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Scientific Article

Stereotactic Body Radiation Therapy (SBRT) for Hepatocellular Carcinoma (HCC) With Single Photon Emission Computed Tomography (SPECT) Functional Treatment Planning in Patients With Advanced Hepatic Cirrhosis

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Purpose: We report on the feasibility and outcomes of liver stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) with single-photon emission computed tomography (SPECT) functional treatment planning in patients with Child-Pugh (CP) B/C cirrhosis.

Methods and Materials: Liver SPECT with ^{99m}Tc-sulfur colloid was coregistered to treatment planning computed tomography (CT) for the guided avoidance of functional hepatic parenchyma during SBRT. Functional liver volumes (FLVs) obtained from SPECT were compared with anatomic liver volumes defined on the planning CT. Radiation dose constraints were adapted exclusively to FLV. Local control, toxicity, and survival were reported with at least 6 months of radiographic follow-up. Pre- and posttransplant outcomes were analyzed in a subset of patients who completed SBRT as a bridge to liver transplant. Model of End-Stage Liver Disease was used to score hepatic function before and after SBRT completion.

Results: With a median follow-up of 32 months, 45 patients (58 lesions) with HCC and CP-B/C cirrhosis received SBRT to a median dose of 45 Gy (3-5 fractions). FLV loss (34%, $P < .001$) was observed in all patients, and the functional and anatomic liver volumes matched well in a control group of noncirrhotic/non-HCC patients. Despite marked functional parenchyma retraction, the amount of FLV on SPECT exposed to the threshold irradiation was significantly less than the CT liver volumes ($P < .001$) because of the optimized beam placement during dosimetry planning. Twenty-three patients (51%) successfully completed orthotopic liver transplant, with a median time to transplant of 9.2 months. With 91% in-field local control, the overall 2-year survival was 65% (90% after the orthotopic liver transplant), with no incidence of radiation-induced liver disease observed within 3 to 4 months or accelerated

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CP class migration from B to C within the first 6 months post-SBRT. Mean Model of End-Stage Liver Disease-Na score was not significantly elevated at 3-month intervals after SBRT completion.

Conclusions: Functional treatment planning with ^{99m}Tc sulfur colloid SPECT/CT allows identification and avoidance of functional hepatic parenchyma in patients with CP-B/C cirrhosis, leading to low toxicity and satisfactory transplant outcomes.

Introduction

Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer-related death in the United States and has a 5-year survival prediction below 20%.[1] The number of new cases and deaths from liver cancer is predicted to increase by >55% by 2040.[2] The choice of curative liver resection is limited by the presence of hepatic cirrhosis, and the most appropriate therapy for patients with HCC is liver transplantation, with a 5-year survival rate approaching 90%; however, only 10% of patients are eligible for a transplant.[3]

Stereotactic body radiation therapy (SBRT) is a treatment for unresectable hepatoma in patients with compensated hepatic cirrhosis that provides local control (LC) rates of 75% to 95% and low toxicity.[4-8] It can be applied as a bridging therapy for patients awaiting liver transplantation[9-11] or used in combination with transarterial hepatic chemo-embolization (TACE) for advanced HCC with curative intent.[12,13] However, patients with advanced Child-Pugh (CP)-B hepatic cirrhosis are at a higher risk of developing radiation-induced liver disease (RILD) than patients with hepatic tumors and CP-A cirrhosis.[8,14-23] With active proliferation of fibrotic tissue, it is possible that cirrhotic liver defined on the treatment planning computed tomography (CT) may not adequately represent functional hepatic parenchyma, and CT-based dose volume constraints developed for noncirrhotic liver may be inappropriate for patients with advanced hepatic cirrhosis. Therefore, to ameliorate hepatotoxicity of liver SBRT in patients with CP-B or CP-C cirrhosis, it was recommended that the mean liver dose be decreased to half of the accepted dosimetric parameters in CP-A patients or in the absence of hepatic cirrhosis, which ultimately required reduction of the prescription dose to centrally located or multiple tumors.[16,20,24,25] Liver SBRT for HCC has become an effective treatment modality to bridge patients with hepatic cirrhosis to a liver transplant.[9-11] There is a critical need for a personalized, innovative, and reliable treatment planning strategy for liver SBRT in patients with CP-B/C hepatic cirrhosis. This planning strategy also needs to minimize the risk of individual hepatotoxicity while targeting hepatic tumors with ablative irradiation based on visualization and conformal avoidance of residual functionally active liver parenchyma.

There are several functional liver imaging modalities in patients with HCC, including indocyanine green hepatic extraction rate in correlation with dynamic contrast-enhanced CT and magnetic resonance imaging (MRI) of hepatic perfusion,[26-28] gadoxetate disodium-enhanced MRI of hepatic function,[29] liver single-photon emission CT (SPECT) with galactosyl human serum albumin (GSA) to assess liver fibrosis,[30,31] hepatobiliary iminodiacetic acid SPECT, and gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid SPECT to assess the hepatocyte-specific bilirubin pathway.[32,33] Functional liver imaging for SBRT in our study was performed with ^{99m}Tc-sulfur colloid (SC) liver SPECT—a US Food and Drug Administration–approved nuclear medicine imaging technique for assessment of hepatic cirrhosis severity through the uptake of ^{99m}Tc-SC by the hepatic sinusoidal macrophages or Kupffer cells residing within well-perfused, functionally active volumes of hepatic parenchyma.[34,35] SC-SPECT imaging of hepatic Kupffer cell masses has been used to direct beam placement during radiation therapy (RT) planning in patients with HCC and liver cirrhosis, resulting in reduced hepatic toxicity.[6,7,9,23,36]

The goals of our study were to: (1) Assess the effect of liver SPECT functional imaging on liver dose-volume constraint determination for development of a liver SBRT planning platform in patients with advanced CP-B/C cirrhosis; (2) report on the toxicity, LC, and survival after liver SBRT with CT/SPECT functional treatment planning; and (3) analyze pre- and posttransplant outcomes in a subset of patients with advanced cirrhosis who completed SBRT as a bridge therapy to liver transplant.

