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Total Pancreatectomy – Indications, Early Morbidity, and Perioperative Strategy. Own Experience of 36 Consecutive Patients and Literature Review

Elena Vrabie[1], Mara Mardare[2,3], Mihai Eftimie[1,3], Octav Ginghina[2,3], Traian Dumitrascu[1,3]*

[1]Department of General Surgery, Fundeni Clinical Institute, Bucharest, Romania
[2]3rd Department of Surgery, Alexandru Trestioreanu Institute of Oncology, Bucharest, Romania
[3]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

***Corresponding author:**
Traian Dumitrascu, MD, PhD
E-mail: traian.dumitrascu@umfcd.ro

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Rezumat

Pancreatectomia totală – indicații, complicații postoperatorii precoce și strategie perioperatorie. O experiență de 36 de pacienți consecutivi și recenzia literaturii

Introducere: Pancreatectomia totală (PT) este un tip mai puțin frecvent întâlnit de rezecție pancreatică, chiar şi în centrele cu volum mare de pacienți. Indicațiile PT nu sunt pe deplin definite, iar rezultatele sunt controversate. Studiul îşi propune să evalueze frecvența de utilizare, indicațiile şi rezultatele precoce ale PT într-o serie consecutivă contemporană de 36 de pacienți.
Pacienți şi Metodă: Datele tuturor pacienților cu PT elective consecutive efectuate de trei chirurgi pancreatici experimentați între 1 februarie 2017 şi 31 decembrie 2024 au fost extrase retrospectiv dintr-o bază de date electronică prospectivă de rezecții pancreatice. Datele pacienților care au necesitat PT au fost analizate pentru indicații, tehnică chirurgicală şi rezultate precoce.
Rezultate: Pacienții au fost predominant bărbați (20 de pacienți, 56%), cu o vârstă mediană de 67 de ani (interval 44-76 de ani). Adenocarcinomul ductal pancreatic a fost principala indicație (24 de pacienți, 67%). Principalele motive pentru efectuarea unei PT au fost leziunile multicentrice (14 pacienți, 39%), hipoplazia/ hipotrofia pancreasului distal (8 pacienți, 22%), anastomozele cu risc crescut (7 pacienți, 19%) şi marginile pancreatice pozitive (6 pacienți, 17%) după duodenopancreatectomie cefalică. Splenectomia a fost efectuată la 23 de pacienți (64%), în timp ce rezecțiile venoase şi arteriale au fost efectuate la 4 pacienți (11%) şi, respectiv, la doi pacienți (6%). Ratele globale, respectiv severe de morbiditate (Dindo ≥ gradul 3) au fost de 83%, respectiv 25%, cu o mortalitate la 90 de zile de 6%. Principalele surse de morbiditate chirurgicală au fost staza gastrică relevantă clinic (5 pacienți, 14%) şi fistula biliară (4 pacienți, 11%).
Concluzii: PT are indicații rare şi specifice, incluzând tumori multicentrice, hipotrofia distală a pancreasului, margini pozitive ale bontului pancreatic şi

anastomoza cu risc crescut după duodenopancreatectomie cefalică. În mâini experimentate, ratele severe de morbiditate şi mortalitate sunt acceptabile pentru o procedură chirurgicală atât de complexă.

Cuvinte cheie: pancreatectomie totală, indicații, anastomoză cu risc crescut, morbiditate precoce, mortalitate, diabet postoperator, chirurg experimentat

Abstract

Background/ Aim: Total pancreatectomy (TP) is an uncommon type of pancreatic resection, even in high-volume centers. The indications of a TP are not fully defined, and the outcomes are controversial. The study aims to assess the frequency of use, indications, and early outcomes of TP in a contemporary consecutive series of 36 patients.
Patients and Methods: The data of all consecutive elective TP performed by three experienced pancreatic surgeons between February 1 2017 and December 31 2024 were retrospectively extracted from a prospectively maintained electronic database of pancreatic resections. The data of patients requiring TP were analyzed for indications, surgical technique, and early outcomes.
Results: The patients were predominantly males (20 patients, 56%) with a median age of 67 years (range 44-76 years). Pancreatic ductal adenocarcinoma was the main indication (24 patients, 67%). The main reasons for a TP were multicentric lesions (14 patients, 39%), distal pancreas hypoplasia/ hypotrophy (8 patients, 22%), high-risk anastomoses (7 patients, 19%), and positive pancreatic margins (6 patients, 17%) following pancreaticoduodenectomy. Splenectomy was performed in 23 patients (64%), while venous and arterial resections were performed in 4 patients (11%) and two patients (6%), respectively. Overall and severe (i.e., ≥ grade 3 Dindo) morbidity rates were 83% and 25%, respectively, with a 90-day mortality of 6%. The primary sources of surgical morbidity were clinically relevant delayed gastric emptying (5 patients, 14%) and bile leak (4 patients, 11%).
Conclusions: TP has rare and specific indications, including multicentric tumors, distal pancreas hypotrophy, positive pancreatic neck margins, and high-risk anastomosis after pancreaticoduodenectomy. In experienced hands, severe morbidity and mortality rates are acceptable for such a complex surgical procedure.

