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ENDOSCOPY

Endoscopic Ultrasound-Guided Choledochoduodenostomy vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction to Prevent Postprocedural Pancreatitis: A Randomized Trial

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BACKGROUND & AIMS: Postprocedural pancreatitis is the most common adverse event (AE) associated with endoscopic retrograde cholangiopancreatography (ERCP). Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) using a lumen-apposing metal stent is emerging as a promising approach for managing malignant distal biliary obstruction, offering the potential to lower the risk of postprocedural pancreatitis. **METHODS:** This was a multicenter randomized study, enrolling consecutive patients admitted for obstructive jaundice due to malignant distal biliary obstruction with dilated common bile duct (≥15 mm). Patients were randomly allocated to receive EUS-CDS or ERCP for primary biliary drainage. This was a superiority trial with postprocedural acute pancreatitis as primary outcome. Other outcomes included technical success, clinical success, AEs, 6-month stent patency rate, and overall survival. Analyses were performed according to intention-to-treat principles. **RESULTS:** Between April 2021 and October 2023, 220 patients were enrolled in the study (EUS-CDS, 111; ERCP, 109). EUS-CDS group showed a lower risk for postprocedural acute pancreatitis (1.8% in EUS-CDS vs 7.3% in ERCP; relative risk, 0.25; 95% confidence interval, 0.07–0.88). Technical success was achieved in 94.6% in EUS-CDS group vs 78.9% ERCP group ($P < .001$), in a mean procedural time of 13.5 ± 11.6 minutes and 24.7 ± 14.9 minutes, respectively ($P < .001$). No differences were found in other AEs (19.8% in EUS-CDS vs 21.1% in ERCP; relative risk, 0.94; 95% confidence interval, 0.56–1.58), clinical success, stent patency, or overall mortality. **CONCLUSIONS:** EUS-CDS is superior to ERCP in reducing postprocedural acute pancreatitis risk. However, the overall risk of AEs was not significantly different and warrants further investigation. Additionally EUS-CDS showed improved technical success and comparable clinical efficacy. These results support a potential role of EUS-CDS as primary approach in selected patients with dilated common bile duct (ClinicalTrials.gov, Number: NCT04099862).

Keywords: Pancreas; Cancer; Jaundice; Interventional EUS.

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most widespread procedures, yet remains among the most risky endoscopic interventions, primarily due to the considerable risk of procedure-related acute pancreatitis.[1,2] This fearsome event seems to be related to several factors, such as traumatic manipulation of the papilla of Vater and injection of contrast agents into the pancreatic duct (PD). Several advancements — such as the use of rectal nonsteroidal anti-inflammatory drugs, pancreatic stenting, and aggressive intravenous fluid hydration[3–5] — have been developed to reduce the risk of post-ERCP pancreatitis, however, it continues to pose a significant challenge in clinical practice, contributing substantially to morbidity and mortality, with consistent annual healthcare

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Abbreviations used in this paper: **CBD, common bile duct; CI, confidence interval; CRO, Clinical Research Organization; CT, chemotherapy; EC, electrocautery-enhanced; ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; EUS-BD, endoscopic ultrasound-guided biliary drainage; EUS-CDS, endoscopic ultrasound-choledoco duodenostomy; LAMS, lumen apposing metal stent; LR, lactated Ringer's; MDBO, malignant distal biliary obstruction; PD, pancreatic duct; PPP, postprocedural acute pancreatitis; RR, relative risk; SEMS, self-expandable metal stent.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Postprocedural pancreatitis is one of the most frequent adverse events after endoscopic retrograde cholangiopancreatography (ERCP) for managing malignant distal biliary obstruction, delaying oncolocic tretment.

NEW FINDINGS

This study established the superiority of endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) over ERCP in minimizing the risk of postprocedural acute pancreatitis.

LIMITATIONS

Main limitations are the lack of blinding due to the interventional nature of the trial, and the lack of a cost-effective analysis.

CLINICAL RESEARCH RELEVANCE

The findings advocate for the adoption of EUS-CDS as a potential primary approach for selected patients with dilated common bile duct in clinical practice. However, further research is needed to evaluate the long-term impact of EUS-CDS in oncologic patients, given the robust, long-term evidence supporting ERCP as a standard procedure.

BASIC RESEARCH RELEVANCE

Although the risk of pancreatitis has been reduced—potentially due to the different anatomic access—the risk of other adverse events remains improvable and warrants further research focused on enhancing device design, optimizing bile flow, and minimizing biofilm formation and bile contamination.

expenditures.[1,2,6,7] This issue is particularly relevant in patients with malignant distal biliary obstruction (MDBO). In these cases, ERCP with stent placement is considered the gold standard to allow an effective biliary decompression, essential for administering chemotherapy (CT) in patients with unresectable tumors and, in selected cases, as a bridge to surgery.[8] However, in this patient population, post-ERCP pancreatitis remains one of the leading causes of delays in oncologic treatment.[9] Additionally, in patients with papillary infiltration, ERCP fails in up to 15% of cases, necessitating alternative decompression strategies.[10,11]

