Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection in chronic pancreatitis: the multicentre randomised controlled ChroPac trial (ISRCTN38973832)

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**Summary**

**Background**

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

**Methods**

This multicentre, randomised, controlled, parallel-group superiority trial was conducted in 18 European hospitals. Patients with chronic pancreatitis were randomly allocated to DPPHR or PD. The primary endpoint was QoL during 24 months after operation (EORTC QLQ-C30). Secondary endpoints included mortality, morbidity, reoperations, hospital stay, and exocrine and endocrine insufficiency. Assuming a 10% difference in QoL, a total sample size of 200 patients was planned. Analysis was done by intention to treat. Patients and outcome assessors were blinded to group assignment. The trial was registered in advance: ISRCTN38973832.

**Findings**

250 patients were randomised between September 2009 and September 2013, of whom 226 patients (DPPHR n=115; PD n=111) were analysed. There was no difference between groups in QoL during 24 months postoperatively (p=0.282). With regard to the secondary outcome parameters, morbidity and short- and long-term mortality did not differ significantly. Operating time was shorter for DPPHR (p=0.008). DPPHR showed a higher rehospitalisation rate due to chronic pancreatitis (p=0.002). New onset of diabetes mellitus did not differ, but new onset of exocrine insufficiency occurred more frequently after PD (p=0.034).

**Interpretation**

DPPHR and PD result in similar QoL, mortality and morbidity after surgery for chronic pancreatitis. While DPPHR has benefits in terms of operating time and exocrine insufficiency, PD represents the more definitive treatment, as shown by the lower rate of rehospitalisation. Results from single-centre trials demonstrating superiority of DPPHR were not confirmed in the multicentre setting.

**Funding**

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**Introduction**

Chronic pancreatitis (CP) 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 function. The most common form of CP is the calcifying type, characterised by the development of intraductal stones; the predominant causative agent is alcohol.1 The progressive functional impairment can be delayed by surgical decompression of the dilated main pancreatic duct.2 Furthermore, due to the inflammatory enlargement of the pancreatic head a high proportion of patients 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 and/or endoscopic treatment in terms of pain relief, loss of pancreatic function and impairment of quality of life.3-5 Moreover, surgical treatment is highly cost-effective compared with endoscopic treatment.6

There are several surgical treatment options for CP, which can be categorised into drainage procedures and resective procedures. For a long time, pancreatoduodenectomy (PD) was established as the main surgical approach for removal of the pancreatic head in patients with CP and enlargement of the pancreatic head. As a parenchyma-sparing approach, Hans G. Beger developed a technique of duodenum-preserving pancreatic head resection (DPPHR) in the early 1970s.7,8 In the intervening years two modifications of the original Beger DPPHR have been introduced that specifically avoid dissection of the pancreas from the portal and superior mesenteric vein, because this can be especially difficult and a source of 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 consists of 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 also 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 of DPPHR have been compared with PD in several small-scale randomised controlled trials.11-14 The individual trials and meta-analyses thereof have suggested superiority of DPPHR over PD for several short-term outcome parameters, e.g. duration of surgery, blood loss, length of hospital stay, postoperative pancreatic function and quality of life (QoL).15 However, there is substantial uncertainty regarding the robustness of these results owing to the potential sources of bias in small single-centre trials.

The ChroPac trial was designed to compare DPPHR with PD in terms of QoL over a period of 24 months after surgery in pragmatic fashion, including all modifications of DPPHR and PD in the respective groups.

**Methods**

**Trial design**

ChroPac was a randomised controlled trial with a parallel-group superiority design. The trial was conducted in 18 European centres for pancreatic surgery located in Germany (n=16), Slovenia (n=1) and the UK (n=1).

Before inclusion of the first subject, the protocol and additional 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. To guarantee transparency of the trial, ChroPac was registered in advance (ISRCTN38973832) and the trial protocol has been published.16 All steps of the trial were conducted in accordance with the ethical principles set out in the current version of the Declaration of Helsinki17 and the principles of Good Clinical Practice (ICH-GCP E6). The reporting of the trial complies with the recommendations of the CONSORT statement.18

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

**Participants**

Patients scheduled for primary elective surgery for chronic pancreatitis of the pancreatic head at one of the trial centres who possessed the ability to understand the nature and consequences of trial participation were considered eligible for inclusion in the trial. All patients provided written informed consent before inclusion. Participation in any other interventional trial that could potentially interfere with the procedures or outcomes of the ChroPac trial led to exclusion of the patient concerned.

**Randomisation and masking**

A central web-based randomisation process (www.randomizer.at) was used to allocate patients to either PD or DPPHR. To achieve balanced group sizes, block randomisation was performed stratified for each centre. Block sizes were unknown to the clinical trial personnel. The randomisation process was performed at each centre by trial personnel not involved in the treatment or outcome assessment of the participants.

Patients and outcome assessors were blinded to the assigned intervention. The operating surgeon could not be blinded.

**Procedures**

Detailed information on the surgical procedures can be found in the published protocol.16

PD, performed either as pylorus-preserving PD (ppPD) or classical PD (cPD; with distal gastrectomy), was considered the control intervention.

All types and modifications of DPPHR, e.g. Beger’s original procedure and the Frey and Berne modifications, were permissible as experimental intervention.

In a pragmatic approach, the choice of ppPD/cPD 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. Furthermore, operative details were not explicitly specified in the protocol, leaving the surgeons free to perform the procedures according to local standards at each participating centre.

