Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Methods: Study Design, Participants, Randomization and Masking, Early Surgery, Endoscopy-First Approach, Outcomes, Data Collection, Safety Monitoring, and Statistics

Methods

Study Design

The ESCAPE trial was conducted as unblinded multicenter parallel randomized clinical superiority trial (see protocol in supplement 1[1]). The study was approved by the medical ethics committee of the Amsterdam UMC, location AMC and by all participating centers. All patients provided written informed consent before randomization.

Participants

Adult patients with severe pain due to obstructive chronic pancreatitis with a dilated pancreatic duct, who recently started opioids because of progressive pain under non-opioid medication were eligible for enrollment. Maximal period of opioid use before inclusion was 6 months for weak opioids (codeine, tramadol and hydrocodone) and 2 months for strong opioids (other opioids) in the last two years. Patients were screened for the detailed eligibility criteria (eTable 1) in six university medical centers and 24 large teaching hospitals of the Dutch Pancreatitis Study Group (DPSG) with computed tomography (CT) and/or magnetic resonance imaging (MRI) and, if needed, endoscopic ultrasonography. Once the Dutch Chronic Pancreatitis Expert Panel confirmed eligibility, patients were randomized between early surgery and the endoscopy-first approach. All interventions in both treatment groups were discussed and performed by multidisciplinary teams in 7 predefined chronic pancreatitis expert centers.

Randomization and Masking

Randomization was performed with varying block size (2, 4 or 6) by the study coordinators using an automatic assignment system that concealed allocation. Randomization was stratified for pancreatic head enlargement (≥4cm / <4cm). Owing to the unfeasibility of masking, all participants and physicians were aware of treatment allocation.

Early Surgery

A surgical drainage procedure was performed within six weeks after randomization. Surgery was performed by experienced pancreatic surgeons who performed at least 25 pancreatic operations specifically for CP. Patients with a non-enlarged pancreatic head (<4cm) underwent surgical drainage of the entire length of the pancreatic duct by a lateral pancreatojejunostomy according to Partington and Rochelle.[2] Patients with an enlarged pancreatic head (≥4 cm) underwent a duodenum-preserving pancreatic head resection as described by Frey and Smith, and Beger and colleagues.[3,4]

Lateral pancreatojejunostomy

The pancreatic duct was incised over the full length, from the tip of the tail up to two cm from the ampulla. For removal of stones, when necessary, a V-shaped incision of the head was performed. For reconstruction, one longitudinal pancreatojejunostomy was constructed, draining the full-length opened pancreatic duct.[2] The length of the anastomosis was measured during the operation (see additional results section). If no pancreatic head enlargement was seen on preoperative imaging, but during the operation an enlarged pancreatic head was found (≥ 4 cm), a Frey or Beger procedure was performed.

Duodenum-preserving pancreatic head resection

A duodenum-preserving pancreatic head resection, combined with a longitudinal pancreatojejunostomy, was performed. The duodenum-preserving pancreatic head resection is performed by coring-out the pancreatic head, leaving a cuff of around 10mm of the pancreas along the inner aspect of the duodenum. For the pancreatojejunostomy, the pancreatic duct was incised over the full length from the distal end of the tail to two cm from the ampulla. For reconstruction, one longitudinal pancreatojejunostomy is constructed, draining the resection

cavity of the head and the full-length opened pancreatic duct.[3] The length of the anastomosis was measured during the operation. A biliodigestive anastomosis was performed in case of stenosis of the intrapancreatic segment of the common bile duct.

Endoscopy-First Approach

The protocol for optimal endoscopy-first approach was designed in consensus by the Dutch Chronic Pancreatitis Expert panel and according the recent treatment guidelines.[5-7] All interventions in both treatment groups were discussed and performed by multidisciplinary teams in 7 predefined chronic pancreatitis expert centers, although patient referral was nationwide.

Step 1: Medical treatment

Optimal medical management was performed using the following guidelines:[8,9]

- Optimal pain medication according to the World Health Organization pain ladder. This starts with non-opioid medication (paracetamol, non-steroidal anti-inflammatory drugs), followed by weak opioids (tramadol, codeine), and ends with strong opioids (morphine, fentanyl, oxycodone etc.). The type and dose of medication is decided at the judgement of the treating physician and based on the clinical situation of the patient. As a guideline the physician aimed to maintain the pain according VAS of the patient below a score of four.
- Co-medication for neuropathic pain: When patients had persisted high pain scores (VAS >4) for more than 2 weeks, the treating physician was advised to refer the patient to the pain specialist. In consultation with the pain specialist co-medications for neuropathic pain such as pregabaline, gabapentin or amitriptyline could be started.
- Dietary advice: Consultation with a dietician was advised for analysis of nutritional status and starting of any necessary dietary program.
- Screening and management of pancreatic insufficiency at baseline and during follow up.

Failure of step 1

The patient remained in step 1 as long as pain control was achieved, defined as having a pain score ≤ 4 on the visual analog scale (VAS). Failure of medical treatment, defined as pain score > 4 for more than six weeks or unacceptable side effects of the medication, was indication for endoscopic treatment.

Step 2: Endoscopic treatment

Patients who failed for medical treatment were referred for endoscopic intervention. Endoscopic intervention was performed by experienced endoscopists who performed at least 50 therapeutic endoscopic interventions specifically for CP.

Stones in the pancreatic duct less than seven mm were treated by endoscopic retrograde pancreatography (ERP) using a balloon or Dormia basket. After sphincterotomy, complete stone removal was attempted. In case of incomplete stone removal, one or more plastic stents were inserted and a following ERP was planned. In case of large intraductal stones (diameter of ≥ 7 mm) extracorporeal shock-wave lithotripsy sessions were performed once a day for three days. All lithotripsy's were performed in the Erasmus Medical Center in Rotterdam using a lithotripter (Dornier lithotripter S) that provided 2000 shock waves per session on intensity level seven. After this three-day lithotripsy therapy, stone fragments were removed during a subsequent endoscopic retrograde pancreatography (ERP) after sphincterotomy. In case the stone fragmentation proved unsuccessful during ERP, a plastic stent was inserted as marker next to the stone and a new lithotripsy session was planned.

In case of strictures, the decision for need of dilatation, with either a balloon catheter or a Soehendra catheter, was made by the treating endoscopist. After sphincterotomy and the dilatation, one or more 10-French plastic stents were inserted. If this was impossible one or more 7-French stents were inserted. After stent insertion, patients underwent an elective endoscopic pancreatogram every three months. If pain was remaining, the following endoscopic pancreatogram was performed earlier. When complete runoff of contrast material was observed after stent removal and a 12-15mm extraction balloon could be passed through the pancreatic duct, endoscopic treatment was completed

and stenting was stopped. Persistent strictures were treated by repeated endoscopic dilatations and sequential insertion of new stents for a maximal period of one year, after which stenting was stopped.

Failure of step 2

Failure of endoscopic treatment was assessed from eight weeks onwards after each performed endoscopic therapy. When a patient had a VAS score above four for more than six weeks, the endoscopist was informed about the failure. When the pain persisted despite a maximum of three endoscopic interventions, the patient failed for the endoscopic treatment. In case stenting was needed to provide pain relief, this was allowed for a maximum duration of one year. If stenting was still needed after one year of stenting, patients failed also for the endoscopic treatment.

Step 3: Surgical treatment

If endoscopic treatment failed, patients underwent surgical intervention. Surgical intervention was performed as described in the early surgery section.