Keywords: total pancreatectomy, indications, high-risk anastomosis, early morbidity, mortality, postoperative diabetes, experienced surgeon

Introduction

Total pancreatectomy (TP) is a surgical procedure that is sometimes used to treat benign but more commonly malignant lesions of the pancreas when more classical pancreatic resections, such as pancreaticoduodenectomy (PD) or distal pancreatectomy, are unsuitable (1,2). Historically, surgeons were reluctant to perform a TP because it was associated with very high mortality rates; thus, Ihse et al., analyzing the outcomes of 89 patients with TP performed between 1959 and 1984, reported an unacceptable mortality rate of 27% (3). Furthermore, significant functional deficiencies in the early and long-term outcomes, including endocrine and exocrine insufficiencies (brittle diabetes that may lead to death and diarrhea), impaired quality of life, and difficulties in managing metabolic consequences, represent important concerns when using TP (4-15). Thus, for a long time, TP was abandoned by many surgeons (16). Even nowadays, pancreatic surgeons are somewhat reluctant to use TP (17), which represents an uncommon type of pancreatic resection, even in high-volume centers; however, the mortality rates after TP have evolved over the years, and contemporary reports of outcomes after TP present far lower mortality rates than the historical ones (1,2,6,18-27).

Considering the indications, TP was initially proposed as an alternative to PD in pancreatic ductal adenocarcinomas (PDAC) to decrease perioperative mortality, increase radicality (i.e., negative resection margins rates), and improve long-term survival. However, historical reports of using TP have shown disappointing survival rates (median overall survival between 7 and 13 months, with 5-year survival rates of only 4.5% to 7%) (3,28,29) in the context of very high mortality rates (3,28,30,31), without increasing negative resection margin rates. Interestingly, the use of TP as an alternative to PD to potentially decrease mortality

and severe morbidity rates, particularly for patients with high-risk pancreatic anastomoses after PD, has been brought again to attention in a few studies in recent years, albeit the results of these studies reached conflicting conclusions (32-44).

Nowadays, advances in imaging, studies leading to a better understanding of tumor biology, and improvements in postoperative care have enabled the establishment of elective TP indications. Thus, TP is suggested to be mainly indicated for a few patients with multifocal tumors or locally advanced PDAC, main duct or mixed-types of intrapapillary mucinous neoplasms (IPMN), or when an arterial resection is performed (2,6, 8-10,19-22,27,45-48). Intraoperative positive pancreatic neck margins and high-risk anastomoses after PD were also considered as an indication for a TP, hoping to avoid local recurrence and, respectively, the potentially harmful consequences of a postoperative pancreatic fistula (9,16,27,35,39, 47-49). Nevertheless, TP indications remain controversial even among experienced pancreatic surgeons (8,9,17,45,50).

Considering the controversies surrounding the use of TP in current practice and conflicting results about its morbidity and mortality rates, the present study aims to add value to the current literature addressing the frequency of use of TP, indications, and early morbidity in a contemporary series of consecutive patients with elective TP performed by three experienced pancreatic surgeons.

Patients and Methods

The data of patients in the present series were extracted and retrospectively analyzed from a prospectively maintained voluntary database of the Romanian Association of HBP Surgery Registry for pancreatic resections established in 2017 (51), which includes multicentric registries for standard pancreatectomies, such as TP, partial PD, and distal pancreatectomies. The inclusion period was February 1 2017 to December 31 2024. Thus, 74 TP were included in the multicenter registry during the analyzed period, with data extracted and analyzed for those procedures performed by three experienced pancreatic surgeons who consented to publish their data (T.D., O.G., and M.E.). It is worth mentioning that during the analyzed period, the three high-case-load surgeons (T.D., O.G., and M.E.) performed 322 standard pancreatic resections, as reported in the registries mentioned above (data not shown). A high-case-load surgeon was defined as one who performed at least six pancreatectomies per year (52).

Inclusion Criteria

The inclusion criteria were adult patients (>18 years), patients who underwent primary TP with or without splenectomy performed by the three experienced pancreatic surgeons (T.D., O.G., and M.E.), elective surgeries, the availability of imaging and blood test results before and after the surgery, available pre- and intraoperative data, histopathological results, and complete early postoperative follow-up.

