

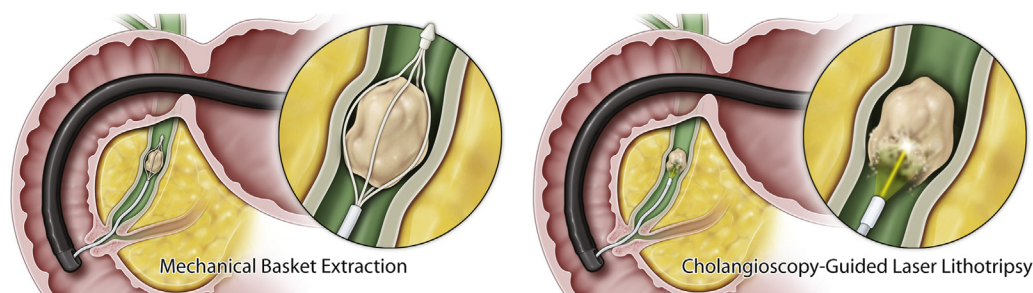


Randomized trial of cholangioscopy-guided laser lithotripsy versus conventional therapy for large bile duct stones (with videos)

James Buxbaum, MD,¹ Ara Sahakian, MD,¹ Christopher Ko, MD,¹ Preeth Jayaram, MD,¹
 Christianne Lane, PhD,² Chung Yao Yu, MD,¹ Ravi Kankotia, MD,¹ Loren Laine, MD^{3,4}

Los Angeles, California; West Haven, Connecticut, USA

GRAPHICAL ABSTRACT



Background and Aims: Bile duct stones >1 cm have a decreased incidence of successful endoscopic extraction and often require lithotripsy. Although previous guidelines suggested mechanical lithotripsy for large common bile duct stones, current guidelines suggest cholangioscopy-guided lithotripsy as an adjunct with or without balloon dilation or mechanical lithotripsy. However, no randomized trials have assessed the usefulness of this practice.

Methods: Patients with bile duct stones >1 cm in diameter were randomized in a 2:1 ratio to cholangioscopy-guided laser lithotripsy versus conventional therapy only. Conventional therapies such as mechanical lithotripsy or balloon dilation were also allowed in the laser lithotripsy group. Randomization was stratified by history of ERCP in the past 3 months. The primary outcome was endoscopic clearance of the bile duct stones.

Results: Endoscopic clearance was achieved in 39 (93%) of 42 patients treated with cholangioscopy-guided laser lithotripsy and 12 (67%) of 18 treated with conventional therapy only ($P = .009$). The 9 patients in whom ERCP was unsuccessful underwent surgical common duct exploration with stone removal. Mean procedure time was 120.7 ± 40.2 minutes for the cholangioscopy-guided laser lithotripsy group compared with 81.2 ± 49.3 minutes for the conventional therapy group ($P = .0008$). There was no significant difference in fluoroscopy time, number of procedures, or adverse events (cholangitis) (cholangioscopy, 2; conventional, 1) and post-ERCP pancreatitis (cholangioscopy, 2; conventional, 1).

Conclusion: Cholangioscopy-guided laser lithotripsy increases the incidence of endoscopic clearance of large bile duct stones and decreases the need for surgery compared with conventional therapy alone. However, it is associated with longer procedure times. (Clinical trial registration number: NCT0175997.) (Gastrointest Endosc 2018;87:1050-60.)

(footnotes appear on last page of article)



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INTRODUCTION

Management of bile duct stones is most commonly the responsibility of biliary endoscopists.^{1,2} Although ERCP with conventional methods, including sphincterotomy, mechanical basket lithotripsy, and balloon extraction, is successful in most cases, certain stones are difficult or impossible to manage with these maneuvers. These include large stones, those with a barrel or piston shape, which makes them difficult to capture with a basket, and stones that become impacted in a narrowed or sigmoid-shaped bile duct.³⁻⁵

Similar to urologists’ approach to nephrolithiasis, gastroenterologists have used a number of techniques to address difficult bile duct stones. These include extracorporeal shock-wave lithotripsy and percutaneous transhepatic, fluoroscopic-guided, or cholangioscopy-guided intraductal therapy using laser or electrohydraulic lithotripsy. Although treatment using direct visualization with cholangioscopes appeared to be safe and effective, the use of intraductal approaches did not become widespread given that the available cholangioscopes were fragile, expensive, and very difficult to operate.⁶⁻⁸

Recently, disposable single-operator cholangioscopy systems have been widely introduced in referral and large community centers. Large cohort studies report favorable results for intraductal treatment of large bile duct stones guided by these new cholangioscopes.⁹⁻¹¹ In this randomized controlled trial, we aimed to determine whether cholangioscopy-guided laser lithotripsy improves clearance of large bile duct stones compared with conventional approaches.

METHODS

Patients

Patients were enrolled at Los Angeles County and University of Southern California Medical Center after approval from the University of Southern California Health Sciences Institutional Review Board and registration of the study with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01759979). We obtained informed consent from all patients before randomization. Patients were blinded to the treatment group. They gave consent for conventional as well as cholangioscopy-guided stone removal. Adult patients with an extrahepatic (common bile or common hepatic) duct stone greater than 1 cm in diameter based on ultrasonography, computed to-

mography, magnetic resonance imaging, or previous ERCP were eligible for inclusion. We excluded those with a history of pancreaticobiliary malignancy or bile duct diversion surgery; age less than 18 years; or who were pregnant, incarcerated, or lacked capacity to give informed consent. Data on baseline laboratory tests, vital signs, demographics, comorbidities, and detailed information regarding the size and number of bile duct stones were collected prospectively.

