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Early and enduring nutritional and functional results of pylorus preservation vs classic Whipple procedure for pancreatic cancer

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Abstract *Background and aims:* There have been many supportive data that the pylorus-preserving pancreatoduodenectomy (PPPD) might be equal to the classic Whipple pancreatoduodenectomy (PD) in terms of oncological radicality. However, few reports are available on the early postoperative and enduring functional changes, nutritional status, body composition, and quality of life years after surgery. The aim of this study was to compare nutritional and functional results of the different techniques in a retrospective evaluation and prospective cohort study. *Patients and methods:* In May 1998, the standard surgical approach in the Department of Surgery, University-Hospital Mannheim, changed from PD to PPPD. The early postoperative and enduring functional changes, quality of life, oncological radicality, and nutritional status after years were compared between 128 patients after PD and 111 patients after PPPD. In a retrospective manner, the intra- and postoperative course was evaluated. In survivors, we prospectively analyzed the functional, nutritional, and oncological outcomes after 54 months (mean) in PD and after 24 months (mean) in PPPD patients. *Results:* The PPPD and PD groups did not differ according to age, gender, preoperative condition, or tumor localization. The PPPD group demonstrated favorable results ($p<0.05$) for operation time (PPPD 341±74 vs PD 386±89 min), blood loss (793±565 vs 1,000±590 ml), blood transfusions (416±691 vs 653±776 ml), delayed gastric emptying (6 vs 13%), and hospital stay (20 vs 24 days). However, a possible bias has to be mentioned since more T4 stages were diagnosed in the PD group (3 vs 11%), and even more extended (venous) resections were performed in the PD group (7 vs 24%). Morbidity (32 vs 30%) and mortality (5 vs 3%) did not differ between the two groups. After 24 months (PPPD, n=22) and 54 months (PD, n=16), there was no difference in global quality of life in recurrence-free patients. While the preoperative body weight was reached after 4 months (median) in the PPPD group, it was reached after 6 months ($p<0.05$) in the PD group. Bioelectrical impedance analysis (BIA) revealed a significantly ($p<0.05$) lower total body water (55 vs 60%) and significantly higher total body fat (26 vs 18%) in PPPD than in PD patients. Long-term follow-up showed no significant statistical differences in survival between both groups. *Conclusion:* Besides favorable postoperative outcome in specific aspects and equal oncological outcome of PPPD, pylorus preservation seems to have advantages in enduring functional and nutritional status years after surgery for pancreatic cancer.

Keywords Whipple · PPPD · Quality of life · Nutrition · Gastrointestinal function

Introduction

The incidence of ductal adenocarcinoma of the pancreas has been increasing worldwide in recent years, and it is now the fifth leading cause of death from cancer in industrialized countries [1, 2]. About 5–25% of all pancreatic cancers are resectable, and only curatively resected (R0) patients enjoy a favorable outcome [2–6]. Nowadays, pancreatic resections represent the only chance for cure or the best chance for palliation since chemotherapy or radiation failed as alternatives [2, 7, 8]. As long-term survival is rare and nutritional and functional disorders are frequent, the quality of life for the remaining months or years is of paramount importance [9]. Complications, delayed gastric emptying (DGE), and long-term nutritional and functional disorders thereby markedly compromise quality of life after major pancreatic head surgery [9–16]. Besides the classic Whipple pancreatoduodenectomy (PD), there have been many supportive data that the pylorus-preserving pancreatoduodenectomy (PPPD) might be equal in terms of oncological radicality [17–21]. However, few reports are available on the early postoperative and enduring functional changes, nutritional status, body composition, measured by bioelectrical impedance analysis (BIA), and quality of life for long-term survivors [14, 17]. This study was performed to assess whether the results of PPPD are equal to those of the classic PD, especially with respect to early and long-term nutritional and functional results, long-term quality of life, and long-term survival.

