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Endoscopic ultrasound-guided drainage using LAMS of malignant afferent limb syndrome in patients with previous Whipple surgery: A multicenter study (with video).

Short running title: EUS drainage of afferent limb syndrome.

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ABSTRACT

OBJECTIVES

Endoscopic ultrasound-guided digestive anastomosis (EUS-A) is a new alternative under evaluation in patients presenting with afferent limb syndrome (ALS) after Whipple surgery. The aim of the present study is to analyze the safety and effectiveness of EUS-A in ALS.

METHODS

This is an observational multicenter study. All patients ≥18 years-old with previous Whipple surgery presenting with ALS who underwent an EUS-A using a lumen apposing metal stent between 2015 and 2021 were included. The primary outcome was clinical success, defined as resolution of the ALS or ALS-related cholangitis. Furthermore, technical success, adverse event rate and mortality were evaluated.

RESULTS

Forty-five patients (mean age: 65.5±10.2 years, 44.4% male) were included. The most common underlying disease was pancreatic cancer (68.9%). EUS-A was performed at a median of 6 weeks after local tumor recurrence. The most common approach used was the direct/freehand technique (66.7%). Technical success was achieved in 95.6%, with no differences between large (≥15mm) and small LAMS (97.4% vs. 100%, p=0.664). Clinical success was retained in and 91.1% of patients. A complementary treatment by dilation of the stent followed by ERCP through the LAMS was performed in three cases (6.7%). There were six recurrent episodes of cholangitis (14.6%) and two procedure-related adverse events (4.4%) after a median follow-up of 4 months. Twenty-six patients (57.8%) died during the follow-up due to disease progression.

CONCLUSIONS

EUS-A is a safe and effective technique in the treatment of malignant ALS, achieving high clinical success with an acceptable recurrence rate.

Key-words: Endoscopic ultrasound, LAMS, stent, anastomosis, gastrojejunostomy.

INTRODUCTION

The endoscopic ultrasound (EUS)-guided creation of a gastrointestinal anastomosis is a new minimally invasive alternative under evaluation for an increasing number of indications. Most data have been collected in the setting of gastric outlet obstruction. In this particular context, EUS has shown a high technical and clinical success rate when performed in expert centers[1], with lower adverse events compared to laparoscopic gastrojejunostomy[2-4].

Indications for EUS-guided gastrointestinal anastomosis have expanded and may also be used for patients with malignant afferent limb syndrome (ALS). In a subgroup of patients with previous Whipple surgery, some patients will develop malignant ALS where increased intraluminal pressure through the bilioenteric anastomosis may lead to subsequent reflux cholangitis. In these cases, therapeutic options have been limited and included percutaneous drainage, enteral stenting, and surgery in the past. To date, some case series with EUS-guided digestive anastomosis (EUS-A) have been published, with favorable outcomes[5]. Especially in this specific clinical setting, minimally invasive therapy by EUS-A may carry significant theoretical advantages, such as the higher clinical success[6] and lower need for reintervention compared to enteral stents [7, 8], and lower morbidity compared to surgery. Despite these potential advantages, EUS-A procedures can be challenging, data on effectiveness are limited to case series, and procedure-related adverse events can be severe, such as bleeding and peritonitis[9].

The present multicenter study aims to analyze the safety and effectiveness of EUS-A in patients with malignant ALS following Whipple surgery.

METHODS

Patients

This is an observational, international retrospective multi-center study. All patients ≥18 years old with previous Whipple surgery presenting with a local tumoral recurrence and ALS who underwent an EUS-A by gastro-jejunostomy or jejuno-jejunostomy using a lumen apposing metal stent (LAMS) between October 2015 and May 2021 were included. The protocol was submitted to the Local Ethical Committee (CERUPHO).

Patients with previous surgical treatment for the palliation of malignant ALS and those with surgically modified anatomies other than Whipple's resection were excluded.

