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## Stereotactic body radiation therapy in patients with hepatocellular carcinoma: A mini-review

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### Abstract

Stereotactic body radiation therapy (SBRT) is an emerging treatment for hepatocellular carcinoma. This technique results in excellent local control rates with favorable toxicity profile despite being predominantly used in heavily pretreated patients or those unsuitable for other local therapies. SBRT may be used as a sole treatment or in combination with other local therapies as well as a bridging strategy for patient awaiting liver transplants. This brief review describes current practice of SBRT with respect to radiation technique, patient selection and treatment concepts. It summarizes available evidence from retro- and prospective studies evaluating SBRT alone, SBRT in combination with other treatments and SBRT compared to other local treatment approaches.

**Key words:** Hepatocellular carcinoma; Stereotactic body radiation therapy; Local-ablative treatment; Combination approaches; Mini-review

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**Core tip:** Stereotactic body radiation therapy (SBRT) is an emerging treatment for hepatocellular carcinoma. It may be used as a sole treatment or in combination with other local therapies as well as a bridging strategy for patient awaiting transplants and results in excellent local control rates with low toxicity. This mini-review describes

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current concepts of SBRT and summarizes the available evidence evaluating SBRT alone, SBRT in combination with other treatments and SBRT compared to other local treatment approaches.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and ranking as the third most common cause of cancer death<sup>[1]</sup>. Tumour resection or liver transplantation is the main curative treatment options. However, only a minority of patients are suitable candidates for surgical treatment due to major vascular involvement, large multifocal lesions or accompanying comorbidities such as poor liver function or associated problems<sup>[2]</sup>. In the past, inoperable cases have traditionally been regarded as incurable. Treatment paradigms have changed dramatically in favor of local treatments in the last decades though. Even in inoperable patients, there is now emerging evidence of survival benefit or potential cure in inoperable patients receiving local treatments<sup>[3,4]</sup>. In consequence, local therapies should be considered in patients not eligible for curative surgery, or as a part of a strategy to bridge patients awaiting liver transplantation according to common guidelines<sup>[5]</sup>. Local treatments are broadly classified into two categories: Arterially-directed and locally ablative therapies. Arterially directed therapies include transarterial chemoembolization (TACE), transarterial chemoembolisation with drug eluting beads (DEB-TACE), and selective internal radiotherapy (SIRT). Locally ablative techniques include radiofrequency ablation (RFA), percutaneous alcohol injection, microwave or (less invasive) Stereotactic body radiation therapy (SBRT). However, potential benefits of these treatments need to be weighed against the potential treatment-induced impairment of liver function or even liver failure especially in the presence of underlying liver disease as a primary cause of most primary hepatic malignancies<sup>[4]</sup>. All of these treatments also have limitations and appropriate patient selection is crucial to achieve positive outcomes: Patients with multiple comorbidities or inadequate liver function are usually poor candidates for surgical interventions<sup>[4]</sup>, patients with lesions directly adjacent to major vessels or bile ducts are not well suited for RFA<sup>[6]</sup>, and patients with portal vein thrombosis rarely qualify for TACE or SIRT<sup>[7]</sup>.

SBRT is an additional locally ablative treatment option for patients with HCC who are not eligible for resection or other local treatments. It can also be used to bridge waiting time in patients qualifying for transplantation or as part of multi-modality treatments with other liver-directed therapies<sup>[3]</sup>. In the absence of level I evidence, SBRT is not considered a standard in many guidelines, unfortunately. This mini-review describes current SBRT techniques and summarizes published evidence regarding efficacy and toxicity as a single treatment or in combination with other liver-directed therapies.

