

Comparing palliative treatment options for cholangiocarcinoma: photodynamic therapy vs. radiofrequency ablation

Tayyaba Mohammad, Michel Kahaleh

Division of Gastroenterology and Hepatology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Referral to an endoscopist is often done once curative resection is no longer an option for cholangiocarcinoma management. In such cases, palliation has become the main objective of the treatment. Photodynamic therapy and radiofrequency ablation can be performed to achieve palliation, with both procedures associated with improved stent patency and survival. Despite the greatly increased cost and association with photosensitivity, photodynamic therapy allows transmission to the entire biliary tree. In contrast, radiofrequency ablation is cheaper and faster to apply, but requires intraductal contact. This paper reviews both modalities and compares their efficacy and safety for bile duct cancer palliation.

Keywords: Ablation treatment; Bile duct neoplasms; Cholangiocarcinoma; Photodynamic therapy

INTRODUCTION

Cholangiocarcinoma is a rare cancer of the biliary tree. Cholangiocarcinoma may involve intrahepatic or extrahepatic bile ducts, excluding the ampulla of Vater or the gallbladder. Risk factors for the development of cholangiocarcinoma include biliary pathology, malformations, cholelithiasis, choledocholithiasis, cholecystitis, cholecystectomy, cirrhosis, alcoholic liver disease, hepatitis B or C infection, type II diabetes, chronic pancreatitis, and smoking, among others.¹ This disease carries a poor prognosis, with a median survival of less than 24 months.²

Classification of tumor locations help in the determination of appropriate treatment modalities. The Bismuth-Corlette

classification is used to define the longitudinal tumor extension of perihilar cholangiocarcinoma.³ Extrahepatic cholangiocarcinoma can be classified by its location in the upper, middle, and lower third of the bile duct or simply by perihilar vs. distal cancer.⁴ Conversely, lateral tumor extension is defined by using the TNM staging of the American Joint Committee on Cancer (AJCC) cancer staging system. Tumor resectability can be determined by the Blumgart T-staging system as well as the AJCC cancer staging system.⁴ Bismuth type I tumors are defined as lesions located below the confluence of the right and left hepatic ducts, and can be treated through extrahepatic bile duct resection. In contrast, Bismuth type II tumors extend to the hepatic ducts and can be treated with bile duct resection, hepaticojejunostomy, and lymph node dissection. Bismuth type IIIa extends to the bifurcation of the right hepatic duct, while IIIb extends to the bifurcation of the left hepatic duct. General management for type III tumors involves hilar resection and hemihepatectomy with lymph node dissection.³ Bismuth type IV tumors extend to the bifurcation of both right and left hepatic ducts, or are multicentric. Often, they are inoperable, with the exception of liver transplantation.⁴

Surgery and/or hepatic transplantation is the curative treat-

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Correspondence: Michel Kahaleh

Division of Gastroenterology and Hepatology, Rutgers Robert Wood Johnson Medical School, 125 Paterson St. New Brunswick, NJ 08901, USA

E-mail: mkahaleh@gmail.com

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ment for cholangiocarcinoma. However, these modalities are rarely pursued in cases of advanced disease. In more widespread and unresectable cholangiocarcinoma, options range between a combination of biliary stenting, chemotherapy, immunotherapy, and other locoregional therapies. These include external beam radiation therapy (EBRT), radiofrequency ablation (RFA), trans-arterial chemoembolization, and photodynamic therapy (PDT).⁵ This review focuses on the use of PDT and RFA in the palliation of cholangiocarcinoma.

PALLIATIVE TREATMENT OPTIONS

Biliary stenting

Biliary stenting is the most commonly used palliation technique for patients with nonresectable cholangiocarcinoma. This is performed to relieve jaundice and symptoms of biliary obstruction. The two types of biliary stents commonly used are plastic stents (PS) and self-expandable metal stents (SEMSs). Primarily, PS is used to serve as a temporary bridge to surgery in cases of hilar or extrahepatic resectable tumors, while SEMS is preferred in cases with nonresectable tumors such as malignant hilar obstruction.⁶ In terms of clinical success, morbidity, and mortality, the short-term results of SEMS and PS are comparable.⁶ However, results differ with respect to long-term outcomes. In a retrospective analysis of 480 patients with cholangiocarcinoma, SEMS was observed to have higher technical and clinical success rates and fewer complications compared to PS placement.⁷ In the same study, the patency of bilateral SEMS and PS was significantly higher than that of unilateral SEMS or PS, with lower occlusion rates. Another randomized controlled trial comparing endoscopic retrograde cholangiopancreatography with SEMS vs. PS placement in patients with unresectable hilar cholangiocarcinoma reported that SEMS provided better drainage and longer survival compared to PS.⁸ The decision to offer unilateral or bilateral stenting is often made after imaging with magnetic resonance imaging, allowing selective drainage when specific segments of the biliary tree are non-dilated or atrophic.

