Review Article

Stereotactic body radiation therapy (SBRT) in patients with hepatocellular cancer—a narrative review and expert opinion

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Background and Objective: Stereotactic body radiation therapy (SBRT) is a highly conformal technique of external beam radiotherapy precisely delivering high total (ablative) doses in a small number of fractions to clearly defined target volumes. Its development enabled efficient and safe radiation treatments in patients with localized hepatocellular cancer (HCC) unsuitable for other local treatment options. Moreover, it can be easily combined with several other therapy approaches. Thus, the aim of this narrative review is to outline the current role of SBRT in the multifocal treatment of HCC patients.

Methods: We searched PubMed for articles dealing with SBRT alone, in combination with other local or systemic treatments or in comparison to other local treatments in patients with HCC. This included original articles, reviews and conceptional articles dealing with the technique of SBRT. All articles were analysed for suitability by two independent reviewers.

Key Content and Findings: This review summarizes the currently available evidence for SBRT as a definitive treatment for HCC as well as its role within combination approaches including bridging to transplantation. SBRT is an effective and safe definitive treatment option in patients with localized HCC unsuitable for surgery and/or other local therapies based on retrospective and prospective series. Its combination with other local treatments yields superior results compared to single modality treatment based on non-randomized data. A growing number of prospective trials confirmed at least similar if not superior rates of local control with low toxicities compared to well established other local treatments even in non-selected patients.

Conclusions: SBRT is a promising tool in the treatment of HCC. It can be used either as definitive treatment, within combination approaches or as a bridging tool. Several phase III trials comparing SBRT with other local options are ongoing, which will further clarify its encouraging role.

Keywords: Hepatocellular cancer (HCC); stereotactic body radiation therapy (SBRT); local-ablative treatment; combination approaches; bridging

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Introduction

Hepatocellular cancer (HCC) is the sixth most common cancer worldwide and the most common malignant liver tumour with reported high cancer related mortality (1). Additionally, patients often suffer from liver cirrhosis commonly caused by viral hepatitis (hepatitis B and C), alcohol or non-alcoholic fatty liver disease, which can affect liver function and thus indirectly influence treatment decisions (2,3).

The Barcelona Clinic Liver Cancer (BCLC) staging system incorporates liver function with performance status and is therefore predominantly used as the staging system to guide the treatment. Surgical resection or orthotopic liver transplantation (OLT) remain the standard of care with 5-year survival rates of up to 60% after resection and 50–70% after transplantation in suitable patients, respectively (3-5). However, only about 20% of cases are eligible for these curative treatments due to limiting factors such as lack of donor organs, comorbidities, technical reasons or advanced tumor situation (2). In cases of comorbidities or poor liver function, other locoregional therapies should be offered as definitive treatment or explored as bridging option in patients suitable for OLT. Each of the possible local treatments [arterial directed therapies like transarterial chemoembolization (TACE), transarterial chemoembolisation with drug eluting beds (DEB-TACE) and selective internal radiotherapy (SIRT) or local ablative techniques like radiofrequency ablation (RFA), microwave ablation (MWA) or minimal invasive stereotactic body radiation therapy (SBRT)] must be considered individually depending on their limitations and underlying liver function (Child Pugh/BCLC stage). Medical treatments including tyrosine kinase inhibitors (like sorafenib, lenvatinib or bevacizumab) or checkpoint inhibitors (like atezolizumab, durvalumab or nivolumab) as monotherapies or in various combinations are mainly reserved for patients with very locally advanced or metastatic lesions (4,6-8).

In this review we focus on SBRT as an encouraging local treatment option either as a sole definitive therapy, in combination with other local therapies or as bridging to OLT. We included considerations for optimal patient selection, treatment technique, dose and fractionation regimens, constraints for adjacent organs at risk and multimodal combinations as well as a summary of the available evidence with regard to treatment efficacy, possible side effects and quality of life. We present this article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-771/rc).

Methods

We searched PubMed for articles published between 1990 and 2023 dealing with SBRT alone, in combination with other local or systemic treatments or in comparison to other local treatments in patients with HCC. This included original articles, reviews and conceptional articles dealing with the technique of SBRT. The focused key words were “stereotactic body radiation therapy”, “stereotactic body radiotherapy”, “stereotactic ablative radiotherapy”, “stereotactic ablative body radiotherapy” and “hepatocellular carcinoma”. All articles were analysed for suitability by two independent reviewers. Eligible articles were limited to full-text publications in English (*Table 1*).

