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ORIGINAL ARTICLE

Long-term quality of life and exocrine and endocrine insufficiency after pancreatic surgery: a multicenter, cross-sectional study

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Abstract

Background: Data regarding long-term quality of life and exocrine and endocrine insufficiency after pancreatic surgery for premalignant and benign (non-pancreatitis) disease are lacking.

Methods: This cross-sectional study included patients ≥ 3 years after pancreatoduodenectomy or left pancreatectomy in six Dutch centers (2006–2016). Outcomes were measured with the EQ-5D-5L, the EORTC QLQ-C30, an exocrine and endocrine pancreatic insufficiency questionnaire, and PAID20.

Results: Questionnaires were completed by 153/183 patients (response rate 84%, median follow-up 6.3 years). Surgery related complaints were reported by 72/153 patients (47%) and 13 patients (8.4%) would not undergo this procedure again. The VAS (EQ-5D-5L) was 76 ± 17 versus 82 ± 0.4 in the general population (p < 0.001). The mean global health status (QLQ-C30) was 78 ± 17 versus 78 ± 17, p = 1.000. Fatigue, insomnia, and diarrhea were clinically relevantly worse in patients. Exocrine pancreatic insufficiency was reported by 62 patients (41%) with relieve of symptoms by enzyme supplementation in 48%. New-onset diabetes mellitus was present in 22 patients (14%). The median PAID20 score was 6.9/20 (IQR 2.5–17.8).

Conclusion: Although generic quality of life after pancreatic resection for pre-malignant and benign disease was similar to the general population and diabetes-related distress was low, almost half suffered from a range of symptoms highlighting the need for long-term counseling.

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Introduction

Pancreatic surgery is predominantly performed in patients with cancer, and increasingly for premalignant diseases, such as intraductal papillary mucinous neoplasm (IPMN) or mucinous cystadenoma. Moreover, pancreatic surgery is also sometimes performed for benign diseases, either because preoperative characterization cannot always distinguish between benign and (pre)malignant abnormalities or intentionally for chronic

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pancreatitis. Since patients who underwent pancreatic surgery for benign or premalignant diseases should have a nearly normal life expectancy, they are especially susceptible to the long-term consequences of pancreatic surgery, including exocrine and endocrine pancreatic insufficiency. Endocrine pancreatic insufficiency (i.e., new-onset diabetes mellitus (DM)) develops in 16−20% of patients after pancreatoduodenectomy, regardless of the final histopathological diagnosis.[1−3] Endocrine pancreatic insufficiency requires daily treatment with antidiabetic agents and carries a risk for long-term micro- and macrovascular complications, both potentially negatively affecting quality of life (QoL).[4] Exocrine pancreatic insufficiency (EPI) develops in approximately 25% of all patients after pancreatic surgery for benign diseases.[1] It results in maldigestion of fat, deficiencies in micronutrients, and deficiencies in fat-soluble vitamins.[4] Patients with EPI often present with steatorrhea, weight loss, or bowel complaints (e.g., pain and cramps), which again can negatively impair QoL.[5]

Overall QoL and exocrine and endocrine pancreatic insufficiency have been studied in patients after pancreatic resections for cancer but data on patients who underwent pancreatic surgery for premalignant and benign indications are lacking.[1,2,6] Therefore, we aimed to assess long-term QoL and exocrine and endocrine pancreatic insufficiency in patients after pancreatic surgery for premalignant or benign (non-pancreatitis) diseases.

