Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients With Chronic Pancreatitis The ESCAPE Randomized Clinical Trial

Dutch Pancreatitis Study Grp; Issa, Yama; Kempeneers, Marinus A.; Bruno, Marco J.; Fockens, Paul; Poley, Jan-Werner; Ahmed Ali, Usama; Bollen, Thomas L.; Busch, Olivier R.; Dejong, Cees H.

Published in:
JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

DOI:
10.1001/jama.2019.20967

Publication date:
2020

JAMA | Original Investigation

Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients With Chronic Pancreatitis
The ESCAPE Randomized Clinical Trial

Yama Issa, MD, PhD; Marinus A. Kempeneers, BS; Marco J. Bruno, MD, PhD; Paul Fockens, MD, PhD; Jan-Werner Poley, MD, PhD; Usama Ahmed Ali, MD, PhD; Thomas L. Bollen, MD, PhD; Olivier R. Busch, MD, PhD; Cees H. Dejong, MD, PhD; Peter van Duijvendijk, MD, PhD; Hendrik M. van Dullemen, MD, PhD; Casper H. van Eijck, MD, PhD; Harry van Goor, MD, PhD; Muhammed Hadithi, MD, PhD; Jan-Willem Haveman, MD, PhD; Yolande Keulemans, MD, PhD; Vincent B. Nieuwenhuijs, MD, PhD; Alexander C. Poen, MD, PhD; Erik A. Rauws, MD, PhD; Adriaan C. Tan, MD, PhD; Willem Thijs, MD; Robin Timmer, MD, PhD; Ben J. Witteman, MD, PhD; Marc G. Besselink, MD, PhD; Jeanin E. van Hooft, MD, PhD, MBA; Hjalmar C. van Santvoort, MD, PhD; Marcel G. Dijkgraaf, PhD; Marja A. Boermeester, MD, PhD; for the Dutch Pancreatitis Study Group

IMPORTANCE For patients with painful chronic pancreatitis, surgical treatment is postponed until medical and endoscopic treatment have failed. Observational studies have suggested that earlier surgery could mitigate disease progression, providing better pain control and preserving pancreatic function.

OBJECTIVE To determine whether early surgery is more effective than the endoscopy-first approach in terms of clinical outcomes.

DESIGN, SETTING, AND PARTICIPANTS The ESCAPE trial was an unblinded, multicenter, randomized clinical superiority trial involving 30 Dutch hospitals participating in the Dutch Pancreatitis Study Group. From April 2011 until September 2016, a total of 88 patients with chronic pancreatitis, a dilated main pancreatic duct, and who only recently started using prescribed opioids for severe pain (strong opioids for ≤2 months or weak opioids for ≤6 months) were included. The 18-month follow-up period ended in March 2018.

INTERVENTIONS There were 44 patients randomized to the early surgery group who underwent pancreatic drainage surgery within 6 weeks after randomization and 44 patients randomized to the endoscopy-first approach group who underwent medical treatment, endoscopy including lithotripsy if needed, and surgery if needed.

MAIN OUTCOMES AND MEASURES The primary outcome was pain, measured on the Izbicki pain score and integrated over 18 months (range, 0-100 [increasing score indicates more pain severity]). Secondary outcomes were pain relief at the end of follow-up; number of interventions, complications, hospital admissions; pancreatic function; quality of life (measured on the 36-Item Short Form Health Survey [SF-36]); and mortality.

RESULTS Among 88 patients who were randomized (mean age, 52 years; 21 (24%) women), 85 (97%) completed the trial. During 18 months of follow-up, patients in the early surgery group had a lower Izbicki pain score than patients in the group randomized to receive the endoscopy-first approach group (37 vs 49; between-group difference, −12 points [95% CI, −22 to −2]; $P = .02$). Complete or partial pain relief at end of follow-up was achieved in 23 of 40 patients (58%) in the early surgery vs 16 of 41 (39%)in the endoscopy-first approach group ($P = .10$). The total number of interventions was lower in the early surgery group (median, 1 vs 3; $P < .001$). Treatment complications (27% vs 25%), mortality (0% vs 0%), hospital admissions, pancreatic function, and quality of life were not significantly different between early surgery and the endoscopy-first approach.

CONCLUSIONS AND RELEVANCE Among patients with chronic pancreatitis, early surgery compared with an endoscopy-first approach resulted in lower pain scores when integrated over 18 months. However, further research is needed to assess persistence of differences over time and to replicate the study findings.

TRIAL REGISTRATION ISRCTN Identifier: ISRCTN45877994

Visual Abstract

Editorial page 219

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 274

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Dutch Pancreatitis Study Group members appear at the end of the article.

Corresponding Author: Marja A. Boermeester, MD, PhD, Department of Surgery, Amsterdam UMC, location AMC, Meibergdreef 9, Ste G4-132.1, 1105AZ Amsterdam, the Netherlands (m.a.boermeester@amsterdamumc.nl).

JAMA. 2020;323(3):237-247. doi:10.1001/jama.2019.20967

Pain is the most important clinical problem in chronic pancreatitis, occurring in 80% to 90% of patients.[1,2] It is thought to be caused by obstruction of the pancreatic duct. In current practice, these patients are treated using an endoscopy-first approach. This approach includes treatment with opioids followed, if necessary, by multiple endoscopic interventions including stone removal and stenting of ductal strictures. Surgical intervention is postponed until other treatments have failed and pain becomes unmanageable.[3-5] During the disease course of chronic pancreatitis, 30% to 75% of patients ultimately undergo surgery, usually in the end stage of the disease.[1,6-8] A randomized clinical trial (RCT) in patients with chronic pancreatitis in a late disease phase showed that surgical treatment was more effective than endoscopic treatment for midterm and long-term pain relief in patients with refractory pain and long-term opioid dependency.[6,9] Observational studies have suggested that earlier surgery could mitigate disease progression, providing better pain control and preserving pancreatic function.[10-13] Therefore, the Dutch Pancreatitis Study Group conducted a multicenter RCT to investigate whether early surgical intervention is more effective than the endoscopy-first approach for improving clinical outcomes.

Key Points

Question For patients with painful chronic pancreatitis, is early surgery more effective than the endoscopy-first approach in reducing pain?

Findings In this randomized clinical trial that included 88 patients with obstructive painful chronic pancreatitis, early surgery compared with an endoscopy-first approach resulted in significantly less pain over 18 months (area under the curve, 37 vs 49 points measured with the Izbicki pain score (range, 0-100 [increasing score indicates more pain severity]).

Meaning Although early surgery resulted in less pain over 18 months, because of study limitations, further research is needed to assess persistence of differences over time, as well as to replicate the study findings.

Methods

Study Design

The ESCAPE trial was conducted as an unblinded, multicenter, parallel-group randomized clinical superiority trial (see study protocol in Supplement 1).[14] 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 despite nonopioid 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 2 years. Patients were screened for the detailed eligibility criteria (eTable 1 in Supplement 2) in 6 university medical centers and 24 large teaching hospitals of the Dutch Pancreatitis Study Group 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 into the early surgery group or the endoscopy-first approach group. All interventions in both treatment groups were discussed and performed by multidisciplinary teams in 7 predefined chronic pancreatitis expert centers.

Randomization

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 (≥4 cm vs <4 cm).