Radiation for HCC in the past

Radiation treatment of unresectable HCC has historically included irradiation of nearly the entire liver using conventionally fractionated or hypofractionated regimens with total doses of 20–24 Gy with or without concomitant chemotherapy. In this context, the clinical results were dismal [median overall survival (OS) 4.9 months, any tumor response in 50%] with high toxicity rates (9,10). Therefore, radiotherapy (RT) has long been considered as a palliative option for advanced HCC because the high toxicity of radiation to almost the entire liver limits the dose that can be administered, resulting in poor efficacy, as mentioned above.

With the development of 3D conformal RT and improvements in imaging techniques the focus shifted to the necessity to deliver an efficient dose of radiation to the tumor without inducing liver injury to the surrounding hepatic tissue. As a result of technical improvements, Cheng *et al.* applied higher radiation doses (40–60 Gy) and achieved increased response rates (partial response was observed in 58% of the patients, and minimal response in another 25%) (11). They (and others) concluded that 3D reconstruction of the tumor and surrounding organs made RT safer and opened up the possibility of treating unresectable HCC efficiently with RT alone or in combination with other treatments (11,12). Furthermore, Matsuura *et al.* investigated conformal RT in patients with residual or recurrent HCC after transarterial embolization (TAE) and found local control (LC) rates of 75% at 6 months and 45% at 1 and 2 years, respectively. Depending on liver function, radiation doses of 58–64 Gy in conventional fractionation following TAE were tolerable with increasing survival rates compared to initial reports from Stillwagon *et al.* (9,10,13).

From the 90s onwards, a further technical development step significantly improved the precision of RT and consequently the ability of dose escalation within shortened treatment times. Blomgren *et al.* first described and applicated SBRT using an extracorporeal stereotactic body

Table 1 The search strategy summary

Items	Specification
Date of search	2023/06/07
Databases and other sources searched	PubMed
Search terms used	"stereotactic body radiation therapy", "stereotactic body radiotherapy", "stereotactic ablative radiotherapy", "stereotactic ablative body radiotherapy" and "hepatocellular carcinoma"
Timeframe	Between 1990 and 2023
Inclusion criteria	Eligible articles were limited to full-text publications in English
Selection process	All articles were analysed for suitability by two independent reviewers (Dr. Gerum and Dr. Roeder)

frame system with mounted indicators covering the body from the head up to the thighs. Patients were immobilized using a vacuum pillow, diaphragmatic motions were evaluated with fluoroscopy and an abdominal compression device was developed to minimize breathing motion. Conformal RT techniques consisting of 4–8 non coplanar stationary beams were used during treatment planning. The beams were generally distributed in a large angle, taking into account the location of all relevant organs at risk. Treatments were administered in 1–4 fractions, using high tumor doses and steep gradients outside the tumor. Although the focus was not on HCC treatment, this was the first report on the clinical value of high-dose SBRT for patients with extracranial metastases (14).

SBRT: history and technical considerations

Based on the technical developments in the 1990s, SBRT has now emerged as an "ablative" local treatment modality for lesions in different body sites. This highly conformal technique of external beam radiation therapy (EBRT) delivers very high-doses in a small number of fractions to clearly defined, usually rather small target volumes. The primary goal of this technique is the "ablation" of the lesion by killing of all tumor cells using adequate biologically effective doses, while sparing dose to adjacent organs at risk due to the sharp dose fall-off outside the target (15,16). Therefore, SBRT has been already successfully introduced into the curative intent treatment of primary and secondary brain and lung tumors and has shown to result in low toxicity and comparable outcome to surgery (17). When performing SBRT, patient immobilization (for example with indexed vacuum pillows), daily image guidance for set-up correction [like cone beam computed tomography (CT)] and motion management strategies to adjust for breathing and other motions are required. Tumor motion can be taken into account for example by treating the whole volume of lesion motion instead of the lesion itself [so called internal target volume (ITV) concept] based on 4DCT. Other options include breath-hold techniques or free-breathing with gated or tracked beam delivery. In addition, abdominal compression can be useful to reduce intrafractional motion (15,16). Due to the poor visibility in non-contrast-enhanced CT scans, HCC lesions can usually not be safely identified on standard LINAC based imaging. Therefore, upfront placement of fiducials is commonly required (3,15,16) unless surgical clips from prior resections are available. In general, 1–4 commercially available gold or platin markers are placed CT- or ultrasound guided inside or near the lesion to treat. They can be used for patient set-up as well as for motion management as they can be easily identified with all commonly used image guidance strategies during radiation therapy (for example such as cone beam CT (3-5). Another option to adequately mark the lesion for set-up or motion management purposes is to perform a TACE with lipiodol or other radiopaque substances prior to SBRT.

