Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection in chronic pancreatitis: the multicentre, randomised, controlled, double-blind ChroPac trial

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Summary

Background There is substantial uncertainty regarding the optimal surgical treatment for chronic pancreatitis. Short-term outcomes have been found to be better after duodenum-preserving pancreatic head resection (DPPHR) than after partial pancreatoduodenectomy. Therefore, we designed the multicentre ChroPac trial to investigate the long-term outcomes of patients with chronic pancreatitis within 24 months after surgery.

Methods This randomised, controlled, double-blind, parallel-group, superiority trial was done in 18 hospitals across Europe. Patients with chronic pancreatitis who were planned for elective surgical treatment were randomly assigned to DPPHR or partial pancreatoduodenectomy with a central web-based randomisation tool. The primary endpoint was mean quality of life within 24 months after surgery, measured with the physical functioning scale of the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire. Primary analysis included all patients who underwent one of the assigned procedures; safety analysis included all patients who underwent surgical intervention (categorised into groups as treated). Patients and outcome assessors were masked to group assignment. The trial was registered, ISRCTN38973832. Recruitment was completed on Sept 3, 2013.

Findings Between Sept 10, 2009, and Sept 3, 2013, 250 patients were randomly assigned to DPPHR (n=125) or partial pancreatoduodenectomy (n=125), of whom 226 patients (115 in the DPPHR group and 111 in the partial pancreatoduodenectomy group) were analysed. No difference in quality of life was seen between the groups within 24 months after surgery (75·3 [SD 16·4] for partial pancreatoduodenectomy *vs* 73·0 [16·4] for DPPHR; mean difference –2·3, 95% CI –6·6 to 2·0; p=0·284). The incidence and severity of serious adverse events did not differ between the groups. 70 (64%) of 109 patients in the DPPHR group and 61 (52%) of 117 patients in the partial pancreatoduodenectomy group had at least one serious adverse event, with the most common being reoperations (for reasons other than chronic pancreatitis), gastrointestinal problems, and other surgical morbidity.

Interpretation No differences in quality of life after surgery for chronic pancreatitis were seen between the interventions. Results from single-centre trials showing superiority for DPPHR were not confirmed in the multicentre setting.

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Introduction

Chronic pancreatitis is a fibro-inflammatory disease of the exocrine pancreas leading to permanent structural damage of the gland. Eventually, this process results in impairment of the gland's exocrine and endocrine functions. The most common form of chronic pancreatitis is the calcifying type, characterised by the development of intraductal stones; the predominant causative agent is alcohol.[1] Progressive functional impairment can be delayed by surgical decompression of the dilated main pancreatic duct.[2] Because of inflammatory enlargement of the pancreatic head, many patients with chronic pancreatitis develop local complications that require further treatment, such as stenosis of the pancreatic or bile duct, duodenal obstruction, or compression of retropancreatic vessels. In such cases, surgery is superior to conservative or endoscopic treatment in terms of pain relief and preservation of pancreatic function and quality of life.[3–5] Moreover, surgical treatment is more cost-effective than endoscopic treatment.[6]

Several surgical treatment options exist for chronic pancreatitis, which can be categorised into drainage or resectional procedures. For a long time, partial pancreatoduodenectomy was the main surgical approach for removal of the pancreatic head in patients with chronic pancreatitis and enlargement of the pancreatic head. As a parenchyma-sparing approach, Beger and colleagues[7,8] developed a technique of duodenum-preserving pancreatic head resection (DPPHR) in the early 1970s. In the

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See **Comment** page 1007

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Research in context

Evidence before this study

We searched PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials from inception to Feb 5, 2017, to identify trials comparing partial pancreatoduodenectomy with duodenum-preserving pancreatic head resection (DPPHR) for the treatment of chronic pancreatitis. The search strategy used for PubMed was "chronic pancreatitis AND (pancreaticoduodenectomy OR pancreatoduodenectomy OR duodenum-preserving OR duodenum preserving OR pancreatic head resection OR pancreatectomy) AND random". We searched the reference lists of the retrieved articles for additional publications. No restrictions were applied to language or date of publication. Five trials were identified, all of which were single-centre studies with no masking. Four trials compared a specific type of DPPHR (two Beger, one Frey, and one Berne) with partial pancreatoduodenectomy, whereas the trial by Keck and colleagues compared DPPHR (either Beger or Frey) with partial pancreatoduodenectomy. Farkas and colleagues and Izbicki and colleagues showed a significant benefit for DPPHR in terms of quality of life during the early period after surgery. However, the long-term results (≥24 months) for all domains of quality of life in the trial by Izbicki and colleagues and in those by Büchler and colleagues and Keck and colleagues were similar for DPPHR and partial pancreatoduodenectomy. No measure of quality of life was presented in the trial by Klempa and colleagues. The pooled results of the trials before ChroPac showed no differences in quality of life (mean difference −0·28, 95% CI −0·75 to 0·18; p=0·24), new onset of endocrine (odds ratio [OR] 0·78, 95% CI 0·32 to 1·92; p=0·59) or exocrine (0·39, 0·06 to 2·46; p=0·32) insufficiency, or reoperation due to chronic pancreatitis (3·82, 0·6 to 24·54; p=0·16).

Added value of this study

We found no difference in quality of life and incidence of serious adverse events between the interventions. However, partial pancreatoduodenectomy was associated with fewer readmissions than DPPHR during the 24 month follow-up. In an updated meta-analysis of the five previous trials and ChroPac (with a total of 481 patients with chronic pancreatitis, including 239 who received partial pancreatoduodenectomy and 243 who received DPPHR), there were still no significant differences in quality of life and new onset of endocrine or exocrine insufficiency between the interventions, although the results were more precise (shown by the narrower 95% CI of the pooled effect estimate). Reoperation due to chronic pancreatitis shifted in favour of partial pancreatoduodenectomy (OR 5·21, 95% CI 1·09–24·94; p=0·0388; appendix).

