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Will There Be a Clinically Significant Role for Protons in Patients With Gastrointestinal Malignancies?

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Gastrointestinal malignancies inherently arise amidst visceral organs that are very radiation sensitive. While radiation therapy is an integral part of cancer treatment, its use has historically been limited by normal tissue toxicity. Proton therapy is a form of external-beam radiation associated with several dosimetric advantages as compared to photon therapy. Proton radiation may allow for the delivery of tumoricidal doses while minimizing side effects by decreasing the dose to adjacent organs at risk. We discuss the rationale for and challenges of using protons in the treatment of gastrointestinal cancers. We describe the available data and ongoing trials using proton radiation to treat these tumors. Finally, we discuss the unique challenges of using protons to treat gastrointestinal malignancies.
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Introduction

Gastrointestinal malignancies are a significant cause of cancer mortality, with an estimated 157,700 deaths in the United States in 2017.[1] An essential role exists for treatments that can improve the chances of cure while minimizing morbidity.

Proton radiation therapy (PRT) has clear dosimetric advantages over photon radiotherapy. While photons are absorbed exponentially, protons have a finite range dependent on the initial proton energy and do not deposit dose beyond the tumor target, resulting in great conformality. In addition to the promise of dose escalation, treatment with PRT may decrease normal tissue toxicity, minimizing treatment breaks and improving long-term outcomes. Although generally sparse, the literature supporting the use of protons in hepatobiliary cancers is more robust as compared to that of other gastrointestinal malignancies.

Here, we discuss the rationale for and challenges of using PRT in the treatment of gastrointestinal cancers. We describe the available data and ongoing trials using PRT for the treatment of these tumors. Finally, we discuss the particular challenges of using PRT to treat gastrointestinal malignancies.

Hepatobiliary Cancers

Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) are aggressive gastrointestinal malignancies with poor outcomes. HCC has a median survival of about 20 months.[2] The majority of patients are diagnosed with advanced disease, frequently in the setting of underlying cirrhosis.[3] CCs are rare malignancies, comprising only 2% of all cancers in the United States.[4] They are characterized by early lymph node and distant metastatic spread.

Surgery, including liver transplantation, traditionally provided the only possibility of cure for primary hepatobiliary cancers. Unfortunately, only a minority of patients are candidates for resection for medical or anatomical reasons. The treatment of unresectable hepatocellular and CC has been palliative, with therapies including transarterial chemoembolization (TACE), radiofrequency ablation, or systemic therapy. In the past, external-beam radiotherapy was an ineffective treatment of hepatic tumors because the radiation doses required to kill these tumors surpassed the normal liver's tolerance to radiation.[5] However, improved technical capabilities have allowed for potentially ablative doses of radiation to be safely delivered to the tumor while sparing the adjacent liver, renewing enthusiasm for radiation therapy.

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However, there are instances in which dose escalation using even sophisticated photon techniques is not possible owing to size or location of the lesion. Patients with portal venous thrombosis, for instance, often require large volumes of the liver to be irradiated. Further adding to this challenge is that hepatobiliary tumors often arise within injured livers. Preserving liver function is therefore of utmost importance. With the use of PRT, ablative doses can be delivered to more of these challenging patients.

Several groups have studied the utility of PRT for primary liver cancers. One of the first prospective trials of protons for HCC included 30 patients with solitary tumors and either Child-Pugh class A or B cirrhosis.[6] Patients were treated with 76 CGE in 20 fractions and the median tumor size was 4.5 cm (range: 2.5-8.2 cm). Twelve patients had vascular invasion and the median follow-up was 31 months. Only 1 patient experienced a local recurrence. The 2-year overall survival was 66% and there was minimal acute toxicity.

In another prospective study by Fukumitsu et al,[7] 51 patients with HCC ≤ 10 cm in size and greater than 2 cm away from the porta hepatis or the gastrointestinal tract received PRT to 66 CGE in 10 fractions. The median tumor size was 2.8 cm (range: 0.8-9.3 cm) and patients had either Child-Pugh class A or B cirrhosis. Radiation was delivered using a rotation gantry under respiratory gating through 1-3 ports with coplanar angles. The 5-year local control and survival rates were 87.8% and 38.7, respectively. For patients with Child-Pugh class A cirrhosis, 5-year survival was 42.1%. Posttreatment serum α-fetoprotein values were significantly reduced as compared to pretreatment values ($P < 0.0001$). Patients experienced only minor toxicity, with no grade 2 or higher acute reactions. Furthermore, 3 patients developed ≥grade 2 late sequelae.

