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Advances in SBRT for hepatocellular carcinoma

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Abstract

SBRT is an emerging effective treatment for hepatocellular carcinoma (HCC) associated with acceptable rates of toxicity in appropriately selected patients. Despite often being reserved for patients unsuitable for other local treatments, prospective and retrospective studies have demonstrated excellent long-term control. SBRT may be used as a stand-alone treatment, or as an adjunct to other HCC therapies. Based on available data, SBRT appears to complement existing local liver therapies. Randomised and non-randomized comparative studies are required to better determine the optimal role of SBRT in HCC treatment.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of cancer death[1]. Following resection or transplant of early stage HCC, 5-year survival is around 50-70%[2]. Unfortunately, only about 30% of HCC patients are suitable, as a result of poor liver function, poor general condition and/or the locally advanced nature of HCC[3]. In patients unsuitable for transplant or resection with smaller tumours, ablative therapies such as radiofrequency ablation (RFA) may result in long term control, with 5-year survival rates over 60% for tumours <3 cm, in selected patients[4]. Larger HCC and lesions adjacent to major vessels are less well suited for RFA. For patients inappropriate for curative options, some may be candidates for hepatic arterial transarterial chemoembolization (TACE) or drug eluting beads (DEB). Conventional TACE improves survival from 11-27% to 24-63% at 2 years[5] and DEB may provide additional benefit[6]. Sorafenib is another treatment that improves survival from 33% to 44% at 1 year compared to placebo in patients with intact liver function[7].

Traditionally, radiotherapy was not considered appropriate for HCC as the whole liver radiation tolerance is lower than the doses required for HCC ablation[8]. In addition, HCC most often occurs on a background of liver disease, and there is a fine balance between adequate treatment of the HCC and avoidance of liver toxicity. Modern radiotherapy and imaging, however, permit ablative doses to be delivered to HCC, without excessive dose to normal liver. HCC SBRT was first described in 1995 by Blomgren et al.[9]. Robust target delineation, highly conformal planning, online image guidance and methods to minimise respiratory motion are required for optimal delivery. Despite often being reserved for patients unsuitable for other treatments, and in whom poor outcomes are expected, studies of SBRT in HCC have demonstrated excellent long-term control. SBRT may be used as a stand-alone treatment for patients unsuitable for standard treatments, and there is interest in its use as an alternative or adjunct to other HCC therapies. Due in part to a lack of level 1 evidence, SBRT is currently not considered as standard treatment in most HCC management guidelines[10-12]. This review examines clinical advancements in SBRT for HCC.

Clinical evidence: Prospective data

A number of early phase trials specifically examining SBRT for HCC have been reported, amounting to more than 250 patients and in excess of 350 HCC lesions[13-17]. Key prospective studies are summarised in Table 1 and discussed below.

Mendez Romero et al published the first prospective trial in 2006[13]. Eight HCC patients, with 11 liver lesions measuring up to 7cm, ineligible for other local treatments, were included. The prescription dose was based on lesion size and presence of cirrhosis. Local control and overall survival at one year were both 75%. Local failure was only observed at the lowest dose (25Gy in 5 fractions).

There was one episode of high-grade toxicity in a patient with Child-Pugh (CP) B cirrhosis who developed fatal radiation-induced liver disease.

Kang et al, in 2012, published outcomes of a phase II trial of SBRT for HCC including 47 patients with incomplete responses to TACE and mainly CP A disease[14]. The 2-year local control and overall survival rates following SBRT (42-60Gy in 3 fractions) were 95% and 69% respectively. Grade 3+ toxicity included grade 3 hyperbilirubinaemia (4%), ascites (4%) and thrombocytopaenia (11%) and grade 3/4 gastrointestinal (GI) ulceration (11%). Progression from CP A to CP B disease occurred in 13% of patients.

