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Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial)

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BACKGROUND & AIMS: Endoscopic ultrasound–guided choledochoduodenostomy with a lumen-apposing metal stent (EUS-CDS) is a promising modality for management of malignant distal biliary obstruction (MDBO) with potential for better stent patency. We compared its outcomes with endoscopic retrograde cholangiopancreatography with metal stenting (ERCP-M). **METHODS:** In this multicenter randomized controlled trial, we recruited patients with MDBO secondary to borderline resectable, locally advanced, or unresectable peri-ampullary cancers across 10 Canadian institutions and 1 French institution. This was a superiority trial with a noninferiority assessment of technical success. Patients were randomized to EUS-CDS or ERCP-M. The primary end point was the rate of stent dysfunction at 1 year, considering competing risks of death, clinical failure, and surgical resection. Analyses were performed according to intention-to-treat principles. **RESULTS:** From February 2019 to February 2022, 144 patients were recruited; 73 were randomized to EUS-CDS and 71 were randomized to ERCP-M. The mean (SD) procedure time was 14.0 (11.4) minutes for EUS-CDS and 23.1 (15.6) minutes for ERCP-M ($P < .01$); 40% of the former was performed without fluoroscopy. Technical success was achieved in 90.4% (95% CI, 81.5% to 95.3%) of EUS-CDS and 83.1% (95% CI, 72.7% to 90.1%) of ERCP-M with a risk difference of 7.3% (95% CI, –4.0% to 18.8%) indicating noninferiority. Stent dysfunction occurred in 9.6% vs 9.9% of EUS-CDS and ERCP-M cases, respectively ($P = .96$). No differences in adverse events, pancreaticoduodenectomy and oncologic outcomes, or quality of life were noted. **CONCLUSIONS:** Although not superior in stent function, EUS-CDS is an efficient and safe alternative to ERCP-M in patients with MDBO. These findings provide evidence for greater adoption of EUS-CDS in clinical practice as a complementary and exchangeable first-line modality to ERCP in patients with MDBO. ClinicalTrials.gov, Number: NCT03870386.

HEPATOBILIARY

Keywords: Endoscopic Ultrasonography; Stent; ERCP; Pancreatic Cancer; Biliary Obstruction.

Malignant distal biliary obstruction (MDBO) is a common complication of periampullary cancers.[1] Achieving effective biliary decompression is essential for administration of hepatotoxic chemotherapy[2] and has a direct impact on patients' quality of life.[3] Although endoscopic retrograde cholangiopancreatography (ERCP) is the current gold standard, the transpapillary route is associated with significant risk of adverse events (AEs), including post-ERCP pancreatitis.[4–6] In addition, stent dysfunction due to obstruction from tumor tissue ingrowth or overgrowth remains common, despite the use of self-expanding metal stents, and occurs in 20%–30% of cases.[6–9] This can lead to serious complications, such as cholangitis; delays in chemotherapy; and a considerable cost burden.[10]

Endoscopic ultrasound–guided choledochoduodenostomy (EUS-CDS) is an emerging technique that was first described in 2002.[11] This approach aims to access the extrahepatic bile duct from the duodenum with a transluminal stent, thereby establishing a choledochoduodenal anastomosis. EUS-CDS is especially relevant in MDBO because a biliary bypass is created away from the tumor and pancreatic duct (Figure 1). Thus, the risk of stent dysfunction due to tumor tissue ingrowth or overgrowth is theoretically reduced and the risk of postprocedural pancreatitis is mitigated.[12] The advent of dedicated biliary lumen-apposing metal stents (LAMSs) has greatly simplified the technique for greater clinical adoption with promising results.[13–16]

This randomized controlled trial (RCT) aimed to ascertain whether EUS-CDS leads to more sustainable effective biliary drainage than ERCP over a 1-year period. We hypothesized that EUS-CDS is associated with more robust biliary drainage, as measured by lower rates of subsequent stent dysfunction with comparable technical success.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Endoscopic ultrasound–guided choledochoduodenostomy using a lumen-apposing metal stent (EUS-CDS) is a promising modality with a recent randomized controlled trial finding outcomes comparable with endoscopic retrograde cholangiopancreatography (ERCP) and metal stenting in unresectable malignant distal biliary obstruction.

NEW FINDINGS

Although not superior to ERCP and metal stenting in stent dysfunction, EUS-CDS is more efficient and facilitates same-session EUS-guided tissue diagnosis with technical success comparable with ERCP and metal stenting, even in operators with limited EUS-CDS experience. There were no significant differences noted in adverse events, quality of life, and pancreaticoduodenectomy outcomes. To our knowledge, our results are the first to provide quality-of-life data and go beyond unresectable disease to include borderline resectable and locally advanced malignant distal biliary obstruction undergoing neoadjuvant chemotherapy.

LIMITATIONS

Lack of cost-effectiveness data to further guide clinical implementation was a limitation.

CLINICAL RESEARCH RELEVANCE

Our data support the clinical adoption of EUS-CDS as a safe and efficient first-line modality alternative to ERCP in patients with malignant distal biliary obstruction not undergoing upfront surgical resection. The generalizability of our findings goes beyond unresectable disease and is applicable even in operators with limited EUS-CDS experience.

Materials and Methods

Study Design

After Research Ethics Board approval and registration at ClinicalTrials.gov (Number, NCT03870386), we initiated a multicenter RCT comparing EUS-CDS with ERCP-M in patients with MDBO who were not considered candidates for up-front oncologic resection. This was a patient- and outcome assessor–blinded superiority study involving 11 referral centers from Canada (n = 10) and France (n = 1). A noninferiority analysis was also performed on the secondary outcome of technical success. An independent Data and Safety Monitoring Board monitored the study's safety and quality. Moreover, the primary and secondary outcomes were adjudicated by a blinded independent committee. Our protocol was published previously[17] and can be found in the Supplementary Material. All authors had access to the study data and reviewed and approved the final manuscript.

Selection Criteria

We included adult (older than 18 years) patients with a radiologic diagnosis of borderline resectable, locally advanced, or unresectable malignant distal (>2 cm from hilum) biliary obstruction. In addition, patients were required to have an elevated serum bilirubin level of at least 3 times the upper limit of normal, a dilated extrahepatic bile duct (>1.2 cm), a Karnofsky index >30, and an American Society of Anesthesiologists physical status classification less than IV. In September 2020, due to several discordant bile duct sizes measurements when comparing radiologic and EUS studies, the Data and Safety Monitoring Board recommended EUS confirmation of a bile duct size diameter of at least 1.2 cm as an additional inclusion criterion. Patients were excluded if there was clinical and radiologic evidence of gastric outlet obstruction, liver cirrhosis

Abbreviations used in this paper: **AE, adverse event; ERCP-M, endoscopic retrograde cholangiopancreatography with metal stenting; EUS-BD, endoscopic ultrasound–guided biliary drainage; EUS-CDS, endoscopic ultrasound–guided choledochoduodenostomy with a lumen-apposing metal stent; LAMS, lumen-apposing metal stent; MDBO, malignant distal biliary obstruction; RCT, randomized controlled trial; SEMS, self-expandable metal stent.**

