant resection of the portal vein being found in this group may also reflect cautious patient selection to avoid older patients with advanced pancreatic cancer because of their postoperative life expectancy (17).

To date, several studies have evaluated the long-term survival of elderly patients undergoing PD. Most of the studies showed a lower 5-year survival or shorter median survival in the elderly group, although the difference often did not reach significance, possibly because of small sample sizes (3, 8, 18, 19). One interpretation for the lower overall long-term survival of group C may be due to chronological age because there were no differences in cancer-specific survival between the three groups. However, there is still a possibility of lowered long-term survival due to cancer-related death because there was a tendency for poorer cancer-specific survival of group C as compared to the other two groups. Elderly patients are expected to be less likely to tolerate chemotherapy and the drop-out rate will be higher. In fact, patients aged 75 years or over are reported to be less likely to be treated with adjuvant therapy (9). Lahat and colleagues reported that only 15% of patients aged 70 years and over who underwent PD for pancreatic cancer received chemotherapy as compared to 68% of patients aged 69 years and younger ($p=0.003$) (19).

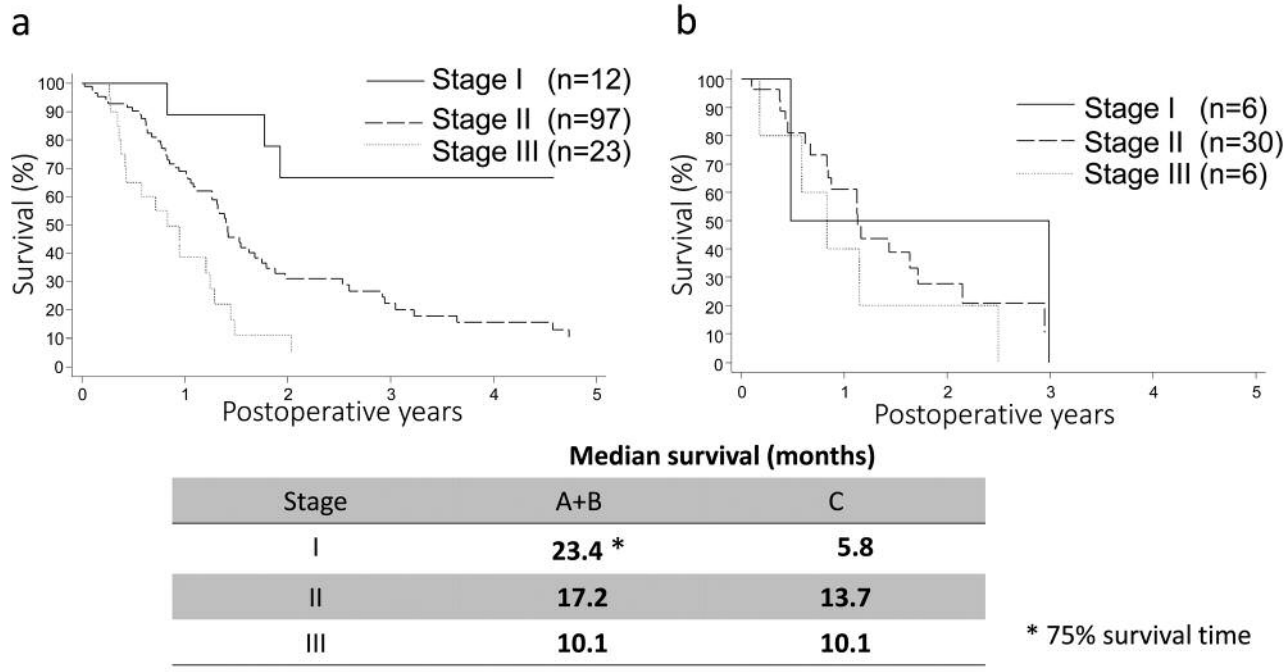


Figure 4. *Five-Year overall survival rates of pancreatic cancer according to staging of the Union for International Cancer Control. a: Age <75 years. The differences in survival rates by stage were significant (stage I vs. II: p=0.006; stage II vs. III: p=0.004). b: Age ≥75 years. The differences in survival rates by stage were not significant (stage I vs. II: p=0.38; stage II vs. III: p=0.29; stage I vs. III: p=0.38).*

Table II. *Short-term outcomes by age.*

Factor	Group A Age <65 years (n=115)	Group B Age (65-74) years (n=144)	Group C Age (≥75) years (n=81)	*p*-Value
Postoperative hospital stay (days), median (interquartile range)	26.5 (22-35)	30 (23-38)	30 (25-38)	0.36
Postoperative complication				
POPF (grade B or C), n (%)	18 (15.7%)	22 (15.3%)	13 (16.5%)	0.96
DGE (grade B or C), n (%)	24 (20.9%)	42 (29.2%)	17 (21.0%)	0.20
Bile leakage, n (%)	4 (3.5%)	8 (5.6%)	0	0.08
Intra-abdominal abscess, n (%)	12 (10.4%)	15 (10.4%)	7 (8.6%)	0.92
Intra-abdominal fluid collection, n (%)	6 (5.2%)	13 (9.0%)	3 (3.7%)	0.26
Intra-abdominal complications*, n (%)	25 (21.7%)	40 (27.8%)	17 (21.0%)	0.38
Reoperation, n (%)	0	11 (7.6%)	4 (4.9%)	0.003
Mortality	1 (0.9%)	3 (2.1%)	5 (6.3%)	0.04
Pseudoaneurysm rupture	0	1	1	
Liver metastasis	1	0	1	
Myocardial infarction	0	1	0	
Bone marrow hypoplasia	0	1	0	
Pneumonia	0	0	2	
Catheter infection	0	0	1	

POPF: Postoperative pancreatic fistula; DGE: delayed gastric emptying. *Intra-abdominal complications included pancreatic fistula, bile leakage, intra-abdominal abscess, intra-abdominal fluid collection, and intra-abdominal bleeding.

