Prijic *et al. Hepatoma Res* 2023;9:42
DOI: 10.20517/2394-5079.2023.20

Hepatoma Research

Review

Open Access

Strategy for ERCP stenting in cholangiocarcinoma

Radovan Prijic[1], Agata Ladic[2], Pave Markos[2]

[1]Department of Internal Medicine, Affoltern Hospital, Affoltern am Albis 8910, Switzerland.
[2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, University Hospital Center Zagreb, Zagreb 10000, Croatia.

Correspondence to: Dr. Radovan Prijic, Department of Internal Medicine, Affoltern Hospital, Sonnenbergstrasse 27, Affoltern am Albis 8910, Switzerland. E-mail: radovan.prijic@gmail.com

How to cite this article: Prijic R, Ladic A, Markos P. Strategy for ERCP stenting in cholangiocarcinoma. *Hepatoma Res* 2023;9:42. https://dx.doi.org/10.20517/2394-5079.2023.20

Received: 14 Mar 2023 **First Decision:** 9 Aug 2023 **Revised:** 4 Sep 2023 **Accepted:** 21 Sep 2023 **Published:** 26 Sep 2023

Academic Editors: Guang-Wen Cao, Nan Li **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

Considering the steadily growing incidence of cholangiocarcinoma (CCA) worldwide, there is a constant need to re-evaluate and re-think its pathophysiology, diagnostic modalities, and mostly important, its treatment. No matter the histopathological appearance, endoscopic procedures - mainly Endoscopic Retrograde Cholangiopancreatography (ERCP) with stenting - are often used in the treatment of CCA complications, such as biliary obstruction when biliary drainage is indicated. Indications for preoperative biliary drainage in surgical cases are adjusted to each patient's status. On the contrary, palliative drainage is the first option for relieving symptoms and improving the quality of life in the context of locally advanced and unresectable CCA. Further, concern about stenting techniques depends on the stricture location: Bismuth-Corlette types I and II are usually endoscopically drained with one stent placed in biliary tract, while for types III and IV, even bilateral stenting may prove inadequate. Stents used in ERCP are either plastic or self-expandable metallic stents (SEMS). Though plastic stents show some advantages over SEMS in terms of removability and possibility to adapt to a biliary tree which allows potential reinterventions, SEMS are better in terms of patency, lower complications number, and success of drainage. Besides ERCP, echo-endoscopic drainage is also an option, especially when ERCP approach has not yielded a successful drainage. The aim of this study was to show the potential of ERCP stenting in CCA treatment, its possible pitfalls, and the need to consider multiple levels of ERCP-related care.

Keywords: Cholangiocarcinoma (CCA), endoscopic stenting, biliary drainage, self-expandable metallic stents (SEMS)

INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive, heterogenous biliary tract carcinoma with rising incidence

worldwide[1]. It is divided into intrahepatic (iCCA) and extrahepatic cholangiocarcinoma (eCCA) - based on the anatomic tumor localization. The latter is further subdivided into hilar (hCCA - "Klatskin tumor") and distal cholangiocarcinoma (dCCA) [Figure 1]. Histopathologically, there are two predominant disease subtypes: cancers with cylindrical, mucin-producing glands and those with cuboidal, non-mucin-producing glands[2]. Another recognized entity is mixed hepatocellular - cholangiocarcinoma (HCC-CCA), a tumor with a "bi-phenotypic" property, i.e., a heavy burden of extremely aggressive behavior and a poor prognosis for both HCC and CCA[3].

Although CCA is the most common type of biliary tract carcinoma, the knowledge of its biology is still unveiled. The traditional belief is that CCA originates from biliary epithelia, considering its' pathohistological presentation (glandular morphology, expression of mucin, and biliary cytokeratins 7 and 19)[4]. Research done during the last few decades has brought about a new perspective of CCA origin and appearance, accentuating its diversity - such as bipotential hepatic progenitor cells (HPSc) as a cellular source of ICC, as well as novel research on cancer-related fibroblast subpopulations[5] and glycosphingolipid marker identified in cholangiocarcinoma - Ganglioside GM2[6].

As already mentioned, CCA is a very aggressive disease characterized by its silent clinical character, which prevents early diagnosis. The majority of patients present with an advanced-stage disease with symptoms that reflect it - such as jaundice, cachexia, and weakness[7].

Additionally, contemporary serum markers include CA 19-9 and carcinoembryonic antigen, which both have low sensitivity and specificity[8] and thus are quite useless in the early course of the disease.

Although most patients with cholangiocarcinoma develop this malignancy *de-novo,* certain clinical conditions and risk factors have been associated with an elevated risk of developing CCA: primary sclerosing cholangitis (PSC) is the first of these conditions and is associated with a prevalence of cholangiocarcinoma of 51%[9]. Others include liver fluke infection with *Opistorchis viverrini* and *Clonorchis sinensis,* hepatolithiasis, biliary tract malformations (such as choledochal cysts), hepatitis C, cirrhosis, toxins and others[8].

Since most patients come with the advanced disease, treatment options are insufficient. For extrahepatic CCA, surgery is the only curative treatment, with the goal of R0 resection. Recent studies suggest that neoadjuvant therapy followed by liver transplantation may result in long-term survival in selected patients with localized, node-negative cholangiocarcinoma[10]. However, surgical procedures (including liver transplantation) are not the result of prospective studies.

According to data, approximately 35% of patients have an early-stage disease and are candidates for surgical resection[7]. On the other side, more than 50% of patients with jaundice are inoperable at the time of the diagnosis[11] and require some form of palliative care, such as systemic chemotherapy, targeted radiation therapy, and endoscopic procedures.

Regarding everything mentioned, each patient needs a personalized approach - preferably through multidisciplinary treatment. In patients who suffer from pain, jaundice and pruritus, an indication exists for palliative endoscopic drainage, whose intention is to relieve the aforementioned symptoms. There are two possible types of endoscopic drainage:

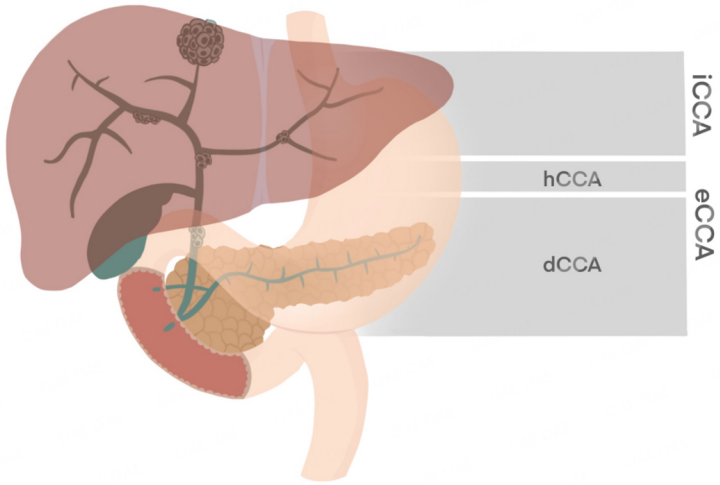

Figure 1. Division of cholangiocarcinoma according to anatomical location. iCCA: intrahepatic cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; hCCA: hilar cholangiocarcinoma ("Klatskin tumor"); dCCA: distal cholangiocarcinoma.

1. Perioperative in a potentially curable disease and;

2. Palliative drainage in a setting of non-curable malignant disease.

Both are technically demanding procedures but provide efficient drainage. The aim of this article was to show the best strategies for endoscopic intervention in all types of CCA.

Epidemiology

As already mentioned, the incidence of CCA is steadily rising worldwide[9]. This is especially true for iCCA, while eCCA prevalence is stable or slightly decreasing[12]. However, some authors debate the actual number of different types of carcinoma, as they believe that hilar CCA is misclassified into "i" and not into "e" CCA[13]. This could also be happening with the misclassification of hilar CCA based on the old ICD codes. In the USA, hCCA is the largest group which accounts for approximately 50%-60% of all CCAs[12]. This is followed by dCCA accounting for up to 30% and iCCA for 10%-20%[12].

The incidence of CCA is 0.3-6 per 100,000 inhabitants per year, while mortality counts from 1-6 per 100 000 inhabitants per year worldwide[14]. Eastern countries, such as South Korea, China and Thailand, exhibit more than 6 per 100,000 habitants per year, due to standard liver fluke infection with the aforementioned parasites[14]. A recent deep analysis of the mortality rates from CCA showed that, in the early 2000s, the mortality rates from ICC were below 1/100,000 among men in most countries[14], but between 2002 and 2012, mortality increased in all countries except for Finland. Some newer data point to the rising CCA incidence in the USA, with a greater increase in iCCA, contrary to eCCA.

In order to emphasize the adequacy of a certain - mainly endoscopic - therapeutical approach, we evaluated different strategies for managing biliary drainage in CCA.

Consequences of the biliary obstruction

Biliary obstruction causes liver dysfunction that, in the long run, has many consequences. Hepatic cell dysfunction leads to reduced protein synthesis and hypoalbuminemia[15]. The blockage of bile drainage to small intestine leads to the damage of the mucosal barrier, which subsequently leads to endotoxemia and

proinflammatory state[16]. Retained bilirubin in the system also contributes to the enhanced inflammatory response in these patients. These pathophysiological changes finally cause failure of other organs, immune suppression, coagulation, and nutritional impairment[16]. Hypoalbuminemia is an independent negative predictive factor for postoperative complications[17]. Reestablishing the biliary drainage in time implies preserving the liver function and enabling the patients to undergo chemotherapy[15].

ERCP STENTING FOR CHOLANGIOCARCINOMA

Preoperative biliary drainage

There is a lot of controversy regarding the question of whether preoperative biliary drainage should be done and how it should be done prior to laparotomy in patients with obstructive jaundice and resectable cholangiocarcinoma.

Firstly, it should be emphasized that stents can induce artifacts in imaging, and all diagnostic imaging procedures should be done before stent placement in order to assess tumor resectability[18,19]. ERCP and stent placement can cause main bile duct inflammation, making the R0 resection that includes radical hepatic operation and lymphadenectomy more complicated[20]. Additionally, stent-induced inflammation can alter the intraoperative macroscopic appearance of tumor, making it look inoperable because of the impossibility of visualizing borders of tumor spreading and making an accurate diagnosis of vascular invasion[21].

The goal of preoperative biliary drainage is to reduce surgical complications, but usually should be done in the settings of acute cholangitis, biliary sepsis, liver dysfunction, scheduled neoadjuvant chemotherapy, and planned radical and extensive resection of the liver[19,22].

In non-jaundiced patients, timing between diagnosis and surgery should not be the only reason for preoperative biliary stenting. Regarding the bilirubin levels, total serum bilirubin > 300 μmol/l was associated with a high risk of postoperative complications, so in that case, preoperative drainage should usually be done, even without clinical signs of sepsis or cholangitis[23].

Special consideration must be given to PSC because of a difficult differentiation between symptoms and findings of early stages of CCA complicating PSC from PSC alone.

