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Stereotactic body radiotherapy for hepatocellular carcinoma: meta-analysis and International Stereotactic Radiosurgery Society practice guidelines

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Disclaimer:

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Society of Stereotactic Radiosurgery assume no liability for the information, conclusions, and recommendations contained in this report.

Abstract

Purpose: This systematic review and meta-analysis reports on outcomes and hepatic toxicity rates following stereotactic body radiotherapy (SBRT) for liver confined hepatocellular carcinoma (HCC), and presents consensus guidelines regarding appropriate patient management.

Methods and Materials: Using the Preferred Reporting Items for Systemic Review and Meta-analyses guidelines, a systematic review was performed from articles reporting outcomes at ≥5 years published prior to October 2022 from the Embase, MEDLINE, Cochrane, and Scopus databases using the key words terms ("Stereotactic body radiotherapy" OR "SBRT" OR "SABR" OR "Stereotactic ablative radiotherapy") AND ("Hepatocellular carcinoma" OR "HCC"). An aggregated data (AD) meta-analysis was conducted to assess overall survival (OS) and local control (LC) using weighted random effects models. In addition, an individual patient data (IPD) analysis incorporating data from 6 institutions was conducted as its own subgroup analyses.

Results: Seventeen observational studies, comprising 1889 HCC patients treated with ≤9 SBRT fractions, between 2003 and 2019, were included in the AD meta-analysis. The 3- and 5- year OS rates after SBRT were 57% (95% confidence interval [CI], 47-66%) and 40% (95% CI, 29-51%). The 3- and 5- year LC rates after SBRT were 84% (95% CI, 77-90%) and 82% (95% CI, 74-88%), respectively. Tumor size was the only prognostic factor for LC. Tumor size and region were significantly associated with OS. Five-year LC and OS rates of 79% (95% CI, 0.74-0.84) and 25% (95% CI, 0.20-0.30), respectively, were observed in the IPD analyses. Factors prognostic for improved OS were tumor size <3 cm, eastern region, Child-Pugh score ≤B7, and the Barcelona Clinic Liver Cancer stage of 0 and A. The incidence of severe hepatic

toxicity varied according to the criteria applied.

Conclusions: SBRT is an effective treatment modality for HCC patients with mature follow up. Clinical practice guidelines were developed on behalf of the XXXX.

Keywords: Hepatocellular carcinoma, meta-analysis, stereotactic radiotherapy

Introduction

Hepatocellular carcinoma (HCC), the most common primary liver cancer, is the sixth most common cancer and the third leading cause of cancer death worldwide.[1] Cirrhosis is the primary underlying etiology for HCC and is attributed to chronic viral hepatitis, alcohol and other causes.[2] The optimal management of HCC is determined by both the status of tumor burden and patient factors (e.g., age, underlying liver disease, and liver function), and a multidisciplinary assessment is critical to determine the best treatment strategy.[3,4]

Historically, the role of external beam radiation therapy (EBRT) for the treatment of HCC has been restricted to a low dose of palliative-intent conventional EBRT to respect both the tolerance of the otherwise considered radio-sensitive normal liver tissue, and the technical uncertainties in tumor delineation and RT delivery.[5] Advances in imaging-guidance, RT delivery and treatment planning software and a mature understanding of the liver tolerance with dose-volume-histogram based constraints, now allow for curative intent doses delivered with stereotactic body radiotherapy (SBRT).

Blomgren et al.[6] reported the first clinical use of SBRT to liver lesions in patients with HCC at the Karolinska Institute in Stockholm in 1995. Since then, numerous prospective and retrospective studies have reported a promising local control (LC) rates at 2 years ranging from 68–95% and low risks of hepatic toxicity.[7] Based on these observational studies, several meta-analyses showed SBRT efficacy for HCC with treatment outcomes ≤3 years.[8-12] However, there is lack of evidence demonstrating durable long-term LC and overall survival (OS) 3- to 5-years after SBRT.

The purpose of this systematic review of the literature is to describe the demographics, patient characteristics, treatment details, long-term survival outcomes, and hepatic toxicity

rates for HCC patients treated with SBRT. Consensus recommendations for treatment were made in an effort to provide clinical guidance and more uniform management on behalf of the XXXX.

Methods and Materials

Study protocol

This systematic review was conducted according to criteria of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) 2020 statement.[13] A literature search was performed using the Embase, MEDLINE, Cochrane, and Scopus databases. The following keywords were used: ("Stereotactic body radiotherapy" OR "SBRT" OR "SABR" OR "Stereotactic ablative radiotherapy") AND ("Hepatocellular carcinoma" OR "HCC"). Full text articles published in the English language up until October 2022 were identified. The initial query identified 3085 articles which were subsequently screened for relevance to the objectives of the present study by thorough review of the article titles, abstracts, and full texts as necessary. Two reviewers (XXX and XXX) independently performed the search and screened studies to identify eligible studies, with significant discrepancies settled by an independent third reviewer (XXX).