The largest prospective data series was published by Bujold et al in 2013[15]. This phase I/II study included 102 patients, all CP A and unsuitable for other local liver therapy, most often with locally advanced HCC (55% with major portal vein invasion) and 12% had extra-hepatic disease. Local control and overall survival at one year following 24-54Gy in 6 fractions were 87% and 55% respectively. Grade 3+ toxicity occurred in 30%, with 7 deaths occurring 1.1-7.7 months after SBRT, all considered possibly related to treatment (liver failure in 5, 2 with progressive HCC in the portal vein, cholangitis in 1, and upper GI bleed in 1). In addition, 29% of patients experienced a decline in CP class at 3 months.

The above group also published outcomes for a combination of 29 prospective (n=14), and retrospective (n=15) patients with CP B and CP C disease, 76% with HCC portal vein thrombosis and 76% with extra hepatic disease[18]. The median prescribed dose was 30Gy in 6 fractions. Overall survival was 32% at 1 year, and was better in patients with CP B7 scores compared to higher, and in patients with

AFP levels ≤4491ng/ml. The rate of progression at 12 months was 45%. A decline in CP score of ≥2 were observed in 63% at 3 months.

More recently, Lasely et al, in 2015, reported Phase I/II trial results for 38 CP A and 21 CP B patients with 65 lesions[16]. Up to three lesions with a combined diameter of ≤6cm and ≥0.5cm away from bowel or stomach wall were eligible. Patients had to be ineligible for resection or transplant, although not necessarily ineligible for other therapies. Prescription doses were initially 36-48Gy in 3 fractions. After the observation of increased toxicity in CP B7+ patients, the dose for CP B patients was changed to 40Gy in 5 fractions and CP B8+ patients were excluded from the trial. Local control at 1 and 3 years was 91% in CP A patients, and 82% in CP B. Grade 3/4 liver toxicity was observed in 11% of CP A patients, and 38% of CP B. For CP B patients, those who experienced grade 3+ toxicity had higher mean liver doses, higher doses to 1/3 of the normal liver and larger volumes of liver receiving up to 15Gy.

Also in 2015, Scorsetti et al published outcomes for 23 CP A and 20 CP B patients with 63 HCC lesions[17]. Lesions <3cm received 48-75Gy in 3 fractions and those 3-6cm received 36-60Gy in 6 fractions. Local control at one year was 86%. No patients with GTVs <5cm who received a biologically equivalent dose >100Gy (n=24) experienced local progression. Grade 3 liver enzyme elevation occurred in 7 patients (16%), accompanied by ascites in 5 CP B patients.

Clinical evidence: Retrospective data

Several retrospective series have been published. Those including more than 60 patients are summarised in Table 2. The two largest studies are reviewed below.

Sanuki et al in 2013 reported on 185 patients with 185 HCC lesions, all ≤5cm[19]. Patients were unsuitable for surgery or percutaneous ablative therapies. Planned prescription doses were 40Gy and 35Gy for patients with CP A and CP B disease respectively, in 5 fractions, reduced, as necessary, to meet constraints. Local control and overall survival at 3 years were 91% and 70% respectively, with no difference between 35Gy and 40Gy. Grade 3+ acute toxicities occurred in 13%. There were two episodes (1%) of grade 5 liver failure at 3 and 6 months, both in CP B patients. Patients who received 35Gy had more acute toxicities, likely reflecting the higher proportion of CP B disease (52%) in this group compared to the 40Gy group (1% CP B). CP score worsened by 2 points in 10%.

Su et al reported on 114 CP A and 18 CP B patients unsuitable for surgery and percutaneous ablative therapies, with 175 HCC lesions, all ≤5cm[20]. Most patients (97%) received 42-46Gy in 3-5 fractions. Local control and overall survival at 1 year were 91% and 94% respectively. Grade 3+ toxicity developed in 8% (73% with CP B disease) including grade 3+ encephalopathy, grade 3-5 upper GI bleeding, grade 5 hepatic failure and grade 5 hepatic haemorrhage. Multivariate analysis demonstrated that CP B disease was the only significant predictor of inferior survival.