Most current article

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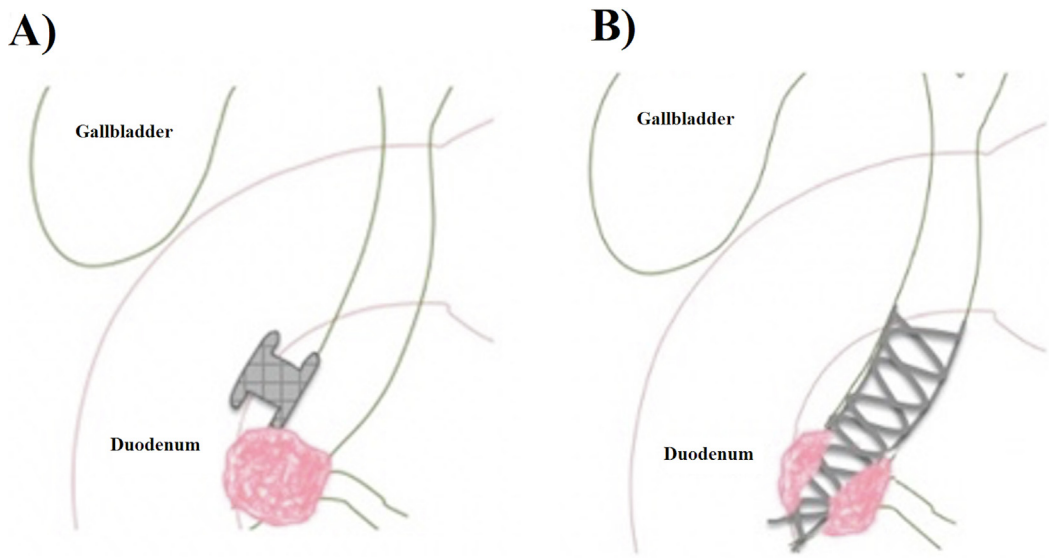

Figure 1. (*A*) EUS-CDS: LAMS deployed via EUS connecting the duodenum and bile duct. (*B*) ERCP with insertion of traditional metal stent through the natural papillary orifice and tumor.

with portal hypertension or ascites, refractory coagulopathy or thrombocytopenia, liver metastasis >30% of its volume, prior biliary sphincterotomy or biliary stent placement, or surgically altered pancreaticobiliary anatomy.

Trial Interventions

All procedures were performed by an experienced endoscopist with or without trainee involvement under conscious sedation or general anesthesia. As a requirement for entry into the trial, before study participation all EUS operators had completed in vitro training with a pig model for EUS-CDS, at least 2 human EUS-CDS cases, transluminal drainage of pancreatic collections using LAMS in at least 5 patients, and at least 10 transluminal EUS procedures of any kind using any type of stents. All EUS-CDS operators in the study were expert endosonographers practicing in referral centers, however, their specific experience with EUS-CDS using LAMS was limited, with a median of only 2 clinical procedures performed before participation in the trial. All ERCP-M operators in the trial had performed more than 1000 career ERCPs before participating in the study.

Endoscopic ultrasound–guided choledochoduodenostomy with a lumen-apposing metal stent. A therapeutic linear echoendoscope was inserted orally and advanced to the duodenal bulb (Supplementary Video). Biliary accessibility was confirmed via EUS from the bulb with Doppler application to rule out any intervening vessels. The LAMS (Hot AXIOS, Boston Scientific, Marlborough, MA) was then inserted freehand using cautery assistance into the bile duct, followed by deployment of the stent. The decision to insert a guide wire after entry of the LAMS catheter into the bile duct before stent deployment was left to the discretion of the endoscopist, as was the choice of stent size (8-mm diameter × 8-mm length or 6-mm diameter × 8-mm length).

Endoscopic retrograde cholangiopancreatography with metal stenting. A duodenoscope was inserted orally and advanced to the papilla. The bile duct was then cannulated with a sphincterotome and guide wire (Figure 2). A cholangiogram was then performed, followed by insertion of a self-expanding metal biliary stent. The decision for biliary sphincterotomy before stent insertion was left to the discretion of the endoscopist, as was the choice of stent size (10 × 40 mm, 10 × 60 mm, or 10 × 80 mm) and stent coverage (uncovered, partially covered, or fully covered). This operator variability in choice of stent coverage was chosen to increase generalizability, as it reflects the current practice of ERCP, with data suggesting no differences in stent dysfunction outcomes with the use of uncovered or covered stents.[18–20]

Participant Allocation

Patients were randomly allocated to 1 of the 2 approaches in a 1:1 ratio using a block size of 4. If EUS-guided tissue acquisition was needed at the time of study enrollment, randomization occurred during the diagnostic EUS procedure. If tissue acquisition had already been performed before enrollment, then randomization occurred immediately before the index biliary drainage procedure. Allocation was stratified by site and tumor stage (stage 3 vs stage 4). Stage 3 lesions included tumors characterized by their surgeons as locally advanced or borderline tumors, and stage 4 included patients with distant metastases. Patients deemed resectable were excluded from the study. Confidential centralized random number allocation was accessed by the local research personnel via a secure internet-based software (randomize.net). Crossovers to the other modality were allowed in cases of technical failure. Based on previous ERCP crossover studies[21–23] and the available literature on difficult biliary cannulation,[24,25] crossovers from ERCP-M to EUS-CDS were allowed after cannulation attempts totalling more than 15 minutes with at least 1 advanced biliary access technique (eg, pancreatic guide wire–assisted biliary cannulation, conventional precut biliary sphincterotomy, needle knife fistulotomy, and/or pancreatic septotomy[25]). Crossovers from EUS-BD to ERCP were allowed in cases of failure to achieve adequate EUS positioning for stent insertion, or if a stent was misdeployed. A medical effectiveness

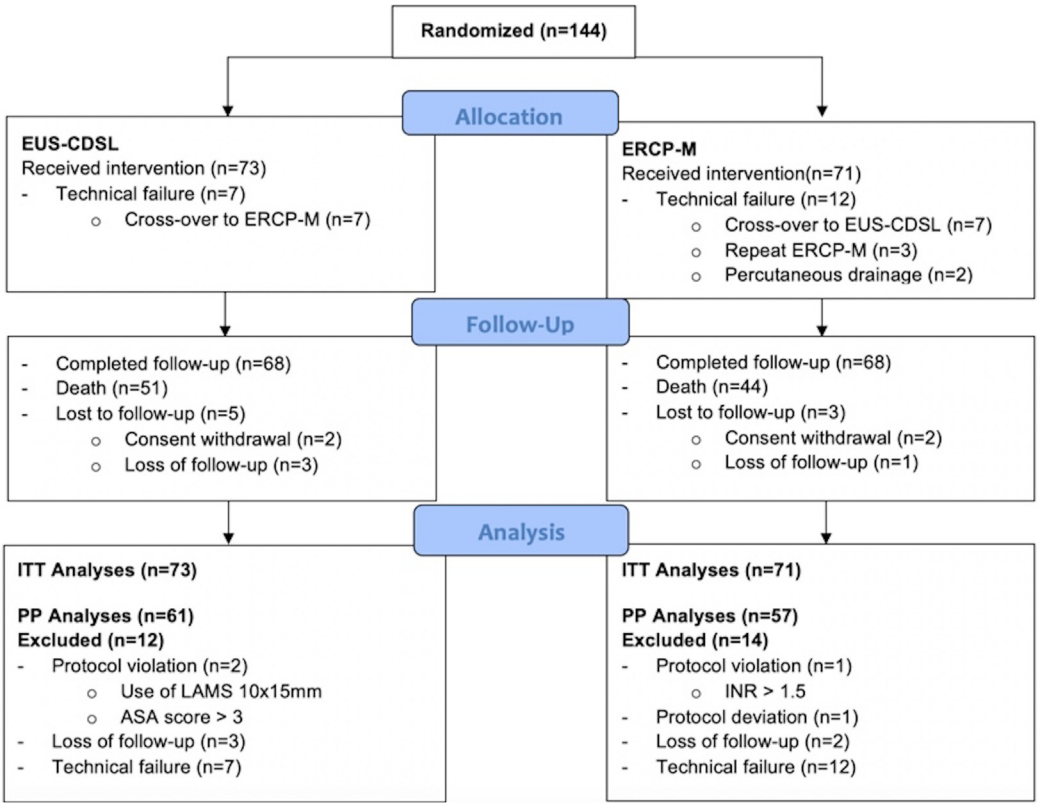

Figure 2. Consolidated Standards of Reporting Trials diagram. ASA, American Society of Anesthesiologists; EUS-CDSL, endoscopic ultrasound–guided choledochoduodenostomy with a lumen-apposing metal stent; INR, international normalized ratio; ITT, intention to treat; PP, per protocol.

approach was adopted, that is, the trial protocol only dictated initial randomized allocation and not the subsequent management decisions. More specifically, in cases of technical failure, crossover to the other treatment group was not mandated, and other approaches, including a repeat ERCP attempt or percutaneous drainage, could be chosen as per the endoscopist and treating team.