Intervention

Immediately before ERCP, patients were randomized in a 2:1 ratio to cholangioscopy-guided laser lithotripsy versus conventional therapy only. The randomization schedule was computer generated by an individual uninvolved in the conduct of the study. The allocation assignments were concealed. Randomization was stratified based on whether or not the procedure was a first or repeat ERCP. Those in the repeat group had undergone an ERCP in the previous 3 months in which a large bile duct stone (>1 cm) was identified but not removed. Perioperative antibiotics were given to all patients, with the choice of antibiotics at the discretion of the attending physician.

During the initial study ERCP, the bile duct was fully opacified with contrast and a radiograph obtained immediately before therapy to confirm that at least one stone was greater than 1 cm and to enable standardized assessment of stone diameter and volume. The dimensions of each stone were determined from a radiograph of the initial cholangiogram using Synapse radiographic software (Fujifilm USA, Valhalla, NY), and the geometric function of Excel (Microsoft, Redmond, Wash) was used to calculate the volume of each stone based on shape (sphere, rhomboid, cylinder). Total stone volume per patient was the sum of individual stones. Extrahepatic bile duct diameter was determined during ERCP with the use of fluoroscopy. Extrahepatic bile duct diameter was measured at the site of the cystic duct insertion or at the level of surgical clips in those who had undergone previous cholecystectomy.

In those randomized to cholangioscopy, a single-operator disposable cholangioscope with a reusable fiberoptic probe (Boston Scientific, Natick, Mass) was used to target laser lithotripsy as the first therapeutic maneuver (Fig. 1; Videos 1 and 2, available online at www.giejournal.org). A coherent VersaPulse holmium laser lithotripsy system (Lumenis, San Jose, Calif) was used to deliver continuous (non-interval) laser therapy at 10 W power (1 J energy, 10 Hz frequency). It was

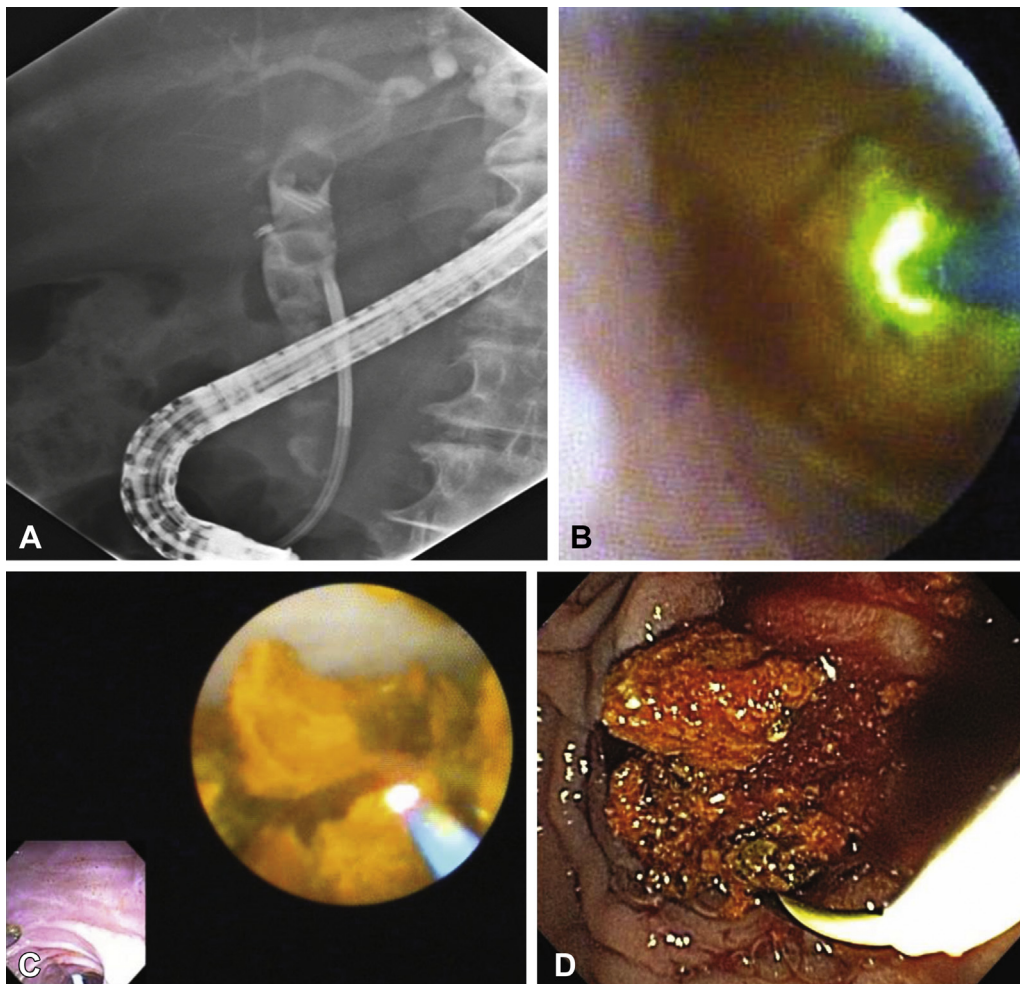


Figure 1. Use of cholangioscopy to target (A) large stones for holmium laser lithotripsy (B and C) (Videos 1 and 2), enabling complete removal from the duct in the form of fragments and debris (D).

delivered via a Smart Identification System enabled for gastroenterology indications with a 365 μ m fiber passed through the cholangioscope biopsy channel and aimed using the cholangioscope. In those randomized to conventional therapy, techniques included baskets for mechanical lithotripsy, papillary dilation, and balloon extraction to facilitate stone removal, and in some cases simply balloon or basket (non-lithotripsy) extraction without papillary dilation.

