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Long-Term Outcomes of Early Surgery vs Endoscopy First in Chronic Pancreatitis

Follow-Up Analysis of the ESCAPE Randomized Clinical Trial

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IMPORTANCE Patients with painful chronic pancreatitis and a dilated pancreatic duct can be treated by early surgery or an endoscopy-first approach.

OBJECTIVE To compare long-term clinical outcomes of early surgery vs an endoscopy-first approach using follow-up data from the ESCAPE randomized clinical trial.

DESIGN, SETTING, AND PARTICIPANTS Between April 2011 and September 2018, 88 patients with painful chronic pancreatitis were randomly assigned to early surgery or an endoscopy-first approach in 30 hospitals in the Netherlands collaborating in the Dutch Pancreatitis Study Group as part of the ESCAPE randomized clinical trial. For the present cohort study, long-term clinical data were collected after the initial 18-month follow-up. Follow-up was completed in June 2022, and data analysis was performed in June 2023.

EXPOSURE Patients with chronic pancreatitis were randomly assigned to early surgery or an endoscopy-first approach.

MAIN OUTCOMES AND MEASURES The primary end point was pain, assessed by the Izbicki pain score; secondary end points included patient-reported complete pain relief and satisfaction. Predefined subgroups included patients who progressed from endoscopy to surgery and those with ductal clearance obtained by endoscopy. Analysis was performed according to the intention-to-treat principle.

RESULTS In this cohort study, 86 of 88 overall patients could be evaluated, with a mean (SD) follow-up period of 98 (16) months. Of 88 initial patients, 21 patients (24%) were female, and mean (SD) patient age was 61 (10) years. At the end of long-term follow-up, the mean (SD) Izbicki pain score was significant lower (33 [31] vs 51 [31]) in the early surgery group, as was the rate of patient-reported complete pain relief (14 of 31 patients [45%] vs 6 of 30 patients [20%]), compared to the endoscopy-first group. After the initial 18-month follow-up, 11 of 43 patients in the early surgery group (26%) underwent reinterventions vs 19 of 43 patients in the endoscopy-first group (44%). At the end of follow-up, more patients in the early surgery group were "very satisfied" with their treatment (22 of 31 patients [71%] vs 10 of 30 patients [33%]). Patients who progressed from endoscopy to surgery (22 of 43 patients [51%]) had significantly worse mean (SD) Izbicki pain scores (33 [31] vs 52 [24]) compared to the early surgery group and had a lower rate of complete pain relief (55% for early surgery vs 12% for endoscopy first). In the endoscopy-first group, patients with endoscopic ductal clearance had similar mean (SD) Izbicki pain scores as the remaining patients (49 [34] vs 53 [28]).

CONCLUSIONS AND RELEVANCE In this cohort study evaluating long-term outcomes of the ESCAPE randomized clinical trial, after approximately 8 years of follow-up, early surgery was superior to an endoscopy-first approach in patients with painful chronic pancreatitis and a dilated main pancreatic duct in pain scores and patient satisfaction. Notably, patients who progressed from endoscopy to surgery had worse outcomes compared to patients undergoing early surgery, and obtaining endoscopic ductal clearance did not improve outcomes.

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Invited Commentary
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Abdominal pain is the predominant clinical symptom in many patients with chronic pancreatitis, resulting in poor quality of life.[1-6] The mechanism for this pain is complex and poorly understood. Obstruction of the pancreatic duct, resulting in increased pressure, is thought to cause abdominal pain. Several studies have shown that surgical and endoscopic ductal decompression reduce abdominal pain and should be considered before the development of opioid dependence and neuropathic pain, which is the result of postponing interventions.[7-10] Traditionally, pain symptoms have been treated by medical treatment (eg, opioids) first and, when unsuccessful, endoscopic therapy, with surgery often reserved as a last resort. However, early surgery has been proposed as an alternative strategy to improve pain, quality of life, and pancreatic function in an early stage.[11-18]

The initial report of the ESCAPE multicenter randomized clinical trial at 18 months follow-up found early surgery superior to an endoscopy-first approach in patients with painful chronic pancreatitis in terms of pain scores.[19,20] However, it has been questioned whether the favorable outcomes of early surgery are sustainable in the long term. In addition, many centers still start with an endoscopy-first approach, as this is considered less invasive than abdominal surgery, and because subgroup analysis of the initial ESCAPE trial showed no benefit of surgery when endoscopic complete ductal clearance was achieved. Consequently, an endoscopy-first approach is typically advised to patients if complete ductal clearance is considered feasible. However, it is also unknown how this approach influences patient outcomes in the long term. A longer duration of pain might result in central sensitization for pain and a decrease in the benefit of future surgery.