## SBRT: INDICATIONS AND TECHNIQUES

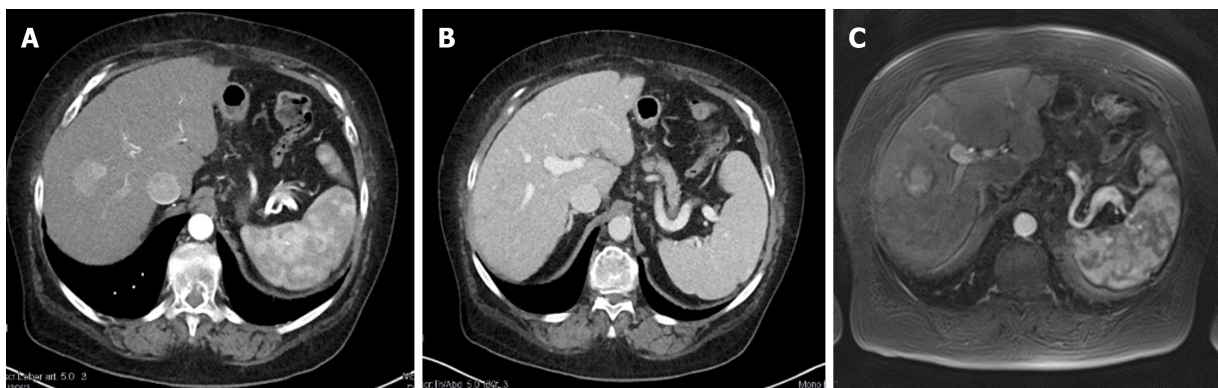
SBRT is a highly conformal technique of external beam radiation therapy (EBRT) delivering high radiation doses in a small number of fractions<sup>[8]</sup>. Tumour control is achieved by high doses per fraction leading to high biological effectiveness and hence increased cell kill. Due to sharp dose gradients outside the target volume, dose to adjacent organs at risk is effectively limited maintaining adequate organ function. Stereotactic radiotherapy was initially developed for treatment of small cerebral lesions as stereotactic radiosurgery (SRS), the same principle was developed further in order to treat extracranial lesions (SBRT = stereotactic body radiation therapy). SRS and SBRT have now been widely accepted as standard of care for the treatment of limited brain or lung metastases as well as for early stage non-small-cell lung cancer. Clinical studies could show that SRS/SBRT and surgical approaches yield comparable results<sup>[8-10]</sup>. Meanwhile, SBRT is increasingly used for treatment of liver, lymph node or bony lesions<sup>[4,11,12]</sup>.



In liver lesions, SBRT is usually indicated in patients with 1-3 lesions with a maximum diameter of 5-6 cm<sup>[13]</sup> who are not eligible for resection or other local therapies either as definitive or bridging therapy prior to transplantation<sup>[13]</sup>. Preservation of adequate liver function is mandatory, which is estimated individually based on total liver volume, lesion size and number, prior treatments and current liver function<sup>[4,13]</sup>. In general, patients with liver cirrhosis Child Pugh class A and early B are suitable candidates. In contrast to RFA/TACE treatment, patients with lesions located close to the liver surface, directly adjacent to large vessels, or portal vein thrombosis as well as patients presenting with extensive ascites are still candidates for SBRT. In contrast, However, patients with lesions directly adjacent to structures with low radiation tolerance like small bowel or stomach are less good candidates because dose reduction may be necessary<sup>[4,14,15]</sup>.

Technically, SBRT is a form of precision external beam radiation therapy using minimal safety margins<sup>[8]</sup>. In consequence, accurate target delineation and treatment planning, precise patient positioning, careful image guidance and adequate motion management strategies are mandatory. Target delineation usually includes multi-modality imaging such as multi-phase contrast-enhanced computed tomography (CT) and magnetic resonance imaging preferably with liver-specific contrast-agents (see [Figure 1](#)). Patient positioning may include supportive vacuum pillows or other immobilization devices. Treatment planning is usually performed using multi-field or rotational techniques (see [Figure 2](#)). On-board imaging usually includes at least three-dimensional cone beam CT prior to each fraction. Unfortunately, HCCs are poorly visible in native CT scans and can therefore rarely be identified by linac-based imaging, hence perilesional placement of fiducials prior to treatment planning is commonly necessary<sup>[4,16,17]</sup>. Depending on respective SBRT strategy, 1-4 gold or platinum markers are placed near the lesion under CT or ultrasound guidance. These markers can be easily identified with all common image-guidance procedures (especially cone beam-CT) and used for patient set-up as well as gating or tracking strategies<sup>[4]</sup>. Exceptions can be made if SBRT is applied shortly following TACE and there is still adequate contrast enhancement of lipiodol or if clips from prior surgical resections are present in direct proximity to the current lesions<sup>[3,4]</sup>, (see [Figure 2](#)).