Endoscopic ultrasound-choledoco duodenostomy (EUS-CDS) has emerged as an alternative approach in case of ERCP failure due to its favorable outcomes in terms of technical success and safety.[12–14] This procedure involves accessing the extrahepatic bile duct from the duodenum using a stent to create a choledochoduodenal anastomosis, establishing a biliary bypass away from the papillary region and PD, which theoretically reduces the risk of postprocedural pancreatitis.[15–18] On the other hand, the main barrier to the widespread adoption of this technique has been its technical complexity, which may result in a higher risk of stent maldeployment. The development of single-step, cautery-enhanced lumen-apposing metal stents for creating an EUS-CDS has further simplified the procedure by minimizing the need for device exchanges. Consequently, endoscopic ultrasound-guided biliary drainage (EUS-BD) is increasingly being considered earlier in the treatment workflow and may be adopted as a primary drainage method for patients with MDBO, based on promising results in technical success and procedural time, although early trials have failed to demonstrate its superiority in terms of stent patency.[19,20] In fact, the rationale behind the initial trials was to demonstrate improved stent patency by using a drainage route distant from the malignant area, theoretically reducing the risk of tumor ingrowth or overgrowth. However, the lack of significant differences, along with more recent data, suggests that the risk of stent dysfunction—and subsequent cholangitis—may depend not only on the drainage route but also on other factors (ie, stent design). Furthermore, previous trials did not find any difference in the risk of pancreatitis, likely due to limited sample sizes that were not powered to detect such an outcome.

We hypothesize that primary EUS-CDS has a clinically relevant lower risk of postprocedural pancreatitis as compared with ERCP. Therefore, the goal of our randomized controlled trial is to focus on this aspect, comparing EUS-CDS with cautery-enhanced lumen-apposing metal stents to ERCP with the placement of a covered self-expandable metal stent (SEMS) in patients with MDBO.

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Methods

Ethical Statement

This randomized, multicenter trial was performed in 6 high-volume institutions in Italy. The Institutional Review Board of the Humanitas Research Hospital (Rozzano, Italy) approved the study (approval number: 2844/2021). Subsequently, the protocol received approval from all participating centers. The study has been registered on ClinicalTrials.gov (NCT04099862) and reported according to CONSORT guidelines. The study adhered to the principles of the Declaration of Helsinki, as well as the International Conference on Harmonization's Good Clinical Practice guidelines. A Clinical Research Organization (CRO) regularly monitored the study. All authors had access to the study data, participated in the review, and approved the final manuscript. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Individual participant data will not be shared.

Study Population

We considered for enrollment all consecutive patients aged 18 years or older, admitted with obstructive jaundice due to MDBO. Eligible patients had elevated serum bilirubin levels at least 3 times the upper limit of normal, a dilated extrahepatic bile duct ($\geq$15 mm) at computed tomography, magnetic resonance imaging or EUS. Exclusion criteria included coagulopathy or thrombocytopenia at the time of the procedure (International Normalized Ratio $\geq$1.5 or platelet count $<$50,000/μL), or antithrombotic therapies precluding the procedure according to European Society of Gastrointestinal Endoscopy (ESGE) guidelines,[21] pregnancy, life expectancy $<$3 months, prior biliary sphincterotomy or stent placement, surgically altered pancreaticobiliary anatomy,[22] and inability to sign the informed

consent. Patients with a history of, current symptoms of, or radiologic evidence of gastric outlet obstruction (extensive duodenal invasion and/or gastrectasia) were excluded. However, radiologic signs suggestive of marginal duodenal involvement were not considered an exclusion criteria.

Randomization

After being included in the study, patients were randomized to either EUS-CDS or ERCP. Confidential, centralized random number allocation was accessed by local research personnel with allocation concealment via a secure web-based software specifically developed for the study and provided by the CRO. Randomization was performed without stratification, using permuted blocks of 4 to ensure balanced group sizes within each participating center throughout enrollment. If EUS-guided tissue acquisition was needed at the time of enrollment, randomization occurred during the diagnostic EUS procedure. If tissue acquisition had been performed before enrollment, randomization took place immediately before the index biliary drainage procedure.

Study Intervention

All procedures were performed with patients under deep sedation or general anesthesia, in a fluoroscopy-equipped room using carbon dioxide insufflation. Endoscopists with proven experience in ERCP and interventional EUS, defined as more than 200 ERCPs, and 10 EUS-CDSs over the 12-month period before the study, performed the procedures (trainees did not have a direct operative role in the procedures). Acute pancreatitis prophylaxis was performed by routine intravenous hydration with lactated Ringer (LR) solution and rectal administration of 100 mg of indomethacin immediately before each procedure in all patients without contraindication, as recommended by the updated ESGE guideline.[6] In particular, the LR protocol consists of an infusion at 3 mL/kg/h during and after the procedure, continued for up to 6–8 hours. However, the infusion rate was adjusted at the discretion of the anesthesiologist, based on the patient's condition and risk of fluid overload. Crossovers to the alternative intervention was permitted in cases of technical failure. Patients were not blinded to the intervention. Procedure details are as follows (Figure 1).

Endoscopic ultrasound-guided choledochoduodenostomy. EUS-guided biliary drainage was performed using a lumen apposing metal stent (LAMS) mounted on an electrocautery-enhanced (EC) delivery system (Hot-AXIOS, Boston Scientific Corp., Natick, Massachusetts). After EUS identification of the dilated common bile duct (CBD), a window without interposing vessels was found by the endosonographer. Transduodenal puncture of the CBD was performed directly with the EC delivery system (free-hand technique). The diameter and length of the stent (8 mm × 8 mm or 6 mm × 8 mm) and the modality of placing the stent (under exclusive EUS view, or with endoscopic or fluoroscopic guidance) were chosen at the discretion of the endoscopist performing the procedure. No coaxial double pigtail plastic stents were deployed within the LAMS.

