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ORIGINAL SCIENTIFIC REPORT

A Contemporary Evaluation of the Cause of Death and Long-Term Quality of Life After Total Pancreatectomy

Wenchuan Wu[1,2] · Rebecca Dodson[1] · Martin A. Makary[1] · Matthew J. Weiss[1] · Kenzo Hirose[1] · John L. Cameron[1] · Nita Ahuja[1] · Timothy M. Pawlik[1] · Christopher L. Wolfgang[1] · Jin He[1]

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Abstract

Objective Total pancreatectomy (TP) may be considered for diffuse disease of the pancreas. However, the quality of life (QOL) implications of TP have not been well studied in the contemporary era. We report the QOL and cause of death after TP.

Methods 186 patients underwent TP between 2000 and 2013. The 100 who were still alive at last follow-up were sent a questionnaire including the Short Form-36 (SF-36), the Audit of Diabetes Dependent QoL (ADD QoL), and the European Organization for Research and Treatment in Cancer Pancreas 26 (EORTC-PAN-26). The cause of death was determined for the 86 patients who were dead at last follow-up.

Results While the majority of deaths of the 86 patients were cancer related ($n = 65$), only one patient died of diabetes complications. Among the 100 surviving patients, the median follow-up was 5.9 years. Among the 36 patients who responded to the survey, every patient required pancreatic enzymes and insulin; four patients required seven total hospitalizations for hypoglycemia. The SF-36 survey indicated a worse QOL in six domains compared with a national population matched with age and gender. However, only physical and emotional domains were decreased compared with self-matched preoperative state ($p < 0.01$ and $p < 0.05$, respectively). The ADD QoL survey showed an overall decrease in diabetes-related QoL ($p < 0.01$). When compared to other types of insulin-dependent diabetes, no significant difference in QoL were found in 14 of 19 domains. The EORTC-PAN-26 survey demonstrated that more than 50 % of patients had moderate to severe changes in three of seven domains.

Conclusions Mortality from diabetic complications following TP is uncommon. The decreasing QoL after TP is comparable to self-matched preoperative assessment or insulin-dependent diabetes from other causes. Accounting for the overall health changes, TP should be considered in carefully selected patients.

Introduction

Total pancreatectomy (TP) is currently a safe operation with mortality and morbidity similar to partial pancreatectomy [1–3]. It is often indicated in the treatment of diffuse pancreatic disease such as intractable pain caused by chronic pancreatitis, multicentric hereditary neuroendocrine tumors, hereditary chronic pancreatitis [4] or pancreatic cancer [5, 6], and multifocal intraductal papillary mucinous neoplasm (IPMN). Completion salvage pancreatectomy for postoperative complications, recurrent IPMN, or pancreatic cancer

✉ Jin He
jhe11@jhmi.edu

[1] Department of Surgery, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

[2] Present Address: Department of General Surgery, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China

also results in a total pancreatectomy [7]. In fact, some surgeons have advocated TP because the increased incidence of IPMN and its unique multicentricity [8]. However, the postoperative care for patients with TP can be challenging because the complete loss of both exocrine and endocrine functions [9–11]. The risk of hypoglycemia is a constant challenge with the brittle apancreatic diabetes [12].

Recent advances in insulin formulations [such as long- and short-acting insulin preparations, pramlintide acetate (a new injectable synthetic analog of human amylin)] [13], the glucagon rescue therapy, and the affordable, and more user-friendly glucometers allow better glucose control and less risk of hypoglycemia for these patients. Furthermore, high-quality pancreatic enzyme formulations are readily available to help relieve exocrine pancreatic insufficiency and improve the malabsorption after TP. Although the management of pancreatic endocrine and exocrine insufficiencies has improved in the last decade [14], quality of life (QoL) following TP remains poorly characterized in the current era. As such, we sought to define the QoL of patients after TP in a single center.