Patients and methods

Patients

In the Department of Surgery, University-Hospital Mannheim, standard surgical approach for pancreatic head masses changed in May 1998 from the classic Whipple PD [2, 4] to PPPD [22]. Since May 1998, the classic Whipple technique (PD) was performed only for pylorus or stomach infiltrating tumors. In a 4 years and 4 months period from January 1994 to April 1998, we performed PD in 164 patients, of which 128 patients were included into the study. Between May 1998 and December 2001 (3 years and 8 months period), 172 pancreatic head resections (PPPD and PD) were performed, of which 111 PPPD patients were included into the study. All patients with PD procedures in the latter period have been excluded. Furthermore, all patients with rare pancreatic neoplasms or chronic pancreatitis were excluded. Data examined comprised (1) demographics, (2) pathology report, (3) TNM stage, (4) UICC classification, (5) preoperative presenting symptoms and history, (6) details of the surgical therapy (including blood loss, blood transfusions, etc.), (7) hospital course (including complications, DGE, etc.), (8) survival, and (9) follow-up examinations of long-term survivors. All deaths occurring within 30 days after surgery or while the patient was still in hospital were classified as surgical mortality.

Surgical technique

Both procedures include resection of the following structures: pancreas head together with distal bile duct and gallbladder, duodenum with the proximal 2–5 cm of the jejunum, and lymph node dissection (peripancreatic, at the hepatoduodenal ligament and to the right of the superior mesenteric artery). With the PD, the distal half of the stomach and the right half of the major omentum are resected. In contrast, in PPPD, the duodenum is removed approximately 2 cm postpylorically, and passage is reconstructed by means of a duodenojejunostomy. The reconstruction consists of an end-to-side pancreaticojejunostomy in a two-row suture with inner duct-to-mucosa suture and invaginating outer pancreas capsule-to-serosa suture without intraductal or intraluminal drainage [9]. The hepaticojejunostomy is applied approximately 5 cm distal to the pancreaticojejunostomy. The jejunum is opened antimesenterially, and the anastomosis is made end-to-side. The gastrojejunostomy (PD) or duodenojejunostomy (PPPD) is formed 40 cm distal to the hepaticojejunostomy. The gastrojejunostomy (PD) is made as an antecolic, end-to-side anastomosis with Braun's anastomosis. The duodenojejunostomy (PPPD) is also made antecolically and stitched continuously.

Follow-up

Follow-up consisted of personal contact with the patient in our outpatient clinic or with the patients' primary physician and was terminated in January 2003 or at patients' death. Besides regular oncological follow-up, the recovery of nutritional parameters (gain of body weight and serum albumin) were examined. In recurrence-free patients, we conducted a special follow-up examination in April 2002 after 54 months (mean, range 43–99 months) in PD and after 24 months (mean, range 4–43 months) in PPPD for analyzing long-term functional and nutritional outcomes. This examination consists of patients' medical history and demographic data (Karnofsky index, reflux, meteorism, medication, body weight and height, endocrine and exocrine insufficiencies), EORTC quality of life questionnaire (QOL-C30, pancreatic module), laboratory work-up, body mass index (BMI), and BIA.

Statistical analysis

Survival analyses were calculated by the Kaplan–Meier method; differences among subjects of the PD or PPPD group were compared by the log-rank test, both by using

Table 1 Demographic and pathological data

	PPPD (n=111)	PD (n=128)	p
Male/female	58:53	83:45	0.0484
Age (years)	64.5±10.6	62.2±10.5	0.1032
ASA I and II	62 (56%)	67 (52%)	0.6109
ASA III and IV	49 (44%)	61 (48%)	0.6109
Ductal adenocarcinoma	73 (66%)	76 (60%)	0.6443
Carcinoma papilla	23 (21%)	33 (26%)	0.5313
Carcinoma distal bile duct	13 (12%)	15 (12%)	0.9664
Duodenal cancer	2 (2%)	4 (3%)	0.5770
Tumor size (cm)	2.6±1.3	2.6±1.6	0.7991
Nodal positive	65 (59%)	65 (51%)	0.2831
Distant metastases[a]	3 (3%)	6 (5%)	0.5146
Gradings 1 and 2	82 (74%)	72 (56%)	<0.001
Grading 3	29 (26%)	56 (44%)	<0.001
Lymphangiosis	30 (27%)	49 (38%)	0.1192
Perineural infiltration	27 (24%)	28 (22%)	0.7426
Negative margins (R0)	104 (94%)	109 (85%)	0.0251