Selection criteria

The following inclusion criteria were used: (1) clinical studies including retrospective or prospective studies specific to liver-confined HCC; (2) inclusion of >10 patients with HCC treated with SBRT; (3) SBRT performed in <10 fractions; and (4) reporting of at least ≥5 years LC and/or OS rates. When numerical data were absent, LC and/or survival rates were indirectly estimated from the descriptive plots. In cases of multiple studies from one institution with overlapping patients, the following criteria were applied, to determine inclusion and are prioritized by numerical order: (1) study that reports exclusively on treatment outcomes of HCC patients following SBRT; (2) study with the largest number of patients; and (3) most recently published study. Studies from the same institution were

independently categorized if they were conducted in different periods. The following exclusion criteria were used: (1) SBRT intentionally planned as a bridge to liver transplantation; (2) SBRT combined with other treatment modalities simultaneously, however, if the treatment interval between each modality was >1 month then it was allowed.

Six of 17 eligible studies agreed to provide deidentified individual patient data (IPD) for more detailed analyses. Data transfer agreements or ethical approvals were obtained according to each institutional policy.

Data extraction and quality assessment

Data extraction was performed using a standardized form with the following data obtained: (1) study, patient and tumor characteristics; (2) treatment; and (3) survivals, and (4) hepatic toxicity rates. Survival included 1- to 5-year survival rates, which were either reported in the studies or derived from the survival curves. Hepatic toxicity was defined according to Common Terminology Criteria for Adverse Events (CTCAE) version 4 or 5 and/or radiation-induced liver disease (RILD), of which there are 2 types: classic RILD and non-classic RILD.

Because most (16/17) of the included studies were retrospective, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies [14]. Studies with a score of 7-9 are considered high quality and studies with a score of 4-6 are considered medium quality.

Statistical analysis

For the aggregated data (AD) meta-analyses, the heterogeneity among the studies was assessed by Higgins I^2 statistic.[15] An I^2 value of ≥50% was considered to represent substantial heterogeneity. Given the variation in treatment decision making, time periods for which the

study was applicable to, and geographical location which influences etiology, the random effects model was considered superior to the fixed effects model when calculating pooled estimates. The DerSimonian and Laird method was used for random-effect analysis and we report both estimates in the tables.[16] Publication bias was assessed by funnel plots and the Egger's regression tests. If the funnel plot was symmetrical or the *P* value was > .05 in Egger's test, then the null hypothesis of no publication bias was accepted. For comparison between subgroups, a Q test based on analysis of the variance and random effects model was used. Values of $P < .05$ were considered statistically significant. All statistical analyses were performed using Rex Excel-based statistical analysis software, ver. 3.6.0 (RexSoft, Korea, http://rexsoft.org/).

For the IPD analysis, survival was estimated using the Kaplan-Meier method and compared between groups using the log-rank test. All statistical analyses were performed using Statistical Package for the Social Sciences software (version 27.0; SPSS Inc., Chicago, IL, USA), and a value of $P < .05$ was considered statistically significant.

Results

An initial search of the 4 databases provided a total of 3085 studies. After removing 746 duplicate articles and 1239 irrelevant articles, 1100 studies were selected for title and abstract screening, of which 238 studies were selected for a full-text review. Finally, 17 studies comprising 1889 patients were found to fit the inclusion criteria for the AD meta-analysis. Among these, 6 studies comprising 665 patients were included for the IPD analysis. The selection process is summarized in Figure 1.

All 17 studies were either retrospective or prospective observational studies. Therefore, the quality of the studies according to the NOS criteria was rated medium. Most were conducted in eastern regions (China, Japan, Korea, Saudi Arabia, Taiwan, and Thailand), and 2 in western regions (Canada, United States, and France). The median proportion of viral etiology was 81% (range: 12-100%). The median proportion of Child-Pugh (CP) class A was 86% (range: 52-100). The median tumor size was 2.8 cm (range: 1.3-5.3 cm). Four studies were for specific to patients with early stage HCC with a 0 or A according to the Barcelona Clinic Liver Cancer (BCLC) classification. Thirteen studies included patients with various BCLC stages, and the proportion of patients with portal vein tumor thrombosis ranged from 0-59%.

