REVIEW

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Endoscopic Ultrasound Biliary Drainage in Pancreatic Cancer

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ABSTRACT

Endoscopic ultrasound (EUS) guided biliary drainage (BD) is an accepted salvage procedure in patients with distal malignant biliary obstruction (DMBO) when endoscopic retrograde cholangiopancreatography (ERCP) is unsuccessful. The potential advantages of EUS-BD include gastric or duodenal biliary access, utilization of novel biliary stents and stent placement away from the area of stenosis, resulting in longer stent patency. These features make EUS-BD very appealing as a primary procedure for biliary drainage. There is a growing body of evidence supporting the utilization of EUS as a primary drainage procedure instead of ERCP, with comparable outcomes.

Key words: pancreatic cancer – endoscopic ultrasound – biliary drainage – lumen apposing metal stents.

Abbreviations: AE: adverse event; BD: biliary drainage; CBD: common bile duct; CDS: choledochoduodenostomy; DMBO: distal malignant biliary obstruction; EC-LAMS: electrocautery self-expanding lumen apposing metal stent; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; EUS-BD: EUS guided biliary drainage; EUS-GBD: EUS guided gallbladder drainage; FNA: fine needle aspiration; HGS: hepatico-gastrostomy; LAMS: self-expanding lumen-apposing metal stents; PTBD: percutaneous transhepatic biliary drainage; RCT: randomized controlled trial; SEMS: self-expanding metal stent.

INTRODUCTION

Pancreatic ductal adenocarcinoma carries a poor prognosis with an overall 5-year survival of 11% [1]. At presentation, only 15-20% are suitable for surgical resection [2]. Jaundice is frequently the presenting sign and is encountered in up to 75% of patients with lesions pertaining to the pancreatic head [3]. Thus, biliary drainage (BD) is fundamental in inoperable patients to administer chemotherapy. For surgically resectable cases, BD is also indicated when surgery is delayed or to permit the administration of neo-adjuvant chemotherapy which is very often utilized in these patients [4]. The standard of care to achieve biliary drainage is endoscopic retrograde cholangiopancreatography (ERCP), with percutaneous transhepatic biliary drainage (PTBD) as a backup approach, when ERCP is unsuccessful or not technically feasible.

Despite the primary role of ERCP in this setting, the occurrence of severe adverse events (AEs), especially pancreatitis may delay or preclude subsequent treatment. Percutaneous transhepatic BD is also associated with significant AEs rates, reported to be as high as 34% in some studies [5-8]. After Giovannini et al. [9] reported for the first time in 2001 the possibility to perform endoscopic ultrasound (EUS)-guided BD, this procedure has emerged as a valid alternative approach to PTBD to achieve biliary drainage when ERCP fails [10, 11]. Possible advantages of EUS-BD include biliary access from the stomach or duodenum irrespective of the accessibility of the papilla; utilization of novel design stents designed for transmural biliary drainage away from the site of obstruction, which may be associated with prolonged stent patency.

The present paper will review the technical and clinical data related to the use of EUS-guided methods for achieving BD in patients with malignant distal bile duct obstruction. After a thorough review of the literature, we found it impossible to extrapolate these data, in particular outcome data, only for pancreatic cancer patients, as distal biliary malignancies are considered in all studies together. In fact, even histopathologically, it is often very difficult or even impossible to differentiate a pancreatic from a distal biliary duct cancer.

TECHNICAL ASPECTS

The technique of EUS-BD has evolved over time and has been repeatedly reported to be clinically relevant in studies with a significant number of patients. Endoscopic ultrasound-guided BD can be broadly classified into 3 approaches: rendezvous, antegrade and transmural stenting [12]. Endoscopic ultrasound-guided rendezvous and antegrade stenting follow the principles of ERCP with placement of a transpapillary drainage. Endoscopic ultrasound-guided transmural stenting is a technique in evolution with new devices being continuously developed and refined to improve safety and outcomes.

Endoscopic ultrasound-guided BD can be performed via a transgastric-transhepatic [hepatico-gastrostomy, (HGS)], or a transduodenal-transcholedochal approach [choledochoduodenostomy, (CDS)]. Initially, EUS-BD was performed using biliary self-expanding metal stents (SEMS) borrowed from the ERCP armamentarium. Recently, small (6-8 mm in diameter) self-expandable lumen-apposing metal stents (LAMS) specifically designed for EUS-CDS has been developed and now equipped with a cystotome capability on the tip of the device, which permits a single step procedure without accessories exchange. Moreover, partially covered tubular metal stents or with antimigration features designed for EUS-HG have also become available.