Methods

Patients and data collection

Patients undergoing total pancreatectomy at the Johns Hopkins Hospital from 2000 to 2013 were selected from a pancreatectomy database which was prospectively maintained. Patients with islet cell auto-transplantation were excluded. We analyzed clinical data including demographics, surgery type, morbidity, and mortality. The in-hospital mortality was defined as patients who died of complications from pancreatectomy during their index admission. For those patients who died at outside hospitals, we obtained the date of death from searching the Social Security Death Index. The cause of death of those patients was obtained from the National Death Index/Centers for Disease Control and Prevention (CDC). This study was approved by our institutional review board.

Quality of life assessment

Social Security Death Index was used to confirm those patients with TP in our hospital were alive before we mailed them the questionnaires of QoL. If we did not receive response within 1 month after the first mailing, we would contact them by phone to inform them of this study. The second mail was then sent to those patients who we successfully contacted on the phone but had not responded to the first mailing as a final attempt.

Our QoL questionnaires including the Short Form-36 (SF-36), the Audit of Diabetes Dependent QoL (ADD QoL), and the European Organization for Research and Treatment in Cancer Pancreas 26 (EORTC-PAN-26) have been described and used in patients after total pancreatectomy [10, 15–17]. The usage of these survey instruments were briefly described as below:

1. The SF-36 evaluates QoL in eight separate domains from the patient's aspect [18]. These eight domains of SF-36 can be summarized into two separate composite scores of overall health in physical aspect and mental aspect. The SF-36 is normalized to a score of 50 for the age- and gender-matched controls. Self-matched preoperative data were also collected and compared with postoperative data.
2. The ADD QoL uses a mean weighted score to analyze 18 separate areas related to the effects of diabetes [19, 20]. A standardized response from patients with insulin-dependent diabetes ($n = 795$) is used as controls.
3. The EORTC-PAN-26 investigates ten categories of well-being among patients with pancreatic cancer specific to the treatment. This pancreas-specific survey has currently no ''normal'' controls available in the US for analysis of the responses [21, 22]. The raw score was standardized by a linear transformation, and a score ranging from 0 to 100 was produced. Higher scores for functional scale represent higher QoL, while a high score for a symptom scale represents a high level of symptoms. Responses to three categories involving symptoms of metastasis (hepatic symptoms, ascites, and cachexia) were removed from the final analysis of our study because most alive patients had TP for benign pancreatic disease.

Statistical analysis

Continuous variable, such as the age, was dichotomized and displayed as age above and below 80. Categorical variables, such as gender and pathologic diagnosis, were displayed as numbers and percentages. Chi-square test was used for comparative analyses of dichotomized or categorical variables. p values <0.05 (two tailed) were deemed statistically significant. Odds ratios were presented with 95 % confidence interval. All statistical analyses were done with SPSS version 19.0 for Windows (SPSS, Chicago, IL).

Results

Clinical material

One hundred eighty-six consecutive cases undergoing TP from 2000 to 2013 at our institution were identified. One hundred seventy-six patients underwent primary resections and completion pancreatectomies were performed on the other ten patients. There were 85 men and 101 women with a median age

of 62 (range from 19 to 85) years. Clinicopathological characteristics (Table 1) showed significant differences between those who responded to the survey and those who did not.

The in-hospital mortality was 4/186 (2 %). Survival was evaluated for the remaining 182 patients. The 5-year survival of 130 patients with pancreatic malignancy was 38 %. The median overall survival was 31 months [95 % confidence interval (CI) 18–44 months].

Eighty-two patients died during follow-up. The most common cause of death in this cohort of 82 patients was cancer related ($n = 65$). Other cause of death included cardio-cerebral vascular disease ($n = 9$), infectious disease ($n = 3$), and other [5]. Only one patient died of complications secondary to diabetes at 3 months postoperatively.

In the 100 surviving patients, the median follow-up was 5.9 years. Thirty-six patients returned the survey. All 36 patients required pancreatic enzymes and insulin. Seventeen patients have insulin pumps after TP. Four patients required total seven hospitalizations for hypoglycemia (average 1.8 hospitalization per patient).