Radiofrequency ablation

RFA is a common palliative treatment modality for patients with unresectable cholangiocarcinoma. This has been utilized for tumor ablation in various types of gastrointestinal malignancies, including esophageal, rectal, and hepatic cancer. RFA works through the delivery of thermal energy within the tissue, leading to coagulative necrosis and cell death.⁹ Cholangioscopy

can be used to assess necrosis (Fig. 1).

For years, RFA procedures have been performed surgically and percutaneously. However, intrabiliary RFA through endoscopy has been observed to be safe and effective. The most commonly used devices for intrabiliary RFA are the Habib HPB-RF probe (Boston Scientific, Natick, MA, USA) and ELRA RF catheter (Taewoong, Medical USA, Los Angeles, CA, USA).⁹

The use of RFA in cholangiocarcinoma improves stent patency by decreasing tumor ingrowth and benign epithelial hyperplasia.¹⁰ The first study demonstrated its safety and efficacy, and reported improved stricture after RFA treatment with minimal complications.¹⁰ Another early study of 20 patients with malignant biliary obstruction, 11 of which were due to cholangiocarcinoma, revealed the safety and efficacy of RFA in conjunction with stenting in improving biliary stricture.¹¹ In a later retrospective analysis examining the efficacy of RFA compared to stenting alone, RFA was shown to be an independent predictor of survival (hazard ratio, 0.29; $p=0.012$).¹²

In recent years, randomized trials analyzing RFA treatment combined with stenting compared to stenting alone in cholangiocarcinoma have emerged. In a study of 65 patients with unresectable cholangiocarcinoma, the overall mean survival time was significantly better in patients who underwent RFA with stenting compared to those who underwent stenting alone (13.2% vs. 8.3%; $p<0.001$).¹³

Photodynamic therapy

PDT achieves local tumor ablation through the accumulation of a photosensitizer in the region of interest and supplying light energy of a specific wavelength and intensity to activate the photosensitizer.¹⁴ Photofrin (Pinnacle Biologics, Bannockburn, IL, USA) is the most frequently used photosensitizer due to its preferential uptake into malignant biliary tissue as opposed to

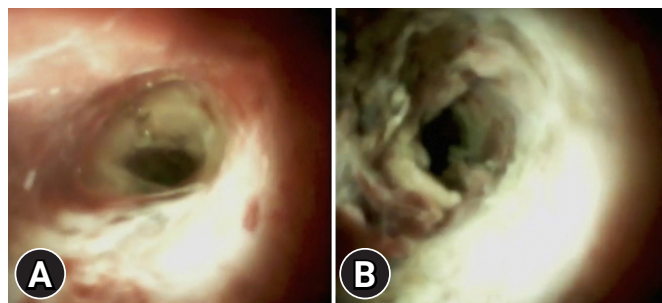


Fig. 1. Biliary cancer (A) pre- and (B) post-radiofrequency ablation treatment seen by cholangioscopy.

normal tissue. Other photosensitizers such as Foscan (Biolitec Pharma Ltd, Jena, Germany), LS11, MACE, and 5-aminolevulinic acid (5-ALA), have also demonstrated uptake into biliary tissue. After uptake, the next step in PDT is the activation of the photosensitizer through delivery of light energy. This is performed through the use of fiber optics that pass through endoscopes to the target area. In the case of Photofrin, this is generally delivered intravenously at 2 mg/kg with illumination at 48 hours postinfusion at around 180–200 J/cm via 630 nm red light.¹⁴ Repeat PDT may be done at 3–6 months if clinically indicated. Cholangioscopy can be utilized to center the fiber, which will administer red light to the cancerous lesion (Fig. 2).

The use of PDT in cholangiocarcinoma first emerged through the lens of a case report by McCaughan et al.¹⁵ and has since become a fundamental technique in the management of unresectable cholangiocarcinoma. Similar to RFA, PDT is often used as an adjunct to stenting to allow tumor shrinkage with concurrent resolution of biliary obstruction. However, PDT is associated with photosensitivity.¹⁴

