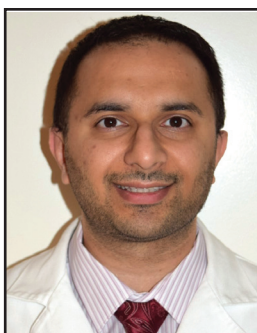


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# Photodynamic Therapy for Perihilar Cholangiocarcinoma



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**Cholangiocarcinoma of the biliary hilum is an uncommon disease but increasing in incidence. Patients affected by this frequently fatal disease often succumb to complications including liver failure and cholangitis secondary to progressive biliary obstruction. The current standard of care in the United States is chemotherapy with gemcitabine and cisplatin that offers a survival benefit just in excess of three months. Endoscopic ablation with photodynamic therapy (PDT) has been used effectively to palliate patients and is considered the standard of care in some European countries. PDT has been demonstrated to resolve jaundice, improve quality of life, and prolong life with favorable outcomes when compared to other treatment options. This has led to other novel applications including using PDT as part of a neoadjuvant protocol to downstage tumors. A multicenter trial is currently being performed to study the role of PDT compared to chemotherapy for perihilar cholangiocarcinoma.**

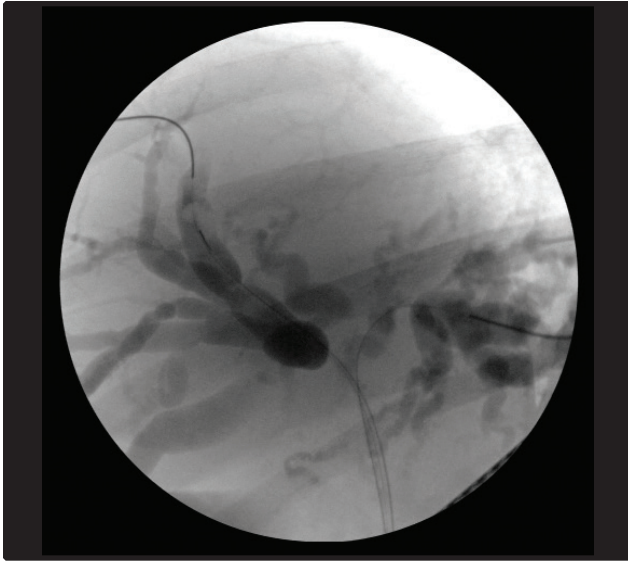
## INTRODUCTION

**C**holangiocarcinoma (CCA) is an uncommon malignancy arising from the biliary epithelium with an estimated annual incidence between 5000 and 8000 cases. The incidence of the disease has been steadily increasing in the U.S. although the factors driving the rise are unknown. CCA is classified according to anatomic location in the biliary tree: intrahepatic, perihilar, or extrahepatic/distal.<sup>1</sup> Perihilar CCA, also known as the Klatskin tumor, is most common and accounts for approximately 70% of

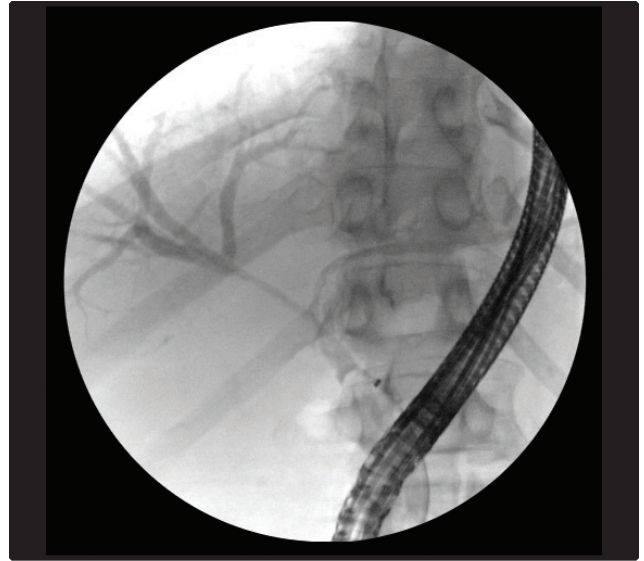
biliary cancers. The Bismuth-Corlette staging system classifies perihilar tumors by the extent and location of proximal ductal infiltration.<sup>2</sup> Unfortunately the majority of patients present with advanced disease that precludes surgical resection either due to local vascular involvement, hepatic extension, or lymphatic metastasis. The median survival is estimated at 6 months for inoperable, untreated CCA.<sup>3</sup> Even when resection is feasible, 5-year survival is achieved in only one-third of individuals.<sup>4,5</sup> Because the goals of care are more often palliative rather than curative, strategies to manage biliary obstruction and its attendant complications of jaundice, cholangitis, and liver failure are the mainstays of therapy. Control of tumor burden is generally a secondary goal of therapy and downstaging of primary tumors is rarely achieved. Traditionally, endoscopic or percutaneous drainage procedures have been performed,

