

# Total Pancreatectomy for Primary Pancreatic Neoplasms

## *Renaissance of an Unpopular Operation*

Werner Hartwig, MD,\* Alexander Gluth, MD,\* Ulf Hinz, MSc,\*† Frank Bergmann, MD,‡  
Pauline E. R Spronk, MSc,\* Thilo Hackert, MD,\* Jens Werner, MD,\* and Markus W. Büchler, MD\*

**Objective:** To assess the long-term survival and quality of life in total pancreatectomies and to identify risk factors for perioperative morbidity and mortality.

**Background:** Total pancreatectomy may be required in locally advanced or centrally located pancreatic neoplasms to achieve complete tumor clearance, but available data on short- and long-term results are limited.

**Methods:** A total of 434 consecutive total pancreatectomies for primary pancreatic or periampullary tumors were performed between October 2001 and September 2012 at the authors' institution and were prospectively documented and analyzed. Long-term outcome was assessed using Kaplan-Meier and quality of life analysis (EORTC-QLQ-C30 and PAN26). Uni- and multivariate analysis was performed to identify perioperative risk factors and predictors for long-term survival.

**Results:** Extended total pancreatectomies were performed in 54% of cases, with arterial and portal vein resections in 15% and 32%, respectively. Overall 30-day and in-hospital mortality rates were 3.7% and 7.8%, respectively. High blood loss, long operative time, and arterial resections were independently associated with increased perioperative mortality ( $P \leq 0.018$ ). In malignant disease, median and 5-year survival were good for standard total pancreatectomies (28.6 months and 24.3%, respectively) and were significantly impaired after vascular resections ( $P < 0.001$ ). Poor tumor grading, high American Joint Commission on Cancer tumor stage, age more than 70 years, and an R1 resection were independent prognostic parameters. Long-term global quality of life was comparable with a matched healthy control group.

**Conclusions:** Standard total pancreatectomy, if needed, is associated with good long-term outcome in pancreatic cancer. Marked surgical morbidity and impaired survival associated with vascular resections reflect the invasiveness of extended total pancreatectomies and the underlying advanced malignant disease.

**Keywords:** adenocarcinoma, morbidity, pancreas, prognosis, extended, resection, surgery

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Pancreatic resections play an essential role in the multimodal therapy of pancreatic cancer and remain the only potential hope of cure for locoregional disease.<sup>1</sup> Whereas standard pancreatic head or tail resections are established procedures with well-documented

short- and long-term outcome, the role of total pancreatectomy is less well understood. Total pancreatectomy was attempted to improve the survival of patients with pancreatic cancer with the rationale to avoid anastomosis-related morbidity and mortality and to reduce tumor recurrence rates.<sup>2–4</sup> However, no benefit could be recorded, and long-term prognosis was hampered by the difficulties of insulin and pancreatic enzyme supplementation.<sup>5</sup> With the establishment of improved long-acting insulin formulations, the manageability of brittle diabetes mellitus has improved substantially, but published data on the quality of life (QOL) after total pancreatectomy remain limited.<sup>6–8</sup>

Today, improved perioperative morbidity and mortality rates in pancreatic surgery are due to several factors, including better surgical techniques, improvements in perioperative care, and establishment of high-volume pancreatic centers with advanced complication management.<sup>9–11</sup> These surgeon- and hospital-related factors are the prerequisite for the implementation of more extended pancreatic resections. Although total pancreatectomies that are performed as a rescue procedure in an emergency situation need to be avoided because of poor outcome with in-hospital mortality rates of up to 40%,<sup>7</sup> recent reports about total pancreatectomy in the elective situation have described encouraging results.<sup>6,12,13</sup> Extensive pancreatic head or body cancers may require total pancreatectomy to achieve complete tumor resection with negative margins. Furthermore, with paramount evidence on intraductal papillary mucinous neoplasms (IPMNs) being a precursor lesion of pancreatic adenocarcinomas, there is an increasing need for total pancreatectomy in patients with extensive main duct IPMNs or in multifocal branch duct IPMNs.<sup>14</sup>

In the present study, we describe the short- and long-term outcome of a large cohort of patients with total pancreatectomy performed in the elective situation for benign and malignant primary pancreatic tumors. The study includes a multivariate perioperative risk and long-term survival analysis and an evaluation of the QOL and of nutrition/metabolic parameters within the first 5 postoperative years after total pancreatectomy.

## PATIENTS AND METHODS

### Patient Selection

From a total of 596 consecutive total and completion pancreatectomies that have been performed between October 2001 and September 2012 at the Department of General Surgery, University of Heidelberg, Germany, 434 patients with pancreatic or periampullary tumors and elective primary pancreatectomy were identified from a prospectively maintained database. Patients who underwent completion pancreatectomy because of tumor recurrence ( $n = 49$ ) or in the emergency situation ( $n = 40$ , eg, anastomotic complication, necrotizing pancreatitis of the remaining pancreas after partial pancreateoduodenectomy), total pancreatectomy for nontumorous indications ( $n = 34$ , eg, chronic pancreatitis), or for extrapancreatic tumors infiltrating the pancreas or metastasis to the pancreas ( $n = 39$ ) were excluded from the present analysis.

From the \*Department of General, Visceral, and Transplantation Surgery; and †Division of Biostatistics, and ‡Institute of Pathology, University of Heidelberg, Heidelberg, Germany.

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Reprints: Markus W. Büchler, MD, Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany. E-mail: markus.buechler@med.uni-heidelberg.de.

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## Surgical Eligibility

Standard preoperative evaluation included physical examination, routine laboratory testing including serum levels of carbohydrate antigen 19-9 (CA19-9), chest radiography, contrast-enhanced multidetector computed tomography, and/or state-of-the-art magnetic resonance imaging. Endosonographic ultrasound with/without fine needle aspiration was an optional diagnostic procedure. In general, tumors were excluded from exploration if the presence of metastatic disease was identified by presurgical imaging studies. Ductal adenocarcinomas with singular liver metastasis, as identified by preoperative cross-sectional imaging or intraoperatively, were resected only in selected patients who were young or in otherwise extraordinarily healthy condition. Adjuvant therapy was generally performed in all patients with histology-proven adenocarcinoma of the pancreas, excluding those patients with a postoperatively poor Karnofsky index. Patients with locoregional extended disease (involvement of the hepatic artery, superior mesenteric artery, celiac axis, or in some patients with a long-segment infiltration of the portomesenteric vein) potentially underwent neoadjuvant chemoradiotherapy or, infrequently, chemotherapy.