Therefore, we compared the long-term outcomes of patients with painful chronic pancreatitis randomized to either early surgery or an endoscopy-first approach in the ESCAPE randomized clinical trial. Outcomes were also assessed in 3 subgroups: (1) patients who progressed from endoscopy to surgery, (2) patients with endoscopic complete ductal clearance, and (3) trends in pain scores over time.

Key Points

Question In patients with painful chronic pancreatitis with dilated pancreatic duct, does an early surgical approach result in improved clinical outcomes compared with an endoscopy-first approach?

Findings In this cohort study, long-term outcomes of the ESCAPE randomized clinical trial were evaluated in 86 patients during a mean (SD) follow-up period of 98 (16) months. Early surgery resulted in a lower mean (SD) pain score (33 [31] vs 51 [31]), a higher rate of complete pain relief (55% vs 12%), and increased patient satisfaction (71% vs 33%) at the end of follow-up.

Meaning In patients with painful chronic pancreatitis with dilated pancreatic duct, early surgery resulted in superior outcomes compared with an endoscopy-first approach.

Methods

Study Design

Between April 2011 and September 2018, 88 patients with symptomatic chronic pancreatitis were enrolled in the ESCAPE multicenter randomized clinical trial.[19] Patients with a dilated main pancreatic duct who only recently started using opioids for pain (within 6 months for weak opioids and 2 months for strong opioids) were eligible for inclusion. (Details on treatment are summarized in the initial report of the ESCAPE trial).[19] The study was conducted in 30 hospitals in the Netherlands collaborating in the Dutch Pancreatitis Study Group. Patients were randomly assigned 1:1 to early surgery (n = 44) and the endoscopy-first approach (n = 44). In the endoscopy-first group, lifestyle modifications and medical treatment were the first step, endoscopic therapy the second step, and surgical intervention the last step. In the early surgery group, patients were treated surgically after randomization.

Long-Term Follow-Up Protocol and Data Collection

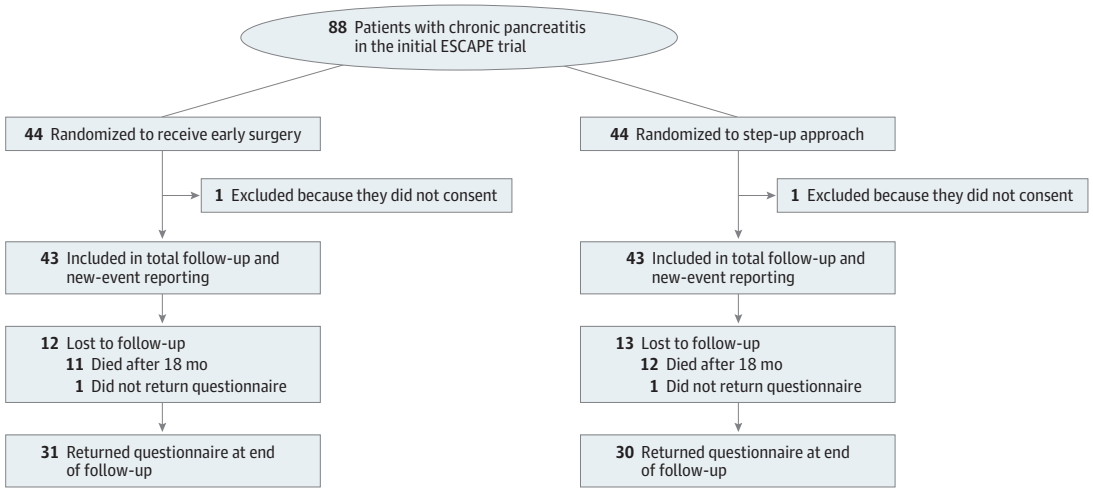
Eligible patients were evaluated at 1 single measurement moment in June 2022, following the initial ESCAPE longitudinal 18-month follow-up. After obtaining written informed consent, clinical data were retrieved retrospectively from medical records or via treating specialists or general practitioners. The choice of additional treatment (ie, type and timing of interventions) was left to the treating medical team, as no particular follow-up criteria were formulated to guide physicians' decisions.

