



Case Report

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# Brachytherapy Boost to Tumor Bed Prior to Adjuvant Chemoradiation in Margin Positive Resected Cholangiocarcinoma

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## Abstract

**Importance:** The role of adjuvant therapy in resected cholangiocarcinoma patients is unproven despite poor survival rates even in completely resected patients. Most relapses occur locally and within a relatively short window from time of resection. R1 resection and lymph node positive patients are particularly at high risk for local relapse.

**Observation:** Adjuvant modalities have not been compared head to head against one another in cholangiocarcinoma patients. The recent phase III PRODIGE 12-ACCORD 18 trial assessing adjuvant chemotherapy with gemcitabine and oxaliplatin in this group of patients was a negative study. Adjuvant radiation has been shown in some retrospective series to improve overall survival in R1 resected and lymph node positive patients. Other retrospective studies suggest adjuvant chemoradiation also carries an overall survival benefit in this setting. Interestingly some of these latter studies suggest the negative prognosis of undergoing an R1 resection may be overcome with adjuvant chemoradiation with regards to overall survival. Two R1 resected cholangiocarcinoma patients at our institution achieved exceptional PFS after receiving brachytherapy boosts prior to external beam chemoradiation with infusional 5-fluorouracil. The first patient was progression free for 91 months prior to succumbing to an unrelated illness while the second patient remains progression free at 65 months currently.

**Conclusions and Relevance:** There remains a significant need for randomized phase III studies looking at the role of chemoradiation in resected cholangiocarcinoma patients, particularly in R1 resected patients. Given the remarkable PFS in these two patients, the addition of brachytherapy boosts to external beam based chemo radiation should be evaluated prospectively. Our anecdotal experience suggests there may be improved local control and potential for prolonged PFS in patients who receive brachytherapy boosts.

## Background

Cholangiocarcinoma is a rare tumor with a dismal five-year survival rate of less than 15% [1]. Anatomic location is prognostic in the disease as patients with distal bile duct tumors have improved outcomes compared to those with proximal bile duct and intrahepatic

tumors. Surgical resection offers the only chance of cure; however, less than 40% of patients are amenable to resection. Even with complete resection five-year survival rates range from 19-47% [2]. Most relapses occur locally and there is limited prospective data to guide choice of optimal adjuvant therapy to improve relapse free survival. Retrospective studies suggest improved overall survival in patients who receive adjuvant radiation post resection, particularly in patients with high risk features such as positive margins and lymph nodes [3,4]. The data about the benefit of chemotherapy in the adjuvant setting is less clear. The results from the PRODIGE 12-ACCORD 18 phase III trial of adjuvant gemcitabine plus oxaliplatin vs. surveillance in resected local biliary tract cancer patients demonstrated no significant difference in relapse free survival between the two arms [5]. Adjuvant chemo radiation has also been successfully utilized in published series to suggest improved overall survival in resected cholangiocarcinoma patients [6,7]. The type of radiation utilized in most of these studies is external beam radiotherapy (EBRT). Few studies have looked at the benefit of adding intraluminal brachytherapy (ILBT) to EBRT in the adjuvant setting.

We describe the cases of two patients with margin positive (R1) resected cholangiocarcinoma who underwent ILBT boost prior to concurrent fluorouracil based chemoradiation. To our knowledge, our first patient had the third longest disease free survival of any R1 resected cholangiocarcinoma patient treated with adjuvant chemoradiation documented in existing literature [8].

