ORIGINAL PAPERS

Endoscopic biliary drainage in unresectable biliary obstruction: the role of endoscopic ultrasound-guidance in a cohort study

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ABSTRACT

Background and study aims: the use of endoscopic ultrasound-guided biliary drainage (EUS-BD) has increased in cases of failed endoscopic retrograde cholangiopancreatography (ERCP) and there are some concerns. The main aim of the study was to determine the role of EUS-BD in a palliative case cohort. The secondary aim was to compare the efficacy, safety and survival of EUS-BD and ERCP procedures.

Patients and methods: this was an observational study at a single tertiary institution, with a consecutive inclusion from January 2015 to December 2016. The inclusion criteria were unresectable tumors of the biliopancreatic region with an indication of BD. Statistical comparison analysis was performed between the ERCP and EUS-BD groups. The incidence between groups was compared using the Chi-square and Fisher exact tests. The log rank test was used to compare the risk of death.

Results: fifty-two cases with an indication of palliative BD were included in the study. Transpapillary drainage via ERCP was possible in 44 procedures and EUS-BD was required in eight cases; 15.4% of the cohort and seven using lumen apposing metal stent (LAMS). The technical and clinical success of global endoscopic BD was 100% and 88.5% (ERCP: 84.6% and 78.9%; EUS-BD: 100% and 62.5%, respectively). Pancreatitis was the most frequent adverse event (AE) in the ERCP group (9.62%) and bleeding in the EUS-BD (25%). There were fatal AEs in ERCP (1.9%) and EUS-BD (25%) cases. Patient survival was higher with ERCP transpapillary stents compared to EUS-guided stents, which was statistically significant (p = 0.007).

Conclusions: the requirement of EUS-BD in palliative biliopancreatic pathology is not marginal. EUS-BD is associated with a lower survival rate and a higher rate of fatal AE, which argues against its use as a first choice procedure.

Key words: Biliary drainage. Endoscopic ultrasound. Endoscopic retrograde cholangiopancreatography. Pancreatic cancer. Biliopancreatic diseases.

INTRODUCTION

Transpapillary access by endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice for biliary drainage (BD) in patients with unresectable malignant tumors of the biliopancreatic region (1-4). However, this procedure is not always successful as 4% to 16% of ERCPs fail due to the impossibility of biliary cannulation (5-7). In patients with biliopancreatic neoplasias, the main reasons for failure are tumor invasion and the inability to reach the papilla due to duodenal obstruction. Percutaneous transhepatic biliary drainage (PTBD) has been used in cases where ERCP fails. However, this technique is associated with significant morbidity and a lower quality of life due to the external drainage.

In recent years, endoscopic ultrasound-guided biliary drainage (EUS-BD) has been increasingly used as an alternative when ERCP fails. Recently, a great number of studies relating the experiences of different centers have been published. However, the correct strategy for EUS-BD has not been clearly established (8). Despite the doubts about its efficacy and safety, the increased use of EUS-BD has even led to the proposal of this procedure as a first-line treat-

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ment for patients with distal malignant biliary obstruction (9). Nevertheless, the optimal proportion of patients with malignant biliopancreatic disease in whom ERCP fails and EUS-BD is required is unknown. In addition, there are obvious differences from country to country (4). Furthermore, the recent innovations in this field such as lumen apposing metal stents (LAMS) have helped to expand the role of EUS-BD as an attractive option to simplify some technical steps. However, some serious concerns exist related to the safety and real clinical success of this option (10).

The main aim of this study was to determine the role of EUS-BD in palliative patients with biliopancreatic tumors, which is the most frequent scenario in our setting. The secondary aims were to compare the efficacy and safety of the endoscopy BD approach and the survival of patients with ERCP-transpapillary stents *vs* EUS-guided transmural stents.

MATERIAL AND METHODS

This was an observational cohort study at a single tertiary-care public institution in Barcelona, in an endoscopy unit with a high volume of ERCPs (more than 700 per year). All patients with biliary obstruction due to unresectable or inoperable malignant tumors, with indication of BD, were consecutively recruited into the study and data was stored in a dedicated database. Exclusion criteria were a benign pathology, a previous BD, resectable borderline cancer, severe coagulopathy (protombin time > 1.5), severe thrombocytopenia (platelet count < 50 x 10^9/l) and a lack of data or follow-up. The inclusion period was 24 months (from January 2015 through December 2016), with a follow-up period of at least one year after the procedure.

