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Long-term outcomes of pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones

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Authors

Florence E.M. de Rijk[1,2], Pauline M.C. Stassen[1,2], Sophia E. van der Wiel[1], Marja A. Boermeester[3,4], Yama Issa[3,4], Marinus A. Kempeneers[3,4], Robert C. Verdonk[5], Marco J. Bruno[1], Pieter Jan F. de Jonge[1]

Institutions

1 Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands
2 Department of Research and Development, St. Antonius Hospital, Nieuwegein, The Netherlands
3 Amsterdam UMC, location University of Amsterdam, Department of Surgery, Amsterdam, The Netherlands
4 Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
5 Department of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands

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Corresponding author
Florence E.M. de Rijk, MD, Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
Fax: +010-7040704
f.derijk@erasmusmc.nl

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ABSTRACT

Background and study aims Pancreatoscopy-guided electrohydraulic lithotripsy (EHL) has proven to be an effective first-line therapy in symptomatic chronic pancreatitis (CP) patients with obstructing pancreatic duct (PD) stones [1]. However, long-term outcomes of endoscopic EHL remain unknown. The aim of the present study was to evaluate the long-term treatment effects of EHL as first-line therapy and to compare with those obtained in a historical cohort of patients who underwent extracorporeal shockwave lithotripsy (ESWL) as primary treatment.

Patients and methods An observational retrospective single-center long-term follow-up study was performed including 19 consecutive patients who previously underwent endoscopic EHL compared to 18 patients who underwent ESWL followed by endoscopic retrograde pancreatography (ERP). The primary endpoint was long-term treatment success after EHL or ESWL defined as no recurrence of symptomatic intraductal stones confirmed on imaging. Secondary endpoints for the EHL-population included long-term clinical success (i. e., a similar or lower Izbicki Pain Score or reduction in opiate usage as compared to 6-month follow-up), quality of life (QoL), pancreatic function and hospital re-admission rate.

Results In the EHL group, 37 % of the patients developed recurrent symptomatic PD stones versus 61 % in the ESWL group after a median follow-up of 35.0 and 76.5 months. Of the patients with recurrence, 71 % versus 100 % underwent a reintervention. Median time to recurrence was 12.0 versus 13.0 months. Clinical success sustained in 58 % of the EHL patients. QoL was not significantly different compared with 6-month follow-up and baseline.

Conclusions Also at long-term follow-up, endoscopic EHL as first-line treatment is moderately effective for symptomatic CP patients with treatment success rates that seems at least equally effective as ESWL.

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disease characterized by irreversible morphological characteristics such as pancreatic atrophy, fibrotic tissue replacement and pancreatic calcifications [1]. Obstructive pancreatic duct (PD) stones can be the culprit responsible for (recurrent) pain relapses or chronic pain most likely due to pancreatic ischemia caused by an increased intraductal and parenchymal pressure [2]. In current practice, patients with obstructive PD stones are treated using an endoscopy-first approach [3, 4]. Extracorporeal shock wave lithotripsy (ESWL) followed by endoscopic extraction of stone fragments is recommended as first-line treatment for stones larger than 5 mm [4]. ESWL involves careful targeting of the pancreatic stone with shock waves generated by a strong electromagnetic lithotripter [5]. Pancreatoscopy-guided intraductal lithotripsy is a relatively new promising technique which may serve as an alternative treatment for ESWL [6]. With pancreatoscopy-guided intraductal electrohydraulic lithotripsy (EHL), fragmentation of stones is achieved under direct visualization by the absorption of shockwave pulses generated by a bipolar probe in an aqueous medium [7]. We recently evaluated the efficacy and safety of pancreatoscopy-guided EHL as first-line therapy in consecutive patients with obstructive chronic calcifying pancreatitis (PELSTONE study) [8]. When PD cannulation was achieved, pancreatoscopy was technically successful in 92 % of patients defined as complete (100 %) or partial ductal clearance (50 % to 99 %) based on post-EHL pancreatoscopic imaging and fluoroscopic pancreatogram. At 6-month follow-up compared with baseline, a significant improvement in Izbicki Pain Score and reduction in opioid usage was observed. However, the long-term clinical outcomes of pancreatoscopy-guided EHL as first-line treatment of obstructing PD stones are unclear and, since CP is a chronic disease, a longer clinical follow-up for such studies is required. Therefore, the aim of the present study is to evaluate the long-term clinical success of pancreatoscopy-guided EHL as first-line treatment in patients with symptomatic CP due to obstructive distal PD stones and to compare outcomes to a historical cohort of patients who underwent ESWL as a primary treatment.

Patients and methods

Study design and population

An observational retrospective long-term follow-up study of patients who underwent pancreatoscopy-guided EHL was conducted at the Erasmus MC University Medical Center Rotterdam, the Netherlands, an academic tertiary referral center for pancreaticobiliary diseases. In this study, we report and primarily focus on the long-term outcomes of pancreatoscopy-guided EHL as first-line treatment for patients with CP and symptomatic obstructive PD stones. In addition, to put these outcomes into perspective, we describe the long-term outcomes of patients who underwent ESWL followed by ERP as primary treatment (historical cohort), which is the recommended treatment in current guidelines.

