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CHAPTER 10

Clinical outcomes after total pancreatectomy: a prospective multicenter pan-European snapshot study

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ABSTRACT

Objective: To assess outcomes among patients undergoing total pancreatectomy (TP) including predictors for complications and in-hospital mortality.

Background: Current studies on TP mostly originate from high-volume centers and span long time periods and therefore may not reflect daily practice.

Methods: This prospective pan-European snapshot study included patients who underwent elective (primary or completion) TP in 43 centers in 16 European countries (June 2018-June 2019). Subgroup analysis included cut-off values for annual volume of pancreatoduodenectomies (<60 vs. ≥60). Predictors for major complications and in-hospital mortality were assessed in multivariable logistic regression.

Results: In total, 277 patients underwent TP, mostly for malignant disease (73%). Major postoperative complications occurred in 70 patients (25%). Median hospital stay was 12 days (IQR 9-18) and 40 patients were readmitted (15%). In-hospital mortality was 5% and 90-day mortality 8%. In the subgroup analysis, in-hospital mortality was lower in patients operated in centers with ≥60 pancreatoduodenectomies compared <60 (4% vs. 10%, p=0.046). In multivariable analysis, annual volume <60 pancreatoduodenectomies (OR 3.78, 95%CI 1.18-12.16, p=0.026), age (OR 1.07, 95%CI 1.01-1.14, p=0.046), and estimated blood loss ≥2L (OR 11.89, 95%CI 2.64-53.61, p=0.001) were associated with in-hospital mortality. ASA ≥3 (OR 2.87, 95%CI 1.56-5.26, p=0.001) and estimated blood loss ≥2L (OR 3.52, 95%CI 1.25-9.90, p=0.017) were associated with major complications.

Conclusion: This pan-European prospective snapshot study found a 5% in-hospital mortality after TP. The identified predictors for mortality, including low-volume centers, age, and increased blood loss, may be used to improve outcomes.

INTRODUCTION

Total pancreatectomy (TP) is mostly performed for diseases involving the entire pancreas, for example, main duct intraductal papillary neoplasm (IPMN), chronic pancreatitis, or pancreatic cancer.[1–3] There is, however, a reluctance to perform TP, because of high postoperative mortality, and the resulting life-long endocrine and exocrine pancreatic insufficiency.[4,5]

Current data on major morbidity and in-hospital mortality after TP are conflicting. A recent systematic review reported that overall morbidity ranged from 36% to 69% and mortality from 0% to 27%.[6] In contrast, a study that only included patients from 2 high-volume centers reported a low 2.1% 30-day mortality after TP in the years 2000-2014.[7] These study results are clearly heterogeneous and may not reflect current practice in recent years. Furthermore, the influence of center volume is unclear. This lack of data is inherent to the fact that TP is a relatively rare procedure. To properly inform patients, reliable and recent real-world data are required.

The relatively new snapshot study is a cross-sectional study design which enables an actual insight into current practice by collecting data in a short period of time in a large number of centers and therefore creates greater generalizability than randomized controlled trials or longitudinal studies.[8,9] Snapshot studies are based on collaborative research and supported by the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). The aim of this pan-European snapshot study was to assess short-term postoperative outcomes after elective TP.

METHODS

Patients and design

A prospective multicenter pan-European study was conducted according to the snapshot design. The aim was to collect a large dataset in a short time period using collaborative research and to create greater generalizability than single-center studies running over longer periods of time.[8,9] All members of the European-African Hepato-Pancreato-Biliary Association were invited to participate. The participating centers included all consecutive patients who underwent elective TP for either malignant or non-malignant disease between June 1, 2018 until June 30, 2019. Patients undergoing elective primary TP, elective completion (after a previous partial pancreatic resection) TP, and in whom an intraoperative decision to extend the planned resection to TP were included. Patients who underwent TP in an emergency setting were excluded. This study is reported in accordance with the STROBE guidelines.[10] The ethics committee of the University Hospital of Guadalajara, Spain waived the need for informed consent.

