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Long-term outcomes of endoscopic ultrasound-guided hepaticogastrostomy in patients with malignant biliary obstruction

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Abstract

Background: Hepaticogastrostomy drainage through endoscopic ultrasound (EUS-HGS) has emerged in the 2010s as a new technique for biliary decompression in cases of endoscopic retrograde cholangiopancreatography (ERCP) failure for malignant biliary obstruction (MBO). Substantial technical and procedural progress in performing EUS-HGS has been achieved, allowing high technical and clinical success and an acceptable risk of adverse events in studies mainly focusing on short-term outcomes. However, the long-term effects of EUS-HGS and the risk of recurrent biliary obstruction (RBO) have not been fully evaluated.

Objectives: To evaluate the long-term effects of EUS-HGS and the risk of RBO.

Methods: Data from 211 patients undergoing technically successful EUS-HGS in three academic centers were retrospectively collected. Clinical success, adverse events, RBO, and reinterventions were evaluated.

Results: In total, 198 patients underwent technically successful EUS-HGS for MBO. The median overall survival was 144 days [108, 2011] after the procedure. Mean patient age was 69.39 (12.91) years. The cause of MBO was pancreatic cancer (n = 98, 49.5%) followed by cholangiocarcinoma (n = 29, 14.6%). The location of MBO was distal in 27.6% of cases and proximal in 68.4%. Adverse events were observed during the follow-up in 65 patients (33%). On multivariate analysis, the use of partially covered self-expandable metal stents (PCSEMS) was associated with a lower risk of RBO (HR = 0.47 [0.24–0.95], p = 0.034). Additionally, patients with distal stenoses had a trend toward better stent patency (HR = 0.06[0—0.77], p = 0.031). RBO developed in 38 cases (19.1%) mainly due tumor ingrowth (36.8%) with a high success rate of endoscopic management.

Conclusions: While RBO occurred in a notable proportion of patients, the primary cause of mortality was progression of the underlying malignancy rather than stent dysfunction. The efficiency of stents, particularly PCSEMS, and the high success rate

of endoscopic management for RBO underscore the effectiveness and reliability of these treatments in managing biliary complications.

KEYWORDS
biliary drainage, endoscopic ultrasound, hepaticogastrostomy, stent patency

INTRODUCTION

Biliary obstruction by malignancy leads to major clinical impairment and degradation of quality of life. It arises mostly from primary cholangiocarcinoma and pancreatic cancer, but also from metastatic tumors. Most patients are inoperable due to the typically advanced stage of the disease at the time of diagnosis and require biliary drainage.[1] Transpapillary drainage via endoscopic retrograde cholangiopancreatography (ERCP) is the first-line treatment for biliary obstruction and is mostly successful.[2] However, severe duodenal obstruction, surgically altered anatomy (after Whipple's resection or Roux-en-Y gastrojejunal anastomoses) as well as in some cases of hilar obstruction, conventional endoscopic management fails even at high-volume centers with expert endoscopists.[3,4] Endoscopic ultrasound-guided biliary drainage (EUS-BD) is a set of interventional techniques which has recently expanded the scope of endoscopic access methods and emerged as valuable alternatives to percutaneous decompression in case of ERCP failure.[5–9] Hepaticogastrostomy (EUS-HGS) is one such technique. Recent trials have suggested EUS-BD non-inferiority when compared to transpapillary biliary drainage or percutaneous transhepatic biliary drainage (PTBD) as a primary decompression method.[10–12]

While several studies have evaluated early adverse event rates such as stent migration or bile leakage, few studies have evaluated the effectiveness of the technique over the longer term. In this retrospective study, long-term outcomes of EUS-HGS were evaluated in a multicenter cohort including a focus on stent dysfunction.

Key summary

Summarize the established knowledge on this subject

- Hepaticogastrostomy drainage via endoscopic ultrasound (EUS-HGS) is a newer technique for biliary decompression in cases of ERCP failure for malignant biliary obstruction (MBO). EUS-HGS has shown high technical and clinical success with acceptable risk in short-term outcomes. Few studies have assessed the long-term efficacy and risks associated with EUS-HGS.

What are the significant and/or new findings of this study?

- This is the largest cohort study evaluating long-term patency of EUS-HGS in patients with MBO, encompassing nearly 200 patients.
- Adverse events post-EUS-HGS were observed in 33% of cases, with a median overall survival post-procedure of 144 days. Recurrent biliary obstruction was observed in 19.1% of cases, with stent patency rates decreasing from 88.9% at 30 days to 61.7% at one year.
- Most patients died from the progression of the underlying disease rather than from the procedure, with the majority of recurrent biliary obstruction (RBO) cases being treatable endoscopically. The use of partially covered self-expandable metal stents was associated with a lower risk of RBO (HR = 0.47 [0.24–0.95], $p = 0.034$). Additionally, patients with distal stenoses had a trend towards better stent patency (HR = 0.06[0 – 0.77], $p = 0.031$).

METHODS

Study population and inclusion criteria

In this multi-center study, we retrospectively reviewed the prospectively collected data on all patients referred for EUS-HGS to three academic tertiary referral centers from 2010 to January 2022. The study period from 2010 to January 2022 was chosen because it aligns with the implementation of a new computerized system in Parisian hospitals, ensuring better data accuracy. Additionally, this timeframe excludes the initial, less representative years of our practice, marked by rarer and less frequent cases before 2010. Patients with MBO secondary to unresectable, histologically proven tumor undergoing technically successful EUS-HGS were identified over the study period. Data from the electronic medical record of each patient, including information about the indication, past medical history, technical aspects of EUS-HGS, adverse events, laboratory measurements and other follow-up data, were collected until patient's death or date of last available information. Quality of life and subsequent oncologic treatment data were too scarce to be analyzed. All patients who underwent an EUS-HGS procedure with technical success were included. Patients were excluded in case of primary stent dysfunction as well as in the absence of non-objection agreement or formal objection during their lifetime with regard to data extraction. Primary stent malfunction (occlusion/migration) was defined as the absence of clinical success and the absence of any improvement in liver function following stent placement. Distal MBO was defined as biliary stenosis located more than 2 cm distal to the

biliary hilum. Proximal MBO was defined as a biliary stenosis located less than 2 cm proximal to the biliary hilum based on imaging studies and/or aspect on fluoroscopy.

