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Systematic Review

Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: A systematic review and meta-analysis of observational studies

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A B S T R A C T

Background and purpose: Stereotactic body radiotherapy (SBRT) is an emerging ablative modality for hepatocellular carcinoma (HCC). This study aimed to synthesize available evidence to evaluate the clinical feasibility and efficacy of SBRT for HCC.

Materials and methods: A systematic search was performed of the PubMed, Medline, Embase, and Cochrane Library databases. Primary endpoints were overall survival (OS) and local control (LC), and the secondary endpoint was grade ≥3 complications.

Results: Thirty-two studies involving 1950 HCC patients who underwent SBRT were included. Pooled 1-, 2-, and 3-year OS rates were 72.6% (95% confidence interval [CI]: 65.7–78.6), 57.8% (50.9–64.4), and 48.3% (40.3–56.5), respectively. Pooled 1-, 2-, and 3-year LC rates were 85.7% (95% CI: 80.1–90.0), 83.6% (77.4–88.3), and 83.9% (77.6–88.6), respectively. The median value of median tumor sizes among studies was 3.3 cm (range: 1.6–8.6). Median radiation doses, calculated in dose equivalent with 2 Gy per fraction, ranged from 48 to 114.8 Gy_{10} (median 83.3 Gy_{10}). Subgroup comparison regarding tumor size showed significant differences for 1- and 2-year OS rates and 1-, 2-, and 3-year LC rates, and that regarding radiation dose showed no difference for OS and a marginal difference for 1-year LC rate. Pooled rates of hepatic and gastrointestinal grade ≥3 complications were 4.7% (95% CI: 3.4–6.5) and 3.9% (2.6–5.6), respectively. Child-Pugh class was significantly correlated with hepatic complication of grade ≥3 in meta-regression analysis ($p = 0.013$).

Conclusion: SBRT for HCC was a feasible option conferring excellent LC persisting up to 3 years. Both OS and LC were affected by tumor size, and radiation dose marginally affected LC. Severe complications rarely occurred, but liver function should be considered to avoid serious hepatic toxicity.

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor and the third most common cause of cancer-related death worldwide, accounting for 600,000 deaths per year [1]. The preferred curative modality is surgical resection; however, only 30% of patients with HCC are suitable candidates for surgery because of inadequate liver function, poor performance status, or locally advanced tumors [2,3]. Radiofrequency ablation (RFA) is another curative option, which might yield long-term tumor control and exhibit comparable results to primary resection for small HCCs [4,5]. Microwave ablation (MWA) has the physical advantage of being affected less by heat-sink effect, and showed comparable oncologic outcomes to those of RFA [6,7]. Trans-arterial chemoembolization showed survival outcomes comparable to those of RFA, in treating small HCCs, although tumor remission or control might be inferior [8–10].

Radiotherapy has not been considered a preferred treatment for HCC, as whole liver radiation tolerance is lower than the dose required for ablation [11]. Furthermore, there has been concern that radiotherapy might impair liver function, as HCC often occurs on a background of chronic liver disease [3]. However, modern radiotherapy based on CT imaging has enabled the delivery of ablative doses to tumors while sparing a sufficient portion of normal liver [12]. Stereotactic body radiotherapy (SBRT), an emerging radiotherapy treatment modality, requires planning for highly conformal delivery, image guidance, and methods to minimize errors due to respiratory motion [13]. Despite being reserved for cases inappropriate for other treatment modalities, local control (LC) rates for SBRT have been found to be excellent, ranging from 82

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to 95% in prospective series [14–17]. SBRT is commonly performed for a duration of <2 weeks, and can be applied to tumors not suitable for RFA, such as those near major vessels or adjacent to the diaphragm [18]. Although MWA is less affected by the heat-sink effect, but to treat tumor near major vessels, biliary trees, or diaphragms might be still difficult [19,20].

Considering the advantages listed above, numerous institutions have performed SBRT for HCC and reported their experiences. As many of the published studies were observational and provided heterogeneous information, pooled analyses have been performed by several authors. Qi et al. [21] conducted pooled analyses of studies published before August 2014 that used radiotherapy (RT) modalities including SBRT. Ohri et al. [22] assessed tumor control rates in relation to radiation dose in studies including five SBRT series for HCC. However, about two-third of studies of SBRT for HCC were published later than 2014 (Fig. 1), and neither of the aforementioned pooled analyses studies covered the majority of studies published to date (Fig. 2).

As clinical experiences with SBRT for HCC have accumulated, it has become necessary to synthesize the updated results to provide conclusive information that can be useful in clinical practice. Therefore, we performed a systematic review and meta-analysis of published clinical trials of SBRT for HCCs to integrate available evidence and evaluate clinical feasibility and efficacy.

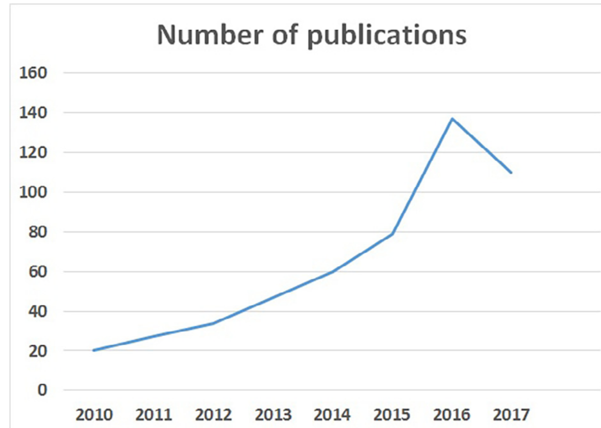

Fig. 1. Number of publications searched with terms "HCC AND SBRT" in Embase, according to year of publication, until August 21, 2018.

