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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