Study endpoints

The primary study endpoint was the duration of stent patency.

Secondary endpoints included overall survival since initial drainage and stent insertion, the rate of procedure-related complications and periprocedural laboratory changes.

1. Stent patency was defined as the duration from the insertion of the stent until the date of the first clinically relevant stent dysfunction or "EUS-HGS-related events." If the cause of death was related to stent failure (i.e. jaundice or increased bilirubin in biology or dilated biliary duct on US or CT imaging), the date of death was defined as the time of the stent occlusion. If no stent failure occurred, stent patency was considered as censored at the date of death.
2. A clinically relevant stent dysfunction was an occlusion or a migration identified as such in the patient's files with clinical and/or biological manifestations (jaundice, cholangitis, sepsis, pruritus) requiring medical action in the form of antibiotic therapy or endoscopic intervention.
3. Technical success was defined as correct insertion of a covered SEMS between left (or exceptionally right) hepatic ducts and the gastric (exceptionally duodenal or jejunal) lumen, with satisfactory radiographic positioning and evidence of immediate bile outflow.
4. Clinical success was defined as an improvement of symptoms such as jaundice or pruritus as reported in electronic health records, or total bilirubin decrease to less than 50% if its initial value at 2 weeks.
5. Overall survival was calculated from the date of the first procedure until the date of death

The major adverse events that were assessed included bleeding, infection, pancreatitis, and abdominal pain occurring within 30 days of the EUS-HGS procedure.

Procedure

All EUS-HGS procedures were performed with the patient under general anesthesia in the supine or left lateral position with combined endoscopic, fluoroscopic and ultrasound guidance using therapeutic echoendoscopes with large working channels of 3.8 mm. The procedures were carried out under CO_2 insufflation. The tip of the echoendoscope with the inflated balloon was positioned in the stomach. Liver segment II or III was punctured with a 19-G access needle (EchoTip® Ultra 19-A, Cook Medical) or with a standard 19-G needle (EchoTip® Ultra 19, Cook Medical). Then, contrast was injected for cholangiography, and the needle was exchanged for a 6-Fr cystotome (Endo-Flex Company) over a 0.035-inch guidewire (Jagwire, Boston Scientific), allowing the creation of a biliodigestive fistula. Finally, we deployed the stent between the left hepatic bile duct and the gastric lumen. Through time, different types of stents were used. Initially, conventional fully covered metallic stents (FCSEMS) were used (Wallflex). Later on, dedicated EUS-HGS stents, mainly the Giobor™ stent (initially half covered and half uncovered Niti-S biliary stents, later proximal third uncovered and distal two-thirds covered, 10 × 80 mm and 10 × 100 mm, Giobor, Taewoong Medical) or, later, the HANAROSTENT™ (proximal third uncovered and distal two-thirds covered, Mi-TECH-Medical Co.) were used. Furthermore, the Giobor™ stent was modified during the last few years with regard to the development of an anti-migration flange on its gastric side. All procedures were performed by three interventional endoscopists (FP, SK, EP) with expertise in ERCP and interventional EUS (>300 therapeutic EUS procedure/years and >300 ERCPs/year).

Statistical analysis

Descriptive statistics were calculated using the mean +/− SD for normally distributed data or median [IQR] in the case of numerical variables when appropriate. Basic characteristics were summarized by absolute and relative frequencies and compared using Chi^2 or Fisher's exact test (categorical variables) when appropriate and continuous characteristics compared using the Student's *t*-test or Mann–Whitney's test when applicable. Stent patency and overall survival were evaluated by Kaplan–Meier's methodology, and differences in survival were evaluated using the log-rank test. Relationships between survival parameters were modeled using one-dimensional Cox regression models and described using a risk ratio (HR) of 95% CI for HR and a *p*-value corresponding to the relevant regression coefficient. We used a multivariate analysis approach using multivariate linear regression. The primary objective was to investigate the relationship between various predictors and two key outcomes: stent patency and overall survival. The variables included in the model were those associated with a significance level of alpha <10% on univariate analysis. This threshold was chosen to ensure a comprehensive inclusion of potentially relevant variables while maintaining statistical rigor. Analyses were performed using R software version 4.2.2 (released on 2022-10-31) (wwwc.cranR.com).

RESULTS

Patient demographics

Among the 211 EUS-HGS procedures, 13 patients were excluded (6 transferred to rehabilitation unit without follow-up data, 1 eventually found to have benign condition, and 6 for primary stent dysfunction), and data from 198 patients were analyzed. The flow chart is depicted in Figure 1. Among 198 patients who underwent EUS-HGS, 107 were men and 91 were female. Mean patient age was 69.39 (12.91) years. Causes of biliary obstruction were pancreatic

