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The Clinical Outcomes after Total Pancreatectomy

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Key Words
Total pancreatectomy · Morbidity · Mortality · Synthetic insulin · Pancreatic enzymes

Abstract
Background: Total pancreatectomy (TP) is not more beneficial than less aggressive resection techniques for the treatment of pancreatic neoplasms and is associated with high morbidity and mortality. However, with advances in surgical techniques and glycemic monitoring, and the development of synthetic insulin and pancreatic enzymes for postoperative treatment, TP has been increasingly indicated. This is a review of the recent literature reporting the clinical outcomes after TP. ***Methods:*** We reviewed the publications reporting the use of TP starting 2007. The clinicophysiological and survival data were analyzed. ***Results:*** Few studies evaluated the differences in clinical outcomes between TP and pancreaticoduodenectomy (PD) with inconsistent results. It was reported that while the perioperative morbidity did not decrease, the mortality decreased compared to previous literature. All patients who underwent TP required insulin and high dose of pancreatic enzyme supplements. The 5-year survival rates after TP and PD for pancreatic cancer were similar. ***Conclusion:*** The perioperative mortality decreased in patients who underwent TP with advances in the operative procedures and perioperative care. The long-term survival rates were similar for TP and PD. Therefore, treating pancreatic neoplasms using TP is feasible. Patients undergoing TP should receive adequate treatment with synthetic insulin and pancreatic enzyme supplements.

Introduction

The first successful total pancreatectomy (TP) for pancreatic adenocarcinoma was performed by Rockey [1] in 1943, which resulted in early perioperative death due to a bile duct leak. TP was attempted in patients who required total resection of their pancreatic diseases to reduce the incidence of morbidity and mortality, to avoid anastomosis related to pancreatic fistulae, and to reduce tumor recurrence rates as an extension of oncological radicality [2–5]. However, using TP in the resection of pancreatic neoplasms has not been shown to confer any benefit over the less aggressive techniques of resection. Furthermore, TP has been associated with high morbidity and mortality rates [6–8].

TP also has a strong influence on the patient quality of life (QOL) compared to organ preserving pancreatectomy because it causes volatile and difficult-to-control blood sugar levels [9–12].

The 5-year survival rates after TP for pancreatic cancer ranged from 0 to 10% [6, 8, 13–15] until about the year 2000. Patients undergoing TP for adenocarcinoma

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showed shorter survival rates than those undergoing pancreaticoduodenectomy (PD; 7.9 vs. 17.2 months; $p < 0.001$) or distal pancreatectomy (7.9 vs. 14.2 months; $p = 0.02$) [15]. There is no proven oncologic benefit for routine TP over PD, even though specific exceptions have been reported [16].

After advances made in the surgical techniques and glycemic monitoring as well as the development of synthetic insulin and pancreatic enzymes, the medical management after TP has improved. However, there have been few published reports on QOL after TP [9, 17]. Recent studies have demonstrated acceptable QOLs after TP for neoplastic disease [2, 9, 18]. However, more recently, the interest in TP has been shifted to alternative indications for the procedure, owing to the increasing recognition of multifocal parenchymal diseases including intraductal papillary mucinous neoplasms (IPMNs), multifocal renal cell metastases, multifocal neuroendocrine tumors (NETs), chronic pancreatitis (CPs), and even pancreatic ductal adenocarcinoma (PDAC), thereby prompting clinicians to reevaluate the role of TP [19, 20]. In this context, there has once again been renewed interest in TP for the treatment of neoplastic disease over the past 10 years [21]. Recently, the number of cases with clinical indications for TP has been significantly increasing (1998, $n = 384$ vs. 2006, $n = 494$; $p < 0.01$) [22].

This study aimed at evaluating the recent literature that reported the clinical outcomes after TP without islet transplantation.

A literature review was performed on the studies that were published from 2007 to date. In order to identify the relevant publications, a database search was performed on PubMed/Medline using the keywords 'total pancreatectomy, excluding islet autotransplantation'. The search was extended to the references listed in the selected reviews and papers.

