Long-Term Quality of Life after Pancreatic Surgery for Intraductal Papillary Mucinous Neoplasm

Helwig Valentin Wundsam^a Christiane Sophie Rösch^a Patrick Kirchweiger^a
Ines Fischer^a Michael Weitzendorfer^b Holger Rumpold^c Reinhold Függer^a

^aDepartment of Surgery, Ordensklinikum Linz, Linz, Austria; ^bDepartment of Surgery, Paracelsus Medical University Salzburg, Salzburg, Austria; ^cDepartment of Gastrointestinal Cancer Center, Ordensklinikum Linz, Linz, Austria

Keywords

Quality of life · Long-term follow-up · Pancreatic resection · Intraductal papillary mucinous neoplasm

Abstract

Introduction: Intraductal papillary mucinous neoplasms (IPMNs) represent the most common precancerous cystic lesions of the pancreas. The aim of our study was to investigate if resection for non-invasive IPMNs alters quality of life (QoL) in a long-term follow-up. **Methods:** Patients ($n = 50$) included in the analysis were diagnosed and resected from 2010 to 2016. QoL was assessed at a median of 5.5 years after resection. At that point in time, the current QoL as well as the QoL before resection was evaluated retrospectively. The standardised European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Pancreatic Cancer (EORTC QLQ – PAN26) was applied for the QoL assessment. **Results:** After a median of 66 months postoperatively, the total QoL score significantly worsened (92.13 vs. 88.04, $p = 0.020$, maximum achievable score = 100) for patients (median age at surgery 68.0 years), mostly due to digestive symptoms. During the same follow-up period, median Eastern Cooperative Oncology Group (ECOG) perfor-

mance status did not worsen ($p = 0.003$). **Conclusions:** Long-term QoL statistically significantly worsened after pancreatic resection for IPMN. The extent of worsening, however, was small, and QoL still remained excellent. Therefore, resection in cases of IPMN is appropriate, if indicated carefully.

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Introduction

During the last 2 decades, the increased use of magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) techniques has led to an increase in the detection of cystic lesions of the pancreas. Consequently, guidelines for follow-up and resection criteria have had to be continuously adapted [1]. Clinical decision-making with the aim of avoiding surgical overtreatment and detecting potentially curable malignant or precancerous pancreatic lesions in an early state is challenging. Centralization of treatment lowers postoperative mortality rates significantly and improves long-term survival in cases of pancreatic adenocarcinoma [2]. Nevertheless, postoperative morbidity and mortality remain significant factors to

be considered when balancing treatment options for benign diseases. In cases of proven malignancy and potentially curable situations, patients are most likely to consent to surgical treatment [3]. The postoperative quality of life (QoL) for benign diseases has also to be taken into account. To address this, we investigated whether resection of suspicious pancreatic lesions that proved to be benign would subsequently alter patient self-reported QoL.

Regarding what is known in the published literature, in February 2020, only 8 papers had been published that included an analysis of standardised QoL data assessment following pancreatic resection. However, these studies were lacking in the number of cases (only 4 included >34 patients [4–7]) or preoperative comparative groups (only 2 [5, 8]), or, with regard to homogeneity, in the indication for resection including pancreatic adenocarcinoma, neuroendocrine tumours, and chronic pancreatitis. Only 1 study [7] was restricted to benign diseases but it included only non-surgical patients in its analysis. Our objective was to conduct the first validated long-term QoL evaluation in patients who underwent pancreatic surgery for a benign indication of non-invasive IPMN.

Materials and Methods

Patients

We conducted an observational cohort study. Demographic data was collected retrospectively from electronic medical records by the same physician who conducted the telephone survey to obtain follow-up data on QoL and insulin dependence. Median call duration was 15 min and interviews were held in the local language, with the physician providing clarification on questions posed by the patients related to the study. We included all patients with histologically verified non-invasive IPMN who underwent pancreatic surgery at our institution between 2010 and 2016 and consented to respond to the survey conducted in 2020.