Outcomes

Primary outcome

The primary outcome was pain, measured by the Izbicki pain score every two weeks during the follow-up period of 18 months. The Izbicki pain score is a validated, CP specific, pain score with a scale ranging from zero to 100, with 100 as the most worse pain score. It consists of four items regarding frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work.[10,11]

Secondary outcomes

Secondary outcomes were pain relief, VAS score, Büchler pain score, post hoc Izbicki pain score at end of follow-up, quality of life, disease progression including development of pseudocysts, chronic use of opioids and hospital admissions for CP flare-ups; exocrine and endocrine pancreatic insufficiency, hospital admissions, number of interventions, complications of interventions, and death. Secondary outcomes that were prespecified in the protocol but not included in the manuscript were duodenum obstruction, total direct and indirect costs and the EQ5D quality of life scores. Data on duodenum obstruction was by mistake not collected during study follow-up. Total direct and indirect costs and the EQ-5D will be reported in a separate manuscript with the cost-effectivity analysis of the ESCAPE trial.

Pain relief

Pain relief was measured at end of follow-up and was classified as complete (Izbicki pain score ≤10), or partial (Izbicki pain score >10 but a decrease >50% compared to baseline).[10] We used the mean score of the last 5 Izbicki pain scores (3 months) to calculate the pain relief since the pain in these CP patients is very fluctuating (see Lasagna plot in figure 3 of main manuscript). Measuring the last 3 months (5 Izbicki pain scores) instead the last 2 weeks (1 Izbicki pain score) is therefore a better representation of pain relief. Post hoc, pain relief was also investigated in the using another definition. If pain VAS (derived from Izbicki pain score) was lower than four, pain relief was reached. If pain VAS was higher than four, no pain relief was reached. See eResults section for the outcomes.
Thereby we visualized pain relief (based on the Izbicki score classification) during the 18 months of follow-up in a lasagna plot, which is a graphical tool that can display longitudinal outcomes.[12]

Büchler pain score

The Büchler pain score during follow-up consist of only the frequency and intensity items from the Izbicki pain score. It ranges from zero to 100, with 100 as the most worse pain score. [13]

Quality of life

Quality of life was measured during follow-up by the Short-Form 36 questionnaire (SF-36).[14] It is scaled from 0 (maximum disability) to 100 (no disability), a score of 50 represents general Dutch population. Only the Physical Component Scale (PCS) and Mental Component Scale (MCS) are reported in the main manuscript since these are the summary scores of the other subdomains. The subdomains are reported in the eTables.

Disease progression

Disease progression included: development of pseudocysts, chronic use of opioids and hospital admissions for CP flare-ups. See eTable 13 for definitions. Exocrine pancreatic function was assessed by the fecal elastase-1 function test and a level of <200µg/g was defined as exocrine insufficient. Endocrine insufficiency was determined by the use of diabetes medication. Glycated hemoglobin level was assessed during follow-up and treatment was advised to the treating physician when levels were above 7%.

Complication of interventions

Complication of interventions were derived from endoscopic complications and surgical complications. Endoscopic complications were: (acute) pancreatitis flare-up, cholangitis, acute cholecystitis, retroperitoneal or bowel perforation, hemorrhage. Surgical complications were: anastomotic leakage, bleeding, sepsis, intra-abdominal abscesses, burst abdomen, pneumonia, severe wound infection requiring prolonged hospital stay, severe delayed gastric emptying. See eTable 13 for definitions.

Data Collection

The primary outcome was assessed using a web questionnaire. Patients without email filled in the questionnaire at home and were reminded by telephone to complete the questionnaire and return it to the trial coordinators. The questionnaire could not be changed once it was send to the trial coordinators. Besides the secondary outcomes that were based on the Izbicki pain score, Laboratory investigations and all other were collected during scheduled visits to the outpatient clinic at baseline and at six, 12 and 18 months. Questionnaires were mailed prior to follow-up visits and collected during the visits. All medical data were collected regarding any hospital admissions, diagnostics and interventions during the study period. CT and MRI imaging before randomization were reassessed by a blinded pancreatic radiologist (TLB). To measure the accomplished duct clearance, imaging and imaging report of the last endoscopic intervention was reassessed for every treated patient by an experienced pancreatic endoscopist (JWP). Complete duct clearance was issued when all intraductal stones and strictures were completely solved on imaging of the last endoscopic intervention. A standardized case record form (CRF) was used to collect the medical data. A designated study nurse monitored the data collection at all sites.

Safety Monitoring

After every 25 included patients, an independent data and safety monitoring committee unaware of the treatment assignment evaluated the trial progress and safety parameters. Serious adverse events were evaluated by the data and safety monitoring committee and reported online to the Central Committee on Research involving Human subjects.

Statistics

Sample size

The hypothesis of the study was that early surgery results in an early and persistent reduction of pain complaints during the 18 months follow-up. Therefore, the average reduction of pain during this period was our primary outcome. A sample size calculation based on the hypothesized difference was not possible because such published data was not available. Therefore, we decided to base this calculation on detecting the minimal clinically relevant difference of the Izbicki pain score. In a consensus meeting the Chronic Pancreatitis Expert Panel hypothesized that in the ESCAPE trial the early surgical intervention will achieve better pain control, probably in the range of 10 to 20 points. Therefore, the Expert Panel agreed that the trial should aim to detect a difference of 15 points or more on the Izbicki pain score (minimal clinically relevant difference) during follow-up. In previous studies, the average within group standard deviation of the Izbicki pain score was in the order of 20 points. Based on these assumptions, it was determined that 39 patients per group are needed to detect the minimal clinically relevant difference of 15 points on

average, based on alpha of 0.05 with a power of 90%. Taking into account a loss to follow-up of 10%, a total sample size of 88 patients were randomized.

Imputation of missing data

Missing data were considered to be missing at random since they were a random subset and had all comparable distributions. Only missing data in the pain score outcomes and quality of life were imputated as these outcomes were measured during follow-up. Missing data were imputed according the original study protocol.[1] Single missing values were imputed using linear interpolation. Multiple consecutive missing values were imputated using multiple imputation. In patients who were lost to follow-up, only missing values till date of lost to follow-up were imputated. Multiple imputation of the primary outcome was based on the following variables: randomization result, pancreatic head enlargement, sex, age, etiology, pain pattern, duration of CP and all Izbicki pain scores during follow-up. Multiple imputation of quality of life was based on the following variables: randomization result, pancreatic head enlargement, sex, age, etiology, pain pattern, duration of CP and all quality of life scores during follow-up.

In addition to this imputation method for the primary outcome, we performed several other imputation scenarios to assess if there were big differences in results. We presented this in the eResults and eTable 3. In the first scenario we imputed all missing data using multiple imputation including missing data of lost to follow-up patients. In the second scenario we imputed all missing data using multiple imputation and removed the imputed data of lost to follow-up patients. In the third scenario we imputed single missing values using linear interpolation and multiple missing values using multiple imputation, including missing data of patients that were lost to follow-up.

Analysis

All analyses were performed according a strict intention-to-treat principle. In addition, for the primary outcome and pain relief at end of follow-up a post hoc per-protocol analysis was performed. For this per-protocol analysis patients were excluded if inclusion was not according the criteria in the protocol or when medical, endoscopic, or surgical treatment was not according the protocol and clinical guidelines. Primary outcome was analyzed using an 'linear trapezoidal area under the curve' (AUC) analysis. It was presented as mean AUC per follow-up moment to present a score that is comparable with the average Izbicki score during follow-up. All other repeated measurement outcomes (pain score outcomes and quality of life) were analyzed as mean scores during follow-up. The primary outcome analysis was performed by a blinded statistician (MGD). As post hoc analysis, adjustment for age and pancreatic head enlargement was performed for the primary outcome using a generalized mixed model with Tweedie distribution. The reason to adjust the primary outcome for these two factors was that age was statistically significant in the baseline characteristics and pancreatic head enlargement was the stratification factor for randomization. Correcting for the baseline Izbicki pain score was not possible since this score was missing in 6 patients. This would have led to selection of patients with only 82 included patients in the corrected primary outcome. In the eResults and eTable 2 the corrected primary outcome with and without baseline Izbicki pain score is reported. A generalized mixed model with Tweedie was used since the distribution of the primary outcome data was bimodal in both groups. This is because of local dependence in the items of the Izbicki pain score questionnaire. No adjustment for centers was performed since individual patients were treated in different hospitals and since >70% of the endoscopy and >80% of the surgery was performed in 1 center (surgery: Amsterdam UMC, location AMC; endoscopy: Erasmus MC Rotterdam). Analysis of secondary outcomes was conducted by one of the study coordinators (MAK), under supervision of the independent statistician. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Dichotomous outcomes were presented as numbers and percentages and compared using the Chi-squared test or Fisher's exact test where appropriate. Normally distributed continuous measures were expressed as means with standard deviation (SD) and analyzed using the Students t-test. Continuous data that were not normally distributed were presented as medians with inter-quartile ranges (IQR) and compared using the Mann-Whitney U test. A two-tailed $P<0.05$ was considered statistically significant. All analyses were presented with 95% confidence intervals. The Hodges-Lehman method was used to calculate 95% confidence intervals for medians. Data analysis was performed using SPSS version 25 (SPSS, Chicago, Illinois, USA) and the R Project software (http://www.r-project.org).