Methods and Materials

Study design

Between October 2012 and August 2022, a total of 45 patients with isolated HCC in the absence of distal metastases, including 41 patients with CP-B and 4 with CP-C cirrhosis, were analyzed in an institutional review board–approved outcome study. All patients received liver SBRT after prospective review of each individual case by our weekly multidisciplinary hepatobiliary and liver transplant tumor board. Patients eligible for liver transplant were included in the study. Prior liver-directed therapies, such as radiofrequency ablation, TACE, or prior liver SBRT were allowed.

CT-SPECT simulation and contouring

Patients were immobilized in a custom molded VacLoc vacuum bag (Bionix). A free-breathing CT with intravenous contrast was acquired, immediately followed by a 4-dimensional (4D) CT to estimate the internal tumor volume (4D-ITV). Sixteen (35%) patients had a target motion above 1 cm, and the patients could hold their breath for at least 20 seconds. The active breathing coordinator (ABC; Elekta Inc) was applied to manage the target motion. For these patients, 3 sets of breath hold (BH) CT scans were done to define BH-ITV. Liver volume on CT (CT-LV) was contoured on the planning CT. For the patients who could not tolerate the ABC, the free-breathing CT was used for planning. For patients who could tolerate ABC, the BH CT scan was used for planning.

After CT simulation, the patients were led to the nuclear medicine department and positioned in the same vacuum bag on a SPECT scanner. The SPECT hepatic images were acquired over a fixed, time-averaged frame mode with a dual head gamma camera (GE Medical Systems) 20 minutes after an intravenous injection of 7 mCi (259 MBq) ^{99m}Tc- SC. In the MIM 6.6 software (MIM Software Inc), the free-breathing CT and SPECT images were rigidly coregistered using a point-based registration algorithm, aligning the radioactive and radiopaque markers on the SPECT and planning CT scans, respectively, as previously described.[7,37] The functional hepatic parenchyma (excluding the intrahepatic vascular structures) was identified as the photogenic area on the SPECT with a consistent window leveling and intensity thresholding approach across all patients and contoured as the functional liver volume (FLV-SPECT). It is a qualitative rather than a quantitative approach to define the FLV-SPECT. The gross tumor volume (GTV) was outlined on the contrast-enhanced FB or BH planning CT images. The ITV was defined with either a 4D-CT or multiple BH CTs, depending on the motion management method. The planned target volume (PTV) included the ITV and a minimum 0.3-cm isotropic expansion. All images and structures were transferred to a MONACO (Elekta) treatment planning system.

The information drawn from SPECT was neither used to delineate GTV nor to derive expansion margins. It was primarily used for the conformal avoidance of the regions of best functioning hepatic parenchyma during treatment planning.

Treatment planning and delivery

Three-dimensional conformal RT (3D-CRT) plans were designed using multiple coplanar and noncoplanar beam arrangements or dynamic conformal arc therapy. It is established that liver cirrhosis is characterized by significant variations in LVs; therefore, FLV-SPECTs for avoidance during SBRT were individually calculated from predicted FLVs (pFLV) derived from an equation used in transplant surgery[38] and for ^{90}Y radioembolization dosimetry[39]:

$$pFLV = -794.41 + 1268.28 \times BSA \quad (1)$$

where *BSA* is the body surface area.

The biologic equivalent dose (BED) was calculated according to the following equation:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad (2)$$

where n is the number of treated fractions, d is the dose per fraction, and α/β = 3 Gy for the liver.

This corresponds to EQD2 (equivalent dose in 2 Gy fractions) calculated from the following equation:

$$\mathrm{EQD2} = \mathrm{BED} = \mathrm{D} \cdot (1 + 2/\alpha/\beta) \quad (3)$$

where α/β = 3 Gy for the liver.

Hepatic dose constraints were imposed exclusively on FLV-SPECT corresponding to at least 30% of the pFLV receiving a BED equal to or less than 40 Gy_3, based on the liver tolerance to the whole liver irradiation, regardless of the adopted fractionation schedule.[40-42] For example, when liver SBRT is to be delivered to 50 Gy in 5 fractions to a patient with a body surface area of 2.45 m^2 (pFLV = 2300 cc), at least 700 cc of their FLV-SPECT (30% pFLV) should receive equal to or less than 18 Gy (EQD2, 4 Gy; BED, 40 Gy_3) with a mean dose to FLV-SPECT of ≤16 Gy. Other constraints included heart/pericardium V30 < 10 cc (max <35 Gy); stomach V25 < 10 cc (max <30 Gy); and small bowel V20 < 20 cc (max <30 Gy), where V20, V25, and V30 are the corresponding organ volumes receiving at least 20, 25, or 30 Gy, respectively.

