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REVIEW

Advances in endoscopic retrograde cholangiopancreatography for the treatment of cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is a malignancy of the bile ducts that carries high morbidity and mortality. Patients with CCA typically present with obstructive jaundice, and associated complications of CCA include cholangitis and biliary sepsis. Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable treatment modality for patients with CCA, as it enables internal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains debate as to if bilateral (or multi-segmental) hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice and good clinical outcomes. Endoscopic therapy for malignant biliary strictures from CCA has advanced to include ablative therapies *via* ERCP-directed photodynamic therapy (PDT) or radiofrequency ablation (RFA). While ERCP techniques cannot cure CCA, advancements in the field of ERCP have enabled us to improve upon the quality of life of patients with inoperable and incurable disease. ERCP-directed PDT has been used in lieu of brachytherapy to provide neoadjuvant local tumor control in patients with CCA who are awaiting liver transplantation. Lastly, mounting evidence suggests that palliative ERCP-directed PDT, and probably ERCP-directed RFA as well, offer a survival advantage to patients with this difficult-to-treat malignancy.

Key words: Endoscopic retrograde cholangiopancreatography; Cholangiocarcinoma; Stents; Self-expandable metal stents; Photodynamic therapy; Photodynamic therapy; Radiofrequency ablation; Radiofrequency ablation

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable treatment modality for patients with cholangiocarcinoma (CCA), as it enables

luminal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains some debate as to if bilateral hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice. Although ERCP interventions cannot cure CCA, advancements in the field of ERCP, including ERCP-directed photodynamic therapy and radiofrequency ablation, likely confer a survival advantage and improve upon the quality of life of patients with incurable disease.

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INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary neoplasm of the liver[1]. It arises from malignant transformation of cholangiocytes, which are the epithelial cells that line the biliary tree. CCA may be classified based on location as intrahepatic, perihilar, or extrahepatic[1]. Perihilar lesions are further sub-classified depending on their proximal tumor extension according to the classification proposed by Bismuth[2]. Seventy percent of tumors present with bilateral hilar involvement - termed "Klatskin tumors" - and are unresectable cancers[2]. Although CCA is a rare malignancy with 3500 to 5000 cases diagnosed annually in the United States[3], mortality from this cancer is high due to a typically late presentation and limited curative therapies[3].

In patients with inoperable, incurable CCA, initial management usually involves drainage of malignant biliary obstruction and palliation of jaundice. Nevertheless, systemic or locoregional therapies do exist that offer the potential for tumor control, in part to mitigate the complications of further biliary obstruction. Chemotherapeutic agents and radiation therapies have been utilized to achieve this end, although their efficacy is limited, with partial response rates with chemotherapy demonstrated to be 35.9%, and with a stable disease rate of only 26.9%[4].

Over the past two to three decades, the management of CCA has evolved. While surgery remains a curative option for early disease, most cases of CCA are unresectable at the time of presentation. The typical presenting sign of CCA is jaundice. As such, decompressive biliary drainage techniques can help bridge symptomatic patients to surgery, and they can also be used for palliation by treating jaundice and pruritus and by reducing the risk of cholangitis. Various strategies have been employed for biliary drainage, including surgical drainage, percutaneous drainage, and endoscopic decompression *via* nasobiliary drainage or internal biliary stenting. Other mainly palliative modalities for treatment of CCA involve chemoradiation, transarterial chemoembolization, and ablative therapies such as brachytherapy, photodynamic therapy (PDT), and radiofrequency ablation (RFA), which can be applied intraoperatively, percutaneously, or endoscopically[5]. Herein, we will focus on endobiliary therapies for the treatment of CCA and its complications, and the majority of this review will pertain to interventions delivered *via* endoscopic retrograde cholangiopancreatography (ERCP).

BILIARY DECOMPRESSION

While surgical resection is the only treatment that offers curative intent to patients with CCA, the morbidity and mortality associated with liver resection is significantly higher in patients with obstructive jaundice than in patients with normal liver function[6]. Therefore, preoperative biliary drainage is routinely performed to reverse cholestatic liver dysfunction and reduce mortality after selective hepatectomy[7].

Historically, surgical bypass (hepaticojejunostomy or choledochojejunostomy) was the primary modality of biliary drainage prior to percutaneous and endoscopic advancements[8-11]. With advances in endoscopic therapy, particularly the development and refinement of ERCP, endoscopic decompression of obstructive jaundice due to malignant biliary stricturing from CCA should be considered the standard of care[12-16]. While adverse events are influenced by the clinical scenario, the risks associated with ERCP are well documented and uncommon. An American Society for Gastrointestinal Endoscopy guideline on "Complications of ERCP" reports a post-ERCP pancreatitis rate of about 3.5% (range 1.6%-15.7%), a rate of hemorrhage of 1.3%, and a perforation rate of 0.1%-0.6%[17]. Typically, the rate of post-ERCP cholangitis is 1% or less, but this risk does increase in situations of ERCP for drainage of malignant biliary obstruction[17].

In circumstances where biliary decompression is not possible or is incomplete by ERCP, percutaneous transhepatic biliary drainage (PTBD) can be an effective adjunctive therapy. However, PTBD is also associated with its own risks, including intra-procedural death in 1.7% of cases[18].

Many variables must be considered when endoscopic biliary drainage is pursued in patients with obstructive jaundice from CCA. Decisions include whether to use plastic stents (PS) *vs* self-expandable metal stents (SEMS) and whether to pursue unilateral *vs* bilateral biliary stenting.

