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Review

Stereotactic body radiation therapy in hepatocellular carcinoma: Optimal treatment strategies based on liver segmentation and functional hepatic reserve

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ABSTRACT

Aim: To discuss current dosage for stereotactic body radiation therapy (SBRT) in hepatocellular carcinoma (HCC) patients and suggest alternative treatment strategies according to liver segmentation as defined by the Couinaud classification.

Background: SBRT is a safe and effective alternative treatment for HCC patients who are unable to undergo liver ablation/resection. However, the SBRT fractionation schemes and treatment planning strategies are not well established.

Materials and methods: In this article, the latest developments and key findings from research studies exploring the efficacy of SBRT fractionation schemes for treatment of HCC are reviewed. Patients' characteristics, fractionation schemes, treatment outcomes and toxicities were compiled. Special attention was focused on SBRT fractionation approaches that take into consideration liver segmentation according to the Couinaud classification and functional hepatic reserve based on Child–Pugh (CP) liver cirrhosis classification.

Results: The most common SBRT fractionation schemes for HCC were 3×10–20 Gy, 4–6×8–10 Gy, and 10×5–5.5 Gy. Based on previous SBRT studies, and in consideration of tumor size and CP classification, we proposed 3×15–25 Gy for patients with tumor size <3 cm and adequate liver reserve (CP-A score 5), 5×10–12 Gy for patients with tumor sizes between 3 and 5 cm or inadequate liver reserve (CP-A score 6), and 10×5–5.5 Gy for patients with tumor size >5 cm or CP-B score.

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Conclusions: Treatment schemes in SBRT for HCC vary according to liver segmentation and functional hepatic reserve. Further prospective studies may be necessary to identify the optimal dose of SBRT for HCC.

1. Background

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and is the leading cause of cancer death in Taiwan, regardless of gender.[1] Traditional treatment modalities include surgical intervention, transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and the use of targeted agents. Policy decisions regarding treatment options are limited by the different stages of cancer or underlying co-morbidities. Only 20–40% of HCC patients are eligible for surgery.[2–4] Surgical resection offers a 5-year survival rate of 60–70% and 3-year recurrence rate of 50%.[3]

Orthotopic liver transplantation offers a 5-year survival rate exceeding 70% and recurrence rates of 17%.[4] For small HCC, RFA and other ablative techniques can achieve excellent local control. However, for tumors >4 cm or those near portal vessels, local recurrence is common.[5,6] For advanced HCC, TACE has been shown to provide modest improvement in overall survival (OS) compared with supportive care.[7]

In previous decades, the role of radiotherapy (RT) for HCC has been limited due to the risk of radiation-induced liver disease (RILD) which can increase when the radiation dosage to the whole liver exceeds 35 Gy. Due to advances in technology, partial liver irradiation has been successful in reducing the risk of RILD. Three-dimensional (3-D) conformal RT has shown encouraging results with a 1-year survival of 40–60%.[8–12] Stereotactic body radiation therapy (SBRT), which can deliver high doses of radiation in a few fractions, has also been used safely, predominantly in primary HCC and cases with small liver metastases that require radiation to less than 25% of the liver.[13–20] SBRT, accompanied by a high degree of accuracy in target delineation, can provide tighter margins. By image-guided radiation therapy (IGRT) and the use of flattening filter-free (FFF) beams, setup accuracy and treatment delivery can minimize radiation-induced toxicity.[21–23] The preliminary results of SBRT treatment of HCC are encouraging.[24,25] SBRT may provide an alternative treatment option for early stage HCC patients or those ineligible for ablative procedures.[26]

In the present study, we aimed to review current dosage schemes for SBRT in HCC patients and to suggest alternative treatment strategies according to liver segmentation (as defined by the Couinaud classification) and functional hepatic reserve.

2. SBRT for HCC: general considerations

2.1. Current SBRT dosage

The most common SBRT fractionation schemes for HCC from the current literature are summarized in Table 1. They include 3 × 10–20 Gy, 4–6 × 8–10 Gy, and 10 × 5–5.5 Gy.

