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PANCREAS

Endoscopic Versus Surgical Step-Up Approach for Infected Necrotizing Pancreatitis (ExTENSION): Long-term Follow-up of a Randomized Trial

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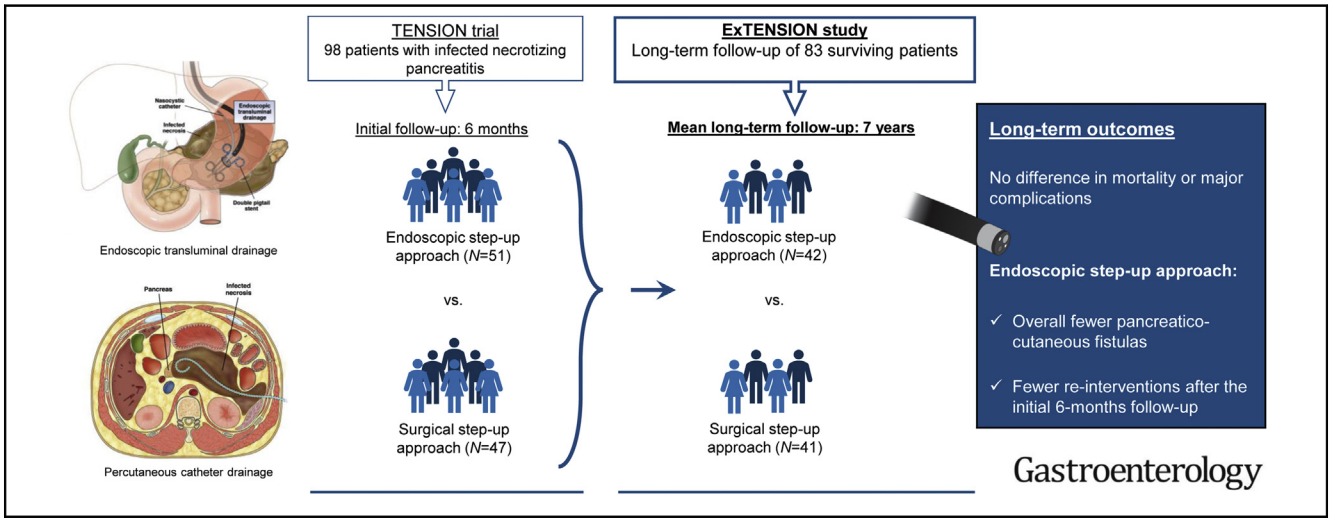

See editorial on page 578.

BACKGROUND & AIMS: Previous randomized trials, including the Transluminal Endoscopic Step-Up Approach Versus Minimally Invasive Surgical Step-Up Approach in Patients With Infected Pancreatic Necrosis (TENSION) trial, demonstrated that the endoscopic step-up approach might be preferred over the surgical step-up approach in patients with infected necrotizing pancreatitis based on favorable short-term outcomes. We compared long-term clinical outcomes of both step-up approaches after a period of at least 5 years. **METHODS:** In this long-term follow-up study, we reevaluated all clinical data on 83 patients (of the originally 98 included patients) from the TENSION trial who were still alive after the initial 6-month follow-up. The primary end point, similar to the TENSION trial, was a composite of death and major complications. Secondary end points included individual major complications, pancreaticocutaneous fistula, reinterventions, pancreatic insufficiency, and quality of life. **RESULTS:** After a mean follow-up period of 7 years, the primary end point occurred in 27 patients (53%) in the endoscopy group and in 27 patients (57%) in the surgery group (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.65–1.32; $P = .688$). Fewer pancreaticocutaneous fistulas were identified in the endoscopy group (8% vs 34%; RR, 0.23; 95% CI, 0.08–0.83). After the initial 6-month follow-up, the endoscopy group needed fewer reinterventions than the surgery group (7% vs 24%; RR, 0.29; 95% CI, 0.09–0.99). Pancreatic insufficiency and quality of life did not differ between groups. **CONCLUSIONS:** At long-term follow-up, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing death or major complications in patients with infected necrotizing pancreatitis. However, patients assigned to the endoscopic approach developed overall fewer pancreaticocutaneous fistulas and needed fewer reinterventions after the initial 6-month follow-up. Netherlands Trial Register no: NL8571.

Keywords: Endoscopy; Surgery; Minimally Invasive Step-up Approach; Necrotizing Pancreatitis; TENSION trial.

Approximately 20% of patients with acute pancreatitis develop a severe disease course with organ failure or necrotizing pancreatitis, or both.[1,2] Infection of pancreatic necrosis or peripancreatic necrosis worsens the prognosis and requires a multidisciplinary management.[3,4] A previous randomized trial confirmed the superiority of a minimally invasive step-up approach over open necrosectomy in select patients with infected necrotizing pancreatitis in both short- and long-term outcomes.[5,6]

The Transluminal Endoscopic Step-Up Approach Versus Minimally Invasive Surgical Step-Up Approach in Patients With Infected Pancreatic Necrosis (TENSION) trial was the first multicenter randomized controlled trial that compared the endoscopic and surgical step-up approach for treatment of infected necrotizing pancreatitis. The approach consisted of an endoscopic transluminal or image-guided percutaneous drainage procedure as the first step, followed by minimally invasive necrosectomy in absence of clinical improvement.[7] At 6 months of follow-up, no differences in death or major complications were found between both approaches. The endoscopic approach was, however, associated with fewer pancreaticocutaneous fistulas and a shorter hospital stay.[7] These favorable short-term outcomes were confirmed by a second randomized trial that compared the endoscopic step-up approach with minimally invasive surgery.[8]

On the basis of these results, the endoscopic approach is now widely regarded as the preferred treatment for patients with infected necrotizing pancreatitis. Nonetheless, long-term clinical outcomes are unknown because the

Abbreviations used in this paper: **CI, confidence interval; EQ-5D, EuroQol 5D; FE-1, fecal elastase 1; HbA_{1c}, hemoglobin A_{1c}; RR, relative risk; SF-36, 36-Item Short Form Health Survey; TENSION, Transluminal Endoscopic Step-Up Approach Versus Minimally Invasive Surgical Step-Up Approach in Patients With Infected Pancreatic Necrosis.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Infected necrotizing pancreatitis is a potentially lethal disease. Short-term outcomes demonstrated that an endoscopic step-up approach is preferred over a surgical approach because of fewer pancreaticocutaneous fistulas and shorter hospital stay.

NEW FINDINGS

This long-term follow-up study found no differences in mortality and major complications between groups. The endoscopic approach lowered the risk of developing pancreaticocutaneous fistulas and resulted in fewer reinterventions during long-term follow-up.

LIMITATIONS

Patients' follow-up periods were not standardized and varied between 5 and 9 years. Therefore, longer follow-up periods may have increased the likelihood on identifying complications unrelated to necrotizing pancreatitis.

IMPACT

While not superior in reducing death or major complications, the endoscopic step-up approach seems to be the preferred treatment for infected necrotizing pancreatitis based on both short-and long-term outcomes.

endoscopic approach is relatively new, and the trial's initial 6-month follow-up period may have been too short to detect all associated complications. We therefore performed this long-term follow-up study to evaluate the long-term clinical outcomes after an endoscopic or surgical step-up approach for infected necrotizing pancreatitis.

Patients and Methods

Study Design

The TENSION trial was a randomized, multicenter, superiority trial conducted in 19 hospitals (7 academic and 12 teaching hospitals) of the Dutch Pancreatitis Study Group. Between September 2011 and January 2015, 98 consecutive patients with infected necrotizing pancreatitis were included in the TENSION trial and randomized to the endoscopic step-up approach (n = 51) or surgical step-up approach (n = 47) (treatment details are summarized in the Supplementary Appendix).[7] The present investigator-initiated study is the long-term follow-up study of these patients (ExTENSION study). The study protocol was approved by the Ethical Committee of the Amsterdam UMC, Academic Medical Centre, Amsterdam, the Netherlands.

Surviving participants from the TENSION trial were invited to participate in the study and were enrolled after providing written consent. Clinical trial monitoring was performed by an independent monitor. There was no patient or public involvement in the recruitment, conduct, or reporting of this study. Patient representatives from the Dutch patient association for pancreatic diseases ("Alvleeskliervereniging"), however, attended research meetings of the Dutch Pancreatitis Study Group and approved the study design before the start of this study. All authors had access to the study data and reviewed and approved the final manuscript. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Follow-up Protocol

Eligible patients were prospectively evaluated until August 2020, after completing a follow-up period of at least 5 years after the trial's initial 6-month follow-up. After providing informed consent, patients were invited for an outpatient appointment or a telephone consultation between June and August 2020 with the coordinating investigator (A.M.O.). Pancreatic endocrine and exocrine function and quality of life were evaluated during these visits. Pancreatic endocrine and exocrine function were determined by hemoglobin A_{1c} (HbA_{1c}) values and function fecal elastase 1 (FE-1) values, respectively.[9-13] Quality of life was evaluated by the EuroQol-5D, 3L (EQ-5D) questionnaire and the 36-Item Short Form Health Survey (SF-36) during the initial TENSION trial (at 3 and 6 months after randomization) and at the end of long-term follow-up.[14-16] Data on clinical outcomes were collected from medical records from health care institutions, general practitioners, and pharmacy drug lists.