Outcomes

The primary outcome was the rate of stent dysfunction (due to migration or stent blockage) requiring re-intervention, as defined by the following criteria: endoscopic or radiologic re-intervention confirming stent blockage or migration needing stent cleaning, stent change, and/or additional stent insertion, and at least 1 of the following: (1) suspected cholangitis (Tokyo consensus definition[26]); (2) definite cholangitis (Tokyo definition[26]); (3) $\geq$50% increase in bilirubin from the lowest level post index procedure; and (4) $\geq$20% increase in bilirubin from the lowest-level, post index procedure, as well as evidence of obstruction on imaging. Patients with a bilirubin that never decreased post index stenting were not classified as experiencing stent dysfunction but rather were categorized as not achieving initial clinical success (see below).

Secondary outcomes included technical success, defined as successful insertion of a transpapillary stent or choledochoduodenostomy stent at the index procedure[6,27]; initial clinical success, defined as a 50% decrease in bilirubin within 2 weeks post stent insertion or achieving a value of $<$25% of preprocedure bilirubin levels within 4 weeks post stent insertion[6,27,28]; and AEs, according to objective criteria set by the American Society for Gastrointestinal Endoscopy lexicon for endoscopic AEs.[29] Additional end points included rate and time to chemotherapy; modality of management used in case of stent dysfunction or technical failure at index procedure; rate of LAMS stent misdeployments, classified as type I (distal flange misdeployment), type II (proximal flange misdeployment), type III (contralateral bile duct wall cautery injury), or type IV (double mucosal puncture); quality of life measurements; procedure and fluoroscopy time[30]; mortality; and rate of hospitalization and length of stay.

Data were collected at the index procedure and at days 14, 30, 90, 180, 270, and 365. Quality of life questionnaires (EQ-5D-5L[31]) were administered on the day of the index procedure and repeated at days 90 and 180. Patients were followed until death or a total of 1-year follow-up.

Sample Size and Data Analysis

The sample size calculation was based on the primary end point of stent dysfunction. Sample size calculation was also performed for the secondary end point of technical success to ensure that the trial was adequately powered for several outcomes. For the primary end point, based on available data,[6,15,16] we estimated a stent dysfunction risk of 30% vs 10% with ERCP and EUS-BD, respectively, up to a 1-year follow-up. To achieve a statistical power of 80% with a 2-sided type I error of 5%, a sample size of 130 patients (65 in each arm) was needed,

including a 5% loss to follow-up. In March 2021, based on recommendations set forth by the Canadian Institute of Health Research grant review committee, a decision was made by our Data and Safety Monitoring Board to increase the sample size to account for competing risks. This was driven largely by the "risk" for surgical resection, initial clinical failure, and high mortality rates before the 1-year follow-up. Based on current data on survival for both metastatic[32,33] and regional disease[34] and surgical resection rates in borderline resectable and locally advanced disease,[35–37] we estimated the cumulative incidence of competing risk factors of death, surgery, and initial clinical failure to be 40%, 5%, and 5%, respectively. After accounting for these competing risks and loss to follow-up, a revised sample size of 144 patients (72 patients in each arm) was established (nQuery, Boston, MA).

For the secondary end point of technical success, we presumed a success rate of 95% in the ERCP cohort.[6] A noninferiority margin of 10% was implemented. To achieve a statistical power of 80% with a 1-sided type I error of 5% a total of 118 patients (59 in each arm) was required.

An intention-to-treat analysis was carried out. A secondary per-protocol analysis was also performed. Descriptive statistics summarized patient characteristics using mean (SD) or median (interquartile range) for continuous variables and proportions (%) with 95% CI for categorical variables. Kaplan-Meier curves and Fine and Gray proportional hazards models[38] were used to compare the primary end point (ie, stent dysfunction) between the EUS-CDS and ERCP-M stratifying by center and tumor stage and accounting for competing risks (initial stent clinical failure, mortality, and surgery). Stent patency was estimated from the primary survival analyses. Secondary end points were compared between the 2 groups using χ^2 tests or Fisher exact tests when appropriate. The EQ-5D-5L questionnaire was used to calculate health utility scores, using the preferred model for the Canadian population as developed by Yan et al.[39] Changes in health status over time were compared between baseline and 90 days, as well as between baseline and 180 days, using *t* tests or nonparametric Wilcoxon tests when applicable. These analyses were performed to assess variations in health status improvement or worsening over time. Subgroup analyses were

Table 1. Baseline Patient Demographic Characteristics

Characteristic	All patients (n = 144)	EUS-CDS (n = 73)	ERCP-M (n = 71)
Age, *y*, mean (SD)	72.0 (10.9)	73.3 (10.4)	70.6 (11.2)
Sex, *female*, n (%)	47 (32.6)	26 (35.6)	21 (25.6)
ASA physical status classification, n (%)			
I	19 (13.2)	5 (6.9)	14 (19.7)
II	89 (61.8)	46 (63.0)	43 (60.6)
III	35 (24.3)	21 (28.8)	14 (19.7)
IV[a]	1 (0.7)	1 (0.7)	0 (0.0)
Karnofsky index score, mean (SD)	73.8 (18.7)	71.9 (19.4)	76.9 (17.2)
Initial laboratory values, mean (SD)			
Total bilirubin, *μmol/L*	259.8 (138.4)	243.1 (123.6)	277.0 (151.0)
ALT, *U/L*	258.8 (194.5)	278.9 (224.7)	237.5 (155.4)
AST, *U/L*	179.5 (106.0)	191.2 (105.1)	167.5 (106.8)
ALK P, *U/L*	726.8 (514.7)	745.7 (473.2)	707.4 (557.0)
Platelet count, 10^9/*L*	269.4 (94.2)	282.2 (85.6)	256.0 (101.3)
INR	1.16 (0.27)	1.19 (0.35)	1.13 (0.15)
PTT, *s*	34.4 (7.5)	34.4 (7.8)	34.4 (7.3)
Etiology of biliary obstruction, n (%)			
Pancreatic cancer	130 (90.3)	63 (86.3)	67 (94.4)
Cholangiocarcinoma	4 (2.8)	4 (5.5)	0 (0.0)
Gallbladder cancer	0 (0.0)	0 (0.0)	0 (0.0)
Ampullary cancer	4 (2.8)	2 (2.7)	2 (2.8)
Other	6 (4.2)[b]	4 (5.5)	2 (2.8)
Staging			
Borderline resectable/locally advanced	56 (38.9)	31 (42.5)	25 (35.2)
Unresectable	88 (61.1)	42 (57.5)	46 (64.8)
Maximum tumor size, *mm*, mean (SD)	34.7 (13.7)	34.5 (14.1)	35.0 (13.3)
Common bile duct diameter on axial imaging, *mm*, mean (SD)	17.8 (4.3)	17.7 (3.6)	18.0 (5.0)

ALK P, alkaline phosphatase; ALT, alanine transaminase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; INR, international normalized ratio; PTT, partial thromboplastin time.
[a]Protocol deviation.
[b]Other etiology (n = 6): metastatic lung cancer; metastatic adenocarcinoma with colorectal origins; metastatic adenocarcinoma of unknown primary with periportal lymph nodes causing obstruction; metastatic colon cancer with peri-portal lymph nodes causing biliary obstruction; cholangiocarcinoma or duodenal cancer; diffuse large B cell lymphoma of the stomach.

performed for borderline resectable or locally advanced tumor stage and unresectable disease for the primary end point of stent dysfunction. $P \leq .05$ was considered statistically significant. All analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

Additional Material and Methods are available in the Supplementary Material.

