Original Article

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Age does not affect complications and overall survival rate after pancreaticoduodenectomy: Single-center experience and systematic review of literature

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Summary **We aimed to evaluate the feasibility of pancreaticoduodenectomy (PD) in elderly patients. We retrospectively analyzed data from 206 patients who underwent PD between 2008 and 2015. The patients were divided into two groups: patients aged < 70 years (n = 117) and those aged ≥ 70 years (n = 89). To update the outcome of PD in elderly patients, we performed a systematic review of published work. The preoperative patient characteristics were similar between the two groups except for hypertension, which was significantly more frequent in the older group (25% *vs.* 52%; $p < 0.001$). There was no difference in the mortality (0% *vs.* 1%; $p = 0.43$) or morbidity (26% *vs.* 20%; $p = 0.41$) rates between the two groups. The overall survival rate in patients with pancreatic cancer between the two groups did not differ ($p = 0.40$). Twenty-one studies, including our own, were identified in the published work. The overall median morbidity and mortality rates of the elderly patients were 41.5% (range, 20-78%) and 5.8% (range, 0-10.5%), respectively. PD is feasible in elderly patients with acceptable morbidity and mortality rates.**

Keywords: Pancreaticoduodenectomy, elderly, complication, mortality, pancreatic neoplasm

1. Introduction

In the early 1990s, pancreaticoduodenectomy (PD) was rarely performed in elderly patients because of the high postoperative morbidity and mortality rates, even in young patients. During the last two decades, the mortality rates after pancreatic resection have decreased to no more than 2% in experienced centers (*1,2*), with an acceptable morbidity rate.

Several reports have shown that postoperative complication rates of surgical resection in elderly patients are similar to those in younger patients, and the overall survival is comparable (*3-5*). Others have shown the contrary, *i.e.*, elderly patients have a higher mortality rate, have a tendency to stay longer in the intensive care unit, have higher incidences of postoperative cardiac events, experience more nutritional and functional difficulties, and show a higher rate of readmission compared to younger patients (*6-8*).

The aim of the present study was to compare the postoperative complication rate and overall survival between patients younger and older than 70 years old who underwent PD. Moreover, we performed a systematic review of the literature related to complications of PD in elderly patients.

2. Materials and Methods

2.1. *Patients*

A prospectively collected database of 206 patients who underwent PD from January 2008 to December 2015 in our department was retrospectively analyzed. The patients who had a performance status of 2 or more,

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symptomatic cardiac or pulmonary insufficiency, renal failure with dialysis, or dementia were considered as contraindicated for PD regardless of age in our department. Neoadjuvant chemotherapy or radiotherapy was not performed.

Patients who underwent PD were divided into two groups: patients aged < 70 years (young group) and patients aged ≥ 70 years (old group). The two groups were compared in terms of preoperative demographic features, comorbidities, surgical procedures, postoperative outcomes, nutritional status, and survival. Preoperative comorbidities included diabetes mellitus, chronic obstructive pulmonary disease, hypertension, coronary artery disease, cardiac insufficiency, renal insufficiency, and cerebrovascular disease.

The surgical procedure included exploration, tumor resection and regional lymph node dissection. Subtotal stomach-preserving PD with reconstruction through pancreaticojejunostomy or pancreaticogastrostomy was performed. Pancreaticogastrostomy was performed in patients with soft pancreatic texture or a small pancreatic duct. In patients with portal vein invasion, portal vein resection was associated with PD. One of the two staff surgeons in our institution always participated in the operation as either the operator or instructor, and PD was performed in the same manner for all patients.