All modalities should be used to differentiate benign from malignant stricture (cross-sectional imaging, ERCP + cytological brush, and cholangioscopy). In cases of cholestasis, biliary sepsis and confirmation of malignant stenosis, a plastic stent should be placed with additional antibiotic prophylaxis[24]. In hilar PSC stenosis, percutaneous or EUS-guided biopsies should be avoided due to the risk of tumor seeding[25].

As the major treatment role of ERCP in PSC patients covers dominant strictures management, some centers propose prophylactic dilation of dominant strictures to prevent complications and extend the time to liver transplantation. In a study by Rupp *et al.*, annual ERCP in PSC patients was associated with longer transplantation-free survival in comparison to on-demand therapy[26]. Therefore, we propose timely dilations and ERCP drainage as this approach could possibly prevent chronic liver damage and infectious complications.

Regarding the extrahepatic distal cholangiocarcinoma, a recently published multicenter study demonstrated no clear benefit of preoperative bile duct drainage; even more, it was associated with a survival rate decrease[27]. If it is needed to plan bile duct drainage for the above-mentioned reasons, the endoscopic

approach is preferred over PTBD due to the higher success rate and lower risk of cholangitis[28,29]. Due to the lower rate of endoscopic reintervention, a 10mm diameter self-expandable metal stent should be used as a first line for biliary drainage[30].

Regarding hilar cholangiocarcinoma, the operation always requires a concomitant major liver resection, so obstructive jaundice is a big risk factor for postoperative failure of the liver remnant. Regarding the large prospective cohort studies, bile duct drainage performed before surgery in non-jaundiced patients did not change survival rate, surgical postoperative complications, R0 resections, and length of hospital stay. In addition, there was no effect on mortality or morbidity rates after radical surgery[31-33]. However, for patients with bile duct obstruction, adequate bile duct decompression before surgery reduced mortality due to improved postoperative liver function and regeneration[11].

Indications for preoperative biliary drainage are made taking into consideration benefits and intervention risks for each case. Usually, patients for planned resection of the left liver lobe do not need preoperative biliary drainage because rates of mortality are elevated due to the high incidence of postoperative sepsis[34]. On the contrary, it has been shown that liver failure and death after right hepatectomy are more frequent in jaundiced patients without preoperative biliary drainage due to a higher volume of resected liver parenchyma, so there is a clear benefit of performing bile duct decompression to keep the adequate function of the remnant left liver lobe[34].

In the complex cases of hilar malignant strictures (Bismuth-Corlette type III and IV) with a need for preoperative biliary drainage before hepatic resection or before neoadjuvant chemotherapy, the choice of drainage technique (percutaneous or endoscopic approach) should be made within the multidisciplinary team. There are three options for percutaneous approach: (1) external biliary drainage; (2) internal-external drainage; and (3) percutaneous SEMS[35].

In hilar cholangiocarcinoma, although endoscopy could be the technique of choice because it is slightly less invasive, several meta-analyses have shown an advantage of preoperative percutaneous over endoscopic drainage regarding safety, with lower rates of pancreatitis and cholangitis[36-38].

One possible long-term complication in patients with resectable hilar cholangiocarcinoma treated with a percutaneous approach is tumor seeding. One retrospective study showed 5.2% recurrence after percutaneous drainage, with risk rising with a longer time to surgery after the drainage[39]. That makes avoidance of this complication another reason not to delay surgery in these patients[35].

According to European guidelines, there is no universal standard follow-up schedule for patients with cholangiocarcinoma. Usually, it is recommended to follow up on these patients with visits every 3-6 months during the first 2 years with laboratory controls, tumor markers, and CT of thorax, abdomen and pelvis[40]. As the infection (acute cholangitis) after the biliary stenting reduces stent patency and overall survival[41], early recognition and treatment could improve outcomes in these patients[40]. Therefore, early recognition of infective complications after biliary stenting should be implemented in the cancer surveillance schedule every 3 months, allowing early treatment in the case of complications.

Palliative drainage

In the setting of locally advanced and unresectable cholangiocarcinoma (CCA), endoscopic drainage is the first option[11] for palliation with the goal of relieving the disease symptoms and significantly improving overall life quality[19,42,43]. There are different indications for palliative biliary drainage. These include

enabling the patient to undergo further systemic treatment (chemotherapy or radiotherapy), treating or preventing complications (cholangitis), relieving symptoms (jaundice, pruritus, pain), and improving quality of life[35,44].

When talking about eCCA, the criteria for non-resectability are diverse. Those include distant metastases and lymph node involvement outside the region of hepatoduodenal ligament, bilateral ductal extension to the secondary biliary branches, occlusion of the main portal vein proximal to the bifurcation, lobar atrophy with contralateral involvement of secondary biliary branches or vascular structures (portal vein or hepatic artery)[45]. In the setting of palliative drainage, we should think of two eCCA locations: the hilar cholangiocarcinoma (hCCA) and distal cholangiocarcinoma (dCCA). Biliary ERCP drainage is easier in distal CCA than in hilar CCA[11,18,19,42]. For hilar obstruction, guidelines recommend different approaches for different subtypes of hCCA.

Bismuth-Corlette types I and II strictures should be treated through transpapillary approach (ERCP). On the other hand, types III and IV are recommended to be treated individually in accordance with the conclusion of the multidisciplinary team and depending on local expertise through a combination of percutaneous and endoscopic approaches [Figure 2][46,47]

For patients with a failed transpapillary approach, one can consider percutaneous transhepatic biliary drainage (PTBD), endoscopic ultrasound-guided biliary drainage (EUS-BD), or surgical bypass[48]. Further, the percutaneous approach consists of two subtypes: ultrasound- or radiologically-guided transhepatic drainage[35].

The standard procedure for biliary drainage is the implantation of biliary drainage stents during the ERCP[18,19]. This method is preferred over surgical procedures as it has similar success and survival rates, but less morbidity[49], and is also preferred over PTBD, as it has lower adverse event rates and shorter hospitalization in the palliative setting[33,47]. Some studies have also shown lower overall survival and increased risk of tumor seeding with the PTBD approach[50].

Major issues with transpapillary biliary drainage are the necessary extent of biliary decompression to achieve sufficient drainage, stent placement approach, choice of the different types of stents (different plastic and metallic stents), and avoidance of complications (especially acute cholangitis)[11].

The main goal is to drain more than half of biliary tree using target stenting according to available radiological imaging[51]. This should lead to a 50% drop in bilirubin levels in patients without liver dysfunction[52]. With cholangitis, the goal is to drain all presumably infected intrahepatic biliary branches[11].

In complex cases, a bimodal approach can be considered, using transpapillary and percutaneous drainage[11].

On the other hand, PTBD is indicated in cases of altered GI tract anatomy, inaccessible biliary ducts, or when ERCP-guided drainage is insufficient[46]. In cases of the more complex hilar strictures, both approaches can be used to achieve biliary drainage: PTBD drain can be used as a guide for ERCP-stenting in such cases. This technique is called Rendez-vous technique[53].

Regarding complex hilar malignant strictures, it is important to apply a multidisciplinary decision-making process, including all the specialties involved in the diagnostic process and treatment of cholangiocarcinoma patients (endoscopist, hepatobiliary surgeon, oncologist, and interventional

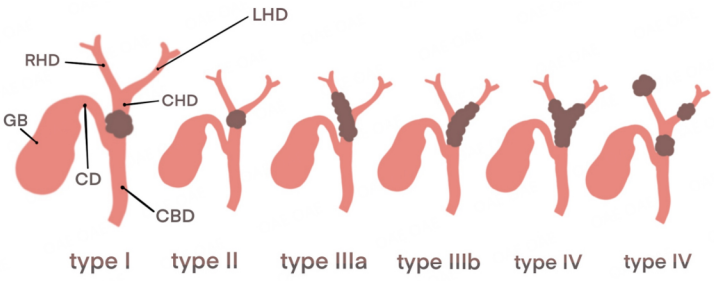

Figure 2. Bismuth-Corlette classification of hilar cholangiocarcinoma (hCCA). Type I is located distally to the hepatic duct confluence; type II involves the confluence. Type III also involves the confluence and the proximal right hepatic duct (type IIIa) or proximal left hepatic duct (type IIIb). Type IV involves bilateral proximal hepatic ducts or is multicentric. hCCA: hilar cholangiocarcinoma; GB: gall bladder; CD: cystic duct; RHD: right hepatic duct; LHD: left hepatic duct; CHD: common hepatic duct; CBD: common biliary duct.

radiologist) to choose the best approach in every individual case[46]. Before any biliary intervention, it is important to carry out appropriate radiological staging, as the foreign material (stents) can interfere with radiological assessment[54].

ERCP and biliary drainage for complex hilar strictures should be done in expert centers with enough patient volumes[47]. Studies showed that this approach results in better success rates and lower adverse event rates for advanced endoscopic procedures[55].

Stent placement technique - unilateral vs. bilateral stenting

Malignant biliary obstruction resulting from strictures from dCCA and hCCA Bismuth-Corlette types I and II can usually be drained endoscopically using one stent [either plastic stent or self-expandable metallic stent (SEMS)][35] [Figure 3]. With bilateral stenting in Bismuth-Corlette II hCCA, one can expect complete biliary drainage. On the other hand, the data regarding the approach in the case of malignant strictures of Bismuth-Corlette types III and IV of hCCA are not so clear.

In these scenarios, sometimes even bilateral stenting could not suffice for adequate biliary drainage[46].

The importance of a thorough pre-procedural radiological assessment cannot be overstated, particularly when considering both the amount of liver volume to be drained and the specific liver segments that require drainage to effectively alleviate jaundice through adequate biliary drainage. Furthermore, adequate planning is necessary to reduce the risk of complications, especially post-interventional cholangitis, by refraining from injecting contrast into the undrained biliary ducts[46,47]. Another important point is to use preprocedural radiological imaging to identify complications, as portal vein thrombosis could possibly result in liver atrophy. This enables avoidance of the unnecessary drainage of the atrophied liver segments, which does not increase biliary drainage or liver function, has no positive effect on survival, and could only lead to an increased risk of infective complications[46,56]. It should be emphasized that both computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) have significant roles in the diagnostic process and pre-interventional planning. CT is appropriate in assessing the primary tumor, vascular infiltration and distant metastases, while MRCP has a role in defining the intraductal involvement and extension of the malignant disease[8,57].

Unilateral stenting

It is considered that unilateral stent placement is enough for biliary drainage, as 25%-30% of the liver should be drained to alleviate jaundice[58-60]. This approach is easier from a technical point of view and financially

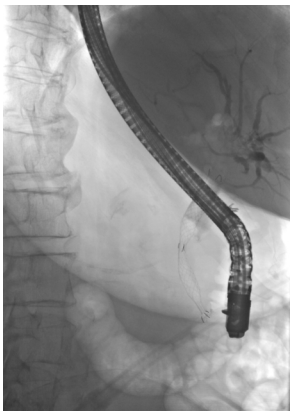

Figure 3. SEMS for dCCA. SEMS: self-expandable metallic stent; dCCA: distal cholangiocarcinoma.

more affordable in comparison to bilateral stenting[52], although with an increased risk of development of acute cholangitis because of the remaining contrast in undrained biliary tree[52].

