UTILITY OF PALLIATIVE EUS-GUIDED BILIARY DRAINAGE USING LUMEN APPOSING METAL STENTS – A PROSPECTIVE MULTICENTRE FEASIBILITY STUDY

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Abstract

Background and aims:

Biliary drainage with ERCP is successful in only 80-90% of extra-hepatic cholangiocarcinoma and pancreatic cancer. We present the results of a multi-centre prospective study assessing the safety, feasibility and quality of life of patients following EUS guided biliary drainage (EUS-BD) with LAMS, after failed ERCP.

Methods:

All consecutive adults with a dilated common bile duct (CBD) ≥14mm secondary to inoperable malignant distal common bile duct (CBD) stricture and failed ERCP biliary drainage were screened and recruited from three tertiary UK centres. Technical success of EUS-BD using lumen-apposing metal stents (LAMS) was the primary endpoint. Improvement in serum bilirubin, 30-day mortality, procedure-related complications and quality of life were secondary endpoints. The quality of life improvement was measured using a validated questionnaire (EORTC QLQ-BIL21).

Results:

Twenty patients were included in analysis. EUS-BD was technically successful in all patients and the clinical success was 95% (19/20) at day 7 (>50% reduction in bilirubin) and 92.3%(12/13) at day 30 (bilirubin <50 µmol/l). There were significant improvements in overall quality of life score (49 vs. 42, p=0.03) at day 30. All cause 30-day mortality was 20% and the moderate adverse event rate was 10% (one cholangitis and one stent migration).

Conclusion:

EUS-BD has acceptable technical success and safety as a second line palliative treatment for inoperable malignant distal CBD strictures. Randomised controlled studies comparing EUS-BD with percutaneous transhepatic biliary drainage (PTBD) are needed to determine their effectiveness in clinical practice.

Introduction:

Almost all extra-hepatic cholangiocarcinoma and about 75% of head of pancreas cancers present with obstructive jaundice[1,2]. Around 10% of these cases are complicated by cholangitis[1-3]. Furthermore, jaundice impairs cellular immunity and may aid the dissemination of cancer[4,5]. Hence, relieving biliary obstruction is time critical in the management of hepato-pancreato biliary (HPB) cancers and in improving symptoms.

Endoscopic retrograde cholangio-pancreatography (ERCP) is the first line management for extra-hepatic biliary and pancreatic malignancy[6]. A Dutch national registry study of 8575 patients reported an overall success rate of 85% for successful biliary cannulation[7]. Approximately one in seven need an alternative mode of biliary drainage.

Endoscopic ultrasonography-guided biliary drainage of extrahepatic bile duct (EUS-BD, also known as choledocho-duodenostomy; CDD) was first described in 2001[8]. It is a recognised alternative mode of biliary drainage for patients with inoperable distal biliary strictures and failed ERCP drainage. A systematic review on 17 studies involving 686 patients reported a cumulative technical success of 87% and 20% adverse event rate for EUS-BD[9].

For CDD, an electrocautery-enhanced lumen-apposing stent has been introduced for the treatment of malignant biliary obstruction. Electrocautery-enhanced lumen-apposing stents have been introduced for the treatment of malignant biliary obstruction. The technical and clinical success from one retrospective study was 93% and 87% respectively[10]. We report the results of an open label multi-centre prospective observational study on the safety, feasibility and quality of life (QOL) following EUS-BD with LAMS.

Patients and Methods:

All consecutive adult patients with an inoperable malignant distal common bile duct (CBD) stricture in whom ERCP biliary drainage failed were eligible for inclusion into the study. Patients were either recruited 1) after previously failed ERCP in another centre or 2) were consented for recruitment if attending for contemporaneous EUS and ERCP, in the event of failed biliary drainage with initial ERCP (consort diagram, Figure 2). Only patients considered surgically unresectable, suitable for either palliative chemotherapy or best supportive care were eligible to be included into the study.