## Surgical Intervention

En bloc pancreatotomy was anticipated in tumors that were located in the pancreatic corpus to avoid intraoperative spillage of tumor cells or in main duct IPMNs with nodular involvement of the Ductus Wirsungianus all along the pancreas. In cases in which a partial pancreatotomy was primarily performed, an intraoperative frozen section of the pancreatic transection margin was taken. An extension of the pancreatic resection was eventually performed when invasive carcinoma or high-grade dysplasia (PanIN 3 lesions) was identified in patients with pancreatic cancer or when moderate dysplasia (PanIN 2 lesions) was detected in younger patients with main duct IPMN and no verified carcinoma. Total pancreatotomy for suspected carcinoma included a standard radical lymphadenectomy, with complete soft tissue removal along the hepatoduodenal ligament, the hepatic artery, the left and/or right side of the mesenteric artery, the retropancreatic tissue, the lymph nodes, and soft tissue around the splenic artery and the splenic hilus (almost always in combination with splenectomy). Extended total pancreatotomy with resection of adjacent organs was performed when mandatory in locally advanced tumors. In some cases, a total pancreatotomy was performed to minimize the risk of eventually anastomosis-related complications, in particular in cases in which arterial resections with reconstruction were performed or in patients with high comorbidity. The technique of total pancreatotomy has recently been described in detail.<sup>15</sup>

## Data Collection

All parameters were prospectively collected in an electronic database. The study was approved by the University of Heidelberg Institutional Review Board. All pancreatic adenocarcinomas were classified according to the TNM criteria of the American Joint Commission on Cancer (AJCC) 2010 cancer system.<sup>16</sup> IPMN histology was confirmed by a specialized pancreatic pathologist (F.B.). The margin resection status (R-status) was defined according to general recommendations before July 2005 when R1 was defined as tumor formations invading the resection margin. Starting July 2005, pathologic reporting included a standardized examination of resection specimens with inking of the resection margins, and R1 was defined as a distance of the tumor from the resection margin of 1 mm or less.<sup>17,18</sup> CA19-9 serum levels were measured using an electrochemiluminescence-based assay (Elecsys, Roche Diagnostics, Mannheim, Germany) and were expressed as U/mL. Follow-up was updated from patient charts of the hospital's pancreatic outpatient clinic in January and February

2013. For patients who were not included in our follow-up program, patients themselves, the patients' general practitioners, relatives, and insurance companies were contacted by telephone and interviewed for patient survival or to determine the documented day of death. Follow-up for survival data was complete in 92.4% of patients (33 patients lost to follow-up). Median follow-up time of 174 patients who were alive at last contact was 21.5 months (range: 1.4–131.5 months, interquartile range: 11.4–43.6 months).

## Quality of Life

QOL was assessed prospectively in a subgroup of 81 patients who had follow-up examinations in our outpatient clinic, with data up to the fifth postoperative year. Regular follow-up checkups were offered to patients at 3-, 6-, or 12-month intervals depending on the diagnosis and the time from surgery. Patients with malignant diseases were offered more frequent follow-up examinations than patients with benign diseases, and as time progressed from surgery, the frequency of checkups was decreased. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC-QLQ-C30) and the EORTC QLQ-30 PAN26 (version 3) modules were used. For comparisons with a "healthy" control population, the linear regression models from Schwarz and Hinz<sup>19</sup> were used to calculate mean reference QOL values from the German general public. Patients were matched for the variables age and sex.

## Fat-Soluble Vitamins and Glycosylated Hemoglobin

The fat-soluble vitamins A, E, and 25-hydroxy-vitamin D and the glycosylated hemoglobin (HbA<sub>1c</sub>) were measured preoperatively and during regular follow-up examinations at 1 year ( $\pm 6$  months), 2 years ( $\pm 6$  months), and 3 or more years postoperatively. Vitamins A and E were measured in serum by high-pressure liquid chromatography (Chromsystems Instruments & Chemicals GmbH, Gräfelfing, Germany), and the results were expressed as  $\mu\text{mol/L}$ . 25-hydroxy-vitamin D by chemiluminescence assay (Diasorin Germany GmbH, Dietzenbach, Germany) and the results were expressed as ng/mL. HbA<sub>1c</sub> was measured in EDTA blood by high-pressure liquid chromatography (BioRad, München, Germany) and results were expressed as mmol/mol.

## Statistical Analysis

SAS software (Release 9.1, SAS Institute, Inc, Cary, NC) was used for statistical analysis. The quantitative variables age, serum levels of CA19-9, hospital stay, operation time, and blood loss were expressed as median with interquartile range. The nonparametric Mann-Whitney *U* test was used to compare these quantitative variables between malignant and benign pancreatic neoplasms. Variables with a categorical score level are presented with absolute and relative frequencies. Subgroups of patients were analyzed by using the Fisher exact test and the  $\chi^2$  test, when appropriate. Overall survival was defined as the time from the date of surgery to either death from any cause or last follow-up. Patients alive at the last follow-up were censored. Follow-up time was given as median with interquartile range. Survival curves were calculated by using the Kaplan-Meier estimate. The 1-, 3-, and 5-year survival rates and the median survival time are presented. Survival differences between subgroups of patients were analyzed by the log-rank test. A multivariate Cox regression analysis was performed to examine the impact of vascular resection on long-term survival. The hazard ratios with its 95% confidence interval are given. The associations between patient/tumor characteristics and the in-hospital mortality were assessed by univariate and multivariate logistic regression analysis. The resulting odds ratios with its 95% confidence intervals were presented. An explorative analysis of the variables vitamins A and E and of 25-hydroxy-vitamin D,

HbA<sub>1c</sub> levels, and of the QOL data was performed using box-and-whisker plots, descriptive statistics, and descriptive *P* values of the Wilcoxon signed rank test and the Mann-Whitney *U* test for all scales of the EORTC C-30 questionnaire and for the questions in the PAN26 part. Two sided *P* values were considered statistically significant at *P* < .05.

## RESULTS

### Patient and Tumor Characteristics

Patient and tumor characteristics are presented in Table 1. Primary benign and malignant tumors of the pancreas were present in 57 (13%) and 377 (87%) cases, respectively. The large majority of malignant tumors were pancreatic ductal adenocarcinomas (*n* = 289), whereas the majority of benign cases were IPMNs (*n* = 44). The main tumor location was the head of the pancreas (*n* = 197), or there were extended or multifocal tumors with invasion of more than 1 pancreatic segment (*n* = 170). Fifty-two patients with malignant tumors underwent neoadjuvant therapy. In benign cases, the tumors extended into more than 1 pancreatic segment in the majority of cases (*n* = 43). Patients with malignant tumors were more often jaundiced and had higher CA19-9 levels (*P* < 0.0001, Table 1). Histopatho-

logic analysis demonstrated that most malignant tumors were T3 (*n* = 296), N1 (*n* = 279), R1 (*n* = 236), G2 (*n* = 214), or AJCC stage IIB (*n* = 219).