Exclusion Criteria

Exclusion criteria included partial PD; completion of pancreatectomy for complications or recurrence after partial PD; incomplete pre-, intra-, or postoperative data; emergency surgeries; and TP performed by surgeons other than the three mentioned above (T.D., O.G., and M.E.). Patients with completion of pancreatectomy were excluded because they represent a particular subset of patients, and this procedure is technically more demanding, particularly in the context of postoperative complications after partial PD being associated with very high mortality rates (up to 56%) (53). Furthermore, although exceptional, pancreatectomies in an emergency setting were also excluded, as they are widely accepted to be also associated with very high mortality rates (54,55).

Preoperative data included age, gender, body mass index, comorbidities, presence and types of symptoms and signs, type of imaging explorations, presence and type of preoperative biliary drainage and neoadjuvant therapy, American Society of Anesthesiologists (ASA) score, and bioumoral data.

Intraoperative data included the type of resection and approach, the association of splenectomy or vascular resections, the indication for TP, the operative time, estimated blood loss, and the need for perioperative transfusions.

Early postoperative data, defined as in-hospital complications, included the grading and types of complications, their treatment, length of postoperative and intensive care unit stays, and glycemic control values on discharge. Furthermore, the results of the final pathological examinations were assessed.

Complications were assessed using the Clavien-Dindo classifications and grading system. For postoperative delayed gastric emptying and hemorrhage, the definitions and grading system of the International Study Group of Pancreatic

Surgery were employed. Severe complications were considered those ≥ grade 3, while clinically relevant delayed gastric emptying/ hemorrhage were considered those having grade B or C. Mortality was assessed at 90 days.

Statistical Analysis

The statistical analysis was performed using R, a software package devloped by the R Foundation for Statistical Computing (R Core Team, 2024). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; version 4.42, Copyright (C) 2024; https://www.R-project.org. Continuous variables were expressed as medians (ranges), and categorical ones were presented as numbers (percentages).

Results

Overall, the present cohort comprised 36 patients who underwent TP, representing 11.2% of the 322 standard pancreatic resections performed by the three surgeons during the analyzed period.

The patients included in the study had a median age of 67 years (range, 44-76), and 20 patients (56%) were male, with a median body mass index of 24.3 kg/m² (range, 13.6 – 34.9). Cardiovascular comorbidities were present in 25 patients (69%), while 18 patients (50%) had pre-operative diabetes mellitus.

The main clinical symptoms and signs at diagnosis were weight loss (26 patients, 72%), jaundice (24 patients, 67%), abdominal pain (21 patients, 58%), upper digestive stenosis (3 patients, 8%), cholangitis (3 patients, 8%), and upper digestive hemorrhage (2 patients, 6%). A pre-operative biliary drainage was performed in 19 patients (53%) (endoscopic biliary drainage – 17 patients, 47%; choledoco-duodenostomy – 2 patients, 6%). Neoadjuvant chemotherapy was used for 10 patients (28%).

When calculating the ASA score, 22 patients (56%) were classified as ASA 3, 11 patients (31%) as ASA 2, 2 patients (6%) as ASA 1, and 1 patient (3%) as ASA 4.

The diagnostic methods performed in the present cohort were computed tomography (32 patients, 89%), magnetic resonance imaging (20 patients, 56%), ultrasound endoscopy (19 patients, 53%), endoscopic retrograde cholangiopancreatography (16 patients, 44%), and positron emission tomography (1 patient, 3%).

Table 1. Preoperative tumor characteristics in 36 patients with TP.

Variable	N (%)
Malignant vs. benign pathology	
- Malignant	26 patients (72%)
- Benign	1 patient (3%)
- Uncertain	9 patients (25%)
Localization	
- Pancreas	30 patients (83%)
- Distal choledocus	4 patients (11%)
- Ampulla of Vater	1 patient (3%)
- Duodenum	1 patient (3%)

The most frequent suspected preoperative imaging diagnosis is presented in *Table 1*.

The serum biological parameters of the patients prior to surgery are illustrated in *Table 2*.

The reasons to perform a TP in the present cohort were represented by multicentric lesions (14 patients, 39%), hypotropia/ hypoplasia of the remnant pancreas (8 patients, 22%), high-risk pancreatico-digestive anastomosis after PD (7 patients, 19%), intraoperative pancreatic neck positive margins after PD (6 patients, 17%) and associated arterial resection (1 patient, 3%).

All TPs in the present cohort were performed by an open approach in an elective setting, and technical details are presented in *Table 3*. In the group of patients with venous resection, segmental resection with end-to-end anastomosis was performed in 3 patients (8%), while in one patient (3%), a tangential resection with suture was performed. The two patients (6%) with an arterial resection underwent segmental resection of a replaced right hepatic artery originating from

Table 2. Serum biological parameters prior to surgery in 36 patients with TP.

