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Review

Endoscopic treatment of unresectable perihilar cholangiocarcinoma: beyond biliary drainage

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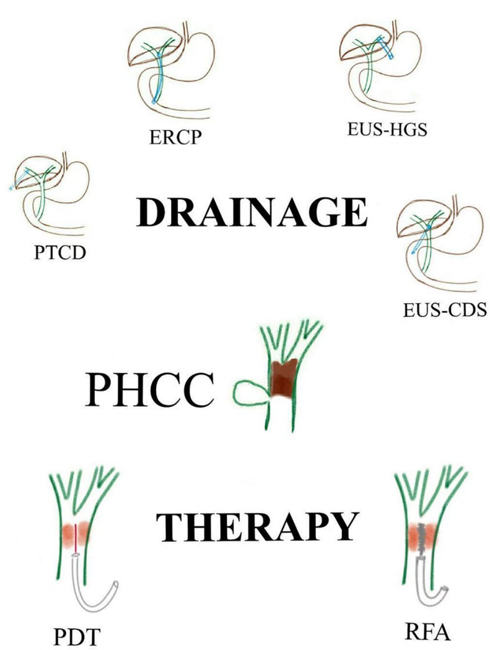
Abstract

Perihilar cholangiocarcinoma (PHCC) is an aggressive biliary malignancy originating from the epithelial cells of the bile duct, typically located in the extrahepatic biliary tree, proximal to the cystic duct. PHCC often presents with a rapid onset of jaundice. While radical surgical resection remains the only curative treatment, only a minority of patients are eligible due to early metastasis and challenges associated with preoperative evaluations. Comprehensive treatments, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, are crucial for managing PHCC. However, in advanced stages, complications such as cholestatic liver injury, malnutrition, and biliary infections pose significant obstacles to these treatments. Therefore, biliary drainage (BD) is essential in the management of PHCC. In addition to external drainage methods like percutaneous transhepatic biliary drainage (PTBD), endoscopic biliary drainage (EBD), particularly endoscopic retrograde cholangiopancreatography (ERCP), offer an effective option for internal drainage, which is more physiologically compatible and better tolerated. Furthermore, the integration of various endoscopic techniques has expanded the management of PHCC beyond mere drainage. Techniques such as radiofrequency ablation (RFA), photodynamic therapy (PDT), and endoscopic ultrasound (EUS) based methods present new therapeutic avenues, albeit with variable results. This review aims to summarize current advancements and ongoing debates in the field of endoscopic treatment for unresectable PHCC.

Graphical abstract



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Introduction

Perihilar cholangiocarcinoma (PHCC), also known as Klatskin tumor, refers to cholangiocarcinoma located between the second-order bile ducts and the junction of the cystic duct. It represents the most prevalent form of cholangiocarcinoma, accounting for 40%–60% of all cases.[1] Common classification systems for PHCC include Bismuth-Corlette, AJCC, Blumgart T-staging, and Memorial Sloan-Kettering Cancer Center (MSKCC) T-staging systems. The Bismuth-Corlette classification emphasizes the tumor's location and extent along the bile duct system. It is primarily used for preliminary endoscopic diagnosis, staging, and guiding surgical planning, and is widely applied to direct localized treatment during endoscopy. However, it lacks information on vascular invasion, metastasis, and liver lobe atrophy, which limits its predictive capability concerning resectability and prognosis[2,3] (Figure 1). The Blumgart T-staging system classifies tumors based on the extent of invasion, portal vein involvement, and ipsilateral liver lobe atrophy, providing better predictive validity for resectability and the likelihood of achieving R0 resection. Nonetheless, it does not consider lymph nodes or distant metastases, which limits its prognostic value.[4,5] In 2001, the MSKCC proposed a T-staging system that integrates local tumor factors, including portal vein involvement and liver lobe atrophy, demonstrating good predictive value for resectability.[6] The AJCC staging system is based on pathological findings, including vascular invasion, lymph node involvement, and distant metastases, providing improved prognostic value and guidance for postoperative treatment.[7–9]

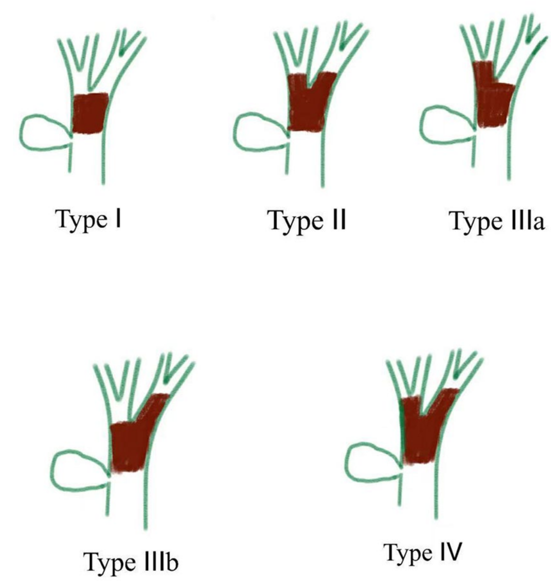

Figure 1. The Bismuth-Corlette classification of PHCC.
PHCC, perihilar cholangiocarcinoma.

The incidence of PHCC varies considerably worldwide, with a notably higher incidence in Asia, ranging from 1 to 70 per 100,000 population, and showing an increasing trend over the years.[10] Surgical resection remains the only curative treatment. However, due to the partial patency of the common bile duct in the early stage, many patients are asymptomatic or present with nonspecific symptoms. Once complete biliary obstruction occurs, patients typically exhibit symptoms such as jaundice (80%–90%), abdominal pain, dark urine, pale stools, pruritus, and often fever. Unfortunately, these symptoms usually indicate disease progression, resulting in missed surgical opportunities. Consequently, only 20%–30% of PHCC patients are candidates for R0 resection, with a median survival of 1–4 years. By contrast, only 5–9 months for those unresectable ones.[10,11] Therefore, adequate biliary drainage (BD) combined with systemic treatments can significantly improve survival outcomes.

BD by endoscopic techniques

The importance and significance of BD in unresectable PHCC

In advanced PHCC, patients frequently succumb not to widespread metastasis but rather to severe cholangitis and liver failure due to biliary obstruction. Although comprehensive treatments can prolong overall survival,[12] they typically require total bilirubin levels to be maintained below

50 μmol/L for effective administration.[13] Therefore, BD serves not only as a palliation treatment but also as a prerequisite for other therapies. Unlike malignant distal biliary obstruction (MDBO), PHCC often leads to the isolation of segmental bile ducts, which complicates BD and increases the likelihood of reintervention. Thus, developing rational strategies, selecting appropriate drainage methods, and advancing new endoscopic treatments are critical areas of research.

Currently, there exists a guideline and a consensus on endoscopic treatment for hilar biliary obstruction,[14,15] alongside several other guidelines and consensuses that address biliary obstruction or strictures, incorporating aspects of hilar obstruction treatments.[16–19] While these guidelines universally emphasize the necessity of BD; however, they vary in their recommendations related to the types, numbers, and selection strategies for stenting in the context of PHCC. These considerations hinge not only on the critical Bismuth classification but also on the available facilities, the expertise of the center, and the individual patient's conditions (e.g., the presence of infection or the need for subsequent treatments).

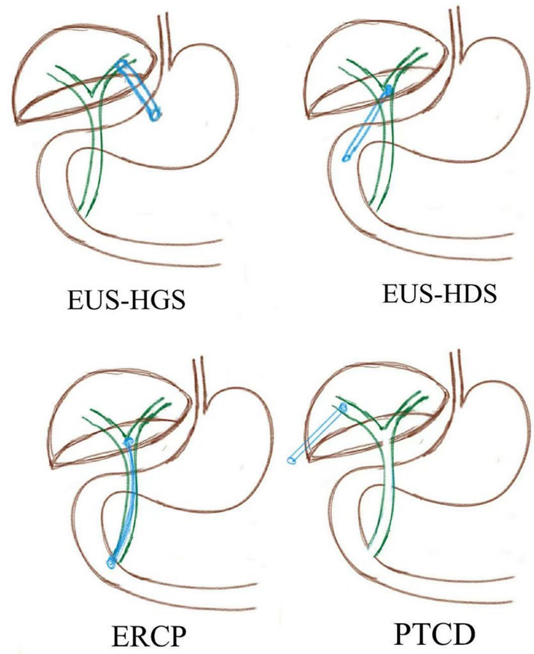

Figure 2. Graphical explanation of ERCP, PTBD, EUS-HGS, and EUS-HDS.
ERCP, endoscopic retrograde cholangiopancreatography; EUS-HGS, endoscopic ultrasound-hepaticogastrostomy; EUS-HDS, endoscopic ultrasound-hepaticoduodenostomy; PTBD, percutaneous transhepatic biliary drainage.

The methods for BD—EBD or PTBD?

BD can be categorized into internal and external drainage. Internal drainage includes endoscopic biliary stenting (EBS) and internal percutaneous transhepatic biliary drainage (iPTBD), while external drainage encompasses endoscopic nasobiliary drainage (ENBD) and external PTBD (ePTBD). Similar to the treatment of MDBO, internal drainage has the advantage of reconstructing the enterohepatic circulation of bile acids, which is more physiologically compatible and improves nutritional status.[20] However, high-level biliary obstructions present unique challenges, such as segment bile duct isolation and intrahepatic metastases, complicating the percutaneous BD.

The selection of appropriate drainage methods should consider factors such as the Bismuth classification, bile duct anatomy, and the overall condition of the patient, including any concurrent infections or the need for future treatments. For Bismuth type I and II PHCC, the preferred approach is the placement of an internal drainage stent via ERCP, the presence of biliary infections may necessitate a direct choice of PTBD or ENBD for external drainage. Thus, simultaneous placement of both a metal stent and ENBD may also be considered to achieve both internal and external drainage. For Bismuth type III and IV PHCC, the primary objective is to drain as many liver segments as possible. While existing guidelines do not provide definitive conclusions on this matter, there remains an ongoing debate regarding the optimal approach (Figure 2).

Technical and clinical success of EBD and PTBD

Technical success refers to the successful placement of a catheter or tube within the bile duct. However, due to complex obstructions and factors such as intrahepatic metastasis, drainage tubes may fail to provide adequate drainage and may exacerbate liver function by triggering biliary infections. Thus, technical success does not translate into clinical success. Clinical success is characterized by the regression of jaundice, restoration

Table 1. Comparison of the clinical success rates of EBD and PTBD.

