

Stereotactic body radiation therapy: A novel treatment modality for inoperable hepatocellular carcinoma

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Summary

Hepatocellular carcinoma (HCC) is the most common malignancy in the world and the most common cause of cancer-related death. Surgical resection is the standard of care for solitary liver-confined HCC and provides the best long-term survival, however, most HCCs are diagnosed at an intermediate to advanced stage, and few meaningful therapeutic options are available at this point. Stereotactic body radiation therapy (SBRT) is a type of external beam radiation therapy (EBRT) that delivers radiotherapy (RT) accurately and precisely to the tumor, more so than conventionally fractionated RT. Several series report high rates of local control and low incidence of complications in SBRT for inoperable HCC. Herein, we discuss the emerging role of SBRT as well as current indications, implementation, efficacy and toxicities after SBRT. It was noted that SBRT was a safe and effective therapeutic option for HCC lesions unsuitable for standard locoregional therapies, with acceptable local control rates and low treatment-related toxicity. The significant correlation between local control (LC) and higher doses and between LC and overall survival (OS) supports the clinical value of SBRT in these patients.

Keywords: Stereotactic body radiation therapy, inoperable hepatocellular carcinoma, local control, overall survival, toxicities

1. Introduction

Hepatocellular carcinoma (HCC) is the most common malignancy in the world and the most common cause of cancer-related death. In the USA, the incidence is low compared with that in Eastern Asia because the majority of cases occur due to the increasing prevalence of viral infection (1,2). Surgical resection is the standard of care for solitary liver-confined HCC and provides the best long-term survival, as it treats both cancer and the underlying cirrhosis (3). However, most HCCs are diagnosed at an intermediate to advanced stage, and few meaningful therapeutic options are available at this point such as transcatheter arterial chemoembolization

(4-6). Even though progress has been achieved for HCC diagnosis and treatment, the overall 5-year survival rate for all patients with HCC has remained steady at 3% to 5% (7). Therefore, it is important to depend upon a palliative treatment option for patients with inoperable HCC. In addition, radiation-induced liver disease (RILD) was the main issue that limited use of RT for HCC treatment, until technological advances provided improvements on the application of radiation therapy (8).

Stereotactic body radiation therapy (SBRT) is a type of external beam radiation therapy (EBRT) that delivers radiotherapy (RT) accurately and precisely to the tumor, more so than conventionally fractionated RT. It can be delivered either using a traditional linear accelerator or using a robotic arm (*i.e.* CyberKnife). Currently, the role of SBRT is not defined in the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer (EASL-EORTC), and National Comprehensive Cancer Network (NCCN) guidelines for HCC treatment, while

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several series report high rates of local control and low incidence of complications in SBRT for inoperable HCC (9-33). Herein, we discuss the emerging role of SBRT as well as current indications, implementation, outcomes and toxicities after SBRT.

2. The indications of SBRT for inoperable HCC

Although the indications of SBRT for inoperable HCC have evolved, the role of SBRT in inoperable HCC is less clear. Currently, certain requirements and restrictions for patients with inoperable HCC who receive SBRT are as follows: (i) the number of tumor lesions (typically ≤ 3); (ii) the tumor size (the longest individual tumor diameter was less than 6 cm); (iii) no extrahepatic metastases, and (iv) Child-Pugh score A or B, *etc.* In addition, a number of other requirements and restrictions to assess the patient situation including a Karnofsky performance score ≥ 70 ; patient's life expectancy was more than 3 months; serum liver enzymes concentration was twice less than the upper limit of the normal range (34-36). Therefore, careful patient selection is required and SBRT should be considered only after thorough discussion within a multi-disciplinary team, with all legitimate treatment options also considered.