In total, six trial visits took place, including a screening visit and a visit on the day of surgery. Follow-up visits with assessment of the trial outcome parameters took place on the day of discharge and at 6, 12 and 24 months after the index operation. The detailed schedule is provided in tabular form in the protocol publication.16

An Electronic case report form (eCRF) was used for data documentation within the ChroPac trial.

**Outcomes**

The primary endpoint of the ChroPac trial was average QoL in the 24 months after surgery, measured at 6, 12 and 24 months and assessed using the “physical functioning” scale of the EORTC QLQ-C30 questionnaire.

Secondary endpoints included further functional and symptom scales of the EORTC QLQ-C30 as well as PAN-26 questionnaires, mortality, general morbidity (wound infection, pulmonary infection) and pancreas-associated morbidity (postoperative pancreatic fistula, delayed gastric emptying). Furthermore, perioperative measures (duration of surgery, intraoperative blood loss), postoperative hospital stay (index admission, total hospital stay due to chronic pancreatitis during 24 months), readmissions and reoperations due to chronic pancreatitis, weight course and new onset of exocrine or endocrine insufficiency were assessed as secondary outcome parameters. Detailed information, including endpoint definitions, is available in the published protocol.16

Assessment of safety was performed with respect to frequency of serious adverse events of all randomised participants (safety population). For each patient, safety evaluation started on the day of written informed consent and continued until the regular end of the trial at 24 months or until premature trial termination. Serious adverse events were classified by intensity, outcome and whether or not they were caused by the trial intervention. To permit timely evaluation, serious adverse events had to be reported to the principal investigator within 24 h after the investigator at the individual centre became aware of them.

**Statistical analysis**

ChroPac was designed as a superiority trial assuming a mean difference of 10% in the “physical functioning” scale of the EORTC QLQ-C30 questionnaire between the trial groups in favour of DPPHR and a standard deviation of 20%, based on the results of two previously completed randomised controlled trials.12,19 Applying a two-sided Student’s t-test, 86 patients per intervention group would have been required to detect this difference with a two-sided significance level α=5% and a power of 1-β=90%. To allow for drop-outs, withdrawals and losses to follow-up, it was planned to include a total of 200 patients in the trial.

The intention-to-treat principle (ITT) was applied for the primary, confirmatory analysis of the trial.

An analysis of covariance adjusting for age, centre and EORTC QLQ C-30 “physical functioning” scale before surgery was applied for analysis of the primary endpoint. Multiple imputation methods were used to deal with missing data.20

Secondary outcome parameters were analysed by methods of descriptive data analysis21 and presented with appropriate measures of the empirical distribution together with the corresponding p-values derived by the Mann-Whitney U-test for continuous variables and the chi-square test or exact unconditional test for categorical variables.22

Several sensitivity analyses were conducted for different populations (per-protocol population, complete cases), with different imputation methods for missing data, and different statistical techniques considering covariates. Furthermore, a safety analysis including frequencies and rates of serious adverse events in the intervention groups was performed.

All statistical analyses were performed with SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA).

The trial was overseen by a data safety monitoring board (DSMB), which received regularly written safety reports during the course of the trial.

To render the results of the ChroPac trial comparable with existing data, a post-hoc meta-analysis was performed comparing PD with DPPHR considering the endpoints ‘global health status/QoL’, new onset of endocrine and exocrine insufficiency and reoperations due to chronic pancreatitis (Review Manager, Version 5.3, The Cochrane Collaboration).

**Role of funding source**

ChroPac was an investigator-initiated trial funded by the German Research Foundation (DFG; support code DI 1484/2-2). The funder of the trial 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 the data in the trial and bore final responsibility for the decision to submit the manuscript for publication.

**Results**

Between 10 September 2009 and 3 September 2013, 250 patients were randomised to either PD (n=125) or DPPHR (n=125). Fourteen patients of the PD group and ten patients of the DPPHR group were excluded from analysis because the inclusion criteria were not fulfilled intraoperatively, e.g. intraoperative diagnosis of pancreatic cancer instead of chronic pancreatitis with subsequent performance of a completely different operative procedure from the two randomized methods, such as total pancreatoduodenectomy or only biopsy in cases of metastatic cancer. The reasons for exclusion are given in the CONSORT flow diagram (Fig. 1). Finally, 226 patients (PD: n=111; DPPHR: n=115) were included in the ITT analysis. Fourteen patients randomised to PD actually underwent DPPHR (Berne n=10, Beger n=2, Frey n=2), and 20 patients randomised to DPPHR underwent PD (ppPD n=18, cPD n=2) (Table 1). For 55 patients the trial was terminated prematurely during the 24-month trial period (Fig. 1).

Table 1 depicts the baseline characteristics of the trial participants. Gender, age, body mass index, smoking status, alcohol consumption and preoperative pain were well balanced between the two intervention groups. Indigestion and preoperative weight loss were more frequent in the PD group. Less than one third of all patients presented with pre-existing diabetes mellitus (total 64/226 [28·3%], PD 29/111 [26·1%], DPPHR 35/115 [30·4%]), but more than half had exocrine insufficiency preoperatively (total 120/226 [53·1%], PD 52/111 [46·8%], DPPHR 68/115 [59·1%]). In the PD group, 79 of 111 patients (71·2%) underwent ppPD, 17 of 111 (15·3%) underwent cPD and 15 of 111 (13·5%) underwent procedures other than PD. In the DPPHR group, 55 of 115 patients (47·8%) underwent the Berne modification, 21 of 115 (18·3%) underwent the Frey modification, 16 of 115 (13·9%) underwent the Beger procedure, and 23 of 115 (20·0%) underwent procedures other than DPPHR. 11 of the 226 patients (4·9%) in the ITT population, eight in the DPPHR group (7·0%) and three in the PD group (2·7%), were diagnosed with pancreatic cancer in the final histological workup.

