

Advances in the endoscopic management of malignant biliary obstruction

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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. Finally, we propose an algorithm that can facilitate management decisions in these patients.

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

Ann Gastroenterol 2020; 33 (4): 1-11

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 [1]. 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 [2], whereas 20-30% of all CCAs are found distally [3]. Other less common etiologies of obstructive jaundice include ampullary carcinoma, gallbladder

carcinoma, duodenal adenocarcinoma, lymphoma, and metastatic disease [4-6].

Concerning hilar CCAs, they account for 60% of all biliary tract cancers and include tumors that originate between the cystic duct and the second order biliary radicals, and are therefore prone to causing proximal MBO. The Bismuth-Corlette (BC) classification (Supplementary Fig. 1) has been traditionally introduced to describe the extension of hilar CCAs along the biliary tree and to assess their resectability. Thus, lesions BC I-IIIa can be resected in more than 80% of the cases, whereas lesions staged as BC IIIb have a 55.6% chance for a curative resection [7].

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 [8,9], thus having a negative impact on these patients' quality of life (QoL). The late symptom appearance, combined with the aggressive nature of the pancreatobiliary malignancies as well as the high operation risk, particularly in elderly patients, poses an ongoing therapeutic challenge. For example, only 20% of periampullary tumors are resectable at the time of first presentation [10,11].

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,

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Conflict of Interest: None

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Received 23 February 2020; accepted 28 April 2020; published online 25 May 2020

DOI: <https://doi.org/10.20524/aog.2020.0497>

but also seems to improve the diagnostic accuracy of (pre-) cancerous lesions. Cholangioscopy and intraductal ultrasound are recent novel endoscopic techniques increasingly being implemented in the diagnostic workup of pancreatobiliary malignancies.

In this article we review the endoscopic approach to MBO, according to the level and nature of obstruction. Furthermore, we discuss future endoscopic perspectives based on recent and ongoing trials in the field of pancreatobiliary malignancies (Table 1).

Diagnostic endoscopic modalities

The early diagnosis and characterization of pancreatobiliary malignancies is the cornerstone for successful treatment. Typically, noninvasive imaging and laboratory tests comprise the first approach for the initial evaluation, followed by more invasive endoscopic techniques such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS).

ERCP

ERCP traditionally plays an important role in the diagnosis of the etiology of MBO. Although its diagnostic use has been limited by noninvasive radiologic modalities such as computed tomography (CT) scan and magnetic resonance imaging cholangiopancreatography (MRI-MRCP), ERCP also provides a radiographic visualization of the stricture(s) and thus provides important information about their length, location and extent. A long, irregular stricture with the presence of a “double duct sign” is considered typical for an underlying malignancy [12]. Once a suspicious stricture is detected by other imaging modalities, brushing and forceps biopsies during the ERCP can establish the diagnosis. However, the sensitivity of brush cytology ranges from 44-80% for CCA [13] and 30-60% for pancreatic cancer [14,15]. Navaneethan *et al.* reported in a meta-analysis of 9 studies and 730 patients that brushings

and intraductal biopsies show a similar diagnostic yield for malignant biliary strictures, only moderately increased when both methods are combined: sensitivity 0.59 (95% confidence interval [CI] 0.54-0.65), specificity 1.00 (95%CI 0.90-1.00) [14].

EUS

EUS has proven to be at least as accurate in detecting ampullary carcinoma as CT scan or MRCP. Cannon *et al.* evaluated 50 patients with ampullary cancer and showed a superiority of EUS for the characterization of T staging compared to MRI and CT scan (78% vs. 46% vs. 24%, respectively [16]). However, this accuracy was limited to 71% when a biliary stent was present [16]. In the case of MBO due to pancreatic cancer or distal CCA, EUS with the use of fine-needle aspiration (FNA) can reach a sensitivity of 92% and a specificity of 96% [17] in pancreatic cancer, and up to 100% detection in distal CCA [18]. Hilar strictures appear more challenging in the establishment of diagnosis, since multiple studies demonstrated a wide range of sensitivity of EUS-FNA between 47% and 89% [12,18-20].

