Endoscopic treatment options for cholangiocarcinoma

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Practice Points

- Most cholangiocarcinomas are locally advanced or have metastasized at the time of diagnosis.
- Endoscopic treatment options have previously been limited to biliary decompression via stenting. Self-expanding metal stents are preferred for distal malignant biliary obstruction.
- Recent developments in locoregional therapy, such as photodynamic therapy and, more recently, radiofrequency ablation, have shown promising results, particularly in improving patient outcomes for those with locally advanced or unresectable disease.
- Further studies are needed to confirm the benefits of photodynamic therapy and radiofrequency ablation on long-term biliary stent patency and survival rates.

SUMMARY Cholangiocarcinomas are often locally advanced or have metastasized, and at the time of diagnosis individuals often have a poor prognosis. Endoscopic treatment options traditionally include biliary decompression via stenting to allow for systemic chemotherapy and radiotherapy, with self-expanding metal biliary stents being preferred. Recent developments in locoregional therapy delivered endoscopically, such as photodynamic therapy and radiofrequency ablation, have shown promising results in improving patient survival.

Cholangiocarcinoma is an epithelial carcinoma arising from the intra- and extra-hepatic biliary tree. Since the 1970s, the incidence of cholangiocarcinoma has increased steadily in western societies and now accounts for 3% of all gastrointestinal malignancies [1,2]. In the USA, the incidence rate has been reported as one to two cases per 100,000 patients, with most patients being older than 65 years of age [3]. Cholangiocarcinomas are classified into three different subgroups based on their anatomic location: intrahepatic, perihilar and distal cholangiocarcinoma [4].

The only curative treatment for cholangiocarcinoma is surgical resection with negative margins. Unfortunately, more than 80% of patients present with unresectable disease at the time of diagnosis [5]. The prognosis at this stage is poor, as the median survival for nonsurgical candidates is 4–7 months [6,7]. Successful palliation of biliary obstruction is the main goal, but alleviating jaundice through biliary stenting alone has not been proven to prolong survival. Systemic chemotherapy and radiotherapy have also been relatively ineffective for prolonging survival or relieving jaundice for patients with inoperable

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Table 1. Plastic versus metal stents (self-expanding metal stents) for distal malignant stricture.

Study (year)	Plastic stents	SEMS	p-value	Ref.
Choi <i>et al.</i> (2012)	Stent occlusion: median 94.6 days	Stent occlusion: median 233.6 days	0.006	[16]
Yoon <i>et al.</i> (2009)	Stent occlusion: mean 133 days	Stent occlusion: mean 278 days	0.0004	[14]
Soderlund <i>et al.</i> (2006)	Stent occlusion: median 1.1 month	Stent occlusion: median 3.5 months	0.007	[17]
Kaassis <i>et al.</i> (2003)	Stent occlusion: median 5 months	Median not reached	0.007	[18]
Prat <i>et al.</i> (1998)	Stent occlusion: median 3 months	Stent occlusion: median 4.8 months	NS	[19]
Knyrim <i>et al.</i> (1993)	43% stent failure rate	22% stent failure rate	0.0035	[20]

NS: Not significant; SEMS: Self-expanding metal stents.

tumors. This has led to a push for novel locoregional therapies directed at improving patient survival and palliation of symptoms.

Biliary stenting

Biliary obstruction develops in 90% of patients with unresectable disease, ultimately leading to jaundice, pruritus, abdominal pain and cholangitis [8]. Biliary decompression palliates these symptoms but has not been shown to affect survival [9]. Surgical bypass used to be the primary method of palliation of jaundice in patients with unresectable cholangiocarcinoma but in the last 20 years has been largely replaced by less invasive nonsurgical procedures such as percutaneous or endoscopic biliary stent placement. Endoscopic stenting costs significantly less and was associated with longer survival than surgical treatment (19 vs 16.5 months), suggesting that endoscopic

stenting is the procedure of choice for palliative biliary drainage [10]. In patients who are operative candidates, however, preoperative biliary drainage is controversial. A meta-analysis did not show any significant differences in mortality, morbidity or complications in patients who received preoperative biliary drainage versus the patients who received surgery directly [11], and currently, the majority of data on preoperative drainage pertain to obstructive jaundice in malignancies other than cholangiocarcinoma. Currently, preoperative drainage is not recommended on a routine basis except in cases of acute suppurative cholangitis [12].