The Indications for TP

After the initial enthusiasm for TP, its disadvantages became obvious [9]. Several centers reported that the perioperative mortality and morbidity rates for TP were equal to or higher than those for the Whipple operation; however, any improvement in the long-term survival was not reported [23]. In addition, TP resulted in major metabolic problems [11]. Insulin-dependent diabetes mellitus (DM) with unstable and difficult-to-control blood glucose levels contributed significantly to morbidity and mortality in the long-term follow-up after TP.

However, recent reports have demonstrated lower TP-associated morbidity and mortality rates, which combined with the development of synthetic insulin and pancreatic enzymes, have reinvigorated the interest in TP owing to the improvement of postoperative medical management. In addition, new indications for pancreatic surgery have been identified in the past decade that require total rather than partial pancreatectomy [24].

Currently, TP is indicated in patients with large invasive tumors, multifocal IPMNs, multifocal islet cell neoplasms, multifocal NET, and CP [24–26].

The PDAC patients exhibit local recurrence and tumor resection with negative margins, which is an important prognostic indicator [27–30]. In patients undergoing pancreatectomy for PDAC, TP improved survival in isolated neck margin–positive patients and was associated with a survival benefit because peri- and postoperative complication rates are comparable to those for pancreatectomy, TP is recommended for patients having cancer spread to the left part of the pancreas [4]. IPMNs involving brunch duct multifocal IPMNs and main duct IPMNs, which are associated with high malignancy rates, and the presence of a positive surgical margin for high-grade dysplasia or carcinoma, might require extended resection to TP [31, 32]. In patients with diffuse noninvasive disease, TP should be considered for select patients to minimize the chance of recurrent, invasive disease [25]. The analyses conducted more recently suggested that the course of disease progression for endocrine tumors is not as benign as previously thought, and that aggressive resection might be warranted, including TP [25]. Several large retrospective studies conducted on CP showed that only 30–60% of the patients undergoing TP experienced significant pain relief, and a large percentage of patients were readmitted for diabetic complications [33–36]. Intractable pain associated with CP refractory to medical management has been shown to significantly improve after TP [22].

Additionally, TP might serve a role in diseases likely affecting the entire gland including familial PDAC, NET [25], and metastatic disease [37]. Survival rates for TP patients with malignant pathology were similar to that of a recently published series [17] and to that of patients undergoing a pancreatoduodenectomy for ductal adenocarcinoma [9]. Furthermore, survival after TP for benign disease was similar to that previously published in patients who underwent TP or partial pancreatectomy [9]. The recent advances in the long-acting insulin formulations and the improvement of pancreatic enzyme supplementation offered TP patients safety without severe fluc-

Table 1. Comparison between the morbidity and mortality for TP and PD

Author	Methods	Number	Morbidity, %	p value	Mortality, %	p value
Müller et al. [9]	TP	87	31	N.S.	6	N.S.
	PD	87	23		3	
Schmidt et al. [4]	TP	33	36	N.S.	6.1	N.S.
	PD	28	54		7.1	
McPhee et al. [38]	TP	63	N.D.	N.D.	8.3	N.S.
	PD	1,260	N.D.		6.6	
Nathan et al. [39]	TP	292	N.D.	N.D.	9	0.11
	PD	2,988	N.D.		6.5	
Reddy et al. [40]	TP	100	69	0.0007	8	<0.0001
	PD	1,286	39.6		1.5	
Bhayani et al. [16]	TP	198	38	0.02	6.1	0.02
	PD	6,314	30		3.1	
Nikfarjam et al. [41]	TP	15	87	0.029	N.D.	N.D.
	PD	150	57		N.D.	
Satoi et al. [42]	TP	45	31.1	N.S.	0	N.S.
	PD	885	40.2		0.2	

N.S. = Not significant; N.D. = not described.

tuations and intestinal malabsorption problems. Therefore, we only reviewed the published articles that reported the use of TP since 2007.