Table III. *The results of the univariate and multivariate analyses of prognostic factors for survival by age after pancreaticodudenectomy.*

	Age <65 years (n=114)					Age (65-74) years (n=141)					Age (≥75) years (n=76)				
	Median survival (days)	Univariate *p*-Value	HR	Multivariate 95%CI	*p*-Value	Median survival (days)	Univariate *p*-Value	HR	Multivariate 95%CI	*p*-Value	Median survival (days)	Univariate *p*-Value	HR	Multivariate 95%CI	*p*-Value
Gender															
Male	1066	0.45				925	0.96				563	0.89			
Female	593					805					598				
Diabetes mellitus															
Yes	541	0.58				743	0.62				563	0.24			
No	1074					842					598				
Indication															
Ampullary cancer	N.A.	0.001	Ref.			3077	0.0002	Ref.			757	0.03	Ref.		
Bile duct cancer	918		2.82	0.52-15.20	0.23	1100		2.16	0.78-5.94	0.14	820		0.91	0.25-3.21	0.88
Pancreatic cancer	518		2.75	0.63-12.08	0.18	511		4.06	1.55-10.58	0.004	412		3.20	1.09-9.42	0.03
Stage															
0, I	N.A.	<0.0001	Ref.			3077	0.0001	Ref.			1091	0.01	Ref.		
II	518		3.40	4.48e+09-2.58e+11	0.001>	681		2.87	1.31-6.26	0.01	598		1.34	0.47-3.83	0.58
III	454		3.54	6.61e+09-4.64e+11	0.001>	470		5.13	2.13-12.37	0.001>	558		2.01	0.60-6.72	0.26
Operative time															
≤Median	638	0.31				947	0.71				412	0.02	0.31	0.15-0.65	0.01>
>Median	1066					743					912				
Blood loss															
≤Median	506**	0.01	Ref.			925	0.49				626	0.88			
>Median	517		1.19	0.60-2.37	0.61	784					563				
Resection of portal vein															
Yes	344	0.001	3.24	1.09-9.61	0.03	511	0.16				N.A.	0.83			
No	1074					947					563				
POPF															
Yes	N.A.	0.07				972	0.47				820	0.97			
No	638					784					598				
DGE															
Yes	506	0.19				585	0.09	1.61	0.96-2.67	0.07	558	0.89			
No	1066					947					563				
Intra-abdominal complications*															
Yes	2965	0.04	0.72	0.29-1.81	0.49	1100	0.12				820	0.78			
No	614					721					598				
Reoperation															
Yes	N.A.	N.A.				N.A.	0.80				226	0.02	12.09	2.39-61.11	0.01>
No		918					805					626			

HR: Hazard ratio; CI: confidence interval; N.A.:not available; POPF: postoperative pancreatic fistula; DGE: delayed gastric emptying. *Intra-abdominal complications included pancreatic fistula, bile leakage, intra-abdominal abscess, intra-abdominal fluid collection, and intra-abdominal bleeding. **75% Survival time.

Recent studies have highlighted the clinicopathological factors influencing overall survival following PD, such as disease for PD indication, tumor size, lymph node metastases, and histological grade (20, 21). Among these factors, pancreatic cancer and UICC stage were highlighted in the present study. Regarding PD for non-pancreatic cancer, patients aged 75 years and over could have a relatively favorable long-term survival, while only non-elderly patients could yield a favorable long-term survival following PD for pancreatic cancer, but only in those with early-stage disease. The median survival for patients treated by radiochemotherapy alone was 8.9 months (22). Considering the impact of the disease, patients with pancreatic cancer should be separated from those with other types of cancers when considering PD. Another prognostic factor detected in the present study was cancer stage. In groups A and B, the effect of UICC stage on median survival for those with pancreatic cancer was obvious. On the other hand, in the patients aged 75 years and over, no impact of stage was found. With regard to pancreatic cancer in the elderly, the indication for PD, particularly in advanced cases, should be decided very carefully because additional chemotherapy is often not feasible (9). Particularly for those aged 75 years and over, performance of reoperation was the third prognostic factor in this study. A higher rate of reoperation in the elderly has been reported (23) and surgical complications that lead to reoperation are responsible for high mortality in elderly patients (10). Comorbidity, concomitant systemic disorders, reduced functional reserve, and subsequent poor tolerance to repeated surgical stress are the possible factors responsible for the high mortality rate after reoperation in elderly patients (24).

The limitations of the current study are its retrospective nature and the inability to evaluate frailty-related factors including comorbidities, such as cardiovascular diseases, ASA score, and preoperative nutritional status. These factors have been shown to affect patient outcome (22). Some patient data regarding adjuvant chemotherapy are also missing. Thereby, it was not possible to determine the contribution of cancer-related deaths to the lower overall survival.

Conclusion

We confirmed the validity of PD for bile duct cancer and ampullary cancer as a treatment option if appropriate preoperative evaluation and postoperative management are applied in elderly patients. Mortality associated with infectious diseases was high in patients over 75 years of age, and their long-term outcomes tended to be worse than those in the non-elderly. On the other hand, caution should be exercised for selection of PD in patients with pancreatic cancer, particularly in those with advanced stages.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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Received July 10, 2017
Revised July 30, 2017
Accepted August 1, 2017