In our evaluation, 50 patients were included with fully analysed data sets prior to elective surgical intervention as well as data on long-term follow-up (Fig. 1). Selection of the study cohort was visualised using the CONSORT template [9–11].

QoL Assessment

The standardised European Organisation for Research and Treatment of Cancer Quality of Life questionnaire for pancreatic cancer (EORTC QLQ – PAN-26) was utilised to measure preoperative and postoperative QoL via a telephone survey. The EORTC QLQ-PAN-26 was originally developed to measure QoL after pancreatic cancer, but it can also provide invaluable information about pancreatic function and QoL after pancreatic surgery [12]. The tool examines overall QoL where higher levels indicate higher QoL, and symptom scales (pancreatic pain, digestive symptoms, hepatic function, altered bowel habits, and body image) and functional scales (sexuality and satisfaction with health care) where

Fig. 1. Consort flow diagram. PDAC, pancreatic ductal adenocarcinoma; MCN, mucinous cystic neoplasia; SCN, serous cystic neoplasia; SPT, serous papillary tumour; NET, neuroendocrine tumour; IPMN, intraductal papillary mucinous neoplasia; MD, main duct; BD, branch duct.

higher scores represent higher levels of suffering these symptoms from a total of 26 items. When answering the questions for each symptom complex, patients were requested to score from 1 (applies not at all) to 4 (applies very much), which can be transformed to a calculated score of 0–100% by using the formula given in the manual provided by the EORTC. A higher score represents a higher level of symptoms (a poorer outcome) or a higher level of functioning (a better outcome) [12].

The Eastern Cooperative Oncology Group performance status (ECOG PS) [13] scored from 0 (fully active, able to carry on all pre-disease performance without restriction) to 4 (completely disabled, cannot carry on any self-care, and totally confined to a bed or chair) was also evaluated.

Statistical Analysis

Metric parameters are generally given as means and SD. Assuming non-normal distribution, the Wilcoxon signed-rank test was used for group comparisons and the Student *t* test was applied for normally distributed metric data. Analyses and remaining visualisations were performed using SPSS v24.0 software (2019, IBM, Armonk, NY, USA). Additionally, a 2-sided significance level of $p < 0.05$ was applied; we reacted to multiple testing by adapt-

ing the level of significance for symptom and functional scales using the Bonferroni correction. Missing values were generally <5% and thus not addressed in the statistical analysis. The power levels were 0.92 based on the Wilcoxon signed-rank test (Mann-Whitney U test) and 0.93 when the Student *t* test was applied, respectively. Power analysis (1- β) was conducted using G*Power v3.1.9.6 (2017, HHU Düsseldorf, Germany).

Results

Patients' Demographics

Our study cohort, consisting of 50 patients, had a median age of 68.0 years on the date of surgery. Patients presented with a mean Charlson Comorbidity Index (CCI) of 4. Preoperative diabetes mellitus type 2 rate was 12%; mean preoperative body mass index (BMI) was 26.05. Gender was equally distributed between male and female. As expected in benign indications, the mean serum levels of carcino-embryonal antigen (CEA) and carbohydrate-antigen 19.9 were not elevated. Mean levels of both serum bilirubin (used as a marker for cholestatic disease) and C-reactive protein (CRP, to indicate chronic pancreatitis or malignant tumours) were within the normal range at diagnosis of IPMN. The most frequent localisation of the cystic lesion was the pancreatic head, followed by the pancreatic cauda. The main duct and branch ducts were afflicted equally and mixed types of IPMN were seldom found. Detailed preoperative patient characteristics as well as intra-operative and histopathological findings are displayed in Table 1.

In the majority of the 10 patients who underwent total pancreatectomy (TP), a suspected main-duct IPMN with extensive multi-focal involvement was the indication ($n = 7/10$ TP); in 1 patient, the indication was a 2× positive resection margin for IPMN in the frozen section; in 1 patient, it was concurrent chronic pancreatitis; and in 1 patient, it was the presence of multiple other pancreatic cysts that proved not clearly distinguishable from IPMN intra-operatively. There was no case of rescue resection of the pancreatic remnant due to anastomotic failure. Postoperative morbidity exceeding Clavien-Dindo grade 3a was seen in 3 patients (6%), grade 3b in 1, and grade 4b in 2. The 5-year survival rate was 91.8%. We did not diagnose any new carcinomas in the pancreatic remnant in the follow-up period.