Summary: efficacy and safety of SBRT for HCC

SBRT is effective in HCC, resulting in local control rates of 75-100% at 1 year, with responses achieved in the majority (Figure 1), and long-term survival reported[21]. Most patients have CP A disease, and between 1 and 3 lesions[13,16,17,19,22-24], often measuring up to 5-7cm[13,16,17,19,20,22-24]. There is more limited experience of SBRT in patients with CP B disease. SBRT has frequently been employed in patients who have failed or are unsuitable for more established therapies. A wide range of dose-

fractionation schedules have been used, usually with lower doses in the presence of CP B disease.

Grade 3+ toxicity has been reported in up to 30% and up to 38% of CP A and CP B patients respectively[15,16]. Hepatic and luminal toxicities are the most frequent toxicities. Deaths from liver failure are reported in up to 13% (most often in CP B patients) and high-grade luminal toxicities occur in up to 11% of patients[13,14]. Normal liver doses and the severity of cirrhosis are important in predicting hepatic toxicity[15,16,25-27]. Classic and non-classic radiation-induced liver disease (RILD) have been described[28], both of which can progress to fulminant hepatic failure. Patients with underlying cirrhosis are also at increased risk of luminal toxicity[14,15,20-22,29-31].

Current questions: the place of SBRT for HCC

Given the encouraging results in traditionally poor prognosis patients unsuitable for surgery or other local therapies, questions arise as to the role of SBRT as an alternative or adjunct to standard liver therapies. To date, no randomised evidence exists comparing SBRT to other HCC therapies, and selection bias hampers non-randomised comparisons. Small retrospective studies have nonetheless attempted to address these questions and are discussed below.

The addition of SBRT to TACE

The combination of TACE and SBRT offers theoretical advantages: TACE may shrink tumours, creating a smaller target for SBRT, and the chemotherapy may provide radiosensitization; furthermore the lipiodal component is radio-opaque and may help with SBRT image guidance. Kang et al previously demonstrated encouraging results from SBRT following incomplete TACE[14]. Jacob et al and Honda et al, compared SBRT and TACE to TACE alone in tumours ≥3cm and ≤3cm respectively in

retrospective series[32,33]. Both studies found that the addition of SBRT resulted in improved local control with no increase in high-grade toxicity. Furthermore, in tumours ≥3cm, after censoring for liver transplantation, overall survival was significantly better with TACE plus SBRT compared to TACE alone (median survival 33 and 20 months respectively; p=0.02)[32]. There was no overall survival advantage from the combination in tumours ≤3cm, although disease free survival (DFS) was significantly better with the addition of SBRT in treatment naïve patients (1-year DFS 71.4% and 24.8% respectively, p=0.029)[33]. SBRT, therefore, based on this evidence, appears to complement TACE.

Similar outcomes were observed by Paik et al who compared retrospective outcomes in 24 patients with a complete response to TACE (group 1) and 154 patients with an incomplete response to TACE who went on to receive: i) curative treatment (surgery, RFA, percutaneous ethanol injection; n=47; group 2), ii) SBRT (median 56Gy, range 40-60Gy in 3-5 fractions; n=37; group 3) or iii) non-curative treatment (e.g. repeat TACE, sorafenib; n=70; group 4)[34]. Overall survival at 5 years was 50%, 58%, 53% and 28% in groups 1,2,3 and 4 respectively. There were no significant differences in survival between groups 1 to 3 while patients in group 4 fared significantly worse. Based on the above, therefore, following an incomplete response to TACE, SBRT appears competitive with curative therapies, and produces outcomes comparable to those achieved following a complete response to TACE.

SBRT for portal vein thrombosis

Patients with HCC portal vein thrombosis (PVT), a poor prognostic factor, have been included in several of the above studies[13-18,21] where overall outcomes are better than expected. Recanalization of the vascular HCC following SBRT potentially facilitates TACE, which is less effective in the presence of main branch PVT. Where SBRT in

HCC patients with PVT has been specifically examined, complete and partial responses have been reported in up to 37% and 75%, respectively, with recanalization in 44-76% and low rates (≤3.2%) of high-grade toxicity[35-37]. The time to maximal response, however, may be many months (e.g. 6).