PPPD pylorus-preserving pancreatoduodenectomy, *PD* Whipple pancreatoduodenectomy, *ASA* American Society of Anesthesiologists Score
[a]Detected intraoperatively

the SPSS software (Release 10.0, SPSS Inc., Chicago, IL). Other comparisons were examined by the chi-square test or t test. Significance was accepted at the probability level of 0.05.

Results

Demographic and pathological data

The PPPD and PD groups did not differ according to age, gender, preoperative condition and symptoms, or tumor localization. Since PPPD was not performed for pylorus and stomach infiltrating masses, significantly more T4 stages were diagnosed in the PD group (PPPD 3% vs PD 11%, p=0.0082). Furthermore, the tumor size and positive lymph nodes did not differ, whereas in PD patients, dedifferentiated tumors (G3) and positive resection margins were more often diagnosed (Table 1).

Perioperative data and hospital course

The overall morbidity rate was 32% for PPPD and 30% for the PD group (ns, Table 2). The hospital mortality was 5% in the PPPD and 3% in the PD group (ns). The PPPD group was significantly (p<0.05) favorable for (Table 2) operation time (PPPD 341±74 vs. PD 386±89 min), blood loss (793±565 vs 1,000±590 ml), blood transfusions (416±691 vs. 653±776 ml), and median hospital stay (20 vs 24 days). Due to more subjects with extended disease (e.g., more T4 tumors) in the PD group, venous resections (portal vein, superior mesenteric vein, and venous confluence) were overrepresented in the PD group (7 vs 24%, p=0.0004). None of the patients received arterial resection.

Table 2 Perioperative data and hospital course

	PPPD (n=111)	PD (n=128)	p
Operation time (min)	341±74	386±89	0.0001
Blood loss (ml)	793±565	1000±590	0.0097
Blood transfusion (ml)	416±691	653±776	0.0173
Extended venous resection	8 (7%)	31 (24%)	0.0004
Relaparotomy	17 (15%)	13 (10%)	0.2462
Bleeding	14 (13%)	14 (11%)	0.6880
Pancreatitis	5 (5%)	1 (1%)	0.0680
Intra-abdominal abscess	7 (6%)	8 (6%)	0.7833
Leckage PJ	7 (6%)	10 (8%)	0.6422
Leckage HJ	2 (2%)	1 (1%)	0.8363
Postoperative stay (days)	20.6	23.6	0.05
Mortality	6 (5%)	4 (3%)	0.473

PJ Pancreaticojejunostomy, *HJ* hepaticojejunostomy

Table 3 Early nutritional and functional outcomes

	PPPD (n=111)	PD (n=128)	p
DGE[a]	7 (6.3%)	16 (12.5%)	0.01
Start of enteral nutrition (POD)	2.2±1.2	2.8±1.4	0.243
Removal of nasogastric tube (POD)	2±1	3±1.6	0.03
Duration of nasogastric tube (POD)	2.2±1.3	3.1±1.8	0.07
Reinseration of nasogastric tube (n)	3 (2.7%)	4 (3.1%)	0.286
Stimulation due to DGE (n)[b]	5 (4.5%)	5 (3.9%)	0.205
Duration of stimulation (days)	3.6±1.3	6.4±3.4	0.183

DGE Delayed gastric emptying, *POD* postoperative day
[a]Removal of the nasogastric tube after postoperative day 3, reinseration of the nasogastric tube, or medical stimulation due to DGE with metoclopramide, neostigmine, and/or erythromycin
[b]Medical stimulation due to DGE with metoclopramide, neostigmine, and/or erythromycin

Early nutritional and functional outcomes

DGE was defined as removal of the nasogastric tube after postoperative day (POD) 3, reinseration of the nasogastric tube, or medical stimulation due to DGE with metoclopramide, neostigmine, and/or erythromycin (Table 3). DGE was observed more frequently in the PD group than in the PPPD group (PD 12.5% vs PPPD 6.3%, p=0.01, Table 3). Furthermore, extraction of the nasogastric tube was delayed (PD POD 3 vs PD POD 2, p=0.03), and the overall duration of the nasogastric tube was prolonged (PD 3.1 vs PPPD 2.2 days, p=0.07) in the PD group (Table 3). Besides that, the start of enteral nutrition and the need for medical stimulation were not different between both groups.