Apart from implantation of fiducial markers, SBRT represents a non-invasive treatment option. Motion mitigation may be managed by either internal target volume concepts (ITV) or gating/tracking strategies. In order to define the ITV, the lesion is delineated on different respiratory phases based on a contrast-enhanced four-dimensional CT. The ITV corresponds to the resulting enveloping volume, which includes each delineated lesion position during the respiratory cycle and can be treated without breathing control or gating. In patients with large respiratory excursions, abdominal compression devices may be used to reduce motion and therefore limit resulting absolute ITVs<sup>[18]</sup>. In gating strategies, lesion motion is either derived from continuous breathing detection by imaging or patient surface detection or continuously detected through electromagnetic transponders. Radiation is applied only during short phases of the breathing cycle when the specific lesion is within a specified position or corridor, tracking techniques model lesion motion with respect to the breathing cycle. Accuracy of the model is checked and corrected in real time feeding back to the treatment position. In consequence, the radiation beam moves with the target and according to the model utilizing the whole breathing cycle and thereby reducing overall treatment time as compared to gating strategies. Doses are typically prescribed to a lesion-surrounding isodose (*i.e.*, 65% or 80%), resulting in inhomogeneous dose distributions. The lesion center therefore intentionally receives significantly higher doses while doses fall off quite sharply outside of the target volume. In consequence, doses and toxicities in adjacent normal tissue are reduced (see [Figure 2](#)). A variety of dose prescription and fractionation schedules have been employed. Currently most centers use 3-6 fractions of 8-20 Gy each, depending on localization, lesion size and liver function<sup>[4]</sup>. In order to preserve adequate liver function following SBRT, attention needs to be paid to specifying and sparing a threshold volume of uninvolved liver (usually 700 mL). In addition, excessive doses to luminal structures must be avoided by keeping a minimum distance (*i.e.*, 5mm) to the high-dose area within the lesion<sup>[4]</sup>. If adequately performed, acute side effects following SBRT are rare and generally mild. These include fatigue, transient elevation of liver enzymes or unspecific abdominal symptoms. Late toxicities may include radiation-induced liver disease resulting in impaired liver function, gastrointestinal side effects like ulceration or stenosis, biliary complications and rib fractures. However, high-grade toxicities were rare and usually lower than in comparable series using alternative locally-ablative techniques<sup>[19-21]</sup>. Close follow-up evaluations including repeated imaging (see [Figure 3](#)) are necessary in order to evaluate resultant toxicity and to detect early local or distant progression<sup>[3]</sup>. It is of note though that SBRT may induce several and characteristic types of tumor and surrounding tissue



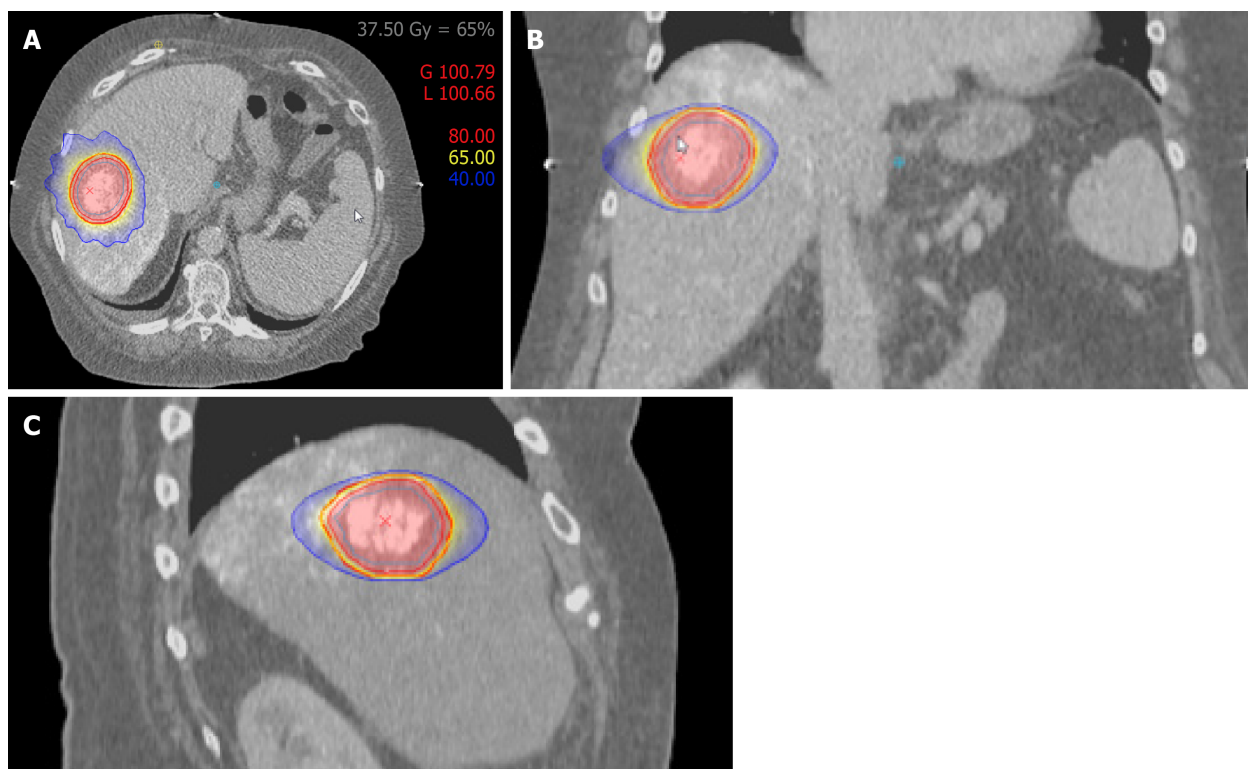
**Figure 1** Hepatocellular carcinoma in segment VIII at diagnosis. A: Contrast-enhanced computed tomography (CT) arterial phase; B: Contrast-enhanced CT venous phase; C: Magnetic resonance imaging with liver-specific contrast agent.