Data collection and definitions

Patient data were collected locally through an online electronic case report form in CASTOR (CIWIT B.V., Amsterdam). Baseline characteristics collected included sex, age, body mass index (kg/m2), previous abdominal surgery, comorbidity (pulmonary, cardiovascular, and gastrointestinal, and hepatic), American Society of Anesthesiologists (ASA) physical status, preoperative diabetes mellitus and neoadjuvant chemo(radio)therapy. Preoperative imaging was reviewed for tumor location and tumor involvement of vascular structures and other organs. Intraoperative outcomes were the type of surgery (open or minimally invasive), type of TP (elective primary, elective completion, intraoperative decision to perform TP), splenectomy, vein resection (portal vein or superior mesenteric vein), arterial resection (common or proper hepatic artery, accessory or aberrant hepatic artery, celiac trunk, or superior mesenteric artery), additional organ resection, estimated blood loss (including a categorical distribution in <2L and ≥2L), and operation time. Pathological outcomes were tumor origin, histology, resection margin, tumor differentiation, T-stage according to the 7th edition of AJCC TNM staging, and lymph node ratio.[11] Postoperative outcomes were collected up to 90 days postoperatively and during readmission when applicable. Collected outcomes included complications (ie, general and pancreas-specific complications), hospital stay (days), readmission, and mortality. Major postoperative complications were defined as a Clavien-Dindo (CD) score ≥3.[12] Pancreatic surgery-specific complications (only grades B and C) included delayed gastric emptying, post-pancreatectomy hemorrhage, and bile leakage and were defined by the International Study Group on Pancreatic Surgery.[13–16] Mortality is presented as in-hospital and 90-day mortality. In-hospital mortality was defined as a patient who deceased during the initial hospital stay or, in case of earlier discharge, within 30 days after TP. Use of adjuvant chemotherapy was recorded. Data about endocrine and exocrine pancreatic insufficiency were collected at 3 and 6 months postoperatively. Annual center volume was based on the mean annual volume of pancreatoduodenectomies in 2018 and 2019. High or lower-volume centers were defined based on two previously used cut-off values, specifically <40 (lower-volume) or ≥40 (high-volume), or <60 (lower-volume) or ≥60 (very high-volume) pancreatoduodenectomies annually.[17–19]

Systematic literature search

To compare our results to the current literature, PubMed was systemically searched for all published series which included at least 100 TPs, regardless of the study period and indication. Systematic reviews and studies with overlapping cohorts were excluded. Outcomes extracted per study included study period, study design, number of patients, indication, the percentages of complications, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, mortality, and long-term survival. Outcomes were compared with our study results.

Statistical analysis

Baseline characteristics are presented using descriptive statistics and compared using the Students t-test, Mann Whitney U test, or Chi-square test, as appropriate. Subgroup analysis were performed to assess the clinical outcomes in patients diagnosed with IPMN, in patients operated in very high-volume, high-volume, and lower-volume centers (cut-offs based on annual volume 60 and 40 pancreatoduodenectomies), and in patients with elective TP compared with patients with an intraoperative decision to perform TP. Predictors within patient characteristics, hospital volume, and intraoperative outcomes for major complications or in-hospital mortality were identified in univariable logistic regression models. Variables with a p-value <0.10 in univariable analyses were entered in the multivariable regression models and backward step selection was used. The results are reported as odds ratio (OR) with corresponding 95% confidence interval (CI). All p-values were based on a 2-sided test and p-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

During the 13-month study period, 277 patients who underwent TP were prospectively included from 43 centers in 16 European countries. The patients had a median age of 68 years (IQR 57-73) and 161 (58%) were male (Table 1). Preoperative diabetes mellitus was present in 101 patients (37%). During the study period, the median number of TPs per hospital was 3 (IQR 2-6) and the median annual number of pancreatoduodenectomies was 32 (IQR 17-78). An annual center volume of ≥40 pancreatoduodenectomies was reached in 18 centers, which performed a total of 217 TPs (78%) with a median of 7 TPs (IQR 5-15) per center. An annual center volume of ≥60 pancreatoduodenectomies was reached in 14 centers, which performed 193 TPs (70%) with a median of 8 TPs (IQR 5-23) per center (eFigure 1).

Perioperative outcomes

Results on intraoperative, pathological, and postoperative outcomes are presented in Table 2-4. TPs were performed by an open approach in 265 patients (96%). Neoadjuvant chemotherapy was given to 42 patients (15%). Vein resection was performed in 58 patients (21%) and arterial resection in 12 patients (4%), both mostly for malignant disease.

Major complications were reported in 70 patients (25%) and mostly consisted of CD grade 3 complications (n=40, 57%). A postpancreatectomy hemorrhage occurred in 11 patients (4%), bile leakage in 17 patients (6%), and delayed gastric emptying in 20 patients (7%). Within 90 days after TP, 40 patients (15%) were readmitted of whom 15 patients (38%) had a complication with CD≥3. The median duration of readmission was 8 days (IQR 5-13). The in-hospital and 90-day mortality were 5%

(n=15) and 8% (n=21), respectively. Causes of death of the 6 patients who died after initial hospital stay but within 90 days, were aspiration pneumonia accompanied by a diabetic ketoacidosis, complication of a second operation for acute arterial ischemia of the lower limb, sepsis with multiorgan failure after start of chemotherapy, multiorgan failure due to cardiac decompensation, portal vein and superior mesenteric vein thrombosis, and early recurrence of pancreatic cancer. At final pathological diagnosis, 202 patients (73%) had malignant disease. Among all patients with adenocarcinoma, 113 received any type of adjuvant chemo(radio)therapy (63%). Patients with a CD score ≥3 had a lower percentage of receiving adjuvant chemo(radio)therapy compared the other patients (40% vs. 72%, p<0.001).