Implications of all the available evidence

The findings of some previous small single-centre trials in favour of DPPHR concerning quality of life and pancreatic function did not hold true in the multicentre setting. We found some interesting new results concerning readmission and reoperation due to chronic pancreatitis, suggesting that partial pancreatoduodenectomy might be the more definite treatment strategy for chronic pancreatitis. Future research should aim to identify individuals who would explicitly benefit from one specific procedure based on preoperative characteristics and imaging findings.

intervening years, two modifications of the original Beger method have been introduced that specifically avoid dissection of the pancreas from the portal and superior mesenteric vein, which can be challenging and result in haemorrhage and complications in patients with portal hypertension. The Frey procedure combines coring out of the inflamed pancreatic head tissue with a lateral incision of the pancreatic duct over its full length. Both the cored-out head and opened duct are subsequently drained into a Roux-en-Y limb of jejunum.[9] The Berne modification of DPPHR involves subtotal resection of the enlarged pancreatic head, leaving just a thin lamella of pancreatic tissue dorsally, towards the duodenum and the portal vein. The pancreatic duct (and, in the presence of cholestasis, the common bile duct) is opened widely and a Roux-en-Y jejunal limb is used to drain the resulting cavity.[10]

The various techniques for DPPHR have been compared with partial pancreatoduodenectomy in several small-scale randomised trials.[11–14] The individual trials and meta-analyses thereof have suggested superiority for DPPHR over partial pancreatoduodenectomy in several short-term outcomes: duration of surgery, blood loss, length of hospital stay, postoperative pancreatic function, and quality of life.[15] However, there is substantial uncertainty regarding the robustness of these results owing to the potential sources of bias in small single-centre trials.

Therefore, we designed the multicentre ChroPac trial to compare DPPHR with partial pancreatoduodenectomy in terms of quality of life in a period of 24 months after surgery, including all modifications of DPPHR and partial pancreatoduodenectomy.

Methods

Study design and participants

ChroPac was a multicentre, randomised, controlled trial with a parallel-group, superiority design. The trial was done in 18 centres for pancreatic surgery located in Germany (n=16), Slovenia (n=1), and the UK (n=1). Patients were eligible if they were scheduled for primary elective surgery for chronic pancreatitis of the pancreatic head at one of the trial centres and were able to understand the nature and consequences of trial participation. All patients provided written informed consent before inclusion. Patients were excluded if they were participating in any

other interventional trial that could potentially interfere with the procedures or outcomes of the ChroPac trial.

The protocol[16] and other relevant documents of the ChroPac trial were approved by the independent ethics committee of the University of Heidelberg and the individual ethics committees of all other participating institutions. The trial was done in accordance with the ethical principles of the Declaration of Helsinki[17] and the principles of Good Clinical Practice (ICH-GCP E6). Reporting of the trial complied with the recommendations of the CONSORT statement.[18]

ChroPac was designed, managed, and analysed by the Study Center of the German Surgical Society with the support of the Institute of Medical Biometry and Informatics of the University of Heidelberg.

Randomisation and masking

A central web-based randomisation process was used to allocate patients before surgery to either partial pancreatoduodenectomy or DPPHR. To achieve balanced group sizes, randomisation was stratified by each centre and with a block size of four, which was unknown to all people involved in trial conduct. The randomisation process was done at each centre by trial personnel not involved in treatment or outcome assessment of the participants. Clinical investigators were not involved in routine care and, thus, were not aware of the procedure done during outcome asssessment. Patients were informed that pancreatic head resection was to be done but were not aware of the specific type of procedure (DPPHR or partial pancreatoduodenectomy). The operating surgeon could not be masked to the intervention.

Procedures

Detailed information about the surgical procedures can be found in the published protocol.[16] Partial pancreatoduodenectomy, done either as pylorus-preserving pancreatoduodenectomy or classic pancreatoduodenectomy (with distal gastrectomy), was the control intervention. All types and modifications of DPPHR (eg, Beger's original procedure, the Frey procedure, or the Berne modification) were permissible as experimental interventions.

In a pragmatic approach, the choice of pylorus-preserving pancreatoduodenectomy or classic pancreatoduodenectomy, or the individual modifications of DPPHR within the randomised groups, was left to the discretion of the operating surgeon, based on the patient's anatomical presentation and the surgeon's skills and preferences. Details of surgery were not explicitly specified, leaving surgeons free to do the procedures according to the local standards at each centre.

Six trial visits took place for each patient: a screening visit; a visit on the day of surgery; and follow-up visits to assess outcomes on the day of discharge and at 6 months, 12 months, and 24 months after surgery. The detailed schedule is provided in the protocol publication.[16] We used electronic case report forms for data documentation.

Outcomes

The primary endpoint was mean quality of life within 24 months after surgery, measured at 6 months, 12 months, and 24 months with the physical functioning scale of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.[19]

Secondary endpoints included all other scales of the EORTC QLQ-C30 questionnaire and the QLQ-PAN26 questionnaire.[19,20] These two questionnaires are composed of several multi-item subscales for general and pancreatic-disease-related quality of life and together form a comprehensive system to assess quality of life in patients with pancreatic diseases. Subscales are global health status/quality of life, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial problems, pancreatic pain, digestive symptoms, altered bowel habits, hepatic symptoms, body image, satisfaction with health care, and sexuality.

For more on the **web-based randomisation process** see www.randomizer.at

Mortality, general morbidity (wound infection, pulmonary infection), and pancreas-associated morbidity (postoperative pancreatic fistula according to the definition of the International Study Group on Pancreatic Fistula[21] and delayed gastric emptying according to the definition of the International Study Group of Pancreatic Surgery[22]) were also assessed as secondary endpoints. Perioperative measures (duration of surgery, intraoperative blood loss), postoperative hospital stay (index admission, total hospital stay due to chronic pancreatitis within 24 months), readmissions and reoperations due to chronic pancreatitis, weight course, and new onset of exocrine or endocrine insufficiency were assessed as secondary outcomes. Detailed information, including endpoint definitions, is available in the protocol.[16]

Assessment of safety was done with respect to the frequency of serious adverse events in all participants who underwent surgical intervention, categorised into groups as treated. For each patient, assessment of safety was started on the day that written informed consent was obtained and continued until completion of the trial at 24 months or until premature trial termination. We classified serious adverse events by intensity, outcome, and whether or not they were caused by the trial intervention. Serious adverse events were reported to the principal investigator within 24 h of the individual centre becoming aware of them.