The use of papillary dilation and dilation balloon size was at the endoscopist's discretion. Sphincterotomy was performed in all patients if it had not been achieved in a previous ERCP. In all cases, papillary dilation was performed after sphincterotomy or in those who had a previous sphincterotomy. Stent placement was at the discretion of the attending physician in both groups. However, the practice of our team of endoscopists is to place bile duct stents after each procedure in which complete stone clearance is not achieved in order to maintain drainage and to promote dissolution therapy. The decision to perform additional endoscopic procedures versus refer for bile

duct surgery was also based on the judgment of the attending endoscopist. If the procedure was unsuccessful but it was deemed that clearance might be achieved with another attempt using the same endoscopic method, an additional procedure was performed. However, if it was felt that endoscopic clearance was impossible or very unlikely, the patient was referred to surgery.

In order to simulate current practice and guideline recommendations, conventional therapies, including mechanical lithotripsy and papillary dilation, were allowed in the laser group.¹ Cholangioscopy and laser lithotripsy were not used in those randomized to conventional methods only. The procedure could be repeated at the discretion of the attending endoscopist, but patients remained in their assigned group; those randomized to conventional treatment could undergo additional attempts with these approaches but not laser lithotripsy. Patients in whom stones could not be cleared using the assigned strategy were referred for surgical common bile duct exploration with stone removal. A dedicated clinical research coordinator was present throughout the procedures to

TABLE 1. Baseline features

	Conventional only (N = 18)	Laser (N = 42)
Female gender	12 (66.7)	29 (69.1)
Hispanic ethnicity	14 (77.8)	32 (76.2)
Previous ERCP	13 (72.2)	31 (73.8)
Comorbidities	7 (38.9)	23 (54.8)
Multiple stones	12 (66.7)	25 (59.3)
Cholesterol stones	16 (89)	42 (100)
Previous cholecystectomy	7 (38.9)	16 (38.1)
Primarily extrahepatic dilation	6 (33)	15 (36)
Intra- and extrahepatic dilation	12 (67)	27 (64)
Age (years), mean (SD)	42.6 (14.5)	51.6 (13.3)
Mean diameter of largest stone (cm), mean (SD)	1.9 (0.9)	1.8 (0.6)
Extrahepatic bile duct diameter (mm), mean (SD)	13.5 (5.5)	12.4 (4.1)
Total stone volume (cm ³), median (IQR)	3.2 (0.9-5.3)	3.3 (1.7-6.5)
Total bilirubin (mg/dL), median (IQR)	1.9 (0.7-3.1)	1.5 (0.5-2.6)
White blood cell count (10 ⁹ /L), median (IQR)	8.4 (6.3-11.3)	7.5 (5.7-9.4)
Alkaline phosphatase (IU/L), median (IQR)	217 (168-277)	184 (127-318)

Values are n (%) except where indicated otherwise.

SD, Standard deviation; IQR, interquartile range.

record the procedure time, fluoroscopy time, success or failure, and the use of specific interventions, including mechanical lithotripsy, papillary dilation, and balloon extraction. All study endoscopists had completed at least 500 ERCP procedures for stone removal using conventional approaches and 20 to 40 cholangioscopy-guided lithotripsy procedures before study initiation.

Endpoints

The primary endpoint was successful endoscopic clearance of bile duct stones with the assigned method. Other efficacy endpoints included procedure time, fluoroscopy time, and number of procedures. Procedure time was defined as the interval between the passage of the duodenoscope into the patient's mouth at the start and removal of the duodenoscope at the end of the procedure. Number of procedures was defined as the total number of ERCPs performed after randomization.

Predefined procedure adverse events assessed included post-ERCP pancreatitis, cholangitis, bleeding, and perforation as defined by the Cotton Consensus criterion.^{12,13} Post-ERCP pancreatitis was defined as hyperamylasemia (amylase >390 U/L, 3 times the upper limit of normal) and development of or increase of epigastric abdominal pain of ≥ 3 on a 0 to 10 visual analog pain scale) persisting for ≥ 24 hours after ERCP.¹³ Bleeding was defined as post-procedure hemorrhage necessitating blood transfusion, and perforation by the development of post-procedure pain accompanied by the presence of air in the retroperitoneum or peritoneum. Criteria from the Tokyo guidelines were used for the diagnosis of post-ERCP cholangitis and

included the following: (1) fever (temperature $>38^{\circ}\text{C}$) or white blood cell count $>10,000$ or $<4000/\text{mm}^3$, or C-reactive protein >1 mg/dL and (2) total bilirubin >2 mg/dL or aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or γ -glutamyl transpeptidase >1.5 times upper limit of normal.¹⁴

We also recorded the use of specific technical maneuvers included as part of conventional therapy. Mechanical lithotripsy was defined as the use of a reinforced baskets to crush stones; use of baskets simply to sweep the duct was not included as mechanical lithotripsy. Rescue lithotripsy was defined as the use of the Soehendra Lithotriptor (Wilson Cook, Bloomington, Ind) when the basket and stone became impacted together in the duct. Papillary dilation was defined as the use of an 8 to 15 mm esophageal or pyloric type balloon (Boston Scientific, Natick, Mass) to dilate the orifice of the bile duct.