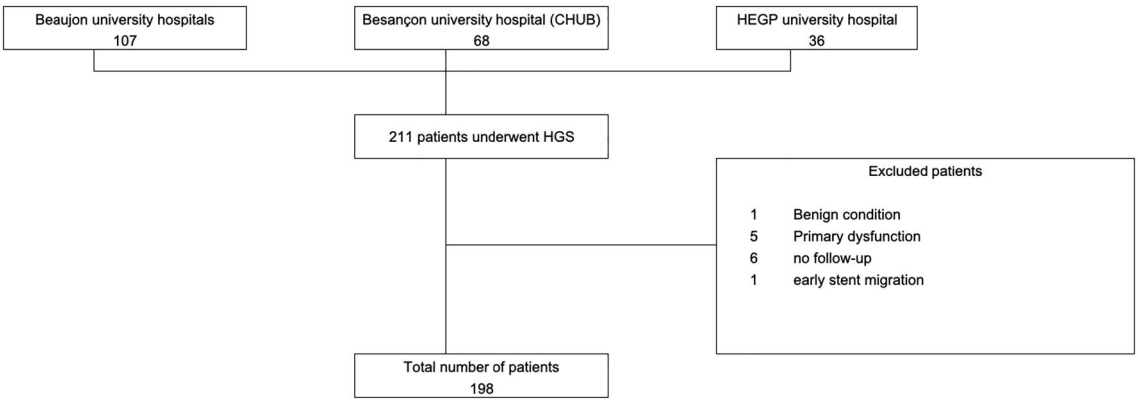

FIGURE 1 Patient flow chart.

adenocarcinoma (n = 98, 49.5%), cholangiocarcinoma (n = 29, 14.6%), and other (n 48, 24.2%). Details on pathology are provided in Table S1. Major reasons for EUS-HGS were duodenal obstruction (61 cases, 31.4%); failed biliary cannulation (n = 58, 29.9%), surgically altered anatomy (n = 35, 18%); tumoral invasion of the papilla (n = 25; 12.9) and clinical need for drainage of the left liver lobe in 8 patients (4.1%). Sixty five (33.5). Sixty-five patients (33.5%) had previously undergone a successful biliary procedure (ERCP + stent). The procedures performed beforehand are detailed in Table 1. At the time of the procedure, the mean baseline total bilirubin level was 185.21 (139.62) mg/dL, mean gamma-glutamyl transpeptidase level was 428.89 (684.71) U/L; mean alkaline phosphatase was 358.14 (474.71) U/L; mean white blood cell count was 5165.61 (6432.12)/μL. At presentation, patients had fever in 74 cases (41.3%), encephalopathy in 5 cases (2.8%), pruritus in 22 cases (12.3%) and renal insufficiency in 15 cases (8.4%). The performance status (PS) score at the time of biliary drainage, categorized as 0, 1, 2, 3, and 4, was observed in 7, 45, 54, 26, and 5 patients, respectively. One hundred and ten patients (57.3%) had metastasis at the time of HGS and 36 (18.2%) had ascites. Regarding procedure details, FCSEMS were used predominantly, with 8 cm length used in 46.6% and 10 cm in 47.2% of cases. Stent diameter was 10 mm for 189 patients (97.4%). The median follow-up was 56.00 [20.75, 186.50] days and 19 patients were alive at the time of data analysis. Patients' baseline characteristics and procedural details are described in Table 1 (Table 2).

Long term post-procedural events

EUS-HGS related events were observed in 65 cases (33%). Major adverse events were infection 18.3% and abdominal pain (12.1%), bilioma (3.2%), bleeding (3.2%) and death related to the procedure (6.1%). Peritonitis developed in 11 cases (5.6%) leading to patient's death in 3 cases. Cholangitis was observed in nine cases: and cholecystitis in 2 patients (1.1%). Thirty patients died within 30 days as a consequence of disease progression, with no evidence of procedure-related complications and despite improvement in liver biology.

Patency rate and recurrent biliary obstruction

Recurrent biliary obstruction developed in 38 cases (19.1%). Kaplan–Meier's curves of stent patency are shown in Figure 2. Stent patency was 88.9 [84.1; 93.9], 82.2 [75.8; 89.1], 69.5 [60.2; 80.1], 61.7 [50.7; 75.2] at 30 days, 90 days, 180 days and 365 days, respectively. Throughout the study period, the survival probability curve did not cross the 50% threshold, indicating that median stent patency was not reached. Consequently, we are unable to report a specific median stent patency duration. Instead, we provide these time-specific patency rates as an alternative way to understand the stent performance over time. The longest follow-up in our study was 510 days. This suggests that the median stent patency likely exceeds the study duration, indicating a prolonged period of effectiveness for the stents used. However, the exact median patency duration cannot be precisely calculated from our data. Univariate and multivariate Cox regression analysis for factors associated with stent patency are presented in Table 4. Interestingly, partially covered self-expandable metallic stent (PCSEMS) were associated with a lower risk of RBO on both univariate and multivariate analysis, with odds ratios of 0.42 (0.21–0.83, p = 0.012) and 0.47 (0.24–0.95, p = 0.034), respectively, indicating a statistically significant reduction in the risk of RBO when using PCSEMS compared to fully covered metallic stent (FCSEMS). Additionally, patients with distal stenoses had a trend toward better stent patency, evidenced by a hazard ratio of 0.13 (p = 0.066) in the univariate analysis and 0.06 (p = 0.031) in the multivariate analysis. No significant difference in stent patency was observed when patients were stratified by age, sex, PS score, level of biliary obstruction, distant metastasis, cause of biliary obstruction, laboratory measure at baseline, stent length or size, or concurrent placement of a duodenal stent.

Overall survival

Median overall survival was 144 [108, 211] days. The Kaplan–Meier's curves of overall survival are shown in Figure 2. Overall survival was 83.3 [78.1; 88.9], 59.8 [52.9; 67.7], 45.8 [38.5; 54.4] and 28.4 [21.5;

TABLE 1 Baseline characteristics of patients treated by EUS-HGS for malignant biliary obstruction.