Age, sex, and demographic variables were collected. Baseline characteristics such as underlying cancer primary site, tumor recurrence size, metastatic status, and presence of peritoneal carcinomatosis were noted. Time elapsed between the Whipple surgery and oncological recurrence, or EUS-A were also considered. Previous percutaneous treatment was also noted.

Procedure

A linear-array echoendoscope was used to create the anastomosis with an electrocautery enhanced LAMS. The EUS-A technique was chosen by the endoscopist based on the patient's characteristics and local experience. All procedures were performed under general anesthesia and CO2 insufflation. All patients received antibiotics periprocedural.

The EUS characteristics (diameter of the afferent limb) and EUS-technique (direct access, wire-guided LAMS placement, previous perforation with a cystotome) were assessed. Procedure time was assessed from the insertion to endoscope removal. The use of radiological guidance, complementary treatment by endoscopic retrograde cholangiopancreatography (ERCP) through the LAMS, and device characteristics (type of needle, type/diameter of the LAMS) were also collected.

Outcomes

The primary outcome was clinical success, defined as the resolution of the ALS or ALS-related cholangitis (using a combination of clinical parameters, C-reactive protein and bilirubin levels) without the need of further endoscopic, radiological or surgical biliary procedures within one week of follow-up.

The secondary outcomes were technical success, adverse event rate, and mortality.

Technical success was defined as the successful placement of the LAMS with the creation of an anastomosis between the jejunal lumen above the hepaticojejunal anastomosis of the afferent limb and the stomach or the proximal jejunum near to the surgical gastrojejunal anastomosis. Procedure-related adverse events were graded using the ASGE lexicon for adverse events[10]. In this study, the LAMS misdeployment was considered as a technical failure and an adverse event if a perforation was done.

Clinical follow-up, as well as delayed adverse events, were evaluated using medical records. Delayed bleeding was defined as the need for transfusion with or without the need for re-intervention (either surgical, endoscopy or interventional radiology). Procedure-related and unrelated mortality was also assessed.

Statistical Analysis

Categorical variables were compared using χ^2 or Fisher-exact tests. Non-normally distributed continuous variables were analyzed by Mann-Whitney U-test or Kruskal-Wallis test. Normal and non-normal variables were presented as mean (SD) and median (range). A survival analysis by Kaplan Meier curves and log-rank test was performed to assess the time to recurrent cholangitis. A two-sided p-value<0.05 was considered statistically significant. The SPSS software v.24 was used (IBM, SPSS Inc, IL, USA).

RESULTS

Patients

Forty-five patients (mean age: 65.5±10.2 years, 44.4% male) from 20 institutions were included. Baseline characteristics are shown in **Table 1**. The most common underlying disease leading to a Whipple resection was pancreatic cancer (68.9%). The median time from Whipple surgery to local recurrence was 13 months (range: 4-39), and metastatic disease was present in half of the patients (53.3%). All of them presented with reflux cholangitis or cholestasis.

EUS-guided anastomosis

The procedure was performed at a median of 6 weeks (range: 1 day – 24 months) after local recurrence diagnosis. Most of the patients (n=30, 66.7%) underwent EUS-guided gastro-jejunostomy (n=40) or jejuno-jejunostomy (n=5) during the nine months following the recurrence. The median time of EUS-A was 25 minutes (range: 5-87) and fluoroscopy was used in most cases (n=33, 73.3%).

The afferent limb measured a median of 35 mm (range: 20-70) by EUS. The different approaches for performing the EUS-guided anastomosis were direct/freehand technique (n=30, 66.7%) (**Video**), wire-guided technique (n=14, 31.1%), and wire-guided technique using a cystostome (n=1, 2.2%). In two patients who underwent the direct approach, EUS-guided needle puncture was performed before LAMS placement, aimed at both filling the afferent limb and fluoroscopic confirmation. Considering patients who underwent the wire-guided LAMS placement, a 19-gauge needle with a 0.025/0.035-inch guidewire was used. There were numerical differences in the procedure times between the direct access and wire-guided techniques (20 min [range: 5-70] vs. 30 min [range: 15-60]), but they were not statistically significant (p=0.078)

Considering LAMS type, the HotAxios (Boston Scientific, MA, USA) was used in 44 cases and Spaxus (Taewoong, Gyeonggi-do, South Korea) in one case. Different LAMS sizes were used: 15x10mm (n=32, 71.1%), 20x10mm (n=5, 11.1%), 10x10mm (n=4, 8.9%), 8x6mm (n=3, 6.7%),

and 16x20mm (n=1, 2.2%). Previous percutaneous drainage of the afferent limb had been performed in two cases prior to EUS-A.