Statistical analysis

We assumed a mean difference of 10% (SD 20%) in the physical functioning scale of the EORTC QLQ-C30 questionnaire between the trial groups in favour of DPPHR on the basis of results from two previously completed trials.[12,23] Applying a two-sided Student's *t* test, 86 patients per intervention group would have been required to detect a 10% difference with a two-sided α value

of 5% and a power of 90%. To allow for dropouts, withdrawals, and loss to follow-up, we planned to include 200 patients. When a third of the planned number of patients had completed follow-up, no post-screening data for the primary endpoint were available for 30% of these patients. To compensate for the higher attrition rate than expected, the number of patients to be included was increased to 250 to obtain enough patients with sufficient information about the primary endpoint.

The modified intention-to-treat (mITT) principle was used for the primary, confirmatory analysis of the trial.[24,25] Patients who underwent no surgery at all or none of the surgical procedures under investigation were excluded from the analysis because they did not provide any information about the examined interventions.[26,27]

ANCOVA, adjusting for age, centre, and EORTC QLQ C-30 physical functioning score before surgery, was used in analysis of the primary endpoint. For missing values, the average value was calculated and used for the primary analysis if quality of life was observed for at least one post-screening timepoint. When no post-screening observations were available, we estimated the postoperative quality-of-life score using multiple imputation with a Markov Chain Monte Carlo method to create 50 imputations[28] based on the variables physical functioning at baseline, age, and body-mass index (BMI). The primary model was estimated on the basis of all imputed datasets and then combined accordingly.[29,30]

We analysed secondary outcomes using methods of descriptive data analysis[31] and presented them with appropriate measures of empirical distribution together with corresponding p values derived with the Mann-Whitney *U* test for continuous variables and with the χ^2 test or exact unconditional test for categorical variables.[32] Odds ratios (ORs) were calculated for binary outcomes and mean differences were computed for continuous endpoints and presented with their 95% CIs. For the analysis of new onset of exocrine or endocrine insufficiency, we considered only patients who did not suffer from exocrine or endocrine insufficiency before surgery.

We did several sensitivity analyses for different populations (per-protocol population, complete cases), with different imputation methods for missing data and with statistical techniques considering different sets of covariates. In particular, if a value for the primary endpoint was missing because of death of the patient, a value of 0 was imputed for all non-observed values in the sensitivity analysis; values that were missing because of any other reason were imputed at every single timepoint (6 months, 12 months, and 24 months after surgery) before calculation of the mean value for every patient across the three measurements. A safety analysis, including frequencies and rates of serious adverse events, was also done

We did all statistical analyses with SAS version 9.4 or higher. The trial was overseen by a data safety monitoring board, who regularly received written safety reports during the course of the trial. To guarantee transparency, ChroPac was registered in advance, ISRCTN38973832.

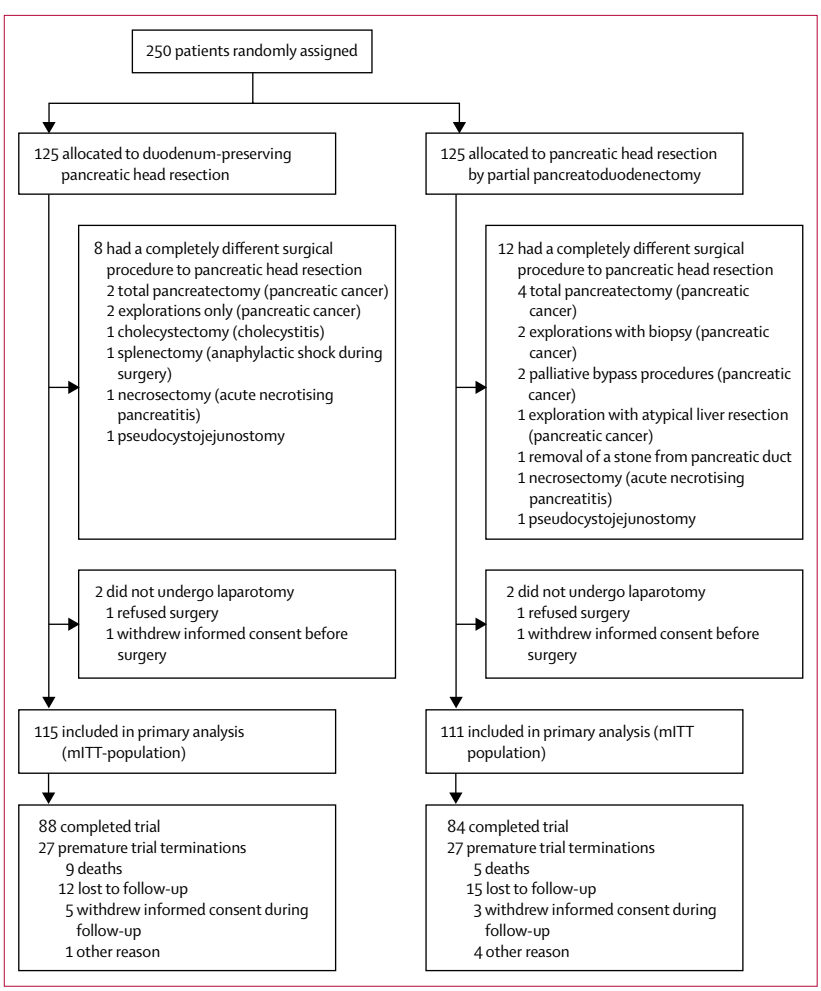

Figure 1: **Trial profile**
mITT=modified intention to treat.