End Points

The primary and secondary end points were similar to the end points of the original TENSION trial.[7] The composite primary end point was death and major complications (ie, new-onset organ failure, incisional hernia, bleeding requiring intervention, perforation of a visceral organ requiring intervention, or enterocutaneous fistula requiring intervention) between randomization and the end of the long-term follow-up. Secondary end points included the individual components of the primary end point, pancreaticocutaneous fistula, biliary strictures, wound infections, recurrent or chronic pancreatitis, pancreatic endocrine or exocrine insufficiency, or both, reinterventions (endoscopic or surgical drainage procedures or necrosectomy), hospital and intensive care length of stay, and quality of life (definitions in Supplementary Appendix Box 1).

Pancreatic endocrine insufficiency was defined as new-onset diabetes after necrotizing pancreatitis, measured by an increased HbA_{1c} level (>53 mmol/mol) or by the need for treatment with insulin or oral antidiabetic agents.[7,17] Pancreatic exocrine insufficiency was defined as FE-1 values <200 μg/g.[9,13] Quality of life scores of the SF-36 and EQ-5D have been implemented in the Dutch health care system by previous translation and validation.[18,19] Treatment duration was a post hoc end point, defined as the time between randomization and the last performed intervention (ie, drainage or necrosectomy) for infected necrosis. End points are given for the overall follow-up period (ie, all events between randomization and the end of long-term follow-up) and for the period after the initial 6-month follow-up (ie, new events beyond the trial's initial 6-month follow-up) to provide a complete overview and accurate comparison.

Statistical Analysis

Analyses were performed according to intention-to-treat principle. Categorical data are presented as counts and

proportions, and continuous data are presented as mean ± standard deviation or medians with interquartile ranges (IQR), depending on distribution. Categorical data were compared with the Fisher's exact test, and continuous data were compared with the Student *t* test or Mann-Whitney *U* test. Results are presented as relative risks (RRs) with corresponding 95% confidence intervals (CIs). Linear mixed models were performed to assess changes in quality of life measurements over time. All tests were 2-sided, and *P* values <.05 were considered statistically significant. *P* values were not adjusted for multiple testing. All statistical analyses were conducted with IBM Statistics SPSS 26.0 software (IBM, Armonk, NY).

Results

Follow-up

During the initial 6-month follow-up of the TENSION trial, 15 of 98 patients died, leaving 83 patients eligible for this long-term follow-up study. The mean period of long-term follow-up was 7 years (84 ± 11 months), in which another 7 patients died (Figure 1). Baseline characteristics originated from the TENSION trial and were comparable between groups (Supplementary Table 1).[7]

Clinical Outcomes

Between randomization and the end of long-term follow-up, the primary end point occurred in 27 patients (53%) in the endoscopy group and in 27 patients (57%) in the surgery group (RR, 0.93; 95% CI, 0.65–1.32; *P* = .688) (Table 1). No differences were observed in the individual major complications, including new-onset organ failure, bleeding, perforation or enterocutaneous fistula, and incisional hernia (Table 1). Overall, 15 of 51 patients (29%) in the endoscopy group and 7 of 47 patients (15%) in the surgery group died (RR, 1.89; 95% CI, 0.89–4.42).

After the initial 6-month follow-up, all deaths occurred after at least 30 months after randomization. None of the deaths were treatment-related or related to necrotizing pancreatitis. In the endoscopy group, 6 of 42 patients (14%) died: 2 of cardiac failure, 1 of metastatic esophageal cancer, 1 of urinary tract cancer, 1 of aspiration pneumonia, and 1 patient died without clear cause at the age of 91. In the surgery group, 1 patient died after multiple cerebral infarctions (6 patients [14%] vs 1 [2%]; RR 5.86; 95% CI, 0.74–46.55). More details are outlined in Supplementary Tables 2 and 3 and Supplementary Figure 1.

Interventions and Hospital Stay

The median number of interventions for infected necrosis (drainage procedures or necrosectomies) did not differ between the endoscopy and surgery group during overall follow-up (3 [IQR, 2–6] vs 4 [IQR, 2–7], *P* = .248) (Table 2). Patients treated in the endoscopy group required fewer drainage procedures (1 [IQR, 1–3] vs 4 [IQR, 2-6], *P* = .003) and had a shorter median treatment duration compared with surgery group (17 days [IQR, 6-46 days] vs 41 days [IQR, 9-162 days], *P* = .029).

After the initial 6-month follow-up, 3 patients (7%) in the endoscopy group and 10 patients (24%) in the surgery group needed reinterventions (RR, 0.29; 95% CI, 0.09–0.99). All 3 patients (100%) in the endoscopy group and 3 of 10 (30%) in the surgery group underwent additional percutaneous catheter drainage. The other 7 patients (70%) in the surgery group underwent additional endoscopic transluminal drainage (Supplementary Table 4).

Total median hospital length of stay during overall follow-up did not differ significantly between the endoscopy and surgery group (52 days [IQR, 27–94 days] vs 72 days [IQR, 50-112 days], *P* = .090). After the initial 6-month follow-up, patients in the endoscopy group were admitted for a median of 12 days (IQR, 3-37 days) compared with a 8 days (IQR, 3-24 days) in the surgery group (*P* = .308).

Pancreatitis-Related Complications

Pancreaticocutaneous fistulas. Fewer pancreaticocutaneous fistulas developed in patients assigned to the endoscopy group compared with patients in the surgery group (4 [8%] vs 16 [34%]; RR, 0.23; 95% CI, 0.08–0.83) during the entire follow-up period (Table 3). Among the 16 patients with a pancreaticocutaneous fistula in the surgery group, persistent pancreaticocutaneous fistulas occurred in 4 patients after the initial 6-month follow-up. New pancreaticocutaneous fistulas developed in another 4 patients after they underwent additional percutaneous drainage (2 patients in both groups; 5% vs 5%; RR, 0.98; 95% CI, 0.14–6.61) (Table 1). Clinical and radiologic signs of a disrupted or disconnected pancreatic duct were present in all 8 patients with a new or persistent pancreaticocutaneous fistula after the initial 6-month follow-up (Supplementary Table 5). These fistulas resolved after endoscopic transluminal drainage (n = 6), transpapillary drainage with pancreatic duct stenting (n = 6), or percutaneous catheter drainage (n = 1).

Endocrine and exocrine pancreatic function. Between randomization and the end of follow-up, 36 patients (19 in endoscopy group [37%] vs 17 in the surgery group [36%]) developed pancreatic endocrine insufficiency (RR, 1.03; 95% CI, 0.61–1.73) (Table 1). Among these patients, 3 (8%) had a spontaneous improved glycemic control without further need for treatment with oral antidiabetic agents or insulin. Meanwhile, 18 patients (9 in the endoscopy group [38%] vs 9 in the surgery group [33%]) developed new-onset endocrine insufficiency after the initial 6-month follow-up (Table 1).

At the end of follow-up, pancreatic endocrine function was reevaluated in the 76 surviving patients (Table 3). In total, 32 patients (16 patients [44%] vs 16 patients [40%]; RR, 1.11; 95% CI, 0.66–1.88) had endocrine pancreatic insufficiency at the long-term follow-up, of whom 1 patient had not yet started with antidiabetic agents, 10 (31%) only used oral antidiabetic agents, and 20 patients (63%) were insulin dependent.

