Impact Factors for Perioperative Morbidity and Mortality and Repercussion of Perioperative Morbidity and Long-Term Survival in Pancreatic Head Resection

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ABSTRACT

Background: The present study analyses complications after pancreatic resections, however, the focus was to reveal any impact factors for perioperative morbidity and mortality as well as repercussion of perioperative morbidity on long-term survival in pancreatic head resection.

Methods: In a retrospective study, altogether 300 patients after pancreatic resections were analyzed for morbidity and mortality. Of these, 240 were pancreatic head resections or total pancreatectomies (PD/TP), 57 left pancreatectomies and three Fray procedures. According to Clavien-Dindo classification, all complications with grade II and more were defined as overall complications (OAC). Clinical-pathologic factors of 240 patients after PD/TP were further analyzed for correlations with morbidity, 30- and 90-day mortality, and long-term survival. Overall complications, all surgical (ASC), all general (AGC), and some specific types of complications like leaks from the pancreatoenteric anastomosis (PL) or pancreatic fistula (PF; type A, B, and C), leaks from other anastomoses (OL), bleeding (BC), and abscesses (AA) were studied for correlation with clinical-pathologic factors.

Results: For all pancreatic resections, the incidence of OAC was 34%, ASC 27%, and AGC 14%. Overall 30- and 90-day mortality were 4.7% and 7.3%, respectively, and decreased to 2.8% and 4.5% in the second period (p=0.025). In left pancreatectomies, the incidence of OAC was 22.8%, ASC 19.3%, and AGC 14%. The 30- and 90-day mortality rates were 3.5% and 5.3%, respectively (in the first and second period), and dropped to 0% in the second period. In PD/TP, the incidence of OAC was 37.1%, ASC 29.2%, and AGC 15.8%. All surgical complications presented themselves as PL, OL, BC and AA in 19% (of 208 PD), 5.8%, 5.8% and 2.5%, respectively. Age, ASA score, amylase on drains, and PF B and C correlated significantly with different types of complications in PD/TP. The 30- and 90-day mortality for PD/TP was 5% and 7.9%, respectively (in the first and second period), and decreased to 3.5% and 5.6% in the second period. In three patients with Frey procedure, there were no complications and no fatalities.

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Conclusions: Morbidity after pancreatic resections remains stable. However, 30- and 90-day mortality decreased. High amylase on drains and higher mean age were independent indicators of morbidity, whereas PL and BC revealed as independent predictor for 30-day mortality, and physical status, OAC and PFC for 90-day mortality.

INTRODUCTION

Pancreatic resection, especially pancreatic head resection or total pancreatectomy (PD/TP), remains a significant challenge for many pancreaticobiliary surgeons. The complications associated with pancreatic procedures are well described (1, 2). They are usually of higher grade than in comparable abdominal surgical procedures. Many attempts have been made to lower these complications (1, 3–7). Some authors have claimed that modifications of the surgical techniques, especially the formation of the pancreatojejunostomy, could have a positive impact on the postoperative course. Others have claimed that a better selection of patients would decrease the morbidity and mortality (8–13). Since perioperative morbidity and mortality are important predictors for long-term survival of patients after PD (14, 15), we performed a retrospective study to determine factors associated with perioperative and specific surgical complications, general complications, and perioperative mortality. The identification of such negative prognostic factors could help to prevent complications or even mortality and could, therefore, have an impact on long-term survival after pancreatic surgery. Factors like postoperative pancreatic fistula, age, and poor general condition have all been determined to have a negative impact on the postoperative course (1, 4, 13, 16, 17). The drawbacks of some of these studies, however, are the small number of included patients, the inclusion of low-volume centers, and the short-term postoperative follow-up of the patients. In our study, we, therefore, evaluated which clinical-pathologic factors significantly influence morbidity, mortality, and long-term results in our reference institution for pancreatic diseases, where meanwhile 40–50 pancreatic procedures are performed annually. Preoperative workup, surgical procedures, and postoperative care became highly standardized. All these factors enabled us to perform a detailed study of factors influencing the perioperative course after pancreatic surgery.

PATIENTS AND METHODS

For the present retrospective study, the data of 300 patients after pancreatic resections performed from January 1, 2008, to March 31, 2017, at the Department of Abdominal Surgery at University Medical Centre Maribor were analyzed. Clinical and pathological data were prospectively stored in a computerized database. Data for the follow-up were obtained by our outpatient follow-up and by the National cancer register of Slovenia. Complete follow-up was obtained up to June 1, 2017. We obtained informed consent from all patients and performed all procedures, according to the guidelines of the Helsinki Declaration. The analysis includes patients having had PD and TP. There are no urgent resections included. The indications for the resection were malignant and premalignant lesions of the region sited in the head of pancreas, and chronic pancreatitis in few cases (Table 1).

PREOPERATIVE WORKUP

Patients' preoperative physical status was expressed by the American Society of Anaesthesiology (ASA) score (18). Before the surgery, all patients were submitted to CT. Additional abdominal MRI or endoultrasonography (EUS) with or without biopsy was done only in selected patients. Beside usual standard laboratory blood tests, tumor markers CEA and CA 19-9 were also evaluated. Preoperative endoscopic biliary drainage (EBD) was done in patients with bilirubin value > 200 mmol/l or in subicteric patients when further preoperative workup was necessary.

