Current Status of Endoscopic Treatment of Advanced Hilar Cholangiocarcinoma
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Abstract
Cholangiocarcinoma is a high-mortality primary hepatic malignancy. A higher incidence of cholangiocarcinoma was reported in Asia, especially Southeast Asia, than in Western countries. Hilar cholangiocarcinoma is a specific type of extrahepatic cholangiocarcinoma that involves the hepatic hilum and has a worse prognosis. More than half of the patients with jaundice are inoperable at the time of first diagnosis. Therefore, biliary drainage is the mainstay of palliative treatment in these patients. Endoscopic biliary drainage via endoscopic retrograde cholangiopancreatoscopy, the modality of choice, for the advanced hilar type is more difficult and complex than those in distal cholangiocarcinoma. Endoscopists should consider many factors before selecting the most appropriate treatment for each patient. Here we discuss the factors systematically. In cases of transpapillary approach failure, other therapeutic modalities should be considered. Percutaneous transhepatic biliary drainage is the most popular method in such cases. At the present, endoscopic ultrasound-guided biliary drainage, especially hepaticogastrostomy, is an alternative procedure with the same efficacy and low complications when it was carried out in the expert hands. Furthermore, recent locoregional therapies for tumor control including trans-luminal photodynamic therapy and radiofrequency ablation also benefit these patients.

Keywords: Unresectable hilar cholangiocarcinoma; Inoperable hilar cholangiocarcinoma; Endoscopic treatment; Biliary stenting; Photodynamic therapy; Radiofrequency ablation; RFA; PDT

Introduction
Cholangiocarcinoma (CCA) is a fatal malignant tumor of the hepatobiliary system with a higher incidence in Eastern countries. The highest incidence of CCA was found in Southeast Asia, especially Thailand, which was 71.3:100,000 in men and 31.6:100,000 in women [1], followed by China and some other countries in Southeast Asia [2], whereas data from the USA, Europe, and Australia showed overall incidences of 0.82:100,000, 0.9–5.5:100,000, and 0.8–1.0:100,000, respectively [3-5]. This discrepancy in disease incidence can be explained according to the pathogenesis of CCA, although cases of CCA were sporadic.

Strong risk factors for CCA include older age, male gender, chronic hepatobiliary tract inflammation such as primary sclerosing cholangitis, chronic hepatitis, choledochal cyst, and chronic parasitic infestations such as Opisthorchis viverrini and Clonorchis sinensis [6-8]. Other recently reported possible risk factors include chronic viral hepatitis infections such as hepatitis B and C, obesity, non-alcoholic steatohepatitis, and metabolic syndrome [9-13]. In the highest incidence area of CCA, O. viverrini plays a very important role in the tumorgenicity of CCA [14].

Understanding the pathogenesis of CCA could be very helpful for tumor screening and providing targeted treatment of CCA in the future. However, CCA currently has a very high mortality rate worldwide. Regarding the clinical characteristics of this silent and slow-growing disease, the lack of a standardized protocol for screening for early-stage disease and the limitations of using CA19-9 as a cancer marker delay the diagnosis in some patients. Even in this era of high-quality imaging studies and improved endoscopic techniques, the ability to achieve a definite cytopathological or histopathological diagnosis in patients with suspected CCA remains at 26–80% [15-17].

Once the diagnosis of CCA is made, R0 resection is the only treatment that provides a potentially curable disease, whereas R1 resection leads to unacceptably low 5-year survival rates and a very high tumor recurrence rate within 2 years [18-20]. Despite the fact that the prognosis of patients with advanced or unresectable cholangiocarcinoma is poor with a median survival time of <6 months [21], it is necessary to ensure a good quality of life and limit the tumor invasion. In this article, we review the endoscopic treatments and techniques in terms of endoscopic biliary drainage and intraluminal procedures for locoregional tumor control that are beneficial for patients with CCA.

Unresectable Cholangiocarcinoma
CCA is classified into extrahepatic and intrahepatic types, the ratios of which vary 0.2–187:1 [2,21,22]. Hilar CCA, an extrahepatic type, was classified by Bismuth and Corlette [23] in 1975 into four subtypes (Figure 1). According to Memorial Sloan Kettering Cancer Center Criteria [20], unresectable CCA is characterized by the presence of at least one of the following: peritoneal or noncontiguous intrahepatic metastasis; perihilar, retroperitoneal, common hepatic, or celiac node involvement; main portal vein involvement or bilateral involvement of the secondary biliary radicles; or unilateral tumor extension to the secondary biliary radicles with contralateral lobar atrophy or portal vein involvement. All of these criteria were applied based on the result of imaging studies performed prior to surgery.

