

ORIGINAL ARTICLE

Patient reported outcomes of duodenum-preserving pancreatic head resection in chronic pancreatitis: high effectivity is impaired by prolonged non-surgical management

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Abstract

Background: Chronic pancreatitis (CP) causes suffering and socioeconomic burden. This study evaluated perioperative results and patient-reported outcomes (PRO) in CP patients treated with duodenum-preserving pancreatic head resection (DPPHR).

Methods: Data were analyzed of CP patients undergoing DPPHR between 01/2001-10/2014. PROs were measured using a specifically designed questionnaire and the EORTC QLQ-C30/PAN26. Associations between treatment variables and PROs were examined.

Results: Of 332 patients who received DPPHR, most (n = 251, 75.6%) underwent the Berne modification. Surgical morbidity was 21.5% (n = 71) and 90-day mortality 1.5% (n = 5). Median follow-up was 79.9 months, 5-year survival 90.5%, and 1.8% of patients developed pancreatic cancer. Of 283 patients alive, 178 (62.9%) returned questionnaires. Referral for surgery was self-initiated (38.0% of cases), by gastroenterologists (27.5%) and by general practitioners (21.1%). QoL improved in 78.7% of patients, remained stable in 12.1%, and worsened in 9.1%. Median Izbicki scores decreased from 90 to 5 points after surgery (p < 0.0001). Time from diagnosis to DPPHR was an independent, proportional predictor of a higher postoperative Izbicki score (p = 0.04).

Conclusion: DPPHR is an effective, safe treatment for CP. A delay in surgery decreases surgical effectivity, hence CP patients should be referred to surgery early to ensure satisfactory outcomes.

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Introduction

Chronic pancreatitis (CP) is a debilitating disease associated with a large health burden and socioeconomic impact.¹ The chronic inflammatory process results in a progressive replacement of pancreatic parenchyma by fibrotic tissue, eventually leading to endocrine and exocrine insufficiency.² Moreover, chronic pain as the predominant symptom results in a reduced quality of life

(QoL) and in the long-term, the risk of developing pancreatic cancer is increased.

In contrast to the Whipple procedure, duodenum-preserving pancreatic head resection (DPPHR) is a less invasive, organ-sparing procedure for surgical treatment of CP.³ At the same time, the removal of the inflammatory mass in the pancreatic head aims to alleviate pain, generally considered the pacemaker of pain in CP.⁴ Initially described by Beger et al., several modifications were proposed in subsequent years, including the Frey and the Berne modification.⁴⁻⁷

PROs are subjective measures of outcomes which help to assess the disease burden, QoL and treatment from a patient's perspective, besides others. They critically complement clinical

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outcomes as they capture the individual patient's perspective in evaluating treatment success and, therefore, constitute an important element to shared decision-making.⁸ Pain is the predominant symptom in CP patients with major impact on QoL and thus PROs represent key outcome measures when evaluating success of DPPHR for treatment of CP.^{9–11} Despite their relevance, PROs in CP patients treated with DPPHR remain largely understudied.^{10,12,13}

Several studies have demonstrated that DPPHR and its different modifications are an effective treatment option for CP.^{4,14–17} Traditionally, a step-up approach has been advocated with surgery as the last option for treatment of CP. However, recent studies including evidence from a randomized controlled trial indicate that this might not be appropriate and surgery should be offered earlier.^{18,19} However, the association between timing of surgery and outcomes of DPPHR – especially PROs – remains unclear.

This study aims to identify treatment-related factors which affect postoperative PROs after DPPHR for painful CP.

Methods

Study design and patient cohort

This retrospective cohort study was approved by the ethics committee of the Medical Faculty in Heidelberg (S-209/2015). All adult patients diagnosed with CP and treated with DPPHR at the Department of General, Visceral and Transplantation Surgery at the Heidelberg University Hospital between 01/2001–10/2014 were identified from a prospectively maintained institutional database. Exclusion criteria were previous pancreatic resections, preoperative suspicion of malignancy, histologically confirmed pancreatic cancer during index operation, and missing informed consent.

Clinical and pathological information of eligible patients were retrieved from the registry or the electronic health record. Medical and surgical complications were noted. Follow-up was carried out via our institution's pancreas outpatient clinic, and by contacting general practitioners and patients by phone or in written form between 01/2016 to 05/2016.

Surgical management

Surgical treatment was dependent on the individual patient's symptoms and radiological findings. The Berne modification is the standard DPPHR procedure at our institution.^{6,16} Briefly, the pancreatic head is resected and the resulting single-cavum anastomosed side to side with a Roux-en-Y jejunal loop. An internal bile duct anastomosis in the excavated head is performed optionally. According to the ISGPS recommendations for description of operations for CP, it corresponds to a duodenum-preserving subtotal pancreatic head resection without transection at neck of pancreas.¹¹ For the Beger

procedure, the resection of the pancreatic head is combined with transection of the pancreas at the portal vein, corresponding to a duodenum-preserving subtotal pancreatic head resection with transection at neck of pancreas according to the ISGPS. Other less common techniques including the Frey procedure (longitudinal pancreaticojejunostomy with partial pancreatic head resection according to the ISGPS) were employed as part of individualized treatment strategies, in particular in cases of CP affecting the tail of the pancreas without a large pseudotumor of the pancreatic head.