Preoperative preparation

Intravenous antibiotic (1.5 g cefuroxime and 0.5 g metronidazole or 0.35 g gentamycin and 0.6 g clindamycin) and subcutaneous antithrombotic (4000 IE

Table 1. Indications for pancreatic resection in 300 patients. PD/TP – pancreatic head resection/total pancreatectomy, MD-IPMN – main duct-intraductal papillary mucinous neoplasm

Indication for pancreatic resection	All	PD/TP
Pancreatic adenocarcinoma	164	135
	54.7%	56.7%
Neuroendocrine tumor of the pancreas	21	9
	7%	3.8%
MD-IPMN	6	3
	2%	0.8%
Franz's tumor	3	1
	1.0%	0.4%
Non-Hodgkin lymphoma	2	2
	0.7%	0.8%
Distal bile duct carcinoma	43	43
	14.3%	17.9%
Adenocarcinoma of the papilla Vateri	30	30
	10%	12.5%
Duodenal adenocarcinoma	8	8
	2.7%	3.3%
Gastric cancer	2	2
	0.7%	0.8%
Chronic pancreatitis	16	7
	5.3%	2.9%
Pancreatic cystadenoma	4	0
	1.3%	0%
Metastasis of renal cell carcinoma	1	0
	0.3%	0%
Total	**300**	**240**

enoxaparin or 3800 nadroparin or 5000 IE dalteparin) prophylaxis were successively used in all patients one hour and 12 hours before operation. Urine catheter and nasogastric tube were usually inserted after induction of anesthesia.

Surgical technique

The usual operative approach was median or bilateral subcostal laparotomy. After confirming respectability (no distant dissemination, no tumor infiltration of the coeliac trunk, hepatic artery or superior mesenteric artery), the strategy was to perform a curable resection (R0) in malignant and premalignant lesions and to relieve symptoms as in chronic pancreatitis. Usually, pylorus-preserving PD, Whipple resection or TP (in patients with very soft texture of the pancreas unsuitable for anastomosis) were performed. In malignant disease, lymphadenectomy was done in hepatoduodenal ligament, around common hepatic artery, superior mesenteric artery (usually 180–270^0), and occasionally between vena cava and aorta. Resection borders on the bile duct and pancreas were checked for neoplastic infiltration by frozen section examination. If infiltration of the superior mesenteric (VMS) or portal vein (VP) was suspected, en bloc resection of the infiltrated vein was done to assure the curability of resection.

Vascular reconstruction was done by direct continuous 6.0 monofilament non-absorbable suture; however, if more extended distance had to be bridged, vascular prosthesis was used. Anastomosis to pancreatic stump was exclusively performed by duct to mucosa end-to-side pancreaticoenteric anastomosis (PEA) using 5.0 monofilament non-absorbable sutures in two layers followed by single-layer bilioenteric anastomosis (BEA) with interrupted 5.0 absorbable poly filament sutures. In selected patients (mostly with thin duct and soft texture of the pancreas), trans-anastomotic lost stent was used. The continuity of the gastrointestinal tract was further established by omega gastroenteric anastomosis (GEA) done with 3.0 absorbable monofilament sutures. In all patients, single-layer continuous enteroenteric anastomosis (EEA) between afferent and efferent loop was done with 4.0 polyfilament absorbable suture. Two drains were placed in the right subhepatic region (one in space of resected head of the pancreas and one above BEA anastomosis) and one in the Douglas region.

Postoperative care

Almost all patients were admitted in the high dependency unit except if admission to the intensive care unit was indicated. Patients started to receive fluid food on the first day. Gastric tube was removed after appearance of bowel movements or the first stools. Amylase was checked in the drained fluid on day 3 and after that when any clinical suspicion for anastomotic leaks was present. In selected patients (soft pancreas remnant) however, parenteral somatostatin (6 mg/24 h) was administrated for 6–10 days.

Definitions and statistical analyses

All complications (OAC) according to Clavien–Dindo classification grade II or more were considered as postoperative morbidity (19). All surgical (ASC), all general (AGC), and all surgical and general complications (SGC) were analyzed. Also, special group of complications like leak from PEA (PL), leaks not from PEA (OL), abdominal abscess (AA) and abdominal or intestinal bleeding (BC) were identified. Any postoperative mortality within 30 and 90 days was considered a probable consequence of surgery and was declared as postoperative mortality (30- and 90-day mortality). Receiver operating curve (ROC) analysis for morbidity and mortality determined the threshold values of amylase secretion on abdominal drains. An area under curve (AUC) of > 0.75 was used to determine the value of significance. The ROC analysis was used to determine sensitivity and specificity of the determined amylase cut-off value, which revealed to be more than seven ukat/L.

Sensitivity and specificity for prediction of pancreatic fistula (PF) type B or C at cut-off seven ng/mL were 100% and 85.4%, respectively. Consequently, any secretion of amylase-rich fluid on drains more than seven ukat/L was defined as elevated. Patients with high amylase on drains from PEA were declared to have PF and were retrospectively classified in three types of PF (A, B, C), respecting clinical picture, therapeutic consequences, and ISGPF (International Study Group of Pancreatic Fistula) recommendations (20).