Early Surgery

A surgical drainage procedure was performed within 6 weeks after randomization by an experienced pancreatic surgeon who had performed at least 25 pancreatic operations specifically for chronic pancreatitis. Patients with a nonenlarged pancreatic head (<4 cm) underwent surgical drainage of the entire length of the pancreatic duct by a lateral pancreaticojejunostomy, according to Partington and Rochelle.[15] Patients with an enlarged pancreatic head (≥4 cm) underwent a duodenum-preserving pancreatic head resection as described by Frey and Smith[16] and Beger and colleagues.[17]

Endoscopy-First Approach

The protocol for optimal endoscopy-first approach was designed in consensus by the Dutch Chronic Pancreatitis Expert Panel and according to recent treatment guidelines.[3,5,18]

Step 1. Medical Treatment

For optimal pain control, pain medication was provided according to the World Health Organization pain ladder.[3,19] If adequate pain control was not achieved by conventional medication, co-medication such as pregabalin for neuropathic pain was prescribed, and a pain specialist or dietitian was consulted. For detailed information about the medical treatment, see the eAppendix (Supplement 2). Failure of medical treatment, defined as a pain score of greater than 4 on the visual analog scale (VAS) for more than 6 weeks, or unacceptable adverse effects from the medication were indications for subsequent endoscopic treatment.

Step 2. Endoscopic Treatment

Endoscopic interventions were performed by experienced endoscopists who had performed at least 50 therapeutic endoscopic interventions specifically for chronic pancreatitis. Stones in the pancreatic duct with a diameter of 7 mm or greater were treated using 3 sessions of extracorporeal shock-wave lithotripsy followed by an endoscopic retrograde pancreatography. In case of small intraductal stones (<7 mm), patients underwent direct endoscopic retrograde pancreatography

without extracorporeal shock-wave lithotripsy. If stone removal during endoscopic retrograde pancreatography was incomplete, 1 or more pancreatic stents (7F to 10F catheter) were inserted and further stone removal was attempted via a subsequent endoscopic retrograde pancreatography.

After sphincterotomy, strictures were treated by dilatation followed by insertion of 1 or more stents in the pancreatic duct. After stent insertion, patients underwent an elective endoscopic retrograde pancreatography every 3 months. When complete runoff of contrast material was observed after stent removal and a 12- to 15-mm 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 1 year.

Failure of endoscopic treatment was considered when a patient had a score above 4 on the visual analog scale for more than 6 weeks, despite a maximum of 3 endoscopic interventions or when stenting was still needed to provide pain relief after 1 year of stenting (see eAppendix in Supplement 2 for a detailed description).

Step 3: Surgical Treatment

Surgical intervention was performed as described in the early surgery section.

Outcomes

The primary outcome was pain, measured on the validated Izbicki pain score and integrated over a follow-up period of 18 months (range, 0-100 [increasing score indicates more pain severity]; see the eAppendix and eFigure 2 in Supplement 2).[9,20]

Secondary pain outcomes were pain relief at end of follow-up (complete relief, Izbicki pain score ≤10; partial relief, Izbicki pain score >10 [but more than 50% decrease compared with the baseline score]) assessed using the visual analog scale pain score, the Büchler pain score, and a post hoc analysis of the Izbicki pain score at the end of follow-up (range for all, 0-100 [increasing score indicates more pain severity).[21] Other secondary outcomes were quality of life assessed using the 36-Item Short Form Health Survey (SF-36; score of 50 represents the Dutch population; score range, 0-100 [lower score indicates more disability]),[22] disease progression including development of pseudocysts, chronic use of opioids (>6 months), hospital admissions for chronic pancreatitis flare-ups, pancreatic exocrine insufficiency (fecal elastase <200 μg/g), endocrine insufficiency (use of diabetes medication), total number of hospital admissions, number of interventions, complications of interventions, and death (eAppendix in Supplement 2).

Data Collection

The primary outcome was assessed every 2 weeks during 18 months using a questionnaire that patients completed either online or on paper. Laboratory investigations and other outcomes were collected during scheduled visits to the outpatient clinic at baseline and at 6, 12, and 18 months. A standardized case record form was used to collect the medical data. A designated study nurse, not involved in patient care, monitored the data collection at all sites. 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 expert pancreatic radiologist (T.L.B.). The duct clearance after endoscopic intervention was reassessed by an experienced pancreatic endoscopist (J.W.P.) by analyzing all images and endoscopic reports of the last endoscopic intervention.

Safety Monitoring

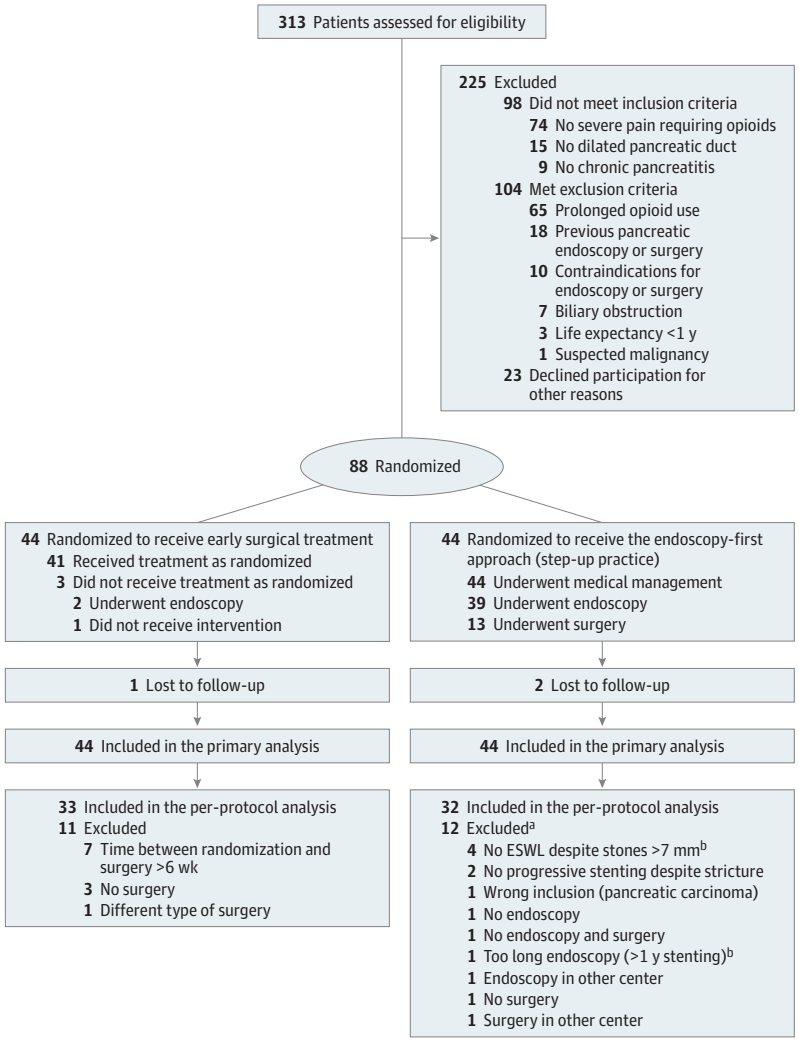
After every 25 included patients, an independent data and safety monitoring committee, unaware of the treatment assignment, evaluated the trial progress and safety parameters. Adverse events were evaluated by the data and safety monitoring committee and reported online to the central committee on research involving human study participants.

Statistical Analysis

The hypothesis of this study was that early surgery would be more effective in pain reduction than the endoscopy-first approach. The sample size calculation could not be based on previously published data. Therefore, the Dutch Chronic Pancreatitis Expert Panel agreed by consensus on a clinically relevant difference of 15 points on the Izbicki pain score with a standard deviation of 20. Together with an expected loss to follow-up of 10%, a power of 90%, and a 2-sided α level of .05, a total of 88 patients were needed.