Patient-reported outcomes

PROs reporting followed the CONSORT-PRO extension when applicable.²⁰ QoL was assessed using the questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30, version 3.0) and the pancreas extension (EORTC QLQ-PAN26) in German language.^{12,21} EORTC QLQ-C30 values were compared to an age and sex matched German reference population.²² Items assessed in the QLQ-C30 are global health status, role functioning, emotional functioning, cognitive functioning, and social functioning. Items measured in the QLQ-PAN26 are pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, as well as other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes).²³

Additionally, a questionnaire in German language was developed for retrospective evaluation of PROs before and after surgery (Suppl. File). Relevant items were chosen based on a review of the literature as well as expert opinions. The questionnaire included the Izbicki pain score as a validated tool for pain assessment in CP.²⁴ Patients had the option of adding documents related to previous hospital stays, e.g., surgery reports, discharge reports, as well as letters from general practitioners and other specialists involved in the treatment. Any uncertainties regarding the questionnaire and other information provided were eliminated by phone interviews.

Statistical analysis

Quantitative parameters are expressed as median and range. The Kaplan-Meier method was used for survival analysis. Overall survival was defined as the time from resection to either death from any cause or last follow-up. Patients alive at last follow-up were censored. Elastic net linear regression was used to regularize regression models to reduce redundant predictors and identify factors associated with the time interval from diagnosis to surgery. Categorical variables were transformed into binary dummy variables. Range of values was scaled from 0 to 1 for all variables. Radar plots were generated using age and sex matched German reference values.²² Missing values for PRO data were imputed using the 'mice' package in R, which is based on Fully Conditional Specification.²⁵ A p value < 0.05 was considered

statistically significant. R statistical programming language (R Foundation, Vienna, Austria) was used for all analysis.

Results

Patient characteristics and perioperative outcomes

After applying the predefined exclusion criteria, 332 patients were identified who underwent DPPHR for CP within the study period. Median age at the time of surgery was 47.6 years (IQR:

Table 1 Demographics and clinical characteristics of chronic pancreatitis patients treated with duodenum-preserving pancreatic head resection

Parameter	Category	Total (n = 332)
Total number of patients		332
Sex	Male	239 (72.0)
	Female	93 (28.0)
Age	Median (IQR)	47.6 (42.4–55.1)
BMI (kg/m ²)	Median (IQR)	21.7 (19.7–24.0)
Surgical Procedure	Berne	251 (75.6)
	Beger	53 (16.0)
	Frey	13 (3.9)
	Others	15 (4.5)
	Missing	10
ASA-score	I	5 (1.6)
	II	212 (65.8)
	III	104 (32.3)
	IV	1 (0.3)
	Missing	10
Etiology	Alcohol	147 (44.3)
	Pancreas divisum	24 (7.2)
	Biliary	11 (3.3)
	Autoimmune	5 (1.5)
	Posttraumatic	5 (1.5)
	Hereditary	2 (0.6)
	Other	11 (3.3)
	Unknown	127 (38.3)
	Missing	10
Follow-up	Alive	283 (85.5)
	Dead	48 (14.5)
	Lost to follow-up	1
	Median in months (IQR)	79.9 (30.6–130.6)
	Missing	1
Subsequent pancreatic surgery	Yes	58 (17.5)
	No	273 (82.5)
	Missing	1
Development PDAC	Yes	6 (1.8)
	No	325 (98.2)
	Missing	1

Legend: IQR: interquartile range; BMI: body mass index; ASA: american society of anesthesiologists; PDAC: pancreatic ductal adenocarcinoma.

42.4–55.1 years) and 72.0% (n = 239) were male (Table 1). Etiologies of CP included alcohol consumption (n = 147, 44.8%), pancreas divisum (n = 24, 7.2%), and biliary etiology (n = 11, 3.3%). In 127 (38.3%) patients, the etiology of CP was unknown. Most patients underwent the Berne procedure (n = 251, 75.6%), while the Beger (n = 53, 16.0%) and Frey procedures (n = 13, 3.9%) were less common. Other less frequent procedures included lateral pancreaticojejunostomies including the Partington-Rochelle (n = 8, 2.4%) and Puestow (n = 3, 0.9%) procedures. Median operating time was 280 min (IQR), 90-day mortality was 1.5% (n = 5), and overall morbidity 28.4% (n = 94) (Table 2). Surgical complications occurred in 71 patients