Drainage of right or left liver lobes was shown to be without difference in terms of survival rate, success rate, complications, or number of reinterventions[61].

Some studies have shown better results for unilateral stenting[58,59,62]. One retrospective study found a significantly higher incidence of liver abscess occurrence in patients who underwent bilateral stenting[59].

De Palma *et al.* described a lower adverse event rate (26.9% *vs.* 18.9 %, $P = 0.026$) and a higher technical success rate (88.6% *vs.* 76.9%, $P = 0.041$)[62] with unilateral stenting.

Another prospective study showed higher rates of early cholangitis in a group of patients with bilateral stenting (16.6% *vs.* 8.8%), but there was no difference in median survival[62].

A recent meta-analysis involving 21 studies showed similar results regarding safety and efficacy for both approaches[63], but the technical success rate was significantly higher in the unilateral stenting group (97% *vs.* 89%, P =0.0003). The limitation of this meta-analysis is the inability to make a subgroup analysis regarding the different Bismuth types of hCCA or the etiology of the malignant strictures. Additionally, the included studies were predominantly observational[63]. A multicenter study by Staub and al. showed higher complication rates for bilateral stenting (11.7% *vs.* 0%, $P = 0.007$) and greater risk of death for the bilateral SEMS group (hazard ratio 1.78, 95% confidence interval 1.09-2.89; $P = 0.02$)[64].

Bilateral stenting

Bilateral stenting is technically more difficult than the unilateral approach[65]. In the case of endoscopic palliative drainage of malignant hilar obstruction, bilateral stenting is indicated in Bismuth III and IV CCA subtypes. Sometimes, there is a need for multiple biliary stenting to achieve adequate drainage in more advanced cases of hilar malignant strictures. Furthermore, in the setting of hilar malignant obstruction, acute cholangitis is more common in comparison to ERCP stenting for distal biliary strictures[66].

Regarding the technical difficulty of bilateral approach, it is recommended to apply bilateral stenting in the setting where unilateral drainage will not suffice to drain 50% of the functioning liver[35]. To avoid the complications resulting from the inability to drain the liver segments after the segmental contrast

opacification of the biliary system, thorough pre-interventional radiological planning is essential[35].

One retrospective study showed a better drainage effect with draining 50% or more of liver volume - particularly in the case of Bismuth III or IV malignant strictures[51], which was associated with longer survival (119 *vs.* 59 days for drainage of < 50% of liver volume). In that context, it has been shown that draining of > 33% of liver volume is enough for effective biliary drainage for patients with preserved liver function, while for patients with impaired liver function, > 50% of liver should be drained to achieve effective biliary drainage[67].

Different techniques describe how to decrease the incidence of post-interventional cholangitis, such as giving the contrast only after the cannulation of the selected obstructed duct, which results in opacification of the ducts that will be subsequently drained or using other types of contrast media such as CO_2[68,69].

One earlier retrospective study showed longer survival for patients with malignant hilar obstruction with bilateral drainage in comparison to unilateral stenting (225 *vs.* 80 days, $P < 0.0001$). The worse outcome was associated with unintended opacification of ducts that were not subsequently successfully drained[70]. Another retrospective study showed a higher rate of stent occlusion in unilateral stenting (31.4% *vs.* 11.9% for bilateral stenting, $P = 0.036$), which also resulted in a higher rate or reintervention. Multivariate analysis identified SEMS placement and bilateral drainage as independent prognostic factors for longer stent patency[71].

It has been well documented that bilateral stenting leads to prolonged stent patency in comparison to unilateral[71,72]. There were no differences in survival rate, technical success, and complication rate between unilateral and bilateral SEMS placement in the randomized prospective multicenter study; however, bilateral stenting was associated with longer stent patency[73].

One meta-analysis indicated an advantage for bilateral stenting in the light of lower rates of reintervention, without difference in complications or technical success rates, compared to unilateral stenting[74]. Another meta-analysis[75] compared side-by-side SEMS bilateral stenting with unilateral stenting in malignant hilar obstruction. Bilateral stenting showed higher stent patency (OR: 1.74; 95%CI: 1.16-2.61, $P = 0.007$) and better clinical success rates (OR: 3.56; 95%CI: 1.62-7.82, $P = 0.002$) in comparison to unilateral stenting. There was a trend towards a lower complication rate in the unilateral stenting group, but this did not reach a statistically significant level[75]. Again, one other meta-analysis confirmed a better effect of bilateral approach for lowering hyperbilirubinemia with SEMS type associated with lower complication rate[76].

In conclusion, to minimize the risk of cholangitis and liver failure, the attempt should be made to drain as much of liver parenchyma as possible[46], which is more possible with bilateral stenting.

Plastic or metallic stents

Biliary drainage can be achieved using either plastic stents or SEMS[11]. Many studies showed the advantages of SEMS regarding complication rate, rate of successful drainage, and stent patency[59,60,71-73,77].

Plastic stents are made of different materials - polyethylene, polyurethane, or Teflon. Plastic stents vary in length and diameter, with length usually between 1 and 18 cm and diameter between 5 and 11.5 Fr[35]. There are different stent configurations as well. These stents can be flanged or curved at the ends. The curved ones can be curved at the distal end (single-pigtail) or both ends (double-pigtail). The flanged plastic stents can have a single flap with side holes or four flaps without side holes on both ends. These can also be straight,

curved, or angled[77].

The advantages of plastic stents are removability and possibility to adapt to biliary tree anatomy regarding length and diameter [Figure 4]. These characteristics allow reinterventions if needed. Multiple plastic stents can be used to achieve biliary drainage[46].

Although plastic stents are inexpensive, there is a higher risk of occlusion[27,29,78] than with the use of SEMS. This risk can be reduced by regular stent exchange, usually every 3-6 months. A different approach is to wait for complication/obstruction to occur and then intervene by means of another ERCP.

Polyethylene plastic stents can become occluded with biliary sludge after forming of biofilm and lead to the development of cholangitis[62,77,79-81]. Other reasons for obstruction are reflux of duodenal dietary content to biliary tree and clotting, with a total incidence of obstruction of plastic stents up to 30%[82]. Longer patency can be expected with a larger plastic stent diameter[83].

In patients whose expected survival exceeds 3 months, the usual approach is to exchange the plastic stent with SEMS[11]. Metallic stents are more expensive and can be irremovable (uncovered), but have longer patency because of the larger diameter. The patency for metallic stents is 8-12 months, while it is much shorter for plastic ones (2-5 months)[74,77,79-81].

On the other hand, in the case of biliary obstruction of metallic stents, it is more challenging to remove the SEMS, especially in the case of uncovered SEMS, or to accomplish the biliary drainage endoscopically again[84].

SEMS are made from diverse metal alloys. They can be uncovered, partially covered, or fully covered. The ones that are fully- or partially covered have a polyurethane or silicone layer. They can be 4 to 12 cm long, with variable diameters between 6 and 10 mm when fully expanded[35]. All SEMS, as well as plastic stents, are designed to be radiopaque[35].

Finally, the choice of stent should consider several key factors, including expected patient survival (life expectancy), quality of life, cost, and physician expertise[11].

Individually, SEMS are more expensive than plastic stents, although it has been shown that total costs are similar to using plastic stents because of the longer patency time and lower reintervention rates[85].

An important thing to have in mind is the stent diameter. Plastic stents with larger diameters have better drainage capability[86]. Plastic stents are limited to 11.5 Fr diameter, because of the caliber of working channel of duodenoscope. SEMS can be passed through the working channel with a 7-8 Fr delivery system and therefore are not limited by the caliber of working channel[87]. The stents are protected by an outer plastic sheath, which is withdrawn after the correct positioning of SEMS, enabling the adequate expansion of the stent[35]. The sharp tip of the SEMS delivery system can also help in traversing through the malignant stricture. Uncovered SEMS have the advantage of draining side branches of the biliary tree through the side holes in SEMS, which can be helpful in the situation of unilateral stenting[35]. The side branches also do not occlude the cystic duct[65].

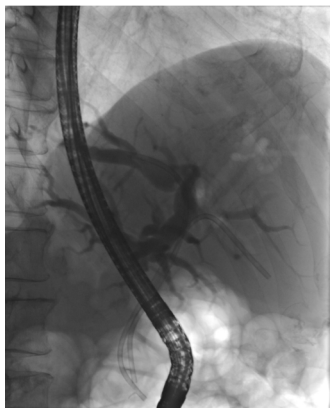

Figure 4. Bilateral plastic stenting for hilar cholangiocarcinoma.

Prospective, randomized-controlled studies have demonstrated the advantages of SEMS in comparison with plastic stents in terms of clinical and technical success -with the need for fewer re-interventions and better cost-effectiveness[60,65,88].

Several meta-analyses have compared plastic stents and SEMS in the treatment of malignant biliary obstruction, yielding different results. All of these studies showed favorable patency in SEMS group[43,77,79-81,89], but overall better survival in SEMS group was demonstrated in only half of the meta-analyses[43,79,81]. One meta-analysis showed lower rates of cholangitis and reduced need for re-interventions for SEMS[80].

An overview of the results of the meta-analyses is shown in Table 1.

It has been shown that SEMS are associated with overall lower failure rates (OR 0.43; 95%CI: 0.27-0.67), lower occlusion rates (OR 0.28; 95%CI: 0.19-0.39), and lower re-intervention rates (WMD = 0.59; 95%CI: 0.28-0.90; $I2 = 76.4\%$)[35,81,90].

Regarding the overall advantages shown in different studies, SEMS are the preferred choice in the scenario of endoscopic transpapillary biliary drainage of hilar CCA[46].

Types of metallic stents - covered and uncovered SEMS

A standard approach for patients with distal cholangiocarcinoma (dCCA) and intact gallbladder is to use uncovered SEMS[19]. In the case of earlier cholecystectomy, the choice is individual and depends on the location and other characteristics of stenosis[11].

Regarding intrinsic tumor growth, covered stents may have an advantage in reducing the risk of tumor ingrowth[19,91,92]. The outer membrane of covered SEMS prevents tumor ingrowth, and these stents are therefore easily removed[65].

One disadvantage of uncovered SEMS is the inability to remove it in the case of complications or the need for re-intervention. Therefore, in the case of biliary sludge obstruction, re-intervention usually consists of balloon sweep and extraction. In the case of tumor ingrowth, placement of another stent is usually necessary[46].