Plastic versus metal stents

Both plastic and metal stents can be used for the palliation of malignant bile duct obstruction. Plastic stents have been used since the

Figure 1. Metal biliary stenting in cholangiocarcinoma. (A) Tumor ingrowth in a previously placed uncovered self-expandable metallic stent in a 67-year-old man with advanced cholangiocarcinoma. (B & C) Insertion of a partially covered self-expandable metallic stent inside the previously placed stent to relieve the obstruction.

Table 2. Covered versus uncovered self-expanding metal stents for distal malignant stricture.

Study (year)	Covered SEMS patency	Uncovered SEMS patency	p-value	Ref.
Isayama <i>et al.</i> (2004)	Mean 304 days	Mean 106 days	0.0032	[22]
Yoon <i>et al.</i> (2006)	Mean 398 days	Mean 319 days	0.578	[23]
Park <i>et al.</i> (2006)	Mean 148 days	Mean 143 days	0.531	[24]
Telford <i>et al.</i> (2010)	Median 357 days	Median 711 days	0.530	[21]
Kullman <i>et al.</i> (2010)	154 days (when a quarter of stents failed)	199 days (when a quarter of stents failed)	0.348	[25]
Lee <i>et al.</i> (2013)	Median 15.4 months	Median 26.3 months	0.61	[26]

SEMS: Self-expanding metal stents.

1980s and are made from materials including Teflon®, polyurethane and polyethylene, ranging in multiple diameters and sizes. They are effective and inexpensive compared with their metallic counterparts. However, plastic stents have a shorter duration of stent patency (about 3 months), often requiring repeat endoscopic retrograde cholangiopancreatographies (ERCP) for stent occlusion that can develop in the setting of sludge, tumor overgrowth or biofilm formation [13,14].

Self-expanding metal stents (SEMS) have been made from three materials: stainless steel, nitinol (a nickel and titanium alloy) and platinum (platinum and nitinol alloy). SEMS are more expensive than plastic stents and may be difficult to remove because of tumor and tissue ingrowth. SEMS, however, are larger in diameter, thus leading to an extended duration of stent patency (approximately 6–12 months) [10]. Metal stents are also associated with fewer ERCPs, a shorter hospital stay and fewer complications than plastic stents in patients who survive more than 6 months [10–15]. Moss *et al.* evaluated the outcomes of surgical bypass, endoscopically placed plastic stents and endoscopically placed metal stents

in 24 studies including almost 2500 patients in a large meta-analysis that showed similar rates of biliary decompression but improved patency rates for SEMS [13]. Numerous studies have compared plastic stents with SEMS for distal malignant biliary strictures and confirm longer patency, decreased hospitalizations, decreased number of endoscopic procedures and reduced overall cost in the SEMS group (Table 1). Thus, SEMS are thought to be the treatment of choice in patients with unresectable distal malignant biliary obstruction.

■ Uncovered SEMS versus covered SEMS

SEMS can be uncovered, partially covered, or fully covered. The covering is a silicone, polycaprolactone, polyether polyurethane, polyurethane or expanded polytetrafluoroethylene fluorinated ethylene propylene lining. Disadvantages of uncovered metal stents include being difficult to remove endoscopically and tumor ingrowth through the stent mesh, thus causing further problems with biliary obstruction and sepsis (Figure 1). The benefits of covered SEMS are removability and theoretically longer patency rate due to reduced tumor ingrowth.

Table 3. Plastic versus self-expanding metal stents for hilar lesions.

Study (year)	Plastic	SEMS	p-value	Ref.
Knysrim <i>et al.</i> (1993)	Median patency: 5 months Cholangitis incidence 36%	Median patency: 5 months Cholangitis incidence 15%	NS <0.05	[20]
Perdue <i>et al.</i> (2008)	Complication rate at day 30: 32.1% Adverse outcome: 39%	Complication rate at day 30: 8.8% Adverse outcome: 12%	0.027 0.017	[29]
Raju <i>et al.</i> (2011)	Median patency: 1.86 months Complication rate: 7.7%	Median patency: 5.56 months Complication rate: 8.3%	<0.0001 0.79	[30]
Sangchan <i>et al.</i> (2012)	Successful drainage: 46.3% Complication rate: 33.3%	Successful drainage: 70.4% Complication rate: 46.3%	0.011 0.246	[31]
Liberato <i>et al.</i> (2012)	Median patency: 20 weeks Complication rate: 56.4%	Median patency: 27 weeks Complication rate: 24.4%	<0.0001 <0.001	[32]

NS: Not significant; SEMS: Self-expanding metal stents.