Postoperative mortality was defined as death within 30 days after the operation or during hospitalization. A postoperative pancreatic fistula (POPF) was defined according to the criteria of the International Study Group of Pancreatic Fistula (ISGPF) (*9*); postoperative pancreatic hemorrhage (PPH) according to the criteria of International Study Group of Pancreatic Surgery (ISGPS) (*10*); bile leakage according to the International Study Group of Liver Surgery (ISGLS) (*11*), delayed gastric emptying (DGE) according to the ISGPS criteria (*12*). Postoperative abdominal complications were recorded and graded according to the Dindo-Clavien classification (*13*). Grade III or IV complications were categorized as severe complications. Nutritional status was evaluated using prognostic nutritional index (PNI) (*14*). PNI was calculated by the following formula: 10 × serum albumin level (g/dL) × absolute lymphocyte count (number/mm^2). PNI was evaluated preoperatively and 6 months postoperatively.

2.2. *Review of literature*

To understand the outcomes of PD in elderly patients, we performed a systematic review of published work on this topic based on the data available on PubMed (1976-2015). The search strategy used the following terms: "pancreaticoduodenectomy, complication, aged, and 70." Related citations in the retrieved articles were also reviewed. Postoperative mortality and morbidity rates and the length of hospital stay were analyzed.

2.3. *Statistical analysis*

Statistical analysis was performed using JMP 11 software (SAS Institute Inc., Cary, NC). Categorical variables were analyzed using Chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed using the Wilcoxon rank-sum test. The overall survival curves were determined using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were two-tailed and p-values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. *Patient characteristics*

During the study period, 206 patients underwent PD in our department: 117 patients belonged to the young group and 89 patients belonged to the old group. Patients underwent PD for pancreatic cancer (47%), bile duct cancer (26%), intraductal papillary mucinous neoplasm (13%), ampullary cancer (8%), and other diseases (6%). The preoperative patients characteristics were similar between the two groups except for hypertension, which was significantly more frequent in the old group (25% *vs*. 52%; $p < 0.001$), and the preoperative hemoglobin level, which was significantly lower in the old group [12.3 g/dL (interquartile range: 11.4-13.6) *vs*. 11.7 g/dL (interquartile range: 10.7-12.6); $p = 0.005$] (Table 1).

There were no differences in the operative time, pancreatic texture, anastomosis, concomitant other procedures (*e.g.*, colectomy and hepatectomy), or the vascular resection frequency between the two groups (Table 2). However, intraoperative blood loss was larger [823 mL (interquartile range, 548-1269 ml) *vs*. 1020 mL (interquartile range, 655-1564 mL); $p = 0.04$] and the red blood cell transfusion rate was higher in the old group (20% *vs*. 33%; $p = 0.04$).

3.2. *Short-term outcomes*

Of the 206 patients, only one patient died of postoperative pancreatic fistula. There was no difference in the mortality rate (0% *vs*. 1%; $p = 0.43$) and complication rates (26% *vs*. 20% $p = 0.41$) between the two groups (Table 3). The most frequent complication in both groups was pancreatic fistula: grade A [6/117 (5%) *vs*. 2/89 (2%); $p = 0.47$], grade B [24/117 (21%) *vs*. 13/89 (15%); $p = 0.35$] grade C [1/117 (1%) *vs*. 2/89 (2%); $p = 0.57$]. There were no differences in the postoperative length of hospital stay: 23 days (interquartile range, 18-29 days) *vs*. 23 days (interquartile range, 19-31 days); $p = 0.95$.

There were no differences in the mortality rate [0/101 (0%) *vs*. 1/83 (1%); $p = 0.45$] and complication rate [23/101 (26%) *vs*. 17/83 (20%); $p = 0.72$] between the two groups in the malignancy patients sub-group.

