

## Short-term results of pancreatoduodenectomy in patients over 70 years old

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### ABSTRACT

**Objective** — to analyze the immediate results of PDE in patients younger and older 70 years.

**Material and methods.** The study included patients who underwent PDE for various indications from March 2010 to February 2019. All patients are divided into 2 groups: <70 years old and ≥70 years old. Primary endpoints were postoperative mortality and complication rate.

**Results.** There were 110 procedures within 9 years. There were 93 patients aged <70 years (group 1) and 17 patients aged ≥70 years (group 2). ASA (American Society of Anesthesiologists) and PMP scores (Preoperative Mortality Predictor) were higher in group 2: 3 (2—3) vs 2 (1—3) ( $p=0,002$ ) and 12 (6—15) vs 6.5 (5—15) ( $p<0.001$ ), respectively. Mortality rate was higher in group 2 (11.7% vs. 3.2%) without statistical significance ( $p=0.16$ ). Overall morbidity (72% vs 76%;  $p=1.0$ ), incidence of major complications grade ≥IIIa (29% vs 29%), delayed gastric emptying B/C (17.2% vs 17.6%), pancreatic fistula grade B/C (23.6% vs 35.3%,  $p=0.3$ ), biliary fistula grade B/C (7.5% vs 11.8%;  $p=0.62$ ), postoperative hospital-stay [22 (8—165) days vs 23 (9—71) days;  $p=0.92$ ] were comparable in both groups.

**Conclusion.** Short-term results of PDE in patients aged <70 and ≥70 years are comparable despite higher ASA and PMP scores in the group 2. General status and concomitant diseases should be considered during selection of patients with resectable tumors for PDE. Age per se is not a contraindication for surgery.

*Keywords:* pancreatoduodenectomy, mortality, complications, advanced age.

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## Background

Pancreatoduodenectomy (PDE) is preferred for malignant tumors of the pancreatic head and periampullar area. This procedure improves survival and increases life expectancy. Much less often, this intervention is performed for some benign diseases. Postoperative mortality and morbidity are still high despite improvement of surgical technique and concentration of patients in specialized centers (0-5 and 38-52%, respectively) [1-5]. Incidence of pancreatic head cancer is increased with age. The last fact and aging of human population result an increase of the absolute number of advanced age patients. The results of treatment of pancreatic head cancer are still not satisfactory even after R0-resection: 5-year survival is 15–20% [6–8]. High surgical risk and small long-term

survival naturally forces the surgeon to ask the question of the appropriateness of intervention in advanced age patient and weigh the pros and cons. Age is often the factor that convinces you to abandon surgery, even if elderly patient is comparable to a younger patient by other aspects. The purpose of this study was to analyze the immediate results of PDE in patients younger and older 70 years.

## Patients and methods

The study included patients who underwent PDE for various indications from March 2010 to February 2019. All patients are divided into 2 groups: <70 years old and ≥70 years old. Primary endpoints were postoperative mortality and complication rate. Postoperative mortality was defined as mortality within in-hospital period after sur-

Table 1. Diagnoses in both groups.

Characteristics of patients	Group 1 <70 years old n=93	Group 2 ≥70 years old n=17	<i>p</i>
Age	57 (21-69)	74 (71-79)	<0,001
Male gender	46 (49,5%)	6 (35,3%)	NS
Diagnosis			NS
pancreatic cancer (ductal adenocarcinoma)	47 (50,5%)	9 (52,9%)	
MDP cancer	19 (20,4%)	7 (41,2%)	
chronic pancreatitis	7	—	
cystic tumors	5	1	
neuroendocrine neoplasia	4	—	
distal common bile duct carcinoma	3	—	
MDP adenoma	2	—	
metastases	2	—	
duodenal cancer	1	—	
acinar cell carcinoma	1	—	
Bile duct cysts	1	—	
duodenal fistula	1	—	

Table 2. Clinical and surgical characteristics of patients.