Exocrine pancreatic insufficiency developed in 62 patients (31 patients in the endoscopy group [61%] vs 31 patients in the surgery group [66%]) between

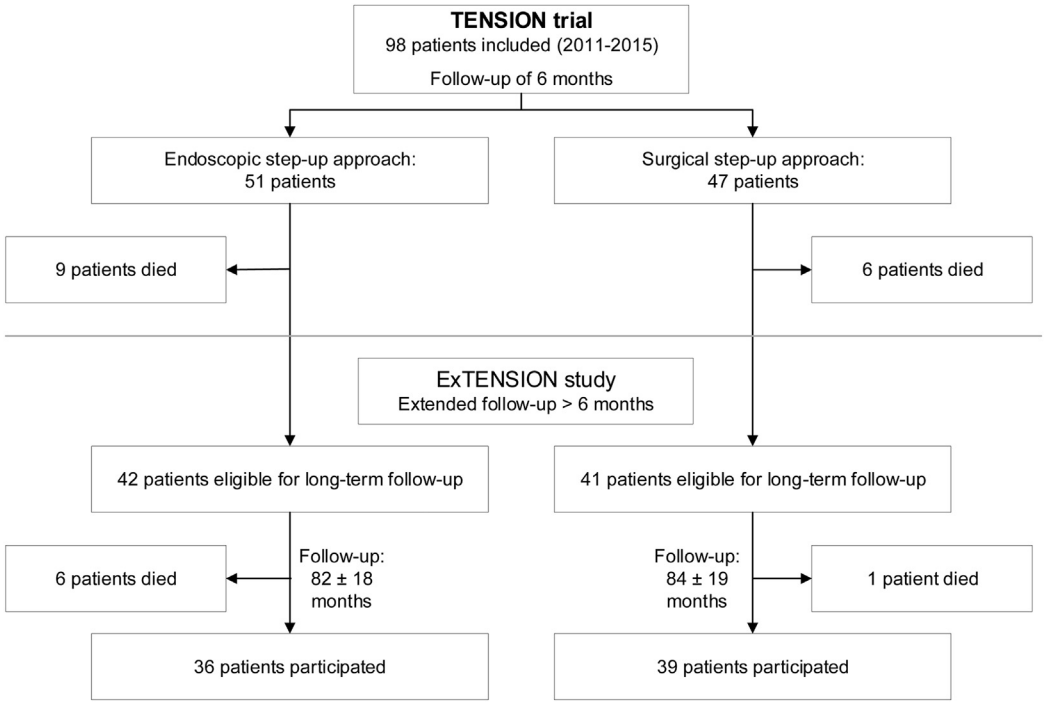

Figure 1. Trial profile.

randomization and the end of long-term follow-up (RR, 0.92; 95% CI, 0.68–1.25) (Table 1). Exocrine pancreatic function improved spontaneously in 13 patients (6 patients [10%] vs 7 patients [11%]) after the initial 6-month follow-up (Supplementary Table 6). However, new-onset pancreatic exocrine insufficiency developed in 17 patients (8 patients in the endoscopy group [40%] vs 9 patients in the surgery group [41%]), of whom only 4 (24%) were treated with supplemental pancreatic enzymes (2 patients [10%] vs 2 patients [9%]) (Table 1). At the end of long-term follow-up, the FE-1 test was performed in 56 of 76 surviving patients (75%) (Table 3). Exocrine pancreatic insufficiency was present in 12 patients in the endoscopy group (44%) and in 12 patients in the surgery group (40%; RR, 1.11; 95% CI, 0.61–2.04).

Recurrent acute pancreatitis and chronic pancreatitis. After the initial 6-month follow-up, 23 patients (28%) experienced recurrent episodes of acute pancreatitis (8 patients [19%] in the endoscopy group and 15 patients [37%] in the surgery group; RR, 0.52; 95% CI, 0.25–1.10) (Table 3). Recurrent acute pancreatitis developed in 12 patients (52%) in the presence of a disrupted or disconnected pancreatic duct. The presumed etiologies of recurrent acute pancreatitis included alcohol (n = 2), biliary (n = 8), idiopathic (n = 10), postendoscopic retrograde cholangiopancreatography pancreatitis (n = 1), pancreatic injury after gastric surgery (n = 1), and unknown (n = 1) (Supplementary Table 7). Signs of chronic pancreatitis eventually developed in 3 patients (13%) with recurrent acute pancreatitis. Chronic pancreatitis developed in 9 patients (11%) after the initial 6-month follow-up (5 patients in the endoscopy group [12%] vs 4 patients in the surgery group [10%]).

Disrupted or disconnected pancreatic duct. A disrupted or disconnected pancreatic duct was diagnosed in 22 patients (27%) after the initial 6-month follow-up (9 patients [21%] in the endoscopy group vs 13 patients [32%] in the surgery group; RR, 0.68; 95% CI, 0.33–1.41) (Table 3). Among the patients with a disrupted or disconnected pancreatic duck, 3 of 9 patients (33%) in the endoscopy group required additional percutaneous drainage for persistent necrotic collections that were not reached by endoscopy and 11 of 13 patients (85%) in the surgery group required additional interventions, 73% of which consisted of endoscopic transgastric or transpapillary drainage (Supplementary Table 8).

Patients with a persistent disrupted or disconnected pancreatic duct developed more complications than those without a disrupted or disconnected pancreatic duct, including pancreaticocutaneous fistulas (8 patients [36%] vs 0 patients [0%], respectively), recurrent pancreatic fluid collections (19 patients [86%] vs 14 patients [23%]; RR, 5.65; 95% CI, 1.96–16.32), and recurrent acute pancreatitis (12 patients [55%] vs 11 patients [18%]; RR, 1.80; 95% CI,1.12–2.89) (Supplementary Table 5). In addition, patients with a disrupted or disconnected pancreatic duct needed more reinterventions (13 patients [59%] vs 2 patients [3%]; RR, 2.36; 95% CI, 1.43–3.92) and had an extended hospital stay (median of 30 days [IQR, 5–60 days] vs 8 days [IQR, 1–24 days]) after the initial 6-months of follow-up.

Quality of Life

In general, all quality of life scores (SF-36 and EQ-5D) improved between the initial follow-up (3 and 6 months

Table 1. Primary and Secondary End Points

Outcome	Overall follow-up (between randomization and the end of long-term follow-up)				New events after the initial 6-month follow-up (excluding events as reported in the TENSION trial)			
	Endoscopic step-up approach (n = 51)	Surgical step-up approach (n = 47)	RR (95% CI)	*P* value	Endoscopic step-up approach (n = 42)	Surgical step-up approach (n = 41)	RR (95% CI)	*P* value
Primary end point[a]								
Major complications or death[a]	27 (53)	27 (57)	0.92 (0.65–1.32)	.688	11 (26)	8 (20)	1.34 (0.60–3.00)	.603
Secondary end points[b]								
Death	15 (29)	7 (15)	1.98 (0.88–4.42)	.096	6 (14)	1 (2)	5.86 (0.74–46.55)	.109
New-onset organ failure[c]	11 (22)	15 (32)	0.68 (0.35–1.32)	.263	4 (10)	2 (5)	1.95 (0.38–10.08)	.676
Multiple new-onset organ failure[c]	4 (8)	6 (13)	0.61 (0.19–2.04)	.513	2 (5)	0 (0)	-	.494
Bleeding requiring intervention	13 (26)	11 (23)	1.09 (0.54–2.19)	1	2 (5)	1 (2)	1.95 (0.18–20.71)	1
Perforation or enterocutaneous fistula requiring intervention	6 (12)	11 (23)	0.5 (0.20–1.25)	.182	2 (5)	3 (7)	0.65 (0.12–3.70)	.676
Incisional hernia	4 (8)	4 (9)	0.92 (0.24–3.48)	1	4 (10)	3 (7)	1.3 (0.31–5.46)	1
Other end points								
Biliary stricture	3 (6)	4 (9)	0.69 (0.16–2.93)	.707	0 (0)	1 (2)	…	.494
Wound infection	3 (6)	4 (9)	0.69 (0.16–2.93)	.707	1 (2)	1 (2)	0.98 (0.06–15.09)	1
Pancreatic fistula	4 (8)	16 (34)	0.23 (0.08–0.64)	.002	2 (5)	2 (5)	0.98 (0.14–6.61)	1
Endocrine pancreatic insufficiency	19 (37)[d]	17 (36%)[d]	1.03 (0.61–1.73)	1	9/24 (38)[e]	9/27 (33)[e]	1.13 (0.54–2.36)	.778
Exocrine pancreatic insufficiency[b]								
FE-1 <200 μg/g	31 (61)	31 (66)	0.92 (0.68–1.25)	.677	8/20 (40)[e]	9/22 (41)[e]	0.98 (0.47–2.04)	1
Use of pancreatic enzymes	19 (37)	19 (40)	0.92 (0.56–1.52)	.836	2/20 (10)[e]	2/22 (9)[e]	1.1 (0.17–7.10)	1

NOTE. Data are n (%). End points were analyzed by the Fisher's exact test according to intention-to-treat principles.
[a]Multiple events in the same patient were scored as one end point.
[b]Individual components of the composite primary end point.
[c]Single or multiple pulmonary, cardiovascular or renal organ failure.
[d]Patients with diabetes before necrotizing pancreatitis were excluded.
[e]Patients who died or who developed endocrine or exocrine insufficiency during the initial 6-month follow-up were excluded from analysis.