As the total SBRT dose and number of fractions was variable among studies, the biologically effective dose (BED) was calculated using an α/β ratio of 10. The median value of all available BED_{10} was 85.8 Gy_{10} (range: 71.4-137.7 Gy_{10}). Study details and treatment outcomes are summarized in Table 1 and Table 2.[17-33]

AD meta-analysis: Treatment outcomes

1889 patients from 17 studies were included in the AD meta-analysis, with a median follow-up of 24 months (range: 12-70 months). The median 3- and 5-year LC rates were 81% (range: 31-100%) and 81% (range: 37-97%), respectively. The median 3- and 5-year OS rates were 64% (range: 29-87%) and 39% (range: 11-80%), respectively. Twelve studies reported a median progression-free survival (PFS) at 3 years of 39% (range: 15-61%), and 9 studies reported a median PFS at 5 years of 32% (range: 13-54%). Using random effects analysis, the pooled 5-year LC and OS estimates were 82% (95% confidence interval [CI], 74-88%) and 40% (95% CI, 29-51%), respectively (Fig. 2). The pooled estimate for 5-year PFS was 33% (95% CI, 24-43%), (Fig. E1). Significant heterogeneity among included studies was present for survival estimates (Table 3 and Table E1), but there was no detection of publication bias except for 5-year PFS (Fig. E2). In subgroup comparison, tumor size <3 cm was the only significantly favorable factor for 1- to 5-year LC rates, and tumor size <3 cm and Eastern region were significantly favorable factors for 1- to 5-year OS rates ($P < .05$), as summarized in Table 3.

IPD analysis: Treatment outcomes

Six hundred sixty-five patients from 6 studies were included in the IPD analysis.[18-20,26,30,33] Roquette et al.[18] provided data for 317 of the 318 patients initially included in their report, as 1 patient withdrew consent following the date of publication. The 3-year and 5-year LC rates were 80% (95% CI, 0.75-0.85) and 79% (95% CI, 0.74-0.84), respectively. The 3-year and 5-year PFS rates were 30% (95% CI, 0.26-0.35) and 22% (95% CI, 0.17-0.28), respectively. The median OS was 31 months, and the 3-year and 5-year OS rates were 45% (95% CI, 0.41-0.49) and 25% (95% CI, 0.20-0.30), respectively. The survival curves are presented in Fig. E3. On univariate analysis, eastern region and BCLC stage of 0 and A were

affected significantly better LC. BED ≥100 Gy_{10} and eastern region were affected significantly better PFS (Table E2). Tumor size <3 cm, eastern region, CP score ≤B7, and BCLC stage of 0 and A were statistically significant prognostic factors for improved OS (Fig. 3 and Table E2).

AD meta-analysis: Hepatic toxicities

Pooled rates using random effects analysis of classic RILD and non-classic RILD were 0% (95% CI, 0-2%) and 8% (95% CI, 5-12%), respectively (Fig. E4). Subgroup analysis was not performed due to the limited number of included studies. Late hepatic toxicity ≥grade 3 was reported in 3 studies and ranged from 0-9%. Toxicity data are summarized in Table 4.

Discussion

To our knowledge, this is the first meta-analysis describing long-term treatment outcomes specific to SBRT for liver confined HCC. Our meta-analysis included 17 studies comprising 1889 patients and reports favorable pooled 5-year LC and OS rates of 82% (95% CI, 74-88%) and 40% (95% CI, 29-51%), respectively. Pooled rates of classic RILD and non-classic RILD were 0% (95% CI, 0-2%) and 8% (95% CI, 5-12%), respectively. While acknowledging the inherent heterogeneity among observational studies, the current meta-analysis confirms durable long-term LC, prolonged OS, and low hepatic toxicity rates after SBRT to HCC.

On subgroup analysis, tumor size was the only significant prognostic factor for both LC and OS. Five-year LC and OS rates for tumors <3 cm were 89% (95% CI, 83-94%) and 51% (95% CI, 37-66%), respectively, which compares favorably with other local modalities including radiofrequency ablation (RFA). The literature suggests for tumors ≤2 cm, surgical resection and RFA offer the same survival benefit with a 70-90% probability of LC.[34] However, RFA for tumors larger than 2 cm is less effective with a lower rate of complete response and a higher rate of local recurrence.[4,35]