UNILATERAL *VS* BILATERAL BILIARY DRAINAGE

In patients with Bismuth I perihilar cholangiocarcinoma,

which involves the extrahepatic bile duct but not the biliary confluence, a single stent that crosses the malignant stricture is usually adequate[12]. However, when considering patients with obstructive jaundice from more advanced CCAs that might involve the biliary confluence but not the second-order radicals (Bismuth Ⅱ), or for those that involve the right (Bismuth ⅢA), left (Bismuth ⅢB), or bilateral (Bismuth Ⅳ) hepatic ducts and higher-order branches, it has been suggested that drainage of as little as 25% of the liver can result in resolution of jaundice[19]. Thus, placement of a single stent into one lobe of the liver can result in sufficient biliary decompression in many cases. In some circumstances, segments of the liver that are inaccessible may be atrophied due to chronic involvement of tumor, making additional stenting unnecessary. However, in cases of Bismuth type II, Ⅲ, or Ⅳ CCA, the optimal location and number of stents remains controversial and has been addressed by a number of studies[12-16,20-31].

Deviere *et al*[12] demonstrated in 1988 that bilateral biliary stenting was associated with significantly improved survival and decreased development of cholangitis compared to unilateral stenting. However, in that study, contrast was injected into both lobes of the liver in all patients making the need for bilateral stenting more critical. In instances where one or more segments of the liver are injected with contrast, cholangitis may develop if adequate drainage is not achieved. This concept underscores an important point that - given the advancements in radiographic imaging - whenever possible, a thinly-sliced computed tomography (CT) scan performed on a multidetector scanner or a contrasted magnetic resonance imaging scan with magnetic resonance cholangiopancreatogram (MRCP) should be obtained prior to ERCP. High resolution cross-sectional imaging can identify areas of obstruction that can be selectively targeted for biliary decompression during ERCP, thereby avoiding over-opacification of the intrahepatic bile ducts[32,33].

In 1998, Chang *et al*[20] reviewed fluoroscopic images from ERCPs conducted for biliary decompression in 141 patients with hilar CCA. Those patients who had either a single lobe opacified and drained (unilateral stenting) or both lobes opacified and drained (bilateral stenting) had a significantly lower incidence of cholangitis and mortality compared with those patients who had both lobes of the liver opacified and only one side drained. These findings highlight that the decision to pursue unilateral *vs* bilateral stenting is greatly influenced by procedure-related issues, such as the extent of intrahepatic biliary opacification as well as the ease/difficulty of cannulating and subsequently draining various intrahepatic segments.

Other reports have suggested that drainage of more than 50% of the liver volume is associated with improved survival[34]. In a large retrospective review of 480 patients receiving endoscopic biliary drainage for hilar CCA, bilateral stenting (with either SEMS or PS) resulted in significantly longer overall stent patency compared with unilateral stenting [18 wk *vs* 17 wk for PS (P = 0.0004) and 27 wk *vs* 20 wk for SEMS (P < 0.0001)][26]. This finding had previously been reported in a smaller retrospective review of 46 consecutive patients undergoing palliative endoscopic biliary stent placement for malignant hilar obstruction. In a subgroup with hilar CCA, significantly greater overall stent patency was found in the group receiving bilateral stenting compared to the unilateral stenting group (P = 0.009)[27].

In 2001, De Palma *et al*[21] randomized patients in Italy with malignant hilar obstruction (about 57% from CCA) to unilateral or bilateral stenting for biliary decompression following a diagnostic cholangiogram. On intention-to-treat (ITT) analysis, patients who received unilateral 10-French (Fr) PS had significantly greater rates of successful stent insertion and drainage and also significantly lower rates of cholangitis (8.8% *vs* 16.6%, P = 0.013) compared to those who got bilateral PS. There were no significant differences between the two groups with respect to 30-d mortality, late complications, and median survival. It is important to note that successful stent insertion was significantly lower in the group randomized to bilateral PS (76.9%) as compared to the unilateral PS group (88.6%, P = 0.041). Bilateral stenting of complex hilar strictures from CCA is challenging and often requires significant device manipulation and repeated opacification of the biliary tree in order to access undrained hepatic segments using a guidewire. In fact, on per-protocol analysis (when only patients with successful unilateral and bilateral drainage were included) there was no difference in outcomes between these two groups, but this secondary analysis was underpowered to detect significant differences.

In considering these somewhat disparate data, it is probably best to be guided by the central tenet of endoscopic retrograde cholangiography, that drainage of any opacified large bile ducts or hepatic segments that do not drain spontaneously should be pursued. In a patient with complex perihilar stricturing, use of cross-sectional imaging to guide ERCP and limit contrast opacification can reduce the risk of cholangitis and other procedure-related complications. Planning an ERCP using cross-sectional imaging can also help one avoid opacifying atrophic segments that are less likely to be functional, which might also be more difficult to access and completely drain. When ERCP is performed using this type of a planned and deliberate approach, unilateral biliary stenting might be sufficient to relieve jaundice from a malignant hilar obstruction.

Lastly, effective treatment of patients with CCA requires multidisciplinary consultation. In patients with potentially resectable disease, the choice of which lobe or segments to drain may not be as simple as going after the largest volume of obstructed liver on cross-

sectional imaging. Indeed, presurgical biliary drainage of the lobe or segments of the liver that will remain after operative resection is key to avoiding atrophy of the liver remnant. If the bile ducts of the designated remnant liver are obstructed and not accessible by ERCP, drainage *via* PTBD should be pursued. In these situations, drainage of the portion of the liver targeted for resection might not be required, as atrophy of these segments is desired (and sometimes pursued by selective portal vein embolization) so as to cause hypertrophy of the future liver remnant, which reduces the risk of post-resection hepatic decompensation[35,36].