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**Figure 1.** Cholangiogram before photodynamic therapy with hilar stricture and bilateral intrahepatic duct dilation.



**Figure 2.** Cholangiogram of the same patient after three treatments of photodynamic therapy with restoration of biliary patency and resolution of duct dilation

but recently endoscopic tumor ablative technologies are emerging. Photodynamic therapy (PDT) is a form of endoscopic ablative therapy for inoperable CCA that has shown promising results since the first application for CCA in 1991.<sup>6</sup> This discussion will focus on the endoscopic palliative management of perihilar CCA with photodynamic therapy.

### Case Report

A 63 year old male developed dark urine, pruritus, and jaundice in December 2011 at which time he was hospitalized and found to have intrahepatic biliary dilation with a normal extrahepatic bile duct. ERCP identified a stricture of the biliary hilum. Cytology brushings confirmed adenocarcinoma and endoprosthesis were placed. Because jaundice failed to resolve, bilateral percutaneous transhepatic drainage was then performed. Surgical resection was unsuccessful due to tumor extension into both right and left lobes as well as regional lymphatic metastasis. Palliative chemotherapy with gemcitabine and cisplatin was initiated and he was then referred to our center for discussion of endoscopic ablative therapies. During consultation it was clear that he desired to resume his active lifestyle as an avid windsurfer and snowboarder. In February 2012, intraductal PDT was delivered under direct cholangioscopic direction and percutaneous drains were replaced. At the time of the second PDT session, there was significant improvement in the biliary

strictures; plastic endoprosthesis were placed and percutaneous drains were permanently removed. With each treatment as soon as his photosensitivity abated, he resumed windsurfing and enjoying the ocean and beach. Over the next three and a half years, PDT was delivered at 3 month intervals, with additional ERCPs required to manage cholangitis when it occurred. During this time he and his wife sailed to the Bahamas, he picked up the sport of paddle board surfing, and in the winter went snowboarding in Montana. In May 2015, he succumbed to progression of his disease manifesting with liver failure, ascites, coagulopathy, and ultimately sepsis.

### Discussion

Photodynamic therapy for cholangiocarcinoma is an intraductal ablative therapy that requires intravenous administration of a photosensitizing medication that preferentially accumulates in dysplastic and neoplastic cells. Forty eight hours after infusion, ERCP with laser illumination is performed causing local tumor necrosis due to microvasculature disturbance and degradation of membranes via cytotoxic radicals.<sup>7,8,9</sup> Laser fiber delivery can be performed endoscopically via ERCP or percutaneously, although the former is preferred due to the ability to select multiple sites for treatment and avoiding percutaneous drains. The dominant complication from PDT is skin photosensitivity that lasts up to 8 weeks following treatment.<sup>10</sup> The major procedure-related complication is recurrent cholangitis