Table 1. Preoperative baseline characteristics of the younger (age < 70) and the elderly (age ≥ 70) groups

Items	Age < 70, *n* = 117	Age ≥ 70, *n* = 89	*p*-value
Age (median (range), y)	63 (40-69)	75 (70-86)	< 0.001
Sex (Male/Female)	70/47 (60/40)	51/38 (57/43)	0.77
Body mass index (median (range), kg/m^2)	21.5 (14-34.3)	21.6 (15.6-31.2)	0.78
ASA score			
1-2	107 (91%)	76 (85%)	0.19
3-4	10 (9%)	13 (15%)	
Comorbidities			
Diabetes mellitus	29 (25%)	24 (27%)	0.75
COPD	23 (20%)	23 (26%)	0.31
Hypertension	29 (25%)	46 (52%)	< 0.001
Coronary artery disease	6 (5%)	8 (9%)	0.40
Cardiac insufficiency	1 (1%)	4 (5%)	0.17
Renal insufficiency	4 (3%)	4 (5%)	0.73
Cerebrovascular disease	5 (4%)	6 (7%)	0.54
Tabacco use	58 (50%)	32 (36%)	0.07
Ethanol use	39 (33%)	33 (37%)	0.66
Hemoglobin level (median (IQR), g/dL)	12.3 (11.4-13.6)	11.7 (10.7-12.6)	0.005
Malignancy	101 (86%)	83 (93%)	0.17
Pancreatic cancer	56 (48%)	42 (47%)	0.92
Bile duct cancer	30 (26%)	25 (28%)	0.69
Ampullary cancer	8 (7%)	9 (10%)	0.40
Other	7 (6%)	7 (8%)	0.59

ASA, American society of anesthesiologist; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table 2. Intraoperative data of the younger (age < 70) and the elderly (age ≥ 70) groups

Items	Age < 70, *n* = 117	Age ≥ 70, *n* = 89	*p*-value
Operative time (median (IQR), min)	435 (IQR, 385-500)	440 (IQR, 378-525)	0.48
Portal vein resection	20 (17%)	21 (24%)	0.29
Pancreatic texture			0.12
Hard	100 (85%)	83 (93%)	
Soft	17 (15%)	6 (7%)	
Anastmosis			1.00
Pancreaticogastrostomy	5 (4.3%)	3 (3.4%)	
Pancreaticojejunostomy	112 (95.7%)	86 (96.6%)	
Additional procedure	18 (15%)	11 (12%)	0.69
Blood loss (median (IQR), mL)	823 (IQR, 548-1269)	1020 (IQR, 655-1564)	0.04
Patients requiring RBC transfusion	23 (20%)	29 (33%)	0.04
Patients requiring FFP transfusion	8 (7%)	12 (13%)	0.15

IQR, interquartile range; RBC, red blood cells; FFP, fresh frozen plasma.

Table 3. Short-term outcomes of the younger (age < 70) and the elderly (age ≥ 70) groups

Items	Age < 70, *n* = 117	Age ≥ 70, *n* = 89	*p*-value
Postoperative complication			
Pancreatic fistula*			
Grade A	6 (5%)	2 (2%)	0.47
Grade B	24 (21%)	13 (15%)	0.35
Grade C	1 (1%)	2 (2%)	0.57
Delayed gastric emptying	1 (1%)	0	1
Hemorrhage	0	0	0
Bile leakage	1 (1%)	0	1
Cholangitis	0	1 (1%)	0.43
Heart failure	0	1 (1%)	0.43
Pneumonia	0	0	0
Overall complication	30 (26%)	18 (20%)	0.41
Postoperative length of stay (median (IQR), d)	23 (IQR, 18–29)	23 (IQR, 19–31)	0.95
Mortality	0 (0%)	1 (1%)	0.43

Grade III to IV according to Dindo *et al*. Classification; *according to the criteria from the International Study Group of Pancreatic Fistula; IQR, interquartile range.