Statistical analysis

Descriptive statistics were used to compare pretreatment clinical measures and patient characteristics in order to ensure balance. Given the stratified design (separate randomization for previous versus no previous ERCP), logistic regression was used for the primary endpoint, endoscopic clearance of stones by assigned modality, as well as the categorical safety outcomes (post-ERCP pancreatitis, cholangitis, perforation, bleeding) and procedure outcomes (mechanical or rescue lithotripsy, papillary dilation). All results reported in the outcomes table (Table 2) are adjusted for the covariate previous/no previous ERCP to account for the stratified randomization.

TABLE 2. Outcomes*

	Laser (N = 42)	Conventional (N = 18)	Odds ratio (95% CI)
Endoscopic stone clearance	39 (92.9)	12 (66.7)	8.0 (1.6-40.2)
Number of procedures†			
1	12 (28.6)	7 (38.9)	Base outcome
2	21 (50.0)	9 (50.0)	1.4 (0.4-4.6)
≥3	9 (21.4)	2 (11.1)	2.6 (0.4-15.8)
Mechanical lithotripsy	21 (50.0)	12 (66.7)	0.5 (0.2-1.6)
Papillary dilation	6 (14.3)	8 (44.4)	0.2 (0.1-0.7)
Basket impaction with rescue lithotripsy	4 (9.5)	4 (22.2)	0.4 (0.1-1.7)
Adverse events	4 (9.5)	2 (11.1)	0.8 (0.1-5.0)
Procedure time (minutes), mean (SD)	120.7 (40.5)	81.2 (49.3)	38.8 (16.7-60.8)‡
Fluoroscopy time (minutes), mean (SD)	9.1 (6.1-14.0)	11 (5.1-13.5)	1.1 (0.7-1.7)‡

Values are n (%) except where indicated otherwise.

CI, Confidence interval; SD, standard deviation.

*All adjusted for covariate of previous ERCP.

†Modeled using multinomial logistic regression; when the ordinal model is used, OR is 1.7 (95% CI, 0.6-4.9) for the number of procedures between randomized groups.

‡Mean difference (95% CI).

Procedure and fluoroscopy times were compared using linear regression, although the latter required a natural log transform of the dependent variable to fulfill the normality assumption. We tested the residuals for normality and equal variance to make certain the model assumptions were fulfilled. Continuous variables were also adjusted for previous/no previous ERCP. Multinomial, ordinal, and exact logistic regression was used to compare the number of study procedures: 1 (comparison group) versus 2 versus ≥3 procedures. Median number of procedures was also compared using the Mann-Whitney U test.

Baseline variables that differed between the groups ($P < .20$) were tested for effect as covariates in multivariate logistic and linear regression models of the main outcomes. Formal subgroup analysis by history of previous ERCP (the factor upon which randomization had been stratified) was not possible given that small sample size and data distribution caused logistic regression models testing the interaction terms to break down. We performed a sensitivity analysis by comparing endoscopic clearance and procedure time of cholangioscopy versus conventional approaches in the 2 groups: previous ERCP versus no previous ERCP. We also performed sensitivity analysis for endoscopic clearance to assess for the impact of duct diameter and stone character (cholesterol versus pigment) on endoscopic clearance both in univariate logistic regression models and by introducing these variables as continuous (duct diameter) or dichotomous (stone character) covariates into the model comparing cholangioscopy versus conventional therapy. As part of an additional sensitivity analysis, we introduced number of ERCP procedures as a variable in the primary outcome model.

As this was the first study to compare single-operator cholangioscopy-guided stone therapy with conventional approaches in a randomized manner, previous controlled

trials were unavailable to inform sample size calculations. We estimated that a sample size of 60 would allow us to demonstrate a significant difference (with $\alpha = 0.05$, 80% power and 2:1 allocation ratio) assuming a 20% difference in endoscopic clearance with the assigned method. We estimated 70% clearance of large >1 cm stones using conventional ERCP methods based on the results at our center as recorded in our prospective research database between September 2010 and July 2012 and 90% clearance for cholangioscopy-guided stone therapy based on the multicenter cohort by Chen et al.^{9,15}

RESULTS

Patients

Among 938 patients with choledocholithiasis assessed for inclusion between March 2013 and March 2016, 789 patients were excluded as the stone size was ≤1 cm on imaging or previous ERCP; 34 had concomitant pancreatico-biliary malignancy, 7 were pregnant, and 9 were less than 18 years old (Fig. 2). In addition, 39 patients refused to participate or were unable to give informed consent (Fig. 2). Forty-two patients were randomized to cholangioscopy-guided laser lithotripsy and 18 to conventional therapy. Baseline characteristics were similar in the study groups although patients in the cholangioscopy group tended to be older ($P = .03$) and have more comorbidities ($P = .18$) (Table 1). Most of the patients were women (68%) and Hispanic (77%). Previous ERCP within the past 3 months had been done in 31 patients (74%) in the cholangioscopy-guided group and in 13 patients (72%) in the conventional therapy group. Forty patients (67%) received periprocedural antibiotic therapy with levofloxacin or ciprofloxacin, 15 patients (25%)