alterations over time which should not be confused with progressive disease. For example, Herfarth *et al*<sup>[22]</sup> described three distinct types of focal reactions on multiphase contrast-enhanced CT following SBRT in their landmark paper. All of those are subject to substantial change over time and correlated to applied dose but have to be distinguished from disease recurrence. Lesions treated by SBRT may show signs of activity like hypervascularisation, wash-out or absence of regression in size up to 12 mo after treatment without residual viable tumor as reported by Mendiratta-Lala *et al*<sup>[23]</sup>. Tétreau *et al*<sup>[24]</sup> compared different criteria for response evaluation and found that RECIST (Response evaluation criteria in solid tumors) criteria were unsuitable for response assessment and were outperformed by EASL (European Association of Study of the liver) criteria at each point of time during available follow-up. Therefore, response assessment including decision-making for salvage treatments following SBRT should preferably be made by a multidisciplinary panel including experienced radiation oncologists.

## SBRT: CLINICAL EVIDENCE

In recent years an increasing number studies have been published, including mainly small retrospective cohorts but also larger series and well-designed phase II trials, see [Table 1](#). Comparison of published data is hampered by varying and inhomogenous inclusion criteria across these studies. In addition, most series include large numbers of patients/lesions receiving SBRT because they were not eligible for other local treatments options (anymore) and/or have been treated with other techniques multiple times before. In consequence, most SBRT series represent a negative pre-selection of patients *ex ante* as compared to series reporting on other local treatments mainly as the primary treatment option. Nevertheless, SBRT resulted in very encouraging local control (1-year LC 65%-100%) and overall survival rates (1-year OS 32%-94%) with low toxicity<sup>[14,25-39]</sup>. In addition to dose and fractionation<sup>[28,34]</sup>, local control appears to be determined by lesion size<sup>[28,34]</sup> and number of lesions<sup>[1]</sup>, while overall survival is strongly associated with general condition and liver function prior to treatment. Several groups have consistently shown clear survival benefits after SBRT in Child-Pugh class A (CP-A) patients when compared to CP-B patients<sup>[14,27,34,39]</sup>. CP-B patients further suffered from significantly increased toxicity despite receiving lower SBRT doses and less aggressive fractionation schemes<sup>[14,27]</sup>, thus possible benefits and risks of SBRT have to be considered carefully when selecting those patients for treatment.

Direct comparisons of SBRT with other local treatment options are limited and analyses most commonly retrospective (see [Table 2](#)). Su *et al*<sup>[40]</sup> compared SBRT with surgery in a propensity score matched cohort. Only patients with adequate liver function (CP-A), relatively small lesions (median 3.3 cm) treated in primary situation were included in the analysis. Despite mature follow-up of these cohorts, the authors could not detect significant differences between these treatment modalities with regard to either local control or overall survival. However, they described significant differences in accompanying toxicity profiles. While surgically treated patients showed less nausea, SBRT patients suffered less often from bleeding and pain. Wahl *et al*<sup>[19]</sup> performed a retrospective comparison of SBRT and RFA in a series of 224 patients. Except for a distinctly higher rate of prior treatments in the SBRT group, both arms seemed comparable with respect to major prognostic factors. Again, no