### Indication for Total Pancreatectomy

The indication for total pancreatectomy in the 434 patients with primary pancreatic neoplasms was as follows (Table 1): (A) Central tumor location in the pancreatic corpus or multifocal tumors with preoperatively planned total pancreatectomy (*n* = 63, 14.5%). (B) The intraoperative finding of an extended tumor that was understaged in the preoperative cross-sectional imaging studies (*n* = 126, 29.0%). (C) Tumor-positive intraoperative frozen pancreatic transection margin with the need for extension of the pancreatic resection (*n* = 156, 35.9%). Of those, 53 patients and 6 patients had a second and third positive frozen section margin after an extension of the pancreatic resection, respectively, before completion of pancreatectomy. (D) Arterial resections of the hepatic artery, celiac trunk, or superior mesenteric artery with the need of arterial reconstruction or graft interposition (*n* = 40, 9.2%). In these patients, the risk of late hemorrhage due to vascular erosion at the site of the arterial reconstruction was aimed to be minimized by total pancreatectomy.

**TABLE 1.** Patient Characteristics

Parameter	All Patients (n = 434)	Benign (n = 57)	Malignant (n = 377)	<i>P</i>
Sex				0.3164
Male	243 (56.0%)	28 (49.1%)	215 (57.0%)	
Female	191 (44.0%)	29 (50.9%)	162 (43.0%)	
Age, yr*	64.3 (56.2–70.4)	64.9 (58.7–68.2)	64.2 (56.1–70.5)	0.5527
ASA score				0.6213
ASA I	10 (2.4%)	2 (3.7%)	8 (2.2%)	
ASA II	233 (55.3%)	28 (51.9%)	205 (55.9%)	
ASA III	177 (42.0%)	24 (44.4%)	153 (41.7%)	
ASA IV	1 (0.2%)	0 (0.0%)	1 (0.3%)	
Diabetes mellitus	138 (32.8%)	15 (27.3%)	123 (33.6%)	0.4413
Jaundice	177 (43.3%)	3 (5.7%)	174 (48.9%)	<0.0001
BMI				1.0
Underweight (BMI <18)	9 (2.1%)	1 (1.9%)	8 (2.2%)	
Normal weight (BMI 18 to <25)	222 (52.7%)	29 (53.7%)	193 (52.6%)	
Overweight (BMI 25 to <30)	146 (34.7%)	19 (35.2%)	127 (34.6%)	
Obesity (BMI ≥30)	44 (10.5%)	5 (9.3%)	39 (10.6%)	
CA19-9, U/mL*	82.5 (15.5–430)	10.8 (6.2–35.3)	118.4 (19.2–495.6)	<0.0001
Tumor location				<0.0001
Head	197 (45.4%)	11 (19.3%)	186 (49.3%)	
Corpus	35 (8.1%)	2 (3.5%)	33 (8.8%)	
Tail	11 (2.5%)	1 (1.8%)	10 (2.7%)	
>1 location	170 (39.2%)	43 (75.4%)	127 (33.7%)	
Bile duct, papilla, duodenum	21 (4.8%)	0 (0%)	21 (5.6%)	
Indication				<0.0001
Planned pre-OP	63 (14.5%)	23 (40.4%)	40 (10.6%)	
Tumor extent intra-OP	126 (29.0%)	11 (19.3%)	115 (30.5%)	
Completion (margin positive)	156 (35.9%)	18 (31.6)	138 (36.6%)	
Arterial resection	40 (9.2%)	2 (3.5%)	38 (10.1%)	
Finding rest pancreas	49 (11.3%)	3 (5.3%)	46 (12.2%)	
Histology				
PDAC	289 (66.6%)	0 (0%)	289 (76.7%)	
Other adenocarcinoma	18 (4.1%)	0 (0%)	18 (4.8%)	
Adenosquamous carcinoma	8 (1.8%)	0 (0)	8 (2.2%)	
Serous cystic neoplasm	4 (0.9%)	4 (7.0%)	0 (0%)	
Acinar cell carcinoma	4 (0.9%)	0 (0%)	4 (1.1%)	
IPMN	75 (17.3%)	44 (77.2%)	31 (8.2%)	
NET	28 (6.5%)	5 (8.8%)	23 (6.1%)	
Other	8 (1.8%)	4 (7.0%)	4 (1.1%)	

Boldface values indicate statistically significant.

ASA indicates American Society of Anesthesiologists; BMI, body mass index; NET, neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma. \*Median (interquartile range). Missing values for ASA score and BMI: *n* = 13 (*n* = 3 benign, *n* = 10 malignant).

(E) The morphology of the otherwise remaining pancreas after partial pancreatectomy (n = 49, 11.3%). Of those, 15 patients had an atrophic small pancreatic tail (in some cases combined with preexisting diabetes mellitus), which was supposed to be not worthwhile for preservation; in 17 cases, the pancreas had a very soft or lipomatous texture, which was thought to harbor an unacceptable high anastomotic risk in combination with preexisting high comorbidity of the patient; in 15 cases, because of acute pancreatitis in the pancreatic tail (in most cases with multifocal necrosis and most frequently after ERCP and stent placement or after fine needle aspiration), which made a safe pancreaticojejunostomy impossible; and in 5 cases because of perfusion problems or other pathologic findings of the small bowel, which mandated avoiding a pancreaticojejunostomy.

### Extent of Resection

Significantly, more pylorus-preserving total pancreatectomies were performed in benign than in malignant tumors (Table 2). Extended total pancreatectomy, as defined by the International Study Group for Pancreatic Surgery,<sup>20</sup> was performed in 233 cases (53.7%). Resections of the superior mesenteric and/or portal vein were performed in 139 cases (32.0%) and of the hepatic or superior mesenteric artery or the celiac trunk in 63 cases (14.5%). Of those, a combination of portomesenteric and arterial resection was performed in 50 patients. Additional other organs were resected in 83 patients (19.1%). Overall, significantly more extended resections were performed in patients with malignant tumors (Table 2). Accordingly, median operative time was longer and blood loss was higher when malignant disease was present. Reflecting the extent of resection in malignant cases, the median number of harvested and histopathologically examined lymph nodes was 34 (interquartile range, 23–47). In 278 patients with tumor-positive lymph nodes, a median number of 5 (interquartile range, 2–9) lymph nodes was positive.