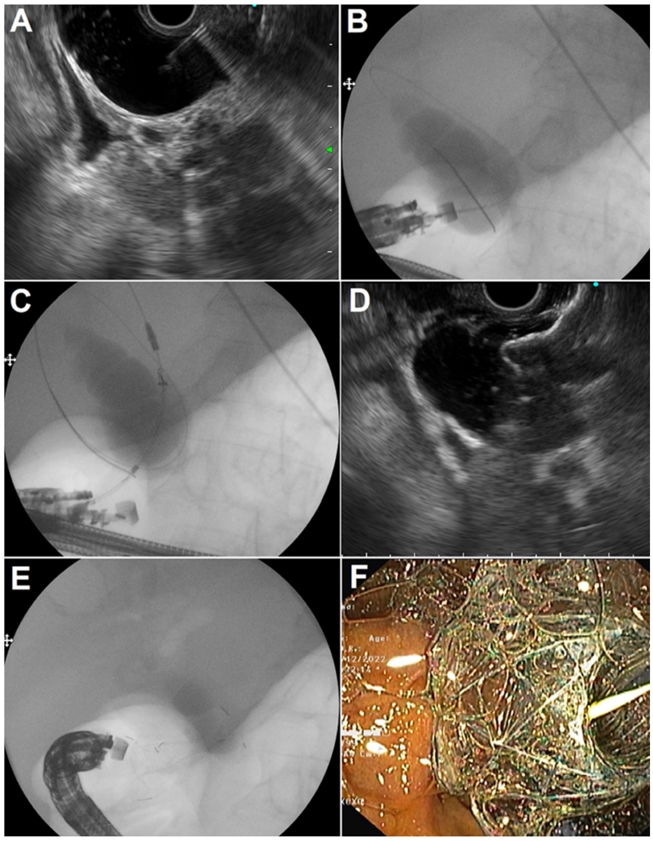

Fig. 1. EUS-guided choledochoduodenostomy in a patient with failed previous ERCP and distal bile duct obstruction from a pancreatic tumor. The dilated common bile duct is punctured with a 19-gauge EUS-FNA needle (A), followed by bile aspiration, contrast injection for cholangiography, and advancement of a guidewire inside the biliary tract (B). An EC-LAMS (10-mm wide/ 20-mm long) is then advanced over-the-guidewire (C), followed by distal flange deployment under EUS guidance (D), stent retraction for apposition of the bile duct and duodenal wall, and proximal flange deployment. Final correct stent position and biliary drainage are controlled radiologically (E) and endoscopically (F).

Endoscopic Ultrasound-guided Choledochoduodenostomy

To achieve transmural drainage of the common bile duct (CBD) (Fig. 1), the echoendoscope is advanced into the duodenal bulb and the CBD located. Access to the CBD has to be done upstream from the obstructive mass, a location that depends on the extent of CBD involvement in the distal/ mid portion. Placement of the LAMS too close to the hilum is usually contraindicated. The subsequent steps are dependent on the choice of the stent, either a LAMS or SEMS. A meta-analysis on 31 studies (820 patients) who underwent EUS-CDS found comparable outcomes between the two stents [13]. The practical advantage of new-generation LAMS is the presence of a cautery-enhanced delivery catheter which permits the transmural puncture and placement of a stent in a single step.

For placement of a SEMS, the CBD is first punctured using a 19-gauge needle that allows placement of a 0.035 or 0.025 and passage of all subsequent accessories. Dilation of the tract can be obtained using a balloon dilation catheter or a cystotome and is followed by stent placement. To reduce the steps needed to complete the procedure, Koga et. al. [14] have recently reported the use of a novel SEMS with a smaller delivery catheter (5.9 F vs. 8.5 F), which does not require dilatation prior to stent insertion [14]. Table I lists the comparison between the utility of LAMS and SEMS for EUS-CDS.

The approach from the duodenal bulb is the preferred route for LAMS placement, even in patients still being considered for surgical resection. For this reason, LAMS should be placed as far as possible from the hepatic hilum. This allows that an adequate length of the CBD after transection remains available for hepatico-jejunostomy, with the stent removed within the surgical resection margin. The procedure can be performed after all the previously described steps of puncturing the CBD over the previously advanced guidewire, or as preferred by many experts, by a free hand technique by which the LAMS is advanced using the electrocautery device directly into the CBD, avoiding accessories exchange and limiting the possibility of errors. A dilated CBD diameter of more than 12 mm (preferably 15mm) is required to avoid the possibility of contralateral bile duct wall injury. In a multicenter prospective study involving a large cohort of patients with unresectable distal malignant biliary obstruction (DMBO), the size of the CBD at the level of the duodenal bulb where EUS-CDS is usually performed was evaluated and found to be smaller than 12 and 15 mm in 21% and 48% of the cases, respectively [15]. This data confirms that in a significant number of jaundiced patients with DMBO, EUS-BD has to be performed using tubular SEMS, especially in non-expert hands.

