

# Malignant Biliary Obstruction; Evolving Endoscopic Diagnostic and Therapeutic Modalities

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## Abstract

Biliary obstruction is common in pancreatobiliary malignancies and has a negative impact on the patient's quality of life, postoperative complications, and survival rates. Particularly in the last decade, there has been enormous progress regarding the diagnostic and therapeutic options in patients with malignant biliary obstruction. Endoscopy has given a new insight in this direction and novel techniques have been developed for the better characterization and treatment of malignant strictures. We herein summarize the available data on the different endoscopic techniques, and clarify their role in the diagnosis and treatment of malignant biliary obstructive disease.

## Keywords

Cholangiocarcinoma, pancreatic cancer, stricture, biliary obstruction, stent, endoscopic ultrasound

## Introduction

Biliary obstruction is a common complication of malignancies of the pancreaticobiliary system that develop either as an extrinsic bile duct compression or an intrinsic growth (Pu et al., 2016). The vast majority of patients with malignant biliary obstruction (MBO) present with an underlying pancreatic adenocarcinoma or cholangiocarcinoma (CCA). Approximately 70% of pancreatic cancer cases are located in the head of the pancreas (Hidalgo M 2010), whereas 20-30% of all CCAs are found distally (Rizvi et al., 2018). Other less common etiologies of obstructive jaundice include ampullary carcinoma, gallbladder carcinoma, duodenal adenocarcinoma, lymphoma, and metastatic disease (Parasher and Lee, 2005 and van Berkel et al., 2005).

Because of its subclinical presentation, MBO is associated with delayed diagnosis and significant morbidity. Weight loss, pruritus, malaise, abdominal discomfort or pain might just be the onset of symptoms in patients with locally advanced or metastatic disease. Furthermore, obstructive jaundice can be complicated by cholangitis, sepsis and hepatic failure (Strasberg et al., 2014 and Boulay and Birg, 2016), thus having a negative impact on these patients' quality of life (QoL).

In this context, endoscopy provides minimally invasive and cost-effective solutions that aim at the long-term drainage of the biliary system and improvement in patients' QoL. Interestingly, endoscopy nowadays not only has a crucial role in palliation but also seems to improve the diagnostic accuracy of pre-cancerous lesions.

In this article we review the Evolving Endoscopic Diagnostic and Therapeutic Strategies of malignant biliary obstruction.

## Advanced Endoscopic Diagnosis

In suspected MBO, based on clinical, imaging or endoscopic (ERCP, EUS) modalities with inconclusive histopathological confirmation obtained by standard techniques such as FNA/FNB samples or biliary brushings and forceps biopsies, novel techniques such cholangioscopy, intraductal ultrasonography (IDUS) or Confocal Laser Endomicroscopy (CLE) have been developed. These

invasive endoscopic procedures are not used routinely and are not largely available, but can be performed during ERCP (**Fernandez and Arvanitakis 2019**).

Cholangioscopy allows direct visualization of the biliary tree. Historically, it was performed with a dual-operator reusable baby endoscope passed through a mother therapeutic duodenoscope. Recently, a single-operator single-use cholangiopancreatroscope (SOCP) was developed, firstly with a fibro-optic based device (FSOCP) and then a digital version (DSOCP). Furthermore, direct peroral cholangioscopy system using an ultra-slim endoscope advancing directly in the ductal system has emerged (**Parsa and Khashab 2019**).

Direct visualization of the biliary tree is useful to distinguish benign and malignant conditions based on the evaluation of the vascular pattern such as irregular, tortuous vessels (PPV 100%), or the presence of nodularity, papillary characteristics and irregular surface (**Itoi et al., 2010 and Robles-Medranda et al., 2018**). Furthermore, cholangioscopy-guided biopsies with dedicated forceps allow targeted tissue sampling (**Parsa and Khashab 2019**).

IDUS involves a radial ultrasound probe being introduced through the duodenoscope on a guidewire during ERCP. IDUS characteristics of malignant strictures include hypoechoic asymmetric wall thickening, irregular borders and abrupt shoulders. IDUS is useful in defining a longitudinal extent and invasion of other structures (**Tabibian et al., 2015**).

Compared to ERCP and MRCP, Domagk and colleagues demonstrated that the combination of ERCP and IDUS correctly diagnosed malignancy in 88% (vs 76% and 58%) (**Domagk et al., 2004**). In term of staging, IDUS showed a low accuracy in nodal evaluation (69%), possibly due to a limited depth of ultrasonic penetration (**Tabibian et al., 2015**).

CLE is performed with a reusable miniprobe, which is also passed through the duodenoscope in the lumen of an ERCP catheter. After administration of 2.5ml to 5ml of 10% intravenous fluorescein dye, it produces live high-resolution images of the biliary epithelium. Nevertheless, it is an expensive technique and not readily available (**Tabibian et al., 2015**).