Tumors >3 cm, location (dome or proximity to gallbladder), and the existence of large abutting vessels leads to a reduction by 50% in the rate of complete necrosis with RFA.[36,37] SBRT is not limited by tumor size or location and more widely applicable. Wahl et al.[38] compared RFA (n = 161) with SBRT (n = 63) for patients with inoperable, nonmetastatic HCC. Two-year LC and OS rates were 80% and 53% with RFA, and 84% and 46% in SBRT, respectively. When stratified according to tumor size, there was no significant difference in LC between RFA and SBRT for tumor <2 cm. However, for tumor ≥2 cm, RFA was associated with significantly worse LC (HR, 3.35; *P* = .025). A recent multinational study

from Asian patients compared RFA (n = 1,568) to SBRT (n = 496) for unresectable HCC ≤6 cm.[39] SBRT resulted in a significantly lower risk of local relapse (LR) as compared to RFA when the entire cohort was analyzed (HR 0.45, *P* < .001), and persisted when the cohort was matched using propensity score methods (HR 0.36, *P* < .001). The 2-year cumulative mortality rates following SBRT and RFA were 26% and 19%, respectively (*P* < .001), and 22% and 29% when matched (*P* = .308). In subgroup analysis, SBRT for tumors ≤3 cm were associated with superior LC regardless of location. For tumors >3 cm located in the subphrenic region, SBRT was associated with significantly lower local relapse rates vs. RFA (19% vs. 32%, *P* = .019, respectively). In terms of gallbladder toxicity, one study showed no relationship between gallbladder dose and toxicity after SBRT to liver tumors, and recommend no specific constraints limiting dose to the gallbladder.[40] In the present meta-analysis, the 5-year LC rate for HCC ≥3 cm was 68% (95% CI, 49-85%) following SBRT. Therefore, we conclude that optimal results following SBRT can be expected for tumors <3 cm, and durable long-term LC is still to be expected for those tumors ≥3 cm.

Over 90% of HCC cases occur in patients with chronic liver disease, and cirrhosis is an important and independent prognostic factor for survival in HCC patients.[41] Therefore, the assessment of liver function is a crucial step in the management of HCC, because some standard therapies could cause collateral damage to the normal liver tissue inducing hepatic decompensation.[42] The CP score has been the most widely adopted system to grade liver function in HCC patients, and categorized patients into 3 grades: A (5-6 points), B (7-9 points), or C (10-15 points). Patients with CP-A have well compensated liver function and are potentially eligible for all treatment modalities. Patients with CP-C have decompensated cirrhosis and are eligible only for liver transplantation or best supportive care. CP-B category

patients have borderline liver function with varying degrees of hepatic impairment, and treatment of HCC should be individualized to balance liver function tolerability with potential benefit.[43] Accordingly, some subdivide CP-B into B7 (well compensated cirrhosis) and B8-9 (decompensated cirrhosis with notable ascites, encephalopathy, or jaundice).

Most SBRT studies for HCC include highly selected patients with CP-A or B7. However, few studies evaluated SBRT results for HCC patients with CP-B7. Culleton et al.[44] reported outcomes in 29 HCC patients with CP-B or C treated with SBRT (median dose 30 Gy in 6 fractions). The median survival was 10 months for CP-B7 and 3 months for CP score ≥8 (*P* = .011). An increase in CP score of ≥2 points occurred in 63% of patients after SBRT, and the authors suggested SBRT dose reduction strategies in those CP-B to minimize hepatic toxicity. Andolino et al.[45] evaluated SBRT for 60 HCC patients with CP-A (median dose 44 Gy in 3 fractions) and B (median dose 40 Gy in 5 fractions). The median survival was 44 months for CP-A and 20 months for CP-B (*P* = .018). There was a significant association between pretreatment CP score, and worsening hepatic dysfunction ≥1 grade (*P* = .008). All 4 patients with CP score ≥8 experienced progressive liver dysfunction: 2 underwent liver transplantation and the other 2 died as a result of progressive liver failure. Therefore, the authors suggest that patients with CP-A or B7 are eligible criteria for SBRT. Additional analysis including phase I and II trials demonstrated the need for strict dose constraints to the residual normal liver.[46] Interestingly, despite the generally lower prescription doses for patients with CP-B, SBRT has shown to offer comparable local control compared with CP-A (ranging from 65 to 100%).[47] Currently, the KLCA-NCC Korea practice guideline and ASTRO Clinical Practice Guideline recommend SBRT for HCC patients with ≤CP-B7.[5,48,49] Although we cannot conduct an AD meta-analysis due to limited number of included studies,

IPD analysis showed long-term survival following SBRT for patients with ≤CP-B7 (P < .001). Therefore, SBRT can be performed when the pretreatment liver function is CP-A or B7. SBRT in patients with ≥CP-B8 should be considered with caution given the paucity of safety evidence.