In a randomized study comparing patients who received stenting with subsequent PDT to those who had stenting alone, there was increased survival in the stenting with PDT group as compared to the stenting only group (493 days vs. 98 days; $p < 0.001$).¹⁶ In an observational study of 48 patients over 5 years, there was increased survival in the PDT plus stenting group compared to the stenting only group (16.2 months vs. 7.4 months; $p < 0.004$).¹⁷ An earlier systematic review demonstrated the efficacy and safety of PDT for the treatment of cholangiocarcinoma with minimal complications.¹⁸ In a more recent meta-analysis examining PDT with stenting vs. stenting alone for treatment and palliation in patients with cholangiocarcinoma, the survival

period was significantly higher in PDT with stenting compared to stenting alone (413 days vs. 183 days; $p = 0.004$).¹⁹

Photodynamic therapy vs. radiofrequency ablation

A review of 54 studies consisting of 1,668 patients undergoing palliative treatment for cholangiocarcinoma with either PDT or RFA was conducted by the authors. The review included 37 studies on PDT consisting of 1,186 patients and 17 studies on RFA consisting of 482 patients. The overall survival rates and adverse events from the studies are detailed in Tables 1^{16,17,20-48} and 2.^{13,38,49-63}

Results from a recent systematic review and meta-analysis on the use of RFA, PDT, and biliary stenting in the treatment of unresectable extrahepatic cholangiocarcinoma showed promising use of PDT over RFA or stenting. This review analyzed 55 studies consisting of 2,146 patients, 1,149 of which were treated with PDT, 545 treated with RFA, and 452 treated with stenting only. The study found that the pooled overall survival rate was 11.9 months (95% confidence interval [CI], 10.7–13.1) with PDT, 8.1 months (95% CI, 6.4–9.9) with RFA, and 6.7 months (95% CI, 4.9–8.4) with stenting alone.⁶⁴ In addition, this meta-analysis demonstrated that the pooled survival rate of patients undergoing endoscopic and percutaneous RFA were 12 months (95% CI, 9.8–14.3) and 5 months (95% CI, 3–6.9), respectively.⁶⁴ The pooled 30-day mortality rate among patients undergoing PDT was 3.3% (95% CI, 1.6%–6.7%) compared to 7% (95% CI, 4.1%–11.7%) among those undergoing RFA.⁶⁴

Adverse events

The PDT and RFA studies cited cholangitis, sepsis, liver abscess, pancreatitis, and phototoxicity as the most frequent ad-

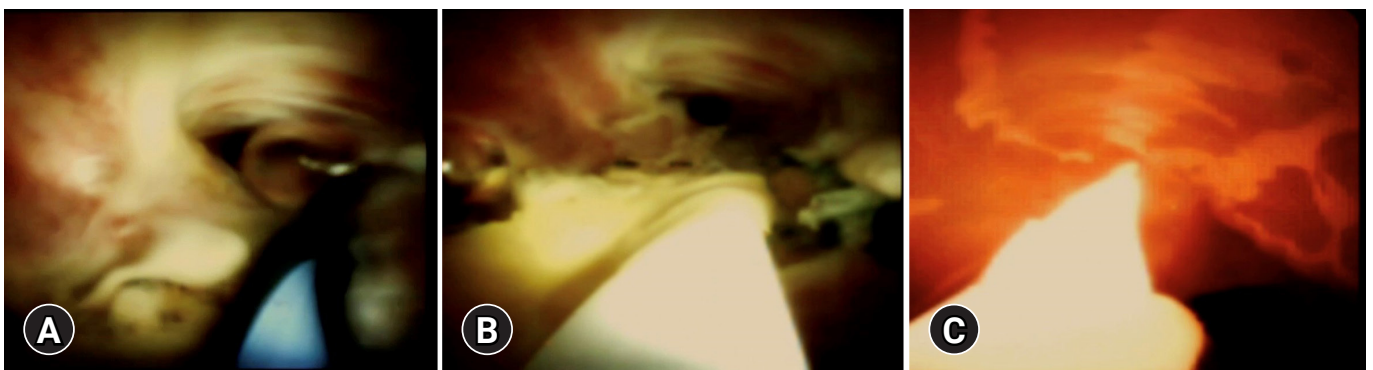


Fig. 2. (A) Cancerous lesion assessed prior to photodynamic therapy. (B) Insertion of the fiber under cholangioscopic vision. (C) Administration of the right light under cholangioscopic control.