TABLE 1. Patient characteristics.

	All patients (n=277)
Male	161 (58%)
Age at operation, median (IQR), years	68 (57-73)
BMI, median (IQR), kg/m^2	24 (22-27)
Indication	
Adenocarcinoma	153 (55%)
IPMN	78 (28%)
Neuroendocrine tumor	9 (3%)
Chronic pancreatitis	14 (5%)
Mucinous cystic neoplasm	2 (0.7%)
Solid pseudopapillary neoplasm	2 (0.7%)
Other	18 (7%)
Missing	1
Previous abdominal surgery	150 (55%)
Missing	5
Comorbidity	
Cardiovascular	124 (45%)
Gastrointestinal and hepatic	47 (17%)
Pulmonary	31 (11%)
ASA score	
I	27 (10%)
II	160 (58%)
III	88 (32%)
IV	2 (1%)
Preoperative diabetes mellitus	101 (36%)
Insulin dependent	51 (50%)
Non-insulin dependent	42 (42%)
Unknown type	8 (8%)
Vascular contact on CT or MRI	72 (27%)
Missing	9
Additional organ involvement on CT or MRI	14 (5%)
Missing	9
Neoadjuvant therapy	42 (15%)
Chemotherapy	29 (69%)
Chemoradiotherapy	13 (31%)
Missing	1

Values are numbers with percentages within parentheses unless indicated otherwise. BMI indicates body mass index.

At 3 months follow-up, 256 patients were alive and questions regarding endocrine and exocrine insufficiency were completed in 238 patients (data were missing in 18 patients). New-onset diabetes mellitus was present in 157 patients (66%), and preoperative diabetes had worsened in 42 patients (16%) and was unchanged in 39 patients (16%). Pancreatic enzyme replacement therapy was given to 230 patients (97%).

TABLE 2. Intraoperative characteristics.

	All patients (n=277)
Type of surgery	
Open surgery	266 (96%)
Minimally invasive surgery	11 (4%)
Type of TP	
Intraoperative decision to perform TP	132 (48%)
Elective primary	127 (46%)
Elective completion	18 (7%)
Splenectomy	214 (77%)
Vein resection	58 (21%)
End-to-end anastomosis	33 (57%)
Wedge	18 (31%)
Segment resection, end-to-end anastomosis with graft	7 (12%)
Missing	4
Arterial resection	12 (4%)
Common or proper hepatic artery	5 (42%)
Superior mesenteric artery	4 (33%)
Accessory hepatic artery	2 (17%)
Celiac trunk	1 (8%)
Additional organ resection	
Partial gastrectomy (beyond Whipple)[a]	16 (6%)
Colon segment resection	2 (1%)
Extended right hemicolectomy	4 (1%)
Other	13 (5%)
Estimated blood loss, median (IQR), L	0.4 (0.3-0.8)
<2L	228 (93%)
≥2L	17 (6%)
Missing	32
Operation time, median (IQR), minutes	405 (303-499)
Missing	4

Values are numbers with percentages within parentheses unless indicated otherwise. [a] Subtotal gastrectomy or antrectomy.

Subgroup analysis

In the 41 patients who underwent TP because of IPMN, major complications occurred in 7 patients (17%), and both in-hospital and 90-day mortality was 0% (Table 5). Patients in high-volume centers (≥40 pancreatoduodenectomies annually) had similar postoperative outcomes compared with lower-volume centers, except for hospital stay (12 days (IQR 8-17) vs. 14 days (11-21), p=0.003). In very high-volume centers (≥60 pancreatoduodenectomies annually) postoperative major complications were similar compared with lower-volume centers but in-hospital mortality was lower (4% vs. 10% in lower-volume

centers, p=0.046), and 90-day mortality was 6% vs. 12%, respectively (p=0.073). There were no differences in outcomes between patients with elective primary TP compared with patients with an intraoperative decision to perform TP, except for diabetes-related hypoglycemia during initial hospitalization or readmission (9% vs. 20%, respectively, p=0.007). The group of 17 patients who underwent elective completion TP was too small to take into account in this subgroup analysis.