Results

Patient Population and Procedures

From February 2019 to February 2022, 144 patients were randomized and 73 patients were allocated to EUS-CDS and 71 patients were allocated to ERCP-M (Figure 2). All patients underwent an attempt at the planned intervention, 5.6% patients were lost to follow-up, and 66% died during the study. Intention-to-treat analysis was conducted for 144 patients and a per-protocol analysis in 118 patients. Baseline characteristics were similar between the 2 arms (Table 1). Mean (SD) age for the entire cohort was 72.0 (10.9) years and 32.6% of patients were female.

The index procedures were performed under conscious sedation in 84.0% of cases and general anesthesia with endotracheal intubation in 16.0% of the cases. EUS-guided tissue diagnosis was performed during the same session as the biliary drainage in 60.3% of the EUS-CDS cases and 37.1% of the ERCP-M cases ($P < .01$). Duodenal tumor invasion was noted during 31.0% of EUS-CDS and 20.5% of ERCP-M ($P = .07$). Additional procedural information is listed in Table 2. The mean (SD) procedure time was 14.0 (11.4) minutes with EUS-CDS vs 23.1 (15.6) minutes with ERCP-M ($P < .01$) and mean (SD) radiation time was 1.15 (2.52) minutes and 4.11 (3.54) minutes, respectively ($P < .01$); 40% of EUS-CDS performed without any fluoroscopy use.

Outcomes

Technical success was achieved in 90.4% (81.5% to 95.3%) of EUS-CDS and 83.1% (72.7% to 90.1%) of ERCP-M cases. The risk difference between the 2 approaches was 7.3% (–4.0% to 18.8%), indicating noninferiority (noninferiority margin of 10%). Stent sizes used for EUS-CDS were 6 × 8 mm (93.9%, n = 62), 8 × 8 mm (4.5%, n = 3), and 15 × 10 mm (1.5%, n = 1, protocol violation). Stent types used for ERCP-M were 47.5% (n = 28) fully covered, 13.6% (n = 8) partially covered, and 39.0% (n = 23) uncovered. For further procedural details, see Supplementary Tables 1 and 2. Technical failures in EUS-CDS were due to stent misdeployment in 3 patients and inaccessible bile duct in 4 patients. All patients experiencing a technical failure at EUS-CDS crossed over to ERCP-M (n = 7, 100%). Technical failures in ERCP-M were due to failed deep cannulation in 8 patients, inability to reach the papilla in 2 patients (due to duodenal tumor involvement without clinical or radiologic evidence of gastric outlet obstruction), and intolerance to conscious sedation in 2 patients. Technical failures with ERCP-M crossed over to EUS-CDS in 7 cases (58.3%) and had repeat successful ERCP-M in 3 cases (25%) and percutaneous drainage in 2 cases (16.7%).

In the intention-to-treat analysis, initial clinical success was achieved in 84.9% (76.5% to 93.3%) of EUS-CDS and 85.9% (77.6% to 94.2%) of ERCP-M cases ($P = .87$) (Figure 3). Stent dysfunction occurred in 9.6% (2.7% to 17.0%) and 9.9% (2.8% to 17.0%) of EUS-CDS and ERCP-M, respectively ($P = .63$) with a mean (SD) follow-up time of 180.5 (132.8) days and 217.9 (134.5) days, respectively ($P = .91$) (Table 3). Mean (SD) stent patency time was 163.9 (128.4) days for EUS-CDS and 200.1 (135.5) days for ERCP-M ($P = .10$). No difference in stent dysfunction was noted

Table 2. Procedural and Periprocedural Data

Variable	EUS-CDS (n = 73)	ERCP-M (n = 71)	*P* value
Tissue diagnosis, n (%)			<.01
Predrainage	29 (39.7)	44 (62.9)	
Intradrainage	44 (60.3)	26 (37.1)	
Rectal indomethacin,[a] n (%)	9 (12.5)	40 (57.1)	<.01
Antibiotics,[a] n (%)	12 (16.7)	13 (18.6)	.77
Procedural sedation, n (%)			.54
General anesthesia	13 (17.8)	10 (14.1)	
Conscious sedation	60 (82.2)	61 (85.9)	
Trainee involved	7 (9.6)	29 (40.9)	<.01
Duodenal invasion, n (%)			.46
None	58 (79.5)	49 (69.0)	
Type I	9 (12.3)	12 (16.9)	
Type II	4 (5.5)	8 (11.3)	
Type III	2 (2.7)	2 (2.8)	
Total radiation time, *min*, mean (SD)	1.15 (2.52)	4.11 (3.54)	<.01
Total procedure time, *min*, mean (SD)	14.0 (11.4)	23.1 (15.6)	<.01

[a]Missing information for 2 patients.

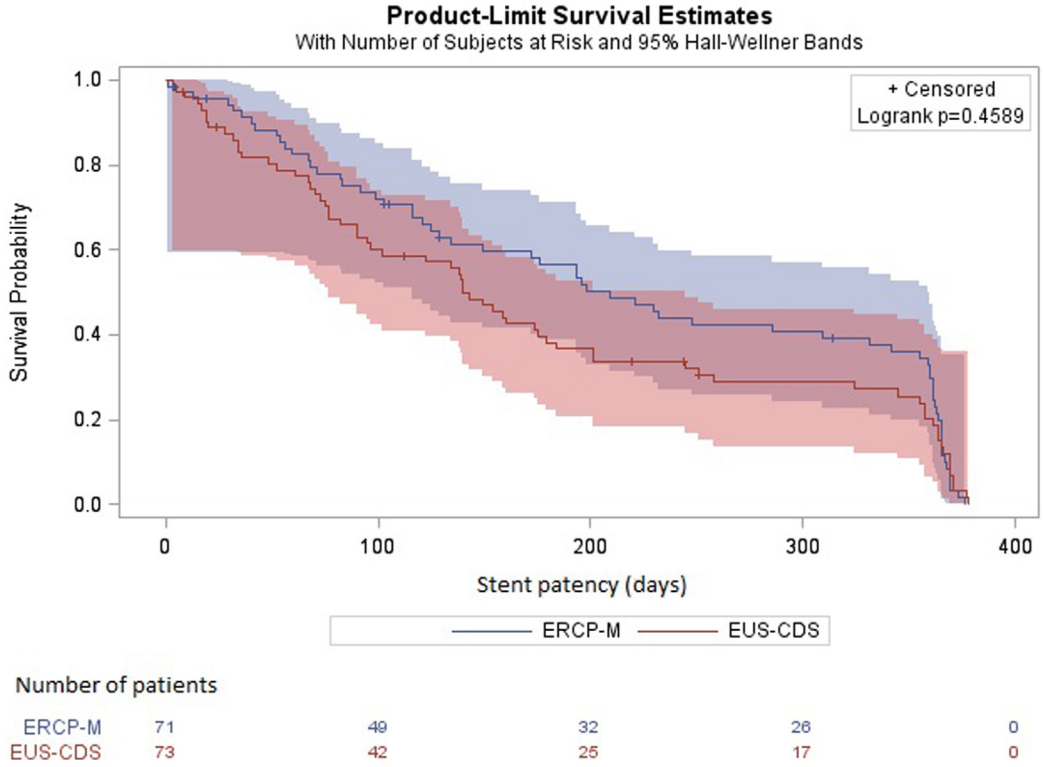

Figure 3. Kaplan-Meier curve for stent dysfunction after EUS-CDS vs ERCP-M.

between the 2 modalities using the Fine and Gray model (subdistribution hazard ratio, 1.04; 95% CI, 0.4–2.96; P = .939) after considering attributable risk factors of clinical failure, surgery, and mortality separately and in combination. Subgroup analyses for stent dysfunction are presented in Supplementary Table 3. In the per-protocol analysis, initial clinical success was achieved in 91.2% (83.7% to 98.8%) of EUS-CDS and 89.1% (80.6% to 97.6%) of ERCP-M (P = .70). Stent dysfunction occurred in 9.8% (2.2% to 17.5%) vs 8.8% (1.2% to 16.3%) of EUS-CDS and ERCP-M, respectively (P = .55).