3. The implementation of SBRT for inoperable HCC

SBRT needs the image-guided radiation treatment planning system to ensure accurate implementation of radiation, and it can be delivered either using a traditional linear accelerator or using a robotic arm (*i.e.* Cyber-Knife). Except for computed tomography (CT), the role of magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) images in SBRT were paid more and more attention because they can clearly display the actual tumor boundaries, and distinguish between edema, tumor and normal liver tissue, as well as help radiation oncologist to seek tumor target. The implementation of SBRT for inoperable HCC included the tumor target confirmation, the prescription dose and fractionation, normal tissues constraints confirmation, and quality control of SBRT.

3.1. The tumor target confirmation of SBRT

The gross target volume (GTV) of inoperable HCC was defined by most radiation oncologists as the visible gross tumor from imaging such as CT, MRI, PET-CT, or the combination. The planning target volume (PTV) was defined as the GTV with some margins in the x, y, and z-axis direction. Theoretically, the PTV was affected by tumor size, location of tumor lesion, the respiratory motion and setup errors, *etc.* The PTV was also amended according to adjacent organs at risk (*e.g.*

duodenum, stomach, and small intestine bowels, *etc.*). In addition, the rapid fall off radiation dose outside the GTV has met the requirements of CTV because of the high SBRT fractionated dose, so the vast majority of studies have adopted that GTV with a margin to generated PTV.

3.2. The prescribed dose and fractionation of SBRT

There are wide variations in dose prescription and fractionation across published series even with the limited number working on the same protocol. The dose is prescribed in nearly all cases to the 80% isodose line covering the PTV (34-36). The dose per fraction and total dose were determined using the dose-volume histogram and organs at risks (OARs) specific report. The normal liver was defined as the volume of liver not included in the PTV (total liver volume minus PTV) and the dose constraints protocol for normal liver and to the OARs should respect the described constraints. In addition, overwhelming evidence confirmed that the prescribed dose and fractionation were specified according to tumor size, location of tumor lesion, the therapeutic purpose, and patient status, *etc.*

3.3. The normal tissue constraints of SBRT

Tolerance of the liver to SBRT derived from experimental models using conventional fractionation schemes and the linear-quadratic model has been well documented. The major dose-limiting concern in the use of SBRT for liver tumors is the risk of radiation-induced liver disease (RILD). The risk is generally proportional to the mean dose of radiation delivered to normal liver tissue because the liver obeys the parallel architecture model of radiobiology.

Although the liver dose limits currently vary, it was agreed that the need to ensure a certain volume of normal liver from the high doses of radiation. Each regimen provided a constraint to roughly one third of normal liver tissue and across all studies, threshold doses ranged from 7 to 21 Gray. Among them, it was generally acknowledged that a critical volume constraint of 700 mL of normal liver should not receive more than 15 Gray in 3 fractions, assuming that the liver volume was at least 2,000 cm³ (29,34). The dose-volume planning objectives for other OARs were defined as follows: stomach, small intestine, maximal dose ≤ 21 Gray in 3 fractions; bilateral kidney, mean dose ≤ 21 Gray in 3 fractions; and spinal cord, ≤ 21 Gray in 3 fractions (21,27).

3.4. The quality control of SBRT

Considering that high doses are delivered in a few numbers of fractions, the movements of the liver during the treatment have to be taken into consideration

(32,35). The need for accurate repositioning from simulation to treatment and rigorous compensation for organ motion require control devices such as abdominal compression or breath-hold maneuvers to maintain the tumor in a reproducible stage of the respiratory cycle. The radiation ray periodically switched when patients received respiration and breathing control devices, and it was noted that it can effectively reduce the normal tissue radiation dose around the tumor. In addition, daily image guidance using on-board cone-beam computed-tomography (CBCT) imaging is mandatory to delocalize the target before each treatment delivery (37). Advanced techniques allow controlling the positioning of the fiducial markers during the irradiation with on-line verification of the positioning of the target.

4. The efficacy of SBRT for inoperable HCC

The treatment efficacy of inoperable HCC is undoubtedly the focus of radiation oncologists and clinical researchers. Currently, SBRT is an effective modality with good LC and acceptable toxicity for inoperable HCC. Further studies in more favorable patients and a longer follow-up period should further elucidate the dose-response relationship, the potential late toxicity profile, and the chances of long-term survival after SBRT. The updated results from the most important series are reported in Table 1.