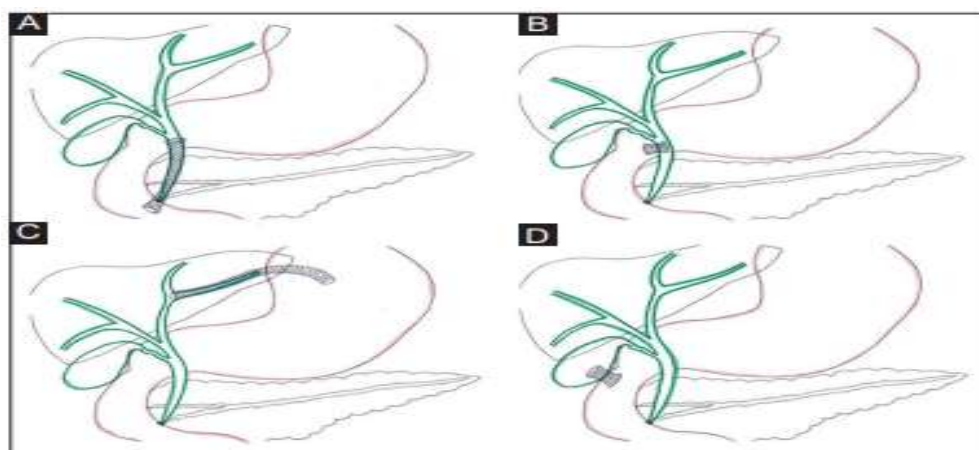
## **Advanced Endoscopic Intervention Modalities**

### **Endoscopic ultrasound-guided biliary drainage (EUS-BD)**

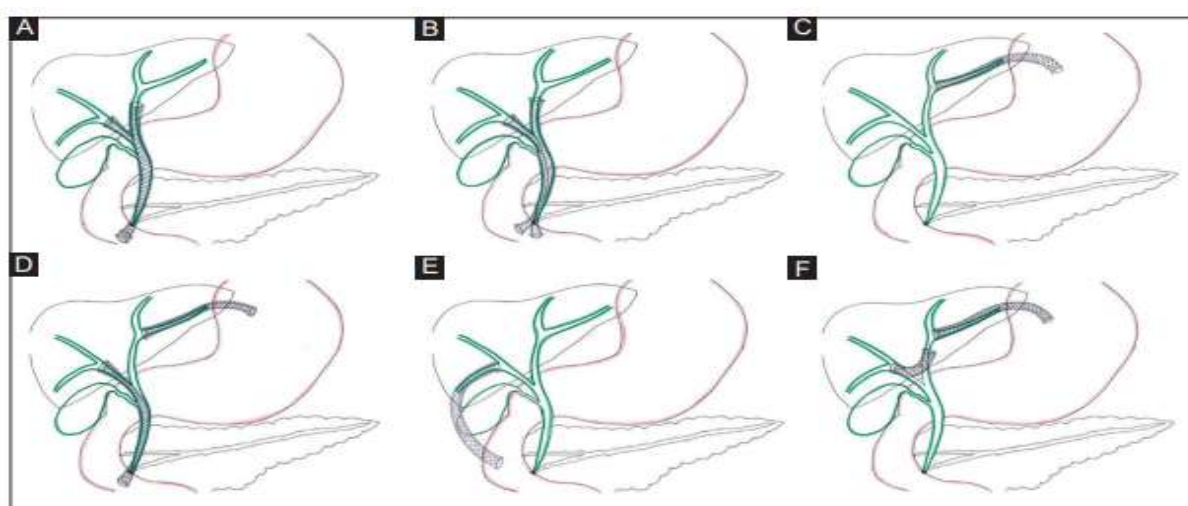
Since its first report in 2001 by Giovannini et al (**Giovannini M et al., 2001**), EUS-BD has evolved rapidly, thanks to the introduction of dedicated devices. The introduction of EUS-BD, as an alternative to or in combination with standard TBD and/or PTBD, has greatly enlarged the spectrum of drainage possibilities for both DMBO and HMBO.

EUS-BD represents a treatment option for the relief of jaundice that can be achieved through an **extrahepatic** or **intrahepatic** approach: the former is represented by direct transluminal stenting from the duodenum (EUS guided choledochoduodenostomy [**EUS-CDS**]), while the intrahepatic approach can involve direct transluminal stenting of the left intrahepatic biliary ducts from the stomach (EUS guided hepaticogastrostomy [**EUS-HGS**]), or the right intrahepatic biliary ducts from the duodenum (EUS-guided hepaticoduodenostomy), or antegrade transpapillary stent placement (**EUS-AS**) (Fig. 1).

In addition, the EUS-assisted rendezvous technique (EUS-RV), using either extra- or intrahepatic access, can provide access to the papilla in cases of ERCP failure, thus permitting subsequent traditional ERCP. Finally, EUS-guided gallbladder drainage (EUS-GBD) has recently become an alternative as a rescue in cases of conventional EUS-BD failure (**van der Merwe SW et al., 2022**).