Table 2. Interventions and Health Care Utilization

	Overall follow-up (between randomization and the end of long-term follow-up)				New events after the initial 6-month follow-up (excluding events as reported in the TENSION trial)[7]			
Outcome	Endoscopic step-up approach (n = 51)	Surgical step-up approach (n = 47)	RR (95% CI)	*P* value	Endoscopic step-up approach (n = 42)	Surgical step-up approach (n = 41)	RR (95% CI)	*P* value
Need for intervention	51 (100)	46 (98)	1.02 (0.98–1.07)	.480	3 (7)	10 (24)	0.29 (0.09–0.99)	**.038**
Interventions, *n*	3 (2–6)	4 (2–7)		.248	0 (0–0)	0 (0–1)		**.039**
Drainage procedures, *n*	1 (1–3)	4 (2–6)		**.003**	0 (0–0)	0 (0–1)		**.039**
Additional ETD	…	9 (19)			1 (2)	7 (17)	0.14 (0.02–1.08)	**.029**
Additional PCD	15 (29)	…			3 (7)	4 (10)	0.73 (0.18–3.07)	.713
Necrosectomy	29 (57)	24 (51)	1.11 (0.77–1.61)	.685	0 (0)	1 (2)	-	.494
Necrosectomies, *n*	1 (0-2)	1 (0-1)		.051	0 (0-0)	0 (0-0)		.311
Treatment duration,[a] *d*	17 (6-46)	41 (9-162)		**.029**				
Length of stay, *d*								
Hospital stay	52 (27–94)	72 (50–112)		.090	12 (3–37)	8 (3-24)		.308
Intensive care unit	2 (0-15)	3 (0-26)		.707	0 (0-0)	0 (0-0)		.134
Readmissions, *n*					3 (1-4)	2 (1-4)		.651
Related to pancreatitis[b]					0 (0-1)	0 (0-2)		.144

NOTE. Data are presented as n (%) or as median (IRQ). Bold *P* values are statistically significant ($P < .05$).
ETD, endoscopic transluminal drainage; PCD, percutaneous catheter drainage.
[a]Median number of days between randomization and last intervention (drainage procedure or necrosectomy).
[b]Defined by the revised Atlanta classification[1] and only episodes of acute pancreatitis with hospital admission were taken into account.

Table 3. Pancreatitis-Related Complications After the Initial 6-Month Follow-up

Outcomes after the initial 6-month follow-up	Endoscopic step-up approach ($n = 42$)	Surgical step-up approach ($n = 41$)	RR (95% CI)	*P* value
Disrupted or disconnected pancreatic duct[a]	9 (21)	13 (32)	0.68 (0.33–1.41)	.328
Recurrent acute pancreatitis[b]	8 (19)	15 (37)	0.52 (0.25–1.10)	.090
Chronic pancreatitis[c]	5 (12)	4 (10)	1.22 (0.35–4.23)	1.000
Pancreaticocutaneous fistulas				
New-onset fistula	2 (5)	2 (5)	0.98 (0.14–6.61)	1.000
Persistent fistula	0 (0)	4 (10)	…	.055
Outcomes at long-term follow-up[d]	**Endoscopic step-up approach[c] ($n = 36$)**	**Surgical step-up approach[c] ($n = 40$)**	**RR (95% CI)**	***P* value**
Endocrine pancreatic insufficiency (HbA_{1c})	16 (44)	16 (40)	1.11 (0.66–1.88)	.817
Oral antidiabetics only	6/16 (38)	4/16 (25)	1.50 (0.52–4.32)	.704
Insulin only	5/16 (31)	4/16 (25)	1.25 (0.41–3.82)	1.000
Combined oral antidiabetics and insulin	5/16 (31)	6/16 (38)	0.83 (0.32–2.18)	1.000
Exocrine pancreatic insufficiency[e]				
FE-1 <200 μg/g	12/27 (44)	12/30 (40)	1.11 (0.61–2.04)	.792
Enzyme use at long-term follow-up[f]	11/36 (31)	12/40 (30)	1.02 (0.51–2.02)	1.000

NOTE. Data are presented as n (%).
[a]Diagnosed by radiologic imaging or persistent pancreatic drain production.
[b]According to the revised Atlanta criteria.[1]
[c]According to the M-ANNHEIM classification.[30]
[d]Pancreatic function of surviving patients at the end of long-term follow-up.
[e]Defined as FE-1 levels <200 μg/g. FE-1 was measured 57 patients at long-term follow-up (27 patients in the endoscopy group vs 30 patients in the surgery group).
[f]Supplemental pancreatic enzyme use in all 76 surviving patients at the end of long-term follow-up.

after randomization) and the long-term follow-up. More details about quality of life are outlined in Table 4, Supplementary Figure 2 (see legends), and Supplementary Table 9. At 3 months after randomization, SF-36 physical functioning scores were higher in the endoscopy group (42 ± 11 vs 36 ± 10, respectively, $P = .037$), but did not differ at the long-term follow-up between groups (45 ± 11 vs 47 ± 10, $P = .475$) (Table 4). Also comparable between groups at long-term follow-up were the SF-36 mental health scores (48 ± 12 vs 52 ± 10, $P = .152$) and EQ-5D scores (0.80 ± 0.23 vs. 0.86 ± 0.17, $P = .237$).

Discussion

In this long-term follow-up study of the TENSION trial, we found no differences in the composite primary end point of mortality and major complications between the endoscopic and surgical step-up approach for patients with infected necrotizing pancreatitis. However, the endoscopic step-up approach overall resulted in fewer pancreaticocutaneous fistulas, and fewer reinterventions were needed after the initial 6-month follow-up.

Although the endoscopic step-up approach did not reduce death or major complications, several long-term benefits were noted for the endoscopy group. In accordance with short-term trial results, the long-term follow-up confirmed that the endoscopic approach results in fewer pancreaticocutaneous fistulas. Pancreaticocutaneous fistulas commonly develop after percutaneous catheter drainage in combination with a pancreatic duct disconnection caused by central gland necrosis.[20] Our results are in line with previous studies reporting that 20% to 45% of patients developed pancreaticocutaneous fistulas after percutaneous catheter drainage or minimally invasive necrosectomy.[8,21,22] Moreover, a quarter of the pancreaticocutaneous fistulas in the surgery group persisted after the initial 6-month follow-up, contributing to a longer treatment duration and more reinterventions in this group during follow-up.

Because most reinterventions in the surgery group consisted of endoscopic transluminal drainage or

Table 4. Quality of Life at 3 Months, 6 Months, and Long-term Follow-up

Outcome	At 3 months after randomization			At 6 months after randomization			At long-term follow-up		
	Endoscopic step-up approach (n = 31)	Surgical step-up approach (n = 27)	*P* value	Endoscopic step-up approach (n = 25)	Surgical step-up approach (n = 34)	*P* value	Endoscopic step-up approach (n = 29)	Surgical step-up approach (n = 30)	*P* value
SF-36									
PCS	42 ± 11	36 ± 10	.037	43 ± 10	39 ± 9	.069	45 ± 11	47 ± 10	.475
MCS	39 ± 13	41 ± 10	.609	49 ± 11	45 ± 11	.213	48 ± 12	52 ± 10	.152
EQ-5D score	0.65 ± 0.31	0.62 ± 0.26	.669	0.76 ± 0.27	0.73 ± 0.18	.643	0.80 ± 0.23	0.86 ± 0.17	.237
Health state score	64 ± 19	59 ± 18	.248	72 ± 18	64 ± 15	.090	72 ± 18	77 ± 13	.263

NOTE. Data are presented as means ± standard deviation. Statistical testing was done using the independent sample *t*-test. The scores on the SF-36 physical and mental health components range from 0 to 100, with higher scores indicating better quality of life. The utilities of the observed health score profiles from the general Dutch population range between −0.330 (indicating serious health problems) and 1.0 (indicating no problems at all). Health state scores range between 0 and 100, with higher scores indicating a better perceived health. The 15 patients who died during the initial follow-up did not complete the quality of life questionnaires. All 3 questionnaires were filled out by 35 patients, and 2 of 3 were filled out by 30 patients. At long-term follow-up, 59 questionnaires of 76 surviving patients were obtained. The n value indicates of patients that filled out the questionnaires at that specific time point. Follow-up was 3 months: mean 97 ± 16 days; 6 months: mean 190 ± 26 days; and long-term: mean 82 ± 11 months.
MCS, Mental Component Scale; PCS, Physical Component Scale.

transpapillary drainage, our findings are in line with previous studies suggesting that an endoscopic approach is of value in both the prevention and treatment of pancreaticocutaneous fistulas.[7,8,23] Nonetheless, it should be noted that not all necrotic collections can be reached endoscopically and that percutaneous drainage and additional necrosectomy are therefore still needed in select cases.[24,25] Endocrine and exocrine pancreatic function did not differ between the groups. Overall, approximately one-third of the patients developed new-onset endocrine pancreatic insufficiency, and approximately two-thirds developed exocrine pancreatic insufficiency. These outcomes are in line with different meta-analyses that have reported on the risk of late-onset endocrine pancreatic insufficiency (30% over 5 years) and exocrine pancreatic insufficiency (60% over 1 year) after necrotizing pancreatitis.[10,26] Remarkably, a substantial percentage of patients (40%) developed exocrine pancreatic insufficiency after the initial 6 months, but only a minority of patients were treated with supplemental pancreatic enzymes. This discrepancy could be explained by the fact that exocrine function was not routinely measured during follow-up. These results underline the importance of monitoring pancreatic function during long-term follow-up.