Study	Study type	Bismuth type	Simple size (EBD/PTBD)	EBD	PTBD	*p* Value
Van Keulen et al. (2022)[13]	Retrospective	I–IV	161/25	45%	24%	0.295
Liang et al. (2021)[25]	Retrospective	III–IV	97/48	52.6%	67.4%	0.097
Walter et al. (2013)[27]	Retrospective	NA	42/87	49%	79%	0.002
Lee et al. (2007)[28]	Retrospective	II–IV	34/66	79.4%	93.9%	0.03
Paik et al. (2009)[23]	Retrospective	III–IV	44/41	77.3%	92.7%	0.049
Zhu et al. (2020)[24]	Retrospective	I–IV	42/40	100%	100%	0.73
Moole et al. (2016)[26]	Meta-analysis	I–IV	348/198	2.53 (95% CI = 1.57–4.08)		$I^2 = 70.8\%$

EBD, endoscopic biliary drainage; NA, not available; PTBD, percutaneous transhepatic biliary drainage; RCT, randomized controlled trial.

of liver function, and improvement in nutritional status.[21–24]

In EBD therapy, challenges in treating MDBO differ from those encountered in PHCC. In cases of MDBO, partial tumor invasion of the papilla often alters its morphology and position, commonly resulting in a dilated common bile duct. By contrast, with PHCC obstruction, the papillary structure typically remains intact, but prolonged disuse of the common bile duct complicates cannulation. PTBD is relatively easier in MDBO since catheter placement in any area above the obstruction can yield effective drainage. If PTBD proves difficult, percutaneous transhepatic gallbladder drainage can often yield satisfactory results and is comparatively simpler to perform. However, this becomes considerably more complex in PHCC.

Few studies have reported technical success rates for PTBD and EBD, possibly because technical challenges have not been the primary focus of research. Most published studies indicated no significant difference in clinical success rates between EBD and PTBD.[13,24–26] Still, some single-center retrospective studies indicated a higher rate of clinical success for PTBD. Walter et al.[27]'s study reported a higher clinical success rate in the PTBD group compared to the EBD group (79% vs 49%, $p = 0.002$), with 51% of EBD patients who failed subsequently undergoing conversion to the PTBD. Paik et al.[23]'s study, which included unresectable Bismuth types III–IV PHCC patients, compared EBS and ePTBD with self-expanding metal stent (SEMS) implantation, finding that the clinical success rate was significantly higher in the ePTBD group than that in the EBS group (92.7% vs 77.3%, $p = 0.049$). Lee et al.[28]'s study demonstrated that compared to the EBD group (79.4%), both the ePTBD group (93.9%) and iPTBD group (97.1%) had higher initial success rates ($p = 0.03$). However, other studies generally supported the absence of significant differences in clinical success rates between the PTBD and EBS groups (Table 1).

The observed differences may be attributed to various factors, including the type and number of stents, as well as the Bismuth type of patients in each study. In addition, PTBD includes both ePTBD and iPTBD, which may represent significant confounding factors affecting the final outcomes.

Overall survival and patency time of PTBD and EBD

Theoretically, stent implantation does not alter the natural course of PHCC, and bile duct drainage should not affect survival time. However, the effectiveness of bile duct drainage is not only closely related to liver function, nutritional status, and immune system improvement, ultimately

Table 2. Comparison of the overall survival and patency time of EBD and PTBD.

Study	Type	Simple size (EBD/PTBD)	Stent	Overall survival		*p* Value	Patency time		*p* Value
				EBD	PTBD		EBD	PTBD	
Liang et al. (2021)[25]	Retrospective	97/48	SEMS	142 days	218 days	0.057	NA	NA	NA
Lee et al. (2007)[28]	Retrospective	34/66	Both	NA	NA	NA	120 ± 16 days	59 ± 6 days	<0.01
Born et al. (2000)[31]	Retrospective	20/39	Plastic	4.5 months	6 months	NA	NA	NA	NA
Paik et al. (2009)[23]	Retrospective	44/41	SEMS	6.2 months	8.7 months	0.125	9.8 months	11.0 months	0.286
Zhu et al. (2020)[24]	Retrospective	42/40	SEMS	237 ± 32.4 days	252.2 ± 21.5 days	0.637	NA	NA	NA

EBD, endoscopic biliary drainage; NA, not available; PTBD, percutaneous transhepatic biliary drainage; SEMS, self-expanding metal stent.

facilitating comprehensive treatments that correlate with quality of life and survival time.[23,29,30]

Existing studies consistently demonstrate no significant difference in overall survival between patients undergoing EBD and those undergoing PTBD (Table 2). Rather, the success of initial drainage and subsequent treatment plays a critical role in determining patient survival. Born et al.[31]'s study indicated that among patients with successful primary drainage, the median survival was 7.5 months, whereas none of the patients with unsuccessful initial drainage survived beyond 6 months. Patients selected for adjuvant radiotherapy, chemotherapy, or both exhibited a median survival of 9 months (range 3–38 months). Liang et al.[25]'s research revealed a survival advantage associated with successful drainage (227 vs 82 days, $p < 0.001$). In addition, Paik et al.[23] found that the median survival of patients with initially successful BD, regardless of procedure type, was significantly longer than that of those with failed drainage (8.7 vs 1.8 months, $p < 0.001$), and this was the factor most associated with long-term survival by univariate and multivariate analyses ($p < 0.001$). Once successful BD was achieved, median survival and stent patency duration were comparable between the two approaches.

Regarding patency duration, only Lee et al.[28]'s study reported statistically different results, in Bismuth type III PHCC, EBD and iPTBD exhibited superior patency rates compared to ePTBD (188 ± 47, 133 ± 21, and 53 ± days, respectively, $p < 0.01$). Cox regression analysis revealed a significant association between the type of drainage procedure and duration of patency (EBD: $p = 0.01$; iPTBD: $p < 0.01$). For patients with Bismuth type IV, the mean patency duration for iPTBD, EBD, and ePTBD were 251 ± 36, 102 ± 19, and 60 ± days, respectively ($p < 0.01$). However, there was no difference for Bismuth type II PHCC (Table 2).

The differences in outcomes may be attributed to factors beyond the drainage technique, as stent patency is influenced not only by the type of drainage method but also by stent characteristics, the number of stents used, and the stent placement strategy (which will be discussed later). Therefore, more rigorous clinical studies are warranted.

Postoperative complications of PTBD and EBD

Regarding postoperative complications, no significant differences were observed between the EBD and PTBD groups (Table 3). Among all complications, pancreatitis and cholangitis are the most extensively studied. Research findings diverge significantly from theoretical expectations. While none of the studies reported a statistically significant difference in the incidence of pancreatitis between the two groups, it is noteworthy that the PTBD group did not have a zero incidence, two studies indicated a higher incidence of pancreatitis in the PTBD group.[23,27] Similar observations have been made concerning postoperative cholangitis. Theoretically, external

Table 3. Comparison of the complications of EBD and PTBD.

Study	Type	Simple size (EBD/PTBD)	Overall complications		p Value	Pancreatitis		p Value	Cholangitis		p Value	Bleeding		p Value
			EBD	PTBD		EBD	PTBD		EBD	PTBD		EBD	PTBD	
Van Keulen et al. (2022)[13]	Retrospective	161/25	12%	12%	1.000	3%	0	1.000	6%	8%	NA	NA	NA	NA
Liang et al. (2021)[25]	Retrospective	97/48	39.2%	39.6%	0.962	NA	NA	NA	27.8%	29.2%	0.867	3.1%	2.1%	1.000
Walter et al. (2013)[27]	Retrospective	42/87	29%	25%	0.79	3%	7%	0.65	25%	21%	0.34	1%	2%	0.54
Choi et al. (2012)[22]	Retrospective	29/31	27.6%	12.9%	0.136	10.3%	0	0.107	17.2%	12.9%	0.727	3.4%	3.2%	>0.999
Born et al. (2000)[31]	Retrospective	20/39	NA	NA	NA	10%	7.7%	NA	5%	5%	NA	NA	NA	NA
Lee et al. (2007)[28]	Retrospective	34/66	38%	20%	NA	2.9%	0%	NA	29.4%	12.1%	NA	5.9%	7.6%	NA
Paik et al. (2009)[23]	Retrospective	44/41	29.5%	31.7%	0.829	0	4.9%	0.138	29.5%	22.0%	0.424	0	4.9%	0.138
Zhu et al. (2020)[24]	Retrospective	42/40	NA	NA	NA	9.5%	0	0.116	52.4%	20%	0.002	NA	NA	NA

EBD, endoscopic biliary drainage; NA, not available; PTBD, percutaneous transhepatic biliary drainage.

drainage should reduce the incidence of postoperative cholangitis; however, apart from Zhu et al.[24]'s study, which showed a significantly lower incidence of cholangitis in the PTBD group, other studies did not find significant differences between the two groups.

These results may be influenced by various factors. First, most studies did not differentiate between iPTBD and ePTBD. Second, the types and numbers of stents utilized in EBD procedures varied. In addition, factors such as sample size and biases inherent in retrospective studies may also affect the results. Furthermore, some studies have combined PTBD with internal drainage via percutaneous biliary stenting.[13,24] This approach leverages the strengths of both approaches while mitigating their weaknesses. Liu et al.[32] reported that combining ENBD and EBS reduces cholangitis rates and improves liver chemistries. Similarly, in our center, we often employ a simultaneous approach using plastic stenting and ENBD tube for Bismuth II/III/IV PHCC to evaluate the effect of BD and liver function recovery. If the drainage effect is satisfactory, the ENBD can be severed for stent transformation via an endoscopic scissor. This two-step technique not only allows for ex vivo assessment but also enhances patient tolerance and psychological outcomes. Our experience indicates that maintaining an ENBD tube can significantly reduce postoperative infections and facilitate ongoing monitoring of bile duct patency through cholangiography.

In summary, there currently exists insufficient evidence to definitively determine where PTBD or EBD has a relative advantage. Only one guideline recommends using ERCP for Bismuth type I and II obstructions while suggesting PTBD or a combination of PTBD and ERCP for type III and IV.[16] Other guidelines and some studies advocate for PTBD due to its similar clinical success and patency duration as compared to EBD, though concerns about the higher incidence of cholangitis and technical challenges associated with EBD exist.[14,33,34] Conversely, other researches highlight the potential drawbacks of PTBD, such as its association with peritoneal metastasis,[35,36] as well as the discomfort and psychological distress it may impose on patients, subsequently increasing the nursing burden. Therefore, the choice

Table 4. Comparison of the technical success and clinical success rates of plastic and metallic stents.