ERCP with covered SEMS. Cannulation of the CBD was performed using a standard ERCP technique, which includes the use of a sphincterotome and guidewire. If difficult biliary cannulation is encountered, as defined by ESGE guidelines,[10] the endoscopist may have employed rescue techniques such as precut biliary sphincterotomy/fistulotomy, the double guidewire technique, cannulation over a pancreatic stent, or transpancreatic biliary sphincterotomy at the discretion of the endoscopist performing the procedure. After successful deep cannulation, a cholangiogram was performed to assess the characteristics of the stenosis, and the length of the stent to be inserted was determined by the endoscopist. All the stents used were fully or partially covered SEMSs with a diameter of 10 mm, and 40 mm or 60 mm in length (Wallflex, Boston Scientific Corp., Natick, Massachusetts). A prophylactic pancreatic stent was placed in patients deemed at high risk for postprocedure pancreatitis, and easy access to the PD according to ESGE guidelines.[10]

Follow-Up

Liver tests were monitored postprocedure at days 1 and 14. Inpatients were clinically evaluated the day after the procedure and daily until discharge. Outpatients received a phone call on days 1 and 7 after the endoscopic procedure. Then, all patients were clinically followed up monthly for up to 6 months or until clinical symptoms arose. Liver tests and radiologic imaging were conducted if recurrent biliary obstruction was suspected. Reintervention procedures were documented, and stent dysfunction was recorded. Patients could receive palliative CT or radiation therapy as recommended by their oncologist.

Outcomes

The primary outcome was the rate of postprocedural acute pancreatitis (PPP) defined according to Cotton's criteria,[23] a widely validated consensus definition. PPP is diagnosed if there was a new onset (or increase) of pain in the upper abdomen, elevation in pancreatic enzymes (of at least 3 times the upper limit of normal) after the procedure, and hospitalisation for at least 2 nights. Severity of PPP was graded according to the American Society for Gastrointestinal Endoscopy lexicon's severity grading system.[24] Requirements for severe pancreatitis included unplanned admission or prolongation for $\geq$10 nights, intensive care unit admission, need for surgery, permanent disability (pancreatic insufficiency), and pancreatitis-related death.

Secondary outcomes included technical success defined as successful biliary drainage through stent placement, clinical success defined as decrease in bilirubin levels to either 50% of the baseline levels, or to $<$3 dL/mg within 2 weeks, and 6-month stent patency rate. Stent dysfunction was defined by endoscopic or radiologic confirmation of stent blockage or migration necessitating stent cleaning, replacement, and/or additional stent insertion, along with specific clinical criteria such as suspected or definite cholangitis or significant increases in bilirubin levels with evidence of obstruction on imaging. Procedural-related adverse events (AEs) were also recorded and graded according to the American Society for Gastrointestinal Endoscopy lexicon's severity grading system.[24] In particular, cholangitis was defined as the presence of fever ($>$38°C) accompanied by evidence of cholestasis; bleeding was defined as hematemesis, melena, or a hemoglobin decrease of $>$2 g/dL. Perforation was defined as the presence of air or luminal contents outside the gastrointestinal

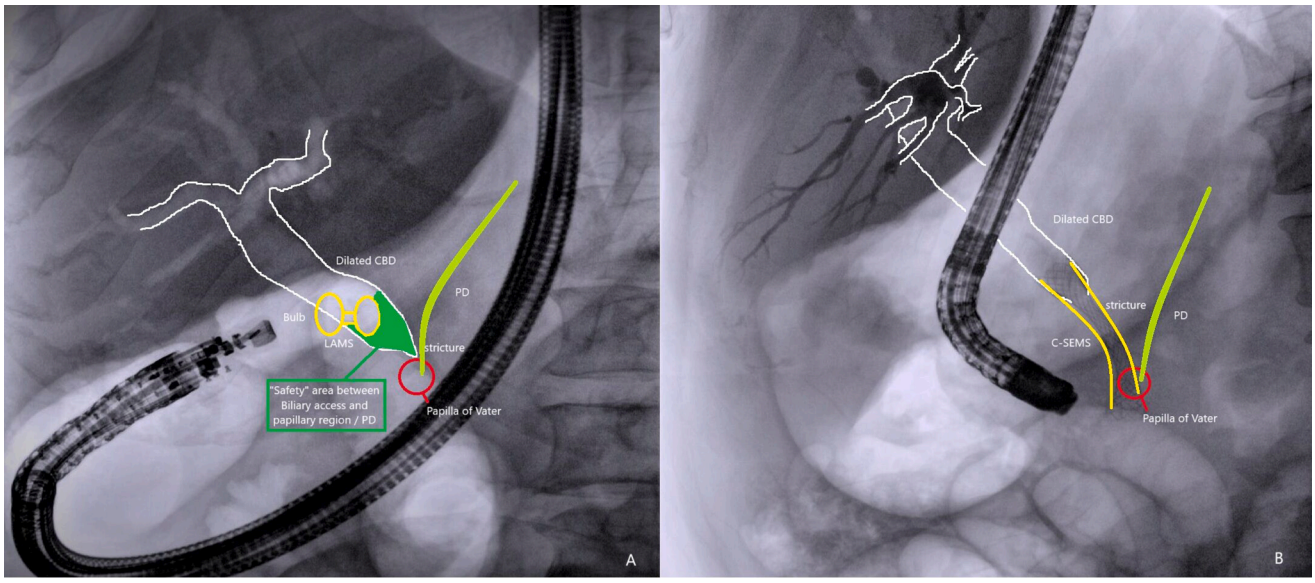

Figure 1. Endoscopic interventions: (*A*) EUS-CDS with LAMS placed in the middle part of the dilated CBD, far from the papilla of Vater and PD. (*B*) ERCP with transpapillary placement of a C-SEMS. C-SEMS, covered self-expandable metal stent.

tract.[24] Additional endpoints were procedural time, hospital stay, modality of management for stent dysfunction or technical failure, and mortality.