All patients completed liver SBRT at a median of 9.1 Gy per fraction (7-12 Gy) prescribed to the isodose line encompassing the PTV (generally ≥90%). Twenty-nine patients were treated on a Siemens Primus linear accelerator with megavoltage cone beam CT for daily setup verifications, and the remaining 16 patients received liver SBRT on Elekta Versa HD with a kilo-voltage cone beam CT.

SPECT and CT liver volume and dosimetry comparison

To analyze the effect of cirrhosis on functional volume loss, there was a control group of 5 patients without hepatic cirrhosis or hepatic dysfunction that were treated for liver metastasis of colorectal or breast cancer primary tumors. The SPECT- and CT-defined normal liver volumes were compared between the control group of non-HCC and noncirrhotic patients (n = 5) and the group of

CP-B/C patients (n = 45). For each group, the mean paired difference among LV-CT, FLV-SPECT, and predicted liver were calculated, and the hypothesis that the difference was consistent with 0 was tested with a repeated analysis of variance (ANOVA) to a significance level of 0.05. In addition, the FLV-SPECT expressed as a percentage of predicted LV was determined for each group, and the hypothesis that it was consistent with 100% was assessed using a 1-sample *t* test with a mean of 100. Finally, CT and FLV-SPECT receiving a BED greater than 40 Gy_3 (EQD2, 4 Gy) were compared, and the statistical significance of the difference between them was assessed with a 2-sampled, paired *t* test. The PTV was excluded from all LV definitions used in this analysis.

SBRT before liver transplant

For our institution, SBRT was the first choice for bridging or downsizing therapy of HCC before liver transplant. Twenty-three patients in this study with 28 HCC lesions received liver SBRT with CT-SPECT treatment planning to the mean dose of 44 Gy (35-50 Gy) delivered in 4 to 5 fractions before orthotopic liver transplant (OLT). Patients with multifocal HCC were treated with simultaneous or sequential SBRT to the lesions ≥2 cm. Sixteen patients were within the Milan criteria for OLT and received liver SBRT as a bridging treatment to OLT. Seven patients were outside of the Milan criteria and received liver SBRT for tumor downsizing before transplant.

Follow-up and outcome data

All patients were analyzed for toxicity every 4 to 5 weeks for the first 3 months and then every 3 months thereafter with clinical examinations, hepatic multiphase contrast MRI or CT, and laboratory tests (complete metabolic panel, coagulation profile, and complete blood count). To score treatment-related hepatic toxicity more accurately in patients with advanced cirrhosis, we applied the Model of End-Stage Liver Disease-Sodium (MELD-Na) scoring system. The MELD-Na score was calculated without the United Network Organ Sharing HCC exception points in transplant-eligible patients.[43] Acute and long-term toxicities were graded according to the Common Terminology Criteria for Adverse Event v4.0.

The local response with either contrast-enhanced multiphase MRI or CT was documented every 3 to 4 months after completion of SBRT, or up until the time of liver transplant. LC was defined as the absence of tumor radiographic progression within or at the PTV margin. New liver lesions arising outside PTV were identified as intrahepatic progression. Actuarial LC and overall survival (OS) curves were generated using the Kaplan-Meier method.

Results

Patient demographics

Forty-five patients with 58 HCCs were included in this study. Forty-one patients had CP-B cirrhosis and a mean MELD-Na score of 13.8 (range, 8-22), and 4 patients had CP-C cirrhosis and a mean MELD-Na score of 20 (range, 13-28). Median follow-up was 32 months (range, 6-28 months). All patients completed CT/SPECT treatment planning and received liver SBRT to hepatic lesions at a mean dose of 45.2 Gy (35-50 Gy). Patient demographics and treatment characteristics are presented in Table 1. Patients had a mean cumulative tumor volume of 28.7 cm^3 (range, 2.5-123 cm^3) and a mean tumor max diameter of 2.93 cm (range, 1.1-6.2 cm). Thirty-six patients (80%) completed liver SBRT for tumor downsizing or as a bridging therapy before OLT, and 23 of them received the transplant with a mean time to transplant of 9.17 months (range, 1-35 months).

SPECT and CT LV and dosimetry comparison

Figure 1 shows fused CT/SPECT images of the liver for noncirrhotic (top) and cirrhotic (bottom) patients. Noncirrhotic patients with normal liver function (control group) had diffuse and homogeneous uptake and distribution of ^{99m}Tc-SC with FLV-SPECT matching LV-CT. Patients with HCC with advanced hepatic cirrhosis had sequestration and retraction of functionally active liver parenchyma. The residual FLV-SPECT was smaller than the anatomic LV derived from treatment planning CT.

There were significant differences among predicted LV, CT-LV, and SPECT volumes in all patients with CP-B/C cirrhosis ($P < .0001$) based on repeated ANOVA results (Table 2), indicating that predicted LVs (mean, 1779.62 cc) were significantly higher than FLVs defined on SPECT (mean, 1003.02 cc). Despite marked retraction of FLV-SPECT, a mean 46.6% of pLV defined on SPECT was exposed to BED ≤ 40 Gy_3 (EQD ≤ 24 Gy), meeting our liver dosimetric objective. Mean dose to FLV-SPECT was 8.2 Gy ± 3.23, and the amount of FLV on SPECT exposed to BED ≥ 40 Gy_3 was less compared with CT with volume difference 99 ± 129 ($P < .001$) based on a paired *t* test (Table 3).