Role of the funding source

ChroPac was an investigator-initiated trial funded by the German Research Foundation. The funder had no role in trial design, data collection, data analysis, data interpretation, or writing of the report. MKD, FJH, and MWB had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

Results

Between Sept 10, 2009, and Sept 3, 2013, 250 patients were randomly assigned before surgery to undergo either pancreatic head resection by partial pancreatoduodenectomy (n=125) or DPPHR (n=125). 14 patients in the partial pancreatoduodenectomy group and ten patients in the DPPHR group were excluded from the primary analysis because they withdrew consent early after randomisation, did not undergo surgery, or did not fulfill inclusion criteria during surgery (ie, a different procedure

to pancreatic head resection was done). Detailed reasons for exclusion are given in figure 1. 226 patients (111 in the partial pancreatoduodenectomy group and 115 in the DPPHR group) were included in the primary analysis. 14 patients assigned to partial pancreatoduodenectomy actually underwent DPPHR (ten underwent the Berne modification and two each underwent the Beger and Frey procedures), and 20 patients assigned to DPPHR underwent partial pancreatoduodenectomy (18 underwent a pylorus-preserving pancreatoduodenectomy and two underwent a classic pancreatoduodenectomy; table 1). For 54 patients, the trial was terminated prematurely during the 24 month trial period for various reasons (figure 1).

Table 1 shows the baseline characteristics of the trial participants. Sex, age, BMI, smoking status, alcohol consumption, and preoperative pain were well balanced between the intervention groups. Indigestion and preoperative weight loss were more frequent in the partial pancreatoduodenectomy group than in the DPPHR group. Less than one-third of all patients presented with pre-existing diabetes, but more than half had exocrine insufficiency before surgery. Of the 111 patients in the partial pancreatoduodenectomy group, 79 (71%) underwent pylorus-preserving pancreatoduodenectomy, 17 (15%) underwent classic pancreatoduodenectomy, and 15 (14%) underwent procedures other than partial pancreatoduodenectomy. Of the 115 patients in the DPPHR group, 55 (48%) underwent the Berne modification, 21 (18%) underwent the Frey modification, 16 (14%) underwent the Beger procedure, and 23 (20%) underwent procedures other than DPPHR (table 1). 11 (5%) of the 226 patients in the mITT population, including eight (7%) patients in the DPPHR group and three (3%) patients in the partial pancreatoduodenectomy group, were diagnosed with pancreatic cancer in the final histological work-up (table 1).

Preoperative medical imaging showed a balanced distribution of pancreatic head enlargement, calcifications, enlargement of the common bile duct or pancreatic duct, duodenal obstruction, and compression of retropancreatic vessels (appendix). More than two-thirds of the patients had undergone at least one (range 1–19) previous endoscopic retrograde cholangiopancreatography: 155 (71%) of 217 patients in the mITT population, including 76 (70%) of 108 patients in the partial pancreatoduodenectomy group and 79 (72%) of 109 patients in the DPPHR group (appendix). Additionally, more than one-third of patients had experienced at least one (1–16) previous stent placement in the pancreatic duct: 85 (38%) of 224 patients in the mITT population, including 36 (33%) of 110 patients in the partial pancreatoduodenectomy group and 49 (43%) of 114 patients in the DPPHR group (appendix).

Quality of life at baseline was not significantly different between the groups (appendix). The primary endpoint (mean EORTC QLQ C-30 physical functioning quality-of-life score within 24 months after surgery) did not differ significantly between the groups: 75·3 (SD 16·4) for the partial pancreatoduodenectomy group compared with 73·0 (16·4) for the DPPHR group (mean difference –2·3, 95% CI –6·6 to 2·0; p=0·284; table 2; appendix). None of the sensitivity analyses changed the

See Online for appendix

	DPPHR (n=115)	Partial pancreatoduodenectomy (n=111)	Total (n=226)
Sex			
Male	95 (83%)	86 (78%)	181 (80%)
Female	20 (17%)	25 (23%)	45 (20%)
Age (years)	52·3 (11·1)	51·5 (10·5)	51·9 (10·8)
Body-mass index (kg/m²)	22·7 (3·7)	22·5 (3·9)	22·6 (3·8)
Smoking status			
Non-smoker	14 (12%)	19 (17%)	33 (15%)
Current smoker	92 (80%)	76 (69%)	168 (74%)
Previous smoker	9 (8%)	16 (14%)	25 (11%)
Alcohol consumption			
Never	17 (15%)	17 (15%)	34 (15%)
Current consumption	30 (26%)	27 (24%)	57 (25%)
Previous consumption	68 (59%)	67 (60%)	135 (60%)
Pain			
No	28 (24%)	20 (18%)	48 (21%)
Yes	87 (76%)	91 (82%)	178 (79%)
Pain duration (months)	42·4 (89·1)	38·1 (48·6)	40·2 (71·2)
Indigestion			
No	78 (68%)	69 (62%)	147 (65%)
Yes	37 (32%)	42 (38%)	79 (35%)
Weight loss*			
No	40 (35%)	26 (24%)	66 (29%)
Yes	75 (65%)	84 (76%)	159 (71%)
Weight loss (kg)	13·5 (12·3)	12·7 (8·6)	13·1 (10·5)
Diabetes			
No	80 (70%)	82 (74%)	162 (72%)
Yes	35 (30%)	29 (26%)	64 (28%)
Exocrine insufficiency			
No	47 (41%)	59 (53%)	106 (47%)
Yes	68 (59%)	52 (47%)	120 (53%)
Procedure done			
Pylorus-preserving pancreatoduodenectomy	18 (16%)	79 (71%)	97 (43%)
Classic pancreatoduodenectomy	2 (2%)	17 (15%)	19 (8%)
Beger	16 (14%)	2 (2%)	18 (8%)
Berne	55 (48%)	10 (9%)	65 (29%)
Frey	21 (18%)	2 (2%)	23 (10%)
Other	3 (3%)†	1 (1%)‡	4 (2%)
Pancreatic ductal adenocarcinoma in final histology			
No	107 (93%)	108 (97%)	215 (95%)
Yes	8 (7%)	3 (3%)	11 (5%)

Data are n (%) or mean (SD). DPPHR=duodenum-preserving pancreatic head resection. *Data for this baseline characteristic were missing for one patient in the partial pancreatoduodenectomy group. †One pylorus-resecting pancreatoduodenectomy, one modified Berne DPPHR with short-longitudinal opening of the pancreatic duct in the neck of the gland, and one modified DPPHR with partial V-shaped resection of the pancreatic body and tail. ‡One modified DPPHR.