Table 1. Overview of meta-analyses comparing plastic stent and SEMS biliary drainage for malignant biliary obstruction

Reference	Year	No. of patients	Included studies	Results
Hong *et al.*[81]	2013	785	10	SEMS: longer stent patency (HR = 0.36; 95%CI: 0.28-0.47); longer patient survival (HR = 0.74; 95%CI: 0.64-0.85)
Zorrón Pu *et al.*[79]	2015	1133	13	SEMS: higher mean survival rate (182 d *vs.* 150 d, $P < 0.0001$); higher patency period (250 d *vs.* 124 d, $P < 0.0001$)
Sawas *et al.*[80]	2015	1989	19	SEMS: lower risk of occlusion (OR 0.38; 95%CI: 0.28-0.53); no difference in 30-d survival
Moole *et al.*[43]	2017	947	11	SEMS: patency 167.7 days (95%CI: 159.2-176.3) *vs.* 73.3 days (95%CI: 69.8-76.9); overall survival 157.3 days (95%CI: 148.9-165.6) *vs.* 120.6 days (95%CI: 114.3-126.9)
Yuan *et al.*[89]	2017	810	10	SEMS: 2.27-fold 6-month stent patency rate (95%CI: 1.30-3.95), 36% reduction in a recurrent obstruction; no difference in 30-d survival
Almadi *et al.*[77]	2017	1713	20	no differences in overall patient survival; SEMS: longer patency 7.70 months (95%CI: 7.14, 8.25)

SEMS: self-expandable metallic stent; HR: hazard ratio; CI: confidence interval; d: day.

It is important to notice that there is no difference in patency rate between the two types of stents, although covered SEMS is less prone to tumor ingrowth[11,93].

Several meta-analyses have found that covered SEMS have a higher risk of tumor overgrowth, occlusion by sludge and food debris, and stent migration[94,95]. Overall, adverse event rate and overall survival did not differ between the two subtypes of SEMS[93-95].

A recent meta-analysis[93] comparing different stent types' efficacy included 21 studies with 2326 patients, of which 11 studies compared the two SEMS subtypes. There were no differences regarding recurrent biliary obstruction [covered SEMS *vs.* uncovered SEMS: RR (95% CI) = 0.93 (0.68-1.26)]. Recurrent biliary obstruction was 23.8% for uncovered SEMS and 23.6% for covered SEMS. Tumor ingrowth occurred in 17.3% (95%CI: 14.5%-20.4%) of uncovered SEMS cases. The reasons for covered SEMS occlusion were sludge (7.5%), tumor overgrowth (7.1%), and stent migration (5.0%)[93]. Cholangitis occurred in 12.1% of uncovered SEMS cases and 5.2% of covered SEMS cases.

The differences between the causes of the biliary obstruction of different stents can be connected to the different designs and builds of stents. The coating membrane of covered SEMS can become a medium for biofilm formation, which could lead to sludge forming and occlusion[94]. The membrane of covered SEMS can also increase the chance of stent migration[93].

Some studies show an increased risk of acute cholecystitis after covered SEMS placement[96,97]: a recent meta-analysis showed the tendency towards increased risk, but the overall incidence of this particular complication was low (1.6% for uncovered SEMS *vs.* 3.1% for covered SEMS)[93]. The tumor invasion of cystic orifice or arterial network of gallbladder could also be the cause of cholecystitis[98]. In theory, SEMS placement could also lead to obstruction of the pancreatic duct by stent compression and potentially result in acute pancreatitis[23,99]. Recent meta-analysis could not confirm this finding, as there was no statistical difference in the risk of pancreatitis among different types of stents (SEMS and plastic)[93].

In the setting of malignant hilar obstruction, stents become occluded in up to 50% of cases[65]. Uncovered SEMS are usually used because the mesh structure of these stents enables the drainage of side branches of the biliary tree[100]. Data supporting the use of other types of SEMS in this setting is limited, and there is

currently no indication for the use of partially covered or fully covered SEMS in palliative biliary drainage of malignant hilar strictures[46]. In the case of placement of more covered SEMS, the outer diameter of stents is decreased, which could have an impact on stent patency[65].

One retrospective study showed the feasibility of using partially covered SEMS in hilar obstruction with the possibility of stent removal in a fraction of patients requiring reintervention, as in these cases, there was no tumor ingrowth of the uncovered part of the stent, but overall median stent patency was just 79 days for all Bismuth CCA subtypes[101]. One other retrospective study analyzed the use of fully covered SEMS for malignant hilar obstruction drainage and showed 94% and 92% technical success rates, with two patients (7%) developing liver abscesses as adverse events, because of intrahepatic bile duct occlusion[102]. One other smaller study using partially and fully covered SEMS showed short mean stent patency (overall 95 days) in this setting[103].

Bilateral stenting approach - stent-in-stent and side-by-side SEMS

In the case of bilateral SEMS stenting in hCCA, there are essentially two approaches. SBS approach consists of the placement of two SEMS parallel to each other, which can be done simultaneously or sequentially. In the SIS approach, the second SEMS is placed after the first SEMS through the mesh structure of the central part of stent [Figure 5][46].

In both approaches, once again, it is essential to plan the procedure in advance with the help of cross-sectional imaging, with the goal of avoiding potential complications and avoiding drainage of atrophied liver segments after prolonged biliary obstruction or because of portal vein thrombosis[30].

In the first approach, stent-in-stent, first SEMS is deployed, usually in the side that is more difficult to cannulate. After this step, the first guidewire is withdrawn to the level of the already-deployed SEMS and then passed through the metallic mesh of the central part of the SEMS and another SEMS is deployed in the contralateral side of the biliary system through the already deployed SEMS[35,104]. The final result of this approach is a Y-shaped configuration of the two SEMS, resulting in bilateral biliary drainage. In more complex strictures, previous balloon dilatation of the first SEMS or balloon dilatation of both hepatic sides before the deployment of stents can be helpful in achieving adequate bilateral drainage. Usually, distal ends of SEMS are placed proximal to the level of papilla[65].

In the SBS approach, two SEMS are placed parallel to each other in both hepatic ducts[105]. Two guidewires are placed in both biliary ducts first. Usually, the first SEMS is then deployed in the duct that was accessed with more difficulty. After that, the second SEMS is deployed beside the first. The advantage is to place SEMS parallel at the same level in CBD or across papilla, which could make future access easier in the case of subsequent obstruction or other complications[35,65]. Two stents can be placed simultaneously using the dedicated 6-Fr delivery system[106]. Otherwise, eventual resistance and difficulty that could be encountered while placing a second SEMS next to one already deployed in cases with severe strictures can be overcome by using balloon dilatation before the deployment of the first SEMS[65].

The structure of different SEMS is very important to consider while performing bilateral biliary stenting. The mesh structure can be divided into two types: small closed–cell and large open-cell. Both types of mesh structures have their advantages.

SEMS with small cell mesh structures have smaller cells, thereby mitigating the vulnerability of the central part of the SEMS, which can be helpful in severe strictures. On the other hand, this leads to more difficult

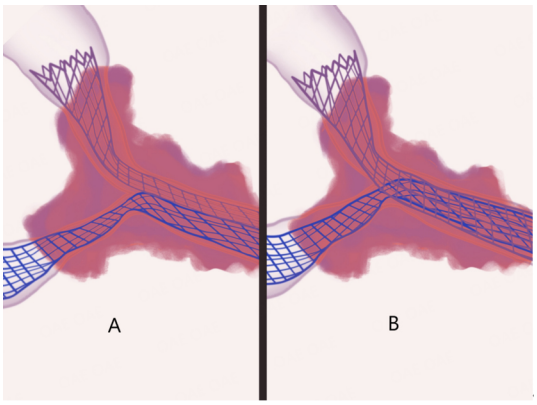

Figure 5. Types of bilateral SEMS stenting approach - A - side-by-side (SBS); B - stent-in-stent (SIS). SEMS: self-expandable metallic stent.

deployment of the second stent or re-intervention in the case of obstruction[65].

SEMS with large open-cell mesh structures can be more easily dilated by using balloon dilatation or placing another SEMS. This characteristic makes them suitable for stenting severe strictures and also subsequent re-intervention in the case of simpler obstruction. On the other hand, these SEMS types have decreased radial force in the central part across the severe strictures and large open-cell structures can lead to reduced patency because of the tumor ingrowth[65,104].

These characteristics of the different SEMS types should be kept in mind when choosing a specific stent for bilateral stenting. Generally, large open-cell types are preferred for the SIS approach, while small closed-cell types are used for the SBS approach[65]. Both approaches have their advantages and require endoscopist experience for technical success.

The SIS approach can prevent reflux of the duodenal content, which could lead to the formation of biliary sludge and obstruction. In addition, it is associated with less pressure on the bile duct wall and surrounding structures[107]. This approach can facilitate multi-sectoral biliary drainage simultaneously or subsequentially, as needed[65,108,109]. On the other hand, the SIS approach can be associated with difficulties when introducing guidewire in a required duct - this can aggravate the deployment of the second stent. Furthermore, in the case of secondary obstruction due to tumor ingrowth, stents that had already been placed with this approach could aggravate the re-introduction of the guidewire or re-deployment of other stents[65].

The SBS approach is technically relatively easier to perform. Additionally, the placement of two SEMS across the papilla enables simpler re-intervention in the case of secondary obstruction[65]. On the other hand, two SEMS placed parallelly can cause compression and subsequent thrombosis of the adjacent portal vein[108]. Small-diameter SEMS can have shorter patency and it could be impossible to achieve complete expansion of the stents in the narrow part of CBD[65].

Studies investigating efficacy reported different results regarding these approaches. In an earlier retrospective study by Naitoh *et al.*, complication rates were higher in SBS group (44% *vs.* 13% in SIS group, $P = 0.016$), with a trend towards longer patency in SBS group[110], but without statistically significant differences.

One more recent study showed similar results regarding adverse event rates, technical and clinical success rates, but without difference in stent patency rates at 3 (85.3% in SIS *vs.* 65.7% in SBS group, $P = 0.059$) and 6 months (47.1% in SIS *vs.* 31.4% in SBS, $P = 0.184$)[111]. A study by Ishigaki *et al.* showed no difference in technical success rates, with a trend towards a higher rate of early adverse events in SBS group (46% *vs.* 23%, $P = 0.09$) and a higher rate of post-ERCP pancreatitis in SBS group (29% *vs.* 0%). There was no statistically significant difference in time to recurrent biliary obstruction (169 days in SIS *vs.* 205 days in SBS)[112]. One meta-analysis included 4 studies and 158 patients and found no difference in the rates of successful placement and drainage, early and late complications, and stent occlusions between the two approaches[113].

Another more recent meta-analysis included 7 studies; the technical success rate was significantly higher in SIS group ($P = 0.04$) and the early complication rate was also lower in SIS group ($P = 0.04$), but the stent patency duration was significantly longer in SBS group ($P = 0.01$). There were no differences between the two approaches regarding functional success rate, overall complication rates, and survival ($P = 0.27$)[114].

Complications of stent placement and re-intervention after stent obstruction

Duodenal biliary reflux occurs when a stent is placed across the papilla. This possibly leads to bacterial colonization and the formation of sludge and biliary stones[35]. Other possible events include duodenal perforation due to the placement of the stent too distally within the duodenal lumen or stent migration leading to impaction. Bowel obstruction after stent migration has also been described[35,65].