The outcomes assessors were not blinded to the intervention group.

Sample Size Calculation and Statistical Analysis

Sample size calculation was based on the primary endpoint of postprocedural acute pancreatitis. Considering that with standard ERCP technique we expected a rate of postprocedural acute pancreatitis of 8.5%[25,26] and with EUS-guided biliary drainage a rate of 0.5%,[27] we established a sample size of 110 patients in each group to observe this difference with a power of 80% and a type I error of 5%, considering a dropout rate of around 5%. Data collected were entered in a web-based electronic data capture system specifically developed for the study and provided by the CRO. Outcomes were evaluated according to the intention-to-treat principle, using appropriate statistical methods. Specifically, categorical data were compared using chi-square or Fisher exact tests, whereas continuous data were analyzed with the Mann-Whitney *U* test for non-normally distributed data or the independent *t* test for normally distributed data. The 6-month stent patency and survival rates were assessed using the Kaplan-Meier method, with the log-rank test applied to compare survival curves between the 2 groups. Patients who did not experience recurrent biliary obstruction were censored at their last follow-up date or at the time of death. For those with stent dysfunction, the time to dysfunction was used in place of the time to death or last follow-up to assess stent patency, and mean stent patency values were calculated for both groups. A per-protocol analysis was conducted by allocating patients based on the actual procedure that was finally performed to achieved biliary drainage, regardless of the initially assigned intervention. This approach accounts for patients who crossed over between groups due to technical failure. All analyses were conducted using STATA, version 18.

Results

Between April 2021 and October 2023, a total of 220 patients were enrolled in the study (111 in the EUS-CDS group and 109 in the ERCP group; Figure 2). All patients with a CBD diameter >15 mm on preprocedural imaging (computed tomography or magnetic resonance imaging) were confirmed to have a CBD >15 mm during EUS evaluation. In 2 patients of the EUS-CDS group the assigned intervention was not attempted. In particular, 1 patient, initially referred for jaundice due to suspected ampullary cancer, during the index procedure was found to have a benign ampullary lesion suitable for endoscopic resection. The other patient did not receive the assigned intervention because of a technical issue with the EUS processor before scope insertion. These patients were excluded from the per-protocol analysis. The baseline characteristics of the 2 groups are presented in Table 1.

Safety Outcomes

Procedural-related acute pancreatitis. The rate of procedure-related AEs was comparable between the 2 groups (EUS-CDS, 22 of 111, 19.8% vs ERCP, 23 of 109, 21.1%; relative risk [RR], 0.94; 95% confidence interval [CI], 0.56–1.58; $P = .81$). Safety outcomes are detailed in Table 2. More specifically, with regard to the study primary outcome, patients enrolled in the EUS-CDS group showed a significant lower risk for procedural-related acute pancreatitis (2 of 111, 1.8% for EUS-CDS group vs 8 of 109, 7.3% for ERCP group; RR, 0.25, 95% CI, 0.07–0.88; $P < .05$), corresponding to an absolute risk reduction of 5.5 percentage points (number needed to treat to prevent 1 episode of postprocedural pancreatitis, 18; Supplementary Figure 1). Six of eight patients (75%) in the ERCP group have at least 1 high-risk factor for post-ERCP pancreatitis. In detail, 5 patients were female (patient-related factor),

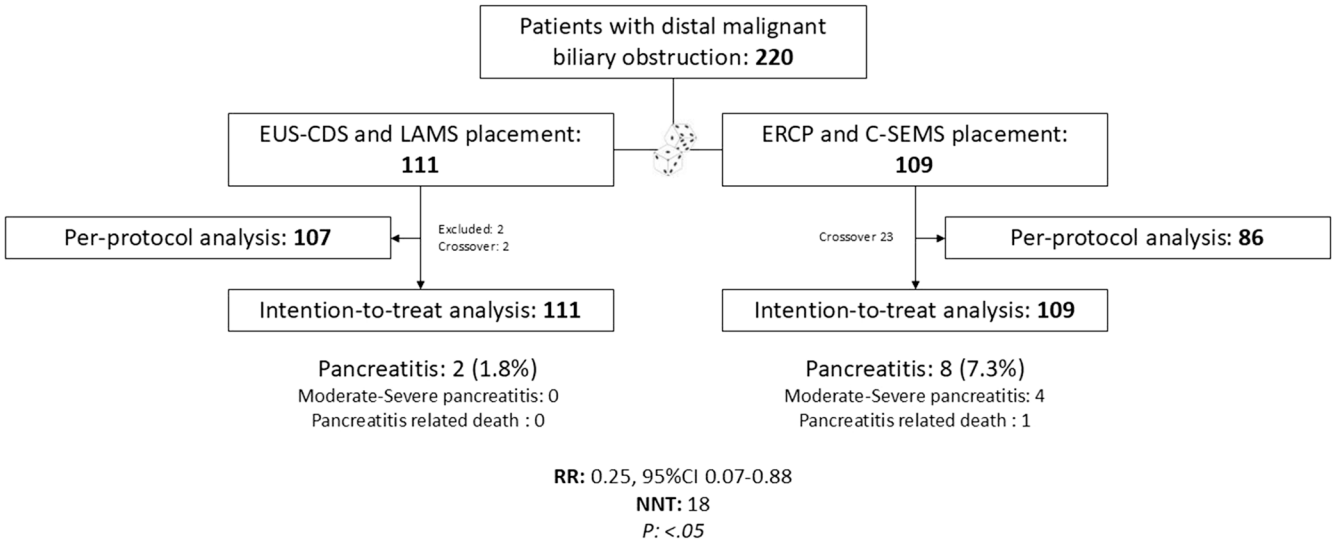

Figure 2. Randomization and study flow chart. NNT, number needed-to-treat.