Outcomes

The primary end point for this follow-up study was pain, assessed by the Izbicki pain score.[21] Secondary end points included the visual analogue scale (VAS) score, complete pain relief, quality of life, disease progression, pancreatic insufficiency (ie, exocrine and endocrine), hospital admissions, reinterventions for chronic pancreatitis, complications following interventions, and death. Furthermore, the use of medication for exocrine and endocrine pancreatic insufficiency was evaluated through a questionnaire. In addition, patients were asked if they would recommend the assigned treatment to both family and friends, and surgically treated patients were asked if they would have preferred to undergo the treatment earlier in the course of disease. Quality of life was evaluated by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36),[22] subdivided into physical and mental summary measures. The primary and secondary end points for this long-term follow-up study were prespecified in the study protocol.

End points were assessed for the period after the trial's initial longitudinal 18-month follow-up until the end of long-term follow-up ("new events after the initial 18-month follow-up") for all surviving patients after the initial follow-up who consented to participate in the current long-term follow-up study. Separately, all events between the time of randomization and the end of long-term follow-up ("total follow-up") were reported, including patients who died in the initial 18-month follow-up and excluding patients who did not consent to participate in this study. This will provide a complete

Figure. Trial Profile



overview of and accurate comparison between the 2 treatment groups.

Definitions

All definitions were according to the initial ESCAPE trial and are explained in detail in eTable 1 in Supplement 1.

Subgroups

Three post hoc subgroup analyses were performed[1]: (1) patients who progressed to surgery in the endoscopy-first group,[2] (2) patients with endoscopic complete ductal clearance, and (3) trends in pain scores over time.[3]

Statistical Analysis

The analysis was performed according to the intention-to-treat principle. Additional post hoc per-protocol analyses were performed for the primary end point and for pain relief, quality of life, and VAS scores in patients with and without duct clearance. End points were expressed as means and SDs or as medians with interquartile ranges, depending on the distributional properties. For normally distributed continuous data, statistical significance was assessed using *t* tests. For nonnormally distributed continuous data, the Mann-Whitney *U* test was performed. For categorical data, the Pearson χ^2 test was used or the Fisher exact test in case of 0-count cells. All reported *P* values are 2 sided, and a *P* value less than .05 was considered statistically significant. *P* values were not adjusted for multiple testing. All statistical analyses were conducted with SPSS version 28.0 (IBM).

Ethics Approval

The medical ethics committee of Amsterdam University Medical Center approved the study protocol of this long-term follow-up study. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and was conducted in accordance with the principles of the Declaration of Helsinki.[23]

Results

Patients

In total, 88 patients with painful chronic pancreatitis were randomized in the ESCAPE trial, of which 2 patients did not provide informed consent for the present study, leaving a total of 86 patients for analysis (**Figure**)—43 patients in the early surgery group and 43 patients in the endoscopy-first group. The mean (SD) total length of follow-up was 98 (16) months. Of 88 initial patients, 21 patients (24%) were female. The follow-up period was 10 years or more in 7 patients, 5 to 10 years in 65 patients, and less than 5 years in 14 patients.

During follow-up, a total of 23 patients died: 11 patients in the early surgery group (26%) and 12 patients in the endoscopy-first group (28%) (relative risk [RR], 0.92; 95% CI, 0.46-1.85; *P* = .81). Two patients died because of new-onset pancreatic cancer, and the other deaths were not directly related to chronic pancreatitis or its complications (details in eTable 2 in Supplement 1). At the end of long-term follow-up, questionnaires were obtained from 61 patients (31 early surgery and 30 endoscopy-first patients). Current smoking was reported in 24 of 31 patients in the early surgery group (77%) and in 16 of 30 patients in the endoscopy-first group (53%) (*P* = .05), and current alcohol use was reported in 9 patients in the early surgery group (29%) vs 5 patients in the endoscopy-first group (17%) (*P* = .15). Baseline characteristics originated from the ESCAPE trial and were comparable between groups (eTable 3 in Supplement 1). All patients had full and equal access to endoscopic and surgical treatment for chronic pancreatitis during the follow-up period.