Methods

Study design and population
This multicenter cohort study included patients at least three years after pancreatoduodenectomy or left pancreatectomy between 2006 and 2016 for a premalignant or benign (non-pancreatitis) disease. Questionnaires were administered cross-sectionally. Patients were included from six Dutch centers for pancreatic surgery: Amsterdam UMC (locations Academic Medical Center and VU University Medical Center), Regional Academic Cancer Center Utrecht (locations St Antonius Hospital Nieuwegein and University Medical Center Utrecht Cancer Center), Catharina Hospital Eindhoven, and Medisch Spectrum Twente Enschede. Patients preoperatively diagnosed with symptomatic chronic pancreatitis (i.e. according to the M-ANNHEIM classification) were excluded because chronic pancreatitis is known to have a distinct impact on QoL and the exocrine and endocrine pancreatic function.[7−9] Patients with an unexpected final histopathological diagnosis of focal pancreatitis/fibrosis, operated for suspected malignancy, were included. Patients with neuro-endocrine tumors were also excluded, because of the potential malignant character. Patients without valid contact information or who were mentally or physically unable to complete the questionnaire were excluded. The medical ethics review committee of the Amsterdam UMC, location Academic Medical Center, granted approval (research not subjected to the WMO (Medical Research Involving Human Subjects Act)). The study was performed in accordance with the STROBE guidelines.[10]

Data collection and definitions
Patient data were collected locally through an online electronic case report form using Castor EDC. Eligible patients were contacted for participation and received, after providing written informed consent, a package of questionnaires assessing long-term QoL and exocrine and endocrine pancreatic insufficiency were sent by post. If patients did not respond within three weeks, they were contacted by telephone. Baseline characteristics, operative, and postoperative data were collected retrospectively from medical charts from all patients who returned the questionnaires. For pancreatic surgery specific complications (i.e., postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy hemorrhage, and chyle leakage) the definitions of the International Study Group on Pancreatic Surgery (ISGPS) were used.[11−14] Bile leakage was scored as defined by the International Study Group of Liver Surgery.[15] Only grade B/C complications were considered as clinically relevant and were reported.

New-onset DM was defined as DM which developed within 6 months after partial pancreatectomy. General practitioners of patients with DM were contacted for their latest HbA1c value and current medication. All patients who used pancreatic enzyme supplementation were considered as diagnosed with EPI.

Questionnaires
Questionnaires included general questions about complaints since surgery, and if so, whether one would undergo the procedure again (Supplementary Text 1). Generic and disease-specific questionnaires were used to assess QoL. The self-rating daily heath status (visual analogue scale (VAS), 0−100 thermometer) from the EuroQoL Five-dimensions (EQ-5D-5L) was assessed and compared to the Dutch general population.[16] The European Organization for Research and Treatment in Cancer Quality of Life Questionnaire Cancer (EORTC QLQ-C30) questionnaire is a multi-dimensional measure with 30 questions concerning the global health status, five functional scales, and nine symptom scales.[17] Each scale was linearly transformed into a score from 0 to 100 and a higher score represented a better QoL on the global health status, better functioning on the functional scales, and a higher level of symptomatology (more symptoms) on the symptom scales. This questionnaire was included, despite being a cancer specific questionnaire, because the questions were also relevant for patients with benign disease, could be easily compared to data from patients after pancreatic resections for malignant indications or the general population, and could be interpreted by a wide readership. Outcomes were compared with corresponding results of the Dutch population of all ages and between 60 and 69 years.[18] Differences in scores of ≥10 were considered clinically relevant. The study-specific questionnaire regarding EPI contained questions about complaints of EPI, burden of disease, and treatment of EPI (Supplementary Text 1). Some study-specific questions about the development of DM and the current treatment were included