As reported by Cardenes et al.,[24] when the dose was increased from 3 × 12 to 3 × 16 Gy for CP-A patients and 5 × 8 Gy for CP-B patients with 1–3 lesions (with cumulative tumor diameters ≤6 cm), a 1-year OS of 75% was noted. The only relevant factor affecting OS, other than grade 3 liver toxicity, was the CP score. Andolino et al.[13] reported that when approximately 40% of patients had a CP-B score, 37% of patients experienced >grade 3 toxicity. In Korea, Kwon et al.[27] reported a 1-year OS of 93% and RILD in 2% of patients treated with either 3 × 13 Gy for tumor volumes <30 cm^3 or 3 × 10–12 Gy for tumor volumes >30 cm^3. For larger tumors, Kang et al.[16] treated 47 patients with tumors which ranged in size from 1.3 to 7.8 cm using a regimen of 3 × 14–20 Gy, with a resulting 2-year OS of 69% and grade 3 RILD of 13%. Mendez-Romero et al.[18] reported a 1-year OS of 75% and grade 3 RILD of 13% after treatment using either 3 × 12.5 Gy for tumors <4 cm or 3 × 10 Gy (or 5 × 5 Gy) for tumors >4 cm in size.

Sanuki et al.[28] reported a 3-year OS of 70% and grade 3 RILD of 13% using a dose of either 5 × 8 Gy for CP-A or 5 × 7 Gy for CP-B. Using a 6 × 4–9 Gy regimen, Bujold et al.[25] reported a 1-year OS of 48%. There was no dose-limiting toxicity, but 29% of the patients had increased grade 3 liver enzymes. Regarding larger tumors, Huang et al.[29] treated 36 patients with tumors ranging in size from 1.1 to 12.3 cm with 25–48 Gy in 4–5 fractions and reported a 2-year OS of 73% and grade 3 RILD of 7%. Using 10 × 5.5 Gy for CP-A and 10 × 5 Gy for CP-B, Iwata et al.[30] reported a 1-year OS of 93% without any grade 3 RILD.

Our institutional regimens were based on our previous SBRT study[19] which took into consideration tumor size and CP class. These regimens included 3 × 15–25 Gy for patients with tumors <3 cm in size and adequate liver reserve (CP-A5); 5 × 10–12 Gy for patients with tumors between 3 and 5 cm or inadequate liver reserve (CP-A 6); and 10 × 5–5.5 Gy for patients with tumors >5 cm in size or CP-B scores.[19]

2.2. SBRT for HCC by liver segmentation

To reduce RILD, SBRT should preserve a sufficient amount of normal liver volume (usually >700 cm^3) in addition to the expected hypertrophy of "normal liver" within 6 months post SBRT. Meticulous delineation of liver segment location is important in SBRT because it affects treatment dose and dose constraints in treatment planning. We defined the liver segments according to the Couinaud classification of liver anatomy (Fig. 1).

The liver is classified into eight functional units which are divided by independent vascular structures, biliary and lymphatic drainage. The liver is anatomically divided by the portal system (the portal vein) into upper and lower segments. Branches of the right and left portal veins project superiorly and inferiorly and converge at the center of each segment. Each segment can be regarded as an isolated functional unit

Table 1 – Stereotactic body radiation therapy for hepatocellular carcinoma.