Patient-Reported Outcomes and Pancreatic Function

At the end of long-term follow-up, the mean (SD) Izbicki pain score was superior in the early surgery group (33 [31]) compared to the endoscopy-first group (51 [31]; *P* = .03). More patients reported complete pain relief in the early surgery group

Table 1. Primary and Secondary End Points at Final Follow-Up

Outcome	Patients at end of long-term follow-up, No. (%)		
	Early surgery (n = 31)	Endoscopy-first approach (n = 30)	*P* value
Primary end point			
Izbicki pain score at end of follow up, mean (SD)	33 (31)	51 (31)	.03
Secondary end points			
Complete pain relief	14 (45)	6 (20)	.04
VAS score pain, mean (SD)	29 (29)	47 (31)	.02
SF-36 Quality of Life score, mean (SD)			
Physical health scale	45 (12)	42 (12)	.39
Mental health scale	42 (7)	42 (8)	.75
Pancreatic function			
Exocrine insufficiency[a]	25 (81)	26 (87)	.53
Endocrine insufficiency[b]	20 (64)	19 (63)	.92
Smoker			
Current	24 (77)	16 (53)	.05
Past	7 (23)	14 (47)	
Never	0	0	
Alcohol consumption			
Current	9 (29)	5 (17)	.15
Past	21 (68)	20 (67)	
Never	1 (3)	5 (17)	
Satisfaction result			
Very satisfied	22 (71)	10 (33)	.003
Partly satisfied	8 (26)	16 (53)	
Not satisfied	1 (3)[c]	4 (13)	
Would recommend treatment to family or friend	27 (87)	14 (47)	<.001

Abbreviations: SF-36, Medical Outcomes Study 36-Item Short-Form General Health Survey; VAS, visual analogue scale.

[a] Exocrine pancreatic function was assessed by the fecal elastase-1 function test, and a level less than 200 µg/g was defined as exocrine insufficient.

[b] Endocrine insufficiency was determined by the use of diabetes medication.

[c] Of all patients who underwent surgery.

(14 of 31 patients [45%]) than in the endoscopy-first group (6 of 30 patients [20%]; *P* = .04), and the mean (SD) VAS score for pain was lower in the early surgery group (29 [29] vs 47 [31]; *P* = .02). Quality of life and pancreatic function were similar in both physical and mental summary measures. At the end of long-term follow up, 22 patients in the early surgery group (71%) vs 10 patients in the endoscopy-first approach (33%) reported they were "very satisfied" with the overall treatment (*P* = .003), and 27 patients (87%) vs 14 patients (47%), respectively, would recommend the received treatment to family and friends (*P* < .001). Primary and secondary end points are summarized in **Table 1.**

New Events and Reinterventions After the Initial 18-Month Follow-Up

Additional interventions (ie, endoscopy and surgery) were required in 11 patients in the early surgery group (26%) and 19 patients in the endoscopy-first approach (44%) (RR. 0.06; 95% CI, 0.31-1.09; *P* = .07). There were no differences between the early surgery and endoscopy-first groups regarding the formation of pseudocysts, chronic opioid use, flare-ups, hospital admissions, and hospital and intensive care unit stay **(Table 2).**

In the early surgery group at long-term follow-up, 9 (additional) patients (21%) underwent endoscopic treatment—8 patients due to a stricture of the common bile duct and 1 patient due to common bile duct stones. Surgical treatment was required in 2 patients: 1 explorative laparotomy was performed due to persistent abdominal discomfort (which turned out to be metastatic pancreatic cancer), and 1 laparotomy was performed due to a perforation of the duodenojejunostomy after repositioning of the percutaneous endoscopic gastrostomy (eTable 4 in Supplement 1).

In the endoscopy-first approach during long-term follow-up, 14 patients (33%) underwent additional endoscopic treatment, and a further 9 patients (21%) also underwent surgery (eTable 5 in Supplement 1).

The total number of additional procedures per treatment group after the initial follow-up period was 19 procedures in the early surgery group vs 57 procedures in the endoscopy-first group (*P* = .03; eTables 4 and 5 in Supplement 1). The rate of treatment-related complications was higher in the endoscopy-first group (2 patients [5%] vs 12 patients [28%]; RR, 0.17; 95% CI, 0.40-0.70; *P* = .007). More details on interventions are outlined in eTables 4 and 5 in Supplement 1.