SBRT as a bridge to transplant

There is interest in the use of SBRT as a bridge to transplant in patients awaiting liver transplantation, since approximately 25% and 44% of patients drop off the waiting list due to HCC progression after 12 and 24 months respectively[38]. SBRT may help reduce this: following SBRT used as a bridging therapy, 63-100% of patients are reported to proceed to transplant, with low rates of toxicity, and with complete and partial pathological responses reported in 14-29% and 23-64% of lesions respectively[39-43]. Mohamed et al recently compared SBRT, TACE, RFA and yttrium-90 microspheres as bridge to transplant therapies in a retrospective series of 60 patients[43]. Mean pathological necrosis was not significantly different between modalities, and toxicities were lowest for SBRT and yttrium-90. Overall, despite small numbers and retrospective data, SBRT appears effective and well tolerated as a bridging therapy, and is competitive with other therapies.

SBRT and sorafenib

Pre-clinical data has suggested that the addition of sorafenib can enhance the tumour response to radiation[44]. Brade et al reported outcomes from a phase I trial of concurrent SBRT and sorafenib[45]. Overall there were 9, 2 and 1 episodes of grade 3, 4 (liver enzyme changes and small bowel obstruction) and 5 (upper GI bleed/ HCC rupture) toxicities, at least possibly attributable to SBRT. It was therefore concluded that the concurrent use of sorafenib and SBRT in HCC is not recommended.

Given the toxicities observed with concurrent therapy, sequential use of SBRT and sorafenib is being investigated in RTOG 1112, a phase III trial comparing SBRT followed by sorafenib with sorafenib alone in HCC patients unsuitable for standard local and regional therapies[46]. Patients must have CP A disease and ≤5 discrete tumour foci, with no one HCC >15cm and the maximum sum of HCC lesions <20cm. Main portal vein invasion and extra-hepatic disease up to a cumulative maximum of 3cm are permissible.

SBRT in comparison to other liver therapies

In the setting of recurrent HCC, Huang et al compared retrospective outcomes between 36 patients (42 lesions) treated with a median of 37Gy (range 25-48) in 4-5 daily fractions and 138 historical controls who received other liver therapies or no therapies[47]. On multivariate analysis, the absence of SBRT, tumour size >4cm, CP B/C and recurrent stage III/IV disease were predictors of inferior overall survival. There was one case of acute grade 3 gastric ulceration in the SBRT group, but no other high-grade acute toxicities. A matched-pair analysis of 28 SBRT patients and 28 historical controls, found overall survival was better in the SBRT group (2-year survival 73% vs 42% in controls) as was time to progression (median 8.6 vs 3.5 months).

Shiowaza et al compared retrospective outcomes between SBRT and RFA, in 35 patients treated with 3-5 fraction SBRT and 38 patients treated with RFA[48]. Patients who received SBRT were significantly older and had larger tumours. There were no significant differences in local control and overall survival. Late adverse events affected 4 patients in the SBRT group, including 2 deaths from hepatic failure, with no adverse events in the RFA group. SBRT therefore appeared competitive with RFA, albeit more toxic.

Wahl et al conducted a similar retrospective comparison between 63 patients (83 tumours) treated with SBRT (median doses: 30Gy in 3 or 50Gy in 4 fractions) and 161 patients (249 tumours) treated with RFA[31]. Patients who received SBRT had lower rates of cirrhosis, higher AFP levels and had received a greater number of previous liver therapies. Statistical methods were employed to adjust for imbalances. Freedom from local progression at 1 year was 97% and 84% for patients treated with SBRT and RFA respectively. For tumours <2cm, there was no difference in local control between RFA and SBRT. For tumours ≥2cm, SBRT was associated with improved local control. On multivariate analysis, RFA, compared to SBRT, was associated with inferior local control. There was no significant difference in overall survival. There were 3 grade 3+ adverse events in the SBRT group (5%), and 18 in the RFA group (11%). The group concluded that there may be an advantage to SBRT in larger (≥2cm) HCC tumours.