Subgroup analysis

A predefined subgroup analysis was performed in patients with continuous pain and in patients with recurrent flare-ups of pain. Thereby post hoc subgroup analyses were performed in patients with an alcoholic and non-alcoholic etiology, and in patients with and without endoscopic duct clearance.

eAppendix 2. Results: Prerandomization Imaging Characteristics, Lost to Follow-up, Early Surgery, Endoscopy-First Approach, and Outcomes

Prerandomization Imaging Characteristics

All patients underwent a CT or MRI scan within six months prior to randomization. 51 patient underwent both a CT and MRI scan, 36 patients only a CT scan, and 1 patient only a MRI scan. In five patients the scans were not available at the end of the study and therefore, the imaging was not reassessed. In 76 patients (92%), the chronic pancreatitis was classified as severe chronic pancreatitis (Cambridge classification score 5). The median maximum diameter of the pancreatic duct was eight mm in both the early surgery as endoscopy-first approach group. 75 patients (90%) had intraductal stones with a median of six stones per patient. The median diameter of the largest stone was eight mm in the early surgery group and 10 mm in the endoscopy-first approach group. 21 patients (25%) had ductal strictures with a median of one stricture per patient. 40 patients (48%) had pseudocysts with a median of two pseudocysts per patient. See detailed information per group in eTable 7.

Lost to Follow-up

85 patients completed the 18 months' follow-up period and three patients were lost to follow up after respectively one, eight and 13 months. One patient in the early surgery group and one patient in the endoscopy-first approach group lost to follow-up because of no interest in the study anymore. Another patient in the endoscopy-first approach group stopped because pancreatic carcinoma was diagnosed, after which he decided to stop participation to the study.

Early Surgery

After randomization, three patients refused for surgery and therefore two of them were treated with endoscopy. The other patient refused also endoscopic treatment and was treated with only pain medication. In the early surgery group, during follow-up 27 patients (61%) were referred to the dietician. 24 patients (55%) were referred to the pain specialist.

In the 41 patients that underwent surgery, the median duration of admission for surgical treatment was eight days (IQR: 7, 10). The median duration of surgery was 247 minutes (IQR: 214, 312) and the median blood loss was 365 milliliters (IQR: 200, 545). An enlarged pancreatic head was found in 18 of 41 patients (44%), for which a pancreatic head resection was performed. The median size of the pancreatic head was five centimeters (IQR: 5, 7). The mean (SD) length of pancreatic-duct anastomosis from head to tail was 10 (4) cm.

Endoscopy-First Approach

For the flowchart of the endoscopy-first approach, see eFigure 1.

Step 1. Optimal medical treatment

As strongest pain medication, 59% of the patients used strong opioids, 34% weak opioids and 7% non-opioids. Only 9% used neuropathic pain medication. In the endoscopy-first approach group, during follow-up 28 patients (64%) was referred to the dietician, 15 patients (34%) were referred to the pain specialist.

Two patients failed for step 1, but were not referred for endoscopic treatment. One patient refused endoscopic and surgical treatment despite high pain scores. In one patient there was a suspicion for pancreatic carcinoma and underwent a pylorus preserving pancreatoduodenectomy where no malignancy was diagnosed. Finally, in another patient pancreatic carcinoma was diagnosed, after which he decided to stop participation to the study.

Step 2. Endoscopic intervention

Thirty-nine patients underwent endoscopy. The first endoscopic intervention was performed a median of 63 days (IQR: 38, 136) after randomization. Seven patients underwent a single endoscopic intervention, of which four

patients underwent lithotripsy because of stones larger than seven mm. Thirty-two patients underwent multiple endoscopic procedures with a median of three procedures (IQR: 2, 4), and 18 of them underwent lithotripsy for stones larger than seven mm (median of one lithotripsy, IQR: 0, 1). Of the 29 of 39 patients which were stented, 55% had a single stent inserted and 45% multiple stents per session.

Of the 29 patients with stones who underwent endoscopy, 16 patients had multiple stones. The median diameter of the largest stone was 10 mm (IQR: 10, 13) and all stones were located in head, neck and corpus of the pancreas. Stone fragmentation by lithotripsy was successful in 82%. Complete stone removal was accomplished in 70% of patients.

Step 3. Surgical treatment

13 patients underwent surgery and the median duration of hospital admission was 10 days (IQR: 7, 14). The median duration of surgery was 280 minutes (IQR: 208, 375) and the median blood loss was 550 milliliters (IQR: 350, 900). The mean (SD) length of pancreatic-duct anastomosis of these procedures was 8 (2) cm from head to tail. An enlarged pancreatic head was found in four of 12 patients (33%), for which a pancreatic head resection was performed. The median size of the pancreatic head was five cm (IQR: 4, 5).

Outcomes

Primary outcome; subdomains

The subdomain scores of the Izbicki pain score are presented in eTable 12 as mean score with standard deviation during follow-up. It is raw data since only the summary Izbicki pain score is imputed, and is therefore somewhat different than the primary outcome in the main manuscript.

Primary outcome; imputation scenarios

9.6% of the measurements in the primary outcome was missing (321 missings in 3344 measurements). As reported in the eMethods, we performed four different imputation scenarios. See eTable 3 for the different results per imputation scenario. We decided to use the imputation scenario according the published protocol. This was the most conservative method as all other scenario's showed a higher contrast between both groups. This resulted in imputation of 7.4% (248 measurements) of the data since the other 2.2% (73 measurements) of the missing data was due to loss to follow-up.

Primary outcome; Primary outcome correction with & without baseline Izbicki pain score

A post hoc primary outcome correction for the baseline Izbicki pain score was not possible since this outcome was missing in 6 patients. This would lead to selection of patients with only 82 included patients in the corrected primary outcome. In eTable 2 we showed the primary outcome correction with and without the baseline Izbicki pain score, with respectively 82 and 88 patients. Selection of patients with a baseline Izbicki pain score (n=82) leaded to a decrease in difference between randomization groups of 2 points in the 2 factors corrected primary outcome compared to the group with all patients included. Therefore, correcting the primary outcome for 3 factors in the all patient group would have theoretically led to a difference between randomization groups of 15 points.

Post hoc per-protocol analysis; primary outcome

There were 24 protocol violations in 23 patients. These patients were excluded for the per-protocol analysis. Per-protocol analysis showed a comparable difference between the early surgery group and the endoscopy-first approach group for both the corrected as non-corrected AUC analysis. Based on the primary outcome, the conclusions of the primary analysis remains the same in this per-protocol analysis. See Table 2 in the main manuscript for the per-protocol analysis and eTable 9 for the protocol violations.