## Case one

61-year old gentleman was noted to have a 4.3 X 3.5 cm enhancing mass in the central aspect of his left hepatic lobe with adjacent porta hepatitis lymphadenopathy. CA 19-9 was elevated at 583, and he underwent right hepatic lobectomy, common bile duct resection, and hepaticojejunostomy. Pathology revealed a Stage II invasive moderately differentiated cholangiocarcinoma with positive bile duct margin and no involved lymph nodes (pT2N0M0, positive lymphovascular invasion [LVI]). He underwent initial boost using a high dose rate (HDR) Iridium-192 remote control afterloading system. Percutaneous biliary drain tubes were replaced with a larger bore catheter to allow placement of the HDR applicator. The patient was treated 500cGy to 0.5cm depth x 3 fractions for a total dose of 1500 cGy. This was followed by EBRT to 4500 cGy given at 180 cGy per fraction over 5 weeks with concurrent continuous infusion fluorouracil at 225 mg/m<sup>2</sup> daily. His post-therapy course over the next two years was complicated by sequelae of biliary strictures (cholangitis) and portal hypertension (hepatic encephalopathy, ascites, spontaneous bacterial peritonitis). He was successfully managed with paracenteses and medical management and ultimately improved with a prolonged course of suppressive antibiotics. He had several instances where there was concern for local recurrence along his intra-hepatic surgical site and abdominal wall incision based on surveillance imaging however biopsy each time was negative. Mr. F passed away in 2013 from uremia secondary to severe sepsis and remained disease free at the time of his demise, 91 months after his initial treatment.

## Case two

71-year-old gentleman was noted to have irregular tapering of the proximal common bile duct on MRCP. ERCP showed possible smooth narrowing of the distal common bile duct, but full cholangiography

was limited technically and deep access to the biliary tree could not be obtained. He underwent left hepatectomy and resection of his intra-hepatic bile duct on 8/19/2011. Pathology revealed a 4.3 cm stage II poorly differentiated invasive cholangiocarcinoma with invasion into hepatic parenchyma and perihilar adipose tissue with LVI and a positive right hepatic duct margin (pT2bN0M0). Mr. V completed his boost consisting of 1500 cGy (500 cGy X 3) HDR brachytherapy with Ir-192 remote control afterloader. This was followed by EBRT to a dose of 4500 cGy and concurrent continuous fluorouracil at 200 mg/m<sup>2</sup> x 5 days weekly during radiation. He remains 65 months free of disease currently.

## Discussion

Both cases represent R1 resected cholangiocarcinoma patients who have done exceptionally well. They suggest a possible role for brachytherapy boost prior to chemoradiation in this subgroup of patients. The benefit to adding ILBT to adjuvant EBRT is controversial. Higher rates of cholangitis, ileus, biliary leak, portal vein obstruction and upper gastrointestinal ulceration have been seen with the addition of intraluminal brachytherapy boosts. The use of EBRT and ILBT has been better explored in the unresectable setting where ILBT improves biliary tract patency in patients with obstructive jaundice and increases survival outcomes. Brachytherapy offers dose escalation opportunities at the site of margin positivity while minimizing toxicity to adjacent healthy tissue. Adjacent tissue toxicity is a major concern because EBRT doses beyond 55 Gy to the peri-hepatic region increase rates of severe bowel toxicity such as obstruction, perforation, and fistula formation [9].

Several retrospective studies indicate adjuvant chemo radiation may play a particularly beneficial role in margin positive cholangiocarcinoma patients. A phase II intergroup study SWOG S0809 assessed 79 resected extrahepatic cholangiocarcinoma patients who subsequently received gemcitabine plus capecitabine chemotherapy followed by capecitabine based chemo radiation. Only 69 patients received radiation. Median overall survival was 35 months and not statistically different between patients with R0 versus R1 resections [10]. Kim et al assessed 91 patients with extra hepatic cholangiocarcinoma who underwent resection followed by EBRT. Seventy-one patients received EBRT to 4000 cGy with concurrent bolus fluorouracil and 61 also received maintenance chemotherapy. The remaining 13 patients received radiation alone for a total of 4000-4500 cGy. Like the SWOG study, there were no differences in five-year survival rates between patients who underwent R0 (35%) vs.

R1 (35%) resections [7]. These studies, along with others, suggest the negative prognosis of having an R1 resection may be overcome with the use of adjuvant chemoradiation. The remarkable disease free survival in the two patients at our institution treated with intraluminal brachytherapy followed by chemoradiation suggest that prospective trials exploring this modality are warranted.

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