Table 2 Perioperative characteristics of the cohort

Parameter	Category	Total (n = 332)
Length of hospital stay (d)	Median (IQR)	9.5 (8–12)
Operating time (min)	Median (IQR)	280 (225–330.5)
Intraoperative blood loss (ml)	Median (IQR)	500 (300–700)
ICU stay	Yes	170 (51.2)
	No	162 (48.8)
ICU stay (d)	Median (IQR)	1 (1–1)
90-day mortality	Yes	5 (1.5)
	No	327 (98.5)
Surgical complications	Yes	71 (21.5)
	No	260 (78.5)
	Missing	1
Postoperative Pancreatic Fistula (ISGPS B or C)	Yes	5 (1.5)
	No	326 (98.5)
Anastomotic leakage	Yes	8 (2.4)
	Pancreaticojejunostomy	5
	Biliodigestive anastomosis	3
	No	323 (97.6)
	Chyle leak	Yes
	No	326 (98.5)
	Delayed gastric emptying	Yes
	No	320 (96.7)
	Surgical site infection	Yes
	No	315 (95.2)
	Relaparotomy	Yes
	No	313 (94.6)
	Incisional hernia	Yes
	No	321 (97.0)
	Missing	1

Legend: d: days; ICU: intensive care unit; IMC: intermediate care unit; IQR: interquartile range; ISGPS: international study group of pancreatic surgery.

(21.5%) with surgical site infection ($n = 16$, 4.8%), and delayed gastric emptying ($n = 11$, 3.3%) being the most frequent. Postoperative pancreatic fistula grade B/C according to ISGPS classification occurred in 5 (1.5%) patients.²⁶ Relaparotomy was rare ($n = 18$, 5.4%), mostly because of postoperative bleeding ($n = 5$, 1.5%), bowel perforation ($n = 3$, 0.9%), leakage at the pancreatic anastomosis ($n = 2$, 0.6%), and burst abdomen ($n = 1$, 0.3%). In total, 29 patients suffered from severe complications corresponding to a Clavien-Dindo grade III or higher. Ten patients (3.0%) developed incisional hernia. Subgroup analysis for the Berne modification versus other DPPHR procedures revealed comparable perioperative results but significantly shorter operating time and ICU stay, respectively (Suppl. Fig. 1, Suppl. Table 1).

Long-term outcomes

Median follow-up was 79.9 months (IQR: 30.6–130.6 months) with a 5-year survival rate of 90.5% and 10-year survival rate of 80.1% (Suppl. Fig. 2). In total, 58 patients (17.5%) had at least one additional surgery related to CP after the initial procedure. Additional surgery occurred at a median of 17.0 months after the index surgery (range 3–133 month), mainly due to continued pain from CP ($n = 24$, 41.4%) in the remnant parenchyma, bile duct stenosis ($n = 22$, 37.9%), as well as suspected malignancy ($n = 10$, 17.2%). Of the latter, 6 patients (1.8%) had developed with pancreatic ductal adenocarcinoma during follow-up.

Patient-reported outcomes survey

Of 283 living patients, 178 (62.9%) returned the questionnaires. Median interval from time of surgery to data collection was 7.6 years and median time from first diagnosis to surgery was 10.2 years (range 1–29.1 years). The majority of patients were not referred for surgical treatment by their doctors but self-initiated surgical presentation ($n = 65$, 36.5%), followed by referral from gastroenterologists ($n = 47$, 26.4%), general practitioners ($n = 36$, 20.2%), and hospitals ($n = 23$, 12.9%) (Suppl. Table 2). In total, 107 (62.2%) patients reported surgery being in time, while 62 (36.0%) reported surgery happening too late. Of note, 3 (1.7%) patients reported that the timing of surgery was too early. Based on patient reporting, general QoL improved by surgery in 137 (78.7%) patients, with no change or decrease in QoL in 21 (12.1%) and 16 (9.2%) patients, respectively. Median Izbicki pain score decreased from 90 points preoperatively to 5 points postoperatively ($p < 0.0001$) (Fig. 1).

Data on self-reported endocrine and exocrine function is depicted in Suppl. Table 2. Prior to surgery, 27 patients (15.4%) reported suffering from diabetes mellitus, while this number increased to 101 (42.9%) postoperatively (Fig. 2a). Contrary, diarrhea and steatorrhea decreased significantly after surgery ($p = 0.03$ and $p = 0.005$, respectively). In parallel, reported pancreatic enzyme replacement therapy went from 34.1% ($n = 56$) to 78% ($n = 131$) after surgery (Fig. 2b). Similarly,