TABLE 3. Pathological outcomes.

		All patients (n=277)
Origin		
	Pancreas	241 (87%)
	Ampulla of Vater	15 (5%)
	Distal bile duct	6 (2%)
	Duodenum	2 (1%)
	Other[a]	13 (5%)
Malignant		202 (73%)
Histology		
	Adenocarcinoma	183 (66%)
	IPMN	41 (15%)
	Neuroendocrine tumor grade 1 and 2	15 (5%)
	Neuroendocrine tumor grade 3	-
	Chronic pancreatitis	14 (5%)
	Metastasis of renal cell carcinoma	10 (4%)
	Mucinous cystic neoplasm	1 (0.4%)
	Solid pseudopapillary neoplasm	1 (0.4%)
	Serous cystadenoma	1 (0.4%)
	Other	10 (4%)
IPMN[b]		
	Mixed type	17 (6%)
	Main duct	15 (5%)
	Side branch	6 (2%)
Missing		3
Resection margin[c]		
	R0	121 (60%)
	R1	74 (37%)
	R2	6 (3%)
Missing		1
Tumor differentiation[d]		
	Well differentiated	16 (9%)
	Moderately differentiated	89 (52%)
	Poorly differentiated	62 (36%)
	Undifferentiated	5 (3%)
Missing		11
T stage[d]		
	T1	15 (9%)
	T2	62 (39%)
	T3	79 (49%)
	T4	5 (3%)
Missing		22
Lymph node ratio[d], median (IQR)		0.08 (0-0.19)

Values are numbers with percentages within parentheses unless indicated otherwise. TNM staging is according to tumor origin and based on the 7th edition of AJCC TNM staging TNM classification. [a] Originating from kidney, stomach, vena cava inferior or gallbladder; [b] IPMN details are based on the preoperative CT or MRI; [c] Only in patients with malignant disease (n=202); [d] Only patients with adenocarcinoma (n=183).

TABLE 4. Postoperative outcomes.

	All patients (n=277)
Patients with a major complication	70 (25%)
Clavien-Dindo grade 3	40 (57%)
Clavien-Dindo grade 4	15 (21%)
Clavien-Dindo grade 5	15 (21%)
Post-pancreatectomy hemorrhage	11 (4%)
Bile leakage	17 (6%)
Delayed gastric emptying	20 (7%)
Other complications	
Abdominal surgical site infection	37 (13%)
Diabetes related hypoglycemia	44 (16%)
Hospital stay[a], median (IQR)	12 (9-18)
Readmission within 90 days	40 (15%)
Missing	2
In-hospital mortality	15 (5%)
90-day mortality	21 (8%)
Adjuvant chemo(radio)therapy[b]	113 (63%)
Missing	5
Diabetes mellitus[c]	238 (100%)
New-onset diabetes mellitus	157 (66%)
Unchanged diabetes mellitus	39 (16%)
Worsened diabetes mellitus	42 (18%)
Postoperative pancreatic enzyme replacement therapy for exocrine insufficiency[c]	230 (97%)

Values are numbers with percentages within parentheses unless indicated otherwise. TNM staging is according to tumor origin and based on the 7th edition of AJCC TNM staging TNM classification. [a] Only calculated in patients who did not die during hospital admission (n= 262); [b] Only in patients with adenocarcinoma (n=183); [c] Data are only presented for patients with a completed 3 month follow-up for endocrine and exocrine insufficiency (n=238).

Multivariable analyses

Based on the results in the subgroup analysis, hospital volume <60 or ≥60 was assessed within the multivariable analysis. Factors associated with major postoperative complications were ASA≥3 (OR 2.87, 95%CI 1.56-5.26, p=0.001), and estimated blood loss ≥2L (OR 3.52, 95%CI 1.25-9.90, p=0.017, eTable 1). In-hospital mortality was related to age (OR 1.07, 95% CI 1.01-1.14, p=0.046), estimated blood loss ≥2L (OR 11.89, 95%CI 2.64-53.61, p=0.001) and lower-volume centers (<60 pancreatoduodenectomies, OR 3.78, 95% CI 1.18-12.16, p=0.026, eTable 1). Vein or arterial resections were not associated with major postoperative outcomes and in-hospital mortality.