PLASTIC *VS* SELF-EXPANDABLE METAL STENTS

The issue of the most appropriate means of biliary decompression is further complicated by the decision to utilize either PS or SEMS. Plastic stents are smaller in caliber and tend to form biofilms, resulting in earlier obstruction than SEMS. On average, PS need to be exchanged at least every 3 mo, while SEMS may remain patent for 6 to 12 mo or longer. Raju *et al*[37] demonstrated median SEMS patency of 5.6 mo compared with 1.9 mo for PS, and they found SEMS to be more cost effective because of reduced need for re-intervention. The advantage of PS is that they are removable, and thus their use may be more attractive in patients with good functional status who might outlive a palliative SEMS. Metal stents are available in uncovered, partially-covered, or fully-covered versions. While fully-covered SEMS are potentially removable, their use across a perihilar stricture can be problematic as they can inadvertently obstruct other intersecting normal bile ducts due to their coating. Covered SEMS are also more prone to migration. Uncovered SEMS are less likely to migrate as tumor ingrowth keeps these stents in place, although tumor ingrowth can also lead to stent occlusion. In clinical practice, many interventional endoscopists tend to favor plastic biliary stenting in situations where the diagnosis remains in question, when surgery might still be possible, and in those patients who are likely to outlive the patency of permanent uncovered SEMS.

Multiple non-randomized and randomized trials have demonstrated greater patency with use of SEMS in patients with inoperable CCA, as compared to plastic stenting[13-16,23,25-30,38-40]. Peters *et al*[16] conducted a small prospective pilot study in 1997 to assess the efficacy of SEMS for palliation of jaundice in patients with malignant hilar strictures. Of the 17 patients included, 11 had CCA, and 9 demonstrated adequate drainage following SEMS placement as reflected by a significant decrease in bilirubin. The 2 patients who did not obtain relief from jaundice had extensive intrahepatic disease. Median stent patency was 12 mo with median survival of 10 mo. While these authors concluded that SEMS appeared to provide durable palliation for high-grade malignant biliary strictures, they cautioned against direct comparison with PS until a controlled trial comparing the two modalities had been completed.

In 2003, Kaassis *et al*[13] published a randomized study that found no significant survival difference in patients with malignant common bile duct strictures who underwent SEMS placement compared with patients who underwent PS placement. However, time to the first episode of biliary obstruction was significantly longer in the group receiving SEMS (P = 0.007). Metal stenting was also noted to be more cost-effective in patients without hepatic metastases, who had longer survival (5.3 mo *vs* 2.7 mo in patients with metastases). These authors recommended that plastic stenting was more appropriate in patients with advanced disease, signified by metastases, due to their shorter expected survival[13].

A large retrospective review of 480 patients who received endoscopic biliary drainage in the setting of hilar CCA over a 15-year period demonstrated greater functional success (defined by a decrease in bilirubin to less than 75% of pre-treatment level) with SEMS placement (97.9%) compared with PS placement (84.8%, P < 0.001)[26]. Furthermore, there were significantly greater rates of early complications (8.3% *vs* 2.0%) and late complications (56.4% *vs* 24.4%) in the group that received PS compared to the group that received SEMS. Interestingly, multivariate analysis using Poisson regression showed that SEMS placement (P < 0.01) and bilateral deployment (P < 0.01) were the only independent prognostic factors associated with stent patency[26].

In 2012, Sangchan *et al*[30] conducted an open-label randomized controlled trial in Thailand that compared PS to SEMS placement for unresectable hilar CCA. 180 patients underwent ERCP with randomization to unilateral placement of a 10-mm-wide SEMS *vs* a 7-Fr or 10-Fr PS into the hepatic duct with the largest area of obstruction based on pre-procedural CT or MRCP. On ITT analysis, the rate of successful drainage in the SEMS group was significantly greater than in the PS group (70.4% *vs* 46.3%, P = 0.011)[30]. Median survival time for the SEMS group (126 d) was also significantly longer compared with the PS group (49 d, P = 0.0021).

In 2013, a randomized controlled trial conducted in Japan compared SEMS to PS for drainage of malignant biliary strictures[15]. This study found the 6-month stent patency in the SEMS group was significantly greater (81%) compared with the PS group (20%, P = 0.0012). Kaplan-Meir analysis demonstrated a 50% patency rate of 359 d in the SEMS group as compared to 112 d in the PS group (P = 0.0002). Furthermore, the mean number of interventions for stent failure was significantly lower in the SEMS group (0.63 times/patient) compared to the PS group (1.80 times/patient, P = 0.0008). Lastly, the overall total cost for the treatment was significantly lower in the SEMS group than in the PS group (P = 0.0222).

Overall, these studies support the use of SEMS over

PS for long-term palliation of patients with malignant biliary obstruction, including from unresectable CCA. Typically, uncovered SEMS should be used for palliation when strictures are found across the biliary confluence, and these SEMS likely have even greater utility and cost-effectiveness when expected survival exceeds 3 mo, such as in those patients without metastatic disease. However, with the advent of ERCP-directed ablative therapies for unresectable CCA, a substantial proportion of patients might now expect to outlive even the patency of SEMS. In these patients, a strategy of repeated ERCPs for plastic stent revision and possibly repeated ERCP-directed ablations for locoregional tumor control is reasonable, particularly while they maintain good functional status and quality of life.