Table I. Comparison of LAMS and SEMS

LAMS	SEMS
Fluoroscopy not required	Fluoroscopy required
Bile duct puncture, fistula creation, and stent deployment possible in a single device (electrocautery enhanced)	Multiple devices required (FNA needle, dilator, stent delivery catheter)
Shorter procedural time	Longer procedural time

There are specific issues related to EUS-CDS. For example, double mucosal puncture is a rare complication of this procedure. This AE can be minimized by filling the lumen with water or utilizing a forward-viewing echoendoscope [16]. There are also concerns about the adequacy of drainage by LAMS, which is placed perpendicular to the axis of the bile duct. Indeed, it has been hypothesized that placement of a coaxial plastic double pigtail stent within a biliary LAMS may be beneficial in EUS-CDS. However, a retrospective study on 41 patients did not find any potential advantages [17]. An ongoing open-label multicenter randomized controlled trial (RCT), the BAMPI study, conducted in three experienced centers in Spain will provide a definitive answer to this important issue [18]. Another specific entity is the sump syndrome, in which refluxed duodenal contents, calculi or debris occlude the stent lumen in the portion of the CBD distal to the placed stent, leading to biliary and/or pancreatic AEs such as ascending cholangitis [19]. It is described for EUS-CDS with a LAMS and generally resolves with antibiotic therapy and temporary placement of a plastic stent inside the previously placed metal stent [20].

Endoscopic Ultrasound-guided Hepaticogastrostomy

EEndoscopic ultrasound-guided HGS is usually performed for palliation of malignant distal biliary obstruction due to pancreatic ductal adenocarcinoma when the duodenum is inaccessible due to malignant infiltration. For this approach, the echoendoscope is positioned in the upper stomach near the cardia, or in the perianastomotic jejunum in patients with prior gastrectomy. Both locations permit access to the left intrahepatic biliary system. The standard steps undertaken are bile ductal puncture, guidewire insertion, tract dilation, and stent deployment (Fig. 2). Intrahepatic bile ducts of segment III are usually chosen as the site of puncture. Segment II puncture is also possible, but there is the potential that the puncture is performed through the distal esophagus, with a subsequent risk of mediastinitis. After Doppler confirmation that no intervening vascular structures are present, the selected dilated biliary radicle of ≥ 5mm is punctured using a 19G needle under EUS guidance. The transducer should be directed towards the liver hilum, with the tip of the echoendoscope in a 90˚ upward angulation visualized on fluoroscopy (a surrogate for the intra-gastric position of scope tip). Successful puncture is confirmed by aspiration of the bile and this is followed by contrast injection to delineate the biliary tree anatomy and the passage of a 0.035" or 0.025" guidewire into the bile duct.

Guidewire manipulation is recognized as one of the rate-limiting steps in the procedure. In a Spanish multicenter retrospective survey of 125 patients who underwent EUS-HGS, unsuccessful guidewire manipulation was responsible for 68.2% of procedural failures [21]. Several potential issues can arise including:

a) Guidewire shearing – this is a risk when the angle between the fine needle aspiration (FNA) needle and the guidewire is acute and can be prevented by positioning the echoendoscope tip in an upward angulation so that the needle access to the bile duct and subsequent guidewire passage is more tangential. The 'liver impaction technique' described by Ogura et al. [22] by withdrawing the fine needle tip into the hepatic parenchyma, can be also useful [22].

b) Penetration of guidewire into the hepatic parenchyma – gentle guidewire manipulation is mandatory to prevent this occurrence. Additionally, selection of a guidewire with a flexible tip but with sufficient stiffness is equally important to facilitate the subsequent passage of accessories after the initial puncture.

c) Guidewire passage into the peripheral bile duct – this can potentially be solved by utilization of a steerable access needle [23].