Long-term nutritional and functional outcomes

Complete nutritional and functional data of recurrence-free patients were available for 16 patients after PD and 22 patients after PPPD (Table 4). After a mean of 24 months (PPPD) and 54 months (PD), there was no difference in global quality of life according to EORTC questionnaire in recurrence-free patients (PPPD 62.88±22.96 vs PD 67.71±15.18, p=0.7248). Furthermore, there was no significant difference in quality of private and family life (24.24± 27.08 vs 32.29±36.24, p=0.6105), loss of appetite (16.67± 30.43 vs 8.33±14.91, p=0.5632), and nausea and vomiting (6.82±12.24 vs 7.29±25.07, p=0.3188) between both groups. While the preoperative body weight was reached after 4 months (median) in the PPPD group, it was reached after 6 months (p=0.001) in the PD group. The rate of postoperative newly diagnosed diabetes, exocrine insufficiency, and gastroesophageal reflux was not different in both groups. However, BIA revealed a significantly lower total body water (55 vs 60%, p=0.0083) and significantly higher total body fat (26 vs 18%, p=0.0029) in PPPD than in PD patients (Table 4).

Long-term oncological outcome

Long-term follow-up by personal contact in our outpatient clinic or with the patients' primary physician showed no significant statistical differences in overall survival between both groups. Furthermore, we found no statistical

Table 4 Long-term nutritional and functional outcomes of recurrence-free patients after PPPD and PD

	PPPD (n=22)	PD (n=16)	p
Duration of preoperative weight (months)[a]	4.1±1.2	6.1±1.3	0.001
Karnofsky index (%)	85.9±17.6	77.5±19.8	0.1769
Postoperative diabetes[b]	3 (14%)	1 (6%)	0.6245
Pancreatin medication[c]	12 (55%)	10 (63%)	0.6239
Symptoms of reflux[d]	7 (32%)	5 (31%)	0.9703
Meteorism	16 (73%)	10 (63%)	0.5031
BMI	27.01±5.3	25.04±5.8	0.4161
Total body water (%)	55±6.5	60±4.7	0.0083
Total body fat (%)	26±9.1	18±5.8	0.0029
BCM (kg)	48±4.4	50±7.9	0.2363
ECV (kg)	27±9.2	29±8.6	0.3223
BCM/ECV quotient	1.1±0.5	1.0±0.4	0.7837

BMI Body mass index, *BCM* body cell mass, *ECV* extracellular volume
[a]Postoperative duration until the preoperative weight is reached
[b]Newly diagnosed postoperative diabetes
[c]Need for regular pancreatin medication due to exocrine insufficiency
[d]Postoperative symptoms of gastroesophageal reflux