Technical success was achieved in 43 cases (95.6%) with no differences between large (≥15mm) and small LAMS (97.4% vs. 100%, p=0.664). A complementary treatment by dilation of the stent followed by ERCP through the LAMS was performed in three patients (6.7%) due to suspicion of local recurrence in hepatico-jejunal anastomosis. There were two adverse events (4.4%). Indeed, two patients confirmed LAMS misdeployment during the procedure This was treated by LAMS extraction and closure of the gastric perforation by an over-the-scope clip in the first case, leading to an unplanned prolongation of hospital stay (mild adverse event). A rescue therapy by stabilization of the LAMS using the technique "stent-in-stent" with the deployment of three 10mm fully covered biliary metal stents was performed in the second case because of the partial opening of the distal flange of the LAMS leading to a higher migration risk. There was no peritonitis in both cases. In addition, no EUS-A related mortality was described.

Clinical success was retained in 41 cases (91.1%), as shown in the flow-chart of **Figure 1**. There were no statistically significant differences in clinical success depending on the EUS-A technique (p=0.907) or the size of LAMS (p=0.775). Regarding the 4 cases with clinical failure: one of them was the patient previously described with a technical failure and perforation closure. In the other case, the LAMS was placed above the malignant stricture. Thus, it was ineffective either, and a new EUS-A was required the day after. There was a persistent cholangitis in the two remaining cases in whom plastic stents through the LAMS were placed in a second procedure.

Follow-up

Overall, the median follow-up was four months (range: 1 week-14 months). Of 41 patients with clinical success, six (14,6%, 5 with a ≥15mm LAMS diameter) developed recurrent cholangitis at a median of 5 months after the procedure (range:1-12) (**Figure 2**). The reasons of recurrent cholangitis were a buried LAMS with stent occlusion (n=3), local recurrence on the

hepaticojejunal anastomosis (n=2), and malignant jejunal stricture distal to the EUS-A due to a peritoneal carcinomatosis nodule. Of note, the buried LAMS leading to recurrent cholangitis were detected at 1,4 and 7 months after EUS-A. These six patients required a new endoscopic intervention as follows: double pigtail plastic stenting through the LAMS (n=3) in case of buried stent, EUS-guided hepatico-gastrostomy/jejunostomy (n=2) in hepaticojejunal recurrence, and coaxial duodenal stent placement (n=1) covering the new jejunal stricture in the last case.

No delayed bleeding or peritonitis was described after initial technical success. Twenty-six patients (57.8%) died during the follow-up due to disease progression.

DISCUSSION

The present multicentre study of 45 patients analyses the role of EUS-A in malignant ALS, revealing high technical and clinical success rates (>90%), with a low rate of procedure-related adverse events during a median follow-up of 4 months. To our knowledge, this study represents the largest series of patients presenting with this condition to date.

EUS-guided digestive anastomoses are a very heterogeneous group of procedures with a wide range of technical difficulty and probably different outcomes depending on several features such as surgical anatomy, clinical presentation, EUS-guided technique, and stent type or diameter. In ALS, EUS-A is gaining ground, although previous studies are limited to case series including heterogeneous groups of patients with different surgical anatomy and baseline conditions. A recent case series[11] reported a technical success of 100% with no related adverse events in 5 patients with ALS and a previous surgery of Roux-en-Y or pancreatoduodenectomy treated by EUS-A using a 15mm stent. Percutaneously assisted EUS-guided gastrojejunostomy[12] and EUS-guided jejuno-jejunostomy[5, 13] have also been described. In our study, we only included patients with previous Whipple surgery without previous surgical or endoscopic treatment of ALS, which seems mandatory to analyze the outcomes of this technique accurately. Furthermore,

the indication for EUS-A was cholangitis or cholestasis in all cases, and most patients underwent EUS-A using freehand 15mm LAMS placement.

