Current status of stereotactic body radiotherapy for the treatment of hepatocellular carcinoma

Jongmoo Park1, Jae Won Park2, Min Kyu Kang1

1Department of Radiation Oncology, School of Medicine, Kyungpook National University, Daegu, Korea
2Department of Radiation Oncology, Yeungnam University College of Medicine, Daegu, Korea

Stereotactic body radiotherapy (SBRT) is an advanced form of radiotherapy (RT) with a growing interest on its application in the treatment of hepatocellular carcinoma (HCC). It can deliver ablative radiation doses to tumors in a few fractions without excessive doses to normal tissues, with the help of advanced modern RT and imaging technologies. Currently, SBRT is recommended as an alternative to curative treatments, such as surgery and radiofrequency ablation. This review discusses the current status of SBRT to aid in the decision making on how it is incorporated into the HCC management.

Introduction

Liver cancer is the sixth most common cancer and the second leading cause of cancer-related mortality in Korea [1]. Hepatocellular carcinoma (HCC) is the major histologic type of primary liver cancers, accounting for 70–85% [2], and has the highest mortality rate among major cancers in Korea [3]. Current treatment guidelines for HCC recommend surgical resection, liver transplantation, and radiofrequency ablation (RFA) as standard treatment options for small HCCs [4,5]. However, hepatic resection is possible in only < 30% of patients due to multifocal disease, unfavorable location, or inadequate functional hepatic reserve, and liver transplantation is associated with many hurdles such as donor availability [6]. RFA is not always safe or effective depending on the tumor size or locations [7].

Stereotactic body radiotherapy (SBRT), or stereotactic ablative radiotherapy, is an advanced form of radiotherapy (RT) that can deliver ablative radiation doses to tumors in a few fractions without excessive doses to normal tissues with the help of advanced modern RT and imaging technologies [8]. Several case series on SBRT have reported high local control rates of over 80% [9]. Current treatment guidelines for HCC recommend SBRT when other liver-directed therapies have failed or are contraindicated [4,5,10]. In addition, it is tried to be combined with other locoregional or systemic therapies.

However, radiation-induced complications in the liver and gastrointestinal (GI) tract prevent the use of SBRT. Patients with HCC often have cirrhotic liver with poor baseline liver function or less recovery ability, which could be related to a higher incidence of radiation-induced liver disease (RILD). The GI tract near the tumors often prevents high-dose irradiation from being delivered to the tumors. Respiratory movement of the liver containing tumors prevents the safe use of SBRT. For these reasons, various efforts have been implemented to understand the risk of toxicities and determine solutions.

This review discusses the current status of SBRT for HCCs in...
terms of technical and clinical aspects to help in the decision making of using SBRT while treating patients with HCC.

Radiotherapeutic considerations

1. Process of stereotactic body radiotherapy

The first step of treatment planning is acquisition of planning computed tomography (CT) images in the treatment position. Immobilization devices, such as stereotactic body frame and vacuum cushions, are usually used to improve the positional reproducibility and reduce the possible movement during the long treatment time of SBRT. Four-dimensional CT (4D-CT) scan with intravenous contrast media is usually used to identify tumor and normal organ movements during respiration. Depending on methods used for tumor localization and respiratory control during treatment, planning CT scans can be performed in various settings: free breathing or breath-hold with or without abdominal compression.

After transferring CT images to the RT treatment planning system, target volumes and normal organs are delineated. Gross tumor volume (GTV) is defined as the tumor(s) seen on imaging studies. In cases of invisible tumor(s) or unclear tumor margin on planning CT images, rigid or deformable registration with diagnostic CT or magnetic resonance imaging (MRI) can be used. The clinical target volume for SBRT is usually the same as for GTV, even though microscopic tumor extension might exist up to several millimeters. The internal target volume (ITV) is the sum of GTVs in all respiratory phases (or some predefined phases for respiratory gating). Planning target volume (PTV) is generated by adding a margin of about 5 mm (up to 10 mm) to ITV [11]. Thereafter, treatment plans are generated while considering tolerance doses of normal organs, especially for the normal liver and GI tract. Typically, 40–50 Gy in 3–5 fractions is prescribed to encompass the edge of PTV [11-14].