The tumors were catalogued as unresectable depending upon the presence of metastatic disease and the vascular invasion, according to the findings of imaging tests (computed tomography, magnetic resonance imaging or EUS). In cases of pancreatic cancer, the consensus of the National Comprehensive Cancer Network was followed (11). The patients were classified as inoperable after the individualized evaluation of each case by a multidisciplinary committee, according to the general clinical condition of the patient, the baseline pathologies and the performance status.

The study was approved by the hospital institutional review board and all patients provided written informed consent. Furthermore, no financial support or free devices were received.

Procedures

Two expert interventional endoscopists, with an experience of more than 100 EUS-guided transmural procedures, performed the procedures. Prophylactic doses of intravenous antibiotics were administered before all procedures, which were performed with an anesthesiologist who provided deep sedation.

The transpapillary approach by ERCP was the procedure of choice in all patients for BD. EUS-DB was considered in cases of a failed ERCP that was due to the inability to reach the papilla or biliary cannulation failure. In the majority of cases, this was performed directly after the failed ERCP in the same session, or in a second programmed procedure if there was any doubt about the palliative attitude, potential resectability or nature of the lesion.

A duodenoscope was used for the ERCP procedures (TJF-145, TJF-Q180V, Olympus, Europe), using the single-operator wire-guided cannulation technique with a standard papillotome plus short-guidewire (Autotome™; 0.035 inch jagwire Boston Sc; 0.025 visiglide). In cases of difficult biliary cannulation due to papilla tumor involvement, a precut needle-knife (MicroKnife™ XL, triple-lumen, Boston SC) or transpancreatic sphicterotomy were considered, which was at the discretion of the endoscopist. The transpapillary stents were self-expandable metal stents (SEMS) or plastic stents in cases of hilar cholangiocarcinoma. The choice of the type (uncovered, partially covered, or fully covered) and size was at the discretion of the endoscopist.

A therapeutic linear echoendoscope (GF-UCT140 or GF-UCT180, Olympus, Europa, or EG-530 UT2, Fujifilm, Tokyo, Japan) was used in EUS-BD procedures. The procedure chosen for performing the EUS-BD was the direct transmural stenting, using the choledochoduodenostomy (CDS) approach as the method of choice and considering the hepatogastrostomy (HGS) in case of non-accessible papilla. A fully covered LAMS was used in all CDS cases (Hot AXIOS™; 6 or 8-mm x 8-mm; Boston Scientific, MA, USA) and a HGS case was performed employing a plastic stent. An example of an EUS-guided BD using LAMS for a pancreatic tumor is shown in figure 1.

Post-procedure care and follow-up

In accordance with the protocol of our center, there was a minimum hospital stay of 24 hours with a blood analysis. On discharge, patients were followed up in outpatient clinics between two and four weeks after the procedure, in order to assess the clinical success of the procedure. Subsequently, patients received oncological or palliative treatment according to the criteria of the Oncology Department and the Palliative Care Unit. Patients were followed up during a period of at least one year after the procedure in order to analyze the results of the different endoscopic approaches such as stent permeability.

Definitions

Technical success was defined as a successful stent placement at the intended position determined by endoscopy and fluoroscopy. Clinical success was defined as a reduction in bilirubin by 50% at 2-4 weeks after stent placement, meaning that the biliary stent was functional. Procedure time was defined from the insertion of the endoscope to its removal. Procedure safety was considered within the first two weeks. Adverse events (AE) were defined and graded according to the ASGE lexicon severity grading system (12).

Statistical analysis

Categorical variables were described using the mean of the number of cases and percentages with respect to the total by category. Continuous variables were described by the