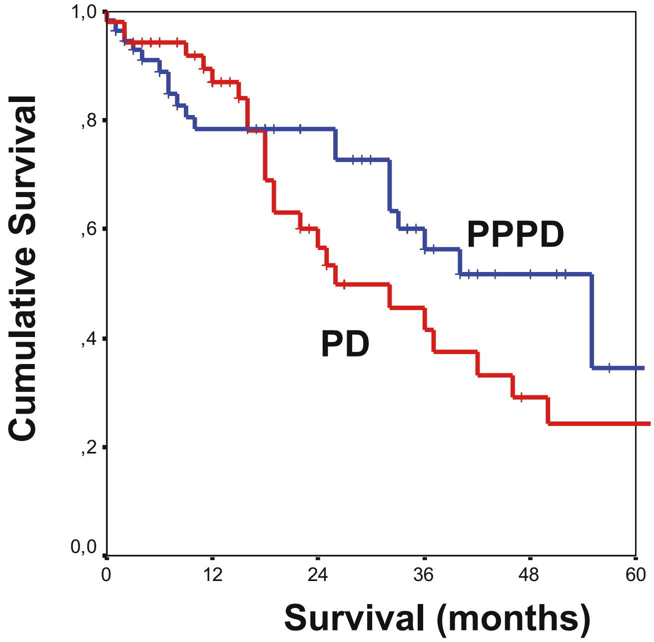

Fig. 1 Cumulative survival analysis for patients with ductal adenocarcinoma that have been resected by either pylorus-preserving pancreatoduodenectomy (PPPD, n=73, *blue line*) or pancreatoduodenectomy (PD, n=76, *red line*) (p>0.05)

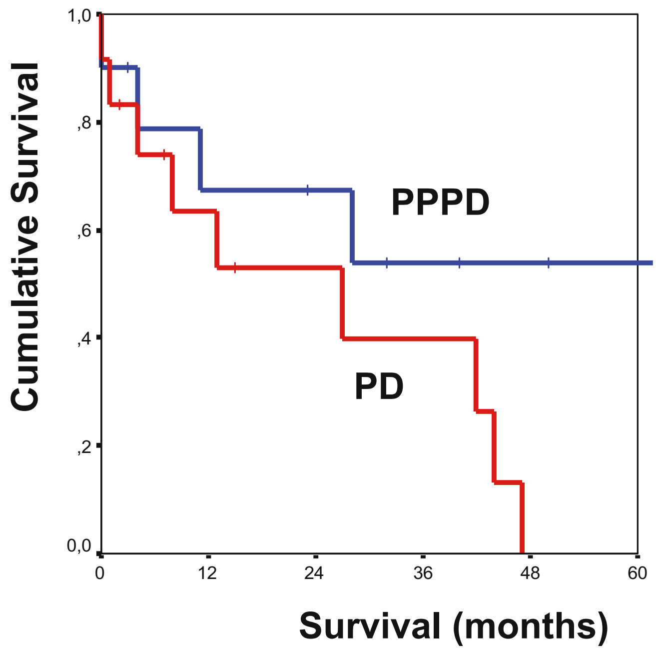

Fig. 3 Cumulative survival analysis for patients with carcinoma of the distal bile duct that have been resected by either PPPD (n=13, *blue line*) or PD (n=15, *red line*) (p>0.05)

significant differences for every specific tumor group after curative resection (ductal adenocarcinoma, carcinomas of the common bile duct or Vater's papilla, and duodenal cancer). Exemplary, cumulative survival analyses of curatively resected (R0) patients with ductal adenocarcinoma and carcinomas of the common bile duct and Vater's papilla are shown in Figs. 1, 2 and 3.

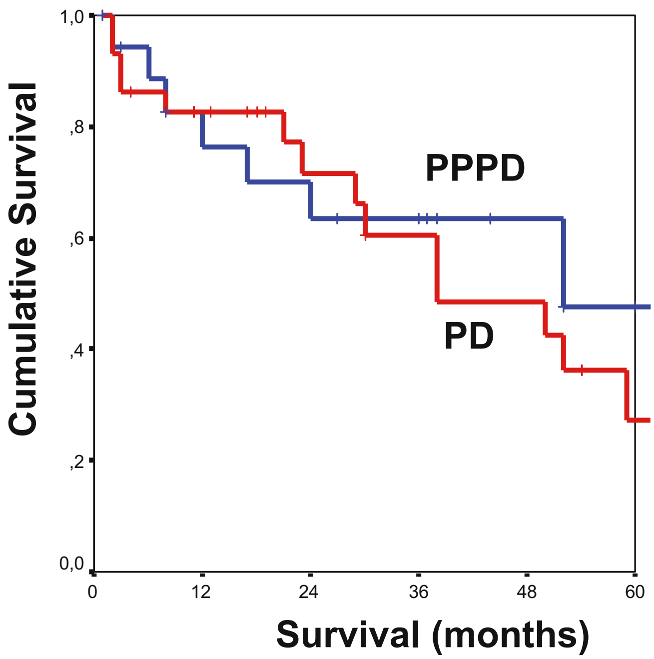

Fig. 2 Cumulative survival analysis for patients with carcinoma of Vater's papilla that have been resected by either PPPD (n=23, *blue line*) or PD (n=33, *red line*) (p>0.05)