For the EHL cohort, we included patients who were technically successful treated with pancreatoscopy-guided EHL as first-line treatment and who participated in the previous PELSTONE study [8]. The EHL technique and protocol we used have been described in detail previously [8]. In short, in all patients a pancreatic sphincterotomy was performed to facilitate introduction of the pancreatoscope (SpyGlass DS Direct Visualization System, Boston Scientific Corp, Natick, Massachusetts, United States). If a stricture was present that precluded the passage of the pancreatoscope, a balloon dilatation was attempted. When the stone was visualized with the pancreatoscope, a 1.9F EHL probe (Nortech AUTOLITH system, Northgate Technologies, Inc., Elgin, Illinois, United States) was introduced and EHL was performed. Depending on characteristics of the stone (i. e., size and hardness), generator settings of the AUTOLITH system were adjusted. Adjustments could be made in power settings varying from low to high and number of shots given per second (i. e., 10 or 15 shots). After lithotripsy was performed, residual stone fragments < 5 mm were extracted using retrieval balloons, baskets or both. Patients with concomitant PD strictures were not excluded from the EHL- nor ESWL cohort. PD strictures were treated endoscopically in both cohorts by exchanging stents on a regular basis (i. e., every 3 months) and insert an increasing number of stents (7Fr or 10F diameter) with each consecutive procedure to further dilate the stricture, during a fixed 1-year stenting period.

In the previous study, patients were included in case of an established diagnosis of CP according to the M-ANNHEIM criteria, and one or more PD stone(s) of ≥ 5 mm in the head or the neck of the pancreas as shown on cross-sectional imaging (i. e., computed tomography (CT), magnetic resonance cholangio-pancreatography (MRCP)) or endoscopic ultrasound (EUS) [9]. Exclusion criteria included, age < 18 years, asymptomatic patients, patients suffering from CP with stones located in the body or tail of the pancreas, previous treatment of PD stones using ESWL, history of surgical treatment of CP and pregnancy. Moreover, patients were not eligible for study inclusion in case endoscopic treatment was not deemed to be possible or successful, due to for example a non-dilated PD or a completely calcified pancreas. Patients were consented for the current study and included when previous pancreatoscopy-guided EHL therapy had been technically successful defined as ductal clearance confirmed with post-EHL pancreatoscopic imaging and fluoroscopic ductal pancreatography.

For the ESWL cohort, we included patients who were successfully treated with ESWL for obstructive PD stones ≥ 5 mm (i. e., ductal clearance confirmed with post-ESWL pancreatoscopic imaging) followed by ERP as first-line treatment at the Erasmus MC University Medical Center Rotterdam, between February 2012 and May 2017. These patients were identified from the Erasmus MC endoscopy registry Endobase, the primary documentation system for endoscopy reports which captures all relevant information about the patient and procedure, including images and videos data, into a centralized database. ESWL was performed on an inpatient basis. Depending on the quantity and size of the PD stones, one to three ESWL sessions were done on consecutive days followed by an ERP on Day 5 to

remove stone fragments. Some of these ESWL patients previously participated in the ESCAPE trial [10]. In the ESCAPE trial, patients with severe pain due to obstructive CP with a dilated PD and who recently started using opioids because of progressive pain (strong opioids for ≤ 2 months or weak opioids for ≤ 6 months) were included.

Written informed consent (IC) was obtained from each participant before participation in this long-term follow-up study. The study was approved by the Medical Ethical Committee/Internal Review Boards of the Erasmus MC University Medical Center.

Follow-up and data collection

As per routine clinical practice, patients were followed up at the out-patient clinic every 3 months.

In case of recurrence of symptoms, cross-sectional imaging (i. e., computed tomography [CT] or magnetic resonance imaging [MRI]/magnetic resonance cholangiopancreatography [MRCP]) was performed to assess presence of recurrent obstructive duct stones or other pancreaticobiliary abnormalities. Standard follow-up imaging was not performed. During follow-up, data on demographic factors, medical history, laboratory tests (i. e., fecal elastase), medication use, radiological imaging, endoscopic or surgical interventions and hospital admissions were extracted from hospital records. In addition, a follow-up questionnaire was sent to all patients to collect information on medication use, hospital admissions, interventions for pancreatic diseases, QoL (SF-12) and pain severity (Izbicki Pain Score).

Study endpoints

The primary study endpoint included long-term treatment success defined as no relapse of symptoms due to intraductal stones confirmed on imaging (i. e., CT, MRI/MRCP, EUS, or endoscopic retrograde cholangiopancreatography) after restoration of pancreatic outflow was achieved with first-line endoscopic treatment (i. e., pancreatoscopy-guided EHL or ESWL followed by ERP with stone extraction).