Analyses were performed according to a strict intention-to-treat principle in which all patients were included. In addition, a post hoc per-protocol analysis was performed for the primary outcome (see the eAppendix in Supplement 2 for patient selection). The primary outcome was analyzed using a 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 mean Izbicki score during follow-up. A corrected primary outcome was calculated post hoc by adjustment for age and pancreatic head enlargement using a generalized mixed model with Tweedie distribution. No adjustment for baseline Izbicki pain score or centers was performed (see the eAppendix and eTable 2 in Supplement 2 for the substantiation). All other repeated measurement outcomes (pain score outcomes and quality of life) were analyzed as mean scores during follow-up. Missing data were considered to be missing at random. Only missing data in the pain score outcomes and quality of life were imputed using linear interpolation and multiple imputation as these outcomes were measured during follow-up (see the eAppendix and eTable 3 in Supplement 2). The primary outcome analysis was performed by a blinded statistician (M.G.D.). Subgroup analyses were performed for pain pattern as stated in the protocol. Post hoc subgroup analyses were performed for etiology and duct clearance after endoscopy (see the eAppendix and eTables 4-6 in Supplement 2 for all subgroup analyses. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Figure 1. Flowchart of Enrollment, Randomization, and Follow-up



[a] To see in which step an exclusion took place, see eTable 9 in Supplement 2.

[b] One patient underwent no extracorporeal shock-wave lithotripsy (ESWL) despite having stones greater than 7 mm, and this same patient also underwent endoscopies for too long (>1 year of stenting).

Dichotomous outcomes were presented as numbers and percentages and compared using the χ^2 test or 2-sided Fisher exact test where appropriate. Normally distributed continuous measures were expressed as means with 95% CIs and analyzed using the *t* test. Continuous data that were not normally distributed were presented as medians with interquartile ranges (IQRs) and compared using the Mann-Whitney *U* test. A 2-tailed *P* value of less than .05 was considered statistically significant. All analyses were presented with 95% CIs. The Hodges-Lehman method was used to calculate 95% CIs for medians. Data analysis was performed using SPSS version 25 and R Project software (http://www.r-project.org).

Results

Participants

Between April 2011 and September 2016, 313 patients were assessed for eligibility, and a total of 88 patients were enrolled and randomized (**Figure 1**). Patients were a mean age of 52 years, 24% were women, and 69% had alcohol use as pancreatitis etiology. Baseline characteristics were comparable except for age (–7 years in favor of early surgery) and are presented in **Table 1**. Median duration of weak opioid use before randomization was 2 months, and median duration was 3 weeks for strong opioid use. Imaging before randomization showed a median diameter of the pancreatic duct of 8 mm (IQR, 6-10). Imaging showed that 16% of patients had both ductal stones and strictures, 74% had only ductal stones, and 10% had only ductal strictures (see eTable 7 in Supplement 2).

Early Surgery

Of the 44 patients randomized to the early surgery group, 41 underwent surgery (median time from randomization to surgery, 40 days [IQR, 32-65]). A lateral pancreatojejunostomy was performed in 24 patients, and 15 patients underwent a duodenum-preserving pancreatic head resection. One patient underwent a distal pancreatectomy and 1 patient had a pylorus-preserving pancreatoduodenectomy. Three patients refused

Table 1. Baseline Characteristics of Patients in the Early Surgery Group vs the Endoscopy-First Approach Group

	Early Surgery (n = 44)	Endoscopy-First Approach (n = 44)
Age, mean (SD), y	49 (10)	56 (9)
Men, No. (%)	33 (75)	34 (77)
Women, No. (%)	11 (25)	10 (23)
Cause of pancreatitis		
Alcohol use	34 (77)	27 (61)
Nonalcoholic	10 (23)	17 (39)
Idiopathic	7 (16)	12 (27)
Hereditary	1 (2)	1 (2)
Other	2 (5)	4 (9)
Body mass index, median (IQR)[a]	22 (20-24)	22 (19-26)
Continuous pain pattern, No. (%)	29 (66)	35 (79)
Recurrent pain pattern, No. (%)	15 (34)	9 (21)
Enlarged pancreatic head, No. (%)	21 (48)	23 (52)
Izbicki pain score, mean (SD)[b]	63 (19)	64 (16)
Strong opioid use, median (IQR), mo[c]	0.8 (0.5-1.5)	0.5 (0.4-1.8)
Weak opioid use, median (IQR), mo[c]	2.0 (1.0-4.0)	1.5 (0.3-3.0)
Duration of chronic pancreatitis, median (IQR), mo[d]	12 (3-60)	12 (5-36)
Smoker, No./total No. (%)		
Current	41/44 (93)	36/42 (86)
Past	3/44 (7)	6/42 (14)
Never	0/44	0/42
Smoking pack-years, median (IQR)[e]	28 (18-43)	23 (9-32)
Alcohol consumption, No./total No. (%)		
Current	9/44 (21)	6/42 (14)
Median (IQR), units/d	5 (2-16)	4 (1-7)
Past	32/44 (73)	33/42 (79)
Never	3/44 (7)	3/42 (7)
Exocrine function[f]		
Insufficiency, No./total No. (%)	33/40 (83)	34/41 (85)
Fecal elastase, median (IQR), µg/g	29 (15-133)	23 (15-122)
Endocrine function[g]		
Insufficiency, No./total No. (%)	8/42 (19)	10/40 (25)
Hemoglobin A_{1c}, median (IQR), mmol/mol	43 (39-50)	43 (39-55)
Hemoglobin A_{1c}, median (IQR), %	6.1 (5.7-6.7)	6.1 (5.7-7.2)
SF-36 quality of life scores, mean (SD)[h]		
Physical health scale	35 (7)	31 (8)
Mental health scale	38 (13)	36 (11)

Abbreviations: IQR, interquartile range; SF-36, 36-Item Short Form Health Survey.

[a] Calculated as weight in kilograms divided by height in meters squared. Assessed in 42 patients in the endoscopy-first approach group.

[b] Assessed in 41 of 44 patients in each study group. Scale ranges from 0 to 100 points (increasing score indicates more pain severity). Questions consist of 4 items regarding frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work. For example, a score of 60 to 65 indicates a patient with weekly pain, a score on the visual analog scale of 50 while prescribed strong opioids, and recent inability to work (eFigure 2 in Supplement 2).

[c] Weak opioids: codeine, tramadol, and hydrocodone. Strong opioids: all other opioids such as morphine, oxycodone, fentanyl, pethidine, and buprenorphine.

[d] Assessed in 42 of 44 patients in each study group.

[e] Assessed in 42 patients in the early surgery group and in 41 in the endoscopy-first approach group.

[f] Exocrine level is insufficient when fecal elastase is less than 200 µg/g.

[g] Endocrine level is insufficient when patient needs diabetes medication.

[h] Physical and mental summary scales were assessed in 42 patients in the endoscopy-first approach group. Scale range: 0 (maximum disability) to 100 (no disability). A score of 50 represents the general Dutch population. Subdomains to physical and mental summary scales are reported in eTable 11A in Supplement 2.

surgery after randomization, of whom 2 patients were treated endoscopically and 1 received only medical treatment.

Endoscopy-First Approach

Step 1. Optimal Medical Treatment

All 44 patients started the endoscopy-first approach with optimal medical treatment. Step 1 was successful in 2 patients (5%) and failed in 42 patients (95%).

Step 2. Endoscopic Intervention

In 39 of 44 patients (89%), endoscopy was performed with a median of 3 endoscopic procedures (IQR, 1-4); 29 patients had stones and 22 of them required extracorporeal shock-wave lithotripsy. Thirty-four of 39 patients undergoing endoscopy had strictures (with or without stones); in 32 patients dilatation was performed. In 29 of 39 patients undergoing endoscopy 1 or more stents were inserted, of which 18 patients underwent multiple stenting procedures for recurrent stenosis. Of the 39 patients who were treated endoscopically, complete duct clearance after the last endoscopy was achieved in 24 patients (62%). Further details about endoscopic treatment are available in the eAppendix (Supplement 2).