QoL Assessment Results

After a median follow-up period of 5.5 years (66 months) post-resection, the total score of QoL decreased slightly, but still significantly (92.13 vs. 88.04, $p = 0.020$).

Table 1. Characteristics pre- and intra-operatively ($n = 50$)

Age at evaluation, years	74 (14.25)
Age at surgery/diagnosis, years	68.0 (13.0)
Males	25 (50)
Females	25 (50)
BMI	26.05 (4.39)
Weight, kg	75.5 (15.44)
Height, cm	171 (9)
CCI	4 (2.00)
ECOG PS ^a	0 (0.00)
Diabetes	6 (12)
Haemoglobin, g/dL	13.40 (6.10)
CRP, mg/dL	0.21 (8.90)
Total serum bilirubin, mg/dL	0.62 (1.40)
CEA, ng/mL	1.80 (6.10)
CA19.9, U/mL	8.00 (892)
Localization	
Caput	17 (34)
Caput-corporis	5 (10)
Corpus	5 (10)
Corpus-cauda	7 (14)
Cauda	8 (16)
Multi-focal	6 (12)
Not declared	2 (4)
Type of IPMN	
Main duct	17 (34)
Branch duct	17 (34)
Mixed-type	6 (12)
Not declared	10 (20)
Pancreatic duct size, mm	2 (3.32)
Procedure	
TP	10 (20)
KW	15 (30)
PPPD	7 (14)
DP	17 (34)
CPR	1 (2)

Values express n (%) or mean (SD), unless otherwise indicated. BMI, body mass index; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; CEA, carcino-embryonal antigen; CA19.9, carbohydrate-antigen 19.9; TP, total duodeno-pancreatectomy; KW, Kausch-Whipple; PPPD, pylorus-preserving partial duodeno-cephalo-pancreatectomy; DP, distal pancreatectomy; CPR, central pancreatic resection.

^a Median (IQR).

According to the symptom scales, pancreatic pain decreased during follow-up (13.66 vs. 7.82, $p = 0.429$), but digestive symptoms, hepatic symptoms, altered bowel habits, and body image worsened. Digestive (7.00 vs. 27.55, $p = 0.000$) and hepatic (0.00 vs. 1.70, $p = 0.040$) symptoms, in particular, were significantly higher post-operatively in the long-term follow-up (Table 2). Functional scales of satisfaction with health care and sexuality, on the other hand, did not alter significantly.

Table 2. Quality of life assessment results ($n = 50$)

	Preoperatively	SD/%	At follow-up	SD/%	<i>p</i> value
Age, years	68.5	8.60	74	8.67	0.003
Males	25	50	25	50	1.000
Females	25	50	25	50	1.000
BMI	26.05	4.39	23.5	4.85	0.018*
Weight, kg	75.5	15.44	67.0	13.52	0.160
Height, m	1.71	0.09	1.71	0.09	1.000
Diabetes	6	12	26	52	0.000*
Metformin intake	2	4	6	12	0.142
Insulin-dependent	0	0	20	40	0.000**
Insulin, U/day	–	–	26	9.88	–
Insulin, U/kg/day	–	–	0.36	0.13	–
HbA _{1c} , %	–	–	6.75	1.06	–
ECOG PS ^a	0	0.00	0	1.00	0.003**
EORTC-PAN26	92.13	8.18	88.04	8.99	0.020*
Symptom scales					
Pancreatic pain	13.66	21.74	7.82	12.55	0.429
Digestive symptoms	7.00	17.85	27.55	22.71	0.000**
Hepatic symptoms	0.00	0.00	1.70	6.13	0.040*
Altered bowel habits	4.33	11.57	9.86	17.98	0.074
Body image	2.67	10.30	5.10	14.11	0.340
Functional scales					
Satisfaction with health care	99.31	18.27	94.79	15.44	0.050
Sexuality	94.67	18.27	89.17	22.96	0.100

Values express n and % or mean and SD, unless otherwise indicated. * $p < 0.05$, ** $p < 0.007$, two-tailed significance.