Lately, technical developments regarding EUS tissue acquisition and evaluation have improved its diagnostic yield. Rapid on-site cytological evaluation (ROSE) is increasingly available in many hospitals. ROSE increases the diagnostic merit of EUS-FNA to 20% and ensures patients' safety by decreasing the number of passes necessary to establish the diagnosis. Furthermore, the introduction of special designed biopsy needles (EUS-FNB) enables the acquisition of better histological samples within few passes, since they procure large volumes of tumor cells and desmoplastic stroma. Comparative studies have reported similar diagnostic accuracy for EUS-FNA and FNB in pancreatic cancer [21,22]. However, recent randomized control trials have shown superiority of EUS-FNB over the FNA method in terms of passes needed, sample adequacy and overall diagnostic yield [23-25].

Other diagnostic endoscopic tools

Recently, novel endoscopic modalities have been developed for the exact characterization of MBO. Direct visualization of the biliary tree is nowadays feasible with the use of a single-operator cholangioscope with integrated digital sensors (SpyGlass™), while specially designed biopsy forceps (SpyBite) allow for directed specimen acquisition. Peroral cholangioscopy (POCS) has shown promising results, with a diagnostic accuracy of more than 80% in both visual inspection and cholangioscopy-guided biopsies [26]. The sensitivity and specificity of the diagnosis of malignancy based on visual impression during POCS is reported to be above 90%, whereas cholangioscopy-targeted biopsies appear to have a slightly lower sensitivity of around 60-85% [27-29]. Intraductal malignant growths can be easily distinguished because of their irregular vascular pattern, nodularity, papillary morphology and bleeding tendency (Fig. 1) [30-32]. However, POCS has certain limitations,

Table 1 Current and future endoscopic perspectives in the management of malignant biliary strictures

Diagnostic procedures
Endoscopic retrograde cholangiopancreatography
Endoscopic ultrasound (EUS) +/- fine-needle aspiration
Peroral cholangioscopy
Intraductal ultrasound
Probe-based confocal laser endomicroscopy
Therapeutic procedures
Endoscopic retrograde cholangiopancreatography
EUS-guided drainage
EUS-choledochoduodenostomy
EUS-hepaticogastrostomy
EUS-rendezvous technique
EUS antegrade biliary stenting
Radiofrequency ablation
Photodynamic therapy

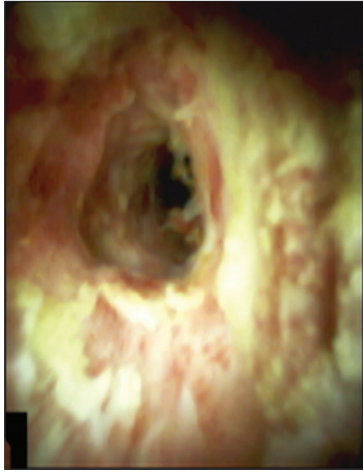


Figure 1 Cholangioscopic image hyperemic of a malignant stricture in the proximal bile duct. The lesion is hyperemic, has irregular borders and shows papillary protrusions

particularly in the case of extrinsic strictures or distal CCAs, due to the unstable scope position [33].

Intraductal ultrasound involves a radial probe being introduced into the bile duct over a guidewire. Although its accuracy for MBO reaches 95% [34], its clinical value is somewhat limited by the reduced maneuverability through the bile tract and the lack of tissue acquisition. Probe-based confocal laser endomicroscopy (pCLE) is a promising endoscopic technique that provides in vivo imaging during ERCP. Fluorescein, a contrast agent, is typically injected intravenously and yields good contrast of vessels and tissue architecture. Meining *et al*, in a prospective trial of 102 patients, reported a sensitivity of 98% and a specificity of 67% [35] in detecting MBO. However, its poor interobserver agreement [36] and high costs have limited its use.