Immediately before treatment, the patient and tumor position are verified with orthogonal radiographs or cone-beam CT scans using various surrogate markers, such as the diaphragm, surgical clips, residual lipiodol after transarterial chemoembolization (TACE) or fiducial markers inserted a few days before planning CT. Recently, the MRI device integrated into the RT machine can be used for real-time tumor tracking during treatment. Finally, treatment starts with respiratory motion management such as active breathing control [15], abdominal compression [16], respiratory gating, and real-time tumor tracking. Respiratory gating is a technique that can treat tumors only at predefined respiratory phases. Tumor-tracking technique is thought to be an ideal method to treat moving targets, which can treat the tumors with the smallest PTV compared to other methods. With the proper use of these techniques, SBRT-related toxicities in the liver and GI tract can be minimized while ensuring enough doses to tumors.

Various imaging tools described above are used to maximize the accuracy and precision throughout the whole process, which is called image-guided radiotherapy (IGRT). The technical aspects of RT for HCC are discussed in detail elsewhere [17,18]. Fig. 1 shows an example of SBRT using tracking intensity-modulated beams.

2. Tumor dose

Radiation oncologists have used various dose fractionation schedules and investigated the impact of total dose and tumor size. For small tumors of < 3 cm (or < 5 cm), a high local control of > 90% has been achieved with a biologically effective dose (BED) of ≥ 100 Gy\(_{10}\) (e.g., 50 Gy in 5 fractions or 45 Gy in 3 fractions), which is considered as an ablative dose [12,19,20]. BED, using a conventional linear-quadratic model assuming \(\alpha/\beta\) of 10 Gy, was calculated as follows: BED = \(nd (1+d/[\alpha/\beta])\), where \(n\) is the number of fractions and \(d\) is the fraction size. In a retrospective study that escalated the radiation dose from 45 Gy in 3 fractions to 60 Gy in 3 fractions for HCCs of < 3 cm, no difference in local control was found between the 2 dose groups [20]. In contrast, several studies have reported lower local control rates in larger tumors [12,19,21]. Although Jang et al. [21] revealed that large tumors needed a higher radiation dose for the same tumor control probability of 90% as small tumors (51.1 Gy in 3 fractions for tumors of ≤ 5 cm vs. 62.1 Gy in 3 fractions for tumors of > 5–7 cm), higher radiation doses would inevitably increase the liver dose related to liver toxicity. Sanuki et al. [13] achieved a high 3-year local control rate of 91% with relatively low doses (40 Gy in 5 fractions in Child–Pugh [CP] A and 35 Gy in 5 fractions in CP B). A pooled analysis of 25 studies on SBRT revealed that overall survival was not different according to radiation doses (equivalent dose in 2 Gy per fractions [EQD2] using the \(\alpha/\beta\) ratio of 10 Gy: < 80 Gy vs. ≥ 80 Gy), where all available median EQD2 estimates ranged from 47.9 Gy to 100 Gy with a median of 83.3 Gy (equal to 100 Gy\(_{10}\) in BED) [9]. Therefore, considering that higher radiation dose and/or larger tumor volume could increase hepatic and/or GI toxicities, the risk adaptive dose–fractionation regimens would be useful to balance both tumor control and toxicities, especially in patients with poor liver function.

3. Charged particle therapy

Charged particles such as proton or carbon ions have a unique beam profile known as Bragg peak, which can prevent irradiation of normal tissues beyond the tumor. Treatment outcomes in patients with HCC treated with proton or carbon ions are promis-
Based on dosimetric studies comparing the proton and photon, proton SBRT was preferred for larger tumors in terms of liver toxicity and could meet liver dose constraints even when photon...
SBRT could not [24,25]. Despite the limited number of particle therapy facilities, charged particle therapy is a promising modality for the treatment of HCC.