The Comparison of TP and PD

The comparison of the mortality and morbidity rates associated with TP and PD is demonstrated in table 1 [4, 9, 16, 38–42] based on published reports from the last 10 years. In these papers, the morbidity rates were 31–87% and included delayed gastric emptying, bleeding, infections, and problems with glycemic control. Nikfarjam et al. [41] reported a higher morbidity rate with a significantly greater number of grade-1 complications according to the Clavien–Dindo classification system, reflecting a high postoperative hypoglycemia rate. The rates of other clinically significant complications were similar between the 2 groups [41]. While 3 reports showed no differences in morbidity between TP and PD [4, 9, 42], 3 showed significant differences between these procedures [16, 40, 41]. While the perioperative mortality rates for TP have decreased in recent years, perioperative morbidity after TP did not decrease significantly (1970–1989: 70.0%; 1990–1999: 70.3%; 2000–2007: 66.0%; p = 1.0) [40]. Although perioperative morbidity was higher after TP compared to PD, most complications (59.0%) were minor (Clavien–Dindo grades 1–2) [40]. Thus, morbidity data between TP and PD were comparable. The evaluation of the differences between TP and PD has not returned consistent results.

In reports comparing TP and PD, the mortality rates were reported in the range 0–9% (table 1). Four reports [4, 9, 38, 39] showed no difference in mortality rates between TP and PD and 2 [16, 40] showed significant differences in the mortality rates of these procedures. Reddy et al. [40] reported higher morbidity and mortality rates for TP compared to PD. However, an increased utilization of TP was noted over time (1970–1989, n = 10; 1990–1999, n = 37; 2000–2007, n = 53) [18]. Although it accounted for the increased utilization of TP, the perioperative mortality for TP decreased over time (1970–1989: 40.0%; 1990–1999: 8.1%; 2000–2007: 1.9%; p = 0.0002) [40]. The operative mortality associated with TP did not differ significantly from PD (1.9 vs. 1.2%, respectively; p = 0.17) [40]. The operative mortality after TP has been decreasing gradually with no changes in the morbidity rates [23, 40]. Portal vein or superior mesenteric vein resection was performed in 11.8–50% of the patients who underwent TP [9, 40–44], and they were performed more commonly than PD [41]. However, the arterial resection of hepatic or superior mesenteric artery or the celiac

Table 2. The morbidity and mortality reported for TP in the last 10 years

Author	Number	Morbidity, %	Mortality, %
Müller et al. [9]	87	31	6
Schmidt et al. [4]	33	36	6.1
McPhee et al. [38]	63	N.D.	8.3
Kulu et al. [24]	147	<40	<5
Murphy et al. [22]	4,013	N.D.	8.5
Stauffer et al. [45]	47	19	2
Casadei et al. [46]	20	25	3
Janot et al. [5]	63	36.5	6.25
Crippa et al. [26]	65	38.5	0
Barbier et al. [2]	56	45	3.6
Epelboym et al. [43]	77	49	2.6
Hartwig et al. [44]	434	37.3	7.8
Johnston et al. [21]	2,582	N.D.	5.5
Watanabe et al. [47]	25	32	5
Satoi et al. [42]	45	31.1	0

N.D. = Not described.

trunk was independently associated with in-hospital mortality in univariate and multivariate analyses. On the other hand, portal vein resection was not associated with in-hospital mortality [44]. Depending on the location of the neoplasms indicating TP, which were neoplasms involving the pancreatic neck region extending to the pancreatic head and body, portal vein involvement is common, explaining the high rate of portal vein resection and reconstruction. Therefore, we reviewed the reports on TP for the last 10 years.

The Results for TP in the Recent Years

In the reports since 2007, the morbidity rates following TP were reported in the range 19–49%, often owing to different operative methods (table 2) [2, 4, 5, 9, 21, 22, 24, 26, 38, 42–47]. Morbidity rates were comparable between TP and PD. The perioperative morbidity rate after TP did not decrease in the last 5 years. The morbidity rates after TP were higher in malignant disease compared to benign disease [44].

It was reported that mortality after TP was 0–8.5% (table 2). Articles comparing TP and PD reported TP mortality rates ranging 6–9%. TP mortality rates appear to have gradually decreased within the last 5 years. Reddy et al. [40] and Murphy et al. [22] reported decreasing trends in TP mortality rates over time, while Crippa et al. [26] reported no mortality in patients who underwent TP. Murphy et al. [22] reported an operative mortality rate of 8.5% that significantly decreased with time (1998–2000: 12.4% vs. 2002–2006: 5.9%; $p < 0.01$). High perioperative morbidity and mortality rates have long been a downside of TP; however, a dramatic decrease in these problems has been achieved over the last several decades [40].