Stent obstruction can be managed with different techniques; plastic stents can be replaced with either new plastic stents or with SEMS. In case of SEMS obstruction due to the sludge or stone formation, stent can be extracted with balloon extraction. On the other hand, the obstruction due to tumor ingrowth or outgrowth can be resolved by placement of another SEMS or plastic stent through previously placed SEMS [Figure 6][35].

In the case of bilateral stenting, the stent obstruction rate is high - between 20%-50%, according to the literature[65]. Therefore, the need for endoscopic re-intervention remains high - although this is technically challenging[65]. The literature regarding different approaches to re-intervention and stent types is scarce.

One review described a similar effect of placing a plastic stent as compared to second SEMS for reintervention in the case of SEMS occlusion. There was no difference in risk of re-occlusion (RR 1.24, $P = 0.16$) and patency rate between the two types of stents used in re-intervention. There was also no difference in survival for patients receiving plastic stents versus SEMS. The limitation of this study was that the included studies were retrospective[115]. On the other hand, other retrospective studies on a small number of patients ($n = 52$) demonstrated a longer patency rate for SEMS used in re-intervention than for plastic stent (131 days *vs.* 47 days, respectively; $P = 0.005$). Multivariate analysis showed SEMS placement as the only independent factor associated with longer time to recurrent biliary obstruction (hazard ratio 0.37; 95%CI: 0.14-0.95; $P = 0.039$)[116].

In this situation of reintervention approach after stent occlusion, larger, prospective randomized studies are needed to answer which is a better approach and give solid recommendations[65].

Infectious adverse events during ERCP are the result of bacterial translocation into the blood via mucosal trauma or contrast injection. Infections have been reported in up to 3 percent of patients undergoing ERCP, usually consisting of gram-negative bacteria[117,118]. Risk factors for post-ERCP cholangitis are incomplete biliary drainage (usually in hilar obstructions), PSC, liver transplant patients, and ERCP including

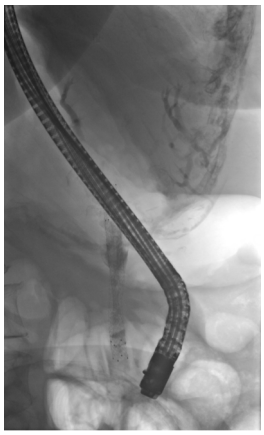

Figure 6. Second SEMS placed through previously placed SEMS for tumor ingrowth. SEMS: self-expandable metallic stent.

cholangioscopy. Most preventive and therapeutic measures consist of performing adequate (complete) biliary drainage and antibiotic prophylaxis[118].

Another approach - echoendoscopic biliary drainage

Echoendoscopy as a method for bile duct drainage (endoscopic ultrasound biliary drainage, EUS-BD) emerged as an additional biliary drainage treatment possibility, especially in cases after failed ERCP or PTBD[119]. There are two different approaches for biliary tree access when using EUS as a method of choice. Usually, distal biliary obstruction is treated with puncturing of the choledocus or common bile duct, but in hilar obstruction, the method of choice is puncturing the intrahepatic bile ducts[120]. Endoscopic ultrasound-guided hepaticogastrostomy is the procedure of choice for extrahepatic malignant strictures since it gives better control and multiple access possibilities in bile duct drainage. Endoscopic ultrasound-guided hepaticogastrostomy is mostly indicated and needed in recurrent bile duct stenosis after previous placement of biliary or duodenal self-expandable metal stents[121,122] or also can be used in situations of failed ERCP and altered anatomy after previous surgery[123].

Endoscopic ultrasound-guided hepticogastrostomy is performed after bile duct puncture, dilatation of the tract, and finished by placing a stent over the bile duct into the lumen of the GI tract. Most studies in literature have demonstrated a high success rate (94.0%) and high intention-to-treat success (90.2%)[122,124-129]. The most frequent complications are bile leakage and cholangitis due to displacement or stent obstruction [122,124-129]. After transmurally placed SEMS, biloma or peritonitis due to bile leak can occur[126,129]. However, most of the above-mentioned complications are usually treated conservatively, without the need for surgical interventions. Bile duct leakage can be minimized by deploying an uncovered metal stent first that is used as a good anchorage and then a covered metal stent inserted coaxially.

Echoendoscopic guided biliary drainage with SEMS had short-term results comparable to bile duct decompression via ERCP in distal cholangiocarcinoma. Even more, the risk of complications like postprocedural pancreatitis was lower in EUS-guided drainage[122,130].

Additionally, comparing echoendoscopic biliary drainage with PTBD, studies clearly revealed EUS-BD as an endoscopic tool of choice for biliary decompression. Regarding patient preference, a multicenter study clearly demonstrated that 80% of patients were more in favor of echo endoscopic biliary drainage than PTBD[33].

There are three types of echoendoscopic biliary drainage that can be done in tumor hilar stenosis: (1) EUS-HGS (echoendoscopic guided hepato-gastrostomy); (2) Bridging therapy; and (3) EUS-HDS (echoendoscopic guided hepatico-duodenostomy). After adequate puncturing and accessing the bile duct via EUSHGS or EUSHDS, there is no standardized choice between performing either transpapillary or transmural drainage.

A more complex method is the transpapillary drainage because it requires all the following: first placement of the guidewire in antegrade direction, second rendez-vous technique to access the papilla, and finally puncture tract dilatation with stent placement. If there is a need for reintervention, biliary access can be easily done by a transmural approach. All of the above-mentioned techniques for EUS-BD are not exclusive and can be used complementary to provide the best drainage[120]. When performing decompression of the left-sided bile ducts, hepaticogastrostomy is performed using an endoscopic ultrasound approach from the stomach (trans-gastric). This procedure involves puncturing and creating a tract between the stomach and the left-sided bile tree, followed by the placement of a stent. Literature data have shown adequate technical (91%-100%) and clinical (75%-100%) success[129,131].

There is a 25% risk of complications and the most common are leakage for the bile ducts, displacement of the stent, GI tract perforation, and cholangitis because only the left lobe of the liver[122,131]. The recent literature has described the "bridging method" that also allows the drainage of the right liver lobe. The procedure is started by forming a tract between the stomach and left bile duct using echoendoscopic puncture, and then, a guidewire is placed to the ducts in the right liver lobe, a stent is placed connecting the left and right intrahepatic ducts and the procedure is finished by performing a hepaticogastrostomy[130]. Approach to the intrahepatic ducts in the right liver lobe can also be done directly (EUSHDS), but it requires puncture from the duodenum (duodenal bulb or D2 part of the duodenum), which can significantly complicate the procedure due to the unstable position of the scope. Due to the above-mentioned reasons, in clinical practice, it is rarely used for drainage in hilar cholangiocarcinoma[132]. In some situations, we can use both of the techniques (ERCP + EUS-BD) to perform complete drainage. First, ERCP is done, and if the self-expandable metal stent is placed in the left intrahepatic bile duct, EUS-HDS for drainage of the right duct can be performed. Vice versa, if the ERCP drainage is done for the right intrahepatic ducts, EUS-HGS is performed for drainage of the left liver lobe[133].

The main reasons for patient preference for EUS-BD compared to percutaneous biliary drainage are better life quality because there is no external biliary drain discomfort (78.1%; 196/251 of the patients), the possibility to perform EUS-BD at the same time with ERCP (28.3% patients) and lower morbidity with a high rate of success[134]. However, there are no studies that have compared the advantages and disadvantages of percutaneous drainage with EUS-BD in bile duct drainage of hilar cholangiocarcinoma. Due to the high complexity of the procedure and limited experience, EUS-BD is still not routinely done in most endoscopic centers. The last option for adequate bile drainage is the surgical bypass procedure, but it should only be reserved when all minimally invasive techniques (ERCP, EUS-BD, and PTBD) have failed, usually due to the location of the tumor, altered anatomy, or as a palliative procedure if intraoperatively tumor is classified as inoperable[8,135,136].

Additional endobiliary treatments

The only definitive and curative treatment for cholangiocarcinoma is radical surgical resection, but only a small proportion of patients are operated on because of locally advanced disease or disease dissemination. Brachytherapy (BT), radiofrequency ablation (RFA) and photodynamic therapy (PDT), which are considered locoregional techniques, are used to improve the survival rate and life quality[137].

Percutaneously, intraoperatively, or endoscopically guided RFA is used as an endo-biliary cholangiocarcinoma therapy. When bile duct cannulation and lesion identification are successfully completed, the guidewire is placed over the stenosis and RFA is performed using a specific catheter that induces tissue necrosis through high temperature and leads to lesion size reduction[46]. The treated tissue and small coagula are removed with the balloon and usually plastic stents are inserted.

A study[138] that included 65 patients with inoperable main bile duct cholangiocarcinoma clearly demonstrated that the patients treated with stenting without RFA had lower mean survival time (8 months) compared to those that were treated with RFA and biliary stenting (13 months). The survival rate at the point of one year was higher in the RFA patients (63%) compared to 12% survival in the stenting without the RFA group. Additionally, the patency of the biliary stent in the RFA group of patients was much longer (7 months compared to 3 months in the group without RFA therapy). There was no significant difference between the RFA and non-RFA groups regarding the complications and adverse events (6% and 9%).

Another meta-analysis that included 505 patients has shown that the patients treated with RFA had longer patency of the endo-biliary stent (mean difference 50.6 days) and improved survival rate[48]. On the contrary, RFA treated patients had a higher risk of abdominal pain after the procedure. Regarding the other possible post-procedural complications (bile duct bleeding, pancreatitis, cholangitis, or cholecystitis), no significant difference was shown between stent only and RFA + stent groups[48]. Another possible application of RFA treatment is intra-biliary ablative therapy in case of self-expandable metal stent occlusion due to the ingrowth of the tumor[139].

Brachytherapy (BT) can be used either percutaneously or by endoscopic approach for treating tumors in left, right hepatic bile duct or main biliary duct by delivering a high dose of local radiation. It can be used for curative treatment in selective early cancer patients (usually small but non-surgically curative tumors combined with chemotherapy and external beam radiotherapy), but is usually indicated for palliative treatment or therapy for postoperative small residual tumoral tissue in a setting of nonradical excision[140]. BT has the advantage of applying a high dose of local radiation therapy without the risk of damaging surrounding tissue, contrary to classical external radiotherapy. The procedure is performed with the placement of a naso-biliary (8,5 or 10Fr) tube during ERCP in the bile duct at least 2 cm over the proximal tumor border[141]. If there is involvement of left and right bile hepatic bile duct, two 10 Fr tubes can be placed. The whole system (tubes and catheter for brachytherapy) is removed after BT is finished. Possible complications described in the literature are abdominal pain, cholangitis, and displacement of the tubes or catheter[141].