The secondary endpoints included the long-term effects of pancreatoscopy-guided EHL on QoL assessed by means of the 12-Item Short Form Health Survey (SF-12), pain severity based on the Izbicki Pain Score, opioid usage, the number of hospital admissions due to acute-on-CP or inadequate pain control and pancreatic function (i. e., exocrine- and endocrine pancreatic insufficiency).

Long-term clinical success was defined as a similar or a lower Izbicki Pain Score *or* reduced opiate usage, as compared to 6-month follow-up after technically successful removal of the intraductal PD stones by pancreatoscopy-guided EHL. Exocrine pancreatic deficiency was scored in case of a fecal elastase-1 test result < 200 µg/g or the use of pancreatic enzyme replacement therapy. Endocrine pancreatic insufficiency was registered when patients used oral antidiabetic medication or insulin therapy.

The primary study endpoint was also described for the historical cohort of ESWL patients. Secondary study endpoints were only assessed for the EHL cohort.

Statistics

Statistical analyses were performed using SPSS version 25 (IBM Corp: Armonk, New York, United States). Dichotomous or categorical outcomes were presented as numbers with percentages and compared using the Chi-square or Fisher's exact test. Continuous data were expressed as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) depending on normality of distribution. Statistical comparison for continuous data was performed using the Student's *t*-test when normally distributed or the Mann-Whitney-U test when not normally distributed. A two-sided alpha < 0.05 was considered statistically significant.

SF-12 and Izbicki Pain Score

Similar to the original PELSTONE study, regression weights that were derived from normative data of the Dutch general population were used to compute the physical and mental component summaries (PCS and MCS) of the SF-12 by using the orthogonal rotation method [8, 11]. These scores range from 0 to 100, with higher scores indicating a better quality of life (QoL). A score of 50 represents the mean in the general population [12]. For all time points (i. e., baseline, 6-month follow-up and long-term follow-up) the mean Izbicki Pain Score, PCS, and MCS were calculated. The mean scores at long-term follow-up were compared to 6-month follow-up and baseline by using the Wilcoxon signed-rank test. $P < 0.05$ was considered statistically significant.