**Figure 2 Treatment plan (prescription dose  $3 \times 12.5$  Gy to 65% surrounding isodose).** A: Isodose plan in axial view; B: Frontal view; C: Sagittal view, broad red line: Planning target volume (PTV), yellow line: PTV-surrounding 65% isodose = 37.5 Gy, light blue line: Internal target volume (ITV), narrow red line: ITV-surrounding 80% isodose = 46.2 Gy, dark blue line: 40% isodose = 23.1 Gy.

significant difference in local control and overall survival was found between the cohorts. While both treatment were similarly efficient in lesions  $< 2$  cm, the analysis showed significantly improved local control in patients treated with SBRT for larger lesions<sup>[19]</sup>. Sapir *et al*<sup>[20]</sup> compared SBRT with TACE in a retrospective series including 209 patients. Both groups were comparable with respect to their baseline characteristics with two exceptions: patients in the SBRT group were more heavily pre-treated, while mean lesion diameter was higher in the TACE group. Keeping those limitations in mind, SBRT resulted in significantly increased local control (1-year LC 97% *vs* 47%) and favourable toxicity profile although this benefit did not translate into a clear survival benefit (1-year OS 75% *vs* 74%)<sup>[20]</sup>.

In summary, SBRT seems to result at least in similar local control and overall survival rates as compared to other local treatments while showing mainly favorable toxicity profiles based on currently available albeit limited evidence. Therefore, SBRT may represent a reasonable alternative to other local treatments and should be considered as potential treatment modality in multidisciplinary evaluations of suitable patients.

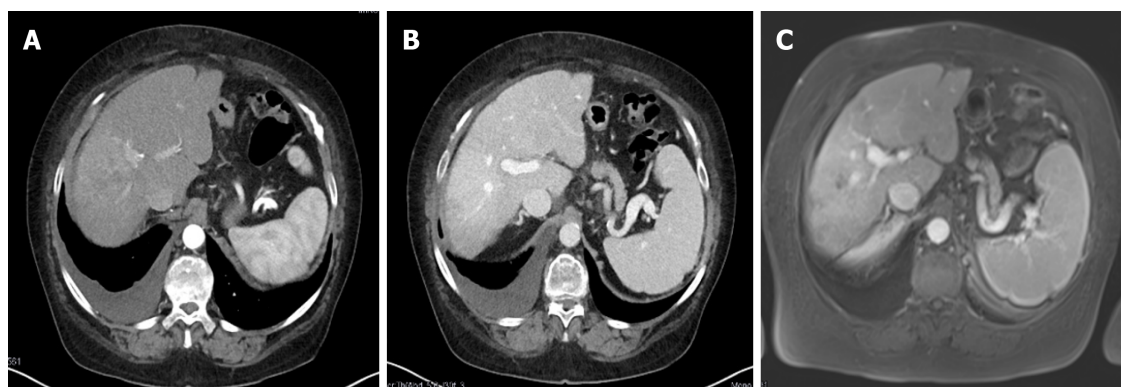
## SBRT COMBINED WITH OTHER TREATMENTS

### RFA/TACE

Combination of SBRT with other local therapies for treatment of either the same or different lesions may result in synergistic effects<sup>[3]</sup>. In case of multifocal disease with several lesions of various sites and size, some lesions may be easily addressed by RFA while others (*i.e.*, due to close proximity to major vessels) may profit from SBRT. When combining different approaches, invasive procedures should be scheduled first, as fiducials (which are often necessary for SBRT) can be implanted in the same session without risks of an additional intervention.

Combining TACE with SBRT in the treatment of the same lesion may offer several advantages (see Figure 1-3). Prior TACE may result in tumour response and hence smaller SBRT volume leading to potentially improved toxicity<sup>[4]</sup>. Chemotherapy as a component of TACE may act as a radiosensitizer also enhancing the radiation effect of SBRT<sup>[4]</sup>, although this might be counterbalanced by tumor hypoxia induced by embolization. Lipiodol deposits placed during embolization can also serve as





**Figure 3** Complete response 9 months after transarterial chemoembolization and stereotactic body radiation therapy. A: Contrast-enhanced computed tomography (CT) arterial phase; B: Contrast-enhanced CT venous phase; C: Magnetic resonance imaging with liver-specific contrast agent.