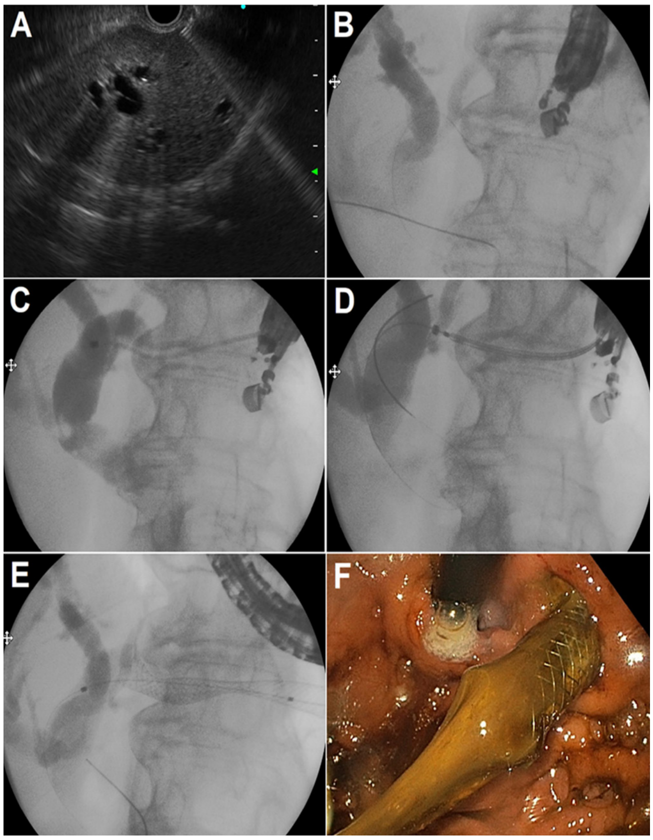

Fig. 2. EUS-guided hepaticogastrostomy performed in a jaundiced patient with tumor infiltration of the duodenum. First, an intrahepatic dilated biliary duct is identified and punctured with a 19-gauge needle (A), followed by bile aspiration, contrast injection for defining the anatomy of the biliary tree and guidewire negotiation and advancement over the stricture (B). Then, the needle is exchanged over-the-guidewire with a 6-Fr cystotome advanced with pure cutting current until the intrahepatic bile duct is reached (C), which is then exchanged again with a tubular partially covered biliary self-expandable metal stent, advanced over-the-guidewire (D) and deployed under radiologic control (E). At the end of the procedure, endoscopic control of the intragastric stent position is performed; its position is at a short distance below the cardia (F).

Following successful guidewire passage, the tract is then dilated with either electrocautery or mechanical devices. Self-expandable metal stents are mostly inserted with minor modifications to conventional stents such as the GIOBOR stent (Taewoong, South Korea) or Hanarostent (M.I.-Tech, South Korea) which have a covered intra-gastric and uncovered intra-biliary segment. The uncovered segment allows for stent anchorage within the biliary tree, avoiding the occlusion of small biliary radicles. However, other types of stents have been developed for this indication, and can be used in different regions, depending on their availability, such as tubular SEMSs with a spring-type stopper or a hook structure on the luminal side (Niti-S Spring Stopper Stent; Taewoong Medical; Hook stents; ZEON Medical), or thin tubular SEMSs loaded onto a thin tapered delivery system (HANAROSTENT Benefit; M.I.Tech) allowing for insertion without the need for electrocautery or prior tract dilation [24]. Prior to stent deployment, the correct position of the stent should be checked fluoroscopically. The intrahepatic portion of the stent is then slowly deployed with fluoroscopic control, followed by adjustments of the stent, if necessary. Finally, the intraluminal portion of the stent is deployed under endoscopic control, leaving at least a 2 cm long stent portion in the upper gastrointestinal tract in order to prevent intraperitoneal stent migration.

Endoscopic-guided Antegrade Stent Placement and Rendezvous Procedures

In these cases, the target bile duct is usually accessed with a 19-gauge FNA needle under real-time EUS guidance, followed by an injection of contrast to obtain a cholangiogram to better define the anatomy of the biliary tree and its ductal stenosis. Subsequently, the guidewire is gently advanced through the needle into the biliary tree and has to be negotiated downwards across the stenosis and/or ampulla and then coiled in the distal bile duct or the intestinal lumen.

In the rendezvous procedure, the target is usually the CBD and once the guidewire passes across the ampulla, the echoendoscope is carefully removed leaving the guidewire in place, and a duodenoscope is advanced alongside till reaching the papilla. Then, the guidewire is captured using a biopsy forceps or a polypectomy snare and pulled out through the working channel of the endoscope. Standard ERCP is then performed in a conventional manner. Cannulation alongside the guidewire is also performed by some operators.

For antegrade stenting, the extra-hepatic left side biliary tree is targeted as in HGS. After needle puncture, contrast injection, and passage of the guidewire, dilation of the newly created fistulous tract is performed using a dilation balloon or a small coaxial electrocautery (of 6 or 7 Fr) with pure cutting current. For metal stent insertion, the tract usually does not require dilatation after cystotome dissection. The biliary SEMS is advanced over the guidewire and deployed in the desired position, usually transpapillary. Radiologic and endoscopic control should be used for stent deployment, using the radiopaque markers of the SEMS to carefully monitor progression of stent deployment in order to achieve a correct final position.