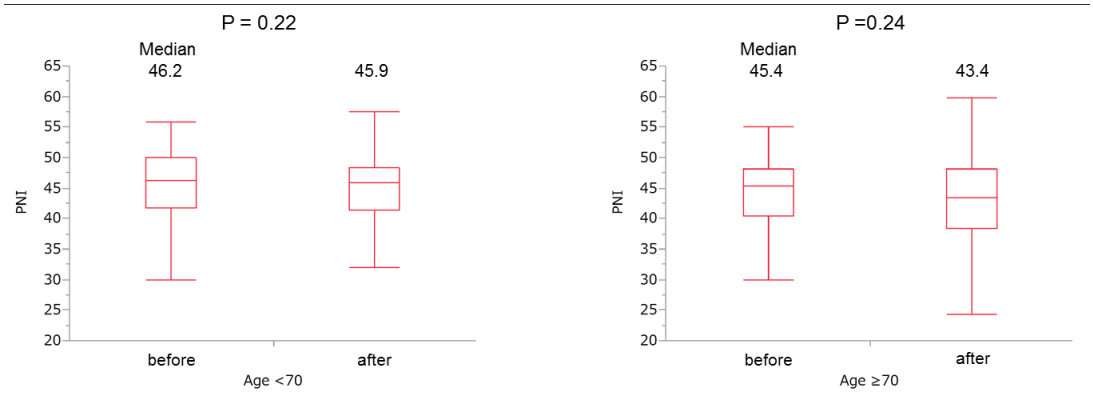

Figure 1. The prognostic nutritional index (PNI) before and after surgery of the younger (age < 70) and the elderly (age ≥ 70) groups.

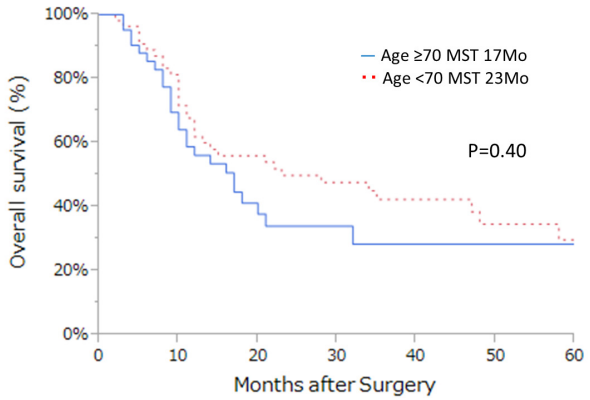

Figure 2. Overall survival of pancreatic cancer patients in the younger (age < 70) and the elderly (age ≥ 70) groups.

3.3. *Long-term outcomes*

Adjuvant chemotherapy was performed in 90 patients. There was no difference in the frequencies of adjuvant chemotherapy between the two groups (54% *vs*. 42%; $p = 0.102$). The preoperative and postoperative PNIs were not different in both groups (Figure 1).

Of the 206 patients, 98 patients underwent PD for pancreatic cancer. Among the 98 patients, there were no differences in the frequencies of R0 resection [45/56 (80%) *vs*. 27/42 (64%); $p = 0.11$], histological papillary or well differentiated adenocarcinoma [16/56 (29%) *vs*. 8/42 (19%); $p = 0.35$], and the Union for International Cancer Control (UICC) cancer stage I or II [5/56 (9%) *vs*. 3/42 (7%); $p = 1.00$] between the two groups.

The median survival time of the young group and old group was 23 and 17 months, respectively (Figure 2). The overall survival between the two groups did not differ ($p = 0.40$). The overall 1-, 3-, and 5-year survival rates of the young group were 62%, 42%, and 25%, respectively, and those of the old group were 56%, 28%, and 28%, respectively.

3.4. *Systematic review*

A review of the published work on the complications of PD in the elderly is shown in Table 4. A total of 21 studies were identified (*15-34*). A total of 6,933 PDs were collected, and of these, 1,931 PDs (27.9%) were performed in elderly patients. The overall median morbidity and mortality rates of the elderly patients were 41.5% (range, 20-78%) and 5.8% (range, 0-10.5%), respectively. Fourteen studies showed that the outcome after PD was not different between the young and old groups. Two studies showed that morbidity and mortality of elderly patients were worse than those of younger patients. Five studies showed that either the morbidity or the mortality of the old group was worse than that of the young group.