Figure 2 shows representative CT/SPECT treatment planning images with dose distribution for a patient with CP-B cirrhosis and centrally located HCC. Functional liver was contoured on ^{99m}Tc-SC SPECT (FLV-SPECT, green color wash), and anatomic LV was contoured on CT (LV-CT, brown color wash). There is 48% FLV-SPECT loss compared with LV-CT. Fifty Gy in 5 fractions was prescribed to the periphery of the ITV (white color wash), with selective avoidance of FLV-SPECT, pursuing

Table 1 Patient and tumor characteristics

Variable	n or mean (range)
Age (years)	64.7 (44-84)
ECOG	1 (0-2)
Hepatitis etiology	
Hepatitis C virus	19
Alcohol	14
NASH	12
Child-Pugh B class	41
MELD-Na score	13.8 (8-22)
Child-Pugh C class	4
MELD-Na score	20 (13-28)
Prior therapies	
SBRT	6
TACE	8
RFA	2
Sequential SBRT for intrahepatic recurrence	10
OLT eligible	36
OLT completed	23
Treated lesions	58
1	32
2	13
Tumor diameter (cm)	
1-2	6
2-3	18
3-4	13
4-6	6
>6	2
Vascular invasion	
Yes	7
No	38
Combined GTV (cc)	28.7 (2.5-123)
Combined PTV (cc)	65.5 (17.5-240)
Dose/fraction (Gy)	9.1 (7-12)
Total dose (Gy)	45.2 (35-50)
Number of fractions	4.8 (3-5)

Abbreviations: ECOG = European Cooperative Oncology Group; GTV = gross tumor volume; MELD-Na = Model of End-Stage Liver Disease-Sodium; NASH = nonalcoholic steatotic hepatitis; OLT = orthotopic liver transplant; PTV = planning target volume; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization.

the goal to keep ≥600 cc of FLV-SPECT (30% predicted) at ≤18 Gy (BED, 40 Gy_3; EQD, 24 Gy). Dose-volume histogram curves reflect a sparing effect on FLV-SPECT.

Liver SBRT as a bridge to transplant

Thirty-six transplant-eligible patients (80% of the entire cohort) received SBRT as a bridging treatment[28] or for tumor downsizing,[8] and 26 patients (58% of the entire cohort) were listed for liver transplant after completion of SBRT. Two patients were removed from the liver transplant waitlist due to de novo intrahepatic lesions. Both patients were initially outside of Milan criteria with tumors successfully downsized after SBRT. A third patient was delisted due to well-controlled HCC and advanced age. He is currently alive and without evidence of intrahepatic progression at 45 months from completion of liver SBRT for a 2.4-cm HCC. Twenty-three patients (51% of the entire cohort) successfully completed OLT, including 7 patients with downsized tumors that were initially outside Milan criteria. Four patients in the transplant-eligible group developed intrahepatic progression outside PTV and received additional liver SBRT with CT/SPECT functional treatment planning before receiving a liver transplant. No patient had recurrence of HCC after liver transplant during this study period.

On pathologic examination of the explanted livers, 9 cases (40%) showed a complete pathologic response, 13 patients (56%) had various degrees of tumor size reduction, and 1 patient (4%) experienced tumor progression at 18 months after completion of SBRT with 40 Gy/5 fractions as a bridge to transplant. Overall, the median viable tumor size in explanted livers was 1.25 cm (0-3.5 cm), which is significantly smaller than the original tumor size defined using MRI before SBRT ($P < .001$). The median wait time for a liver transplant was 9.2 months (range, 1-35 months). One patient had progression of the CP score from B to C at 11 months post-SBRT. With a 45-month (range, 11-127 months) median follow-up after the liver transplant, actuarial survival for the OLT cohort was 91.3%. Two patients died of sepsis and metastatic second primary cancer at 19 months and 4 years after OLT, respectively.

Survival, LC, and toxicity

Median survival was 32 months with a 62% OS rate for the entire group of 45 CP-B/C patients. The transplant patients had an OS rate of 91.3%, whereas the transplant-ineligible patients had an OS rate of 32% (Fig. 3).

Fifteen of 22 patients (68%) in the transplant-ineligible group died of complications of cirrhosis, including 8 patients with intrahepatic progression of HCC and an average survival of 21.06 months (range, 5-58 months) after completion of SBRT. With a median follow-up of 32 months (range, 6-128 months), local tumor control for the entire group was 91%, and 3 patients developed local recurrence within PTV at 11.6, 17, and 48 months after