Yuan et al compared outcomes in 48 patients with stage I HCC, 22 treated with SBRT (median 45Gy, range 39-54 in 3-8 fractions) and 26 who received microscopic complete resections[49]. Local control at 1 and 3 years after SBRT was 93% and 68% respectively. There was no significant difference in overall survival (3-year overall survival: 57% vs 69% for SBRT vs surgery) or progression free survival.

These comparative studies suggest that SBRT is competitive with other, more established treatments. Given the potential for bias, however, randomised comparisons are warranted.

SBRT technique

Patient selection

The most suitable HCC patients for SBRT have CP A disease. CP B patients have also been successfully treated although toxicity is more frequent, and lower doses should be considered for these patients. Preservation of adequate liver function and avoidance of excessive dose to luminal structures are needed: a threshold volume of uninvolved liver[15-17,20] (often 700ml) may be specified, and a minimum distance (e.g. 5mm) between tumours and luminal structures may be mandidated[16,23,50]. Much of the earlier evidence limited lesion size (often to <5-7cm) and number (often ≤3), and patients with vascular invasion or extra-hepatic disease have been excluded in some studies, but there is increasing successful use of SBRT in the setting of larger lesions, more numerous lesions and in the presence of adverse features[15,18].

Respiratory motion management

Breath hold techniques using Activated Breathing Control devices [15,25,29] have been used to reduce respiratory motion[51]. Abdominal compression with 4D-CT have also been used to reduce respiratory motion[19,21,50,52] as has respiratory gating[29,32,41] and intra-fraction tracking of peri-tumoral implanted fiducials[22,30,34,42,48] or external surface markers[20,22,30,43,48] (which requires daily imaging to ensure the adopted breathing model remains satisfactory). Free breathing with 4D-CT, with individualised margins to account for respiration, have also been employed[23].

Simulation and contouring

Intra-venous contrast-enhanced, multi-phasic CT is required for GTV delineation. Tumour enhances on the arterial phase before washing out during venous and delayed phases, obtained during breath hold. 4D-CT can aid in estimation of motion. MRI sequences can further assist with GTV definition. For SBRT, CTV margins are

typically not employed[14,16,19,20]. PTV margins are usually individualised and are ideally ≤5 mm but up to ~10mm may be required, depending on the motion management strategy.

Planning

A multi-beam approach, often including non-coplanar beams, is usually adopted to create highly conformal treatment plans[13,15,16,20,29]. Arc therapies have also been employed[20,29]. For the majority of HCC SBRT, dose has been prescribed to a peripheral isodose (typically 70-85%) covering the majority of the PTV, thus facilitating dose escalation within the PTV and rapid dose fall off beyond.

Dose, fractionation and organ at risk constraints

A variety of dose and fractionation schedules have been employed, most often using 3 to 6 fractions. Both the severity of liver disease and normal tissue doses influence the chosen prescription dose. Some studies have found higher doses to be important for local control and overall survival[13,21,30] but others have not[14,15,18-20,23,29]. Indeed, HCC appears to be a radiosensitive tumour, such that, above a certain threshold dose, there may be little benefit in further dose escalation, and potential for increased toxicity[19].

For small tumours away from luminal GI tissues, a fixed dose may be used (e.g. 40Gy in 5 fractions), but for larger tumours, where doses must be limited because of normal liver tolerance, an individualised strategy, based on escalating dose based on liver constraints, is most appropriate. Varying approaches to dose selection have been adopted and include a biological individualised strategy based on the effective volume of irradiated liver and Lyman normal tissue complication probability (NTCP) estimation of classic RILD[15,53], or a critical volume approach, which limits the dose received by a specified volume of normal liver[14,17,21,23,25] (often 700ml).

Uncertainties remain regarding the optimal HCC SBRT dose and liver constraints, and prospective data is required to define these further[28]. HCC SBRT dosimetry and dose-volume effects are discussed in greater detail elsewhere[28,54].