Author, year	Pt No.	CP B (%)	PVT (%)	Tumor size (cm or mL)	Dose(Gy)/fractions	1 y survival	Toxicity (Gr ≥ 3)	Dose constraint
Sanuki, 2014	185	15	0	1.5–65.3 mL, 7.2 mL (med)	CPA: 40/5 CPB: 35/5	70% (3 y)	RILD 13%	Liver V_{20Gy} < 80% or reduced 5 Gy; stomach, bowels <25 Gy; spinal cord <25 Gy
Wang, 2014	32	6	28	6–848 mL, 86 mL (med)	<3 cm: 45/3 3–5 cm: 50/5 >5 cm: 50/10	74% (0.5 y)	RILD 5%; GI 0%	Liver >700 mL <15 Gy; stomach $V_{37.5Gy}$ < 5%; kidneys V_{15Gy} < 35%; spinal cord V_{22Gy} < 1 mL
Bujoild, 2013	102	0	55	1.3–1913 mL, 117 mL (med)	24–54/6	87%	30%; 7%(Gr5)	Esophagus, stomach, duodenum, bowel V_{30Gy} < 0.5 mL; spinal cord <27 Gy; heart <40 Gy
Huang, 2012	36	29[a]	NA	1.1–12.3 cm, 4.4 cm (med)	25–48/4–5	73% (2 y)	RILD 7%; GI 3%	Liver >700 mL <15 Gy; stomach V_{25Gy} < 5 mL; bowel V_{23Gy} <5 mL; kidney V_{16Gy} < 33%; spinal cord <23 Gy
Kang, 2012	47	13	11	1.3–7.8 cm, 2.9 cm (med)	42–60/3 (by SLTD)	69% (2 y)	RILD 13%; GI 11%	Liver >700 mL <17 Gy; spinal cord <22 Gy and V_{18Gy} < 0.25 mL
Andolino, 2011	60	40	NA	1–6.5 cm, 3.1 cm (med)	CPA: 30–48/3 CPB: 24–48/5	67% (2 y)	37%; RILD: 16%	Liver V_{18Gy} < 66% and V_{12Gy} > 500 mL; bowel V_{12Gy} < 0.5 mL; R't kidney V_{15Gy} < 33%; Lt kindey V_{15Gy} < 33%; spinal cord <18 Gy
Cardenes, 2010	17	NA	18	8–95 mL, 34 mL (med)	CPA: 36–48/3 CPB: 40/5	75%	RILD 18%	Liver V_{15Gy} < 66%; bowel V_{12Gy} < 0.5 mL; R't kidney V_{15Gy} < 33%; Lt kidney V_{15Gy} < 33%; spinal cord <18 Gy; heart <30 Gy
Kwon, 2010	42	10	0	≤100 mL	<30 mL: 39/3 ≥30 mL: 30–36/3	93%	RILD 2%	Liver V_{20Gy} < 50%; stomach, bowel <21 Gy; R't kidney V_{15Gy} < 33%; spinal cord <21 Gy
Iwata, 2010	18[b]	6	NA	19–101 mL, 42 mL (med)	CPA: 55/10 CPB: 50/10	94%	RILD 0%; GI 0%	Stomach, bowel $V_{40Gy} \leq 10$ mL; spinal cord <35 Gy; kidney V_{20Gy} < 33%
Mendez-Romero, 2006	8	25	25	0.5–6.1 cm, 4.5 cm (med)	<4 cm: 37.5/4 ≥4 cm: 25/5; 30/3	75%	RILD 13% (Gr 5)	Liver V_{21Gy} < 33% and V_{15Gy} < 50%; stomach, bowel V_{21Gy} < 5 mL; spinal cord <15 Gy; kidney V_{15Gy} < 33%

CP, Child–Pugh; GI, gastro-intestine; NA, not available; PVT, portal vein thrombosis; RILD, radiation-induced liver disease; SLTD, Sum of longest tumor diameter; V_{XXGy}, the volume or percentage of organ receiving more than or equal to the xx Gy.

[a] Include 1 case with CP-C.

[b] Include 12 cases with liver metastases.