Systematic literature search

The systematic review retrieved 7 studies which included at least 100 TPs (Table 6). All studies were retrospective (including one post-hoc analysis of a prospective database). One study included series from 2 different countries. All studies had an inclusion period beyond 5 years. The number of included patients ranged from 100 to 813. Most studies included both malignant as nonmalignant disease. The pancreatic specific complications postpancreatectomy hemorrhage and bile leakage in our cohort were comparable to literature, but the rate of delayed gastric emptying rate in our study was lower. Mortality

in our study was comparable with most published series, although 1 study had a lower 90-day mortality (3%), whereas 1 other study had a higher rate (11%).

DISCUSSION

This prospective multicenter pan-European snapshot study found a 5% in-hospital mortality after TP. The international snapshot approach allowed for inclusion of 277 patients from 16 countries in a relatively short period of only 13 months, hereby assuring data representative of current clinical practice. The multivariable analysis found an association between in-hospital mortality and annual center volume for pancreatoduodenectomy of <60, age, and estimated blood loss ≥2L.

In this study, the decision to perform TP in patients with malignant disease was mostly made intraoperatively (eg, in order to obtain a radical resection), thus striving for optimal survival outcomes.[20,21] TP is also increasingly considered in patients with main-duct IPMN, which was associated with lower (0%) mortality.[1,20] Generally, TP may be more often considered in recent years because of perceived improved surgical outcomes, increased use of surgery in patients with locally advanced pancreatic cancer, and better management of exocrine and endocrine insufficiency.[7,22,23]

The present study found high rates of postoperative complications and 90-day mortality after TP. In the total cohort, causes for mortality were not only surgery-related but sometimes also disease-related (eg, cancer recurrence). In an earlier series, postoperative complications were associated with a higher age and longer operation time, and there were no independent risk factors identified for mortality.[7] In contrary, a large monocenter series demonstrated that perioperative mortality was related to high blood loss, longer operative time (≥7 hours) and arterial resection.[23] Independent predictors for major complications in the current study were ASA score and estimated blood loss ≥2L, and predictors for in-hospital mortality included center volume, age and estimated blood loss ≥2L. These risk factors should be taken into account during patient selection and the decision to refer patients. We found no association with arterial or vein resections and outcome, which could be related to the low number of 12 patients with arterial resection and 58 patients with vein resection. Also, malignant disease was not related to worse outcomes. No differences were observed in morbidity and mortality between patients who underwent elective primary TP or in whom it was intraoperatively decided to perform TP. An intraoperative decision to perform a TP is therefore feasible. However, because morbidity and mortality after TP are high, this decision should be very well-considered and this option should be discussed with patients prior to surgery.

TABLE 5. Subgroup analysis.

	Total cohort (n=277)	IPMN (n=41)	Center volume based on ≥40 pancreatoduodenectomies annually			Center volume based on ≥60 pancreatoduodenectomies annually			Type of total pancreatectomy		
			High-volume centers (n=217)	Lower-volume centers (n=60)	p-value	High-volume centers (n=193)	Lower-volume centers (n=84)	p-value	Elective primary TP (n=127)	Intraoperative decision to perform TP (n=132)	p-value
Major complications	70 (25%)	7 (17%)	53 (25%)	17 (28%)	0.537	43 (22%)	27 (32%)	0.083	30 (24%)	35 (26%)	0.591
Clavien-Dindo grade 3	40 (57%)	6 (67%)	33 (62%)	7 (41%)		27 (63%)	13 (48%)		15 (50%)	22 (63%)	
Clavien-Dindo grade 4	15 (21%)	1 (22%)	9 (17%)	6 (35%)		9 (21%)	6 (22%)		7 (23%)	6 (17%)	
Clavien-Dindo grade 5	15 (21%)	-	11 (21%)	4 (24%)		7 (16%)	8 (30%)		8 (27%)	7 (20%)	
Post pancreatectomy hemorrhage	11 (4%)	1 (2%)	9 (4%)	2 (3%)	0.775	5 (3%)	6 (7%)	0.075	7 (6%)	3 (2%)	0.176
Bile leakage	17 (6%)	2 (5%)	13 (6%)	4 (7%)	0.847	9 (5%)	8 (10%)	0.121	9 (7%)	7 (5%)	0.551
Delayed gastric emptying	20 (7%)	3 (7%)	16 (7%)	4 (7%)	0.852	16 (8%)	4 (5%)	0.297	8 (6%)	10 (8%)	0.686
Other complications											
Abdominal surgical site infection	37 (13%)	3 (7%)	30 (14%)	7 (12%)	0.664	28 (15%)	9 (11%)	0.394	16 (13%)	19 (14%)	0.673
Diabetes related hypoglycemia	44 (16%)	9 (22%)	38 (18%)	6 (10%)	0.159	38 (20%)	6 (7%)	**0.009**	11 (9%)	27 (20%)	**0.007**
Readmission within 90 days	40 (15%)	7 (17%)	35 (16%)	5 (8%)	0.136	34 (18%)	6 (7%)	**0.024**	14 (11%)	21 (16%)	0.231
Missing	2		1	1		1	1			2	
Hospital stay[a], days, median (IQR)	12 (9-18)	11 (9-14)	12 (8-17)	14 (11-21)	**0.003**	12 (9-17)	14 (10-21)	**0.014**	13 (10-17)	12 (9-19)	0.228
In-hospital mortality	15 (5%)	-	12 (6%)	3 (5%)	0.872	7 (4%)	8 (10%)	**0.046**	8 (6%)	6 (5%)	0.533
90-day mortality	21 (8%)	-	16 (7%)	5 (8%)	0.804	11 (6%)	10 (12%)	0.073	10 (8%)	10 (8%)	0.928