Preoperative medical imaging showed balanced distribution of pancreatic head enlargement, calcifications, enlargement of the common bile duct or pancreatic duct, duodenal obstruction, and compression of the retropancreatic vessels (Table 2). More than two thirds of the patients had undergone at least one (range 1 – 19) previous endoscopic retrograde cholangiopancreatography (total 71·4%, PD 70·4%, DPPHR 72·5%) and more than one third had experienced at least one (range 1 – 16) previous stent placement in the pancreatic duct (total 37·9%, PD 32·7%, DPPHR 43·0%).

The primary endpoint QoL, assessed by the mean score of the scale “physical functioning” of the EORTC QLQ-C30 questionnaire at 6, 12 and 24 months after index operation, did not differ significantly between the PD and the DPPHR group (PD 76·1 ± 19·8, DPPHR 72·3 ± 21·1; p = 0·282). None of the sensitivity analyses changed the results for the primary endpoint (data not shown).

‘Global health status/QoL’ showed significant improvement at 24 months after surgery compared with baseline in both groups (p < 0·0001 in both groups). Furthermore, the symptom scales ‘pain’, ‘pancreatic pain’, ‘nausea/vomiting’ and ‘digestive symptoms’ and the functional scales ‘emotional functioning’ and ‘social functioning’ were significantly improved 24 months after surgery in both groups (Fig. 2). No differences between the PD and DPPHR groups were present in any of the QoL items at any time during the follow-up (data not shown).

Mortality (modified ITT population with cancer cases excluded) at 6 & 12 months (total 6/215 [2·8%], PD 2/108 [1·9%], DPPHR 4/107 [3·7%]; p = 0·401), and 24 months (total 10/215 [4·7%], PD 3/108 [2·8%], DPPHR 7/107 [6·5%]; p = 0·190) was comparable between the intervention groups. Similarly, morbidity in terms of surgical site infections (superficial/deep), pulmonary infections, postoperative pancreatic fistula and delayed gastric emptying and their respective grades showed no differences between the trial groups (Table 3).

Operation time was shorter for DPPHR than for PD (total 5 ± 1·5 h, PD 5·3 ± 1·6 h, DPPHR 4·7 ± 1·3 h; p = 0·008). Intraoperative blood loss was not different between the two groups (total 611·0 ± 600·8 ml, PD 664·7 ± 760·7 ml, DPPHR 560 ± 393·3; p = 0·409). The length of the initial hospital stay did not differ between PD and DPPHR (total 17·1 ± 22·2 days, PD 16 ± 14·6 days, DPPHR 18·1 ± 27·7 days; Table 3).

Readmission due to chronic pancreatitis occurred more frequently in the DPPHR group during the 24-month follow-up period (total 43/226 [19·0%], PD 12/111 [10·8%], DPPHR 31/115 [26·96%]; p = 0·002). However, the difference in length of total hospital stay during the 24-month postoperative period did not reach statistical significance (total 20.6 ± 33.8, PD 17·3 ± 15·7 days, DPPHR 23·7 ± 44·8 days; p = 0·056). Frequency of reoperation due to chronic pancreatitis during the trial period did not differ significantly between PD and DPPHR (total 8/226 [3·5%], PD 2/111 [1·8%] vs. DPPHR 6/115 [5·2%]; p = 0·165; Table 4).

New onset of diabetes mellitus did not show differences and occurred in 18 of 111 (16·2 %) patients after PD compared with 14 of 115 (12·2%) after DPPHR (p = 0·383). New onset of exocrine insufficiency was more frequent after PD than after DPPHR (PD 53/111 [47·8%] vs. DPPHR 39/115 [33·9%]; p = 0·034; Table 4). The course of postoperative body weight was similar for both groups (Fig. 3).

At least one serious adverse event occurred in 138 of 246 patients (56.1%). The rate of serious adverse events did not differ between the PD and DPPHR groups (Table 5). Since all randomised patients were considered in the safety analysis, patients that underwent other operations were also included. More severe serious adverse events were reported for those patients with operations other than PD or DPPHR, which were mainly total pancreatoduodenectomy or merely surgical exploration with biopsy or bypass procedures owing to intraoperative findings of pancreatic cancer or necrosectomy in cases of acute pancreatitis.

**Discussion**

ChroPac is the first randomised controlled trial to compare PD with DPPHR for treatment of chronic pancreatitis in a multicentre setting and with a pragmatic design. The results reveal that the two procedures are comparable in terms of the primary endpoint, long-term postoperative QoL as assessed by the EORTC QLQ-C30 and PAN26 questionnaires.