Studies have shown that 15–29.5% of patients with CCA were deemed unresectable at the time of diagnosis [24-26]. In addition, in some institutes, patients with potentially resectable CCA would undergo laparoscopic evaluation prior to laparotomy. Barlow et al. [27] reported that as many as 45% of patients had inoperable disease and that another 35% of patients who underwent laparotomy for attempted R0 resection

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had inoperable disease. This study provided the overall laparoscopy yield of 45% and accuracy of 71%. Therefore, approximately two thirds of patients with CCA are in the advanced stage of the disease at the time of first diagnosis.

Biliary drainage is the main palliative strategy for patients with advanced CCA. The advantages and disadvantages of endoscopic biliary drainage compared to percutaneous drainage and surgical biliary bypass procedures such as hepaticojejunostomy have been reported and debated [28-30]. Endoscopic procedures are currently the preferred palliative treatment options for patients with advanced CCA worldwide.

Endoscopic Biliary Drainage

Endoscopic biliary drainage of hilar CCA is more difficult compared to that of distal CCA. To achieve the best therapeutic outcome, endoscopists need to answer the following questions: (a) How many segments of the liver should be drained; (b) Should unilateral, multi-segmented unilateral, or bilateral stenting be used; (c) Should plastic or self-expandable metal stents (SEMS) be used; and (d) Which technique is the best? This article discusses these issues as shown below.

How many segments of the liver should be drained and (b) Should unilateral, multi-segmented unilateral, or bilateral stenting be used?

The Asia Pacific consensus [31] recommendation in 2013 stated that the goal for palliative drainage of hilar cholangiocarcinoma is to drain ≥ 50% of the liver volume, although 25% drainage might be enough to relieve jaundice. In terms of estimated hepatic volume, the right (anterior and posterior segment), left, and caudate lobes account for 55–60% (35% and 30%), 30–35%, and 10%, respectively, so draining this according to reference volume alone might not be the “real” liver volume.

To ensure effective biliary drainage, “targeted stent placement” based on pre-procedural imaging studies was found to be cost-effective [32]. Vienne et al. [33] reported cross-sectional imaging studies in which effective drainage consisted of >50% of the liver volume while the factors associated with long survival was >50% drainage (119 days vs. 59 days, p=0.005) and chemotherapy. Therefore, pre-procedural evaluations with cross-sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) are essential.

Liver volume evaluations can be divided according to the usual portal system distribution into three sectors: left (segments II and III), right posterior (segments VI and VII), and right anterior (segments V and VIII). Segment IV was assigned to the left or right posterior segment depending on each patient’s anatomy. The relative area of each sector is calculated as a fraction on each side, while the relative volume of each sector is inferred from the pool surface analysis of all sides. For example, in a patient with Bismuth type IIIa with right lobe atrophy and left lobe hypertrophy as shown in Figure 2, would benefit from unilateral drainage (unilateral placement). In contrast, another patient with Bismuth type IIIa required drainage of at least two segments of the intra-hepatic bile ducts (Figure 3). Therefore, from our perspective, there is no “routine” or “best” approach in terms of unilateral versus bilateral drainage for hilar CCA. However, volume-based drainage is still limited to cases in which no cholangitis occurred.

For patients with cholangitis, drainage of all suspected infected intra-hepatic segmental branches should be performed. Thus, in some cases, multimodality biliary drainage such as transpapillary drainage in combination with percutaneous transhepatic biliary drainage should be offered. Given that three-dimensional CT or MRI might not be possible in all institutes, here we propose an algorithm for adequate biliary drainage based on Klatskin’s classification (Figure 4).

For type I hilar lesions, which are connected to the right and left systems, the placement of only one stent in any functioning liver lobe would be appropriate. Type II lesions, which are also connected to both biliary systems, can also be treated with unilateral drainage, a right-
Demonstrate air cholangiogram.

Adequate biliary drainage based on Klatskin’s classification type.

In 2010, Zhang et al. [35] recently demonstrated a significantly higher rate of post-ERCP cholangitis in patients who underwent CO₂ cholangiography compared to a conventional contrast study (5.6% vs. 33.3%, p=0.04). Thus, we recommend the use of air or CO₂ cholangiography for the treatment of type IV hilar lesions.