In 2018, Brewer Gutierrez et al.[8] reported their multicenter experience with EUS-A in 18 patients with different previous surgical procedures, for a variety of indications and with various LAMS placement techniques. The authors reported a clinical resolution of symptoms in 89% of cases, and a reduced need for re-intervention compared to enteroscopy-assisted luminal stenting. Herein, we describe similar outcomes with a 91% clinical success in a more homogeneous population. Furthermore, all patients with recurrent cholangitis underwent a new successful endoscopic procedure. However, only two adverse events were described in our study (4.4%) compared to the 16.7 % adverse event rate (abdominal pain) described by the beforementioned authors[8]. A potential explanation for this could be that post-procedural abdominal pain has been underestimated in our series due to the study's retrospective nature.

The LAMS size is another important point to consider. Given that the ALS presents with a fluid content, small stents could be enough to achieve clinical success avoiding gastro-jejunal flow of gastric liquids and food to the ALS. Large LAMS could be necessary if an ERCP through the anastomosis is needed, but this scenario is less common as described in the present series.

It's important to highlight that EUS-A may not be possible in situations where the afferent loop is not accessible or local invasion makes EUS-A unfeasible as described by De Bie C et al. [14]. In this setting, EUS-guided hepaticogastrostomy can be an effective alternative, as also illustrated by two patients in the current study suffering recurrent cholangitis following EUS-A. This technique is often easier than a gastrojejunostomy performed for gastric outlet obstruction since the targeted afferent limb is most often distended. However, EUS-A is probably preferable and intrahepatic bile duct is not usually very dilated in this scenario. In addition, more proximal or distal small bowel strictures secondary to carcinomatosis disease may prevent from clinical improvement or EUS-A and lead to a new recurrence of obstructive symptoms.

Long-term outcomes in patients undergoing EUS-guided therapy with limited oncological disease load and longer subsequent survival can be an issue[15]. In total, nine patients required reintervention due to either clinical failure or recurrent cholangitis over time, resulting in an overall reintervention rate of 20%. Notably, a median follow-up of 4 months was achieved, and no procedure-related mortality was described. Indeed, most of reflux cholangitis (66.7%) occurred in patients with >4 months follow-up.

Long-term LAMS placement after EUS-A may be feasible and safe for direct access to the excluded limb, but these patients can require multiple endoscopic sessions across the endoscopic anastomosis[16]. There are several limitations to this study. This is a retrospective study with inherent limitations due to its design. Related to this, the evaluation of post-procedural abdominal pain has probably been underestimated. Furthermore, there are many participating centers with different local protocols, the degrees of severity of cholangitis and bilirubin levels were not assessed, and extrapolation of the current outcomes to the non-expert setting may be difficult. The major strengths of our study are the large sample size, our attempts to limit the heterogeneity by wielding strict inclusion criteria, and the relatively long-term follow-up period.

In conclusion, EUS-A seems safe and effective in treating malignant ALS presenting with cholangitis, achieving high clinical success with an acceptable recurrent rate. The standardization of the EUS-guided technique, type of stent, and timing from cholangitis presentation to EUS-A seems mandatory in the near future.

CONFLICT OF INTEREST

Michiel Bronswijk received grants from Taewoong, Takeda, Prion Medical and has consultancy agreements with Prion Medical – Taewoong. Schalk Van der Merwe holds the Cook and Boston Scientific chair in Interventional endoscopy and holds consultancy agreements with Cook, Pentax and Olympus. Enrique Pérez-Cuadrado-Robles has consultancy agreement with Boston Scientific. Enrique Pérez-Cuadrado-Robles and Alberto Largui are Associate Editors of Digestive Endoscopy. Pierre Deprez is Deputy Editor-in-Chief of Digestive Endoscopy.