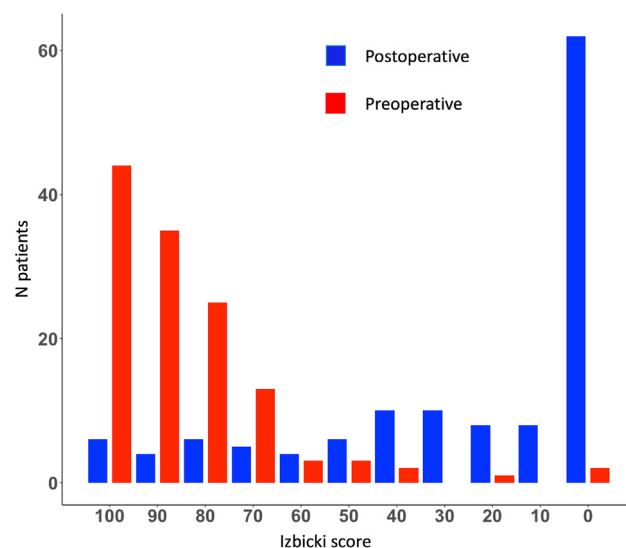


Figure 1 Preoperative versus postoperative Izbicki pain scores demonstrate high effectiveness of duodenum-preserving pancreatic head resection with most patients reporting only minor levels of pain after surgery

episodes of acute pancreatitis and associated interventions decreased after surgery (Fig. 2c) as well as frequency of pain attacks (Fig. 2d).

Next, EORTC QLQ-C30 scores of CP patients after DPPHR were compared to an age and sex-matched German reference population (Fig. 3a and b). Scores were comparable in the separate groups compared to the reference data; however, patients ≤ 49 years were markedly more affected by diarrhea compared to the reference population as well as to other age groups.

Predictors of worse postoperative outcomes as measured by the Izbicki score

Next, we aimed to construct a model to identify factors which predict a worse postoperative outcome as measured by the Izbicki score. Using cross-validated elastic net regression to adjust for potential confounders and select among redundant predictors, longer time interval from diagnosis to surgery predicted a higher postoperative Izbicki score per time unit (OR 1.01; 95%-CI 1.00–1.02; $p = 0.04$) (Fig. 4). Specifically, for every doubling of the time interval from diagnosis to surgery, measured in months, there was an associated one percent increase in the postoperative Izbicki score. Additionally, we conducted two sensitivity analyses. First, we excluded patients who underwent an additional pancreatic surgery after the index surgery to exclude the possibility that the observed effect might be due to the additional surgery (Suppl. Fig. 3). Second, we excluded patients who underwent the Puestow or Partington-Rochelle procedure, as these are not considered classical DPPHR operations (Suppl. Fig. 4). Notably, results remained consistent.