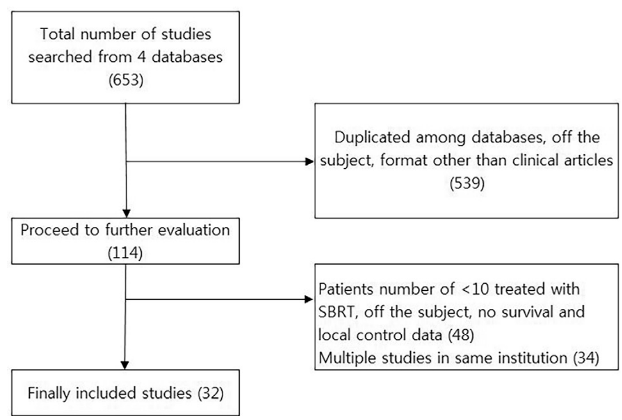

Fig. 2. Study inclusion plot.

Materials and methods

Study protocol

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRIMSA) guidelines. A systematic search was performed of the PubMed, Medline, Embase, and Cochrane Library databases for relevant literature published until April 23, 2018. Unpublished studies were not included in the search. We did not use any language restrictions. The search terms were designed to find studies using SBRT or stereotactic ablative radiotherapy (SABR) to treat HCC, emphasizing clinical outcomes rather than technical perspectives. We used the search terms: ("Stereotactic body radiotherapy" OR SBRT OR SABR OR "Stereotactic ablative radiotherapy") AND ("Hepatocellular carcinoma" OR HCC) AND survival.

Inclusion process and criteria

After initial searching, studies were filtered to exclude duplicated studies, conference abstracts, reviews, letters, editorials, case reports, lab studies, and studies with irrelevant subjects, using titles and citations. The remaining studies were further assessed to determine whether they fully met the inclusion criteria, using abstracts and full texts. The following inclusion criteria were used: (1) clinical trials, including retrospective or prospective studies; (2) inclusion of at least 10 patients with HCC treated with SBRT or SABR; (3) SBRT performed in <10 fractions; and (4) provision of at least one subject from both survival and local control. When numerical data were absent, survival or tumor control rate was estimated from the descriptive graphs. In cases of multiple studies from one institution, the following criteria were used, prioritized in numerical order, to determine inclusion: (1) study that solely reported clinical outcomes of patients with HCC treated with SBRT, rather than including other cancer patients or patients treated with other RT modalities; (2) study with the largest number of patients; and (3) most recently published study. All procedures to identify eligible studies were performed by two independent researchers (CH Rim and HJ Kim). Any disagreement was resolved by discussion and mutual consent of the above two researchers and another researcher (J Seong).

Data extraction

The standardized form for data extraction from studies included the following: (1) general information including authors, year of publication, type of study, number of relevant patients, sex, and age; (2) clinical information including Child-Pugh class, etiology, tumor vascular invasion, extrahepatic metastases, and tumor size; and (3) treatment information and outcomes including SBRT dose, fractionation scheme, overall survival rate, LC rate, and complications of grade $\geq$3. Tumor vascular invasion included invasion of portal vein, hepatic vein, inferior vena cava, and right atrium. Complications reported within 3 months after the end of radiotherapy were classified as acute complications, and those reported later than 3 months or described as "late complication" were classified as late complications. The toxicities were classified into four categories, including gastrointestinal (GI), hematologic, hepatic, and others. GI complications included gastric or duodenal ulcer, nausea and vomiting; hematologic complications included abnormalities of white blood cells, platelets, and hemoglobin; and hepatic complications included abnormalities of liver function profile (alanine transaminase, aspartate aminotransferase, and bilirubin), albumin abnormalities, and liver decompensation (ascites, encephalopathy, and varices). If rates of toxicities in a category were reported separately (e.g., vomiting and nausea were reported separately), the highest values were recorded.

Quality assessment

As most of the included studies were retrospective, we used the Newcastle-Ottawa Scale (NOS) [23] to assess the quality of included studies. Studies with NOS scores of 7–9 were regarded as high-quality studies, and those with scores of 4–6 were considered medium-quality studies.

Statistical analysis

The primary endpoints were overall survival (OS) and LC, and the secondary endpoint was complications of grade ≥3. As the included studies were performed at independent facilities using different RT schedules, we used a random effects model to yield pooled results [24]. Heterogeneity was considered to be present if the p value in Cochran's Q test [25] was <0.1 and the I^2 value was >50%. Publication biases were assessed using visual inspection of funnel plots and quantitatively assessed using Egger's test for the intercept [26]. If the two-tailed p value in Egger's test was <0.1, trimmed results using the Duval and Tweedie method [27] were presented. For comparison between subgroups, categorized by radiation dose or tumor size, a Q test based on analysis of the variance and random effects model were used. Meta-regression was performed to evaluate the correlation between continuous variables, such as Child-Pugh class A (%), tumor size, radiation dose, and oncologic outcomes including survival and complications. A p value of <0.05 was considered statistically significant. All statistical analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat Inc., Englewood, NJ, USA).

Results

An initial search of the four databases identified 653 studies. After exclusion of many duplicate studies, conference abstracts, reviews, letters, editorials, case reports, lab studies, and studies with irrelevant subjects or formats other than clinical article, 114 studies were selected for further screening. The 114 studies were evaluated using abstracts and full texts to determine whether they fully met the inclusion criteria. Multiple studies from a single institution were filtered using the criteria described in the Methods section. Finally, 32 studies comprising 33 cohorts, consisting of 1950 patients, fully meeting the inclusion criteria, were included in the present meta-analysis. The process of study recruitment is described in Fig. 1.

The majority of the included studies (85%) featured a retrospective design. Application of the NOS revealed all of the included studies to be of medium quality. The median proportion of patients with Child-Pugh class A was 82.3% (range: 47.9–100). The median proportion of patients with viral etiology was 76.7% (range: 14.9–100). The overall median tumor size (i.e. the median value of the median tumor sizes found by the studies) was 3.3 cm (range: 1.6–8.6). General information regarding included studies is summarized in Table 1.