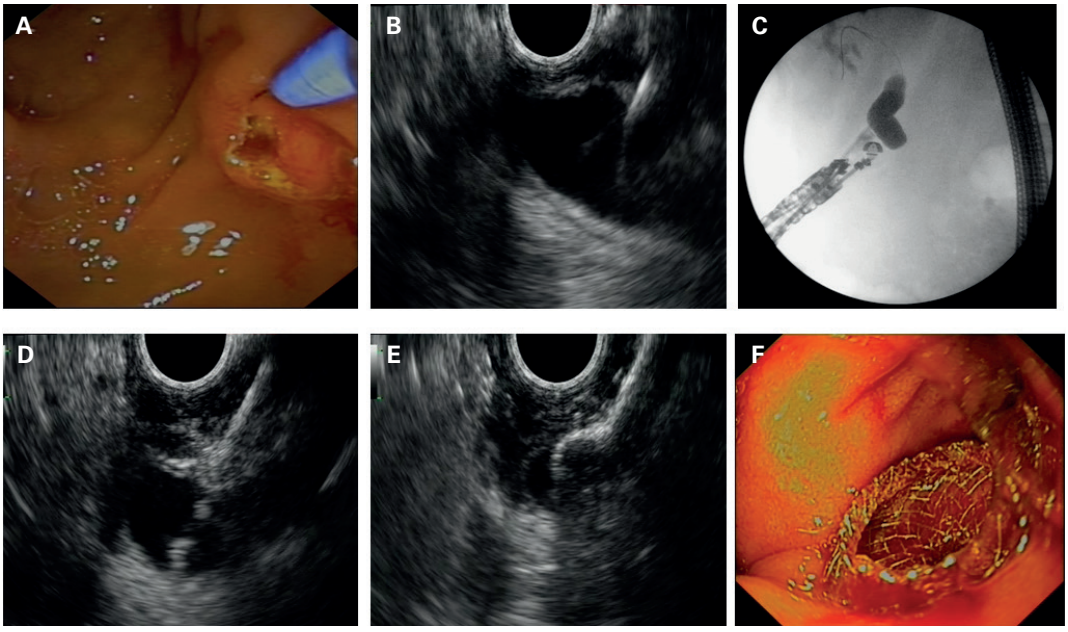

Fig. 1. *Example of EUS-guided biliary drainage in an unresectable pancreatic tumor. A. Duodenal papilla with tumor invasion signs, in a failed ERCP case. B. Common bile duct access by EUS-guided puncture. C. Cholangiography with a dilated common bile duct and a malignant distal stricture. D. EUS-guided transmural bile duct drainage using a cautery-tipped stent delivery system (Hot-AXIOS™). E. EUS image of a lumen-apposing metal stent delivered inside the common bile duct. F. The proximal end of a biliary LAMS located at the duodenum.*

mean of the number of cases, the mean and the standard deviation or the median and the interquartile range (IQR).

The incidences of clinical and technical success and AEs in the two groups of procedures (ERCP and EUS-BD) were compared using the Chi-square test or Fisher's exact test. Time until death was assessed using the Kaplan-Meier estimator. The log rank test was used to compare the risk of death between the study groups. A retrospective statistical analysis was performed. The level of statistical significance was set at 0.05 and the R version 3.4.0 for Windows statistical software was used for data analysis.

RESULTS

Role of EUS-BD

A total of 52 patients with unresectable or inoperable malignant tumors of the biliopancreatic region underwent an endoscopic BD during the study period. In all cases, an attempt was made to perform a transpapillary BD via ERCP. Figure 2 shows a flowchart with the results of accessibility to the papillary area, the biliary cannulation rates and the assignment of patients to each BD modality. EUS-BD was required in 15.4% of patients in the cohort due to six cases of tumoral papilla and two cases of a non-accessible papilla. The CDS approach was performed in 87.5% of cases and the HGS in 12.5%.