Quality of life of patients in both groups was impaired after infected necrotizing pancreatitis but improved as soon patients recovered. Whereas the endoscopy group experienced a more rapid physical recovery during the trial's initial follow-up, the surgery group had the same extent of increase in physical state after the initial 6-month follow-up. Even though a substantial number of patients developed pancreatitis-associated morbidity, such as pancreaticocutaneous fistulas or pancreatic insufficiency, quality of life was preserved at the long-term follow-up without differences between groups. Our findings are in line with a previous study, suggesting that patients may become accustomed to daily adaptations concerning their morbidity.[27,28]

To date, only 1 retrospective study has reported the long-term outcomes of patients with necrotizing pancreatitis treated with an endoscopic step-up approach.[29] The results of this single-center study demonstrated a mortality rate of 7% after a follow-up duration of 4 years. A higher mortality rate was observed in our study; however, all deaths after the initial 6-month follow-up were unrelated to necrotizing pancreatitis. An adjudication committee that was blinded to treatment allocation evaluated the causes of death and concluded that none were treatment-related. The proportion of deaths can be explained by other factors, such as the patients' older age, comorbidities, and the extensive follow-up period.

We acknowledge several limitations of the present study. First, quality of life was not assessed directly after randomization (at baseline) and at predefined time points after the initial 6-month follow-up. Hence, an overall comparison of quality of life between randomization and the end of long-term follow-up could not be performed.

Therefore, when patients experienced an improved quality of life was unclear.

Second, the long follow-up period also increased the likelihood of measuring complications that were not related to necrotizing pancreatitis. Moreover, the long-term follow-up period was not standardized between patients (ie, the first randomized patient had a longer follow-up period compared with the last randomized patient). These differences in time could have affected the patients' clinical outcomes.

Conclusion

We found no differences in mortality and major complications between the endoscopic and surgical step-up approach in patients with infected necrotizing pancreatitis in this long-term follow-up study. However, the endoscopic approach led to overall fewer pancreaticocutaneous fistulas and resulted in fewer reinterventions after the initial 6-month follow-up. These results confirm that, if feasible, the endoscopic approach should be preferred.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2022.05.015.

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Data Availability
The study design was preregistered at the Netherlands Trial Register (https://www.trialregister.nl/trial/8571) before the study was conducted. Requests for data can be made to the corresponding author and will be discussed during a meeting of the Dutch Pancreatitis Study Group. Individual deidentified participant data used in this study will only be shared after approval by the Dutch Pancreatitis Study Group.

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Conflicts of interest
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Supplementary Appendix

ExTENSION: Long-term follow-up study of an endoscopic vs a surgical step-up approach for infected necrotizing pancreatitis

Treatment Algorithm in the Initial TENSION Trial

Step-Up Approach

The initial TENSION trial[1] included patients with a high suspicion or evidence of infected (peri)pancreatic necrosis, an indication for invasive intervention and for whom both the endoscopic and surgical step-up approach was possible after evaluation by a multidisciplinary expert panel. Generally, the first step of the minimally invasive step-up approach is a drainage procedure, followed by necrosectomy in the absence of clinical improvement within 72 hours. Lack of clinical improvement was defined as clinical deterioration, (multiple) organ failure, or increasing inflammatory parameters (temperature, C-reactive protein, and leukocyte count).[2]

Endoscopic Step-Up Approach As Performed in the TENSION Trial

- Step 1: Endoscopic transluminal drainage
  Endoscopic transluminal drainage of infected necrosis was performed as the first step of the endoscopic step-up approach. Using procedural sedation, endoscopic ultrasound was used to visualize the size, location, and content of the necrotic collection. The necrotic collections were punctured through the gastric or duodenal wall, and subsequently, 2 double-pigtail plastic stents (7F) were placed. A nasocystic catheter was inserted in the collection to flush with 1 L saline/24 hours after the procedure. If a patient did not clinically improve and the collection was inadequately drained (as observed on imaging), additional drainage was performed. If this was clinically unsuccessful or when there was no clinical improvement, endoscopic transluminal necrosectomy was performed (step 2).

- Step 2: Endoscopic transluminal necrosectomy
  During endoscopic transluminal necrosectomy, the fistulous tract with the double-pigtail stents in situ was first dilated up to 15 to 20 mm and then entered with a therapeutic gastroscope to remove the remaining necrotic tissue under direct vision. The procedure was completed when most of the necrotic tissue was removed. When there was no clinical improvement after the procedure, imaging was performed and the endoscopic transluminal necrosectomy was repeated.

Surgical Step-Up Approach as Performed in the TENSION Trial

- Step 1: Percutaneous catheter drainage
  Image-guided percutaneous catheter drainage was performed with placement of a 14F drain as the first step of the surgical step-up approach. Multiple drains were allowed. The preferred route was through the left retroperitoneum, thereby facilitating video-assisted retroperitoneal débridement at a later stage, if needed. If drainage through the left retroperitoneum was not possible, transperitoneal drainage was performed. Drains were flushed with 50 mL, 3 times per day. If a collection was inadequately drained after 72 hours, additional drainage (ie, percutaneous or endoscopic) was performed or drains were upsized, or both. If drainage was clinically unsuccessful or when there was no clinical improvement, minimally invasive surgical necrosectomy was performed (step 2).

- Step 2: Video-assisted retroperitoneal débridement
  Video-assisted retroperitoneal débridement (VARD) was the preferred technique for minimally invasive surgical necrosectomy. VARD is a drain-guided, minimally invasive retroperitoneal procedure requiring a small incision. With the retroperitoneal drain used for guidance, the remaining necrosis was removed under video assistance, and 2 large drains with a lavage system were placed into the necrotic collection. When there was no clinical improvement after the procedure, imaging was performed and VARD was repeated. If initial VARD was not possible, débridement by laparotomy was performed.

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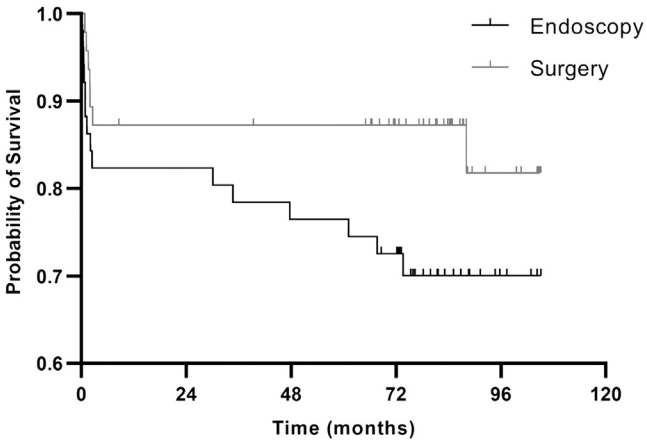
Supplementary Box 1. Definitions of Primary and Secondary End Points