Endoscopy failed in 24 patients (62%). At the end of follow-up, 13 of these patients had undergone surgery and another 6 patients were on the waiting list for surgery. One patient refused surgery and in another patient, surgery was not deemed possible due to an atrophic pancreas. An additional 3 patients still underwent repeated stenting procedures at the end of follow-up.

Table 2. Primary and Secondary Outcomes

	Early Surgery (n = 44)[a]	Endoscopy-First Approach (n = 44)[a]	Early Surgery vs Endoscopy-First, Difference (95% CI)	*P* Value
Izbicki score: primary analysis[b]				
Area under curve	37 (25)	49 (25)	−12 (−22 to −2)	.02
Corrected area under curve[c]	34 (21)	52 (29)	−18 (−29 to −7)	.001
Izbicki score: per protocol[b]				
No. of patients	33	32		
Area under curve	33 (26)	46 (25)	−13 (−25 to −0.1)	.05
Corrected area under curve[c]	30 (21)	50 (30)	−20 (−33 to −7)	.003
Patients with some pain relief at end of follow-up, No./total No. (%)	23/40 (58)	16/41 (39)	19 (−4 to 41)	.10
Complete relief[d]	12/40 (35)	8/41 (20)		
Partial relief[d]	11/40 (23)	8/41 (20)		
Izbicki score at end of follow-up[b]	31 (29)	42 (32)	−11 (−25 to 3)	.13
VAS score during follow-up[e]	28 (22)	36 (17)	−9 (−17 to −1)	.03
Büchler pain score during follow-up[f]	36 (26)	51 (21)	−14 (−24 to −5)	.004
SF-36 quality of life during follow-up[g]				
Physical health scale	39 (12)	36 (9)	3 (−2 to 8)	.21
Mental health scale	44 (11)	41 (11)	3 (−2 to 8)	.21
Disease progression, No./total No. (%)				
Pseudocysts	2/44 (5)	6/44 (14)	−9 (−21 to 3)	.27
Chronic opioid use[h]	20/42 (47)	26/42 (60)	−14 (−35 to 7)	.20
Chronic pancreatitis flare-up	18/44 (41)	20/44 (46)	−5 (−26 to 17)	.67
Flare-ups per patient, median (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	.52
Exocrine insufficiency, No./total No. (%)[i]	37/40 (93)	37/41 (90)	3 (−10 to 15)	>.99
Endocrine insufficiency, No. (%)[j]	12 (27)	19 (43)	−16 (−36 to 4)	.12
Hospital admissions, median No. per patient (IQR)	2 (1 to 2)	2 (1 to 4)	0 (−1 to 0)	.15
Hospital stay, median (IQR), d	11 (7 to 15)	10 (2 to 19)	1 (−3 to 5)	.57
Interventions per patient, median (IQR)	1 (1 to 1)	3 (2 to 4)	−2 (−3 to −1)	<.001
No. of endoscopic procedures ±ESWL[k]	0 (0 to 0)	3 (1 to 4)		
No. of surgical procedures	1 (1 to 1)	0 (0 to 1)		
Treatment complications, No. of patients (%)[l]	12 (27)	11 (25)	2 (−17 to 21)	.81

Abbreviations: ESWL, extracorporeal shock-wave lithotripsy; IQR, interquartile range; SF-36, 36-Item Short Form Health Survey; VAS, visual analog scale.

[a] Values are reported as mean (SD) unless otherwise indicated.

[b] Scale ranges from 0 to 100 points (increasing score indicates more pain severity). Questions consist of 4 items regarding frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work. For example: a score of 30 to 40 indicates a patient with monthly pain, a VAS score of 30 indicates a short inability to work and treatement with nonopioids and with short inability to work (eFigure 2, eTable 12 in Supplement 2).

[c] Post hoc correction by adjustment for age and pancreatic head enlargement using a generalized mixed model with Tweedie distribution. For detailed information see the eAppendix in Supplement 2.

[d] Complete pain relief is defined as having an Izbicki pain score of 10 or less; partial relief is a score of greater than 10 but decreased by more than 50% when compared with baseline.

[e] VAS ranges from 0 (no pain) to 100 (most severe pain imaginable).

[f] Consists of only the frequency and VAS scale derived from the Izbicki pain score. Scale ranges from 0 to 100 points (increasing with severity). A score of 35 to 50 indicates a patient with monthly pain and a VAS score of 30.

[g] Scale range: 0 (maximum disability) to 100 (no disability). A score of 50 represents the general Dutch population. Subdomains to physical and mental summary scales are reported in eTable 11B in Supplement 2.

[h] Indicates a daily need for strong opioids for more than 6 months.

[i] Exocrine level is insufficient when fecal elastase is less than 200 µg/g.

[j] Endocrine level is insufficient when patient needs use of diabetes medication.

[k] ESWL sessions with the subsequent endoscopic retrograde cholangiopancreatography were measured as a single endoscopic procedure; 39 patients underwent endoscopic procedures, of which 22 patients underwent ESWL.

[l] Treatment complications were complications that were caused by endoscopic or surgical interventions. Definition of the complications and number of patients per complication are presented in eTables 10 and 13 in Supplement 2.

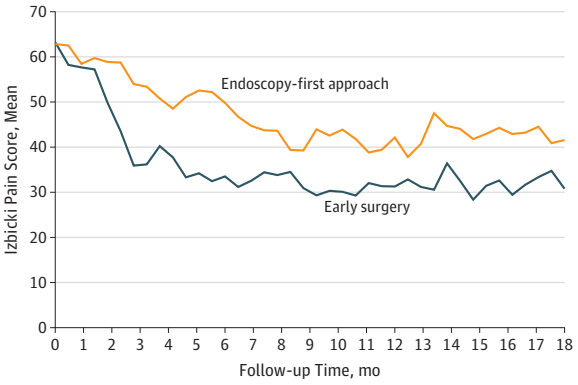
Step 3. Surgical Treatment

Thirteen of the 44 patients in the endoscopy-first approach group (30%) underwent surgery after a median of 299 days (IQR, 230-454); 8 patients had a Frey procedure, 3 patients a lateral pancreatojejunostomy, and 1 patient a pancreatoduodenectomy. Another patient had a pancreatic body and tail resection with a pancreatojejunostomy at the pancreatic head. Of the patients with endoscopic duct clearance, 17% underwent surgery compared with 60% of the patients without endoscopic duct clearance (see eFigure 1 in Supplement 2 for a flowchart of the endoscopy-first approach).

Clinical Outcomes

The primary and secondary outcomes are presented in **Table 2.** The primary outcome, the mean AUC for the Izbicki pain score during follow-up, was 37 (95% CI, 30 to 44) in the early surgery

Figure 2. Mean Izbicki Pain Score During 18 Months of Follow-up



Early surgery																			
No. of patients	44	44	44	44	44	44	44	44	44	43	43	43	43	43	43	43	43	43	43
No. who underwent surgery (cumulative)	10	29	35	40	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
Endoscopy-first approach																			
No. of patients	44	44	44	43	43	43	43	43	43	43	43	43	43	43	42	42	42	42	42
No. who underwent surgery (cumulative)	0	0	0	0	0	1	2	6	6	7	7	7	7	9	10	12	12	12	13

Mean difference during follow-up for the early surgery group vs the endoscopy-first approach group: −12 (95% CI, −22 to −2); $P = .02$. The scale for the Izbicki pain score ranges from 0 to 100 points (increasing score indicates more pain severity). Questions consist of 4 items regarding frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work (see eFigure 2 in Supplement 2 for scoring details).

group and 49 (95% CI, 41 to 57) in the endoscopy-first group, resulting in a difference of −12 points (95% CI, −22 to −2; [$P = .02$]). Directly after early surgery, a clear and constant decrease in Izbicki pain score was observed (**Figure 2**).