Quality of life assessment

The SF-36 survey for generic QoL demonstrated six domains that were decreased compared with a national population matched with age and gender (i.e., an average score of 50) (all $p < 0.05$). These six domains were physical functioning, general health, role physical, role emotional, social functioning, and vitality. The overall composite score for physical and mental fitness was also decreased in the surveyed patients ($p < 0.001$). However, only two domains (role physical and role emotional) were reduced compared with self-matched preoperative data ($p < 0.01$ and $p < 0.05$, respectively) (Fig. 1).

The diabetes-specific ADD QoL (normalized to a value of zero, which suggests diabetes has no impact on perception of QoL) presented an overall negative effect secondary to the diabetes which was induced by TP with a weighted score of -2.29 in average (standard deviation, 0.33; $p < 0.01$). Evaluation of the other 18 individual domains showed a negative impact in every area of life ($p < 0.01$ each) resulted from diabetes (Fig. 2). However, when insulin-dependent diabetes was compared with other causes, only the decrease of QoL in the five domains of "future worries," "travel," "confidence in ability," "finances," and "enjoyment of food" was significant after TP ($p < 0.01$). The other 14 of 19 domains showed no significant change in QoL comparing to insulin-dependent diabetes from other causes.

The pancreas-specific EORTC-PAN-26 instrument showed that more than 50 % patients reported moderate to severe change in domains such as bowel habit, sexuality, and satisfaction with health care (Fig. 3). These three domains are often related to pancreatic surgery rather than diabetes. Less than 50 % patients reported change in other domains such as pain, digestive symptoms, body image, and hepatic function. Unfortunately, comparative analysis of the responses with pancreas-specific instrument had no controls available now.

Table 1 Clinicopathological data of 186 patients with TP from 2000 to 2013

	All patients ($n = 186$)	Died ($n = 86$)	Survived ($n = 100$)	Responder ($n = 36$)	Nonresponder ($n = 64$)	p value
Age						
<80	174	74	100	36	64	ns
≥80	12	12	0	0	0	
Gender						
Male	85	44	41	11	30	ns
Female	101	39	59	25	34	
Benign diagnosis	52	5	47	22	25	
Chronic pancreatitis	19	1	18	7	11	ns
Noninvasive IPMN	20	3	17	10	7	ns
MCN or SCN	4	0	3	1	2	ns
Other	9	1	9	4	5	ns
Malignant diagnosis	134	81	53	14	39	
Pancreatic ductal adenocarcinoma	106	75	31	9	22	ns
Other periampullary cancer	1	0	1	0	1	ns
Metastatic renal cancer	8	2	6	1	5	ns
Neuroendocrine tumor	19	4	15	4	11	ns