Values are numbers with percentages within parentheses unless indicated otherwise. [a] Only calculated in patients who did not die during hospital admission.

TABLE 6. Comparison with published cohorts including at least 100 total pancreatectomies.

Author	Inclusion period	Country	Mono or multicenter	Retrospective or prospective	Patients, n	Indications for TP	Complications, n (%)	PPH, %	BL, %	DGE, %	Mortality, n (%)	Long-term survival
Reddy et al.[22]	1970-2007 37 years	Johns Hopkins Hospital, USA	Monocenter	Retrospective	100	Pancreatic adenocarcinoma	Surgical morbidity 69% CD≥3 28%	14%		11%	30-day 8%	Median survival 13 months 5-year 19%
Nathan et al.[24]	1998-2004 6 years	USA	Multicenter (SEER)	Retrospective	376	Pancreatic adenocarcinoma	-	-	-	-	30-day 7% 90-day 11%	Median survival per location: Head 15 months Body/tail 12 months Unspecified 11 months
Murphy et al.[25]	1998-2006 8 years	USA	Multicenter (NIS)	Retrospective	4013 *Weighted (actual inclusion 813)*	Malignant and non-malignant	Major complications[a] 28%	4%	-	-	In-hospital 9%	-
Johnston et al.[26]	1998-2011 13 years	USA	Multicenter (NCDB)	Retrospective	5726	Pancreatic adenocarcinoma	-	-	-	-	30-day 6%	Median survival 15 months 5-year survival 12%
Hartwig et al.[23]	2001-2012 11 years	University of Heidelberg, Germany	Monocenter	Post hoc analysis of prospective database	434	Malignant and non-malignant	Nonsurgical morbidity 38% Surgical morbidity 37%	7%	6%	18%	30-day 5% In-hospital 12%	Median survival 24 months 5-year non-malignant 94% 5-year adenocarcinoma 15%
Pulvirenti et al.[7]	2001-2013 12 years	Johns Hopkins Hospital, and University of Verona (binational)	Bicenter	Retrospective	329	Malignant and non-malignant	Morbidity 59% CD≥3 23%	6%	2%	14%	30-day 2% 90-day 3%	-
Scholten et al.[4]	2006-2016 10 years	The Netherlands	Multicenter	Retrospective	148	Malignant and non-malignant	CD≥3 32%	5%	3%	14%	30-day 5% 90-day 8%	Median survival per diagnosis: IPMN 98 months PDAC 13 months
Current study	2018-2019 1 year and 1 month	Pan-European (international)	Multicenter	Prospective	277	Malignant and non-malignant	CD≥3 25%	4%	6%	7%	In-hospital 5% 90-day 8%	-

BL indicates bile leakage; DGE, delayed gastric emptying; NCDB, U.S. National cancer Database; NIS, Nationwide Inpatient Sample; PDAC, pancreatic ductal adenocarcinoma; SEER, surveillance, epidemiology, and end results;. [a] Major post-operative complications in this study were defined by specific diagnoses with codes based on their validation as true complications rather than comorbidities by the methods described by Lawthers et al.[32]

To place the current findings in perspective, a systematic literature search was performed. Compared with the included series, this present study stands out because of its prospective and international multicenter design and short inclusion period with a relatively high number of patients. Our findings are comparable to previous literature in terms of morbidity and mortality and thus outcomes of TP seem not to have substantially improved over the latter years. Mortality in 3 registry studies from the USA was similar to our findings (mortality 6-11%).[24–26] Mortality in high-volume centers was lower than in our cohort.[7] Studies from the world's highest volume centers are less useful for daily clinical practice. The association between outcome and volume was confirmed in our subgroup analyses which showed more favorable results in centers with an annual pancreatoduodenectomy volume of ≥60. The rate of major complications did not differ between very high and lower-volume centers (cut-off ≥60), although mortality rates were lower in very high-volume centers. This could be explained by a lower failure to rescue rate (ie, better treatment of patients with a major complications) in very high-volume centers as was already shown for pancreatoduodenectomy.[27,28] These findings further support the concept of centralization of major pancreatic surgery.