Upon identification of patients from each regional HPB multi-disciplinary meeting; patients were approached by the research team, provided with a written patient information sheet (PIS) and consulted either in person or on the phone at least 24 hours before informed consent was obtained. During the baseline visit, patient demographics were collected, and bloods tests were performed including full blood count, renal function, liver function tests and clotting screen.

Informed written consent was obtained either at the baseline visit or on the day of the procedure. After the procedure, patients were followed-up for 30 days (on day 1, 7 and 30). During these appointments, data including occurrence and severity of any adverse events, quality of life (European organisation for research and treatment of cancer-EORTC QLQ-BIL21 questionnaire) and repeat blood tests were collected. EORTC QLQ-BIL21 questionnaire was completed by the patient themselves unless they needed assistance. After the day 30 visit was completed, the patient had completed the study with no further trial follow-up but continued clinical standard of care.

Inclusion criteria:

All adult patients with inoperable distal malignant CBD stricture and failed ERCP drainage were included into the study. For inclusion, minimum CBD diameter was 14mm and distance between the duodenal mucosa and the bile duct walls was $\leq$ 8mm, measured using pre-procedure imaging or during EUS examination.

Exclusion Criteria:

Patients suitable for curative pancreatic or bile duct resection were excluded from the study. Patients who had proximal (i.e. within 1cm from the hilar bifurcation) malignant bile duct strictures and those with a distal CBD stricture with duodenal stent *in situ* occluding access via the first part of the duodenum (where LAMS is placed) were excluded from the study. Patients who were deemed not fit enough to undergo endoscopic drainage with ERCP were also excluded. Patients were also excluded if the distance between bile duct and duodenal wall was >8mm or bile duct diameter was <14mm.

EUS-guided biliary drainage procedure:

Patients referred for ERCP were consented both for ERCP and in the case of failure, for EUS-BD procedure. The EUS procedure was performed under conscious sedation or if not tolerated under deep sedation (e.g. propofol sedation) or general anaesthesia. Procedure was performed by independent endosonographers who had received formal training to place LAMS.

The LAMS (LAMS; Hot-AXIOS®, Boston Scientific Ltd, Marlborough, Massachusetts, US) is a fully-covered (6X8mm or 8X8mm) self-expanding lumen apposing metal stent that is preloaded on a 9Fr catheter, with an electrocautery metal ring at the tip (Figure 1). Using EUS, the most clearly accessible portion of the bile duct adjacent to the first part of the duodenum was selected and the distance between the mucosa of the duodenal wall and bile duct wall was measured. If less than 8mm, and after ensuring there were no intervening vessels on EUS doppler examination, the CBD was punctured using the EC-enhanced LAMS. Once the catheter tip was within the bile duct, a 0.035" or 0.025" diameter guidewire was introduced into the bile duct to anchor position and ensure deep cannulation within the bile duct, at the discretion of endosonographer. LAMS was deployed under real-time EUS ultrasound guidance. Once the LAMS stent was successfully deployed, bile drainage through the stent was confirmed endoscopically and endoscope withdrawn from the patient. The EUS-BD procedure is explained in video 1. In the event of failure to achieve EUS-biliary drainage, the procedure was terminated, and the patient referred for PTBD.

Quality of life (QOL) questionnaire:

The European organisation for research and treatment of cancers EORTC-BIL21 quality of life questionnaire was used for this study. It is an internationally validated questionnaire for patients with jaundice secondary to biliary tract cancer[11]. It has 21 questions addressing 7 different domains; appetite, jaundice, pain, tiredness, anxiety, side effects with treatment, drains and patients' concerns regarding weight loss. Each question has four domains which states responses as "not at all=1, little bit=2, quite a bit=3 and very much=4". The maximum score is 84 and the minimum 21. The questionnaire is attached as supplementary material.

Outcomes:

Primary Outcome:

To assess the feasibility and technical success of LAMS placement in EUS-guided biliary drainage of inoperable malignant distal CBD obstruction.

