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Gallbladder toxicity and high-dose ablative-intent radiation for liver tumors: Should we constrain the dose?

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Abstract

Purpose: Little is known about the risk of gallbladder toxicity from hypofractionated (HFXRT) and stereotactic body radiation therapy (SBRT). We report on gallbladder toxicity and attribution to treatment in a prospective series of patients with primary and metastatic liver tumors receiving ablative-intent HFXRT and SBRT with protons.

Methods and materials: We evaluated 93 patients with intact gallbladders enrolled in either of 2 trials investigating proton HFXRT and SBRT for primary and metastatic liver tumors from 2009 to 2014. Patients received 45 to 67.5 GyE in 15 fractions for primary liver tumors (n = 45) and 30 to 50 GyE in 5 fractions for metastatic tumors (n = 48). No gallbladder dose constraints were used at treatment, and gallbladder volumes and dose-volume histograms were created retrospectively. Attributable toxicity was defined as cholecystitis or perforation without preexisting gallbladder disease. Baseline factors were evaluated using Fisher exact test and the nonparametric K-sample test.

Results: At baseline, 25 patients had preexisting cholelithiasis and 15 underwent biliary stenting before or after RT. Median follow-up after treatment was 11.8 months (range, 0.1-59.2 months). Despite maximum gallbladder doses >70 GyE in 41%, >80 GyE in 31%, and >90 GyE in 13% (equieffective dose at 2 Gy [EQD2], $\alpha/\beta = 3$), there were no attributable cases of gallbladder toxicity. Two patients

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Data presented here represent a secondary analysis from 2 prospective studies: NCT00976898 (Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2016;34:460-468) and NCT01239381 (In press: Hong TS, Wo JY, Borger DR, et al. A phase II study of proton-based stereotactic body radiation therapy for liver metastases. INCI. Accepted February 8, 2017).

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developed grade 3 and 4 cholecystitis 16 and 2 months after treatment, respectively, and both had a strong history of preexisting cholelithiasis and biliary stenting. These patients received relatively low gallbladder doses with mean doses of 0.02 GyE and 5.1 GyE (EQD2, $\alpha/\beta = 3$), well below the 17.1 GyE mean for the remaining cohort (range, 0-81.1 GyE, EQD2).

Conclusions: We identified no relationship between gallbladder dose and toxicity and did not reach the maximum tolerated gallbladder dose in this cohort treated with high-dose radiation. We recommend not constraining dose to the gross tumor volume to protect the gallbladder during ablative HFXRT and SBRT.

Introduction

The gallbladder is a relatively inert, musculomembranous sac situated on the undersurface of the liver, which variably interfaces with liver segments 1, 4, 5, and 6.[1] Many liver tumors occur adjacent to the gallbladder and its fossa, potentially placing this organ in direct contact with liver-directed local therapies.

Liver-directed radiation therapy (RT), including high-dose hypofractionated RT (HFXRT) and stereotactic body RT (SBRT), is an emerging treatment for both primary and metastatic liver tumors.[2] These treatments are capable of delivering ablative tumoricidal doses but are limited by toxicity to surrounding organs, each with a distinct tolerance to ionizing radiation.[3] Although fractionated RT and intraluminal brachytherapy of the gallbladder appear to be safe and well-tolerated,[4-6] little is known about the risk of HFXRT and SBRT to the gallbladder and there are no known dose constraints to this organ in available guidelines.[7,8] In the absence of such knowledge, efforts to protect the gallbladder may compromise dose and coverage of treated tumors.

Since 2009, we have not used gallbladder dose constraints at our institution and here report on gallbladder toxicity and attribution to treatment in a prospective series of patients with primary and metastatic liver tumors receiving ablative-intent HFXRT and SBRT with protons.

Methods and materials

Patient population

We performed a secondary analysis for gallbladder toxicity among patients enrolled in either of 2 prospective trials investigating HFXRT and SBRT with protons, respectively, for primary and metastatic liver tumors at our institution between July 2009 and August 2014. This study was approved by the institutional review board (Protocols NCT00976898[9] and NCT01239381). All patients were >18 years of age and had Eastern Cooperative Oncology Group performance status 0-1, expected survival of >3 months, and 1 to 3 primary liver tumors or 1 to 4 metastatic tumors. Patients with a history of cholecystectomy were excluded from this secondary analysis.

Treatment

Patients were simulated and treated in the supine position using a stereotactic BodyFIX 14 system (Elekta, Stockholm, Sweden, http://www.elekta.com) for immobilization with daily cone-beam computed tomography (CT) image guidance and intrahepatic fiducial marker placement before RT. Target volumes were designed using intravenous contrast-enhanced 4-dimensional CT to account for respiratory motion, as previously described.[10-12] When available, baseline magnetic resonance imaging and positron emission tomography-CT fusion with deformable registration were used to assist with tumor delineation.

All patients received treatment with hypofractionated proton 3-dimensional conformal RT in 15 fractions over 3 weeks for primary liver tumors or in 5 fractions over 2 weeks for metastatic tumors. Target dose and fractionation schema were determined per protocol based on size of tumor, volume of unirradiated liver, and distance from tumor to critical structures and the portal hilum (Table 1). Specifically, primary liver tumors received between 67.5 GyE for peripheral tumors and 45 GyE for central tumors, dosed to maintain a mean liver dose <24 GyE and a liver equivalent uniform dose (EUD) <20 GyE.[9] EUD was defined as the homogeneous dose expected to result in the same degree of cell death as the actual inhomogeneous absorbed dose distribution: $EUD = \left(\sum_i v_i D_i^a\right)^{1/a}$.[13,14] Metastatic tumors received 50 GyE when effective liver volume (Veff) was <0.22, 40 GyE when Veff was between 0.22 and 0.51, and 30 GyE when Veff was >0.51. Veff was used as a measure of volume of normal liver irradiated, as previously described.[15-17]

Follow-up and toxicity endpoints

Patients were followed in clinic every 3 months for 2 years and every 6 months for an additional 3 years until protocol withdrawal, death, or disease progression. Toxicity was assessed prospectively in accordance with the Common Terminology Criteria for Adverse Events 3.0 with additional chart review as indicated.[18] Attributable gallbladder toxicity was defined as any episode of cholecystitis or gallbladder perforation without evidence of preexisting cholelithiasis or gallbladder disease. Nonattributable gallbladder toxicity was defined as any episode cholecystitis or gallbladder