Table 1 Baseline, operative, and postoperative characteristics

	Patients, n (%) n = 153
Female	66 (43%)
Age at operation, median (IQR)	63 (54−70)
Preoperative BMI, median (IQR)	25.9 (23.9−28.7)
Missing	7
American Society of Anesthesiologist score	
I	34 (22%)
II	93 (61%)
III	25 (16%)
IV	1 (1%)
Preoperative comorbidities	111 (73%)
Cardiovascular disease	22 (20%)
Pulmonary disease	20 (18%)
Type of resection	
Pancreatoduodenectomy	99 (65%)
Left pancreatectomy	50 (33%)
Other[a]	4 (3%)
Minimally invasive surgery	
Open	129 (84%)
Laparoscopic	22 (15%)
Robotic	2 (1%)
Conversion	2 (8%)
Postoperative pancreatic fistula, grade B/C	40 (26%)
Missing	0
Delayed gastric emptying, grade B/C	27 (18%)
Missing	1
Bile leakage, grade B/C	16 (11%)
Missing	1
Post-pancreatectomy hemorrhage, grade B/C	19 (13%)
Missing	1
Chyle leakage, grade B/C	6 (4%)
Missing	1
Length of hospital stay, median (IQR)	11 (7−21)
Final histopathological diagnosis	
Intraductal papillary mucinous neoplasm	59 (39%)
Focal pancreatitis/fibrosis	19 (13%)
Serous cystadenoma	18 (12%)
Mucinous cystadenoma	12 (8%)
Adenoma	11 (7%)
Other	33 (22%)
Missing	1
Origin	
Pancreas	128 (85%)

(continued on next column)

Table 1 (*continued*)

	Patients, n (%) n = 153
Ampulla of Vater	12 (8%)
Distal bile duct	5 (3%)
Duodenum	3 (2%)
Other	4 (3%)
Missing	1

[a] Other procedures included central pancreatectomy, radical antegrade modular pancreatosplenectomy, and enucleation.

(Supplementary Text 1). The Problem Areas in Diabetes Scale 20 (PAID20) measures DM-related distress with items scored on a Likert scale of 0−4.[19] The total score was transformed to a 0−100 scale with higher scores indicating higher distress. The modified Worry of Cancer Scale (WOCS) was adjusted to seven questions regarding the worry of recurrence or progression of disease. Each question was scored from 0 to 3 with a maximum score of 21 points and a higher score indicating more worry.

Statistical analysis

Normally distributed continuous data were compared using the t-test and presented as means with standard deviations (SD). Non-normally distributed continuous data were compared using the Mann−Whitney U test or Kruskal Wallis test and presented as medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages and compared using the Chi-square test. A subgroup analysis was performed to assess the impact of patients with focal pancreatitis/fibrosis. A P-value < 0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, N.Y., USA).

Results

Patients

In total, 234 patients after pancreatectomy for premalignant and benign disease were alive and eligible in the six centers between 2006 and 2016. Of all 234 eligible patients, 42 patients had non-valid contact information and 9 patients were excluded due to a language barrier, cognitive impairment, dementia, or hospital admission leaving 183 patients for potential participation. Questionnaires were returned by 153 of 183 patients (response rate 84%) after a median follow-up of 6.3 years (IQR 4.7−8.3) after pancreatic surgery. The median age was 63 years (IQR 54−70) and 66 patients (43%) were female (Table 1). Most patients had undergone pancreatoduodenectomy (n = 99, 65%). Pancreatic specific complications are specified in Table 1. The most common final histopathological diagnosis was IPMN (39%), followed by focal pancreatitis/fibrosis (13%), and serous cystadenoma (12%).