4. Discussion

In the present study, patients aged ≥ 70 years had similar outcomes compared to those aged < 70 years, with no differences in the morbidity, mortality, or pancreatic fistula rates. The older group also had lengths of hospital stay similar to that of the young group. There was no difference in the postoperative nutritional state or tolerance of adjuvant chemotherapy between the two groups. Overall survival after the resection of pancreatic cancer was similar between the two groups. Therefore, PD is feasible and can be safely performed in elderly patients with acceptable postoperative survival.

We set 70 years as the cut-off value, because it was the most frequent value used in the literature. Several papers showed that age is one of the risk factors for postoperative complications. Kimura *et al*. reported that age was a risk factor for mortality using the Japanese national clinical database (*6*). However, the indication of PD in the elderly differs among institutions. One of the reasons why there was no difference in the morbidity rate in the present study may be the appropriate patient selection criteria in our department. The patients who had a performance status of 2 or more, symptomatic cardiac or pulmonary insufficiency, renal failure with dialysis, or dementia were considered as contraindications for PD regardless of age in our department, similar to the criteria proposed by Tzeng

Table 4. Postoperative outcome of pancreaticoduodenectomy for elderly patients published in the English literature

Author	Year	*n*	Mortality (%)	*p*-value	Morbidity (%)	*p*-value	Postoperative hospital stay (d)	*p*-value
Fong (*15*)	1995	350 *vs*. 138	4 *vs*. 6	NS	39 *vs*. 45	NS	20 *vs*. 20	NS
Richter (*16*)	1996	293 *vs*. 45	1.9 *vs*. 4.3	Not reported	22 *vs*. 39	Not reported	Not reported	Not reported
Dicarlo (*17*)	1998	85 *vs*. 33	4 *vs*. 6	NS	33 *vs*. 39	NS	17 *vs*. 17	NS
Bottger (*18*)	1999	300 (total)	3.2 *vs*. 2.3	NS	22.1 *vs*. 30.2	Not reported	Not reported	Not reported
al-Sharaf (*19*)	1999	47 *vs*. 27	4 *vs*. 7	NS	46 *vs*. 45	NS	16 *vs*. 13	NS
Hodul (*20*)	2001	74 *vs*. 48	1.4 *vs*. 0	NS	35 *vs*. 40	NS	11 *vs*. 12	NS
Muscari (*21*)	2006	248 *vs*. 52	8 *vs*. 17	< 0.03	38 *vs*. 42	NS	Not reported	Not reported
Brozetti (*22*)	2006	109 *vs*. 57	3.7 *vs*. 10.5	NS	46 *vs*. 49	NS	16 *vs*.16	NS
Kang (*23*)	2007	66 *vs*. 11	1.5 *vs*. 0	NS	38 *vs*. 73	0.049	23 *vs*. 29	NS
Ouaissi (*24*)	2008	150 (total)	0 *vs*. 16	Not reported	36 *vs*. 56	NS	19 *vs*. 21	NS
Shin (*25*)	2011	36 *vs*. 19	2.7 *vs*. 0	NS	52.8 *vs*. 57.9	NS	30.2 *vs*. 37.8	0.148
de Franco (*26*)	2011	41 *vs*. 41	2.5 *vs*. 5	NS	78 *vs*. 71	NS	29 *vs*. 30	NS
Haigh (*27*)	2011	1633 *vs*. 977	1.7 *vs*. 4.3	< 0.001	34 *vs*. 41	0.001	Not reported	Not reported
Lahat (*28*)	2011	173 *vs*. 120	2.3 *vs*. 5.8	0.02	29 *vs*. 41	0.01	20 *vs*. 28	< 0.0001
Brachet (*29*)	2012	173 (total)	4.1 *vs*. 12	NS	Not available	0.002	Not available	Not available
Kanda (*30*)	2014	272 (total)	0 *vs*. 0	NS	40 *vs*. 35	NS	Not reported	Not reported
Sun (*31*)	2014	208 *vs*. 88	1.0 *vs*. 1.1	NS	61 *vs*. 78	0.003	28 *vs*. 30	NS
Adham (*32*)	2014	228 *vs*. 116	3.9 *vs*. 13	0.003	68 *vs*. 72	NS	23 *vs*. 25	NS
Zhang (*33*)	2015	148 *vs*. 70	3.4 *vs*. 8.8	NS	54 *vs*. 41	NS	20 *vs*. 25	0.013
Urbonas (*34*)	2015	251 (total)	2.8 *vs*. 8.3	NS	22.4 *vs*. 29.6	NS	Not reported	Not reported
Present case	2016	117 *vs*. 89	0 *vs*. 1	NS	26 *vs*. 20	NS	23 *vs*. 23	NS