PERCUTANEOUS TRANSHEPATIC BILIARY DECOMPRESSION

Biliary decompression and stent placement for malignant biliary strictures can also be achieved by a percutaneous approach. In most centers, PTBD is performed by interventional radiologists. Decompression tubes may be inserted into dilated proximal biliary radicals to facilitate drainage of static bile above the level of obstruction. Alternatively, stenting across a malignant stricture can also be achieved by PTBD, which then allows for bile drainage internally into the duodenum. However, several studies have evaluated the use of PTBD with mixed results[14]. Complications associated with PTBD include vascular injury, risk for tumor seeding, and discomfort at the external drain site[28]. Additionally, PTBD has reported intraprocedural hemorrhage and sepsis rates of 2.5% and a death rate of 1.7%[18].

Hamy *et al*[23] evaluated 35 patients with malignant hilar obstruction (most had CCA) who received a palliative SEMS *via* a percutaneous-transhepatic route. They found a 97% rate of adequate biliary drainage with a median survival of 182 d and a 25% rate of recurrent jaundice after 180 d. These results were corroborated by a large retrospective multicenter study of 84 patients that compared the efficacy of percutaneous-transhepatic to endoscopic SEMS placement for initial malignant biliary decompression[28]. In this study, the rate of successful initial biliary decompression was higher in the percutaneous group (92.7%) as compared with the endoscopically-placed SEMS group (77.3%)[28]. However, overall stent patency and survival-once decompression was achieved-were similar between the groups, suggesting that a well-placed stent, irrespective of how it was placed, is the key to durable biliary decompression and improved survival in patients with malignant biliary obstruction.

Oftentimes, the decision to pursue biliary drainage *via* ERCP or PTBD is determined by clinical reasons, such as in patients with surgically altered gastroduodenal anatomy in whom PTBD might offer easier or more reliable access for therapeutic biliary interventions, or by local expertise. PTBD can be a valuable adjunctive therapy to drain obstructed bile ducts not accessible by ERCP, particularly in patients who might be surgical candidates and require drainage of the future liver remnant so as to prevent atrophy. In our experience, most patients favor endoscopic biliary drainage whenever possible, as it obviates the need for an external catheter for drainage or access. In general, if an experienced biliary endoscopist is available who can perform complex ERCP (as treatment of a hilar tumor is considered a level-3-complexity ERCP by American Society for Gastrointestinal Endoscopy guidelines[41]), we suggest attempting biliary decompression *via* ERCP. If adequate biliary drainage by ERCP is not achieved, then PTBD is an important adjunctive therapy in this patient population that should be pursued. Furthermore, once a PTBD track is mature (which typically requires 3-4 wk), a rendezvous-ERCP procedure can be performed to internalize biliary drainage of a previously inaccessible segment, after which the PTBD catheter can be removed.

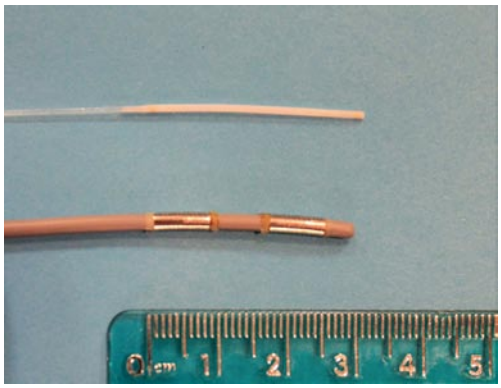

Figure 1 Endoscopic retrograde cholangiopancreatography-directed ablative therapies. Photodynamic therapy is applied *via* a laser fiber (above), whereas radiofrequency ablation is delivered using an 8-Fr catheter with two sets of bipolar rings (below).

ERCP-DIRECTED PHOTODYNAMIC THERAPY

PDT is a well-studied ablative therapy that induces tumor necrosis and apoptosis in treated portions of the biliary tree. The intravenous photosensitizer used in the United States is porfimer sodium (Photofrin, Pinnacle Biologics, Bannockburn, IL). While use of this drug for PDT in patients with CCA is done so off-label in the United States, Medicare and most private insurers in the United States do cover this procedure for palliation of unresectable CCA[42]. Porfimer sodium is typically administered intravenously, at 2 mg/kg, ideally 48 h (but possibly up to 72 h) before ERCP. At the time of ERCP, a 10-Fr bougie catheter (SBDC-10, Cook Medical, Bloomington, IL) or a choledochoscope (SpyGlass, Boston Scientific, Natick, MA) is advanced over a wire to

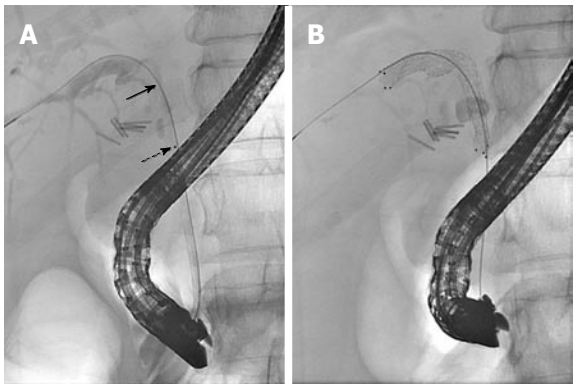

Figure 2 Endoscopic retrograde cholangiopancreatography-directed photodynamic therapy followed by unilateral metal stenting. A: Fluoroscopic view of a photodynamic therapy laser fiber delivered through a 10-Fr-bougie catheter during endoscopic retrograde cholangiopancreatography. The portion of the fiber that emits laser light is demarcated by the black dot (dashed arrow). The proximal-most tip of the fiber is not visible fluoroscopically (solid arrow) but is located near the biliary confluence; B: An 8 mm x 6 cm uncovered self-expandable metal stent was placed across a malignant stricture that involved the right hepatic duct and common hepatic duct.

the level of the malignant stricture and used to pass a laser fiber. This laser fiber (Figures 1 and 2) is then used to deliver activating light (at 630 nm for 750 s, with a light dose of 180 J/cm^2)[43]. When the photosensitizer is activated, oxygen free radicals are released that result in local tissue destruction. Since its first description for biliary tumor ablation in 1991[44], multiple studies have demonstrated that PDT can enable local tumor control and also can result in improved quality of life in this difficult-to-treat patient population[42,45-61]. Metal stent patency has also been shown to be significantly greater with PDT applied immediately prior to stent placement *vs* metal stent placement alone (median time of 244 d *vs* 177 d, respectively, $P = 0.002$)[49].