Study	Study type	Sample size (plastic/metal)	Technical success		p Value	Clinical success		p value
			Plastic	Metal		Plastic	Metal	
Liberato and Canena (2012)[37]	Retrospective	115/99	88.3%	98.8%	<0.001	84.8%	97.9%	<0.001
Kim et al. (2021)[39]	Retrospective	67/35	100%	100%	NA	65.6%	71.4%	>0.05
Sangchan et al. (2012)[38]	RCT	54/54	85.2%	83.3%	0.792	46.3%	70.4%	0.011
Xia et al. (2021)[40]	Retrospective	96/96	100%	100%	NA	71.9%	99.9%	<0.001
Wagner et al. (1993)[41]	RCT	9/11	88.9%	100%	0.27	87.8%	100%	0.24
Raju et al. (2011)[42]	Retrospective	52/48	100%	100%	NA	94.2%	95.8%	NA
Xia et al. (2020)[43]	Retrospective	172/184	100%	100%	NA	68.6%	90.8%	<0.01
Gong et al. (2022)[44]	Retrospective	43/28	60.47%	96.43%	<0.001	NA	NA	NA
Koiwai et al. (2022)[45]	Retrospective	25/24	100%	100%	NA	100%	87.5%	0.11
Mukai et al. (2013)[46]	RCT	30/30	100%	100%	NA	NA	NA	NA

NA, not available; RCT, randomized controlled trial.

between PTBD and EBD should be guided by the experience of local centers, patient preferences, and the specific clinical context.

The selection of stents in EBD

The selection of stents is closely tied to advancements in material science, particularly regarding their patency. In managing unresectable PHCC, the focus shifts from operative area adhesions and edema—critical factors in resectable cases—to the efficacy of drainage procedures. Currently, plastic stents and SEMS are widely employed in the EBD approach. Plastic stents offer various length options and can be trimmed using an ENBD tube to suit clinical needs. By contrast, while SEMS exhibit superior drainage efficiency due to their larger inner diameters, their placement in narrow anatomical spaces poses significant challenges. However, existing researches indicate that the technical success rate in the SEMS group is not lower than that in the plastic stent group, and in some studies, it even surpasses.[37,38] Clinical success rates are predictably higher in the SEMS group, although some studies show no statistically significant differences, a trend favoring metallic stents persists (Table 4).

A body of research (Tables 4 and 5) has demonstrated that SEMS yield better outcomes regarding stent dysfunction, re-intervention rates, and median survival times. For example, Sawas et al.[47] confirmed that SEMS had a lower 30-day occlusion rate compared to plastic stents (odds ratio (OR) 0.16; 95% confidence interval (CI): 0.04–0.62), and a lower long-term occlusion rate in the context of hilar malignant obstruction (OR 0.28; 95% CI: 0.19–0.39). Therapeutic failure was more likely with plastic stents (13%) than with SEMS (7%; OR 0.43; 95% CI: 0.27–0.67). Furthermore, SEMS required fewer reinterventions compared to plastic stents (mean difference, 0.49; 95% CI: 0.8–0.19), and the incidence of cholangitis was statistically lower with SEMS (8% vs 21%; OR 0.41; 95% CI: 0.22–0.76). A randomized controlled trial (RCT) conducted by Sangchan demonstrated a higher successful drainage rate in the SEMS group compared to the plastic stent group (70.4% vs 46.3%, $p = 0.011$), with a median survival time of 126 days in the SEMS group versus 49 days in the plastic stent group ($p = 0.002$).[38]

Several guidelines recommended SEMS as the preferred choice for endoscopic palliation.[15,16]

Table 5. Comparison of survival time, stent patency, and reintervention of plastic and metallic stents.

Study	Type	Sample size (plastic/metal)	Survival time		p Value	Stent patency		p Value	Reintervention		p Value
			Plastic	Metal		Plastic	Metal		Plastic	Metal	
Liberato and Canena (2012)[37]	Retrospective	115/99	46 weeks	45 weeks	0.18	20 weeks	27 weeks	<0.0001	1.043[a]	0.60[a]	<0.001
Kim et al. (2021)[39]	Retrospective	67/35	HR: 1.71, 95% CI (0.93–3.13)[b]		NA	56 days	112 days	0.63	56.7%	40%	0.11
Sangchan et al. (2012)[38]	RCT	54/54	49 days	126 days	0.0021	NA	NA	NA	NA	NA	NA
Xia et al. (2021)[40]	Retrospective	96/96	4.1 months	7.2 months	0.015	9.2 months	4.8 months	NA	9.4%	0%	0.003
Mukai et al. (2013)[46]	RCT	30/30	189 days	220 days	0.283	30% until death	60% until death	0.0185	1.80[a]	0.63[a]	0.0008
Raju et al. (2011)[42]	Retrospective	52/48	8.22 months	9.08 months	0.50	1.86 months	5.56 months	<0.0001	4.60[a]	1.53[a]	<0.05
Xia et al. (2020)[43]	Retrospective	172/184	HR = 0.71; 95% CI: 0.56–0.90		0.006	HR = 0.35; 95% CI: 0.25–0.49		<0.001	2.0 ± 1.4[a]	1.5 ± 0.7[a]	<0.001
Gong et al. (2022)[44]	Retrospective	43/28	8.15 months	11.83 months	<0.05	NA	NA	NA	NA	NA	NA
Wagner et al. (1993)[41]	RCT	9/11	NA	NA	NA	NA	NA	NA	2.4[a]	0.4[a]	0.05
Perdue et al. (2008)[48]	Retrospective	28/34	NA	NA	NA	NA	NA	NA	32%	12%	0.065
Hong et al. (2013)[49]	Meta-analysis	NA	HR = 0.73; 95% CI: 0.56–0.96		$I^2 = 56.9\%$	HR = 0.43; 95% CI: 0.30–0.61		$I^2 = 57.6\%$	WMD = 0.59; 95% CI: 0.28–0.90		$I^2 = 76.4\%$

[a]Times/patient.
[b]Mortality within 12 months.
CI, confidence interval; HR, hazard ratio; NA, not available; RCT, randomized controlled trial; WMD, weighted mean difference.

However, some literature suggested that advancements in chemotherapy, immunotherapy, and targeted therapy may allow the survival of unresectable PHCC patients to exceed the patency duration of SEMS.[50,51] This raises concerns regarding the challenges of endoscopic re-intervention for SEMS, potentially increasing the need for PTBD. And some guidelines suggest that plastic stents might be more appropriate for patients responding to adjuvant therapy.[14] Nevertheless, we disagree with this viewpoint, as reinserting plastic stents or fully covered SEMS into patients is feasible in our center. Due to the increased use of peroral cholangioscopy (POCS) and endoscopic ultrasound (EUS), the difficulties of re-intervention have substantially decreased. Notably, as locoregional therapies continue to evolve, including radiofrequency ablation (RFA) and photodynamic therapy (PDT), which will be discussed in detail subsequently, plastic stents emerge as a commendable alternative. However, when it comes to EUS treatments (as discussed later), metallic stents are primarily preferred.

The strategy of BD in unresectable PHCC

As previously discussed, BD in unresectable PHCC presents significant challenges due to the isolation of segmental bile ducts and the tumor's location. Consequently, a single stent may not provide sufficient or durable drainage. A well-thought-out strategy is therefore essential.

Debate continues over the benefits of unilateral versus bilateral drainage in managing PHCC. Some studies and one guideline[15] suggest that bilateral drainage may offer advantages over unilateral drainage. Specifically, Lee et al.[52]'s multicenter, prospective, randomized study revealed the bilateral group had a significantly longer patency duration (252 vs 139 days, $p < 0.01$), higher clinical success rates (95.3% vs 84.9%, $p = 0.047$), and lower re-intervention rates (42.6% vs 60.3%, $p = 0.049$) compared to the unilateral group. Xia et al.[43] demonstrated that bilateral stent placement resulted in higher clinical success rates ($p = 0.024$), increased stent patency ($p = 0.018$), and improved overall survival ($p = 0.040$) compared to unilateral stenting. Although this study included some non-PHCC patients. Another retrospective study by Liberato and Canena[37] found that the cumulative patency of bilateral SEMS or plastic stents was significantly superior to that of unilateral deployment ($p < 0.01$) and was the only independent prognostic factor associated with stent patency. In addition, the primary re-intervention rate in the bilateral group was lower than that in the unilateral group (42.6% vs 60.3%, $p = 0.049$).

Conversely, a substantial body of research, including three meta-analyses,[53–55] suggests that unilateral drainage is not inferior to bilateral drainage in terms of clinical efficacy and safety, with no significant differences in survival rates between the two groups. An RCT by De Palma et al.[56] argued against the routine insertion of multiple stents, as the success rates for drainage, median survival, complication rates, and mortality did not differ significantly between the two groups. Another RCT conducted by Hakuta et al.[57] found no differences in transient re-obstruction rates and overall survival between the two groups ($p = 0.11$ and $p = 0.78$, respectively), and the bilateral SEMS groups experienced a higher incidence of early adverse events (5.3% vs 28%; $p = 0.11$). A recent meta-analysis led by Wang et al.[53] indicated no significant differences in the technical success rates (OR = 0.93; 95% CI: 0.34–2.54, $p = 0.88$), clinical success rates (OR = 1.03; 95% CI: 0.49–2.15, $p = 0.94$), stent dysfunction (OR = 1.47; 95% CI: 0.91–2.39, $p = 0.12$), or survival rates (hazard ratio (HR) = 0.85; 95% CI: 0.50–1.42, $p = 0.53$) between the groups. The complication rate was notably lower in the unilateral group (OR = 0.34; 95% CI: 0.13–0.88, $p = 0.03$; Table 6).

The discrepancies among these studies can be attributed to variations in disease types, stages, Bismuth classification, liver volume, the types of stents, and the expertise in each center. Current guidelines do not offer specific recommendations regarding unilateral versus bilateral stenting for unresectable PHCC. Nonetheless, they highlight the necessity of adopting a departmental drainage strategy paradigm in clinical practice and future research. And the latest perspectives suggest that the goal of drainage should be to achieve at least 50% liver volume drainage, without overemphasizing the choice between unilateral or bilateral approaches.[14,16–18] Vienne et al.[69] reported in 2010 that drainage of at least 50% liver volume yields better outcomes, longer survival, and fewer instances of cholangitis compared to drainage of less than 50%. Furthermore, a retrospective study by Caillol et al.[70] in 2019 highlighted the advantages of higher liver drainage ratios, showing that

Table 6. Comparison of the overall survival and patency time patency of unilateral and bilateral.