Pain relief; scenarios

In the published protocol we stated that pain relief will be measured at end of follow-up.[1] Pain relief at end of follow-up can be measured using the last Izbicki pain score. This score, however, only showed the pain of the last two weeks, whereas we assessed the Izbicki pain score every two weeks. Pain in chronic pancreatitis is very variable over time (see Lasagna plot in figure 3 of main manuscript), and therefore we decided that this single end-of-follow-up measurement was not reliable. Another way to measure pain relief at end of follow-up is to measure it over the

last three months. Therefore, we decided to use the last five Izbicki pain (which is the last three months) scores for the pain relief analysis.

As stated in the methods above, another frequently used pain relief measurement is to calculate it using the VAS score. We also measured the pain relief based on the VAS score of the last two weeks and last three months. See eTable 10 for the different pain relief scenario's and results.

Pain relief; lasagna plot

We visualized pain relief during follow-up in a lasagna plot, which is a graphical tool that can display longitudinal outcomes.[12] This lasagna plot visualized a much higher complete pain relief during follow-up in the early surgery group compared to the endoscopy-first approach. See figure 3 in the main manuscript for the plot.

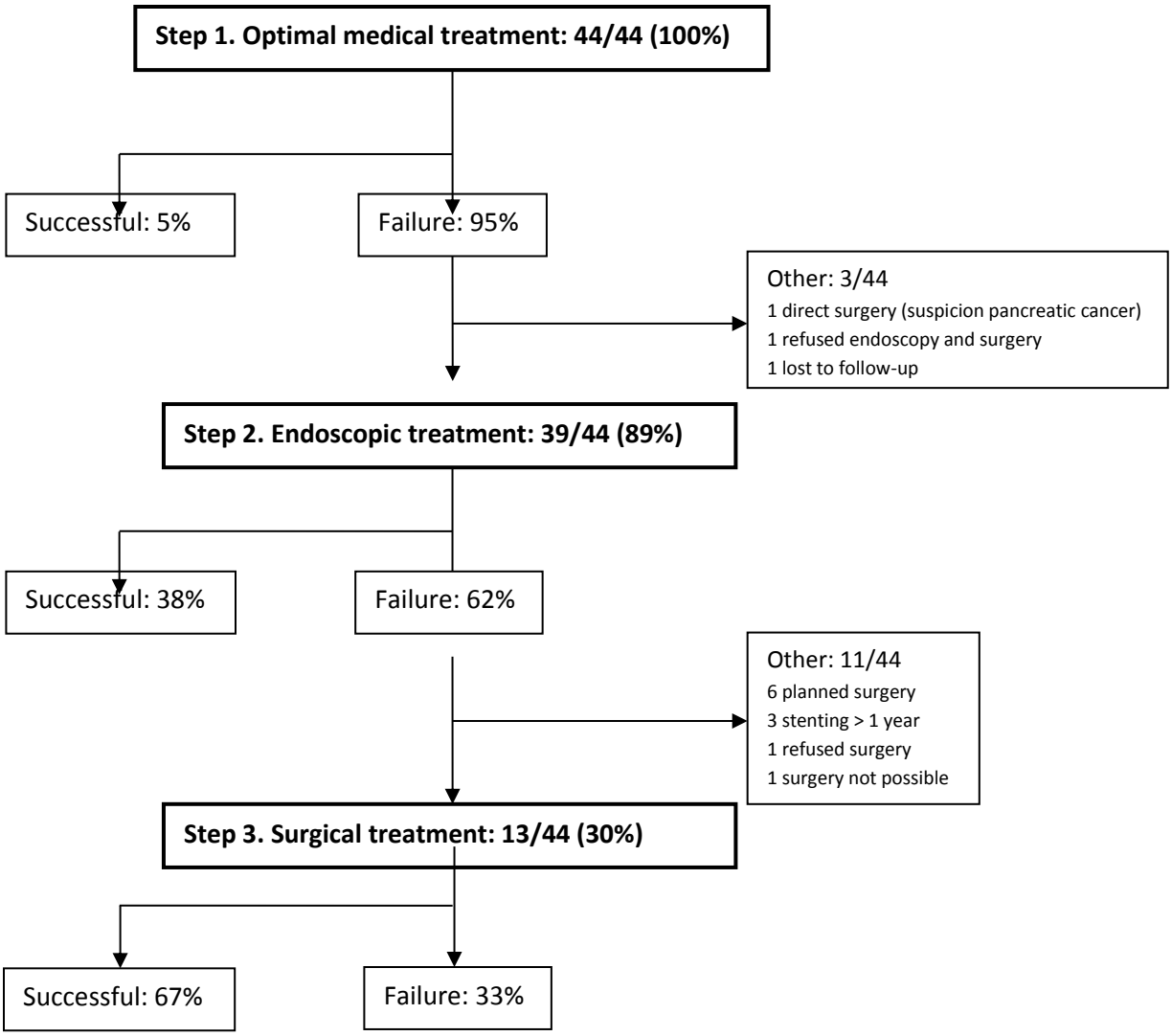
Predefined subgroup: continuous pain vs. recurrent pain

As stated in the published protocol we performed a subgroup analysis in patients with continuous pain and patients with recurrent pain.[1] In patients with continuous pain, the Izbicki pain score during follow-up was significant higher for the early surgical group. In patients with recurrent pain, the Izbicki pain score during follow-up between both groups was comparable (eTable 4). Regression analysis for interaction between pain pattern and the primary outcome was however not significant (P=0.274).

Post hoc subgroup: Alcoholic etiology vs. non-alcoholic etiology

We performed a subgroup analysis in patients with an alcoholic etiology and patients with a non-alcoholic etiology (eTable 5). In the alcoholic etiology group, the difference in the Izbicki pain score during follow-up was 12 points in favor of early surgery, compared to a difference of 20 points in the non-alcoholic etiology group. In the alcoholic etiology group the physical quality of life was significant higher in patients who underwent early surgery. In the non-alcoholic etiology group the mental quality of life was significant higher in patients who underwent early surgery. In the endoscopy-first approach group, patients with an alcoholic etiology underwent a median of 2 interventions compared to 4 interventions in patients with an non-alcoholic etiology.

eFigure 1. **Flowchart of Endoscopy-First Approach**



eFigure 2. Izbicki Pain Score Questionnaire

ESCAPE trial questionnaire

Early Surgery versus Optimal Current Step-up Practice for Chronic Pancreatitis (ESCAPE) trial

		Never	Few times per year	Few times per month	Few times per week	Daily
1	Frequency of pain	1	2	3	4	5

2 Intensity of pain

No pain _____ Worst pain imaginable

		None	Aspirine Paraceta -mol	Ibuprofen Naproxen Diclofenac	Tramal Tramadol	Pethidine	Temgesic	Morfine MS Contin Durogesic
3	Pain medication	1	2	3	4	5	6	7

