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Functional image-guided stereotactic body radiation therapy planning for patients with hepatocellular carcinoma

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ABSTRACT

The aim of the current planning study is to evaluate the ability of gadoxetate disodium-enhanced magnetic resonance imaging (EOB-MRI)–guided stereotactic body radiation therapy (SBRT) planning by using intensity-modulated radiation therapy (IMRT) techniques in sparing the functional liver tissues during SBRT for hepatocellular carcinoma. In this study, 20 patients with hepatocellular carcinoma were enrolled. Functional liver tissues were defined according to quantitative liver-spleen contrast ratios ≥ 1.5 on a hepatobiliary phase scan. Functional images were fused with the planning computed tomography (CT) images; the following 2 SBRT plans were designed using a "step-and-shoot" static IMRT technique for each patient: (1) an anatomical SBRT plan optimization based on the total liver; and (2) a functional SBRT plan based on the functional liver. The total prescribed dose was 48 gray (Gy) in 4 fractions. Dosimetric parameters, including dose to 95% of the planning target volume (PTV $D_{95\%}$), percentages of total and functional liver volumes, which received doses from 5 to 30 Gy (V5 to V30 and fV5 to fV30), and mean doses to total and functional liver (MLD and fMLD, respectively) of the 2 plans were compared. Compared with anatomical plans, functional image-guided SBRT plans reduced MLD (mean: plan A, 5.5 Gy; and plan F, 5.1 Gy; $p < 0.0001$) and fMLD (mean: plan A, 5.4 Gy; and plan F, 4.9 Gy; $p < 0.0001$), as well as V5 to V30 and fV5 to fV30. No differences were noted in PTV coverage and nonhepatic organs at risk (OARs) doses. In conclusion, EOB-MRI–guided SBRT planning using the IMRT technique may preserve functional liver tissues in patients with hepatocellular carcinoma (HCC).

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death in the world.[1] Curative therapy for early-stage HCC involves surgeries such as resection or transplantation.[2,3] However, only 10% to 30% of patients with HCC are eligible for surgery.[4] Accordingly, for patients with HCC with liver dysfunction, underlying cirrhosis, or multifocal tumors, locoregional therapies such as radiofrequency ablation or transarterial chemoembolization are recommended.[3] Although radiation therapy has not been accepted as a therapeutic option for HCC according to the Barcelona Clinic Liver Cancer staging system, several studies have reported good treatment outcomes with stereotactic body radiation therapy (SBRT) for HCC.[5-7] SBRT is a highly conformal radiotherapy (RT) technique used for extracranial tumors, which delivers a very high dose per fraction in a short time while limiting the exposure to adjacent normal tissues.[8,9]

Challenges of HCC treatment include limited liver function in some patients; in previous studies, nonclassic radiation-induced liver disease (RILD) was more common in patients with poor liver function (hepatitis B infection and Child-Pugh classes B and C).[10,11] Therefore, SBRT to the liver should be cautiously planned to prevent RILD. Moreover, the incidence of RILD is strongly correlated with irradiated liver volumes[12] and mean liver doses.[13] Hence, precise assessments of liver function are critical to minimize irradiated volumes and mean doses to functional liver tissues.

Functional imaging techniques are used during RT planning and treatment to minimize irradiated volumes and mean doses to functional tissues while delivering highly conformal doses to the tumor.[14]

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Functional imaging modalities, such as functional magnetic resonance imaging (MRI),[15] [^{18}F]-fluorodeoxyglucose positron emission tomography,[16] single-photon emission computed tomography (SPECT) using 99mTc-labeled iminodiacetic acid,[17] and 4-dimensional computed tomography (CT),[18] have been used during radiation treatment planning. However, functional image-guided RT planning and treatment for HCC remain poorly validated. A few studies investigated the efficacy of SPECT-based RT for HCC[19,20]; however, in clinical practice, SPECT liver imaging for liver SBRT is implemented in several institutions only.