and in 3 cases the biliary cannulation was considered difficult (procedural-related factor). Two acute pancreatitis cases occurring in the ERCP group were graded as severe (EUS-CDS, 0 cases; ERCP, 2 cases; $P = .24$, with 1 of the patients dying 5 days postprocedure due to a multiple-organ failure related to the systemic involvement of the pancreatitis. The remaining cases of pancreatitis were mild (EUS-CDS, 2 cases; ERCP, 4 cases; $P = .44$) or moderate (EUS-CDS, 0 cases; ERCP, 2 cases; $P = .24$). The mean length of hospital stay for patients experiencing a postprocedural pancreatitis was 5.4 + 8.9 days. One patient discharged the same day of the procedure was readmitted the day after, and remained hospitalized 17 days for a severe pancreatitis. Single patients' characteristics are detailed in Supplementary Table 1.

Overall AEs. Regarding other AEs, cholangitis was the most common, reported in 11.7% (13 of 111) of the EUS-CDS group and 7.3% (8 of 109) of the ERCP group (RR, 1.60; 95% CI, 0.69–3.70; $P = .27$). No cases of cholecystitis were recorded. Two cases of bleeding requiring endoscopic treatment were reported in each group (RR, 0.98; 95% CI, 0.56–1.58; 0.14–6.85; $P = .99$). Furthermore, in the EUS-CDS group occurred 2 cases of stent misdeployment (1.8%), 1 of which was salvaged endoscopically with a bridging tubular stent. The other case required surgery due to the maldeployment of the second flange of the stent outside the duodenal lumen, leading to the rapid formation of a periduodenal collection and loss of safe access to the CBD. The event was classified as severe. Overall, the rate of severe procedure-related AEs was comparable between the 2 groups (EUS-CDS, 3 of 111, 2.7% vs ERCP, 4 of 109, 3.7%; RR, 0.74; 95% CI: 0.17–3.21; $P = .68$). Specifically, in the EUS-CDS group, 2 cases of cholangitis and 1 case of stent misdeployment were classified as severe. In the ERCP group, 2 cases of severe pancreatitis and 2 cases of severe cholangitis were reported. Length of hospital stay was comparable between the 2 groups (EUS-CDS, 3.9 ± 10.5 days vs ERCP, 3.7 ± 6.0 days; $P = .87$).

Procedural and Efficacy Outcomes

Technical success was achieved in 105 of 111 patients (94.6%) in the EUS-CDS group and 86 of 109 patients (78.9%) in the ERCP group ($P < .01$). The mean procedural times were 13.5 ± 11.6 minutes for EUS-CDS and 24.7 ± 14.9 minutes for ERCP ($P < .01$).

Technical failures in the EUS-CDS group were due to stent misdeployment in 2 patients. One of these patients had a tubular SEMS inserted through the LAMS as a rescue strategy, and remained asymptomatic after the procedure. The other patient was referred for surgery. The other 2 EUS-CDS failures were caused by inaccessible bile ducts due to diffuse neoplastic infiltration of the duodenal bulb, leading both patients to cross over to the ERCP group. However, in 1 of these cases, ERCP was also unsuccessful due to diffuse infiltration of the ampullary region. Adequate biliary drainage was finally achieved through EUS-guided gallbladder drainage as a rescue strategy. Technical failures in the ERCP group occurred due to failed deep cannulation in 19 patients and inability to reach the papilla in 4 patients due to duodenal tumor involvement, despite no prior clinical or radiologic evidence of gastric outlet obstruction. All patients with technical failure during ERCP crossed over to the EUS-CDS group, where successful endoscopic biliary drainage was achieved in all but 1 case. In that case, biliary drainage was ultimately achieved via EUS-guided antegrade stenting. Procedural features are detailed in Supplementary Material (Supplementary Table 2).

Clinical success was achieved in 96 of 111 patients (86.5%), and 96 of 109 patients (88.1%) of the EUS-CDS group and the ERCP group, respectively ($P = .72$). Six-months stent dysfunction was observed in 8.3% (8 of 96) of patients in the EUS-CDS group and 11.5% (11 of 96) in the ERCP group ($P = .47$), in a comparable mean follow-up period (EUS-CDS, 143.8 ± 57.9 days vs ERCP, 142.9 ± 57.2 days; $P = .90$). No significant difference in stent dysfunction was recorded between the 2 modalities over time (Figure 3). Planned and administered oncologic treatments