^a Median and IQR.

As shown in Table 2, ECOG PS remained at the level of 0 in the course of follow-up 66 months after resection ($p = 0.003$). The total rate of diabetes increased to 52% ($n = 26$), from 12% ($n = 6$) preoperatively, in the follow-up group. A total of 40% of patients ($n = 20$) were insulin-dependent and half of these ($n = 10$) following TP. A mean weight loss of 8.5 kg (75.5 vs. 67.0, $p = 0.160$) and a decrease in BMI of 2.55 (26.05 vs. 23.5, $p = 0.018$) were documented in the long-term follow-up.

The analysis of the surgical subgroups showed that there was no worsening in ECOG PS in patients following either distal pancreatectomy ($p = 0.016$), TP ($p = 0.067$) or resection of the pancreatic head ($p = 0.216$). Improvement in pancreatic pain on the symptom scale found in all types of resection did not reach statistical significance. Deterioration regarding digestive symptoms, on the other hand, was found to be significant, irrespective of the resection technique. Functional scales did not significantly alter in the long-term follow-up according to resection types. Postoperative ECOG PS and QoL scores stratified by the surgical technique applied are displayed in Table 3.

When calculating differences in symptom scales and functional scales for comparing the type of resection, significant findings were seen for postoperative diabetes, which occurred in 34.8% of resections of the pancreatic head, 47.7% of distal pancreatectomies, and 100% of TPs ($p = 0.001$). No other differences between the type of resection and long-term follow-up reached statistical significance.

When analysing the data from the 2 patients with complications classified as Clavien-Dindo grade 4b, we found that both reported a diminished QoL (–11.69 and –27.27% respectively), primarily concerning digestive symptoms and pain.

Discussion

The detection rate of cystic pancreatic lesions seems to grow exponentially. On the one hand, early diagnosis in the case of malignant tumours is essential, but on the other, we face new dilemmas [14]. The IPMN group is heterogenous and indication for resection is not always easy to

Table 3. EOCG PS and EORTC-PAN26 alteration depending on type of resection

Number of patients	TP		PHR		DP	
	PO (n = 10)	FU (n = 10)	p value	PO (n = 22)	FU (n = 22)	p value
EOCG PSa	0 (0.00)	0 (1.00)	0.067	0 (0.00)	0 (0.25)	0.216
EORTC-PAN26	90.00 (11.06)	86.92 (8.41)	0.325	93.01 (7.99)	90.04 (9.15)	0.216
Symptom scales						
Pancreatic pain	22.50 (27.23)	7.50 (15.93)	0.143	10.98 (18.07)	7.58 (13.34)	0.513
Digestive symptoms	6.67 (14.05)	40.00 (29.61)	0.004**	6.82 (19.69)	22.73 (18.93)	0.001**
Hepatic symptoms	0.00 (0.00)	3.33 (7.03)	0.146	0.00 (0.00)	2.27 (7.79)	0.153
Altered bowel habits	11.67 (19.32)	15.00 (22.84)	0.721	3.79 (10.20)	9.09 (15.19)	0.159
Body image	0.00 (0.00)	1.67 (5.27)	0.317	4.55 (14.71)	4.55 (14.71)	0.670
Functional scales						
Satisfaction with health care	96.67 (10.54)	86.67 (23.31)	0.255	100.00 (0.00)	100.00 (0.00)	1.000
Sexuality	100.00 (0.00)	90.00 (16.10)	0.067	90.91 (25.58)	89.39 (26.00)	0.712

Values express mean (SD), unless otherwise indicated. * $p < 0.05$, ** $p < 0.007$, two-tailed significance. TP, total pancreatectomy; PHR, pylorus-preserving partial duodeno-pancreatectomy; DP, distal pancreatectomy; PO, postoperatively; FU, follow-up.
^a Median (IQR).

determine. In which cases is surgery the appropriate treatment? When are we at risk of lowering the QoL of patients with benign lesions by operating on them in order to not miss potential malignancies [15]? To address these questions and meet this ongoing challenge, we are required to continuously adjust our surveillance algorithms and scrutinise the indications for surgery.