As well as liver doses, luminal doses are also important. One trial, with one of the highest high-grade GI toxicity rates, did not specify luminal constraints, which may have contributed to the high toxicity, although pre-existing GI ulceration may have had an impact[14]. Another study observed that all patients with high-grade GI toxicity had lesions <0.5cm from luminal structures[21]. Thus, luminal constraints, and/or specification of minimal distances between targets and lumen, are necessary.

Image guidance

Daily image guidance is necessary[55]. Orthogonal x-rays and cone beam CT (CBCT) are most commonly employed. CBCT matching has been suggested to be superior to orthogonal x-rays[56]. The use of peri-tumoral fiducials, with both x-rays and CBCT can further enhance set-up[21,26,31,32,34,52,57]. The presence of lipiodal following TACE, or surgical clips, have also been used as surrogates for tumour position[21,26]. Depending on the method of respiratory motion compensation, CBCT may be most usefully acquired in breath hold or as a 4D-CBCT to assist in matching.

Future technical developments

The use of intra-abdominal spacers to increase the distance between tumours and luminal structures can be used to reduce GI toxicity. These have been shown to displace the stomach and bowel by ≥2cm, with low complication rates[58]. The clinical implementation of deformable image registration has the potential to improve set-up accuracy in the face of organ deformation, which leads to discrepancies in planned versus delivered doses[59]. It may also have a role in CT and MRI co-registration prior to contouring, and in comparing pre- and post-treatment imaging[59]. The

implementation of daily online image guidance using MRI in the context of the MR-linac will provide enhanced soft tissue information compared to CBCT, thus improving set-up accuracy, without the need for fiducials. The system may also allow intra-fraction motion monitoring. Adaptive radiotherapy would allow creation of 'plans of the day', based on each day's anatomy, which could further improve accuracy. These measures may reduce uncertainties PTV margins, and normal tissue irradiation, hopefully reducing toxicities and improving the therapeutic ratio for HCC SBRT.

Conclusions

SBRT for HCC is effective in early phase trials and retrospective series, with acceptable toxicity, with long-term survival achieved in a proportion. Caution is required when treating patients with CP B disease. SBRT has been shown to complement existing HCC therapies, but comparative trials are required to better determine the place of SBRT amongst more recognised HCC treatments.

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Table 1. Prospective studies of SBRT for HCC

Study, year and type of data	Median follow-up (months)	No. patients	No. lesions	Child-Pugh class B** (%)	PVT (%)	Previous liver therapy (%)	Median GTV diameter (cm, (range))	Dose (Gy)/ no. fractions	1-year Local control (%)	1-year Overall survival (%)	Grade 3+ toxicity (%)
Mendez Romero 2006[13] Phase I/II	12.9	8	11	25	25		3.5 (0.5-7.2)	<4cm, no cirrhosis: 37.5/3 ≥4cm or cirrhosis: 25/5 or 30/3	75	75	12.5
Kang 2012[14] Phase II	17	47	56	13 (all B7)	11	100	2.9 (1.3-7.8)	42-60/3	2-year: 95	2-year: 69	11 (GI ulcer) 9 (ascites) 11 (thrombo-cytopaenia) 4 (hyper-bilirubinaemia)
Bujold 2013[15] Phase I/II	31.4	102	Multiple in 60.8%	0	55	52	7.2 (1.4-23.1)	Median 36 (range 24-54)/6	87	55	

											30
Culleton 2014[18] Mixed on (n=14) and off study		29	Median of 2 lesions	97 (B7/8/9: 69/24/3) (CP10: 3)	76	14	Sum of all lesions: 8.6 (4.1-26.6)	Median 30/6		32	
Lasley 2015[16] Phase I/II	CPA: 33 CPB: 46	59	65	36 (B7/8+: 81/19)	20	15	Volume: 33.6ml (2.0-107.3)	Median 48 (range 36-48)/3 CPB: 40/5*	CPA: 91 CPB: 82	CPA: 94 CPB: 57	CPA: 11 CPB: 38
Scorsetti 2015[17] Observational study	8	43	63	47	20	44	4.8 cm (1.0-12.5)	<3cm: 48-75/3 3-6cm: 36-60/6	86	78	16