Secondary outcome:

To assess clinical success (>50% improvement at day 7 or bilirubin<50 at day 30), procedure-related complications, quality of life before and after EUS-BD (EORTC QLQ-BIL21 questionnaire) and 30-day mortality. Bilirubin of less than 50 was chosen because patients can be considered for chemotherapy and other palliative treatments below this level. The discomfort score (Grade 1-no discomfort, 2-minimal, 3-moderate and 4-severe discomfort) was recorded by endoscopy nursing staff independent of the study, both in the procedure room and in recovery (1-hour post-procedure).The procedure related complications were reported according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon[12].

Ethical approval:

Favourable national research ethical committee (REC) and NHS health research authority approvals (NHS-HRA) were obtained for the study (REC id: 237130). Nottingham University Hospitals NHS trust was the sponsor of the study (study ref: 18GA021). This study was registered with ISCRTN (ISRCTN13196704).

Statistical analysis:

Continuous variables were presented as median and standard deviation. Categorical variables were presented as number and percentage. Paired student's t-test or 2-way ANOVA test was used to study the relationship between continuous variables of baseline and follow-up data. The QOL was compared using Wilcoxon matched-pairs signed rank test. A p value of <0.05 was considered significant. All statistical analyses were performed using PRISM for Windows.

Results:

Thirty-two consecutive patients who met the eligibility criteria were screened for inclusion into the study, of which 21 patients were recruited. Eleven patients had successful biliary drainage with ERCP and were excluded from the study. One patient had a protocol deviation (inclusion criteria) and was therefore excluded from the study. Twenty patients were included in the final analysis (Figure 2).

Eleven (55%) patients were female and 9 patients were male (45%). The median age was 76 years (IQR 16; 65-81). The median eastern cooperative oncology group performance status (ECOG) was 2 (IQR1; 2-3). Twelve (60%) patients had locally advanced pancreatic cancer and 8 (40%) had metastatic disease. Of the patients with metastatic disease, 4 had a duodenal primary tumour, 2 pancreatic, 1 colorectal and 1 breast primary. Fourteen (70%) patients were considered for palliative chemotherapy and 6 (30%) were deemed suitable for best supportive care. The ECOG of all patients except one deemed fit for best supportive care was 3. Patient demographics are illustrated in table 1.

EUS-BD and Technical Success:

EUS-BD was technically successful in all patients with no immediate complications . The clinical success was achieved in 19/20 patients (95%) at day 7 (>50% reduction in bilirubin from base line) and 12/13 (92.3%) at day 30 (serum bilirubin <50). The median length of hospital-stay 2 days (IQR 3; 1-4).

The median bile duct diameter was 18mm (IQR 6; 16-22) and median distance between bile duct and duodenal wall was 4mm (IQR 2; 3-5mm). Seventeen (85%) patients received 8x8mm LAMS, and 3 (15%) 6x8mm LAMS. Two patients also had duodenal stent insertion 72 hours after LAMS insertion. All procedures were performed under conscious sedation and 95% received peri-procedural antibiotics. The median discomfort score during the procedure and in recovery was 1 (IQR 1; 1-2). Procedure details are illustrated in table 1.

Following LAMS placement, there were significant reductions in bilirubin, ALP and ALT both at day 7 and 30 compared to baseline (Figure 3). There was no significant difference in albumin, haemoglobin, white cell count, platelets, urea and creatinine between baseline, day 7 and 30.

Quality of life (QOL- EORTC-BIL21) before and after EUS-BD with LAMS:

QOL data was available on all patients at baseline, 20 patients on day 1, 16 patients on day 7, and 13 patients on day 30. The median (IQR) baseline overall score was 50 (18; 44-62). There was a significant improvement in overall QOL score compared to baseline on day 1 (from 50 vs. 46, p=0.02), day 7 (49 vs. 48.5, p=0.04) and day 30 (49 vs. 42, p=0.03).