Despite the increasing application of SBRT for HCC treatment, the optimal SBRT dose has yet to be determined. Scorsetti et al.[50] reported that patients treated with a BED ≥100Gy_{10} had statistically improved 1-year LC and median OS rates than those treated with a BED <100 Gy_{10} (100% vs. 52% and 27 months vs. 8 months, P < .05, respectively). Jang et al.[33] reported a positive linear relationship between SBRT dose and LC (P = .006) and OS (P = .002). Based on the tumor-control probability model, the authors suggested that a dose of 54.8 Gy in 3 fractions provides a 2-year LC rate with a 90% probability. Su et al.[51] showed higher SBRT dose was associated with improved OS and PSF on both univariate and multivariate analyses (P < .05) from multicenter study including 602 patients with median follow-up of 50 months. They recommend BED ≥100 Gy_{10} as a first-line ablative dose. However, no dose-response relationship with respect to LC was reported by the University of Michigan with a median BED 100 Gy_{10}.[38] From the Princess Margaret Hospital (Toronto, Canada), a dose-response relationship was observed for LC, but there was no significant association on multivariate analysis.[52] The 1-year LC in that series was 87%, despite relatively large tumors (median size 7.2 cm) and lower SBRT doses (median dose 36 Gy in 6 fractions).

Two recently published studies also report contradictory results. From the Asian Liver Radiation Therapy Group Study, a dose-response relationship from 510 HCC patients treated with a BED ≥100 Gy_{10} was observed with significantly favorable 2-year LC and OS rates.[53]

However, Ohri et al.[54] suggests that there is no evidence that LC for HCC is influenced by BED within the range of reported schedules (33-60 Gy in 3-5 fractions, BED 60-180 Gy_{10}) from 7 published studies. Among previously published meta-analysis, only 1 study reported a significant association between SBRT dose and OS.[12] The current meta-analysis also does not show a relationship between BED and LC or OS both on either AD meta-analysis and IPD analysis. There was also no correlation between tumor size and BED from our IPD data (Fig. E5).

The variation of prescription dose reflects the multiple factors that are considered including tumor size, location, radiation tolerance of nearby organs, pretreatment liver function, liver constraints, and organ motion management.[55] Current clinical evidence shows durable long-term LC of 82% at 5 year (95% CI, 74-88%) within a wide range of prescription practices. Further studies would be needed to define the optimal dose without increasing the risk of toxicity. Ongoing phase III NRG Oncology RTOG 1112 trial (NCT01730937) using effective liver volume to aid SBRT dose allocation could be an answer.

To our knowledge, this is a first report demonstrating differences in survival rates following SBRT for HCC according to the geographic location. On AD meta-analysis, 5-year OS rates were better for those patients from the eastern region than from the western region (43% [95% CI, 34-53%] vs.17% [95% CI, 6-32%], P = .0035). However, LC rates tended to increase in the western region than in the eastern region (90% [95% CI, 82-97%] vs. 80% [95% CI, 71-88%], P = .0671). We hypothesize that this potential difference may be related to different etiologies of HCC based on region. Hepatitis B virus (HBV) and hepatitis C virus (HCV)-induced HCC occurred in 68-100% of patients from the eastern region, as opposed to 12-52% from the western region as shown in Table 1. China, South East Asia and Sub-

Saharan Africa are the most high-risk HCC areas, and the key determinant is chronic HBV infection.[1] Alcohol is the most common cause of HCC in Europe and HCV is the most common cause in the high-income Pacific regions (Japan, Australia, and New Zealand).[2] The major risk factors appear to be in transition, with the prevalence of HBV and HCV declining, but non-alcoholic fatty liver disease (NAFLD) caused by excess body weight and diabetes is steadily increasing in western regions, and alcohol consumption is increasing throughout the world.[1]

The underlying etiology of HCC is thought to be associated with tumor biology and can influence response to treatment. For example, Lenvatinib has been shown to result in significantly better OS rates in NAFLD-HCC[56] or in non-viral HCC[57]. A recent meta-analysis of 3 large randomized controlled trials of immunotherapies (CheckMate-459, IMbrave 150, and KEYNOTE-240) also showed that the survival benefit of immunotherapy significantly decreased for non-viral HCC (HR, 0.92: 95% CI, 0.77-1.11) compared with viral HCC (HR, 0.64; 95% CI, 0.48-0.84).[58] Subgroup analysis from the HIMALAYA trial has also demonstrated improved OS in HBV-HCC (HR, 0.64, 95% CI, 0.48-0.86) and non-viral HCC (HR: 0.74, 95% CI, 0.57-0.95) but not in HCV-HCC (HR: 1.06, 95% CI, 0.76-1.49).[59] Further research is required to determine if SBRT dose prescriptions should be adjusted based on the etiology of the HCC.