End point	Definitions
Overall follow-up	Between randomization and the end of long-term follow-up.
Long-term follow-up	Starting from >6 months after randomization.
Primary end point	Composite of mortality or major complications.
Secondary end points	Individual components of the primary end point.
Mortality	All-cause deaths.
New-onset organ failure	First episode of organ failure after randomization. Recurrent organ failure after the initial 6 months follow-up was excluded as a new event during long-term follow-up. • Pulmonary: Pa_{O_2} <60 mm Hg despite F_{IO_2} 30%, or the need for mechanical ventilation. • Cardiovascular: a systolic blood pressure <90 mm Hg despite adequate fluid resuscitation or need for vasopressor support. • Renal: a serum creatinine >177 mmol/L after rehydration or need for hemofiltration or hemodialysis.
Bleeding requiring intervention	Requiring surgical, radiologic, or endoscopic intervention.
Perforation/enterocutaneous fistula requiring intervention	Perforation of a visceral organ or secretion of fecal material from a percutaneous drain/drainage canal after removal of drains or from a surgical wound, either from small or large bowel (confirmed by imaging or during surgery). Requiring surgical, radiologic, or endoscopic intervention.
Incisional hernia	Full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction.
Pancreaticocutaneous fistula	A connection between the pancreas and the cutis, through a percutaneous drain or drainage canal after removal of drains, with output of measurable volume of fluid, confirmed with either an amylase content level >3 times the upper limit of normal serum amylase level or confirmed with imaging or during surgery.
Persistent pancreaticocutaneous fistula	Persistent or recurrent pancreaticocutaneous fistula after the initial follow-up of 6 months.
Exocrine pancreatic insufficiency	Abnormal FE-1 test result (<200 μg/g) or the need for oral pancreatic enzyme supplementation to treat clinical symptoms of steatorrhea (not present before onset pancreatitis).
Endocrine pancreatic insufficiency	Elevated serum HbA_{1c} level (>53 mmol/L) or need for treatment with insulin/oral antidiabetic agents (not present before onset pancreatitis).
Wound infection	A superficial incisional surgical site infection and must meet the following criteria: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following: • Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site • Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision • At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion • An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination • Diagnosis of superficial/deep incisional surgical site infection by the surgeon or attending physician.
Biliary stricture	Biliary stricture requiring ERCP or PTC.
Infected necrosis	One of the following: (a) Gas configurations on contrast-enhanced CT or (b) positive culture from a fine-needle aspiration or the first drainage procedure from the (peri)pancreatic collection/walled-off necrosis.
Pancreatic necrosis	Diffuse or focal area(s) of nonenhancing pancreatic parenchyma as detected on contrast-enhanced CT.

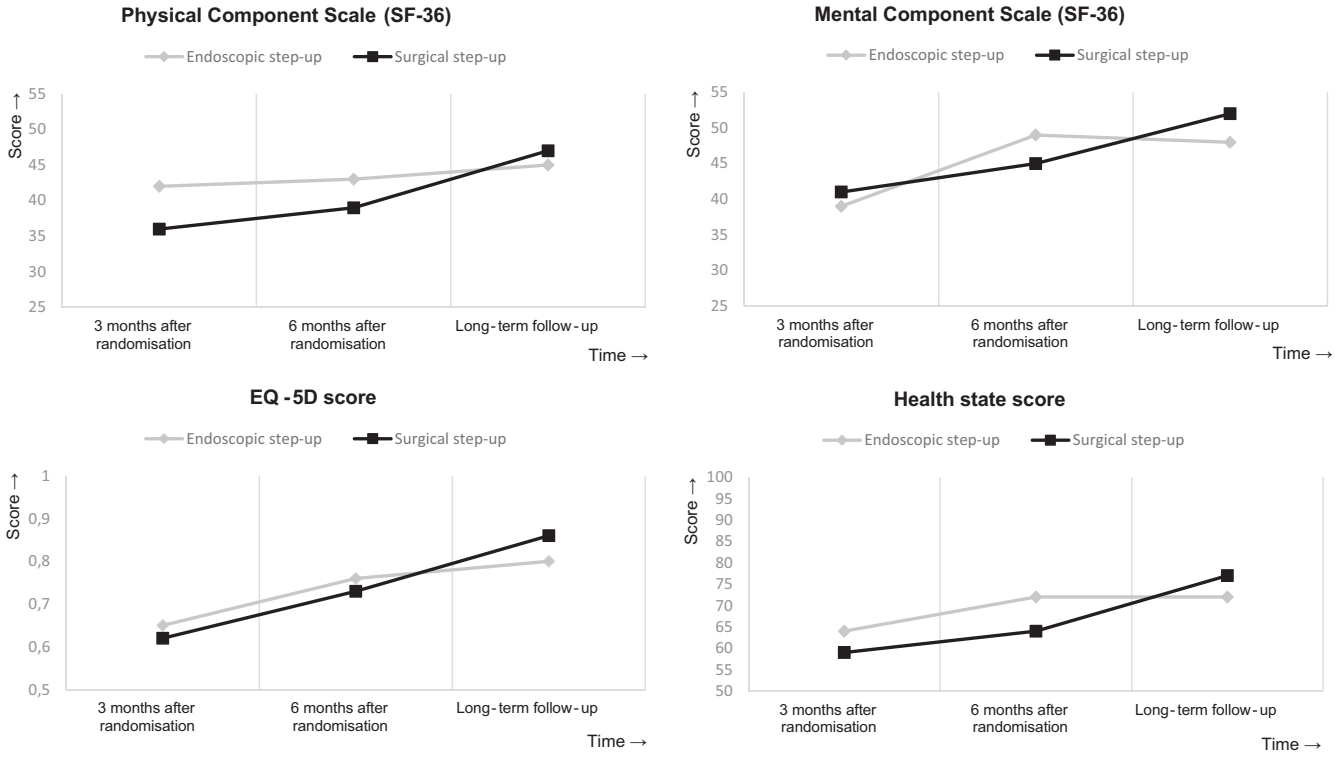
Supplementary Box 1. Continued

End point	Definitions
Acute pancreatitis	According to the 2012 Atlanta classification.[3]
Chronic pancreatitis	According to the M-ANNHEIM criteria.[4]

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PTC, percutaneous transhepatic cholangiography.



Supplementary Figure 1. Long-term survival curve. Probabilities of survival of patients randomized to the endoscopic and surgical step-up approach.



Supplementary Figure 2. Quality of life scores per group during follow-up. Data are presented as observed means per group at 3 and 6 months after randomization and at long-term follow-up. The scores on the SF-36 physical and mental health components range from 0 to 100, with higher scores indicating better quality of life. The utilities of the observed health score profiles from the general Dutch population range between −0.330 (indicating serious health problems) and 1.0 (indicating no problems at all). Health state scores range between 0 and 100, with higher scores indicating a better perceived health.

Supplementary Table 1. Baseline Characteristics of the TENSION Trial[1]

Characteristics	Endoscopic step-up approach (n = 51)	Surgical step-up approach (n = 47)
Age, *y*	63 ± 14	60 ± 11
Male sex	34 (67)	29 (62)
Cause of acute pancreatitis		
Gallstones	26 (51)	30 (64)
Alcohol abuse	7 (14)	7 (15)
Other[a]	18 (35)	10 (21)
Body-mass index,[b] kg/m^2	29 (20–63)	28 (19–33)
Coexisting condition		
Cardiovascular disease	26 (51)	18 (38)
Pulmonary disease	8 (16)	6 (13)
Chronic renal insufficiency	4 (8)	0 (0)
Diabetes	11 (22)	7 (15)
ASA Physical Status on admission		
I: healthy status	17 (33)	18 (38)
II: mild systemic disease	29 (57)	27 (58)
III: severe systemic disease	5 (10)	2 (4)
CT severity index[c]	6 (3–10)	8 (4–10)
Extent of pancreatic necrosis		
<30%	26 (51)	22 (47)
30%–50%	15 (29)	10 (21)
>50%	10 (20)	15 (32)
Necrosis extending >5 cm down the paracolic gutter	20 (39)	22 (47)
Encapsulation of the necrotic collection		
Partial	15 (29)	14 (30)
Complete	36 (71)	33 (70)
Gas configurations within the necrotic collection	23 (45)	27 (57)
Disease severity[d]		
Admitted to the ICU at randomization	21 (41)	25 (53)
SIRS[e]	33 (65)	38 (81)
APACHE II score[f]	9 (2–23)	10 (0–25)
APACHE II score ≥20[f]	3 (6)	4 (9)
Modified Glasgow Coma Score[g]	2 (0–5)	2 (0–7)
Modified MODS[h]	0 (0–8)	0 (0–6)
SOFA score[h]	0 (0–10)	1 (0–8)
C-reactive protein,[i] *mg/L*	168 (8–545)	189 (9–523)
White cell count,[j] $\times 10^9/L$	14.4 (3.8–31.2)	13.1 (4.1–38.9)
Single organ failure	13 (26)	14 (30)
Respiratory	11 (22)	13 (28)
Cardiovascular	11 (22)	7 (15)
Renal	3 (6)	1 (2)
Multiple organ failure	9 (18)	7 (15)
Time since onset of symptoms, *d*	39 (12–159)	41 (17–230)

Supplementary Table 1. Continued

Characteristics	Endoscopic step-up approach (n = 51)	Surgical step-up approach (n = 47)
Antibiotic treatment at randomization	10 (20)	9 (19)
Tertiary referral	35 (69)	35 (75)
Confirmed infected necrosis[k]	46 (90)	46 (98)

NOTE. Data are presented as mean ± SD, median (IQR), or n (%).
APACHE, Acute Physiology and Chronic Health Evaluation; ASA, American Society of Anesthesiologists; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.
[a]Includes, among others, medication, anatomic abnormalities, and unknown etiology.
[b]Data were missing in 34 patients.
[c]Data were derived from the computed tomography performed just before randomization. Scores range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and extrapancreatic collections.
[d]Data were based on maximum values during the 24 hours before randomization, unless stated otherwise.
[e]SIRS was defined according to the consensus conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine.
[f]Scores range from 0 to 71, with higher scores indicating more severe disease.
[g]Scores range from 0 to 8, with higher scores indicating more severe disease.
[h]Scores range from 0 to 24, with higher scores reflecting more severe organ dysfunction.
[i]Data were missing in 10 patients.
[j]Data were missing in 2 patients.
[k]Confirmed infected necrosis was defined as a positive culture of pancreatic or extrapancreatic necrotic tissue obtained by fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the collection on contrast-enhanced computed tomography.