Results

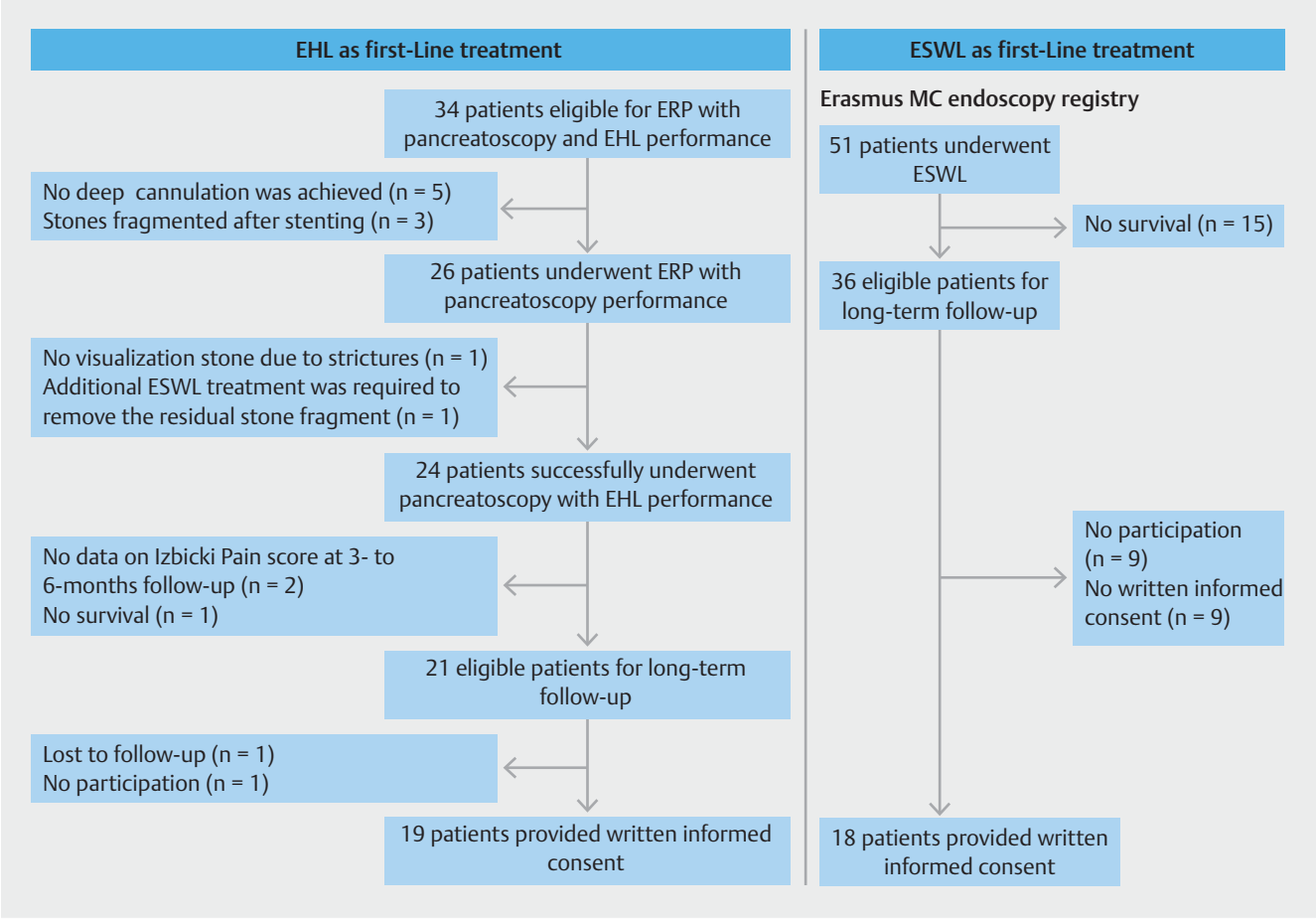
Study population

EHL cohort

Between December 2017 and July 2020, 24 CP patients were technically successfully treated with pancreatoscopy-guided EHL as primary treatment for one or more obstructive PD stone(s) in the head or neck of the pancreas [8]. Data on clinical success (i. e., Izbicki Pain Score) were missing for two patients at 6-month follow-up and one patient died after the initial follow-up period because of metastatic pancreatic carcinoma leaving 21 eligible patients. In total, 19 patients provided written IC for this long-term follow-up study (▶ **Fig. 1**). Patient demographics at baseline are provided in ▶ **Table 1**. In 17 patients the stones were located in the pancreatic head and in two patients in the neck of the pancreas with a median of one stone (range 1 to 3), and a mean stone size of 8.0 mm ± 2.6. At baseline, opioids were used on a daily basis in 53 % of patients.

ESWL cohort

Between February 2012 and May 2017, 51 consecutive patients underwent successful first-line treatment with ESWL for obstructive distal PD stones at the Erasmus MC University Medical Center of whom 17 patients previously participated in the ESCAPE trial [10]. During follow-up 15 patients died leaving 36 patients eligible for the present study of whom 18 patients (50 %) provided written IC. Nine patients refused to participate



▶ **Fig. 1** Flowchart of patient inclusion in the study.

and nine patients who initially indicated their intention to participate did not respond to follow-up reminders. In total, 18 CP patients treated with ESWL followed by ERP as first-line treatment for obstructive calcifying CP were included in the present study (▶ **Fig. 1**). ▶ **Table 1** lists patient characteristics of the ESWL cohort. In the majority of patients (n = 14), the stones were located in the head of the pancreas with a median of one stone (range 1 to 3) and a mean stone size of 9.0 mm ± 2.8. Daily opioid usage was observed in 83 % of patients.

Long-term treatment success

EHL cohort

Long-term treatment success after initial EHL therapy (i. e., no recurrence of symptomatic obstructive PD stones) sustained in 12 of 19 patients (63 %) after a median follow-up period of 35.0 months (IQR 30 to 41).

In this group, seven of 19 patients (37 %) presented with recurrent symptomatic obstructive PD stones. Median time from the last successful ERP to recurrence was 12.0 months (IQR 7.0 to 14.0). Based on imaging (CT/MRI/MRCP or pancreatogram during ERCP) a median of two recurrent stones with a mean stone size of 4.3 ± 1.2 mm was present in these patients (▶ **Table 2**).

In five patients with symptomatic stone recurrence an endoscopic reintervention was performed (71 %). Endoscopic retreatment resulted in complete pain reduction in four of five patients (80 %). A median number of three ERPs (range 3 to 5) was required to achieve pain reduction in these four patients. In three patients the recurrent stone(s) was successfully removed with a basket or balloon of whom one also had developed a recurrent pancreatic stricture, which was successfully treated by progressive pancreatic stenting. One patient was treated successfully with endoscopic dilatation of a PD stricture and stent placement. None of the patients required retreatment with EHL. Endoscopic retreatment was not successful in one of five patients due to a resilient stricture in the pancreatic head impeding cannulation of the PD. This patient was then treated surgically but died after surgery due to long-term postoperative complications (i. e., cachexia and failure to thrive due to dumping syndrome). Finally, in two of seven patients with recurrence (29 %) no reintervention was performed despite stone recurrence. One patient suffered from a metastatic hepatocellular carcinoma and therefore refrained from reintervention and the other patient was scheduled for a reintervention which

▶ **Table 1** Patient and disease characteristics at time of initial treatment with EHL/ESWL.