On analysis of individual components of QOL scale; a significant improvement was noted in jaundice scale on day 1 (9 vs. 8, p=0.03), day 7 (9 vs. 6, p=0.02) and day 30 (8.5 vs. 4.5, p=0.001) of follow-up (figure 4). Similarly, there was a significant improvement in anxiety scale on day 1 (11 vs. 9, p=0.03) and day 30 (12 vs. 10, p=0.02), but not day 7 (10.5 vs. 10, p=0.40) compared to baseline . There was significant difference in oral intake on day 1 but no significant differences in pain or fatigue following drainage (Figure 4).

Adverse events and Mortality:

Three patients experienced pain following EUS-BD, which resolved with simple analgesics within 48 hours. Moderate adverse events were noted in two patients; one delayed stent migration in to the duodenum requiring PTC biliary drainage (classified as moderate according to ASGE lexicon[12])and one post-procedure cholangitis, which resolved during 5 days of intra-venous antibiotics. Three patients were lost to follow up.

A total of 4 (20%) patients died within 30 days' post-procedure; all deaths occurred between day 24 and day 28 post-procedure and were due to disease progression (n=2) or a vascular event (n=2; one thrombotic cerebrovascular accident and one small bowel ischaemia secondary to superior mesenteric vein thrombosis). No deaths were attributed directly or indirectly to EUS-BD.

Discussion:

This is the first multi-centre prospective study to report efficacy as well as sustained improvement in quality of life of patients within 30 days of EUS-BD with LAMS in patients with cancer-related inoperable distal biliary obstruction. We enrolled only those in whom ERCP had failed to decompress the biliary system; 60% of patients had locally advanced cancer and there was evidence of metastatic disease in 40%. EUS-BD was successfully achieved in all patients with resolution of jaundice in 95% by 30-day post-procedure.

The main objective of decompressing the biliary system in patients with advanced cancer-related obstructive jaundice is to bring about symptom relief and improvement in quality of life. QLQ-BIL21 consists of 7 domains and each domain has been validated in an international multicentre Phase IV validation study in patients with biliary malignancy and has been shown to be accurate quantification of quality of life[11]. As 50-78% of patients with pancreatic cancer develop anxiety and depression[13,14], sustained reduction in anxiety scale at 30-day assessment reflects a substantial improvement in the quality of life of our patients. Improvement in bilirubin as shown by the jaundice scale has been associated with improvement in patients' social function[15]. Therefore, our study has demonstrated that EUS-BD has brought about significant symptom relief and improvement in overall quality of life in this patient group.

Resolution of jaundice is another key objective in this patient cohort as persistent jaundice is a contraindication for further treatment such as palliative chemo- or radiotherapy. As expected, this study demonstrated a steady fall in serum bilirubin levels reaching near normal by day 30. ALP and ALT improved with bilirubin. Hepatic dysfunction can affect the drug kinetics including the metabolism, clearance and biliary excretion of the chemotherapy drugs [16] hence, improvement in all aspects of liver function is vital pre-requisite for ongoing management which was achieved by EUS-BD.

The technical success of EUS-BD with LAMS in other studies was between 89 and 100%[10,17-19]. The high technical success rate in this study may be because the median diameter of CBD was 18 mm which will allow the proximal flange to open within the CBD more easily than in a narrower calibre duct in other studies. Another factor was the use of guidewire anchoring within the bile duct after puncture of the bile duct, although this was done at the discretion of endosonographer. Both these factors were recommended in 2 retrospective studies[10,18]. With LAMS; the puncture of bile duct and deployment of the stent is done in a single step, minimising the need for exchange of devices which may lead to higher success rate[10,20]. As the technical success is high, pre-procedure consent for both

EUS guided drainage and ERCP might be considered in those with malignant obstruction and duct size >14mm (4 patients in this study).