Therapeutic endoscopic modalities

Preoperative treatment

Distal MBO

Preoperative biliary drainage (PBD) has been an issue of debate over the last decade. Although hyperbilirubinemia has been associated with increased morbidity and mortality, multiple meta-analyses have demonstrated worse postoperative outcomes in patients with distal obstruction treated with PBD [37-39]. In particular, in a large randomized control trial (RCT) van der Gaag *et al* showed higher complication rates in patients who had PBD compared to those without preoperative treatment (74% vs. 39% [40]).

However, certain conditions, such as cholangitis, severe symptomatic jaundice, delayed surgery and neoadjuvant therapy have been embraced by international guidelines [33,41] as main indications for PBD. Preoperative bilirubin levels above 300 $\mu\text{mol/L}$ serve as a cutoff for severe postoperative

complications and poorer long-term survival, as shown in a recently published retrospective study of 1200 patients [42].

Regarding the preferred route, the endoscopic approach should be favored over the percutaneous approach, since the latter has been associated with tract seeding, lower survival rates, and a higher risk of recurrence [43-45].

Type of stent

The recommended type of stent for PBD has been the subject of investigation in many studies, including some without an oncological primary endpoint [46-48]. The majority of them support the findings of a Dutch RCT conducted in patients with pancreatic cancer: the use of fully covered self-expandable metal stents (fcSEMS) resulted in fewer perioperative adverse events compared with the group treated with plastic stents (PS) (24% vs. 46%) [49]. Compared to uncovered SEMS (uSEMS), fcSEMS seem to have a longer patency and duration as well as fewer days of delay for chemotherapy onset [46]. However, in a recent RCT of 119 patients with distal MBO uSEMS showed equal results in biliary drainage (BD) compared to fcSEMS (72.2% vs. 72.9%) [50].

Proximal MBO

According to the current guidelines of the European Society for Gastrointestinal Endoscopy [41], endoscopists and radiologists should refrain from PBD in hilar malignancies unless cholangitis is present or the predicted future liver remnant volume following surgery is less than 30% [51]. There have been controversial data regarding the preferred route of stenting [52,53]. Nonetheless, we should take into consideration that the technical success in patients with proximal MBO is lower when the endoscopic approach is preferred [54]. The final choice should take into account the available expertise and the exact localization of the stricture. PS are favored over fcSEMS, but further studies are necessary [41].

Palliative treatment

Distal MBO

Surgical bypass was the initial approach to treating cholestasis in patients with distal MBO, given the low rates of recurrent jaundice (2-5%). Nevertheless, surgery was soon replaced by radiographic and endoscopic techniques because of its high risk of postoperative morbidity and mortality [55,56]. Compared to percutaneous transhepatic BD (PTBD), ERCP is the preferred initial approach. It has a lower rate of adverse events (8.6% vs. 12.3%) and shorter hospitalization. Furthermore, it is associated with fewer repeated procedures and lower costs, and it is physically better tolerated by patients [57]. In case of failed access or difficult biliary cannulation, other techniques such as PTBD or EUS-guided BD (EUS-BD) are appropriate.

SEMS are favored over PS, as shown in multiple meta-analyses [58-62]. They demonstrate longer patency and

patient survival, fewer adverse events and lower reintervention rates. Regarding cost efficacy, there seem to be no significant differences between PS and SEMs. Interestingly, in a recent RCT conducted in The Netherlands [63], costs were demonstrated to be similar in both groups, even in patients with a life expectancy of <3 months or metastatic disease.

The big question, however, is whether fcSEMS or uSEMS should be the gold standard for drainage in patients with distal MBO. The data from various meta-analyses have shown conflicting results [64-66]. All of them agree that, compared with uSEMS, fcSEMS have longer patency but are more prone to migration. However, none of these stents have demonstrated a significant survival benefit. Because of the patency benefit, a recently published international consensus expresses a weak preference for fcSEMS for pancreatic MBO [33].