	EHL (n = 19) n, (%)	ESWL (n = 18) n, (%)
▪ Age (year), mean ± SD[1]	60.8 ± 10.5	55.2 ± 9.5
▪ Male gender, no. (%)	12 (63.2)	10 (55.6)
▪ BMI (kg/m^2), mean ± SD	24.0 (4.6)	22.5 (4.3)
ASA classifications, no. (%)[1]		
▪ ASA I	13 (68.4)	1 (5.6)
▪ ASA II	6 (31.6)	12 (66.7)
▪ ASA III	0 (0.0)	5 (27.8)
Smoking, no. (%)		
▪ Yes	9 (47.4)	14 (77.8)
▪ No	4 (21.1)	0 (0.0)
▪ Quit	6 (31.6)	4 (22.2)
Alcohol no. (%)		
▪ Yes	4 (21.1)	2 (11.1)
▪ No	7 (36.8)	4 (22.2)
▪ Quit	8 (42.1)	12 (66.7)
Etiology, no. (%)		
▪ Alcoholic CP	12 (63.3)	11 (61.1)
▪ Non-alcoholic CP	7 (36.8)	7 (38.9)
▪ Genetic	0	
▪ Hypercalcemia	2	0
▪ Idiopathic	4	5
▪ Pancreas divisum and alcohol	1	0
▪ Recurrent acute pancreatitis due to medication use	0	1
Opiate usage, no. (%)	10 (52.6)	15 (83.3)
Exocrine pancreatic insufficiency, no. (%)[1]	12 (63.2)	17 (94.4)
Endocrine pancreatic insufficiency, no. (%)	6 (31.6)	9 (50.0)
Insulin usage	4	8
Oral antidiabetic medication	4	3
Sphincterotomy, no. (%)		
▪ Pancreatic	19 (100.0)	15 (83.3)
▪ Biliary	6 (31.6)	6 (33.3)
Stricture, no. (%)	13 (68.4)	11 (61.1)
Stent placement prior to EHL/ESWL performance, no. (%)[1]	14 (73.7)	7 (38.9)
Prior balloon dilatation of stricture, no. (%)	9 (47.4)	7 (38.9)
Dilated pancreatic duct, no. (%)	19 (100.0)	18 (100.0)
Pancreatic duct diameter (mm), median (range)	10.0 (6–12)	8.5 (6–17)
Stone location based on pancreatogram, no. (%)		
▪ Head	17 (89.5)	14 (77.8)
▪ Neck	2 (10.5)	4 (22.2)
▪ No. stones present based on pancreatogram, median (range)	1.0 (1–3)	1.0 (1–3)
▪ Stone size based on pancreatogram (mm), mean ± SD	8.0 ± 2.6	9.0 ± 2.8

ASA, American Society of Anesthesiologists; BMI, body mass index; CP, chronic pancreatitis; EHL, electrohydraulic lithotripsy; ERP, endoscopic retrograde pancreatography; ESWL, extracorporeal shock wave lithotripsy; PD, pancreatic duct; SD, standard deviation.
[1] Significant difference: $P < .05$.

▶ **Table 2** Long-term outcomes of patients with symptomatic obstructive chronic pancreatitis after initial successful treatment with EHL/ESWL.

	EHL (n = 19) n, (%)	ESWL (n = 18) n, (%)
Main outcomes		
▪ Survival, no. (%)	18 (94.7)	18 (100)
▪ Follow up period (months), median (P25 – P75)	35.0 (30–41)	76.5 (64.8–92.3)
▪ Stone recurrence rate, no. (%)	7 (36.8)	11 (61.1)
▪ Stone recurrence confirmed with imaging (CT/MRCP)	6	7
▪ Stone recurrence diagnosed during ERCP	4	11
▪ Time to recurrence (months), median (P25 – P75)	12.0 (7.0–14.0)	13.0 (8.0–24.0)
▪ Need for an intervention, no. (%)	5 (26.3)	11 (61.1)
▪ Endoscopic reintervention	5	11
▪ Endoscopic treatment success	4	7
▪ Surgical reintervention	1	3
▪ Surgical treatment success	0	2
▪ Size of stones based on imaging/pancreatogram (mm), mean ± SD	4.3 ± 1.2	6.4 ± 4.1
▪ Number of intraductal stones, median (range)	2	2 (1–2)
Secondary outcomes		
▪ Hospitalization rate, no. (%)	9 (47.3)	N/A
▪ No. hospitalizations, mean ± SD	1.6 ± 2.5	N/A
▪ Duration of admission (days), mean ± SD	14.6 ± 12.7	N/A
▪ Exocrine pancreatic insufficiency, no. (%)	16 (84.2)	N/A
▪ Endocrine pancreatic insufficiency, no. (%)	7 (36.8)	N/A
▪ Insulin usage, no.	5	N/A
▪ Oral antidiabetic medication, no.	4	N/A

CT, computed tomography; EHL, electrohydraulic lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; MRCP, magnetic resonance cholangiopancreatography; SD, standard deviation.

was canceled by the patient due to spontaneous regression of pain.