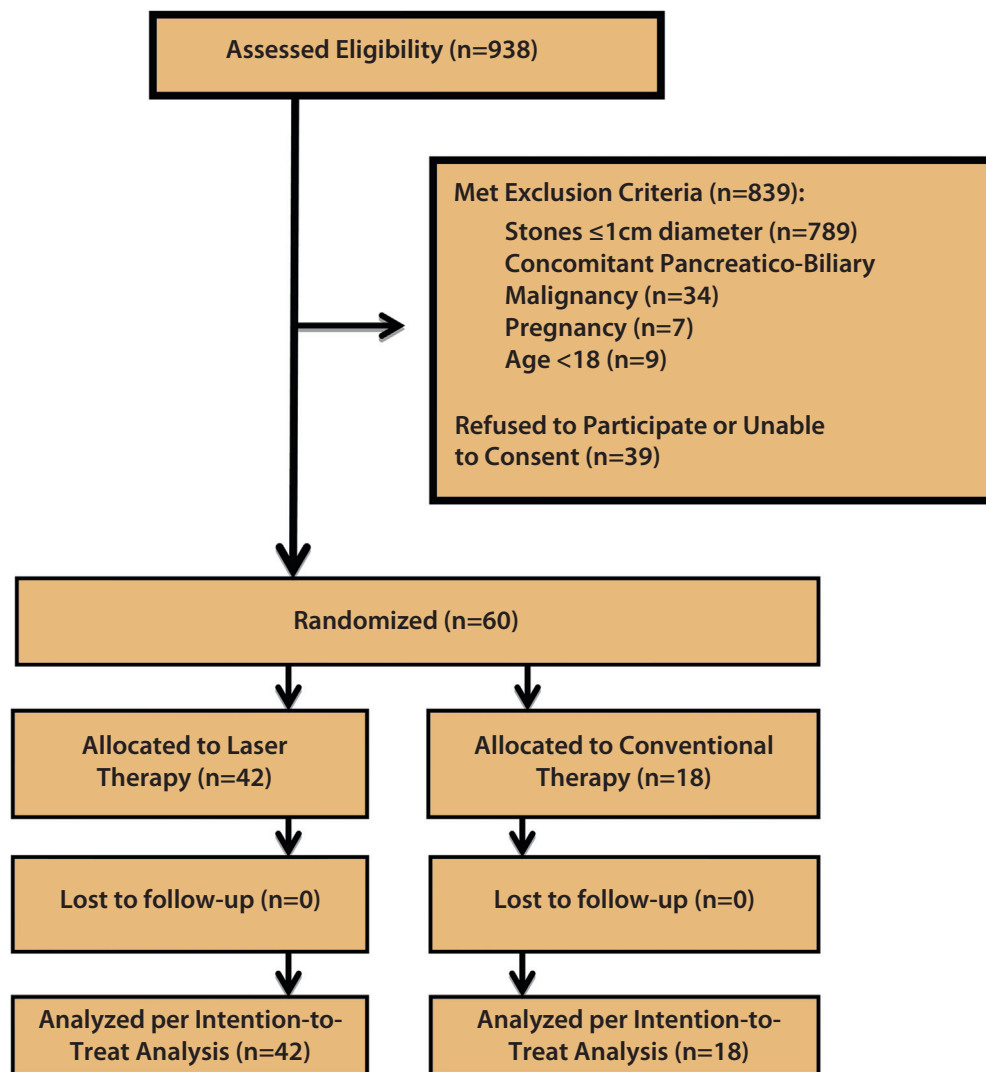


Figure 2. Consort diagram of patient flow through the trial.

received piperacillin-tazobactam, and the remaining patients received a second-generation cephalosporin.

Cholangiogram at the first study ERCP (after randomization) confirmed stone size >1 cm for all patients in the 2 groups. The mean diameter of the largest stone per patient was 1.9 cm and mean total stone volume was 5.1 cm³. In both the conventional therapy and cholangioscopy groups, there were patients with large common hepatic duct stones but relatively decompressed common bile ducts, resulting in the mean extrahepatic bile duct diameter being less than the average stone diameter. Multiple stones were present in 12 patients (67%) in the conventional therapy group and 25 patients (59%) in the cholangioscopy group. Two patients (3%) had black-brown pigment stones; the remainder had classic-appearing cholesterol stones. Among patients managed with cholangioscopy-guided laser therapy, 27 had intra- and extrahepatic dilation and 15 had primarily extrahepatic dilation. A similar

pattern was seen in those managed with conventional therapy; 12 had intra- and extrahepatic dilation and 6 had extrahepatic dilation. Only 2 patients had ductal strictures both in the proximal common bile duct and both managed by laser lithotripsy.

At the time of randomization, 44 patients had undergone ERCP in the previous 3 months to address the stones, whereas 16 had never undergone ERCP. During the previous ERCP, stent placement without attempted stone removal was performed because of cholangitis in 34% (n = 15) and prolonged bile duct cannulation in 11% (n = 5). In 56% (24/44) of patients with previous ERCP, unsuccessful stone removal attempts with extraction balloon only (n = 10) or extraction balloon combined with mechanical lithotripsy (n = 7) or papillary dilation (n = 7) prompted referral to the study. Among those in the previous ERCP group, 4 (9%) had undergone a more remote ERCP (range, 2-5 years) for clearance of previous bile duct stones.