### Morbidity and Mortality

Surgical and nonsurgical morbidity were 37.3% and 37.6%, respectively. The most frequent complications were delayed gastric

emptying, intra-abdominal abscess, anastomotic insufficiency (hepaticojejunostomy, n = 24; esophago-/gastrojejunostomy, n = 8; colon anastomosis, n = 4), and bleeding in 18.1%, 11.1%, 7.8%, and 7.1%, respectively. Relaparotomy was needed in 17.1% of patients. Surgical morbidity and herein delayed gastric emptying occurred more frequently in malignant than in benign disease (Table 2). Likewise, the hospital stay was significantly longer in patients with malignant tumors.

Overall, 30-day and in-hospital mortality rates were 3.7% and 7.8%, respectively (Table 2). Parameters associated with in-hospital mortality in univariate analysis were American Society of Anesthesiologists (ASA) score of 3 or 4, resection of additional organs (such as colon, small bowel, adrenal gland, liver, and/or kidney), arterial resections, blood loss of 2000 mL or more, and operative time of 420 minutes or more (Table 3). In multivariate analysis, a long operative time, high blood loss, and arterial resections were independently associated with in-hospital mortality (Table 4). The 2 lethal cases associated with benign tumors were caused by fulminant pulmonary embolism and therapy-resistant sepsis on the basis of superinfected hematoma and splenic vein thrombosis with subsequent spleen infarction.

### Long-term Survival

Median survival of all patients after total pancreatectomy was 24.4 months, with 1-, 3-, and 5-year survival rates of 67.8%, 40.7%, and 27.8%, respectively. Five-year survival rates of patients with benign tumors, adenocarcinomas, and other carcinomas were 93.8%, 15.2%, and 69.1%, respectively (Fig. 1A). In the subgroup of pancreatic adenocarcinomas, median survival and 5-year survival rates were significantly impaired in R1 resections ( $P \leq 0.0001$ , Fig. 1B) or when arterial or portomesenteric vein resections were performed ( $P < 0.001$ , Fig. 1C). When perioperative mortality was excluded, the median survival of 36.7 months and a 5-year survival rate of 25.7% were encouraging in the subgroup of patients with adenocarcinomas without vascular resection (vs 18.8 months and 14.1% for arterial resections, respectively). Univariate analysis identified poor

**TABLE 2.** Surgical Intervention and Perioperative Morbidity

Parameter	All Patients (n = 434)	Benign (n = 57)	Malignant (n = 377)	P
Type of total pancreatectomy				<b>0.0016</b>
With distal stomach	231 (53.2%)	19 (33.3%)	212 (56.2%)	
Pylorus preserving	203 (46.8%)	38 (66.7%)	165 (43.8%)	
Extended total pancreatectomy	233 (53.7%)	7 (12.3%)	226 (59.9%)	<b>&lt;0.0001</b>
With portal vein resection	139 (32.0%)	2 (3.5%)	137 (36.3%)	<b>&lt;0.0001</b>
With arterial resection	63 (14.5%)	2 (3.5%)	61 (16.2%)	<b>0.0081</b>
With resection of other organs*	83 (19.1%)	4 (7.0%)	79 (21.0%)	<b>0.0109</b>
Operative time, min†	350 (285–425)	285 (259–385)	360 (295–435)	<b>&lt;0.0001</b>
Blood loss, mL†	900 (500–1500)	700 (400–1000)	1000 (500–1600)	<b>0.0002</b>
Morbidity (nonsurgical)	163 (37.6%)	21 (36.8%)	142 (37.7%)	<b>1.0</b>
Morbidity (surgical)	162 (37.3%)	13 (22.8%)	149 (39.5%)	<b>0.0182</b>
Anastomotic insufficiency	34 (7.8%)	3 (5.3%)	31 (8.2%)	0.5998
Intra-abdominal abscess	48 (11.1%)	2 (3.5%)	46 (12.2%)	0.0666
Peritonitis	14 (3.2%)	1 (1.8%)	13 (3.4%)	1.0
Bleeding	31 (7.1%)	6 (10.5%)	25 (6.6%)	0.2738
Wound infection	17 (3.9%)	3 (5.3%)	14 (3.7%)	0.4777
DGE	76 (18.1%)	3 (5.3%)	73 (20.1%)	<b>0.0050</b>
Relaparotomy	74 (17.1%)	8 (14.0%)	66 (17.5%)	0.7052
30-d mortality	16 (3.7%)	2 (3.5%)	14 (3.7%)	1.0
In-hospital mortality	34 (7.8%)	2 (3.5%)	32 (8.5%)	0.2888
Hospital stay, d*	14 (10–21)	13 (8–16)	14 (10–21)	<b>0.0150</b>

Boldface values indicate statistically significant.

\*Additional resection of colon, liver, small bowel, adrenal gland, and/or kidney.

†Median (interquartile range).

DGE indicates delayed gastric emptying.

**TABLE 3.** Results From Univariate Logistic Regression Analyses of Variables Associated With In-hospital Mortality in 396 Patients With Pancreatic Tumors After Total Pancreatectomy (37 Patients Were Deleted From Analysis Due to Missing Values)

Variables	N	Events	OR	95% CI	P
Age					0.6764
<70 yr	289	23	1		
≥70 yr	108	10	1.18	0.52–2.51	
Sex					0.3686
Male	223	21	1		
Female	174	12	0.71	0.33–1.47	
Body mass index					
<18.5	9	2	3.13	0.45–13.69	0.1662
18.5 to <30	347	29	1		
≥30	41	2	0.56	0.09–1.97	0.4431
ASA					<b>0.0053</b>
1/2	227	11	1		
3/4 (n = 1)	170	22	2.92	1.40–6.42	
Carcinoma					0.1077
No	52	1	1		
Yes	345	32	5.21	1.08–93.72	
Total pancreatectomy					0.0510
Pylorus preserving	186	10	1		
With distal stomach	211	23	2.15	1.02–4.85	
Other organs*					<b>0.0430</b>
No	319	22	1		
Yes	78	11	2.22	0.99–4.71	
Arterial resection					<b>0.0011</b>
No	335	21	1		
Yes	62	12	3.59	1.62–7.66	
Resection of portal vein					0.6678
No	266	21	1		
Yes	131	12	1.18	0.55–2.44	
Blood loss					<b>0.0016</b>
<2000 mL	325	20	1		
≥2000 mL	72	13	3.36	1.55–7.10	
Operative time					<b>&lt;0.0001</b>
<420 min	284	11	1		
≥420 min	113	22	6.00	2.86–13.30	

Boldface values indicate statistically significant.

ASA indicates American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio.

\*Additional resection of colon, liver, small bowel, adrenal gland, and/or kidney.