The significant improvements in ‘global health status/QoL’ and pain scales show that both procedures are effective in the treatment of chronic pancreatitis. Four out of five previous trials provided information on QoL.11-13,23 Two of these trials found similar QoL in DPPHR and PD, thus agreeing with our results.23,24 The trial by Farkas et al. showed a benefit in QoL in favour of DPPHR during a follow-up of 1 year after surgery.12 The initial report of the trial by Izbicki et al.13 demonstrated superiority of DPPHR over PD in terms of QoL, but the long-term results revealed no significant difference between the two procedures.25,26 In a quantitative summary, the pooled results of the meta-analysis of RCTs within this report corroborate the finding that DPPHR and PD result in equal QoL (see panel 1).

Concerning the secondary endpoints, there were no differences between DPPHR and PD in terms of mortality and morbidity. DPPHR resulted in lower operating time and fewer cases of new onset of exocrine insufficiency during the 2-year follow-up, as suggested by previous small RCTs.12,13,23 However, other secondary outcome parameters of this trial distinctly favoured PD, which might influence future clinical decision making: First, patients treated with DPPHR were more frequently readmitted to hospital due to chronic pancreatitis during the 24-month trial period. Second, it bears mentioning that in the PD group no reoperations due to chronic pancreatitis were necessary more than 6 months after index surgery. Close inspection of the long-term results of previous trials comparing PD and DPPHR reveals similar patterns, although statistical significance was not attained owing to low sample sizes.24-26 Meta-analysis of reoperations due to chronic pancreatitis in these three trials combined led to a significant result in favour of PD (panel 1; Fig. 4). Thus, PD seems to be the more definitive treatment for patients with chronic pancreatitis.

The findings concerning QoL at baseline in this trial correlate well with those of other studies in similar patient populations; this confirms the external validity of the results.27-29 Furthermore, the baseline parameters of the trial population are typical for the intended patient population. Interestingly, even though surgical intervention has been shown to be superior to endoscopic treatment in chronic pancreatitis, it is still the case that a majority of patients treated by surgery have undergone previous ERCP and a large proportion have even undergone pancreatic stenting before being referred for surgical treatment. Despite the increasing evidence that early surgery in chronic pancreatitis is effective in reducing pain and preserving pancreatic function, this demonstrates that most patients are still not managed in this way.30 A Dutch randomised controlled trial comparing early surgery with a step-up approach is currently in progress, and the results may shed more light on this matter with potential implications for current clinical practice.31

Regarding pancreatic function, DPPHR results in fewer cases of new-onset exocrine insufficiency. For new onset of diabetes mellitus, however, there was no statistically significant difference between DPPHR and PD. Former trials with sufficient follow-up showed similar rates of exocrine and endocrine insufficiency after PD and DPPHR (see panel 1). This may indicate that the progressive parenchymal destruction in chronic pancreatitis, rather than an individual surgical procedure, is mainly responsible for the impairment of pancreatic function.

The strength of the current 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 assure high data quality.

Nevertheless, some limitations should be kept in mind when interpreting the results. Hence, the aggregation of modifications of the PD and DPPHR techniques in the comparison groups rules out discrimination of the individual techniques. This may be a drawback, given that most centres focus on one individual modification. However, this issue was debated intensely during protocol development. Since none of the techniques in use showed clear superiority over the others, the aim of the ChroPac trial was to provide a pragmatic comparison of two surgical strategies. This could form the baseline for a further refinement of the decision which of the two strategies to follow in individual cases (tailored approach). The incidental detection of pancreatic cancer in the ChroPac trial of 6.9% (4.9% in ITT population with pancreatic cancer in final histology and at least 6 of 20 patients that were excluded because total pancreatoduodenectomy or biopsy/bypass procedures were performed due to intraoperative finding of pancreatic cancer) underlines that this situation is not a rare event in this patient collective. If pancreatic cancer cannot be ruled out with certainty, PD should be performed, as it represents adequate oncological treatment and avoids the need for reoperation. On the other hand, in patients with compression or occlusion of the portal vein system — 12.1% of the trial cohort — DPPHR should be the procedure of choice to avoid major bleeding and other intraoperative complications. In the remaining cases, surgeons can stick with their preferred procedure, since PD and DPPHR are similarly effective means of treating chronic pancreatitis. Furthermore, ChroPac provides trustworthy evidence on which to base discussion of the harms and benefits of individual strategies with patients.

In conclusion, PD and DPPHR are both effective in the treatment of chronic head pancreatitis, resulting in similar QoL with comparable mortality and morbidity. While DPPHR offers advantages with regard to operating time and new onset of exocrine insufficiency, PD seems to be the more definitive treatment, resulting in fewer readmissions and in the meta-analysis even less reoperations due to chronic pancreatitis in the long term. Pancreatic surgeons should be competent in both DPPHR and PD to be able to offer the optimal treatment to all individual patients. Future trials should aim at identifying subgroups of patients, based on preoperative clinical and imaging characteristics that will profit specifically from particular procedures.

**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 CDH carried out trial management and contributed to data interpretation, proof reading and writing. MD, RG, UW, RS, H-MH, JW, AK, C-DH, AT, CH, TJW, MB, KTB, TB, MG, US, FT, LS, and JW participated in patient recruitment. PK participated in patient recruitment and trial design. KT was responsible for onsite monitoring. MK and TB participated in trial design, data analysis and data interpretation.

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**Conflict of interest**

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All authors declare that they have no conflicts of interest in relation to this trial. None of the authors has had any financial and personal relationships with funding bodies or any other people or organisations that could inappropriately influence their work within this project.