Photodynamic therapy (PDT) uses specific wavelength irradiation after photosensitizer injection, which induces cytotoxic effects on tumor cells. In clinical practice, it is usually used for palliative approach or in post-surgical recurrence[142]. PDT is applied either during ERCP or cholangioscopy (via transhepatic percutaneous route- PTSC). If PDT is performed during ERCP, a specific optical fiber is placed into the malignant stenosis. Photosensitizer is injected and light through the fiber is applied to the tumor tissue that is destroyed by forming oxygen free radicals[143]. Two randomized prospective studies performed in patients with inoperable cholangiocarcinoma clearly reported better life quality, longer overall survival rate in a group of patients undergoing PDT, without the difference in adverse events between two groups: one group undergoing PDT and another group receiving only stent placement[144,145]. However, there is no impact of PTD (no matter the delivery route- ERCP or PTCS) on the total patient survival rate or placed biliary SEMS patency[146].

CONCLUSION

In conclusion, ERCP-stenting in malignant CCA strictures is a much-appreciated method, which demands highly skilled endoscopists willing to consider indications, advantages, drawbacks, and patient needs. No matter the availability of a certain stent type or its cost-effectiveness, the priority is always to recognize the adequate timing of stenting, as well as tailoring endoscopic treatment exclusively to each patient. The crucial role of a multidisciplinary approach and detailed planning is emphasized, especially in patients with complex hilar strictures and in patients in the preoperative setting. We also presented available research comparing individual endoscopic techniques of biliary drainage, as well as types of stents. Thus, we have shown that, in the case of choice of endoscopic biliary drainage of more advanced hilar CCA, research so far emphasizes the advantage of bilateral stenting and the use of SEMS. It is clear that recommendations and practices in this area are rapidly changing with the development and implementation of new techniques. Therefore, in the last part of this review, we also presented data on the echoendoscopic possibilities of biliary drainage, where the indications and application will certainly expand significantly in the future. Finally, the possibilities of local endobiliary treatment of patients in the palliative setting, such as RFA, brachytherapy and PDT, enable today a greater choice in the approach to the care of these patients.

DECLARATIONS

Authors' contributions

Searched the literature and drafted and wrote the paper: Prijic R, Ladic A, Markos P
Revised the article and contributed their opinion to the concept of the paper: Prijic R, Ladic A, Markos P
Provided the endoscopic images from his collection: Markos P
Designed the graphic figures: Ladic A
Approved the final article version to be published: Ladic A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist* 2016;21:594-9. DOI PubMed PMC
2. Cardinale V, Bragazzi MC, Carpino G, et al. Cholangiocarcinoma: increasing burden of classifications. *Hepatobiliary Surg Nutr* 2013;2:272-80. DOI
3. Brunt E, Aishima S, Clavien PA, et al. cHCC-CCA: consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentation. *Hepatology* 2018;68:113-26. DOI

4. Guest RV, Boulter L, Kendall TJ, et al. Cell lineage tracing reveals a biliary origin of intrahepatic cholangiocarcinoma. *Cancer Res* 2014;74:1005-10. DOI PubMed PMC
5. Affo S, Nair A, Brundu F, et al. Promotion of cholangiocarcinoma growth by diverse cancer-associated fibroblast subpopulations. *Cancer Cell* 2021;39:866-82.e11. DOI PubMed PMC
6. Talabnin K, Talabnin C, Kumagai T, et al. Ganglioside GM2: a potential biomarker for cholangiocarcinoma. *J Int Med Res* 2020;48:0300060520903216. DOI PubMed PMC
7. Jarnagin W, Winston C. Hilar cholangiocarcinoma: diagnosis and staging. *HPB* 2005;7:244-51. DOI PubMed PMC
8. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. *Nat Rev Gastroenterol Hepatol* 2011;8:512-22. DOI PubMed PMC
9. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2004;99:523-6. DOI PubMed
10. Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer* 2016;122:1349-69. DOI PubMed
11. Tantau AI, Mandrutiu A, Pop A, et al. Extrahepatic cholangiocarcinoma: current status of endoscopic approach and additional therapies. *World J Hepatol* 2021;13:166-86. DOI PubMed PMC
12. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020;17:557-88. DOI PubMed PMC
13. Khan SA, Emadossadaty S, Ladep NG, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? *J Hepatol* 2012;56:848-54. DOI
14. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019;71:104-14. DOI
15. Ramadori G, Cameron S. Effects of systemic chemotherapy on the liver. *Ann Hepatol* 2010;9:133-43. DOI PubMed
16. Pavlidis ET, Pavlidis TE. Pathophysiological consequences of obstructive jaundice and perioperative management. *Hepatobiliary Pancreat Dis Int* 2018;17:17-21. DOI PubMed
17. Golse N, Nunez J, Mazzotta A, et al. Personalized preoperative nomograms predicting postoperative risks after resection of perihilar cholangiocarcinoma. *World J Surg* 2020;44:3449-60. DOI
18. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 2018;15:95-111. DOI PubMed PMC
19. Brandi G, Venturi M, Pantaleo MA, Ercolani G; GICO. Cholangiocarcinoma: current opinion on clinical practice diagnostic and therapeutic algorithms: a review of the literature and a long-standing experience of a referral center. *Dig Liver Dis* 2016;48:231-41. DOI PubMed
20. Kurahara H, Maemura K, Mataki Y, et al. Preoperative biliary drainage-related inflammation is associated with shorter survival in biliary tract cancer patients. *Int J Clin Oncol* 2016;21:934-9. DOI
21. Szary NM, Al-Kawas FH. Complications of endoscopic retrograde cholangiopancreatography: how to avoid and manage them. *Gastroenterol Hepatol* 2013;9:496-504. PubMed PMC
22. Liu F, Li Y, Wei Y, Li B. Preoperative biliary drainage before resection for hilar cholangiocarcinoma: whether or not? a systematic review. *Dig Dis Sci* 2011;56:663-72. DOI PubMed
23. Tringali A, Hassan C, Rota M, Rossi M, Mutignani M, Aabakken L. Covered vs. uncovered self-expandable metal stents for malignant distal biliary strictures: a systematic review and meta-analysis. *Endoscopy* 2018;50:631-41. DOI PubMed
24. Hilscher MB, Tabibian JH, Carey EJ, Gostout CJ, Lindor KD. Dominant strictures in primary sclerosing cholangitis: a multicenter survey of clinical definitions and practices. *Hepatol Commun* 2018;2:836-44. DOI PubMed PMC
25. Bowlus CL, Lim JK, Lindor KD. AGA clinical practice update on surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis: expert review. *Clin Gastroenterol Hepatol* 2019;17:2416-22. DOI PubMed
26. Rupp C, Hippchen T, Bruckner T, et al. Effect of scheduled endoscopic dilatation of dominant strictures on outcome in patients with primary sclerosing cholangitis. *Gut* 2019;68:2170-8. DOI PubMed PMC
27. Miura F, Sano K, Wada K, et al. Prognostic impact of type of preoperative biliary drainage in patients with distal cholangiocarcinoma. *Am J Surg* 2017;214:256-61. DOI
28. George C, Byass OR, Cast JE. Interventional radiology in the management of malignant biliary obstruction. *World J Gastrointest Oncol* 2010;2:146-50. DOI PubMed PMC
29. Paik WH, Park YS, Hwang JH, et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. *Gastrointest Endosc* 2009;69:55-62. DOI PubMed
30. Zhou WZ, Liu S, Yang ZQ, et al. Percutaneous stent placement for malignant hilar biliary obstruction: side-by-side versus stent-in-stent technique. *BMC Gastroenterol* 2020;20:174. DOI PubMed PMC
31. Gouma DJ. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma (Br J Surg 2013; 100: 274-283). *Br J Surg* 2013;100:283-4. DOI PubMed
32. Zhao XQ, Dong JH, Jiang K, Huang XQ, Zhang WZ. Comparison of percutaneous transhepatic biliary drainage and endoscopic biliary drainage in the management of malignant biliary tract obstruction: a meta-analysis. *Dig Endosc* 2015;27:137-45. DOI PubMed
33. Inamdar S, Slattery E, Bhalla R, Sejpal DV, Trindade AJ. Comparison of adverse events for endoscopic vs percutaneous biliary