**Figure 1** Endoscopic drainage of DMBO. (A) TBD with SEMS; (B) EUS-guided choledocoduodenostomy with LAMS; (C) EUS-guided hepaticogastrostomy with SEMS; (D) EUS-guided gallbladder drainage DMBO, distal malignant biliary obstruction; TBD, transpapillary endoscopic biliary drainage; SEMS, self-expanding metal stent; EUS, endoscopic ultrasound; LAMS, lumen-apposing metal stent. **(Binda C et al., 2024)**



**Figure 2** Endoscopic drainage of HMBO. (A) TBD with bilateral stent-in-stent technique; (B) TBD with bilateral stent-by-stent technique; (C) EUS-guided hepaticogastrostomy; (D) CERES (Combined ERCP and endosonography); (E) EUS-guided hepaticoduodenostomy; (F) Bridging method HMBO, hilar malignant biliary obstruction; TBD, transpapillary endoscopic biliary drainage; EUS, endoscopic ultrasound; CERES, combined endoscopic retrograde cholangiopancreatography and EUS. **(Binda C et al., 2024).**

## Novel Biliary Stents

Stent migration and re-occlusion due to tumor ingrowth are major disadvantages of covered and uncovered SEMS, respectively; therefore, special strategies have been developed. **Paclitaxel-eluting stents** showed no apparent benefits in a recent RCT involving 72 patients (Lee TH et al., 2019). In 2 RCTs of 23 and 55 patients (Zhu HD et al., 2012) (Hasimu A et al., 2017), **SEMS combined with radioactive seeds (I125)** showed promising results regarding patency and survival (mean survival of 8 months vs. 3 months) compared to a similar nonradioactive stent.

To overcome the problem of migration, SEMS with anchoring flaps, flared ends or differential radial expansive forces have been studied. Park et al showed that stents with anti-migration flaps migrate less often than flared-end stents (Park DH et al., 2011).

Furthermore, a double pigtail PS could serve as an anchor and prevent migration when inserted through a fcSEMS. Duodenal biliary reflux has also been described as a result of the impaired sphincter function due to the inserted SEMS (Misra SP, et al., 2009). Novel stents with an antireflux valve have been developed and have shown promising results in 2 RCTs (Hu B et al., 2014) (Lee YN, et al., 2016). However, latest data from Japan point out the need for further investigation and technical improvement (Hamada T et al., 2017).

## Novel endoscopic techniques

### Radiofrequency ablation (RFA) and photodynamic therapy (PDT)

Recently, local therapies such as RFA or PDT have been developed for the treatment of MBO. Intraductal RFA can be performed either endoscopically or percutaneously, through the insertion of a bipolar catheter over a guidewire that delivers alternating currents and thus causes localized thermal injury and necrosis. RFA has been described before stent placement, or even after, in order to ablate the tumor in growth in occluded stents. It has shown significant clinical outcomes in distal and proximal MBO, as well as a benefit in terms of patients' survival. In a meta-analysis from Sofi *et al*, the application of RFA led to longer stent patency (50 vs. 37 days,  $P<0.002$ ) and patients' survival (285 vs. 248 days,  $P<0.001$ ) (Sofi AA et al., 2018). Similarly, a recent trial from Japan demonstrated a median time to obstruction recurrence of 230 days in hilar tumors when RFA was combined with bilateral stenting (Inoue T et al., 2020). Stent patency was significantly longer in strictures  $\geq 15$  mm (Inoue T et al., 2020). However, the majority of the studies in the literature had a retrospective design and the only 2 RCTs were performed with PS after RFA (Hu BGD et al., 2016) (Yang J et al., 2018).

PDT is a 2-step process that requires the injection of an intravenous porphyrin photosensitizing agent followed by selective intraductal laser photo-radiation during endoscopy. PDT has been reported to increase stent patency, QoL, and survival (Berr F et al., 2000) (Kahaleh M et al., 2008). Systemic photosensitivity occurs in 10% of cases as the most important adverse event. Nonetheless, its role in the palliation of MBO is limited by significant costs and need for operator expertise (Ortner ME et al., 2003). Both of these adjunctive techniques might also be promising, but are still considered investigational therapies for MBO (Nakai Y et al., 2019).

## Conclusion

Endoscopy has brought a new era in the field of management of MBO. It provides patients with minimally invasive diagnostic and therapeutic tools that improve the QoL in the palliative setting, and ensure lower postoperative complication rates and longer survival. Cholangioscopy and CLE are promising diagnostic modalities, which in combination with tissue-based genetic tests (fluorescence *in situ* hybridization and flow cytometry) seem to have a role to play in future diagnostics. Furthermore, the introduction of EUS-assisted drainage has shown a new way of successful and safe management of MBO. We believe that future perspectives of EUS-BD will also include the primary decompression of the obstructive ducts. However, further studies are necessary to optimize the indications and technical flaws of the material used.

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