Another challenging issue in patients affected by distal tumors is concomitant biliary and duodenal malignant obstruction. These are classified into 3 different types [67]: type I, in which duodenal strictures are present in the first part of the duodenum; type II, in which the duodenal stenosis involves the papilla; and type III, in which duodenal stenosis occurs distally from the papilla. Unlike type I and III lesions, where the duodenal and biliary stents do not interact with each other, in type II lesions accessing the ampulla, especially the native ampulla, through the mesh of the duodenal uSEMS is associated with a percentage of failure up to 60% [68]. Therefore, endoscopic transpapillary BD before duodenal stent insertion is recommended if the duodenoscope can pass through the duodenal stricture [69]. Otherwise, combination with PTBD, removal of some of the wires of the duodenal mesh with rat-tooth forceps, or destroying the mesh wire using argon plasma coagulation might be useful to gain access to the biliary orifice. Recently, a novel duodenal SEMs with expandable lattices in the mid portion has been reported to facilitate biliary stent deployment in 91.7% of the cases [70]. Nevertheless, the choice of the endoscopic approach is based on expertise and exact location of the tumor.

Proximal MBO

In patients with hilar MBO, stenting aims to ensure drainage of $\geq 50\%$ of the total liver volume, associated with prolonged survival and improved QoL [71]. Although PTBD has been shown to have greater technical success than stenting via ERCP [54], its major drawbacks—inconvenience to the patient, leaking, seeding and infection risk, reduced QoL—have given endoscopy the role of primary intervention in the palliative setting.

Similarly to studies in distal MBO, several RCTs in patients with hilar malignancy demonstrated a superiority of SEMs over PS in patients with a life expectancy of over 4 months [72-74]. uSEMS are to be preferred, because occlusion of small bile ducts by an fcSEMS might increase the risk of cholangitis.

The choice between unilateral or bilateral stents is based on the morphology of the hilar malignancy and the segments that need to be drained. Although Bismuth I tumors can be approached similarly to distal MBO, Bismuth II-IV tumors still remain a field of controversy. CT scan can assess the

percentage of the total liver volume affected by the strictures and therefore justify the choice of bilateral drainage, especially in Bismuth type III or IV lesions. Unilateral drainage appears to be technically less challenging, and it demonstrates similar outcomes with bilateral stenting according to 2 RCTs [74,75]. However, in 2 recent Asian RCTs, bilateral stenting for Bismuth type III-V strictures showed a higher clinical success rate (84.9 vs. 95.3%, $P=0.047$) and a lower reintervention rate (60.3 vs. 42.6%, $P=0.049$) compared to unilateral [76,77].

In any case, endoscopic drainage of complex malignant hilar strictures is technically demanding and might require multiple SEMs. In a recent large retrospective Italian study, SEMs malfunction was usually attributed to sludge formation, in 65.9% of the cases, or to overgrowth and ingrowth (34.1% [78]). Such cases require recannulation of the duct through the occluded stent. Sludge and clots can be mechanically removed with the ERCP balloon, whereas ingrowth and overgrowth can be treated by placing another uSEMS inside the previous one.

There are 2 methods for bilateral endoscopic drainage. In the stent-in-stent (SIS) technique a second uSEMS is placed through the mesh of the first one into the contralateral hepatic duct, whereas in the stent-by-stent (SBS) technique both of the stents are inserted and placed, simultaneously or one after the other, side by side into the left and the right hepatic duct. The branch more difficult for cannulation should be selected as the first stent placement target, to ensure easy insertion of the second stent. Otherwise, balloon dilation of the contralateral hepatic duct immediately before the first stenting might facilitate second SEMs insertion.

Both techniques are considered equivalent in terms of successful drainage, complications and occlusion rates [79-81]. However, unpublished data from Korea indicate that the SIS method might have a tendency towards a higher rate of stent patency compared to SBS. Hence, each case has to be assessed individually and evaluated regarding expertise, pros and cons.