Clinical evidence for SBRT

As a highly precise treatment option, SBRT has become increasingly important especially, if other local treatment options such as surgical resection, RFA or MWA cannot be performed. In general, SBRT is suitable for patients with 1–3 lesions with a maximum diameter of 5–6 cm (18,19). A variety of dose prescription and fractionation schedules have been employed, with most centers using 3–6 fractions of 8–20 Gy each (prescribed to the surrounding 65% to 89% isodose), depending on localization, lesion size and liver function (2,3,19). The preferred regimes used in prospective trials consisted of 3–5 fractions for small or 15 fractions for

larger lesions (19-23). Liver function must be considered before treatment as it may limit treatment options. In this regard, patients with Child-Pugh Class A and early B are usually suitable candidates for SBRT, while Child-Pugh Class C is considered as a contraindication by most authors due the risk of fatal liver failure. Further limitations (at least to the use of ablative doses) might be caused by adjacent organs at risk with low radiation tolerance (stomach, small bowel, heart, esophagus) (2).

The available literature mainly consists of retrospective series with only a few prospective trials. Moreover, those series usually contain heavily pretreated recurrent patients and/or patients not suitable for all other local standard approaches including surgery, RFA, MWA and TACE, thus representing a negative selection. Nevertheless, most series showed encouraging results with 2-year LC rates of 68–95% depending on inclusion criteria. The 1- and 2-year OS rates ranged from 55–95% and 45–91% (2,20-22,24-30). Recently, two comparative studies and one randomized trial compared SBRT (photons or protons) with surgery, RFA or TACE and found at least non-inferior overall results regarding LC and OS (31-34).

Based on the growing evidence, SBRT was recently included at least as an option in most updates of multidisciplinary guidelines for HCC [National Comprehensive Cancer Network (NCCN) (8), European Society for Medical Oncology (ESMO) (35); Korean Liver Cancer Association (KLCA) (36); American Association for the Study of Liver Diseases (AASLD) (37); Eastern Canadian Gastrointestinal Cancer Consensus Conference (ECGCCC) (38); Gastroenterological Society of Australia (GESA) (39), Hong Kong guideline (40), Taiwan guideline (41)], while some still refer to SBRT as a method under investigation without robust evidence [EASL (42), APASL (43)]. Due to the limited number of randomized trials showing a clear benefit compared to other local options, SBRT is mainly listed as an alternative approach in situations not suitable for other local treatments, especially in western guidelines [NCCN (8), ESMO (35)]. In contrast, most Asian guidelines describe a more pronounced role for SBRT (44) as a general alternative to other liver-directed therapies in unresectable patients or as a bridging to transplant [KLCA (36), Hong Kong guideline (40), Taiwan guideline (41)]. Moreover, the American society for therapeutic radiation oncology (ASTRO) has published recommendations for the use of EBRT including SBRT for HCC within a consensus guideline (19).

Specific situations

Unifocal or limited multifocal HCC

Outside a transplant approach, surgical resection remains the treatment of choice in patients with one or at least a limited number of HCC lesions. If patients are medically unfit for major liver surgery due to comorbidities or poor liver function, all other locally ablative techniques should be considered. Same is true if lesions are present in surgically unsuitable regions (for example central lesions) or if surgery would result in unacceptable loss of liver tissue. RFA is usually considered as an adequate choice at least in HCC smaller than 3 cm based on comparable disease free survival (DFS) and OS compared to surgery in the prospective trial by Chen *et al.* (45). However, SBRT demonstrated at least similar efficacy compared to other locally ablative treatments in retrospective series and prospective phase I/II trials including unresectable and often pretreated patients with predominant single and small HCC lesions (1–6 cm). Most trials reported 2- and 5-year LC rates of >90% (21,26,29,46,47). Several comparative studies and one meta-analysis reported similar outcomes in terms of LC and OS comparing SBRT with surgery or RFA (32,33). In the study by Wahl *et al.*, SBRT even resulted in significantly higher LC rates than RFA in lesions >2 cm (33). Sapir *et al.* further showed in their comparative study that SBRT was clearly more effective (2-year LC: 91% *vs.* 23%) and less toxic compared to TACE (34). A propensity score-based analysis of Shen *et al.* comparing SBRT *vs.* TACE in patients with the novo or recurrent medium size HCC (3–8 cm) showed superior results for SBRT with regard to LC and OS (48). Méndez Romero *et al.* (49) recently published the results of a randomized phase II trial comparing TACE and SBRT. The trial was closed early after inclusion of 30 patients due to slow accrual. The primary endpoint of time to progression favored SBRT in absolute figures (19 *vs.* 12 months) but was not significantly different (P=0.15). However, LC rates were significantly improved for SBRT *vs.* TACE according to a posthoc analysis (2-year LC: 100% *vs.* 48%). For a summary of prospective trials see *Table 2*.