Variable	Value
Hemoglobin, g/ dl	12.4 (9.3 – 15.6)
Leukocytes, / mmc	7560 (4370 - 22280)
Thrombocytes, / mmc	269500 (153000 - 720000)
Total bilirubin, mg/ dl	0.9 (0.2 – 22.7)
Glycaemia, mg/ dl	109 (72 - 282)
ALT, U/ l	36 (12 – 354)
AST, U/ l	33 (13 – 307)
Amylase, U/ l	57 (16 – 146)
Lipase, U/ l	44 (10 – 688)
Urea, mg/ dl	37 (9 – 127)
Creatinine, mg/ dl	0.8 (0.4 – 1.7)
INR	1.02 (0.88 – 1.27)
Sodium, mmol/ l	140.9 (128 – 146)
Potassium, mmol/ l	4.3 (3.1 – 5.3)
CA 19-9, U/ l	83 (6.5 – 6040)

Table 3. Technical surgical characteristics in 36 patients with TP.

Variable	N (%)
Type of intervention	
Pylorus resecting TP	24 patients (69%)
Whipple TP	9 patients (25%)
Pylorus preserving TP	2 patients (6%)
Splenectomy	
Yes	23 patients (64%)
No	13 patients (36%)
Venous resection	
Yes	4 patients (11%)
No	32 patients (89%)
Arterial resection	
Yes	2 patients (6%)
No	34 patients (94%)
Approach	
Posterior approach	11 patients (31%)
Other types of artery-first approach	13 patients (36%)
Standard	12 patients (33%)
Gastro-jejunal anastomosis	
Precolic	30 patients (83%)
Transmesocolic	6 patients (17%)
Hepatico-jejunal anastomosis	
In situ	18 patients (50%)
Transmesocolic	18 patients (50%)

the superior mesenteric artery with end-to-end anastomosis.

The median operative time in the present cohort of TPs was 360 minutes (range, 230 – 480), with a median estimated blood loss of 475 mL (range, 200 – 1500). Intraoperative blood transfusions were administered to 12 patients (33%), while fresh-frozen plasma was considered in 2 patients (6%).

Table 4 illustrates the complications of the present cohort according to the Clavien-Dindo grading and classification system. The overall morbidity rate was 83%, while the severe morbidity rate (i.e., ≥ grade III) was 25%. The 90-day mortality rate was 6%.

Five patients (14%) had clinically relevant delayed gastric emptying, four patients (11%) had clinically relevant bile leak, and one patient (3%) had clinically relevant postoperative hemorrhage. One patient (3%) of the present cohort underwent re-exploration for choleperitoneum secondary to hepatico-jejunal anastomosis dehiscence.

The median postoperative hospitalization was 15 days (range, 10-70), while the median intensive care unit stay was 3 days (range, 1-16).

The median glycemia value at discharge was 163 mg/ dl (range 57-302), and the median insulin requirement was 30 units/ day (range 10-45). None of the patients experienced symptomatic hypoglycemia during the hospitalization period.

Table 4. Complications in 36 patients with TP, according to the Clavien-Dindo grading and classification system.

Clavien-Dindo	N (%)
Grade I	8 patients (22%)
Grade II	13 patients (36%)
Grade IIIa	3 patients (8%)
Grade IIIb	1 patient (3%)
Grade IVa	2 patients (6%)
Grade IVb	1 patient (3%)
Grade V	2 patients (6%)

The final histopathological results of the present cohort are presented in *Table 5*.

Table 5. Final histopathological results in 36 patients with TP.

Variable	N (%)
Final histopathological result	
Pancreatic cancer	22 patients (61%)
Distal choledochus cancer	5 patients (14%)
IPMN (2 patients with malignant transformation)	4 patients (11%)[†]
Other	5 patients (14%)
Type of pathology	
Malignant	32 patients (89%)
Benign	4 patients (11%)
T stage	
1	4 patients (13%)[#]
2	9 patients (28%)[#]
3	19 patients (59%)[#]
N stage	
0	14 patients (44%)[#]
1	18 patients (56%)[#]
M stage	
0	31 patients (97%)[#]
1	1 patient (3%)[#]
R status	
R0	24 patients (75%)[#]
R1	7 patients (22%)[#]
R2	1 patient (3%)[#]
Differentiation grade	
G1	10 patients (31%)[#]
G2	16 patients (50%)[#]
G3	6 patients (19%)[#]
Vascular emboli	
Yes	17 patients (53%)[#]
No	15 patients (47%)
Perineural invasion	
Yes	22 patients (69%)[#]
No	10 patients (31%)[#]

[†]Two patients with malignant transformation;
[#]% of the patients with malignant pathology.