landmarks for image guidance in SBRT, which may potentially render fiducial placement unnecessary<sup>[3,4]</sup>. Indeed, small retrospective series have shown significant improvements regarding treatment response, local control, progression-free survival, and even overall survival by the addition of SBRT to TACE compared to TACE alone at least if lesion size exceeded 3 cm<sup>[41,42]</sup>. Kang *et al*<sup>[28]</sup> reported a prospective phase II trial using SBRT following TACE. Fifty patients with lesion size < 10 cm and CP-A or early CP-B cirrhosis were enrolled. Patients received SBRT in 3 fractions with 14-20 Gy per fraction. The group reported very encouraging 2-year local and overall survival rates of 95% and 69%. Toxicities of grade III or higher were observed in only 10% despite comparatively high doses. In summary, combination of TACE and SBRT seems to be a very promising approach, which is currently evaluated in several prospective trials.

### Sorafenib

Although preclinical data suggested radiation-sensitizing effects of sorafenib<sup>[43]</sup>, combination of Sorafenib with SBRT does not appear advisable. Prospective clinical trials reported discouraging toxicities: Brade *et al*<sup>[44]</sup> conducted a phase I trial investigating SBRT with concurrent Sorafenib in CP-A patients unsuitable for standard local therapies. Nine out of 16 patients showed grade 3+ toxicity including 2 deaths. While 15 of 16 patients completed SBRT as planned, adherence to Sorafenib treatment was poor: Only 3 out of 16 patients completed treatment for the first 12 wk without modifications. The authors concluded that concurrent use of SBRT and Sorafenib should not be recommended. Based on the preclinical data they advocated in favor of evaluating a sequential approach, which is currently under investigation within a randomized trial (RTOG 112).

## SBRT AS BRIDGING TO TRANSPLANT

Many patients who were initially eligible for liver transplantation unfortunately drop off waiting lists due to tumour progression. As a result, increasing attention is paid to bridging approaches to reduce this number. Based on limited evidence from retrospective analyses, SBRT seems to be a reasonable option. For example, Katz *et al*<sup>[45]</sup> reported 18 patients treated with SBRT as bridging approach. All patients received 50 Gy in 10 fractions. 6 patients were delisted due to various reasons while the remaining 12 finally received major surgery or transplant after a median of 6.3 months. No grade 3+ toxicities were reported. Pathologic complete response rate in explanted organs following SBRT was 20%. Local control until transplantation was achieved in all patients. With a median follow-up of 20 mo, all patients are disease-free and alive. O'Connor *et al*<sup>[46]</sup> similarly described a series of 11 patients with median lesion size of 3.4 cm who received SBRT with 33-54 Gy in 3 fractions as bridging. Patients underwent liver transplantation after a median interval of 113 d. Again no patient experienced grade 3+ toxicity. Pathologic complete response was found in 27% and 5-year DFS and OS after transplantation were 100%. Interestingly, patients receiving 54 Gy in 3 fractions showed a distinctly higher pathologic complete response rate of 60%. Mohamed *et al*<sup>[21]</sup> evaluated various bridging strategies including RFA, TACE, SBRT and SIRT. They found high pathologic complete response rates for all bridging treatments but noticed favorable toxicity profiles for SBRT and SIRT (no grade 3+ toxicity). Finally, Murray *et al*<sup>[4]</sup> noted in a recent review

**Table 1 Prospective trials and large (> 100 patients) retrospective series evaluating stereotactic body radiation therapy in hepatocellular carcinoma**