Study	Study type	Simple size (Uni/Bil)	Bismuth type	Stent	Overall survival		*p* Value	Patency time		*p* Value
					Uni	Bil		Uni	Bil	
Lee et al. (2017)[52]	RCT	66/67	II–IV	SEMS	178 days	270 days	0.053	139 days	252 days	<0.01
Staub et al. (2020)[58]	Retrospective	57/137	I–IV	SEMS	HR = 1.78 (95% CI: 1.09–2.89)		0.02	22.5 weeks	22.0 weeks	0.81
Xia et al. (2020)[43]	Retrospective	178/178	II–IV	Both	HR = 0.77; 95% CI: 0.61–0.97		0.025	HR = 0.63; 95% CI: 0.44–0.88		0.008
Yin et al. (2019)[59]	Retrospective	51/42	II–IV	SEMS	222 days	202 days	0.755	189 days	198 days	0.887
Liberato and Canena (2012)[37]	Retrospective	35/42	II	Both	NA	NA	NA	168 days	203 days	<0.001
De Palma et al. (2001)[56]	RCT	79/78	I–III	Plastic	143 days	144 days	0.442	NA		NA
Iwano et al. (2011)[60]	Retrospective	65/17	II–IV	SEMS	170 days	184 days	0.4908	133 days	125 days	0.322
Naitoh et al. (2009)[61]	Retrospective	17/29	I–IV	SEMS	166 days	205 days	0.559	210 days	488 days	0.009
Hakuta et al. (2021)[57]	RCT	38/39	II–IV	SEMS	9.7 months	7.9 months	0.79	11.1 months	4.3 months	0.11
Wang et al. (2021)[53]	Meta-analysis	215/309	I–IV	Both	HR = 0.85 (95% CI: 0.50–1.42)		0.53	OR = 1.47 (95% CI: 0.91–2.39)		0.12
Hong et al. (2019)[54]	Meta-analysis	NA	I–IV	Both	HR = 0.75; (95% CI: 0.31–1.80)		$I^2 = 94.3\%$	HR = 0.57;95% CI: 0.19–1.73		$I^2 = 91.1\%$

Bil, bilateral; CI, confidence interval; HR, hazard ratio; NA, not available; OR, odds ratio; RCT, randomized controlled trial; SEMS, self-expanding metal stent; Uni, unilateral.

maximal drainage greater than 80% was associated with longer survival compared to drainage of less than 80% (HR = 2.46; 95% CI: 1.16–5.23, $p = 0.02$).

In addition to bilateral drainage, the optimal between stent-in-stent and side-by-side remains unclear. Published studies are limited, resulting in low evidence quality. An RCT performed by Lee et al.[71] revealed no significant differences between these two approaches regarding clinical success, complications, stent dysfunction, or overall survival. And two other meta-analyses reached the same conclusion.[72,73] It is noteworthy that some studies have explored the use of smaller metallic stents (6 mm) for multisite drainage like plastic stents.[74,75]

Regarding suprapapillary and transpapillary approaches, Borges et al.'s[76] study found that while technical success, occlusion rates, reintervention rates, adverse events, and 30-day mortality were similar between the two techniques, the 90-day mortality and postoperative infection indicators were higher in the transpapillary group. Based on our center's experience, transpapillary procedures are relatively straightforward, with convenient stent retrieval; however, this approach increases the risk of reflux. By contrast, suprapapillary stenting carries a higher risk of stent migration.

In conclusion, developing a comprehensive drainage strategy is more critical than merely selecting the materials or quantity of the drainage tubes itself.

The role of EUS techniques in PHCC

First, EUS can also be utilized as a diagnostic tool for PHCC. Although ERCP brush cytology is the standard method for diagnosing malignant biliary strictures, it has a relatively low sensitivity. In cases of negative ERCP brush cytology, EUS-guided fine-needle aspiration biopsy can achieve higher sensitivity and specificity[77,78] and has gradually become a first-line diagnostic method for hilar strictures.[79] And with advancements in artificial intelligence (AI) and image analysis systems, the integration of AI into EUS significantly simplifies for endoscopists.[80]

In addition to BD, EUS-BD has emerged as a viable alternative, particularly in patients who have failed ERCP or surgically altered anatomy.[81–84] EUS-BD may even outperform PTBD in certain scenarios,[17,85,86] and one study indicates that patients show a preference for EUS-BD over PTBD[87] (Figure 2), (Table 7).

In contrast to MDBO, where the obstruction is typically located lower and often accompanied by significant dilation of the common bile duct and intrahepatic bile ducts, EUS-BD can be effectively performed via puncture drainage from the duodenum or stomach, yielding generally positive outcomes.[88,89] However, the complexity of EUS-BD significantly increases when addressing PHCC due to anatomical constraints, making puncturing the right liver lobe particularly challenging. In Bismuth type I, drainage can be effective, as the right and left hepatic ducts are interconnected, resulting in outcomes comparable to ERCP. Thus, EUS-guided hepaticogastrostomy (EUS-HGS) serves as a viable alternative when ERCP fails. In Bismuth type II, although the primary bile duct branches are involved, it is still possible to navigate a guidewire through the narrowed segment and position a multi-side hole stent, facilitating drainage of both liver lobes. Similarly, for type IIIA, EUS-HGS can effectively drain the left liver lobe, particularly if the left lobe is dominant and the drainage volume exceeds 50%, which leads to satisfactory results.[63] However, for types IIIB and IV, the difficulty of puncture is significantly increased, and single-lobe drainage often proves insufficient for effective drainage.[62] Nonetheless, Ogura et al.[67] demonstrated that among 10 patients who failed ERCP-guided reintervention (nine with type IV and one with type IIIB), EUS-BD was carried out with a technical success rate of 100%, and no adverse events were reported. To preserve as much viable liver parenchyma as possible, Kongkam et al.[90] first proposed the CERES approach (EUS-HGS with right biliary SEMS via ERCP or EUS-HDS with left biliary self-expanding stent via ERCP). The same team conducted a multicenter, open-label, observational study comparing the CERES technique with PTBD for MHBO, which included 33 cases of Bismuth type III or IV PHCC and some other cancers. This study demonstrated similar technical success, clinical success, and complication rates between the two methods. The rates of recurrent biliary obstruction and reintervention were significantly lower in CERES groups (26.7% vs 88.2% within 3 months and 22.2% vs 100% in 6 months, $p < 0.05$). In addition, the median

Table 7. Success rates, complications, patency time, and survival time of EUS-BD.

Study	Study type	Sample size	Diagnosis	Bismuth type	Intervention	TS	CS	Adverse events	Patency time (days)	Survival time (days)
Minaga et al. (2017)[62]	Retrospective	30	Cholangiocarcinoma 12 Gallbladder carcinoma 6 Pancreatic carcinoma 5 Hepatocellular carcinoma 1 Liver metastasis 5 Lymph node metastasis 1	Type II 5 Type III 13 Type IV 12	EUS-IBD	96.7%	79.5%	10%	62.5	64
Moryoussef et al. (2017)[63]	Prospective	18	Pancreatic adenocarcinoma 8 Hilar cholangiocarcinoma 5 Colorectal adenocarcinoma 3 Gastric adenocarcinoma 2	I–II 7 III 7 IV 1	EUS-HGS	94%	72.2%	16.7%	79 (5–390)	210 (32–390)
Park et al. (2010)[64]	Case study	5	3 Klatskin (II, IIIB, IV) 1 distal CBD cancer 1 pancreatic head cancer	NA	EUS-HGS	100%	100%	0	NA	NA
Panpimanmas et al. (2013)[65]	Retrospective	10	Cholangiocarcinoma	3 IIIA 7 IV	HGS	80%	70%	0	NA	123
Ogura et al. (2015)[66]	Retrospective	11	3 Pancreatic cancer 6 cholangiocarcinoma 1 colon cancer 1 gastric cancer	NA	7 bridging, 4 HDS	100%	100%	0	NA	NA
Ogura et al. (2017)[67]	Retrospective	10	NA	9IV 1 IIIb	8 HGS, 2 HDS	100%	90%	0	152 (median)	NA
Kanno et al. (2017)[68]	Retrospective	7	3 ICC IV 4 PHCC (1 II, 3 IV)	NA	HGS	100%	57%	0	112 (43–147)	179 (99–273)

AEs, adverse events; CBD, common bile duct; CS, clinical success; EUS-BD, endoscopic ultrasound-biliary drainage; EUS-CDS, endoscopic ultrasound-guided choledochoduodenostomy; EUS-HGS, endoscopic ultrasound-guided hepaticogastrostomy; EUS-IBD, endoscopic ultrasonography-guided intrahepatic biliary drainage; ICC, intrahepatic cholangiocarcinoma; NA, not available; PHCC, perihilar cholangiocarcinoma; RCT, randomized controlled trial; TS, technical success.

drainage patency period was longer in the CERES group compared to the PTBD group (92 vs 40 days, $p=0.06$).[90] However, it is worth noting that this technique involves a higher degree of difficulty.[91]

While ERCP-BD remains the standard drainage approach for PHCC, EUS-BD is primarily utilized in patients who have failed or impossible ERCP. There is a noticeable lack of reports comparing initial EUS-BD versus ERCP-BD for PHCC.[14,81] Current studies have predominantly focused on MDBO.[88,89,92] Consequently, high-quality RCTs are needed to address the comparison of initial EUS-BD versus ERCP-BD in patients with PHCC.

The applications of POCS in unresectable PHCC treatment

POCS can significantly enhance the diagnostic efficiency for indeterminate biliary strictures (IDBS) through direct visualization and targeted multi-site biopsy sampling.[93–97] And a recent meta-analysis demonstrated the high sensitivity and specificity of POCS in the visual interpretation of IDBS and malignancies.[98]

Another important application of POCS is in guiding direct visual biliary selection cannulation. Conducting these procedures solely under digital subtraction angiography guidance can be challenging, and "false passages" may occur even during guidewire selection, exacerbating potential complications. Utilizing POCS in this context reduces the occurrence of stent-related complications and enhances the drainage efficacy of multiple stents during ERCP.[99]

Furthermore, POCS allows for a visual assessment of local treatment effects of PHCC, such as RFA and PDT. A study by Talreja et al.[100] included 45 PHCC patients, consisting of Bismuth Type I–IV, who underwent PDT treatment guided by either ERCP or POCS. The results indicated that the median survival time in the ERCP group was lower (200 days) compared to the POCS group (386 days), although this difference was not statistically significant ($p = 0.45$). In addition, POCS significantly reduced fluoroscopy time, with averages of 21.1 min for ERCP compared to 11.1 min for POCS ($p < 0.0001$).

In recent years, AI has demonstrated great potential in the endoscopic assessment and management of biliary cancer, with several studies exploring its application in diagnosing biliary malignancies. For example, Saraiva et al.[101] developed a convolutional neural network (CNN)-based system in 2022 that accurately detects and differentiates malignant strictures in benign biliary diseases. Similarly, Marya et al.[102] developed a CNN model in 2023 that exhibited greater accuracy for biliary stricture classification compared to traditional ERCP-based sampling techniques.

RFA and PHCC treatment

Current status of RFA in cholangiocarcinoma treatment

RFA through two primary mechanisms in tumor treatment. First, it induces thermal damage that directly destroys tumors through coagulative necrosis and cell death. Second, the release of intracellular components can activate both local and systematic anti-tumor immunity. Percutaneous RFA has been routinely employed in various malignancies, including hepatocellular carcinoma, liver metastases, intrahepatic cholangiocarcinoma, and non-small-cell lung cancer. The advent of flexible catheters, such as Habib HPB-RF probe (Boston Scientific, America) and ELRA RF catheter (Taewoong, Korea), has made endoscopic RFA procedures feasible[103–106] (Table 8).