Clinical and surgical characteristics	Group 1 <70 years old n=93	Group 2 ≥70 years old n=17	<i>p</i>
ASA	2 (1-3)	3 (2-3)	<b>0,002</b>
ASA I	7 (7,5)	0	0,6
ASA II	52 (56%)	3 (17,6%)	<b>0,007</b>
ASA III	34 (36,5%)	14 (82,4%)	<b>&lt;0,001</b>
Revised Cardiac Risk Index	1 (0-3)	1 (1-3)	0,49
PMP score	6,5 (5-15)	12 (6-15)	<b>&lt;0,001</b>
Diabetes mellitus, n (%)	15 (16%)	8 (47%)	<b>&lt;0,001</b>
Total bilirubin prior to surgery, μmol/l	18 (5,5-221)	27,1 (4,9-119)	0,59
Preoperative jaundice (total bilirubin >21 μmol/l)	40 (43%)	9 (52,9%)	0,6
Total bilirubin >50 μmol/l, n (%)	19 (20,4%)	4 (23,5%)	0,75
Cholangitis, n (%)	10 (10,8%)	2 (11,8%)	1
Preoperative biliary drainage, n (%)	54 (58%)	13 (76,5%)	0,18
Albumin	40 (26-53)	38 (31-43)	0,09
BMI, kg/m <sup>2</sup>	25 (17-42,6)	24,4 (21-33,7)	0,8
BMI ≥30 kg/m <sup>2</sup> , n (%)	16 (17,2%)	3 (17,6%)	0,59
Fistula Risk Score	3 (0-8)	2 (0-5)	0,25
Blood loss, ml	400 (100-2500)	300 (200-1000)	0,94
Duration of surgery, min	375 (240-690)	360 (240-540)	0,2
Portal vein resection	11	0	0,2

ger regardless length of hospital-stay. Major complications (Clavien-Dindo grade ≥ IIIa [9]) and PDE-specific complications (gastrostasis, pancreoenterostomy failure and bleeding) in accordance with ISGPS definitions were compared [10-12]. The following prognostic scales were used to unify and compare severity of initial conditions of patients considering concomitant diseases: ASA (American Society of Anesthesiologists) [13], PMP (Preoperative Mortality Predictor) [14] and RCRI (Revised Cardiac Risk Index) [15]. Risk of pancreoenterostomy failure was assessed in all patients in accordance with the

Fistula Risk Score system proposed by ISGPS (International Study Group of Pancreatic Surgery) [16].

### Statistical analysis

All numerical variables are shown as median, minimum and maximum values (Me (min-max)). Quantitative data were compared using Mann-Whitney test, qualitative variables —  $\chi^2$  or Fisher's exact test (for sample size <5). Between-group differences were significant at *p*-value <0.05. Statistical analysis was performed using Statistica 8.0 software package.

**Table 3. Postoperative mortality and complications.**

Postoperative outcomes	Group 1 <70 years old n=93	Group 2 ≥70 years old n=17	<i>p</i>
Mortality	3 (3,2%)	2 (11,7%)	0,16
Complications	67 (72%)	13 (76%)	1,0
max grade ≥IIIa	27 (29%)	5 (29%)	
max grade ≥IIIb	17 (18,3%)	4 (23,5%)	0,73
Specific complications	48 (51,6%)	10 (58,8%)	0,6
Specific complications B/C	40 (43%)	9 (52,9)	0,6
Gastrostasis	24 (25,8%)	5 (29,4%)	0,76
B/C	16 (17,2%)	3 (17,6%)	
Pancreatoenterostomy failure	24 (25,8%)	6 (35,3%)	0,4
B/C	22 (23,6%)	6 (35,3%)	0,3
Hepaticoenterostomy failure	7 (7,5%)	2 (11,8%)	0,62
B/C	7 (7,5%)	2 (11,8%)	
Intra-abdominal bleeding	11 (11,8%)	1 (5,9%)	0,68
B/C	11	1	
Gastroenterostomy failure (grade IIIb)	2 (2,1%)	0	1,0
Myocardial infarction	1	2	
Stroke	0	1	
Pneumonia	1	0	
Postoperative hospital-stay	22 (8-165)	23 (9-71)	0,92