We acknowledge that the current meta-analysis has several limitations. First, the studies included were either observational or retrospective, and this composition is controversial for meta-analysis.[60] The heterogeneity of the study and selection bias might affect pooled analysis. Second, although the studies included were conducted spanning long-term time intervals, the median follow-up was only 24 months (range: 12-70 months). We indirectly

estimated LC or survival from the descriptive graphs when numerical data were absent in 5 studies and this may overestimate treatment outcomes. Third, we conducted an IPD analysis because each study reported different research endpoints. We tried to contact all corresponding authors of this meta-analysis, however, only 6 authors (35%) replied and agreed with data sharing for IPD analysis. Our IPD analysis of 665 patients from diverse regions including Asia and Europe, is the largest amongst those published studies specific to HCC SBRT and showed similar results on subgroup analysis. Lastly, subgroup analysis on hepatic toxicity was challenging because there were limited data and the definition of hepatic toxicity was variable among studies. Classic RILD and non-classic RILD is a useful categorization to compare historical SBRT studies, and the use of hepatic toxicity according to CTCAE is recommended to standardize reporting.[61]

Conclusions

From this systemic review and meta-analysis, we proposed key recommendations for SBRT to HCC in Table 5 on behalf of the XXXX. Pooled analyses showed durable long-term LC and OS rates, with a low risk of serious hepatic toxicity, after SBRT to HCC.

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Figure legends

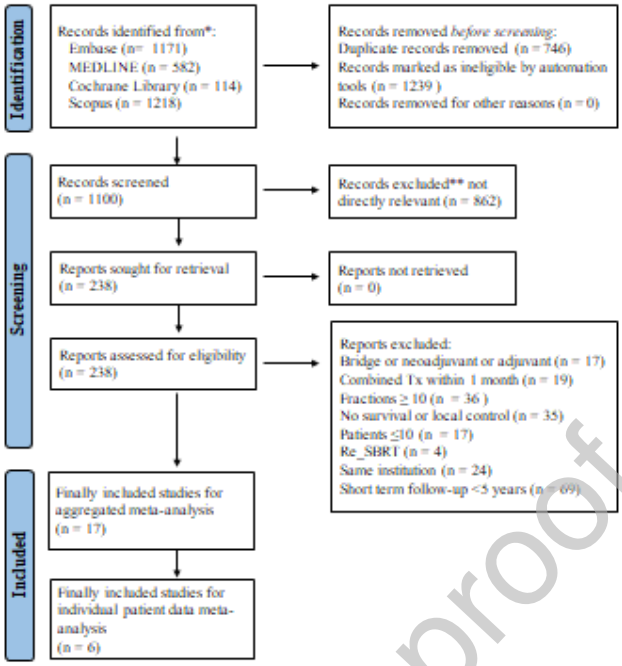
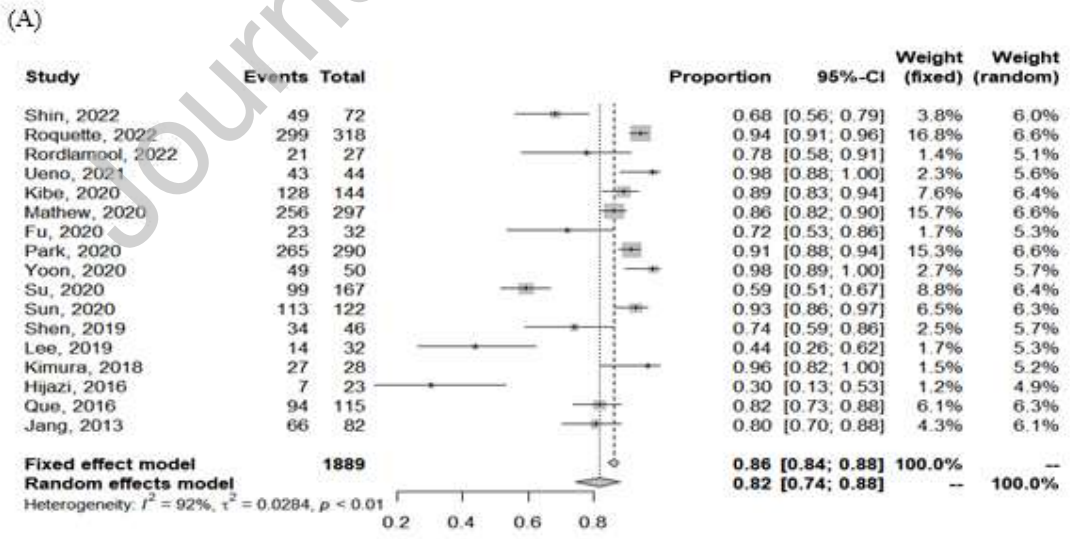