Supplementary Table 2. Mortality Within 5 Years of Follow-up

Outcome	Endoscopic step-up approach (n = 42)	Surgical step-up approach (n = 41)	RR (95% CI)	*P* value
Death <5 years after randomization	3 (7)	0 (0)	…	.241
Death >5 years after randomization	3 (7)	1 (2)	2.93 (0.32–27.02)	.616

NOTE. Data are presented as n (%).

Supplementary Table 3. All-Cause Mortality

Patient and group	Cause of death	Age, *y*	Pancreatitis related[a]	Time,[b] *mo*
1: endoscopy	Cardiac failure (ischemic cardiomyopathy)	79	No	30
2: endoscopy	Metastatic esophageal cancer	63	No	34
3: endoscopy	Cause of death unclear	91	No	47
4: endoscopy	Urinary tract cancer	71	No	61
5: endoscopy	Aspiration pneumonia (due to diabetic gastroparesis)	58	No	67
6: endoscopy	Cardiac failure (decompensation cordis)	68	No	73
1: surgery	Multiple cerebral infarctions	81	No	88

[a]Cause of death was discussed by an adjudication committee that was blinded to treatment allocation.
[b]Time between randomization and date of death.

Supplementary Table 4. Interventions During Long-term Follow-up

Patient group	Type of intervention	Indication
Patients in endoscopy group		
1	• PCD	• Psoas abscess and new pancreaticocutaneous fistula
2	• PCD	• Paracolic necrotic collections
3	• PCD	• Paracolic necrotic collection
	• ETD	• New pancreaticocutaneous fistula
Patients in surgery group		
1	• PCD • ETD with pancreatic duct stenting	• Persistent pancreaticocutaneous fistula
2	• ETD with pancreatic duct stenting	• Persistent pancreaticocutaneous fistula
3	• ETD	• Persistent pancreaticocutaneous fistula
4	• ETD with pancreatic duct stenting	• Persistent pancreaticocutaneous fistula
5	• ETD with pancreatic duct stenting	• New pancreaticocutaneous fistula
6	• PCD	• New pancreaticocutaneous fistula
7	• PCD	• Infected collection pancreatic tail
8	• PCD • VARD	• Ongoing treatment (persistent necrotic collections)
9	• ETD	• Recurrent pancreatic fluid collection
10	• ETD	• Recurrent pancreatic fluid collection

NOTE. Patients per group who required re-interventions (ie, drainage procedures or necrosectomy, or both) during long-term follow-up. Persistent pancreaticocutaneous fistula was defined as recurrent or persistent fistula after the initial 6 months of follow-up.
ETD, endoscopic transluminal drainage; PCD, percutaneous catheter drainage; VARD, video-assisted retroperitoneal débridement.

Supplementary Table 5. Comparison of Patients With and Without a Disrupted or Disconnected Pancreatic Duct After the Initial 6-Month Follow-up

Variable	Patients with a DPD (n = 22)	Patients without a DPD (n = 61)	RR (95% CI)
Pancreaticocutaneous fistulas[a]	8 (36)	0 (0)	…
New pancreaticocutaneous fistula	4 (18)	0 (0)	…
Persistent pancreaticocutaneous fistula	4 (18)	0 (0)	…
Recurrent fluid collection	19 (86)	14 (23)	5.65 (1.96–16.32)
Recurrent acute pancreatitis	12 (55)	11 (18)	1.80 (1.12–2.89)
Chronic pancreatitis	4 (18)	5 (8)	1.12 (0.91–1.39)
Need for intervention	13 (59)	2 (3)	2.36 (1.43–3.92)
Need for additional drainage procedure (PCD/ETD)	12 (55)	1 (2)	2.16 (1.37–3.42)
PCD	6 (27)	1 (2)	1.35 (1.05–1.75)
ETD	8 (36)	0 (0)	…
Necrosectomy	0 (0)	1 (2)	…
Transpapillary drainage	8 (36)	1 (2)	1.55 (1.13–2.12)
Pancreatic surgery[b]	1 (5)	1 (2)	1.03 (0.94–1.14)
Readmissions, *n*	5 (2–8)	1 (1–3)	…
Hospital length of stay, *d*	30 (5–60)	8 (1–24)	…
Endocrine pancreatic insufficiency[c]	9 (41)	27 (44)	0.94 (0.62–1.43)
Exocrine pancreatic insufficiency[d]	19 (86)	39 (64)	2.65 (0.88–7.97)

NOTE. Data are presented as n (%) or median (IQR).
DPD, disrupted or disconnected pancreatic duct; ETD, endoscopic transmural drainage; PCD, percutaneous catheter drainage.
[a]New pancreaticocutaneous fistulas developed after the initial 6-month follow-up. Persistent pancreaticocutaneous fistulas developed during the initial TENSION trial with persistence after the initial 6-months follow-up.
[b]Open cystogastrostomy.
[c]As measured by elevated HbA_{1c} levels and the need for oral antidiabetic agents or insulin, or both.
[d]Based on FE-1 values <200 μg/g.

Supplementary Table 6. Exocrine Pancreatic Insufficiency at Long-term Follow-up

Variable	Endoscopic approach[a] (n = 36)	Surgical approach[a] (n = 40)	RR (95% CI)	*P* value
FE-1 <200 μg/g[b]	12/27 (44)	12/30 (40)	1.11 (0.61–2.04)	.792
FE-1 <100 μg/g[b]	8/27 (30)	9/30 (30)	0.99 (0.45–2.19)	1.000
Enzyme use at long-term follow-up[c]	11/36 (31)	12/40 (30)	1.02 (0.51–2.02)	1.000
Complaints (steatorrhea)[c]	7/36 (19)	5/40 (13)	1.56 (0.54–4.47)	.532
Patients with improved FE-1 >200 μg/g[d]	6/25 (24)	7/27 (26)	0.93 (0.36–2.38)	1.000

NOTE. Data are presented as n/N (%).
[a]Pancreatic function was reevaluated in the 76 patients who were alive at the long-term follow-up.
[b]FE-1 test was repeated in 57 patients.
[c]Supplemental pancreatic enzyme use and clinical complaints of steatorrhea in all 76 surviving patients at the end of long-term follow-up.
[d]Normalization of FE-1 values to >200 μg/g among surviving patients who were initially diagnosed with exocrine pancreatic insufficiency (FE-1 <200 μg/g).