Comparison was performed between responder group and nonresponder group

ns not significant

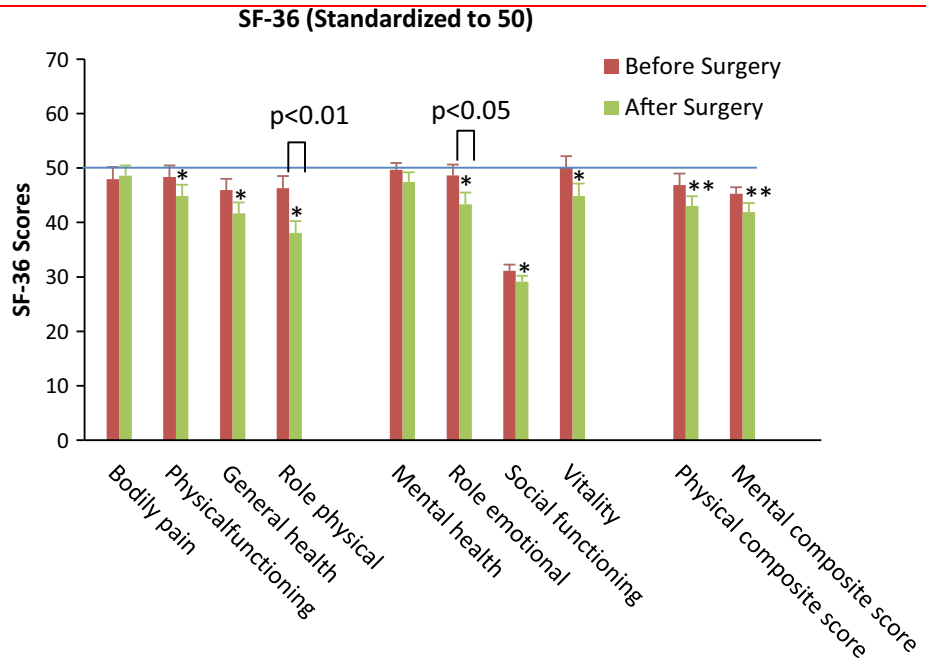

Fig. 1 The comparison of QOL in 36 patients using the SF-36 survey. The score of 36 patients is displayed in mean ± SEM. We demonstrated six domains that were decreased compared with an age- and gender-matched national population (a mean score of 50) (*$p < 0.05$). The composite score for physical and mental health was also lower (**$p < 0.01$). However, only two domains (role physical and role emotional) were decreased comparing with self-matched preoperative data ($p < 0.01$ and $p < 0.05$, respectively)

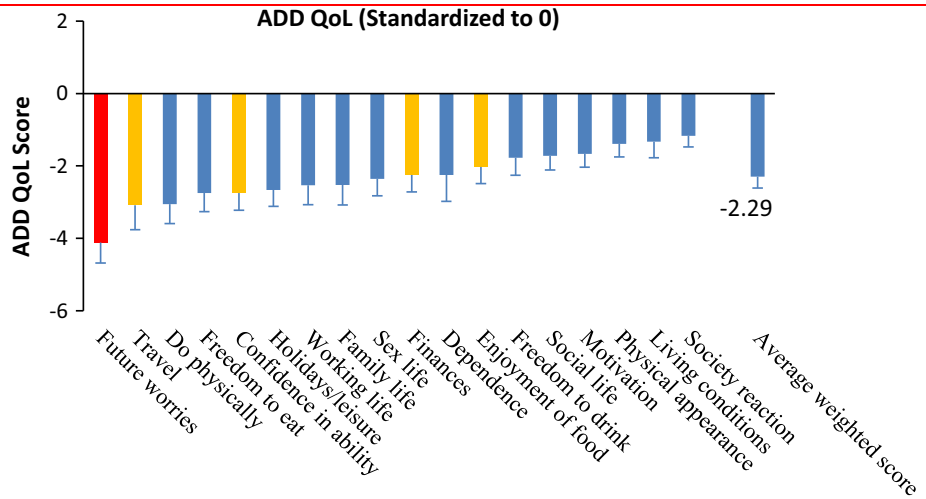

Fig. 2 The comparison of QOL in 36 patients using the ADD QoL survey. The ADD QoL score of 36 patients is displayed in mean ± SEM. The average weighted score of −2.29 (SD 0.33; $p < 0.01$) demonstrated an overall negative impact secondary to the diabetes induced by TP. However, when compared with insulin-dependent diabetics from other causes, only the QoL decrease in the domains of "future worries," "travel," "confidence in ability," "finances," and "enjoyment of food" (highlighted in *red* and *yellow*) is significant. The remaining domains (highlighted in *blue*) showed no significant difference comparing to insulin-dependent diabetics from other causes

Discussion

Among 186 patients undergoing TP in this series, there was 2 % in-hospital mortality, which is consistent with other contemporary data [6, 23]. Among the patients leaving the hospital, the cause of death was mainly related to the primary pathology. Only one patient died directly from complications of poorly controlled diabetes.