EORTC QLQ-C30 Functioning Subscales
Higher score indicates better functioning

a

Figure legend: —●— Patients —●— General population —●— General population (age 60-69)
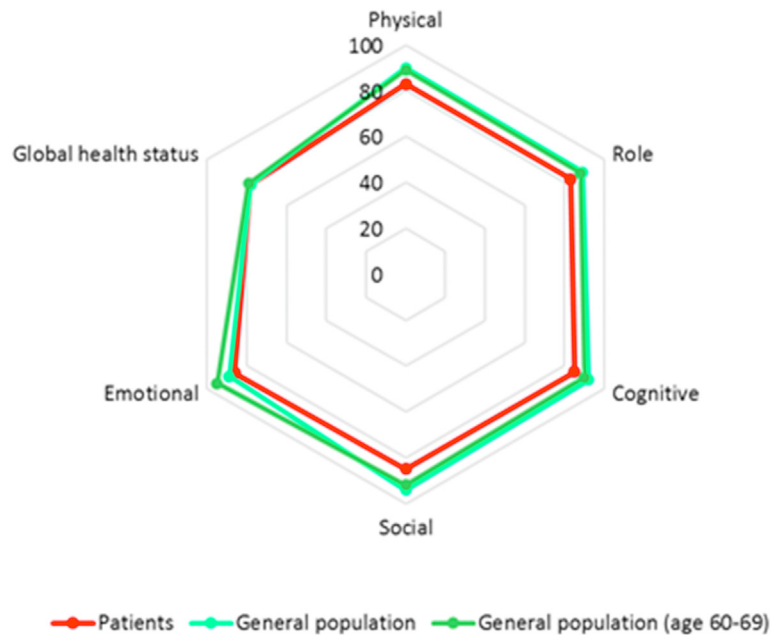
	Patients, mean (SD)	General population, mean (SD)	p-value	General population (age 60-69), mean[#]
Physical	83 (18)	90 (15)	**<0·001**	89
Role	83 (23)	89 (21)	**0·005**	88
Cognitive	85 (20)	92 (15)	**<0·001**	90
Social	85 (19)	94 (16)	**<0·001**	92
Emotional	86 (21)	89 (16)	**0·004**	95
Global health status	78 (17)	78 (17)	1·000	79

Bold numbers indicate statistical significance; # SD not presented in reference values and consequently unable to calculate p-values. Physical functioning is missing in one patient (n = 152), role functioning is missing in one patient (n = 152).

Figure 1 EORTC QLQ-C30 mean scores in patients after a pancreatic surgery for premalignant and benign (non-pancreatitis) disease versus a reference population. a. EORTC QLQ-C30 Functional scales. b. EORTC QLQ-C30 Symptom scales

Quality of life

Pancreatic surgery related complaints, not further specified, were reported by 72 of 153 patients (47%) and 13 of 153 patients (8.4%) would, in hindsight, not undergo this procedure again because of these complaints. The mean daily health status (VAS) of the EQ-5D-5L was 76 (SD 17) versus 82 (SD 0.4) for all ages in the general population (p < 0.001) and 81 (SD 1) for the general population aged 55–64 years (p < 0.001). The results from the QLQ-C30 are shown Fig. 1. On all functional subscales, patients scored significantly worse compared to the general population of all ages but none of the differences was clinically relevant. The mean global health status was 78 (SD 17) and comparable with the general population (all ages mean 78 [SD 17], p = 1.000).