Discussions

Billroth apparently performed the first TP in the pre-insulin era in 1884 (4,5), while Rockey performed the first TP in the modern era in 1943 for PDAC (4). However, Priestley's merit is in performing the first successful TP in 1944 for an insulinoma (5).

The current TP rate worldwide ranges from 3% to 17.3% of pancreatic resections performed in high-volume centers or by high-case-load surgeons (7,18,22,24,29,45,54–60). In our experience, TP accounted for 11.2% of the total pancreatic resections during the analyzed period.

Nowadays, major morbidity rates after TP vary between 11% and 34.5%, while mortality rates are reported between 0% and 11.8% (1,6–8,18,20–27, 38–43,45,56,58,60–66) (*Table 6*). It is worth mentioning that recently published real-world data from a German Registry of 756 patients with TP have shown higher-than-expected mortality rates (30-day – 9.5%, and 90-day – 18%) (50). At the same time, in a Japanese registry that included 2888 patients with TP, an in-hospital mortality rate of only 2.7% was reported (23). Surgical risk calculators were proposed to predict severe complications after TP, but their performance was considered poor (41). Individual surgical expertise, as well as peri- and postoperative management quality, are significant determinants of low severe and low mortality rates after TP (27).

Several studies have demonstrated the beneficial effects of high hospital volume and high-case-load surgeons on postoperative morbidity and mortality rates after pancreatic resections. However, different cut-offs defined high-volume or high-case-load (26,52,54,65,67-70). Although the mortality of pancreatic resections has decreased in the last years with performing pancreatectomies, including TP, in high-volume centers and by high-case-load surgeons (54,70), however, reports at a national level, including both low and high-volume centers and low and high-case load surgeons are still showing high mortality rates after pancreatic resections in general (around 9%) (70) and TP in particular (up to 22.9%) (50,57,71). It is also worth mentioning that a few patient-dependent factors, such as advanced age, heart or renal failure, liver disease, and ASA scores, were associated with increased mortality rates after TP (6,26,27,50,58,70). At the same time, other studies have found no differences in mortality after TP between high- and low-volume centers (62).

Table 6. Early morbidity and mortality in a series of patients with TP published in the last 5 years.

Author, year	Study	No of patients	Period	Mortality	Major morbidity	CR_DGE	CR_PPH	Re-exploration rate
Stoop, 2020	single-center, Karolinska, Sweden	145	2008 - 2015	5.5%	34.5%	20%	13.1%	12.4%
Hempel, 2021	single-center, Dresden, Germany	41	2008 - 2017	7.3%	31.7%	NA	NA	8%
Beltzer, 2022	two-centers, Germany	92	NA	5.4%	18.5%	NA	NA	9.9%
Johansen, 2022	multicenter, Sweden	20	2020 - 2021	0%	0%	2%	0%	NA
Jung, 2022	single-center, Samsung Medical Center, Korea	142	1995 - 2015	2.1%	17.6%	3.5%	2.8%	NA
Latenstein, 2022	multicenter, Europe	277	2018 - 2019	5%	25%	7%	4%	NA
Loos, 2022	single-center, Heidelberg, Germany	1451	2001 - 2020	6.1%	NA	19.7%	5.9%	14.9%
Marchegianni, 2022	single-center, Verona, Italy	86	2017 - 2019	3%	19%	12%	12%	7%
Hohn, 2023	multicenter, registry, Germany	408	2014 - 2018	10.3%	32%	18.9%	NA	20.6%
Shabunin, 2023	single-center, Moscow, Russia	37	2010 - 2021	18.9%	43.2%	21.6%	21.6%	NA
Stoop, 2023	single-center, Karolinska, Sweden	268	2008 - 2021	3.4%	28%	13.9%	7.5%	6.7%
Ailhaud, 2023	single-center, Grenoble, France	26	2014 - 2023	0%	15%	7%	0%	4%
Balzano, 2023	two-centers, Italy	30	2010 - 2019	3.3%	23.3%	10%	13.3%	10%
Umman, 2023	single-centre, Izmir, Turkiye	47	2017 - 2022	8.5%	25.5%	NA	4.3%	NA
Ukegjini, 2024	single-center, St. Gallen, Switzerland	17	2011 - 2023	11.8%	29.4%	11.8%	5.9%	NA
Zohar, 2024	single-centre, Philadelphia, USA	60	2013 - 2023	5%	27%	8%	3%	7%
Capretti, 2025	five-centers, Italy	75	2016 - 2022	4%	23.3%	6.7%	8%	NA
Current series, 2025	three-surgeons, Bucharest, Romania	36	2017 – 2024	6%	25%	14%	3%	3%

CR_DGE – clinically relevant delayed gastric emptying; CR_PPH – clinically relevant postoperative hemorrhage