Endoscopic Ultrasound-guided Gallbladder Drainage

Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) is an attractive option to achieve drainage in biliary obstruction due to pancreatic cancer (Fig. 3). A mandatory pre-requisite is patency of the cystic duct which should also not be in the vicinity of the tumor. This approach follows the steps of transmural stent insertion described above for draining the CBD and has been highly facilitated by the development of dedicated fully covered bi-flanged stents or electrocautery LAMS (EC-LAMS) [25].

Final Radiologic and Endoscopic Control

At the end of the procedure, radiologic control of the stent position and adequate drainage of the contrast in the gastrointestinal lumen and/or presence of air in the bile ducts need to be confirmed. The last step of the procedure involves also endoscopic control of the gastrointestinal side of the fistula, which is mandatory to confirm proper stent positioning, adequate biliary drainage, and to exclude ongoing bleeding.

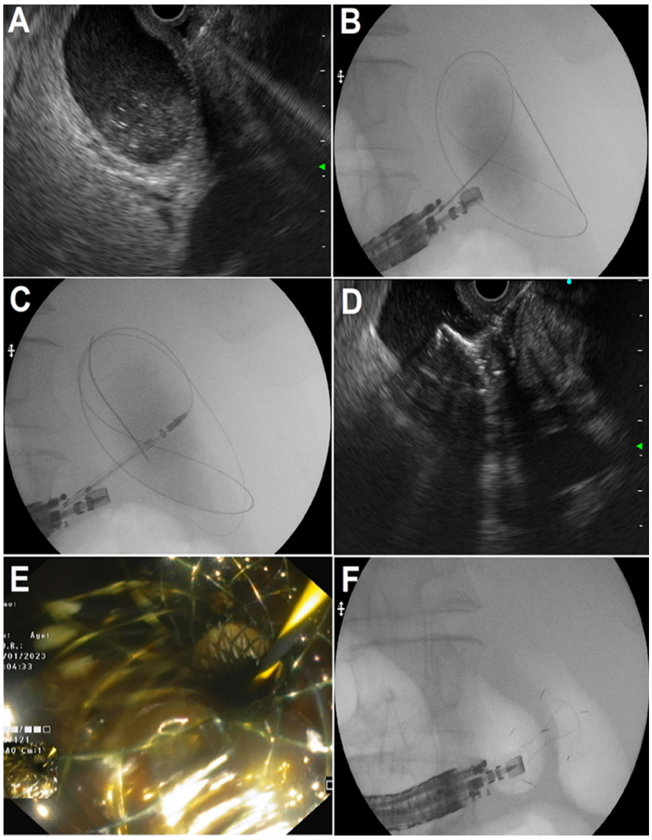

Fig. 3. EUS-guided gallbladder drainage for palliation of jaundice in a patient with peritoneal carcinomatosis from pancreatic cancer in which ERCP failed and an endosonographic window for draining the common bile duct could not be found. The gallbladder is accessed from the duodenal bulb under EUS guidance with a 19-gauge FNA needle (A), bile is aspirated, contrast is injected and a guidewire coiled inside the gallbladder (A and B), followed by over-the-guidewire EC-LAMS advancement using pure cut current (C), deployment of the distal flange under EUS guidance (D), stent retraction for achieving correct apposition, and then intra-channel proximal flange release. Endoscopic and radiologic control of the correct stent position is performed at the end of the examination (E, F).

Pre- and Post-operative Care and Follow-up

Prophylactic antibiotics given intravenously are routinely administered before and for at least 48 hours after the procedure [26]. Their use may be helpful in decreasing the incidence of sepsis, but no controlled studies on this matter are available. The preferred choices include third generation cephalosporins or fluoroquinolones.

Patients are kept fasting for at least 24 hours after the procedure, with resumption of the oral intake if they do not experience any procedural-related abdominal pain, signs of sepsis, or frank signs of stent dislocation. The clinical success of the procedure in patients with biliary obstruction is generally defined as a reduction in bilirubin of at least 50% at 2 weeks or below 3 mg/dL at 1 month [27]. The latter value allows chemotherapy to be started, when indicated. However, there is a subset of patients who fail to reach these values despite evidence of good drainage and in whom the proper therapeutic strategy remains elusive.

ADVERSE EVENTS

Common AEs that are reported during or at short-term after EUS-BD are gastrointestinal perforation, bile leakage (4%), bleeding (4%), stent malpositioning or migration (7.1%), cholangitis (4%), and abdominal pain (18%, usually reported as mild) [32]. Most of these AEs are either self-limited or can be managed conservatively. However, in a single center study on 101 procedures, six procedure-related deaths occurred mostly during HGS, five of which were among the initial 50 treated patients [28]. Moreover, there were also several procedural-related deaths reported in other studies [21]. However, significant morbidity and mortality tended to decrease with the experience of the operators [21]. In addition, the development of specifically designed EC-LAMS which has reduced the need for multiple accessories in a one-step procedure has further reduced AEs.