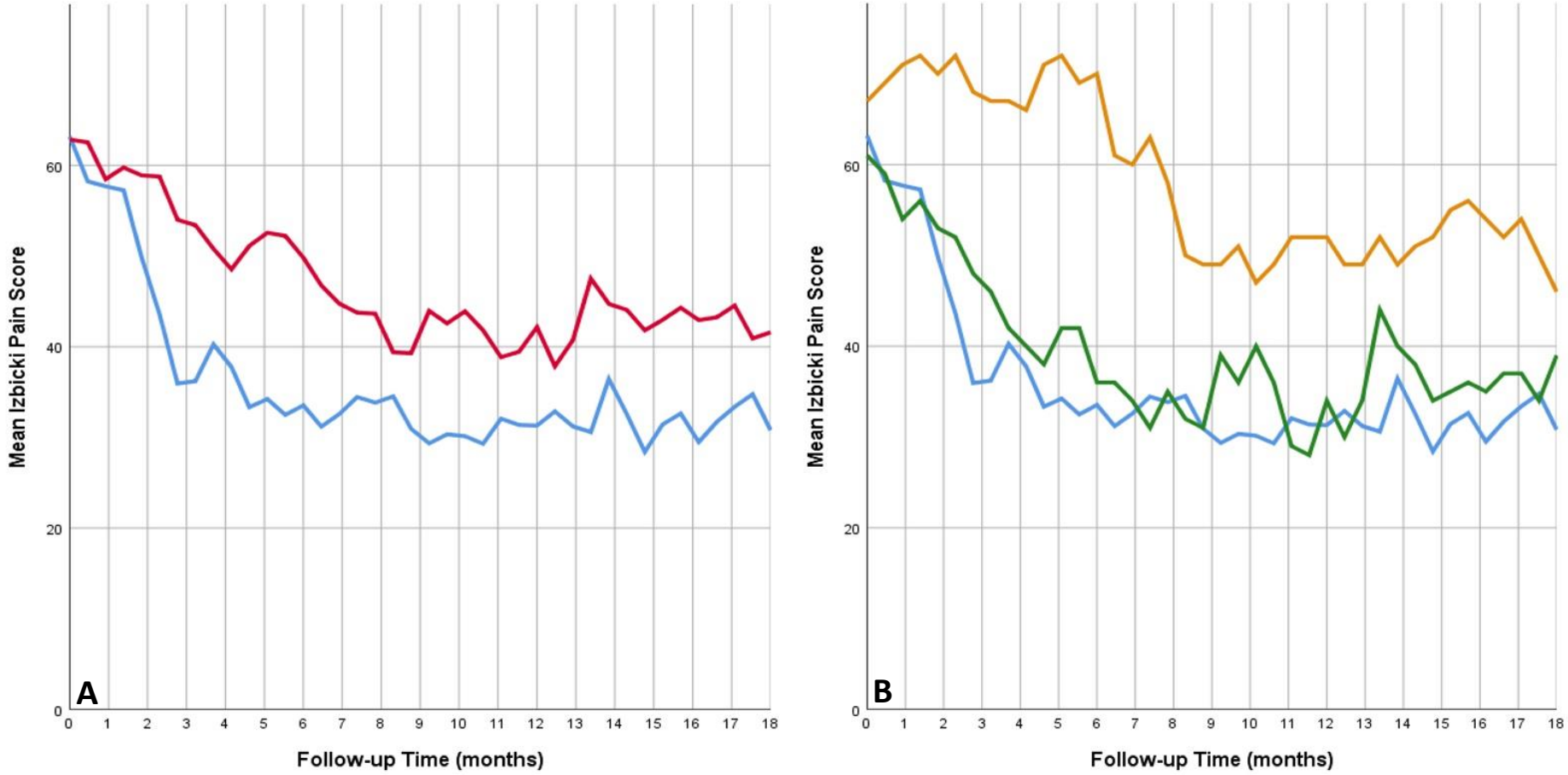
		Never	Shorter than 1 week	Between 1 week and 1 month	Between 1 month and 1 year	Permanent
4	Chronic pancreatitis related inability to work	1	2	3	4	5

Calculation:

Frequency of pain: 1=0 / 2=25 / 3=50 / 4=75 / 5=100
Intensity of pain: Scale 0-100
Pain medication: 1=0 / 2=1 / 3=3 / 4=15 / 5=20 / 6=80 / 7=100
Inability to work: 1=0 / 2=25 / 3=50 / 4=75 / 5=100

Total score / 4 = Izbicki pain score

eFigure 3. Izbicki Pain Score During 18 Months of Follow-up; Effect of Endoscopic Duct Clearance



LEGEND:

- Endoscopy-first approach (figure A)
- Endoscopy-first approach with Duct Clearance (figure B)
- Endoscopy-first approach without Duct Clearance (figure B)
- Early Surgery (figure A + B)

Mean Izbicki pain score is presented per arm for every month during the 18 months' follow-up. The Izbicki pain scores ranges from 0 to 100.

eTable 1. Eligibility Criteria

Inclusion criteria
- Age > 18 yr
- Confirmed diagnosis of chronic pancreatitis according the M-ANNHEIM diagnostic criteria*: ▪ Typical clinical history of chronic pancreatitis And one or more of the following criteria: ▪ Calcifications or moderate / marked ductal lesions on imaging ▪ Marked and persistent exocrine insufficiency
- Dilated pancreatic duct of ≥5 mm on imaging
- Severe pain requiring weak or strong opioids for at least 3 days a week during at least 2 weeks in a row **
Exclusion criteria
- Prolonged use of opioids: ▪ Use of weak opioids for more than 6 months in 2 years prior randomization ** ▪ Use of strong opioids for more than 2 months in 2 years prior randomization **
- Previous pancreatic surgery or endoscopic treatment of pancreatic duct (dilatation or stenting)
- Autoimmune pancreatitis
- Biliary obstruction in 2 months prior randomization (defined as jaundice or bilirubin level ≥25 µmol/l
- Intraductal stones fully impacting the entire pancreatic duct or exclusively located in pancreatic tail
- Contra-indications for surgery or endoscopy, as judged by the expert panel
- Suspected or confirmed pancreatic malignancy
- Life expectancy of < 1 year
- Pregnancy

* criteria published by Schneider et al[27] ** Weak opioids: codeine, tramadol and hydrocodone, Strong opioids: all other opioids such as morphine, oxycodone, fentanyl, pethidine, buprenorphine.

eTable 2. Primary Outcome Correction With and Without Baseline Izbicki Pain Score

All patients (N=88)	**Early surgery (N=44)**	**Endoscopy-first approach (N=44)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Area Under Curve – mean (SD)	37 (25)	49 (25)	-12 (-22 to -2)	0.024
2 factors corrected Area Under Curve – mean (SD)	34 (22)	52 (29)	-18 (-29 to -7)	0.001
3 factors corrected Area Under Curve – mean (SD)	NP	NP	NP	NP
Only patients with baseline Izbicki score (N=82)	**Early surgery (N=41)**	**Endoscopy-first approach (N=41)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Area Under Curve – mean (SD)	37 (25)	48 (25)	-11 (-22 to 0.2)	0.054
2 factors corrected Area Under Curve – mean (SD)	35 (22)	51 (29)	-16 (-28 to -5)	0.005
3 factors corrected Area Under Curve – mean (SD)	36 (20)	49 (25)	-13 (-23 to -4)	0.006

Correction with 2 factors: Age, Pancreatic head enlargement; Correction with 3 factors: Age, Pancreatic Head Enlargement; Baseline Izbicki pain score; NP = not possible; Correction with 3 factors not possible for 88 patients since the baseline Izbicki pain score was missing in 6 patients.

eTable 3. Primary Outcome Imputation Scenarios

	Early surgery (N=44)	**Endoscopy-first approach (N=44)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
SCENARIO 1: Izbicki score **(final)**				
Area Under Curve – mean (SD)	37 (25)	49 (25)	-12 (-22 to -2)	0.024
Corrected Area Under Curve – mean (SD)	34 (21)	52 (29)	-18 (-29 to -7)	0.001
SCENARIO 2: Izbicki score				
Area Under Curve – mean (SD)	37 (24)	48 (24)	-11 (-21 to -1)	0.030
Corrected Area Under Curve – mean (SD)	34 (21)	51 (28)	-17 (-27 to -7)	0.001
SCENARIO 3: Izbicki score				
Area Under Curve – mean (SD)	37 (24)	49 (25)	-12 (-22 to -2)	0.022
Corrected Area Under Curve – mean (SD)	34 (22)	52 (29)	-18 (-29 to -7)	0.001
SCENARIO 4: Izbicki score				
Area Under Curve – mean (SD)	37 (24)	48 (24)	-12 (-22 to -1)	0.027
Corrected Area Under Curve – mean (SD)	34 (21)	51 (29)	-17 (-28 to -7)	0.001

Scenario 1: linear interpolation for single missing values, multiple imputation for multiple missing values, and only observed values for patients who were lost to follow-up

Scenario 2: all missing's were multiple imputed (including lost to follow-up patients)

Scenario 3: all multiple imputation and only observed values for patients who were lost to follow-up.