One-year mortality rates were 69.9% (59.1% to 80.6%) among EUS-CDS patients and 62.0% (40.5% to 73.5%) among ERCP-M patients (P = .32). Chemotherapy was administered in 46.6% (34.9% to 58.3%) of EUS-CDS patients and 60.6% (48.9% to 72.2%) of ERCP-M patients (P = .10). Mean (SD) time to chemotherapy was 54.9 (35.3) days and 49.6 (37.2) days in EUS-CDS and ERCP-M, respectively

Table 3. Clinical Outcomes

Variable	EUS-CDS (n = 73)	ERCP-M (n = 71)	*P* value
Clinical success, n (%)			
ITT	62/73 (84.9)	61/71 (85.9)	.87
PP	52/57 (91.2)	49/55 (89.1)	.70
Stent dysfunction (1-y follow-up), n (%)			
ITT	7 (9.6)	7 (9.9)	.63
PP	6/61 (9.8)	5/57 (8.8)	.55
Stent patency time, *d*, mean (SD)	163.9 (128.4)	200.1 (135.5)	.10
Rate of chemotherapy, n (%)	34 (46.6)	43 (60.6)	.10
Time from index procedure to chemotherapy, *d*, mean (SD)	54.9 (35.3)	49.6 (37.2)	.53
Rate of pancreaticoduodenectomy, n (%)	6 (8.2)	4 (5.6)	.54
Mortality rate, n (%)	51 (69.9)	44 (62.0)	.32
Time to mortality, *d*, mean (SD)	118.1 (89.7)	145.0 (99.3)	.17

ITT, intention to treat; PP, per protocol.

Table 4. Adverse Events

Variable	EUS-CDS (n = 73)[a]	ERCP-M (n = 71)[a]	*P* value
Procedure-related AEs ≤14 d from index procedure	9 (12.3)	9 (12.7)	.95
Type of complication			
Cholangitis	5 (71.4)	3 (37.5)	.32
Pancreatitis	0 (0.0)	4 (50.0)	.08
Bleeding	1 (14.3)	0 (0.0)	.47
Other[a]	1 (14.3)	1 (12.5)	1.00
Intraprocedural	2 (2.7)	1 (1.4)	1.00
Gastrointestinal perforation	2 (2.7)	0 (0.0)	.50
Bleeding requiring additional intervention (endoscopic or nonendoscopic)	0 (0.0)	1 (1.4)	.50
Severity grade			
Fatal	0 (0.0)	1 (11.1)	1.00
Severe	0 (0.0)	1 (11.1)	1.00
Moderate	6 (66.7)	2 (22.2)	.15
Mild	3 (33.3)	5 (55.6)	.64
Time to AE, *d*, mean (SD)	6.0 (3.8)	3.3 (2.3)	.11
AEs >14 d, n (%)	11 (15.1)	12 (16.9)	.76
Type of AE, n (%)			
Cholangitis	8 (72.7)	9 (75.0)	1.00
Bleeding	0 (0.0)	1 (8.3)	1.00
Other	3 (27.3)	2 (16.7)	.64
Severity grade, n (%)			
Fatal	2 (18.2)	1 (8.3)	.59
Severe	1 (9.1)	5 (41.7)	.16
Moderate	8 (72.7)	5 (41.7)	.21
Mild	0 (0.0)	1 (8.3)	1.00
Time to AE, *d*, mean (SD)	169.7 (94.6)	125.2 (105.5)	.30

[a]Patients may have experienced more than 1 AE.

($P = .53$). The rate of pancreaticoduodenectomy was 8.2% (1.8% to 14.7%) with EUS-CDS vs 5.6% (1.4% to 11.1%) with ERCP-M ($P = .54$). No differences in surgical outcomes were noted (Supplementary Table 4). There were no significant differences in quality-of-life scores between the 2 groups from baseline to 90 days or from baseline to 180 days (Supplementary Tables 5–7).

Procedure-related AEs (occurring 14 or fewer days from index procedure) occurred in 12.3% (6.6% to 21.8%) of EUS-CDS and 12.7% (6.8% to 22.4%) of ERCP-M ($P = .95$) (Table 4). More specifically, in EUS-CDS, there were 5 cholangitis (n = 1 mild and n = 4 moderate), 2 perforations (n = 2 mild), 1 bleeding (n = 1 moderate), and 1 other (leukocytosis, n = 1 moderate). In ERCP-M, procedural AEs were 4 pancreatitis (n = 2 mild, n = 2 moderate), 3 cholangitis (n = 1 mild, n = 1 severe, n = 1 fatal), 1 bleeding (n = 1 mild), and 1 other (fever) (n = 1 mild). Of these AEs, 2.7% (2 perforations due to stent misdeployments, both mild) in EUS-CDS and 1.4% (bleeding) in ERCP-M occurred intraprocedurally ($P = 1.00$). Delayed or stent-related AEs (more than 14 days post index procedure) was observed in 15.1% (8.6% to 25.0%) of EUS-CDS and 16.9% (9.9% to 27.3%) of ERCP-M ($P = .76$) with cholangitis as the most common event.

There were 7 stent misdeployments with EUS-CDS. All stent misdeployments were salvaged endoscopically without need for surgery or radiologic intervention. Two stent misdeployments led to AEs, which were categorized as perforations, rated as mild. Six of the stent misdeployments occurred in patients allocated to EUS-CDS, with 1 case occurring in a patient allocated to ERCP-M who then crossed over to EUS-CDS. Overall, there were 5 type I distal flange misdeployments, 1 type II proximal flange misdeployment, and 1 type III contralateral bile duct wall injury during cautery-assisted LAMS tip advancement. The type I misdeployments were salvaged with a bridging tubular stent (n = 1), cross over to ERCP with fully covered self-expanding metal stent insertion and duodenal defect closure (n = 3), and insertion of a second LAMS after removal of the misdeployed stent (n = 1). The type II misdeployment was salvaged with a bridging stent and type III misdeployment was treated conservatively with antibiotics.

A total of 9 patients experienced severe and/or fatal events, 2 in the first 14 days after the index procedure at randomization. Both latter 2 patients were randomized to ERCP, with the first experiencing 2 bouts of cholangitis during the same hospitalization: an early event due to clots

from postprocedural hemorrhage and a later one resulting from malignant tissue stent overgrowth leading to death. The second of these patients experienced cholangitis requiring a hospital stay longer than 10 days. Among the 7 patients who experienced a severe and/or fatal AE after 14 days, 4 were allocated to ERCP-M: 1 patient crossed over to EUS-CDS but in time developed cholangitis due to a sump syndrome and the other 3 patients developed cholangitis complicated by septic shock and death in 1, cholangitis caused by delayed postprocedural hemorrhage (hemobilia) in another, and the third patient required percutaneous drainage of liver abscesses. Of the remaining 3 patients who were all randomized to EUS-CDS, all developed cholangitis; this AE was further complicated by gastric outlet obstruction in 1 and the last patient also developed percutaneous liver abscesses, eventually requiring duodenal stent placement for gastric outlet obstruction and subsequently passed away during the same hospitalization.

There were 7 stent dysfunctions in the ERCP group; these included 1 patient who underwent percutaneous drainage; 6 patients were managed endoscopically, with placement of fully covered self-expandable metal stents (SEMSs) in 5. The sixth patient experienced stent blockage initially because of clots that were cleaned out; a second ERCP performed 1 week later showed extensive tumor overgrowth, at which point sole supportive measures were provided. Of the 7 patients experiencing stent dysfunction in the EUS group, 1 underwent percutaneous drainage, 3 had stent cleaning followed by insertion of co-axial double pigtail plastic stents through the LAMS, 1 had insertion of a coaxial fully covered SEMSs through the LAMS, and the remaining 2 underwent ERCP with SEMS insertion (fully covered in 1 and uncovered in 1).

