Endoscopy

EUS-guided choledochoduodenostomy using single step lumen-apposing metal stents for primary drainage of malignant distal biliary obstruction (SCORPION-p): a prospective pilot study

Jeska A Fritzsche, Paul Fockens, Marc G Besselink, Olivier Busch, Freek Daams, Nahid S Montazeri, Johanna W Wilming, Rogier P Voermans, Roy L.J. van Wanrooij.

Affiliations below.

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Trial registration: NL9757, Netherlands National Trial Register (http://www.trialregister.nl), Prospective

Abstract:
Background and study aims: To assess the safety and feasibility of EUS-guided choledochoduodenostomy (EUS-CDS) using lumen-apposing metal stents (LAMS) as primary drainage strategy in patients with distal malignant biliary obstruction (MBO).

Patients and methods: Prospective single center pilot study in patients with a pathology confirmed MBO without gastric-outlet obstruction. Primary outcome was technical success. Secondary outcomes included clinical success, adverse events (AEs) and re-interventions. The study was registered in the Netherlands Trial Registry (registry number NL9757).

Results: Overall, 22 patients were enrolled (median age 69.5 years [IQR 64-75.2]. Technical success was achieved in 20/22 patients (91%). Adverse events occurred in one patient, namely a perforation occurred due to inadequate deployment (5%), treated in the same procedure. Clinical success was achieved in 19/22 patients (86%). Stent dysfunction was observed in 11 of the 20 patients after technically successful EUS-CDS (55%). Two patients were treated conservatively, in 9 patients re-intervention(s) were performed. One patient died <30 days due to fulminant disease progression.

Conclusions: This study confirms safety and feasibility of EUS-CDS using LAMS as the primary drainage strategy. The high incidence of stent dysfunction should be improved before EUS-CDS with LAMS can be seen as a valid alternative to ERCP.

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Disclosures
Jeska A. Fritzsche, Marc G. Besselink, Nahid S.M. Montazeri, Olivier R. Busch and Freek Daams have no conflicts of interest or financial ties to disclose. Paul Fockens performed as a consultant for Olympus and Cook Endoscopy. Johanna W. Wilmink reports research grants from Servier, Celgene, Halozyne, Merck, Roche, Pfizer, Amgen and Novartis, and nonfinancial support from MSD and AstraZeneca. Rogier P. Voermans reports research grants from Boston Scientific and Prion Medical, performed as a consultant for Cook Medical and Boston Scientific, and received speaker’s fee from Mylan and Zambon. Roy L.J. van Wanrooij performed as a consultant for Boston Scientific. All outside the submitted work.

Author contributions
This study was primarily designed by PF, RV and RvW. The study was conducted by JF, PF, RV and RvW. The data were collected and analysed by JF who also drafted the manuscript under supervision of RV and RvW. All authors contributed to the interpretation of the data and to the draft of the manuscript. All authors have approved of the final manuscript. The guarantor of the article is RvW.

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Conclusions This study confirms safety and feasibility of EUS-CDS using LAMS as the primary drainage strategy. The high incidence of stent dysfunction should be improved before EUS-CDS with LAMS can be seen as a valid alternative to ERCP.
Introduction

Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) is a relatively new technique that allows the endoscopist to create a biliodigestive anastomosis. Due to bypassing the tumor, EUS-CDS simplifies the efforts required to obtain biliary access compared with endoscopic retrograde cholangiopancreatography (ERCP). Moreover, EUS-CDS obviates manipulation of the papilla in order to gain biliary access, nor does the stent cause acute obstruction of the pancreatic duct, thereby precluding the risk of post-procedural pancreatitis.

EUS-CDS has already been shown to be superior to percutaneous approaches in patients with distal malignant biliary obstruction (MBO).[1-3] Based on these promising results EUS-CDS is now also being compared to ERCP. Current prospective studies however all used biliary self-expandable metal stents (SEMS), while electrocautery-enhanced lumen-apposing metal stents (LAMS) simplify the procedure.[1, 2, 4, 5]

Therefore, the aim of this prospective pilot study was to assess the safety and feasibility of EUS-CDS using LAMS as the primary drainage strategy in MBO.