Treatment outcomes

Total dose of SBRT and fractionation schemes were available in all included studies. We calculated median EQD2 (dose equivalent to treatment with 2 Gy per fraction) estimates using the median or prescribed doses and number of fractionations. The calculation used the α/β ratio of 10, to consider tumor radiobiology rather than that of normal tissues. The median value of all available median EQD2 estimates was 83.3 Gy (range: 48–114.8). The median values of 1-year OS, 2-year OS, and 3-year OS rates were 80.2% (range: 36.0–99.2), 56.2% (range: 30.6–87.0), and 47.5% (range: 22.0–83.8), respectively. The median values of 1-year, 2-year, and 3-year LC rates were 92.2% (range: 25–100), 89.8% (range: 39.0–100.0), and 89.3% (range: 30.0–100.0), respectively. Treatment schemes and outcomes are summarized in Table 2.

Pooled rates using random effects analyses of 1-year, 2-year, and 3-year OS were 72.6% (95% confidence interval [CI]: 65.7–78.6), 57.8% (95% CI: 50.9–64.4), and 48.3% (95% CI: 40.3–56.5), respectively. Significant heterogeneities among included studies were present in all three OS rates. In subgroup comparisons, differences between subgroups categorized by tumor size (median value of 5 cm) were statistically significant for 1-year OS rate (p < 0.001) and 2-year OS rate (p = 0.020), and tended to be significant for 3-year OS rate (p = 0.070). For subgroup comparisons categorized by radiation dose (median EQD2 estimates of 80 Gy_{10}), no statistically significant difference was found among all three comparisons regarding OS.

Pooled rates using random effects analyses of 1-year LC, 2-year LC, and 3-year LC were 85.7% (95% CI: 80.1–90.0), 83.6% (95% CI: 77.4–88.3), and 83.9% (95% CI: 77.6–88.6), respectively. Significant heterogeneities among included studies were present in all three LC rates. In the subgroup comparisons regarding tumor size (median value of 5 cm), the differences were statistically significant for 1-year, 2-year, and 3-year LC rates (p < 0.001, 0.001, and 0.001, respectively). In the subgroup comparisons regarding radiation dose (median EQD2 estimates of 80 Gy_{10}), the difference was marginally significant for 1-year LC rate (p = 0.071), and not significant for 2- and 3-year LC rates. The results of pooled analyses for OS and LC rates are summarized in Table 3.

Complications

The interpretation of complications was available in 23 of 33 cohorts. The most commonly reported complications of grade ≥3 were GI or hepatic toxicities. For GI toxicities, the rates of grade ≥3 complications were less than 5% in 16 of 17 cohorts (94.1%), and were not reported in other 6 cohorts. The pooled rate using random effects analysis was 3.9% (95% CI: 2.6–5.6). Regarding hepatic toxicities, the rates of grade ≥3 complications were <10% in 23 of 24 cohorts (95.8%). The pooled rate was 4.7% (95% CI: 3.4–6.5). Among subgroup comparisons regarding tumor sizes and radiation dose, none were found to be statistically significant. Acute and late complication rates among all studies are shown in Table 4. Pooled complication rates are summarized in Table 5. Forest plots of all primary and secondary endpoints analyses are presented in Supplemental Fig. 1.

Publication biases

Using Egger's test quantitatively and visual inspections of funnel plots, publication biases were identified from 1-year OS rates of all studies; the subgroup with tumor size <5 cm; the subgroup with median EQD2 estimates <80 Gy; 2-year OS rate of the subgroup with tumor size ≥5 cm; 1- and 2- year LC rates of all studies; the subgroup with tumor size <5 cm; the subgroup with median EQD2 estimates ≥80 Gy; 3-year LC rate of the subgroup with tumor size <5 cm; the acute hepatic and GI grade ≥3 complication rates of all studies, the subgroup with tumor size <5 cm; and the subgroup with median EQD2 estimates ≥80 Gy. All above rates were presented as trimmed results using the Duval and Tweedie method.

Meta-regression analyses

We performed meta-regression analyses to identify the correlation between toxicities and Child-Pugh class, median EQD2 estimates, and tumor size; also between overall survival and Child-Pugh class and tumor size. Child-Pugh class showed

Table 1
General information from the included studies.