**Investigators**

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**Legends of Figures**

Figure 1 Trial profile (CONSORT)

Abbreviations: ITT = intention-to-treat analysis

Figure 2 Radar charts of QoL: (a) functional scales; (b) symptom scales

Abbreviations: PD = partial pancreatoduodenectomy; DPPHR = duodenum-preserving pancreatic head resection;

p-values given for the comparison of score at baseline to score at 24 months after surgery (Students t-test)

Figure 3 Weight course

Abbreviations: DPPHR = duodenum-preserving pancreatic head resection; PD = partial pancreatoduodenectomy

Time point ‘0’ is weight at screening visit (preoperatively).

Figure 4 Meta-analysis of randomised trials comparing PD with DPPHR in the treatment of chronic pancreatitis: (a) Global health status/QoL; (b) reoperations due to chronic pancreatitis

Abbreviations: PD = partial pancreatoduodenectomy; DPPHR = duodenum-preserving pancreatic head resection; SD = standard deviation; IV = inverse variance method; CI = confidence interval; M-H = Mantel-Haenszel method

**Panels**

**Panel 2:** Research in context

*Systematic review*

PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (Central) were searched to identify randomised controlled trials comparing PD with DPPHR for the treatment of chronic pancreatitis. The following search strategy was used for PubMed, with similar strategies for the other databases: “chronic pancreatitis AND (pancreaticoduodenectomy OR pancreatoduodenectomy OR duodenum-preserving OR duodenum preserving OR pancreatic head resection OR pancreatectomy) AND random\*”.

The last search was conducted on 5 February 2017. Reference lists of the retrieved publications were searched for additional publications. No restrictions were applied to language or date of publication. Only fully published studies were considered, no conference abstracts or incomplete reports were assessed. Meta-analyses were performed for the endpoints ‘global health status/QoL’ of the EORTC QLQ-C30, endocrine/exocrine insufficiency and reoperation due to chronic pancreatitis (> 6 months postoperatively). Odds ratios pooled by the Mantel-Haenszel random effects model were calculated for binary outcomes, while the inverse variance method standardised mean difference was calculated for continuous outcomes (Review Manager Version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

*Interpretation*

Apart from ChroPac, five trials including data on a total of 255 patients (127 PD, 128 DPPHR) were identified by the literature search and included in the systematic review/meta-analysis.11-14,23 Including the current results, a total of 481 patients (238 PD, 243 DPPHR) were meta-analysed. All trials except ChroPac were single-centre studies with no blinding. Four trials compared a specific type of DPPHR with PD (two Beger vs. PD; one Frey vs. PD; one Berne vs. PD),11-14 whereas the trial by Keck et al. compared DPPHR (either Beger or Frey) with PD.23 Two trials showed a significant benefit of DPPHR in terms of QoL during the early postoperative period.12,13 However, the long-term results (≥ 24 months) of one of those25,26 and two further trials23,24 showed comparable results for all domains of QoL. One trial did not report any measure of QoL.14

The pooled results of the trials before ChroPac showed no differences in QoL, new onset of endocrine or exocrine insufficiency, or reoperation due to chronic pancreatitis. After inclusion of the ChroPac results, there were still no differences in QoL and new onset of endocrine or exocrine insufficiency but the results were more precise. The meta-analysis of reoperation due to chronic pancreatitis shifted to a significant difference in favour of PD after inclusion of the ChroPac results (OR 5·21, 95% CI 1·09 – 24·94; p=0·04; Fig. 4).

The findings of some previous small single-centre trials in favour of DPPHR concerning QoL and pancreatic function did not hold true in the multicentre setting. Furthermore, ChroPac revealed some interesting new findings concerning readmission and late reoperation due to chronic pancreatitis, suggesting that PD is the more definitive treatment strategy for chronic pancreatitis.