Regarding evidence from the published literature, papers fulfilling the MeSH terms “pancreas” OR “pancreatic” AND “quality of life” AND one of the following: “IPMN,” “mucinous cystic neoplasm,” “serous cystic neoplasm,” “solid pseudopapillary neoplasm,” “cystic pancreatic lesion,” “benign pancreatic lesion” were screened in February 2020, resulting in a total of 57 papers. The majority reported on very low case numbers. Only 4 papers [4–7] included >45 patients. However, these 4 studies could not be compared to ours, for several reasons. Two of them [4, 5] compared different operation techniques measuring postoperative QoL.

When Müller et al. [5] prospectively evaluated the peri-operative and long-term results of total pancreatectomy versus the pylorus-preserving (pp)-Whipple procedure, they included multiple benign and malignant entities, and the long-term follow-up was limited to a median of 23 months. We faced the same problem with the study by Kwon et al. [4], that retrospectively compared early/late clinical results and functional outcomes in terms of QoL and nutrition between conventional laparoscopic distal pancreatectomy (LDP) and laparoscopic spleen-preserving distal pancreatectomy (LSPDP). Indication for resection, however, was very heterogenous, comprising at least 9 different entities (mucinous cystic neoplasm [MCN], solid pseudopapillary neoplasm [SPN], IPMN, serous cystic neoplasm [SCN], neuroendocrine tumour, pancreatic cancer, pseudocyst, metastatic cancer, and others). Moreover, the long-term follow-up was confined to a median of 25 months. Pezzilli and Calculli [7], on the other hand, analysed 2-year follow-up results in consecutive conservatively treated patients with BD-IPMNs, to assess symptoms at presentation and their morphological progression, and found that branch-duct IPMNs did not worsen the QoL of affected patients. Unfortunately, this paper addressed only non-surgical patients and thus cannot contribute to the question of whether surgery, per se, alters QoL. Pulvirenti et al. [6] recently published their findings on QoL in 94 patients with a median follow-up of 63 (IQR 20–109) months. The most common indication for resection within the cohort was very heterogenous and included chronic pancreatitis as well. Further-

more, we could not assess to what extent QoL changed within the operation group, due to the lack of preoperative QoL data.

Our study provides preoperative and long-term follow-up data within the same cohort, i.e., it served as its own control group. By restricting the included patients to a single, non-malignant, non-inflammatory indication, we were able to avoid the bias on QoL represented by adjuvant chemotherapies in cases of cancer as well as chronic pain experienced by patients with a history of chronic pancreatitis. With a mean CCI of 4 at the time of operation, our patients represent an average cohort of pancreatic surgery patients according to the literature [16, 17]. The preoperative diabetes mellitus type 2 rate of 12% was comparable to the rate found in elderly patients in Europe [18]. Thus, our patient population is comparable to the average age-adjusted patient collective.

As we can see from our analysis, total QoL score worsened slightly but significantly in a long-term follow-up of patients resected for benign IPMN. New onset of diabetes, occurring in 40% of the resected patients within 66 months, as well as digestive symptoms, hepatic symptoms, and altered bowel function might be responsible for these findings. Pain was shown to be reduced after resection, but this trend should not be overestimated as it was not statistically significant. The indication for resection was IPMN, but coincidental pancreatitis was not totally excluded. In total, our cohort included 3 patients with coincident chronic pancreatitis, all in the TP group. This could explain this trend.

However, as expected, digestive and hepatic symptoms were aggravated postoperatively. Digestive symptoms are to be explained by the altered postoperative situs and recurrent complaints due to postoperative adhesions. The postoperative increase in hepatic symptoms like icterus can be explained by cholangitis, which occurred in 6.6% of our patients with biliodigestive anastomoses. This correlates with the literature data. For example, Yamaguchi et al. [19] observed postoperatively, and/or in the further course, recurrent cholangitis in 8.9 and 6.7%, respectively, following resection of the pancreatic head. Moreover, the worsening of hepatic symptoms was not observed in the patients who underwent distal pancreatectomy. Therefore, anastomotic strictures of the hepatico-jejunostomy causing recurrent cholangitis may be involved. As the indication for resection was solely benign IPMN, the complete absence of these afflictions preoperatively is easily explained.