EORTC QLQ-C30 Symptom Subscales
Higher score indicates worse symptoms

b

● Patients   ● General population   ● General population (age 60-69)
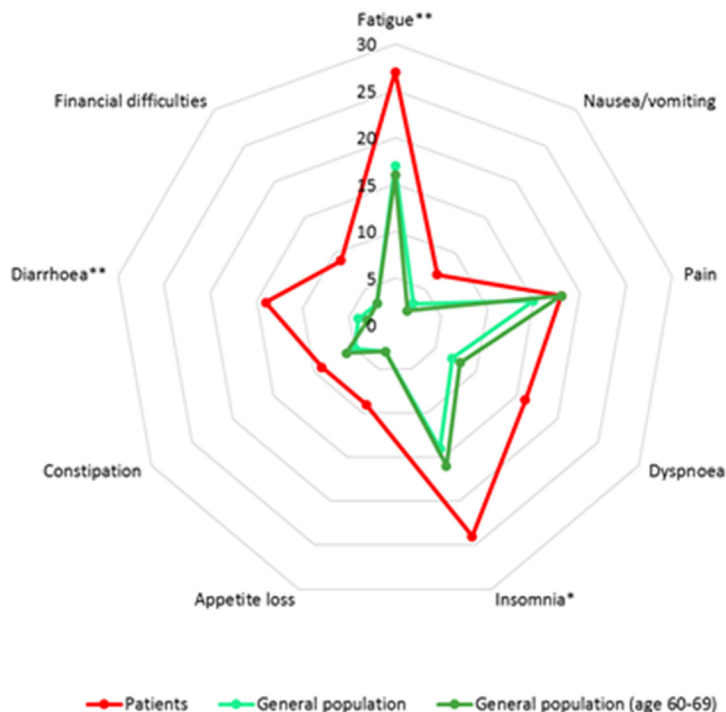
	Patients, mean (SD)	General population, mean (SD)	p-value	General population (age 60-69), mean#
Fatigue**	27 (25)	17 (20)	**<0·001**	16
Nausea/vomiting	7 (16)	3 (10)	**<0·001**	2
Pain	18 (23)	15 (22)	0·107	18
Dyspnoea	16 (25)	7 (17)	**<0·001**	8
Insomnia*	24 (30)	14 (23)	**<0·001**	16
Appetite loss	9 (21)	3 (12)	**<0·001**	3
Constipation	9 (19)	5 (14)	**0·001**	6
Diarrhoea**	14 (23)	4 (14)	**<0·001**	3
Financial difficulties	9 (19)	3 (13)	**<0·001**	3

Bold numbers indicate statistical significance; # SD not presented in reference values and consequently unable to calculate p-values. Insomnia is missing in one patient (n = 152), constipation is missing in one patient (n = 152).

* Clinically relevant difference compared to general population of all ages
** Clinically relevant difference compared to general population of all ages and aged 60-69 years
Reference mean values of EORTC QLQ-C30 for healthy population from reference values manual

Figure 1 (continued)

Table 2 Exocrine pancreatic insufficiency

	Patients with pancreatic enzymes, n (%) n = 62	Patients without pancreatic enzymes, n (%) n = 91	p-value
Abdominal complaints			
Abdominal rumbling	20 (32%)	21 (23%)	0.208
Abdominal cramps	14 (23%)	20 (22%)	0.930
Excessive flatulence	30 (48%)	32 (35%)	0.102
Fatty stools	31 (50%)	24 (26%)	**0.003**
Foul smelling stools	15 (24%)	14 (15%)	0.172
Unintentional weight loss	7 (11%)	2 (2%)	**0.019**
No symptoms	16 (26%)	39 (43%)	**0.013**
Abdominal pain			
No pain	33 (54%)	62 (69%)	**0.037**
Slightly	26 (43%)	22 (24%)	
Moderate	1 (2%)	6 (7%)	
Missing	1	1	
Use of proton pump inhibitor	36 (59%)	41 (45%)	0.104
Missing	1	1	
Stool frequency			
≤1 times week	–	1 (1%)	0.380
1–3 times/week	4 (7%)	5 (6%)	
4–7 times/week	38 (62%)	46 (51%)	
2–3 times/day	17 (28%)	37 (41%)	
≥4 times/day	2 (3%)	1 (1%)	
Missing	1	1	
Dosage of pancreatic enzyme capsules (FIP-E), median (IQR)[a]			
Breakfast	25.000 (25.000–50.000)	NA	
Lunch	40.000 (25.000–50.000)		
Dinner	50.000 (25.000–56.250)		
Snacks	0 (0–25.000)		
Determination of optimal dosage			
Based on amount of fat percentage in meal	8 (13%)	NA	
In consultation with dietician	8 (13%)		
Fixed dose	40 (65%)		
Combination of the above	6 (10%)		

Bold numbers indicate statistical significance.
EPI: exocrine pancreatic insufficiency, IQR: interquartile range.
[a] Number of missing patients was 15, 13, 15, and 12 for breakfast, lunch, diner, and snacks, respectively.