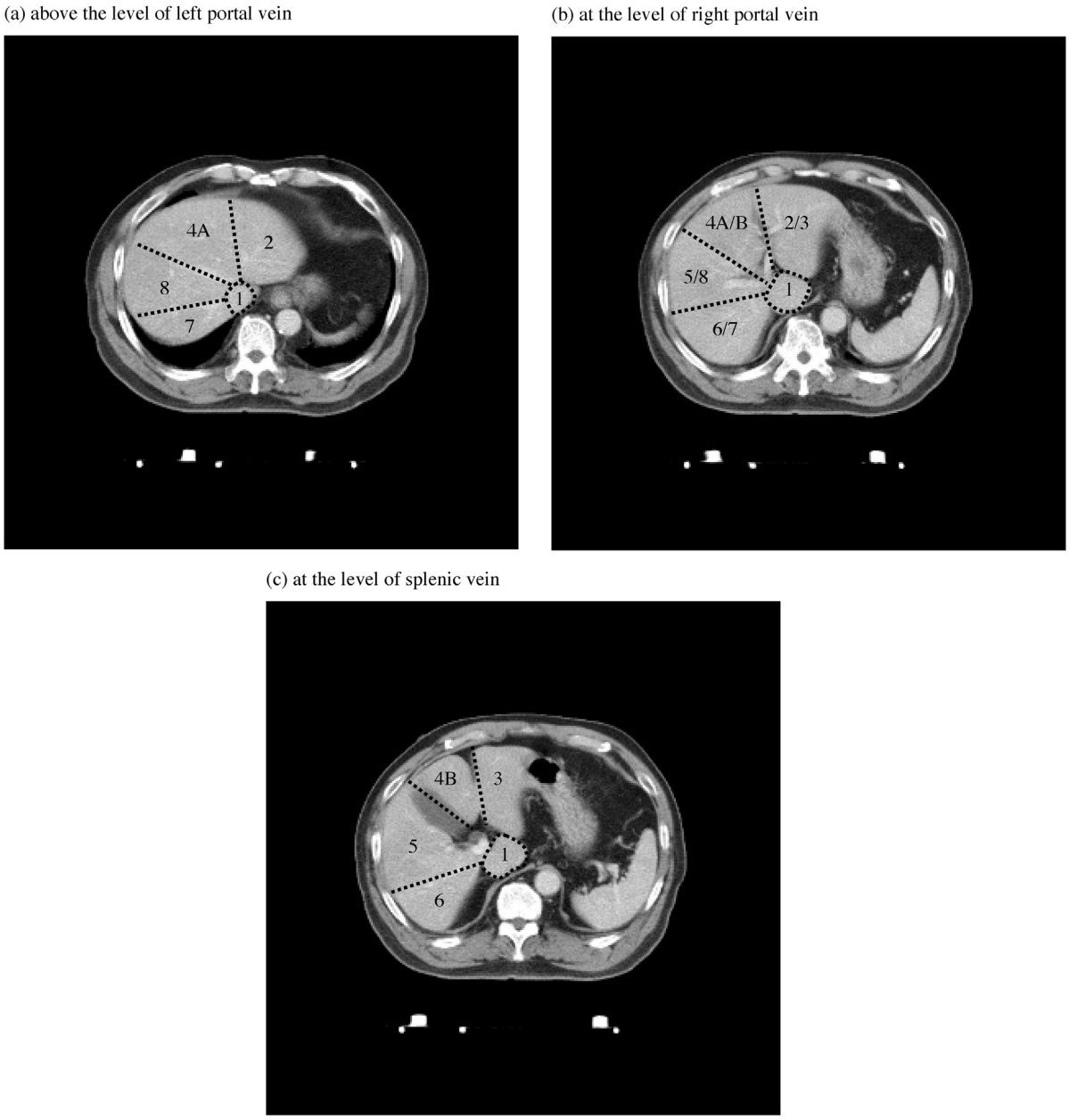

Fig. 1 – Anatomy of liver according to the Couinaud classification (a) above the level of left portal vein; (b) at the level of right portal vein; (c) at the level of splenic vein. Numerics indicate the segmentation of liver.

that may be individually resected without damage to other adjacent segments.

2.2.1. *Segment 1 (caudate lobe)*

The caudate lobe (or segment 1) is located within the posterior lobe of the liver and is considered the most dangerous zone for SBRT when combined with main portal vein thrombosis (MPVT). In this territory, the most critical organ at risk (OAR) in treatment planning is the neighboring gastro-intestinal (GI) tract, specifically the duodenum. Cone beam CT (CBCT) should be performed for repositioning accuracy and quality assurance before each fraction. The so-called "cone-down" technique is also required because of changes in the target contour or variation in the position of normal organ interfraction. A shrinkage field technique is mandatory to avoid radiation-induced GI ulcer (Fig. 2).

2.2.2. *Segment 2 (left superior lateral segment)*

Segment 2 is located lateral to the falciform ligament and superior to the left portal vein. The OAR in this zone is the stomach. When lesions are located within this area, the points of concern regarding SBRT targeting and contouring are similar to those encountered in segment 1. Cone-down technique and CBCT are important with respect to interfraction. In addition, when performing SBRT, fasting for at least 3 h before treatment to empty the stomach may help to minimize the volume of GI tract that is irradiated.