although bleeding and pancreatitis are additional risks. There have been two prospective, randomized controlled trials comparing biliary stenting alone to PDT in addition to biliary stenting for unresectable CCA, both performed in Europe. Ortner et al. performed a rigorously designed study and found over a 1 year survival advantage (493 days vs 98 days;  $p < 0.0001$ ) for those patients who received PDT compared to stents alone.<sup>11</sup> The study was halted as the data safety monitoring board determined it unethical to withhold PDT from the group randomized to stents without PDT. This study also reported improved biliary drainage and quality of life indices in the PDT group, a benefit seen in other studies as well. Zoepf et al. conducted a randomized controlled trial of 32 patients, and found a median survival of 630 days in the PDT group versus 210 days for biliary stenting alone cohort ( $p = 0.0109$ ).<sup>12</sup> A prospective cohort study of 40 patients compared chemotherapy to PDT. In this cohort, all patients had ERCP with stent exchanges. The PDT group fared better with a median survival of 425 days, compared to 169 days for those receiving chemotherapy.<sup>13</sup> These data are contrasted by the 3.5 months of survival benefit afforded by the current standard of care in the US, which is a combination chemotherapy with gemcitabine and cisplatin.<sup>14</sup> Performing PDT sooner in the clinical course may be more beneficial as Prasad et al. demonstrated that a visible mass on imaging studies or a lag between diagnosis of hilar cholangiocarcinoma and initiating PDT predicted poorer survival after PDT.<sup>15</sup> Surgical literature has shown that PDT and subsequent stenting resulted in a similar survival time compared with resection if there was residual postoperative disease.<sup>16</sup> PDT has also been used as neoadjuvant therapy. In a small study of 7 patients with unresectable CCA, PDT was initially performed and complete resection was able to be performed in all patients. 83% of patients were recurrence free at 1 year with a 5-year survival of 71%.<sup>17</sup> Recently, endoscopic radiofrequency ablation has been developed for tumor ablation, and randomized trials are pending.

## CONCLUSION

This case highlights the application of PDT for unresectable cholangiocarcinoma. Cholangiocarcinoma is typically diagnosed at an advanced stage and is usually inoperable resulting in a poor prognosis. PDT in addition to biliary stenting, has been shown repeatedly in observational and randomized studies to provide

significant survival benefit, improved biliary drainage and improved quality of life. For our patient who survived four years from the time of his diagnosis, his quality of life was enhanced with a durable resolution of jaundice and most importantly, successful removal of percutaneous drains allowing him to resume his active lifestyle. The successes observed with PDT outside the United States have led to the current multicenter trial to assess the benefits of PDT in combination with chemotherapy. When possible, patients should be considered for multidisciplinary cancer strategies with photodynamic therapy playing a central role. ■

## References

1. Bridgewater J, Gall PR, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of Hepatology*, 2014; 60:1268-1289.
2. Bismuth H, Castaing D, Traynor O. Resection or palliation: priority of surgery in the treatment of hilar cancer. *World J Surg* 1988; 12:39-47.
3. Grove MK, Hermann RE, Vogt DP, Broughan TA. Role of radiation after operative palliation in cancer of the proximal bile ducts. *Am J Surg* 1991; 161 (4):454-458.
4. Rea DJ, Muno-Juarez M, Farnell MB, et al. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. *Arch Surg* 2004; 139:514-523.
5. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; 234:507-517.
6. McCaughan JS, Mertens BF, Cho C, Barabash RD, Payton HW. Photodynamic therapy to treat tumors of the extrahepatic biliary ducts. A case report. *Arch Surg* 1991; 126:111-113.
7. Dougherty TJ, Gomer CJ, Henderson BW, Jori G et al. Photodynamic therapy. *J Natl Cancer Inst* 1998; 90:889-905.
8. Zoepf T. Photodynamic therapy of cholangiocarcinoma. *HPB* 2008; 10:161-163.
9. Tomizawa Y, Tian J. Photodynamic Therapy for Unresectable Cholangiocarcinoma. *Dig Dis Sci* 2012; 57:274-283.
10. Baron TH. Photodynamic therapy: standard of care for palliation of cholangiocarcinoma? *Clin Gastroenterol Hepatol* 2008; 6:266-267.
11. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003; 125:1355-63.
12. Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterology* 2005; 100:2426-2430.
13. Quyn AJ, Ziyaie D et al. Photodynamic therapy is associated with an improvement in survival in patients with irresectable hilar cholangiocarcinoma. *HPB* 2009; 11:570-577.
14. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362:1273-1281.
15. Prasad GA, Wang KK, Baron TH et al. Factors associated with increased survival after photodynamic therapy for cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2007; 5:743-748.
16. Witzigmann H, Berr F, Ringel U, et al. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. *Ann Surg* 2006; 244:230-239.
17. Wiedmann M, Caca K, Berr F, et al. Neoadjuvant photodynamic therapy as a new approach to treating hilar cholangiocarcinoma: a phase II pilot study. *Cancer* 2003; 97:2783-2790.