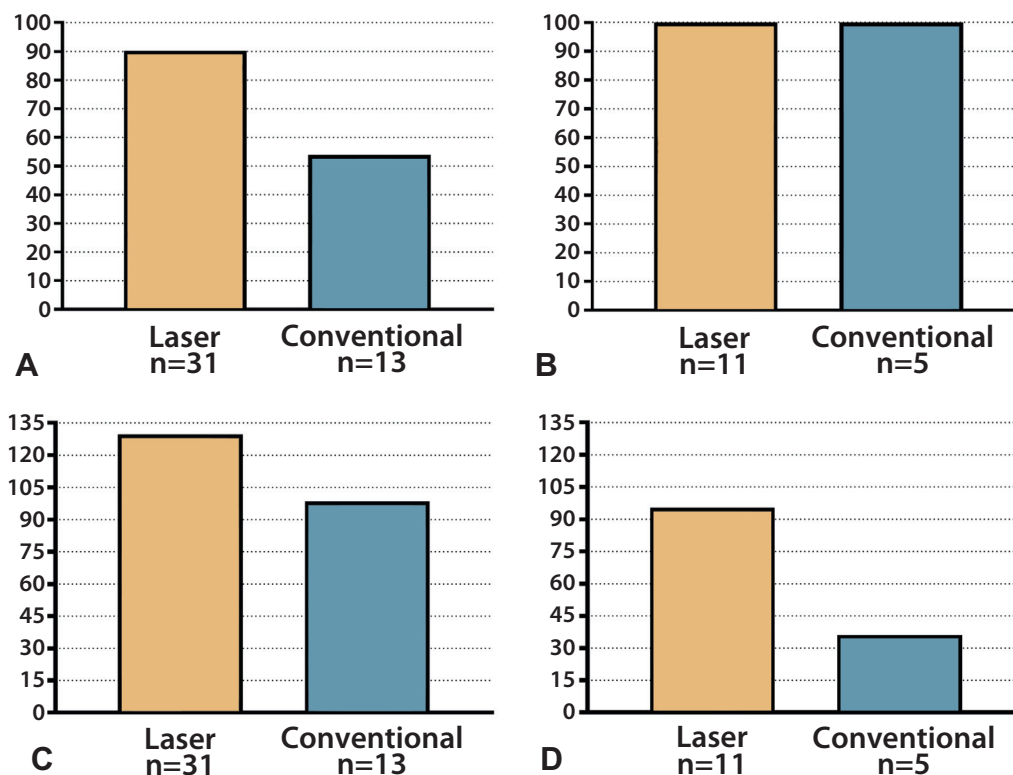


Figure 3. Successful endoscopic clearance (A and B) and mean procedure time (C and D) by previous versus no previous ERCP. **A,** Successful endoscopic clearance (%) with previous ERCP. **B,** Successful endoscopic clearance (%) no previous ERCP. **C,** Mean procedure time (minutes) with previous ERCP. **D,** Mean procedure time (minutes) with no previous ERCP.

Primary outcome: endoscopic stone clearance

Endoscopic stone clearance using the assigned strategy was successful in 39 of 42 patients (93%) undergoing cholangioscopy compared with 12 of 18 (67%) using conventional therapy only ($P = .009$) with an odds ratio (OR) adjusted for the covariate of previous ERCP of 8.0 (95% confidence interval [CI], 1.6-40.2) (Table 2). The 9 patients for whom ERCP for stone clearance was not successful underwent surgical common bile duct exploration with stone removal. Multivariate regression analysis adjusting for the 2 independent baseline variables with $P < .20$ on univariable comparison of the study groups (age and comorbidities) demonstrated consistent results: OR, 8.7; 95% CI, 1.1-69.7.

Additional procedure outcomes

The mean procedure time was greater in the cholangioscopy arm (120.7 minutes) compared with 81.2 minutes in the conventional arm ($P = .0008$), which remained significant after adjusting for age and comorbidities ($P = .0014$). The mean cholangioscopy time in the cholangioscopy-guided laser lithotripsy arm was 50.0 ± 27.1 minutes. Fluoroscopy times were similar in the 2 groups. There was also no significant difference in the median number of ERCs after randomization; it was 2 for both groups with the same interquartile range of 1. Nevertheless, 9 (21%) of

those in the cholangioscopy group underwent 3 or more ERCs compared with 2 (11%) in the conventional therapy group.

In the cholangioscopy-guided laser lithotripsy group, mechanical lithotripsy and/or papillary dilation was also used in 25 patients (61%). In the conventional therapy group, balloon extraction alone was successful in 3 patients, whereas mechanical lithotripsy and/or papillary dilation was used in the remaining 15 patients (83%). Papillary dilation was used less frequently among patients in the cholangioscopy arm (6/42 [15.3%]) compared with those receiving only conventional therapy (8/18 [44.4%]; OR, 0.2; 95% CI, 0.1-0.7), whereas mechanical lithotripsy (OR, 0.5; 95% CI, 0.2-1.6) and basket impaction requiring rescue lithotripsy (OR, 0.8; 95% CI, 0.1-5.0) were not (Table 2).

Among the 14 patients who underwent papillary dilation, a balloon diameter of 10 mm was used in 9 (64%), 12 to 15 mm in 4 (29%), and 8 mm in 1 patient. At the time of enrollment, bile duct stents were in place in all patients in the previous ERCP group ($n = 44$). Bile duct stents were placed after each study ERCP in which clearance was not achieved. Thus, the only patients who received no stent therapy were 6 patients with no previous ERCs who achieved stone clearance in the first procedure. All patients referred to surgery had at least one session of stent dissolution therapy.

Adverse events

Adverse events were similar in the 2 treatment groups (OR, 0.8; 95% CI, 0.1-5.0) (Table 2). There were 6 adverse events: 3 episodes of cholangitis (2 in the cholangioscopy group) and 3 episodes of post-ERCP pancreatitis (2 in the cholangioscopy group). One patient developed fatal post-procedure cholangitis after conventional therapy only; the other adverse events were successfully managed with intravenous hydration and antibiotics.