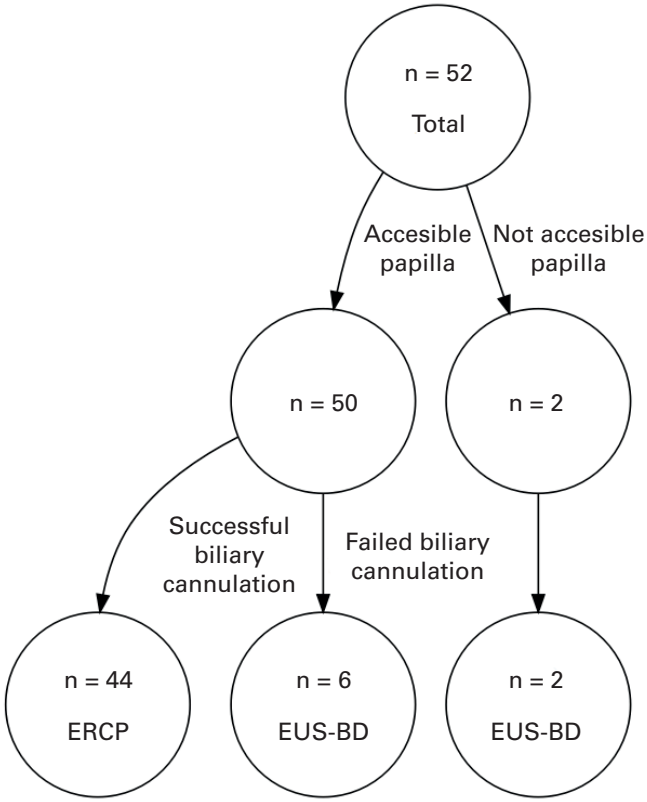

Fig. 2. *Flowchart of all endoscopic biliary procedures.*

Technical aspects

Transpapillary biliary cannulation with a sphincterotome and guidewire was used in 50% of cases, a needle-knife precut in 36.4% and a transpancreatic sphincterotomy in 13.6%. The transpapillary stent types used were fully covered SEMSs

Supplementary Table. *Procedure details of the EUS-guided transmural biliary drainage cases*

Case	Sex	Age	Tumour	Papilla	EUS-BD approach	Stent	AE (in 2 weeks)	Survival (days)
1	M	63	Pancreas	Tumoral	CDS	HXS 06-08	Yes	6
2	F	58	Pancreas	Tumoral	CDS	HXS 06-08	No	56
3	F	79	Urothelial/kidney	Not accessible	CDS	HXS 06-08 Enteral SEMS	No	163
4	F	80	Pancreas	Tumoral	CDS	HXS 06-08	No	6
5	M	86	Pancreas	Tumoral	CDS	HXS 08-08 + DPT 10 Fr, 5 cm	No	18
6	F	62	Pancreas	Tumoral	CDS	HXS 06-08 + DPT 10 Fr, 5 cm	No	161
7	F	83	Pancreas	Tumoral	CDS	HXS 06-08 + DPT 10 Fr, 5 cm	Yes	1
8	F	70	Pancreas	Not accessible	HGS	Plastic 7 Fr, 9 cm	No	124

AE: adverse event; CDS: choledochoduodenostomy; DPT: double-pigtail stent; EUS-BD: endoscopic ultrasound guided biliary drainage; M: male; F: female; HGS: hepatogastrostomy; HXS: Hot-AXIOS™ stent; SEMS: self-expandable metal stent.

(15.9%), partially covered SEMSs (72.7%), uncovered SEMSs (2.3%) and plastic stents (9.1%) (WallFlex™, Advanix; Boston SC, MA, USA). The details of the EUS-guided transmural biliary drainage procedures are presented in the supplementary table.

Efficacy and safety of ERCP and EUS-BD

Table 1 summarizes the technical and clinical success, the AEs and their degree of severity in the ERCP and EUS-BD approach. No statistically significant differences were detected between the groups. Excluding the not-accessible papilla cases, the technical and clinical success of the ERCP was slightly higher than that reflected in the table (88% and 82%, respectively). The global technical and clinical success of the endoscopic BD (ERCP plus EUS-BD) was 100% and 88.5%, respectively.

Table 1. *Technical success, clinical success and adverse events rate of ERCP and EUS-BD procedures*

	ERCP n = 52*	EUS-BD n = 8	p value
Technical success, n (%)	44 (84.6)	8 (100)	0.582
Clinical success, n (%)	41 (78.9)	5 (62.5)	0.374
Adverse events†, n (%)	8 (15.4)	2 (25.0)	0.610
Pancreatitis rate, n (%)	5 (9.6)	0 (0)	-
Bleeding rate, n (%)	2 (3.8)	2 (25)	-
Infection rate, n (%)	1 (1.9)	0 (0)	-
Severity of adverse events, n (%)			0.128
Mild	4 (7.7)	0 (0)	-
Moderate	3 (5.8)	0 (0)	-
Fatal	1 (1.9)	2 (25)	-

*All cases, including non-accessible papilla. †Adverse events within the first two weeks.

Pancreatitis was the most frequently observed AE in the ERCP group (9.62% of cases, 80% mild), whereas bleeding (25%) was the most frequent in the EUS-BD group. In the ERCP group, most of the AEs were mild (7.7%) and fatalities were unusual (1.9%). In contrast, all AEs observed were fatal in the EUS-BD group (25%). However, this difference was not statistically significant. No intra-procedure AEs were reported and all appeared during the post-procedure period.