Patients and methods

Study design

Consecutive patients between October 2021 and June 2022 were screened for eligibility in Amsterdam UMC. Patients with a distal MBO confirmed by histology or cytology (including rapid onsite evaluation [ROSE] strongly suggestive of malignancy) with an indication for biliary drainage were considered eligible. Main exclusion criteria were surgically altered anatomy, cancer extending into the antrum or proximal duodenum, extensive liver metastases, WHO performance score of 4, uncorrectable coagulopathy, or clinically relevant gastric-outlet obstruction (GOO). The study was approved by the medical ethics committee of Amsterdam UMC. All patients provided written
informed consent before inclusion. An independent monitor performed clinical trial monitoring. The SCORPION-pilot was registered in the Netherlands Trial Registry (NL9757).

Study procedures

All patients received a single dose of prophylactic broad-spectrum intravenous antibiotics in line with ESGE guideline recommendations.[6] Anticoagulants were stopped if applicable, an INR <1.5 was accepted. Antiplatelet monotherapy was allowed, in case of dual antiplatelet therapy one of two drugs needed to be discontinued 5 days prior to the procedure and was restarted 24 hours post-procedurally.

Procedure was performed using linear endoscopic ultrasound (Olympus GF-UCT180) with the patient in the left lateral or prone position. In case a tissue diagnosis was lacking, a fine needle biopsy (FNB) and/or fine needle aspiration (FNA) was performed to confirm malignant obstruction. The common bile duct (CBD) was identified proximal to the level of the tumor obstruction and at least 2 cm below the hilum. Subsequently the origin of the cystic duct from the CBD was visualized. Care was taken to avoid intervening blood vessels. To allow safe stent deployment the minimal bile duct diameter at the puncture site was set at 12mm considering all procedures were performed by experts in LAMS placement.[6, 7] If the diameter was smaller than 12mm a standard ERCP was performed. EUS-CDS was performed using the 'free-hand technique', meaning that the electrocautery enhanced LAMS was directly introduced into the bile duct using pure-cutting current (100W). In this study the Hot AXIOS™ stent 6x8mm was used. In case the LAMS catheter could not be advanced deep enough into the bile duct, a guidewire was advanced towards the hilum to redirect the catheter and facilitate further advancement. In small diameter bile ducts the distal flange was deployed in a stepwise manner. The biliary system was visualized following LAMS placement by contrast injection via a diagnostic catheter through the LAMS, in order to confirm adequate stent position and exclude contrast leakage. The procedure is illustrated in Figure 1. Three gastroenterologists (PF, RV, RW)
experienced in both EUS and ERCP, performed all study procedures with two of them being present in the endoscopy suite during the procedure.

Follow-up was performed after 2 weeks, 4 weeks, 3 months and 6 months.

Outcome

Primary outcome was technical success. Secondary outcomes were clinical success, defined as at least 50% decrease of bilirubin and/or relief of symptoms without the need for re-intervention within 30 days, procedure time measured from introduction of the endoscope until visual flow of bile through the LAMS. When FNB or FNA was required, time was measured after completion of this procedure. (Serious) adverse events (AEs) <30 days after the procedure were reported. Periprocedural AEs were events that occurred during the procedure. Severity of AEs was graded according to the AGREE classification.[8] Stent dysfunction was defined as recurrent jaundice (conjugated bilirubin ≥35 umol/L [2.0 mg/dL]) after initial clinical success, persisting of jaundice and dilatation of the bile ducts, or cholangitis. Reason of stent dysfunction was classified according to the Leuven-Amsterdam-Milan Study Group classification of EUS-CDS dysfunction.[9] Time to recurrent biliary obstruction was calculated from the moment of stent insertion until stent dysfunction. Re-interventions in case of stent dysfunction were reported. Dysfunction-free survival was defined as the number of days after EUS-CDS until death without experiencing stent dysfunction.

Statistical analysis

Descriptive statistics were used to report proportions and characteristics of the results using R version 4.0.1. Categorical variables were expressed as absolute and relative frequencies, 95% confidence intervals (95%CI) were constructed using the exact binomial distribution approximation. Continuous data were presented as medians and interquartile ranges. (Dysfunction-free) survival was
estimated using Kaplan-Meier survival analysis, since all patients who were still undergoing follow-up were censored at 6 months only a point estimate without 95% CI was provided.

**Results**

**Baseline characteristics**

Overall, 22 consecutive patients with MBO were enrolled. A total of 30 patients signed informed consent, yet in 3 patients ROSE could not confirm malignancy, in 2 patients the CBD diameter was less than 12 mm, and 3 patients were excluded because there was no safe window to perform the procedure, either because the tumor was too close to the hilum (n=2) or because of ascites (n=1). The full screening- and selection process is depicted in Supplementary Figure 1. Baseline characteristics of the included patients are summarized in Table 1.