ESWL cohort

Of the 18 patients who were successfully treated with ESWL followed by ERP, seven patients (39 %) reported no recurrence of symptoms after a median follow-up period of 76.5 (IQR 64.8 to 92.3). The recurrence rate of symptomatic obstructive PD stones in the ESWL group was 61 % (n = 11). Median time from the last successful interventional procedure (i. e., ESWL session or ERP) to recurrence was 13.0 months (IQR 8.0 to 24.0). Based on imaging (CT/MRI/MRCP or pancreatogram during ERCP) a median of two recurrent stones (range 1 to 2), with a mean stone size of 6.4 ± 4.1 mm, were present (▶ **Table 2**).

All recurrent patients underwent an endoscopic reintervention, which was clinically successful in seven of 11 patients (64%). A median number of two ERPs (range 1 to 6) was required for the restoration of pancreatic duct outflow. Endoscopic retreatment was not clinically successful in four patients. One patient remained symptomatic despite technically successful endoscopic removal of the recurrent intraductal stone. In one patient with a complete pancreas divisum, drainage via the papilla minor failed because it was not possible to cannulate the accessory PD due to a swollen duodenal papilla. One patient rapidly developed a new symptomatic recurrence and also suffered from a refractory benign biliary stricture. In these three patients, endoscopic therapy was therefore successfully followed by pancreatic surgery. The final patient developed multiple stones recurrences during follow-up despite various endoscopic reinterventions. This patient, however, was not considered a suitable candidate for pancreatic surgery due to prolonged opioid usage and addiction problems.

Izbicki Pain Score

The mean Izbicki Pain scores and number of EHL patients who used opioids at the three different time points (baseline, 6-month and long-term follow-up) are listed in ▶ **Table 3**. There was a non-significant increase in mean Izbicki Pain Score at long-term follow-up as compared to 6-month follow-up (P = .334). However, long-term follow-up scores were still significantly lower as compared to those at baseline (P = .001). (**Supplementary Appendix**, **Table 1**.) At long-term follow-up, a similar or reduced Izbicki Pain Score in contrast to baseline and

▶ **Table 3** Izbicki pain scores, opioid use and quality of life at baseline and follow-up of the 19 patients who successfully underwent pancreatoscopy and electrohydraulic lithotripsy.

	Baseline	6 months	Follow-up
Clinical success			
▪ Izbicki pain score[1]	64.2 ± 22.4	25.9 ± 33.0	35.8 ± 33.5
▪ Opioid usage	10 (53 %)	3 (16 %)	6 (32 %)
Quality of life (Short Form Health Survey)			
▪ Physical Component Summary[2]	39.3 ± 9.7	43.3 ± 10.1	39.9 ± 12.9
▪ Mental Component Summary[2]	41.1 ± 12.4	46.2 ± 11.8	46.6 ± 11.6

Values are mean ± standard deviation (n/N) or n (%) (n/N).
[1] Scale ranges from 0 to 100 points (increasing scores indicating more pain severity). Questions consist of 4 items: frequency of pain, intensity of pain, use of pain medication and disease-related inability to work.
[2] These scores range from 0 to 100, with higher scores indicating a better quality of life. A score of 50 represents the mean in the general population.

6-month follow-up was reported by 79 % and 58 % of patients, respectively. (**Supplementary Appendix**, **Table 2**.)

Quality of life

▶ **Table 3** shows the mean PCS and MCS at baseline, 6-month and long-term follow-up for the 19 patients who successfully underwent pancreatoscopy with EHL. At long-term follow-up, only physical QoL was lower compared with the normative data from the Dutch general population, whereas mental QoL was comparable to the Dutch general population. No significant differences were observed in the mean PCS and MCS scores at long-term follow-up compared to 6-month follow-up and baseline. (**Supplementary Appendix**, **Table 3**.)

Hospital readmissions and pancreatic function

Data on pancreatic function and re-admission rate for the EHL cohort are presented in ▶ **Table 2**. During long-term follow-up, nine patients were readmitted because of acute-on-chronic pancreatitis episodes or inadequate pain control with a mean number of hospital admissions of 1.6 ± 2.5 and hospital duration of 14.6 ± 12.7 days. Cross-sectional imaging was performed in all patients who were readmitted during long-follow-up. Stone recurrence on imaging was found in six of the nine patients. After the initial 6-month follow-up post-EHL, for patients developed new-onset pancreatic exocrine insufficiency and one patient was newly diagnosed with diabetes.

Discussion

This was the first study to assess the long-term outcomes of pancreatoscopy-guided EHL as primary treatment for symptomatic obstructive distal PD stones located in the head or neck of the pancreas.

After a median follow-up of 35 months, treatment success (i. e., no symptomatic stone recurrence) sustained in more than half of patients treated successfully with EHL (63 %). In addition, in those patients with symptomatic stone recurrence, repeat endoscopic therapy was effective in 80 %. Overall, long-term clinical success (i. e., lower or similar Izbicki Pain Score or reduction in opioid usage) also sustained in a small majority of patients previously treated with EHL (58 %).