drainage in the treatment of malignant biliary tract obstruction in an inpatient national cohort. *JAMA Oncol* 2016;2:112-7. DOI
34. Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 2013;100:274-83. DOI
35. Mocan T, Horhat A, Mois E, et al. Endoscopic or percutaneous biliary drainage in hilar cholangiocarcinoma: when and how? *World J Gastrointest Oncol* 2021;13:2050-63. DOI PubMed PMC
36. Tang Z, Yang Y, Meng W, Li X. Best option for preoperative biliary drainage in Klatskin tumor: a systematic review and meta-analysis. *Medicine* 2017;96:e8372. DOI PubMed PMC
37. Liu JG, Wu J, Wang J, et al. Endoscopic biliary drainage versus percutaneous transhepatic biliary drainage in patients with resectable hilar cholangiocarcinoma: a systematic review and meta-analysis. *J Laparoendosc Adv Surg Tech A* 2018;28:1053-60. DOI
38. Al Mahjoub A, Menahem B, Fohlen A, et al. Preoperative biliary drainage in patients with resectable perihilar cholangiocarcinoma: is percutaneous transhepatic biliary drainage safer and more effective than endoscopic biliary drainage? *J Vasc Interv Radiol* 2017;28:576-82. DOI
39. Takahashi Y, Nagino M, Nishio H, Ebata T, Igami T, Nimura Y. Percutaneous transhepatic biliary drainage catheter tract recurrence in cholangiocarcinoma. *Br J Surg* 2010;97:1860-6. DOI PubMed
40. Vogel A, Bridgewater J, Edeline J, et al; ESMO Guidelines Committee. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34:127-40. DOI
41. Xia MX, Wang SP, Wu J, et al. The risk of acute cholangitis after endoscopic stenting for malignant hilar strictures: a large comprehensive study. *J Gastroenterol Hepatol* 2020;35:1150-7. DOI
42. Prachayakul V, Chaisayan S, Aswakul P, Deesomsak M. Clinical characteristics and treatment outcomes of patients with unresectable cholangiocarcinoma in Thailand: are there differences dependent on stent type? *Asian Pac J Cancer Prev* 2013;14:529-32. DOI PubMed
43. Moole H, Jaeger A, Cashman M, et al. Are self-expandable metal stents superior to plastic stents in palliating malignant distal biliary strictures? *Med J Armed Forces India* 2017;73:42-8. DOI PubMed PMC
44. Squadroni M, Tondulli L, Gatta G, Mosconi S, Beretta G, Labianca R. Cholangiocarcinoma. *Crit Rev Oncol Hematol* 2017;116:11-31. DOI PubMed
45. Zaydfudim VM, Rosen CB, Nagorney DM. Hilar cholangiocarcinoma. *Surg Oncol Clin N Am* 2014;23:247-63. PubMed
46. Boškoski I, Schepis T, Tringali A, et al. Personalized endoscopy in complex malignant hilar biliary strictures. *J Pers Med* 2021;11:78. DOI PubMed PMC
47. Dumonceau JM, Tringali A, Papanikolaou IS, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European society of gastrointestinal endoscopy (ESGE) clinical guideline - updated October 2017. *Endoscopy* 2018;50:910-30. DOI PubMed
48. Sofi AA, Khan MA, Das A, et al. Radiofrequency ablation combined with biliary stent placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis. *Gastrointest Endosc* 2018;87:944-51.e1. DOI PubMed
49. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994;344:1655-60. DOI PubMed
50. Uppal DS, Wang AY. Advances in endoscopic retrograde cholangiopancreatography for the treatment of cholangiocarcinoma. *World J Gastrointest Endosc* 2015;7:675-87. DOI PubMed PMC
51. Vienne A, Hobeika E, Gouya H, et al. Prediction of drainage effectiveness during endoscopic stenting of malignant hilar strictures: the role of liver volume assessment. *Gastrointest Endosc* 2010;72:728-35. DOI
52. Kerdsirichairat T, Arain MA, Attam R, et al. Endoscopic drainage of > 50% of liver in malignant hilar biliary obstruction using metallic or fenestrated plastic stents. *Clin Transl Gastroenterol* 2017;8:e115. DOI PubMed PMC
53. Neu B, Nennstiel S, von Delius S, et al. Endoscopic rendez-vous reconstruction of complete biliary obstruction. *Dig Liver Dis* 2017;49:769-72. DOI
54. Mansour JC, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. *HPB* 2015;17:691-9. DOI PubMed PMC
55. Keswani RN, Qumseya BJ, O'Dwyer LC, Wani S. Association between endoscopist and center endoscopic retrograde cholangiopancreatography volume with procedure success and adverse outcomes: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2017;15:1866-75.e3. DOI PubMed
56. Gwon DI, Ko GY, Sung KB, et al. Percutaneous biliary metallic stent placement in patients with unilobar portal vein occlusion caused by advanced hilar malignancy: outcome of unilateral versus bilateral stenting. *AJR Am J Roentgenol* 2011;197:795-801. DOI
57. Masselli G, Manfredi R, Vecchioli A, Gualdi G. MR imaging and MR cholangiopancreatography in the preoperative evaluation of hilar cholangiocarcinoma: correlation with surgical and pathologic findings. *Eur Radiol* 2008;18:2213-21. DOI
58. Yasuda I, Mukai T, Moriwaki H. Unilateral versus bilateral endoscopic biliary stenting for malignant hilar biliary strictures. *Dig Endosc* 2013;25 Suppl 2:81-5. DOI PubMed
59. Iwano H, Ryozawa S, Ishigaki N, et al. Unilateral versus bilateral drainage using self-expandable metallic stent for unresectable hilar biliary obstruction. *Dig Endosc* 2011;23:43-8. DOI
60. Mukai T, Yasuda I, Nakashima M, et al. Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. *J Hepatobiliary Pancreat Sci* 2013;20:214-22. DOI
61. Polydorou AA, Chisholm EM, Romanos AA, et al. A comparison of right versus left hepatic duct endoprosthesis insertion in malignant hilar biliary obstruction. *Endoscopy* 1989;21:266-71. DOI

62. De Palma GD, Galloro G, Siciliano S, Iovino P, Catanzano C. Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. *Gastrointest Endosc* 2001;53:547-53. DOI PubMed
63. Aghaie Meybodi M, Shakoor D, Nanavati J, et al. Unilateral versus bilateral endoscopic stenting in patients with unresectable malignant hilar obstruction: a systematic review and meta-analysis. *Endosc Int Open* 2020;8:E281-90. DOI PubMed PMC
64. Staub J, Siddiqui A, Murphy M, et al. Unilateral versus bilateral hilar stents for the treatment of cholangiocarcinoma: a multicenter international study. *Ann Gastroenterol* 2020;33:202-9. DOI PubMed PMC
65. Lee TH, Moon JH, Park SH. Biliary stenting for hilar malignant biliary obstruction. *Dig Endosc* 2020;32:275-86. DOI PubMed
66. Nomura T, Shirai Y, Hatakeyama K. Cholangitis after endoscopic biliary drainage for hilar lesions. *Hepatogastroenterology* 1997;44:1267-70. PubMed
67. Takahashi E, Fukasawa M, Sato T, et al. Biliary drainage strategy of unresectable malignant hilar strictures by computed tomography volumetry. *World J Gastroenterol* 2015;21:4946-53. DOI PubMed PMC
68. Singh V, Singh G, Verma GR, Singh K, Gulati M. Contrast-free unilateral endoscopic palliation in malignant hilar biliary obstruction: new method. *J Gastroenterol Hepatol* 2004;19:589-92. DOI
69. Sud R, Puri R, Choudhary NS, Mehta A, Jain PK. Air cholangiogram is not inferior to dye cholangiogram for malignant hilar biliary obstruction: a randomized study of efficacy and safety. *Indian J Gastroenterol* 2014;33:537-42. DOI
70. Chang WH, Kortan P, Haber GB. Outcome in patients with bifurcation tumors who undergo unilateral versus bilateral hepatic duct drainage. *Gastrointest Endosc* 1998;47:354-62. DOI PubMed
71. Liberato MJ, Canena JM. Endoscopic stenting for hilar cholangiocarcinoma: efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients. *BMC Gastroenterol* 2012;12:103. DOI PubMed PMC
72. Naitoh I, Ohara H, Nakazawa T, et al. Unilateral versus bilateral endoscopic metal stenting for malignant hilar biliary obstruction. *J Gastroenterol Hepatol* 2009;24:552-7. DOI
73. Lee TH, Kim TH, Moon JH, et al. Bilateral versus unilateral placement of metal stents for inoperable high-grade malignant hilar biliary strictures: a multicenter, prospective, randomized study (with video). *Gastrointest Endosc* 2017;86:817-27. DOI PubMed
74. Ashat M, Arora S, Klair JS, Childs CA, Murali AR, Johlin FC. Bilateral vs unilateral placement of metal stents for inoperable high-grade hilar biliary strictures: a systemic review and meta-analysis. *World J Gastroenterol* 2019;25:5210-9. DOI PubMed PMC
75. Chen ZK, Zhang W, Xu YS, Li Y. Unilateral versus side-by-side metal stenting for malignant hilar biliary obstruction: a meta-analysis. *J Laparoendosc Adv Surg Tech A* 2021;31:203-9. DOI PubMed
76. Puli SR, Kalva N, Pamulaparthy SR, et al. Bilateral and unilateral stenting for malignant hilar obstruction: a systematic review and meta-analysis. *Indian J Gastroenterol* 2013;32:355-62. DOI
77. Almadi MA, Barkun A, Martel M. Plastic vs. self-expandable metal stents for palliation in malignant biliary obstruction: a series of meta-analyses. *Am J Gastroenterol* 2017;112:260-73. DOI PubMed
78. Coelen RJS, Roos E, Wiggers JK, et al. Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2018;3:681-90. DOI PubMed
79. Zorrón Pu L, de Moura EG, Bernardo WM, et al. Endoscopic stenting for inoperable malignant biliary obstruction: a systematic review and meta-analysis. *World J Gastroenterol* 2015;21:13374-85. DOI PubMed PMC
80. Sawas T, Al Halabi S, Parsi MA, Vargo JJ. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. *Gastrointest Endosc* 2015;82:256-67.e7. DOI PubMed
81. Hong WD, Chen XW, Wu WZ, Zhu QH, Chen XR. Metal versus plastic stents for malignant biliary obstruction: an update meta-analysis. *Clin Res Hepatol Gastroenterol* 2013;37:496-500. DOI PubMed
82. Kwon CI, Lehman GA. Mechanisms of biliary plastic stent occlusion and efforts at prevention. *Clin Endosc* 2016;49:139-46. DOI PubMed PMC
83. Schmassmann A, von Gunten E, Knuchel J, Scheurer U, Fehr HF, Halter F. Wallstents versus plastic stents in malignant biliary obstruction: effects of stent patency of the first and second stent on patient compliance and survival. *Am J Gastroenterol* 1996;91:654-9. PubMed
84. Weber A, Mittermeyer T, Wagenpfeil S, Schmid RM, Prinz C. Self-expanding metal stents versus polyethylene stents for palliative treatment in patients with advanced pancreatic cancer. *Pancreas* 2009;38:e7-e12. DOI PubMed
85. Walter D, van Boeckel PG, Groenen MJ, et al. Cost efficacy of metal stents for palliation of extrahepatic bile duct obstruction in a randomized controlled trial. *Gastroenterology* 2015;149:130-8. DOI
86. Speer AG, Cotton PB, MacRae KD. Endoscopic management of malignant biliary obstruction: stents of 10 French gauge are preferable to stents of 8 French gauge. *Gastrointest Endosc* 1988;34:412-7. DOI PubMed
87. Luigiano C, Ferrara F, Cennamo V, et al. A comparison of uncovered metal stents for the palliation of patients with malignant biliary obstruction: nitinol vs. stainless steel. *Dig Liver Dis* 2012;44:128-33. DOI
88. Perdue DG, Freeman ML, DiSario JA, et al; ERCP Outcome Study ERCOST Group. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. *J Clin Gastroenterol* 2008;42:1040-6. DOI PubMed
89. Yuan TW, Liu HQ, Wang SB, Cao J. Comparison of plastic stents with self-expandable metal stents in palliative treatment of malignant biliary obstruction: a meta-analysis. *Eur Rev Med Pharmacol Sci* 2017;21:2847-57. PubMed
90. Xia MX, Pan YL, Cai XB, et al. Comparison of endoscopic bilateral metal stent drainage with plastic stents in the palliation of

unresectable hilar biliary malignant strictures: Large multicenter study. *Dig Endosc* 2021;33:179-89. DOI