Table 1. Baseline Features

	Total (220)	ERCP (109)	EUS-CDS (111)
Age (*y*), mean (SD)	73.28 (10.06)	72.72 (10.09)	73.82 (10.03)
Sex, female, n (%)	100 (45.5)	47 (43.1)	53 (47.7)
ASA score, mean (SD)	2.3 (1.0)	2.3 (1.0)	2.3 (0.9)
Etiology of biliary obstruction, n *(%)*			
Pancreatic cancer	189 (85.9)	94 (86.2)	95 (85.6)
Cholangiocarcinoma	13 (5.9)	6 (5.5)	7 (6.3)
Ampullary cancer	7 (3.1)	3 (2.8)	4 (3.6)
Other	11 (5.0)	6 (5.5)	5 (4.5)
Neoplastic staging, n *(%)*			
Resectable	30 (13.6)	16 (14.7)	14 (12.6)
Borderline/locally advanced	106 (48.2)	47 (43.1)	59 (53.2)
Unresectable/metastatic	84 (38.1)	46 (42.2)	38 (34.2)
Lesion size (*mm*), mean (SD)	34.1 (12.8)	34.4 (13.0)	33.7 (12.5)
Duodenal involvement, n *(%)*[a]	43 (19.5)	22 (20.2)	21 (18.9)
CBD diameter (*mm*), mean (SD)	18.25 (3.48)	17.99 (3.49)	18.50 (3.49)
Preprocedure laboratory results[b]			
Total bilirubin (*mg/dL*), mean (SD)	14.17 (7.53)	14.62 (7.55)	13.73 (7.54)
GGT (*U/L*), mean (SD)	936.32 (422.12)	932.35 (418.11)	938.75 (427.57)
AlkP (*U/L*), mean (SD)	761.54 (486.12)	749.32 (478.22)	770.12 (490.43)
Concomitant EUS-guided tissue acquisition	146 (66.4)	80 (73.4)	66 (59.5)
Sedation, n *(%)*			
Deep sedation	136 (61.8)	68 (62.4)	68 (61.3)
General anesthesia	84 (38.2)	41 (37.6)	43 (38.7)

AlkP, alkaline phosphatase; ASA, American Society of Anesthesiologists; BD, biliary drainage; GGT, gamma-glutamyl transferase; SD, standard deviation.
[a]In most cases (18 of 22 in the ERCP group and 19 of 21 in the EUS-BD group), duodenal involvement was marginal and did not hinder access to the second portion of the duodenum with the endoscope.
[b]Within the 7 days preceding the procedure.

are reported in Supplementary Table 3. Six-month mortality rates were similar between the EUS-CDS (32.4%; 36 of 111) and ERCP groups (34.9%; 38 of 109; $P = .70$). Procedural and efficacy outcomes are summarized in Table 3. Per-protocol analysis is reported in Table 4.

Discussion

Our multicenter randomized controlled trial demonstrated that primary EUS-CDS for MDBO is superior to ERCP in reducing the risk of postprocedural pancreatitis by 75%, with a corresponding number needed to treat of 18, while showing no significant impact on the overall risk of AEs. Additionally, our findings confirmed that EUS-CDS offers favorable procedural outcomes, including a higher rate of technical success and shorter procedural times compared with the standard transpapillary approach, while showing no significant difference in terms of clinical success, stent patency, and mortality.

Our findings have a much relevant impact on clinical management of patients with MDBO compared with previous trials,[19,20] showing how to reduce the risk of delaying or compromising systemic oncologic treatments as well as potentially curative surgical approaches. This is due to key differences of our study design, such as considering postprocedural pancreatitis as primary outcome. This led us to enroll a larger cohort of patients, providing a sample specifically powered to test the hypothesis that a biliary bypass away from the papillary region and PD would reduce the risk of the most common ERCP-related AEs. In our cohort, the incidence of acute pancreatitis was significantly higher in the ERCP group (8 cases; 7.3%) compared with the EUS-CDS group (2 cases; 1.8%). This result is particularly noteworthy considering that experienced biliopancreatic endoscopists were involved in the trial. Given that the risk of post-ERCP AEs is closely tied to the endoscopist's experience, we compared EUS-CDS with a best-case scenario regarding the risk of post-ERCP pancreatitis. Moreover, we implemented all prophylactic measures to minimize the risk, including the administration of rectal indomethacin and hydration with LR solution. In cases of difficult biliary cannulation, a pancreatic stent was placed when pancreatic access was feasible, following ESGE guidelines. Thus, in a real-life setting we might expect a higher rate of post-ERCP pancreatitis.[1] On the other hand, the 2 cases of postprocedural pancreatitis in the EUS-CDS

Table 2. Safety Outcomes

	ERCP (109)	EUS-CDS (111)	*P* value
Primary outcome, n *(%)*			
Procedural-related pancreatitis	8 (7.3)	2 (1.8)	<.05
Moderate or severe pancreatitis	4	0	.06
Severe pancreatitis	2	0	.24
Pancreatitis-related death	1	0	.50
Secondary outcomes, n *(%)*			
Overall procedure-related AEs	23 (21.1)	22 (19.8)	1
Cholangitis	8 (7.3)	13 (11.7)	.27
Bleeding	2 (1.8)	2 (1.8)	.99
Stent misdeployment/migration	0 (0)	2 (1.8)	.98
Other	5 (4.6)	3 (2.7)	.46
Overall AEs severity			
Severe[a]	4 (3.7)	3 (2.7)	.68
Moderate	10 (9.2)	10 (9.0)	.97
Mild	9 (8.2)	9 (8.1)	.97
Hospital stay (*d*) (SD)	3.7 (6.0)	3.9 (10.5)	.87

[a]Severe AEs were 2 pancreatitis and 2 cholangitis for the ERCP group, and 1 stent misdeployment and 2 cholangitis in the EUS-BD group.

group (1.8%) exceeded the previous reports. This, while strengthening the statistical significance of our finding, may also lead to underestimation of the actual magnitude of postprocedural pancreatitis risk reduction that could be achieved by adopting the EUS-CDS approach as the primary option. Speculating on the possible causes of pancreatitis in the EUS-CDS group, considering the complete absence of papillary manipulation, we may point the finger at the EUS-guided fine-needle biopsy performed in the same-session in both of the cases.[28] However, considering the relative novelty of the procedure, we cannot rule out other still unknown pathogenetic mechanisms potentially explaining a remaining (very low) risk of post EUS-CDS pancreatitis.