Figure 1. PRISMA flow chart of study selection



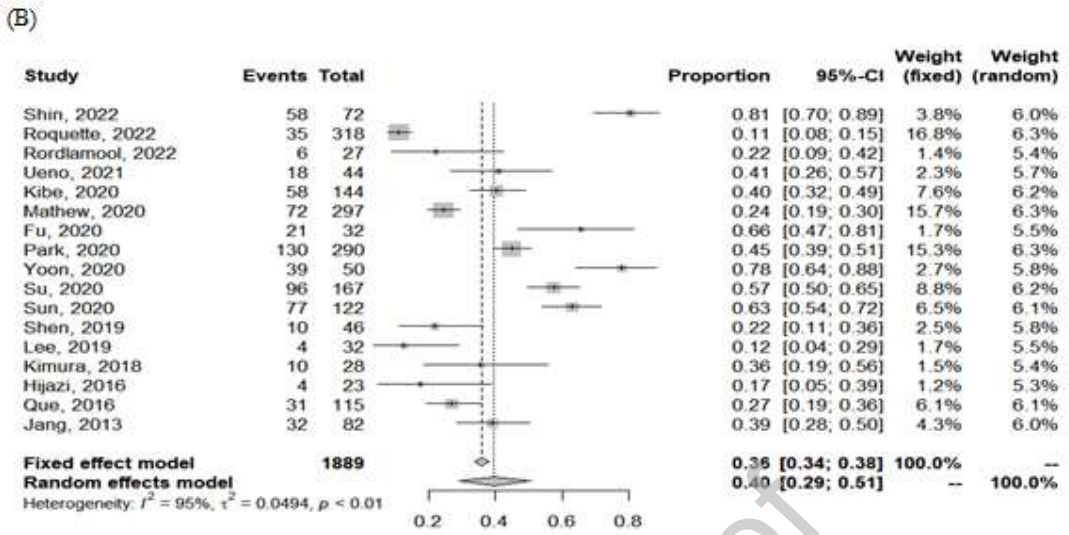
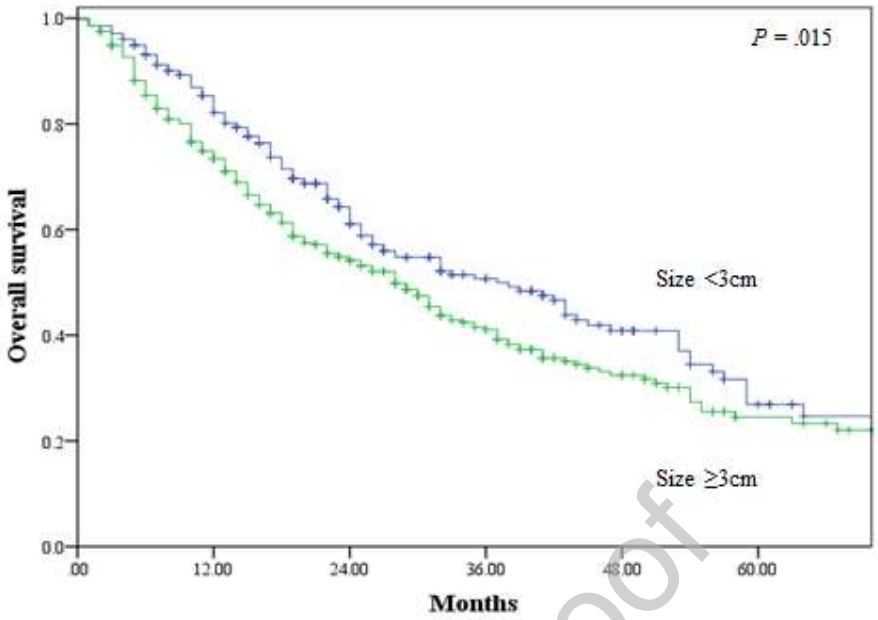
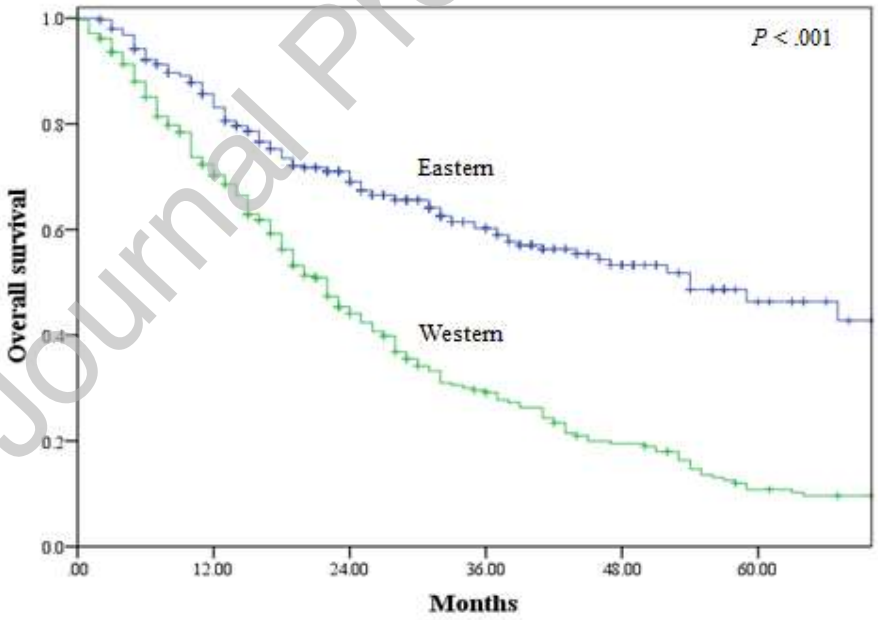