Endocrine and Exocrine Replacement after TP

We reviewed the endocrine and exocrine replacement therapies and clinicophysiological parameters after TP (table 3) [2, 9, 26, 43, 45–48]. All patients required insulin and exocrine pancreatic enzyme replacement. The median number of total insulin units (U) reported for previous studies ranged 25–34 U and the median number of long-acting insulin units ranged 7–16 U. The median number of rapid-acting insulin units reported for previous studies ranged 18–21 U. The requirement for insulin was usually less than expected after TP because of an increase in the expression of peripheral insulin receptors [49–51]. In previous studies, it was reported that patients with apancreatic diabetes required less insulin per day compared to those with type 1 DM [52–54].

The endocrine abnormalities associated with TP included glucagon and pancreatic polypeptide deficiency in addition to insulin abnormalities and thus were different from the conventional types 1 and 2 DM [47]. TP patients are thought to have been more vulnerable to severe hypoglycemic episodes, tend to be resistant to ketosis, and have higher plasma levels of gluconeogenic precursors, which include lactate and alanine, owing to the absence of glucagon [55, 56]. The pancreatic polypeptide might play a key role in the induction of hepatic sensitivity to insulin and insulin receptor regulation [57, 58].

The median glycated hemoglobin levels for patients who underwent TP were reported in the range 6.7–8.2%. The similarities between the glycated hemoglobin levels of patients who underwent TP and PD, and the episodes of hypoglycemia or ketoacidosis showed no evidence that diabetes control was worse in patients who underwent TP [59]. Jamil et al. [49] and Casadei et al. [46] reported that glycemic control after TP could be managed well. In ad-

Table 3. Endocrine and exocrine replacements and the long-term outcomes after TP

Author	Median total insulin, U	Long-acting insulin, U	Rapid-acting insulin, U	Median HbA1c, %	Median daily intake of pancreatic enzymes supplements (lipase U)	Median body weight loss, kg	Weight loss of patients, %	Diarrhea, %
Müller et al. [9]	N.D.	N.D.	N.D.	Malignant 7.5 Benign 6.7	N.D.	13.5	41	Malignant 64 Benign 10
Stauffer et al. [45]	N.D.	10 (0–80)	N.D.	7.7 (6.6–8.8)	N.D.	8.8	40.4	N.D.
Casadei et al. [46]	25 (20–52)	7 (4–20)	18 (15–32)	8	8 (6–11)*	15	84.6	N.D.
Parsaik et al. [48]	37	N.D.	N.D.	7.9	N.D.	N.D.	N.D.	N.D.
Crippa et al. [26]	32 (18–52)	N.D.	N.D.	N.D. (7–9.56)	80,000 (30,000–160,000)	5	45	13
Barbier et al. [2]	N.D.	16 (7–48)	21 (7–70)	7.8	150,000 (75,000–450,000)	9	60	33
Epelboym et al. [43]	29.8	N.D.	N.D.	7.23	N.D.	N.D.	N.D.	N.D.
Watanabe et al. [47]	N.D.	6 (0–16)	17 (10–28)	7.4 (6.2–11.2)	150,000	4.5	68	29

N.D. = Not described.
* Number of pancreatic enzyme units not discribed.

dition to improved endocrine control, exocrine insufficiency might be improved using modern pancreatic enzyme formulations and pylorus-preserving or subtotal stomach-preserving TP [14, 60].

Although in the past, patients who underwent TP were considered to be at a high risk for hypoglycemia [61, 62], recent studies have reported that diabetes after TP is not necessarily associated with poor glycemic control and in the majority of patients, it resulted in equivalent biochemical control compared to the normal type 1 diabetic population [63]. In the follow-up, hospital readmission because of hypoglycemia occurred in 8.7–25% of the patients [9, 43–45]. However, almost none of these patients had life-threatening diabetes-related problems in the recent studies [2, 9, 17, 26, 40, 46]. Advances in glucose monitoring systems, insulin delivery systems, and insulin formulations might contribute to superior glycemic control in these patients [25].