4.1. Local control rate

At present, most studies show 1-year and 2-year LC rates of inoperable HCC treated with SBRT was about 72-89.8% and 64% in the best cases, respectively. In general, fixed doses of 40-60 Gray/3-5 fractions are employed for relatively small tumors with a median diameter of approximately 3 cm. In contrast, modified doses are employed for relatively larger targets according to normal liver tolerance depending on tumor size and normal liver volume (Table 1). Current evidence shows that many important factors affecting LC rate include total dose and per fractionation, BED, and tumor size, etc.

Several studies demonstrated that a dose-response relationship seems to be associated with local control. In the setting of HCC, Andolino *et al.* (22) compared their results (with a median total dose between 40 and 44 Gray) with those reported by Tse *et al.* (median dose 36 Gray) (38). The former reported a local control rate of 90% at 2 years, while the latter reported a local control of 65% at 1 year. The most likely explanation could be a higher median dose per fraction and a lower median tumor volume. Similarly, a Korean series of 108 patients suffering from inoperable HCC treated with an escalated dose from 33 Gray in 3 fractions to 60 Gray in 3 fractions demonstrated the role of the dose in a multivariate analysis for LC rate (15). Based on a

tumor control probability model, the dose of 54.8 Gray is associated with 90% probability of local control at 2 years. However, in a study of 185 patients with HCC (median diameter, 27 mm) treated with SBRT of 35 Gray or 40 Gray in 5 fractions, both local control (91% and 89%, respectively; $p = 0.99$) rates were equivalent between the two dose groups (11). The reason for these discrepancies may in part be attributed to the histology, patient selection, and other treatments used. In any case, the vast majority of studies have shown that a higher total dose of SBRT should be set if patients' general condition permitted and the surrounding normal tissues could be tolerated.

Scorsetti *et al.* (9) also demonstrated that a dose-response relationship between BED and LC in inoperable HCC and a higher more intense BED and dose contribute to higher LC. They conducted prospective clinical trial in 43 inoperable HCC patients with treatment pattern of 48-75 Gray/3f and 36-60 Gray/6f and the results showed actuarial LC rate at 6, 12, 24 months with BED > 100 Gray were much higher than that with BED < 100 Gray. So they preliminarily thought there would be a certain relationship between BED and LC rate. Though there is no approved definite total dose and fractionation pattern, most researchers thought that SBRT could cure tumors with BED > 100 Gray.

In addition, Mendez *et al.* found (29) that using doses ranging from 25 Gray (tumor size at least 4 cm) to 37.5 Gray (tumor larger than 4 cm) in 3 fractions, the 1-year and 2-year local control were 94% and 82%, respectively. Concurrent with the above study, Scorsetti *et al.* (9) conducted prospective clinical trials in 43 inoperable HCC patients with a treatment pattern of 48-75 Gray/3f and 36-60 Gray/6f and the results showed actuarial LC rate with GTV < 5 cm was much higher than that with GTV ≥ 5 cm. So these preliminary outcomes demonstrated that there would be a certain relationship between tumor size and prescription dose/fractionation, thus affecting the LC rate. Other factors may also affect treatment outcomes including primary tumor histological type, progression free survival, and number of lesions. For example, our previous pooled analyses showed that SBRT combined with TACE significantly improved local control rate (39).

4.2. Overall survival

There existed apparent differences in overall survival of inoperable HCC patients for influencing factors such as dose and fractionation pattern. Sanuki *et al.* (34) summarized that currently for inoperable HCC patients 1-year OS and 2-year OS were 21-69% and 30-38% after SBRT, respectively.