Two chronologically successive groups of patients (period 1 (P1): from January 1, 2008, to December 31, 2012 (124 patients); and period 2 (P2): from January 1, 2013, to March 31, 2017 (176 patients) were compared for perioperative morbidity, and 30- and 90-day mortality.

Continuous data are expressed as mean ± standard deviation, and categorical variables are given as percentages. Continuous variables were compared with Student's t-tests for parametric data and Mann-Whitney U tests for nonparametric data. Chi-square tests were used for comparisons of discrete variables.

All of the predictors that were significant on univariate analysis ($p > 0.05$) were included in the multivariate analysis. In the multivariate analysis, a binary logistic model was used. Survival analysis was performed with the Kaplan-Meier method. The differences between groups were compared with the log-rank test. P-values < 0.05 were defined as the limit of significance. For statistical analysis, SPSS version 22.0 for Windows 7 (IBM Analytics, Armonk, NY) was used.

Our study aimed to evaluate the incidence of morbidity and mortality and to reveal any correlations with clinical-pathologic factors. In addition to morbidity and mortality, the impact of morbidity and mortality on survival was studied. The second aim was to reveal any differences between two chronologically successive groups (P1 and P2).

RESULTS

Altogether 300 patients had pancreatic resection (male 160, female 140, mean age 66.4 years). The indications for resections and characteristics of the analyzed patients after all pancreatic resections, left pancreatectomy and PD/PT are presented in Table 1 and Table 2a–d. For all pancreatic resections, the incidence of OAC was 34%, ASC 27%, and AGC 14%. Overall 30- and 90-day mortality were 4.7 and 7.3%, respectively, and decreased to 2.8 and 4.5% (p=0.025) in P2. In left pancreatectomies, the incidence of OAC was 22.8%, ASC 19.3%, and AGC 14%. The 30- and 90-day mortality rates were 3.5 and 5.3%, respectively (P1 and P2), and dropped to 0% in P2. In three patients with Frey procedure, there was no complications and no fatalities.

Table 2a. Clinical-pathologic features in 300 patients after pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), ASA – American Society of Anaesthesiologists score

		P1	P2	All	p-value
Gender	male	62	98	160	0.4
		50%	55.7%	53.3%	
	female	62	78	140	
		50%	44.3%	45.7%	
Age	mean (years)	66.1 ± 9.9	65.98 ± 10.1	66.4	0.9
ASA	1	25	57	82	0.06
		20.2%	32.4%	27.3%	
	2	70	83	153	
		56.5%	47.2%	51%	
	3	29	36	65	
		23.4%	20.5%	21.7%	
Hospital stay (n = 278)	mean (days)	20.2 ± 13.6	18.7 ± 12.4	19.3	0.3
Overall complications (OAC)		42	60	102	0.5
		33.9%	34.1%	34%	
Surgical complications (ASC)		30	51	81	0.2
		24.2%	29%	27%	
General complications (AGC)		22	20	42	0.08
		17.2%	11.4%	14%	
30-day mortality		9	5	14	0.06
		7.3%	2.8%	4.7%	
90-day mortality		14	8	22	0.025
		11.3%	4.5%	7.3%	

Table 2b. Clinical-pathologic features in 57 patients after left pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), ASA – American Society of Anaesthesiologists score

		P1	**P2**	**All**	**p-value**
Gender	male	11	16	27	0.17
		50%	55.2%	53.3%	
	female	17	13	30	
		50%	43.3%	45.7%	
Age	mean (years)	59.4 ± 13.4	58.5 ± 12.2	58.9	0.8
ASA	1	8	12	20	0.58
		28.6%	41.4%	35.1%	
	2	17	14	31	
		60.7%	48.3%	54.4%	
	3	3	3	6	
		10.7%	10.3%	10.5%	
Hospital stay (n=278)	mean (days)	16.8 ± 9.4	18.4 ± 16.3	17.7	0.68
Overall complications (OAC)		8	5	13	0.24
		28.6%	17.2%	22.8%	
Surgical complications (ASC)		6	5	11	0.47
		21.4%	17.2%	19.3%	
General complications (AGC)		5	3	8	0.33
		17.9%	10.3%	14%	
30-day mortality		2	0	2	0.23
		7.1%	0%	3.5%	
90-day mortality		3	0	22	0.035
		10.7%	0%	7.3%	

The incidence of OAC in PD/TP was 37.1%, ASC occurred in 29.2% whereas AGC in 14.2%. All surgical complications presented themselves as PL, OL, BC and AA in 19% (of 208 PD), 5.8%, 5.8% and 2.5%, respectively. In case of OL, five were from GEA and ten from BEA. Bleeding occurred in altogether 14/240 patients. Two patients had early intestinal bleeding, and 12 occurred after 24 hours. Other rare surgical complications occurred in altogether 4.5% (Table 3). All general complications in PD/TP are described in Table 4.

Drained fluid was checked for amylase in 189/207 patients after PD. Elevated amylase more than seven ukat/L on drains was found in 73 patients (38.6%). In 63 patients (33.3%), the high amylase on drains originated from PEA whereas in 10 patients amylase-rich secretion evidently did not originate from PEA (six bile leaks, two leaks from GEA, one ileus, and one strangulation of the mobile cecum). The rate of PF A was 14.4%, PF B 9.6%, and PF C 9.6%. Determination of PF in groups A, B and C did not correlate with means of amylase value in discharged secretion on drains in ordinal fashion; it was rather the consequence of clinical factors and therapeutic measures.