Author	Yr	Type	n	Size	VI	PVT	mf	PT	CP class	f/u	Dose	1y-LC	1y-OS
Méndez Romero <i>et al</i> <sup>[25]</sup>	2006	phase I/II	8 (11)	3.5 (0.5-7) cm	38%	25%	25%	NR	A: 63%, B: 25%, UK: 12%	13	25-37.5/3-5Fx	75%	75%
Tse <i>et al</i> <sup>[26]</sup>	2008	phase I	31 (NB)	173 (9-1913) mL	52%	NR	NR	61%	A: 100%	18 <sup>1</sup>	24-54/6Fx	65% <sup>1</sup>	48%
Cárdenes <i>et al</i> <sup>[27]</sup>	2010	phase I	17 (25)	34 (8-95) mL	NR	18%	30%	24%	A: 35%, B: 65%	24	36-48/3-5Fx	100%	75%
Kang <i>et al</i> <sup>[28]</sup>	2012	phase II	47 (56)	15 (2-214) mL	NR	29%	17%	100% <sup>2</sup>	A: 87%, B: 13%	17	42-60/3Fx	95% <sup>4</sup>	69% <sup>4</sup>
Price <i>et al</i> <sup>[29]</sup>	2012	phase I/II	26 (29)	NR (21-253) mL	NR	12%	12%	27%	A: 54%, B: 46%	13	36-48/3-5Fx	96%	77%
Huang <i>et al</i> <sup>[30]</sup>	2012	phase II	36 (NB)	4.8 (1.1-12.3) cm	NR	NR	NR	NR	A: 78%, B: 19%, C: 3%	14	25-48/4-5Fx	88%	64% <sup>4</sup>
Bujold <i>et al</i> <sup>[31]</sup>	2013	phase I/II	102 (NB)	117 (1-1913) mL	55%	NR	61%	52%	A: 100%	31	24-54/6Fx	87%	55%
Culleton <i>et al</i> <sup>[32]</sup>	2014	phase II	29 (NB)	9 (4-27) cm	NR	76%	NR	14%	B: 97%, C: 3%	NR	21-49/5-15Fx	NR	32%
Sanuki <i>et al</i> <sup>[33]</sup>	2014	retro	185 (185)	8 (1.6-65) mL	NR	NR	0%	68% <sup>2</sup>	A: 85%, B: 15%	23	35-40/5Fx	99%	95%
Lasley <i>et al</i> <sup>[14]</sup>	2015	phase I/II	59 (65)	34 (2-107) mL	NR	NR	NR	NR	A: 64%, B: 36%	33/46 <sup>3</sup>	36-48/3-5Fx	NR	91%/82% <sup>3</sup>
Scorsetti <i>et al</i> <sup>[34]</sup>	2015	phase II	43 (63)	5 (1-13) cm	NR	20%	43%	65%	A: 53%, B: 47%	8	36-75/3-6Fx	86%	78%
Su <i>et al</i> <sup>[35]</sup>	2016	retro	132 (175)	3 (1.1-5) cm	NR	NR	28%	30%	A: 86%, B: 14%	21	42-46/3-Fx	91%	94%
Takeda <i>et al</i> <sup>[36]</sup>	2016	phase II	90 (90)	NR (1-4) cm	NR	NR	0%	64%	A: 91%, B: 9%	42	35-40/5Fx	96% <sup>5</sup>	67% <sup>5</sup>
Moon <i>et al</i> <sup>[37]</sup>	2018	phase II	11 (NB)	23 (3-145) mL <sup>1</sup>	NR	NR	13% <sup>1</sup>	48% <sup>1</sup>	NR	13 <sup>1</sup>	27.5-45/3-5Fx	82%	36%
Nabavizadeh <i>et al</i> <sup>[38]</sup>	2018	retro	146 (146)	NR	NR	10%	0%	92%	A: 46%, B: 41%, C: 13%	23	50/5Fx <sup>6</sup>	97%	NR
Jeong <i>et al</i> <sup>[39]</sup>	2018	retro	119 (139)	1.7 (NR) cm	0%	0%	NR	97%	A: 91%, B: 9%	26	30-60/3Fx	99%	99%

<sup>1</sup>All patients (including different histologies);<sup>2</sup>TACE 1-2 mo prior to SBRT;<sup>3</sup>Reported separately for CP-A and CP-B patients;<sup>4</sup>2-year rate;<sup>5</sup>3-year rate;<sup>6</sup>Patients with poor liver function were treated with hypofractionated radiation therapy (45 Gy in 18 fractions).

n: Number of patients (lesions); cm: Cm diameter; mL: Milliliter volume; VI: Vascular invasion; PVT: Portal vein thrombosis; mf: Multifokal; PT: Prior treatment; CP: Child-Pugh; f/u: Median follow-up in months; dose: Total dose in Gy; Fx: Number of fractions; 1y-LC: 1-year local control rate; 1y-OS: 1-year overall survival rate; retro: Retrospective; UK: Unknown; NR: Not reported.

that 63%-100% of patients treated with SBRT as bridging proceeded to transplantation with explants showing pathologic complete and partial responses in 14%-27% and 23%-64% of lesions.

In summary, SBRT seems to be another suitable option to bridge patients scheduled for liver transplant, which shows similar response rates but very modest toxicity profiles as compared to other local treatment options and should be considered in the multidisciplinary evaluation.

