Commentary (Small): Radiation Therapy in the Treatment of Cholangiocarcinoma

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The prognosis of patients with biliary cancers is poor. Although surgery is potentially curative in selected patients, local recurrence is a common pattern of failure. Adjuvant or neoadjuvant radiation therapy improves local control and possibly survival. In locally advanced patients, radiation therapy provides palliation and may prolong survival. Concurrently administered chemotherapy may further enhance these results. Newer radiation therapy techniques, including intraluminal transcatheter brachytherapy, intraoperative radiation therapy, intensity-modulated radiation therapy, and three- and four-dimensional treatment planning, permit radiation dose escalation without significant increases in normal tissue toxicity, thereby increasing the effective radiation dose. Preliminary results of studies employing hepatic transplantation with radiation therapy are encouraging. Although these new approaches hold promise, the prognosis in patients with biliary cancers remains poor, and the integration of novel therapeutic strategies is indicated.

Drs. Czito, Anscher, and Willet do an excellent job of reviewing the available literature regarding the use of radiotherapy in the treatment of cholangiocarcinoma. Cholangiocarcinomas and gallbladder cancers are uncommon malignancies, but the incidence in the United States appears to be rising with 8,570 estimated cases in 2006.[1] Surgical resection remains the cornerstone of curative therapy. Even with apparent complete resection, however, the ultimate outcome of patients remains unfavorable, with locoregional recurrences and distant metastasis common after surgery alone. Treatment of nonsurgical candidates remains particularly challenging, with limited chance for sustained tumor control.

Resectable Disease

The use of radiotherapy in the treatment of resected cholangiocarcinoma must be based on “first principles” of oncology and available nonrandomized outcome data. Surgery alone has been associated with significant rates of locoregional recurrence. In a series reported by Park et al, locoregional recurrence was noted in 13 of 14 proximal extrahepatic bile duct cancers treated with resection.[2] It seems reasonable that the addition of radiotherapy can reduce the chance of recurrence. The impact of local recurrence on ultimate survival will be increasingly important if the rate of distant metastasis can be reduced with improved systemic therapy. The authors do a nice job of summarizing the available literature regarding the adjuvant use of radiotherapy in resected cholangiocarcinoma. Radiotherapy should be considered in resected patients, given the high rates of locoregional recurrence, the overall poor prognosis, and data suggestive of improved outcome with adjuvant therapy. The majority of adjuvantly treated patients have received postoperative therapy, but there are a number of theoretical advantages to the use of preoperative therapy. A series reported by McMasters et al noted a 30% complete pathologic response rate in cholangiocarcinoma patients treated with preoperative combined-modality therapy.[3] This response rate is similar to that seen in neoadjuvantly treated rectal cancer patients and suggests a possible role for preoperative therapy. Given the overall poor prognosis of cholangiocarcinoma it would seem that this is an approach in need of investigation. In hopes of improving the margin-negative resection rate and ultimate outcome, we have utilized preoperative infusional fluorouracil (5-FU) and localized radiotherapy in patients who are thought to be "borderline" resectable.

Unresectable Disease

Radiotherapy is frequently utilized in the treatment of patients with locally advanced/unresectable disease. Local progression and associated complications of biliary obstruction often lead to fatal complications. It would be hoped, therefore, that local therapy could extend survival by preventing
or delaying biliary obstruction. Traditional radiotherapy in doses of 45 to 50.4 Gy, even when combined with chemotherapy, is unlikely to provide local control of disease. The authors’ review attempts to intensify radiotherapy, primarily with intraluminal brachytherapy. As summarized in Table 3 of the paper by Dr. Czito et al, boost with either intraoperative radiotherapy or intraluminal brachytherapy appears to be associated with improved outcome compared to external-beam radiotherapy alone. Although the data suggest that higher radiotherapy doses are associated with improved outcome, selection bias favoring boost therapy for better-prognosis patients likely influences this conclusion. Despite the nonrandomized nature of the data, I favor intraluminal boost therapy whenever possible.

Transplant

The only curative therapy for cholangiocarcinoma is complete surgical resection. In patients with significant intrahepatic disease or severe underlying liver disease, resection without liver transplantation is not feasible. In theses patients, resection associated with liver transplantation may allow extended disease-free survival and possibly cure. At Northwestern, we have delivered preoperative hyperfractionated radiotherapy with concurrent chemotherapy in patients with extrahepatic cholangiocarcinoma and primary sclerosing cholangitis. The radiotherapy consists of 1.5 Gy per fraction twice a day to a total dose of 45 Gy over 3 weeks combined with 5-FU as a continuous infusion. Three to six weeks later, patients with living donors undergo transplantation. If a donor is not available, we consider a brachytherapy boost and await a cadaveric liver. At last report, five patients had undergone this therapy. Of the five explanted livers, three had complete pathologic responses and two had partial responses, with no recurrences at the time of last report.[4] The pathologic response rate and initial tumor control is encouraging.

Future Directions

The authors review improved radiation techniques, including intensity-modulated radiation therapy (IMRT), four-dimensional treatment planning, and therapy with charged particles. In addition to advancement of radiotherapy techniques, improved outcome may be seen with novel systemic therapeutic agents combined with radiotherapy. As discussed by Dr. Czito and colleagues, 5-FU has been the most commonly used radiosensitizing agent in the treatment of cholangiocarcinoma. A number of newer cytotoxic agents have been combined with radiotherapy in other malignancies, showing evidence of improved outcomes, and may be candidates for combined therapy in cholangiocarcinoma. These agents include oxaliplatin (Eloxatin), taxanes, and gemcitabine (Gemzar). Molecularly targeted agents may also be candidates for novel therapeutics, including the vascular endothelial growth factor (VEGF) antibody bevacizumab (Avastin), which has been successfully combined with capecitabine (Xeloda) and radiotherapy in locally advanced pancreatic cancer.[5]

Conclusions

Drs. Czito, Anscher, and Willet do an excellent job of reviewing the literature regarding the role of radiotherapy in cholangiocarcinoma. Overall, these malignancies carry a poor prognosis, with surgery the mainstay of curative therapy. Radiotherapy seems to play a critical role in both resectable and unresectable groups of patients. As novel therapeutics and improved radiotherapy techniques continue to advance therapy, it is hoped that outcomes will improve.

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