In 2003, Ortner *et al*[52] conducted a prospective, open-label, randomized, multicenter study of patients with unresectable CCA that compared PDT (using porfimer sodium) in addition to endoscopic or percutaneous stenting by using two 10-Fr endoprostheses *vs* stenting alone and demonstrated significant improvement in survival times (median 493 d *vs* 98 d, respectively, $P < 0.0001$)[52]. Improvement in cholestasis and quality of life indices were also reported. Another randomized controlled trial by Zoepf *et al*[60] in 2005 compared PDT (using Photosan-3, SeeLab, Wesselburenerkoog, Germany) and stenting *vs* stenting alone in patients with unresectable CCA. These investigators demonstrated significantly improved survival in the group that received PDT (21 mo) compared to the group that received only stents (7 mo, $P = 0.0109$). In this study, PDT was delivered *via* ERCP (transpapillary) or by percutaneous biliary access.

The survival benefit associated with PDT in patients with unresectable CCA has also been demonstrated by multiple heterogeneous cohort studies, which were mostly retrospective in nature[45,47,54,62,63]. In 2012, Leggett *et al*[50] conducted a meta-analysis that included six studies that contributed 170 patients with unresectable CCA who received PDT and biliary stenting *vs* 157 patients with CCA who underwent stenting alone. This meta-analysis found that PDT was associated with a statistically significant survival advantage (weighted mean difference of 265 d, $P = 0.01$) and significantly improved quality of life as reflected by improvement in Karnofsky score (weighted mean difference of 7.74, $P = 0.01$). While there appears to be sufficient data to support that at least one round of PDT offers a survival advantage to patients with incurable CCA, it is not clear if multiple rounds of PDT (done every few months) adds to the survival advantage[62]; nor is it clear if bilateral PDT is superior to unilateral PDT in the case of Bismuth IV tumors.

The merits of PDT are tempered somewhat by its potential side-effects. Although a study evaluating the safety and long-term efficacy of PDT using porfimer sodium reported no treatment-related mortality or grade-4 toxicity, complications including photosensitivity resulting in burns (Figure 3) and to a lesser extent bleeding, stenosis, and bile leak have been reported[46]. Cholangitis is usually the most commonly encountered problem that arises in patients with CCA who have undergone biliary intervention, and as expected cholangitis following PDT does occur. A major drawback with ERCP-directed PDT is the need for patients to avoid direct or indirect sunlight for 4-6 wk, which may significantly affect their quality of life. Efforts to limit light toxicity have also resulted in use of a newer photosensitizer meta-tetra(hydroxyphenyl)chlorin (Foscan, Biolitec AG, Jena, Germany) that has demonstrated efficacy in a small study while potentially removing the detrimental side-effects of prolonged skin photosensitivity[48]. Another major drawback of PDT is that the cost of a single-dose of porfimer sodium in a 75 kg patient is about USD $37208, which can be prohibitively high[43].

Nevertheless, PDT has several advantages including: (1) porfimer sodium preferentially accumulates in malignant cells, potentially reducing damage to non-malignant epithelium; and (2) laser light can refract through bile, which can transmit the PDT effect to malignant strictures that are not directly adjacent to (and might be inaccessible to) the laser fiber[43]. Because PDT is dependent on the transmittance of laser light, and does not require the laser fiber to directly make contact with tumor tissue, successful delivery of PDT through metal stents has been reported with appropriate adjustment of the light dose[64].

ERCP-DIRECTED RADIOFREQUENCY ABLATION

Percutaneously- and intraoperatively-directed RFA have been demonstrated by several studies to be efficacious for local tumor control in patients with

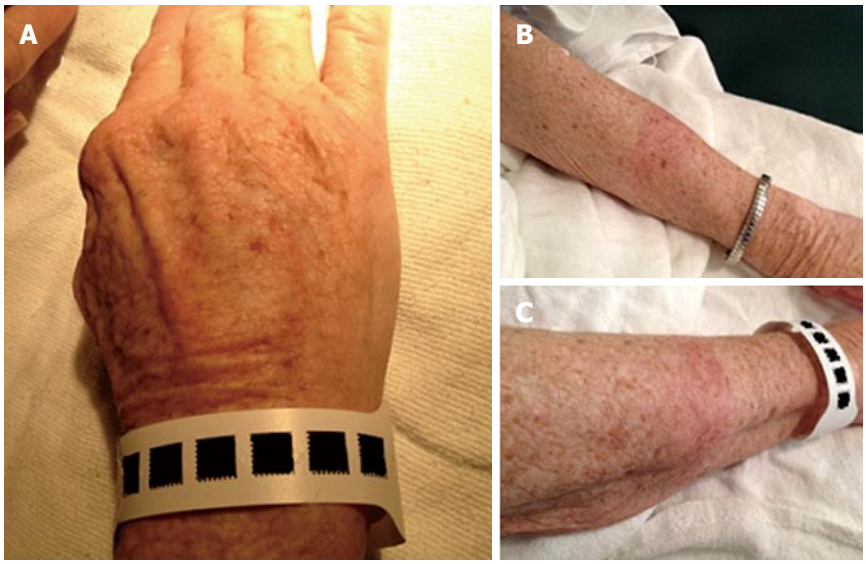

Figure 3 Photosensitivity following photodynamic therapy. A patient with unresectable cholangiocarcinoma was treated with photodynamic therapy. After 4 wk, a test dose of 10 min of exposure to direct sunlight on small areas of uncovered skin resulted in moderate burns on hands (A) and forearms (B, C). Two additional weeks of avoidance to even indirect sunlight was required.