Table 1: **Baseline and clinical characteristics of the modified intention-to-treat population**

results for the primary endpoint. For example, the sensitivity analysis in which 0 was imputed for values missing because of death, and values missing because of any other reason were imputed via multiple imputation before calculation of the mean of the primary endpoint across three timepoints after surgery, showed reduced mean quality-of-life scores for both groups, but the outcome was not significantly changed (appendix).

Scores of the global-health-status/quality-of-life scale were significantly improved at 24 months after surgery compared with baseline in both groups (p<0·0001 in both groups). Furthermore, scores of the symptom scales for pain, pancreatic pain, and digestive symptoms and the functional scale for assessment of emotional functioning were significantly improved after surgery in both groups (figure 2). The mean score of the constipation scale at 24 months after surgery was significantly lower for the partial pancreatoduodenectomy group (11·8 [SD 18·6]) than for the DPPHR group (17·2 [18·6]; mean difference 5·4, 95% CI 0·5–10·2; p=0·030; appendix) indicating fewer symptoms of constipation after partial pancreatoduodenectomy. All other subscales did not show any significant differences between the partial

	DPPHR (n=115)	Partial pancreatoduodenectomy (n=111)	Treatment difference (95% CI)	p value
Quality of life (mean physical functioning score)	73·0 (16·4)	75·3 (16·4)	−2·3 (−6·6 to 2·0)*	0·284†
Mortality (with cancer cases excluded)				
6 months	4 (4%) of 107 patients	2 (2%) of 108 patients	2·1 (0·3 to 23·1)‡	0·401
12 months	4 (4%) of 107 patients	2 (2%) of 108 patients	2·1 (0·3 to 23·1)‡	0·401
24 months	7 (7%) of 107 patients	3 (3%) of 108 patients	2·5 (0·5 to 15·0)‡	0·190
Wound infection			1·6 (0·7 to 3·8)‡	0·206
No	92 (82%)	97 (88%)	..	..
Yes	20 (18%)	13 (12%)	..	..
Missing data	3	1	..	..
Pulmonary infection			1·4 (0·4 to 5·8)‡	0·574
No	105 (94%)	105 (95%)	..	..
Yes	7 (6%)	5 (5%)	..	..
Missing data	3	1	..	..
Postoperative pancreatic fistula	10 (9%)	10 (9%)	1·0 (0·3 to 2·7)‡	0·949
Grade A	7 (6%)	3 (3%)	..	..
Grade B	2 (2%)	3 (3%)	..	..
Grade C	1 (1%)	4 (4%)	..	..
Missing data	4	3	..	..
Delayed gastric emptying	10 (9%)	9 (8%)	1·1 (0·4 to 3·2)‡	0·842
Grade A	5 (4%)	6 (5%)	..	..
Grade B	3 (3%)	2 (2%)	..	..
Grade C	2 (2%)	1 (1%)	..	..
Missing data	3	1	..	..
Duration of operation (h)	4·7 (1·3)	5·3 (1·6)	−0·6 (−0·98 to −0·21)*	0·008
Intraoperative blood loss (mL)	560·4 (393·3)	664·7 (760·7)	−104·3 (−289·3 to 80·7)*	0·409
Length of initial hospital stay (days)	18·1 (27·7)	16·0 (14·6)	2·1 (−3·80 to 7·94)*	0·710
Recurrent hospital stay due to chronic pancreatitis				
From discharge until 6 months postoperatively	7 (7%)	7 (7%)	..	..
Missing data	13	8	..	..
6–12 months postoperatively	18 (19%)	3 (3%)	..	..
Missing data	19	18	..	..
12–24 months postoperatively	13 (15%)	4 (5%)	..	..
Missing data	27	27	..	..
During entire follow-up	31 (27%)	12 (11%)	0·3 (0·1 to 0·7)‡	0·002

(Table 2 continues on next page)

	DPPHR (n=115)	Partial pancreatoduodenectomy (n=111)	Treatment difference (95% CI)	p value
(Continued from previous page)				
Length of total hospital stay in 24 months (days)	23·7 (44·8)	17·3 (15·7)	6·4 (–2·5 to 15·3)*	0·056
Reoperation due to chronic pancreatitis				
From discharge until 6 months postoperatively	1 (1%)	2 (2%)	..	..
Missing data	13	8	..	..
6–12 months postoperatively	1 (1%)	0 (0%)	..	..
Missing data	19	18	..	..
12–24 months postoperatively	4 (5%)	0 (0%)	..	..
Missing data	27	27	..	..
During entire follow-up	6 (5%)	2 (2%)	0·3 (0·0 to 1·9)‡	0·165
New onset of diabetes§	3 (4%) of 80 patients	4 (5%) of 82 patients	1·3 (0·2 to 9·3)‡	0·724
New onset of exocrine insufficiency¶	19 (40%) of 47 patients	29 (49%) of 59 patients	1·4 (0·6 to 3·3)‡	0·370

Data are n (%) or mean (SD) unless otherwise specified. DPPHR=duodenum-preserving pancreatic head resection. *Data are mean difference (95% CI). †Analysis of covariance adjusted for age, centre, and European Organisation for Research and Treatment of Cancer QLQ C-30 physical functioning scale before surgery. ‡Data are odds ratio (95% CI). §Cases of pre-existing diabetes excluded. ¶Cases of pre-existing exocrine insufficiency excluded.