Complete or partial pain relief at the end of follow-up was observed in 23 of 40 patients (58%) in the early surgery group and in 16 of 41 (39%) in the endoscopy-first group (difference, 19% [95% CI, −4% to 41%]; $P = .10$). Pain relief during follow-up is visualized in **Figure 3**. The early surgery group underwent significantly fewer interventions (between-group difference, −2 [95% CI, −3 to −1]; $P < .001$). There was no significant difference between groups for death (0% [95% CI, 0% to 0%]), hospital admissions (0 [95% CI, −1 to 0]; $P = .15$), exocrine pancreatic insufficiency (3 [95% CI, −10 to 15]; $P > .99$), endocrine pancreatic insufficiency (−16 [95% CI, −36 to 4]; $P = .12$), and quality of life (physical component, 3 [95% CI, −2 to 8]; $P = .21$ and mental component, 3 [95% CI, −2 to 8]; $P = .21$).

Adverse Events

Adverse events during follow-up occurred in 12 of 44 patients (27%) in the early surgery group vs 11 of 44 patients (25%) in the endoscopy-first approach group, which was comparable. All adverse events in the early surgery group were postoperative complications. In the endoscopy-first approach group, 7 patients (16%) had a complication after endoscopy and 5 patients (38%) had a postoperative complication. In the early surgery group, 3 patients had a anastomotic leakage after surgery compared with 2 patients in the endoscopy-first group. Abdominal bleeding after surgery occurred in 3 patients in the early surgery group and in 1 patient of the endoscopy-first group. Nine patients in the endoscopy-first group had a pancreatitis flare-up requiring hospitalization (vs 0 patients in the early surgery group) (severe treatment complications are given in eTable 8 in Supplement 2).

Post Hoc Analyses

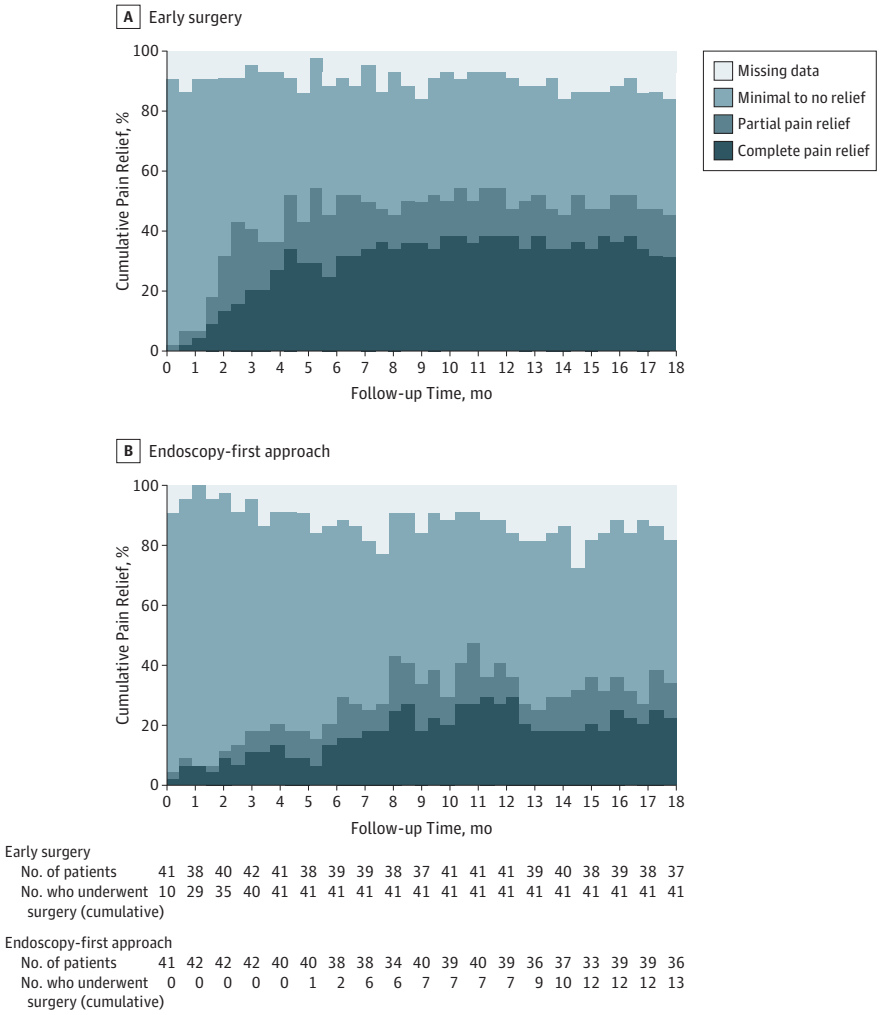
On a post hoc basis, a per-protocol analysis of the primary outcome was performed that showed the same difference between the early surgery group vs the endoscopy-first approach group (−13 points [95% CI, −25 to −0.1]; $P = .048$). Izbicki pain score at the end of follow-up showed a difference of −11 points (95% CI, −25 to 3; [$P = .13$]). Subgroup analysis showed that in the endoscopy-first group, patients with endoscopic duct clearance had a mean AUC Izbicki pain score during total follow-up of 40 (95% CI, 31 to 50) compared with 60 (95% CI, 48 to 72) in patients without endoscopic duct clearance (eFigure 3 and eTable 6 in Supplement 2).

Discussion

In this multicenter RCT among patients with chronic pancreatitis, early surgery compared with an endoscopy-first approach resulted in lower pain scores with fewer interventions when integrated over 18 months. At the end of follow-up, single time point pain scores and proportion of patients with complete or partial pain relief were not significantly different. Pancreatic function and quality of life were not significantly different between groups.

The findings on the primary outcome, the Izbicki pain score during 18 months' follow-up, were consistent with previous observational studies that concluded early surgery results in better pain relief compared with postponed surgery in patients with chronic pancreatitis.[10,12] Previous opioid use and multiple endoscopic interventions before surgery were associated with less pain relief, as compared with surgical intervention in an early phase of the disease.[10] These factors could be possible explanations for the beneficial outcome of early surgery in this study. First, short-term opioid use before surgery

Figure 3. Pain Relief During 18 Months of Follow-up



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Early surgery																			
No. of patients	41	38	40	42	41	38	39	39	38	37	41	41	41	39	40	38	39	38	37
No. who underwent surgery (cumulative)	10	29	35	40	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
Endoscopy-first approach																			
No. of patients	41	42	42	42	40	40	38	38	34	40	39	40	39	36	37	33	39	39	36
No. who underwent surgery (cumulative)	0	0	0	0	0	1	2	6	6	7	7	7	7	9	10	12	12	12	13

Complete relief is defined as having an Izbicki pain score of 10 or less; partial relief is a score of greater than 10 but decreased by more than 50% when compared with baseline. Average pain relief during follow-up was 44% in the early surgery group and 30% in the endoscopy-first approach group (difference, 14% [95% CI, −7% to 35%]; P = .18). Other pain relief scenarios at the end of follow-up are presented in eTable 10 in Supplement 2.

could have led to better pain control since long-term opioid use leads to opioid dependency. Furthermore, prolonged opioid use is associated with central sensitization and hyperalgesia, which can lead to a self-perpetuating state that is impossible to treat with interventions such as endoscopy or surgery.[23] Second, in this study, endoscopy failed in two-thirds of patients, and one-third of the patients from the endoscopic group were referred to undergo surgery within a follow-up of 18 months. This number of endoscopy failures and referrals to undergo surgery were because not all stenoses could be treated successfully, and strictures and stones often recurred. By directly performing pancreatic drainage surgery, all stenoses can be treated in a single intervention, which may lead to a more definitive result.