Most symptom scores were significantly worse (i.e., higher scores) compared the general population of all ages, except for pain (Fig. 1B). For fatigue, insomnia, and diarrhea, this difference was clinically relevant. The median modified WOCS score was 1 (IQR 0–5) and indicated very little worries about recurrence of disease.

Exocrine pancreatic insufficiency
Usage of pancreatic enzymes, indicating the presence of exocrine pancreatic insufficiency, was reported by 62 patients (41%, Table 2) and more often present in patients after pancreato-duodenectomy as compared to patients after left pancreatectomy (50 (51%) vs. 10 (20%), p < 0.001) After starting enzyme supplementation, EPI related complaints disappeared in 29/62 patients (48%), decreased in 21 patients (35%) and were unchanged in 10 patients (17%, missing data in 2 patients). At the moment of administering the questionnaire, patients with pancreatic enzyme replacement therapy had more complaints of fatty stools (50% vs. 26%, p = 0.003) and unintentional weight loss (11% vs. 2%, p = 0.019) than those without pancreatic

Table 3 Timing of enzyme supplementation in 62 patients with exocrine insufficiency following pancreatic surgery

	Before	During	After	None
Breakfast	11 (18%)	38 (61%)	5 (8%)	8 (13%)
Lunch	15 (24%)	39 (63%)	5 (8%)	3 (5%)
Snacks[a]	5 (8%)	13 (21%)	7 (11%)	36 (58%)
Dinner	20 (32%)	37 (60%)	5 (8%)	–

[a] Data are missing in one patient.

enzyme therapy. All patients used capsules for the administration of pancreatic enzymes, of which only two patients opened their capsules before administration. Most patients used enzymes during their meal (range 60–63% per meal) but also before or after (Table 3). More than half of all patients did not use enzymes while having a snack (n = 36, 58%, missing data in 1 patient). In the past three months, 13 patients (21%) with EPI had consulted a dietician. The initial reason was weight loss in 2 patients (15%), DM in 6 (46%), weight loss and DM in 1 (8%), or another reason in 4 (31%). Ten patients (16%) reported to use a low-fat diet. Side effects of enzyme supplementation were noted by 13 patients (21%) but these were not further specified.

Endocrine pancreatic insufficiency

New-onset DM was present in 22 patients (40% of all patients with DM, and 14% of the total cohort). In the group of patients who pancreatoduodenectomy, 11 patients (11%) developed new-onset DM and 10 patients (20%) who underwent left pancreatectomy (p = 0.141). Table 4 shows details about endocrine pancreatic insufficiency. The median HbA1c value of all 55 patients with DM was 60 mmol/mol (IQR 54–60). The HbA1c value did not differ between patients with preoperative DM, new-onset DM, and DM diagnosed later than 6 months after pancreatic surgery (p = 0.079) with 62 mmol/mol (IQR 57–68), 64 mmol/mol (IQR 56–68), and 53 mmol/mol (IQR 48–64), respectively. The median HbA1c value was 56 mmol/mol (IQR 50–59) in patients who used tablets and 64 mmol/mol (IQR 57–69) in patients who used insulin with or without tablets (p = 0.004).

Subgroup analysis

A subgroup analysis excluding patients with focal pancreatitis/fibrosis showed similar results (Supplementary Table 1).

Discussion

This multicenter study found that more than six years after pancreatic surgery for premalignant and benign (non-pancreatitis) disease, generic QoL was comparable to the general population and diabetes related distress was low. However, almost half of all patients reported surgery related complaints and 8% of all patients would not undergo surgery again because of these

Table 4 Endocrine pancreatic insufficiency

	Patients, n (%) n = 55
Diabetes mellitus	
Preoperative diabetes mellitus	21 (38%)
New-onset diabetes mellitus	22 (40%)
Diabetes mellitus developed >6 months after pancreatic surgery	12 (22%)
HbA1c value (mmol/mol), median (IQR)	60 (54–68)
Missing	1
Antidiabetic medication	
Tablets	19 (36%)
Insulin	16 (30%)
Tablets and insulin	18 (34%)
Missing	2
PAID20	
Median value (IQR)	6.9 (2.5–17.8)
Mean (SD)	12.4 (14.2)
Missing	5

complaints. Especially, pancreatic enzyme replacement therapy, used by 41% of patients, led to insufficient relieve of symptoms in the majority of these patients.