Total Follow-Up

During the total follow-up (combining the initial 18 months and the current additional long-term follow-up), 40 of 43 patients in the early surgery group (93%) underwent surgical treatment for chronic pancreatitis, and 13 patients (30%) underwent endoscopic reintervention after having received surgery. In the endoscopy-first approach, 39 of 43 patients (91%) underwent endoscopic treatment, and 22 patients (51%) progressed from endoscopy to surgery.

Table 2. End Points in Patients After Early Surgery vs Optimal Step-Up Approach for Chronic Pancreatitis[a]

End point	Events during initial 18-mo follow-up, No. (%)		New events after the initial 18-mo follow-up, No. (%)[a]		Total follow-up (between randomization and the end of long-term follow-up)[b] No. (%)			
	Early surgery (n = 44)	Endoscopy-first approach (n = 44)	Early surgery (n = 43)	Endoscopy-first approach (n = 43)	Early surgery (n = 43)	Endoscopy-first approach (n = 43)	Relative risk (95% CI)	*P* value
Secondary end point								
Disease progression								
Pseudocysts	2 (5)	6 (14)	4 (9)	3 (7)	5 (12)	9 (21)	0.56 (0.20-1.52)	.33
Chronic opioid use	20 (47)	26 (60)	12 (28)	12 (28)	25 (58)	30 (70)	0.83 (0.61-1.15)	.26
Chronic pancreatitis flare-up	18 (41)	20 (46)	13 (30)	13 (30)	25 (58)	27 (63)	0.93 (0.66-1.30)	.66
No. of flare-ups, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	1 (0-2)	1 (0-2)	NA	.53
No. of hospital admissions, median (IQR)	2 (1-2)	2 (1-4)	0 (0-1)	0 (0-2)	2 (1-4)	3 (2-5)	NA	.08
Hospital stay, median (IQR), d	11 (7-15)	10 (2-19)	0 (0-5)	0 (0-12)	13 (8-21)	17 (6-35)	NA	.63
Interventions per patient, median (IQR)	1 (1-1)	3 (2-4)	0 (0-1)	0 (0-2)	1 (1-2)	4 (2-5)	NA	<.001
No. of endoscopic procedures, median (IQR)	0 (0-0)	3 (1-4)	0 (0-0)	0 (0-1)	0 (0-1)	3 (2-5)	NA	<.001
No. of surgical procedures, median (IQR)	1 (1-1)	0 (0-1)	0 (0-0)	0 (0-1)	1 (1-1)	1 (0-1)	NA	<.001
No. of reinterventions								
0	NA	NA	32 (74)	24 (56)	NA	NA	NA	NA
1	NA	NA	8 (18)	7 (16)	NA	NA	NA	NA
≥2	NA	NA	3 (7)	12 (28)	NA	NA	NA	NA
No. of patients with treatment complications	12 (27)	11 (25)	2 (5)	12 (28)	14 (33)	19 (44)	0.74 (0.43-1.27)	.27
Mortality	0	0	11 (26)	12 (28)	11 (26)	12 (28)	0.92 (0.46-1.85)	.81

Abbreviation: NA, not applicable.

[a] Excluding events as reported in the ESCAPE randomized clinical trial. Multiple events in the same patient were scored as 1 end point.

[b] Two patients (of 88 originally included patients) from the ESCAPE trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis.

The occurrence of pseudocysts, chronic opioid use, chronic pancreatitis flare-ups, number of hospital admissions, and duration of hospital (and intensive care unit) stay was similar between treatment groups (Table 2).

Significantly fewer median (IQR) interventions per patient were required in the early surgery group (1 procedure [1-2]) than the endoscopy-first group (4 procedures [2-5]). Overall, the rate of complications did not differ significantly (early surgery, 14 patients [33%] vs endoscopy first, 19 patients [44%]; RR, 0.74; 95% CI, 0.43-1.27; *P* = .27). All deaths occurred after the initial 18-month follow-up and were similar, as previously reported.