The optimal timing of endoscopy versus pancreatic surgery in symptomatic patients with CP is still a matter of debate. According to the latest guidelines, endoscopic treatment, including ESWL, is recommended as first-line treatment for patients with symptomatic obstructive CP due to pancreatic strictures or intraductal stones, whereas surgery should preferably be reserved for patients who fail endoscopic treatment [3, 4]. As recurrences of both pancreatic strictures and stones are not uncommon in these patients, multiple endoscopic procedures are often needed to maintain pancreatic outflow and pain relief. Current evidence suggests that multiple endoscopic procedures and opioid usage prior to pancreatic surgery are associated with poorer outcomes. This may indicate that pancreatic surgery should be considered early in disease course and not be postponed until endoscopic treatment has failed [10, 13].

In some studies, however, physicians did not apply endoscopic treatment as outlined in the protocol and therefore these cases should be regarded as non-compliant. Since these patients were included in the intention-to-treat analysis and hence are discounted in the results, this implies that there is ample room to improve the outcome of endoscopic therapy. In the meantime, intraductal pancreatoscopy combined with lithotripsy has become available. All this may offer new perspectives in the endoscopic treatment of symptomatic CP patients.

EHL has several benefits compared with the standard treatment involving ESWL. EHL allows for stone and stricture treatment during the same procedure, is relatively less expensive since hospitalization is no longer needed, and there is no need to consult a urologist because stone fragmentation is performed under direct visualization. In the past decade, multiple studies have been performed to examine the potential value of pancreatoscopy-guided lithotripsy as an alternative treatment for obstructive PD stones. In a recent meta-analysis of ten studies including 302 patients (67.72 % male; mean age 55.10 ± 3.22 years; mean stone size of 10.66 ± 2.19 mm) a pooled technical success rate of 91 % with an overall fragmentation success of 86 % was found [6]. Most of the included studies, however, were in nature retrospective and used pancreatoscopy-guided

lithotripsy as secondary treatment after failure of ESWL. Therefore, we have prospectively evaluated the technical and clinical success of per-oral pancreatoscopy-guided EHL as first-line treatment in a consecutive series of patients [8]. In this study, a total of 34 patients were included of whom 25 underwent EHL, which was followed by complete or partial stone clearance in 24 patients. Clinical success according to the criteria of the original PELSTONE (i. e., > 50 % pain reduction or reduction in opioid usage) was achieved in 72 % (16 of 22) of the EHL patients whose Izbicki Pain scores were available at 6-month follow-up. The initial follow-up period of this study, however, covered a period of only six months which is relatively short for a benign chronic disease such as CP.

The results of this long-term follow-up study suggest that pancreatoscopy-guided EHL is a moderately effective first-line treatment modality. However, this only applies to a selected group of patients, as patients with a non-dilated PD were excluded from treatment. It should be noted that also in patients with a dilated PD, pancreatoscopy can be challenging, especially in patients with a native papilla and those with a very distally located stone in the PD. We therefore amended our treatment strategy by placing a pancreatic stent first for difficult and prolonged PD cannulation followed by pancreatoscopy and EHL in 4 to 6 weeks, which has been described in detail previously [8]. Despite these measures, the technical success of pancreatoscopy with EHL was most limited by the inability to achieve deep cannulation of the PD. Here, when cannulation of the PD was achieved, pancreatoscopy was technically successful in 92 % of patients. In general, free-floating stones are technically easier to treat as compared to impacted stones, however, in this study our experiences with treating impacted stones were relatively good. Based on these findings we conclude that for a selected group of patients, pancreatoscopy-guided EHL seems to be a safe and effective treatment. To put our long-term follow-up EHL results into perspective to the current standard of care of the treatment of large PD stones (≥ 5 mm), results were compared with a historical cohort of patients who underwent ESWL.

The recurrence rate of symptomatic stones in the ESWL group was 61 %, which was higher as compared to those in the EHL cohort (37 %). This could not be related to inadequate treatment with ESWL, as only patients in whom ESWL-treatment was considered successful, defined as restoration of PD flow followed by post-treatment self-reported pain relief, were included. All recurrent ESWL patients underwent endoscopic therapy, which was clinically successful in seven patients (64 %). Median follow-up times for the EHL-group and ESWL group were 35.0 and 76.5 months, respectively. Interestingly, although the follow-up period was longer for the ESWL group, the median time to stone recurrence was approximately one year in both cohorts. Based on the current non-randomized comparison, EHL seems to be a valuable and effective alternative for ESWL as first-line therapy for symptomatic obstructing PD stones.