Stent evolution

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 [82]. In 2 RCTs of 23 and 55 patients [83,84], SEMs combined with radioactive seeds (I125) showed promising results regarding patency and survival (mean survival of 8 months vs. 3 months [83]) 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 [85]. 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 [86]. Novel stents with an antireflux valve have been developed and have shown promising results in 2 RCTs [87,88]. However, latest data from

Japan point out the need for further investigation and technical improvement [89].

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 ingrowth 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, $P < 0.001$) [90]. 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 [91]. Stent patency was significantly longer in strictures ≥ 15 mm [91]. However, the majority of the studies in the literature had a retrospective design and the only 2 RCTs were performed with PS after RFA [92,93].

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 [94-96]. 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 [95]. Both of these adjunctive techniques might also be promising, but are still considered investigational therapies for MBO [33].

EUS-BD

Since 1996, when Wiersema reported the first EUS-guided cholangiopancreatography [97], and 2001, when Giovannini performed the first EUS-assisted choledochoduodenostomy (CDS) [98], there has been an increased interest in the utility of EUS-BD in patients with benign and malignant biliary obstructions. EUS-BD is further categorized, according to the route of approach and the site of BD, as CDS, hepaticogastrostomy (HGS), rendezvous technique (RV), and antegrade biliary stenting. Briefly, a sectorial echoendoscope identifies the dilated hepatic ducts or the bile duct. The duct of interest is then punctured with a 19-G needle and a guidewire is placed to guide the stent through the gastric or duodenal wall (Fig. 2). Alternatively, the guidewire can be exteriorized through the papilla into the second part of the duodenum and a SEMS can be forwarded in an antegrade fashion transpapillary. In the RV technique, once the guidewire is guided through

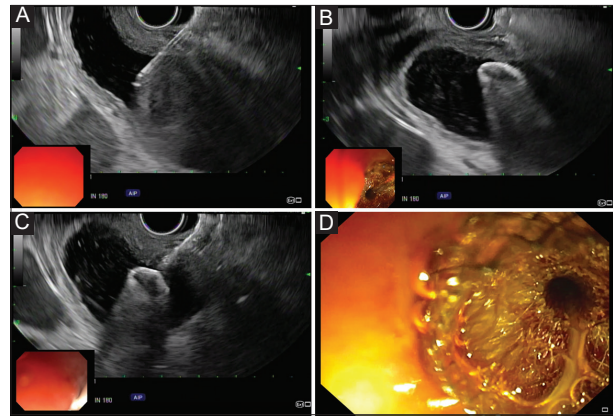


Figure 2 Steps of EUS-CDS. The dilated bile duct is punctured under EUS-guidance with a 19-g FNA needle (A). The distal end of the LAMS is deployed in means of an electrocautery enhanced delivery system in the dilated lumen (B). The distal part of the deployed LAMS is pulled closed to the wall of the bile duct (C). Deployment of the proximal end of the LAMS in the duodenal lumen under endoscopic guidance (D) EUS, endoscopic ultrasound; FNA, fine-needle aspiration; CDS, choledochoduodenostomy; LAMS, lumen-apposing metal stent

the papilla the echoendoscope is withdrawn and the stent is advanced in the obstructed duct by means of a duodenoscope.

Compared to PTBD, EUS-BD is similarly effective but is associated with a lower rate of adverse events and fewer reinterventions [99,100]. EUS-BD has high technical and clinical success rates [101], is less expensive than PTBD and improves patients' QoL, since external drainage might cause skin irritations, infections or leakage. Therefore, current international consensus guidelines recommend EUS-BD after failed ERCP if the expertise is available [102,103].

The efficacy of EUS-BD as a first-line treatment for malignant decompression is the subject of recent and ongoing studies. Emerging data from 3 recent prospective trials and 1 meta-analysis [104-107] described similar technical success rates and clinical outcomes between EUS- and ERCP-assisted primary BD. There was no significant difference in terms of procedure time or the risk of stent occlusion; however, EUS-BD was associated with a lower risk of pancreatitis (risk ratio 0.22, 95%CI 0.05-1.02) [107]. These results remain to be confirmed in the ELEMENT trial, an ongoing multicenter prospective RCT that involves 9 Canadian centers [108].