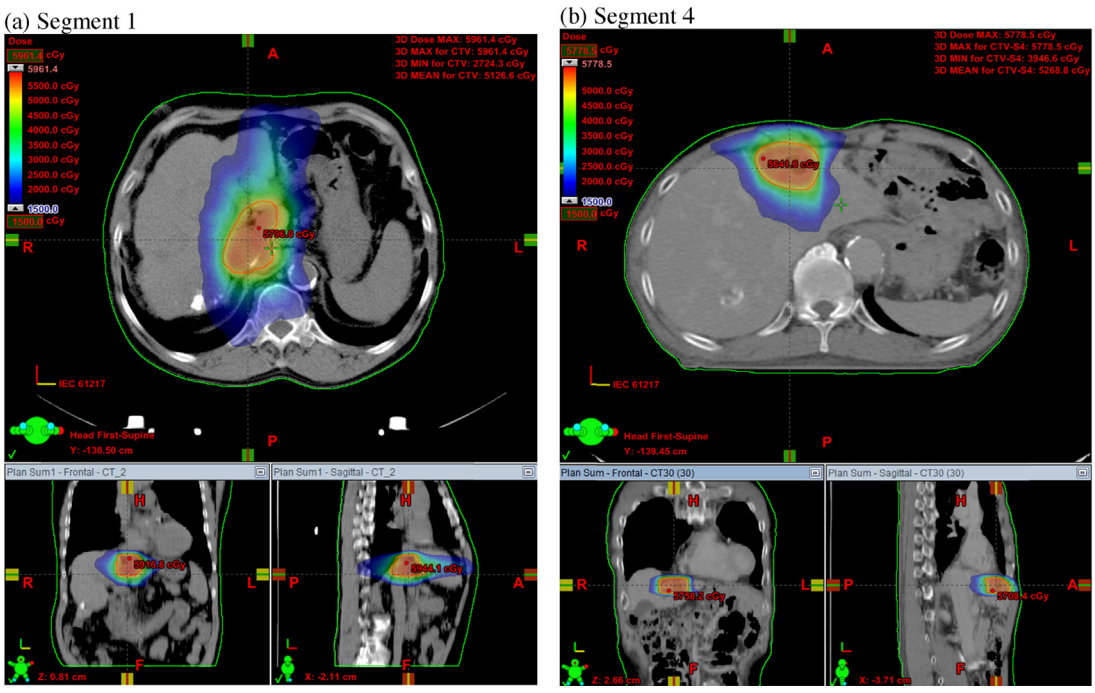

Fig. 2 – Isodose distributions for typical patients in coronal, sagittal and axial planes. The tumor located in (a) segment 1; (b) segment 4. Color-wash threshold was set to 15 Gy.

2.2.3. *Segment 3 (left inferior lateral segment)*

Segment 3 is located lateral to the falciform ligament and inferior to the left portal vein and is adjacent to the stomach. CBCT should be performed prior to each treatment. It allows for easy identification of the gastric wall by reference to the air density shown on the image. Once the air density moves toward the target or the OAR shifts position toward the high dose target area, re-planning with non-coplanar arc technique should be applied to avoid high radiation to the OAR or GI tract that can led to radiation-induced ulcer. At the same time, more of the normal liver will be preserved by this technique.

2.2.4. *Segment 4A (left superior medial segment)*

Segment 4A is separated from segment 2 by the left hepatic vein and fissure of the round ligament on CT longitudinal images and is a relatively safe segment for SBRT. The critical organs such as GI tract, kidney, and spinal cord are relatively far away from this location. In SBRT of HCC with left portal vein thrombosis (LPVT), non-coplanar arc beam angle along with the LPVT axis will preserve more of the normal right liver volume and should be considered.

2.2.5. *Segment 4B (left inferior medial segment)*

Similar to 4A, segment 4B is located between segments 3 and 5 over the inferior liver. Tumor in segment 4B with LPVT is also a dangerous zone for SBRT. The OARs are the pylorus and the second portion of duodenum (near the superior duodenal flexure). The SBRT technique for segment 4B is similar to that used for segment 3, reducing the percentage of critical organs irradiated in order to minimize GI toxicity.

2.2.6. *Segment 5 (right anterior inferior segment)*

Segment 5 is a relatively safe segment. The right lobe of the liver has a much larger volume compared with the left lobe of the liver. Through careful planning, it is feasible to spare adjacent normal segment 8 and to ensure an adequate liver reserve. The OAR in the treatment planning for this area is often the colon. Unlike radiation-induced gastric and duodenal ulcers, radiation-induced colonic ulcer, or radiation colitis, is less severe and primarily self-limited. Mucosal or submucosal damage will heal and change to telangiectasia several months after conservative and supportive treatment.