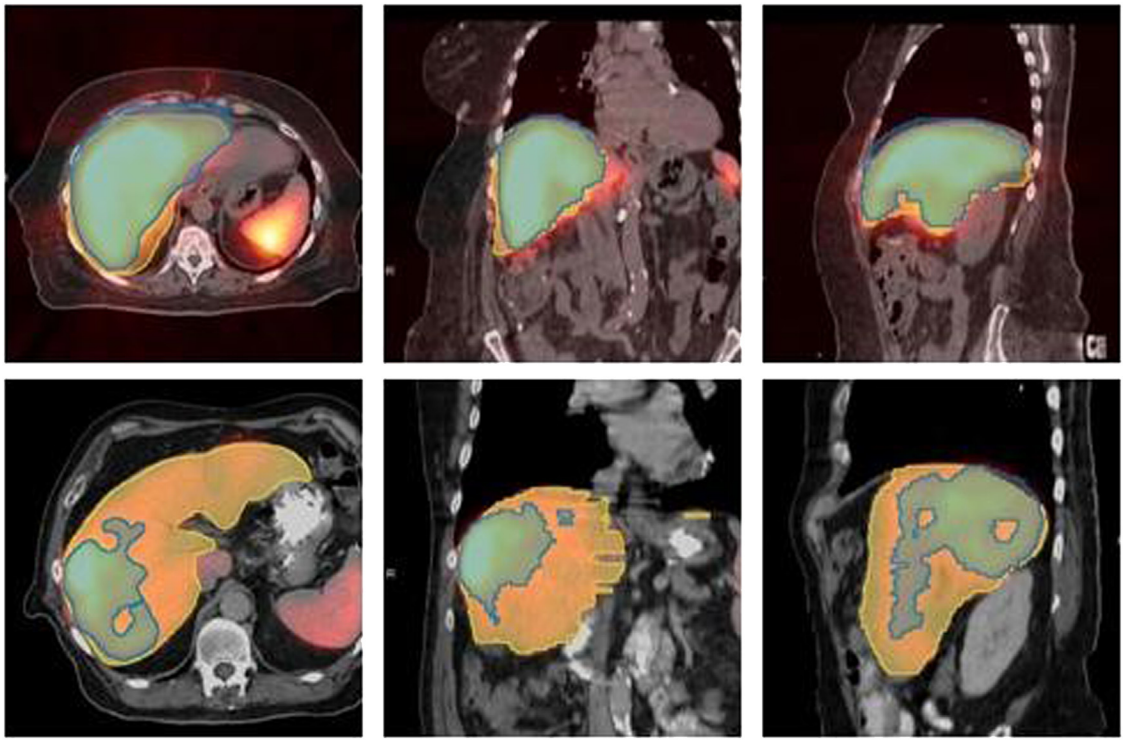

Figure 1 From left to right: Axial, coronal, and sagittal fused single-photon emission computed tomography/computed tomography liver images for noncirrhotic (top) and Child-Pugh B cirrhotic (bottom) patients. Anatomical liver contours defined on planning computed tomography are shown in yellow, and the single-photon emission computed tomography defined functional liver is shown in blue.

completion of SBRT, respectively. This also included 1 patient in the transplant group with evidence of tumor progression in the explanted liver at 18 months after completion of SBRT as a bridge to liver transplant.

Overall, 17 patients (38%) developed intrahepatic progression outside PTV (mean time to recurrence, 17.6 months; range, 4.3-32 months). Fifteen patients with intrahepatic progression received additional salvage liver SBRT with CT/SPECT functional treatment planning, and 4 of them successfully received a liver transplant.

None of the patients received radiation doses exceeding FLV tolerance. No incidence of classic or nonclassic RILD (defined as rapid elevation of bilirubin or liver enzymes >5x upper limit of normal) was observed in the entire group within 3 months post-SBRT.[16] Two incidences of >grade 1 gastrointestinal toxicity were observed (nausea/vomiting controlled with medication). Grade ≤2 fatigue (45% grade 1, 15% grade 2, and 0% grade 3) was the most prevalent toxicity and did not correlate with severity of hepatic cirrhosis based on the MELD-Na score.

Table 2 SPECT- and CT-defined liver volume comparison between patients with advanced cirrhosis and noncirrhotic controls

Mean liver volumes (range)	HCC Child-Pugh B&C (n = 45)	Non-HCC, noncirrhotic control (n = 5)
LV-CT (cc)	1506.31 (889-2502)	1289 (1132-1369)
FLV-SPECT (cc)	1003.02 (498-1657)	1300 (1137-1460)
Difference (cc)	503.29 ± 319.65 $P < .0001$	−11 ± 61 $P = .71$
FLV-SPECT reduction (%pFLV)	795.10 ± 351.42 $P < .0001$	3 ± 19 $P = .76$

Abbreviations: CT = computed tomography; FLV = functional liver volume; HCC = hepatocellular carcinoma; LV = liver volume; pFLV = predicted functional liver volume; SPECT = single-photon emission CT.

Table 3 Liver dose-volume characteristics for patients with HCC with Child-Pugh B/C cirrhosis (n = 45)

	LV-CT	FLV-SPECT	Difference
Overall volume (range) (cc)	1506.31 (889-2502)	1003.02 (498-1657)	503.29 ± 319.65 $P < .0001$
Volume receiving BED ≥ 40 Gy_3 (cc)	309 (40-1098)	205 (11-698)	99 ± 129 $P < .001$
Mean dose (Gy)	8.91 (1.6-15.62)	8.2 (1.36-15.26)	0.56 ± 1.39 $P = .0471$

Abbreviations: BED = biologic equivalent dose; FLV-SPECT = functional liver volume on single-photon emission computed tomography; HCC = hepatocellular carcinoma; LV-CT = liver volume on computed tomography.