Table 1. Studies using PDT for treatment of cholangiocarcinoma

Study	Study design	No. of patients	OS (mo)	Adverse events
Berr et al. (2000) ²⁰	Prospective	23	9.1	Cholangitis (8), phototoxicity (3)
Dumoulin et al. (2003) ²¹	Prospective	24	9.9	Cholangitis (2), phototoxicity (1), peritonitis (1)
Ortner et al. (2003) ¹⁶	RCT ^{a)}	39	16.43	Cholangitis (3), phototoxicity (2)
Wiedmann et al. (2004) ²²	Prospective	23	9.3	Cholangitis (13), phototoxicity (3)
Shim et al. (2005) ²³	Prospective	24	18.6	Phototoxicity (7), sepsis (1), abscess (1)
Zoepf et al. (2005) ²⁴	RCT ^{b)}	32	21	Infection (4)
Witzigmann et al. (2006) ²⁵	Prospective	68	12	Cholangitis (38), phototoxicity (8)
Prasad et al. (2007) ²⁶	Retrospective	25	7.13	Pancreatitis (2), cholangitis (1)
Kahaleh et al. (2008) ¹⁷	Prospective	19	16.2	Cholangitis (7), phototoxicity (3)
Fuks et al. (2009) ²⁷	Prospective	14	13.8	Cholangitis (8), phototoxicity (2)
Quyn et al. (2009) ²⁸	Prospective	23	14.16	Sepsis (5), phototoxicity (4)
Gerhardt et al. (2010) ²⁹	Prospective	8	12.3	Cholangitis (1), abscess (1)
Hoblinger et al. (2011) ³⁰	Retrospective	10	47.6	Cholangitis (2), phototoxicity (1)
Cheon et al. (2012) ³¹	Retrospective	72	9.8	Phototoxicity (10), sepsis (1), abscess (1)
Lee et al. (2012) ³²	Retrospective	18	11.8	Cholangitis (1), phototoxicity (1)
Pereira et al. (2012) ³³	Prospective	36	12	Sepsis (5), phototoxicity (4)
Bahng et al. (2013) ³⁴	Prospective	11	4.68	-
Talreja et al. (2013) ³⁵	Retrospective ^{c)}	A: 25 B: 29	8.57 6.1	Cholangitis (28), abscess (6), phototoxicity (3), other (7) -
Hong et al. (2014) ³⁶	Retrospective ^{d)}	A: 16 B: 58	17.93 11.13	Cholangitis (1) Cholangitis (3), phototoxicity (2), abscess (2)
Park et al. (2014) ³⁷	RCT ^{e)}	A: 21 B: 22	17 8	Phototoxicity (2), abscess (1) Phototoxicity (2), abscess (2)
Strand et al. (2014) ³⁸	Retrospective	32	7.5	Cholangitis, abscess
Hauge et al. (2016) ³⁹	RCT ^{f)}	10	7.9	Cholangitis (5)
Wagner et al. (2015) ⁴⁰	Prospective	29	15.4	Phototoxicity (5), cholangitis (4), abscess (2), cholecystitis (2)
Lee et al. (2016) ⁴¹	Retrospective ^{g)}	A: 24 B: 13	11.6 9.5	- -
Wentrup et al. (2016) ⁴²	Retrospective ^{h)}	A: 33 B: 35	17.33 12.47	Cholangitis (25) Cholangitis (27)
Yang et al. (2016) ⁴³	Prospective	39	13.8	Cholangitis (1)
Dolak et al. (2017) ⁴⁴	Prospective	88	12.4	Cholangitis (21), sepsis (1), abscess (1)
Pereira et al. (2018) ⁴⁵	RCT ⁱ⁾	92	6.2	Sepsis (2), cholangitis (1), pancreatitis (1)
Gonzalez-Carmona et al. (2019) ⁴⁶	Retrospective ^{j)}	A: 36 B: 34	20 15	Cholangitis (20), abscess (5), phototoxicity (4), other (4) Cholangitis (15), phototoxicity (3), other (2)
Shiryaev et al. (2019) ⁴⁷	Case series	33	14	Cholangitis (11)
Wu et al. (2019) ⁴⁸	Retrospective	59	17.6	-

PDT, photodynamic therapy; OS, overall survival; RCT, randomized controlled trial; RT, radiotherapy; PTCS, percutaneous transhepatic cholangioscopy; ERCP, endoscopic retrograde cholangiopancreatography.

^{a)}PDT+stenting vs. stenting alone; ^{b)}PDT vs. endoprosthesis; ^{c)}PDT+chemo/RT (A) vs. PDT alone (B); ^{d)}PDT+chemo (A) vs. PDT alone (B); ^{e)}PDT+ S-1 (A) vs. PDT alone (B); ^{f)}PDT+chemo/stent vs. chemo/stent alone; ^{g)}PTCS-directed PDT (A) vs. ERCP-directed PDT (B); ^{h)}PDT+chemo (A) vs. PDT alone (B); ⁱ⁾PDT+stenting vs. stenting alone; ^{j)}PDT+chemo (A) vs. PDT alone (B).

verse events. Cholangitis was the most common adverse event in both modalities, reported in 21% and 9.3% of patients who received PDT and RFA, respectively. Sepsis, liver abscess, and pancreatitis were also reported in both modalities. In addition,

phototoxicity was reported in 5.6% of patients undergoing PDT. Many of these adverse events may not be intrinsic to the treatment modalities themselves, but may be related to the method of delivery.