One of the common consequences of complications was significantly prolonged hospital stay (OAC: 30.9 ± 16 vs. 14.2 ± 4.5 days; $p < 0.0001$). Overall 30- and 90-day mortality was 5% and 7.9%.

Table 2c. Observed clinical-pathologic features in patients after pancreatic head resection and total pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), ASA – American Society of Anesthesiologist score

		P1	P2	All	p-value
Gender (n=240)	male	51	80	131	0.4
		53.1%	55.6%	54.6%	
	female	45	64	109	
		46.9%	44.4%	45.4%	
Age (n=240)	mean (years)	66.1 ± 9.9	65.98 ± 10.1	66.4	0.91
ASA (n=240)	1	17	43	17	0.103
		17.7%	29.9%	17.7%	
	2	53	68	53	
		55.2%	47.2%	55.2%	
	3	26	33	26	
		27.1%	22.9%	27.1%	
Preoperative histology (n=240)		4	32	36	0.0001
		4.2%	22.2%	15.0%	
Hospital stay (n=222)	mean (days)	21.2 ± 14.5	19 ± 11.6	19.8	0.138
Preoperative total bilirubin (n=240)	mean (mmol/L)	67.6 ± 71.5	79.0 ± 85.5	74.7	0.028
Preoperative endoscopic biliary drainage (n=240)		34	51	85	0.554
		35.4%	35.4%	35.4%	

Correlation of clinical-pathologic factors and perioperative morbidity in pancreatic head resection and total pancreatectomy

Age and physical status

Patients with OAC and AGC were older, and their physical status according to ASA was worse. Physical status was worse also in a group of patients with PL (29.5% vs. 16.1%; p=0.042). Regarding this, no correlations were found in other subsets of complications (AA, BC, and OL) (Table 5).

Preoperative bilirubin value and endoscopic biliary drainage

At our disposal were only bilirubin values from the period within a week before the PD, and the majority of patients was transferred to our institution with already placed EBD more than one week before the operation. This prevented us to make any conclusive analysis on this issue. Patients with preoperatively placed EBD had lower mean preoperative bilirubin values than those without EBD (57.4 ± 66 vs. 83.8 ± 86mmol/L; p=0.005). Increased mean bilirubin level was noted in BC (134.7 ± 104 vs. 70.7± 71.6 mmol/L; p=0,005). Endoscopic biliary drainage was in 37.6% of our patients associated with the occurrence of ASC and in 30% with PL (ASC: 37.6% vs. 24.5%, p=0,024, PL: 30% vs. 12.5%, p=0,004), but there have been no correlations of EBD with other settings of complications (Table 5).

Type of resection and vascular resections

All clinical-pathologic factors were comparable in patients that underwent PD or TP, except AA which was more likely after TP (1% vs. 12.1%; p=0.004). Resections of VMS/VP correlated only with AGC revealing even less complications if vascular resection has been done (2.5% vs. 16.5%; p=0.011). This correlation was difficult to explain since patients with vascular resection were comparable regarding the age and physical status (mean age: 65.2 vs. 66.1 years; p=0.556; ASA3 vs. ASA1/2: 22.2% vs. 25%; p=0.456) (Table 5).

Type and size of the tumor

Data of tumor dimensions were available for 201 patients. There was a high correlation between tumor size and tumor type revealing non-pancreatic carcinomas (NPCs) to be smaller and pancreatic adenocarcinomas (PACs) to be larger. In groups of OAC, ASC, and PL, smaller size of tumor significantly predicted the onset of complications. Calculation revealed that patients with NPC were more prone for onset of OAC than those with PAC (Table 5).

Amylase on drains

Complications after PD were associated with amylase rates more than seven ukat/L. The mean amylase value was increased only in OAC and ASC (OAC: 150.6 ± 252 vs. 21 ± 62; p < 0.0001, ASC: 179.9 ± 270 vs. 24 ± 73; p < 0.0001). Since PF A has never been noticed, it did not have any negative impact on any complications. There is an inverse correlation of mean amylase level and AA (1.1 ± vs. 72.5 ± 177 ukat/L; p < 0.0001) proving that abscesses did not originate from pancreatic leak. Smaller size of the tumor proved to be a predictor for the occurrence of PL (30.3 ± 18 vs. 22.5 ± 9; p=0.001). Amylase rates more than 7 ukat/L and PF B were more often noted in NPCs (amylase < 7 ukat/L: 48.4% vs. 25.3%; p=0.002, PF B: 17.2% vs. 6.3%; p=0.029), but there was no correlation at the whole between PF C and type of tumour (Table 5).