Author/year		Study type	n	Male (%)	Age (median, range)	CPC A (%)	Viral etiology (%)	TVI (%)	EHM	Tumor size (median [in cm], range)
Shiozawa K	2015	R	35	68.6	m75.2 (55–89)	80	77.1		0	m2.86 (1.2–5)
Huertas A	2015	R	77	75.3	71 (44–91)	85.7				2.4 (0.7–6.3)
Yoon SM	2013	R	93	80.6	62 (42–86)	74.2	87.1	0.0	0	2.0 (1.0–6.0)
Jeong Y	2018	R	119	81.5	60 (36–90)	90.8	87.4	0.0	0	1.7 (0.8–6.0)
Bibault JE	2013	R	75	84.0	70 (44–86)	88	14.9		0	3.7
Kubo K	2018	R	65	67.7	73 (49–90)	86.2	90.8			1.6 (0.5–4.7)
Sanuki N	2014	R	48	67.0	73 (40–86)	47.9	77.0			2.7 (1.0–5.0)
Sanuki N-2	2014	R	137	64.0	74 (48–89)	98.5	84.0			2.4 (0.8–5.0)
Andolino DL	2011	R	37	81.1	63 (24–85)	64.9	51.3		0	3.5 (1–6.5)
Jang WI	2013	R	82	73.0	60 (39–79)	90.2	76.0	10.0		3.0 (1.0–7.0)
Yamashita H	2014	R	79	75.9	73 (38–95)	84.8				2.7 (0.6–7.0)
Kwon JH	2010	R	42	76.2	m60.1	90.5	85.7			3.1*, 15.4cc
Ibarra RA	2012	R	21	76.2	72 (47–88)				9.5%	8.6*, 334.2cc
Feng M	2018	P	69	70	62 (34–85)		40.0	18		3 (0.5–13)
Bujold A	2013	P	102	78.4	69.4 (40.4–90.3)	100	76.4	54.9	11.8	7.2 (1.4–23.1)
Lo C.-H.	2017	R	89	73	68 (36–87)	77.5	83.2	49.4	0	6.2 (1.2–18.5)
Scorsetti M	2015	R	43	72.1	m72 (46–87)	53	69.8	20.0		4.8 (10–12.5)
Kim JW	1905	P	18	77.8	59.5 (42–83)	94.4	83.3	0.0	0	1.95 (1.0–3.3)
Hasan S	2017	R	40	82			68.0			3.5 (1.5–8.9)
Madhavan R	2017	R	10		61.5 (52–69)	80		50		5.1, 69.3cc
Zhang T	2018	R	28	75	49 (22–65)	85.7	100.0	0	0	2.1 (1.1–3.0)
Que J	2016	R	115	76.5		90.4	87.8	29.6		(1.8–18)
Hijazi H	2016	R	23			52				5 (2–9)
Gkika E	2018	R	40	83	69 (29–84)	55	30.0	28		7 (1.7–22)
Kim M	2017	R	72	79.2	62 (37–81)	72.2	75.0	31.9	0	7 (5–10)
Uemoto K	2018	R	121	57.9	75 (44–91)	78.8		7		4.4*, 45.3cc
Lam MHC	2017	R	39	79.5	72 (54–90)	89.7	89.7			1.9 (0.6–5.0)
Sapir E	2018	R	125	81	60.8 (46.2–83.2)		50.9	7	0	2.9 (0.7–15.0)
Moon DH	2018	P	11		65.5 (23–86)					3.5 (1.7–6.5)
Guarneri A	2016	R	29	79	70 (55–88)	66	65.0			4.7 (3.1–12)
Weiner AA	2016	P	12	46	72 (51–95)					5 (1.6–12.3)
Baumann BC	2018	R	37	84	65 (41–88)	70	68.0		0	2.7 (1.1–5.6)
Hanazawa H	2017	R	17	76.5	77 (63–75)	82.3			0	4.7*, 54.6cc

Abbreviations: CPC, Child-Pugh class; TVI, tumor vascular invasion; EHM, extrahepatic metastases; R, retrospective; P, prospective.
m' heading indicates mean value.
* Diameter is calculated from volume, assuming tumor is spherical.

significant correlation with hepatic toxicity ($p = 0.013$), and tumor size was significantly correlated with 1-, 2-, and 3- year OS rages ($p < 0.0001$, $p = 0.0022$, and $p = 0.0002$). A correlation trend was observed between Child-Pugh class and 1-year OS rate, but not 2- and 3-year OS rates. The results with scatterplots are shown in Fig. 3.

Discussion

In the present study, we performed a meta-analysis of 32 studies encompassing 1950 patients who were treated with SBRT for HCC. Pooled results of 1-year, 2-year, and 3-year LC rates were 85.7% (95% CI: 80.1–90.0), 83.6% (95% CI: 77.4–88.3), and 83.9% (95% CI: 77.6–88.6), respectively, and grade ≥3 complication rates were 4.7% (95% CI: 3.4–6.5) for hepatic and 3.9% (95% CI: 2.6–5.6) for GI complications. Despite inherent heterogeneity among observational studies, these results showed that SBRT is a feasible local ablative modality with potent tumor control ability.

Subgroup analyses were performed for tumor size and radiation dose (EQD2), which are known clinical and treatment factors affecting oncologic outcomes [17,28–30]. Subgroup comparison regarding tumor size showed significant difference for both OS and LC rates, although the comparison could not fully resolve statistical heterogeneity. These results correspond to the findings of previous studies showing that patients with larger HCCs were more likely to die owing to recurrences in the liver or distant metastases [31,32]. Additionally, four studies with tumor vascular invasion (TVI) rate >30% were all categorized into the subgroup of tumor size ≥5 cm, and the higher TVI rate might affect the difference in clinical outcomes. Larger tumors were shown to exhibit portal vein thromboses with higher frequency in other previous studies [33,34].

As an ablative method for localized HCCs, SBRT has often been compared with RFA. Advantages of RFA include the potential to perform ablation with a single procedure and the greater accumulated level of evidence for the method than exists for SBRT. In particular, RFA for tumors <3 cm in size showed survival outcomes comparable to surgical resection [35,36]. SBRT has the advantage of being a non-invasive modality, along with the ability to treat tumors regardless of their location, including those adjacent to major vessels, bile ducts, or the diaphragm [37–39]. Wahl et al. [40] compared treatment outcomes of RFA and SBRT for inoperable non-metastatic HCC using propensity matching methods. No difference was shown in the LC rate for tumors smaller than 2 cm, but a statistically significant difference in favor of SBRT was observed for tumors >2 cm (hazard ratio: 3.35; $p = 0.025$). In the present meta-analysis, the median tumor sizes were >2 cm in the majority of studies in the subgroups of those with tumor size <5 cm. The pooled LC rates of these subgroups were 85.7%, 83.6%, and 83.9%, respectively; the pooled LC rate was excellent at 1 year and remained favorable until 3 years. Additionally, tumors >5 cm are generally considered to be beyond the indication for RFA [41]. In our meta-analysis, the 1- and 2-year pooled LC rates were 73.9% and 66.3% for the subgroup with tumor size ≥5 cm. Despite the inclusion of several patients with TVI in this subgroup, SBRT

Table 2
Clinical information from the included studies.