Scenario 4: linear interpolation for single missing values, multiple imputation for multiple missing values (including lost to follow-up patients)

eTable 4A. Subgroup Analysis; Continuous Pain vs Recurrent Pain; Continuous Pain

CONTINUOUS PAIN: Main outcomes				
	Early surgery (N=29)	**Endoscopy-first approach (N=35)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Izbicki score				
Area Under Curve – mean (SD)	38 (25)	51 (25)	-13 (-26 to -0.7)	0.040
Corrected Area Under Curve – mean (SD)	34 (20)	54 (28)	-21 (-32 to -9)	<0.001
Pain relief at end follow-up – no. (%)[a]	15 (58)	12 (38)	20 (-6 to 47)	0.125
Complete	8 (31)	8 (25)		
Partial	7 (27)	4 (13)		
No relief	11 (42)	20 (63)		
SF-36 quality of life during follow-up – mean (SD)				
Physical health component score	39 (12)	35 (9)	4 (-1 to 9)	0.099
Mental health component score	46 (11)	42 (10)	3 (-2 to 8)	0.228
Disease progression – no. (%)				
Pseudocysts	1 (3)	5 (14)	-11 (-25 to 4)	0.209
Chronic opioid use[b]	13 (46)	20 (59)	-13 (-38 to 13)	0.330
CP flair-up	10 (34)	15 (43)	-9 (-33 to 16)	0.494
Exocrine insufficiency – no. (%)[a]	25 (96)	29 (91)	5 (-8 to 19)	0.620
Endocrine insufficiency – no. (%)	9 (31)	16 (46)	-15 (-4 to 10)	0.231
Interventions per patient – median (IQR)	1 (1, 1)	3 (2, 4)	2	<0.001
No. of endoscopic procedures	0 (0, 0)	3 (1, 4)	3	
No. of surgical procedures	1 (1, 1)	0 (0, 1)	0	
Treatment complications – no. (%)	9 (31)	8 (23)	8 (-14 to 31)	0.461
Mortality – no. (%)	0 (0)	0 (0)	0	

CP = chronic pancreatitis, [a] = missing in 6 patients, [b] = missing in 2 patients

eTable 4B. Subgroup Analysis; Continuous Pain vs Recurrent Pain; Recurrent Pain

RECURRENT PAIN: Main outcomes				
	Early surgery (N=15)	**Endoscopy-first approach (N=9)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Izbicki score				
Area Under Curve – mean (SD)	36 (24)	42 (24)	- 10 (-27 to -16)	0.586
Corrected Area Under Curve – mean (SD)	38 (27)	41 (26)	- 2 (-23 to 18)	0.812
Pain relief at end follow-up – no. (%)[a]	8 (57)	4 (44)	13 (-33 to 59)	0.680
Complete	4 (29)	0 (0)		
Partial	4 (29)	4 (44)		
No relief	6 (43)	5 (56)		
SF-36 quality of life during follow-up – mean (SD)				
Physical health component score	38 (12)	40 (11)	-2 (-12 to 9)	0.766
Mental health component score	41 (11)	36 (13)	5 (-5 to 15)	0.297
Disease progression – no. (%)				
Pseudocysts	1 (7)	1 (11)	-4 (-30 to 21)	1.000
Chronic opioid use	7 (47)	6 (66)	-19 (-65 to 25)	0.423
CP flair-up	8 (53)	5 (55)	-2 (-48 to 43)	1.000
Exocrine insufficiency – no. (%)	12 (86)	8 (89)	-3 (-35 to 28)	1.000
Endocrine insufficiency – no. (%)	3 (20)	3 (33)	-13 (-52 to 26)	0.635
Interventions per patient – median (IQR)	1 (1, 1)	2 (2, 4)	-1	0.018
No. of endoscopic procedures	0 (0, 0)	2 (1.5, 4)	-2	
No. of surgical procedures	1 (1, 1)	0 (0, 0)	1	
Treatment complications – no. (%)	3 (20)	3 (33)	-13 (-52 to 26)	0.635
Mortality – no. (%)	0 (0.0)	0 (0.0)		

CP = chronic pancreatitis, [a] = missing in 1 patient

eTable 5A. Subgroup Analysis; Alcoholic vs Nonalcoholic: Alcoholic

ALCOHOLIC ETIOLOGY: Main outcomes				
	Early surgery (N=34)	**Endoscopy-first approach (N=27)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Izbicki score				
Area Under Curve – mean (SD	41 (25)	53 (25)	-12 (-25 to 1)	0.068
Corrected Area Under Curve – mean (SD)	39 (22)	56 (28)	-17 (-29 to -4)	0.007
Pain relief at end follow-up – no. (%)[a]	14 (47)	8 (32)	6 (-12 to 42)	0.269
Complete	9 (30)	4 (16)	14	
Partial	5 (17)	4 (16)	1	
No relief	16 (53)	17 (68)	-15	
SF-36 quality of life during follow-up – mean (SD)				
Physical health component score	38 (11)	37 (9)	1 (-4 to 6)	0.714
Mental health component score	44 (11)	37 (11)	6 (0.5 to 12)	0.033
Smoking – no. (%)[b]	27 (90)	19 (70)	20 (-1 to 40)	0.061
Disease progression – no. (%)				
Pseudocysts	2 (6)	4 (15)	-9 (-24 to 7)	0.392
Chronic opioid use[c]	16 (49)	17 (63)	-14 (-40 to 12)	0.262
CP flair-up	13 (38)	13 (48)	-10 (-36 to 16)	0.437
Exocrine insufficiency – no. (%)[a]	27 (90)	23 (92)	-2 (-18 to 14)	1.000
Endocrine insufficiency – no. (%)	8 (24)	7 (26)	-2 (-25 to 20)	0.829
Interventions per patient – median (IQR)	1 (1, 1)	2 (1, 4)	-1 (-2 to -1)	<0.001
No. of endoscopic procedures	0 (0, 0)	2 (1, 3)		
No. of surgical procedures	1 (1, 1)	0 (0, 1)		
Treatment complications – no. (%)	12 (35)	5 (19)	16 (-6 to 40)	0.147
Mortality – no. (%)	0 (0)	0 (0)	0 (0 to 0)	1.000

CP = chronic pancreatitis, [a] = missing in 6 patients, [b] = missing in 4 patients, [c] = missing in 1 patient

eTable 5B. Subgroup Analysis; Alcoholic vs Nonalcoholic: Nonalcoholic

NON-ALCOHOLIC ETIOLOGY				
	Early surgery (N=10)	**Endoscopy-first approach (N=17)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Izbicki score				
Area Under Curve – mean (SD)	22 (18)	42 (25)	- 20 (-37 to -3)	0.026
Corrected Area Under Curve – mean (SD)	24 (17)	43 (25)	- 19 (-35 to -2)	0.026
Pain relief at end follow-up – no. (%)[a]	6 (100)	6 (55)	46 (-0.1 to 92)	0.102
Complete	2 (33)	2 (18)		
Partial	4 (67)	4 (36)		
No relief	0 (0)	5 (45)		
SF-36 quality of life during follow-up – mean (SD)				
Physical health component score	42 (13)	34 (8)	8 (-1 to 16)	0.079
Mental health component score	46 (10)	47 (8)	-1 (-8 to 6)	0.736
Smoking – no. (%)[b]	5 (56)	11 (65)	-9 (-52 to 34)	0.692
Disease progression – no. (%)				
Pseudocysts	0 (0)	2 (12)	-12 (-34 to 10)	0.516
Chronic opioid use	4 (40)	9 (56)	-16 (-59 to 27)	0.420
CP flair-up	5 (50)	7 (41)	9 (-33 to 51)	0.706
Exocrine insufficiency – no. (%)	10 (100)	14 (88)	13 (-10 to 35)	0.508
Endocrine insufficiency – no. (%)	4 (40)	12 (71)	-31 (-73 to 11)	0.224
Interventions per patient – median (IQR)	1 (1, 1)	4 (3, 5)	-3 (-4 to -1)	0.003
No. of endoscopic procedures	0 (0, 0)	0 (0, 1)		
No. of surgical procedures	1 (1, 1)	3 (2, 4)		
Treatment complications – no. (%)	0 (0)	6 (35)	-35 (-68 to -3)	0.057
Mortality – no. (%)	0 (0)	0 (0)	0 (0 to 0)	1.000