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FIGURE LEGENDS

Figure 1: Flow-chart of patients presenting with afferent limb syndrome who underwent endoscopic ultrasound-guided entero-enterostomy. Of 6 patients presenting with recurrent cholangitis during the follow-up, four underwent "stent in stent technique" through the LAMS, and two underwent EUS-guided hepatico-gastrotomy. LAMS, lumen-apposing metal stent.

Figure 2: (a) This Kaplan Meier curve represents the time to recurrent cholangitis (months). **(b)** Late recurrences were probably due to new malignant stenosis, but no statistically significant differences were found between patients presenting with carcinomatosis (p=0.125).

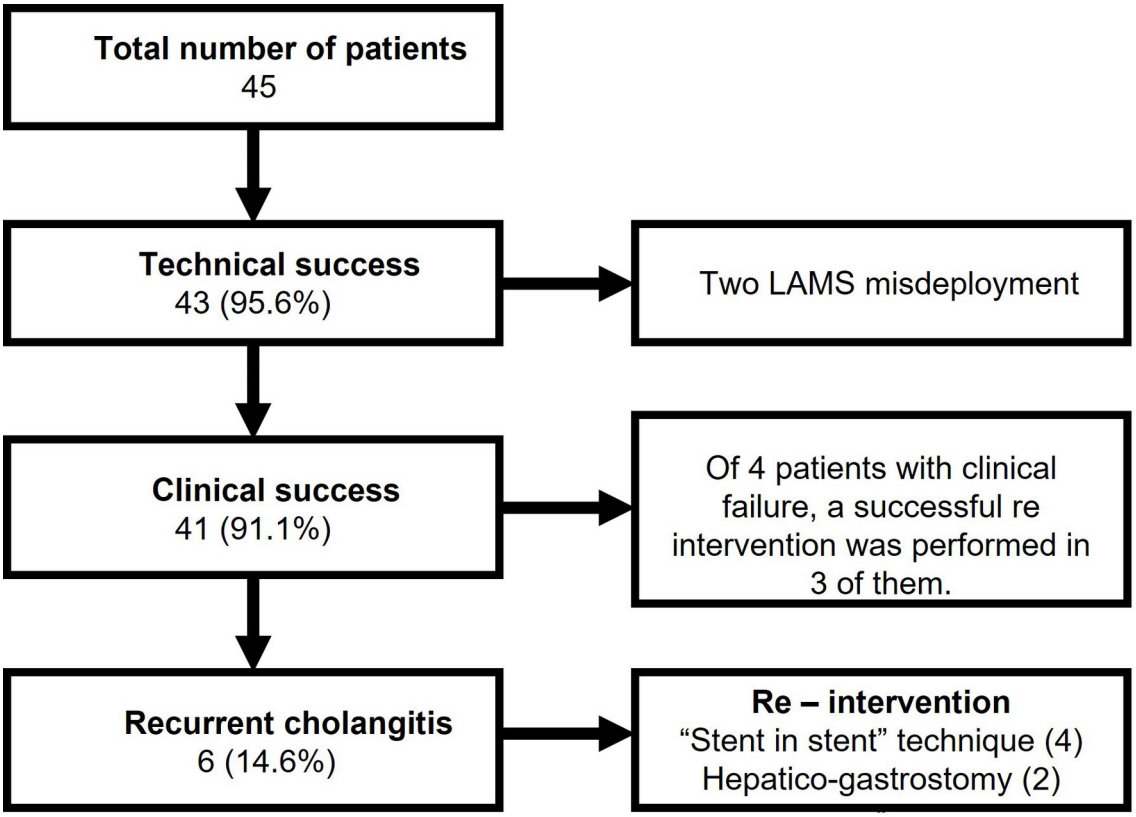
SUPPLEMENTARY MATERIAL - VIDEO LEGEND

Endoscopic ultrasound-guided gastro-jejunostomy using the direct technique in a patient with afferent limb syndrome and cholangitis. Placement of a 15x10mm lumen apposing metal stent.