Regarding the recommended route of approach, EUS-RV seems to be the safest of all procedures—should conditions permit—because it respects the patients' anatomy. Experts agree that the access and drainage routes in EUS-assisted biliary interventions should be chosen depending on the indication, the level of the biliary obstruction, the anatomical condition of the upper gastrointestinal tract and the operator's experience [103]. However, EUS-RV involves certain pitfalls, since it is associated with a risk of pancreatitis due to the manipulation of the papilla, it requires a longer intervention time and it is technically more challenging.

The choice between CDS and HGS has mostly to do with the level of obstruction and the patient's anatomy. CDS is well

tolerated with shorter intervention time, whereas EUS-HGS has a higher level of difficulty and a longer learning curve: the targeted duct lies most commonly in segment 3 of the liver and the puncture is performed through the thick gastric wall.

Over the last decade, SEMs have been introduced in EUS-BD. Recently, the use of lumen apposing metal stents for CDS has been increasing, since they provide lower migration rates and a smaller risk of bile leakage [109]. Furthermore, specially designed SEMs and PS have been proposed for use in HGS [110,111]. These stents are mostly 8-10 cm long, because a longer luminal length seems to be associated with long-term stent patency [112].

Concluding remarks

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 pCLE 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 (Fig. 3, 4). However, further studies are necessary to optimize the indications and technical flaws of the material used. The bottom line is that MBO is a complex entity and the decision concerning its diagnostic and/or therapeutic management should be based on personalized criteria, the location of the stricture, and the operator’s expertise.