Stent alone versus RFA plus stent treatment in PHCC

In addition to inducing tumor necrosis and immune activation, RFA has demonstrated a synergistic effect when combined with BD via stent implantation. Survival rates associated with RFA combined with stenting are generally superior to those of stenting alone. A large cohort study by Xia et al. in 2021[121] demonstrated that combined RFA significantly improves overall survival in extrahepatic cholangiocarcinoma compared to stenting alone (9.5 vs 6.1 months, $p < 0.01$). A multi-center RCT conducted by Gao et al.[115] revealed that combined endoscopic RFA significantly improved overall survival (14.3 vs 9.2 months, $p < 0.01$) and quality of life, although this study included some distal cholangiocarcinoma cases. Additional research supported the notion that combining RFA with stent implantation can prolong overall survival and stent patency (Table 9). Despite discrepancies in results across different studies, the therapeutic effect of RFA combined with stenting shows potential advantages in diverse contexts, particularly among specific patient populations. Future studies should further explore the applicability of different types of stents to optimize treatment strategies.[116]

RFA plus chemotherapy/targeted therapy/immunotherapy in PHCC treatment

Limited studies have explored the combination of RFA with other therapies for PHCC. A retrospective study by Gonzalez-Carmona et al.[127] compared conventional RFA combined with first-line chemotherapy (gemcitabine plus platinum derivatives) for advanced extrahepatic biliary tract cancer. The results revealed that the combination group significantly improved overall

Table 8. Efficacy and safety of endoscopic radiofrequency ablation.

Study	Study type	Type of stent	Simple size	Median OS	Stent patency	Complications
Laleman et al. (2017)[107]	Retrospective	Both	9	NA	Median 4.6 months (range: 1.7–11.2)	4 cholangitis, 2 PEP
Han et al. (2020)[108]	Prospective	Both	16	147 days (92–487)	90 days (35–483)	1 cholangitis, 1 Cholecystitis
Inoue et al. (2020)[109]	Retrospective	Metal	41	244	230 days	1 cholangitis, 1 Cholecystitis
Tal et al. (2014)[110]	Retrospective	Plastic	16	6.4 months (95% CI: 0.05–12.7)	6.4 months (95% CI: 0.05–12.7)	3 cholangitis, 3 bleeding
Wang et al. (2016)[111]	Retrospective	Plastic	9	100 days (95% CI: 85–115 days)	5.3 months (95% CI: 2.5–8.1)	4 cholangitis
Dolak et al. (2014)[112]	Retrospective	Both	58	17.9 months (95% CI: 10.3–25.6)	170 days (95% CI: 63–277)	5 cholangitis, 3 bleeding
So et al. (2021)[113]	Retrospective	SEMS	11	50 days (95% CI: 34–NA)	289 days (95% CI: 107–NA)	None

CI, confidence interval; NA, not available; OS, overall survival; SEMS, self-expanding metal stent; PEP, post-operative pancreatitis.

survival (17.3 vs 8.6 months, $p=0.004$) and progression-free survival (12.9 vs 5.7 months, $p=0.045$). Another retrospective study by Inoue et al.[109] evaluated the efficacy of RFA combined with gemcitabine plus cisplatin for unresectable extrahepatic biliary tract cancer, showing longer periods of biliary obstruction recurrence (10.7 vs 5.2 months, $p=0.048$) and higher overall survival (23.1 vs 16.6 months, $p=0.032$) for locally advanced tumors, with no significant difference in the incidence of various toxicities between the groups. An RCT by Yang et al.[128] demonstrated that RFA combined with the novel drug S-1 resulted in significantly longer overall survival (16.0 vs 11.0 months, $p<0.001$), stent patency time (6.6 ± 1.5 vs 5.6 ± 0.1 months, $p=0.014$), and higher Karnofsky Performance Status scores at 9 months (51.6 ± 17.0 vs 40.4 ± 16.4, $p=0.012$) and 12 months (35.2 ± 18.3 vs 23.9 ± 11.4, $p=0.014$) compared to RFA alone, with no significant difference in ERCP-related complications. Gou et al.[129] conducted a multi-center retrospective cohort study comparing the efficacy and safety of RFA combined with hepatic arterial infusion chemotherapy (oxaliplatin and 5-fluorouracil) and stent placement against stent placement alone for treating advanced biliary tract cancer with biliary obstruction. The results showed that the combination therapy group had a significantly longer stent patency time (8.2 vs 4.3 months, $p<0.001$) and overall survival (13.2 vs 8.5 months, $p<0.001$) compared to the stent-alone group, with no statistically significant difference in the incidence of procedure-related adverse events between the two groups. Further studies are needed to evaluate the efficacy of combining RFA with chemotherapy, immunotherapy, and targeted therapy for PHCC.

Endoscopic PDT in PHCC treatment

PDT was first demonstrated by Ortner et al.[130] in 1998 as an effective method for restoring BD, improving quality of life, and prolonging survival in patients with unresectable cholangiocarcinoma. In a subsequent prospective randomized study conducted in 2003, which included 39 patients with unresectable Bismuth types II–IV PHCC, it was shown that PDT significantly extended the median survival time (493 vs 98 days, $p<0.0001$) while also enhancing BD and quality of life[131]. A RCT conducted by Zoepf et al.[132] in 2005 involved 31 patients with unresectable Bismuth type IV cholangiocarcinoma and

Table 9. Comparison of the overall survival and stent patency of RFA plus stent and stent alone.

Study	Study type	Stent type	Simple size (plus/alone)	Overall survival		*p* Value	Stent patency		*p* Value
				RFA+ stents	Stents alone		RFA+ stents	Stents alone	
Gao et al. (2021)[115]	RCT	Plastic	87/87	14.3 months (95% CI: 11.9–16.7)	9.2 months (95% CI: 7.1–11.2)	<0.01	3.7 months (95% CI: 2.8–4.5)	4.1 months (95% CI: 3.7–4.5)	0.674
Andrasina et al. (2021)[117]	RCT	Metal	21/22	12.3 months (95% CI: 5.7–14.4)	12.3 months (95% CI: 8.4–17.5)	0.908	9.3 ± 2.2	5.0 ± 3.1	0.029
Kong et al. (2022)[118]	Retrospective	Metal	150/127	12.3 months (95% CI: 11.6–13.4)	11.8 months (95% CI: 11.2–13.1)	0.352	NR	NR	NR
Bokemeyer et al. (2019)[119]	Retrospective	Both	20/22	342 ± 57 days	221 ± 26 days	0.046	NR	NR	NR
Cui et al. (2017)[120]	Retrospective	Metal	25/39	6.7 months	4.5 months	0.307	7.6	5.4	0.009
Xia et al. (2021)[121]	Cohort	Both	124/496	9.5 months (95% CI: 7.7–11.3)	6.1 months (95% CI: 5.6–6.6)	<0.001	NR	NR	NR
Yang et al. (2018)[121]	RCT	Plastic	32/33	13.2 ± 0.6 months (95% CI: 11.8–14.2)	8.3 ± 0.5months (95% CI: 7.3–9.30	<0.001	6.8 months (95% CI: 3.6–8.2)	3.4 months (95% CI: 2.4–6.5)	0.02
Kang et al. (2021)[122]	RCT	Metal	24/24	244 days (95% CI: 117.8–370.0)	180 days (95% CI: 27.8–332.2)	0.281	132 days (95% CI: 99.6–164.4)	116 days (95% CI: 52.4–179.6)	0.440
Kang et al. (2022)[123]	RCT	Metal	15/15	230 days (95% CI: 77.0–383.0)	144 days (95% CI: 0–323.1)	0.643	178 days (95% CI: 96.2–259.8)	122 days (95% CI: 111.2–132.8)	0.154
Oh et al. (2022)[124]	Retrospective	SEMS	28/51	311 ± 46.9 days	311 ± 24.7 days	0.73	140 ± 53.7 days	192 ± 39.2 days	0.41
Jong et al. (2022)[125]	Meta-analysis	Both	217/294	9.5 months [95% CI, 6.3-12.6]	7.0 months [95% CI, 5.7-8.2]	HR = 0.65 [95% CI, 0.50-0.84] $I^2=38\%$	NR	NR	NR
de Oliveira Veras et al. (2024)[126]	Meta-analysis	Both	481	MD 85.70 (95% CI: 34.29–137.10) days		$I^2=98\%$ $p=0.001$	MD 22.25 (95% CI: 17.38–61.87) days		$I^2=97\%$ $p=0.27$

BPS, bilateral plastic stent; CI, confidence interval; MD, mean difference; RCT, randomized controlled trial; RFA, radiofrequency ablation; SEMS, self-expanding metal stent; NR, not reported.

1 patient with type II lymph node involvement. This study found that the combination of stent placement and PDT significantly improved overall survival (21 vs 7 months, $p=0.01$). In addition, the PDT group exhibited a notable reduction in bilirubin levels (decreasing from an average of 2.75 to 1.3 mg/dL), with no significant difference in adverse events between the two groups. A large retrospective study by Dolak et al.[133] in 2017 included 88 patients who underwent a total of 150 PDT procedures. Among these patients, 79 had Klatskin tumors (including 4 Bismuth type I, 3 type II, 15 type III, and 57 type IV). The results indicated that the median duration of stent patency was 246 days (95% CI: 203–289), with median survival from the first PDT being 12.4 months (95% CI: 9.7–14.9). Cox regression analysis identified the number of PDT treatments as the only independent prognostic factor for survival in multivariate analysis ($p=0.048$). Notably, among these patients, 24 received chemotherapy and 9 underwent curative liver surgery. A meta-analysis conducted by Moole et al.[134] in 2017, compared the outcomes of PDT combined with biliary stenting versus biliary stenting alone. The results indicated that the PDT group achieved better BD, with an OR of 4.39 (95% CI: 2.35–8.19), and prolonged survival, as well as higher Karnofsky scores compared to the stenting alone group, alongside a lower incidence of cholangitis (OR = 0.57, 95% CI: 0.35–0.94), although this analysis exhibited higher heterogeneity. Other studies have also supported the notion that combining PDT with stenting can prolong survival, improve quality of life, and restore BD without increasing adverse events. While PDT may cause phototoxicity, no fatal events have been reported, and most side effects can be managed locally (Tables 10 and 11).

In comparison, RFA offers advantages such as lower cost and no phototoxicity but requires direct access to lesions for effective ablation. PDT, conversely, allows for repeated interventions and can target peripheral or inaccessible lesions, making it a potential downstaging therapy prior to surgery or transplantation. Overall, both RFA and PDT have demonstrated efficacy in improving survival outcomes for patients with unresectable PHCC.[145] Some guidelines recommend both RFA and PDT for patients with PHCC.[14,17] But limitations exist, their use may not be permitted in certain countries as off-label treatments; for example, France does not recommend their implementation outside of clinical trial settings[18] and PDT may not be FDA approved.