Discussion

This multicenter RCT aimed to ascertain the clinical outcomes of EUS-guided choledochoduodenostomy with LAMS vs ERCP with a SEMS in patients with MDBO stemming from unresectable, locally advanced, or borderline resectable periampullary cancers. The results showed no evidence of superiority in terms of stent dysfunction or patency attributable to EUS-CDS over ERCP-M. EUS-CDS is nevertheless noninferior to ERCP-M in terms of technical success. In addition, there were no significant differences noted in safety or clinical success. EUS-CDS was associated with a significantly shorter procedural time and lower radiation exposure than ERCP-M, with 40% of procedures performed without fluoroscopy. In terms of oncologic end points, there were no differences in rates of chemotherapy, time to chemotherapy, and rates of pancreaticoduodenectomy or its outcomes. Lastly, quality-of-life data did not differ between the 2 modalities.

Our findings are consistent with a recent RCT from Hong Kong[40] that found no significant difference between EUS-CDS and ERCP-M in terms of major clinical end points. There exist, however, key differences in our study design that provides additional important information, while also increasing the generalizability of our findings. First, unlike the previous trial, which only included patients with unresectable MDBO, our study population also encompassed patients with borderline resectable and locally advanced disease, making our results applicable to patients in the neoadjuvant chemotherapy setting, with potential for subsequent oncologic resection. To our knowledge, our trial is the first RCT to include pancreaticoduodenectomy outcomes after EUS-CDS vs ERCP-M. In addition, operators in our study were relatively recent adopters of EUS-CDS, with a median number of prestudy enrollment procedures performed of only 2; this is in contrast with the RCT that included only expert endoscopists in EUS-CDS with more than 20 procedures performed by each before study initiation. The relative inexperience of our EUS-CDS endoscopists was more akin to the current limited clinical adoption of this modality in clinical practice, as demonstrated by our recent international survey on EUS-guided biliary drainage (EUS-BD).[41] Our results, therefore, have greater generalizability to the current "real-world" practice setting. In addition, the high EUS-CDS technical success achieved in our study by relatively inexperienced operators underscores the procedure's ease of use and potential for widespread adoption. Our trial also provides RCT evidence addressing quality of life in this setting for the first time.

Due to the anatomic bypass provided by EUS-CDS that is farther away from the primary tumor site than that established with ERCP-M, we hypothesized a potential for decreased risk of subsequent stent dysfunction. Previous small RCTs using nondedicated EUS stents have suggested better stent patency with EUS-BD compared with ERCP-M.[42] Our data, however, failed to reject the null hypothesis. Taken together with the RCT from Teoh and colleagues,[40] there does not appear to be an advantage in terms of stent patency over time when using EUS-CDS. It is important to note, however, that the rate of stent dysfunction in our study was particularly low compared with previous ERCP-M literature.[28] This may be due to the implementation of robust methodology to limit detection bias and misclassification, including the use of objective criteria for stent dysfunction and adjudication by a centralized blinded committee.

The fear of complicating subsequent oncologic resection has been identified as a barrier to clinical implementation of EUS-CDS in patients undergoing neoadjuvant chemotherapy with possible subsequent pancreaticoduodenectomy.[41] Anatomically, however, a choledochoduodenostomy is located within the surgical resection margins of a pancreaticoduodenectomy, therefore, minimizing its impact on surgical resection outcomes. To our knowledge, our trial is the first RCT to include patients who underwent pancreaticoduodenectomy post EUS-CDS. Rates of pancreaticoduodenectomy did not differ between the 2 arms, at 8.2% (1.8% to 14.7%) with EUS-CDS vs 5.6% (1.4% to 11.1%) with ERCP-M ($P = .54$). Although limited by the small sample size, no differences were noted in terms of operating room time, length of hospitalization post surgery, or subsequent 30-day AEs. In addition, recent large retrospective studies comparing the pancreaticoduodenectomy outcomes of patients undergoing EUS-BD vs ERCP showed better outcomes with the former.[43,44] However, these studies are limited by their retrospective nature with case selection bias

and heterogenous use of stent types, including plastic stents in the ERCP cohorts. Nevertheless, taken together with the plausible anatomic argument, EUS-CDS likely does not hinder subsequent pancreaticoduodenectomy.

Fear of AEs and the perceived risk of severe complications from stent misdeployment has also limited the clinical adoption of EUS-CDS.[41] Our study found nonsignificant differences in procedural-related and stent-related AEs between the 2 modalities—and this despite the relative inexperience of the operators in the EUS-CDS arm. One notable technical mishap that was specific to EUS-CDS was the risk for stent misdeployment. There were 7 stent misdeployments, but only 2 of them led to AEs, both were rated as mild and managed successfully using conservative treatment. All stent misdeployments were salvaged endoscopically without needing surgery or interventional radiology rescue. In addition to stent misdeployments, fatal bleeding from EUS-CDS has been reported previously.[16] Notably in our study, only 1 case of bleeding, which was mild, occurred at the CDS stent site and resolved without endoscopic therapy. The previously published case of catastrophic bleeding[16] was observed in an acutely septic patient with multiorgan failure, duodenal vascular collaterals, and coagulopathy. Our trial excluded such critically ill patients, and the safety of EUS-CDS in this highly selected patient population requires better characterization.

In addition to safety, EUS-CDS was associated with a shorter mean (SD) procedure time of 14.0 (11.4) minutes compared with 23.1 (15.6) minutes with ERCP-M ($P < .01$); 40% of cases did not require fluoroscopy. The EUS approach also facilitated same-session EUS-tumor needle sampling. Indeed, EUS-guided tissue diagnosis was performed more often during the same session as biliary drainage in the EUS-CDS arm (60.3% vs 37.1% with ERCP-M; $P < .01$). This is an important aspect of management, as patients with suspected MDBO require EUS-guided tissue diagnosis and biliary decompression before commencing oncologic treatments. It is important to note that in Canada, many units perform EUS in a separate room from ERCPs. As such, most patients undergo EUS-guided tissue acquisition and ERCP at 2 separate sessions during the same day or over a few days. This likely explains the higher rates of same-session EUS-guided tissue sampling in the EUS-CDS arm, as the endosonographer can immediately perform the biliary drainage without needing to move the patient to a fluoroscopy room. In addition, most procedures in both arms were performed under endoscopist-directed conscious sedation, which remains the standard of care in Canada and many parts of the world, including the United Kingdom. This further highlights the ease with which EUS-CDS can be performed safely, even with conscious sedation. When considered as a whole, EUS-CDS appears to be a dynamic first-line alternative to ERCP that is associated with a shorter procedural time, greater flexibility, and better radiation safety, while facilitating same-session tissue diagnosis without the need to change operators and/or process additional duodenoscopes to achieve biliary decompression.

A survey by our group, on the current practice of EUS-BD, identified the limited access to dedicated EUS stents and devices as a key barrier to clinical adoption of EUS-BD.[41] LAMS are presently exceedingly more expensive than the SEMSs used in ERCP. Whether benefits such as faster procedure time, ease of same-session tissue diagnosis, and avoidance of fluoroscopy when performing EUS-CDS can lead to improvements in cost-effectiveness requires further study. The current high cost of LAMS is likely to limit EUS-CDS adoption as a first-line approach in many constituencies, highlighting the need for alternative device options that can reduce cost and make EUS-CDS a financially viable initial modality of biliary drainage.

Limitations of our study include its single-blinded design. As with other interventional trials, blinding of the operator was not feasible, which can lead to possible performance and detection bias. To limit performance bias, strict cross-over rules were put in place before study initiation. Detection bias was minimized using objective criteria to define the primary and secondary outcomes, along with the use of blinded assessors and a blinded centralized committee who adjudicated all stent dysfunctions and AEs. In addition, although our study was adequately powered to detect superiority in stent dysfunction and noninferiority in technical success, it was not powered for the determination of noninferiority in AE rates. Strengths of our RCT include its multicenter design; its novelty in studying EUS-CDS as it applies to patients who have locally advanced or borderline resectable peri-ampullary cancers, making this the first RCT to report pancreaticoduodenectomy outcomes; the generalizability of the results to a real-world setting using nonexpert EUS-CDS operators; and strong methodology considering competing risks of death, initial clinical failure, and surgery for the primary outcome of stent dysfunction.