Center						
		Overall ($n = 198$)	Beaujon ($n = 104$)	CHUB ($n = 61$)	HEGP ($n = 33$)	p
Sex male (%)		107 (54.0)	62 (59.6)	28 (45.9)	17 (51.5)	0.222
Age		69.39 (12.91)	67.42 (12.89)	73.52 (10.63)	68.03 (15.24)	0.011
Follow up, day (median [IQR])		56.00 [20.75, 186.50]	52.50 [27.00, 212.25]	50.00 [10.00, 144.00]	96.00 [54.00, 217.00]	0.110
Overall survival, day (median [IQR])		74.50 [29.75, 208.75]	53.00 [28.00, 204.25]	93.00 [37.00, 185.00]	100.00 [34.00, 443.00]	0.187
PS (0,1,2,3,4)		(7/45/54/26/5)	(3/21/27/16/3)	(1/13/17/7/2))	(3/11/10/3/0)	0.635
BMI		21.96 (5.60)	22.05 (6.23)	22.39 (5.05)	20.98 (4.26)	0.654
Histological diagnosis (%)	Cholangiocarcinoma	29 (14.6)	15 (14.4)	9 (14.8)	5 (15.2)	0.020
	Colorectal adenocarcinoma	16 (8.1)	6 (5.8)	5 (8.2)	5 (15.2)	
	Duodenum adenocarcinoma	6 (3.0)	4 (3.8)	0 (0.0)	2 (6.1)	
	Esophageal cancer	1 (0.5)	1 (1.0)	0 (0.0)	0 (0.0)	
	Other	48 (24.2)	36 (34.6)	10 (16.4)	2 (6.1)	
	Pancreatic adenocarcinoma	98 (49.5)	42 (40.4)	37 (60.7)	19 (57.6)	
Metastasis		110 (57.3)	62 (60.8)	27 (47.4)	21 (63.6)	0.188
Ascitis		36 (18.2)	29 (27.9)	5 (8.2)	2 (6.1)	0.001
Previous history of biliary drainage		65 (33.5)	42 (40.4)	9 (15.8)	14 (42.4)	0.003
Indication of EUS-HGS (%)	Duodenal obstruction	66 (4)	20 (19.3)	24 (42.1)	18 (54.5)	<0.001
	Failed biliary cannulation	59 (30.4)	30 (28.8)	18 (31.6)	10 (30.3)	
	Pyloric stenosis	5 (2.6)	2 (1.9)	3 (5.3)	0 (0.0)	
	Surgically altered anatomy	35 (18.0)	25 (24.0)	5 (8.8)	5 (15.2)	
	Tumoral invasion of papilla	25 (12.9)	22 (21.2)	3 (5.3)	0 (0.0)	
	Unclear	1 (0.5)	0 (0.0)	1 (1.8)	0 (0.0)	
	Need for complimentary drainage of left lobe	8 (4.1)	5 (4.8)	3 (5.3)	0 (0.0)	
Bilirubin (mg/dl),		185.21 (139.62)	166.62 (138.59)	212.12 (139.85)	184.68 (138.03)	0.179
GGT, UI/L		677.41 (700.98	558.92 (588.62)	797.08 (878.49)	658.67 (425.26)	0.159
ALP,UI/L		727.86 (764.41)	869.57 (1019.28	625.27 (537.81)	587.62 (337.45)	0.194
WBC UI/L		5165.61 (6432.12)	1880.89 (4783.01)	10,431. (5218.38)	9.89 (7.65)	<0.001
Fever (%)		74 (41.3)	56 (58.3)	15 (27.3)	3 (10.7)	<0.001
Encephalopathy (%)		5 (2.8)	1 (1.0)	1 (1.8)	3 (10.7)	0.021
Pruritus (%)		22 (12.3)	15 (15.6)	5 (9.1)	2 (7.1)	0.333
Renal insufficiency (%)		15 (8.4)	8 (8.3)	6 (10.9)	1 (3.7)	0.543
Stent length (%)						
	10 cm	91 (47.2)	11 (11.0)	50 (83.3)	30 (90.9)	
	6 cm	12 (6.2)	12 (12.0)	0 (0.0)	0 (0.0)	<0.001
	8 cm	90 (46.6)	77 (77.0)	10 (16.7)	3 (9.1)	

TABLE 1 (Continued)

Center		Overall (n = 198)	Beaujon (n = 104)	CHUB (n = 61)	HEGP (n = 33)	p
Stent diameter (%)						
	10 mm	189 (97.4)	95 (95.0)	61 (100.0)	33 (100.0)	0.306
	7Fr	2 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)	
	8 mm	3 (1.5)	3 (3.0)	0 (0.0)	0 (0.0)	
Stricture location (%)						
	Hilar	42 (27.6)	24 (30.8)	14 (27.5)	4 (17.4)	0.084
	IH	6 (3.9)	3 (3.8)	0 (0.0)	3 (13.0)	
	CBD	104 (68.4)	51 (65.4)	37 (72.5)	16 (69.6)	
Stent dysfunction during follow-up		44 (22.3)	28 (26.9)	10 (17)	6 (18.2)	0.16

Abbreviations: ALP, Alkaline phosphatase; BMI, Body mass index; GGT, Gamma-glutamyl transferase; PS, Performance status; WBC white blood cells.