**Technical success**

Immediate technical success was achieved in 18/22 patients. In two patients the distal flange was initially inadequately deployed in the bile duct wall leading to minor bile spill, which was immediately solved after manipulation (n=1) or replacement with a second LAMS (n=1), without clinical consequences. In two patients the procedure was unsuccessful leading to an overall technical success rate of 91% (95% CI [71-99]%). In one patient the stent was unintentionally placed in the cystic duct. In the other patient the distal flange was deployed outside the bile duct wall. An ERCP with closure of the defect in the duodenum with a through-the-scope clip was performed in the same procedure and the patient recovered uneventfully. In one patient a double pigtail stent (DPS) was placed through the LAMS to prevent stent obstruction by blood clots after a self-limiting intraprocedural bleeding. Median procedure time was 11 minutes (IQR 7-16)
Clinical success

Clinical success was achieved in 19/22 patients (86%; 95% CI [65-97]%). The patient in whom the stent was unintentionally placed in the cystic duct required a (successful) second EUS-CDS procedure due to inadequate biliary drainage. The other two patients underwent successful additional DPS placement to achieve adequate biliary drainage because of early cholangitis (n=1) or suspected stent obstruction (n=1).

Adverse events

Besides the previous described endoscopically treated perforation, no periprocedural AEs occurred. Eight patients (36%) experienced a possible related AE <30 days. Two adverse events were unrelated to stent dysfunction: one patient had mild intermittent abdominal pain which resolved after placement of a DPS through the LAMS and one patient developed rhabdomyolysis and kidney failure <2 weeks after the procedure of unknown relation to the procedure which completely resolved. Six patients developed cholangitis due to stent dysfunction. None of the patients developed pancreatitis or delayed bleeding.

One patient died <30 days due to fulminant disease progression, unlikely related to the procedure (Table 2).

Stent dysfunction (n=20)

Eleven patients out of 20 patients with a technically successful procedure (55%) experienced stent dysfunction <6 months, presenting with either cholangitis (n=10) or jaundice (n=1). Stent dysfunction occurred after a median of 6 days (IQR 5-87.5). Median estimated dysfunction-free survival was 140 days. Reason and grading of stent dysfunction is shown in Supplementary Table 1.
In 2 patients cholangitis was sufficiently treated with antibiotics while 9 patients needed a re-intervention. Overall, endoscopic re-interventions were successful in 8/9 patients (89%). In patients who developed GOO due to disease progression (n=3), concomitant surgical (n=1) or endoscopic gastroenterostomy (n=1) was performed or left untreated according to patients’ wishes. Re-interventions are summarized in Supplementary Figure 2.

Follow-up (n=20)

Median total follow-up was 149 months (IQR 62.5-180). Five patients underwent surgical resection after a median of 34 days (IQR 23.5-49.75). Eight patients died after a median of 80 days (IQR 71-157). The remaining 7 patients were still undergoing follow-up after 6 months. Estimated median survival was 172 days.

Discussion

This pilot study prospectively evaluates the use of EUS-CDS with LAMS as the primary drainage strategy in patients with MBO. EUS-CDS showed high technical and clinical success rates in combination with minimal periprocedural AEs. The high rate of stent dysfunction (55%) however provides a challenge that first needs to be addressed in order to realize the potential benefits of EUS-CDS with LAMS.