Comparative patient survival

In order to assist in the assessment of the equivalence of the two groups, table 2 summarizes the demographic data and the characteristics of the biliopancreatic tumors in ERCP transpapillary stents and EUS-guided stents. No significant differences were found with regard to the clinical parameters such as ASA, albumin, bilirubin levels or the existence of metastasis. Table 3 summarizes the procedure details and the outcomes of the different stent approaches. The procedure time was slightly longer in the transpapillary group and the functional success was higher compared to the EUS-guided transmural stents (93.2% *vs* 62.5%). This difference was statistically significant (p = 0.04).

Patient survival was longer with ERCP transpapillary stents compared to EUS transmural stents and this difference was statistically significant, with a median survival of 203 days *vs* 37 days (p = 0.007). Survival was recalculated after excluding the cases of fatal AE in order to rule out the influence of the AEs on survival. A statistically significant longer survival rate was maintained in the group with the stents placed via ERCP (median survival of 203 days *vs* 90 days, p = 0.047). Figure 3 shows the Kaplan-Meier curves of survival, compared with the log rank test.

Table 2. *Comparative demographic data and characteristics of the biliopancreatic region tumors, transpapillary* vs *transmural stents*

	Transpapillary nstents n = 44*	EUS-guided stents n = 8	p value
Age, mean (SD), years	69.9 (10.8)	73.0 (10.9)	0.482
Sex, n (%)			0.262
Female	22 (50)	6 (75)	-
Male	22 (50)	2 (25)	-
ASA, n (%)			0.249
I	2 (4.55)	0 (0)	-
II	19 (43.2)	1 (12.5)	-
III	21 (47.7)	7 (87.5)	-
IV	2 (4.55)	0 (0)	-
Bilirubin, median (Q1; Q3) mg/dl	12.3 [3.39;21.4]	15.6 [10.6;18.4]	0.577
Albumin, median (Q1; Q3) g/dl	3.3 (2.65; 3.78)	3.15 [2.98;3.37]	0.611
Clinical manifestation, n (%)			0.892
Obstructive jaundice	32 (72.7)	7 (87.5)	-
Acute cholangitis	4 (9.09)	1 (12.5)	-
Cholestasis	5 (11.4)	0 (0)	-
Constitutional syndrome	2 (4.55)	0 (0)	-
Abdominal pain	1 (2.27)	0 (0)	-
Tumors, n (%)			0.371
Pancreas	34 (77.3)	7 (87.5)	-
Cholangiocarcinoma	7 (15.9)	0 (0)	-
Others†	3 (6.8)	1 (12.5)	-
Metastatic disease, n (%)			0.458
Yes	20 (45.5)	5 (62.5)	-
No	24 (54.5)	3 (37.5)	-
Unresectable tumors, n (%)	40 (90.9)	8 (100)	1.000
Inoperable patients, n (%)	4 (9.09)	0 (0)	1.000

ASA: American Society of Anesthesiologists physical status classification. *Excluding the failed ERCP cases. †Other tumors, including biliopancreatic involvement due to colorectal cancer, urothelial/kidney cancer and osteosarcoma.