**TABLE 4.** Results From Multivariate Logistic Regression Analyses of Variables Associated With In-hospital Mortality in 396 Patients With Pancreatic Tumors After Total Pancreatectomy (37 Patients Were Deleted From Analysis Due to Missing Values)

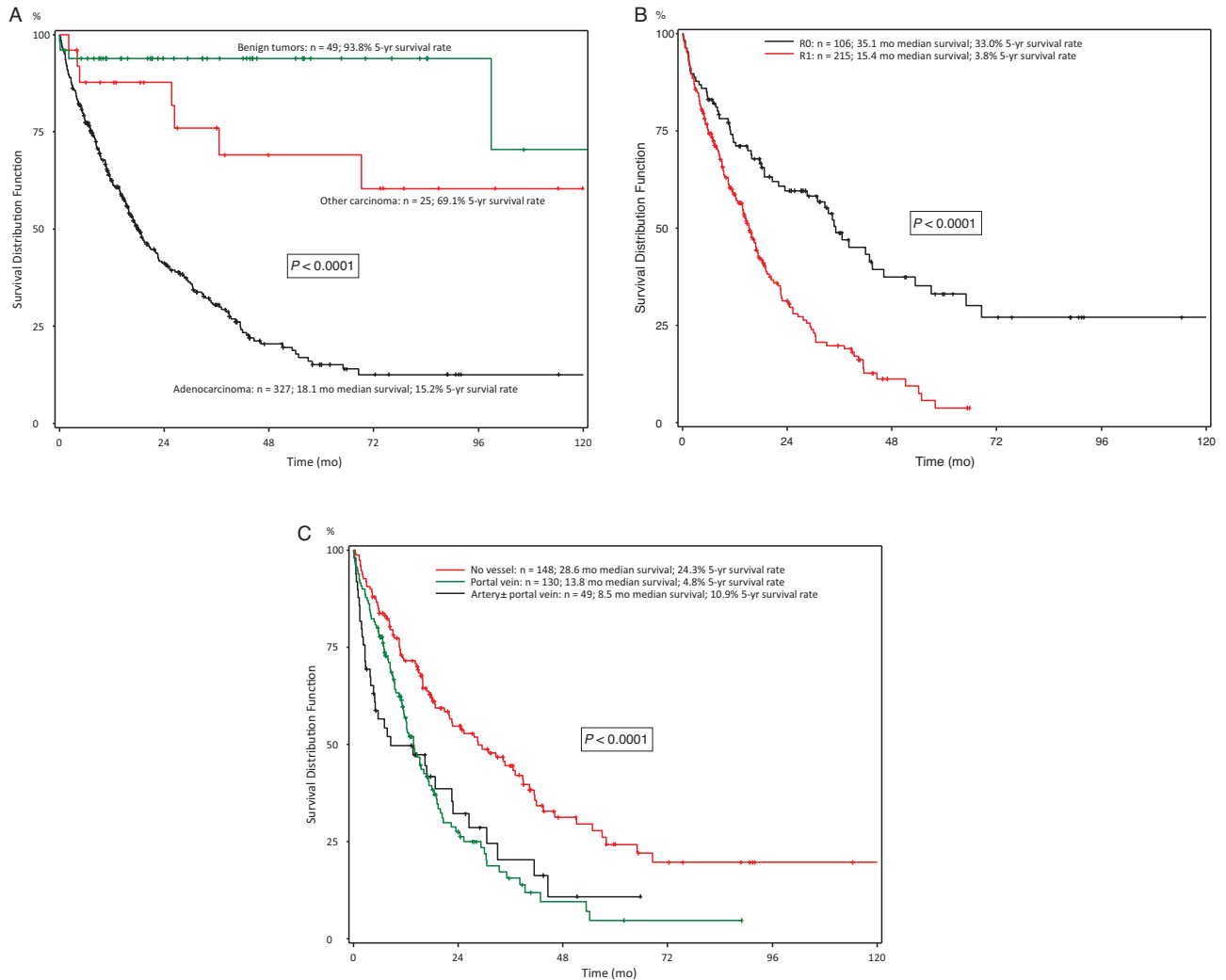
Variables	OR	95% CI	P
Operative time ≥420 min vs <420 min	4.69	2.16–10.67	0.0001
Blood loss ≥2000 mL versus <2000 mL	2.98	1.38–6.89	0.0069
Arterial resection yes versus no	2.76	1.17–6.34	0.0179

Likelihood ratio test:  $P < 0.0001$ .  
CI indicates confidence interval; OR, odds ratio.

tumor grading, high American Joint Commission on Cancer tumor stage, age 70 years or more, an R1 resection, and arterial and portomesenteric vein resection to be prognostic parameters for long-term outcome. In multivariate analysis, vascular resections lost their statistical significance (Table 5).

### Quality of Life Analysis

Long-term global QOL was evaluated in 81 patients who had undergone total pancreatectomy. Of those, 25 had benign and 56 had malignant disease. No differences in age and sex were present between the 2 groups. When data were compared with an age- and sex-matched “healthy” German control population, no differences in global health status were found (Fig. 2). However, patients with benign disease and who had undergone total pancreatectomy had a significant lower global health status in the first postoperative year ( $P = 0.012$ ), but no differences were present between the groups in the later follow-up (data not shown). The functioning scale showed lower score levels in patients who underwent total pancreatectomy for benign and malignant tumors than in the control group during the entire postoperative follow-up time ( $P < 0.03$  and  $P < 0.006$ , respectively, Fig. 3A). No relevant changes were seen over time and between malignant and benign diseases ( $P \geq 0.3$ ). Similarly, patients who underwent total pancreatectomy for malignant disease had significant worse score levels in the symptom scale within the first 2 postoperative years compared with the control group ( $P < 0.001$ ), whereas no differences were seen between benign disease and controls ( $P \geq 0.2$ ). When differences for specific symptoms between benign and malignant were analyzed, the only variable that showed consistently worse values over time for malignant disease was diarrhea ( $P < 0.05$ ,



**FIGURE 1.** A–C, Overall survival of patients with pancreatic tumor undergoing total pancreatectomy: the role of histopathologic dignity (A), R1 resection (B), and vascular resection (C). Excellent survival was identified in benign or premalignant tumors and to a lesser degree also in other carcinomas as compared with pancreatic adenocarcinoma (A). In the subgroup of pancreatic adenocarcinomas, survival was significantly impaired when an R1 resection (B) or when arterial or portomesenteric vein resections were performed (C). Patients who died perioperatively are included in the figures.

Fig. 3B). Insomnia was worse for benign disease in the first follow-up period, without differences later on. For other parameters (eg, pain, fatigue, loss of appetite) no significant differences could be identified.