A frequently encountered long-term AEs in both EUS-CDS and EUS-HGS is stent occlusion, which leads to jaundice recurrence with endoscopic and/or radiologic evidence of biliary obstruction. Causes of stent occlusion include clogging of the stent, food impaction, and ingrowth or overgrowth by tissue hyperplasia or, less frequently, tumor. Reintervention is achieved by stent replacement or placement of a second stent within the existing one. Repeat procedures are usually more technically demanding after EUS-HGS than after EUS-CDS.

CLINICAL OUTCOME

Biliary drainage is mandatory prior to the administration of chemotherapy for locally advanced or metastatic pancreatic cancer with jaundice. For potentially resectable patients, biliary drainage is generally not recommended apart from the following circumstances: administration of neo-adjuvant chemotherapy, cholangitis, and delayed surgery generally related to co-morbidities requiring pre-operative workup or lack of operating theatre capacity. Another indication for biliary drainage even in operable patients is severe jaundice with very high serum bilirubin levels.

EUS-BD vs PTBD after ERCP Failure: What Is the Evidence?

Percutaneous transhepatic BD is widely performed worldwide but is associated with significant morbidity and mortality [29]. As such, an alternative method is preferable, and several studies have evaluated the role of EUS-BD in comparison to PTBD.

In an RCT including 66 patients, comparable clinical success was accompanied by a significantly lower incidence of AEs in the EUS-BD arm [30]. These results were further confirmed in a meta-analysis of nine studies including 483 patients, which demonstrated comparable technical success between the two procedures [31], but with EUS-BD found to be more cost-effective, as well as associated with a significantly higher clinical success [odds ratio (OR)=2.22), fewer post-procedural side effects (OR=0.23), and fewer need for reintervention (OR=0.13) than PTBD. In a more recent meta-analysis enclosing 10 articles (567 patients in the EUS-BD group and 564 patients in the PTBD group) [10], technical and clinical success rates were comparable between the two groups. However as pointed out in the previous meta-analysis, procedural AEs ($p=0.03$) and total AEs ($p<0.01$) occurred less frequently in the EUS-BD group.

Therefore, where EUS-BD expertise is available, this procedure should be preferred over PTBD, as recently stated in the European Society for Gastrointestinal Endoscopy (ESGE) guideline for interventional EUS [32]. Moreover, internal biliary drainage has other advantages over PTBD because it provides better absorption of nutrients by maintaining bile secretion in the gastrointestinal tract, thus obviating nutrient and electrolyte loss. Moreover, it avoids the social stigmata associated with the presence of an external drain and has a better effect on patient quality of life.

EUS-BD vs ERCP for Primary Biliary Drainage: What Is the Evidence?

Evidence from RCTs and retrospective trials assessing the role of EUS-BD in comparison to ERCP as a primary drainage modality has demonstrated comparable success rates and AEs [33-37]. Unfortunately, these studies may be underpowered due to inadequate sample size [38]. Despite this limitation, these studies have provided an essential insight into the utility of the primary role of EUS-BD in this clinical setting, instead of being predominantly a 'salvage' procedure. More importantly, pancreatitis is rarely seen in patients who have undergone EUS-BD, while there are AEs that are unique to EUS-BD such as bile leakage and peritonitis, which will likely decrease with better training and development of dedicated devices.

Three RCTs provided the best evidence in support of EUS-BD. Bang et al. [33] assessed only EUS-CDS in various stages of pancreatic cancer. There was no significant difference in the rates of technical success (90.9% vs 94.1%, $p = 0.67$), treatment success (97% vs 91.2%, $p = 0.61$), or reinterventions (3.0% vs 2.9%, $p = 0.99$) between EUS-BD and ERCP cohorts, respectively. Endoscopic ultrasound-guided BD did not impede or make subsequent pancreaticoduodenectomy more difficult in 5 of 33 patients (15.2%) who underwent the procedure [33].

Park et. al. [35] conducted a single center RCT comparing EUS-BD and ERCP with 15 patients included in each arm.

Technical (EUS-BD 93% vs ERCP 100%, p=1) and clinical success (EUS-BD 100% vs ERCP 93%, p=1) were similar. The authors noted that stent dysfunction following EUS-BD was mainly due to food impaction and stent migration as opposed to tumor ingrowth noted with ERCP [35].