Table 2: **Summary results of primary and secondary endpoints**

pancreatoduodenectomy and DPPHR groups during follow-up (appendix).

Mortality (mITT population with cancer cases excluded) at 6 months and 12 months (two [2%] of 108 patients in the partial pancreatoduodenectomy group *vs* four [4%] of 107 patients in the DPPHR group; OR 2·1, 95% CI 0·3–23·1; p=0·401) and 24 months (three [3%] of 108 patients in the partial pancreatoduodenectomy group *vs* seven [7%] of 107 patients in the DPPHR group; 2·5, 0·5–15·0; p=0·190) was similar between the intervention groups. Similarly, morbidity in terms of incidence and severity of surgical site infections (superficial or deep), pulmonary infections, postoperative pancreatic fistula, and delayed gastric emptying was not different between the trial groups (table 2).

The operation time was shorter for DPPHR (4·7 h [SD 1·3]) than for partial pancreatoduodenectomy (5·3 h [1·6]; mean difference –0·6, 95% CI –0·98 to –0·21; p=0·008; table 2). Intraoperative blood loss was not different between the groups. The length of initial hospital stay did not differ between the partial pancreatoduodenectomy group (16·0 days [14·6]) and the DPPHR group (18·1 days [27·7]; 2·1, –3·80 to 7·94; p=0·710; table 2).

Readmission due to chronic pancreatitis occurred more frequently in the DPPHR group (31 [27%] of 115 patients) than in the partial pancreatoduodenectomy group (12 [11%] of 111 patients) during the 24 month follow-up (OR 0·3, 95% CI 0·1–0·7; p=0·002; table 2). However, the difference between the interventions in length of total hospital stay during the 24 month follow-up was not significant (17·3 days [SD 15·7] for the partial pancreatoduodenectomy group *vs* 23·7 days [44·8] for the DPPHR group; mean difference 6·4, 95% CI –2·5 to 15·3; p=0·056). The frequency of reoperation due to chronic pancreatitis during the trial did not differ significantly between the groups (two [2%] of 111 patients in the partial pancreatoduodenectomy group *vs* six [5%] of 115 patients in the DPPHR group; OR 0·3, 95% CI 0·0–1·9; p=0·165; table 2).

The incidence of new-onset diabetes did not differ significantly between the groups, occurring in four (5%) of 82 patients after partial pancreatoduodenectomy and in three (4%) of 80 patients after DPPHR (OR 1·3, 95% CI 0·2–9·3; p=0·724; table 2). Similarly, the incidence of new-onset exocrine insufficiency was not significantly different between the groups, occurring in 29 (49%) of 59 patients after partial pancreatoduodenectomy and in 19 (40%) of 47 patients after DPPHR (1·4, 0·6–3·3; p=0·370; table 2). The course of bodyweight after surgery was similar for both groups (appendix).

At least one serious adverse event occurred in 138 (56%) of the 246 patients included in the safety analysis. The incidence of serious adverse events did not differ between the intervention groups (table 3; appendix). Because all patients who underwent surgical intervention were considered in the safety analysis, patients who underwent completely different operations to pancreatic head resection were also included. More severe serious adverse events were reported for patients who underwent completely different operations to pancreatic head resection—mainly total pancreatoduodenectomy and surgical exploration with biopsy, with or without bypass procedures, after intraoperative findings of pancreatic cancer or necrosectomy in cases of acute necrotising pancreatitis—than for those who underwent partial pancreatoduodenectomy or DPPHR (appendix).