**Vitamin and HbA<sub>1c</sub> Analysis**

The number of patients for whom vitamin A data were available preoperatively and during regular follow-up examinations at 1, 2, and 3 or more years postoperatively were as follows: n = 62, 61, 29, and 16, respectively; for vitamin E, patient numbers were as follows: n = 59, 59, 29, and 16, respectively; for 25-hydroxy-vitamin D, patient numbers were as follows: n = 75, 67, 32, and 17, respectively; and for HbA<sub>1c</sub>, patient numbers were as follows: n = 51, 93, 38, and 17, respectively. There was a nonsignificant trend to lower vitamin levels in malignant versus benign disease preoperatively (data not shown). In comparison with preoperative serum levels, vitamin A and E levels showed a significant decrease within the first postoperative year in both benign and malignant diseases, with no further decrease

thereafter (Fig. 4). No significant changes were found for 25-hydroxy-vitamin D between groups and over time. In contrary, HbA<sub>1c</sub> levels increased within the first postoperative year in benign and malignant diseases, with no further increase thereafter (Fig. 4).

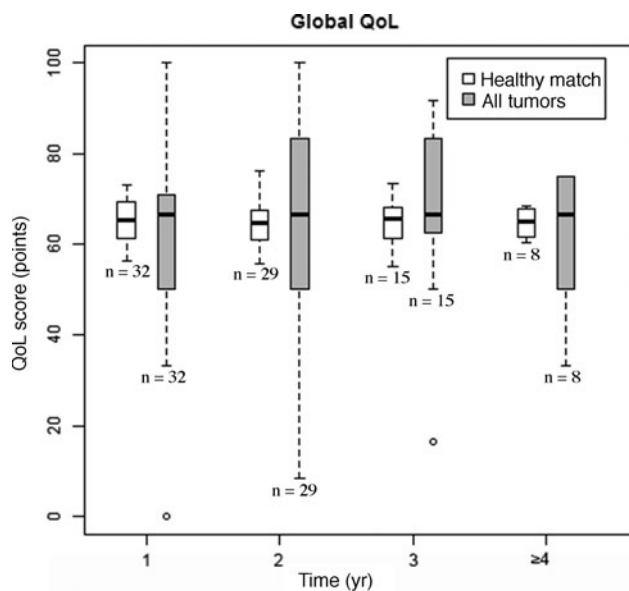
**DISCUSSION**

With increasing evidence in pancreatic carcinogenesis and improvements in perioperative management of patients who undergo pancreatic resection, the indications for electively performed total pancreatectomies have been extended in recent years. Indications include tumors in patients with a history of familial pancreatic cancer, multicentric or extensive pancreatic endocrine tumors, IPMNs with diffuse ductal involvement or multicentricity, locally advanced pancreatic head or body adenocarcinomas that require total pancreatectomy to achieve complete tumor resection, or to minimize complications in patients with a soft and fragile pancreatic remnant that was thought to be associated with unacceptable anastomotic risks.<sup>4,15,21</sup>

**TABLE 5.** Multivariate Analysis of Prognostic Factors for Overall Survival in 258 Patients With Total Pancreatectomy for Pancreatic Adenocarcinoma Among Complete Data sets [Exitus Cases (n = 20), Missing Grading (n = 33), and R2 Resection (n = 5) Excluded]

Variable	Category	HR	95% CI	P
Grading	G3 vs G2	1.67	1.21–2.30	0.0020
AJCC stage	IIB vs IIA/I/0	1.84	1.14–2.97	0.0122
	3/4 vs IIA/I/0	2.39	1.25–4.59	0.0086
Age, yr	≥70 vs <70	1.68	1.20–2.35	0.0025
R classification	R1 vs R0	1.76	1.20–2.58	0.0042
Vessel resection	Artery versus no vessel	0.93	0.52–1.65	0.7962
	Portal vein versus no vessel	1.37	0.97–1.93	0.0707

AJCC indicates American Joint Commission on Cancer; CI, confidence interval; HR, hazard ratio.



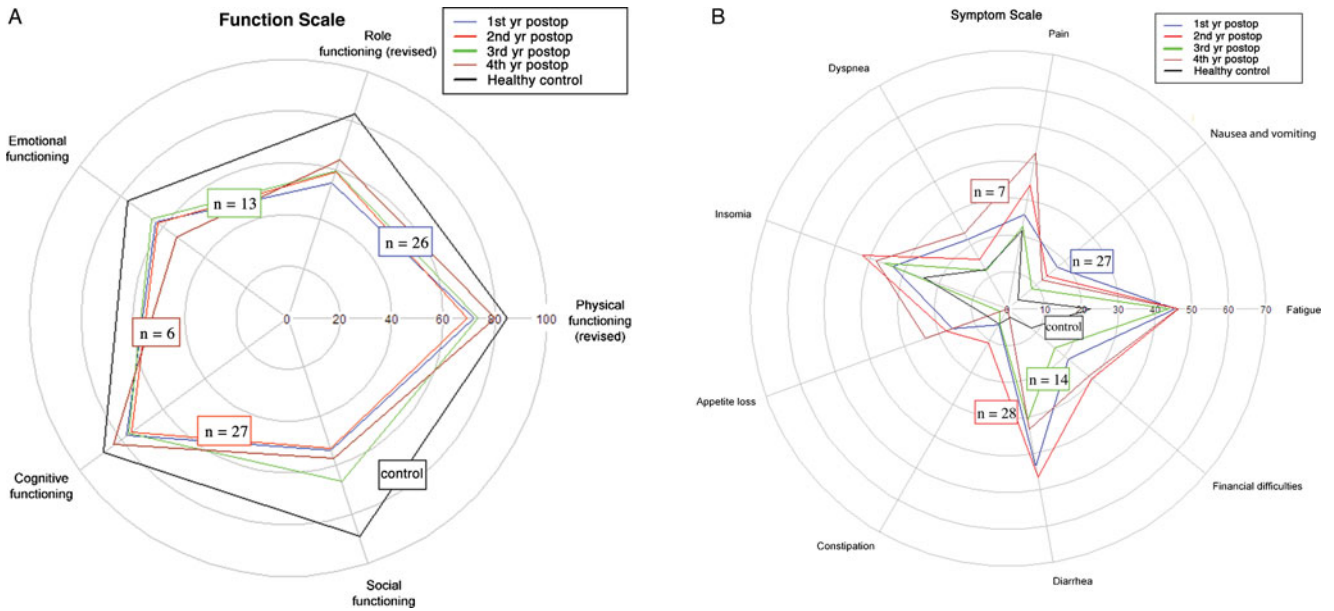
**FIGURE 2.** Global QoL: Comparison with a matched healthy control group. No differences in global health status are present when patients with total pancreatectomy were compared with an age- and sex-matched “healthy” German control population.