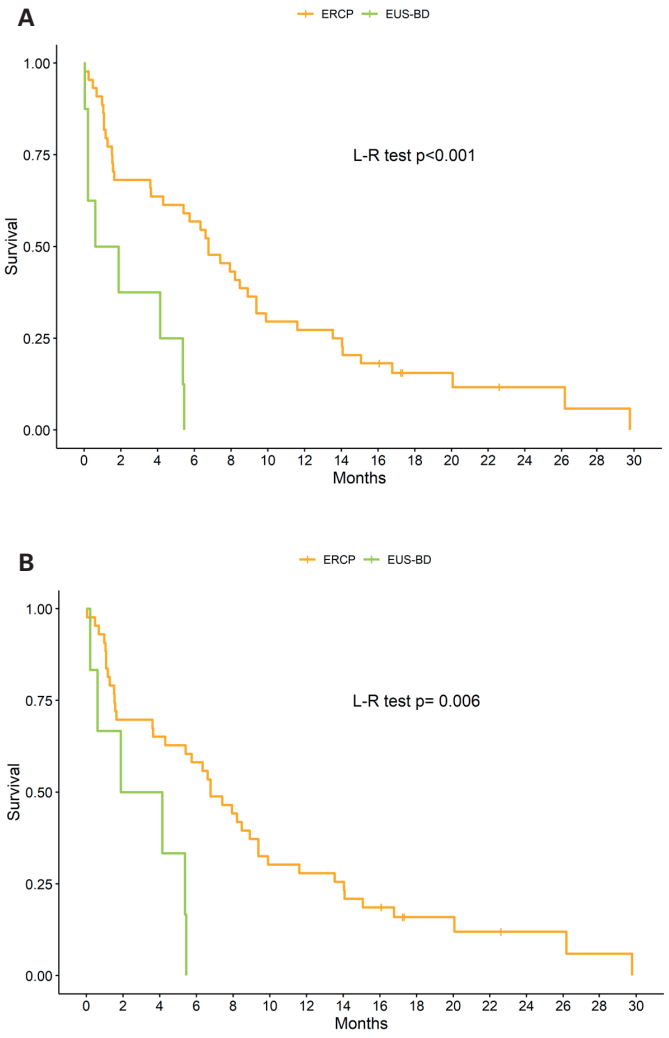

Fig. 3. *A. Kaplan-Meier survival curve of the time until death in the two groups, compared with the log rank test. B. Kaplan-Meier survival curve of the time until death in the two groups, compared with the log rank test and excluding fatal adverse events.*

Table 3. *Procedure details and outcomes of the transpapillary ERCP stents compared with the EUS-guided stents*

	ERCP transpapillary stents n = 44*	EUS-guided stents n = 8	p value
Procedure time, mean (SD), minutes	40.4 (12.4)	29.2 (11.0)	0.105
Clinical success, n (%)	41 (93.2)	5 (62.5)	0.040
Number of drainage interventions required, mean (SD)	1.39 (0.92)	1.25 (0.46)	0.533
Number of cases requiring re-intervention, n (%)	9 (20.4)	2 (25)	-
Survival, mean (SD), days	250 (224)	67 (71) [0.20; 4.44]	< 0.001
Survival, median (Q1; Q3) days	203 (46; 410)	37 (6; 133) [0.20; 4.44]	0.007
Survival, mean (SD), days†	256 (224)	88 (71) [0.20; 4.44]	0.001
Survival, median (Q1; Q3) days†	203 (47; 414)	90 (28; 152)	0.047

*Excluding the failed ERCP cases. †Excluding fatal adverse events.

DISCUSSION

Palliative BD, which is required in patients with unresectable malignant biliopancreatic tumors, is a demanding procedure. Transpapillary access via ERCP continues to be the procedure of choice. However, despite the development of new instruments and devices for performing advanced cannulation techniques, the rate of failed ERCP in these patients is not negligible (4). In recent years, EUS-BD has been proposed as an option to increase the endoscopic BD rate when ERCP fails.

Several EUS working groups have considered EUS-BD as a priority research topic, in an effort to accelerate its development and standardize the procedure (13). In recent years, a large number of studies have been reported with the aim of establishing the role of EUS-BD in the clinical practice and compare the effectiveness and safety of its different modalities. Despite the enthusiasm associated with this technique, the recently updated guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) still recommend restricting the use of EUS-BD to cases where standard ERCP techniques have failed (strong recommendation, low quality evidence) (4). Due to this lack of available evidence, we feel that the implementation and extended use of EUS-BD must be evaluated with caution. Furthermore, this must also be supported by strong evidence, in terms of safety and effectiveness, combined with an adequate comparison with the alternatives already available.

Holt et al. published their experience with the aim to determine how often EUS-BD is really needed in a tertiary-level care center. The overall ERCP failure rate was 1.7% in 524 cases of native papilla and there was an EUS-BD indication in 0.6% of cases (7). Along the same lines, Tonozuka et al. reported the need for EUS-BD in only 3% of a total of 634 cases from a referral center in Japan (14), while Nakai et al. reported a similar rescue EUS-BD rate of 3.1% (15). In our unit, the failed biliary cannulation rate was around 2.3% in native papilla, similar to reported experiences (16). According to the data reported from referral centers, the need for EUS-BD is quite low. Furthermore, serious AEs may occur and should therefore not be used as a substitute for a limited ERCP technique. In addition, the initial aim should be the perfection of ERCP skills.