Bujold *et al.* (13) conducted phase I and II combined clinical trials in 102 inoperable HCC patients with a treatment pattern of 24-54 Gray/6f and the results showed the median follow-up time and the median

Table 1. Stereotactic body radiation therapy for inoperable HCC (sample ≥ 38)

Ref.	Type	Patient/ lesion number	Child-Pugh A/B/C number	Median volume (mL)	Median size (cm)	Median dose/fraction, Gy	Median follow-up (mo)	LC	OS	Toxicity ≥ G3 (%)
Bujold <i>et al.</i> (13)	Pro LA	102/-	A and B; 35/ C; 67	117	7.2	24-54/6	31.0	87% (1-yr)	Median 17.0 months	26.5
Kang <i>et al.</i> (19)	Pro CK	47/56	41/6/0	29	-	57/3	17	94.6% (2 yr)	68.7% (2 yr)	10.7
Scorsetti <i>et al.</i> (9)	Pro LA	43/63	A/B; all patients	-	4.8	48-75/3 36-60/6	8.0	85.5% (1 yr) 64.4% (2 yr)	77.9% (1 yr); 45.3% (2 yr)	16
Seo <i>et al.</i> (23)	Pro CK	38/-	34/4/0	40.5	-	33-57/3-4	15	78.5% (1 yr) 66.4% (2 yr)	68.4% (1 yr) 61.4% (2 yr) 42.1% (3 yr)	2.7
Sanuki <i>et al.</i> (11)	Retro LA	185/185	158/27/0	8	-	CPA:40/5 CPB:35/5	24	99% (1 yr) 93% (2 yr) 91% (3 yr)	95% (1 yr) 83% (2 yr) 70% (3 yr)	13.0
Jang <i>et al.</i> (15)	Retro LA	82/95	74/8/0	-	3	51/3	30	87% (2 yr) 82% (5 yr)	63% (2 yr) 39% (5 yr)	7
Yamashita <i>et al.</i> (10)	Retro LA	79/-	67/9/1/2	-	-	48/4	21.0	-	52.9% (2 yr)	4.6
Huerts <i>et al.</i> (33)	Retro CK	77/97	35/6/36	11.7	2.4	45/3	12.0	99% (2 yr)	81.8% (1 yr); 56.6% (2 yr)	5.2
Andolino <i>et al.</i> (22)	Retro LA	60/71	36/24/0	29	3.2	CPA:44/3 CPB:40/5	27	90% (2 yr)	67% (2 yr)	0
Kwon <i>et al.</i> (24)	Retro CK	42/-	38/4/0	15.4 cc	-	30-39/3	28.7	72% (1 yr) 67.5% (3 yr)	92.9% (1 yr); 58.6% (3 yr)	2.3
Xi <i>et al.</i> (14)	Retro LA	41/-	-	65	-	36/6	10.0	-	50.3% (1 yr)	2.4

Abbreviations: Retro, Retrospective; Pro, Prospective; CK, CyberKnife; LA, linear accelerator; Gy, Gray; LC, Local control; OS, Overall survival; Yr, Year.

survival time were 31.0 and 17.0 months, respectively. Similar to above results, Andolino *et al.* (22) conducted a prospective phase I/II clinical trial study with total dose range from 24-48 Gray in 6-16 fractions showing that 2-year OS rates were 67%. Until now, the best LC rate provided by a large sample study, and 3-year LC rate was up to 91% when the patients received SBRT of 35 Gray/5 fractions (11).

Similarly, a Scorsetti *et al.* (9) study also demonstrated that there was a significant correlation between OS and BED as well as tumor size, with a median OS of 27 months in patients treated with BED > 100 Gray versus 8.1 months in those patients treated with BED < 100 Gray ($p < 0.05$). In addition, OS decreased significantly in the subgroup of patients with cumulative GTV > 5 cm (1-year OS rate of 48%), while patients with GTV < 5cm presented a 1-year OS rate of 85% ($p = 0.046$). Furthermore, several studies were consistent with the results of Scorsetti *et al.*, which showed that tumor size was an independent prognostic factor for OS of patients (15,18). These results support the use of ablative dose in the treatment of inoperable HCC, not only to increase the local response, but also to improve the prognosis of these patient populations, even if there is no candidate for effective alternative care.