Author	SBRT dose (Gy) (median [range], or prescribed)	No. of fractions	Median EQD2 estimate	Median f/u (month)	OS at 1/2/3 years (%)			LC at 1/2/3 years (%)		
Shiozawa K	60	3–5	>100	12.6	95.2			97.1	89.6	74.7
Huertas A	45	3	93.75	12	81.8	56.6	44.2	99.0	99.0	
Yoon SM	45 (30–60)	3–4	93.75	25.6	86.0	63.3	53.8	94.8	92.8	92.1
Jeong Y	45 (30–60)	3–4	93.75	25.8	99.2	87.0	83.8	98.5	97.0	97.0
Bibault JE	45 (24–45)	3	93.75	10	78.5	50.4	37.8	89.8	89.8	89.8
Kubo K	48	4	88	41.0	90.0	72.0	56.3	100	100	100
Sanuki N	35	5	49.6		91.5	82.1	66.0	97.5	90.7	90.7
Sanuki N-2	40	5	60	24	95.7	82.5	72.1	100	94.2	91.6
Andolino DL	44 (24–48)	3	84	27.3	74.3	47.0	40.0		87.0	
Jang WI	51 (33–60)	3	114.75	30	83.7	63.0	54.7	93.4	87.0	82.0
Yamashita H	48 (40–60)	4	88	15.9		52.9		78.5	74.8	74.8
Kwon JH	33 (30–39)	3	57.75	28.7	92.9	77.2	58.6	72.0	72.0	67.5
Ibarra RA	30 (21–45)	3	50	12.9	87.0	55.0	27.0	64.0	61.2	61.2
Feng M	49 (23–60)	3–5	80.85	37.0	63.0	36.0	22.0	99.0	95.0	95.0
Bujold A	36 (24–54)	6	48	31.4	55.0	34.0	23.8	87.0	74.0	71.8
Lo C.-H.	45 (38–48)	3–12	71.2	19.0	45.9	30.6	24.3	77.0		
Scorsetti M	(36–75)	3–6		8	77.9	45.3	22.6	85.8	64.4	64.4
Kim JW	52 (36–60)	4	100	23 (11–38)	94.4	69.3	69.3	77.8	71.3	71.3
Hasan S	45 (40–50)	4–5	71.25	24.0	92.0	60.0	45.0	98.0	98.0	
Madhavan R	40 (35–60)	5	60		87.5	56.3	56.3	25.0		
Zhang T	(35–60)	3–6		36.0	92.9	85.7	78.6	96.4	92.9	89.3
Que J	(26–40)	3–5		15.5	63.5	41.3		85.3	81.6	
Hijazi H	45 (16–50)	5 (2–6)	71.25	12.0	47.0	35.0	35.0	85.0	85.0	30.0
Gkika E	45 (21–66)	3–12		14.3	40.0			79.0		
Kim M	50 (33–60)	3–10		12.8	70.1	45.2		57.0	39.0	
Uemoto K.	45 (30–64)	5 (4–20)	71.25		78.0	66.8	50.0	95.0	91.5	91.5
Lam MHC	54 (30–54)	6–7	85.5	17.8	73.6	56.1	35.0	82.8	80.0	80.0
Sapir E	BED 100	3–5		12.4	74.1	34.9		96.5	91.3	91.3
Moon DH	45 (27.5–45)	3 (3–5)	93.75	12.7	36.0			82.0	53.0	53.0
Guarneri A	48 (36–48)	3–5		18.0	71.7	56.2		100	100	
Weiner AA	55 (40–55)	5	96	8.8	38.0			91.0		
Baumann BC	50 (21–50)	5 (3–5)	83.33	14.0	87.0	50.0	43.0	95.0	95.0	95.0
Hanazawa H	50 (45–50)	5 (5–10)	83.33	16.0	82.0	68.0	68.0	100	100	100

Abbreviations: SBRT, stereotactic body radiotherapy; EQD2, equivalent dose in 2 Gy per fraction; OS, overall survival; LC, local control; BED, biologically equivalent dose.

yielded moderate tumor control rates for relatively large HCCs. In summary, our study provides support for the use of SBRT not only in HCCs with anatomical contraindications to RFA, but also for tumors >2–3 cm.

MWA is another method of ablation, which has physical advantage of rapid heating to avoid heat-sink effect than RFA. It also enables larger size of ablation than RFA, which might overcome the limitations of RFA regarding tumor size [4,5]. However, possible difficulties treating tumors close to or invading major vessels, biliary trees, or diaphragm are still hindrances [19,20]. Until recently, MWA has been mainly compared with RFA but not with SBRT; future studies are warranted to determine optimal indications for each ablative treatment, including MWA, RFA, and SBRT.

Regarding the radiation dose (EQD2), better LC rates were achieved with higher radiation doses, with marginal significance, but the OS rate was not significantly different among the subgroups. OS might be affected by various clinical characteristics and treatment modalities other than SBRT; thus, the difference in radiation dose might not directly affect OS. Jang et al. [42] showed differences in the LC and OS rates, among subgroups treated with >54, 45–54, and <45 Gy of 3-fractions SBRT, along with a positive linear correlationship between dose and LC. On the other hand, Ohri et al. [22] did not find a significant difference between tumor control and dose, after comparing biologically effective doses (BED) of <100 Gy_{10} and >100 Gy_{10}, for primary liver cancer. Currently, no evidence firmly supports the minimal or identical dose of SBRT for HCCs. Also, dose-escalation is largely affected by tumor size, liver function, and anatomical consideration with other organs (e.g. duodenum). Further studies are warranted to clearly identify this issue.

Since SBRT generally uses a relatively high dose of radiation, there have been concerns regarding hepatic or GI complications. In our meta-analysis, the reported rates of grade ≥3 hepatic and GI complications were 4.7% (95% CI: 3.4–6.5) and 3.9% (95% CI: 2.6–5.6), respectively, supporting the feasibility of SBRT. These rates are consistent with the results of previous meta-analyses including the use of SBRT for HCC cases [21,43]. In subgroup comparison according to radiation dose, the subgroup with higher EQD2 had higher numerical values of hepatic and GI complications, but these differences were not statistically significant. Generally, radiation oncologists perform more meticulous planning considering clinical conditions, using advanced techniques such as image-guided radiotherapy, gating, and tracking modalities, when prescribing higher doses. Therefore, significant differences in subgroup comparisons might not be observed.