Discussion

The preservation of the pylorus is an old element of pancreatic surgery and was first described by Watson [23] in 1944, before Traverso and Longmire [24] took up this idea in 1978 and made it popular. In contrast to the PD, here, the duodenum is dissected approximately 2 cm distal to the pylorus, and passage is reconstructed by duodenojejunostomy [22, 24, 25]. Potential advantages are discussed like shortened surgery time due to the absence of the distal gastrectomy with corresponding reconstruction, as well as the nearly physiological passage and the greater patient acceptance by stomach preservation [9, 12, 14, 17, 18, 21, 26, 27]. Disadvantages like DGE and reduced overall survival are often mentioned by surgeons advocating the classic Whipple [28, 29]. These factors are at present the subject of controversial discussion. Long-term effects of pylorus preservation in terms of nutrition, gastrointestinal function, and recurrence are still not well defined. By analyzing our nonrandomized data of two time periods (PD 1994–1998 and PPPD 1998–2001), we are able to substantially support the indication for PPPD based on nutritional and functional results.

As previously described by other institutions, the postoperative course regarding morbidity and mortality of

PPPD is comparable to PD [13, 14, 20, 21, 26]. We found favorable results for PPPD concerning operation time, hospital stay, blood loss, and need for transfusion. The latter two aspects, however, might be a result of less subjects with extended venous resections in the PPPD group. Some institutions report on up to 70% DGE (range 4–70%), and DGE represents almost half of all complications and is therefore the leading cause of postoperative morbidity [10, 15, 16, 30, 31]. DGE is usually not associated with higher mortality, but its occurrence results in longer hospitalization, reduced quality of life, and increasing costs [32]. DGE has been mentioned as one disadvantage of PPPD compared with the classic Whipple (PD) [33]. In contrast, our data show reduced DGE in PPPD (PPPD 6.3% vs PD 12.5%) and an earlier removal of the nasogastric tube, as described by other authors [12, 18, 22]. Several factors have been suggested for the pathogenesis of DGE. The most important risk is the presence of other intra-abdominal complications, such as pancreatic fistula, anastomotic leakage, and intra-abdominal abscess [12, 31]. From our point of view, DGE almost exclusively occurs as a consequence of other complications or reasons. Therefore, DGE should not be used as an argument to advocate hemigastrectomy. An additional factor thought to play a role is the radicality of the resection, including the lymph node dissection. Cameron et al. [34] demonstrated that after extended retroperitoneal lymphadenectomy, DGE is significantly increased. This observation supports the idea that the complication is caused by gastric atony resulting from disruption of the gastroduodenal neural network [35]. It has also been demonstrated that pancreatic fibrosis and increased gastric fluid production correlate with this complication after pancreaticoduodenectomy. Progressive pancreatic fibrosis correlates with elevated gastric fluid production postoperatively and is therefore associated with DGE [30]. Other authors suggest that the ischemic injury to the antropyloric muscle plays a role in DGE. They argue to preserve the right gastric artery because of its supply to the pylorus and the proximal duodenum [36, 37]. However, it has been demonstrated that ligation of this vessel does not result in an increased DGE [30]. Resection of the duodenum, the primary production site of most gastrointestinal hormones, might also play a role in the pathogenesis of this complication. The consequence is a reduced circulation level of motilin. For prokinetic drugs, it was demonstrated that low doses of erythromycin reduce the incidence of DGE by 75% [38], but it is still debatable whether to apply this to every patient prophylactically or not. We prefer to start the medication when DGE persists for more than 5 days. According to our data, the problem of gastric emptying disorders following PPPD is to be avoided by means of the antecolic reposition of the stomach and a duodenojejunostomy in the mid-abdomen. It has the advantages of gravity-assisted gastric emptying in the upright patient, the spatial removal of the stomach from possible inflammatory complications of the pancreas, and the reduction of the danger of kinking. Our own favorable results could be confirmed in a smaller randomized study by means of scintigraphic documentation of gastric emptying [39] and by Kozuscheck et al. [13].