## Results

There were 110 PDEs for 9-year period (March 2010 — February 2019) in the department of liver and pancreatic surgery of the Petrovsky National Research Centre of Surgery. Median age of patients was 59 (21-79) years. There were 52.7% of men. Malignancies of pancreatic head (50.9%; 56/110) and major duodenal papilla (23.6%; 26/110) were predominant diseases. Overall mortality was 4.5% (5/110). A complicated postoperative period (at least one complication) was observed in 80 patients (72.7%). A total of 154 complications were observed. Major (≥IIIa) complications occurred in 29% (32/110) of patients, specific complications — in 52.7% (58/110) of patients. Specific complications grade B or C were noted in 44.5% (49/110) of cases. The first group (<70 years old) enrolled 93 patients, the 2nd group (≥70 years old) — 17 patients. There were 6 patients aged 75-79 years. Diagnoses in both groups are shown in Table 1. Ductal adenocarcinoma was the most common pancreatic head tumor. The second common neoplasm was cancer of the major duodenal papilla (MDP). Incidence of various diagnoses was similar in both groups. Nevertheless, proportion of patients with cancer of the major duodenal papilla was 2 times higher in the 2nd group. Chronic pancreatitis was an indication for PDE only in 7 cases (7.5%; 7/93) in group 1.

Comparison of clinical and surgical characteristics (Table 2) revealed significantly higher ASA score and PMP score in the 2nd group. Patients with ASA score 3 prevailed among those older 70 years (82.4%, 14/17). At the same time, this value was noted only in 36.5% (34/93) of patients in the 1st group ( $p<0.001$ ). PMP score was significantly higher in group 2 compared with group 1:

12 (6-15) vs. 6.5 (5-15), respectively ( $p<0.001$ ). Diabetes mellitus was more common in group 2 compared with group 1 (47 vs. 16%,  $p<0.001$ ). Blood loss, duration of surgery and Fistula Risk Score were similar in both groups.

Early postoperative results are summarized in Table 3. Mortality was higher among patients older 70 years (11.7%, 2/17). Three patients died in the 1st group (mortality rate 3,2%, 3/93). Differences were not significant ( $p=0.16$ ). Complication rate was similar in both groups: 72% (67/93) vs. 76% (13/17) ( $p=1.0$ ). This is true for overall and major (grade ≥IIIa) morbidity. Incidence of specific complications was also similar in both groups. Myocardial infarction, cerebrovascular accident and pneumonia were noted in single cases.

All deceased patients were characterized by a combination of several severe concomitant or consequent complications (Table 4). The only common sign in these patients was specific high grade complications (grade C). Pancreatoenterostomy failure was observed in 3 out of 5 patients, persistent gastrostasis — in 2 patients. All these patients required re-laparotomy (1-5). In patient No. 1, pancreatic stump necrosis resulted failure of pancreatoenterostomy and recurrent intra-abdominal bleeding. In patient No. 2, failure of pancreatoenterostomy was followed by arrosive bleeding from the stump of gastroduodenal artery (in 7 days after surgery). This complication resulted death of the patient despite re-laparotomy and stopping the bleeding. In patients No. 3 and No. 4, persistent gastrostasis was an indication for reconstructive interventions. In patient No. 3, reconstruction of gastroenterostomy was complicated by bowel perforation, peritonitis, sepsis, that required several re-laparotomies.

Table 4. Fatal outcomes.