Correlation of clinical-pathologic factors and perioperative mortality in pancreatic head resection and total pancreatectomy

Patients who suffered complications in terms of OAC, ASC, AGC, BC, PL and PF C were at a significant

Table 2d. Observed clinical-pathologic features in patients after pancreatic head resection and total pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), PD – pancreatic head resection, TP – total pancreatectomy, VMS – superior mesenteric vein, VP – portal vein

		P1	**P2**	**All**	**p-value**
Type of pancreatic head resection (n=240)	PD	92	115	207	0.0001
		95.8%	79.9%	86.3%	
	TP	4	29	33	
		4.2%	20.8%	14.2%	
Resection of VMS/VP (n=240)		12	28	40	0.17
		12.5%	19.4%	16.7%	
Type of vascular reconstruction (n=240)	Direct suture	10	14	24	0.043
		10.4%	9.7%	10.0%	
	Vascular graft	2	14	16	
		2.1%	9.7%	6.7%	
Overall complications (OAC) (n=240)		34	55	89	0.383
		35.4%	38.2%	37.1%	
30-day mortality (n=240)		7	5	12	0.152
		7.3%	3.5%	5.0%	
90-day mortality (n=240)		11	8	19	0.080
		11.5%	5.6%	7.9%	

Table 3. Surgical complications in patients after pancreatic head resection and total pancreatectomy. PF – pancreatic fistula. GEA – gastroenteroanastomosis

Type of all surgical complications (n=240)	n	%	% 90-day mortality
No surgical complications	169	70.4	3
PF B or C	28	11.7	25
PF B or C and bleeding	8	3.3	62.5
Bleeding in the intestines	2	0.8	0
Intraabdominal bleeding – no PF	4	1.7	25
Bile leak	10	4.2	0
Leak from GEA	5	2.1	20
Dehiscence of laparotomy	3	1.3	0
Intraabdominal abscess	6	2.5	0
Ileus	1	0.4	0
Thrombosis of vascular graft	2	0.8	0
Volvulus coeci	1	0.4	0
Stenosis of coeliac trunk	1	0.4	0
Total	**240**	**100.0**	**7.9**

Table 4. General complications in patients after pancreatic head resection and total pancreatectomy

Type of all general complications (n = 240)	n	%	% 90-day mortality
No general complications	202	84.2	5.0
Pneumonia	8	3.3	25
Cardiorespiratory decompensation	3	1.3	100
Heart failure	9	3.8	11.1
Pulmonary embolism	4	1.7	25
Different infections	10	4.2	10
Renal failure	1	0.4	100
Brain stroke	1	0.4	0
Miscellaneous	2	0.8	0
Total	**240**	**100.0**	**7.9**

higher risk for postoperative mortality (OAC 30-day: 13.5% vs. 0%; $p < 0.0001$, OAC 90-day: 20% vs. 0.7%; $p < 0.0001$, ASC 30-day: 14.3% vs. 1.2%; $p < 0.0001$, ASC 90-day: 20% vs. 2.9%; $p < 0.0001$, AGC 30-day: 14.1% vs. 4.3%; $p < 0.0001$, AGC 90-day: 20% vs. 2.9%; $p < 0.0001$, BC 30-day: 35.7% vs. 3.1%; $p < 0.0001$, BC 90-day: 34.3% vs. 7.2%; $p < 0.0001$, PL 30-day: 22.2% vs. 2%; $p < 0.0001$, PL 90-day: 33.3% vs. 3.2%; $p < 0.0001$, PF C 30-day: 33.3% vs. 2.9%; $p < 0.0001$, PF C 90-day: 50% vs. 4.7%; $p < 0.0001$). On the other hand, OL and AA did not impact the 30- and 90-day mortality.

Age did not correlate to 30- or 90-day mortality; however, ASA physical status did (30-day: 11.9% vs. 2.8%; p=0.011, 90-day: 18.6% vs. 4.4%; p=0,001).

Table 5. Correlation of clinicopathological factors and perioperative morbidity and mortality in 240 patients after pancreatic head resection and total pancreatectomy. OAC – overall complications, ASC – all surgical complications, BC – bleeding complications, OL – other anastomotic leak, AA – intraabdominal abscess, PL – pancreatic leak anastomosis, AGC – all general complications, NC – no complications, WC – with complications, ASA – American Society of Anaesthesiologists score, EBD – external biliary drainage, PD/TP – pancreatic head resection/total pancreatectomy, PAC – pancreatic adenocarcinoma, NPC – non-pancreatic carcinoma, PF C/B/A – pancreatic fistula type C/B/A, P1 – first study period (2008–2012), P2 – second study period (2013–2017)