There was no accelerated (within 6 months) CP class migration from B to C based on our calculations and an independent assessment by the hepatology and transplant surgery teams. The mean MELD-Na score before SBRT was 14.18 and was significantly different ($t = -2.32$, $P = .0232$; $t = -2.89$, $P = .0051$) within 6 months (mean, 15.14) and 1 year (mean, 15.20) but not within a 3-month interval after completion of SBRT ($P = .0733$) (Table 4). There was no significant difference in the mean MELD-Na scores between 3 to 4 months, 6 months, and 1 year after SBRT. In the subgroup of transplant patients, there was a significant difference in the mean MELD-Na score before SBRT and at the time of liver transplant (mean, 17.21) based on paired t test results with $t = -2.35$, $P = .0280$ (Table 4).

Discussion

For most of the patients with compensated hepatic cirrhosis who received liver RT with 3D-CRT planning, the observed incidence of RILD correlates well with the dose/volume effects and the mean radiation dose to the liver.[8,16,48,49] However, patients with advanced hepatic cirrhosis are at higher risk of developing classic and nonclassic RILD from the same radiation dose than patients with metastatic hepatic tumors in the absence of cirrhosis.[8,14-22] Lawrence et al[50] demonstrated the effect of nondosimetric biologic parameters on RILD with liver TD50 for treating primary versus metastatic hepatic malignancy with 39.8 and 45.8 Gy, respectively, Further data indicate that severity of hepatic cirrhosis in patients with HCC undergoing 3D-CRT correlates with the incidence of lethal RILD,[14,15,17,51] and the prediction of RILD by the Normal Tissue Complication Probability model for patients with advanced cirrhosis can be underestimated.[18]

Higher sensitivity of cirrhotic liver to irradiation could be linked to the proliferation of fibrotic tissue with loss of hepatic functional reserve representing combined function of hepatocytes and nonparenchymal cells residing within sinusoids (Kupffer cells, endothelial cells, stellate, and pit cells). Preoperative quantitation of a hepatocyte mass using ^{99m}Tc-GSA SPECT was used for selecting patients for safe hepatic resection.[52] Imaging functional hepatic parenchyma with ^{99m}Tc-GSA SPECT helped to direct beam placement during liver 3D-CRT for advanced

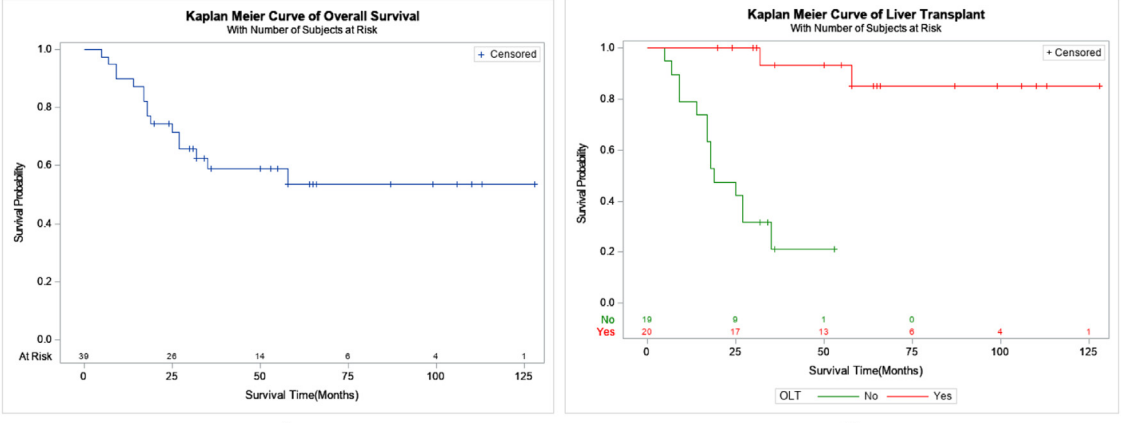

Figure 2 Kaplan-Meyer estimates of overall survival for the entire group (A) and for patients by orthotopic liver transplant status (B).