Group 1	Gender, age	Diagnosis	Scores	Vascular procedures	Complications	Death, day after surgery
No.1	f, 65	Pancreatic head cancer	ASA – II RCRI – 1 PMP – 7,5	Portal vein resection	Pancreatic stump necrosis; failure of pancreaticoenterostomy (grade C); intra-abdominal bleeding (grade C); multiple organ failure;	35
No.2	m, 62	Pancreatic head cancer	ASA – III RCRI – 1 PMP – 11	No	Failure of pancreaticoenterostomy (grade C); intra-abdominal bleeding (grade C);	8
No.3	f, 57	MDP cancer	ASA – II RCRI – 1 PMP – 6	No	Gastrostasis (grade C); bowel perforation, peritonitis, sepsis; intra-abdominal bleeding;	105
Group 2						
No.4	f, 71	MDP cancer	ASA – III RCRI – 3 PMP – 12	No	Gastrostasis (grade C); abdominal abscess; ischemic stroke;	71
No.5	m, 75	MDP cancer	ASA – III RCRI – 2 PMP – 15	No	Failure of pancreaticoenterostomy (grade C); pulmonary embolism; myocardial infarction;	47

In patient No. 4, reconstruction of gastroenterostomy was complicated by stroke (in 2 days after re-laparotomy) and subsequent death. In patient No. 5, failure of pancreaticoenterostomy required two re-laparotomies. The 2nd re-laparotomy was followed by pulmonary embolism, myocardial infarction and death of the patient.

## Discussion

Increased life expectancy and aging of population are observed in all developed countries. Incidence of tumors is also increased with age. Prevalence of malignant tumors in patients older 65 years is 11 times higher compared with young people. It is expected that 70% of all malignancies and 85% of deaths associated with malignant tumors will be in population over 65 years old by 2030. Therefore, the need for the treatment of advanced age patients will be only increased [17–20]. Pancreatic cancer accounts 3.3% among other malignancies in Russia. Mean age of sick men is 64.6 years, women — 70.3 years [21]. Incidence of pancreatic cancer is rapidly increased after 50–54 years old with maximum values in patients aged 80–85 years. A similar situation is typical for other periampullary adenocarcinomas [6]. Surgery is preferable for these diseases. A five-year survival after PDE for pancreatic head cancer is only 15–20%. This value is higher in patients with cancer of distal common bile duct (20–25%), major duodenal papilla (30–40%) and duodenum (50–60%) [6–8].

Advanced age patients naturally have more concomitant diseases. An objective assessment and comparison of comorbid status is not an easy task. We chose several scales for this purpose: ASA, RCRI, PMP. Significant differences were found for ASA and PMP scales. Mean ASA score was higher in patients older 70 years (ASA III). There were 82.4% (14/17) of patients with ASA III. In the 1st group, this value was 36.5% (34/93). We used PMP scale despite the fact that there is an age factor in this system. Moreover, age of 70–79 years increases the final value by 1 score.

This scoring system includes simplified assessment of cardiovascular and respiratory systems, liver, kidney, nutritional status. In patients older 70 year, PMP score was 11, in patients younger than 70 years — 6.5 (5–15) scores ( $p < 0.001$ ).

PDE is technically difficult and extended surgery. It is logical to assume that advanced age patients with various concomitant diseases have advanced risk of postoperative complications and mortality. Contradictory data are obtained in various researches. The authors use different threshold age (70 or 75 years as a rule). However, there are reports devoted to surgical outcomes in patients older than 80 [22] or 90 years [5]. Some authors found similar mortality in different age groups [22–27]. On the contrary, this correlation was observed in other series [5, 28–32]. Many of these studies had small sample size. Current meta-analyses confirm certain differences in mortality and complication rate. One of these meta-analyses (2012) included 11 trials and 5186 patients. It was found that patients older 75 years are characterized by higher postoperative mortality and incidence of pneumonia. In addition, patients older 80 years have higher complication rate [33]. The results of PDE in patients older 80 years were estimated in another meta-analysis (2017). Analysis of 18 trials confirmed higher 30-day mortality, complication rate, incidence of pneumonia, gastrostasis and hospital-stay in these patients [34]. We have adopted the age of 70 years as a threshold for two reasons. First, there were only 6 patients aged 75 years and over and no patient older than 80 years in our sample. Secondly, in our opinion, age of 70 years is a psychological barrier in the mind of many surgeons influencing decision making about surgery.