Conclusion

The continuous advancement of endoscopic technology has increasingly underscored its pivotal role in the diagnosis and treatment of PHCC. In terms of diagnosis, combining traditional ERCP imaging and cytological brushing with POCS-guided biopsy and EUS-guided puncture sampling can significantly enhance the diagnostic yield for PHCC. In treatment, bile duct drainage remains the primary therapeutic approach for PHCC, as it is essential for improving liver function and paving the way for chemotherapy and targeted therapies. Contrary to common belief, PTBD does not show a clear advantage over endoscopic internal drainage techniques in reducing the incidence of biliary infections, according to multiple studies. However, PTBD carries a risk of complete bile loss, which can adversely affect digestion and absorption, thereby significantly impacting survival and treatment outcomes. By contrast, endoscopic bile duct drainage more effectively aligns with physiological needs by reconstructing the enterohepatic circulation of bile acids. When combined with ENBD, it can reduce the risk of infection. If necessary, this approach can be converted to a biliary stent in a secondary procedure or performed alongside a biliary stent in a single procedure to balance the benefits of internal and external drainage. Furthermore, ERCP can safely and effectively place multiple stents to improve liver function when conducted under direct endoscopic visualization using POCS.

In cases where ERCP fails, EUS-BD serves as a viable supplementary technique. Beyond bile duct drainage, integrating endoscopic with catheter-based RFA, PDT, and systemic treatments can further prolong stent patency and overall survival. The emergence of innovative endoscopic diagnostic and therapeutic techniques has significantly expanded treatment options for unresectable PHCC patients. Nevertheless, further large-scale RCTs are necessary to validate the therapeutic efficacy of these techniques in the context of unresectable PHCC.

Table 10. Efficacy and safety of photo dynamic therapy.

Study	Study type	Simple size	Overall survival months (95% CI)	Median TB before PDT (mg/dl)	Median TB after PDT (mg/dl)	Cholangitis	Phototoxicity
Ortner et al. (1998)[130]	Single arm	9	14.6 (9.3–16.6)	18.6 ± 4.18 (mean)	6.0 ± 2.0 (mean)	0	1 (11%)
Berr et al. (2000)[135]	Single arm	23	11.0 (9.5–12.5)	11.2 (5.8–21.8)	1.1 (0.4–4.8)	8 (35%)	3 (13%)
Rumalla et al. (2001)[136]	Single arm	6	NA	2.7 (1.5–3.7)	1.3 (0.9–2.3)	2 (33%)	2 (33%)
Dumoulin et al. (2003)[137]	Single arm	24	9.9 (6.4–13.4)	13.3 (7.6) (mean)	2.6 (3.4)	5 (21%)	2 (8%)
Ortner et al. (2003)[131]	Non-randomized	31	14.2 (10.3–16.9)	11.8 ± 1.75	3.1 ± 0.9	6 (19%)	3 (10%)
Harewood et al. (2005)[138]	Single arm	8	9.2	7.7	1.1	2 (25%)	2 (25%)
Witzigmann et al. (2006)[139]	Single arm	68	12.0 (8.8–15.3)	12 (0.5–45.7)	4.1	38 (56%)	8 (12%)
Prasad et al. (2007)[140]	Single arm	25	10.8 (7.6–17.1)	6.1 ± 1.1 (mean)	3.5 ± 1.2	2 (8%)	1 (4%)
Shim et al. (2004)[141]	Prospective	24	18.6 ± 6.0	14.0 ± 9.1 (mean)	2.7 ± 3.2	0	0
Dolak et al. (2017)[133]	Retrospective	84	12.1 (9.7–14.9)	NA	NA	20	NA

CI, confidence interval; NA, not available; PDT, photodynamic therapy; TB, total bilirubin.

Table 11. Comparison of the overall survival of PDT plus stent and stents alone.

Study	Type of study	Simple size	PDT plus stents	Stents alone	*p* Value
Li et al. (2020)[142]	Retrospective	62	14.2 months, 95% CI: 11.8–16.6 (*n* = 30)	9.8 months (95% CI: 7.0–12.6) (*n* = 32)	0.003
Lee et al. (2012)[143]	Retrospective	33	356 ± 213 (163–1330) days (*n* = 18)	230 ± 73 (56–687) days (*n* = 15)	0.006
Ortner et al. (2003)[131]	RCT	39	493 days (95% CI: 276–710) (*n* = 20)	98 days (95% CI: 87–107) (*n* = 19)	<0.0001
Zoepf et al. (2005)[132]	RCT	32	21 months (3–31) (95% CI: 13–19) (*n* = 16)	7 months (1–24) (95% CI: 1–13) (*n* = 16)	0.01
Witzigmann et al. (2006)[139]	Retrospective	124	12.0 months (95% CI: 8.8–15.3) (*n* = 68)	6.4 months (95% CI: 4.2–8.5) (*n* = 56)	<0.01
Kahaleh et al. (2008)[144]	Retrospective	48	16.2 ± 2.4 months (*n* = 19)	7.4 ± 1.6 months (*n* = 29)	<0.003

CI, confidence interval; PDT, photodynamic therapy; RCT, randomized controlled trial; TB, total bilirubin.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Di Zhang: Investigation; Writing – original draft.

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Competing interests
The authors declare that there is no conflict of interest.

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References
1. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. *Am J Med* 1965; 38: 241–256.
2. Bismuth H and Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 1975; 140: 170–178.
3. Bismuth H, Nakache R and Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg* 1992; 215: 31–38.
4. Burke EC, Jarnagin WR, Hochwald SN, et al. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998; 228: 385–394.
5. Matsuo K, Rocha FG, Ito K, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. *J Am Coll Surg* 2012; 215: 343–355.
6. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; 234: 507–517; discussion 517–509.
7. Yamada M, Mizuno T, Yamaguchi J, et al. Superiority of clinical American Joint Committee on Cancer T classification for perihilar cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2022; 29: 768–777.
8. Gaspersz MP, Buettner S, van Vugt JLA, et al. Evaluation of the New American Joint Committee on Cancer Staging Manual 8th Edition for perihilar cholangiocarcinoma. *J Gastrointest Surg* 2020; 24: 1612–1618.
9. Chun YS, Pawlik TM and Vauthey JN. 8th edition of the AJCC Cancer Staging Manual: pancreas and hepatobiliary cancers. *Ann Surg Oncol* 2018; 25: 845–847.
10. Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. *Lancet (London, UK)* 2021; 397: 428–444.
11. Rerknimitr R, Angsuwatcharakon P, Ratanachu-ek T, et al. Asia-Pacific consensus recommendations for endoscopic and interventional management of hilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2013; 28: 593–607.
12. Liu Q, Chen Y, Hu Y, et al. Clinical research progress of targeted therapy

combined with immunotherapy for advanced cholangiocarcinoma. *Cancer Treat Res Commun* 2023; 37: 100771.

13. Van Keulen A-M, Gaspersz MP, van Vugt JLA, et al. Success, complication, and mortality rates of initial biliary drainage in patients with unresectable perihilar cholangiocarcinoma. *Surgery* 2022; 172: 1606–1613.
14. Angsuwatcharakon P, Kulpatcharapong S, Chuncharunee A, et al. The updated Asia-Pacific consensus statement on the role of endoscopic management in malignant hilar biliary obstruction. *Endosc Int Open* 2024; 12: E1065–E1074.
15. Qumseya BJ, Jamil LH, Elmunzer BJ, et al. ASGE guideline on the role of endoscopy in the management of malignant hilar obstruction. *Gastrointest Endosc* 2021; 94: 222–234.e22.
16. 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: 910–930.
17. Elmunzer BJ, Maranki JL, Gomez V, et al. ACG Clinical Guideline: diagnosis and management of biliary strictures. *Am J Gastroenterol* 2023; 118: 405–426.
18. Neuzillet C, Decraecker M, Larrue H, et al. Management of intrahepatic and perihilar cholangiocarcinomas: guidelines of the French Association for the study of the liver (AFEF). *Liver Int* 2024; 44: 2517–2537.
19. Nagino M, Hirano S, Yoshitomi H, et al. Clinical practice guidelines for the management of biliary tract cancers 2019: the 3rd English edition. *J Hepatobiliary Pancreat Sci* 2021; 28: 26–54.
20. Gu J, Guo X, Sun Y, et al. Efficacy and complications of inoperable malignant distal biliary obstruction treatment by metallic stents: fully covered or uncovered? *Gastroenterol Rep (Oxf)* 2023; 11: goad048.
21. Arnstein E. Oculogyric crisis: a distinct toxic effect of carbamazepine. *J Child Neurol* 1986; 1: 289–290.
22. Choi J, Ryu JK, Lee SH, et al. Biliary drainage for obstructive jaundice caused by unresectable hepatocellular carcinoma: the endoscopic versus percutaneous approach. *Hepatobiliary Pancreat Dis Int* 2012; 11: 636–642.
23. 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.
24. Zhu J, Feng H, Zhang D, et al. Percutaneous transhepatic cholangiography and drainage and endoscopic retrograde cholangiopancreatograph for hilar cholangiocarcinoma: which one is preferred? *Rev Esp Enferm Dig* 2020; 112: 893–897.
25. Liang XY, Li W, Liu F, et al. A retrospective study of biliary drainage strategies for patients with malignant hilar biliary strictures. *Cancer Manag Res* 2021; 13: 4767–4776.
26. Moole H, Dharmapuri S, Duvvuri A, et al. Endoscopic versus percutaneous biliary drainage in palliation of advanced malignant hilar obstruction: a meta-analysis and systematic review. *Can J Gastroenterol Hepatol* 2016; 2016: 4726078.
27. Walter T, Ho CS, Horgan AM, et al. Endoscopic or percutaneous biliary drainage for Klatskin tumors? *J Vasc Interv Radiol* 2013; 24: 113–121.
28. Lee SH, Park JK, Yoon WJ, et al. Optimal biliary drainage for inoperable Klatskin's tumor based on Bismuth type. *World J Gastroenterol* 2007; 13: 3948–3955.
29. Cassani LS, Chouhan J, Chan C, et al. Biliary decompression in perihilar cholangiocarcinoma improves survival: a single-center retrospective analysis. *Dig Dis Sci* 2019; 64: 561–569.
30. Abraham NS, Barkun JS and Barkun AN. Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life. *Gastrointest Endosc* 2002; 56: 835–841.
31. Born P, Rosch T, Bruhl K, et al. Long-term outcome in patients with advanced hilar bile duct tumors undergoing palliative endoscopic or percutaneous drainage. *Z Gastroenterol* 2000; 38: 483–489.
32. Liu H, Shi C, Yan Z, et al. A single-center retrospective study comparing safety and efficacy of endoscopic biliary stenting only vs. EBS plus nasobiliary drain for obstructive jaundice. *Front Med (Lausanne)* 2022; 9: 969225.
33. Chen M, Wang L, Wang Y, et al. Risk factor analysis of post-ERCP cholangitis: a single-center experience. *Hepatobiliary Pancreat Dis Int* 2018; 17: 55–58.
34. Rerknimitr R, Kongkam P and Kullavanijaya P. Outcome of self-expandable metallic stents in low-grade versus advanced hilar obstruction. *J Gastroenterol Hepatol* 2008; 23: 1695–1701.