inoperable CCA[65-70], including as an adjunct to surgery[71-73]. RFA has been used for local control of tumor recurrence following surgery in patients who may no longer be good operative candidates or for whom no other surgical intervention is possible[68,72], including those who have already undergone protocol liver transplantation for CCA[74]. However, complications following the percutaneous delivery of RFA are not trivial and have included gastrohepatic fistula[75], hemorrhage necessitating transarterial embolization[76], hepatic vein pseudoaneurysm[77], acute liver failure or abscess formation[78], and needle-tract seeding of tumor[79].

ERCP-directed RFA was developed to enable endoscopists to treat malignant biliary strictures *via* a mechanism of coagulative necrosis induced by thermal energy that is delivered *via* contact using a bipolar catheter[43]. One commercially available RFA catheter (Figure 1) is an 8-Fr device with two electrodes spaced 8 mm apart at the end of the catheter that can be passed over a guidewire (Habib EndoHPB; EMcision, London, United Kingdom)[80]. This device passed United States Food and Drug Administration 510[k] premarketing clearance in 2009. This RFA catheter can be passed through the accessory channel of a duodenoscope and into the bile duct (Figure 4). Fluoroscopic guidance is used to center the two sets of bipolar rings across a malignant stricture for RFA treatment (Figures 5 and 6).

In 2011, Steel *et al*[81] conducted a single-center open-label pilot study that demonstrated that ERCP-directed RFA could be performed safely and efficaciously in patients with malignant biliary strictures from unresectable pancreas cancer or CCA. In this initial study, all but one of 21 patients who had RFA followed by SEMS placement maintained stent patency at 30 d. One patient had asymptomatic biochemical pancreatitis, 2 patients required percutaneous gallbladder drainage, and 1 patient developed rigors. At 90-d follow-up, 3 patients had occluded biliary stents. Subsequently, in a retrospective series of 12 patients (9 with CCA) with malignant intraductal or perihilar biliary strictures, Tal *et al*[80] performed 19 successful RFA applications *via* ERCP followed by PS placement. These investigators used a setting of 8 W for treatment of intrahepatic and perihilar biliary strictures and 10 W for extrahepatic bile duct strictures using an ERBE electrosurgical generator (VIO 200D, ERBE Elektromedizin, Tübingen, Germany). However, biliary bleeding was observed at 4-6 wk in 3 patients (2 of whom died of hemorrhagic shock), and cholangitis developed in 4 patients, which was amenable to stent exchange. Finally, Figueroa-Barojas *et al*[82] reported on the use of ERCP-directed RFA in 25 patients with malignant biliary structures (11 patients had CCA). Procedures were performed using a RITA 1500X RF generator (Angiodynamics, Latham, NY) set at 7-10 W for a time period of 2 min. These investigators reported a resultant significant increase in mean bile duct diameter of 3.5 mm ($P < 0.0001$)[82]. In this series, 5 patients presented with pain after the procedure, one patient developed mild post-ERCP pancreatitis, and one patient developed cholecystitis following endobiliary RFA.

In 2014, Sharaiha *et al*[83] published a retrospective series of 66 patients with malignant biliary strictures (36 with CCA) who underwent either SEMS placement alone or RFA followed by SEMS placement. They reported 100% technical success in both groups. While these investigators found that rates of stent patency were similar between the two groups, on multivariate analysis, RFA was found to be an independent predictor of survival (HR = 0.29, 95%CI: 0.11-0.76, $P = 0.012$). Finally, RFA has been described as a means of treating tumor ingrowth of uncovered SEMS in the bile duct[84].

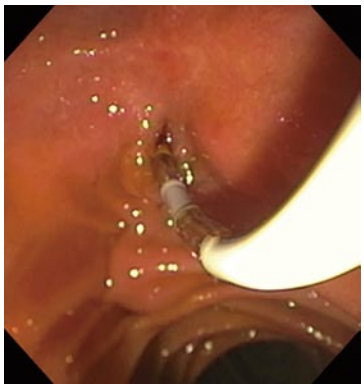

Figure 4 Endoscopic view of a radiofrequency ablation catheter being inserted into the bile duct by using a duodenoscope. A biliary sphincterotomy had been performed during a prior endoscopic retrograde cholangiopancreatography procedure in this patient with an unresectable cholangiocarcinoma to enable easier access to the bile duct. Note: this is not a depiction of radiofrequency ablation (RFA) actively being performed, as RFA is not typically applied with the bipolar coils exposed in the duodenal lumen, in order to avoid thermal injury to the duodenal wall.

Typically, the RFA catheter can be passed into a blocked stent and used under fluoroscopic guidance to ablate any tumor ingrowth, which is then removed by retrieval balloon sweep. This ablation may be followed by placement of an indwelling plastic stent or a second uncovered SEMS, in appropriate situations (Figure 6).