Figure 2. Cholangiogram demonstrating placement of bilateral self-expanding metal stents allowing for maximum drainage in a patient with advanced hilar cholangiocarcinoma.

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Covered SEMS also have also been reported to have a higher migration rate [21]. Multiple studies have compared the patency of covered versus uncovered SEMS in distal pancreaticobiliary malignancy (Table 2). In a meta-analysis including five trials, Saleem *et al.* showed that covered SEMS have prolonged stent patency (weighted difference plus 60.56 days) and prolonged survival (weighted mean difference plus 68.76 days) compared with uncovered SEMS [27]; however, in a more recent meta-analysis, Almadi *et al.* calculated the mean difference in the stent patency duration on two studies to be 67.9 days longer for covered SEMS than for uncovered SEMS (95% CI: 60.3–75.5) with a summary analysis showing no difference in patency of covered versus uncovered SEMS after 6 and 12 months [28]. The choice of covered versus uncovered SEMS in patients with distal malignant biliary obstruction should be made on an individual basis.

Similarly, for nonresectable hilar tumors, SEMS are preferred over plastic stents, due to increased patency rates and a decrease in the number of endoscopic sessions (Table 3). Uncovered SEMS are recommended for hilar and intrahepatic regions as to avoid blocking the drainage of other intrahepatic segments with covered SEMS, as it would lead to segmental cholangitis [33].

Unilateral versus bilateral drainage: hilar cholangiocarcinoma

There is currently no consensus on whether bilateral or unilateral (single vs multiple) drainage is more effective in the setting of hilar lesions, as various studies have demonstrated conflicting data. Approximately 55–60% of the liver volume is drained via the right hepatic duct, 30–35% by the left hepatic duct, and 10% from the caudate lobe. Only 25% of the liver volume requires drainage to see improvement in jaundice [34]. Earlier studies found that bilateral stent placement was associated with improved outcomes compared with unilateral stenting, but contrast material was injected into both lobes, leading to bacterial contamination of undrained areas and an increased risk of cholangitis [35]. In the only randomized trial to address this question, De Palma *et al.* reported that unilateral SEMS insertion was effective in biliary palliation in unresectable hilar cholangiocarcinoma, with higher rates of successful endoscopic stent insertion than bilateral stents (88.6 vs 76.9%; $p = 0.041$) [36] and lower rates of complication (18.9 vs 26.9%; $p = 0.026$) [37]. Unilateral drainage has also been associated with a lower incidence of liver abscess as well as a comparable outcome with regard to stent patency and complication-free survival compared with bilateral drainage [38]; however, more recent studies have found bilateral stenting may still be needed to allow for adequate drainage of liver volume (Figure 2). Chang *et al.* demonstrated that the survival rate was highest in patients who underwent bilateral drainage, with the lowest survival rate in patients who had cholangiographic filling of both lobes but drainage of only one [35]. Cumulative stent patency was also higher in patients who had bilateral stents placed [39]. A recent retrospective study of 107 patients with hilar tumors found that the most important predictor of effective drainage (defined as a decrease in serum bilirubin by 50% after 1 month) was stents draining a volume greater than 50%, which often did require bilateral stents. A drainage of >50% was also

Figure 3. Photodynamic therapy light probe. (A) A photodynamic therapy light diffuser probe for use in the bile duct. (B) Uniform illumination can be achieved despite curvature of the probe. Reproduced with permission from Medlight, Switzerland.

associated with a longer median survival (119 vs 59 days; $p = 0.005$), whereas intubating an atrophic sector ($<30\%$) was not helpful and increased the risk of cholangitis (odds ratio: 3.04; $p = 0.01$) [40]. Therefore, in malignant hilar obstruction, cross-sectional imaging is important to identify the dominant biliary system before endoscopic decompression of malignant hilar obstruction, and biliary drainage should be maximized, either through unilateral or bilateral stenting.

