

## Role of Chemoradiation in Intrahepatic Cholangiocarcinoma

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Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer following hepatocellular cancer. Although it is uncommon, worldwide incidence showed a significant rise over the last several decades. Comparing with hepatocellular cancer, ICC tends to spread to lymph nodes early, and is rarely limited to the regional lymph nodes, with a frequent postoperative recurrence. Curative resection is the most effective treatment and the only therapy associated with long-term survival. Macroscopic tumor type of mass forming and periductal infiltration, positive resection margin (RM), lymph node metastases, and vascular invasion are poor prognostic factors. Therefore, post-operative therapeutic strategies are required for these high risk patients. Regarding radiotherapy, a small retrospective series showed an increased 5-year survival in patients with positive RM receiving postoperative RT (34% vs. 13.5%). However, these results have not been supported by other studies and there is a lack of prospective randomized trials. Chemotherapy has so far not been shown to substantially improve survival in patients with resected or unresected cholangiocarcinoma. Most studies have used 5-fluorouracil (5-FU) alone or in combination with older agents such as methotrexate and cisplatin. Further those studies are small, retrospective, and single-centered, resulting in poor quality data. Therefore, there is currently no role for adjuvant radiotherapy or chemotherapy outside a trial setting. Radiosensitizing effect of 5-FU suggests that combination of radiation and chemotherapy would be more effective. This approach has been used in some early studies with encouraging results, but there are no prospective trials of this combined treatment and a retrospective case study showed no benefit with adjuvant chemoradiation therapy.

However, progress has been made recently in the area of chemotherapy and in understanding molecular mechanism of carcinogenesis. Gemcitabine and platinum chemotherapy provided a better survival compared to fluoropyrimidine-based chemotherapy. It is also reported that angiogenesis and

EGFR signaling are activated in subset of cholangiocarcinoma and addition of angiogenesis or EGFR inhibitor to chemotherapy showed a higher response rate in advanced cholangiocarcinoma. Therefore, integration of newer anticancer agents into chemoradiation needs to be investigated in near future.