Prospective phase III trials comparing photon SBRT with other local treatments are not yet available but two ongoing randomised trials compare SBRT with RFA in small HCCs in a definitive and recurrent setting (NCT03898921, NCT04047173) (2). Nevertheless, SBRT seems at least comparable to other (more established)

Table 2 Prospective trials evaluating SBRT in HCC

Author	Year	Type	Stage (BCLC)	n	F/U (months)	Dose and fractionation	LC	OS	Study conclusion
Kang (24)	2012	Prospective phase II	A-C	47	17	42–60 Gy/3 Fx	2-year: 95%	2-year: 69%	SBRT after incomplete TACE provides promising response and LC
Bujold (25)	2013	Prospective phase I/II	A-C	102	31	24–54 Gy/6 Fx	1-year: 87%	1-year: 55%	SBRT in HCC should be studied in prospective randomised phase III trials
Scorsetti (27)	2015	Prospective phase II	A-C	43	8	36–75 Gy/3–6 Fx	2-year: 64%	2-year: 45%	SBRT is a safe treatment with acceptable LC
Takeda (50)	2016	Prospective phase II	0-C	90	42	35–40 Gy/5 Fx	3-year: 96%	3-year: 67%	SBRT achieved high LC with acceptable toxicity in solitary HCC
Chen (51)	2021	Prospective pilot study	A-C	26	28	30–50 Gy/5 Fx	1-year: 86%; 2-year: 64%	1-year: 79%; 2-year: 42%	SBRT is feasible and safe in patients unresponsive or ineligible for TACE. Doses ≥45 Gy yields better local control
Durand-Labrunie (21)	2020	Prospective phase II	A-C	43	48	45 Gy/3 Fx	2-year: 94%	2-year: 69%	SBRT resulted in promising LC and OS
Yoon (28)	2020	Prospective phase II	0-A	50	48	45 Gy/3 Fx	2-year: 100%; 5-year: 97%	5-year:78%	SBRT in small HCC (median 1.3 cm) resulted in high LC with minimal toxicity
Lasley (20)	2015	Prospective phase I/II	A-C	59	33	36–48 Gy/3–5 Fx	3-year: 82–91%	3-year: 26–61%	SBRT is a safe treatment for HCC
Jang (22)	2020	Prospective phase II	0-C	65	41	60 Gy/3 Fx	2-year: 97%	2-year: 84%	SBRT for unresectable HCC is well tolerated and effective, treatment assoc. severe toxicity <3%
Buckstein (23)	2022	Prospective phase II	A	32	37	35–50 Gy/5 Fx	ORR: 91%	n.r.	Promising ORR when combining TACE + SBRT in large (4–7 cm), unresectable solitary HCC
Méndez Romero (49)	2023	Phase II rand. DEB-TACE *vs.* SBRT	Only CP A	30	28	48–54 Gy/6 Fx	2-year: 100%; 3-year: 100%	Median OS 37 *vs.* 41 months (SBRT)	TTP after DEB-TACE was not sig. improved by SBRT, SBRT showed higher local antitumoral activity than DEB-TACE
Kim (31)	2021	Phase phase III randomized. proton-RT *vs.* RFA	0-C	72	52	66 Gy/10 Fx	2yr: 93%	2-year: 92%	Proton beam therapy was non-inferior to RFA and was tolerable
Comito (52); NCT02323360	2022	Phase III randomised SBRT *vs.* TAE/TACE	A-B	40	20	60 [30–75] Gy/ 6 [3–10] Fx	1-year: 84% *vs.* 23%	2-year: 64% *vs.* 57%	SBRT was correlated with significantly higher LC rates as compared to rechallenge with TAE/TACE
RTOG 1112	Ongoing	Phase III randomised SBRT + sorefenib *vs.* sorafenib							
NCT03898921; NCT04047173	Ongoing	Phase III SBRT *vs.* RFA in small HCC							

SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer Classification; n, number of patients; F/U, median follow-up; LC, local control; OS, overall survival; CP, Child-Pugh class; TACE, transarterial chemoembolisation; ORR, objective response rate; TTP, time to progression; DEB-TACE, drug eluting beads transarterial chemoembolization; RFA, radiofrequency ablation; TAE, transarterial embolisation.

treatments based on the available literature and therefore represents a reasonable treatment alternative. Whether a patient with HCC should be treated most appropriately by SBRT or other locally ablative options should be decided within a multidisciplinary board depending on individual lesion and patient factors, which may only slightly favor one option over another (47). Such factors may include lesion size, lesion localization within the liver, involvement of liver surface, vessels or bile duct, adjacent organs at risk, presence of portal vein thrombosis (PVT) and overall liver function. For example, American Society for Radiation Oncology (ASTRO) clinical guidelines recommend EBRT, mostly used as ultrahypofractionated radiation (SBRT) as potential first line treatment alternative if surgery or thermal ablation is not applicable due to medical comorbidities, poor liver function, size, localization or lack of ultrasound echogenicity/visibility (19).