	n		OAC	p-value	ASC	p-value	BC	p-value	OL	p-value	AA	p-value	PL	p-value	AGC	p-value
Age (years)	240	NC WC	**64.6 ± 10** **68.4 ± 9.1**	**0.005**	65.3 ± 10.3 67.9 ± 9.1	0.051	66.2 ± 10 63.5 ± 12	0.452	66 ± 10 67.1 ± 8	0.665	65 73	0.056	65.7 ± 10 67.3 ± 8	0.256	**65.4 ± 10** **70.1 ± 9**	**0.007**
Age (<70 and >69)	240	<70 >69	28.6% 43.7F%	**0.011**	23.8% 33.3%	0.071	8.6% 3.7%	0.094	4.8% 6.7%	0.369	**0%** **100%**	**0.030**	16.3% 21.4%	0.234	**8.6%** **18.5%**	**0.021**
ASA 1+2 vs. 3	240	ASA 1+2 ASA 3	**32%** **52.5%**	**0.004**	**23.8%** **33.3%**	**0.042**	5.5% 6.8%	0.465	5.5% 6.8%	0.465		0.457	**16.1%** **29.5%**	**0.042**	**10.5%** **25.4%**	**0.006**
Total bilirubin (mmol/l)	240	NC WC	70.1 ± 74 82.9 ± 89	0.271	68.3 ± 73.6 89.5 ± 93.1	0.062	**71 ± 77** **134 ± 104**	**0.005**	74..4 ± 78 75.5 ± 108	0.969		0.231	68.1 ± 70 91.4 ± 99	0.195	**79 ± 82** **47.4 ± 61**	**0.033**
EBD (no/yes)	240	No Yes	33.5% 43.5%	0.082	24.5% 37.6%	**0.024**	5.8% 5.9%	0.594	7.1% 3.5%	0.203		0.640	**12.8%** **30%**	**0.004**	11.6% 18.8%	0.092
PD/TP	240	PD TP	37.2% 36.4%	0.545	29.5% 27.3%	0.488	6.3% 3%	0.400	5.8% 6.1%	0.600	**1%** **12.1%**	**0.004**	-	-	13% 21.2%	0.126
Vascular resection (yes/no)	240	No Yes	39.5% 27.5%	0.115	30.0% 25.0%	0.334	4.5% 12.5%	0.063	6% 5%	0.578		0.738	21.1% 7.7%	0.083	**16.5%** **2.5%**	**0.011**
Size of tumor (mm)	201	NC WC	**32.3 ± 19** **24.6 ± 12**	**0.001**	**31.7 ± 18.8** **23.7 ± 10.1**	**0.002**	29.5 ± 17 25 ± 10	0.187	29.4 ± 17 25.1 ± 13	0.320		0.069	30.3 ± 18 22.5 ± 9	0.001	29.7 ± 17 25.7 ± 15	0.211
Type of tumor PAC/NPC	216	PAC NPC	**34.1%** **46.9%**	**0.042**	26.7% 37.0%	0.074	6.7% 4.9%	0.421	5.9% 7.4%	0.435		0.403	16.2% 25.7%	0.092	69.8 ± 183 83.5 ± 127	0.094
Amylase level (ukat/L)	187	NC WC	**21.3 ± 62.1** **150.6 ± 252**	**0.0001**	**24.0 ± 73** **179.9 ± 270**	**0.0001**	68.6 ± 175 128.1 ± 199	0.333	72.3 ± 180 62.5 ± 100	- 0.773	**72.5 ± 177** **1.1 ± 1**	**0.0001**	**22.2 ± 70** **260 ± 310**	**0.0001**	69.8 ± 183 83.5 ± 127	0.640
Amylase (>7 ukat/L)	187	< 7 > 7	**20.2%** **69.8%**	**0.0001**	**11.4%** **61.6%**	**0.0001**	**3.5%** **12.7%**	**0.022**	**1.7%** **60.3%**	**0.0001**		0.529	**19.1%** **100%**	**0.0001**	35.6% 57.7%	0.033
PF C (yes/no)	187	No Yes	**33.1%** **100%**	**0.0001**	**23.7%** **100%**	**0.0001**	**3%** **38.9%**	**0.0001**		0.318		0.818	**10.7%** **100%**	**0.0001**	-	0.464

	n		OAC	p-value	ASC	p-value	BC	p-value	OL	p-value	AA	p-vlue	PL	p-value	AGC	p-value
PF B (yes/no)	187	No Yes	**33.1%** **100%**	**0.0001**	**23.7%** **100%**	**0.0001**	6.5% 5.6%	0.676		0.318		0.818	10.7% 100%	**0.0001**	-	0.221
PF A (yes/no)	187	No Yes	**42.5%** **22.2%**	**0.035**	**36.3%** **0**	**0.0001**		0.148		0.171		0.734	**24%** **100%**	**0.0001**	-	0.141
PF B+C	187	No Yes	25.2% 100%	**0.0001**	**14.6%** **100%**	**0.0001**	**2.6%** **22.2**	**0.0001**		0.088		0.655				
Period of the study	240	P1 P2	35.4% 38.2%	0.383	25.0% 31.9%	0.155	**2.1%** **8.3%**	**0.036**	5.2% 6.3%	0.485		0.230	16.9% 21.2%	0.292	17.7 11.8	0.137
Hospital stay (days)	240		**14.2 ± 4** **31.4 ± 16**	**0.0001**	**15.2 ± 6** **32.9 ± 17**	**0.0001**	**19.3 ± 13** **31.9 ± 8**	**0.003**	**18.1 ± 9** **44.9 ± 29**	**0.0001**	19.6 ± 13 29 ± 10	0.075	**17.8 ± 12** **30.7 ± 9**	**0.0001**	**18.4 ± 12** **30.9 ± 10**	**0.0001**

Patients with amylase-rich secretion more than 7 ukat/L were also at a higher risk to die within 30 or 90 days after operation (amylase > 7ukat/l 30-day: 14.3% vs. 1.7%; p=0.002, amylase > 7ukat/L 90-day: 20.6% vs. 3.4%; p < 0.0001). However, mean value of amylase on drains was significantly higher in patients that died within 90 days compared to those who died in 30 days (90-day: 172 ± 231 vs. 59.1 ± 170ukat/L; p = 0.013). Tumor type or size of the tumor, mean preoperative total bilirubin, EBD, and PF A and B did not correlate with 30- and 90-day mortality.

Multivariate analysis in pancreatic head resection and total pancreatectomy

Predictors found to be significant for morbidity and 30- and 90-day mortality in the univariate analysis were included in the multivariate logistic regression analysis.