Conversely, proportion of complete or partial pain relief at the end of follow-up was not significantly different between early surgery and the endoscopy-first practice. It is possible that early surgery may be beneficial primarily in the short term and may become comparable with the endoscopy-first practice in the long term, when in both groups, patients have undergone surgery. Also in that case, it is questionable if the multiple steps of the endoscopy-first approach are worth doing since they fail at a high rate. Furthermore, optimal medical management as first-step treatment failed in nearly all patients in the endoscopy-first approach group. This first step should, therefore, only be used as a short bridging period to interventional therapy.

Two previous RCTs compared surgery with endoscopy in patients with chronic pancreatitis, and both concluded that surgery was more effective in pain relief than endoscopy.[9,24] In contrast with the present study, which included patients in the early phase of treatment with short-term opioid use, the previous studies included patients in a much later phase of chronic pancreatitis, with refractory pain and long-term opioid dependency. Cahen et al showed that when compared with endoscopy, better pain relief was provided with mid-term surgery (75% vs 32%; P = .007) and also with long-term surgery (80% vs 38%; P = .04).[6,9] These studies have not changed clinical practice since endoscopic therapy is still preceding surgery in many cases. What did change is that surgery is considered more often after failed endoscopy, instead of years of stent exchanges.

There is no consensus as to the optimal treatment of patients with an enlarged pancreatic head. In a recent survey among pancreatologists, 58% preferred a surgical treatment vs 42% who would perform endoscopic therapy.[25] In a previous RCT comparing surgery with endoscopy, patients with an enlarged pancreatic head were explicitly excluded, which made it difficult to extrapolate the results to all patients with ductal obstruction.[9] In the present study, patients with an enlarged pancreatic head were also included. The results can therefore also be extrapolated to patients with an enlarged pancreatic head and ductal obstruction.

Among patients who received endoscopic treatment, post hoc analysis showed that complete duct clearance was associated with a much lower Izbicki pain score—almost as low as in the early-surgery group. This might leave the option open for endoscopy to be tried first in a subgroup of patients, but complete duct clearance and pain reduction should be obtained and confirmed at short-term follow-up. New endoscopic techniques such as intraductal pancreaticoscopy and endoscopic laser or electrohydraulic lithotripsy are under consideration for future use, which may lead to higher complete duct clearance rates in the future.

Previous studies have suggested that early surgical intervention can mitigate disease progression and specific loss of pancreatic function.[13,26,27] These findings were not shown in this trial. Most patients already had pancreatic exocrine insufficiency at randomization, and therefore, no benefit from either treatment could be obtained. More patients developed endocrine insufficiency in the endoscopy-first approach group, as compared with the early-surgery group, but no significant differences were found. Potentially, there is no beneficial effect of early surgery on endocrine and exocrine function in patients who recently started prescription use of opioids because of progressive pain, or the 18 months' follow-up was not sufficient to achieve a significant difference.

Despite lower pain scores during follow-up for the early surgery group, quality of life was not significantly different between both groups. Potentially, the differences in pain scores between both groups were too small to distinguish differences in quality of life. The fact that both the pain relief during follow-up (Figure 3) and pain relief at end of follow-up were not statistically different supports this concern.

Limitations

This study has several limitations. First, the high frequency of pain score assessment, together with the subjectivity of the pain score, could have led to observer bias. The pain score that was used is a validated pain score that was specifically designed for chronic pancreatitis and used in previous trials.[9] Nevertheless, the effect of treatment could have been underestimated since repetitive asking about pain potentially results in patients reporting higher pain scores.

Second, the combination of an unblinded design with the subjective outcome could have led to biased results. Concerns have been raised that studies on invasive interventions in chronic pancreatitis never included a sham control group.[3] The beneficial effect of interventions may therefore, in theory, be a placebo effect. Sham-controlled trials are subject to debate because it is ethically questionable to withhold patients with severe pain from interventions that have shown to be successful without sham comparison.

Third, the inclusion of 88 patients in this study was based on power calculation for the primary outcome, but this small sample size precluded definitive conclusions regarding secondary outcomes because of a lack of statistical power. Therefore, findings for analyses of secondary end points should be interpreted as exploratory.

Fourth, although it is a strength of this study that all patients enrolled from 30 participating hospitals were treated by experts working in multidisciplinary teams, and consequently, these results may not generalize to outcomes at centers that have less expertise, it can be difficult to have patients referred for surgery in this early phase of treatment. Multidisciplinary teams, including gastroenterologists and surgeons, are crucial early in the disease course to successfully treat these patients without large delays.

Conclusions

Among patients with chronic pancreatitis, early surgery compared with an endoscopy-first approach to treatment resulted in lower pain scores when integrated over 18 months. However, further research is needed to assess persistence of differences over time and to replicate the study findings.

ARTICLE INFORMATION

Accepted for Publication: December 4, 2019.

Author Affiliations: Department of Surgery, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Issa, Kempeneers, Ahmed Ali, Busch, Besselink, Boermeester); Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, Amsterdam, the Netherlands (Bruno, Poley); Department of Gastroenterology and Hepatology; Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Fockens, Rauws, van Hooft); Department of Radiology, St Antonius Hospital, Nieuwegein, the Netherlands (Bollen); Department of Surgery, Maastricht University Medical Center+, Maastricht, the Netherlands (Dejong); Department of Surgery, Universitätsklinikum Aachen, Aachen, Germany (Dejong); Department of Surgery, Gelre Hospital, Apeldoorn, the Netherlands (van Duijvendijk); Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (van Dullemen); Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, the Netherlands (van Eijck); Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands (van Goor); Department of Gastroenterology and Hepatology, Maasstad Hospital, Rotterdam, the Netherlands (Hadithi); Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Haveman); Department of Gastroenterology and Hepatology, Zuyderland Hospital, Sittard/Heerlen, the Netherlands (Keulemans); Department of Surgery, Isala Hospital, Zwolle, the Netherlands (Nieuwenhuijs); Department of Gastroenterology and Hepatology, Isala Hospital, Zwolle, the Netherlands (Poen); Department of Gastroenterology and Hepatology, Canisius-Wilhemina Hospital, Nijmegen, the Netherlands (Tan); Department of Gastroenterology and Hepatology, Martini Hospital, Groningen, the Netherlands (Thijs); Department of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, the Netherlands (Timmer); Department of Gastroenterology and Hepatology, Gelderse Vallei Hospital, Ede, the Netherlands (Witteman); Department of Surgery, St Antonius Hospital, Nieuwegein, the Netherlands (van Santvoort); Department of Surgery, University

Medical Center Utrecht, Utrecht, the Netherlands (van Santvoort); Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Amsterdam Public Health, Amsterdam UMC, University of Amsterdam, the Netherlands (Dijkgraaf).