Locally recurrent unifocal or limited multifocal HCC

Patients with local recurrence after primary locally directed treatment are usually suitable for further locally directed therapies. The role of SBRT has been studied in retrospective analyses, but it is difficult to generalize these data to all patients with recurrent disease due to differing initial treatment approaches, different overall situations and different number of patients with recurrent HCC included in these analyses (19). Shen *et al.* for example performed a propensity score based comparative subgroup analysis of SBRT with TACE in patients with recurrent HCC and found superior LC at 3 years (75% *vs.* 57.5%) and OS (58.3% *vs.* 5.9%) favoring SBRT (19,48). A prospective phase II trial of Jang *et al.* included only patients with recurrent HCC and confirmed the promising results with SBRT after 1–5 TACE sessions. The authors reported a 3-year LC rate of 95% and a 3-year OS rate of 76%. Treatment related severe toxicities (≥ G3) were very low (3% after 1 year) (19,22). Kim *et al.* published the only phase III trial comparing proton beam radiotherapy (PBR) *vs.* RFA in patients with locally recurrent HCC with a non-inferiority design. Patients with up to two lesions with a maximum size of 3 cm were eligible. Non-inferiority of PBR in terms of 2-year local progression-free survival was statistically confirmed, with the absolute rates even favouring for the PBR approach (93% *vs.* 83%) (31). These results indicate the promising role for SBRT in recurrent HCC, however further prospective randomized trials comparing SBRT to TACE or other local options especially in patients with recurrent disease are warranted to further define the role of the different treatment approaches.

Distinctly multifocal inoperable liver confined HCC

Patients with multifocal HCC including a large number of lesions are usually poor candidates for surgery and outside the criteria justifying a transplant approach. Systemic therapy or local techniques capable of covering larger hepatic areas like TACE or SIRT represent the standard of care in most cases. However, locally ablative techniques including also SBRT might be useful in properly selected cases within a multimodal approach.

TACE is the preferred treatment in distinctly multifocal HCC, although there seems to be a role for SBRT even in advanced situations based on suitable lesion numbers, lesion sizes and lesion distribution. Several retrospective and prospective reports showed the feasibility of SBRT with LC rates of 65–95% after 2 years and OS rates between 40–80% in more advanced situations, although patient cohorts varied widely in terms of dose prescription, prior treatments and baseline liver function (20,22,25,27-29,31).

Patients with PVT and multifocal disease show even poorer outcome. Therefore, systemic therapy is the preferred treatment (2,19). However, combinations with additional local therapies have also been studied. For example, Yoon *et al.* (53) prospectively studied the addition of RT and TACE to medical treatment with sorafenib in a randomized trial. Roughly 80% of the included patients showed multifocal lesions, median tumor size was 9 cm and all patients had portal vein invasion. They observed an improved PFS (86.7% *vs.* 34.3% after 1 year), higher longer median time to progression (31.0 *vs.* 11.7 weeks), and a significantly longer OS (55.0 *vs.* 43.0 weeks) for the combination approach (53). Bettinger *et al.* similarly demonstrated an improved median survival (17 *vs.* 9.6 months) comparing SBRT with sorafenib in a propensity score based retrospective analysis evaluating patients with multifocal disease and portal vein invasion initially treated with TACE (6).

Combination with other local treatments

Combination of SBRT with other local therapies for treatment of either the same or different lesions may result in synergistic effects (3). Therefore, SBRT should be considered as potential treatment modality depending on individual lesion localizations, overall situation and