Comparison of our results with patients after pancreatoduodenectomy in the Dutch and German audit, showed similar rates of postpancreatectomy hemorrhage and lower rates of delayed gastric emptying. This may be surprising since post-pancreatectomy hemorrhage is related to postoperative pancreatic fistula, which by definition cannot occur after TP. In-hospital mortality after pancreatoduodenectomy was 4.3% and 3.9% in respectively the German and Dutch audit and thus lower than after TP, except for very high-volume centers.[29] Results after pancreatoduodenectomy within the Swedish registry showed a lower major complication (15.3%) and 90-day mortality (3.5%) as compared with the current study.[30] A systematic review comparing TP and pancreatoduodenectomy confirmed these suggestions and showed that TP had worse outcomes as compared with pancreatoduodenectomy.[31]

A recent systematic review concluded that treatment of endocrine and exocrine insufficiency after TP remains challenging.[5] In our cohort, some data on endocrine and exocrine insufficiency were collected but due to the short follow-up an accurate reflection of treatment and burdens of endocrine and exocrine insufficiency could not yet be demonstrated. Regarding exocrine insufficiency after TP, some patients did not receive pancreatic enzyme supplementation, which should be improved. The impact of long-term endocrine, exocrine insufficiency, and quality of life will have to be assessed in a longer term follow-up study.

The findings of this study should be interpreted considering some limitations. First, since participation in this study was voluntary, some selection bias toward higher-volume centers may have occurred. This

bias, if present, would only further strengthen our findings of a high 90-day mortality after TP. Second, in retrospect, some data could have been collected otherwise. TNM staging should have been scored according to the 8th edition. Third, registration bias cannot be excluded. Although all variables were defined in the online Castor system, the relatively low rate of delayed gastric emptying in our study could be related to registration bias. This could be improved by an external control, but this is obviously highly challenging in 43 centers and 16 countries, let alone the current strict privacy laws. Fourth, pancreatic surgery expertise was based on center volume of pancreatoduodenectomy, which is common in pancreatic surgery literature. The relationship between pancreatoduodenectomy and TP volume is, however, not constant and symmetrically predictable between centers. Moreover, expertise increases with other resections, such as left sided resections and enucleations, and is also depending on the capability of the intensive care unit and interventional radiology. It might be possible that expertise is underestimated based on only pancreatoduodenectomy.

The international multicenter snapshot design is one of the main strengths of the study and allowed for the inclusion of a large number of patients in a very short time period. Snapshot studies require effort from physicians and residents to register data, but also extensive study coordination to ensure complete data collection. Especially, prospective follow-up within a snapshot study complicates the ease and should be excluded from study protocols if possible. A better alternative would be to perform a second snapshot study within the same cohort with (long-term) follow-up. The large advantage of this novel design is the accurate reflection of current practice and these results add substantially to those from studies with a selected cohort, such as randomized controlled trials or series from high-volume centers. The results from our study form a solid basis for discussion about how to improve outcomes after TP.

In conclusion, this pan-European prospective snapshot study found a 5% in-hospital mortality after TP across Europe. Several risk factors for mortality and major complications were identified which could be useful for patient selection and selective patient referral.