Author Contributions: Dr Boermeester had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Issa and Mr Kempeneers contributed equally as co–first authors.
Concept and design: Issa, Bruno, Fockens, Ahmed Ali, Busch, Dejong, van Eijck, van Goor, Nieuwenhuijs, Witteman, Besselink, van Hooft, Van Santvoort, Dijkgraaf, Boermeester.
Acquisition, analysis, or interpretation of data: Issa, Kempeneers, Bruno, Fockens, Poley, Ahmed Ali, Bollen, Busch, Dejong, van Duijvendijk, van Dullemen, van Eijck, van Goor, Hadithi, Haveman, Keulemans, Nieuwenhuijs, Poen, Tan, Thijs, Timmer, Witteman, Besselink, van Hooft, Van Santvoort, Dijkgraaf, Boermeester.
Drafting of the manuscript: Issa, Kempeneers, Bruno, Ahmed Ali, van Eijck, Nieuwenhuijs, van Hooft, Van Santvoort.
Critical revision of the manuscript for important intellectual content: Issa, Kempeneers, Bruno, Fockens, Poley, Ahmed Ali, Bollen, Busch, Dejong, van Duijvendijk, van Dullemen, van Eijck, van Goor, Hadithi, Haveman, Keulemans, Nieuwenhuijs, Poen, Tan, Thijs, Timmer, Witteman, Besselink, van Hooft, Van Santvoort, Dijkgraaf, Boermeester.
Statistical analysis: Issa, Kempeneers, Ahmed Ali, Van Santvoort, Dijkgraaf, Boermeester.
Obtained funding: Issa, Ahmed Ali, Van Santvoort, Dijkgraaf, Boermeester.
Administrative, technical, or material support: Issa, Kempeneers, Ahmed Ali, Dejong, van Goor, Poen, Timmer, Besselink, van Hooft, Van Santvoort.
Supervision: Issa, Bruno, Poley, Ahmed Ali, Busch, Dejong, van Duijvendijk, van Goor, Haveman, Nieuwenhuijs, Tan, Witteman, Besselink, van Hooft, Van Santvoort, Boermeester.

Conflict of Interest Disclosures: Dr Ahmed Ali reports receipt of grants from ZonMW (governmental agency, nonprofit, Ministry of Health), MLDS (nongovernmental organization, national gastrointestinal disease association, nonprofit), and Alvleesklliervereniging (patient association of pancreatic disease, nongovernmental organization, nonprofit) during the conduct of the study. Dr Boermeester reports receipt of grants from Mylan, Acelity/KCI, Johnson & Johnson, Bard, New Compliance, and Alvleesklliervereniging; and other from Acelity/KCI (speaker, instructor, advisory board), Johnson & Johnson (speaker and advisory board), Bard (speaker), Gore (speaker and instructor), and Smith & Nephew outside the submitted work. Dr Bruno reports receipt of grants for investigator-initiated studies from Cook Medical, Pentax Medical, 3M, and Mylan; grants for industry and investigator-initiated studies from Boston Scientific; and personal fees for consultancies and lectures from Boston Scientific, from Cook Medical, Pentax Medical, 3M, and Mylan outside the submitted work. Dr Fockens reports receipt of grants from Boston Scientific and personal fees from Olympus, Cook, and Ethicon Endosurgery outside the submitted work. Dr Poley reports receipt of personal fees and other from Cook Endoscopy, Boston Scientific, and Pentax outside the submitted work. Dr van Hooft reports receipt of grants from Cook Medical and Abbott and personal fees from Boston Scientific outside the submitted work. No other disclosures were reported.

Funding/Support: The ESCAPE trial was funded by grants from the Netherlands Organization for Health Research and Development (ZonMw; 17110216), and the Dutch Digestive Diseases Foundation (WO10-21, Maag Lever Darm Stichting).

Role of the Funder/Sponsor: The Netherlands Organization for Health Research and Development and the Dutch Digestive Diseases Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: None of the collaborators received compensation for their work for the ESCAPE trial. Department of Gastroenterology, Albert Schweitzer Hospital Dordrecht: Pieter Honkoop, MD, PhD; and Annemieke Y. Thijssen, MD, PhD. Department of Internal Medicine, Alrijne Hospital Leiderdorp: Tessa Kooistra, MD, PhD. Department of Gastroenterology, Amsterdam University Medical Centers, location AMC: Sebastiaan Balkema, MD; Noor Bekkali, MD, PhD; Karam S. Boparai, MD, PhD; Liesbeth M. Kager, MD, PhD; Jaap J. Kloek, MD, PhD; and R. Bart Takkenberg, MD, PhD. Department of Surgery, Amsterdam University Medical Centers, location AMC: Dirk J. Gouma, MD, PhD; Thomas M. van Gulik, MD, PhD; and Willem A. Bemelman, MD, PhD. Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Amsterdam University Medical Centers, location AMC: A. H. (Koos) Zwinderman, PhD. Department of Gastroenterology, Amphia Hospital Breda: Alexander G. L. Bodelier, MD, PhD; and Tom C. J. Seerden, MD, PhD. Department of Gastroenterology, Canisius Wilhelmina Hospital Nijmegen: Conny van Enckevort, MD; and Nienke van Gils, MD. Department of Gastroenterology, Catharina Hospital Eindhoven: Erik Schoon, MD, PhD. Department of Gastroenterology, Deventer Hospital: Lauran Vogelaar, MD, PhD; and Roland S. de Vries, MD. Department of Gastroenterology, Diakonessenhuis Utrecht: Annet M. Voorburg, MD, PhD. Department of Surgery, Elisabeth-Tweesteden Hospital Tilburg: Joos Heisterkamp, MD, PhD. Department of Gastroenterology, Erasmus Medical Center Rotterdam: Geert Bezemer, MD, PhD; Henri Braat, MD, PhD; Paul Didden, MD, PhD; Neda Farahani, MD, PhD; Hajo J. Flink, MD, PhD; Arjun D. Koch, MD, PhD; Cindy Postma, MD, PhD; Paul G. van Putten, MD, PhD; Jurriën G. P. Reijnders, MD, PhD; Robert Roomer, MD, PhD; and Ubbo Wiersema, MD, PhD. Department of Gastroenterology, Gelderse Vallei Hospital Ede: G. Lieneke Homans, MS; Wout G. N. Mares, MD; and Ruby Meiland, MD, PhD. Department of Gastroenterology, Gelre Hospital Apeldoorn: G. Willemien Erkelens, MD, PhD; Hans van Maanen; and Gudrun Muller, MD. Department of Gastroenterology, Haaglanden Medical Center: Erwin van Geenen, MD, PhD; and Lars E. Perk, MD. Department of Internal Medicine, Ijsselland Hospital Capelle a/d Ijssel: Johan de Raaf, MD. Department of Gastroenterology, Isala Hospitals Zwolle: Karin Fransen, MD, PhD; Reinier Hoedemaker, MD; Maarten A. C. Meijssen, MD, PhD; and Dorien Oude Hergelink, MD. Department of Gastroenterology, Jeroen Bosch Hospital 's Hertogenbosch: Ivo P. van Munster, MD, PhD; and Tessa E. H. Römkes, MD, PhD. Department of Surgery, Leiden University Medical Center: Andries E. Braat, MD, PhD; and A. F. M. (Sandro) Schaapherder, MD, PhD. Department of Gastroenterology, Maasstad Ziekenhuis Rotterdam: Frank J. G. M. Kubben, MD, PhD. Department of Gastroenterology, Maastricht University Medical Center: Chantal Hoge, MD; and Ad Masclee, MD, PhD. Department of Surgery, Maastricht University Medical Center: Laurents P. S. Stassen, MD, PhD. Department of Gastroenterology, Meander Medical Center Amersfoort: Menno A. Brink, MD, PhD; and Lotte van Vlerken, MD, PhD. Department of Gastroenterology, Medisch Spectrum Twente Enschede: Jeroen J. Kolkman, MD, PhD; and Niels G. Venneman, MD, PhD. Department of Gastroenterology, Noordwest ziekenhuisgroep Alkmaar: A. P. J. (Lex) Houdijk, MD, PhD; and Bas van der Spek, MD, PhD. Department of Gastroenterology, OLVG Amsterdam: Jeroen M. Jansen, MD, PhD; and Olle The, MD, PhD. Department of Surgery, OLVG Amsterdam: Michael F. Gerhards, MD, PhD. Department of Surgery, Radboud University Medical Center Nijmegen: Hein G. Gooszen, MD, PhD. Department of Anesthesiology, Radboud University Medical Center Nijmegen: Oliver Wilder-Smith, MD, PhD. Department of Gastroenterology, Reinier de Graaf Groep Hospital Delft: Jildou Hoekstra, MD, PhD; and Daniëlle F. G. M. Josemanders, MD. Department of Gastroenterology, Rijnstate Hospital Arnhem: B. W. Marcel Spanier, MD, PhD. Department of Gastroenterology, Slingeland Hospital Doetichem: Sybrand Y. de Boer, MD, PhD; and Edith de Vries, MS. Department of Gastroenterology, St Antonius Nieuwegein: Abdulbaqi Al-toma, MD, PhD; Bert van Ramshorst, MD, PhD; and Bas L. A. M. Weusten, MD, PhD. Department of Surgery, St Antonius Nieuwegein: Djamila Boerma, MD, PhD. Department of Gastroenterology, University Medical Center Groningen: A. (Rina) Bijlsma, MD; Eleonora A. M. Festen, MD, PhD; Ilona Kerkhof, MD, PhD; Jan H. Kleibeuker, MD, PhD; and Eva Kouw, MD. Department of Surgery, University Medical Center Groningen: H. Sijbrand Hofker, MD; and R. Ploeg, MD. Department of Anesthesiology, University Medical Center Groningen: Ulrich Beese, MD, PhD. Department of Gastroenterology, University Medical Center Utrecht: Peter D. Siersema, MD, PhD; and Frank P. Vleggaar, MD, PhD. Department of Surgery, University Medical Center Utrecht: I. Quintus Molenaar, MD, PhD. Department of Gastroenterology, Ziekenhuis Groep Twente Almelo: Huseyin Aktas, MD, PhD; and Iris Guchelaar, MD.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We would like to thank all participants and their families. We thank Anneke Roeterdink, BS; Bernadette Schutijser, MS; Steven Groeneveld, BS; Ellen Laluan, BS; Margot van der Hoek, BS; and Vanita Mathura, BS (Department of Surgery, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, the Netherlands) for their help as study research nurse/assistants and all the medical and nursing staff at the participating centers. The study research nurses and assistants received financial compensation for their work.