With a 5.9 years' median follow-up, we reported the QoL of 36 patients who returned their surveys. All required management with pancreatic enzymes and insulin. Seventeen patients have insulin pumps. Our study provides the

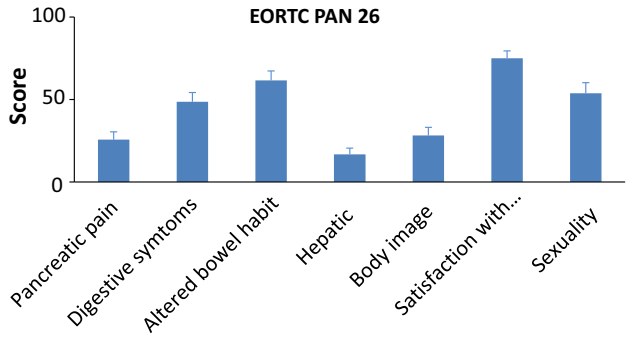

Fig. 3 The QOL in 36 patients using the EORTC-PAN-26 instrument. The EORTC-pan-26 score of 36 patients is displayed in mean ± SEM. More than 50 % patients had moderate to severe change in three of seven domains such as bowel habit, sexuality, and satisfaction with health care

updated QoL data in a cohort of apancreatic patients using three widely used QoL survey instruments to cover generic, diabetes-specific, and pancreas-specific variables. Although all three surveys showed some degree of decreasing QoL, our data show that most domains in SF-36 were similar compared with self-matched preoperative controls. When compared to insulin-dependent diabetes from other causes, most domains in ADD QoL showed no significant difference.

Diabetes after TP can be classified as type 3c diabetes, which testified insufficiency of pancreatic exocrine and the lack of diabetes-associated antibodies. [24, 25] In contrast to type 1 diabetes, diabetes after TP has no glucagon and decreased hepatic insulin sensitivity [26]. In 2004, Landoni et al. [27] reported the QoL of 20 patients after TP surveyed with the EORTC QLQ. A median insulin dosage of 30 IU/day is required for the patients with only one insulin infusion-dependent patient. 72 % patients claimed to experience hypoglycemic episodes at least once a week. The median scores of QOL and health status were paralleled to age-matched patients suffering from type 2 diabetes. In 2005, Billings et al. [15] reported the QoL of 34 patients after TP at the Mayo Clinic. Multiple QoL instruments were used in the survey and patients were found to have similar QoL scores compared with an age- and sex-matched control group. These authors reported three patients who died of late hypoglycemic episodes.

Although the management of type 3c diabetes has significantly improved in the last decade with current treatment of pancreatic exocrine and endocrine replacement [16, 17], we have to make a careful personalized decision weighing the benefit of surgery versus the risks of living with apancreatic diabetes due to its negative impact on QoL. For example, most patients with a benign pancreatic tumor, such as noninvasive IPMN, MCN, or SCN, will undergo a parenchymal preserving partial pancreatectomy pending on the location of the disease without sacrificing the oncological principle. When a young patient presents with diffuse disease such as multifocal IPMN or familiar syndrome that makes the patient prone to malignancy transformation, total pancreatectomy is a reasonable choice.

There are a number of limitations that need to be considered when interpreting the QoL data from survey instruments. Recall bias in QoL is inevitable; however, the bias was likely random with regard to the preoperative versus postoperative groups. With relatively a small number of patients returned the survey, response bias may have been a factor although the clinicopathologic data are similar between responders and nonresponders. Our study cohort is a heterogeneous group of patients with different pathology. This likely affects the QoL as some patients with malignancy were likely undergoing chemotherapy or radiotherapy and suffered from associated side effects.

In conclusion, the risk of death secondary to apancreatic diabetes is low; however, episodes of hypoglycemia remain a threat. The QoL of apancreatic diabetes after TP is not remarkably different when compared with diabetes from other causes. Concerns of the difficulty in management of postoperative apancreatic diabetes are not supported by our data. With better management of diabetes, the apancreatic state after TP is not a major problem in the majority of survivors. TP is now a safe operation with mortality and morbidity similar to those of partial pancreatectomy. Thus, in those who were carefully selected with adequate medical support and appropriate education about all the effects of the apancreatic state, TP should remain an acceptable option when patients have the oncologic, technical, prophylactic, or complication-related reasons [28].

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