For OAC, higher mean age and drained amylase more than 7 ukat/L (age: CI 95%: 1.019–1.103; p=0.004, amylase > 7ukat/L: 95% CI: 0.045–0.204; p < 0.0001) were predictive. For ASC, higher mean amylases and drained amylase more than 7 ukat/L (mean amylase: 95% CI: 1.000–1.007; p=0.047, 95%, amylase > 7 ukat/L: 95% CI: 0.070–0.427; p < 0.0001) were specific. Moreover, for AGC, physical status, mean age and mean level of total bilirubin preoperatively (ASA: 95% CI: 1.007–1.121; p=0.028, mean age: 95% CI: 1.042–6.715; p < 0.041, mean total bilirubin: 95% CI: 0.981–0.999; p < 0.027) revealed as independent predictors.

For 30-day mortality, PL and BC revealed as independent predictors (PL: 95% CI: 0.026–0,522; p=0.005, BC: 95% CI: 0.024–0 537; p=0.006). In case of 90-day mortality, physical status, OAC and PF C (ASA: 95% CI: 1.404–16.514; p=0.012, OAC: 95% CI: 1.622–117.599; p=0.016, PF C: 95% CI: 2.030–28.244, p=0.003) were noticed as predictive factors.

Survival analyses in pancreatic head resection and total pancreatectomy

Patients who had OAC, ASC, AA, OL or AGC have had comparable expectation for long-term survival to those without complications (OAC: 866 ± 139 vs. 760 ± 174 days, Log Rank: p=0.242; ASC: 866 ± 134 vs. 901 ± 216 days, Log Rank: p=0.234; AA: Log-rank: p=0,048, OL: 836 ± 123 vs. 1159 ± 673 days; Log-rank: p=0.760, AGC: 866 ± 135 vs. 760 ± 197 days, Log Rank: p=0.431). Complications like PL in PD and BC in all resected patients seriously compromised the expected long-term survival (PL: 938 ± 67 vs. 499 ± 146 days; Log Rank: p=0.010, BC: 901 ± 128 vs. 409 ± 457 days; Log Rank: p=0.046). On the other hand, in patients who survived complications, the long-term survival was not impacted by any complications.

Differences between two chronologically successive groups in pancreatic head resection and total pancreatectomy

Two chronologically successive groups of patients were comparable on most clinical-pathologic factors except for preoperative gained histology, preoperative total bilirubin, and type of resection (Table 2). The indications for TP were: postoperative bleeding from the pseudoaneurysm of the proximal part of the common hepatic artery combined with leak of the PEA (one patient); PAC and main duct IPMN (nine patients); diffuse main duct IPMN (one patient); very soft pancreas (10 patients); positive resection margins (five patients); tumour extending to the body of the pancreas (five patients); and formerly removed left pancreas (two patients) (Table 1). Five out of 10 patients with extremely soft pancreas also had vascular reconstructions with prosthetic interposition, and three already had insulin-dependent diabetes. The overall (P1 and P2) 30- and 90-day mortality in our cohort were 5 and 7.9%, respectively. In P2, the rates for 30- and 90-day mortality became lower, 3.5% and 5%, respectively, but the statistical difference between P1 and P2 reveals only borderline statistical value (p=0.08) (Table 2).

DISCUSSION

Pancreatic resections present the only curative option for patients with malignant and premalignant diseases and relief of symptoms in selected group of patients with chronic pancreatitis. However, due to high morbidity and mortality, the treatment should not be worse than the disease (21).

Despite marked progress on the field of pancreatic resections, morbidity remains quite high for decades whereas mortality rates gradually improved (22–27).

There was no exception in our study with morbidity, irrelevant of type of resection, remained stable within the two observed periods. On the other hand the 30- and 90-day mortality for all resections together decreased in the second period (30-day: 2.8%, p=0.06; 90-day: 4.5%, p=0.025). Almost the same, decrease can be observed in PD/TP in P2, but the difference in 90-day mortality tightly misses the statistical significance (30-day: 3.5%, 90-day: 5.6%, p=0.06). This result is well comparable to the reports of other authors. In many studies, postoperative mortality was defined traditionally as mortality within 30-days or during the initial hospitalization. This might had led to an underestimated postoperative morbidity and mortality rates. As shown by some meta-analyses, even in centers of excellence, the 90-day mortality rate is double of the 30-day mortality rate and significantly differs regarding the hospital volume. One of the consequences of postoperative morbidity for patients who survive the complication was significantly prolonged hospitalization (5, 15, 26, 18). In our study, it was ranging between 30 and 44 days.

It has often been documented that higher age and low physical status can significantly affect the occurrence of postoperative complications (12, 13). In our study, higher mean age and higher ASA score impacted the incidence of OAC and AGC. American Society of Anaesthesiologists score alone impacted ASC and PL. Regarding our results, higher mean age was an independent predictor for OAC and AGC whereas ASA score was for AGC. On the other hand, specific complications like BC, AA, and OL did not correlate with age or physical status. Age did not prove as an independent prognostic factor for any complications; however, ASA score did for 90-day mortality. Therefore, our results support the conclusion not to restrain patients from PD or TP only because of their age; however, caution is needed while selecting the patients for PD or TP.

