Chronic pancreatitis is a common inflammatory disease with a prevalence of 26.4 cases per 100,000 population. It is characterized by the progressive fibrosis of pancreatic parenchyma. Alcohol consumption is the leading cause of CP in Western countries (70% to 90%), followed by biliary lithiasis, autoimmune or individual genetic predisposition, and anatomic variants, such as pancreas divisum.

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Chronic pancreatitis has an enormous personal and socioeconomic impact; the annual treatment costs are approximately $17,000 per patient and, compared with a population without CP, life expectancy is shortened by 10 to 20 years and mortality is increased 3.6-fold. The principal symptom is chronic pain resulting in reduced quality of life and inability to work. Despite improvements in conservative, interventional, and surgical procedures, the treatment of CP remains challenging.

Because randomized controlled trials (RCTs) have shown that surgery is superior to endoscopic treatment, there is no doubt as to the need for surgical intervention in patients with CP. A wide variety of surgical interventions has been used in CP, ranging from simple drainage procedures to extensive resections, especially pancreatectoduodenectomy. However, it has been shown that simple drainage procedures do not ensure sufficient pain relief in...
patients with enlargement of the pancreatic head. Therefore, resection of the pancreatic head should be a central feature of any surgical procedure. On the other hand, the major disadvantage of pancreaticoduodenectomy is that surrounding nondiseased organs, such as the duodenum and the distal common bile duct, are sacrificed, along with loss of continuity of the alimentary tract. Because of the complexity of the resection and reconstruction, the operation is technically demanding.

Duodenum-preserving pancreatic head resections (DPPHRs) combine the advantages of both procedures: the “pacemaker” of the disease, the pancreatic head is subtotally resected and the continuity of the alimentary tract is preserved.12 Duodenum-preserving resections were found to be superior to Whipple procedures at short-term follow-up in RCTs,14,15 and these organ-sparing procedures have gained wide acceptance.

This study was conducted to evaluate for the first time the long-term (ie, 16-year) outcomes of an RCT comparing 2 different methods of duodenum-preserving resection of the pancreatic head, the Beger and the Frey procedures. The analysis is focused on the long-term results with regard to survival, endocrine and exocrine function, pain control, and quality of life. In a recently published long-term follow-up, significantly lower long-term mortality was found after DPPHR compared with pancreaticoduodenectomy.16

METHODS

The data presented are the results of a 16-year long-term follow-up of a closed RCT that was approved by the Ethics and Research Committee of the Hamburg Medical Association.17,18

Patients

The design of the randomized trial, the inclusion and exclusion criteria, as well as patient assessment, treatment assignment, technical aspects of the operative procedures, in-hospital morbidity and mortality, and early postoperative results, are reported elsewhere, as are data of the 8-year follow-up.17,18

Briefly, inclusion criteria were as follows: an inflammatory mass in the head of the pancreas of >35 mm in diameter; severe recurrent pain attacks (at least 1 pain attack per month requiring opiates); history of pain attacks for at least 1 year; or coexisting complications from adjacent organs.

Disease-related exclusion criteria were CP without involvement of the pancreatic head, small-duct disease, pseudocysts without duct pathology, and portal vein thrombosis. Patient-related exclusion criteria were detection of a malignant pancreatic tumor, coexisting malignancy of other organs, or myocardial infarction within 6 months.

Preoperatively, all patients were seen by a panel of gastroenterologists and surgeons who decided on the indication for surgery.

The primary end points of the study were pain control and improvement of quality of life. Quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire,17,19 and an additional module of 20 specific items incorporating a disease-specific symptom scale, a Treatment Strain scale, and an Overall Hope and Confidence scale. This scoring system has previously been validated for patients with CP.20 Pain was assessed using the validated Izbicki pain score (Table 1), which included the following components: frequency of pain attacks, a visual analogue scale of pain, analgesic medication used, and inability to work.18,20 Secondary outcomes were definitive control of complications arising from adjacent organs, mortality and morbidity rates, exocrine and endocrine pancreatic function, and occupational rehabilitation.21

A total of 80 patients were randomized, but 6 patients had to be excluded because of intraoperative detection of a pancreatic adenocarcinoma in frozen section. Therefore,
74 patients were included in this trial (Frey procedure, \( n = 36 \); Beger procedure, \( n = 38 \)) (Fig. 1). The 2 groups of patients were comparable in terms of incidence of complications from adjacent organs, pancreatic morphology, and clinical features.\(^\text{17,18}\)

After short-term follow-up and reassessment after 8 years, all patients were reassessed for the trial after a median of 16 years postoperatively by investigators who were unaware of group allocation. Patients were contacted by mail to fill out the quality of life questionnaire and the pain score forms. For each patient who did not answer by mail, the family practitioner and the local government administration were contacted to ascertain whether the patient had died. Patients whose data could not be acquired by these methods were declared to be lost to follow-up.