■ Complications

Complications are inherent in the performance of endoscopy, arising from the procedure itself

(e.g., bleeding, pancreatitis, perforation or cardiopulmonary events) or are stent related (e.g., occlusion, migration, infection, cholangitis or cholecystitis). Selective endoscopic stenting into the appropriate bile duct is still a challenge, and is one of the technical limitations to performing effective biliary drainage in hilar cholangiocarcinoma.

Stent migration is usually seen in covered metal stents, with reported rates ranging from 6 to 8% [14,41,42]. Uncovered metal stents have a much lower migration rate, approximately 1% [27], likely secondary of tumor and tissue growth within the stent interstices. Stents can become

Table 4. Results of photodynamic therapy in cholangiocarcinoma.

Study (year)	Patients (n)	Study type	Serum bilirubin before and after PDT	Median survival (months)	Adverse events; n (%) [†]	Ref.
Ortner <i>et al.</i> (1998)	9	Single arm	18.6, 6	14.6	1(11), 0(0)	[51]
Berr <i>et al.</i> (2000)	23	Single arm	11.2, 1	11.1	3(13), 8(35)	[52]
Rumalla <i>et al.</i> (2001)	6	Single arm	2.7, 1.3	6	2(33), 2(33)	[53]
Dumoulin <i>et al.</i> (2003)	24	Single arm	13.3, 2.6	9.9	2(8), 5(21)	[54]
Ortner <i>et al.</i> (2003)	20	Randomized	Decreased	16.4	2(10), 5(25)	[50]
Harewood <i>et al.</i> (2005)	8	Single arm	7.7, 1.1	9.2	2(25), 2(25)	[55]
Zoepef <i>et al.</i> (2006)	32	Randomized	Decreased	21	NR	[56]
Witzigmann <i>et al.</i> (2006)	68	Single arm	Decreased	12.0	8(12), 38(56)	[57]
Prasad <i>et al.</i> (2007)	25	Single arm	6.1, 3.5	13.4	1(4), 2(8)	[58]
Kahaleh <i>et al.</i> (2008)	19	Comparative	6.3, 3.5	16.2	3(16), 7(37)	[59]
Quyn <i>et al.</i> (2009)	23	Comparative	Decreased	14.2	4(17), 5(21)	[60]
Cheon <i>et al.</i> (2012)	72	Comparative	9.9, 1.8	9.8	10(14), NR	[61]
Lee <i>et al.</i> (2012)	33	Comparative	8.5, 1.3	11.7	1(6), 1(6)	[62]

[†]Phototoxicity, cholangitis.

NR: Not reported; PDT: Photodynamic therapy.

Figure 4. Photodynamic therapy with choledochoscopy. (A) Radiograph of SpyGlass™ (BSCI, Inc., MA, USA) choledochoscope insertion. **(B)** Choledochoscopic-guided insertion of photodynamic therapy probe.

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occluded from debris, tumor ingrowth or overgrowth, and plastic stents are particularly vulnerable. As mentioned earlier, patency of plastic stents is reported to be around 3 months, and they require frequent replacement, whereas SEMS have patency rates of nearer to 9 months. Uncovered SEMS are prone to tissue or tumor ingrowth (Figure 1), and may be difficult to remove, thus necessitating placement of a second stent within the lumen of the occluded stent [43]. Covered SEMS have also been associated with cholecystitis by causing cystic duct occlusion, although two retrospective studies have shown no significant differences in the rate of cholecystitis between uncovered SEMS and covered SEMS [44,45]. However, tumor involvement at the orifice of the cystic duct is a significant risk factor for cholecystitis [46,47]. Rates of pancreatitis with SEMS have been reported to be approximately 6% [48], and cholangiocarcinoma, contrast injection into the pancreatic duct [44] and hilar cholangiocarcinoma [49] have been independent predictive factors for pancreatitis after SEMS placement.

Locoregional therapies

■ Photodynamic therapy

Photodynamic therapy (PDT) is an investigational procedure using a photosensitizing agent (such as Photosan-3® and Photofrin®) activated by a laser (at a specific wavelength) introduced via ERCP (Figure 3). The activation leads to

creation of reactive oxygen species that subsequently causes necrosis of tumor cells to a depth of 4–6 mm and an antiangiogenic effect [50]. PDT has been shown to increase survival in patients with unresectable cholangiocarcinoma compared with historic controls in multiple studies (Table 4).