In conclusion, EUS-CDS using a LAMS is not superior to ERCP with SEMS insertion in reducing stent dysfunction in the management of MDBO in borderline resectable, locally advanced, and unresectable peri-ampullary cancers. Nevertheless, it appears to be an efficient, effective, and safe first-line alternative to ERCP-M with comparable technical success. EUS-CDS is associated with a shorter procedure time, even when used by operators with low EUS-CDS experience, and can be performed without fluoroscopy, while facilitating same-session tissue diagnosis. No significant differences were noted in terms of safety, oncologic results, pancreaticoduodenectomy outcomes, and quality of life. Additional data, including meta-analyses, are needed to further characterize safety and other performance characteristics of EUS-CDS, while cost-effectiveness studies are needed to better define implementation issues in clinical practice.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.07.024

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Conflicts of interest
These authors disclose the following: Yen-I Chen is a consultant for Boston Scientific, has received research funding from Boston Scientific, and is the co-founder of Chess Medical Inc. Anand Sahai is a consultant for Boston Scientific. Sarto Paquin is a consultant for Boston Scientific. Nauzer Forbes is a consultant and speaker for Boston Scientific. Gary May is a consultant for Boston Scientific. Ali Bessissow is a consultant for Boston Scientific and is a co-founder of Chess Medical. Mouen Khashab is a consultant for Boston Scientific and Chess Medical, and receives research support from Boston Scientific. Rastislav Kunda is a consultant, speaker, and medical advisory board member of Boston Scientific and M.I.Tech. The remaining authors disclose no conflicts.

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Data Availability
Data, analytic methods, and study materials will not be made available to other researchers.

Supplementary Table 1. Procedure Details for Endoscopic Ultrasound–Guided Choledochoduodenostomy With a Lumen-Apposing Metal Stent

Variable	EUS-CDS (n = 73)
CBD diameter on EUS, *mm*	
Mean (SD)	17.4 (3.5)
Minimum–maximum	10.0–26.0
Median	16.0
Technical success (n = 66), n (%)	
Use of safety wire preloaded in the LAMS	29 (43.9)
If yes: was wire advanced into the bile duct?	9/29 (31.0)
Use of needle puncture and wire guidance	2 (1.5)
Use of bridging stent	2 (3.0)
10 × 600 mm	1/2 (50.0)
10 × 400 mm	1/2 (50.0)
Axios stent size	
6 × 8 mm	62 (93.9)
8 × 8 mm	3 (4.5)
Hot axis stent used 15 × 10 mm	1 (1.5)
Stent dilated	0 (0.0)
Double pigtail plastic stent insertion	5 (7.6)
Technical failure (n = 7), n (%)	
How was biliary drainage attained?	
ERCP-M	7 (100.0)
Percutaneous drainage	0 (0.0)
Surgery	0 (0.0)
Other	0 (0.0)
Reason for technical failure	
Stent misdeployment	3 (42.9)
Other	4 (57.1)[a]

CBD, common bile duct.

[a]Multiple reasons:

1. Small window of CBD 13 mm with dilated gallbladder proximally and large mass distally, ++ vasculature in EUS window, >8 mm distance between duodenal lumen and CBD lumen.
2. Only small window with cross-section of CBD 13 mm. EUS-guided entry with Axios into CBD but concern regarding able to safely deploy stent. Therefore, aborted procedure.
3. Bile duct <12 mm.
4. Distance between CBD and duodenum >12 mm.

Supplementary Table 2. Procedure Details for Endoscopic Retrograde Cholangiopancreatography With Metal Stenting

Variable	Data, n (%)
Technical success (n = 59)	
Need for advanced biliary access technique	
None	34 (57.6)
Access sphincterotomy	24 (40.7)
Double wire	1 (1.7)
Biliary sphincterotomy	56 (94.9)
Biliary stent type	
Fully covered SEMS	28 (47.5)
Partially covered SEMS	8 (13.6)
Uncovered SEMS	23 (39.0)
Stent diameter	
10 × 400 mm	5 (8.5)
10 × 600 mm	48 (81.4)
10 × 800 mm	6 (10.2)
Pancreatic stent insertion	2 (3.4)
Technical failure (n = 12)	
How was biliary drainage attained?	
EUS-CDS	7 (58.3)
Percutaneous drainage	2 (16.7)
Repeat ERCP-M	3 (25.0)
Reason for technical failure	
Deep cannulation failure	8 (66.7)
Inability to reach papilla	2 (16.7)
Procedure intolerance with conscious sedation	2 (16.7)

Supplementary Table 3. Stent Dysfunction Subgroup Analyses

Variable	EUS-CDS, n (%) (n = 73)	ERCP-M, n (%) (n = 71)	*P* value
Stent dysfunction (1-y follow-up)			
Unresectable	2/42 (4.8)	5/46 (10.9)	.93
Locally advanced/borderline resectable	5/31 (16.1)	2/25 (8.0)	.31

Supplementary Table 4. Pancreaticoduodenectomy Outcomes

Variable	EUS-CDS, mean (SD) (n = 73)	ERCP-M, mean (SD) (n = 71)	*P* value
Operating time, *h*	7.29 (2.22)	8.10 (1.27)	.65
Hospitalization post pancreaticoduodenectomy, *d*	7.40 (1.50)	11.30 (9.30)	1.00

Supplementary Table 5. Quality of Life Questionnaire (EQ-5D-5L) Data

Variable	Baseline				90 d				180 d			
	All patients (n = 141)	EUS-BD (n = 72)	ERCP-M (n = 69)	*P* value	All patients (n = 84)	EUS-BD (n = 41)	ERCP-M (n = 43)	*P* value	All patients (n = 56)	EUS-BD (n = 24)	ERCP-M (n = 32)	*P* value
Mobility baseline visit, n (%)				.19				.12				.11
I have no problems in walking	80 (56.7)	37 (51.4)	43 (62.3)		38 (45.2)	15 (36.6)	23 (53.5)		28 (50.0)	9 (37.5)	19 (59.4)	
I have problems in walking	61 (43.3)	35 (48.6)	26 (37.7)		46 (54.8)	26 (63.4)	20 (46.5)		28 (50.0)	15 (62.5)	13 (40.6)	
Self-care, n (%)				.25				.95				.01
I have no problems washing or dressing myself	113 (80.1)	55 (76.4)	58 (84.1)		53 (63.1)	26 (63.4)	27 (62.8)		38 (67.9)	12 (50.0)	26 (81.3)	
I have problems washing or dressing myself	28 (19.9)	17 (23.6)	11 (15.9)		31 (36.9)	15 (36.6)	16 (37.2)		18 (32.1)	12 (50.0)	6 (18.8)	
Usual activities (eg, work, study, housework, family, or leisure activities), n (%)				.21				.14				.12
I have no problems doing my usual activities	70 (49.7)	32 (44.4)	38 (55.1)		33 (39.8)	13 (31.7)	20 (47.6)		18 (32.1)	5 (20.8)	13 (40.6)	
I have problems doing my usual activities	71 (50.4)	40 (55.6)	31 (44.9)		50 (60.2)	28 (68.3)	22 (52.4)		38 (67.9)	19 (79.2)	19 (59.4)	
Pain/discomfort, n (%)				.22				.58				.02
I have no pain or discomfort	52 (36.9)	23 (31.9)	29 (42.0)		27 (32.1)	12 (29.3)	15 (34.9)		25 (45.5)	6 (26.1)	19 (59.4)	
I have pain or discomfort	89 (63.1)	49 (68.1)	40 (58.0)		57 (67.9)	29 (70.7)	28 (65.1)		30 (54.6)	17 (73.9)	13 (40.6)	
Anxiety/depression, n (%)				<.01				.08				<.01
I am not anxious or depressed	60 (42.6)	22 (30.6)	38 (55.1)		43 (51.2)	17 (41.5)	26 (60.5)		23 (41.1)	5 (20.8)	18 (56.3)	
I am anxious or depressed	81 (57.5)	50 (69.4)	31 (44.9)		41 (48.8)	24 (58.5)	17 (39.5)		33 (58.9)	19 (79.2)	14 (43.8)	
EQ-VAS, mean (SD)	63.5 (21.3)	59.8 (24.2)	67.3 (17.1)	.04	64.0 (19.6)	58.1 (18.6)	69.7 (19.1)	<.01	65.5 (17.0)	61.3 (16.5)	68.5 (17.0)	.12
Health index,[a] mean (SD)	0.77 (0.18)	0.74 (0.19)	0.80 (16.9)	.03	0.75 (0.22)	0.71 (0.23)	0.78 (0.20)	.14	0.78 (0.17)	0.69 (0.21)	0.84 (0.11)	<.01