Our present study showed that clinical success (i. e., > 50 % pain reduction or reduction in opioid usage) sustained in 58 % of EHL patients (11 of 19) at long-term follow-up. Stone recurrence was only confirmed in three of the eight patients who reported increased Izbicki Pain Scores compared with 6-month follow-up. The increase in pain scores in non-recurrent patients could be explained by the fact that pain in CP is often multifactorial and pathophysiological mechanisms such as alterations in pancreatic sensory nerves and central sensitization also play an important role in patients' experience of pain [14, 15].

Another important finding of this study is that QoL was not significantly different at long-term follow-up compared with 6-month follow-up and baseline. This finding highlights the fact that pain is not the only factor determining QoL and our present study confirms that treatment success does not necessarily lead to improvement of QoL, even if pain scores did decrease. This underscores the importance of discussing with individual patients what can potentially be expected from endotherapy at which costs (e. g., number of procedures and potential complications). Perhaps even more importantly, definition of treatment success should not only be looked upon as from technical perspectives (i. e., stone removal or restoration of ductal flow), but also from a patients' perspectives on the impact of treatment on their lives in terms of QoL, pain severity and social participation (i. e., holistic point of view). However, whether current QoL assessment tools are adequate to detect the relevant clinical difference for individual patients, especially when there are relatively few patients in a study, remains a subject of debate. On top of that, despite extensive insights regarding factors impacting QoL (i. e., pain, disability, current smoking, alcohol consumption, low body mass index, use of opioids, associated comorbidities, bowel symptoms and pancreatic dysfunction), a large proportion of variance in physical and mental QoL scores among patients with CP still remains unexplained [16]. Therefore, it is necessary to have a better understanding of QoL and how patient-reported outcomes can be used to assess and define treatment success. The Dutch Pancreatitis Study Group is currently performing the COMBO trial, a nationwide stepped-wedge cluster randomized controlled trial to investigate if patients' education and an integrated therapeutic approach, covering the four main domains of disease management (e. g., lifestyle modifications and psychological support, pancreatic function, nutritional support, and pain management), improves QoL and pain severity as compared to current practice [17].

Our study has several strengths, including its long-term follow-up, well-defined patient population, comparison with a historical ESWL cohort, and clinically relevant endpoints, including QoL. Some limitations of this study should however be acknowledged. First, the number of patients in this retrospective analysis of a prospective cohort series with historical controls is limited. Due to the small size of both the EHL and ESWL cohorts, these groups could not be suitably matched. As a result, we have chosen to describe the primary endpoint for both cohorts without performing any statistical comparison to evaluate between-group differences. In a larger, preferably randomized controlled, multicenter study this should be tailored according to a proper sample calculation for which the current study may serve as input and also would circumvent and avoid the risk of bias that is inherent to the current study approach. We, therefore, look forward to seeing the results of this recently an-

nounced trial which directly compares per-oral pancreatoscopy-guided lithotripsy to ESWL for treating refractory main PD stones in CP [18]. Second, due to the non-randomized retrospective nature of the present long-term follow-up study there is a possibility of selection bias. Third, contrary to ESWL in the ESCAPE trial, opioid usage was not required to start treatment with EHL. Patients not using opioids may have less disease severity and therefore the comparison might not be optimally balanced. Finally, follow-up cross-sectional imaging after initial successful treatment with EHL or ESWL was not routinely performed, unless in case of symptom recurrence. The rates of stone recurrence may therefore be higher in both cohorts than found in our present study. Furthermore, in this study ESWL and EHL were performed according to the standard treatment protocol of the Erasmus MC University Medical Center. In clinical practice, however, protocols may vary including the technical success rates of EHL and ESWL depending on the local experience and available equipment. Our results may therefore not be generalizable to non-tertiary referral centers. Besides economic considerations, availability, and local expertise most likely will impact the choice and hence experience with each treatment option.

Conclusions

In conclusion, at long-term follow-up, endoscopic EHL as first-line treatment for obstructive PD stones performed in an expert treatment center is a moderately effective treatment for symptomatic CP patients, with a sustained long-term clinical success in more than half of the patients. Our results suggest that EHL is at least equally effective as ESWL, which is considered the current standard of first-line care for large PD stones. Future studies should aim at a direct comparison between EHL and ESWL, focus on clinically relevant outcome parameters (e. g., QoL) and cost-effectiveness, preferably within large prospective multicenter trials.

Competing interests

M.A. Boermeester: institutional grants from J&J/ Ethicon, KCI/3M, and New Compliance; and is an advisory board member and/or speaker and/or instructor for KCI/3M, Johnson & Johnson/Ethicon, LifeCell/ Allergan, Bard, Gore, TelaBio, Medtronic, GD Medical, and Smith & Nephew. M.J. Bruno: consultant for Boston Scientific, Cook Medical, and Pentax Medical, financial support from Boston Scientific, Cook Medical, Pentax Medical, InterScope, ChiRoStim, 3M, and Viatris.

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
NTR6853
TRIAL REGISTRATION: Long-term FU of a prospective single-center consecutive case series NTR6853 at ClinicalTrials.gov (http://www.clinicaltrials.gov/)

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