Meta-regression analyses found a significant correlation between Child-Pugh class and hepatic toxicity of grade ≥3 ($p = 0.013$), and a correlation trend between GI toxicity and radiation dose. These results corroborate previous reports of association between liver function (presented as Child-Pugh class) and hepatic toxicities [15,44]. Minimization of the target size using image-guidance, gating, and abdominal compression may be needed, especially for patients with poor liver function. Dose escalation should be performed carefully considering the anatomical consideration with intestinal tracts. Charged particle therapy might be an option to reduce toxicity, as it has physical advantage to reduce dose directed to normal tissues, and might have lower late toxicity than SBRT as reported by a previous meta-analysis [21].

Although rates of grade ≥3 complications were mostly mild, some studies reported relatively high complication rates. Scorsetti et al. [17] reported grade ≥3 hepatic toxicity rates of 16.3%, and all reported cases were transient elevation of liver enzymes. Large tumor size and poor liver function were assumed to be possible

Table 3
Pooled rates of overall survival among studies and subgroups.

Groups	Cohorts (n)	Patients (n)	*p*, He	I^2	Egger's test, *p*	Events (95% CI)	p^* (between subgroups)
1-Year OS							
All	32	1871	<0.001	84.5%	0.003	72.6% (65.7–78.6)	
Size < 5 cm	22	1369	<0.001	74.0%	0.009	79.5% (73.4–84.5)	<0.001
Size ≥ 5 cm	9	387	<0.001	74.7%	0.190	60.1% (47.6–71.3)	
mEQD2 < 80	10	633	<0.001	90.9%	0.043	78.1% (63.5–88.0)	0.956
mEQD2 ≥ 80	15	786	<0.001	75.8%	0.294	81.1% (71.7–87.9)	
2-Year OS							
All	29	1852	<0.001	86.6%	0.149	57.8% (50.9–64.4)	
Size < 5 cm	21	1402	<0.001	85.9%	0.249	62.4% (55.2–69.0)	0.020
Size ≥ 5 cm	7	335	0.025	58.4%	0.079	38.6% (29.6–48.5)	
mEQD2 < 80	10	633	<0.001	91.1%	0.803	59.3% (46.9–70.6)	0.930
mEQD2 ≥ 80	13	807	<0.001	80.0%	0.678	60.0% (49.4–69.7)	
3-Year OS							
All	24	1432	<0.001	87.4%	0.691	48.3%(40.3–56.5)	
Size < 5 cm	18	1169	<0.001	86.3%	0.518	51.9% (43.6–60.2)	0.070
Size ≥ 5 cm	6	263	0.004	70.8%	0.058	35.4% (23.7–49.1)	
mEQD2 < 80	10	633	<0.001	89.1%	0.582	45.5% (33.4–58.1)	0.557
mEQD2 ≥ 80	12	728	<0.001	86.3%	0.941	50.6% (39.3–61.8)	
1-Year LC							
All	32	1913	<0.001	80.5%	0.0002	85.7% (80.1–90.0)	
Size < 5 cm	22	1411	<0.001	72.2%	0.00005	91.0% (86.2–94.2)	<0.001
Size ≥ 5 cm	9	387	<0.001	75.3%	0.873	73.9% (60.3–84.1)	
mEQD2 < 80	10	633	<0.001	83.1%	0.32	85.5% (74.8–92.2)	0.071
mEQD2 ≥ 80	15	828	<0.001	66.8%	0.003	89.3% (82.5–93.7)	
2-Year LC							
All	29	1799	<0.001	85.0%	0.003	83.6% (77.4–88.3)	
Size < 5 cm	23	1448	<0.001	75.7%	0.008	87.1% (81.9–91.0)	0.001
Size ≥ 5 cm	5	236	<0.001	84.8%	0.567	66.3% (47.2–81.2)	
mEQD2 < 80	8	534	<0.001	81.8%	0.305	85.6% (75.6–91.9)	0.392
mEQD2 ≥ 80	15	853	<0.001	73.3%	0.031	87.4% (80.6–92.0)	
3-year LC							
All	23	1429	<0.001	83.0%	0.164	83.9% (77.6–88.6)	
Size < 5 cm	19	1265	<0.001	78.2%	0.075	86.3% (80.8–90.4)	0.001
Size ≥ 5 cm	4	164	0.005	76.7%	0.424	59.7% (39.9–76.7)	
mEQD2 < 80	7	494	<0.001	89.8%	0.811	76.9% (59.9–88.1)	0.119
mEQD2 ≥ 80	13	739	<0.001	75.5%	0.082	85.6% (80.0–90.9)	

Abbreviations: CI, confidence interval; OS, overall survival; LC, local control; mEQD2, median EQD2 estimate; EQD2, equivalent dose in 2 Gy per fractions.
* Q test based analysis of variance.

risk factors by the authors. In the studies by Kim et al. [45] and Weiner et al. [46], grade ≥3 hematologic toxicity rates were 28 and 27%, respectively. The former study reported mostly thrombocytopenia and the latter study reported only lymphopenia. In the former study, six of the seven patients who experienced grade ≥3 hematologic toxicities had prior hematologic problems. As thrombocytopenia is commonly observed with chronic liver disease and cirrhosis [47], SBRT might incite an aggravation, but the background liver condition might be the major cause of the thrombocytopenia. Lymphopenia occurs following radiotherapy as a result of direct destruction of circulating cells, not only in treatment of the liver, but also in treatment including the lungs [48] and brain [49]. Poor replenishment and defective thymopoiesis in cirrhosis might be another cause [50]. Considering both the pooled rates of complications and the fact that complications at high rates were mostly transient and might be caused by chronic liver disease, we support the use of SBRT as a feasible treatment for HCC.