Our study on 434 electively performed total pancreatectomies in patients with primary periampullary or pancreatic tumors mirrors this situation. Around 80% of total pancreatectomies were performed because of pre- or intraoperatively confirmed advanced or multifocal tumors. Here, the finding that in a large percentage of patients the indication for total pancreatectomy cannot be made earlier than intraoperatively has also been described by other groups.<sup>3,12,13</sup> In case of an isolated positive neck margin identified by intraoperative frozen section, a survival benefit may justify the conversion of pancreatoduodenectomy to total pancreatectomy to achieve an R0 resection.<sup>3</sup> The remaining 20% of total pancreatectomies in our series were performed because of the morphology of the otherwise remaining pancreas: atrophic with preexisting diabetes mellitus; extremely soft or lipomatous pancreas or a pancreas with inherent pancreatitis that would be associated with a presumably unacceptable high risk of anastomosis-related complications; or because of the high risks of combined arterial reconstructions and potential pancreatic fistulas (around 10% each). In our earlier experience, we had some cases

with severe late hemorrhage from arterial anastomosis in patients who developed pancreatic fistulas after partial pancreatectomies. This made us reluctant to preserve smaller parts of the pancreas in this situation.

High perioperative morbidity and mortality rates have long been a downside of total pancreatectomy, but a dramatic decrease has been achieved over the last decades.<sup>12</sup> The morbidity and mortality rates found in the present study were higher in malignant than in benign disease and appear higher than in series that reported about standard pancreatoduodenectomy.<sup>22</sup> Importantly, the high number of extended total pancreatectomies that were performed in 54% of cases in the present series, with portomesenteric vein, arterial, or additional organ resection in 32%, 16%, and 19% of cases, respectively, reflect the mostly advanced tumors and the scale of performed resections. Univariate analysis identified higher ASA score, high blood loss, long operative time, resection of additional organs other than the main vascular structures, and arterial resection as risk factors for in-hospital mortality. Operative time longer than 420 minutes, blood loss of more than 2000 mL, and arterial resections remained independent risk factors in multivariate analysis. These results confirm the increased perioperative risks that have been described for extended pancreatectomies and arterial resections.<sup>23–25</sup> Considering the large quantity of extended total pancreatectomies, the 30-day mortality rate of 3.7% in the present series compares favorably with other reports.

Long-term survival justifies the surgical approach of total pancreatectomy in patients with advanced malignant or multifocal premalignant neoplasms. In the present series, the subgroup of 327 patients with adenocarcinomas and completed follow-up had a median survival of 18.1 months and a 5-year survival rate of 15.2%. Our data are similar to that on total pancreatectomy from the Johns Hopkins group<sup>12</sup> or to that of the CONKO-001 or ESPAC-3 trials that evaluated adjuvant gemcitabine after pancreatic cancer resection.<sup>26,27</sup> Importantly, these data compare favorably with respect to a median survival of 11.1 months and an 18-month survival rate of 18.6% in patients with metastatic pancreatic cancer who undergo FOLFIRINOX therapy,<sup>28</sup> or a median survival of 8.6 months and a 1-year survival rate of 32% in patients with locally advanced tumors who undergo intensive induction chemoradiotherapy, followed by gemcitabine.<sup>29</sup> For the subgroup of benign tumors, which consisted predominantly of extended main duct or multifocal branch duct IPMNs, the 5-year survival rate of 93.8% has to be seen in context with the potentially halted progression of premalignant lesions to malignancy. However and importantly, patients with benign or not yet malignant tumors substantiate the need for accurate, conclusive, and nonhazardous diagnostics to adequately weigh the risks of a potentially harmful operation with the benefits of cancer prevention.



**FIGURE 3. A,B, Functional Scale (A) and symptom scale (B):** Comparison with a matched healthy control group. Functional and symptom scores were significantly impaired as compared with an age- and sex-matched control group. Most significantly, diarrhea was marked in patient after total pancreatectomy for malignant tumors (not shown).

A substantial number of patients in the present series had locally advanced tumors that required portomesenteric vein or arterial resections. Both patients with portomesenteric vein or arterial resections had a significantly impaired prognosis compared with patients who did not require vascular resections. The latter subgroup was characterized by a favorable median survival of 28.6 months and 5-year survival rate of 24.3%, which increased to 36.7 months and 25.7% when perioperative mortality was excluded. In multivariate analysis, arterial and portal vein resection did not have a significant effect on long-term prognosis. Based on this and previous data,<sup>25</sup> the perioperative risks of arterial resections must not be underestimated, but in selected patients, the potential long-term benefit may outweigh the perioperative risks, especially when long-term results are compared with those of palliative chemo- or chemoradiotherapy.<sup>28,29</sup> The moderate perioperative risks of portal vein resection<sup>30,31</sup> justify its application in combination with total pancreatectomy. Whether the pathologic grade of portal vein infiltration may determine long-term survival, as suggested recently,<sup>32</sup> needs to be validated by larger studies.