The procedure technique has become standardized, as PDT is typically offered to patients as part of a neoadjuvant regimen or those with unresectable cholangiocarcinoma. Two to four days after administration of the photosensitizing agent, the patient undergoes ERCP. A cholangiogram is performed to delineate the distribution of malignant disease, and stricture dilation is performed to facilitate the subsequent placement of the cylindrical diffuser (with a laser) within the stricture. Photoactivation is performed at 630 nm with a light dose of 10 J/cm², fluence of 0.250 W/cm² and irradiation time of 750 s [63]. Multiple segments can be treated at once, and placement of an endoprosthesis is performed after PDT to prevent cholangitis. Photosensitivity effects of the drug last for 4–6 weeks [58], and as these agents can also deposit in the skin, phototoxicity is a side effect and all patients must be educated regarding sun exposure. PDT can be repeated at 3-month intervals, at which time all stents should be replaced [48].

The first successful report of PDT in unresectable cholangiocarcinoma was by McCaughan in 1991, where a patient was treated over the course

of 4 years with seven sessions of PDT [64]. Many subsequent studies (Table 4) have had promising results, particular when used in conjunction with metal stenting. At this time, there have been two prospective randomized controlled trials comparing PDT after stent insertion compared with stents alone. Ortner *et al.* demonstrated that median survival was 493 days in the PDT group versus 98 days in the non-PDT group ($p < 0.0001$), and was thus terminated early (although this study was limited to enrollment in patients in whom biliary decompression was not successful via stents alone) [50]. Zoepf's study of 32 patients also demonstrated higher survival in patients who underwent PDT compared with stents alone (median survival 630 vs 210 days; $p < 0.01$) [56]. The presence of a visible mass on imaging, and increased time between diagnosis and PDT treatment session was associated with a lower survival rate after PDT [65], suggesting that early treatment with PDT after diagnosis may be preferred. Two small cases series (totaling 17 patients) have also demonstrated some promising results for adjuvant and neoadjuvant use of PDT [66,67]. In a systemic review of 20 studies published in 2010, Gao *et al.* concluded that PDT offered benefit on survival and quality of life with few adverse effects and should be offered to patients with unresectable cholangiocarcinoma [68].

More recently, PDT has been performed under direct visualization with single-operator cholangioscopy and peroral cholangioscopy. Cholangioscopy-guided PDT allows for the identification of tumor margins and determination of the appropriate location for placement of the diffuser (Figure 4); it also allows for evaluation of the response to therapy (Figure 5). Talreja *et al.* compared patients undergoing PDT with those undergoing cholangioscopy with direct PDT [69]. While the median survival time between the groups was not different, there was a statistically significant difference between the groups in terms of fluoroscopy time, as median time was 21.1 min with PDT and 11.1 min with cholangioscopy with direct PDT, thus allowing for decreased radiation exposure for both patients and healthcare professionals. Choi *et al.* also reported on their preliminary experience with peroral cholangioscopy with an ultraslim upper endoscope for patients with inoperable cholangiocarcinoma and an 88% success rate in performing PDT (Figure 6) [70]. In addition, PDT has also been

found in a retrospective study to prolong metal stent patency (median 244 ± 66 days for PDT and metal stent vs 177 ± 45 days for metal stent alone; $p = 0.002$) [59].

Although many studies have been published about PDT use in cholangiocarcinoma, questions remain whether PDT in combination with chemoradiation therapy is beneficial with regard to long-term survival and whether this modality can be used as a bridge to definitive therapy, such as surgery or transplantation.

■ Radiofrequency ablation

Radiofrequency ablation (RFA) has been used effectively for years in the management of primary and secondary hepatic malignancies by causing tissue necrosis. RFA involves the delivery of alternating currents that leads to thermal injury to abnormal cells, thus causing necrosis, and an endoscopic bipolar RFA catheter has been developed for the palliation of human malignant biliary obstruction. The Habib Endo HPB (EMcision UK, London, UK) catheter is a bipolar 8F catheter with a 180 cm working length, with two electrodes 8 mm in length and 8 mm apart, and has a 5-mm leading tip (Figure 7). The catheter can

Figure 5. Effects of photodynamic therapy as seen with choledochoscopy. Endoscopic (SpyGlass™ choledochoscope; BSCI, Inc., MA, USA) evaluation of the photodynamic therapy effect 3 months after treatment.