**Should plastic stents or self-expandable metal stents (SEMS) be selected?**

To answer this question, endoscopists who perform the procedures must know the advantages and limitations of both stent types. Plastic stents are less expensive and technically easier to insert, remove, and exchange if stent malfunction or occlusion occurs. SEMS, which are composed of either stainless steel or nickel shape-retaining titanium (Nitinol), are designed and produced in many different styles and have advantages such as better stent patency than plastic stents as well as the ability to drain the side branches through the mesh. However, SEMS are much more expensive than plastic stents.

Prior to selecting a stent, endoscopists should consider patient life expectancy, cost effectiveness, stent patency, and the need for stent revision. The patency of SEMS and plastic stents in hilar cholangiocarcinoma were previously reported in many studies as 3.4–5.5 months and 1.2–1.86 months, respectively [21,36]. A meta-analysis by Hong et al. [37,38] demonstrated that SEMS had a higher successful drainage rate with an odds ratio (OR) of 0.26 and 95% confidence interval (CI) of 0.16–0.42, lower early complication OR of 2.92 (95% CI, 1.65–5.17), longer stent patency with a hazard ratio (HR) of 0.43 (95% CI, 0.30–0.61), and longer patient survival HR of 0.73 (95% CI, 0.56–0.96).

Sangchan et al. [36] reported a model based on a cost utility analysis and demonstrated that SEMS is more cost effective than plastic stents, while the median survival time of SEMS and plastic stents in this study was 129 and 49 days, respectively. Therefore, SEMS, rather than plastic stents, should be considered for patients with a life expectancy of >3 months. Other factors worthy of consideration include procedure cost compared to stent cost (plastic stents might require more revisions than SEMS), the possibility of complications during follow-up (such as acute cholangitis due to stent dysfunction), and patient ability to undergo a second procedure. Thus, stent type is an individual consideration.

Considering both factors (stent types and bilateral or unilateral drainage), Liberato and Canena [39] reported a retrospective study of 480 patients with CCA who underwent bilateral and unilateral biliary stenting and found a higher cumulative stent patency for bilateral stenting, either SEMS or plastic. Naitoh et al. [40] revealed a higher cumulative stent patency rate in the bilateral biliary stenting group. However, few studies from Japan [41,42] failed to demonstrate the clinical benefits of SEMS over plastic stents. Although data were inconclusive, we believed that bilateral stenting with or without SEMS was preferable for type III and IV CCA.

**Which stenting technique is better?**

The endoscopic technique for both methods can be described as shown in Figures 6A and 6B. With the stent in stent technique (Y stenting), the stricture site would first be negotiated with the guidewire after successful selective cannulation into the desired intra-hepatic segment (most commonly the left system). The first stent is inserted and deployed, after which the second guidewire is passed through the middle part of the first stent (through the mesh) into the second desired biliary segment. The mesh is then dilated using a balloon followed by second stent insertion and deployment. Using the Y-stent technique, some studies have shown an 86.7% technical success rate and a 100% functional success rate regardless of stent type [43].
Using the side-by-side technique, given the difficulty of the stent-in-stent technique using the guidewire to cannulate the contralateral duct, more time is needed to create the fenestration of the first stent mesh including the challenge of dilatation of the tight stent mesh. This technique requires the placement of two guidewires into two desired ducts in side-by-side fashion (subsequently or in parallel). Lee et al. [44] reported a study of the feasibility of using the side-by-side stenting technique in hilar CCA and showed a 91% technical success rate and a 100% functional success rate. This study also used small-caliber introducer (7 Fr introducer, 8-mm diameter) stents for the parallel deployment technique. Interestingly, the data showed no statistically significant difference between stent patency and median survival of the 8-mm and 10-mm groups.

Law and Baron [45] reported the use of a small (6-mm) introducer SEMS for bilateral biliary stenting for both techniques which found no difference in terms of technical success, procedural time, rate of stent revision, and revision success rate. This might refer to the benefit of using SEMS with a smaller introducer. Therefore, the choice of stent insertion technique was according to endoscopist preference. However, the stent type that should be selected in these procedures is summarized in Table 1. With regard to the endoscopic techniques for hilar CCA, we postulate an algorithm for endoscopic biliary drainage based on ERCP approach as shown in Figure 7.