In 2011, Bush et al,[8] published a phase II trial of 76 patients with HCC and cirrhosis. Fifty-four percent (54%) of the patients were outside of Milan criteria, 24% had Child-Pugh class C cirrhosis, and 16% had a model of end-stage liver disease score >15. Almost half of the patients had tumors greater than 5 cm in size. Patients underwent PRT to 63 CGE in 15 fractions. Median progression-free survival was 36 months, with a 3-year progression-free survival rate of 60% for patients within the Milan criteria. The median time to failure was 18 months and the local control rate was 80%. Eighteen (18) patients underwent liver transplantation, and of these, 6 had pathologic complete response and 7 had microscopic residual disease. Acute toxicity was minimal.

The same group recently reported on a randomized trial comparing TACE with PRT delivered in 70.2 CGE over 15 fx.[9] Of 69 patients meeting either Milan or San Francisco transplant criteria, 36 were randomized to TACE and 33 to PRT. Total days of hospitalization within 30 days of the procedures was 166 vs 24, in favor of protons ($P < 0.001$). Although not statistically significant, the pathologic complete response rate of 25% compared to 10% was in favor of proton therapy. The median survival (30 months) and the 2-year survival rates (59%) did not differ between the groups. However, there was a trend toward improved 2-year local control rates favoring PRT (88% vs 45%; $P = 0.06$).

Makita et al,[10] published a retrospective study detailing the clinical outcomes and toxicity of PRT in 28 patients with advanced CC. The study included patients with intrahepatic or peripheral CC ($n = 6$), hilar CC or Klatskin tumor ($n = 6$), distal extrahepatic CC ($n = 3$), gallbladder cancer ($n = 3$), and local or lymph node recurrences ($n = 10$). The median follow-up was 12 months (range: 3-29 months), the median tumor size was 5.2 cm (range: 2.0-17.5 cm), and the median radiation dose was 68.2 CGE (range: 50.6-80 CGE) in 2.0-3.2 CGE per fraction. Overall survival, progression-free survival, and local control rates at 1 year were 49.0, 29.5, and 67.7%, respectively. At 1 year, local control was better in those patients who were treated with a biologically equivalent dose (BED10) higher than 70 CGE as compared to those who received less than 70 CGE (83.1 vs 22.2%). Tumor size and performance status were associated with survival. Eleven (11) patients experienced cholangitis and 7 patients had late grade 2 or higher gastrointestinal toxicities.

In 2014, Hong et al[11] at the Massachusetts General Hospital published feasibility study of respiratory-gated PRT for patients with HCC ($n = 11$), intrahepatic CC ($n = 3$), and hepatic metastases ($n = 1$). Fifteen (15) patients with Childs Pugh class A or B cirrhosis and 1-3 lesions ≤6 cm in size were treated with a dose of 45-75 CGE in 15 fractions. Of the 15 patients enrolled, 10 had a single lesion, 3 had 2 lesions, and 2 had 3 lesions. Radiation dose was based on the amount of radiation to the uninvolved liver, as well as other normal tissue constraints. The 3-year progression-free survival and overall survival rates were 27%, and 33%, respectively. One patient developed a marginal recurrence, 3 had hepatic recurrences in other parts of the liver, and 2 had extrahepatic recurrences. Two (2) patients (both Child-Pugh class B) had grade 3 hyperbilirubinemia, and 1 patient had a grade 3 gastrointestinal bleed treated with conservative management. One patient with a congenital single ventricle and long-standing portal hypertension died after a stomach perforation adjacent to his treated liver lesion. Another patient developed hepatic encephalopathy.

More recently, Hong et al,[12] published a multi-institutional phase II trial of high-dose hypofractionated proton radiotherapy in patients with localized, unresectable HCC and intrahepatic CC. Eighty-three (83) patients with Childs Pugh class A or B, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, no extrahepatic disease, and no prior radiation were evaluable. Patients underwent PRT with 67.5 CGE delivered in 15 fractions. The median radiation dose was 58.0 CGE, the median tumor size was 5 cm (range: 1.9-12 cm), and the median follow-up was 19.5 months among survivors. The 2-year local control rates were above 94% for patients with HCC and intrahepatic CCs. The 2-year overall survival rates were 63.2% for patients with HCC and 46.5% for patients with intrahepatic CC. There were no grade 4 or higher toxicities, suggesting that the use of high-dose hypofractionated PRT is safe.

The data supporting the use of PRT in hepatobiliary malignancies is more robust as compared to tumors in other parts of the gastrointestinal tract. Additional studies will be needed to evaluate the utility of radiation as compared to traditional nonradiation treatment modalities such as