2.2.7. *Segment 6 (right posterior inferior segment)*

Segment 6 is located at the right posterior portion of the liver (also known as the “tip” of the liver). The normal liver volume in this segment is small. The OARs in segment 6 are bowel and right kidney. To spare more of the bowel and right kidney and attain better target dose conformity, the adjacent rib cage is often inevitably irradiated. Complications of soft tissue fibrosis or rib fracture are sometimes encountered.

2.2.8. *Segment 7 (right superior posterior segment)*

Segment 7 is a relatively safe segment. The main OARs in this segment are the upper pole of the right kidney and the spinal cord. A prudent assessment of spinal cord dose constraints and volume is mandatory.

2.2.9. *Segment 8 (right superior anterior segment)*

Segment 8 is regarded as the safest segment in SBRT for HCC. In our experience, HCC as large as 8 cm (protruding in an outward or upward direction) can be safely treated with SBRT.[19] Although a portion of the right lung base will be irradiated,

especially for tumors located within the dome of the liver, the risk of radiation pneumonitis is tolerable and limited.

2.3. *Tumor targeting and dose constraints for normal tissue*

Tri-phase four-dimensional CT (4-D CT) has been suggested for use in SBRT planning. For some patients whose lesions are not easily detected by CT, incorporation of magnetic resonance imaging (MRI) in planning may be necessary for a more precise target delineation.

Gross tumor volume (GTV) is defined as a primary tumor plus abnormal portal areas showed on 4-D gated CT. Clinical target volume (CTV) is defined as GTV plus a 0.5–1.0 cm margin for subclinical disease. Internal target volume (ITV) is defined as the envelope of all CTVs from the different respiratory phases and is used for treatment planning as the equivalent of the planning target volume (PTV). In addition to the target volume, the entire liver, the normal liver (whole liver minus ITV), both kidneys, the stomach, the duodenum, and the spinal cord are meticulously outlined and taken into consideration during SBRT planning optimization.

The following explicit planning objectives were defined: (1) $V_{30Gy} < 60\%$ for the total liver; (2) for normal liver, the volume receiving less than 15 Gy should be $>700\,cm^3$; (3) regarding OAR, dose constraints should include $V_{37.5Gy} < 5\%$ for the stomach and duodenum, $V_{15Gy} < 35\%$ for the kidneys: and $D_{1cm^3} < 22$ Gy for the spinal cord.

Individualized optimization should be performed using single or multiple, coplanar or non-coplanar, mono-isocentric arcs. Gated technique should be performed using the respiratory cycle in order to deliver treatment only during the selected respiratory phase (end-expiration with a duty cycle of 30–70%). Image guidance during treatment should be exploited by means of daily cone-beam CT acquisition to verify the proper positioning of the patient in three dimensions.

2.4. *Toxicity*

Because of advancements in radiation therapy techniques and proper dose constraints, GI toxicity (i.e., toxicity to the stomach, duodenum, and small intestine) and spinal cord toxicity (as noted in Sections 2.2 and 2.3) has been reduced. However, RILD is still an important issue in treating HCC patients by radiotherapy. In addition to dose-related factors affecting RILD, such as higher total dose or larger fraction size, Cheng et al.[31] reported that patients with CP-B or hepatitis B virus (HBV) are also at a significant risk of developing RILD. Patients with CP-B had worse hepatic insufficiency compared with those with CP-A[32]. The CP classification not only reflects hepatic functional reserve, but is also a prognostic factor in patients with HCC. SBRT may partially damage hepatic reserve resulting in RILD susceptibility.

In a multi-institutional phase I dose escalation study, Cardenes et al.[24] also reported that CP-B has a higher hepatic toxicity compared with CP-A. HBV [rather than hepatitis C virus (HCV) infection] was also associated with higher RILD.[33] Because HBV carriers have poor tolerance to partial liver irradiation, RILD risk increases at even low doses.[33] Huang et al.[34] reported that serum HBV DNA levels and some dosimetric parameters related to normal liver (such as normal liver volume, the volume of liver receiving more than 20 Gy, and the mean dose) were predictors of HBV reactivation during radiation therapy. Thus, patients with CP-B liver cirrhosis or HBV infection should be carefully evaluated prior to SBRT.