Sensitivity analyses

Previous versus no previous ERCP. Overall, successful endoscopic clearance was less likely among those who underwent previous ERCP (35/44 [80%]) versus those with no previous ERCP (16/16 [100%]). Thirty-one of the 42 patients managed by cholangioscopy-guided laser therapy and 13 of the 18 managed by conventional therapy had undergone previous ERCP. Among those who had a previous ERCP, successful endoscopic clearance was achieved in 28 (90%) of 31 treated with cholangioscopy compared with 7 (54%) of the 13 treated conventionally (OR, 8.0; 95% CI, 1.6-40.2) (Fig. 3). ERCP with stone removal was successful in all patients in both arms among those who had undergone no previous ERCP. Among those who had a previous ERCP, the mean procedure time was 129.7 ± 46.8 minutes for cholangioscopy versus 98.5 ± 39.8 minutes for conventional therapy (mean difference, 31.1 minutes; 95% CI, 3.2-59.1 minutes). The mean procedure time in those who had not undergone a previous ERCP was 95.4 ± 31.8 minutes for cholangioscopy versus 36.2 ± 7.5 minutes for conventional therapy (mean difference, 59.2 minutes; 95% CI, 26.3-92.0 minutes).

One (6.3%) of the 16 patients who had not undergone previous ERCP developed post-ERCP pancreatitis, whereas 5 (11.4%) of the 44 patients with previous ERCP developed adverse events.

The incidence of stones >2 cm was 43.2% (19/44) in patients who had undergone a previous ERCP and 25.0% (4/16) in those who had not undergone a previous ERCP. Cholangioscopy enabled endoscopic clearance in all patients who had previous and no previous ERCP (15/15) with stone diameter of >2 cm compared with half (4/8) of those managed with conventional approaches; the failures were in the previous ERCP group.

Stone type, bile duct diameter, and number of study ERCP procedures. Endoscopic clearance was successful in both cases with brown stones (both in the conventional therapy group) versus 82.7% (48/58) with cholesterol stones ($P = .69$). Controlling for stone type did not affect the increased endoscopic clearance with cholangioscopic versus conventional therapy (adjusted OR, 8.7; 95% CI, 1.8-41.4).

Duct diameter did not predict successful endoscopic clearance. When duct diameter was included as a covari-

ate, the significantly higher odds of endoscopic stone clearance for cholangioscopic versus conventional therapy remained at a similar level (adjusted OR, 8.7; 95% CI, 1.7-45.4). When the number of study ERCP procedures was introduced as a covariate, the odds of endoscopic stone clearance with cholangioscopic versus conventional therapy also did not change materially (adjusted OR, 9.3; 95% CI, 1.7-50.5).

DISCUSSION

We report the first randomized controlled trial of cholangioscopy-guided laser lithotripsy compared with conventional approaches for the management of large bile duct stones. We found that cholangioscopy-guided lithotripsy increased the rate of endoscopic clearance of large bile duct stones and thereby decreased the necessity for surgery. Nevertheless, cholangioscopy increased the procedure time.

ERCP with conventional techniques, such as mechanical lithotripsy and balloon extraction, achieves complete endoscopic stone removal in 86% to 90% of cases.^{16,17} However, the likelihood of success is lower, in the range of 68% to 79%, for large (>1 cm) stones and those with other features making them difficult to capture with baskets, including piston shape or impaction in a narrowed distal common bile duct.^{3,4,18} A number of approaches for difficult bile duct stones have been proposed, including extracorporeal shock-wave lithotripsy as well as intraductal approaches using laser or electrohydraulic probes to fragment stones using light energy or high-voltage electrical shocks.^{19,20}

Laser and electrohydraulic probes may be introduced into the duct via a percutaneous transhepatic approach, guided retrogradely into the duct by fluoroscopy, or advanced into the duct using a cholangioscope. The latter offers the advantage of direct visualization and targeting of the stone. A randomized trial demonstrated superior performance of intraductal (cholangioscopic guidance) laser lithotripsy compared with extracorporeal shock-wave lithotripsy (97% vs 73% stone clearance).²¹ Cohort studies demonstrated that cholangioscopic introduction of the laser probe is associated with fewer serious adverse events than percutaneous passage and fewer misfires than fluoroscopic guidance.^{6,7}

Nevertheless, until recently, cholangioscopy-guided laser lithotripsy was available in very few centers. Technical problems with available cholangioscopes limited the popularity of this approach. Mother-baby (duodenoscope-cholangioscope) systems required 2 operators, were fragile, expensive, and had limited tip deflection.^{22,23} Ultraslim scopes may be introduced directly into the bile duct to perform laser lithotripsy but require a continuously inflated intraductal balloon to maintain access in most procedures.^{8,24,25}

Recently, disposable single-operator cholangioscopy systems have been introduced. Cohort studies have demonstrated that laser lithotripsy using this system enables stone clearance in >90% of patients.⁹⁻¹¹ Our success rate in this prospective randomized trial was comparable with the cohort studies, with 93% of patients achieving stone clearance. Importantly, cholangioscopy-guided therapy did not increase the rate of adverse events compared with conventional therapy. However, as mentioned, a longer procedure time is required to achieve the improvement in efficacy.