In addition, patients were asked to report to our outpatient clinic or their general practitioner for the assessment of exocrine pancreatic function and endocrine function as described elsewhere.\(^\text{22,23}\)

**Surgical procedures**

The procedures have been described elsewhere.\(^\text{10,24}\) Basically, the Beger operation included a subtotal resection of the pancreatic head after transection of the pancreas above the portomesenteric axis. The reconstruction was performed with one Roux-en-Y loop with an end to end pancreaticojejunostomy and another side to side anastomosis between the resection cavity in the pancreatic head and the same jejunal loop.\(^\text{24}\)

The Frey procedures included a limited excision of the pancreatic head and drainage of the main pancreatic duct by longitudinal pancreaticojejunostomy of the body and tail of the pancreas in a manner similar to the Partington-Rochelle procedure.\(^\text{10}\)

In both procedures, the gastroduodenal and the bilioenteric passage remained intact.

**Statistical analysis**

SPSS software, version 13.0 (SPSS Inc) was used for statistical analysis. Quality of life scores, including function and symptom scales and items as well as pain scores, were evaluated using the Mann-Whitney U test. Survival curves were plotted using the Kaplan-Meier method and survival data were analyzed using the log-rank test. Categorical data were compared using chi-square test. Statistical analysis was performed on an
intention-to-treat basis. Descriptive analysis is expressed as median and range. Significance statements refer to p values of 2-tailed tests that were <0.05.

RESULTS
Hospital course and early postoperative results and the data of an 8-year follow-up are reported elsewhere.17,18

Follow-up and mortality
Median (range) follow-up time for the current study was 16 years (range 14 to 18 years). One patient in the Frey group and 2 patients in the Beger group were lost to follow-up. Twenty-six patients died during follow-up (12 of 35 Frey; 14 of 36 Beger; mean survival was 13.0 ± 1.1 years and 13.3 ± 0.9 years, respectively; p = 0.660). In the majority of patients, the cause of death was cardiovascular disease commonly associated with diabetes (n = 14), but 5 patients died from the consequences of cancer, 2 patients died from liver cirrhosis, and 1 from trauma. In 4 patients, cause of death was unknown. Survival curves are presented in Figure 2.

Pain and quality of life
In the surviving patients, median pain score was found to be 3 (range 0 to 94) in those who had undergone the Beger procedure and 4 (range 0 to 96) in those with the Frey procedure (p = 0.936) (Table 2). For quality of life, physical status, ability to work, cognitive functioning, emotional functioning, social functioning, and global quality of life were analyzed. This revealed no statistically significant difference between the 2 treatment groups (Table 3). Additionally, scores on the symptom scales showed no statistically significant differences between the groups (Table 4).

Need for reintervention
As reported previously in the 8-year follow-up, 3 patients in the Beger group underwent reintervention because of stenosis of the common bile duct or recurrent CP of the organ remnant. In the Frey group, 1 patient underwent reintervention after 10 years because of recurrent CP.

Occupational rehabilitation
Overall, 26 of the 45 surviving patients in this study were employed full-time at follow-up (Beger, 13 of 22 patients; Frey, 13 of 23 patients), 17 patients were retired, and 2 patients in the Frey group were unemployed. No significant differences were found between the Beger and Frey groups.

Impact of endocrine and exocrine insufficiency and continuing alcohol consumption
After 8 years, endocrine insufficiency was found in 56% of patients after the Beger procedure and in 60% after the Frey procedure. In this 16-year long-term follow-up, this rate had increased to 77% (Beger) vs 83% (Frey) (p = 0.655).

Table 2. Beger vs Frey Procedure: Follow-Up Results of the Pain Score of the Surviving Patients at 16-Year Follow-Up

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Beger (n = 22)</th>
<th>Frey (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of pain attacks</td>
<td>0</td>
<td>0</td>
<td>0–100</td>
</tr>
<tr>
<td>Visual analogue scale</td>
<td>10</td>
<td>0</td>
<td>0–75</td>
</tr>
<tr>
<td>Analgetic medication</td>
<td>0</td>
<td>0</td>
<td>0–100</td>
</tr>
<tr>
<td>Inability to work</td>
<td>0</td>
<td>0</td>
<td>0–100</td>
</tr>
<tr>
<td>Pain score</td>
<td>3</td>
<td>4</td>
<td>0–94</td>
</tr>
</tbody>
</table>