Supplementary Table 7. Patients With Recurrent Acute Pancreatitis After the Initial 6-Month Follow-up

Patient and group	Initial etiology	Presumed etiology of recurrent episode(s)	Presence of DPD	Treatment	Endocrine insufficiency	Exocrine insufficiency	Development of chronic pancreatitis
1: endoscopy	• Biliary	• Traumatic (pancreatic injury during gastric surgery)	No	Conservative	Yes	No	No
2: endoscopy	• Alcohol	• Alcohol	No	Conservative	Yes	Yes	Yes
3: endoscopy	• Biliary	• Idiopathic	No	Open cystogastrostomy after infected fluid collection (due to dislocated pigtail stent)	Yes	Yes	No
4: endoscopy	• Idiopathic	• Idiopathic	No	Systemic antibiotics	Yes	No	No
5: endoscopy	• Idiopathic	• Idiopathic	No	Conservative	No	No	No
6: endoscopy	• Idiopathic	• Post-ERCP	Yes	1) PCD 2) ETD	No	Yes	Yes
7: endoscopy	• Idiopathic	• Idiopathic	Yes	Conservative	Yes	Yes	No
8: endoscopy	• Alcohol	• Biliary	No	Laparoscopic cholecystectomy	No	No	No
1: surgery	• Idiopathic	• Idiopathic	No	Conservative	Yes	No	No
2: surgery	• Idiopathic	• Idiopathic	Yes	1) PCD 2) ETD with transpapillary drainage	Yes	Yes	No
3: surgery	• Biliary	• Biliary	Yes	1) PCD 2) ETD with transpapillary drainage	Yes	Yes	Yes
4: surgery	• Biliary	• Biliary	Yes	PCD	Yes	No	No
5: surgery	• Alcohol	• Alcohol	No	Conservative	No	Yes	No
6: surgery	• Idiopathic	• Biliary	Yes	1) PCD 2) ERCP with trans-papillary drainage 3) No cholecystectomy	Yes	Yes	Yes
7: surgery	• Biliary	• Idiopathic	Yes	1) PCD 2) ETD	No	No	No

Supplementary Table 7. Continued

Patient and group	Initial etiology	Presumed etiology of recurrent episode(s)	Presence of DPD	Treatment	Endocrine insufficiency	Exocrine insufficiency	Development of chronic pancreatitis
8: surgery	• Biliary	• Biliary	Yes	Conservative	No	No	No
9: surgery	• Post-ERCP	• Biliary	Yes	1) ETD with transpapillary drainage 2) Surgical (open) cystogastrostomy	No	No	No
10: surgery	• Biliary	• Biliary	Yes	ERCP with sphincterotomy	Yes	No	No
11: surgery	• Biliary	• Idiopathic	Yes	ETD	No	Yes	No
12: surgery	• Biliary	• Idiopathic	No	Conservative	Yes	Yes	No
13: surgery	• Biliary	• Unknown	No	Conservative	Yes	Yes	No
14: surgery	• Idiopathic	• Idiopathic	No	Conservative	No	No	No
15: surgery	• Biliary	• Biliary	Yes	ERCP with sphincterotomy • No cholecystectomy	Yes	No	No

DPD, disrupted or disconnected pancreatic duct; ERCP, endoscopic retrograde cholangiopancreatography; ETD, endoscopic transmural drainage; PCD, percutaneous catheter drainage.

Supplementary Table 8. Patients Diagnosed With a Disrupted or Disconnected Pancreatic Duct After the Initial 6-Month Follow-up

Patient and group	Complications	Diagnosis	Endocrine pancreatic insufficiency	Exocrine pancreatic insufficiency	Treatment after the initial 6-month follow-up
1: endoscopy	• Recurrent pancreatic fluid collection	Imaging (CT-scan)	No	No	Conservative
2: endoscopy	• Recurrent pancreatic fluid collection	Imaging (MRI/MRCP)	Yes	Yes	Conservative
3: endoscopy	• Recurrent pancreatic fluid collection	Imaging (MRI/MRCP)	Yes	No	Conservative[a]
4: endoscopy	• New pancreaticocutaneous fistula	Imaging (CT/MRI)	Yes	Yes	1) PCD
5: endoscopy	• Recurrent pancreatic fluid collection	Imaging (CT/MRI)	Yes	Yes	Conservative
6: endoscopy	• Recurrent pancreatic fluid collection	Imaging (CT scan)	Yes	Yes	Conservative
7: endoscopy	• Recurrent pancreatic fluid collection	Imaging (CT scan)	Yes	Yes	1) PCD
8: endoscopy	• Recurrent pancreatic fluid collection • New pancreaticocutaneous fistula • Recurrent acute pancreatitis • Chronic pancreatitis	Imaging (CT/MRI)	No	Yes	1) PCD 2) ETD with transpapillary drainage
9: endoscopy	• Recurrent pancreatic fluid collection • Recurrent acute pancreatitis	Imaging (CT/MRI)	Yes	Yes	Conservative
1: surgery	• Recurrent (infected) pancreatic fluid collections • Persistent pancreaticocutaneous fistula • Recurrent acute pancreatitis	Functional: persistent high amylase in drain fluid	Yes	Yes	1) PCD 2) ETD with transpapillary drainage[a]
2: surgery	• Recurrent pancreatic fluid collection • Persistent pancreaticocutaneous fistula • Recurrent acute pancreatitis • Chronic pancreatitis	Functional: persistent high amylase in drain fluid	Yes	Yes	1) ETD with transpapillary drainage[a]
3: surgery	• Recurrent (infected) pancreatic fluid collections • Recurrent acute pancreatitis	Imaging CT scan)	Yes	No	1) PCD
4: surgery	• Recurrent pancreatic fluid collection • Gastrointestinal (pancreatic-colonic) fistula	Functional: persistent high amylase in drain fluid	Yes	Yes	1) Surgery (hemicolectomy)
5: surgery	• New pancreaticocutaneous fistula • Recurrent acute pancreatitis	Imaging (MRI/MRCP)	Yes	Yes	1) PCD 2) ERCP with trans-papillary drainage
6: surgery	• Recurrent pancreatic fluid collection • Persistent pancreaticocutaneous fistula • Recurrent acute pancreatitis	Functional: persistent high amylase in drain fluid	No	No	1) PCD 2) ETD

Supplementary Table 8. Continued

Patient and group	Complications	Diagnosis	Endocrine pancreatic insufficiency	Exocrine pancreatic insufficiency	Treatment after the initial 6-month follow-up
7: surgery	• Recurrent pancreatic fluid collection • Chronic pancreatitis	Imaging (CT scan	Yes	Yes	1) ERCP with trans-papillary drainage
8: surgery	• Recurrent pancreatic fluid collection • Recurrent acute pancreatitis	Imaging (MRI/MRCP)	No	No	Conservative
9: surgery	• Recurrent pancreatic fluid collection • Recurrent acute pancreatitis	Imaging (CT scan)	No	No	1) ETD with transpapillary drainage 2) Surgical (open) cystogastrostomy
10: surgery	• New pancreaticocutaneous fistula • Recurrent acute pancreatitis	Imaging (MRI/MRCP)	Yes	Yes	1) ETD with transpapillary drainage
11: surgery	• Recurrent pancreatic fluid collection • Recurrent acute pancreatitis	Functional: persistent high amylase in drain fluid	No	Yes	1) ETD
12: surgery	• Recurrent pancreatic fluid collection • Recurrent acute pancreatitis	Functional: persistent high amylase in drain fluid	Yes	No	Conservative
13: surgery	• Recurrent pancreatic fluid collection • Persistent pancreaticocutaneous fistula	Functional: persistent high amylase in drain fluid	Yes	No	1) ETD with transpapillary drainage[a]

NOTE. New pancreaticocutaneous fistulas developed after the initial 6-months follow-up. Persistent pancreaticocutaneous fistulas developed during the initial TENSION trial with persistence after the initial 6-month follow-up.
CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; ETD, endoscopic transmural drainage; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PCD, percutaneous catheter drainage.
[a]Patients with indwelling plastic pigtail stents after endoscopic transluminal drainage.

Supplementary Table 9. Comparison of Quality of Life Scores Within Treatment Groups

	Mean score differences (standard error)					
Approach	3 vs 6 months	*P* value	6 months vs long-term follow-up	*P* value	3 months vs long-term follow-up	*P* value
Endoscopic step-up approach						
PCS (SF-36)	1.75 (2.21)	0.433	3.72 (2.21)	.112	5.47 (2.20)	.017
MCS score (SF-36)	7.39 (3.03)	0.019	−0.71 (3.11)	.820	6.68 (3.03)	.033
EQ-5D score	0.08 (0.06)	0.205	0.07 (0.06)	.279	0.14 (0.06)	.018
Health state score	5.28 (3.84)	0.175	0.98 (3.89)	.802	6.27 (3.84)	.109
Surgical step-up approach						
PCS score (SF-36)	2.52 (1.78)	0.163	8.80 (1.76)	<.001	11.32 (1.85)	<.001
MCS score (SF-36)	3.82 (2.50)	0.131	7.57 (2.47)	.003	11.39 (2.61)	<.001
EQ-5D score	0.11 (0.04)	0.015	0.14 (0.04)	.001	0.25 (0.05)	<.001
Health state score	5.39 (3.14)	0.092	12.65 (3.08)	<.001	18.04 (3.28)	<.001

NOTE. The comparison of quality of life scores within treatment groups were calculated by linear mixed models based on estimated marginal mean scores. Score differences are represented with corresponding *P* values. The 65 patients who filled out at least 2 of 3 questionnaires were included in this model with time as the fixed effect.
MCS, Mental Component Scale; PCS, Physical Component Scale.