Paik et. al. [34] evaluated the role of EUS-BD in the primary palliation of malignant distal biliary obstruction in a multi-center setting. In this study, the authors utilized a tubular SEMS with a 15 mm uncovered segment positioned inside the biliary tree to favor anchoring and avoid blockage of the small radicals and a 35-85 mm length covered segment that extented transmurally to prevent bile leak. This stent was utilized for both CDS (32 patients) and HGS (32 patients). Reported technical and clinical success were similar between the two groups (93.8% and 90% for EUS-BD and 90.2% and 94.5% for ERCP). Lower rates of overall AEs (6.3% vs 19.7%, p=0.03) including post-procedure pancreatitis (0 vs 14.8%, p=0.001) and need for reintervention (15.6% vs 42.6%, p=0.001) was noted with EUS-BD. Stent patency rate was longer (85.1% vs 48.9%, p=0.001) and quality of life (QOL) preserved in patients who underwent EUS-BD as compared to the ERCP group.

A systematic review and meta-analysis conducted by Han et. al. [37] including 3 RCTs and 7 retrospective studies for a total of 756 patients, assessed the utility of EUS-BD for primary drainage compared to ERCP [37]. Cumulative technical and clinical success rates were high for both procedures (94.8% and 93.8% for EUS-BD versus 96.5% and 95.7% for ERCP). Cumulative AEs rates were similar (16.3% for EUS-BD versus 18.3% for ERCP). In the subgroup analysis including only patients without duodenal invasion, cumulative technical and clinical success, and AEs were comparable between EUS-CDS and ERCP.

Based on all results of RTCs and meta-analysis, the ESGE guideline for interventional EUS recommended ERCP as a primary therapeutic intervention to relieve jaundice in patients with biliary obstruction. EUS-BD could be utilized as a primary treatment in expert centers for patients with unresectable malignant disease [32].

EUS-CDS or EUS-HGS?

Most of the data comparing EUS-CDS and EUS-HGS for EUS-BD come from observational retrospective studies, and as also described in RCTs and meta-analyses, reported comparable technical and clinical success rates between the two techniques. Data from a few studies directly comparing the two techniques in 329 and 303 patients, also found comparable high technical and clinical success rates (96% and 87.5% for EUS-HGS versus 94.7% and 88.4%% for EUS-CDS) [39-41] with no significant difference in procedure-related AE rates [42].

A recent multicenter study involving 12 centers with 14 years of follow-up [43] compared the two techniques. A total of 182 patients were included, of whom more than half (54.3%) had pancreatic cancer. Superior long-term stent patency defined as a need for repeat stenting 30 days post-procedure was observed in patients who underwent EUS-CDS, which however was associated with a higher rate of AEs. A meta-analysis by Li et.al. [44] involving 12 studies with 693 patients concluded that both techniques have equal technical and clinical success. They also noted shorter procedural times and fewer early AEs when EUS-CDS was performed [44].

Despite the above-reported results, the ESGE guideline recommends utilization of EUS-CDS over EUS-HGS due to the lower rates of AEs [32]. This recommendation, however, was rated as weak and of low quality. Thus, it is still unclear which EUS-BD approach should be used preferentially in these patients, and usually, the use of one over the other relies on the preference of the endosonographer. Besides, EUS-CDS and EUS-HGS may have different indications depending on the anatomic situations as well as on the cause of biliary obstruction. For example, a pancreatic cancer with biliary obstruction close to the liver hilum or presenting with duodenal malignant stenosis is an indication for EUS-HGS, while the presence of massive liver metastases to the left liver usually represents an indication for EUS-CDS.

Is Surgery after EUS-BD Feasible?

This is an important question that has limited the utilization of EUS-BD in patients with resectable and unresectable disease undergoing neo-adjuvant chemotherapy because of the concerns of making surgery more difficult or impossible. Available data indicate that EUS-BD, when performed prior to curative surgery for pancreatic adenocarcinoma, is safe [45-48]. Tyberg et. al. [48] conducted an international, multicenter retrospective comparative study of 145 patients who underwent hepatobiliary surgery after having undergone EUS-BD or ERCP in 6 tertiary care centers (EUS-BD 58, ERCP 87). Surgical technical and clinical success were significantly higher in the EUS-BD group compared with the ERCP group (97% vs. 83%, 97% vs. 75%). Adverse event rates were similar in both groups: EUS-BD (n=10, 17%) and ERCP (n=23, 26%). The total length of hospital stay was significantly higher in the ERCP group (19 vs. 10 days, p=0.0082). Thus, it appears that EUS-BD can be safely utilized also in resectable patients and in those who can become resectable after neoadjuvant chemotherapy. Moreover, if retrospective data from Tyberg et al. [48] is confirmed in prospective and/or randomized controlled trials, EUS-BD can become the first treatment of choice in these patients due to the lower rates of endoscopic reinterventions, shorter duration between endoscopy and surgical intervention, higher rates of surgical clinical success, and shorter length of hospital stay after surgery as compared to those who undergo ERCP.