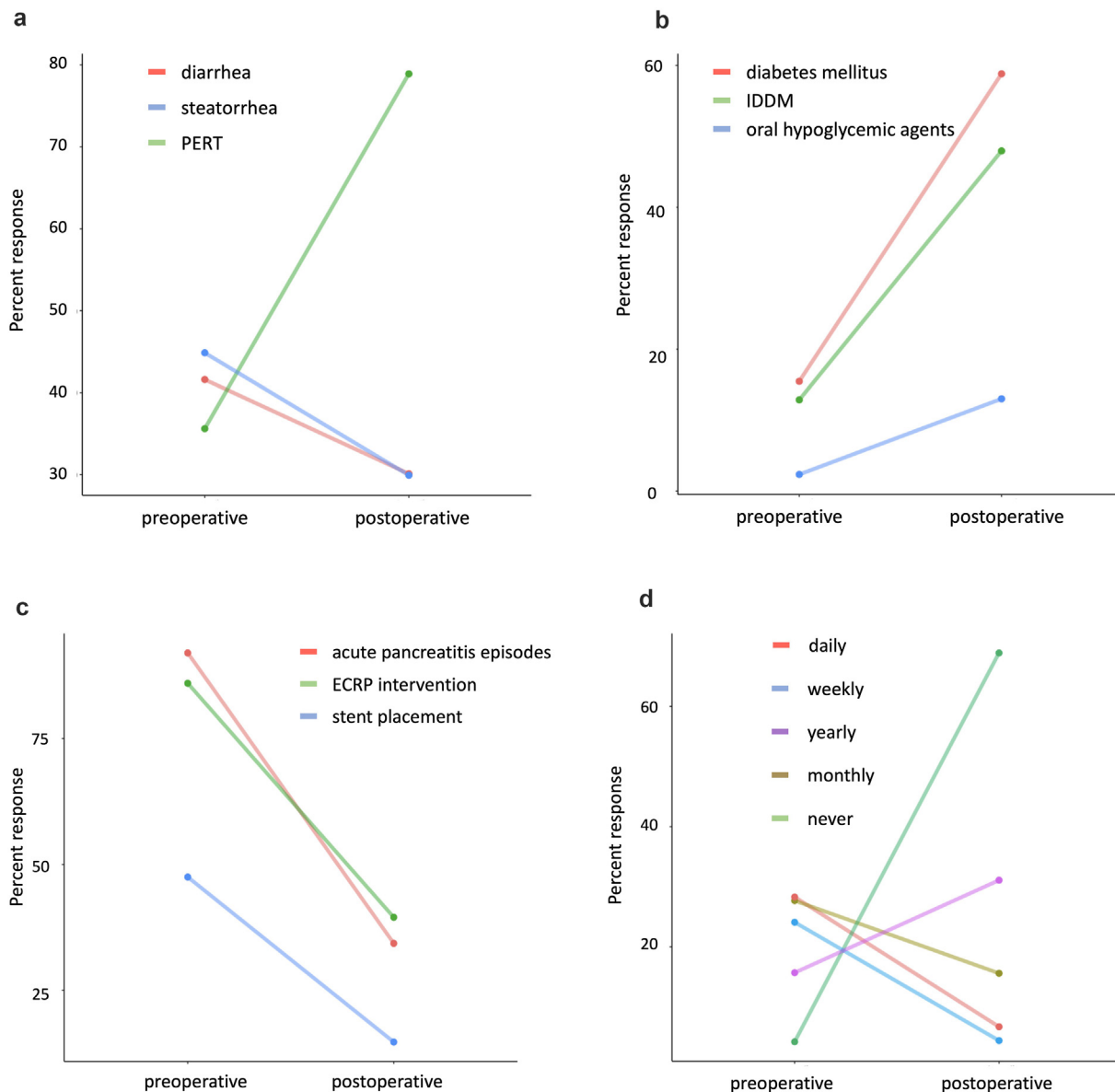


Figure 2 Before-after plots of endocrine (a) and exocrine (b) function after duodenum-preserving pancreatic head resection. Additionally, before-after plots of acute pancreatitis episodes and clinical interventions (c) as well as pain frequency (d) after duodenum-preserving pancreatic head resection indicate good outcomes

Discussion

The present study comprehensively evaluated perioperative outcomes and PROs in CP patients treated with DPPHR. DPPHR was highly effective in reducing pain levels and improving QoL and is a safe treatment option for CP associated with low mortality and acceptable morbidity. Importantly, a prolonged time interval from diagnosis to surgery was proportionally associated with a worse postoperative outcome as measured by the Izbicki pain score.

Most of the patients included in the current study underwent the Berne modification, making it the largest cohort for this

procedure in the literature including the assessment of PROs. PROs including general QoL are highly relevant in CP patients, and postoperative evaluation should consider the individual patient's self-assessment as decisive outcomes of treatment success.²⁷

Consistent with a previous randomized controlled trial, the Berne modification was associated with shorter ICU stay as well as shorter operating time compared to other DPPHR procedures in our cohort.¹⁶ However, as this was a retrospective cohort, a selection bias in favor of the Berne procedure in patients with less advanced CP cannot be ruled out, as the Berne procedure is