A study published in 2025, which included 86,073 pancreatic resections performed in 921 hospitals in Germany, shows that in high-volume centers (i.e., ≥ 50 pancreatic resections per year), in-hospital mortality is significantly lower compared to low-volume centers (5.5% vs. 10.1%) (70). Performing more than 20 TP per year was associated with improved severe morbidity rates in a recent study (65). Differences in failure to rescue rates of patients from severe complications after pancreatectomies may explain, at least in part, these mortality rate discrepancies (72). In the present cohort, the severe morbidity rate was 25%, while 90-day mortality was 6%, which is in line with those reported in other high-volume centers worldwide, even though more than 50% of the patients had at least an ASA score of 3. The two deaths occurred, one in a patient with associated arterial resection who developed hepatic artery and portal vein thrombosis. In contrast, the other patient developed a choleperitoneum due to hepatico-jejunal anastomosis insufficiency and underwent redo anastomosis, but later, on post-operative day 50, developed massive hemorrhage from the hepatic pedicle, most likely in the context of a local septic source.

PDAC represents the primary indication of a TP (24-27,43,47,48,50,58,60,64,65,73), as it was the case in the present cohort. Multicentric tumors indicate TP in 16% to 53.4% of the patients in series published worldwide (56,60,63,73). In the present series, multicentric tumors represented the reason for TP in 39% of the patients.

Intraoperative pancreatic neck positive resection margins after PD for PDAC represent a matter of concern, and a few studies have shown that conversion of PD to TP, aiming to obtain negative resection margins, was associated with statistically significant improved survival without any increase in morbidity and mortality rates (61). Negative resection margins represent an important goal after pancreatectomies for PDAC, being associated with lower local recurrence rates and improved survival compared to resections with positive margins (74,75); however, a few studies discuss the benefits of negative resection margins on overall survival for only PD and not for distal pancreatectomies and TP (59,73,74). Furthermore, the oncological benefit of conversion to TP for intraoperative positive margins after partial pancreatectomies, particularly in PDAC, remains controversial (49,59,76). At the same time, a few studies have shown no oncological benefit of TP over PD and distal pancreatectomy for PDAC of the pancreatic neck (77–80). Nevertheless, intraoperative pancreatic neck positive resection margins after PD represent an indication for TP in 22.3% to 35.9% of the patients in series published worldwide (20,24,56,60,73). In the present series, intraoperative positive pancreatic neck margins after PD represented the reason for TP in 17% of patients.

Several studies have shown the benefits of TP replacing PD for patients with high-risk remnant pancreas anastomoses in terms of severe morbidity and mortality rates (33,34,36-40,43). TP eradicates the potential complications related to distal pancreatic stump anastomoses after PD, which represents the primary source of surgical complications. Indeed, as our study reveals (no mortality in patients with TP for high-risk anastomoses after PD, data not shown), TP can be an alternative to PD for high-risk anastomoses. However, precise and objective criteria for selecting patients who might benefit from a TP over a PD remain unclear (33,36,37), as they depend on the surgeon's expertise and subjective assessment and preference, as was the case in the present series. Nevertheless, a few studies have shown increased rates of major morbidity and mortality for TP compared to PD (1,18), while other studies have not found any significant differences between the two types of pancreatectomies (32,34-36,38,42,44,66,79,81). In Karolinska's experience, high-risk anastomosis after PD indicated TP in 15.9% of the cases (24), whereas in the present series, it represented 19% of patients.

Difusely dilated main-duct IPMN has been considered an indication of TP; however, recent studies have shown that partial PD is not associated with earlier progression after surgery (82). In the present cohort, IPMN represented an indication for TP in 11% of patients, two patients associated with malignant transformation at the pancreatic neck (*Fig. 1*). An atrophic pancreatic tail indicated conversion from PD to TP in 29.4% of the cases in a study (35), while in the present series represented 22% of patients.

A venous resection during TP was reported in 4% - 21.8% of patients in series worldwide (22,26, 27,43,58,64). In the present cohort, a venous resection was associated with TP in 11% of patients.

Although rarely associated with pancreaticoduodenectomies for PDAC, a few experienced pancreatic surgeons consider an arterial resection an indication for conversion from PD to TP, thereby avoiding potential hemorrhagic complications resulting from an arterial anastomosis source secondary to erosion in the context of postoperative