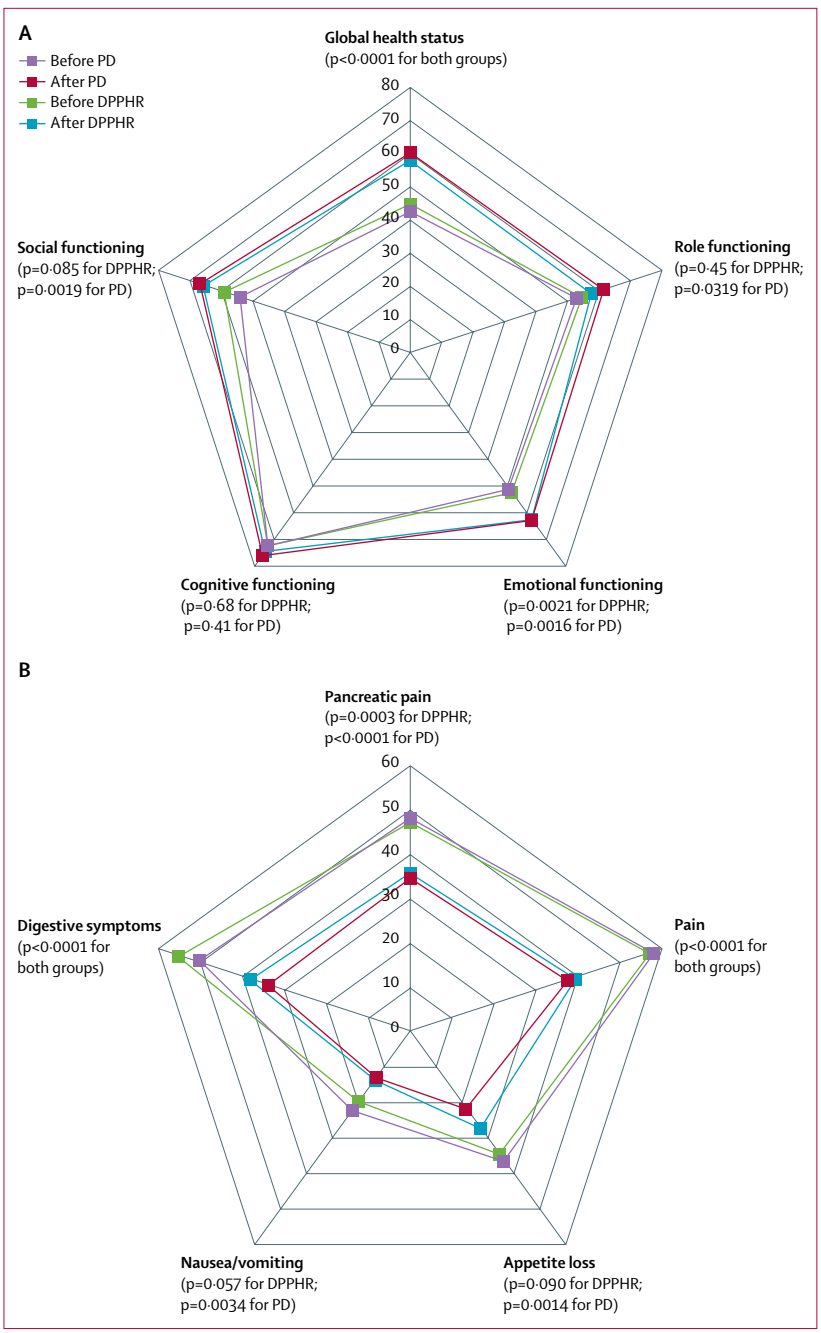

Figure 2: **Radar charts of quality of life**
p values are given for the comparison of the score at baseline to the mean score within 24 months after surgery (calculated with Students *t* test). (A) EORTC QLQ-C30 functional scales (higher scores mean better quality of life). (B) EORTC QLQ-C30 and PAN26 symptom scales (lower scores mean fewer symptoms). PD=partial pancreatoduodenectomy. DPPHR=duodenum-preserving pancreatic head resection. EORTC=European Organisation for Research and Treatment of Cancer.

Discussion

ChroPac is the first randomised controlled trial to compare partial pancreatoduodenectomy with DPPHR for treatment of chronic pancreatitis in a multicentre setting with a pragmatic design. The results showed that DPPHR was not superior to partial pancreatoduodenectomy in terms of the primary endpoint, long-term postoperative quality of life assessed with the EORTC QLQ-C30 and PAN26 questionnaires. The validity of this result was corroborated by several prespecified sensitivity analyses.

Significant improvements in scores of global health status/quality of life and pain scales in both groups showed that both procedures were effective in the treatment of chronic pancreatitis. Four of five previous trials comparing DPPHR with partial pancreatoduodenectomy for chronic pancreatitis provided information about quality of life.[11–13,33] Two of these trials[33,34] found that quality-of-life scores were similar for DPPHR and partial pancreatoduodenectomy, thus agreeing with our results. Farkas and colleagues[12] showed a benefit for quality of life in favour of DPPHR during 1 year follow-up after surgery. The initial report of the trial by Izbicki and colleagues[13] showed superiority for DPPHR over partial pancreatoduodenectomy in terms of quality of life, but the long-term results suggested no significant difference between the two procedures.[35,36] In a quantitative summary, the pooled results of the meta-analysis of trials within this report corroborated the finding that DPPHR and partial pancreatoduodenectomy lead to similar quality of life (appendix). In line with the results of this study, both a 2016 Cochrane meta-analysis[37] and a network meta-analysis[38] of DPPHR versus partial pancreatoduodenectomy for the treatment of chronic pancreatitis concluded that there were no differences in medium-term or long-term quality of life between the two procedures.

Concerning the secondary endpoints, no differences in mortality, morbidity, and new onset of exocrine insufficiency or diabetes were seen between the two interventions. DPPHR resulted in a shorter operating time than partial pancreatoduodenectomy, as shown in previous smaller trials.[12,13,33] However, other secondary outcomes of this trial favoured partial pancreatoduodenectomy, which might influence future clinical decision making. First, patients treated with DPPHR were more frequently readmitted to hospital because of chronic pancreatitis during the 24 month trial. Second, in the partial pancreatoduodenectomy group, no reoperations due to chronic pancreatitis were necessary at more than 6 months after index surgery. Close inspection of the long-term results of previous trials[34–36] comparing partial pancreatoduodenectomy with DPPHR revealed similar patterns, although statistical significance was not attained owing to low sample sizes. Our meta-analysis of reoperations due to chronic pancreatitis in these three trials led to a significant result in favour of partial pancreatoduodenectomy (appendix). Thus, partial pancreatoduodenectomy might be the more definitive treatment for patients with chronic pancreatitis. However, in the interpretation it should be noted that the ChroPac trial was not explicitly powered for these secondary endpoints.

The findings concerning quality of life at baseline in this trial correlated well with those of other studies in

similar patient populations,[39–41] confirming the external validity of our results. Furthermore, the baseline characteristics of the trial population were typical for the intended patient population. Alcohol consumption and smoking were frequent baseline characteristics and were the presumed primary causes of chronic pancreatitis in the trial population. The representative patient population, together with the multicentre, pragmatic trial design, permit wide generalisability of our results.

Although surgical intervention has been shown to be superior to endoscopy for the treatment of chronic pancreatitis,[3–5] and there is increasing evidence that early surgery is effective in reduction of pain and preservation of pancreatic function,[42] most patients treated with surgery have undergone previous endoscopic retrograde cholangiopancreatography, and a large proportion have even undergone pancreatic stenting before being referred for surgical treatment. The results of an ongoing Dutch trial[43] comparing early surgery with a step-up approach might shed more light on the importance of early surgery, with potential implications for clinical practice.

Regarding pancreatic function, DPPHR and partial pancreatoduodenectomy did not differ significantly in terms of new onset of exocrine insufficiency or diabetes. However, some patients with exocrine or endocrine insufficiency before surgery had functional improvement after surgery. Previous trials[33–36] with sufficient follow-up also showed similar incidences for exocrine and endocrine insufficiency after partial pancreatoduodenectomy and DPPHR. This finding might indicate that progressive parenchymal destruction in chronic pancreatitis, rather than an individual surgical procedure, is mainly responsible for the impairment of pancreatic function.

The strength of this trial is its multicentre, randomised, double-blind design, by which systemic bias was reduced to a minimum. Furthermore, clear definition of endpoints, publication of the protocol, and strict assessment assured high-quality data.