Recent studies indicate that gadoxetate disodium (EOB; EOB Primovist; Bayer Yakuhin Ltd., Osaka, Japan)-enhanced MRI (EOB-MRI) is effective for detecting hepatic lesions and may indicate hepatic function.[21,22] Some studies have demonstrated the clinical utility of EOB-MRI as a predictive parameter to assess the changes in hepatic function after SBRT.[23,24] Thus, it is a promising imaging technique for assessing liver dysfunction and predicting changes in hepatic function after SBRT. Therefore, we believe that the EOB-MRI–guided liver functional imaging modality can be applied to SBRT for liver cancer to spare the functional liver region using intensity-modulated radiation therapy (IMRT) planning and lead to safer and more efficacious treatment.

Here we investigated the ability of EOB-MRI–guided SBRT planning using IMRT techniques to reduce functional liver mean dose and functional liver volumes, which received doses from 5 to 30 Gy.

Methods and Materials

Patient characteristics

A total of 20 subjects were recruited after curative SBRT for HCC at Hiroshima University Hospital between May 2009 and May 2013. The study was approved by the university's Human Ethics Review Committee, and written informed consent was obtained from all patients.

The inclusion criteria of our institution for curative SBRT for HCC are as follows: (1) Eastern Cooperative Oncology Group Performance Status of 0 to 2; (2) Child-Pugh score A or B; (3) < 3 HCC nodules, each less than 5 cm in diameter, with or without vascular invasion; (4) luminal gastrointestinal tract should be far from tumor more than 2 cm; (5) inoperability; and (6) unsuitability for radiofrequency ablation because of tumor location, invisibility on ultrasonography, or bleeding tendency. The exclusion criteria were uncontrolled ascites and gastrointestinal tract-adjacent tumor.

Patient and tumor characteristics are summarized in Table 1.

EOB-MRI acquisition

MRI was performed before SBRT planning for all patients using 1.5-T imagers (Signa Excite HD; GE Healthcare, Milwaukee, WI) and an 8-channel body-phased array coil. Respiratory motion was controlled using the breath-hold method at the end of the expiratory phase. Dynamic MRI was performed with fat-suppressed T1-weighted gradient-echo imaging and 3-dimensional (3D) acquisition sequences (liver acquisition with volume acceleration). After pre-enhanced scanning, EOB was administered intravenously and 4-phase EOB-enhanced scans of the liver were obtained during the arterial, portal venous, transitional,[25] and hepatobiliary phase (HBP). Scanning during the HBP was performed from 20 minutes after the start of EOB injections.

Table 1
Patient and tumor characteristics

Age	Median/(range)	73/(55-84)
Sex	Male/Female	12/8
Performance status	0/1	18/2
Type of virus infection	HCV/HBV/NBNC	18/1/1
Child-Pugh class	A/B	17/3
Child-Pugh score	5/6/7/≥ 8	10/7/3/0
Clinical stage [UICC Seventh]	I/II	14/6
TMN	T1N0M0/T2N0M0	14/6
Tumor location	S3/S4/S5/S6/S7/S8	2/3/1/4/4/6
GTV (cm^3)	Median/(range)	1.7/(0.03-27.6)
PTV (cm^3)	Median/(range)	16.2/(2.4-87.3)

GTV, gross tumor volume; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, nonhepatitis B nonhepatitis C; PTV, planning target volume; S, segment of liver; UICC, International Union Against Cancer.

EOB (25 μmol/kg) was administered at a rate of 2.0 mL/s and then flushed using 20 mL of saline with a power injector (Sonic Shot 50; Nemoto Kyorindo, Tokyo, Japan). All of the images were obtained in the transverse plane with an acquisition time of 20 seconds, and 3-mm-thick HBP images were used to generate a functional liver map.

CT acquisition for SBRT planning

Patients were immobilized with a vacuum cushion (Vac-Lok with Wingboard; CIVCO, Orange City, Iowa), and respiratory motion was coordinated by voluntary breath-holding in the end of the expiratory phase using an Abches device (Apex Medical, Tokyo, Japan) that allows patients to control the respiratory motion of the chest and abdomen. For the simulations, dynamic CT scans (LightSpeed QX/I; GE Medical Systems, Waukesha, WI) included noncontrast enhancement, and images in the arterial, portal, and venous phases were collected following the bolus injections of nonionic iodinated contrast material (100 mL at 3 mL/s). CT slice thicknesses were 1.25 to 2.5 mm.