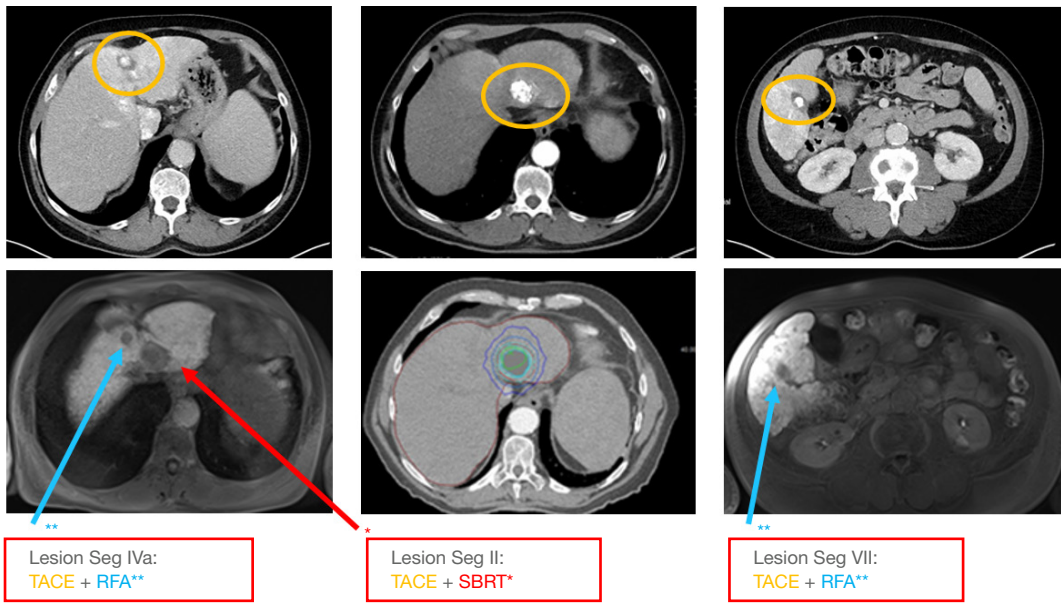

Figure 1 Multifocal HCC with combined treatment to all lesions. Upper row: upfront TACE with lipiodol; lower row: additional local treatment with either RFA or SBRT without fiducials. HCC, hepatocellular carcinoma; TACE, trans arterial chemoembolisation; SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation.

suitability of every lesion for other local treatments, especially in case of limited multifocal disease. SBRT can be combined with surgery and/or RFA/MWA based on multidisciplinary pretreatment evaluation. For example, some of our patients with limited multifocal disease received surgery for easily resectable superficial lesions, while deep lesions were treated with MWA/RFA and central lesions with broad contact or infiltrations of large intrahepatic vessels were treated by SBRT, often proceeded by TACE (see *Figure 1*). From a practical point of view, it is often advantageous to schedule invasive procedures first, as fiducials (which are often used for SBRT) can be implanted in the same session without the risks of additional interventions or TACE with radiopaque materials can be used instead. Same is true if combination approaches are used in single lesions. Incomplete response rates after thermal ablation or catheter-based treatments have been reported in up to 61% (19). This often-triggered repeated procedures to the same lesion and/or resulted in poor survival. An alternative to repeated procedures with the same modality might be the upfront combination with SBRT. There is increasing evidence, that combinations of TACE and SBRT or MWA and SBRT yield superior results than one modality alone (3,4,23,24,54-57).

For example, Buckstein *et al.* (54) retrospectively analysed patients with either upfront (planned group) immediate combination of TACE and SBRT and patients who received SBRT in case of recurrence after TACE (unplanned group). They observed significantly improved CR rates within the planned group (80% *vs.* 43%, P=0.006). Moreover, an absolute increase in one year survival was achieved for the planned SBRT group (71% *vs.* 61%, P=0.052), although not statistically significant (54). Another retrospective study including patients with large, unresectable HCC (median tumor size 8.5 cm) treated with SBRT alone or TACE followed by SBRT showed improved OS rates after 5 years for the combined treatment group (33% *vs.* 47%) (55). Based on their promising retrospective results from 2018, Buckstein *et al.* conducted a phase II prospective trial for patients with a single HCC lesion from 4 to 7 cm not suitable for resection or liver transplantation. Patients received 2 sessions of drug-eluting based DEB–TACE followed by immediate SBRT in 5 fractions (35–50 Gy total doses) within 1 month. Response rates in the treated lesions was 91% (63% CR, 28% PR), median time to CR was 10 months, translating into median PFS of 35 months. No severe toxicity was reported (23). Takeda *et al.* (50) conducted a phase II trial on SBRT, which allowed the inclusion of treatment naïve patients as well as patients with SBRT immediately after TACE or in

case of recurrence after previous TACE. Of 90 evaluable patients, only 32 were treatment-naïve. Prescription dose for SBRT was 35–40 Gy in 5 fractions. They reported a 3-year LC rate of 96% and a 3-year OS rate of 68% with limited toxicity. Several meta-analyses have also confirmed increased complete response rates as well as improved OS rates in patients receiving TACE and SBRT to the same lesion compared to TACE alone (56,57).