There is an on-going debate on whether jaundiced patients with obstructive lesion and higher bilirubin in the head of the pancreas should be drained or not (29–34). Since only relevant laboratory data from the immediate preoperative period were at our disposal for the study, we can hardly profoundly discuss this issue. Based on our data, however, we observed higher mean total bilirubin values in patients with BC and lower for the group with AGC. The results regarding EBD match with the results from others revealing higher incidence of ASC and PL in patients with EBD (31, 35–38). There was no correlation of mean total bilirubin or EBD with 30- and 90-day mortality (32, 39, 40).

Our study confirms comparable results regarding the perioperative morbidity and mortality between PDs and TPs except for abdominal abscesses, which occurred more often in TP. This fact could speak for TP in selected cases of patients with pancreas remnant, untenable for PEA, especially in elderly in less good general condition who do not tolerate this kind of complications at all (41–43). In patients with preexisting insulin-dependent diabetes, this decision could be even easier. Relevant criteria for decision-making in this regard are still missing. Further analyses are needed for long-term quality of life, especially concerning insulin-dependent diabetes (44–46).

Resection of VMS or VP for infiltration was formerly regarded as a relative contraindication for the PD. However, nowadays it presents a standard treatment and was performed in 16.7% of our patients. In our study, neither type of pancreatic resection nor the incidence of VMS/VP resection influenced the occurrence of postoperative morbidity and mortality (47–52).

The proportion of chronic pancreatitis in PACs and NPCs included in the reports can differ significantly, and if cases with predominantly hard pancreas remnant predominate, as in patients with chronic pancreatitis, the overall risk for postoperative morbidity and mortality rates could reveal at a lower rates. In our collective of patients, chronic pancreatitis and PAC contributed to 2.9% and 56.7% of patients, respectively, remaining more than 40% of patients with diseases where the pancreas remnant could be softer (Table 1) (9, 53–55).

To our results, concerning only PACs and NPCs, OACs were more likely to occur in NPCs and tumours of smaller size. Moreover, the majority of NPCs were also smaller than PACs. The size of tumor affects the onset of OAC, ASC, and PL; however, neither 30- nor 90-day mortality were statistically impacted by type or size of the tumor (56–58).

Patients with amylase more than seven ukat/L on drains and pancreatic fistula were retrospectively classified in three types of PF (A, B, C) respecting clinical picture, therapeutic consequences, and ISGPF PF recommendations (20). Mean values of amylase in discharged secretion did not differ between PF A, B, and C. There is consensus among all reports that PF negatively affected the postoperative course in patients after PD (59, 60).

Our experience with PF was similar. In PD, the high mean amylase on drains or amylase more than seven ukat/L predicted the onset of complications, especially if surgical complications were involved (OAC, ASC, and PL). However, exception was AA where the mean amylases on drains were low proving that abscesses did not originate from pancreatic leak. Pancreatic fistula type A was not associated with any serious morbidity in postoperative course of our patients. Patients with OAC, ASC, AGC, BC, PL, PF C and high mean amylase or amylase more than seven ukat/L are at a higher risk to die within 30 or 90 days. Although most studies agree about the impact of PF on morbidity and mortality, there are fewer consensuses on how to prevent the occurrence of PF. Most effort is focused on how to perform a save anastomosis in case of soft, friable pancreas texture with a thin pancreatic duct (5–7, 10, 61, 62).

Both periods (P1 and P2) were comparable regarding almost all clinical-pathologic factors except for type of pancreatic resection and vascular reconstructions, and the count of performed TPs. There were more TPs in P2 as in P1 (20.8% vs. 4.2%). Both types of pancreatectomies were comparable regarding age, physical status, tumor markers, mean bilirubin value, morbidity, and mortality. Logically, there were no PF in TP. In addition to other indications, TP was performed in 11 patients with pancreas remnant unsuitable for anastomosis. Our results regarding perioperative mortality is good (30- and 90-day mortality was 0%); however, the indications for TP must be posed very responsible, and the inform consent must be done preoperatively in this issue (24, 41, 43).

Most subtypes of complications did not compromise the long-term survival in our cohort of patients. The exceptions were PLs in PDs and BCs in PDs and TPs where the 5-year survival was significantly compromised. On the other hand, in patients who survived any of these complications, the long-term survival was not impacted by any complications (59, 60, 63, 64).

In conclusion, the present study indicates that amylase-rich secret on drains and higher mean age are independent indicator for OAC whereas, PL and BC proved as an independent predictor for 30-day mortality, and physical status, OAC and PF C for 90-day mortality. Endoscopic biliary drainage, smaller size of tumor and NPC can provoke complications, however; there was no repercussion on postoperative mortality. Even though the decrease in 30- and 90-day mortality (3.5% and 5.6%) tightly missed the significance, the trend of better surgery in pancreatic resections in our institution seemed to be encouraging and can also be based on significant decrease in perioperative morbidity in all pancreatic resections together. Most subtypes of complications did not compromise the long-term survival in our cohort of patients. The exceptions were specific complications like PLs and BCs where the 5-year survival was significantly compromised. On the other hand, in patients who survived these complications, the long-term survival was not impaired by any complication. The worse scenario in pancreatic resection is an older patient in bad physical condition having small tumor or NPC, amylase reach output on drains after resection, and eventually BC.

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