Clinical considerations

1. Clinical outcomes of stereotactic body radiotherapy
Many institutions have reported their clinical outcomes after SBRT for HCC after the first report by Blomgren et al. [26]. Even though dose schedules and patient/tumor characteristics were heterogeneous, clinical outcomes were promising in terms of tumor control and toxicities. Recently, Kim et al. [9] conducted a meta-analysis on the results of 32 studies, including 1,950 patients, published in between 2010 and 2018. The median proportion of CP A was 82.3% (range, 47.9–100%). The median of the median tumor sizes was 3.3 cm (range, 1.6–8.6 cm). The median of the median EQD2 estimates was 83.3 Gy (range, 48.0–114.8 Gy). Pooled 1-, 2-, and 3-year overall survival rates were 72.6% (95% confidence interval [CI], 65.7–78.6), 57.8% (95% CI, 50.9–64.4), and 48.3% (95% CI, 40.3–56.5), respectively. Pooled 1-, 2-, and 3-year local control rates were 85.7% (95% CI, 80.1–90.0), 83.6% (95% CI, 77.4–88.3), and 83.9% (95% CI, 77.6–88.6), respectively. Larger tumor size of ≥ 5 cm was a significant factor for worse local control and overall survival rates. Hepatic and GI complication rates of grade ≥ 3 were 4.7% (95% CI, 3.4–6.5) and 3.9% (95% CI, 2.6–5.6), respectively. Overall, these results imply that SBRT is a safe and effective local ablative therapy.

2. Selection of local modalities
Tumors unsuitable for ablation or surgical resection or with failed treatments have usually been treated with SBRT; however, deciding whether a patient is a proper candidate for SBRT or which is the best modality is difficult. Data below would help the multidisciplinary team to recommend SBRT for a given patient, even though the evidence level is low.

Overall local control rates of SBRT and RFA have been reported to be comparably high [27,28]. SBRT was notably achieved a higher local control rate than RFA for tumors of ≥ 2 cm in Wahl et al.’s study [28], which may be related to the better radiation dose coverage of SBRT and limited heat transfer to long distances from the heat source of RFA. In addition, tumor control was not influenced by the tumor size after SBRT in two studies with a median tumor size of 2.2 cm (range, 0.10.0 cm) and 7.2 cm (range, 1.4–23.1 cm) [28,29], which implies that SBRT could be a preferred treatment option for large tumors.

RFA is less effective or contraindicated in the following situations: tumors close to the major vessels (due to the heat sink effect); tumors abutting the diaphragm (due to the risk of diaphragmatic injury); tumors on the liver capsule (due to the risk of rupture or track seeding); centrally located tumors (due to the risk of bile duct injury); and invisible tumors on ultrasonography [30]. Instead, SBRT is less influenced by tumor location, except its distance from the GI tract.

An important difference between RFA and SBRT is repeatability. In contrast to RFA, repeated use of SBRT is limited for new HCC lesions due to the decreased liver function after SBRT [31]. Considering that frequent intrahepatic recurrences of HCC require repeated treatments, SBRT might be spared for lesions unsuitable for other liver-directed treatments. In contrast, Lee et al. [32] reported the treatment outcomes after a repeated SBRT for recurrent HCCs with a median tumor size of 1.7 cm (interquartile range, 1.4–2.2 cm) in 85 patients. The 3-year local control rates were not different between the first and second SBRT (94.9% vs. 90.4%, p = 0.667). None of the 73 patients with CP A experienced RILD after the second SBRT, whereas 2 of the 12 patients with CP B experienced irreversible liver function deterioration. Although the use of repeated SBRT has been limited so far, SBRT can be reapplied to highly selected patients with good liver function.

The superiority in the survival aspect between SBRT and other treatments has been controversial. RFA showed superior survival compared to SBRT in a study based on a large number of patients from the National Cancer Database [33]. When comparing SBRT with surgical resection, survival was comparable or superior in the surgery group, depending on the studies [34,35]. However, a firm conclusion cannot be made because of both the retrospective design and potential selection bias in these studies.

Toxicities after stereotactic body radiotherapy

1. Liver
Liver toxicities, or RILD, is the most important dose-limiting factor for the treatment of liver tumors [36]. Patients with HCC are more vulnerable to the development RILD, because HCC frequently occurs in a cirrhotic liver susceptible to radiation injury. Non-classic RILD (elevation of liver transaminases or decline of CP score) is usually reported after SBRT, rather than classic RILD (anicteric hepatomegaly and ascites or elevation of alkaline phosphatase). The RILD rate of grade ≥ 3 was as low as 4.7% (95% CI, 3.4–6.5) in a pooled analysis of 23 studies, which was generally transient [9]. Since worse baseline liver function is correlated with higher risk of severe RILD [13,37–40], caution is warranted in deciding the treatment and SBRT planning in patients with poor liver function. Although no definite guidelines
were available for liver constraints, the following guidelines have been used: limiting SBRT to CP A or B7 patients [5]; adjusting prescription dose using the normal tissue complication probability of the liver [39]; limiting the normal liver dose (e.g., mean normal liver dose: < 13–18 Gy in 3–6 fractions for CP A vs. ≤ 6 Gy in 4–6 fractions for CP B) [36]; or sparing the critical residual liver volume (e.g., ≥ 700 mL of normal liver receives ≤ 15 Gy in 3–5 fractions) [36].