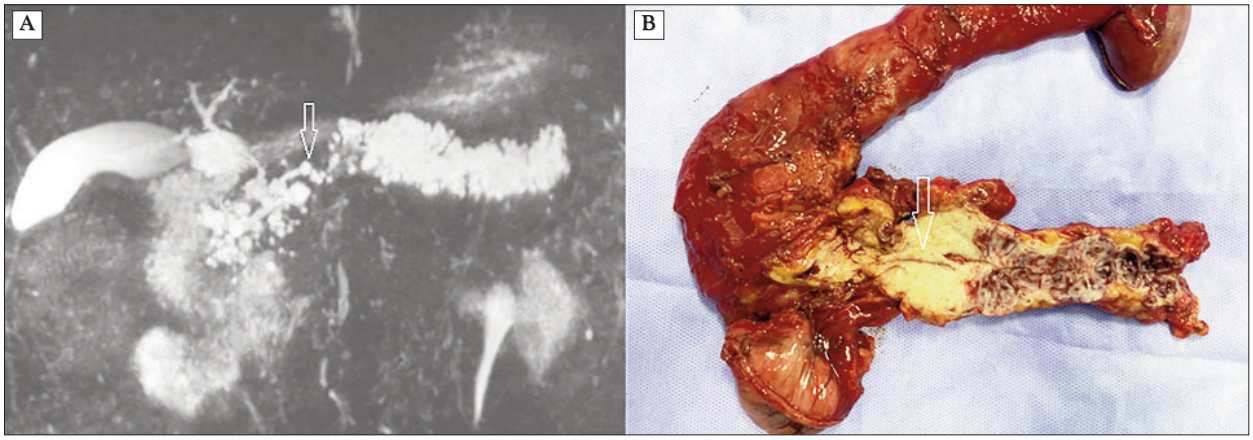

Figure 1. **(A)** Magnetic resonance cholangiography showing a diffuse main duct IPMN with malignant transformation at the pancreatic neck; **(B)** Operative specimen of TP in a patient with diffuse main duct IPMN with malignant transformation at the pancreatic neck (the white arrow marks the malignant transformation).

pancreatic fistula after PD (20,27,46). An arterial resection during TP was reported in 0.9% to 11.4% of patients (22,24,26,27,58,60), and it was associated with statistically significant increased mortality rates (20,27,58) and low survival rates (83). In the present cohort, 6% of patients underwent an arterial resection associated with TP; notably, one of the two deaths in the present series occurred in a patient who had an arterial resection.

Splenectomy can be omitted in a few patients with TP, even for PDAC, as several studies have shown its feasibility and oncological safety (64). In European and US multicenter studies, a splenectomy rate of 44.1% to 77% was reported in TP (26,58). In the present cohort, 64% of patients had an associated splenectomy with TP.

Although the open approach is primarily used for TP (26,58,60), as was the case in the present series, a minimally invasive approach has emerged in recent years, showing, in experienced centers, improved rates of blood loss and major morbidity compared to the open approach (84-87).

The metabolic consequences of a TP are essential in both early and long-term settings (11,13,15, 48,88,89), and managing both endocrine and exocrine insufficiencies still requires further improvement (11). Shortly after the surgery, TP is considered safer than PD, avoiding the complications related to remnant pancreas anastomosis, but long-term metabolic effects, represented mainly by diabetes mellitus, are significant. Even in an immediate postoperative setting, there is an approximately 41% risk of severe life-threatening hypoglycemia, and this remains a cause of late mortality in approximately 3% of cases. On the other hand, the lack of optimal glycemic control with persistent hyperglycemia leads to diabetic retinopathy, neuropathy, nephropathy, and cardiovascular and cerebrovascular diseases. Patients who undergo TP must have a complex insulin regimen and diet plan to maintain optimal blood glucose levels and avoid the severe consequences of variations. Additionally, in these cases, an insulin infusion pump may be the solution to achieve better glycemic control and prevent hypoglycemia episodes (8,10,90).

A systematic review and a meta-analysis have shown that after TP, 80% of the patients will experience a hypoglycemic episode, including 40% with severe hypoglycemia symptoms, leading to related morbidity and mortality rates of 25% to 45% and 0% to 8%, respectively (91,92). A Japanese nationwide multicentre prospective study showed that in the first year after TP, 41.7% of patients experienced one or more moderate or severe hypoglycemic events (89), while a study performed at Karolinska showed that during a median follow-up of approximately 2 years after TP, 90.6% of patients experienced at least one episode of symptomatic hypoglycemia and 25% of patients had at least one episode of loss of consciousness (11).

Diabetes after TP represents a particular type (9,93) that requires insulin and exposes the patient more frequently to mild or even severe postprandial hypoglycemia after insulin administration (5,9,15,94), a situation that explains the long-term reluctance of pancreatic surgeons to use TP. Diabetes may also have a detrimental effect on

early morbidity after pancreatic resections, albeit a few studies show no significant impact (95). Recent advances in the management of patients with insulin-dependent diabetes, including those after TP, have significantly improved the management and outcomes of these patients (12,14,15,92, 96-98), showing similar glycemic control rates to those of patients with type I diabetes (94), and, thus, bringing again to attention the potential role of TP. Using an artificial pancreas has been demonstrated to reasonably control perioperative glycemia in patients with TP, including those at high risk of developing brittle diabetes (99,100). Islet autotransplantation also represents a potential strategy to mitigate the consequences of TP (12).