Unfortunately, one phase III trial comparing SBRT versus standard re-TAE/TACE for the curative treatment of intermediate stage HCC with incomplete response after initial TAE/TACE was closed due to slow accrual. Evaluation of the included patients (n=40) showed significantly higher LC rates for SBRT as compared to rechallenge with TAE/TACE. This result translated into extended PFS while the likelihood of new lesions outside the treated region was not different. However, an OS advantage for the SBRT group could not be shown, probably due to the small number of patients (52). Another phase III trial (TASABR) comparing clinical outcomes between TACE + SABR and TACE + re-TACE for HCC patients with post-prior-TACE residual tumors is still ongoing (58). ASTRO Guidelines concluded that the combination therapy of EBRT/SBRT sequenced with TACE should be recommended as a treatment option (19).

Bridging to transplant

Liver transplantation is the most promising treatment in case of irreversible liver disease, but often patients drop out because of tumor progression during prolonged waiting times. Local treatment modalities can be used for bridging, e.g., to downsize the tumor and prevent tumor progression (3,4,19,59,60). Bridging therapy before transplantation helps to decrease drop out rates and increases OS (61). All patients have to be evaluated in a multidisciplinary team and usually SBRT is selected only if a patient is not well suited for other local treatments (19).

Despite the small number of patients who have been treated with SBRT as bridging upfront to liver transplantation, some case series/observational studies are available. These retrospective series included usually less than 30 patients, mainly with poor liver function and no possibility for other treatment options. Therefore, actual SBRT series generally represent a negative selection compared to reports dealing with other local modalities. Reported pathological complete response (pCR) rates in explanted livers varied widely from 14–89% after SBRT (4,7,59,60,62,63), but were generally similar compared to RFA (21–75%) and often superior to TACE (24–44%).

Sapisochin *et al.* (60) reported a direct comparison of different modalities and observed pCR rates of 49.2% with RFA, 24.3% with TACE, and 13.3% with SBRT, respectively. However, those results are difficult to interpret due to the mentioned selection bias. Patients treated with SBRT on this series were ineligible for the other options, mainly due to poor baseline liver function, technical limitations, or progression after TACE/RFA. In addition, the prescription dose of the used SBRT treatment was relatively low (36 Gy/6 fractions). OS rates after 1, 2 and 5 years remained similar (60). In contrast, Garg *et al.* (59) described a much higher pCR rate of 62% after more dose intense SBRT treatments (median 50 Gy in 5 fractions), although they could not establish a direct dose-response relationship. Time interval from bridging treatment to transplantation seems also crucial for the comparison of pCR rates. Due to the different mechanism of action, SBRT usually needs at least some months to achieve a verifiable pCR, while TACE and especially RFA may achieve a pCR much earlier. Again, combination approaches might be superior to single modality treatments. Bauer *et al.* compared different strategies in a multicentric retrospective analysis and found significantly improved pCR rates in patients who received TACE followed by SBRT (89%) versus TACE or SBRT alone (0% and 25%) (7).

In summary, reported pCR rates vary widely with all locally ablative treatment options depending on multiple factors. Nevertheless, encouraging OS rates of 61% to 73% for the overall approach have been reported with no significant differences between the bridging modality (19,60,62,63). Therefore, no definitive conclusions can be made in terms of superiority of any of the currently used bridging regime in the absence of randomized direct comparisons. SBRT seems to be a suitable method for bridging patients waiting for OLT and can be recommended on a case-by-case bases after multidisciplinary evaluation (19). Results of a completed phase II study (NCT02182687) comparing SBRT *vs.* TACE as bridging to transplant are awaited. One Phase III randomized trial comparing both treatment approaches is also ongoing (NCT03960008) (2).

Toxicity and quality of life

The safety profile of SBRT is highly dependent on the patient's baseline liver function (based on CHILD-Pugh Classification), localization and size of the lesion(s) and