2. Gastrointestinal tract
Because tolerance doses of luminal structures such as the esophagus, stomach, or intestine are much lower than ablative doses used for SBRT, special concerns are required for lesions close to luminal structures. In one case series, all 5 patients who experienced grade 3 or 4 GI toxicities had lesions within 0–0.4 cm from the GI tract [21]. Radiation oncologists generally recommend SBRT for lesions with enough distance from GI tract (e.g., > 1–2 cm) [14,41]. To overcome this limitation, various techniques are attempted, including 4D-CT, abdominal compression, gated RT, tracking RT, or intensity-modulated beam. Real-time tumor tracking, using fiducial markers (Fig. 1A) or MRI images, is the current most advanced method used to avoid the GI tract close to tumors. Fig. 1 shows an example of a patient undergoing follow-up without GI complication at 33 months after receiving tracking SBRT for a tumor at 5 mm from the bowel. Tolerance doses of luminal structures are discussed in detail elsewhere [42-45].

3. Bile duct
Biliary stricture has been occasionally reported at the rate of 0–3% [12,28,32,46-48]. Eriguchi et al. [49] found biliary stenosis in 2 out of 50 patients irradiated with over 20 Gy to the central biliary system; 1 patient experienced biliary stricture at the area irradiated with > 80 Gy after the second SBRT and the stenotic site of the other patient was outside the area irradiated with > 20 Gy. In addition, even in a study that investigated the relationship between the central hepatobiliary tract dose and hepatobiliary toxicity rate (not only for biliary tract complications), no biliary stricture was observed in 20 patients with HCC unlike the intrahepatic cholangiocarcinoma with high rate of biliary stricture (38.8% of 26 patients) [50]. Therefore, SBRT seems to be a feasible modality for centrally located tumors unsuitable for other treatments.

Additional indications of stereotactic body radiotherapy

1. As a bridge therapy
Bridge therapies can be used to prevent tumor progression while waiting for transplantation or to downstage tumors into the Milan criteria. SBRT as a bridge therapy has also been reported as safe and effective. O’Connor et al. [51] and Andolino et al. [52] reported that SBRT did not increase surgical complications. Sapioschin et al. [53] revealed that drop-out, post-transplant survival, and HCC recurrence rates after liver transplantation were similar among SBRT, TACE, and RFA. Mohamed et al. [54] showed that acute toxicities of SBRT and yttrium-90 radioembolization were lower than those of TACE or RFA. These results suggest that SBRT is a viable option as bridge to transplantation.

2. In advanced hepatocellular carcinoma
HCC with portal vein tumor thrombosis (PVTT) has poor prognosis; however, the standard treatment strategy remains to be established. RT has been used to restore the portal flow and facilitate subsequent treatments such as surgery or TACE. The response rate was 39–57% with conventional RT using a small fraction size of 1.8–3 Gy, which requires a long treatment period (e.g., 45–50 Gy in 25 fractions over 5 weeks) [55]. Advanced RT techniques such as intensity-modulated RT or IGRT facilitate giving higher radiation doses without increasing GI toxicities, with which higher tumor response and better survival would be expected [56]. Although advanced tumor characteristics related to PVTT, poor liver function, or close distance to GI tract often limit the use of SBRT for PVTT [57], recent studies have reported high PVTT response rates (70–76%) after SBRT using relatively low dose regimens (e.g., 40 Gy in 5–6 fractions over 1–2 weeks) [58-60]. Therefore, SBRT, which ends in a short treatment period, is worth of future investigation for the treatment of PVTT, especially in combination with recently developed systemic agents.

Large or multiple HCCs not suitable for curative treatments are often treated with TACE with or without RT [4,5]. A meta-analysis by Meng et al. [61], comparing TACE plus RT to TACE alone, revealed that the adding RT to TACE improved the tumor response and survival, where small doses per fraction or lower total doses were usually used for fear of toxicities in the liver and GI tract. As SBRT has a higher capability of sparing normal tissues as compared to RT techniques used before, SBRT could be assumed to increase the clinical outcomes when combined with TACE for large HCCs. Jacob et al. [62] reported that TACE plus SBRT (45 Gy in 3 fractions) achieved better local control and survival rates than TACE alone in HCCs of ≥ 3 cm. Paik et al. [63] confirmed the comparable survival outcomes among the three treatment groups (complete TACE alone, incomplete TACE followed by curative treatments, and incomplete TACE followed by SBRT [46–60 Gy in 3–5 fractions]).
results imply that SBRT is an effective adjuvant treatment for HCCs showing an incomplete response to TACE.