A number of studies have demonstrated that the primary histological type, progression free survival, number of lesions, tumor size and systematic treatment except for total radiation dose and fractionation pattern also affected the OS of patients with inoperable HCC receiving SBRT. Therefore, we expect to have more meticulous and comprehensive studies to further understand and correctly evaluate the curative effect of SBRT for inoperable HCC patients.

4.3. SBRT for inoperable BCLC-C stage HCC

There are recently published reports of various treatment modalities for BCLC-C stage. The median survival time of BCLC-C stage was 2-28 months. One-year and 3-year OS rates were 6-70% and 1-41%, respectively (40-45). Although the best treatment outcome was associated with surgery, however, surgery is indicated in highly selected patients among the BCLC-C stage.

Culleton *et al.* (46) conducted pooled analysis of prospective (14/29, 48.28%) and retrospective (15/29, 51.72%) clinical study in 29 patients, and most of them were BCLC-C stage inoperable HCC (CP class B; 28 and CP class C; 1). The median dose was 30 Gray in 6 fractions, and the median OS and the 1-year survival rate were 7.9 months and 32.3%, respectively. There was no significant difference in OS between prospective and retrospective groups of patients ($p = 0.308$). Though Bae *et al.* (47) treated 35 inoperable BCLC-C stage HCC patients (CP class A; 32 and CP class B; 3) with a totally different fractionation pattern (30-60 Gray/3-5 fractions), they obtained better OS rates with 52% for 1-year

and 21% for 2-years, respectively. The reason they analyzed was that patients with CP class A were the best candidates and at least SBRT dose of BED > 80Gray was required for BCLC-C stage. It is clear that SBRT would be considered a treatment option for BCLC-C stage, especially in Asian countries. We suggest that CP class A is the best candidate for SBRT in patients with BCLC-C stage. In addition, SABR dose of at least BED > 80 Gray would be required to achieve a considerable treatment outcome.

4.4. SBRT successful bridge to transplantation for unresectable HCC

Importantly and interestingly, there is always a waiting period between listing and transplantation, and this varies among institutions. Because of prolonged wait times on transplantation lists, the incidence of disease progression while listed for organ transplantation ranges from 10% to 23%. Many therapies have been used as a "bridge" to transplantation, and SBRT has also been evaluated as a means to bridge to transplantation. As a bridging therapy, SBRT has been reported to be feasible and well tolerated (48-50). Therefore, future studies should focus not only on maximizing efficacy, but also on determining how SBRT should be used in the context of other previously established therapies.

4.5. SBRT combination with TACE for inoperable HCC

Numerous clinical studies of TACE plus SBRT for patients with inoperable HCC have emerged recently. Among these trials, two strategies of combining SRT with TACE have been studied. The most common approaches included the use of SBRT follow by TACE procedures and TACE procedure follow by SBRT. The first involves using RT to treat portal vein and inferior vena cava tumor thrombus to complement TACE. The rationale for this approach is that TACE is less effective in patients with portal vein tumor thrombus, and RT may make TACE more effective if portal vein disease can be eradicated. A second approach is to deliver RT as a "consolidation" planned procedure to target residual hepatic tumor after TACE. The rationale for this approach is that RT targets cancer cells at the tumors periphery that may remain viable through blood supply from collateral circulation or recanalization of the embolized artery (51). The third approach, tumor shrinkage after TACE allows the use of smaller irradiation fields, which permits higher tumor doses and improves normal liver tolerance (52). Furthermore, the TACE anticancer drugs retained in the tumor may have a radiosensitizing effect (53,54). Hence, we asserted that the combination of TACE with RT may remedy the limitation of each alone and have synergistic effects.