Table 3 Recommended dose constraints for liver SBRT

Structure	Metric	Diez *et al.* (65)				Timmerman (66)				Endpoint
		3 fractions		5 fractions		3 fractions		5 fractions		
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Liver-GTV	$V_{10\ Gy}$			70%						Grade 3+ liver dysfunction, classic/non-classic RILD
	D_{mean}	13 Gy	15 Gy	13 Gy						
	$D_{>700\ cc}$	15 Gy	17 Gy	15 Gy	15.2 Gy		17.7 Gy		21.5 Gy	
Stomach	$D_{0.1\ cc}$		22.2 Gy	33 Gy	35 Gy		30.0 Gy		35 Gy	Grade 3+ ulceration, fistula
	$D_{10\ cc}$		16.5 Gy	25 Gy						
	$D_{5\ cc}$						22.5 Gy		26.5 Gy	
Small bowel	$D_{0.1\ cc}$		25.2 Gy	30 Gy	35 Gy		28.5 Gy		34.5 Gy	Grade 3+ enteritis, obstruction
	$D_{5\ cc}$		17.7 Gy							
	$D_{30\ cc}$						20.7 Gy		24 Gy	
Duodenum	$D_{0.1\ cc}$		22.2 Gy	33 Gy	35 Gy		30.0 Gy		35 Gy	Grade 3+ ulceration
	$D_{10\ cc}$		11.4 Gy	25 Gy						
	$D_{5\ cc}$						22.5 Gy		26.5 Gy	
Common bile duct	$D_{0.1\ cc}$	50 Gy		50 Gy			36 Gy		41 Gy	Stenosis
Kidney cortex combined	$D_{>200\ cc}$	8.5 Gy		10.0 Gy			14.7 Gy		17.5 Gy	Grade 3+ renal dysfunction
Kidney_Cortex (individual/combined)	D_{mean}		16 Gy	17.5 Gy						Grade 3+ renal dysfunction

D_x, threshold dose, or higher, that can be given to a specified volume (x) of the organ or structure, with the remaining volume receiving less than the threshold dose; V_x, maximum critical volume (percentage or absolute) of the organ or structure, that can receive the specified threshold dose x or higher; $D_{>x}$, minimal critical volume of the organ or structure that must receive a specified threshold dose or lower; D_{mean}, mean dose to organ or structure. SBRT, stereotactic body radiation therapy; GTV, gross tumor volume; RILD, radiation induced liver disease.

dose-fractionation regimen. Most patients with CP class A and selected patients with early CP class B stage are usually deemed suitable for SBRT treatments, while CP class C is regarded as contraindication for SBRT in most centers. Typical acute side effects including fatigue, transient elevation of liver enzymes or unspecific abdominal symptoms, which are generally mild if treatment is performed according to modern standards after adequate patient selection (2-4). Severe late complications (Grade 3+) may include radiation-induced liver disease (RILD), gastrointestinal side effects like ulceration or stenosis, biliary complications and rib fractures but are typically rare based on prospective series (3,20,22,24,25,64). Classic RILD is caused by venoocclusive disease and occurs in less than 5% of patients, while non-classic RILD is more common (10–30%), but occurs primarily in patients with preexisting liver function impairment (2). Patients with non-classic RILD often develop worsening liver function (increase of >2 points CP class) in the first 3–6 months after therapy. Lasley *et al.* demonstrated the need to differentiate between CP class A and B patient with regard to the applied dose in a prospective trial. They recommended different dose schedules, namely 48 Gy in 3 fractions for CP class A and 40 Gy in 5 fractions for CP class B) (20). If application of ablative doses is not feasible, EBRT with moderate hypofractionation (12–15 fractions) is also an alternative treatment option, especially in combination with prior TACE (19,53). However, the detailed discussion if such approaches is beyond the scope of this review. Regarding adjacent non-liver organs at risk, general recommendations (65,66) for dose constraints should be followed to avoid severe side effects (see *Table 3*).

Data on quality of life following liver SBRT is generally scarce. Klein *et al.* prospectively assessed the quality of life in patients receiving SBRT for liver lesions (nearly 50% suffered on HCC). Treatment was well tolerated, only temporary effects occurred (appetite loss and fatigue) and no significant decline in quality of life has been documented (67). A prospective observational trial (HERAKLES) found a preserved quality of life while and after SBRT with no differences to patients treated by TACE. SBRT resulted in high LC rates with low to moderate severe toxicity (17%) (64).

Conclusions

In summary, SBRT is a valuable treatment option especially in patients unsuitable for other local treatment approaches. It can be used either as definitive treatment or as bridging in OLT candidates. In both situations, SBRT resulted in high LC rates with acceptable OS and usually low toxicity rates, especially if the negative selection of patients within SBRT reports compared to other more established modalities is taken into account. There is increasing evidence, that SBRT has at least similar efficacy compared to surgery or other local treatments also in patients with more favorable factors. Moreover, combination approaches using SBRT and other modalities seem to further increase efficacy while maintaining low toxicity rates. While combinations of RFA or TACE with SBRT seem to increase response rates and LC, combinations with medical treatments may reduce the risk of outfield intrahepatic failures commonly seen especially in patients with multifocal disease. Patients should be scheduled for SBRT based on multidisciplinary evaluation. Technical execution, dose and fractionation schemes as well as organ at risk constraints should follow published guidelines to ensure optimal efficacy with low toxicity.

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