One could argue that this reduction in pancreatitis did not translate into differences in mean hospital stays or mortality between the groups. Currently, most cases of postprocedural pancreatitis are mild, typically requiring only short hospital stays for symptom management and intravenous hydration. In our cohort, 6 of 10 patients developed mild pancreatitis (ERCP group, 4; EUS-CDS group, 2). However, severe pancreatitis can necessitate prolonged hospitalization and intensive care. Notably, in our study, there were 4 cases of moderate to severe pancreatitis in the ERCP group, 1 of which resulted in a patient's death 5 days postprocedure.

On the other hand, safety encompasses more than just the risk of postprocedural pancreatitis, and no significant differences were observed regarding the risk of developing other AEs. Most AEs in both groups were infection-related, such as cholangitis and fever, consistent with previous trials.[18–20,29] In particular, the risk of cholangitis after EUS-CDS with LAMS is emerging as a relevant concern.[30] Although no significant difference in cholangitis rates was observed between the EUS-CDS and ERCP groups in our cohort, our study was not designed or powered to detect differences in this specific outcome. Given the potential clinical impact of postprocedural cholangitis, high-quality evidence is urgently needed, and further studies should focus on this important issue. Moreover, our cohort noted 2 instances of stent misdeployment with EUS-CDS, 1 requiring surgical intervention and classified as severe. We assert that the risk of severe complications must always be considered, even with a procedure seemingly endoscopist-friendly like EUS-CDS. Despite reports suggesting the feasibility of this procedure by nonexperts, we recommend it be performed only by physicians with dedicated training in biliopancreatic endoscopy.

Our safety findings are clinically significant for several reasons. Historically, ERCP has been regarded as the optimal approach for MDBO, but its major drawback has been the substantial risk of pancreatitis, a complication that can delay CT or impede curative surgery. Our study demonstrates the efficacy of an alternative strategy offering comparable clinical benefits without these primary disadvantages, challenging the notion that ERCP with transpapillary stenting should be the first-line treatment for patients with suitable CBD dilation for EUS-CDS. Second, the perceived risk of severe complications with transmural access has been a barrier to EUS-CDS adoption. Although the risk of stent misdeployment is not negligible, our analysis showed no difference in the severity profile of AEs between EUS-CDS and ERCP.

Besides safety, EUS-CDS is more efficient than ERCP, evidenced by higher technical success and shorter procedural times. EUS-CDS also proved to be an effective rescue strategy in nearly all ERCP failures (22 of 23 cases), aligning with studies suggesting that alternative biliary drainage routes can mitigate transpapillary access

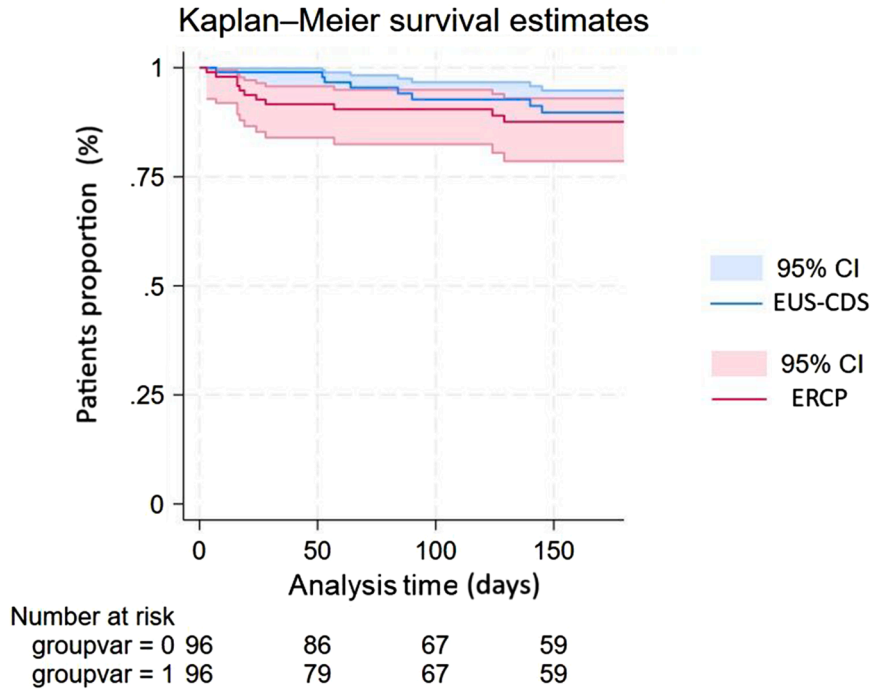

Figure 3. Loss of stent patency. Kaplan-Meier failure estimates analysis.

challenges. Furthermore, EUS-CDS offers the potential for same-session tissue acquisition and biliary drainage, reducing overall endoscopy time; more than 65% of our patients underwent both procedures, highlighting the growing popularity of this approach. Despite no demonstrated significant advantage in preventing long-term stent dysfunction, we confirmed that EUS-CDS and ERCP outcomes are comparable in immediate clinical success and stent patency, with anticipated similar mortality rates given the critical role of effective biliary drainage. A recent prospective study[30] raised concerns about the need for reintervention due to poor stent patency, potentially related to LAMS design. Although the reported 55% rate of stent dysfunction in that study may be overly pessimistic—significantly higher than data from this trial and 2 other RCTs[19,20] on the topic—it highlights the importance of technical adjustments to enhance stent durability The placement of a coaxial double pig-tail plastic stent has been proposed as a strategy to improve long-term drainage.[31,32] However, at the time this study was designed, evidence supporting its potential role was limited, and the practice was not widely adopted. Even now, conclusive evidence remains lacking. With this in mind, although the results are promising, additional research is necessary to assess the long-term outcomes of EUS-CDS in oncologic patients, particularly considering the well-established long-term evidence supporting ERCP as a reliable option.