Technical and clinical success rate were comparable with previous studies performing EUS-CDS with LAMS after unsuccessful ERCP, range of 89-100% and 82-100%, respectively.[2, 9-17] The stent dysfunction rate in this study was however considerably higher compared with the 6-37% reported previously for EUS-CDS with LAMS.[9-17] This discrepancy may be partially explained by the fact that the majority of studies on this topic were retrospective and may have underestimated the rate of stent dysfunction. Secondly, a relatively strict, though clinically relevant, definition of stent dysfunction was used in this study.
dysfunction was used in this study, including cholangitis as well as persisting or recurrent jaundice. Thirdly, despite GOO being an exclusion criterion, 3 patients developed GOO during the course of the disease which may have contributed to the occurrence of cholangitis. [9, 18] Fourthly, the use of a relatively small diameter LAMS (6x8mm) may have contributed, as there currently is some evidence that larger diameter stents may reduce the risk of stent dysfunction. [16] Lastly, in our study DPS were not routinely placed through the LAMS while recent data showed that this may be beneficial. On the other hand, the fact that 5 patients underwent surgical resection after a median of 34 days could have led to an underestimation, however considering stent dysfunction occurred after a median of 6 days, this factor is expected to be of limited influence. Data on surgical resection after EUS-CDS is still scarce however we believe the available data shows no reason to be reluctant with EUS-CDS in operable patients while awaiting further studies in this specific patient category. [19] Although the rate of cholangitis due to stent dysfunction was high, the course of the disease was generally mild. The vast majority of patients were successfully treated with antibiotics and/or endoscopic re-intervention. Stent dysfunction after ERCP with SEMS is, though lower than EUS-CDS in the current study, also substantial with a range of 3-43%. [4, 5] Yet, with regards to other AEs such as pancreatitis, cholecystitis and delayed bleeding, the safety profile of EUS-CDS seems superior over ERCP. [20] Moreover, periprocedural AEs of EUS-CDS in this study were limited and were managed endoscopically in the same session without clinical implications.

EUS-CDS, using the current technique, is however unable to fully replace ERCP as EUS-CDS was not feasible in 17% of our patients. The main reason being insufficient bile duct dilatation which is in line with a recent study on pre-procedural cross-sectional imaging that identified a sufficiently (>12mm) dilated CBD in only 78.8% of patients. [7] Furthermore, EUS-CDS should not be conducted in patients with GOO due to the high risk of influx of gastric contents in this specific group. Thus, endoscopists should be well trained in both EUS and ERCP in order to switch from EUS-CDS to ERCP when indicated, as well as to adequately handle periprocedural AEs.
The findings of this study are limited by the small sample size and the lack of a control group. Future studies should directly compare the overall impact of AEs and stent dysfunction of either technique on clinical condition, quality of life and delay or annulment of treatment. However, in order to conduct such a trial, the EUS-CDS procedure should first be further optimized to lower the risk of stent dysfunction.

In conclusion, the present study supports the safety and feasibility of EUS-CDS using LAMS as the primary drainage strategy in patients with MBO. However, the high incidence of stent dysfunction currently limits the use of EUS-CDS with LAMS as a valid alternative to ERCP with SEMS. Further studies on the benefit of coaxial stent placement through the LAMS or alternative stent designs are necessary to reduce the risk of stent dysfunction.
References


Figure 1. EUS-guided choledochoduodenostomy with electrocautery-enhanced lumen-apposing metal stent and confirmation of technical success by cholangiogram.

(a) sonographic identification of the common bile duct (CBD) proximal of the tumour. A window with a common bile duct (CBD) ≥12mm without intervening vessels or ascites was identified. With purecutting current the lumen-apposing metal stent (LAMS) was introduced into the bile duct using the free hand technique. (b) The distal flange was deployed in the CBD under endosonographic control. (c) The proximal flange was subsequently deployed under endoscopic control which results in immediate bile flow from the LAMS. (d) Cholangiogram via the LAMS confirms adequate position of the LAMS.
SUPPLEMENTARY MATERIAL

“EUS-guided choledochoduodenostomy using single step lumen-apposing metal stents for primary drainage of malignant distal biliary obstruction (SCORPION-p): a prospective pilot study”

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*Contributed equally to the work
Supplementary Table 1. Grading and cause of stent dysfunction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of stent dysfunction, n (%)</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Grade II</td>
<td>2 (10)</td>
</tr>
<tr>
<td>• Grade IIIa</td>
<td>8 (40)</td>
</tr>
<tr>
<td>• Grade IVa</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Cause of stent dysfunction, n (%)</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Type 2a: Sludge impaction</td>
<td>1 (5)</td>
</tr>
<tr>
<td>• Type 2b: Food impaction</td>
<td>2 (10)</td>
</tr>
<tr>
<td>• Type 3a: LAMS compression on biliary side</td>
<td>4 (20)</td>
</tr>
<tr>
<td>• Type 5: GOO</td>
<td>3 (15)</td>
</tr>
<tr>
<td>• Unknown</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Other interventions, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>• Percutaneous drainage of liver abscesses</td>
<td>1 (5)</td>
</tr>
<tr>
<td>• Diagnostic laparoscopy including percutaneous drainage of liver abscess&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (5)</td>
</tr>
<tr>
<td>• EUS-guided gastrojejunostomy</td>
<td>1 (5)</td>
</tr>
<tr>
<td>• Surgical gastrojejunostomy</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; GOO, gastric outlet obstruction; EUS, endoscopic ultrasound.