EQ-VAS, EuroQoL visual analog scale.
[a]Derived from the Canadian model from Yan et al.[39]

Supplementary Table 6. EQ-5D-5L Patient Health Index Variation

Variable	Health index Δ (baseline – 90 d) All patients (n = 82)	EUS-BD (n = 40)	ERCP-M (n = 42)	*P* value	Variable	Health index Δ (baseline – 180 d) All patients (n = 55)	EUS-BD (n = 23)	ERCP-M (n = 32)	*P* value
Δ (health index), mean (SD)	0.05 (19.5)	0.07 (0.21)	0.03 (0.18)	.45	Δ (health index), mean SD	0.03 (15.6)	0.07 (0.19)	0.01 (0.13)	.13
Patient status, n (%)				—	Patient status, n (%)				—
Worsen	34 (41.4)	17 (42.5)	17 (40.5)		Worse	23 (41.8)	7 (30.4)	16 (50.0)	
No change	8 (9.7)	3 (7.5)	5 (11.9)		No change	4 (49.1)	2 (8.7)	2 (6.3)	
Better	40 (48.8)	20 (50.0)	20 (47.6)		Better	28 (50.9)	14 (60.9)	14 (43.8)	

Supplementary Table 7. EQ-5D-5L Domain Description

Variable	Baseline, n (%)			90 d, n (%)			180 d, n (%)		
	All patients (n = 141)	EUS-BD (n = 72)	ERCP-M (n = 69)	All patients (n = 84)	EUS-BD (n = 41)	ERCP-M (n = 43)	All patients (n = 56)	EUS-BD (n = 24)	ERCP-M (n = 32)
Mobility baseline visit									
I have no problems in walking about	80 (56.7)	37 (51.4)	43 (62.3)	38 (45.2)	15 (36.6)	23 (53.5)	28 (50.0)	9 (37.5)	19 (59.4)
I have slight problems in walking about	28 (19.9)	16 (22.2)	12 (17.4)	18 (21.4)	10 (24.4)	8 (18.6)	12 (21.4)	5 (20.8)	7 (21.9)
I have moderate problems in walking about	24 (17.0)	14 (19.4)	10 (14.5)	18 (21.4)	10 (24.4)	8 (18.6)	11 (19.6)	6 (25.0)	5 (15.6)
I have severe problems in walking about	6 (4.3)	3 (4.2)	3 (4.4)	8 (9.5)	4 (9.8)	4 (9.3)	5 (8.9)	4 (16.7)	1 (3.1)
I am unable to walk about	3 (2.1)	2 (2.8)	1 (1.5)	2 (2.4)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Self-care									
I have no problems washing or dressing myself	113 (80.1)	55 (76.4)	58 (84.1)	53 (63.1)	26 (63.4)	27 (62.8)	38 (67.9)	12 (50.0)	26 (81.3)
I have slight problems washing or dressing myself	12 (8.5)	8 (11.1)	4 (5.8)	17 (20.2)	4 (9.8)	13 (30.2)	8 (14.3)	5 (20.8)	3 (9.4)
I have moderate problems washing or dressing myself	11 (7.8)	6 (8.3)	5 (7.3)	9 (10.7)	7 (17.1)	2 (4.7)	8 (14.3)	5 (20.8)	3 (9.4)
I have severe problems washing or dressing myself	2 (1.4)	1 (1.4)	1 (1.5)	3 (3.6)	2 (4.9)	1 (2.3)	2 (3.6)	2 (8.3)	0 (0.0)
I am unable to wash or dress myself	3 (2.1)	2 (2.8)	1 (1.5)	2 (2.4)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Usual activities (eg, work, study, housework, family, or leisure activities)									
I have no problems doing my usual activities	70 (49.7)	32 (44.4)	38 (55.1)	33 (39.8)	13 (31.7)	20 (47.6)	18 (32.1)	5 (20.8)	13 (40.6)
I have slight problems doing my usual activities	35 (24.8)	22 (30.6)	13 (18.8)	16 (19.3)	6 (14.6)	10 (23.8)	16 (28.6)	5 (20.8)	11 (34.4)
I have moderate problems doing my usual activities	23 (16.3)	10 (13.9)	13 (18.8)	24 (28.9)	18 (43.9)	6 (12.3)	16 (28.6)	10 (41.7)	6 (18.8)
I have severe problems doing my usual activities	8 (5.7)	5 (6.9)	3 (4.4)	6 (7.2)	2 (4.9)	4 (9.5)	3 (5.4)	3 (12.5)	0 (0.0)
I am unable to do my usual activities	5 (3.6)	3 (4.2)	2 (2.9)	4 (4.8)	2 (4.9)	2 (4.8)	3 (5.4)	1 (4.2)	2 (6.3)
Pain/discomfort									
I have no pain or discomfort	52 (36.9)	23 (31.9)	29 (42.0)	27 (32.1)	12 (29.3)	15 (34.9)	25 (45.5)	6 (26.1)	19 (59.4)
I have slight pain or discomfort	38 (27.0)	19 (26.4)	19 (27.5)	31 (36.9)	16 (39.0)	15 (34.9)	20 (36.4)	11 (47.8)	9 (28.1)
I have moderate pain or discomfort	32 (22.7)	16 (22.2)	16 (23.2)	17 (20.2)	8 (19.5)	9 (20.9)	7 (12.7)	4 (17.4)	3 (9.4)
I have severe pain or discomfort	17 (12.1)	12 (16.7)	5 (7.3)	8 (9.5)	4 (9.8)	4 (9.3)	3 (5.5)	2 (8.7)	1 (3.1)
I have extreme pain or discomfort	2 (1.4)	2 (2.8)	0 (0.0)	1 (1.2)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety/depression									
I am not anxious or depressed	60 (42.6)	22 (30.6)	38 (55.1)	43 (51.2)	17 (41.5)	26 (60.5)	23 (41.1)	5 (20.8)	18 (56.3)
I am slightly anxious or depressed	51 (36.2)	31 (43.1)	20 (29.0)	19 (22.6)	10 (24.4)	9 (20.9)	17 (30.4)	8 (33.3)	9 (28.1)
I am moderately anxious or depressed	17 (12.1)	12 (16.7)	5 (7.3)	13 (15.5)	9 (22.0)	4 (9.3)	13 (23.2)	8 (33.3)	5 (15.6)
I am severely anxious or depressed	11 (7.8)	5 (6.9)	6 (8.7)	8 (9.5)	4 (9.8)	4 (9.3)	2 (3.6)	2 (8.3)	0 (0.0)
I am extremely anxious or depressed	2 (1.4)	2 (2.8)	0 (0.0)	1 (1.2)	1 (2.4)	0 (0.0)	1 (1.8)	1 (4.2)	0 (0.0)