The primary strength of our study lies in its robust methodology, combining a randomized controlled design with external oversight on data collection and outcome assessment. We focused on critical issues, such as postprocedural pancreatitis, stent dysfunction, and mortality, significantly impacting the oncologic treatment pathway for these patients. This rigorous approach allowed us to draw evidence-based conclusions that could shift the management of MDBO patients. Our multicenter setting ensures the reproducibility of the findings.

Despite its strengths, our study has limitations. First, due to the interventional nature, operators were not blinded, introducing potential performance bias, especially with the ERCP group's 80% technical success rate, lower than expected, but aligned with existing research comparing ERCP to EUS-guided approaches. Although this may reflect real-world outcomes more accurately than previous studies involving only postcannulation phases, we minimized detection bias with objective criteria and external data management. Furthermore, the early decision by the endoscopist to switch to EUS-guided approaches in cases of difficult biliary cannulation is now a well-recognized and increasingly adopted strategy in clinical practice (for both benign and malignant indications), aimed at reducing the risk of AEs.[33–35] However, we consider the overall risk of bias as high, common in interventional endoscopy trials, thus downgrading to "moderate" our evidence quality. Second, when examining the baseline characteristics of patients in the 2 groups, the only imbalance observed was in the rate of concomitant EUS-guided tissue acquisition, which was more frequently performed in the ERCP group (80 vs 66 patients). Although the risk of pancreatitis associated with EUS-guided biopsy is considered very low,[28] we cannot entirely exclude the possibility that it may have had a marginal influence on the development of postprocedural pancreatitis. Third, although powered to detect intergroup differences in term of the primary outcome, our sample size limits statistical inferences regarding specific features that might enhance outcomes with either approach. However,

Table 3. Procedural and Efficacy Outcomes

	ERCP (109)	EUS-CDS (111)	*P* value
Technical success (%)	86 (78.9)	105 (94.6)	<.01
Procedural time (SD) (*min*)	24.7 (14.9)	13.5 (11.6)	<.01
Crossover (%)	23 (21.1)	2 (1.8)	<.01
Successful crossover (%)	22 (20.2)	1 (0.9)	<.01
Clinical success (%)	96 (88.1)	96 (86.5)	.72
6-mo loss of patency rate (%)	11 (11.5)	8 (8.3)	.47
6-mo death rate (%)	38 (34.9)	36 (32.4)	.70

given the minimal postprocedural pancreatitis risk with EUS-CDS, we speculate that adopting EUS-BD first in patients at high risk for post-ERCP pancreatitis (eg, young, female patients with previous pancreatitis episodes) could maximize benefits. Last, the study lacks a cost-effectiveness analysis, a relevant limitation considering the high cost of LAMS may restrict EUS-CDS adoption as a first-line approach. Future research should focus on economic aspects to efficiently implement EUS-CDS in real-world settings, possibly identifying the subgroup of patients who may benefit the most from EUS-CDS (ie, patients at high risk of pancreatitis). This analysis must take into account long-term data that reflect the true impact of different endoscopic techniques on access to and tolerance of oncologic treatments, as well as ultimately on patient survival. In this context, postprocedural pancreatitis—and safety outcomes more broadly—should be considered clinically meaningful proxies for the risk of delaying or even losing the opportunity to initiate oncologic therapy. Our findings are thus essential for laying the groundwork for future studies specifically designed to evaluate more definitive long-term outcomes, such as delays in systemic treatment, disease progression, or overall survival.

In conclusion, EUS-CDS with LAMS is superior to ERCP with SEMS placement in reducing the risk of postprocedural acute pancreatitis. However, the overall risk of AEs was not significantly different and warrants further investigation. Additionally, EUS-CDS demonstrates favorable technical efficiency and preserved clinical efficacy. These results support the potential role of EUS-CDS as a primary approach in selected patients with dilated common bile ducts (≥15 mm).

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.09.003.

Table 4. Per-Protocol Analysis: Safety, Procedural, and Efficacy Outcomes

	ERCP (88)	EUS-CDS (130)	*P* value
Primary outcome, n (%)			
Procedural-related pancreatitis	6 (6.8)	4 (3.1)	.20
Moderate or severe pancreatitis	2	1	
Severe pancreatitis	1	1	
Pancreatitis-related death	1	0	
Secondary outcomes, n (%)			
Safety			
Overall procedure-related AEs	18 (20.5)	28 (21.5)	.85
Cholangitis	7 (8.0)	17 (13.1)	.24
Bleeding	2 (2.3)	2 (1.5)	.69
Stent misdeployment/migration	0 (0)	2 (1.5)	.52
Other	3 (3.4)	3 (2.3)	.63
Overall AEs severity, n (%)			
Severe	2 (2.3)	5 (3.8)	.52
Moderate	8 (9.1)	13 (10.0)	.82
Mild	8 (9.1)	10 (7.7)	.83
Hospital stay (SD) (*d*)	3.7 (5.8)	4.2 (10.6)	.72
Procedural/efficacy			
Technical success (%)	87 (98.9)	127 (97.7)	.53
Procedural time (SD) (*min*)	25.1 (15.2)	19.3 (12.6)	.04
Clinical success (%)	77 (87.5)	113 (86.9)	.90
6-mo loss of patency rate (%)	9 (10.2)	10 (7.7)	.52
6-mo death rate (%)	26 (29.5)	48 (36.9)	.26

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