Re-intervention for Biliary Drainage

Successful endoscopic biliary drainage with SEMS carries the chance of stent dysfunction either through tumor ingrowth, tumor overgrowth, or stent migration. The reported rate of SEMS dysfunction following hilar CCA biliary drainage was 45–57%. The success rate of endoscopic SEMS revision was 75–93.2% [44]. Ridtitid et al. [46] reported longer median stent patency of second SEMS than plastic stents (150 days vs. 60 days, p<0.05). Thus, SEMS is the preferable option for re-intervention in cases of SEMS dysfunction.

Drainage Options for Failed ERCP

Since failed ERCP or incomplete drainage after ERCP accounted for 5–10% of all procedures, multi-modality drainage should be considered. The combination of ERCP and percutaneous drainage was acceptable. The use of endoscopic ultrasound-guided biliary drainage (EUS-BD) was also feasible for a left system drainage procedure in patients with advanced cholangiocarcinoma who failed transpapillary drainage [47,48]. EUS-BD was a novel endoscopic-based approach for patients in whom conventional biliary drainage failed. For hilar CCA, the procedure of choice is EUS-guided hepaticogastrostomy, which allows left system access only.

Prachayakul and Aswakul [49] reported a case series of EUS-BD by using non-cauterization and a non-balloon dilatation technique that showed a lower complication rate of 6% compared to other techniques that reported 11–35% with comparable technical and clinical success rates. However, with regard to EUS working group recommendations [50], the performance of EUS-guided biliary drainage is limited to

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<tr>
<th>Stent-in-stent</th>
<th>Side-by-side</th>
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<td>Technical success</td>
<td>++ ++</td>
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<tr>
<td>Clinical success</td>
<td>++ ++</td>
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<tr>
<td>Ease of stent revision</td>
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<th>Technical tips</th>
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<tr>
<td>Need dilation of the first stent’s mesh using balloon or dilators</td>
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<td>First stent insertion into more difficult side</td>
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<td>Using large-open cell type stent will be easier for second stent insertion and stent revision in case of first stent occlusion</td>
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<th>Preferable stent types</th>
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<tr>
<td>First stent should be large-open cell type mesh or special designed stent for Y-configuration</td>
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<td>Second stent should be large-open cell type mesh</td>
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<td>Second stent should be small introducer</td>
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| Table 1: Technical tips and preferable stent types to be considered for stent-in-stent and side-by-side technique. |
PDT is a preferable standard of therapy for unresectable hilar CCA. PDT using intravenous Photofrin II 2 mg/kg (Axcan Pharma, Quebec, Canada) in 2012 [55] reported a cohort study of 18 patients who underwent seven PDT sessions in the span of 4 years [52]. Only a handful of data exists regarding intraductal RFA for hilar CCA. Monga et al. [58] reported a clinical case report of successful therapy of intraductal CCA, while Steel et al. [59] reported the feasibility of using intraductal therapy for malignancy, of which only six of 21 cases were diagnosed as CCA. Therefore, more information regarded the efficacy and safety of this particular therapy is still needed; however, it was considered a potential "new tool" for the endobiliary treatment of hilar CCA.

**Locoregional Tumor Control**

**Photodynamic therapy (PDT)**

PDT is a relatively new therapeutic approach for local tumor control. Based on the mechanism that the photosensitizing agent concentrates in the lesion, the photosensitizer is activated by non-thermal laser light of an appropriate wavelength, which leads to subsequent damage of the neoplastic tissue by generated free oxygen radicals [51]. Four photosensitizing agents are currently used for CCA. The most commonly used include hematoporphyrin derivatives (Photofrin and Photosan), δ-aminolevulinic acid, and meso-tetra(hydroxyphenyl) chlorin. However, the use of some photosensitizing substances such as photofrin had considerable disadvantage, including strong phototoxic skin reactions that can persist for weeks. On the other hands, δ-aminolevulinic acid which is a second generation photosensitizer had advantage over the first -generation photosensitizers such as photofrin, including a lack of prolonged photosensitization and laser light exposure. Nevertheless, the data which demonstrate the efficacy of this new agent in hilar cholangiocarcinoma was still limited. The first case report of successful PDT was published in 1991 of a patient who underwent seven PDT sessions in the span of 4 years [52].