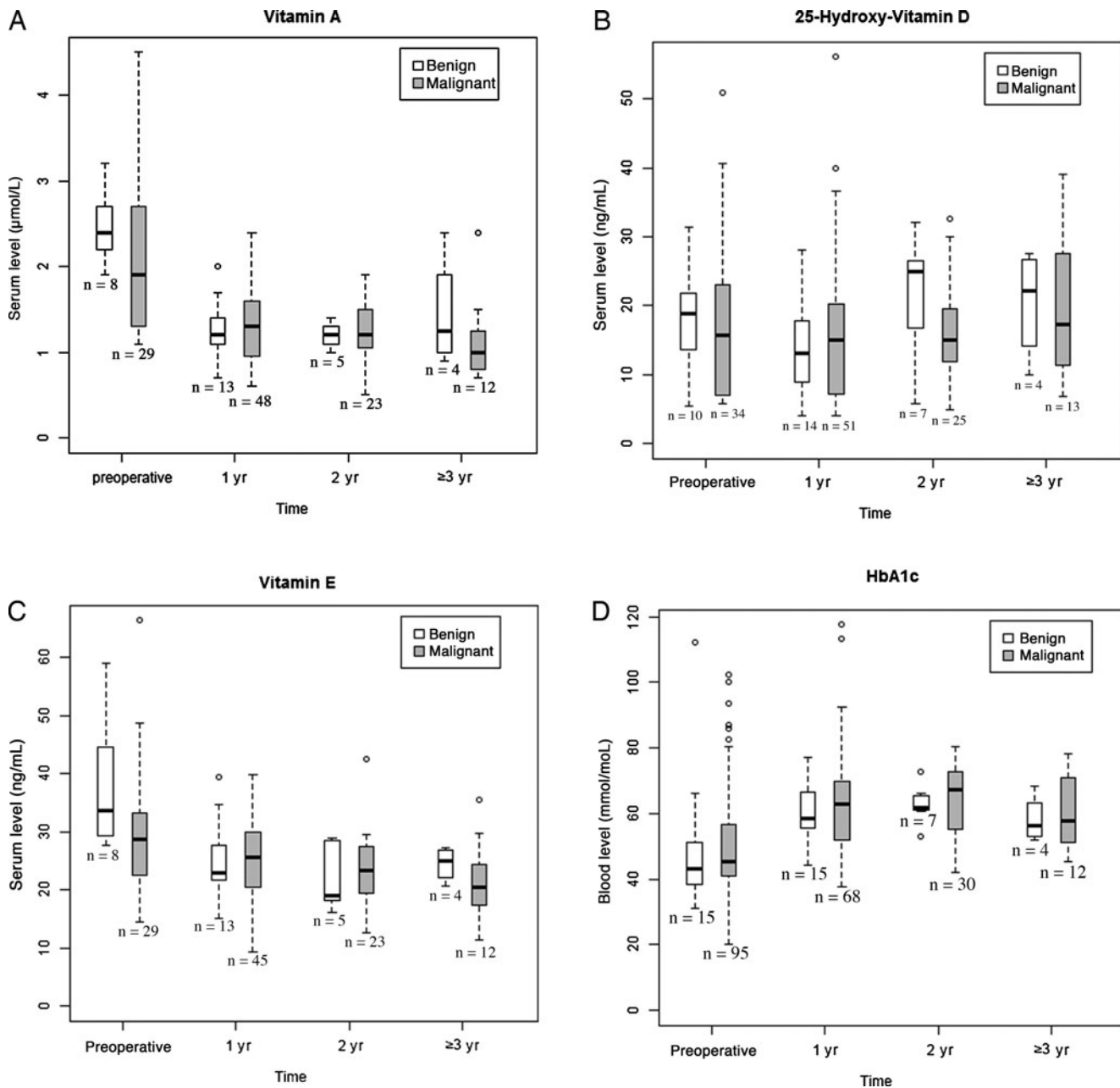
With application of histopathologic reporting as suggested by the Royal College of Pathologists and R1 definition as microscopic evidence of tumor extension within 1 mm of resection margins,<sup>33</sup> survival of patients with R0 resection is significantly better than that with R1 resection.<sup>34,35</sup> This finding is confirmed by data of the present study. Importantly, about two-thirds of patients had R1 resections despite of a generous attitude toward extension of the pancreatic resection in case of a tumor positive frozen pancreatic transection margin. Whether the medial resection margin is the prognostic most relevant one and conversion of pancreatoduodenectomy to total pancreatectomy may be dispensable in patients with a positive pancreatic transection margin (with the advantage of lowering perioperative morbidity and mortality and avoiding brittle diabetes) remains controversial.<sup>3,36</sup>

Relatively little published data are available about QOL after total pancreatectomy. A previous series from our institution described a cohort of 46 patients in which global health status was not

different compared with a matched group who underwent a pylorus-preserving pancreatoduodenectomy.<sup>7</sup> In 27 patients with no recurrent malignancy after total pancreatectomy from the Mayo group, QOL was decreased compared with age- and sex-matched controls but not with diabetes from other causes.<sup>6</sup> The present series with data from 25 patients with benign and 56 patients with electively resected malignant tumors demonstrated that global health status was similar to that of an age- and sex-matched “healthy” control population. However, patients with benign tumors were temporarily affected by the operations’ side effects because patients had a significant lower global health status in the first postoperative year but not thereafter. Using the EORTC-QLQ-C30 module, the functioning and symptom scores were altered after total pancreatectomy within the first 4 postoperative years. Patients with malignant but not benign disease had significantly worse score levels in the symptom scale, as compared with controls. When differences for specific symptoms between benign and malignant were analyzed, the only variable that showed consistently worse values over time for malignant disease was diarrhea. One may conclude from these data that the malignant disease itself is responsible for the major effects on long-term QOL impairment after total pancreatectomy. The more aggressive approach of soft tissue removal in malignant disease frequently including the resection of the nerve plexus around the coeliac trunk and the superior mesenteric artery may contribute to the symptom of diarrhea in patients who undergo total pancreatectomy for malignant tumors.

In the present study, serum levels of the fat-soluble vitamins A and E were identified to be altered after total pancreatectomy, which is explainable by the observed digestion disorder. In comparison with preoperative levels, vitamin A and E decreased within the first postoperative year in both benign and malignant diseases, but concentrations remained stable at these reduced levels in the consecutive years. Similarly, HbA<sub>1c</sub> as the long-term marker of blood glucose levels, increased within the first postoperative year but remained mostly unchanged thereafter. HbA<sub>1c</sub> levels around 60 mmol/mol, as observed in the present study, confirm that the blood glucose





**FIGURE 4.** Vitamin A, D, E, and HbA<sub>1c</sub> in patients undergoing total pancreatectomy: Comparison of benign and malignant disease. Serum levels of the fat-soluble vitamins A and E decreased significantly within the first postoperative year and remained stable in the later years (A,C). Unlike vitamins, HbA<sub>1c</sub> increased within the first postoperative year and remained at tolerable levels around 60 mmol/mol thereafter (D).

concentrations can be kept within a tolerable range after total pancreatectomy by the usage of well-established long-acting insulin formulations.<sup>37</sup> Further studies with long-term follow-up data of patients who undergo total pancreatectomy for premalignant pancreatic tumors are needed.

A major challenge in pancreatic cancer therapy is the identification of patients who will probably not benefit from pancreatectomy because of poor tumor biology. Like in the present study, tumor grading, serum CA19-9 levels, American Joint Commission on Cancer tumor

stage, and R1 resection have been identified as independent prognostic markers for long-term survival.<sup>34,38,39</sup> Notably in locally advanced tumors, as assessed by imaging studies or by extraordinarily high CA19-9 levels, neoadjuvant therapy may further select patients who are good candidates for surgery by excluding those who develop systemic disease or by minimizing the necessity of vascular resections because of tumor shrinkage. It is hoped that various randomized controlled trials that are currently enrolling patients will provide more insights.

## CONCLUSIONS

Overall, favorable survival rates, acceptable QOL scores, and stabilized vitamin and HBA<sub>1c</sub> levels in the mid-term follow-up demonstrate that total pancreatectomy is a justifiable operation when needed in patients with premalignant or malignant tumors. Relevant perioperative morbidity and mortality rates, in particular when total pancreatectomy is combined with vascular resections, illustrate that extensive experience in surgical technique and complication management is mandatory. Patients with locally advanced pancreatic cancer should properly be selected for such an incisive surgical intervention.

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Werner Hartwig, MD, and Alexander Gluth, MD, contributed equally to this work.

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