TP can cause severe physiologic abnormalities, manifested by acutely disordered intestinal function, and DM, because of the lack of insulin and glucagon secretion [64]. After TP, the patients were at risk for osteopenia development manifested by radial bone mineral content after surgery that decreased with time [65]. Hartwig et al. [44] reported that the fat-soluble vitamins A, E, and D were measured preoperatively and during regular follow-up examinations until 3 or more years postoperatively. The vitamins A and E levels decreased significantly within the first postoperative year compared to the preoperative serum levels, and showed no further decrease thereafter. No significant changes in the levels of vitamin D were reported over time [31]. Pancreatic enzyme replacement therapy (at least 20,000 U of lipase/major meal), routine calcium and vitamin supplementation, and adherence to a regimen of multiple calorie-dense meals per day could prevent nutritional deficiencies, loss of weight [64], and osteoporosis associated with the apancreatic state [25]. It was reported that the efficacy of pancreatic enzyme supplementation depended on adequate mealtime enzyme replacement [66, 67].

Exocrine replacement via the daily intake of pancreatic enzyme supplements (median 80,000–150,000 U) was reported between 2007 and 2016. Weight loss was observed in 40.4–84.6% of the patients and the median weight loss was 5–15 kg (table 3) [2, 26]. Diarrhea was reported in 10% of the patients with benign diseases and up to 64% of the patients with malignant diseases, who frequently underwent nerve and lymph node dissection that increased the incidence of diarrhea (table 3). Diarrhea after TP mainly resulted from exocrine insufficiency [2]. Therefore, a high dose of pancreatic enzyme supplementation was required to reduce diarrhea and prevent weight loss. The current availability of long-acting insulin and the development of modern pancreatic enzyme preparations have enabled the control of endocrine and exocrine pancreatic insufficiency [46]. Long-term assessments showed that exocrine insufficiency impacted everyday life in 20% of the patients; however, it was reported that nutri-

Table 4. Long-term survival rates (the 3-, 5-year, and median survival times) after TP

Author	Diseases	Number	Methods	3-year survival rates, %	5-year survival rates, %	MST, months
Schmidt et al. [4]	PDAC	33	TP	34	14	17.9
Müller et al. [9]	PDAC, SCN, IPMN, NET, others	147	TP	Malignant 36.6 Benign 88.3	N.D.	Malignant 21.9
Stauffer et al. [45]	PDAC, SCN, IPMN, NET, others	47	TP	65 (PDAC 34)	N.D.	N.D.
Reddy et al. [40]	PDAC	100 1,286	TP PD	27.5 26.8	18.9 18.5	12.6 21
Kulu et al. [24]	PDAC, IPMN	147	TP	36.6	N.D.	21.9
Nathan et al. [39]	PDAC	292 2,988	TP PD	15.3 19.6	11.3 13.4	15 15
Crippa et al. [26]	PDAC, SCN, IPMN, NET, others	65	TP	76	71	Not reached
Barbier et al. [2]	IPMN, NET, PDAC, metastases, CP	56	TP	62	55	122
Hartwig et al. [44]	PDAC, SCN, IPMN, NET, others	434	TP	40.7	27.8	24.4
Johnston et al. [21]	PDAC	2,582	TP	22	13	15
Watanabe et al. [47]	PDAC, IPMN, NET, others	44	TP	64	48	51
Satoi et al. [42]	PDAC	45 885	TP PD	20 32	15 21	17 24

SCN = Serous cystic neoplasm; N.D. = not described.

tion issues after TP are now managed better due to diabetic education [2], and that the QOL could be improved by endocrine and exocrine replacement after TP.