The endoscopic PDT technique involves intravenous 48-hour administration of the photosensitizing agent prior to the laser light illumination. Commonly used agents are shown in Table 2. These agents are cleared from normal tissue in 48–72 hours but retained for longer intervals within the skin and tumor tissues. The laser light sources that deliver the appropriate wavelengths have been used for intraluminal illumination. A power density of 300–400 mW/cm and a power energy of 180–200 J/cm (of the diffuser length) is delivered through the fiber, while the irradiation time is 400–600 s [51]. This leads to 2–6-mm tumor necrosis depth. After selective cannulation in the desired intrahepatic duct, the catheter will be placed over the guidewire, which is then retrieved and replaced by the light laser fiber across the stricture site. However, this light laser fiber was stiff and prone to breakage, which can occur in up to one third of the procedures, making the procedure a bit more cumbersome and affecting treatment cost.

A meta-analysis of 24 studies by Gao et al. [53] showed that PDT prolonged survival (493 vs. 98 days) (p<0.0001) and improved biliary drainage and quality of life. Complications were reported in 0.3–27% of cases and cholangitis was the most common complication (27.5%). Another systematic review conducted by Tomizawa and Tian [54] confirmed that the benefit of PDT for survival (630 vs. 210 days for PDT and endoprosthesis alone, respectively, p<0.01). A study by Lee et al. in 2012 [55] reported a cohort study of 18 patients who underwent PDT using intravenous Photofrin II 2 mg/kg (Axcan Pharma, Quebec, Canada) showed longer patient survival in the PDT group (median survival time, 356 ± 213 days vs. 230 ± 73 days, p=0.006). Therefore, PDT is a preferable standard of therapy for unresectable hilar CCA.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Dosage (mg/Kg Body weight)</th>
<th>Time before activation</th>
<th>Light dose (J/cm²)</th>
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<tbody>
<tr>
<td>Photofrin-2</td>
<td>2</td>
<td>48 hrs</td>
<td>150-250</td>
</tr>
<tr>
<td>Photosan-3</td>
<td>2</td>
<td>48 hrs</td>
<td>200</td>
</tr>
<tr>
<td>5-ALA60</td>
<td>60</td>
<td>48 hrs</td>
<td>200</td>
</tr>
<tr>
<td>mTHPC</td>
<td>0.15</td>
<td>48 hrs</td>
<td>10-50</td>
</tr>
</tbody>
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Table 2. Photosensitizing agents which commonly used.

**Radiofrequency ablation (RFA)**

Percutaneous image-guided RFA has received increasing attention as a promising technique for the treatment of liver cancer. An RFA catheter that is suitable for endoscopic delivery into the biliary tree over a 0.035-inch guidewire was recently produced. The Habib Endo HPB+ (EMcision Ltd., London, UK) consists of a 2.6-mm catheter with a 180-cm working length. The distal end has a 5-mm leading tip proximal to two circumferentially placed, 8-mm-wide stainless steel electrodes. The distance between the proximal and distal electrodes was 8 mm, which allows for a coagulative effect of approximately 2.5 cm between the distal and proximal electrode margins [56]. The catheter is a bipolar device and enables connection to the power source. Tissue damage, both depth and length, after RFA treatment occurs according to the power setting and treatment duration.

The endoscopic technique for RFA consists of the following: After selective intra-hepatic duct cannulation, the 0.035-inch guidewire is placed across the stricture point. Full cholangiography is then performed to delineate the target lesion. A sphincterotomy is performed and the RFA catheter is advanced into the bile duct. RFA is applied at 7 W in 120-s bursts with a pause of 60 s before catheter movement. RFA application should be performed from the upstream stricture margin to the downstream stricture margin to cover the entire area of tumor invasion. Once the RFA catheter is removed, a balloon sweep should be performed to remove all the coagulated tissue from the biliary system. The stent is then subsequently inserted according to regular technique [57].

Only a handful of data exists regarding intraductal RFA for hilar CCA. Njei B (2013) The Changing Pattern of Epidemiology in Intrahepatic Cholangiocarcinoma. Hepatology. Endoscopic therapy for advanced hilar CCA results in better quality of life and longer survival. Adequate biliary drainage should be the most important factor, and a good plan should be prepared for each patient to ensure the best clinical outcome. Photodynamic therapy is accepted as an effective local therapy option, while newer modalities such as endobiliary RFA treatment awaits further supportive data.

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