35. Hirano S, Tanaka E, Tsuchikawa T, et al. Oncological benefit of preoperative endoscopic biliary drainage in patients with hilar cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2014; 21: 533–540.

36. Wang L, Lin N, Xin F, et al. A systematic review of the comparison of the incidence of seeding metastasis between endoscopic biliary drainage and percutaneous transhepatic biliary drainage for resectable malignant biliary obstruction. *World J Surg Oncol* 2019; 17: 116.

37. Liberato MJ and 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.

38. Sangchan A, Kongkasame W, Pugkhem A, et al. Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial. *Gastrointest Endosc* 2012; 76: 93–99.

39. Kim JY, Lee SG, Kang D, et al. The comparison of endoscopic biliary drainage in malignant hilar obstruction by cholangiocarcinoma: bilateral metal stents versus multiple plastic stents. *Gut Liver* 2021; 15: 922–929.

40. 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: 179–189.

41. Wagner HJ, Knyrim K, Vakil N, et al. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. *Endoscopy* 1993; 25: 213–218.

42. Raju RP, Jaganmohan SR, Ross WA, et al. Optimum palliation of inoperable hilar cholangiocarcinoma: comparative assessment of the efficacy of plastic and self-expanding metal stents. *Dig Dis Sci* 2011; 56: 1557–1564.

43. Xia M-X, Cai X-B, Pan Y-L, et al. Optimal stent placement strategy for malignant hilar biliary obstruction: a large multicenter parallel study. *Gastrointest Endosc* 2020; 91: 1117–1128.e9.

44. Gong M, Li Q, Xu Y, et al. The evaluation of clinical status of endoscopic retrograde cholangiography for the placement of metal and plastic stents in cholangiocarcinoma therapy. *Comput Math Methods Med* 2022; 2022: 5741437.

45. Koiwai A, Hirota M, Katayama T, et al. Self-expandable metal stents have longer patency and less cholangitis than inside stents in malignant perihilar biliary obstruction. *JGH Open* 2022; 6: 317–323.

46. 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: 214–222.

47. Sawas T, Al Halabi S, Parsi MA, et al. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. *Gastrointest Endosc* 2015; 82: 256–267.e7.

48. Perdue DG, Freeman ML, DiSario JA, et al. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. *J Clin Gastroenterol* 2008; 42: 1040–1046.

49. Hong WD, Chen XW, Wu WZ, et al. Metal versus plastic stents for malignant biliary obstruction: an update meta-analysis. *Clin Res Hepatol Gastroenterol* 2013; 37: 496–500.

50. Jiang Y, Zeng Z, Zeng J, et al. Efficacy and safety of first-line chemotherapies for patients with advanced biliary tract carcinoma: a systematic review and network meta-analysis. *Front Oncol* 2021; 11: 736113.

51. Ottaiano A, Santorsola M, Diana A, et al. Treatments, prognostic factors, and genetic heterogeneity in advanced cholangiocarcinoma: a multicenter real-world study. *Cancer Med* 2024; 13: e6892.

52. 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: 817–827.

53. Wang Y, Liu PP and Yang LL. Stent insertion for hilar cholangiocarcinoma: a meta-analysis of comparison between unilateral and bilateral stenting. *Prz Gastroenterol* 2021; 16: 383–389.

54. Hong W, Sun X and 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: 1105–1112.

55. 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–E290.

56. De Palma GD, Galloro G, Siciliano S, et al. 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: 547–553.

57. Hakuta R, Kogure H, Nakai Y, et al. Unilateral versus bilateral endoscopic nasobiliary drainage and subsequent metal stent placement for unresectable malignant hilar obstruction: a multicenter randomized controlled trial. *J Clin Med* 2021; 10: 206.

58. 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: 202–209.

59. Yin X, Li DM, Yang F, et al. Self-expanded metallic stent insertion for hilar cholangiocarcinoma: comparison of unilateral and bilateral stenting. *J Laparoendosc Adv Surg Tech A* 2019; 29: 1501–1506.

60. 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: 43–48.

61. Naitoh I, Ohara H, Nakazawa T, et al. Unilateral versus bilateral endoscopic metal stenting for malignant hilar biliary obstruction. *J Gastroenterol Hepatol* 2009; 24: 552–557.

62. Minaga K, Takenaka M, Kitano M, et al. Rescue EUS-guided intrahepatic biliary drainage for malignant hilar biliary stricture after failed transpapillary re-intervention. *Surg Endosc* 2017; 31: 4764–4772.

63. Moryoussef F, Sportes A, Leblanc S, et al. Is EUS-guided drainage a suitable alternative technique in case of proximal biliary obstruction? *Therap Adv Gastroenterol* 2017; 10: 537–544.

64. 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: 413–419.

65. Panpimanmas S and Ratanachu-ek T. Endoscopic ultrasound-guided hepaticogastrostomy for advanced cholangiocarcinoma after failed stenting by endoscopic retrograde cholangiopancreatography. *Asian J Surg* 2013; 36: 154–158.

66. 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: 72–75.

67. 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: 163–168.

68. Kanno Y, Ito K, Koshita S, et al. EUS-guided biliary drainage for malignant perihilar biliary strictures after further transpapillary intervention has been judged to be impossible or ineffective. *Intern Med (Tokyo, Japan)* 2017; 56: 3145–3151.

69. 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: 728–735.

70. Caillol F, Bories E, Zemmour C, et al. Palliative endoscopic drainage of malignant stenosis of biliary confluence: efficiency of multiple drainage approach to drain a maximum of liver segments. *United European Gastroenterol J* 2019; 7: 52–59.

71. 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: 222–230.

72. Cao Q, Sun L, Li Z-Q, et al. Bilateral stenting for hilar biliary obstruction: a meta-analysis of side-by-side versus stent-in-stent. *Minim Invasive Ther Allied Technol* 2022; 31: 525–530.

73. Hong W, Chen S, Zhu Q, et al. Bilateral stenting methods for hilar biliary obstructions. *Clinics (Sao Paulo)* 2014; 69: 647–652.

74. 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: 352–357.

75. 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: 548–555.

76. Borges AP, Silva AV and Donato P. Comparison between suprapapillary and transpapillary uncovered self-expandable metallic stent placement for perihilar cholangiocarcinoma. *J Vasc Interv Radiol* 2023; 34: 1400–1408.

77. DeWitt J, Misra VL, Leblanc JK, et al. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. *Gastrointest Endosc* 2006; 64: 325–333.

78. Fritscher-Ravens A, Broering DC, Knoefel WT, et al. EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. *Am J Gastroenterol* 2004; 99: 45–51.

79. Tellez-Avila FI, Bernal-Mendez AR, Guerrero-Vazquez CG, et al. Diagnostic yield of EUS-guided tissue acquisition as a first-line approach in patients with suspected hilar cholangiocarcinoma. *Am J Gastroenterol* 2014; 109: 1294–1296.

80. Yao L, Zhang J, Liu J, et al. A deep learning-based system for bile duct annotation and station recognition in linear endoscopic ultrasound. *EBioMedicine* 2021; 65: 103238.

81. Nakai Y, Kogure H, Isayama H, et al. Endoscopic ultrasound-guided biliary drainage for unresectable hilar malignant biliary obstruction. *Clin Endosc* 2019; 52: 220–225.

82. Kitamura H, Hijioka S, Nagashio Y, et al. Use of endoscopic ultrasound-guided biliary drainage as a rescue of re-intervention after the placement of multiple metallic stents for malignant hilar biliary obstruction. *J Hepatobiliary Pancreat Sci* 2022; 29: 404–414.

83. Binda C, Dajti E, Giuffrida P, et al. Efficacy and safety of endoscopic ultrasound-guided hepaticogastrostomy: a meta-regression analysis. *Endoscopy* 2024; 56: 694–705.

84. Alsakarneh S, Madi MY, Dahiya DS, et al. Is endoscopic ultrasound-guided hepaticogastrostomy safe and effective after failed endoscopic retrograde cholangiopancreatography?—a systematic review and meta-analysis. *J Clin Med* 2024; 13: 3883.

85. Giri S, Seth V, Afzalpurkar S, et al. Endoscopic ultrasound-guided versus percutaneous transhepatic biliary drainage after failed ERCP: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2023; 33: 411–419.

86. Moole H, Bechtold ML, Forcione D, et al. A meta-analysis and systematic review: success of endoscopic ultrasound guided biliary stenting in patients with inoperable malignant biliary strictures and a failed ERCP. *Medicine (Baltimore)* 2017; 96: e5154.

87. 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.

88. Khoury T, Sbeit W, Fumex F, et al. Endoscopic ultrasound- versus ERCP-guided primary drainage of inoperable malignant distal biliary obstruction: systematic review and meta-analysis of randomized controlled trials. *Endoscopy* 2024; 56: 955–963.

89. Gopakumar H, Singh RR, Revanur V, et al. Endoscopic ultrasound-guided vs endoscopic retrograde cholangiopancreatography-guided biliary drainage as primary approach to malignant distal biliary obstruction: a systematic review and meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2024; 119: 1607–1615.

90. Kongkam P, Tasneem AA and Rerknimitr R. Combination of endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography-guided biliary drainage in malignant hilar biliary obstruction. *Dig Endosc* 2019; 31(Suppl. 1): 50–54.

91. Yoon SB, Yang MJ, Shin DW, et al. Endoscopic ultrasound-rendezvous versus percutaneous-endoscopic rendezvous endoscopic retrograde cholangiopancreatography for bile duct access: systematic review and meta-analysis. *Dig Endosc* 2024; 36: 129–140.

92. Chen YI, Sahai A, Donatelli G, et al. Endoscopic ultrasound-guided biliary drainage of first intent with a lumen-apposing metal stent vs endoscopic retrograde cholangiopancreatography in malignant distal biliary obstruction: a multicenter randomized controlled study (ELEMENT Trial). *Gastroenterology* 2023; 165: 1249–1261.e5.

93. Tyberg A, Raijman I, Siddiqui A, et al. Digital pancreaticocholangioscopy for mapping of pancreaticobiliary neoplasia: can we alter the surgical resection margin? *J Clin Gastroenterol* 2019; 53: 71–75.

94. Nishikawa T, Tsuyuguchi T, Sakai Y, et al. Preoperative assessment of longitudinal extension of cholangiocarcinoma with peroral video-cholangioscopy: a prospective study. *Dig Endosc* 2014; 26: 450–457.

95. Nishikawa T, Tsuyuguchi T, Sakai Y, et al. Comparison of the diagnostic accuracy of peroral video-cholangioscopic visual findings and cholangioscopy-guided forceps biopsy findings for indeterminate biliary lesions: a prospective study. *Gastrointest Endosc* 2013; 77: 219–226.