**Tables**

Table 1 Baseline/clinical characteristics of the intention-to-treat population

|  |  |  |  |
| --- | --- | --- | --- |
| **N (%) or mean (SD)** | **DPPHR (N=115)** | **PD** **(N=111)** | **Total** **(N=226)** |
| **Gender** |  |  |  |
| Male | 95 (82.6%) | 86 (77.5%) | 181 (80.1%) |
| Female | 20 (17.4%) | 25 (22.5%) | 45 (19.9%) |
|  |  |  |  |
| **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 (12.2%) | 19 (17.1%) | 33 (14.6%) |
| Current smoker | 92 (80.0%) | 76 (68.5%) | 168 (74.3%) |
| Previous smoker | 9 (7.8%) | 16 (14.4%) | 25 (11.1%) |
|  |  |  |  |
| **Alcohol consumption** |  |  |  |
| Never | 17 (14.8%) | 17 (15.3%) | 34 (15.0%) |
| Current consumption  | 30 (26.1%) | 27 (24.3%) | 57 (25.2%) |
| Previous consumption | 68 (59.1%) | 67 (60.4%) | 135 (59.7%) |
|  |  |  |  |
| **Pain** |  |  |  |
| No | 28 (24.3%) | 20 (18.0%) | 48 (21.2%) |
| Yes | 87 (75.7%) | 91 (82.0%) | 178 (78.8%) |
|  |  |  |  |
| **Pain duration (months)** | 42.4 (89.1) | 38.1 (48.6) | 40.2 (71.2) |
|  |  |  |  |
| **Indigestion** |  |  |  |
| No | 78 (67.8%) | 69 (62.2%) | 147 (65.0%) |
| Yes | 37 (32.2%) | 42 (37.8%) | 79 (35.0%) |
|  |  |  |  |
| **Weight loss** |  |  |  |
| No | 40 (34.8%) | 26 (23.6%) | 66 (29.3%) |
| Yes | 75 (65.2%) | 84 (76.4%) | 159 (70.7%) |
|  |  |  |  |
| **Weight loss (kg)** | 13.5 (12.3) | 12.7 (8.6) | 13.1 (10.5) |
|  |  |  |  |
| **Diabetes mellitus** |  |  |  |
| No | 80 (69.6%) | 82 (73.9%) | 162 (71.7%) |
| Yes | 35 (30.4%) | 29 (26.1%) | 64 (28.3%) |
|  |  |  |  |
| **Exocrine insufficiency** |  |  |  |
| No | 47 (40.9%) | 59 (53.2%) | 106 (46.9%) |
| Yes | 68 (59.1%) | 52 (46.8%) | 120 (53.1%) |
|  |  |  |  |
| **Procedure performed**  |  |  |  |
| Pylorus-preserving Whipple | 18 (15.7%) | 79 (71.2%) | 97 (42.9%) |
| Classical Whipple | 2 (1.7%) | 17 (15.3%) | 19 (8.4%) |
| Beger | 16 (13.9%) | 2 (1.8%) | 18 (7.9%) |
| Berne | 55 (47.8%) | 10 (9.0%) | 65 (28.8%) |
| Frey | 21 (18.3%) | 2 (1.8%) | 23 (10.2%) |
| Other | 3 (2.6%)# | 1 (0.9%)\* | 4 (1.8%) |
|  |  |  |  |
| **PDAC in final histology** |  |  |  |
| No | 107 (93.0%) | 108 (97.3%) | 215 (95.1%) |
| Yes | 8 (7.0%) | 3 (2.7%) | 11 (4.9% |
|  |  |  |  |

Abbreviations: DPPHR = duodenum-preserving pancreatic head resection; PD = pancreatoduodenectomy; PDAC = pancreatic ductal adenocarcinoma; # one pylorus-resecting Whipple, 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 2 Imaging techniques, findings and endoscopic data

|  |  |  |  |
| --- | --- | --- | --- |
| **N (%) or mean (SD)** | **DPPHR (N=115)** | **PD** **(N=111)** | **Total** **(N=226)** |
| **CT scan** |  |  |  |
| No | 11 (9.6%) | 14 (12.6%) | 25 (11.1%) |
| Yes | 104 (90.4%) | 97 (87.4%) | 201 (88.9%) |
|  |  |  |  |
| **MRI** |  |  |  |
| No | 58 (50.4%) | 56 (50.5%) | 114 (50.4%) |
| Yes | 57 (49.6%) | 55 (49.5%) | 112 (49.6%) |
|  |  |  |  |
| **Enlargement of pancreatic head** |  |  |  |
| No | 33 (28.7%) | 24 (21.6%) | 57 (25.2%) |
| Yes | 82 (71.3%) | 87 (78.4%) | 169 (74.8%) |
|  |  |  |  |
| **Pancreatic calcifications** |  |  |  |
| No | 39 (34.2%) | 33 (29.7%) | 72 (32.0%) |
| Yes | 75 (65.8%) | 78 (70.3%) | 153 (68.0%) |
| Missing data | 1 | 0 | 1 |
|  |  |  |  |
| **Enlargement of bile duct** |  |  |  |
| No | 72 (63.7%) | 61 (55.5%) | 133 (59.6%) |
| Yes | 41 (36.3%) | 49 (44.5%) | 90 (40.4%) |
| Missing data | 2 | 1 | 3 |
|  |  |  |  |
| **Enlargement of pancreatic duct** |  |  |  |
| No | 32 (27.8%) | 24 (21.6%) | 56 (24.8%) |
| Yes | 83 (72.2%) | 87 (78.4%) | 170 (75.2%) |
|  |  |  |  |
| **Compression of retropancreatic vessels** |  |  |  |
| No | 98 (85.2%) | 99 (90.8%) | 197 (87.9%) |
| Yes | 17 (14.8%) | 10 (9.2%) | 27 (12.1%) |
| Missing data | 0 | 2 | 2 |
|  |  |  |  |
| **Duodenal obstruction** |  |  |  |
| No | 98 (86.0%) | 93 (86.1%) | 191 (86.0%) |
| Yes | 16 (14.0%) | 15 (13.9%) | 31 (14.0%) |
| Missing data | 1 | 3 | 4 |
|  |  |  |  |
| **Previous ERCP (frequency)** |  |  |  |
| None | 30 (27.5%) | 32 (29.6%) | 62 (28.6%) |
| 1 - 5 | 69 (63.3%) | 67 (62.0%) | 136 (62.7%) |
| 6 - 10 | 8 (7.3%) | 8 (7.4%) | 16 (7.4%) |
| > 10 | 2 (1.8%) | 1 (0.9%) | 3 (1.4%) |
| Missing data | 6 | 3 | 9 |
|  |  |  |  |
| **Previous pancreatic stent implantation (frequency)** |  |  |  |
| None | 65 (57.0%) | 74 (67.3%) | 139 (62.1%) |
| 1 - 5 | 42 (36.8%) | 33 (30.0%) | 75 (33.5%) |
| 6 - 10 | 5 (4.4%) | 3 (2.7%) | 8 (3.6%) |
| > 10 | 2 (1.8%) | 0 (0%) | 2 (0.9%) |
| Missing data | 1 | 1 | 2 |
|  |  |  |  |