3. SBRT for HCC: special considerations for patients with hepatitis and liver cirrhosis

The majority (approximately 75%) of HCC patients in Asian countries are HBV or HCV carriers. Sinn et al.[35] reported that HBV-related HCC and HCV-related HCC have different oncogenic pathways. In HBV infection, the integration of HBV DNA into the patient's hepatocyte DNA will transactivate human oncogenes, while in HCV infection, chronic inflammation is the major pathway in oncogenesis.[35–37] Although HCV-related HCC has a higher recurrence rate than HBV-related HCC[38], HBV-related HCC is more aggressive than HCV-related HCC, especially in the advanced stages.[35,39]

In patients with underlying HBV or HCV infection, hepatitis reactivation is a concern as such patients are at a much higher risk of RILD during treatment. Patients with HBV have a significantly greater susceptibility to RILD after radiotherapy than patients with HCV.[31] Thus, HBV or HCV infection and liver cirrhosis status must be considered when contemplating SBRT for HCC.

Recent data have shown that CP score is more important than CP classification for predicting survival.[40–43] In patients who received sorafenib, Kim et al.[42] reported that OS was significantly better in CP-A5 compared with CP-A6 patients (8.4 vs. 5.1 months, respectively). Okajima et al.[43] also suggested that CP-A5 had better OS and disease-free survival (DFS) rates than CP-A6 patients who had undergone a curative hepatic resection. Kudo et al.[41] reported that CP score (i.e., CP-5 vs. CP-6 or higher) was the only independent risk factor for OS in patients with solitary hepatocellular carcinoma $\leq$5 cm.

Because patients with CP-A6 have more inflammation and fibrogenicity than those with CP-A5[43], CP-A6 is associated with a higher potential for liver dysfunction compared with CP-A5. Thus, SBRT is considered safe for patients with CP-A5 but, for patients with CP-A6, the individual CP scoring items have different weights with regard to the incidence of RILD. In the order of decreasing weight, these items include prolonged prothrombin time (PT), total bilirubin, hepatic encephalopathy, ascites, and albumin. Prolonged PT is the most important score when determining the incidence of RILD during SBRT in patients with CP-A6. Thus, a prolonged PT >4 s indicates severe liver decompensation and higher RILD risk. Thus, SBRT should be performed with care in CP-A6 patients with PT prolongation.

Minor GI tract bleeding or constipation may sometimes alter the serum ammonia level. Hepatic encephalopathy induced by high serum ammonia level may be relieved by lactulose administration. For patients with GI bleeding or ulceration, endoscopic cryotherapy may be beneficial in reducing high serum ammonia levels. Albumin supplementation may also be helpful in patients with lower albumin levels. In most situations, minimal ascites can be treated with diuretics.

The mechanism underlying HBV infection reactivation may be related to a bystander effect on irradiated endothelial cells which release cytokines, including interleukin-6.[44] This cytokine release may account for some cases of non-classical RILD after RT. Quantitative polymerase chain reaction for HBV DNA copy number before (and 3 months after) SBRT is necessary to exclude the possibility of HBV infection reactivation. Although lamivudine (Zeffix) is considered the drug of choice for acute fulminant HBV infection, entecavir (Baraclude) or telbivudine (Sebivo) seem to have less drug resistance. Both entecavir and telbivudine showed similar antiviral potencies and led to a rapid and profound suppression of HBV DNA.[45] Thus, the HBV-related HCC patient should receive entecavir or telbivudine from 7 to 14 days prior to SBRT to one year after the completion of RT as prophylactic treatment for HBV infection reactivation in order to minimize the risk of RILD.

4. Conclusions

SBRT is a safe and effective alternative treatment for HCC patients who are unable to undergo liver ablation or resection. However, optimal SBRT fractionation schemes and treatment planning strategies that take into consideration the OAR need to be established. The OAR and treatment concerns vary depending on the liver segment involved with HCC. Treatment strategies also require adjustment when the patient has either HBV or HCV infection and/or liver cirrhosis. Further multi-institutional prospective studies may be warranted to validate the optimal dose of SBRT for HCC.

Conflict of interest

None declared.

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