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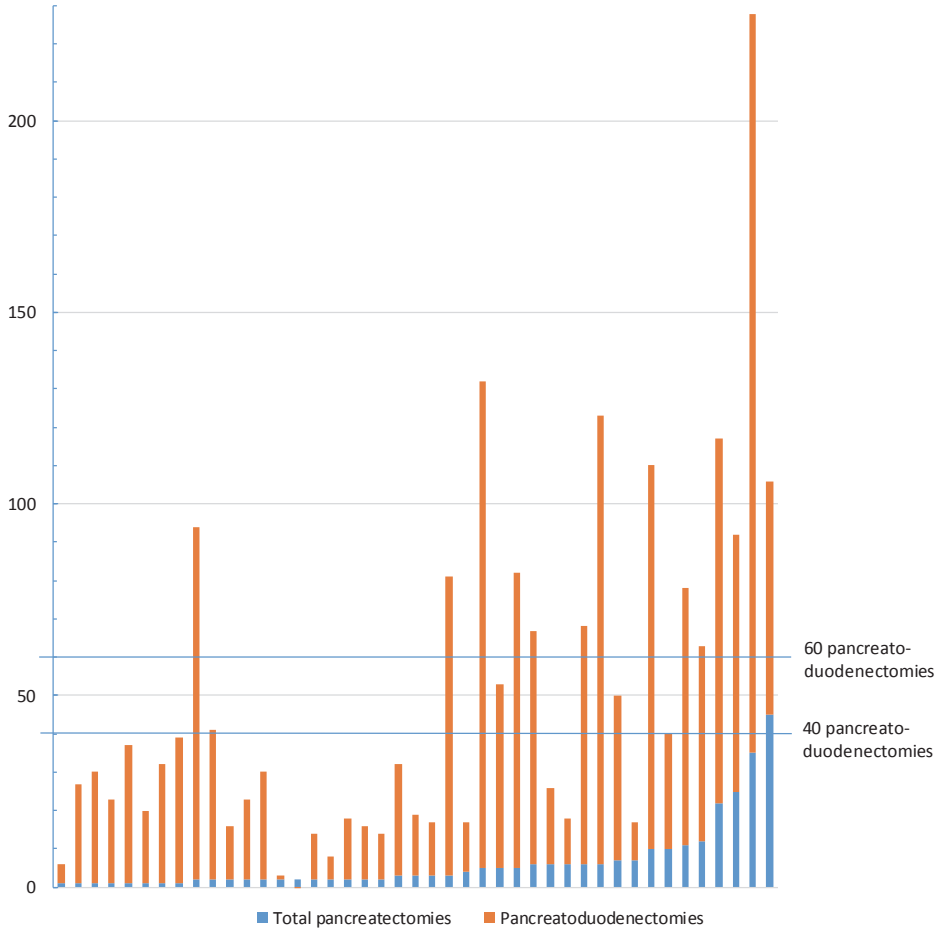
SUPPLEMENTARY MATERIAL

eFIGURE 1. Number of total pancreatectomies and pancreatoduodenectomies per center.



eTABLE 1. Multivariable logistic regression analyses with backward step selection.

	Major postoperative complications				In-hospital mortality			
	Univariable analyses OR (95%CI)	p-value	Multivariable analyses[ab] OR (95%CI)	p-value	Univariable analyses OR (95%CI)	p-value	Multivariable analyses[ab] OR (95%CI)	p-value
Male	1.53 (0.87-2.70)	.138			2.05 (0.64-6.62)	.228		
Age at operation	1.01 (0.99-1.03)	.434			**1.05 (1.00-1.11)**	**.068**	**1.07 (1.01-1.14)**	**0.046**
BMI	1.05 (0.99-1.12)	.115			**1.11 (1.01-1.23)**	**.038**		
ASA ≥3	**3.00 (1.71-5.26)**	**<.001**	**2.87 (1.56-5.26)**	**.001**	**2.51 (0.88-7.15)**	**.085**		
Neoadjuvant therapy	1.05 (0.50-2.23)	.893			2.13 (0.65-7.05)	.214		
Malignant disease	1.35 (0.71-2.54)	.359			2.51 (0.55-11.40)	.233		
Type of TP								
Elective primary	1.00 (reference)				1.00 (reference)			
Elective completion	1.24 (0.41-3.77)	.700			0.88 (0.10-7.44)	.903		
Intraoperative conversion to TP	1.17 (0.66-2.05)	.592			0.71 (0.24-2.10)	.534		
Splenectomy	1.40 (0.71-2.76)	.337			1.19 (0.33-4.35)	.795		
Any vein resection	0.80 (0.40-1.59)	.526			1.37 (0.42-4.48)	.559		
Any arterial resection	1.51 (0.44-5.17)	.514			3.88 (0.77-19.54)	.101		
Additional organ resection	0.90 (0.36-2.17)	.796			2.18 (0.58-8.20)	.251		
Operation time	1.00 (1.00-1.00)	.296			1.00 (1.00-1.00)	.556		
Estimated blood loss ≥2L	**3.81 (1.40-10.36)**	**.009**	**3.52 (1.25-9.90)**	**.017**	**6.71 (1.84-24.31)**	**.004**	**11.89 (2.64-53.61)**	**.001**
Lower-volume center (<60 pancreatoduodenectomies)	**1.65 (0.94-2.92)**	**.084**			**2.80 (0.98-7.98)**	**.055**	**3.78 (1.18-12.16)**	**.026**

All bold results of the univariable analyses were included in the multivariable analyses (p <.10). TP: total pancreatectomy; ASA: American Society of Anesthesiologist. [a] n=245 patients, because estimated blood loss was missing in 32 patients selection. [b] Results after backward step selection.