3. In combination with systemic therapies

Despite the high local control rates of SBRT, there is a demand to combine SBRT with systemic agents due to frequent intrahepatic or extrahepatic recurrences after SBRT. Sorafenib, a multikinase inhibitor, was attempted to be combined with SBRT based on improved overall survival in patients with advanced HCC treated with sorafenib (vs. best supportive care group) in SHARP phase III trial [64] and in vitro and in vivo radiosensitizing effect of sorafenib in HCC cell lines [65]. However, the addition of sorafenib to SBRT is not currently recommended due to increased risk of GI toxicities [66,67].

Recently, immunotherapy has been successfully employed for the treatment of solid tumors such as melanoma and non-small cell lung cancer, and the combination of immunotherapy with RT is an active field of clinical investigation [68]. SBRT using a high radiation dose per fraction is known to have an immunomodulatory effect, which can potentially improve tumor response and survival outcomes of immunotherapy [69]. Notably, abscopal effect, or tumor regression outside the RT field, has been increasingly reported when RT was combined with immunotherapy, even though it was a rare phenomenon before the era of cancer immunotherapy. Mechanisms of abscopal effect, related to systemic effect of radiation, are also being revealed [70,71]. In 2017 and 2018, 2 immune checkpoint antibodies, nivolumab and pembrolizumab, have been approved to be used as a second-line therapy for HCC by the Food and Drug Administration. Preclinical data showed that the combination of programmed death ligand 1 blockade and RT significantly suppressed the tumor growth in a murine HCC model compared with single treatments [72]. And, there are several ongoing phase I or II trials combining immunotherapy and SBRT for patients with HCC (NCT03203304, NCT03316872, NCT03482102, and NCT03817736). With this new strategy, the prognosis of both early and advanced HCCs is anticipated to improve via enhanced local and systemic effects.

Conclusion

Current evidences support the use of SBRT as an alternative or complement to curative treatments based on its high local control rates and low toxicity profiles. There is also an emerging interest in combining SBRT with other locoregional or systemic therapies to potentially maximize treatment outcomes. Clinical uses of SBRT are summarized in Table 1. However, optimal dose-fractionation regimens balancing tumor control and toxicities and methods to overcome the current limitations of SBRT should be determined. Given that clinical presentations of patients with HCC are significantly heterogeneous, a multidisciplinary team approach could determine the best candidates who would benefit from SBRT with or without combined treatments.

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

ORCID

Jongmoo Park, https://orcid.org/0000-0002-7004-8128
Jae Won Park, https://orcid.org/0000-0003-1100-5301
Min Kyu Kang, https://orcid.org/0000-0002-7962-7054

References

5. Korean Liver Cancer Association; National Cancer Center. 2018

Table 1. Clinical uses of stereotactic body radiotherapy for hepatocellular carcinoma

| 1. Recommended by major guidelines for HCC management |
| - As an alternative to curative treatment options for single tumors or multiple small lesions with a limited number (BCLC stage 0–A) |
| 2. Based on small case series |
| - As a bridge therapy to prevent tumor progression or to downstage tumors into the Milan criteria |
| - As an adjuvant therapy after incomplete transarterial chemoembolization for large tumors (BCLC stage A) or multiple lesions (BCLC stage B) |
| - As palliative therapy to restore the portal flow and facilitate subsequent treatments in HCC with portal vein thrombosis (BCLC stage C) |
| 3. Promising |
| - In combination with immunotherapy with the potential to enhance local and systemic control |

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer.


30. Rhim H, Yoon KH, Lee JM, Cho Y, Cho JS, Kim SH, et al. Major complications after radio-frequency thermal ablation of he-


54. Mohamed M, Katz AW, Tejani MA, Sharma AK, Kashyap R, Noel MS, et al. Comparison of outcomes between SBRT, yttre-
um-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. Adv Radiat Oncol 2015;1:35–42.