*lower dose for CPB patients introduced after safety committee review, **percentage breakdown of CPB patients by CP score provided in parentheses if available, other patients mainly CPA or occasionally had no cirrhosis, unless otherwise stated, CP: Child Pugh, CR: complete response,
GI: gastrointestinal; HCC: hepatocellular carcinoma, PR: partial response, PVT: portal vein thrombosis, RECIST: Response Evaluation Criteria in Solid Tumours, SBRT: stereotactic body radiotherapy, SD: stable disease

Table 2. Retrospective studies of SBRT for HCC including >60 patients

Study and year	Median follow-up (months)	No. patients	No. lesions	Child-Pugh class B** (%)	PVT (%)	Previous liver therapy (%)	Median GTV diameter (cm, (range))	Dose (Gy) (range)/ fractions	1- year Local control (%)	1-year Overall survival (%)	Grade 3+ toxicity (%)
Bibault 2013 [30]	10	75	96	12 (B7/8: 67/33)		51% of lesions	3.7 (3.0-4.4)	45(24-45) /3	90	79	9.3%
Jang 2013[21]*	30	82	95	10 (all CPB7)	10	100	3.0 (1.0-7.0)	51(33-60)/3	2-year: 87	2-year: 63	>54Gy: Bowel: 3.1% Other: 3.1%
Sanuki 2013[19]	35Gy: 31 40Gy: 23	185	185	15		68	35Gy: 2.7 (1.0-5.0) 40Gy: 2.4 (0.8-5.0)	CPA: 40 (35-40)/5 CPB: 35 (35-40)/5	99	95	13%
Yoon, Jung 2013[23,26]	26	93	103	26		99	2.0 (1.0-6.0)	45/3 (30-60/3-4),	95	86	6.5% (hepatic)
Takeda 2014[50]	31	63	63	16		68	2.6 (1.0-5.0)	40 (35-40)/5 CPB: 35/5	100	100	21% at 6-12 months
Huestas	12	77	97	14		16	2.4	45(15-60)/3	99	82	Acute: 2.6%

2015[22]				(B7/8: 73/27)			(0.7-6.3)				Late 6.5%
Kimura 2015[24]	26	65	74	14 (B7/8: 56/44)	0	≥92	1.6 (0.5-5.4)	48/4	100	92	23.1% at 6-12 months
Yamashita 2015[29]	21	79	79	11 (CPC: 1%)		67	2.7 (0.6-7.0)	48 (40/4-60/10)	At median FU: 82%	2-year: 53	4.6% (all GI)
Su 2016[20]	21	132	175	14		30	3 (1.1-5.0)	42-46/3-5 28-30/1	91	94	8.3% (8/11 CPB)
Wahl 2016[31]	13	63	83	29 (B7/8/9: 38/46/17) (CPC: 2%)		Median of 2 prior therapies	2.2 (0-10.0)	30/3 or 50 /5	97	74	5% at ≤30 days, 5.4% luminal , 3.3% biliary at 1 year

* Retrospective series but includes patients reported in Kang et al prospective trial, **percentage breakdown of CPB patients by CP score provided in parentheses if available, other patients mainly CPA or occasionally no cirrhosis, unless otherwise stated, CP: Child Pugh, CR: complete response, FU: follow-up, GI: gastrointestinal; HCC: hepatocellular carcinoma, PR: partial response, PVT: portal vein thrombosis, RECIST: Response Evaluation Criteria in Solid Tumours, SBRT: stereotactic body radiotherapy, SD: stable disease

Figure 1. Patient with HCC with venous invasion showing reduction in size and alpha-fetoprotein (AFP) in response to SBRT, 45Gy in 5 fractions: a) Pre-SBRT venous phase CT, b) SBRT plan (PTV for different respiratory phases shown in sold light green, cyan and pink) and c) 3-month post-SBRT venous phase CT