Although long-term QoL has been studied after surgery for pancreatic cancer, studies solely including patients with premalignant and benign diseases or distinguishing these from patients with malignant disease are scarce. Huang *et al.* compared patients with other benign diseases who (i.e. cystic neoplasms, endocrine tumors, n = 24) who underwent pancreatoduodenectomy between 1981 and 1997 with patients after laparoscopic cholecystectomy and found no differences in physical, physiological, and social scores.[9] The functional assessment (e.g. weight loss, abdominal pain, fatigue, and foul stool) showed worse results in patients after pancreatoduodenectomy. A more recent series (2006–2010) demonstrated that in 42 patients after pancreatoduodenectomy for non-malignant diseases, QoL was negatively impacted by complaints such as pain and diarrhea (4.9% and 7.3%, respectively).[20] An Italian cohort from three centers pointed out that QoL, 24 months after pancreatoduodenectomy in 30 patients with benign diseases was better than in patients with malignant disease.[21] However, none of the studies compared outcomes with the general population. We found that generic quality of life (mean global health status QLQ-C30) scores was comparable between patients after pancreatic surgery and the general population. However, the EQ-5D-5L VAS score was worse in patients after pancreatic surgery compared with the general population. The EQ-5D-5L VAS score only questions "health today" on a scale from 0 to 100, whereas the QLQ-C30 questions both "health today" and "quality of life today", both on a scale from 0 to 7. This might explain the difference of both score with the general population as the health

status was worse but the experienced quality of life was comparable. Most function and symptom subscales (QLQ-C30) in patients were significantly worse in patients after pancreatic surgery but these difference were not clinically relevant. A clinically relevant difference was found for fatigue, insomnia, and diarrhea. This was also found in the study comparing patients after pancreatoduodenectomy with patients after laparoscopic cholecystectomy. In addition, fatigue has been indicated as a common problem after pancreatoduodenectomy (and other major operations), regardless of a malignant or non-malignant indication for the operation.[9]

The frequency of EPI (41%), defined as patients receiving pancreatic enzymes, in the present study was higher than previously reported in a systematic review which included patients with non-malignant diseases (25%), and was more comparable to patients with malignant disease.[1,3,22] Few data are available concerning EPI in patients with benign or premalignant diseases and therefore, it is difficult to reliably compare the prevalence found in this study. Physicians, however, should be aware of the risk on developing EPI after pancreatic surgery, especially in patients after pancreatoduodenectomy. Patients receiving pancreatic enzyme supplementation at least three years after surgery (i.e., considered as having EPI) had more complaints of fatty stools and unintentional weight loss on the long-term compared to those without EPI. This could be caused by incorrect dosing or intake of pancreatic enzymes, a phenomenon frequently observed in patients with EPI. First, the median enzyme dose was 40.000 FIP-E during lunch and 50.000 FIP-E during dinner. This means that 50% of the patients used less. The advised starting dose with breakfast, lunch, or dinner is 40.000−50.000 FIP-E for patients and therefore dosing is insufficient in half of our patients.[23] Second, 20.000 FIP-E is recommended for snacks and 58% of patients did not use any enzymes while having a snack. Third, the moment of enzyme administration is important and preferably enzymes are taken during the meal.[24,25] Sixty to 63% of our patients took their enzymes during the main meals but the optimal effect of supplementation might not be accomplished in the other patients. Increased attention for these aspects is required and personalized care should be delivered by a dietician or nurse practitioner. In the current cohort only 21% of patients with EPI had consulted a dietician in the past three months and only in three patients this was probably related to EPI (i.e., referral for weight loss). This should be improved in current postoperative care, because even on the long-term patients still experience symptoms. Future studies should assess to what extent the guidance of a specialist dietician or nurse practitioner in the management of EPI treatment can improve symptoms of EPI.