The Evidence for EUS Guided Gallbladder Drainage

Two retrospective studies have evaluated the results of EUS-GBD after ERCP and EUS-BD failure in the setting of DMBO, mostly caused by a pancreatic tumor. The first study by Imai et al. [49] involved 12 patients who underwent EUS-GBD using serial accessories to puncture and dilate the fistulous tract before placement of a partially covered biliary SEMS in conjunction with a coaxial plastic double pigtail stent in 7 (58%) of cases. Technical and clinical success were met in 100% and 91.7% of cases, while two (16.7%) patients developed AEs (peritonitis and failure of jaundice resolution due to disease progression), and an additional one patient (8.3%) suffered from stent dysfunction related to entrapment of the cystic duct by the growing tumor. The median survival of patients was 105 days which did not allow for assessment of the long-term patency of the stent utilized for EUS-GBD.

In the second multicenter retrospective study by Issa et al. [25], the 28 involved patients represented 0.11% and 7.3% of the 24,720 and 384 patients who underwent attempted ERCP or EUS-BD for MDBO during a 6-year study period [25]. Drainage was performed in all but two patients using LAMS. Technical and clinical success were achieved in 100% and 93% of cases. Adverse events occurred in 5 patients (18%) after 24 hours and included 3 cases of acute cholecystitis due to food impaction of the stent that was managed endoscopically and 2 cases of delayed bleeding in patients who were on anticoagulation. Median follow-up was 33 months and no additional patients required reintervention for recurrent jaundice or other adverse events. Stent patency at >30 days was 82%.

The results of this second study are very promising, especially regarding the duration of follow-up that extended over a 2-and-half-year period. If confirmed in larger multicenter and comparative studies, this approach can become a very important technique in cases of DMBO [50]. At present, however, the method of EUS biliary drainage through the gallbladder is likely to be reserved as a 'salvage' method when ERCP or other EUS-BD approaches fail.

CURRENT PLACE

Current guidelines advocate ERCP as the primary method of choice for malignant distal biliary obstruction [32, 51]. Endoscopic ultrasound-guided BD, utilized as a salvage method has been demonstrated to be safer than PTBD with fewer AEs [10]. The choice of procedure performed for EUS-BD is dependent on multiple factors including the site of obstruction, accessibility to the papilla (absence or presence of duodenal obstruction, surgically altered anatomy), and patient performance status/ clinical fitness to undergo an extended procedure. At present, the accepted indications for EUS-BD drainage for malignant CBD obstruction include [52]:

- failed standard ERCP performed in experienced centers;
- altered upper gastrointestinal anatomy in the context of previous surgery making access to the papilla impossible;
- failure to reach or access the papilla secondary to deformation or malignant involvement of the pylorus-duodenal region;
- as a primary drainage procedure in expert centers for patients with unresectable tumor.

Endoscopic ultrasound-guided BD is contraindicated in severe coagulopathy, presence of intervening blood vessels at the access site, significant ascites, and insufficiently dilated bile ducts. Importantly, EUS-DB should only be performed by operators highly trained in pancreaticobiliary endoscopy, with mandatory 24/7 interventional radiology and surgical backup, given the possibility of severe AEs associated with this procedure [32].

FUTURE PERSPECTIVE

It is envisaged that in the future, EUS will likely supersede ERCP in achieving biliary drainage in the setting of pancreatic cancer presenting with DMBO, independent of the resectability status and accessibility to the papilla. To achieve this goal, there must be an emphasis on the development of dedicated devices specific to EUS. There is also a need to set the minimum requirements for training in EUS-BD before being able to perform the procedure unsupervised, given its technical complexity and the potential for severe AEs. There is agreement that training in interventional EUS should be performed together with training in ERCP. However, the minimal number of procedures needed in order to become proficient in EUS-BD needs to be better specified.

The possibility to perform a 'one-stop shop' approach has been proposed where tissue acquisition and drainage can be performed with the same endoscope in a single session [53]. Tissue acquisition will be performed with an FNB needle where samples are acquired for the following: confirmation of diagnosis by an onsite pathologist and molecular laboratory analysis for cancer subtyping. Subsequently, biliary stenting can proceed with dedicated fully covered metallic self-expandable biliary stents mounted on cautery-enhanced delivery devices.

CONCLUSIONS

There is no doubt that EUS-BD has a huge potential to achieve effective BD in patients with pancreatic cancer, with longer stent patency due to its' placement away from the tumor site. Current evidence would support similar efficacy when compared with ERCP and found it to be superior to PTBD. The profile of procedure-related AEs seem is also more favorable than ERCP or PTBD, but the possibility of severe AEs exists. To recommend EUS-BD over ERCP as a primary technique of biliary drainage, there should be further development of dedicated accessories, a better standardization of the procedure and availability of a more robust evidence-base.

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