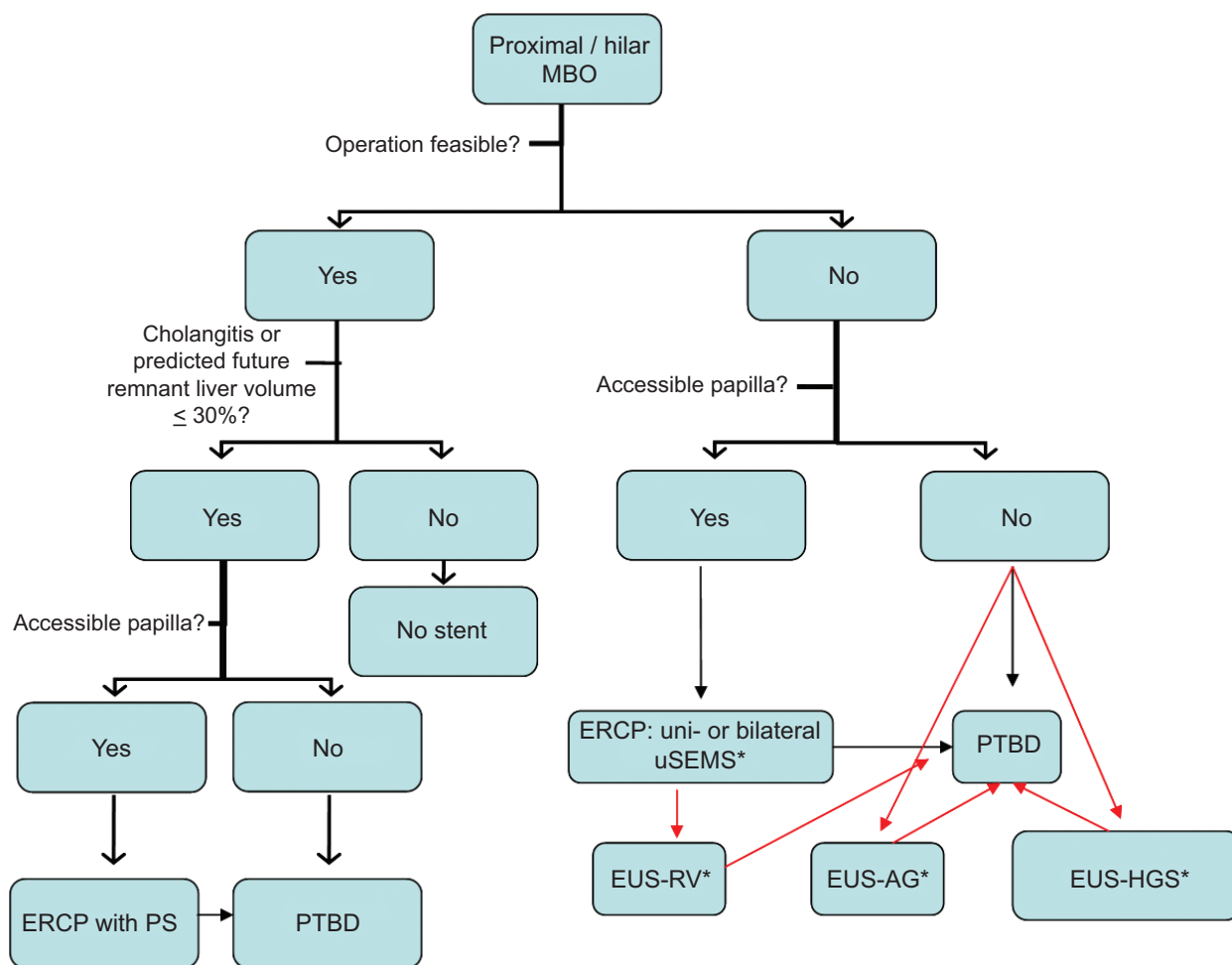


Figure 3 Simplified algorithm of management for patients with proximal/hilar MBO. The red arrows indicate future tendencies
 *Taking into account the level of obstruction and expertise
 MBO, malignant biliary obstruction; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; uSEMS, uncovered self-expandable metal stents; PS, plastic stents; EUS-RV, endoscopic ultrasound rendezvous technique; EUS-AG, endoscopic ultrasound antegrade biliary stenting; EUS-HGS, endoscopic ultrasound hepaticogastrostomy