TABLES

Table 1: Baseline characteristics of patients presenting with a malignant afferent limb syndrome due to a local recurrence.

Male, sex, n (%)	20 (44.4%)
Age, mean (SD), years	65.5 (10.2)
Underlying disease, n (%)	
Pancreatic cancer	31 (68.9%)
Distal cholangiocarcinoma	7 (15.6%)
Ampullary cancer	5 (11.1%)
Gastric cancer	1 (2.2%)
Pancreatic neuroendocrine tumor	1 (2.2%)
Tobacco use, n (%)	11 (24.4%)
Diabetes, n (%)	11 (24.4%)
Size of local recurrence, median (range), mm	25 (20-60)
Metastatic disease, n (%)	24 (53.3%)
Peritoneal carcinomatosis, n (%)	21 (46.7%)



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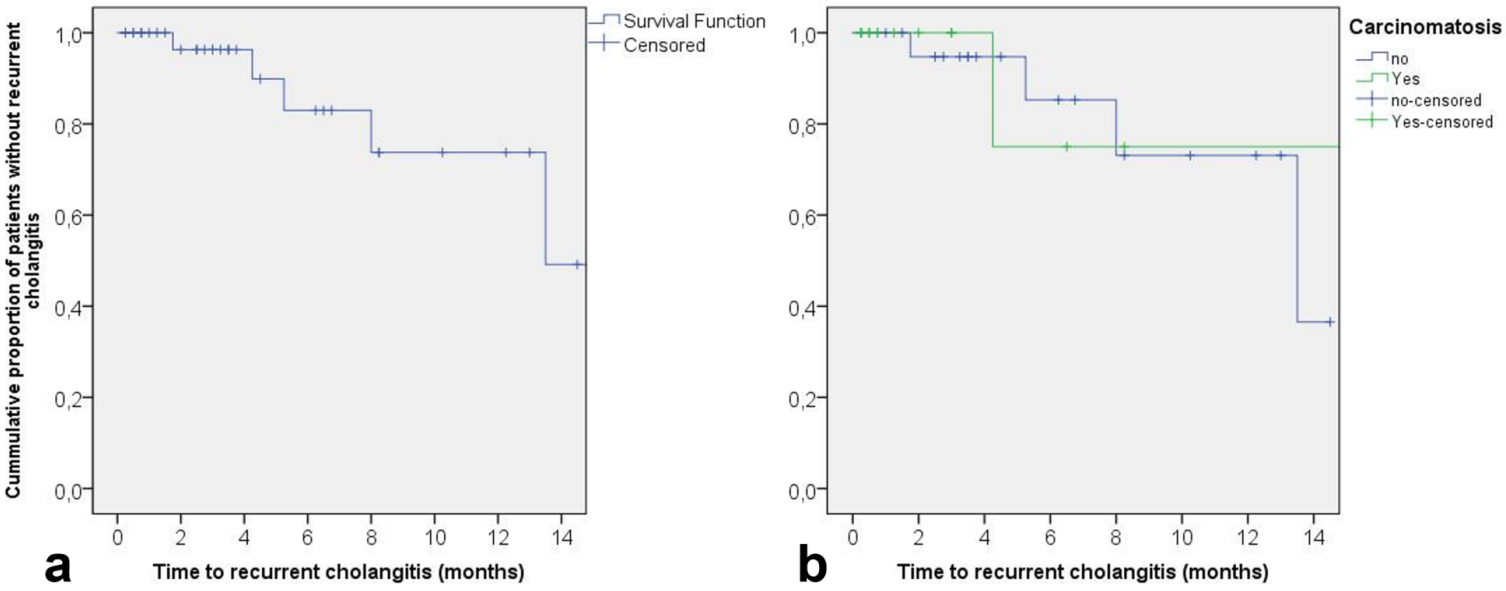

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