Table 3. Beger vs Frey Procedure: Follow-Up Results of the Functioning Scale Scores of the Surviving Patients at 16 Years

<table>
<thead>
<tr>
<th>Functioning scale</th>
<th>Beger (n = 22)</th>
<th>Frey (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Status</td>
<td>100</td>
<td>100</td>
<td>0–100</td>
</tr>
<tr>
<td>Working Ability</td>
<td>100</td>
<td>100</td>
<td>0–100</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>100</td>
<td>100</td>
<td>0–100</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>75</td>
<td>83</td>
<td>0–100</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>92</td>
<td>67</td>
<td>0–100</td>
</tr>
<tr>
<td>Global Quality of Life</td>
<td>88</td>
<td>67</td>
<td>0–100</td>
</tr>
</tbody>
</table>

*Scores range from 0 to 100, with a higher score representing a higher level of functioning, items corresponding to questionnaire.
Concerning exocrine insufficiency, for the Beger group the rate was 88% of patients after 8 years and 87% after 16 years postoperatively, and in the Frey group, the rate had increased from 78% at 8 years to 86% at 16 years. The intergroup comparison of the 16-year data revealed no significant difference in endocrine and exocrine insufficiency (p = 0.953). The presence of endocrine and exocrine insufficiency was not associated with reduced quality of life or increased pain.

No significant differences concerning the rate of patients with continuing consumption of alcohol (defined as mean daily consumption of >12 g alcohol[25,26]) were detected when the 2 groups were compared (Beger, 2 of 22; Frey, 4 of 23; p = 0.413). When the impact of continuing consumption of alcohol on long-term outcomes was analyzed, a strong decrease in quality of life was detected. Scores for cognitive functioning, emotional functioning, and global quality of life were significantly lower in patients with continuing consumption of alcohol (Table 5). The pain score was also significantly lower in nondrinkers (3; range 0 to 66 vs 50; range 24 to 96; p < 0.001) (Table 6).

**DISCUSSION**

This is the first 16-year long-term follow-up of an RCT comparing 2 different methods for duodenum-preserving resection of the pancreatic head. In this trial, it was shown that the Beger and the Frey procedures have equivalent outcomes with regard to pain and quality of life. Mortality and mean survival are comparable after both procedures. Additionally, no significant differences were found concerning exocrine and endocrine insufficiency and occupational rehabilitation. Interestingly, it was shown that the continuing consumption of alcohol was associated with greater pain and lower quality of life. The presence of endocrine or exocrine insufficiency had no impact on the outcomes. The good long-term outcomes of DPPHR is confirmed by the findings of a recently published long-term follow-up comparing pancreaticoduodenectomy and Frey procedure.

**Table 4. Beger vs Frey Procedure: Follow-Up Results of the Symptom Scale Scores of the Surviving Patients (Median and Range)**

<table>
<thead>
<tr>
<th>Symptom scale and/or items</th>
<th>Beger (n = 22)</th>
<th>Frey (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Median 56 Range 0–100</td>
<td>Median 33 Range 0–100</td>
<td>0.057</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Median 0 Range 0–67</td>
<td>Median 0 Range 0–100</td>
<td>0.262</td>
</tr>
<tr>
<td>Pain</td>
<td>Median 0 Range 0–83</td>
<td>Median 0 Range 0–67</td>
<td>0.815</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>Median 0 Range 0–100</td>
<td>Median 0 Range 0–100</td>
<td>0.798</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Median 0 Range 0–100</td>
<td>Median 0 Range 0–100</td>
<td>0.867</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>Median 0 Range 0–100</td>
<td>Median 33 Range 0–100</td>
<td>0.432</td>
</tr>
<tr>
<td>Constipation</td>
<td>Median 0 Range 0–100</td>
<td>Median 0 Range 0–100</td>
<td>0.787</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Median 0 Range 0–100</td>
<td>Median 0 Range 0–100</td>
<td>0.955</td>
</tr>
<tr>
<td>Financial Strain</td>
<td>Median 0 Range 0–100</td>
<td>Median 0 Range 0–100</td>
<td>0.978</td>
</tr>
<tr>
<td>Loss of Body Weight</td>
<td>Median 0 Range 0–100</td>
<td>Median 0 Range 0–100</td>
<td>0.872</td>
</tr>
<tr>
<td>Fever or Shivering</td>
<td>Median 0 Range 0–33</td>
<td>Median 0 Range 0–33</td>
<td>0.677</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Median 0 Range 0–67</td>
<td>Median 0 Range 0–33</td>
<td>0.307</td>
</tr>
<tr>
<td>Bloating</td>
<td>Median 0 Range 0–100</td>
<td>Median 33 Range 0–100</td>
<td>0.083</td>
</tr>
<tr>
<td>Thirst</td>
<td>Median 0 Range 0–67</td>
<td>Median 0 Range 0–100</td>
<td>0.172</td>
</tr>
<tr>
<td>Itching</td>
<td>Median 0 Range 0–33</td>
<td>Median 0 Range 0–67</td>
<td>0.442</td>
</tr>
<tr>
<td>Treatment Strain</td>
<td>Median 33 Range 0–100</td>
<td>Median 33 Range 0–100</td>
<td>0.711</td>
</tr>
<tr>
<td>Hope and Confidence</td>
<td>Median 100 Range 0–100</td>
<td>Median 83 Range 0–100</td>
<td>0.389</td>
</tr>
</tbody>
</table>