Endocrine pancreatic insufficiency was present in 14% and this was comparable to previous literature.[1−3] This is higher than the estimated crude incidence of diagnosed diabetes in United States adults (45−64 years) in 2018 which is 9.9 per 1000 persons.[26] Guidelines on DM generally recommend an HbA1c level

≤53 mmol/mol and thus glycemic control should be improved.[27,28] The median HbA1c in the present study was 60 mmol/mol and even in patients who were only treated with oral antidiabetics (i.e., which indicates less severe DM) the HbA1c value was above 53 mmol/mol. On the other hand, in a large study with patients with DM type I and II from the United States and the Netherlands the mean HbA1c value was 61 mmol/mol showing that tight glycemic control is difficult to achieve.[19] The mean PAID20 score was 24.6 and 22.5 in Dutch patients for DM type I and type II, respectively. This was higher than the mean score of 12.4 in our cohort. This may be explained by the fact that the results of Snoek et al. are 20 years old and DM treatment has improved over the last two decades causing less distress. A more recent study from 2012 showed a mean PAID20 score of 22 in both patients with DM type I and type II patients.[29] This was still higher than our population, indicating little emotional distress regarding diabetes. Another point of interest are risk factors for new-onset DM, e.g. preoperative BMI, smoking, abdominal fat, and inactivity. These could not be properly assessed in our retrospective data set, but would require a prospective approach. One hypothesis that could be tested is that with decreasing risk factors and improving insulin sensitivity, comparable to diabetes type II, the incidence of new-onset diabetes mellitus could decrease.

The findings of this study should be interpreted in light of some limitations. First, the retrospective collection of patients' and (post)operative characteristics might have been influenced by information bias. Also, the exact indication of surgery was missing and at least a proportion of patient was operated because of suspicion of malignancy.[30] These data were difficult to retrieve in retrospect and to maintain remain as objective as feasible the pathological diagnosis was used. We believe that this did not substantially affect the long-term outcomes. Second, we compared outcomes with the general population but the ideal design would have included a QoL measurement at baseline and during follow-up. Third, the inclusion period of 10 years was relatively long and surgical technique and postoperative care could have improved during this period. This was inherent to the relative rarity of pancreatic resections for premalignant and benign diseases. Fourth, details about enzyme dosage should be interpreted with caution. Dosing of enzyme supplementation can vary per day and per meal, depending on the amount of fat ingested. However, most patients reported that dosage per meal was based on a fixed scheme and therefore we believe that the gathered data is valid. This, again, showed that flexibility in dosing should be more stimulated. Fifth, EPI was defined as using enzyme supplementation. It is known that EPI is currently underdiagnosed and probably, the actual prevalence of EPI is even higher.[8,31] Fatty stools were reported by 26% of patients without EPI and this supports the presence of under diagnosis and treatment.

Strengths of the study are the relatively large cohort, the high response rate and the long follow-up. Data regarding the consequences of exocrine and endocrine pancreatic insufficiency in

patients after pancreatic surgery for benign or premalignant diseases were lacking and the presented data is therefore valuable when consulting patients.[1]

Conclusions

Long-term generic QoL after pancreatic surgery for premalignant and benign (non-pancreatitis) disease was similar to the general population and diabetes related distress was low, but nearly half of all patients reported surgery related complaints and 8% would, in retrospect, not undergo pancreatic surgery again. The current treatment of EPI needs further attention, potentially by personalized treatment schemes given by dieticians or nurse practitioners. The current should be used in the shared-decision making process in case surgery is considered for benign non pancreatitis or premalignant pancreatic diseases.

Conflict of interest
AL has received research funding from Mylan and Allergan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.04.012.