96. Gerges C, Beyna T, Tang RSY, et al. Digital single-operator peroral cholangioscopy-guided biopsy sampling versus ERCP-guided brushing for indeterminate biliary strictures: a prospective, randomized, multicenter trial (with video). *Gastrointest Endosc* 2020; 91: 1105–1113.

97. Kulpatcharapong S, Pittayanon R, Kerr SJ, et al. Diagnostic performance of digital and video cholangioscopes in patients with suspected malignant biliary strictures: a systematic review and meta-analysis. *Surg Endosc* 2022; 36: 2827–2841.

98. de Oliveira P, de Moura DTH, Ribeiro IB, et al. Efficacy of digital single-operator cholangioscopy in the visual interpretation of indeterminate biliary strictures: a systematic review and meta-analysis. *Surg Endosc* 2020; 34: 3321–3329.

99. Bokemeyer A, Gross D, Bruckner M, et al. Digital single-operator cholangioscopy: a useful tool for selective guidewire placements across complex biliary strictures. *Surg Endosc* 2019; 33: 731–737.

100. Talreja JP, DeGaetani M, Sauer BG, et al. Photodynamic therapy for unresectable cholangiocarcinoma: contribution of single operator cholangioscopy for targeted treatment. *Photochem Photobiol Sci* 2011; 10: 1233–1238.

101. Saraiva MM, Ribeiro T, Ferreira JPS, et al. Artificial intelligence for automatic diagnosis of biliary stricture malignancy status in single-operator cholangioscopy: a pilot study. *Gastrointest Endosc* 2022; 95: 339–348.

102. Marya NB, Powers PD, Petersen BT, et al. Identification of patients with malignant biliary strictures using a cholangioscopy-based deep learning artificial intelligence (with video). *Gastrointest Endosc* 2023; 97: 268–278.e1.

103. Teng LS, Jin KT, Han N, et al. Radiofrequency ablation, heat shock protein 70 and potential anti-tumor immunity in hepatic and pancreatic cancers: a minireview. *Hepatobiliary Pancreat Dis Int* 2010; 9: 361–365.

104. Chen M, Tan Y, Hu J, et al. Injectable immunotherapeutic thermogel for enhanced immunotherapy post tumor radiofrequency ablation. *Small* 2021; 17: e2104773.

105. Huang KW, Tan CP, Reebye V, et al. MTL-CEBPA combined with immunotherapy or RFA enhances immunological anti-tumor response in preclinical models. *Int J Mol Sci* 2021; 22: 9168.

106. Yin L, Li XY, Zhu LL, et al. Clinical application status and prospect of the combined anti-tumor strategy of ablation and immunotherapy. *Front Immunol* 2022; 13: 965120.

107. Laleman W, van der Merwe S, Verbeke L, et al. A new intraductal radiofrequency ablation device for inoperable biliopancreatic tumors complicated by obstructive jaundice: the IGNITE-1 study. *Endoscopy* 2017; 49: 977–982.

108. Han SY, Kim DU, Kang DH, et al. Usefulness of intraductal RFA in patients with malignant biliary obstruction. *Medicine (Baltimore)* 2020; 99: e21724.

109. Inoue T, Naitoh I, Kitano R, et al. Endobiliary radiofrequency ablation combined with gemcitabine and cisplatin in patients with unresectable extrahepatic cholangiocarcinoma. *Curr Oncol (Toronto, ON)* 2022; 29: 2240–2251.

110. Tal AO, Vermehren J, Friedrich-Rust M, et al. Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. *World J Gastrointest Endosc* 2014; 6: 13–19.

111. Wang Y, Cui W, Fan W, et al. Percutaneous intraductal radiofrequency ablation in the management of unresectable Bismuth types III and IV hilar cholangiocarcinoma. *Oncotarget* 2016; 7: 53911–53920.

112. Dolak W, Schreiber F, Schwaighofer H, et al. Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. *Surg Endosc* 2014; 28: 854–860.

113. So H, Oh CH, Song TJ, et al. Feasibility and safety of endoluminal radiofrequency ablation as a rescue treatment for bilateral metal stent obstruction due to tumor ingrowth in the hilum: a pilot study. *J Clin Med* 2021; 10: 952.

114. Xia MX, Wang SP, Yuan JG, et al. Effect of endoscopic radiofrequency ablation on the survival of patients with inoperable malignant biliary strictures: a large cohort study. *J Hepatobiliary Pancreat Sci* 2022; 29: 693–702114.

115. Gao D-J, Yang J-F, Ma S-R, et al. Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. *Gastrointest Endosc* 2021; 94: 91–100.e2.

116. Schmidt C, Zapf A, Ozga AK, et al. Radiofrequency ablation via catheter and transpapillary access in patients with cholangiocarcinoma (ACTICCA-2 trial)—a multicenter, randomized, controlled, open-label investigator-initiated trial. *BMC Cancer* 2024; 24: 931.

117. Andrasina T, Rohan T, Panek J, et al. The combination of endoluminal radiofrequency ablation and metal stent implantation for the treatment of malignant biliary stenosis—randomized study. *Eur J Radiol* 2021; 142: 109830.

118. Kong YL, Zhang HY, Liu CL, et al. Improving biliary stent patency for malignant obstructive jaundice using endobiliary radiofrequency ablation: experience in 150 patients. *Surg Endosc* 2022; 36: 1789–1798.

119. Bokemeyer A, Matern P, Bettenworth D, et al. Endoscopic radiofrequency ablation prolongs survival of patients with unresectable hilar cholangiocellular carcinoma—a case-control study. *Sci Rep* 2019; 9: 13685.

120. Cui W, Wang Y, Fan W, et al. Comparison of intraluminal radiofrequency ablation and stents vs. stents alone in the management of malignant biliary obstruction. *Int J Hyperthermia* 2017; 33: 853–861.

121. Yang J, Wang J, Zhou H, et al. Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. *Endoscopy* 2018; 50: 751–760.

122. Kang H, Chung MJ, Cho IR, et al. Efficacy and safety of palliative endobiliary radiofrequency ablation using a novel temperature-controlled catheter for malignant biliary stricture: a single-center prospective randomized phase II TRIAL. *Surg Endosc* 2021; 35: 63–73.

123. Kang H, Han SY, Cho JH, et al. Efficacy and safety of temperature-controlled intraductal radiofrequency ablation in advanced malignant hilar biliary obstruction: a pilot multicenter randomized comparative trial. *J Hepatobiliary Pancreat Sci* 2022; 29: 469–478.

124. Oh D, Chong J, Song TJ, et al. The usefulness of endobiliary radiofrequency ablation before metal stent placement in unresectable malignant hilar obstruction. *J Gastroenterol Hepatol* 2022; 37: 2083–2090.

125. de Jong DM, Fritzsche JA, Audhoe AS, Yi SSL, Bruno MJ, Voermans RP, van Driel LMJW. Comparison of Intraductal RFA Plus Stent versus Stent-Only Treatment for Unresectable Perihilar Cholangiocarcinoma-A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 Apr 21;14(9):2079. doi: 10.3390/cancers14092079. PMID: 35565209; PMCID: PMC9099890.

126. de Oliveira Veras M, de Moura DTH, McCarty TR, et al. Intraductal radiofrequency ablation plus biliary stent versus stent alone for malignant biliary obstruction: a systematic review and meta-analysis. *Endosc Int Open* 2024; 12: E23–E33.

127. Gonzalez-Carmona MA, Mohring C, Mahn R, et al. Impact of regular additional endobiliary radiofrequency ablation on survival of patients with advanced extrahepatic cholangiocarcinoma under systemic chemotherapy. *Sci Rep* 2022; 12: 1011.

128. Yang J, Wang J, Zhou H, et al. Endoscopic radiofrequency ablation plus a novel oral 5-fluorouracil compound versus radiofrequency ablation alone for unresectable extrahepatic cholangiocarcinoma. *Gastrointest Endosc* 2020; 92: 1204–1212.e1.

129. Gou Q, Wu L, Cui W, et al. Stent placement combined with intraluminal radiofrequency ablation and hepatic arterial infusion chemotherapy for advanced biliary tract cancers with biliary obstruction: a multicentre, retrospective, controlled study. *Eur Radiol* 2021; 31: 5851–5862.

130. Ortner MA, Liebetruth J, Schreiber S, et al. Photodynamic therapy of nonresectable cholangiocarcinoma. *Gastroenterology* 1998; 114: 536–542.

131. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003; 125: 1355–1363.

132. Zoepf T, Jakobs R, Arnold JC, et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 2005; 100: 2426–2430.

133. Dolak W, Schwaighofer H, Hellmich B, et al. Photodynamic therapy with polyhematoporphyrin for malignant biliary obstruction: a nationwide retrospective study of 150 consecutive applications. *United European Gastroenterol J* 2017; 5: 104–110.

134. Moole H, Tathireddy H, Dharmapuri S, et al. Success of photodynamic therapy in palliating patients with nonresectable cholangiocarcinoma: a systematic review and meta-analysis. *World J Gastroenterol* 2017; 23: 1278–1288.

135. Berr F, Wiedmann M, Tannapfel A, et al. Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. *Hepatology (Baltimore, MD)* 2000; 31: 291–298.

136. Rumalla A, Baron TH, Wang KK, et al. Endoscopic application of photodynamic therapy for cholangiocarcinoma. *Gastrointest Endosc* 2001; 53: 500–504.

137. Dumoulin FL, Gerhardt T, Fuchs S, et al. Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma. *Gastrointest Endosc* 2003; 57: 860–867.

138. Harewood GC, Baron TH, Rumalla A, et al. Pilot study to assess patient outcomes following endoscopic application of photodynamic therapy for advanced cholangiocarcinoma. *J Gastroenterol Hepatol* 2005; 20: 415–420.

139. Witzigmann H, Berr F, Ringel U, et al. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. *Ann Surg* 2006; 244: 230–239.

140. Prasad GA, Wang KK, Baron TH, et al. Factors associated with increased survival after photodynamic therapy for cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2007; 5: 743–748.

141. Shim CS, Cheon YK, Cha SW, et al. Prospective study of the effectiveness of percutaneous transhepatic photodynamic therapy for advanced bile duct cancer and the role of intraductal ultrasonography in response assessment. *Endoscopy* 2005; 37: 425–433.

142. 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: 5655–5664.

143. Lee TY, Cheon YK, Shim CS, et al. Photodynamic therapy prolongs metal stent patency in patients with unresectable hilar cholangiocarcinoma. *World J Gastroenterol* 2012; 18: 5589–5594.

144. Kahaleh M, Mishra R, Shami VM, et al. Unresectable cholangiocarcinoma: comparison of survival in biliary stenting alone versus stenting with photodynamic therapy. *Clin Gastroenterol Hepatol* 2008; 6: 290–297.

145. Mohammad T and Kahaleh M. Comparing palliative treatment options for cholangiocarcinoma: photodynamic therapy vs. radiofrequency ablation. *Clin Endosc* 2022; 55: 347–354.