CP = chronic pancreatitis, [a] = missing in 10 patients, [b] = missing in 1 patient

eTable 6. Subgroup Analysis; Early Surgery vs Endoscopy-First Approach (Duct Clearance Y/N)

	Early surgery (N=44)	Endoscopy-first approach (N=39)	
		Endoscopic duct clearance (N=24)	No endoscopic duct clearance (N=15)
Izbicki score			
Area Under Curve – mean (SD)	37 (25)	40 (22)	60 (22)
Pain relief at end follow-up – no. (%)[a]	23 (58)	12 (52)	3 (21)
Complete	12 (35)	5 (22)	2 (14)
Partial	11 (23)	7 (30)	1 (7)
No relief	17 (43)	11 (48)	11 (79)
SF-36 quality of life during follow-up – mean (SD)			
Physical health component score	39 (12)	37 (9)	33 (7)
Mental health component score	44 (11)	43 (10)	40 (12)
Smoking – no. (%)[b]	32 (82)	16 (67)	12 (80)
Morphology			
Max diameter pancreatic duct (mm) – median (IQR)	8 (6-10)	8 (7-12)	6 (5-9)
Number of stones – median (IQR)	6 (3-6)	6 (1-6)	6 (3-6)
Max diameter stone (mm) – median (IQR)	8 (6-11)	10 (4-16)	7 (4-10)
Number of strictures – median (IQR)	1 (1-2)	1 (1-2)	1 (1-1)
Disease progression – no. (%)			
Pseudocysts	2 (5)	2 (8)	3 (20)
Chronic opioid use	20 (47)	13 (54)	11 (73)
CP flair-up	18 (41)	11 (46)	7 (47)
Exocrine insufficiency – no. (%)[a]	37 (93)	19 (83)	14 (93)
Endocrine insufficiency – no. (%)	12 (27)	11 (46)	5 (33)
Surgical intervention – no. (%)	41 (93)	4 (17)	9 (60)
Interventions per patient – median (IQR)	1 (1, 1)	3 (2, 4)	3 (2, 4)
No. of endoscopic procedures	0 (0, 0)	3 (2, 4)	2 (1, 3)
No. of surgical procedures	1 (1, 1)	0 (0, 0)	1 (0, 1)
Treatment complications – no. (%)	12 (27)	6 (25)	5 (33)
Mortality – no. (%)	0 (0)	0 (0)	0 (0)

CP = chronic pancreatitis, [a] = missing in 6 patients, [b] = missing in 5 patients

eTable 7. Prerandomization Imaging Characteristics

	Early surgery (N=44)	Endoscopy-first approach (N=44)	Early Surgery results vs. Endoscopy-first results
CT and MRI – no. of pt (%)	23 (52)	28 (64)	-12
Only CT – no. of pt (%)	20 (46)	16 (36)	10
Only MRI – no. of pt (%)	1 (2)	0 (0)	2
Most relevant imaging* – pt[a]	N=44	N=39	
Max diameter PD – mm – median (IQR)	8 (6.25, 10.00)	8 (6.00, 11.00)	0
Max diameter pancreatic head – mm – mean (SD)	43 (10)	43 (9)	0
Peripancreatic infiltration – no. of pt (%)	33 (75)	20 (51)	24
Atrophic pancreas – no. of pt (%)	15 (34)	19 (49)	-15
Calcifications – no. of pt (%)b	39 (93)	34 (90)	3
Irregular PD – no. of pt (%)[b]	42 (98)	36 (97)	1
Severity (classified according the Cambridge criteria)			
Cambridge 4 – no. of pt (%)	3 (7)	4 (10)	-3
Cambridge 5 – no. of pt (%)	41 (93)	35 (90)	3
Ductal stones and strictures – no. of pt (%)	6 (14)	7 (18)	-4
Only ductal stones – no. of pt (%)	34 (77)	28 (72)	5
Only ductal strictures – no. of pt (%)	4 (9)	4 (10)	-1
Ductal stones – no. of pt (%)	40 (91)	35 (90)	5
No. of stones – median (IQR)	6 (3, 6)	6 (3, 6)	0
Diameter largest stone – median (IQR)	8 (6, 11)	10 (5, 14)	2
Location largest stone[c]			
Head – no. of pt (%)	39 (98)	32 (97)	1
Body – no. of pt (%)	1 (2)	1 (3)	-1
Tail – no. of pt (%)	0 (0)	0 (0)	0
Ductal strictures – no. of pt (%)	10 (23)	11 (28)	-5
No. of strictures – median (IQR)	1 (1, 2)	1 (1, 2)	0
Location of strictures			
Diffuse – no. of pt (%)	4 (40)	3 (27)	13
Head – no. of pt (%)	4 (40)	6 (55)	-15
Body – no. of pt (%)	1 (10)	1 (9)	1
Tail – no. of pt (%)	1 (10)	1 (9)	1
Pseudocysts – no. of pt (%)	22 (50)	18 (46)	4
No. of pseudocysts – median (IQR)	2 (1, 3)	2 (1, 3)	0
Diameter largest pseudocyst – median (IQR)	20 (12, 30)	16 (9, 24)	4
Location largest pseudocyst[c]			
Head – no. of pt (%)	19 (86)	15 (94)	-8
Body – no. of pt (%)	1 (5)	1 (6)	-1
Tail – no. of pt (%)	2 (9)	0 (0)	9

CT = computed tomography, MRI = magnetic resonance imaging, PD = pancreatic duct, * most relevant = imaging nearest to randomization date that is reassessed by the pancreatic expert radiologist, [a] missing in 5 patients, [b] missing in 3 patients, [c] missing in 2 patients

eTable 8. Severe Treatment Complications

	Early Surgery (N=44)	Endoscopy-first approach (N=44)	Early Surgery results vs. Endoscopy-first results (95% CI)	P value
Treatment complications – no. of patients (%)	12 (27)	11 (25)	2 (-17 to 21)	0.808
Treatment complications – total no.	14	18	4	1.000
Type of complications:				
- Anastomotic leakage - pancreatojejunostomy	3	2		
- Bleeding	1	1		
- Bleeding with relaparotomy	2	0		
- Cholangitis	0	1		
- Incisional hernia	2	0		
- Pancreatitis flare-up	0	9		
- Pneumonia	2	0		
- Diagnostic relaparotomy	1	1		
- Duodenum perforation with relaparotomy	0	1		
- Sepsis	1	1		
- Severe delayed gastric emptying	2	1		
- Wound infection	0	1		

eTable 9. Protocol Violations

	No. of patients*
Early Surgery	
- Duration randomization till surgery	7
- No surgery	3
- Different type of surgery	1
Endoscopy-first approach	
- Wrong inclusion (pancreatic carcinoma)	1
Step 2: Endoscopic treatment	
- No endoscopy	1
- No endoscopy and surgery	1
- No ESWL despite stones >7mm	4
- No progressive stenting despite stricture	2
- Too long endoscopy (>1 year stenting)	1
- Endoscopy in other center	1
Step 3: Surgical treatment	
- No surgery	1
- Surgery in other center	1

ESWL = extracorporeal shock-wave lithotripsy, *23 patients underwent in total 24 protocol violations.

eTable 10. Pain Relief Scenarios

* Visual Analog Scale from 0 (no pain) to 100 (most severe pain imaginable), [a] missing in 7 patients, [b] missing in 15 patients, [c] missing in 4 patients, [d] missing in 12 patients