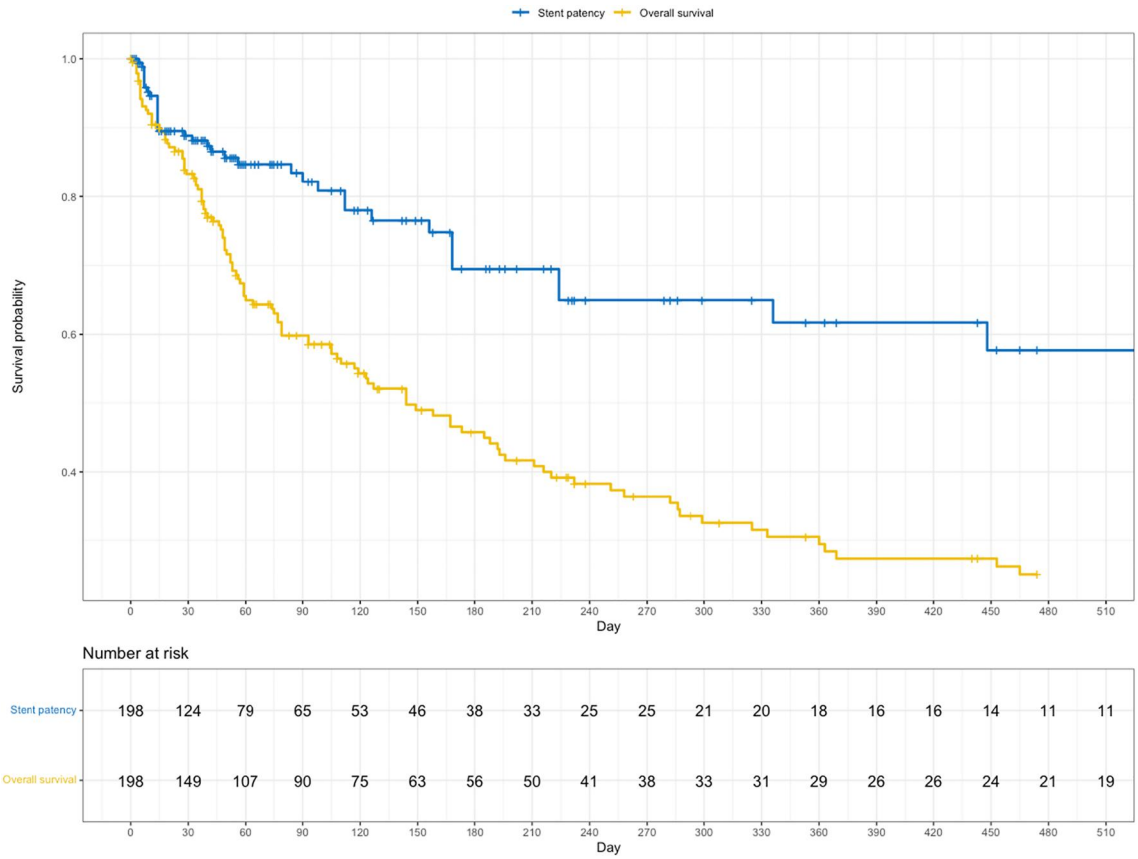

FIGURE 2 Kaplan-Meir curve of overall survival (yellow) and stent patency (blue).

37.6] at 30 days, 90 days, 180 days and 365 days, respectively (Table 3). Univariable and multivariable Cox regression analysis for factor associated with overall survival are presented in Table 4. Metastasis was observed in 110 cases, accounting for 57.3% of the total. The presence of metastasis was significantly associated with overall survival, with an odds ratio of 1.93 (1.30–2.87, p = 0.001), indicating a nearly two-fold increased risk of mortality in patients with metastasis. The PS score showed a significant association with overall survival in both univariate and multivariate analyses. The odds ratios were 1.75 (1.35–2.27, $p < 0.001$) in univariate analysis

TABLE 2 Post-procedure adverse events.

	Overall (n = 198)	Beaujon (n = 104)	CHUB (n = 61)	HEGP (n = 33)	p
Any adverse event (%)	65 (33.0)	34 (33.0)	19 (31.1)	12 (36.4)	0.877
Abdominal pain(%)	24 (12.1)	12 (11.5)	8 (13.1)	4 (12.1)	0.956
Infection (%)	36 (18.3)	27 (26.2)	8 (13.1)	1 (3.0)	0.005
Peritonitis (%)	11 (5.6)	2 (1.9)	6 (9.8)	3 (9.1)	0.063
Cholecystitis (%)	2 (1.1)	0 (0.0)	2 (3.3)	0 (0.0)	0.118
Cholangitis (%)	9 (4.5)	1 (1.0)	6 (9.8)	2 (6.1)	0.027
Bilioma (%)	6 (3.2)	6 (5.8)	0 (0.0)	0 (0.0)	0.077
Bleeding (%)	12 (6.1)	6 (5.8)	2 (3.3)	4 (12.1)	0.226

TABLE 3 Survival at different time point.

	Stent patency		Overall survival	
Time (days)	Number at risk	Survival probability [95% CI]	Number at risk	Survival probability [95% CI]
30	124	0.889 [0.841; 0.939]	149	0.833 [0.781; 0.889]
90	65	0.822 [0.758; 0.891]	90	0.598 [0.529; 0.677]
180	38	0.695 [0.602; 0.801]	56	0.458 [0.385; 0.544]
365	17	0.617 [0.507; 0.752]	27	0.284 [0.215;0.376]

and 1.87 (1.40–2.51, $p < 0.001$) in multivariate analysis. These results suggest a substantial impact of PS on survival, where higher PS scores correlate with decreased survival rates. On multivariable analysis, PS, and metastasis at the time of biliary drainage were associated with shorter overall survival. The location of biliary obstruction, stent length and diameter, as well as the concurrent placement of a duodenal stent, were not associated with changes in overall survival.

Causes and outcomes of RBO

Table S2 summarizes outcome measures for 38 cases (19.1%) of RBO occurring during the study follow-up. Causes of biliary obstruction were food impaction or sludge formation was identified in 8 cases (21.1%), while hyperplasia at the uncovered part of the stent was found in 6 cases (15.8%), bleeding or clots were responsible for 3 cases (7.9%), and tumor ingrowth was the most frequent cause, observed in 14 cases (36.8%). Regarding management, endoscopic approaches were predominant, employed in 22 cases (57.9%), which included additional stent placement (stent-in-stent) in 14 patients, stent cleaning in 7 patients and new EUS-HGS in 1 patient. Radiological percutaneous drainage was used in 7 cases (18.4%), and conservative measures, such as antibiotics, were applied in 6 cases (15.8%). Endoscopic management was successful in 20 out of the 22 attempts, indicating a high efficacy rate of 90.9% for these procedures.