The adverse event rate in this study was 10%; there were no procedure-related serious adverse events. The rate of adverse events is comparable to a recently published retrospective study of 11.6%[10]. The cumulative adverse event rate of 20% has been reported for EUS-BD in a systematic review and meta-analysis for EUS-BD[9]. The stent migration rate was 5% which is comparable to the reported literature of 7%[21]. A meta-analysis on EUS-BD reported bile leak as the most common adverse event occurring in 3-7% of patients[22]. This may be due the use of devices not dedicated to EUS-BD procedure, exchange of accessories and leakage of bile alongside the stent. There was 20% all cause 30-day mortality and no procedure-related mortality. There were 2 deaths secondary to vascular event and two to disease progression. The risk of thromboembolism in any cancer is 13% and increases to 21% for pancreato-biliary malignancies[23,24]. Locally advanced and metastatic pancreato-biliary malignancies are aggressive cancers and their median survival is 6-11 and 5-9 months respectively[25]. The life expectancy is considerably shorter if they are considered only for best supportive care, reflecting poor performance status.

The median length of stay (LOS) was 2 (IQR 3; 1-4) days, with admission at least overnight following EUS-BD was mandated as part of the study protocol. A recent retrospective study using LAMS reported a mean length of stay of 6.125 days post procedure[10]. Another retrospective multicentre study reported a median length of stay of 6.6 days with EUS-BD[26]. A retrospective study on PTBD involving 692 patients reported a median overall LOS of 13 days and inter-procedure LOS of 9 days[27]. The length of stay was shorter in this study which along with subjective and objective improvement of jaundice makes it potentially a cost-effective mode of treatment.

The main limitations of this study are that it is an open label trial with relatively small sample size and lack of a PTBD control arm, although this was an exploratory safety and feasibility study. We enrolled only patients with CBD of $\geq$ 14mm because we felt that it may be difficult to deploy LAMS in a duct smaller that 14mm. This we acknowledge is potentially a major limitation as we didn't include all patients with CBD dilation. In our view, we need more flexible delivery systems or use a guidewire to facilitate stent placement in patients with smaller diameter CBD. The small sample size may have also influenced the quality of life assessments. As all therapeutic EUS procedures are generally performed in tertiary referral centres, access for patients to receive EUS-BD following

failed ERCP may not be generalisable throughout the UK. However, it is a procedure in which EUS endoscopists can be trained more easily compared to advanced ERCP[28].

In conclusion, in this prospective multi-centre study, we demonstrate that LAMS can be used safely and effectively for EUS-BD in patients with inoperable malignant distal biliary obstruction where ERCP failed to achieve biliary drainage. The procedure was associated with substantial and sustained improvement in patients' quality of life. Cost-effectiveness of EUS-BD using LAMS in patients who have distal malignant obstruction should be compared to PTBD in prospective multi-centre randomised controlled trials.

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Conflict of Interest:

This was an investigator led study and neither NIHR Nottingham Biomedical Research Centre nor Boston Scientific Ltd had a role in the design, recruitment, analysis and delivery of the study.

Table 1: Patient demographics & procedure details

Patient demographics & procedure details	Values
Male: female	11 (55%): 9 (45%)
Median age (IQR)	76 years (IQR 16, 65-81)
ECOG	2 (IQR 1,2-3)
Locally advanced disease	12 (60%)
Metastatic disease	8 (40%)
Palliative chemotherapy: best supportive care	14 (70%): 6 (30%)
8X8mm: 6X8mm LAMS	17 (85%): 3 (15%)
Diameter on CBD (median, IQR)	18mm (IQR 6, 16-22)
Technical success	100%
Patient discomfort (median, IQR)	1 (IQR 1, 1-2)
Length of stay (median, IQR)	2 days (IQR 3, 1-4).

Figure1: LAMS deployed in bile duct and duodenum

Figure 2: Screening and Recruitment

Figure 3: Changes in liver parameters before and after the procedure

Figure 4: QOL before and after the procedure

Video of EUS-BD procedure

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