Unlike the aforementioned series, this present cohort only included patients with malignant biliopancreatic obstruction, meaning a more difficult biliary cannulation due to the tumoral papilla or non-accessible duodenum. Thus, the need for an EUS-guided technique as a rescue option after an ERCP failure was higher (15.4%), which may explain the more demanded use of EUS-BD.

The use of EUS-BD to date in our center has been performed in individualized cases with rigorous selection criteria. Its use in benign pathologies is well-selected with prior agreement of a multidisciplinary committee. In malignant pathologies, EUS-BD is mainly considered in palliative scenarios. However, the general tendency at our center is to avoid EUS-BD in patients who may be potential candidates for surgical treatment. This is due to the fact that there is some controversy regarding how an EUS-guided transmural BD might alter a potential surgical technique.

The EUS-BD efficacy rates achieved in this study may be distant from some other studies. Three meta-analyses reported that EUS-BD had a clinical success rate of 87-94% (17-19) and a recent review evaluated the feasibility of LAMS in EUS-BD technique, with a clinical success rate of 98.9% (10). However, it is important to note that these data usually come from retrospective case-series studies. The risk of publication bias cannot be excluded and these results should be interpreted with caution. In addition, this technique is not standardized and there is a wide variability of results between centers and a lack of randomized clinical trials to evaluate actual efficacy and safety. The global EUS-BD clinical success rate of this study was acceptable. Furthermore, in our experience, this procedure has a more defined clinical role as a rescue maneuver after a failed ERCP in the same session. This is mainly in cases of palliative biliary drainage and in well-selected benign biliopancreatic scenarios (16,20).

Kawakubo et al. compared EUS-guided CDS and transpapillary BD as first-line procedures in malignant obstructions in a pilot study, with an equivalent clinical success and overall AE rate (9). Post-procedural pancreatitis was only observed in the transpapillary group and therefore, they concluded that an EUS-guided BD approach would be feasible as a first-line treatment. The potential risk of AEs associated with EUS-BD is well known and was well reflected in recent meta-analyses with reported AE rates of 17 and 23% (17,18). In our opinion, this means that EUS-BD should not be recommended as a first-line procedure and its use is restricted to failed ERCP and well-selected cases at expert centers.

In this cohort, there were no statistically significant differences in the comparison of the overall AE rates. The EUS-BD AE rate was 25%, which is similar to the results of the previously reported meta-analysis. However, the mortality rate was higher. This could be explained as an overestimate due to the make-up of our cohort, which consisted of patients with advanced-stage cancers and a poor prognosis. Thus, resulting in a limitation of therapeutic efforts in the management of AEs by avoiding invasive procedures.

With regard to the survival results obtained in our study, the patients with transpapillary stents via ERCP had a statistically significant longer survival compared to the patients with EUS-guided stents. The explanation seems to lie in the stent design, as a transpapillar SEMS via ERCP has a tubular design that offers more physiological drainage, whereas the majority of deployed transmural stents via EUS-BD were LAMS, which has a less anatomical design and associated risks related to the possibility of occlusion. Thus, the question as to whether a double-pigtail stent within the LAMS is recommended to prevent self-occlusion is left open (21).

The appearance of doubts concerning EUS-BD *vs* PTBD may be common in clinical care. A recent meta-analysis found that clinical success was similar with the two techniques, although EUS-BD had a lower AE rate (22). In addition, Khashab et al. observed that EUS-BD had a lower need for re-interventions and lower cost compared to PTBD (23). However, it should be noted that all these data were reported by endoscopists and thus, these comments should be interpreted with caution.

The limitations of this study include a limited number of cases, a retrospective analysis (possibility of loss of cases) and a lack of knowledge about the role of LAMS in the EUS-BD. Questions such as the ideal LAMS size, the role of double-pigtail within LAMS and the actual clinical success and safety remain unanswered. At the same time, it is important to highlight the homogeneity of our cohort, the consecutive inclusion and an internal protocol from an experienced single center.

In conclusion, the need for EUS-guided transmural BD in palliative malignant biliopancreatic pathology is not negligible. In our opinion, the potential severity and the AE rate of EUS-BD suggests that this approach should not be used as the initial modality and its role should be restricted to cases of ERCP failure in expert centers. However, as with any new technique with a great potential, there is a need for scientific evidence to establish its actual role in the clinical practice and its associated safety.

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