DISCUSSION

We hereby report the largest cohort of patients with MBO evaluating long-term patency of extrahepatic hepato-drainage, including nearly two hundred patients. Indications for EUS-BD remain limited to inaccessible papilla because of tumor invasion or surgically altered anatomy, failed biliary cannulation and as an alternative to PTBD.[13,14] Up to now, a large - sized prospective, randomized, controlled trial comparing EUS-BD to PTBD has not been published. Common approaches for EUS-BD are choledochoduodenostomy (EUS-CDS) or hepaticogastrostomy (EUS-HGS); however, there is still no consensus on the technique of choice for EUS-BD. The advent of a lumen-apposing metal stent (LAMS) has made CDS the most widespread approach, although EUS-HGS possesses the advantage of being a viable option in case of inaccessible papilla for surgically altered anatomy or gastric outlet obstruction. However, although the first description of such a technique was proposed in 2003[7], both the technical challenges and the risk of severe adverse events have prevented the diffusion of the procedure, with most of such adverse events being strongly related to the risk of stent migration and the lack of dedicated stents. Similar to a meta-analysis from our group, the rate of early adverse events in our study was 33%.[6]

Few studies have assessed the long-term efficacy of EUS-HGS. In our analysis of long-term outcomes, we observed a stent patency rate of 61.7% [50.7; 75.2] at 1 year, with RBO noted in 38 cases (19.1%). Our findings align with those of Nakai et al.,[15] who, in their evaluation of the long-term outcomes of EUS-HGS, found RBO in a

TABLE 4 Univariate and multivariate analysis of prognostic factors of stent patency and overall survival.

		Stent patency			Overall survival		
		Mean(SD) or *n*(%)	HR (univariable)	HR (multivariable)	Mean(SD) or *n*(%)	HR (univariable)	HR (multivariable)
Age, mean(SD)		69.4 (12.9)	0.97 (0.95–1.00, $p = 0.027$)	0.98 (0.96–1.00, $p = 0.076$)	69.4 (12.9)	0.99 (0.98–1.01, $p = 0.312$)	0.99 (0.97–1.01, $p = 0.306$)
Sex = male (%)		107 (54.0)	1.95 (0.96–3.94, $p = 0.064$)	1.84 (0.93–3.67, $p = 0.082$)	107 (54.0)	1.46 (1.01–2.11, $p = 0.045$)	1.53 (0.96–2.42, $p = 0.072$)
PS, mean(SD)		1.8 (0.9)	0.80 (0.53–1.21, $p = 0.294$)	-	1.8 (0.9)	1.75 (1.35–2.27, $p < 0.001$)	1.87 (1.40–2.51, $p < 0.001$)
BMI lower than 22		68 (34.3)	2.29 (1.17–4.49, $p = 0.016$)	-	68 (34.3)	1.15 (0.79–1.67, $p = 0.460$)	-
Ascitis		36 (18.2)	2.77 (1.27–6.06, $p = 0.011$)	-	36 (18.2)	3.02 (2.00–4.55, $p < 0.001$)	1.66 (0.97–2.86, $p = 0.065$)
Cause of biliary obstruction	Cholangiocarcinoma	29 (14.6)	-	-	29 (14.6)	-	-
	Colorectal adenocarcinoma	16 (8.1)	3.53 (0.92–13.51, $p = 0.066$)	-	16 (8.1)	1.91 (0.85–4.29, $p = 0.119$)	-
	Duodenum adenocarcinoma	6 (3.0)	0.88 (0.10–7.87, $p = 0.906$)	-	6 (3.0)	0.92 (0.27–3.17, $p = 0.892$)	-
	Esophageal cancer	1 (0.5)	0.00 (0.00-Inf, $p = 0.998$)	-	1 (0.5)	9.14 (1.17–71.27, $p = 0.035$)	-
	Other	48 (24.2)	1.71 (0.53–5.49, $p = 0.371$)	-	48 (24.2)	1.83 (1.00–3.35, $p = 0.052$)	-
	Pancreatic adenocarcinoma	98 (49.5)	1.23 (0.40–3.77, $p = 0.722$)	-	98 (49.5)	1.47 (0.83–2.61, $p = 0.189$)	-
Metastasis		110 (57.3)	0.99 (0.49–2.01, $p = 0.988$)	-	110 (57.3)	1.93 (1.30–2.87, $p = 0.001$)	1.89 (1.15–3.11, $p = 0.012$)
History of biliary drainage		65 (33.5)	1.21 (0.61–2.40, $p = 0.593$)	-	65 (33.5)	0.82 (0.56–1.20, $p = 0.306$)	-
Bilirubin (mg/dl), mean(SD)		185.2 (139.6)	1.00 (0.99–1.00, $p = 0.223$)	-	185.2 (139.6)	1.00 (1.00–1.00, $p = 0.868$)	-
GGT UI/L, mean(SD)		428.9 (684.7)	1.00 (1.00–1.00, $p = 0.572$)	-	428.9 (684.7)	1.00 (1.00–1.00, $p = 0.159$)	-
ALP UI/L, mean(SD)		358.1 (474.7)	1.00 (1.00–1.00, $p = 0.156$)	-	358.1 (474.7)	1.00 (1.00–1.00, $p = 0.081$)	-
WBC/mm^3, mean(SD)		5165.6 (6432.1)	1.00 (1.00–1.00, $p = 0.116$)	-	5165.6 (6432.1)	1.00 (1.00–1.00, $p = 0.205$)	-
CRP mg/dL, mean(SD)		444.1 (4048.6)	1.00 (1.00–1.00, $p = 0.019$)	-	444.1 (4048.6)	1.00 (1.00–1.00, $p = 0.733$)	-
Fever		74 (41.3)	2.08 (1.03–4.23, $p = 0.042$)	-	74 (41.3)	1.16 (0.79–1.69, $p = 0.444$)	-
Encephalopathy		5 (2.8)	2.72 (0.64–11.56, $p = 0.176$)	-	5 (2.8)	2.39 (0.87–6.56, $p = 0.090$)	-
Pruritus		22 (12.3)	0.87 (0.33–2.32, $p = 0.785$)	-	22 (12.3)	0.76 (0.45–1.31, $p = 0.325$)	-
Renal insufficiency		15 (8.4)	1.30 (0.40–4.29, $p = 0.662$)	-	15 (8.4)	1.03 (0.50–2.13, $p = 0.928$)	-