While increasing numbers of studies have been published, the majority of studies regarding external beam radiation therapy (EBRT) for HCC are observational. Since these studies differ in research design and patient characteristics, the integration of results to provide information that can be applied to clinical practice is necessary. Therefore, several researchers have performed pooled analyses of EBRT for HCC.

Previously, Qi et al. [21] conducted pooled analyses including studies of SBRT for HCC, published until August 2014. The authors' findings showed results of SBRT comparable to proton therapy, and provided oncologic outcomes such as OS and LC, derived from 500 to 1000 patients. Ohri et al. [22] recently published pooled analyses to assess LC after SBRT for liver tumors. Although the study was well designed to find a relationship between radiotherapy dose and LC, the authors searched only one database and included five studies of SBRT for HCC. Considering previous pooled analyses, the significance of our study is that it included the largest number of studies to date on SBRT for HCC, and provided an integrated long-term oncologic outcome from almost 2,000 patients correlated with radiation dose and tumor size.

Randomized controlled trials have not yet been published in support of the clinical benefits of SBRT, and the utility of SBRT has not been addressed in the updated version of the European Association for the Study of the Liver guidelines [51]. However, in the updated version of the National Cancer Comprehensive Network guidelines for hepatobiliary cancers, safety and efficacy were further confirmed as clinical experiences have accumulated, and the recommendation level as a locoregional modality was raised to 2A from 2B [52]. The Asia-Pacific Primary Liver Cancer Expert meeting (APPLE), an association of liver cancer experts in the Asia-Pacific region, also recommended application of SBRT for early HCC. Early HCC as indication of SBRT was defined as a solitary tumor with ≤5 cm of maximum diameter or as multiple nodules (≤3 in total) measuring ≤3 cm in maximum diameter, without vascular invasion/extrahepatic metastasis and with Child-Pugh A or B, for which RFA or liver transplantation is not feasible [53,54]. Our meta-analysis and systematic review integrate information from

Table 4
Treatment-related toxicities among the included studies.

	Acute toxicity (grade ≥ 3)				Late toxicity (grade ≥ 3)		
	Gastro intestinal (%)	Hemato logic (%)	Hepatic (%)	Undefined or Etc.	Gastro intestinal (%)	Hemato logic (%)	Hepatic (%)
Shiozawa K	0	0	0				11.4
Huertas A	1.3		1.3		2.6		3.9
Yoon SM			6.5				
Jeong Y	1.7	0	8.4				
Bibault JE	1.3		4	4 (Fatigue)			
Kubo K	0	6.2	3.1		0	6.2	6.2
Sanuki N			4.2				
Sanuki N-2							
Andolino DL							
Jang WI	6.1		3.6	1.2 (Soft tissue)			
Yamashita H							
Kwon JH	0	0	0		0	0	2.4
Ibarra RA							
Feng M			8		1.1		
Bujold A							
Lo C.-H.	2.2		2.2				
Scorsetti M			16				
Kim JW	0	28	0				
Hasan S	0	0	0		0	0	0
Madhavan R							
Zhang T	0	0	0				
Que J.	0	5.2	7				
Hijazi H	4.3	0	8.7				
Gkika E							
Kim M							
Uemoto K.			0.7				
Lam MHC			2.5				
Sapir E	3.2		0.8				
Moon DH		3.3	3.3		0	0	0
Guarneri A	3.3	13					
Weiner AA	15	27	8		8	19	4
Baumann BC	3		6				
Hanazawa H			5.9				

Table 5
Pooled analysis of acute grade ≥ 3 complications.

Groups	Cohorts (n)	Patients (n)	p, He	I^2	Egger's test, p	Events (95% CI)	p^* (between subgroups)
Hepatic ≥ G3							
All	23	1304	0.157	23.1%	0.00018	4.7% (3.4–6.5)	
Size < 5 cm	18	1047	0.087	32.9%	0.00016	6.2%(4.0–9.4)	0.871
Size ≥ 5 cm	4	142	0.488	<0.1%	0.995	4.6% (0.2–11.7)	
mEQD2 < 80	6	363	0.362	8.4%	0.141	3.0% (1.5–5.9)	0.217
mEQD2 ≥ 80	13	630	0.887	<0.1%	0.026	5.8% (4.2–8.1)	
Gastrointestinal ≥ G3							
All	17	1011	0.605	<0.1%	0.014	3.9% (2.6–5.6)	
Size < 5 cm	12	754	0.805	<0.1%	0.002	3.6% (2.4–5.4)	0.280
Size ≥ 5 cm	4	142	0.278	22.1%	0.916	4.8% (2.0–10.8)	
mEQD2 < 80	4	194	0.84	<0.1%	0.536	2.2% (0.8–5.8)	0.415
mEQD2 ≥ 80	9	520	0.249	21.8%	0.099	4.3% (2.3–7.8)	

Abbreviations: CI, confidence interval; mEQD2, median EQD2 estimate; EQD2, equivalent dose in 2 Gy per fractions.
[*] Q test based analysis of variance.

a large number of published studies, providing information to support the efficacy and feasibility of SBRT and to assist clinical decision-making, along with increasing trends in the application of this treatment modality.

Examining the temporal view of the main outcomes of the present study, LC rates tend to persist for up to three years, but OS steadily declines. These results mean that many patients die from intrahepatic or systemic metastases even if the target tumor is controlled with SBRT. Until recently, sorafenib was the only proven systemic treatment, but regorafenib [55] has proven to be beneficial as a second treatment after sorafenib failure, and carbozantinib, ramucirumab, and nivolumab have also shown significant results [56–58]. The results of the present meta-analysis not only suggest that SBRT may have potent LC ability, but also that the combination of systemic agents with SBRT might be beneficial. Several ongoing trials regarding combination of SBRT with sorafenib or other systemic treatments (NCT02906397, NCT02989870, NCT02794337, NCT01730937) and immunotherapies (NCT02989870, NCT03203304) were found at Clinicaltrials.gov.