91. Ridtitid W, Rerknimitr R, Janchai A, Kongkam P, Treeprasertsuk S, Kullavanijaya P. Outcome of second interventions for occluded metallic stents in patients with malignant biliary obstruction. *Surg Endosc* 2010;24:2216-20. DOI PubMed
92. Hong W, Sun X, Zhu Q. Endoscopic stenting for malignant hilar biliary obstruction: should it be metal or plastic and unilateral or bilateral? *Eur J Gastroenterol Hepatol* 2013;25:1105-12. DOI PubMed
93. Park CH, Park SW, Jung JH, Jung ES, Kim JH, Park DH. Comparative efficacy of various stents for palliation in patients with malignant extrahepatic biliary obstruction: a systematic review and network meta-analysis. *J Pers Med* 2021;11:86. DOI PubMed PMC
94. Saleem A, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. *Gastrointest Endosc* 2011;74:321-7.e1. DOI PubMed
95. Moole H, Bechtold ML, Cashman M, et al. Covered versus uncovered self-expandable metal stents for malignant biliary strictures: a meta-analysis and systematic review. *Indian J Gastroenterol* 2016;35:323-30. DOI
96. Coté GA, Kumar N, Ansstas M, et al. Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. *Gastrointest Endosc* 2010;72:748-54. DOI
97. Nakai Y, Isayama H, Togawa O, et al. New method of covered wallstents for distal malignant biliary obstruction to reduce early stent-related complications based on characteristics. *Dig Endosc* 2011;23:49-55. DOI
98. Sogabe Y, Kodama Y, Honjo H, et al. Tumor invasion to the arteries feeding the gallbladder as a novel risk factor for cholecystitis after metallic stent placement in distal malignant biliary obstruction. *Dig Endosc* 2018;30:380-7. DOI
99. Kawakubo K, Isayama H, Nakai Y, et al. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. *Surg Endosc* 2012;26:771-6. DOI
100. Costamagna G, Tringali A. Can we insert a covered stent, partially or not, in case of hilar biliary stenosis? *Endosc Int Open* 2017;5:E1218-9. DOI PubMed PMC
101. Kitamura K, Yamamiya A, Ishii Y, Mitsui Y, Nomoto T, Yoshida H. Side-by-side partially covered self-expandable metal stent placement for malignant hilar biliary obstruction. *Endosc Int Open* 2017;5:E1211-7. DOI PubMed PMC
102. Inoue T, Okumura F, Naitoh I, et al. Feasibility of the placement of a novel 6-mm diameter threaded fully covered self-expandable metal stent for malignant hilar biliary obstructions (with videos). *Gastrointest Endosc* 2016;84:352-7. DOI PubMed
103. Yoshida T, Hara K, Imaoka H, et al. Benefits of side-by-side deployment of 6-mm covered self-expandable metal stents for hilar malignant biliary obstructions. *J Hepatobiliary Pancreat Sci* 2016;23:548-55. DOI
104. Lee TH, Lee SJ, Moon JH, Park SH. Technical tips and issues of biliary stenting, focusing on malignant hilar obstruction. *Minerva Gastroenterol Dietol* 2014;60:135-49. DOI PubMed
105. Dumas R, Demuth N, Buckley M, et al. Endoscopic bilateral metal stent placement for malignant hilar stenoses: identification of optimal technique. *Gastrointest Endosc* 2000;51:334-8. DOI
106. Chennat J, Waxman I. Initial performance profile of a new 6F self-expanding metal stent for palliation of malignant hilar biliary obstruction. *Gastrointest Endosc* 2010;72:632-6. DOI PubMed
107. Fukasawa M, Takano S, Shindo H, Takahashi E, Sato T, Enomoto N. Endoscopic biliary stenting for unresectable malignant hilar obstruction. *Clin J Gastroenterol* 2017;10:485-90. DOI PubMed
108. Moon JH, Rerknimitr R, Kogure H, Nakai Y, Isayama H. Topic controversies in the endoscopic management of malignant hilar strictures using metal stent: side-by-side versus stent-in-stent techniques. *J Hepatobiliary Pancreat Sci* 2015;22:650-6. DOI PubMed
109. Kawamoto H, Tsutsumi K, Fujii M, et al. Endoscopic 3-branched partial stent-in-stent deployment of metallic stents in high-grade malignant hilar biliary stricture (with videos). *Gastrointest Endosc* 2007;66:1030-7. DOI PubMed
110. Naitoh I, Hayashi K, Nakazawa T, et al. Side-by-side versus stent-in-stent deployment in bilateral endoscopic metal stenting for malignant hilar biliary obstruction. *Dig Dis Sci* 2012;57:3279-85. DOI
111. Lee TH, Moon JH, Choi JH, et al. Prospective comparison of endoscopic bilateral stent-in-stent versus stent-by-stent deployment for inoperable advanced malignant hilar biliary stricture. *Gastrointest Endosc* 2019;90:222-30. DOI
112. Ishigaki K, Hamada T, Nakai Y, et al. Retrospective comparative study of side-by-side and stent-in-stent metal stent placement for hilar malignant biliary obstruction. *Dig Dis Sci* 2020;65:3710-8. DOI
113. Hong W, Chen S, Zhu Q, Chen H, Pan J, Huang Q. Bilateral stenting methods for hilar biliary obstructions. *Clinics* 2014;69:647-52. DOI PubMed PMC
114. Chen L, Gao GM, Li DL, Chen ZK. Side-by-side versus stent-in-stent bilateral stenting for malignant hilar biliary obstruction: a meta-analysis. *Wideochir Inne Tech Maloinwazyjne* 2022;17:279-88. DOI PubMed PMC
115. Shah T, Desai S, Haque M, Dakik H, Fisher D. Management of occluded metal stents in malignant biliary obstruction: similar outcomes with second metal stents compared to plastic stents. *Dig Dis Sci* 2012;57:2765-73. DOI PubMed PMC
116. Inoue T, Naitoh I, Okumura F, et al. Reintervention for stent occlusion after bilateral self-expandable metallic stent placement for malignant hilar biliary obstruction. *Dig Endosc* 2016;28:731-7. DOI
117. Anderson DJ, Shimpi RA, McDonald JR, et al. Infectious complications following endoscopic retrograde cholangiopancreatography: an automated surveillance system for detecting postprocedure bacteremia. *Am J Infect Control* 2008;36:592-4. DOI
118. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007;102:1781-8. DOI

119. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. *Endoscopy* 2001;33:898-900. DOI PubMed
120. Artifon ELA, Ferreira FC, Otoch JP, Rasslan S, Itoi T, Perez-Miranda M. EUS-guided biliary drainage: a review article. *JOP J Pancreas* 2012;13:7-17. PubMed
121. Baniya R, Upadhaya S, Madala S, Subedi SC, Shaik Mohammed T, Bachuwa G. Endoscopic ultrasound-guided biliary drainage versus percutaneous transhepatic biliary drainage after failed endoscopic retrograde cholangiopancreatography: a meta-analysis. *Clin Exp Gastroenterol* 2017;10:67-74. DOI PubMed PMC
122. Park DH, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. *Gastrointest Endosc* 2011;74:1276-84. DOI PubMed
123. Teoh AYB, Dhir V, Kida M, et al. Consensus guidelines on the optimal management in interventional EUS procedures: results from the Asian EUS group RAND/UCLA expert panel. *Gut* 2018;67:1209-28. DOI
124. Horaguchi J, Fujita N, Noda Y, et al. Endosonography-guided biliary drainage in cases with difficult transpapillary endoscopic biliary drainage. *Dig Endosc* 2009;21:239-44. DOI
125. Bories E, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. *Endoscopy* 2007;39:287-91. DOI PubMed
126. Park DH, Koo JE, Oh J, et al. EUS-guided biliary drainage with one-step placement of a fully covered metal stent for malignant biliary obstruction: a prospective feasibility study. *Am J Gastroenterol* 2009;104:2168-74. DOI
127. Perez-Miranda M, de la Serna C, Diez-Redondo P, Vila JJ. Endosonography-guided cholangiopancreatography as a salvage drainage procedure for obstructed biliary and pancreatic ducts. *World J Gastrointest Endosc* 2010;2:212-22. DOI PubMed PMC
128. Park DH, Song TJ, Eum J, et al. EUS-guided hepaticogastrostomy with a fully covered metal stent as the biliary diversion technique for an occluded biliary metal stent after a failed ERCP (with videos). *Gastrointest Endosc* 2010;71:413-9. DOI
129. Kawakubo K, Isayama H, Kato H, et al. Multicenter retrospective study of endoscopic ultrasound-guided biliary drainage for malignant biliary obstruction in Japan. *J Hepatobiliary Pancreat Sci* 2014;21:328-34. DOI
130. Ogura T, Sano T, Onda S, et al. Endoscopic ultrasound-guided biliary drainage for right hepatic bile duct obstruction: novel technical tips. *Endoscopy* 2015;47:72-5. DOI
131. Park DH. Endoscopic ultrasound-guided biliary drainage of hilar biliary obstruction. *J Hepatobiliary Pancreat Sci* 2015;22:664-8. DOI PubMed
132. Ogura T, Onda S, Takagi W, et al. Clinical utility of endoscopic ultrasound-guided biliary drainage as a rescue of re-intervention procedure for high-grade hilar stricture. *J Gastroenterol Hepatol* 2017;32:163-8. DOI PubMed
133. Kongkam P, Tasneem AA, Rerknimitr R. Combination of endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography-guided biliary drainage in malignant hilar biliary obstruction. *Dig Endosc* 2019;31 Suppl 1:50-4. DOI PubMed
134. Nam K, Kim DU, Lee TH, et al. Patient perception and preference of EUS-guided drainage over percutaneous drainage when endoscopic transpapillary biliary drainage fails: an international multicenter survey. *Endosc Ultrasound* 2018;7:48-55. DOI PubMed PMC
135. Chamberlain RS, Blumgart LH. Hilar cholangiocarcinoma: a review and commentary. *Ann Surg Oncol* 2000;7:55-66. DOI PubMed
136. Dondossola D, Ghidini M, Grossi F, Rossi G, Foschi D. Practical review for diagnosis and clinical management of perihilar cholangiocarcinoma. *World J Gastroenterol* 2020;26:3542-61. DOI PubMed PMC
137. Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 2005;100:2426-30. DOI PubMed
138. Larghi A, Rimbaş M, Tringali A, Boškoski I, Rizzatti G, Costamagna G. Endoscopic radiofrequency biliary ablation treatment: a comprehensive review. *Dig Endosc* 2019;31:245-55. DOI PubMed
139. Nayar MK, Oppong KW, Bekkali NLH, Leeds JS. Novel temperature-controlled RFA probe for treatment of blocked metal biliary stents in patients with pancreaticobiliary cancers: initial experience. *Endosc Int Open* 2018;6:E513-7. DOI PubMed PMC
140. Skowronek J, Zwierzchowski G. Brachytherapy in the treatment of bile duct cancer - a tough challenge. *J Contemp Brachytherapy* 2017;9:187-95. DOI PubMed PMC
141. Mukewar S, Gupta A, Baron TH, et al. Endoscopically inserted nasobiliary catheters for high dose-rate brachytherapy as part of neoadjuvant therapy for perihilar cholangiocarcinoma. *Endoscopy* 2015;47:878-83. DOI
142. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *CA Cancer J Clin* 2011;61:250-81. DOI PubMed PMC
143. Feisthammel J, Mössner J, Hoffmeister A. Palliative endoscopic treatment options in malignancies of the biliopancreatic system. *Viszeralmedizin* 2014;30:238-43. DOI PubMed PMC
144. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003;125:1355-63. DOI
145. Li Z, Jiang X, Xiao H, et al. Long-term results of ERCP- or PTCS-directed photodynamic therapy for unresectable hilar cholangiocarcinoma. *Surg Endosc* 2021;35:5655-64. DOI PubMed PMC
146. Lee TY, Cheon YK, Shim CS. Photodynamic therapy in patients with advanced hilar cholangiocarcinoma: percutaneous cholangioscopic versus peroral transpapillary approach. *Photomed Laser Surg* 2016;34:150-6. DOI PubMed