NS, not significant.

et al. (*35*). Postoperative hemorrhage, pancreatic fistula and delayed gastric emptying are the three most common surgical complications after PD. The incidence of these complications varies among studies. DiCarlo *et al*. (*17*) reported that patients aged ≥ 70 years had more relaparotomies and hemorrhagic complications following pancreatic resection. A French study by Scurtu *et al*. (*36*) demonstrated a statistically higher incidence of delayed gastric emptying in the old group. However, our study showed that there were no significant differences in these three complications between the two groups with similar postoperative length of hospital stay; this result was similar to that reported by Kanda *et al*. (*30*), Usuba *et al*. (*37*), and Hatzaras *et al*. (*38*). However, in our study, the red blood cell transfusion rate was higher in the old group. This may be due to the fact that elderly patients had preoperative anemia more frequently and more intraoperative blood loss than the young patients.

A literature review concerning PD in elderly patients is summarized in Table 4. In the vast majority of studies, the reported postoperative mortality and complication rates after PD were slightly higher in the group defined as elderly, but the difference was not statistically significant (Table 4) (*15-34*). Many of these series concluded that PD is feasible in elderly patients with acceptable morbidity and mortality rates, which is consistent with our conclusion.

Several single-institution studies have described long-term survival following PD in elderly patients for malignancy. The reported median overall survival ranged from 14-38 months and 5-year survival rates ranged from 12-31% (*15,17,27,39*). In the present study, the median survival time of the two groups were 17 months in the old group and 23 months in the young group. Furthermore, the 5-year survival rate was 28.3% and 24.7%, respectively. One of the reasons that the older patients exhibited a good long-term outcome, as well as the younger patients is patient selection. We performed PD for selected patients who were in good condition, without cardio-pulmonary disease and severe renal insufficiency. Thus, the older patients in this study had a good long-term outcome. These results are comparable with the previous reports and justify PD in elderly patients with pancreatic cancer.

A limitation of our study is the relatively small number of elderly patients and the retrospective nature of the study. Therefore, we attempted to overcome this limitation by adding a systematic review of the published work. There may be a selection bias (*i.e*., all subjects were a selected subset of relatively fit patients in the old group): however, the preoperative characteristics were similar between the two groups. As shown in the recent evidence (*33,40*), PD is certainly a feasible procedure in selected elderly patients.

Several studies have shown that age is a risk factor for postoperative morbidity and mortality following PD (*27,41*). However, others (including ours) have demonstrated that there are no differences in the incidence of postoperative complications between the two groups (*3-5*). These results may indicate that the patient selection and preoperative recognition of high-risk patients are important in elderly patients before PD. Several methods for assessing the surgical risk of the old group have been introduced in clinical practice: Charlson comorbidity index (*42*), G8 geriatric screening tool (*43*), and Adult Comorbidity Evaluation-27 (*44*). These scoring systems may be helpful in selecting

elderly patients before PD.

In conclusion, PD is feasible in elderly patients with acceptable morbidity and mortality rates. Moreover, the overall survival rate in patients with pancreatic cancer did not differ between the old and young groups.

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