Abbreviations: DPPHR, duodenum-preserving pancreatic head resection; PD, pancreatoduodenectomy

Table 3 Primary and secondary endpoints

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **N% or mean (SD)** | **DPPHR (N=115)** | **PD** **(N=111)** | **Total** **(N=226)** | **p** |
| **QoL (mean physical functioning)** | 72.3 (21.1) | 76.1 (19.8) | 74.2 (20.5) | **0.2821** |
|  |  |  |  |  |
| **Mortality with cancer cases excluded** |  |  |  |  |
| 6 months | 4/107 (3.7%) | 2/108 (1.9%) | 6/215 (2.8%) | 0.4012 |
| 12 months | 4/107 (3.7%) | 2/108 (1.9%) | 6/215 (2.8%) | 0.4012 |
| 24 months | 7/107 (6.5%) | 3/108 (2.8%) | 10/215 (4.7%) | 0.1902 |
|  |  |  |  |  |
| **Wound infection** |  |  |  |  |
| No | 92 (82.1%) | 97 (88.2%) | 189 (85.1%) | 0.2063 |
| Yes | 20 (17.9%) | 13 (11.8%) | 33 (14.9%) |  |
| Missing data | 3 | 1 | 4 |  |
|  |  |  |  |  |
| **Pulmonary infection** |  |  |  |  |
| No | 105 (93.8%) | 105 (95.5%) | 210 (94.6%) | 0.5743 |
| Yes | 7 (6.3)%) | 5 (4.5%) | 12 (5.4%) |  |
| Missing data | 3 | 1 | 4 |  |
|  |  |  |  |  |
| **POPF** | 10 (9.0%) | 10 (9.3%) | 20 (9.1%) | 0.9493 |
| Grade A | 7 (6.3%) | 3 (2.8%) | 10 (4.6%) |  |
| Grade B | 2 (1.8%) | 3 (2.8%) | 5 (2.3%) |  |
| Grade C | 1 (0.9%) | 4 (3.7%) | 5 (2.3%) |  |
| Missing data | 4 | 3 | 7 |  |
|  |  |  |  |  |
| **DGE** | 10 (8.9%) | 9 (8.2%) | 19 (8.6%) | 0.8423 |
| Grade A | 5 (4.5%) | 6 (5.5%) | 11 (5.0%) |  |
| Grade B | 3 (2.7%) | 2 (1.8%) | 5 (2.3%) |  |
| Grade C | 2 (1.8%) | 1 (0.9%) | 3 (1.4%) |  |
| Missing data | 3 | 1 | 4 |  |
|  |  |  |  |  |
| **Duration of operation (h)** | 4.7 (1.3) | 5.3 (1.6) | 5.0 (1.5) | **0.0084** |
|  |  |  |  |  |
| **Intraoperative blood loss (ml)** | 560.4 (393.3) | 664.7 (760.7) | 611.0 (600.8) | 0.4094 |
|  |  |  |  |  |
| **Length of initial hospital stay (days)** | 18.1 (27.7) | 16.0 (14.6) | 17.1 (22.2) | 0.7104 |
|  |  |  |  |  |
|  |  |  |  |  |

Abbreviations: DGE, delayed gastric emptying; DPPHR, duodenum-preserving pancreatic head resection; PD, pancreatoduodenectomy; POPF, postoperative pancreatic fistula; QoL, quality of life

1: analysis of covariance adjusting for age, centre, and EORTC QLQ C-30 “physical functioning” scale before surgery; 2: exact unconditional test; 3: chi-square test; 4: Mann-Whitney U-test

Table 4. Long-term secondary endpoints

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **N% or mean (SD)** | **DPPHR (N=115)** | **PD** **(N=111)** | **Total** **(N=226)** | **p** |
| **Recurrent hospital stay due to CP** |  |  |  |  |
| From discharge until 6 months postop. | 7 (6.9%) | 7 (6.8%) | 14 (6.8%) |  |
| Missing data | 13 | 8 | 21 |  |
|  |  |  |  |  |
| 6 – 12 months postop. | 18 (18.8%) | 3 (3.2%) | 21 (11.1%) |  |
| Missing data | 19 | 18 | 37 |  |
|  |  |  |  |  |
| 12 – 24 months postop. | 13 (14.8%) | 4 (4.8%) | 17 (9.9%) |  |
| Missing data | 27 | 27 | 54 |  |
|  |  |  |  |  |
| During whole FU | 31 (27.0%) | 12 (10.8%) | 43 (19.0%) | **0.0021** |
|  |  |  |  |  |
| **Length of total hospital stay during 24 months (days)** | 23.7 (44.8) | 17.3 (15.7) | 20.6 (33.8) | 0.0562 |
|  |  |  |  |  |
| **Reoperation due to CP** |  |  |  |  |
| From discharge until 6 months postop. | 1 (1.0%) | 2 (1.9%) | 3 (1.5%) |  |
| Missing data | 13 | 8 | 21 |  |
|  |  |  |  |  |
| 6 – 12 months postop. | 1 (1.0%) | 0 (0%) | 1 (0.5%) |  |
| Missing data | 19 | 18 | 37 |  |
|  |  |  |  |  |
| 12 – 24 months postop. | 4 (4.5%) | 0 (0%) | 4 (2.3%) |  |
| Missing data | 27 | 27 | 54 |  |
|  |  |  |  |  |
| During whole FU | 6 (5.2%) | 2 (1.8%) | 8 (3.5%) | 0.1651 |
|  |  |  |  |  |
| **New onset of diabetes mellitus** | 14 (12.2%) | 18 (16.2%) | 32 (14.2%) | 0.3841 |
|  |  |  |  |  |
| **New onset of exocrine insufficiency** | 39 (33.9%) | 53 (47.8%) | 92 (40.7%) | 0.0341 |
|  |  |  |  |  |