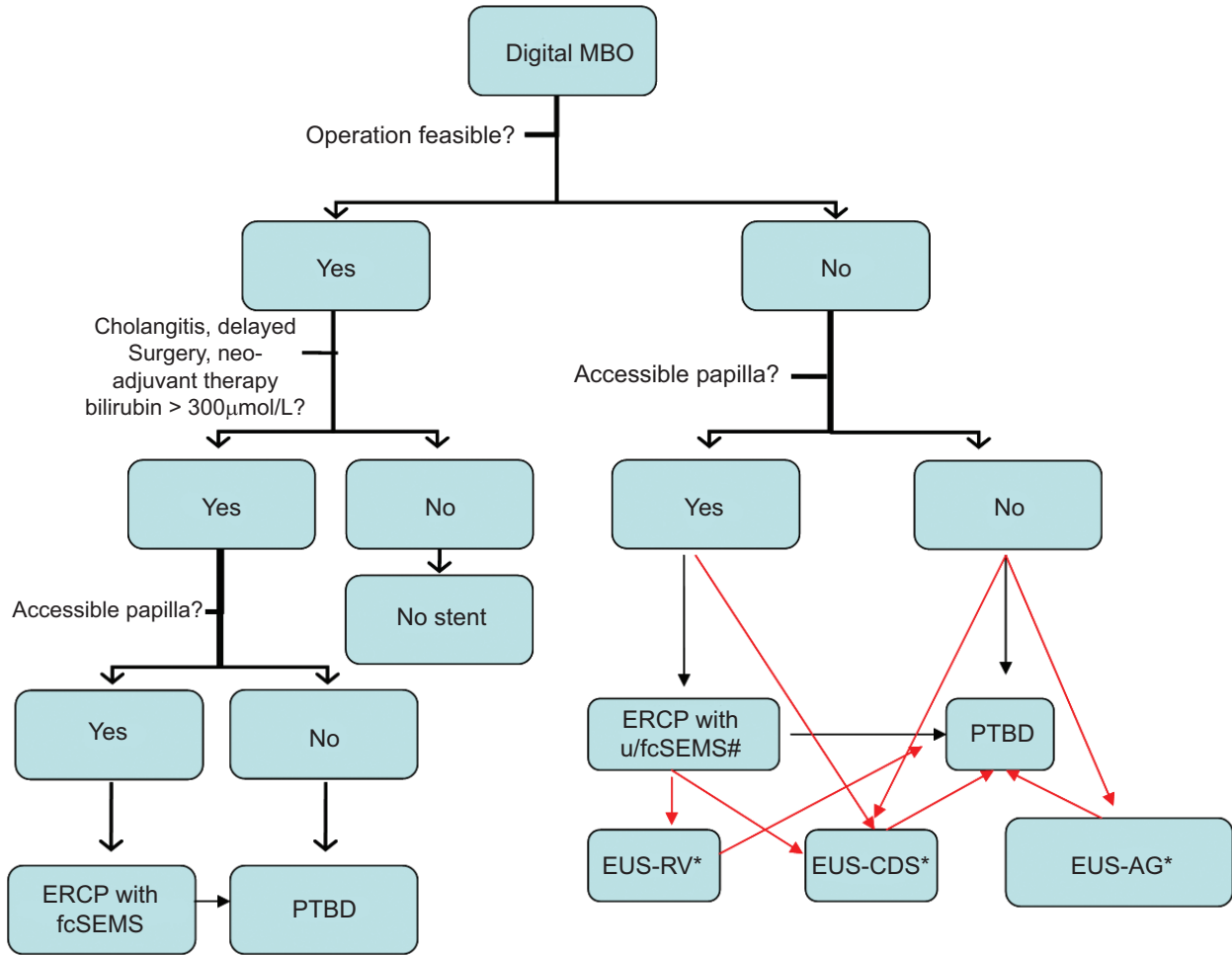


Figure 4 Simplified algorithm of management for patients with distal MBO. The red arrows indicate future tendencies

*Taking into account the level of obstruction and expertise

#weak preference for fcSEMS

MBO, malignant biliary obstruction; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; uSEMS, uncovered self-expandable metal stents; fcSEMS, fully covered self-expandable metal stent; EUS-RV, endoscopic ultrasound rendezvous technique; EUS-AG, endoscopic ultrasound antegrade biliary stenting; EUS-CDS, endoscopic ultrasound choledochoduodenostomy

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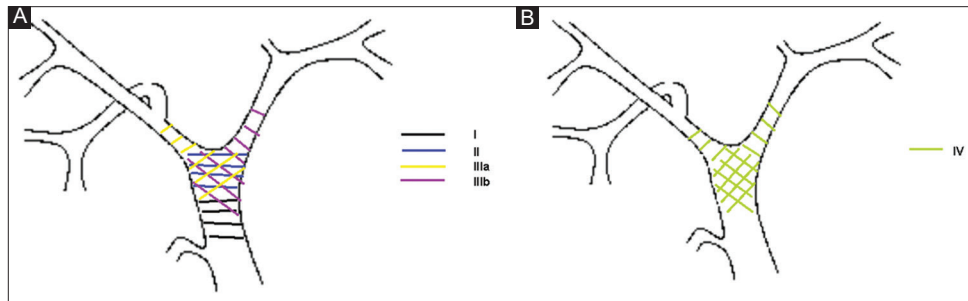
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Supplementary material



Supplementary Figure 1 Bismuth-Corlette classification for hilar malignant lesions. (A) In type I (black) the stricture is in the common hepatic duct, in type II (blue) the stricture interrupts the hepatic bifurcation, in type III the stricture reaches the right (IIIa, yellow), or the left hepatic duct (IIIb, purple). (B) Type IV (green) strictures involve the hepatic confluence and both of the hepatic ducts