

# Is there any role of radiotherapy in intrahepatic cholangiocarcinomas?

## Abstract

Cholangiocarcinoma or bile duct cancer is a rare type of cancer which is prevalent in developed countries and its prevalence is increasing in developing countries. Cholangiocarcinoma is included in the list of lethal cancer. While surgery is the cornerstone of its management, the benefit of adding neoadjuvant or adjuvant treatment in the form of chemotherapy and/or radiotherapy have not been shown to significantly improving the prognosis of the patients. The role of radiotherapy in the management of intrahepatic cholangiocarcinoma remains debated. These cancers usually present at advanced stages and are associated with low rates of local control and overall survival. The indications and implications of radiotherapy in these carcinomas are still not very clear. However, planning target volume and biologically effective dose of radiation have a prognostic value and initial treatment response is helpful in predicting survival time. In this review, we tried to explore various ways and options where radiotherapy can provide some better results in treating resectable and unresectable IHCC.

**Keywords:** intrahepatic, cholangiocarcinoma, radiotherapy, adjuvant, neoadjuvant, palliative, proton

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**Abbreviations:** IHCC, intrahepatic cholangiocarcinoma; EHCC, extrahepatic cholangiocarcinoma; CT, computed tomography; RFS, recurrence free survival

## Introduction

Cholangiocarcinoma is a rare type of hepatobiliary cancer with 5year survival rate of <5% and associated with high mortality rate.<sup>1</sup> It is classified into intrahepatic cholangiocarcinoma (IHCC) and extrahepatic cholangiocarcinoma (EHCC). Hilar cholangiocarcinoma is most common (60%) with distal (30%) and IHCC (10%) being less common.<sup>2</sup> Due to the rarity of incidence of IHCC, there are no established treatment guidelines. Surgical resection remains the main treatment modality in the resectable cases. Role of radiotherapy in neoadjuvant, adjuvant and palliative settings remains uncertain. The addition of radiotherapy to chemotherapy is associated with improved survival in unresectable IHCC.<sup>3</sup> With improvements in systemic therapy and radiation technique including the use of intensity-modulated and stereotactic body radiotherapy, radiotherapy may play an increasingly important role in improving survival.

## Discussion

IHCC is a heterogeneous cancer type and complete surgical resection is the most effective treatment. Majority of the patients undergo postoperative adjuvant treatment in the form of chemotherapy or radiotherapy or combination of both the modalities. Although these adjuvant treatments have demonstrated certain benefit in survival rates and local control rates, the standard guidelines vary, especially regarding radiotherapy.<sup>3</sup> At present, there is no consensus regarding the indications of radiotherapy, target contouring, dose and fractionation schedule of the radiotherapy treatment. Radiological modalities, including magnetic resonance cholangiopancreatography, dynamic computed tomography (CT), and positron emission tomography/CT have become useful for target contouring. Moreover, liver motion is a critical factor that requires consideration during contouring.

Fluoroscopy or 4D-CT is useful taking into consideration the liver motion and thus is helpful in the precise definition of the internal target volume.<sup>4-6</sup> Tao et al have recently demonstrated that radiation dose impacts survival in patients with unresectable IHCC.<sup>7</sup> Higher doses of radiation could have resulted in survival benefit. Also, in metastatic cases, radiotherapy did not confer survival benefit as these patients were more likely treated with palliative courses of radiotherapy.<sup>7</sup>

## Adjuvant therapy

The benefit of adjuvant radiotherapy in patients with resectable IHCC remains controversial though certain factors might affect the treatment outcomes and survival of patients.<sup>1</sup> Tumor histopathology, lymph node metastasis, positive margins, tumor stage are also prognostic factors influencing the outcome of the patient.<sup>8</sup> Horgan et al.,<sup>9</sup> in a meta-analysis suggested that 5-FU based chemoradiation or chemotherapy is better to radiotherapy alone as adjuvant treatment especially in patients who underwent R1 resection or had lymph node positive disease.<sup>9</sup> After R0 resection without any other risk factor, observation alone is appropriate.<sup>9</sup> In another study by Shinohara et al, median OS significantly increases from 6months to 11months when adjuvant radiation therapy is added to surgery.<sup>10</sup>

## Neoadjuvant therapy

The role of neoadjuvant chemoradiotherapy is also controversial, though it might improve OS and recurrence free survival (RFS). Chemoradiation therapy regimen consisted of 3 cycles of full-dose gemcitabine (1000mg/m<sup>2</sup> at days 1, 8, and 15, every 4weeks) with 50-60Gy radiation. This was followed by surgery for IHCC or EHCC. In this study by Kobayashi et al.,<sup>11</sup> the three-year RFS rates in patients treated with and without neoadjuvant therapy were 78% and 58%, respectively (p=0.0263).<sup>11</sup>

## Unresectable IHCC

The prognosis of unresectable patients is poor with a median

survival of 3.9 months with supportive care alone.<sup>12</sup> Chemotherapy is an accepted standard of care for inoperable patients and the role of radiation is less well defined. Radiotherapy may improve bile duct patency and reduce pain in inoperable patients.<sup>2</sup> Radiotherapy in a palliative setting has increased the patients' survival by 4 months in unresectable IHCC. In another study by Chen et al, one- and two-year survival rates for EBRT versus non-EBRT group were 38.5% versus 16.4%, and 9.6% versus 4.9%, respectively.<sup>13</sup> While there has been no randomized evidence for radiotherapy, a phase 2 study showed that radiation with concurrent hepatic artery oxuridine infusion was associated with improved survival over historical controls.<sup>14</sup>

## SBRT for IHCC

Mahadevan et al.<sup>15</sup> treated unresectable IHCC with SBRT and have given radiotherapy dose of 30Gy in 3 fractions with some patients receiving chemotherapy also. After a median follow-up of 38 months, 1-year local control and OS was 88% and 58%, respectively.<sup>15</sup> Jung et al.<sup>16</sup> treated unresectable and recurrent cases of IHCC and EHCC with total doses of SBRT being given as 45Gy in 3 fractions.<sup>16</sup> Some patients have received EBRT prior to SBRT (median 40Gy in 20 fractions). One-year local control and median survival was 85% and 10 months respectively.<sup>16</sup>

## Moderately hypofractionated proton therapy

High dose hypofractionated proton therapy demonstrated better local control rate and overall survival in patients of IHCC. Proton therapy has also demonstrated better local control in IHCC and is especially useful in patients with underlying liver dysfunction. The CONSORT study has delivered 58GyE proton therapy in 15 fractions to unresectable cases of IHCC and hepatocellular carcinomas.<sup>17</sup> Median follow up was of 19.5 months and 2 years local control and overall survival for IHCC was 94.1% and 46.5% respectively.<sup>17</sup>

## Conclusion

To conclude, radiation in combination with chemotherapy results in prolonged overall survival in comparison to chemotherapy alone in patients with unresectable and/or advanced IHCC. SBRT and proton beam RT also have better local control and overall survival in patients ineligible for surgical resection. So, we strongly recommend radiation in the management of intrahepatic cholangiocarcinoma.

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## Conflict of interest

Author declares that there is no conflict of interest.

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