As to oncological radicality, most series agree with our results and report comparable long-term results for PD and PPPD [17, 19, 21]. We archived nearly identical 5-year survival rates for both procedures in patients with ductal adenocarcinoma, carcinomas of the common bile duct, Vater's papilla, and duodenal cancer (Figs. 1, 2 and 3). To our knowledge, the only limitation of the PPPD is posed by large pancreas head masses, which do not allow preservation of the stomach due to their proximity to the pylorus. In these cases, a classic Whipple should be performed. In our series, PPPD was not performed for pylorus or stomach infiltrating masses. Therefore, significantly more T4 stages were diagnosed (PPPD 3% vs PD 11%), and more extended venous resections (7 vs 24%) were performed in the PD group, implying a possible bias in this study. Likewise, there were more microscopically involved margins (R1) and more dedifferentiated tumors (G3) in the PD group. However, this had no effect on the long-term survival (Figs. 1, 2 and 3). Only one group describes less satisfactory long-term results following PPPD, however, in patients with stage III cancer [29]. The only lymph node stations which are not removed during the PPPD are those of the lesser and greater gastric curvature, which are occupied by the tumor only in extremely rare cases and, according to available studies, have never been affected [40]. In a recent prospective, randomized, multicenter study of Tran et al. [17], PPPD finally could demonstrate having no adverse effects on long-term survival. Seiler et al. [21] could also confirm these results in a smaller previous single-center study. Since tumors of the pancreas head generally infiltrate more likely into the retroperitoneum, we consider the PPPD as oncologically equivalent.

Weight loss is most of the time the first symptom of pancreatic carcinoma [41–44]. The depletion of body fat is the reason for the rapid weight loss in cancer cachexia [45], especially in pancreatic cancer [42–44]. Decreased food intake associated with reduction of BCM and body fat differentiate cancer cachexia from chronic starvation. Indeed, body fat is the component that is preferentially depleted in noncancer starvation. The effect of refeeding on body composition in malnourished cancer patients is still debatable [45]. In fact, an inability to use nutrients effectively is one distinguishing feature of cancer cachexia. This may explain weight loss in patients whose food intake is apparently adequate [46]. However, the postoperative loss of body weight after PD and PPPD is a result of postaggressive metabolism and preoperative tumor-induced weight loss. After resection of the tumor, postaggressive metabolism remains as the only source of continuing body weight loss. The restoring of the preoperative body weight depends on a multifactorial genesis. Especially body fat is increased as a consequence of an improvement in appetite and dietary intake. Appetite and dietary intake were limited by gastrointestinal symptoms like nausea, flatulence, epigastric fullness, vomiting, and diarrhea (Table 4). The DGE in the PD group would be a lead to a prolonged intestinal passage problem (Table 3). An intestinal passage problem is resulting in prolonged gastrointestinal symptoms and, therefore, in attenuated dietary intake. The faster normalization of the dietary intake would be the reason for the significantly faster achievement of the preoperative body weight and body fat in the PPPD group (Table 4).

PPPD archives favorable perioperative outcome like in decreased surgery time, DGE, blood loss, need for blood transfusion, and hospital stay. Furthermore, the long-term oncological outcome of PPPD is equal to PD for all pancreatic head masses. For long-term survivors, pylorus preservation has advantages in enduring nutritional and functional status in particular. Adding up prospective data from the literature [11, 14, 17–21, 26] with the results presented here, there is no doubt that pylorus preservation is oncologically equal to the classic Whipple and is the "standard" procedure for pancreatic head malignancies.

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