## FUTURE DIRECTIONS

Future developments regarding SBRT mainly focus on MRI-based treatment planning followed by real-time MRI-guided radiation therapy. The implementation of daily image guidance and replanning using MR-linac technology with enhanced soft-tissue information may not only result in increased set-up accuracy. It may however, allow omission of fiducial placement prior to SBRT, thus rendering SBRT a completely non-invasive treatment option. Furthermore, particle therapy (protons or heavy ions) seems to be a promising option due to higher biological effectiveness (heavy ions) and dosimetric advantages. However, the main benefit of protons (the lack of exit dose) may be offset in liver tumors by several factors: Meticulous motion mitigation techniques are crucial in order to minimize range uncertainties caused by moving air-soft-tissue or air-bony interface. Air-filled cavities in adjacent luminal organs present

Table 2 Studies comparing stereotactic body radiation therapy to other local treatments

Author	Yr	Type	Treat.	n	Size	mf	PT	CP class	f/u	Dose	1y-LC	1y-OS	tox.	Comment
Su et al <sup>[40]</sup>	2017	pm	SBRT	33 (45)	3.3 (NR) cm	36%	0%	A: 100%	42	42-48/3Fx	84% <sup>1</sup>	100%	nausea <sup>4</sup>	LC/OS NS
			OP	33 (45)	3.3 (NR) cm	30%	0%	A: 100%	44		72% <sup>1</sup>	97%	bleed./pain <sup>5</sup>	
Wahl et al <sup>[19]</sup>	2016	retro	SBRT	63 (83)	2.2 (0.1-10) cm	29%	2 (0-7) <sup>2</sup>	A: 69%, B: 29%, C: 2%	13	30-50/3-5Fx	97%	74%	grade3+: 3%	LC/OS NS
			RFA	161 (249)	1.8 (0.6-7) cm	32%	0 (0-7) <sup>2</sup>	A: 50%, B: 42%, C: 8%	20		84%	70%	grade3+: 11%	> 2 cm LC sig↑ with SBRT
Sapir et al <sup>[20]</sup>	2018	retro	SBRT	125 (173)	2.3 (0.1-20.8) cm	NR	2 (NR) <sup>2</sup>	6 (5-9) <sup>3</sup>	12	30-50/3-5Fx	97%	75%	grade3+: 8%	LC sig↑ with SBRT
			TACE	84 (84)	2.9 (0.7-15) cm	NR	0 (NR) <sup>2</sup>	6 (5-9) <sup>3</sup>	23		47%	74%	grade3+: 13%	Tox sig↑ with TACE

<sup>1</sup>Intrahepatic recurrence free survival;<sup>2</sup>Number of prior treatments median (range);<sup>3</sup>CP score median (range);<sup>4</sup>All grades, significantly increased with SBRT;<sup>5</sup>All grades, significantly increased with surgery.

treat.: Treatment; n: Number of patients (lesions); size: Lesion size median(range); cm: Centimeter diameter; mf: Multifokal; PT: Prior treatment; CP: Child-Pugh; f/u: Median follow-up in months; dose: Total dose in Gy; Fx: Number of fractions; 1y-LC: 1-year local control rate; 1y-OS: 1-year overall survival rate; tox: Toxicity, NS: Not significant; pm: Propensity score matched pair analysis; retro: Retrospective; bleed.: bleeding; sig: Significant; OP: Surgery; RFA: Radiofrequency ablation; TACE: Transarterial chemoablation; NR: Not reported.

further challenges<sup>[47]</sup>. Nevertheless, several reports describing early experiences with protons have shown high local control rates and low toxicities<sup>[48,49]</sup>. The potential benefit is currently evaluated in a phase III trial (NRG-GI003) comparing photon and proton SBRT in unresectable HCC<sup>[47]</sup>.

## CONCLUSIONS

Evidence comparing various strategies for the treatment of HCC is limited. Based on available data, SBRT is an effective treatment option for HCC accompanied by low rates of toxicity. Outcomes seem at least comparable to other local treatment options or limited (non-transplantation) surgical approaches. Combination with other local therapies especially TACE appears to be feasible and seems to result in synergistic effects. SBRT may also be reasonably used as a bridging option in patients awaiting liver transplantation. Dose and fractionation should be prescribed individually based on liver volume, lesion size and number, prior treatments, current liver function and adjacent organs at risk and adequate patient selection is crucial.

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