*Scores range from 0 to 100, with a higher score representing a higher degree of symptoms, items corresponding to questionnaire.

**Table 5. Function Scale Scores of the Surviving Patients at 16-Year Follow-Up: Comparison of Patients Who Did or Did Not Continue Alcohol Consumption**

<table>
<thead>
<tr>
<th>Functioning scale</th>
<th>Alcohol (n = 6)</th>
<th>Nonalcohol (n = 39)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Status</td>
<td>Median 80 Range 0–100</td>
<td>Median 100 Range 0–100</td>
<td>0.131</td>
</tr>
<tr>
<td>Working Ability</td>
<td>Median 25 Range 0–100</td>
<td>Median 100 Range 0–100</td>
<td>0.099</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>Median 17 Range 0–100</td>
<td>Median 17 Range 0–100</td>
<td>0.004</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>Median 21 Range 0–83</td>
<td>Median 83 Range 17–100</td>
<td>0.007</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>Median 75 Range 0–100</td>
<td>Median 83 Range 17–100</td>
<td>0.684</td>
</tr>
<tr>
<td>Global Quality of Life</td>
<td>Median 33 Range 0–100</td>
<td>Median 83 Range 0–100</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*Scores range from 0 to 100, with a higher score representing a higher level of functioning, items corresponding to questionnaire.
Table 6. Follow-Up Results of the Pain Score of the Surviving Patients (Comparison of Patients who Did or Did Not Continue Alcohol Consumption)

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Alcohol (n = 6)</th>
<th>Nonalcohol (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Range</td>
<td>Median Range</td>
</tr>
<tr>
<td>Frequency of pain attacks</td>
<td>75 25–100</td>
<td>0 0–100</td>
</tr>
<tr>
<td>Visual analogue scale</td>
<td>73 40–85</td>
<td>10 0–75</td>
</tr>
<tr>
<td>Analgetic medication</td>
<td>8 0–100</td>
<td>0 0–100</td>
</tr>
<tr>
<td>Inability to work</td>
<td>75 0–100</td>
<td>0 0–25</td>
</tr>
<tr>
<td>Pain score</td>
<td>50 24–96</td>
<td>3 0–66</td>
</tr>
</tbody>
</table>

The reliability of the presented results is emphasized by the similar outcomes after Frey procedure in 2 separate collectives of patients, but with identical inclusion criteria in both RCTs.16

There is a general consensus that the primary therapy for CP should be a conservative, symptom-related treatment. In patients with failure of conservative treatment, different interventional procedures have been used, including sphincterotomy, endoscopic stone extraction, and stenting of the pancreatic duct.27–29 These interventions alleviate outflow obstructions of the duct system.6,8,27

Two RCTs have been published that compare endoscopic and surgical treatment. Dite and colleagues found a significantly higher rate of complete pain relief after surgery (34%), compared with 15% after endoscopy in a 5-year follow-up.8

More recently, Cahen and colleagues published the results of another RCT that compared endoscopic drainage procedures and pancreaticojejunostomy (Partington-Rochelle procedure).9 In a 24-month follow-up, surgery was found to be superior for quality of life and pain relief (pain score 53 ± 21 vs 25 ± 15).7 A 79-month follow-up found that symptomatic patients with advanced CP who underwent surgery as the initial treatment for pancreatic duct obstruction had better pain relief compared with patients who were treated endoscopically. In addition, almost half of the patients who were treated with endoscopy initially underwent surgery eventually.7 It is noteworthy that only patients without an inflammatory mass in the pancreatic head (defined as enlargement <4 cm) were included in the analysis of the patient cohort,8 although such an inflammatory mass is a common finding in CP.14,30,31 Results of this trial might be even more salient in patients experiencing an additional inflammatory tumor of the pancreatic head with potential organ complications, such as stenosis of the common bile duct and duodenal outlet obstruction.6