(Continues)

TABLE 4 (Continued)

		Stent patency			Overall survival		
		Mean(SD) or *n*(%)	HR (univariable)	HR (multivariable)	Mean(SD) or *n*(%)	HR (univariable)	HR (multivariable)
Stenosis location							
	Hilar or IH	48 (31.6)	-	-	48 (31.6)	-	-
	CBD	104 (68.4)	0.13 (0.01–1.15, $p = 0.066$	0.06 (0.00–0.77, $p = 0.031$)	104 (68.4)	0.92 (0.59–1.43, $p = 0.703$)	-
Stent length							
	10 cm	91 (47.2)	-	-	1 (0.5)	0.70 (0.08–5.83, $p = 0.739$)	-
	6 cm	12 (6.2)	3.44 (1.09–10.80, $p = 0.035$)	-	91 (47.2)	-	-
	8 cm	90 (46.6)	1.69 (0.78–3.69, $p = 0.187$)	-	12 (6.2)	2.46 (1.26–4.80, $p = 0.008$)	2.03 (0.86–4.76, $p = 0.105$)
Stent diameter							
	10 mm	189 (97.4)	-	-	90 (46.6)	1.90 (1.28–2.82, $p = 0.001$)	1.57 (0.97–2.55, $p = 0.065$)
	7Fr	2 (1.0)	-	-	189 (97.4)	-	-
	8 mm	3 (1.5)	1.80 (0.24–13.31, $p = 0.563$)	-	2 (1.0)	0.00 (0.00-Inf, $p = 0.996$)	-
					3 (1.5)	0.62 (0.15–2.50, $p = 0.498$)	-
Type of stent							
	FCSEMS	50 (25.3	-		50 (25.3)	-	-
	PCSEMS	146 (73,7)	0.42 (0.21–0.83, $p = 0.012$)	0.47 (0.24–0.95, $p = 0.034$)	146 (73.7)	0.42 (0.21–0.83, $p = 0.012$)	0.41 (0.14–1.17, $p = 0.096$)
Duodenal stent		66 (33.3)	0.56 (0.26–1.19, $p = 0.129$)		66 (33.3)	0.99 (0.67–1.44, $p = 0.945$	

Abbreviations: ALP, Alkaline phosphatase; BMI, Body mass index; CBD, Common bile duct; CRP, C-reactive protein; FCSEMS, Fully covered self-expandable metal stents; GGT, Gamma-glutamyl transferase; IH, Intrahepatic; PCSEMS, Partially covered self-expandable metal stents; PS, Performans status; WBC, white blood cells.

third of the patients. They identified hyperplasia of the uncovered portion as the primary cause of biliary obstruction, which was addressed through endoscopic reintervention. In our study, tumor ingrowth was the most frequent cause of biliary obstruction, observed in 14 cases (36.8%) followed by food impaction or sludge formation in 8 cases (21.1%), while hyperplasia at the uncovered part of the stent was found in 6 cases (15.8%) and bleeding or clots were responsible for 3 cases (7.9%). In a separate study by Minaga et al.,[16] involving 211 patients who underwent HGS at eight referral centers in Japan, 16.6% (35/211) experienced RBO,[16] with a median onset time of 104 days [56: 263]. The causes of RBO were gastroduodenal content reflux or sludge formation in 19 (57.6%) patients, hyperplasia at the proximal uncovered stent portion in 9 (27.3%) patients, and additional biliary stricture due to tumor invasion in 5 (15.2%) patients. Minaga et al. found an overall technical and clinical success rate of reintervention for RBO of 100% (33/33 [95% CI, 0.894–1.00]) and 81.8% (27/33 [95% CI, 0.645–0.930]), respectively.

In another study conducted by Poincloux et al.[17] authors reported their 7 years of experience with 66 EUS-HGS procedures. They reported technical and clinical success rates of 98.5% and 93.8%, respectively, with 15 complications (15/65, 22.7%) and 6 RBO due to dysfunctional stents (6/65, 9%). Several improvements of metallic stents were made in order to reduce the risk of stent dysfunction and adverse events, such as GIOBOR™ and Hanarostent BPD™. In a previous pilot study evaluating GIOBOR™ stent conducted by De Cassan et al. of 37 patients, 10 (27%) who underwent EUS-HGS required a BD in the 6-month follow-up after EUS-HGS.[18] Subsequently, the Hanarostent BPDTM, equipped with an anti-migratory system that functions bidirectionally, has an uncovered extremity and four flaps to prevent the migration of the intrahepatic extremity, along with a flanged covered end to prevent the migration of the intragastric extremity. Other authors evaluated the patency of plastic stents. In a more recent prospective study evaluating a new dedicated plastic stent, the authors reported RBO in eight out of 23 patients, accounting for 34.8% of cases.[19] According to a recent study on a large case series using a dedicated plastic stent for EUS-HGS, the stent patency rate after 2 months of stent placement was >90%.[20] However, it's crucial to recognize that these stents have

significant limitations, especially in the context of long-term evaluation. Their design and plastic composition might impact both migration and obstruction risks. While initial findings are promising, longer-term studies are needed to comprehensively assess the effectiveness and safety of these stents in real-world scenarios.