Subgroup 1: Surgery in the Endoscopy-First Group

Of 61 patients who completed the survey at the end of follow-up, 45 patients underwent surgical treatment during follow-up for chronic pancreatitis: 28 patients in the early surgery group and 17 patients in the endoscopy-first group. Patients treated in the early surgery group reported a lower mean (SD) pain score at the end of long-term follow-up (33 [31] vs 52 [24]) (eTable 6 in Supplement 1). Of 17 patients treated by endoscopy first who progressed to surgery, the rate of complete pain relief was 12% vs 55% in the early surgery group. These differences were confirmed by mean (SD) VAS scores (29 [29] vs 50 [30]), whereas quality of life did not differ between these 2 groups (eTable 6 in Supplement 1).

Subgroup 2: Endoscopic Complete Ductal Clearance

During the initial ESCAPE trial, complete ductal clearance was achieved by endoscopy in 24 of 39 patients in the endoscopy-first group (62%). Of these 39 patients, 28 were still alive at the end of long-term follow-up. The mean (SD) Izbicki pain score at the end of long-term follow-up did not significantly differ between patients with and without ductal clearance (49 [34] vs 53 [28], respectively). Also, no significant differences were seen in complete pain relief, VAS score, quality of life, and interventions per patient based on ductal clearance (eTable 7 in Supplement 1). Patients in the early surgery group had improved outcomes compared to patients with ductal clearance in the endoscopy-first group, although these improvements only reached statistical significance for VAS score (29 [29] vs 48 [34]; *P* = .047) (eTable 8 in Supplement 1).

Subgroup 3: Trends in Pain Scores Over Time

Looking at the pain scores at baseline, 18-month follow-up, and end of long-term follow-up, mean (SD) pain scores in the early surgery group remained similar compared with the scores at 18-month follow-up (29 [30]) and the end of long-term follow-up (32 [30]). In the endoscopy-first group, pain scores worsened over time (39 [34] at 18-month follow-up vs 49 [29] at the end of long-term follow-up) (eTable 9 in Supplement 1). Differences for the first and second half of follow-up (participants were grouped by first or second 50%, to avoid a time bias) are provided in eTable 10 in Supplement 1.

Discussion

This approximately 8-year follow-up of the ESCAPE multicenter randomized clinical trial in patients with painful chronic pancreatitis and a dilated main pancreatic duct found early surgery superior over an endoscopy-first approach. Patients in the early surgery group had persistently lower pain scores and a higher rate of complete pain relief (45% vs 20%). Early surgery also resulted in increased patient satisfaction and fewer reinterventions compared to an endoscopy-first approach. Notably, patients who ultimately progressed from endoscopy to surgery had worse outcomes (based on Izbicki pain score, complete pain relief, and VAS scores) than patients assigned up-front to early surgery. Notably, endoscopic ductal clearance (often mentioned as rationale for and feasible target of an endoscopy-first approach) was not associated with improved outcomes, which differs from the initial trial report and may be explained by worsening pain scores over time after endoscopy.

These results are in accordance with 2 previous randomized clinical trials,[11,24] which reported improved outcomes with surgical treatment compared to endoscopy in patients with painful chronic pancreatitis. Both trials, however, enrolled patients in a later stage of their disease course. The international consensus guideline for surgery in chronic pancreatitis[9] supports early surgery over surgery at a more advanced stage of disease to achieve optimal long-term pain relief. Furthermore, a cost analysis in the ESCAPE trial also found early surgery more cost-effective than an endoscopy-first approach.[25]

However, in clinical practice, many patients with painful chronic pancreatitis and a dilated main pancreatic duct still start with an endoscopy-first approach. How can this be explained? For one, surgical treatment has traditionally been considered the more invasive approach. However, endoscopy results in a higher number of reinterventions and increased burden to the patient.[26,27] Importantly, our study provides evidence of superior patient satisfaction with early surgical treatment compared to endoscopy first. Second, many patients with pancreatitis may not be referred to specialized centers, where patients are discussed among a multidisciplinary team (including, for example, gastroenterologists, surgeons, radiologists, and anesthesiologists). Third, the (initial) lack of consensus on timing of surgery in patients with chronic pancreatitis may have contributed to an initial conservative approach. With the current evidence and recent guidelines,[8,9,28] clinical practice may now increasingly change toward a surgery-first approach.