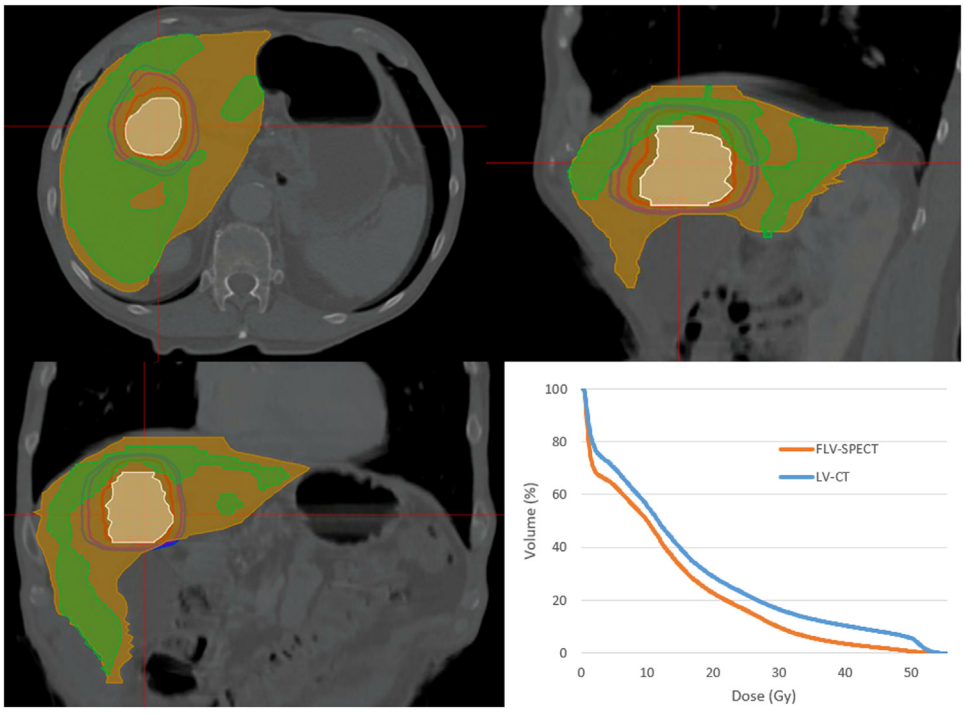

Figure 3 Representative CT/SPECT treatment planning images with dose distribution for a patient with Child-Pugh B cirrhosis. Functional liver contoured on 99mTc-sulfur colloid SPECT (FLV-SPECT, green color wash) and anatomic liver volume contoured on CT (LV-CT, brown color wash). There is 48% FLV-SPECT loss compared to LV-CT. Fifty Gy in 5 fractions prescribed to the periphery of internal target volume (white color wash) with selective avoidance of FLV-SPECT pursuing the goal to keep ≥600 cc of FLV-SPECT (30% predicted) at ≤18 Gy (biologic equivalent dose 40 Gy3). Dose-volume histogram curves reflect sparing effect on FLV-SPECT with V18 equal to 25% (red line) and 33% for LV-CT (blue line). *Abbreviations:* CT = computed tomography; FLV = functional liver volumes; LV = liver volume; SPECT = single-photon emission computed tomography.

HCC with portal vein embolization, which reduced hepatic toxicity in patients with advanced cirrhosis.[30,53,54]

In our study, we used a hepatic functional imaging technique with ^{99m}Tc-SC SPECT to visualize the hepatic sinusoidal Kupffer cells via their uptake of radioactive colloid in proportion to sinusoidal blood flow.[34,35] Hepatic Kupffer cells are highly radiosensitive and play a pivotal role in the initiation and development of RILD[55-58] and may accelerate the progression of liver fibrosis/cirrhosis.[59] Their irradiation leads to the release of reactive oxygen species and numerous proinflammatory cytokines, including tumor necrosis factor a, interleukin-1b, and interleukin-6, causing early apoptosis of hepatocytes and delayed periportal fibrosis with sinusoidal congestion—all characteristics of RILD.[56,57,60] Selective inactivation of hepatic Kupffer cells with intravenous injection of gadolinium chloride before whole-liver irradiation in rats reduced radiation-induced cytokine production and protected the liver against acute radiation-induced damage.[58] At early points after RT, the rats in the experimental group exhibited significantly lower levels of liver enzyme activity, apoptotic response, and hepatocyte micronucleus formation compared with irradiated control.

Our treatment planning with ^{99m}Tc-SC CT/SPECT allowed for the delineation of functionally active hepatic Kupffer cell masses in all patients. For the noncirrhotic patients, we observed diffuse, homogeneous distribution of ^{99m}Tc-SC, and their FLV-SPECT matched LV-CT (Fig. 1, Table 2). In contrast, patients with advanced cirrhosis exhibited significant functional LV loss. For CP-B/C patients in our study, the LV defined on CT was an overrepresentation of the volumes of functionally active liver parenchyma by a factor of 1.5 on average. Compared with predicted LV, CP-B/C patients demonstrated an average FLV-SPECT loss of 44% ($P < .001$) based on repeated ANOVA results (Table 2). Our liver dose/volume constraints were tailored exclusively to residual functionally active LVs on SPECT corresponding to at least 30% of pLV, rather than to the LV defined on CT to maximize guided avoidance of residual functional hepatic parenchyma in cirrhotic liver. Despite marked retraction of FLV-SPECT, a mean 46.6% of predicted LVs defined on SPECT was exposed to BED ≤ 40 Gy_3 (EQD ≤ 24 Gy) at a mean dose 8.2 ± 3.23 Gy, meeting our liver dosimetric objectives. The amount of FLV-SPECT exposed to BED ≥ 40 Gy_3 (EQD ≥ 24 Gy) was significantly less

Table 4 Repeated ANOVA and paired *t* test results of MELD

Variables	F/T value	*P* value
Overall MELD comparison	3.50	.0197
Before SBRT vs 3, 4 months after SBRT	−1.82	.0733
Before SBRT vs 6 months after SBRT	−2.32	.0232
Before SBRT vs 1 year after SBRT	−2.89	.0051
3, 4 months after SBRT vs 6 months after SBRT	−0.85	.3969
3, 4 months after SBRT vs 1 year after SBRT	−1.63	.1079
6 months after SBRT vs 1 year after SBRT	−0.84	.4018
Before SBRT vs before liver transplant	−2.35	.0280

Abbreviations: ANOVA = analysis of variance; F/T = the ratio of two mean squares; MELD = Model of End-Stage Liver Disease; SBRT = stereotactic body radiation therapy.

compared with CT for the entire group, reflecting our ability to spare a critical amount of residual functionally active liver parenchyma by optimizing beam placement process during the treatment planning (Table 3, Fig. 2).