Functional liver map construction

Functional liver maps were generated using a 4-step procedure based on the EOB-MRI and SBRT planning CT images (Fig. 1). Both image types were acquired before the radiation planning, and assessments of liver function were performed using the EOB-MRI and planning CT images as a spatial reference. At first deformable registration, EOB-MRI was spatially aligned using planning CT with an insight segmentation and registration toolkit.[26] For median filtering, the EOB-MRI images were smoothed using a 3D median filter ($15 \times 15 \times 15$ mm). For liver-spleen contrast ratio (LSC) conversion, the MRI signals were then converted to a functional map according to quantitative LSC. The pixels of the EOB-MRI images were divided according to spleen signal intensities, which were measured manually using the volumetric region of interest. Functional liver was defined as quantitative LSC ≥ 1.5 during the HBP as described previously.[27] Functional liver maps were posterized from gradation images to stepped images by rounding of the numbers to the nearest decimal point for ease of analysis (> 1.0 but < 1.1, rounded to 1.0; > 1.1 but < 1.2, rounded to 1.1). Finally, because a treatment planning system does not accommodate decimal numbers on images, the functional map values were multiplied by 1000.

SBRT planning

RT planning CT and EOB-MRI images from 20 patients were transferred to a 3D treatment planning system (Pinnacle3 ver. 9.6; Phillips Medical Systems, Fitchburg, WI). The EOB-MRI images were then fused with the planning CT images that were obtained during the arterial phase.

Gross tumor volumes (GTVs) were defined as those carrying residual lipiodol using transarterial chemoembolization and early enhancement during the arterial phase of dynamic CT. A clinical target volume (CTV) margin of 0 to 5 mm was added to the GTV for subclinical invasions, and a planning target volume (PTV) margin of 5 to 8 mm was added to the CTV based on the reproducibility of respiratory motions and setup errors. Eight ports were selected in all patients, including 4 coplanar and 4 noncoplanar static beams, which were established in directions that avoided the stomach, intestine, gall bladder, and spine, if possible. Treatment plans were delivered using 6- and 10-MV photons generated by a linear accelerator (Clinac iX; Varian Medical Systems, Palo Alto, CA). The total prescribed dose was 48 gray (Gy) in 4 fractions and the prescription dose was delivered to 95% of the PTV.

SBRT plans were subsequently designed using a "step-and-shoot" static IMRT technique for each patient. First of all, the anatomical SBRT plan (plan A) was optimized based on total liver volume using the clinical optimization parameters. Plan A's optimization parameters were copied in the functional SBRT plan (plan F), and then the functional liver map (volume) was added to the dose constraints of plan F. Finally, plan F was re-optimized based on the functional liver volume. Table 2 shows the dose constraints for plans A and F, which had exactly the same IMRT optimized values for each patient but different functional liver values.

IMRT inverse treatment planning was optimized using a direct machine parameter optimization algorithm. Dose calculations were performed using a $2 \times 2 \times 2$ mm dose grid and a dose computation with collapsed cone convolution.

Data analysis and statistical methods

Dosimetric parameters of plans A and F were investigated by (1) PTV doses to 95% of the prescription dose (PTV $D_{95\%}$) and mean PTV dose; (2) calculating mean doses to total and functional liver minus GTVs (MLD and fMLD), respectively; (3) expressing percentages of total and functional liver volumes, which received doses from 5 to 30 Gy (V5 to V30, fV5 to fV30); (4) calculating mean doses, doses to 0.5 cc and to 5 cc volumes (D0.5cc and D5cc) of the stomach, duodenum, and intestine; and (5) calculating monitor units.

Statistical analyses were performed using R-statistics program version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). Differences were identified using paired t-tests and considered significant at values of $p < 0.05$. All quantitative data are expressed as mean ± standard deviation.