When compared to PDT, the advantages of endobiliary RFA include being able to provide ablative treatment without the patient having to come in 2 d in advance for infusion of a photosensitizer, easier delivery of the RFA catheter that can be done over a guidewire, and no requirement to avoid sunlight for several weeks to prevent photosensitivity. However, RFA requires direct contact with neoplastic tissue for ablation, thus it does not offer the "field effect" conferred by the laser light used in PDT, which can refract through bile to treat inaccessible blocked bile ducts.

In 2014, Strand *et al*[43] demonstrated comparable survival following ERCP-directed RFA *vs* ERCP-directed PDT. In this retrospective cohort study, 48 patients with unresectable CCA underwent RFA (n = 16) or PDT (n = 32) followed by plastic or metal biliary stenting. Overall median survival in both treatment groups was not statistically different (9.6 mo following RFA and 7.5 mo following PDT, P = 0.799). Furthermore, patients who underwent RFA had a lower mean number of plastic stents placed per month (0.45 *vs* 1.10, P = 0.001) but also had more episodes of stent occlusion (0.06 *vs* 0.02, P = 0.008) and cholangitis (0.13 *vs* 0.05, P = 0.008) per month, as compared to patients who received PDT.

In addition to the differing advantages and disadvantages of RFA *vs* PDT that were mentioned earlier, a major discriminating factor between these two ablative technologies is cost. Strand *et al*[43] noted that because both procedures required ERCP with sent exchange, the true cost differential is the difference between the cost of a dose of porfimer sodium (USD $37208) and the cost of the RFA catheter (USD $1295), which is $35913[43]. In the current environment of falling reimbursements and the need for cost-containment, this is a significant difference that favors ERCP-directed RFA.

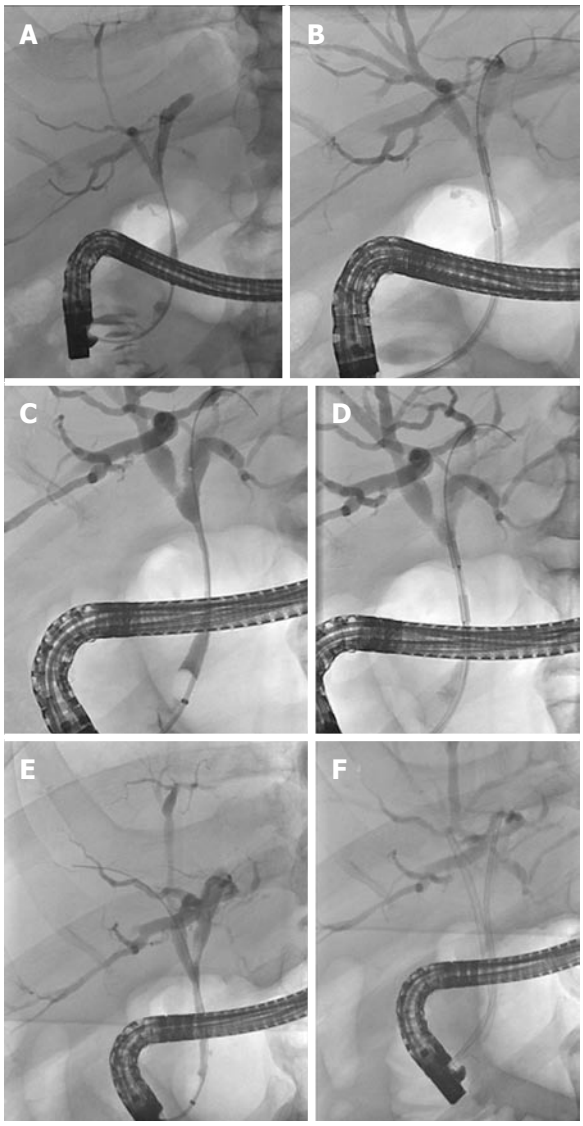

Figure 5 Effect of repeated endoscopic retrograde cholangiopancreatography-directed radiofrequency ablation on a malignant extrahepatic biliary stricture in a patient with unresectable cholangiocarcinoma. A long perihilar stricture is seen involving the extrahepatic duct (A) in a patient who had exploratory laparotomy that showed locally advanced and unresectable Bismuth I cholangiocarcinoma. A cholecystectomy had been performed at the time of laparotomy. Endoscopic retrograde cholangiopancreatography (ERCP)-directed radiofrequency ablation (RFA) was applied to this malignant stricture (B) followed by biliary stenting (not shown). Following two rounds of RFA done at about 3 mo intervals, a third ERCP showed moderate improvement in the stricture's diameter (C). Repeat ERCP-directed RFA was performed (D). After 4 rounds of RFA therapy, an ERCP 1 year later showed marked improvement of the extrahepatic bile duct with no high-grade stricture seen (E), and RFA was not repeated during this procedure. A 10-Fr plastic stent was placed into the right hepatic duct and a 7-Fr plastic stent was placed into the left hepatic duct for more durable biliary drainage (F), as this was an otherwise healthy patient with excellent functional status who would likely outlive metal stenting. While patients with Bismuth I cholangiocarcinoma often do well with a single extrahepatic biliary stent, this patient had previously had premature stent failure and cholangitis with a single plastic stent, thus two biliary stents were required.