REFERENCES

1. Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. *Gastroenterology*. 1999;116(5):1132-1140. doi:10.1016/S0016-5085(99)70016-8

2. Gardner TB, Kennedy AT, Gelrud A, et al. Chronic pancreatitis and its effect on employment and health care experience: results of a prospective American multicenter study. *Pancreas*. 2010;39(4):498-501. doi:10.1097/MPA.0b013e3181c5c693

3. Drewes AM, Bouwense SAW, Campbell CM, et al; Working group for the International (IAP–APA–JPS–EPC) Consensus Guidelines for Chronic Pancreatitis. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatology*. 2017;17(5):720-731. doi:10.1016/j.pan.2017.07.006

4. Forsmark CE. Management of chronic pancreatitis. *Gastroenterology*. 2013;144(6):1282-1291 e3. doi:10.1053/j.gastro.2013.02.008

5. Löhr JM, Dominguez-Munoz E, Rosendahl J, et al; HaPanEU/UEG Working Group. United European gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J*. 2017;5(2):153-199. doi:10.1177/2050640616684695

6. Cahen DL, Gouma DJ, Laramée P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. *Gastroenterology*. 2011;141(5):1690-1695. doi:10.1053/j.gastro.2011.07.049

7. Clarke B, Slivka A, Tomizawa Y, et al. Endoscopic therapy is effective for patients with chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2012;10(7):795-802. doi:10.1016/j.cgh.2011.12.040

8. Nealon WH, Matin S. Analysis of surgical success in preventing recurrent acute exacerbations in chronic pancreatitis. *Ann Surg*. 2001;233(6):793-800. doi:10.1097/00000658-200106000-00009

9. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med*. 2007;356(7):676-684. doi:10.1056/NEJMoa060610

10. Ahmed Ali U, Nieuwenhuijs VB, van Eijck CH, et al; Dutch Pancreatitis Study Group. Clinical outcome in relation to timing of surgery in chronic pancreatitis: a nomogram to predict pain relief. *Arch Surg*. 2012;147(10):925-932. doi:10.1001/archsurg.2012.1094

11. Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database Syst Rev*. 2012;1:CD007884. doi:10.1002/14651858.CD007884.pub2

12. Ke N, Jia D, Huang W, et al. Earlier surgery improves outcomes from painful chronic pancreatitis. *Medicine (Baltimore)*. 2018;97(19):e0651. doi:10.1097/MD.0000000000010651

13. Maartense S, Ledeboer M, Bemelman WA, Ringers J, Frolich M, Masclee AA. Effect of surgery for chronic pancreatitis on pancreatic function: pancreatico-jejunostomy and duodenum-preserving resection of the head of the pancreas. *Surgery*. 2004;135(2):125-130. doi:10.1016/j.surg.2003.09.004

14. Ahmed Ali U, Issa Y, Bruno MJ, et al; Dutch Pancreatitis Study Group. Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE): design and rationale of a randomized trial. *BMC Gastroenterol*. 2013;13:49. doi:10.1186/1471-230X-13-49

15. Partington PF, Rochelle RE. Modified Puestow procedure for retrograde drainage of the pancreatic duct. *Ann Surg*. 1960;152:1037-1043. doi:10.1097/00000658-196012000-00015

16. Frey CF, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. *Pancreas*. 1987;2(6):701-707. doi:10.1097/00006676-198711000-00014

17. Beger HG, Krautzberger W, Bittner R, Büchler M, Limmer J. Duodenum-preserving resection of the head of the pancreas in patients with severe chronic pancreatitis. *Surgery*. 1985;97(4):467-473.

18. Dumonceau JM, Tringali A, Papanikolaou IS, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline—updated October 2017. *Endoscopy*. 2018;50(9):910-930. doi:10.1055/a-0659-9864

19. World Health Organization. *Cancer Pain Relief*. Geneva, Switzerland: World Health Organization; 1986.

20. Izbicki JR, Bloechle C, Broering DC, Kuechler T, Broelsch CE. Longitudinal V-shaped excision of the ventral pancreas for small duct disease in severe chronic pancreatitis: prospective evaluation of a new surgical procedure. *Ann Surg*. 1998;227(2):213-219. doi:10.1097/00000658-199802000-00010

21. Müller MW, Friess H, Martin DJ, Hinz U, Dahmen R, Büchler MW. Long-term follow-up of a randomized clinical trial comparing Beger with pylorus-preserving Whipple procedure for chronic pancreatitis. *Br J Surg*. 2008;95(3):350-356. doi:10.1002/bjs.5960

22. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305(6846):160-164. doi:10.1136/bmj.305.6846.160

23. Demir IE, Friess H, Ceyhan GO. Neural plasticity in pancreatitis and pancreatic cancer. *Nat Rev Gastroenterol Hepatol*. 2015;12(11):649-659. doi:10.1038/nrgastro.2015.166

24. Díte P, Ruzicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy*. 2003;35(7):553-558. doi:10.1055/s-2003-40237

25. Issa Y, van Santvoort HC, Fockens P, et al; Collaborators. Diagnosis and treatment in chronic pancreatitis: an international survey and case vignette study. *HPB (Oxford)*. 2017;19(11):978-985. doi:10.1016/j.hpb.2017.07.006

26. Nealon WH, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression: a longitudinal prospective analysis of the modified puestow procedure. *Ann Surg*. 1993;217(5):458-466. doi:10.1097/00000658-199305010-00005

27. Lamme B, Boermeester MA, Straatsburg IH, et al. Early versus late surgical drainage for obstructive pancreatitis in an experimental model. *Br J Surg*. 2007;94(7):849-854. doi:10.1002/bjs.5722