Our study has identified two key factors that are associated with lower stent patency rates in patients with biliary obstruction. Firstly, we observed that the location of the biliary obstruction significantly influences stent patency. Patients with proximal obstructions (hilar or intrahepatic) demonstrated poorer stent patency compared with those with distal (common bile duct) obstructions. This difference is likely due to the increased anatomical and technical challenges encountered when placing stents in proximal locations.[16] Secondly, our analysis revealed that the type of stent used plays a crucial role in determining stent patency. While PCSEMS showed a significant association with improved stent patency, as evidenced by favorable *p*-values in both univariate ($p = 0.012$) and multivariate ($p = 0.034$) analyses, FCSEMS did not demonstrate the same level of effectiveness. These findings highlight the importance of considering both the location of the biliary obstruction and the type of stent used when planning for optimal patient care and management.

The study's analysis identified several key risk factors impacting overall survival in patients undergoing biliary drainage. Metastasis was a significant predictor, where its presence nearly doubled the risk of mortality (HR = 1.89[1.15–3.11], $p = 0.012$). Additionally, PS was closely linked to survival outcomes, with higher scores indicating decreased survival rates. This correlation was found in both univariate (HR = 1.75[1.35–2.27], $p < 0.001$) and multivariate analyses (HR = 1.87[2.4–2.51], $p < 0.001$). Factors such as the location of the biliary obstruction, stent length and diameter, and the concurrent placement of a duodenal stent did not show a significant association with overall survival. Interestingly, ascites during the procedure was not associated with lower stent patency time and further support the feasibility of this technique in case of ascites.[21] Moreover, Our study found no significant association between the use of concomitant duodenal stenting and RBO or OS in our patient cohort. This suggests that duodenal stenosis and subsequent food impaction potentially have a lesser impact on hepaticogastrostomy as compared to conventional retrograde stenting or CDS.

Our study presents some limitations, such as its retrospective nature. The data were collected from medical records, and some information, especially if patients are hospitalized at other sites, may be missing despite our efforts to recover all the data. Also, we included only patients with technical success in order to evaluate stent patency over a long term period. Therefore, patients with complications such as very early stent dislodgment were not included. Our study does not allow us to assess the clinical success rate of a procedure. Selection bias is inevitable in this setting. Second, there was heterogeneity in the underlying malignancy that led to the development of MBO. Also, the technical aspects of the HGS technique have changed over time and the safety profile as well as clinical efficacy have improved over time. The wide inclusion period necessary for a long-term evaluation inherently introduces a heterogeneity of the population and practices. Additionally, our analysis encompassed patients with heterogeneous causes of biliary obstruction, including those with gastric and hepatobiliary cancers, among other conditions. While our principal aim was not to delve into the specific cancer outcomes, the inclusion of these diverse cancer types warrants a nuanced discussion, particularly given their distinct biological behaviors and treatment responses. Gastric cancers and hepatobiliary malignancies, although both gastrointestinal in origin, exhibit significantly different disease trajectories. Gastric cancers are often diagnosed at an advanced stage and tend to have a more aggressive clinical course. In contrast, hepatobiliary cancers, though also aggressive, might present differently in terms of symptomatology and progression. These inherent differences in disease behavior could potentially influence the outcomes related to stent patency, a key focus of our study. We acknowledge the significance of chemotherapy in influencing stent patency and patient outcomes. Our study did not evaluate this aspect due to data limitations. However, the work of Minaga et al., showing a significant benefit of chemotherapy over Best Supportive Care ($p = 0.02$), highlights its importance. This underscores the need for future research to comprehensively explore the impact of chemotherapy on stent effectiveness and patient prognosis. Nevertheless, the trustworthiness of our results is supported by the high sample size and its multicenter setting. To the best of our knowledge, this study is the first to report the clinical efficacy of HGS over a very long period of time. We hereby found that despite chemotherapy and progress in the treatment of underlying oncologic disease, RBO remains low and most patients die from cancer progression before biliary event. One notable limitation that merits acknowledgment pertains to the potential risk of selection bias within our patient cohort, stemming from our chosen methodology. We chose to exclude six patients who experienced primary stent dysfunction from our analysis as they did not meet our predefined criteria for clinical success. Although we consistently applied these exclusion criteria, this approach may introduce bias by focusing on patients who responded positively to the initial procedure. Consequently, our analysis may not fully capture the full spectrum of outcomes that can occur following EUS-HGS. Furthermore, our study did not account for technical failures, such as instances in which attempted HGS procedures did not result in actual stent deployment. This omission stemmed from our reliance on medical records and databases, which may not comprehensively capture unsuccessful attempts. Additionally, patients who experienced primary clinical failure due to a nonfunctional biliary stent were not included as events in our analysis. Our primary endpoint of interest was stent occlusion, and we excluded primary clinical failure events as they do not contribute to a specific time-to-event outcome. This limitation reflects our study's primary focus on evaluating stent longevity after achieving clinical success, rather than providing an all-encompassing assessment of technical success or the broader clinical success of EUS-HGS procedures. Although our study included a significant number of patients ($n = 198$) and yielded valuable insights

into the specific subgroup of individuals who achieved clinical success following successful stent deployment and bilirubin-level improvement, we acknowledge that the exclusion of technical failures and primary stent dysfunction may introduce potential selection bias, thereby possibly overestimating and limiting the generalizability of our conclusions. Future studies should consider a prospective and comprehensive assessment of EUS-HGS outcomes, encompassing not only long-term clinical success but also technical and short-term stent performance, to provide a more robust and inclusive understanding of this therapeutic approach.

In conclusion, 2 decades of experience have shown that EUS-HGS is still a naturally complex operation. Significant procedural and technical advancements have made it possible to reduce the risk of adverse events and RBO. Our results showed that more patients died of complications of the underlying disease than from recurrent obstruction, which could be treated endoscopically in the majority of cases.

CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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