In clinical practice, particularly at referral centers, cholangioscopy is used in those with large stones (>1 cm) who have undergone previous ERCP as well as those who have not had a previous procedure. However, we suspected that patients who had undergone previous versus no previous ERCP might represent 2 fundamentally different groups of patients, and therefore we stratified our randomization scheme by this variable. Our sensitivity analysis suggested that this may be the case; those who had undergone previous ERCP were less likely to have endoscopic clearance overall. The difference in endoscopic clearance between the 2 methods in this trial was driven by the 36% increase in success in those with a previous ERCP who were randomized to cholangioscopy rather than conventional approaches. Although both methods performed well among those who had no previous ERCP, the mean procedure time was nearly 1 hour longer in those randomized to cholangioscopy. Thus, our results suggest that cholangioscopy-guided therapy may improve success in the treatment of patients with large stones who have undergone a previous ERCP but appears less likely to be beneficial and may increase the procedure time for those who have not undergone previous ERCP. Nevertheless, our study was not powered to compare cholangioscopy versus conventional methods specifically in those who had undergone previous or no previous ERCP; thus, our results must be interpreted with caution. In addition, although cholangioscopy appeared to perform better for very large (>2 cm) stones, this study was also not designed to address this specific question. Given the additional cost of cholangioscopy equipment and technical demands, clinical trials assessing its role in these subpopulations are needed to optimize rational patient selection for this approach.

Our study has several limitations. Although our faculty endoscopists had completed more than 500 ERCP procedures for stone removal using conventional approaches, given its recent introduction, they had only performed between 20 and 40 cholangioscopy-guided ERCP procedures. Nevertheless, this likely biased our results in favor of conventional approaches, and we demonstrated the opposite, improved clearance with cholangioscopy-guided methods. However, this might have contributed to the increased procedure time and trend toward more procedures in the cholangioscopy group.

In addition, papillary dilation was not prescribed by the study protocol, and its use was at the discretion of the endoscopist. At the time the study was designed in 2012, there was residual concern about increased pancreatitis risk stemming from high-profile American trials in which papillary dilation without sphincterotomy was used to remove stones.^{26,27} It was used in a few patients and more frequently in the conventional therapy arm. Recent high-quality studies,^{28,29} including a large randomized trial published by Teoh et al³⁰ in 2013, demonstrate that papillary dilation after sphincterotomy is not associated with pancreatitis and may lower costs and minimize procedure times and the requirement for mechanical lithotripsy.²⁸⁻³⁰ In addition, balloon size was not prescribed by the protocol, and in most patients a 10 mm balloon was used. In trials of papillary dilation stone therapy, large balloons with a diameter ≥ 12 mm are used; thus the use of smaller balloon sizes may have diminished the efficacy of this approach in our trial.²⁸ Future trials of bile duct large stone management will need to integrate large-diameter papillary dilation after sphincterotomy into study protocols.

Another consideration is that digital single-operator cholangioscopy systems have recently been introduced for stone therapy. Our study used the original single-operator system, which uses a disposable cholangioscope fitted with a reusable fiber optic probe. Nevertheless, given reports of improved visualization and flexibility of the new cholangioscopy system, success rates with the digital system are unlikely to be lower than with the fiberoptic cholangioscope.³¹ We did not study cholangioscopy-guided electrohydraulic therapy because we have more extensive experience with laser lithotripsy at our center.

A larger trial at multiple clinical centers would increase generalizability. However, our sample size calculation indicated that a sample size of 60 was required to show significance for a 20% difference in endoscopic clearance, and we demonstrated a 26% difference in success among the methodologies. We anticipated that clearance in the conventional arm would be 70% based on results at our center between 2010 and 2012, which was lower than the reported success rates for large stones (76%-91%).^{3,18,28,30,32} Nevertheless, this ended up being a reasonable estimation of success, likely because mean stone size in our conventional arm was nearly 2 cm, and three-quarters of the patients had undergone previous ERCP in which challenging stones were not removed. In addition, as 97% of our patients had giant cholesterol stones, our results cannot be readily extrapolated to those with pigment stones typical of patients with recurrent pyogenic cholangitis. These stones tend to be soft and more readily amenable to endoscopic removal.

The use of surgical bile duct exploration in those who failed the assigned treatment strategy may not reflect

clinical practice in some centers. At our institution, patients with complicated disease, including those with large bile duct stones, are managed by a specialized pancreaticobiliary surgery team. In addition, two-thirds of our patients had not undergone a previous cholecystectomy, making it more reasonable to use a combined surgical approach to manage gallbladder and bile duct stones. Thus, our threshold to co-manage these patients with the surgical team may be lower than in other centers. At the time the study was initiated, cholangioscopy-guided laser therapy was regarded as an experimental therapy. Since then, it has become available in most referral and large community centers. An alternative design would have been a crossover design in which patients randomized to initial conventional therapy would cross over to cholangioscopy if the conventional methods failed. In patients who have undergone a previous cholecystectomy, especially centers without surgical expertise in bile duct exploration, this strategy represents a logical algorithm.

In conclusion, we demonstrated in this randomized, controlled trial that cholangioscopy-guided laser lithotripsy increases successful large stone (>1 cm) clearance compared with conventional methods. In particular, it is more likely to be successful than conventional approaches in those who have had previous ERCP. Although cholangioscopy-guided laser lithotripsy increases the procedure time, it also increases the likelihood of endoscopic treatment success without an increase in adverse events. It represents an important tool in the biliary endoscopist's armamentarium for the management of difficult bile duct stones.

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Abbreviations: CI, confidence interval; OR, odds ratio.

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Current affiliations: Division of Gastroenterology (1), Department of Preventive Medicine (2), University of Southern California, Keck School of Medicine, Los Angeles, California; Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut (3); VA Connecticut Healthcare System, West Haven, Connecticut, USA (4).

Reprint requests: James Buxbaum, MD, University of Southern California, Keck School of Medicine, D & T Building Room B4H100, 1983 Marengo Street, Los Angeles, CA 90033-1370.

If you would like to chat with an author of this article, you may contact Dr Buxbaum at james.buxbaum@med.usc.edu.

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