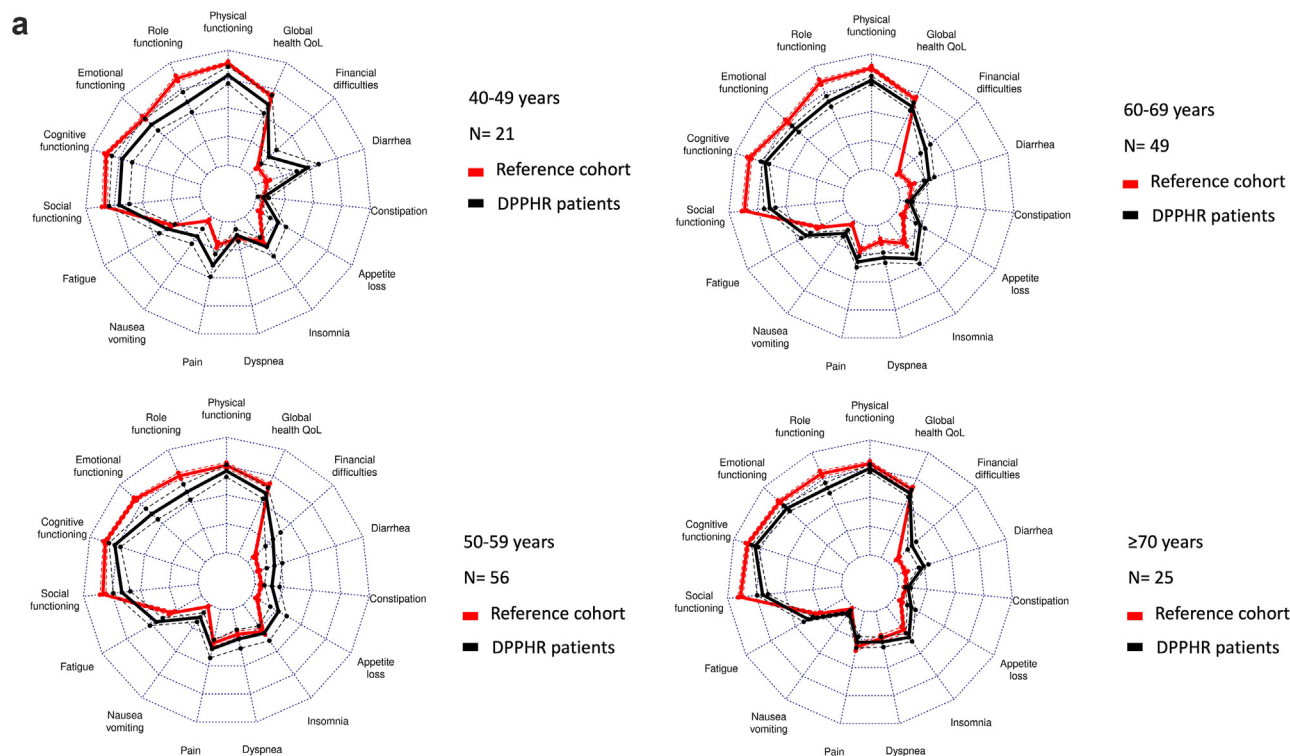


Figure 3 Radar plots demonstrating good Quality of Life measured by EORTC QLQ C30 between male (a) and female (b) chronic pancreatitis patients after duodenum-preserving pancreatic head resection versus an age- and sex-matched reference population. Solid line depicts mean values, dashed line 95% confidence intervals. Diarrhea was markedly more common in younger patients independent of sex

technically less challenging compared to the Beger procedure. Re-operations were less common for the Berne modification compared to the remaining cohort. Of note, in the ChroPac trial comparing pancreaticoduodenectomy (PD) vs DPPHR, no re-operations due to ongoing CP (e.g., bile duct stenosis, pancreatic duct stenosis) were noted in the PD group >6 months after the index surgery in contrast to the DPPHR group.²⁸ It needs to be noted that the Berne and Beger procedure might be particularly beneficial in a German population, as large pseudotumors in the pancreatic head are more frequent in this population than elsewhere.²⁹ At the same time, strictures of the distal pancreas are not addressed by these procedures, emphasizing the need for appropriate preoperative imaging to choose the best procedure.

Consistent with previous reports, the overall incidence of PDAC during the follow-up period was low with a total of 6 patients (<2%), indicating that PROs rather than survival and oncological aspects are the key outcome variables in evaluating treatment success in CP patients.^{10,30}

While DPPHR was highly effective in reducing pain levels, it did not prevent the progression of the disease, eventually resulting in exocrine and endocrine insufficiency in the majority of patients.^{18,31} Interestingly, patients reported less diarrhea and steatorrhea after surgery, presumably due the parallel increase in pancreatic enzyme replacement therapy as well as

successful medical management after DPPHR. Based on comparison to a reference population, the progression of exocrine and endocrine insufficiency did not significantly impair the effectiveness of DPPHR, except patients ≤ 49 years of age. This result is consistent with evidence indicating that QoL is mainly determined by pain levels in CP patients.³² Importantly, early surgery effectively reduces pain levels, as demonstrated in the present study.

The optimal time point of surgery is controversial. The consensus guidelines on pain from the International Association of Pancreatology (IAP) together with the American Pancreatic Association (APA), the Japan Pancreas Society (JPS), and the European Pancreatic Club (EPC) recommend surgery within the first 2–3 years after diagnosis/symptom onset, ≤ 5 endoscopic procedures or in patients who have not yet required opioid analgesics for pain treatment.³³ In contrast, the American College of Gastroenterologist recommends surgery over endoscopic intervention in cases of obstructive CP if first-line endoscopic approaches have been exhausted or unsuccessful without specifying a time interval.³⁴ German S3 clinical practice guidelines recommend early surgery (<2–6 months) after initiation of opioid treatment in cases of considerably dilated pancreatic duct.³⁵ In addition, unsuccessful endoscopic treatment for more than 3 months should lead to surgical treatment.³⁵ Finally, the