Most patients in the early surgery group were adequately treated by 1 single operation (26 of 43 patients [60%]), contrasted with only 5 of 43 patients treated by the endoscopy-first approach (12%), who generally underwent multiple procedures. In 22 of 43 patients (51%), in line with the literature, endoscopic treatment failed and conversion to surgery was required—13 patients during the initial trial and another 9 patients who required additional surgical intervention for chronic pancreatitis during long-term follow-up. Although not statistically significant, more patients needed reinterventions in the endoscopy-first group (11 vs 19 patients) after the initial 18-month follow-up. It is relevant to note that the damage of the pancreatic tissue (ie, exocrine and endocrine insufficiency) was not improved by surgical and endoscopic intervention(s), as it did not differ between the 2 groups at the end of long-term follow-up.[29] Furthermore, again in line with literature,[30,31] at the end of follow-up, 23 patients (27%) had died. The poor long-term survival of patients with chronic pancreatitis has been related to comorbidity and the association with cancer.

Pain scores were not only significantly different between the 2 groups during the initial 18-month follow-up,[19] but remained superior for surgery at the end of the long-term follow-up period spanning more than 8 years. In fact, after the initial 18-month follow-up, pain scores worsened further in the endoscopy-first group. Interestingly, the original ESCAPE trial reported that the proportion of complete pain relief at 18-month follow-up was not significantly different between the 2 groups. However, after longer follow-up, complete pain relief was clearly and significantly superior in the early surgery group (45% vs 20%), which contradicts the theory that early surgery is primarily beneficial in the short term.

Although the numbers of patients were small, our study showed that surgical treatment in the early surgery group resulted in lower pain scores, higher complete pain relief, and lower VAS scores compared to patients in the endoscopy-first group who progressed to surgery. However, is not possible to identify a similar subgroup in the surgery-first group, so no formal comparison can be made.

Interestingly, endoscopic complete ductal clearance (of the main pancreatic duct) did not affect the outcomes at long-term follow-up with regards to pain scores. This is clinically relevant, as it has been previously suggested that if ductal clearance seems obtainable, an endoscopic approach should still be advised, despite the original ESCAPE trial results. Again, some caution is required, as this was not the primary comparison of the trial. On the other hand, all patients randomized in the ESCAPE trial were eligible for endoscopic treatment. In the short term, endoscopic ductal clearance may be effective. However, in the long term, the disease will progress and new strictures and stones will develop, leading to recurrent obstruction and symptoms. A confirmation of this important finding would require a new trial randomizing only patients with high likelihood of complete endoscopic ductal clearance between early surgery and endoscopy first with pancreatoscopy-guided therapy.

Limitations

The present study has several limitations, which should be considered when interpreting the results. First, the long-term follow-up period was not standardized, and as a result, the duration of follow-up differed between the first and last randomized patient, ranging from 128 to 51 months, respectively. However, outcomes did not differ when outcomes within groups were compared for the first and second half of follow-up. Second, a single measurement point (June 2022) was used for pain evaluation in this study in contrast to the initial analyses, which were based on multiple longitudinal measurements. Consequently, interpretation of these results should be done with caution, since it is known that pain patterns differ. and therefore, a single measure does not always reflect the situation adequately.[32] However, to proactively account for this limitation, patients were

asked to fill out the questions regarding their pain over the last 6 months instead of over a shorter period (eg, 2 weeks). Third, some data were collected retrospectively, such as information on interventions and readmission, which may have led to information bias. Fourth, the choice for timing and type of additional intervention after the initial 18 months of follow-up was based on institutional or physician preference, which may have led to different strategies.

Conclusions

In this cohort study, based on a mean (SD) follow-up period of 98 (16) months of the ESCAPE randomized clinical trial, in patients with symptomatic chronic pancreatitis and a dilated main pancreatic duct, early surgery was superior to an endoscopy-first approach in terms of Izbicki pain scores, number of reinterventions, VAS scores, and patient satisfaction. Opioid use at the end of follow-up was comparable between the groups. Notably, endoscopic complete ductal clearance did not improve patient outcomes. Also, outcomes were worse if patients underwent surgery after failed endoscopy compared to up-front early surgery. The current results demonstrate that frequently used arguments for an endoscopy-first approach (eg, less invasive, ductal clearance may be obtained, surgery can always be done later) do not hold up. The present findings clearly strengthen the recommendation that early surgery should be the preferred approach for these patients and leave little room for an endoscopy-first approach.

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