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Figure 6. Endoscopic evaluation of photodynamic therapy with a patient with hilar cholangiocarcinoma. (A) Before and (B) after 3 months of photodynamic therapy.

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be introduced over a 0.035-in. guidewire into the biliary system. The catheter is activated at 10 W of energy for 90 s at a time, causing coagulation necrosis over a 2.5-cm length, and then the device can be removed and subsequently, stents can be inserted. There have been animal studies to assess the power and duration of treatment [71].

There have been two published clinical studies on the efficacy of RFA in cholangiocarcinoma published in full. Steel *et al.*, in an open-label pilot cohort study, treated 22 patients with malignant biliary obstruction (16 with pancreatic cancer and six with cholangiocarcinoma) with RFA [72]. Patients were treated with RFA and had stents placed. Initial successful decompression was achieved in 21 out of 22 patients. Thirty-day stent patency was preserved in 20 patients, and 90-day stent patency was seen in 16 out of 19 living patients. Complications included biochemical but asymptomatic pancreatitis (amylase 1450 IU/l), and two patients developed cholecystitis that required percutaneous drainage. Both patients were septic originally and had evidence of cystic duct involvement of the tumor. Figueroa-Barojas *et al.* treated 20 patients with biliary stents and RFA, 11 of whom had unresectable cholangiocarcinoma (total of 25 strictures) [73]. Mean

stricture diameter before RFA was 1.7 mm while the mean diameter after RFA was 5.2 mm, with a significant increase of 3.5 mm ($p = <0.0001$). Five patients presented with pain after the procedure, but only one developed mild post-ERCP pancreatitis and cholecystitis.

Most recently, Sharaiha *et al.* have also reported, in abstract form, their experience on endobiliary RFA versus stenting alone [74]. A total of 15 patients underwent RFA with metal stenting, while ten patients received stents alone. Overall, 16 of the patients had cholangiocarcinoma, and technical success was reported at 100% for both groups; survival was significantly improved in patients undergoing RFA therapy. One patient in the RFA group had an adverse event (cholecystitis). Strand *et al.* also recently reported their experience with RFA in cholangiocarcinoma and compared it to patients who received PDT [75]. In total, 16 patients who received RFA and 32 patients who received PDT were included, with similar baseline characteristics. Median survival time was 7.5 months (95% CI: 4.3–16.0) for the PDT cohort and 9.6 months (95% CI: 5.1–11.7) for the RFA cohort, and survival was not statistically different in patients who received endobiliary RFA and those who received PDT. Kahaleh

Figure 7. The Habib EndoHPB biopolar radiofrequency ablation catheter, designed for endoscopic treatment of biliary tumors.

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et al. have also recently reported their interim results from using RFA in a multicenter registry (Figure 8); the 25 patients with unresectable cholangiocarcinoma had an increase in stricture diameter after RFA treatment (mean diameter before treatment: 2.21 mm, mean diameter after RFA: 5.26 mm; $p < 0.0001$) [76]. Cholangioscopy-directed RFA has also been used to confirm tissue necrosis and ablation [73,77].

Until recently, PDT was the only evidence-based endoscopic treatment other than stenting that improved the quality of life for patients with cholangiocarcinoma. Endobiliary RFA has demonstrated some promising results, and

further controlled trials are needed to establish survival advantages, improved stent patency and cost-effectiveness.

Conclusion

Most cholangiocarcinomas are locally advanced or have metastasized at the time of diagnosis. Endoscopic treatment options have previously been limited to biliary decompression via stenting, but recent developments in locoregional therapy, such as PDT and, more recently, radiofrequency ablation, have shown promising results, particularly in improving patient outcomes for those with locally advanced or unresectable disease. Further

Figure 8. Radiographic images of radiofrequency ablation in the treatment of cholangiocarcinoma. (A) Left and (B) right intrahepatic systems, (C) followed by bilateral stent placement.

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studies are needed to confirm the benefits of PDT and RFA on long-term biliary stent patency and survival rates.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest

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No writing assistance was utilized in the production of this manuscript.

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