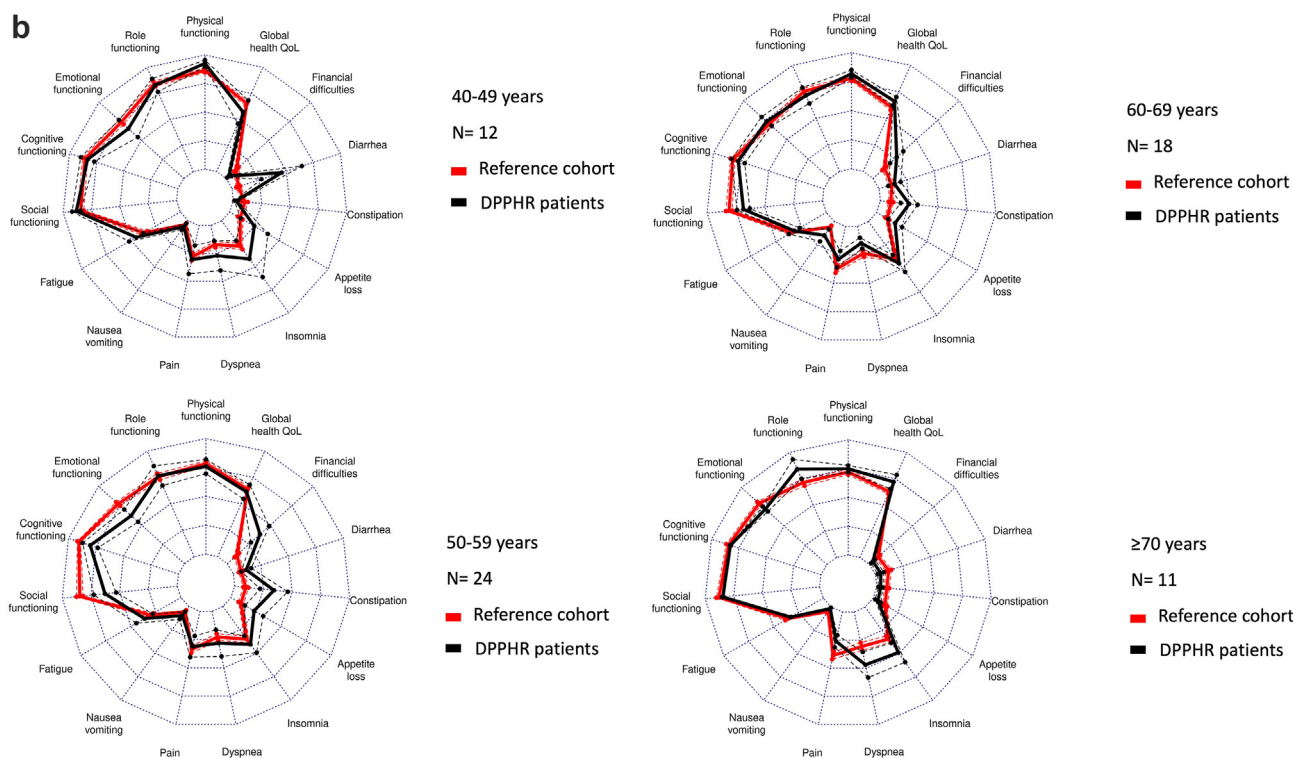


Figure 3 (continued).

2020 IAP-APA-JPS-EPC consensus guideline on timing of surgery recommends surgery <3 years after onset of symptoms.²⁷

The results of the present study support and extend these recommendations as based on postoperative pain relief. However, it indicates that despite these existing national and international guidelines, current clinical practice frequently deviates from these recommendations. Most CP patients were not evaluated for surgical treatment based on referrals from gastroenterologists or general practitioners, but rather based on self-initiation. While this might be influenced by referral patterns specific to the German healthcare system, it emphasizes the importance of early interdisciplinary consultation when treating CP patients and the need for early referral to a surgeon when appropriate. Interestingly, more than one third of patients reported that surgery was performed too late.

A previous study aimed to define an optimal timing for surgery to achieve postoperative pain control.¹⁹ The investigators proposed that the best cut-off point for unadjusted preoperative CP duration based on pain-relief was 26.5 months. Most studies published so far used a 3-year cut-off to differentiate between early and late surgery, without providing a specific reasoning for this threshold.³⁶ The recent randomized controlled ESCAPE trial reported that early surgery was superior to endoscopic intervention based on the Izbicki pain score 18 months after surgery, yet proportions of patients with complete or partial pain relief did not differ significantly between the groups at the end of follow-up^{18, 18}. Early surgery was defined as surgery within 6

weeks of randomization with eligibility based on recently initiated opioid use due to progressive pain, without defining a specific timeframe from diagnosis to surgery.

In contrast, the present study used time of diagnosis instead, as we believe it is more relevant because it is an antecedent to CP specific treatment. It has been estimated that the time interval from onset of symptoms until diagnosis of CP takes a median of approximately 80 months.³⁰ A longer time interval from diagnosis to surgery might result in a central hyperalgesia, making it difficult to alleviate with surgical treatment strategies and hence resulting in a higher postoperative Izbicki score.^{37,38}

The results from this study suggest that defining a specific cut-off might not be possible, but the need of surgical intervention should be based on individual patient's characteristics. The specific treatment strategy needs to be tailored to the individual patient's performance status and comorbidities, as DPPHR is associated with relevant morbidity and mortality, despite being overall a safe and highly effective treatment strategy. Additionally, early surgery compared to endoscopic intervention has been associated with reduced healthcare costs, a matter particularly important in a disease associated with a high socioeconomic burden like CP.³⁹

This study has several strengths. It is the largest cohort describing perioperative outcomes and PROs for the Berne modification and therefore is an important contribution to the literature on DPPHR for CP. Previous results regarding a shorter operating time as well as shorter ICU stay in comparison with