Patients younger ( $n=422$ ) and older ( $n=102$ ) 75 years who underwent surgery within 9 years were compared in a large trials from the University Hospital Southampton (UK). Mortality was higher in the second group (1.9% vs 5.9%,  $p=0.037$ ). The following independent risk factors of mortality were determined in multivariate analysis: ASA

score, postoperative bleeding and pulmonary embolism but not an age [35]. In our study, we found higher mortality in patients older 70 years (11.7% vs. 3.2%,  $p=0.16$ ). The absence of statistical significance may be explained by small size in one of the groups. This value is quite high, since overall mortality after PDE does not exceed 1-5% in the majority of specialized departments.

It is noteworthy that all 5 deceased patients had surgical specific complications: failure of pancreatoenterostomy ( $n=3$ ), intra-abdominal bleeding ( $n=3$ ), gastrostasis ( $n=2$ ). These events served as a trigger for subsequent disorders. In patients older 70 years, subsequent cardiovascular complications (myocardial infarction, pulmonary embolism, cerebrovascular accident) resulted unfavorable outcome. In patients younger 70 years, infectious complications, intra-abdominal bleeding and multiple organ failure caused death.

Incidence of complications after PDE is still high despite improvement of surgical technique (38-52%) [1-5]. We have not found differences in the incidence of all and major complications. Similar data were obtained by other authors [35, 36]. Risk factors of pancreatoenterostomy failure were soft pancreatic parenchyma, pancreatic duct diameter ( $<3$  mm), intraoperative blood loss ( $>1000$  ml) and tumor type (major duodenal papilla, duodenum, neuroendocrine and cystic tumors) [37]. These parameters are included into prognostic model (Fistula Risk Score) [16] for assessment of the risk of this complication. This model was also used in our study. There were no between-group differences in this value. Incidence of pancreatoenterostomy failure (grade B/C) was also similar (35.3% vs. 23.6%,  $p=0.3$ ). Previously, it was shown that age is not a significant predictor of this event [38]. Some authors found higher incidence of postoperative gastrostasis in older patients [5, 34, 39]. Probably, it was associated with impaired gastric motility in advanced age patients [40]. These data are

not confirmed by other researchers [41,42] and our results. Incidence of gastrostasis (B/C) was the same in both groups (17%). Incidence of other specific complications (bile leakage, bleeding) was also similar. These data are consistent with the results of other publications [38,42]. Postoperative hospital-stay was similar in both groups.

Undoubtedly, long-term results of PDE and their dependence on the age of patients are of particular interest. We do not answer this question in this study. Primary endpoints were postoperative mortality and complication rate. Other authors who analyzed mixed group of patients (periampullary malignancies with predominant pancreatic head adenocarcinoma) reported median life expectancy near 22 months in patients younger 75 years ( $n=422$ ) and 19 months in patients older 75 years ( $n=102$ ) ( $p=0.165$ ). The predictors of 5-year survival were vascular resection, positive resection margin, lymphovascular invasion and number of affected lymph nodes, but not an age [35].

It is also important that the results of PDE are influenced by the number of these operations performed in the clinic and individual experience of surgeon. This is true for all major operations. Outcomes of treatment are much better in great centers [43]. It is difficult to take into account the role of this factor in our and in other studies.

Multidisciplinary approach (cardiologists, neurologists, anesthesiologists) should be applied for selection of patients for PDE. Assessment of general condition of patients and comorbidities is essential. The most difficult task is objective analysis of patient's condition and surgical risks. Various scales may be useful for this purpose. However, these systems give only approximate assessment. In each case, the decision should be made in individual fashion with comparison of benefits and risks of surgery. Advanced age per se is not a contraindication for surgical treatment of periampullary tumors.

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