Addressing the differences in the subgroups of operation techniques, we can state that every symptom scale

except pancreatic pain stayed stable or worsened slightly postoperatively, even if statistical significance was only seen in the postoperative occurrence of diabetes due to the extent of resection. The small number of patients and the high number of subgroups represented by the test parameters may also account for this. To reveal significant differences between the 3 types of resection, the number of patients included must be higher. However, all worsening QoL parameters remained <1.55 within a possible range of 1–4, and the overall EORTC-PAN 26 score decreased by 4 points (92.12 vs. 88.08, $p = 0.02$) with a maximum of 100 reachable points after a median 66 months of follow-up in an elderly population.

During the same period, deterioration of ECOG PS was only seen in the change of IQR (0 vs.1), but still did not reach 1 ($p = 0.003$), meaning that patients were fully active and able to carry on all pre-disease activities without restriction. ECOG PS does not include digestive symptoms, which represent the leading cause of diminished QoL. The ECOG PS refers only to a patient's ability to perform self-care and daily activities. There are multiple factors, primarily advancing age itself, which can negatively influence ECOG PS during follow-up. Hence, we cannot directly hold surgery accountable for the marginal decrease in ECOG PS over the course of 66 months. Regarding surgical complications, we found a complication rate of 6% exceeding Clavien-Dindo grade 3a. The median follow-up of 5.5 years allows us to abstract from a merely postoperative decrease in QoL. This is one of the advantages of our study. Moreover, we found postoperative complications leading to multi-organ failure (Clavien-Dindo 4b) in only 2 patients, which underlines the necessity for surgery to be performed by highly experienced surgeons. There was no significant influence of peri-operative complications on long-term QoL for the whole cohort. These findings align with the published literature on this topic [20].

Apart from the retrospective character of our analysis, a drawback of our study, and a potential source of bias, is represented by the fact that patients had to remember their QoL 5.5 years ago and compare this to their current status. Certainly, measurable parts of the questionnaire like insulin dependence and development of diabetes are more reliably reported than sexual function in this memory-based preoperative part of the questionnaire. Digestive symptoms and hepatic symptoms (like jaundice), according to the occurrence of postoperative cholangitis, on the other hand, should be remembered quite well, we assume. We first thought that we would find an age-matched control group, but the published literature does not pro-

vide preoperative QoL data generated prospectively using the EORTC-PAN26 score in a comparable situation. We thus decided to use the cohort as its own control group (before and at a median of 5.5 years after resection), for there is no control group to be found which exactly coincides with the study group. In our opinion, the comparability between study group and control group outweighed the limitation of the study's retrospective character. To address the inherent statistical weakness of a retrospective analysis, prospective trials are needed to assess QoL preoperatively and at follow-up, by using validated questionnaires such as the QLQ PAN26.

Conclusion

Resection following careful indication in cases of benign IPMN represents an appropriate treatment modality, if performed by experienced surgeons, and results in low perioperative complication rates.

Statement of Ethics

The study was approved by the Institutional Ethics Committee (approval No. 1008/2020) and written informed consent was obtained from participating patients at the Ordensklinikum Linz.

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Conflict of Interest Statement

None of the authors has any conflicts of interest or financial ties to disclose.

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Author Contributions

H.V.W.: conception and design of the work; acquisition, analysis, and interpretation of data; and drafting the work and revising it. C.S.R. and P.K.: substantial contributions to the conception and design of the work; acquisition of data; and revising the work critically for intellectual content. I.F.: substantial contributions to the acquisition of data and revising the work critically for intellectual content. M.W., H.R., and R.F.: substantial contributions to the conception and design of the work and revising it critically for intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work (by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved).

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