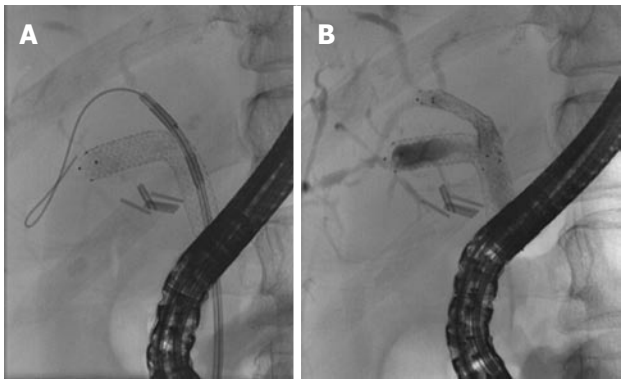

Figure 6 A patient with unresectable cholangiocarcinoma was previously treated with photodynamic therapy followed by placement of an uncovered metal stent (see Figure 2). For persistent symptomatic biliary obstruction due to undrained segments in the right liver, a wire was passed into the previously undrained segments which allowed for 6-Fr bougie dilation followed by 4-mm balloon dilation across the lattices of the existing large-cell uncovered self-expandable metal stent (SEMS) (not shown). After dilation, the 8-Fr radiofrequency ablation (RFA) catheter was deployed over the wire and through the SEMS, and RFA was applied to a malignant stricture that was obstructing drainage (A). Lastly an 8-mm uncovered SEMS was deployed through the previously placed 8-mm uncovered SEMS (B) enabling durable drainage of more of the right liver.

ERCP-DIRECTED NEOADJUVANT ABLATIVE THERAPY FOR CCA PRIOR TO LIVER TRANSPLANTATION

Experience with liver transplantation (LT) for unresectable CCA had previously been disappointing due to frequent cancer recurrence and poor 5-year survival rates[3]. To improve outcomes following LT for CCA, a protocol for neoadjuvant chemotherapy followed by LT was first developed at the University of Nebraska and then at the Mayo Clinic[3,85]. Patients who met the following criteria were included in this LT protocol: (1) perihilar location of suspected CCA; (2) a malignant-appearing stricture on cholangiography with malignant endoluminal brushing or biopsy, carbohydrate antigen 19-9 level > 100 U/mL (in the absence of cholangitis), mass on cross-sectional imaging, and/or polysomy on fluorescence *in situ* hybridization; (3) unresectable disease or disease arising in primary sclerosing cholangitis; (4) completion of neoadjuvant therapy before LT; and (5) medical suitability for LT[85]. Neoadjuvant therapy from the early "Mayo" protocol included administration of external beam radiation therapy (XBRT) and 5-fluorouracil, followed by brachytherapy[85-87]. Use of intraluminal brachytherapy and XBRT in patients with unresectable CCA has been reported for palliation of jaundice and as a treatment to temporarily obviate the need for biliary stenting[88,89]. Furthermore, a retrospective study by Darwish Murad *et al*[85] of 287 patients, 75% of whom received brachytherapy as part of neoadjuvant therapy prior to LT, demonstrated a 5-year ITT survival rate of 53% and post-transplant recurrence-free survival of 65%[85]. In this large series of patients, recurrence-free survival for patients who had received brachytherapy was similar to those who had not (HR = 1.05; 95%CI: 0.60-1.85)[85]. Other studies have also shown no mortality benefit from the addition of brachytherapy[90,91]. In an effort to mitigate side-effects associated with brachytherapy and the complexities associated with delivery of radioactive ribbons in the endoscopy or radiology suite, other endobiliary therapies for neoadjuvant locoregional CCA tumor control prior to LT have been adopted.

In particular, PDT, as mentioned previously, has been demonstrated to be a safe and potentially efficacious modality for locoregional control of perihilar CCA in palliative patients. In a proof-of-concept study performed at our institution, Cosgrove *et al*[42] reported on 4 patients with unresectable CCA who had undergone protocol-driven neoadjuvant chemoradiation followed by ERCP-directed PDT to provide endobiliary and local tumor control in patients who were awaiting LT[42]. Although the sample size of this study was small, none of the patients who received PDT had progressive locoregional disease or distant metastases during the pre-transplant period, and all patients underwent successful LT. ITT disease-free survival was 75% at a mean follow-up of 28.1 mo. Based on these data regarding PDT, as well as our comparable experience with RFA for patients with incurable CCA[43], our institution's protocol allows for the use of either PDT or RFA as an alternative to brachytherapy for locoregional tumor control in patients with inoperable CCA who are awaiting LT. Prospective trials to study these ERCP-directed neoadjuvant modalities for locoregional control in patients with CCA are indicated.

CONCLUSION

CCA is a malignancy with high morbidity and mortality due to its typically late presentation with obstructive jaundice, and its associated complications of cholangitis and biliary sepsis. ERCP is a valuable treatment modality for patients with CCA, as it enables internal luminal drainage of blocked bile ducts and hepatic segments by using plastic or metal stents. While there remains debate as to if bilateral (or multi-segmental) hepatic drainage is required and/or superior to unilateral drainage, the underlying tenant of draining any persistently opacified bile ducts is paramount to good ERCP practice and good clinical outcomes. Endoscopic therapy for malignant biliary strictures from CCA has advanced to include ablative therapies *via* ERCP-directed PDT or RFA. As chemoradiation is of limited efficacy in providing tumor control for this cancer, these endoscopic modalities, which offer the potential for locoregional control and hopefully more durable biliary drainage, are a much needed addition to our therapeutic endobiliary armamentarium. While ERCP techniques cannot cure CCA, advancements in the field of ERCP have enabled us to improve upon the quality of life of patients with incurable disease. ERCP-directed PDT has been used in lieu of brachytherapy to provide neoadjuvant local

tumor control in patients with CCA who are awaiting LT. Lastly, mounting evidence suggests that palliative ERCP-directed PDT, and probably ERCP-directed RFA as well, can offer a survival advantage to patients with this difficult-to-treat malignancy.

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