Nevertheless, some limitations should be considered when interpreting the results. First, although the secondary endpoints were clearly defined, some of them represented complex conditions (eg, diabetes) that could require more intensive assessment. To investigate those complex conditions in detail, laboratory analyses (eg, glycated haemoglobin) or treatment details (eg, dietary treatment, oral medication, insulin therapy) would be of importance. However, such a detailed analysis would have substantially complicated the conduct of this multinational trial. Therefore, clear and transparent but pragmatic definitions for these complex conditions were used because they only represented secondary endpoints. Hence, the conclusions regarding these outcomes have to be judged with consideration of the applied definitions and that the trial was not powered for these endpoints.

Second, the aggregation of modifications of the two surgical techniques in the comparison groups ruled out discrimination between the individual techniques. This approach might be considered a limitation, given that most centres focus on one individual modification. However, this issue was debated intensely during protocol development and it was decided that, because none of the individual techniques showed clear superiority over the others, the aim of the ChroPac trial would be to provide a pragmatic comparison of two surgical strategies (DPPHR and partial pancreatoduodenectomy). The results of this trial could form the baseline for further refinement of the decision of which of the two strategies to follow in individual cases (a tailored approach).

The incidental detection of pancreatic cancer in 11 (5%) of 226 patients in the mITT population underlines that

	DPPHR (n=109)*	Partial pancreatoduodenectomy (n=111)*
Patients with at least one SAE	70/109 (64%)	61/117 (52%)
Number of documented SAEs	142	109
Maximum intensity		
Mild	42/142 (30%)	26/107 (24%)
Moderate	66/142 (46%)	48/107 (45%)
Severe	34/142 (24%)	33/107 (31%)
Missing data	0	2
Causality with intervention		
Unrelated	53/142 (37%)	48/109 (44%)
Possibly related	53/142 (37%)	34/109 (31%)
Probably related	17/142 (12%)	8/109 (7%)
Definitely related	18/142 (13%)	14/109 (13%)
Not assessable	1/142 (1%)	5/109 (5%)
Outcome		
Ongoing	2/142 (1%)	0/108 (0%)
Recovered completely	110/142 (77%)	85/108 (79%)
Recovered with sequelae	20/142 (14%)	13/108 (12%)
Death	7/142 (5%)	7/108 (6%)
Unknown	3/142 (2%)	3/108 (3%)
Missing data	0	1
SAE categorisation†		
Reoperation	22/142 (15%)	16/109 (15%)
Bleeding	5/142 (3%)	8/109 (7%)
Abscess or fluid collection	6/142 (4%)	3/109 (3%)
Cholangitis	4/142 (3%)	0/109 (0%)
Burst abdomen	4/142 (3%)	1/109 (1%)
Wound infection	5/142 (3%)	3/109 (3%)
Other surgical morbidity	16/142 (11%)	14/109 (13%)
Gastrointestinal	35/142 (24%)	19/109 (17%)
Cardiovascular	5/142 (3%)	8/109 (7%)
Pulmonary	7/142 (5%)	9/109 (8%)
Cancer	8/142 (6%)	4/109 (4%)
Renal	4/142 (3%)	1/109 (1%)
Other general variables	11/142 (8%)	12/109 (11%)
Not assessable	12/142 (8%)	11/109 (10%)

Data are n (%). DPPHR=duodenum-preserving pancreatic head resection. SAE=serious adverse event. *Number of patients differ from the primary analysis because only patients categorised as treated were included in the safety analysis. †Number of categorised SAEs exceeds total number of SAEs because of multiple categorisation in three individuals.

Table 3: **Summary of SAEs**

this disease is not a rare occurrence in this patient population. If pancreatic cancer cannot be ruled out with certainty, partial pancreatoduodenectomy should be done, because it is an adequate oncological treatment and it avoids the need for reoperation. Conversely, in patients with compression or occlusion of the portal vein system, which occurred in 27 (12%) of 224 patients in this trial (appendix), DPPHR should be the procedure of choice to avoid major bleeding and other intraoperative complications. In the remaining cases, surgeons can continue their preferred procedure, because both procedures were similarly effective for treatment of chronic pancreatitis. This trial provides evidence on which to base discussion of the harms and benefits of individual strategies with patients.

In conclusion, both partial pancreatoduodenectomy and DPPHR were effective in the treatment of chronic head pancreatitis, with no difference in quality of life, mortality, and morbidity between the interventions. Although DPPHR offered advantages with regard to operating time, partial pancreatoduodenectomy might be the more definitive treatment because it was associated with fewer readmissions. For further individualisation of the available techniques, surgeons need to learn more about the specific reason for readmission or reoperation after DPPHR due to ongoing or recurrent chronic pancreatitis, such as stenosis of the common bile duct or pancreatic duct. Future trials should aim to identify subgroups of patients, on the basis of preoperative clinical and imaging characteristics, who will benefit specifically from a particular procedure. Pancreatic surgeons should be competent in both DPPHR and partial pancreatoduodenectomy to be able to offer the optimal treatment on an individual patient basis.

Contributors

MKD and MWB conceived and designed the trial, supervised trial conduct, participated in data analysis and interpretation, and prepared and wrote the report. FJH participated in trial design, trial conduct, data analysis and interpretation, and prepared and wrote the report. AU, TH, and CD-H managed the trial and contributed to data interpretation and writing of the manuscript. MD, RG, UAW, RS, H-MH, JW, AK, C-DH, AT, TJW, MB, TBe, TBö, MG, US, FT, ALM, and LS participated in patient recruitment and trial conduct. PK participated in patient recruitment, trial design, and trial conduct. CMH participated in patient recruitment and trial conduct and developed the patient information sheet and consent form for the UK arm of the trial. KT was responsible for onsite monitoring. MK and TBr participated in trial design, data analysis, and data interpretation. All authors have proof-read the manuscript.

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Declaration of interests

We declare no competing interests.

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