Long-Term Survival Rates after TP

The long-term survival rates of patients who underwent TP for pancreatic cancer were similar to those for patients who underwent PD at both the 3- and 5-year time points (table 4) [2, 4, 9, 21, 24, 26, 39, 40, 42, 44, 45, 47], which supports the use of TP for the treatment of pancreatic adenocarcinoma in appropriately selected patients [39]. As with most retrospective studies, we were unable to collect prospective data on long-term glycemic control or QOL [40]. Postoperative insulin-dependent diabetes associated with dangerous episodes of hypoglycemia contributed to the long-term morbidity and mortality [11, 63, 68, 69]. Billings et al. [17] showed that there was no difference in QOL for 34 patients who underwent TP compared to the type I diabetic controls. The similar 3- and 5-year survival rates in patients who underwent TP vs. those who underwent PD suggested that the glycemic issues were not major determinants of death in the long-term. The comparison of patients who underwent TP and DP showed no differences in global health, and the overall QOL was acceptable [24].

To date, some long-term follow-up complications after TP had been reported. There are several reports of post TP deaths owing to hypoglycemia [2, 17]. However, the patients have recently been referred to the endocrinology unit after TP for education purposes, which might have resulted in good glycemic control and self-management [2, 47]. Therefore, mortality due to diabetic complications or metabolic consequences of pancreatic resection during long-term follow-up after TP was eliminated [20, 45].

The weight loss might be multifactorial and related to poor oral intake and maldigestion that causes malabsorption [48]. In the early phase after TP, consideration should be given to providing all the patients with supplemental enteral feeding for several weeks postoperatively [45]. A strict follow-up protocol, which includes close endocrine and nutritional supervision, strict adherence to proton pump inhibitor (PPI) intake and pancreatic enzyme replacement therapy, and adequate hydration as well as protein intake, should be available for these patients [43]. The risk of an anastomotic ulcer after TP has been suggested since the 2000s [69–72]. However, no anastomotic ulcer has been observed after starting the routine administration of PPI for all patients who underwent TP [2].

In addition to improved endocrine control, control of exocrine insufficiency might be achieved using modern pancreatic enzyme formulations, PPI therapy. Recent studies on glycemic management and pancreatic enzyme supplementation after TP revealed good QOL and a lower rate of endocrinopathy than purported [17, 63].

The long-term survival rates of patients who underwent TP were recently improved for pancreatic cancer and other pancreatic neoplasms (table 4). Long-term survival justifies the use of TP in patients with advanced malignant or multifocal premalignant neoplasms [44]. Surgical resection remains the most effective treatment for PDAC patients. Perioperative mortality and morbidity dramatically decreased over time in patients who underwent TP [40]. The median overall survival was 12.6–17.9 months, with 3- and 5-year survival rates of 15.3–34 and 11.3–15.9%, respectively. Similarities between TP and PD for PDAC were reported by several studies, supporting the use of TP when oncologically appropriate [7, 21, 38, 40, 42]. The rates of disease recurrence after TP for PDAC or invasive IPMN ranged 4.6–26.8% [2, 4, 26, 47]. The primary site of recurrence for PDAC was the liver with a postoperative liver metastasis rate of 52% [42]. In invasive IPMN, 20% of the patients showed an isolated regional recurrence, and 80% showed metastatic lesions at the time of recurrence [2].

Müller et al. [9] did not report any life-threatening events due to diabetes or hypoglycemic episodes during the long-term follow-up. Long-term functional results showed that the management of insulin-dependent diabetes and complete exocrine insufficiency were less complicated than previously reported, with no deaths owing to diabetes and/or hypoglycemic episodes.

This study had several limitations. First, because all the studies included in the review were retrospective in nature, there was a patient selection bias and deviation. Second, the prospectively maintained database did not include complete data on patient comorbidities or other measures of the preoperative state of health. Finally, although endocrine replacement therapy using long-acting and rapid-acting insulin has been evaluated, a long-term replacement therapy for exocrine dysfunction has not been established to date. Therefore, we analyzed the reported effective doses of enzyme replacement therapy. However, the results of our analyses should be validated in a prospective study.

In conclusion, mortality due to TP has decreased over time and long-term survival following TP was equivalent to that following PD. Therefore, TP can feasibly be used to treat pancreatic neoplasms, which have the potential to spread and affect the entire pancreas. Patients should receive adequate doses of synthetic insulin and pancreatic enzyme supplementation to ensure long-term survival.

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Disclosure Statement

The authors declare no conflicts of interest relevant to this study.

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