At a mean dose of 45 Gy (4-5 fractions) and a median follow-up of 32 months (range, 6-28 months), our in-field local tumor control was 91% with an OS rate of 62%, similar to the rates previously reported,[4,42] and the toxicity profile was similar to or lower than expected compared with other studies.[12,13,15,16,35,36,38]

In 1 study, highly focused liver SBRT without functional treatment planning has been shown to be both safe and effective in selected patients with CP-B/C cirrhosis.[25] However, in a phase 1 to 2 trial of liver SBRT for HCC, CP-B patients experiencing grade 3/4 liver toxicity had a significantly higher mean liver dose, higher dose to one-third normal liver, and larger volumes of liver exposed to doses at or below threshold levels.[17] For CP-A patients, there was no critical liver dose or volume constraint correlated with toxicity.

We believe that implementation of functional treatment planning in patients with advanced hepatic cirrhosis with guided avoidance of residual, functionally active hepatic parenchyma may contribute to amelioration of radiation-induced liver toxicity. Our results are particularly impressive given that all patients in the study had CP-B/C hepatic cirrhosis with a mean MELD-Na score of 14.18 (range, 8-28) and a mean PTV of 65.5 cc (range, 17.5-240), including 21 patients (47%) with a mean tumor diameter of 4.3 cm (3.1-6.2), 13 patients (29%) with ≥2 liver lesions, 14 patients (31%) who received prior TACE[8] or SBRT,[6] and 10 patients (22%) who received a sequential course of liver SBRT with SPECT/CT functional planning for intrahepatic recurrences outside PTV (Table 1). The liver SBRT planning approach in our study was not uniform, but rather personalized, with radiation dose constraints tailored exclusively to individual residual functionally active volumes of cirrhotic liver parenchyma representing at least 30% of predicted functional LVs derived from the equations used in transplant surgery[38] and for ^{90}Y radioembolization dosimetry.[39]

Liver function before and at 3 to 4, 6, and 12 months after completion of SBRT was assessed with the MELD-Na scoring system (incorporating the international normalized ratio, serum creatinine, serum bilirubin, and serum sodium) because it is a more robust predictor of liver failure in patients with advanced cirrhosis compared with CP scoring, as MELD-Na does not include subjective variables, such as recurrent ascites and hepatic encephalopathy, that are present at baseline in all patients with CP-B/C cirrhosis.[39,44-47] Moreover, because 80% of our patients with advanced cirrhosis were transplant-eligible, it was appropriate to evaluate liver toxicity after SBRT by the MELD-Na score as it has been specifically adopted in the United States for the allocation of liver transplant based on its more accurate prediction of hepatic failure progression.[61]

An elevation of MELD-Na scores at 3 and 6 months after SBRT completion was observed. However, this was not clinically significant and did not lead to accelerated CP class migration or influence the interval between transplant listing and liver transplantation. This was also applicable to the 2 patients with CP-B and CP-C cirrhosis whose MELD-Na scores disproportionately increased before OLT at 9 and 12 months after SBRT completion. Both patients are alive and well 6.5 and 4.5 years post-transplant.

Our data indicate that liver SBRT with functional treatment planning is a safe and highly effective modality to control HCC in patients awaiting liver transplant, associated with low toxicity, minimal dropout rate from the transplant list, and no recurrence of HCC after the liver transplant. Regarding pathologic response in the explanted livers, our study yielded 38% (9/23) complete pathologic response, higher than the previously

reported,[62,63] which could be explained by consistently higher SBRT doses used in our study, 45 Gy (35-50 Gy) delivered in 4 to 5 fractions.

Further investigation with prospective, longitudinal studies using personalized liver SPECT/CT functional treatment planning protocol enabling tumor dose intensification with guided avoidance of functional liver parenchyma may improve the therapeutic ratio when managing HCC in CP-B/C patients with ablative RT bridging to liver transplant.

Limitations of this study include its retrospective analysis and absence of deformable registration to align SPECT to the planning CT. SPECT has an intrinsic image penumbra with image attenuation at the edges, and the point-based SPECT/CT rigid registration method used in our study has an uncertainty in the order of 6 mm.[37] In addition, the long acquisition time of SPECT imaging incorporates patient/respiratory motion, which may further degrade image quality. Information drawn from semiquantitative SPECT in our study was neither used to delineate GTV nor to derive expansion margins. It was primarily used for identification and conformal avoidance of the regions of functioning hepatic parenchyma in the beam placement process. To improve diagnostic accuracy in defining GTV and safe volumes of functional hepatic parenchyma for liver RT planning, we have initiated a prospective pilot study that investigates MRI-guided adaptive RT with superparamagnetic iron oxide nanoparticles on an MRI linear accelerator.

In summary, we observed marked individual retraction of Kupffer-cell-rich functionally active volumes of hepatic parenchyma in CP-B and CP-C patients defined on liver SPECT with ^{99m}Tc-SC compared with anatomic LVs defined on CT. Despite significant volumetric difference between functional and anatomic LVs, the amount of residual FLV on SPECT exposed to threshold irradiation was significantly less compared with CT because of the optimized beam placement during dosimetry planning. Treatment planning with ^{99m}Tc-SC SPECT/CT allows identification and guided avoidance of functional hepatic parenchyma in patients with CP-B/C cirrhosis, leading to low toxicity and satisfactory transplant outcomes.

Disclosures

None of the authors have a conflict of interest.

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