For many years, the longitudinal pancreaticojejunostomy introduced by Partington and Rochelle was the favored surgical option for treatment of CP.11 With increasing knowledge about the disease and the mechanisms of pain development, pancreaticoduodenectomy was frequently used, addressing the enlarged pancreatic head as the dominant morphologic pathology and the mainspring of the disease.15,30,31 The first duodenum-preserving resection of the pancreatic head was introduced by Beger in 1972.12 Resection components that address the enlarged pancreatic head without sacrificing the gastroduodenal and bilioduodenal passages are combined with drainage components comparable with the Partington-Rochelle procedure. Subtotal resection of the pancreatic head is performed before transection of the gland above the portal vein.10

A modification of this procedure was suggested in 1985 by Frey. A limited duodenum-preserving excision of the pancreatic head is accomplished by coring out the head of the pancreas, leaving a small cuff along the duodenal wall.10 In contrast to the Beger procedure, the pancreas is not divided above the superior mesenteric portal vein and the main pancreatic duct is open in the body and tail of the organ.

In recent years, 2 other modifications have been suggested. The rationale of the Berne procedure is to combine the advantages of the Frey and the Beger procedures33,34: a deep duodenum-preserving resection of the pancreatic head is done according to the Beger procedure, and the transection of the gland over the superior mesenteric portal vein is avoided.

The Hamburg procedure also combines aspects of the Beger and Frey procedures33,34: subtotal resection of the pancreatic head including the uncinate process is carried out, but the transection of the gland over the superior mesenteric portal vein is again avoided, and the excision is combined with a longitudinal V-shaped excision of the ventral aspect of the body and tail of the pancreas.

There are only 6 RCTs comparing different surgical procedures for the treatment of CP. Four trials comparing DPPHR and pancreaticoduodenectomy have been published.14,15,35,36

The Beger procedure was superior to pylorus-preserving pancreaticoduodenectomy in terms of pain control, quality of life, and gain in body weight in the short-term follow-up published by Buchler and colleagues.14 The 14-year long-term follow-up found no significant differences in the proportion of pain-free patients, in global health status, or in endocrine or exocrine insufficiency, but favorable results for appetite were still present.37 In another randomized trial, Klempa and colleagues found a significant benefit of the Beger...
procedure concerning postoperative hormonal status, it was also superior in terms of recuperation.16

When comparing a modification of the DPPHR to pancreaticoduodenectomy, Farkas and colleagues found the proportions of pain-free patients (86% vs 83%) to be comparable, but the morbidity (0% vs 30%) and increase in body weight (7.8 ± 0.9 kg vs 3.2 ± 0.3 kg) were significantly better after DPPHR. Additionally, operating time (142.5 ± 4.9 minutes vs 278.5 ± 6.9 minutes) and duration of hospital stay (8.5 ± 0.9 days vs 13.8 ± 3.9 days) were longer in the pancreaticoduodenectomy group.15,35

Only 1 RCT has analyzed the results of pancreaticoduodenectomy vs the Frey procedure.15,18 In the short-term follow-up, after 24 months the Frey procedure was superior for the primary end points of pain score (6.1 vs 18.1) and quality of life score (85.7 vs 75.1). In addition, the perioperative morbidity was significantly lower after DPPHR. Additionally, the proportions of pain-free patients (86% vs 83%) to be comparable, but the morbidity (0% vs 30%) and increase in body weight (7.8 ± 0.9 kg vs 3.2 ± 0.3 kg) were significantly better after DPPHR. Additionally, operating time (142.5 ± 4.9 minutes vs 278.5 ± 6.9 minutes) and duration of hospital stay (8.5 ± 0.9 days vs 13.8 ± 3.9 days) were longer in the pancreaticoduodenectomy group.40

CONCLUSIONS

Resections of the pancreatic head that preserve the duodenum offered good and permanent pain relief and substantially increased the quality of life in CP. A 16-year long-term follow-up found overall comparable outcomes after the Beger and the Frey procedures.
Author Contributions

Study conception and design: Bachmann, Bockhorn, Izbicki, Mann

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Drafting of manuscript: Bachmann, Tomkoetter, Erbes, Hofmann, Reeh, Perez, Vashist

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Final approval: Bachmann, Tomkoetter, Erbes, Hofmann, Reeh, Perez, Vashist Bockhorn, Izbicki, Mann

REFERENCES