	Early surgery (N=44)	**Endoscopy-first approach (N=44)**	**Early Surgery results vs. Endoscopy-first results**	**P value**
SCENARIO 1: Pain relief – no. of pt (%)[a]	23 (58)	16 (39)	19 (-4 to 41)	0.098
Complete pain relief	12 (35)	8 (20)	15	
Partial pain relief	11 (23)	8 (20)	3	
No pain relief	17 (42)	25 (61)	-19	
SCENARIO 2: Pain relief – no. of pt (%)[b]	20 (54)	15 (42)	12 (-11 to 36)	0.290
Complete pain relief	14 (38)	10 (28)	10	
Partial pain relief	6 (16)	5 (14)	2	
No pain relief	17 (46)	21 (58)	-12	
SCENARIO 3: Pain relief – no. of pt (%)[c]	32 (76)	28 (67)	9 (-10 to 29)	0.334
Complete pain relief (VAS<10)*	18 (43)	9 (21)	22	
Partial pain relief (VAS<40)*	14 (33)	19 (45)	-12	
No pain relief (VAS>40)*	10 (24)	14 (33)	-9	
SCENARIO 4: Pain relief – no. of pt (%)[d]	29 (75)	26 (71)	4 (-17 to 25)	0.690
Complete pain relief (VAS<10)*	21 (54)	15 (41)	13	
Partial pain relief (VAS<40)*	8 (21)	11 (30)	-9	
No pain relief (VAS>40)*	10 (26)	11 (30)	-4	

Scenario 1: Pain relief at end of follow-up based on mean Izbicki of last 5 Izbicki scores (3 months)

Scenario 2: Pain relief at end of follow-up (Izbicki score at 18 months follow-up) based on Izbicki score

Scenario 3: Pain relief at end of follow-up based on mean VAS* of last 5 Izbicki scores (3 months)

Scenario 4: Pain relief at end of follow-up (VAS score at 18 months follow-up) based on VAS score*

eTable 11A. Quality of Life (SF-36) at Baseline; Subdomains

	Early surgery (N=44)	Endoscopy-first approach (N=42)
Vitality	41 (19)	34 (17)
Physical functioning	60 (25)	48 (22)
Bodily pain	37 (20)	31 (14)
General health perceptions	41 (16)	37 (18)
Physical role functioning	10 (18)	7 (19)
Emotional role functioning	41 (46)	37 (44)
Social role functioning	47 (29)	36 (24)
Mental health	47 (29)	36 (24)
Physical health scale	35 (7)	31 (8)
Mental health scale	38 (13)	36 (11)

eTable 11B. Quality of Life (SF-36) During Follow-up; Subdomains

	Early surgery (N=44)	**Endoscopy-first approach (N=44)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Vitality	*47 (23)*	*42 (18)*	*5 (-0.4 to 11)*	*0.066*
Physical functioning	*63 (26)*	*56 (25)*	*7 (0.1 to 14)*	***0.048***
Bodily pain	*62 (31)*	*52 (26)*	*10 (2 to 18)*	***0.011***
General health perceptions	*47 (25)*	*39 (18)*	*8 (2 to 14)*	***0.009***
Physical role functioning	*39 (44)*	*27 (40)*	*12 (1 to 24)*	***0.031***
Emotional role functioning	*71 (42)*	*55 (46)*	*16 (4 to 28)*	***0.009***
Social role functioning	*58 (32)*	*54 (28)*	*4 (-3 to 13)*	*0.242*
Mental health	*67 (24)*	*63 (22)*	*4 (-2 to 10)*	*0.218*
Physical health scale	*39 (12)*	*36 (11)*	*4 (0.5 to 7)*	***0.024***
Mental health scale	*44 (12)*	*42 (12)*	*3 (-0.8 to 6)*	*0.134*
Physical health scale – imputed	39 *(12)*	36 *(9)*	3 (-2 to 8)	0.208
Mental health scale – imputed	44 *(11)*	41 *(11)*	3 (-2 to 8)	0.205

eTable 12. Primary Outcome; Subdomains in Raw Data*

	Early surgery (N=44)	**Endoscopy-first approach (N=44)**	**Early Surgery results vs. Endoscopy-first results (95% CI)**	**P value**
Izbicki score – raw data – mean (SD)	36.0 (24.6)	46.4 (24.5)	-10.5 (-20.9 to -0.1)	0.049
Subdomain 1: frequency – mean (SD)	45.9 (33.6)	65.5 (27.9)	-19.5 (-32.6 to -6.4)	0.004
Subdomain 2: VAS score – mean (SD)	27.5 (22.7)	35.8 (16.8)	-8.3 (-16.8 to 0.1)	0.053
Subdomain 3: Medication – mean (SD)	34.2 (34.9)	43.8 (35.8)	-9.6 (-24.6 to 5.3)	0.204
Subdomain 1: Work inability – mean (SD)	36.3 (41.5)	40.7 (44.2)	-4.3 (-22.5 to 13.8)	0.637

*Only the summary Izbicki pain score was imputed. Therefore the raw data including the missings are showed here.

eTable 13. Definition of Disease Progression and Complications

Disease progression	**Definition**
Pseudocysts	Fluid-filled collection in the pancreas without epithelial cover proven by CT[a].
Chronic use of opioids	Daily need for strong opioids for a period > 6 months.
Complications	**Definition**
(Acute) pancreatitis flare-up	Episode of upper abdominal pain requiring hospitalization with either increased amylase (>3 normal level) or typical upper abdominal pain recognized by patient from previous episodes.
Cholangitis	1) Body temperature > 38.5°C and 2) Bilirubin > 20 µmol/L and/or common bile duct of > 8 mm for age ≤75 years or > 10 mm for age > 75 years on abdominal ultrasonography or CT[a].
Acute cholecystitis	1) Local signs of inflammation (Murphy's sign, right upper quadrant mass/pain/tenderness), and 2) Systemic signs of inflammation (Fever, elevated CRP[b], elevated WBC[c]), and 3) Gallstones on abdominal ultrasonography.
Perforation	Retroperitoneal or bowel-wall perforation documented by any radiographic technique.
Anastomotic leakage: Pancreatojejunostomy	High amylase level (>3 times serum amylase) in the abdominal drain fluid, or pancreatic leakage proven by imaging or at relaparotomy, often but not necessarily in combination with one or more clinical signs(abdominal pain, peritoneal tenderness, temperature above 38.5°C or WBC[c] above 15 X 109/l).
Anastomotic leakage: biliary leakage	Bilirubin in abdominal drain or dehiscence found at laparotomy, often but not necessarily in combination with one or more clinical signs (abdominal pain, peritoneal tenderness, temperature above 38.5°C or WBCc above 15 x 109/l).
Bleeding/ Hemorrhage	Any bleeding leading to relaparotomy or intervention.
Sepsis	Presence of two or more of the following: fever or hypothermia, leucocytosis or leukopenia, tachycardia, and tachypnea or a supernormal minute ventilation.
Intra-abdominal abscesses	Intra-abdominal fluid collection with positive cultures identified by ultrasonography or CT[a], associated with persistent fever and elevations of white blood cells.
Burst abdomen	Post-operative separation of the abdominal musculo-aponeurotic layers with protruding viscera.
Pneumonia	Combination of clinical signs (coughing, dyspnea), with infiltrative abnormalities on chest X-ray, raised inflammatory parameters (WBC[b] and CRP[c]) and/or positive culture in sputum. In intubated patient a positive endotracheal culture is mandatory.
Severe wound infection	Infection occurring within 30 days after the operative procedure, and requiring hospitalization or intervention with subsequent prolonged hospital stay (otherwise considered as minor complication).
Severe delayed gastric emptying	Persistent need for nasogastric intubation of over 10 days or inability to tolerate solid diet on or after the 14th postoperative day.

[a]CT: computed tomography, [b]CRP: C-reactive protein, [c]WBC: white blood cell count

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