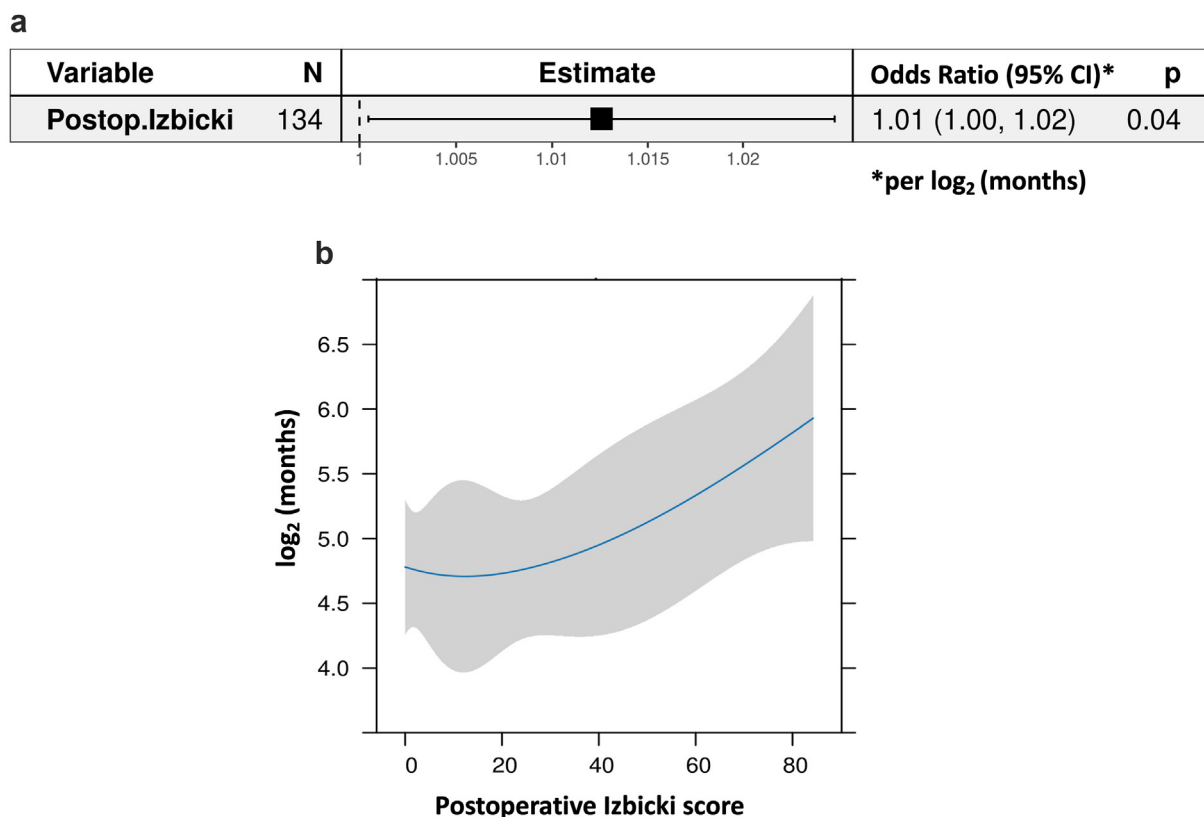


Figure 4 Forest plot (a) showing the odds ratio and 95% confidence interval of the association of time from diagnosis to surgery and increase in postoperative postoperative Izbicki pain score per time unit. Graphical display of change in time interval and resulting postoperative Izbicki score (b)

other DPPHR procedures were confirmed. Combining a condition-specific questionnaire allowed us to better capture symptoms and associated concerns. Not all elements of the questionnaire were psychometrically validated. Yet, the well-established Izbicki pain score was part of the self-designed questionnaire and enables comparisons to previously published results. The questionnaire complements the EORTC QLQ-C30 and the pancreas-specific PAN26 extension, which were previously psychometrically validated in CP.⁴⁰ Using published reference values for the EORTC-QLQ30 questionnaire enabled us to compare scores of the present cohort to an age and sex-matched German reference population. In contrast to previous studies, patients were answering the questionnaires at home in the present study, minimizing observer bias.¹⁸

This study has several limitations. First, the retrospective analysis with a single prospective QoL measurement prevents a true longitudinal analysis and recall bias and non-response bias cannot be ruled out.⁴¹ Notably, 37.1% of patients alive did not return the questionnaire, thus limiting the conclusion of the study as it remains unknown if these patients differed from the ones who responded in a systematic way. Second, the condition-specific questionnaire was not psychometrically validated. Third, in addition to the retrospective design functional outcome measurements were based on PROs using the standardized

questionnaire. While this provides valuable information, a biochemical assessment of endocrine and exocrine pancreatic insufficiency based on fasting glucose, HbA1c, fecal elastase, and others would result in more objective data. Lastly, data from preoperative cross-sectional imaging, which could be useful to assess outcomes of DPPHR dependent on CP morphology was not available for this study.⁹

In summary, this study emphasizes the importance of early referral to a surgeon for the treatment of painful CP and demonstrates excellent perioperative and long-term outcomes based on patient reported outcomes for DPPHR as surgical treatment for patients with chronic pancreatitis.

Acknowledgments

None.

Conflict of interest

None to declare.

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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.2023.10.002>.