Although considerable evidence indicates that TACE plus SBRT is highly beneficial for treating

patients with UHCC. It is still unclear whether the existing evidence is scientifically rigorous enough to recommend its routine use to palliative treatment of UHCC. Hence, the methodological quality of clinical trials with TACE plus SBRT for inoperable HCC needs improvement in accordance with the Consolidated Standards of Reporting Trials statement (CONSORT). In particular, rigorously designed, multi-center, large, randomized, double-blind, controlled trials are required.

5. The toxicities of SBRT for inoperable HCC

The SBRT for inoperable HCC patients was considered to potentially cause risk of RILD. Therefore, how to avoid and predict the occurrence of RILD has become another key of inoperable HCC using SBRT. Some reviews summarized many studies showing normal liver dose was the important factor to predict the occurrence of RILD (22-24). When enough normal liver could avoid irradiation, the highest prescription dose of liver lesion was even up, and in those circumstances the non-irradiated normal liver tissue could maintain function. It was noted that average liver irradiation dose and normal liver volume after SBRT had a close relationship with adverse events, so those limits should be paid attention to when formulating a radiotherapy plan, especially for patients who had small normal liver volume (< 1000 mL) before SBRT.

The toxicities were mild (CTCAE Grade 1-2), with most patients experiencing constitutional symptoms, elevated liver enzyme, and leucopenia, *etc.* These symptoms were transient and resolved with conservative management. It has been reported that adverse events were relatively rarely observed in surrounding liver tissue, particularly in gastrointestinal tissue, but patients had the lesion in close proximity to the gastrointestinal tract and relatively high doses were delivered to the gastrointestinal tract who may experience Grade 3 and 4 gastrointestinal toxicity (15). For example, Tse *et al.* (38) reported several Grade 3 and 4 gastrointestinal complications after escalating the SBRT dose for inoperable HCC. Among these patients with gastrointestinal complication, one patient appearing with duodenal ulcer at the distal stomach and proximal duodenum received 20 Gray/4 fraction irradiation. Therefore, dose-volume constraints for OARs around the liver are strict especially in stomach and duodenum. Currently, the case of biliary stricture after SBRT has not been reported, nonetheless considering the hypofractionated dose compared to conventional radiotherapy are more likely to lead to biliary fibrosis narrow complications. Hence, radiation oncologists should place more emphasis on developing the treatment plan when GTV is close to the bile duct.

Above evidence suggests that we should pay close attention to the irradiation sensitive OARs near the target area in the implementation of SBRT. Meanwhile,

longer follow-up is needed to assess the late adverse events of varieties of SBRT doses and fractionated regimens, to provide reliable evidence for improving efficacy and decreasing normal tissue adverse events.

6. Conclusion

The role of SBRT for inoperable HCC has evolved over the years. The technological advances that provided the means to deliver a tumoral dose to liver lesions while sparing the surrounding normal parenchyma have given new insight into the treatment options for inoperable HCC. The published results of SBRT for inoperable HCC are encouraging; however, the optimal dose, target, and fractionated regimen now remain inconclusive. Combined with the above evidence, the higher dose rate was associated with better OS and LC rate, we recommend the prescription BED dose at least > 100 Gray.

Fortunately, clinical investigators should pay more attention to how to accurately target the tumor lesion and real time monitor the tumor movement, and thus maximize protection of the surrounding normal tissue except for prescribing sufficient doses into tumor lesions. With the extended follow-up time, a considerable number of patients with out-field failure after SBRT, therefore, the multimodality therapy of SBRT, chemotherapy, and targeted therapy may be the future of treatment strategies for these patients. In conclusion, we have successfully moved from the role of SBRT for inoperable HCC to a new era of radiotherapy given as an effective treatment for patients not suitable for other therapeutic approaches. Currently, two Korean Phase II prospective studies have been opened for evaluating SBRT for inoperable HCC (ClinicalTrials.gov IDs: NCT01165346 and NCT01910909, respectively) to determine the optimal fractionation modality.

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