The median insulin requirement at discharge after TP was 10 units/day (range, 0-80) in the Mayo Clinic experience (55). In the present series, the median insulin requirement on discharge was 30 units/day (range, 10-45). Although the median glycemia value on discharge in the present cohort was 163 mg/dL (range 57-302), 33% of patients had a glycemia on discharge of more than 180 mg/dL. However, it is worth mentioning that none of the patients in the present cohort experienced symptomatic hypoglycemia during the hospitalization period.

Other concerns related to the metabolic consequences of TP include exocrine insufficiencies, characterized by abnormal absorption of fat-soluble vitamins, chronic diarrhea with steatorrhea, malabsorption, and weight loss, as well as steatohepatitis (5,9,11,88,101,102). Chronic diarrhea is attributed to exocrine insufficiency and nerve damage around the superior mesenteric artery during TP, which is more significant than PD. A Japanese multicenter study identified steatohepatitis in 19.6% of the patients within one year (101). To improve results and mitigate the adverse effects of endocrine and exocrine deficiencies caused by TP, a comprehensive preoperative nutritional plan should be established. Its aim should be to optimize the preoperative nutritional status, normalize the albumin level, and avoid sarcopenia, which are important prognostic factors, particularly in PDAC. Enteral nutrition is considered more desirable than parenteral nutrition in the preoperative preparation. After the surgery, in the first few days, parenteral nutrition associated with per-protocol insulin treatment improves glycemic control and decreases the risk of postoperative non-infectious complications. Pancreatic enzyme administration is necessary for achieving long-term outcomes, as it is associated with maintaining fat digestion and absorption functions, and promoting nutritional status, while also preventing hepatic steatohepatitis (102). This strategy may increase the chances of receiving optimal chemotherapy by improving the patient's tolerance, reducing the risk of relapse, and prolonging survival (13,14,88).

A few studies show an acceptable long-term quality of life after TP (7,11,19,20,45,62,63,90), although endocrine and exocrine deficiencies following TP can impact quality of life (19,62,63, 66,103). However, lower quality of life has been observed in patients after TP compared with the general population (11,62), patients with type I diabetes (94,104), and those with PD, particularly with increased rates of insomnia and higher interference with functioning (38,42,66,105). In the present cohort, the long-term metabolic consequences and the quality of life after TP were not assessed, as only glycemic control and glycemia-related events were recorded during the in-hospital stay.

Our present study represents a descriptive statistical analysis of the patients treated by TP as a modest added value to the current literature in understanding the frequency of use, the indications of this type of surgery, the profile of these patients, the characteristics of the surgical approach, the postoperative complications, and short-term surgical results. However, the present study has several limitations, including its retrospective design and the relatively small number of patients. Furthermore, the role of TP in chronic pancreatitis, including autologous islet cell transplantation, is not tackled since the authors have no experience with such procedures. Additionally, the long-term metabolic sequelae and quality of life were not assessed in the present cohort.

Conclusions

TP represents an uncommon type of pancreatic resection, even in high-volume centers or for experienced pancreatic surgeons, with limited indications because it is associated with significant morbidity rates, including functional deficiencies such as insulin-dependent diabetes. However, nowadays, postoperative morbidity and mortality have decreased because of the advances in managing diabetes mellitus and also in compensating for exocrine insufficiency. Therefore, well-trained pancreatic surgeons in high-volume

centers, along with highly selected patients, should not avoid the procedure. When performed by experienced surgeons, TP mortality rates are acceptable for such a complex surgical procedure. Furthermore, the potential benefits of an artificial pancreas may lead to increased use of TP in the future. Considering the significant morbidity and mortality associated with TP, the indication must be firmly established based on a comprehensive diagnostic plan, along with complex postoperative management for both endocrine and exocrine insufficiency.

Author's Contributions

Conceptualization, E.V. and T.D.; methodology, E.V., T.D., M.M., M.E. and O.G.; software, T.D., E.V.; validation, T.D., M.E., and O.G.; formal analysis E.V., M.M., M.E., T.D., and O.G.; investigation, E.V., M.M., M.E., T.D., and O.G.; resources, E.V., M.M., M.E., T.D., and O.G.; data curation, T.D., M.E., and O.G.; writing - original draft preparation, E.V., T.D.; writing - review and editing, E.V., M.M., M.E., T.D., and O.G.; visualization, T.D. and O.G.; supervision, T.D.; project administration, T.D.. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ethical Statement

This study was waived for ethical review and approval due to its retrospective design and non-interference with patient management.

Informed Consent Statement

Informed consent for surgery was obtained from all subjects involved in the study.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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