Several limitations should be considered in the interpretation of the present study. The use of meta-analysis for observational studies is controversial [59]. The heterogeneity of patient characteristics and study designs might affect pooled analyses. Moreover, although randomized controlled trials provide the highest level of evidence, the field of oncology does not always have the best evidence, and treatment decisions often rely on multiple small observational studies or clinical experience [60]. Additionally, radiotherapy for HCC, including SBRT, has been commonly

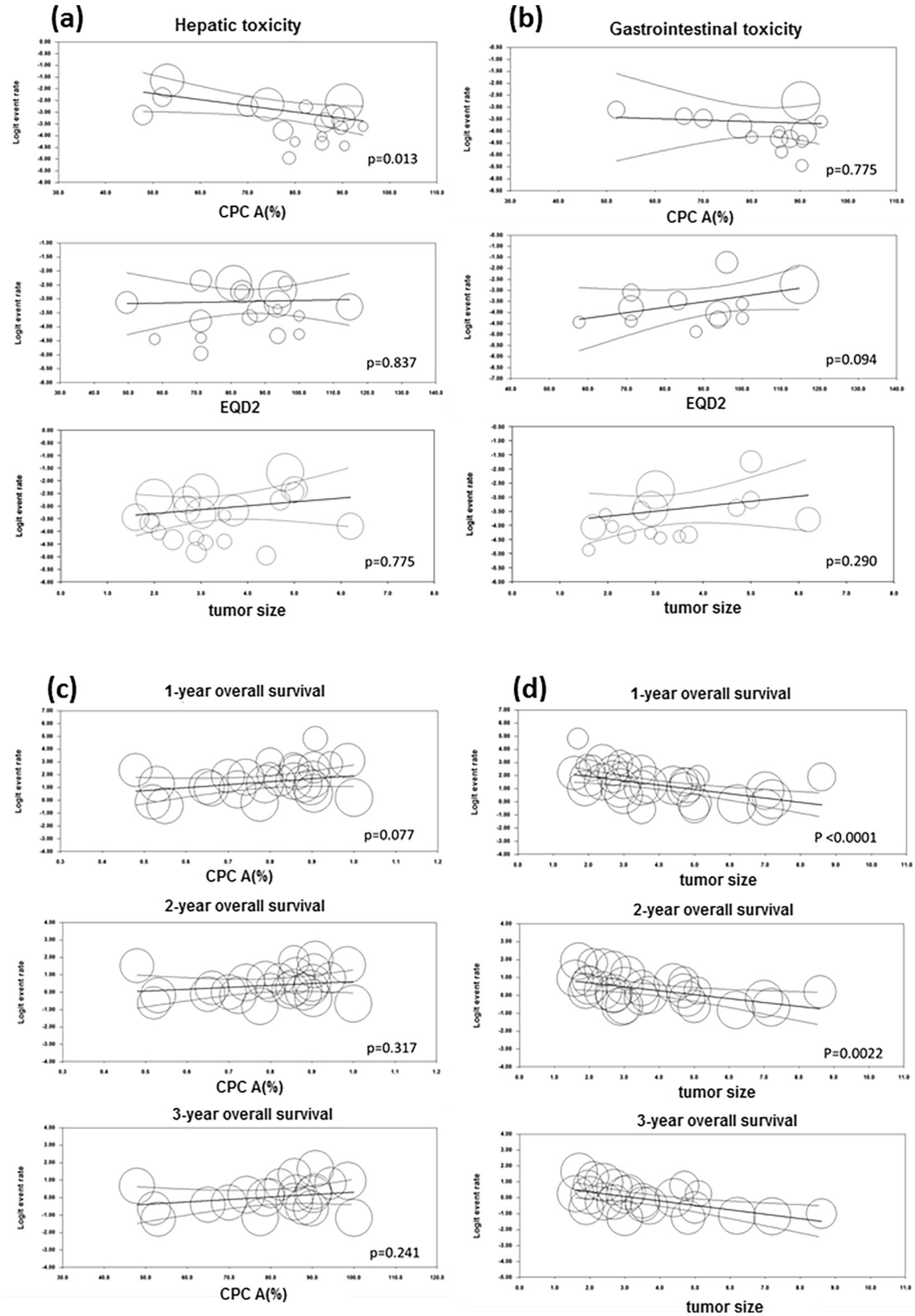

Fig. 3. Scatterplots of meta-regression. (a) analyses between hepatic toxicity and Child-Pugh class A(%), median EQD2 estimate, and tumor size. (b) analyses between gastrointestinal toxicity and Child-Pugh class A(%), median EQD2 estimate, and tumor size. (c) analyses between 1-,2-, and 3- year OS rates and Child-Pugh class A(%). (d) analyses between 1-,2-, and 3- year OS rates and tumor size.

reserved for cases not considered appropriate for other treatment modalities. Considering the above factors, a meta-analysis of observational studies might be one of the best available options to evaluate the feasibility and efficacy of treatment and to provide useful information for clinical decision-making [61].

Conclusion

The present study reported pooled results of oncologic outcomes based on the integration of information from a large number of trials, providing support for the clinical efficacy and feasibility of SBRT for HCC. Both OS and LC were affected by tumor size, and radiation dose marginally affected LC. LC rates for small HCCs were excellent, and moderate efficacy was shown in treatment of tumors $\geq$5 cm. Rates of serious complications were low, either hepatic or GI, suggesting the feasibility of SBRT for HCC. However, liver function should be considered to find patients eligible for SBRT in order to avoid severe hepatic toxicity. Randomized trials are warranted to prove the clinical benefit of SBRT for HCC, and combination use with systemic treatment is another projected subject of future research.

Conflicts of interests

All the authors have no conflicts of interests in terms of employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or any funding.

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Appendix A. Supplementary data

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