Table 2. Studies using RFA for treatment of cholangiocarcinoma

Study	No. of patients	Study design	OS (mo)	Adverse events
Mizandari et al. (2013) ⁴⁹	39	Retrospective	2.98	-
Butros et al. (2014) ⁵⁰	7	Retrospective	38.5	-
Dolak et al. (2014) ⁵¹	58	Retrospective	10.6	Cholangitis (5), hemobilia (3) sepsis (2), empyema (1)
Strand et al. (2014) ³⁸	16	Retrospective	9.6	-
Tal et al. (2014) ⁵²	12	Retrospective	6.4	Hemobilia (2)
Laquiere et al. (2016) ⁵³	12	Case series	12.3	Cholangitis (3), sepsis (1)
Wang et al. (2016) ⁵⁴	12	Retrospective	7.7	Infection (2), pancreatitis (1)
Wang et al. (2016) ⁵⁵	18	Retrospective	6.1	Cholangitis (3)
Wang et al. (2016) ⁵⁶	9	Retrospective	5.3	Cholangitis (4)
Cui et al. (2017) ⁵⁷	50	Retrospective	5	Cholangitis (10), pancreatitis (1)
Wu et al. (2017) ⁵⁸	35	Retrospective	6.97	Hemobilia (3), cholangitis (2)
Xia et al. (2017) ⁵⁹	43	Retrospective	2.68	-
Acu et al. (2018) ⁶⁰	21	Retrospective	2.53	Cholangitis (9), abscess (1)
Yang et al. (2018) ¹³	65	RCT	13.2	Cholangitis (2)
Bokemeyer et al. (2019) ⁶¹	32	Case control	11.4	Cholangitis (6), pancreatitis (2), other (1)
Hu et al. (2019) ⁶²	23	Retrospective	36	Pancreatitis (1)
Lee et al. (2019) ⁶³	30	Prospective	12.7	Pancreatitis (2), cholangitis (1)

RFA, radiofrequency ablation; OS, overall survival; RCT, randomized controlled trial.

CONCLUSIONS

Cholangiocarcinoma is a cancer of the biliary collecting system, with the majority of these tumors being nonresectable at the time of diagnosis. The main objective of palliative treatment for these patients is symptomatic relief through biliary decompression. Biliary stenting combined with ablation techniques such as PDT and RFA are the primary options for palliation.

PDT is a strong modality for palliation, with higher overall survival and lower 30-day mortality rates compared to RFA and/or stenting. The use of PDT requires expertise in the field and a dedicated team. Furthermore, additional effort is needed to prevent photosensitivity and other complications unique to this therapy. In patients who are unable to receive PDT, RFA has been increasingly used as an option for ablation and as an adjunct to biliary stenting.

PDT has some advantages over RFA in the palliative treatment of nonresectable cholangiocarcinoma. It operates through repeated interventions, which allows for additional tumor debulking with each session. Moreover, it is able to treat peripheral and unreachable lesions as it is transmitted through the biliary system and can also be used as downstaging therapy prior to surgery or transplantation. Numerous studies on PDT have demonstrated increased survival rates.

The advantages of RFA include repermeabilization of occluded metal stents and biliary stenoses. RFA also has lower cost

and does not lead to photosensitivity, unlike PDT. However, RFA therapy requires the lesion to be reachable to be ablated, so it cannot be used for peripheral lesions. Recent studies suggest that RFA is less efficacious than PDT in terms of overall survival.

In conclusion, both PDT and RFA seem to have specific advantages and limitations, with PDT being potentially more beneficial. Further randomized controlled trials comparing PDT to RFA using an increased number of patients matched in terms of staging, age, and treatment need to be conducted to confirm this data.

Conflicts of Interest

Michel Kahaleh has received grant support from Boston Scientific, Fujinon, EMCison, W.L. Gore, Apollo Endosurgery, Cook Endoscopy, Merit Medical, and Olympus. He is a consultant for Boston Scientific, ABBvie, Medtronic, and Microtech. Tayyaba Mohammad has no conflicts of interest.

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TM and MK have contributed equally from conceptualization to original draft, review and editing.

ORCID

Tayyaba Mohammad <https://orcid.org/0000-0003-2293-7999>
 Michel Kahaleh <https://orcid.org/0000-0003-0836-6114>

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