<sup>a</sup>Missing in 1 patient who underwent resection after 7 days; <sup>b</sup>In 11 patients experiencing stent dysfunction; <sup>c</sup>According to AGREE classification [1]; <sup>d</sup>According to the Leuven-Amsterdam-Milan Study Group classification of EUS-CDS dysfunction [2]. <sup>e</sup>Liver abscess after diagnostic liver puncture.
References


Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Median age, y (IQR)</td>
<td>69.5 (64-75.25)</td>
</tr>
<tr>
<td>Median BMI, kg/m² (IQR)</td>
<td>24.7 (23.7-26.1)</td>
</tr>
<tr>
<td>Type of tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Pancreatic ductal adenocarcinoma</td>
<td>20 (91)</td>
</tr>
<tr>
<td>• Duodenal carcinoma</td>
<td>1 (5)</td>
</tr>
<tr>
<td>• Distal cholangiocarcinoma</td>
<td>1 (5)</td>
</tr>
<tr>
<td>WHO-score at inclusion, n (%)</td>
<td></td>
</tr>
<tr>
<td>• 0: Fully active</td>
<td>6 (27)</td>
</tr>
<tr>
<td>• I: Restricted in physically strenuous activity</td>
<td>12 (55)</td>
</tr>
<tr>
<td>• II: Ambulatory, but unable to carry out any work activities</td>
<td>2 (9)</td>
</tr>
<tr>
<td>• III: Capable of only limited selfcare</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Use of anticoagulant drugs, n (%)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Tumor stage at inclusion, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Resectable</td>
<td>10 (46)</td>
</tr>
<tr>
<td>• Locally advanced</td>
<td>6 (27)</td>
</tr>
<tr>
<td>• Metastatic</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Median serum total bilirubin, µmol/L (IQR)</td>
<td>225 (130.75-335.25)</td>
</tr>
<tr>
<td>Median diameter common bile duct at EUS, mm (IQR)</td>
<td>16.5 (13.25-20.75)</td>
</tr>
<tr>
<td>Concomitant chemotherapy at inclusion, n (%)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Cholecystectomy prior to intervention, n (%)</td>
<td>4 (18)</td>
</tr>
</tbody>
</table>

BMI, body mass index; WHO, World Health Organization; IQR, interquartile range; EUS, endoscopic ultrasound.

Table 2. Adverse events <30 days including grading
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events ≤30 days, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>• Perforation</td>
<td>1 (5)</td>
</tr>
<tr>
<td>• Pancreatitis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Bleeding</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Cholangitis</td>
<td>6 (27)</td>
</tr>
<tr>
<td>• Other</td>
<td>2 (9)</td>
</tr>
<tr>
<td>o Intermittent abdominal pain</td>
<td>1 (5)</td>
</tr>
<tr>
<td>o Rhabdomyolysis with kidney failure</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Severity of adverse events ≤30 days, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>• Grade II</td>
<td>3 (14)</td>
</tr>
<tr>
<td>• Grade IIIa</td>
<td>5 (23)</td>
</tr>
<tr>
<td>• Grade IVa</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>30-day mortality, n (%)</strong></td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

*According to AGREE classification[8]
60 patients with distal MBO and indication for biliary drainage

30 patients were excluded
- Recent unsuccessful ERCP in referring centre (n=15)
- Reasonable doubt about benign cause at moment of intervention (n=4)
- Gastric outlet obstruction (n=3)
- Patients refused to participate (n=2)
- Missed for screening because of emergency setting (n=2)
- Altered anatomy (n=1)
- Planned drainage referring centre (n=1)
- Ingrowth in duodenal bulb (n=1)
- Language barrier (n=1)

30 patients signed informed consent

8 patients were not enrolled
- No safe window to perform the procedure (n=3)
- On site cytology not representative for malignancy (n=3)
- CBD diameter less than 12 mm (n=2)

22 patients enrolled
9 patients underwent re-intervention(s)

- DPS through LAMS (n=8)*
  - LAMS removed and replaced by two DPS (n=2)
    - Antegrade placement of transpapillary uSEMS (n=3)
      - DPS removed and replaced by FCSEMS (n=1)
    - ERCP and PTCD (n=1)