Abbreviations: CP, chronic pancreatitis; DPPHR, duodenum-preserving pancreatic head resection; FU, follow-up; PD, pancreatoduodenectomy; postop., postoperatively

1: chi-square test; 2: Mann-Whitney U-test

Table 5 Serious adverse events reported

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Other OP****N=20\*** | **DPPHRN=109\*** | **PDN=117\*** | **TotalN=246** |
| **Patients with at least 1 SAE** | 7 (35.0%) | 70 (64.2%) | 61 (52.1%) | 138 (56.1%) |
|  |  |  |  |  |
| **No. of documented SAEs** | 13 | 142 | 109 | 264 |
|  |  |  |  |  |
| **Maximum intensity** |  |  |  |  |
|  Mild | 1 (7.7%) | 42 (26.9%) | 26 (24.3%) | 69 (26.3%) |
|  Moderate | 4 (30.8%) | 66 (46.5%) | 48 (44.9%) | 118 (45.0%) |
|  Severe | 8 (61.5%) | 34 (23.9%) | 33 (30.8%) | 75 (28.6%) |
|  Missing data | 0 | 0 | 2 | 2 |
|  |  |  |  |  |
| **Causality with intervention** |  |  |  |  |
|  Unrelated | 10 (76.9%) | 53 (37.3%) | 48 (44.0%) | 111 (42.0%) |
|  Possibly related | 2 (15.4%) | 53 (37.3%) | 34 (31.2%) | 89 (33.7%) |
|  Probably related | 0 (0.0%) | 17 (12.0%) | 8 (7.3%) | 25 (9.5%) |
|  Definitely related | 0 (0.0%) | 18 (12.7%) | 14 (12.8%) | 32 (12.1%) |
|  Not assessable | 1 (7.7%) | 1 (0.7%) | 5 (4.6%) | 7 (2.7%) |
|  |  |  |  |  |
| **Outcome** |  |  |  |  |
|  Ongoing | 0 (0.0%) | 2 (1.4%) | 0 (0.0%) | 2 (0.8%) |
|  Recovered completely | 6 (46.2%) | 110 (77.5%) | 85 (78.7%) | 201 (76.4%) |
|  Recovered with sequelae | 1 (7.7%) | 20 (14.1%) | 13 (12.0%) | 34 (12.9%) |
|  Death | 3 (23.1%) | 7 (4.9%) | 7 (6.5%) | 17 (6.5%) |
|  Unknown | 3 (23.1%) | 3 (2.1%) | 3 (2.8%) | 9 (3.4%) |
|  Missing data | 0 | 0 | 1 | 1 |
|  |  |  |  |  |
| **SAE categorisation** |  |  |  |  |
|  Reoperation | 2 (15.4%) | 22 (15.3%) | 16 (14.7%) | 40 (15.0%) |
|  Bleeding | 0 (0.0%) | 5 (3.5%) | 8 (7.3%) | 13 (4.9%) |
|  Abscess/fluid collection | 0 (0.0%) | 6 (4.2%) | 3 (2.8%) | 9 (3.4%) |
|  Cholangitis | 0 (0.0%) | 4 (2.8%) | 0 (0.0%) | 4 (1.5%) |
|  Burst abdomen | 0 (0.0%) | 4 (2.8%) | 1 (0.9%) | 5 (1.9%) |
|  Wound infection | 0 (0.0%) | 5 (3.5%) | 3 (2.8%) | 8 (3.0%) |
|  Other surgical morbidity | 1 (7.7%) | 16 (11.1%) | 14 (12.8%) | 31 (11.7%) |
|  Gastrointestinal | 3 (23.1%) | 35 (24.3%) | 19 (17.4%) | 57 (21.4%) |
|  Cardiovascular | 0 (0.0%) | 5 (3.5%) | 8 (7.3%) | 13 (4.9%) |
|  Pulmonary | 0 (0.0%) | 7 (4.9%) | 9 (8.3%) | 16 (6.0%) |
|  Cancer | 7 (53.8%) | 8 (5.6%) | 4 (3.7%) | 19 (7.1%) |
|  Renal | 0 (0.0%) | 4 (2.8%) | 1 (0.9%) | 5 (1.9%) |
|  Other general variables | 0 (0.0%) | 11 (7.6%) | 12 (11.0%) | 23 (8.6%) |
|  Not assessable | 0 (0.0%) | 12 (8.3%) | 11 (10.1%) | 23 (8.6%) |

Number of categorised SAEs exceeds total number of SAEs because of multiple categorisation in three individuals.

\* = patients analysed as treated;

Abbreviations: DPPHR, duodenum-preserving pancreatic head resection; PD, pancreatoduodenectomy; OP, operation; SAE, serious adverse event