Figure 2. Forest plot of 5-year local control (A) and overall survival (B)

(A)



(B)



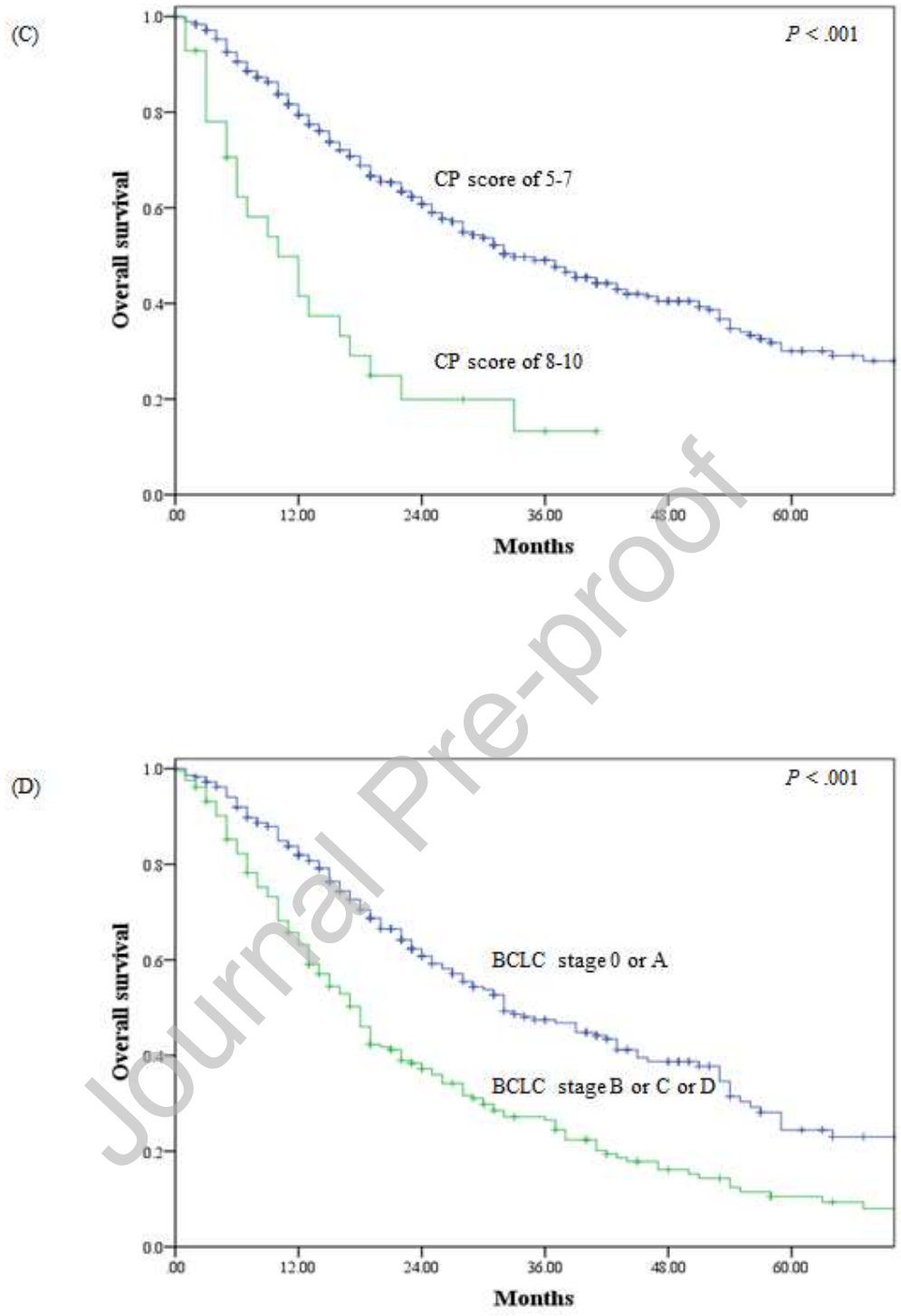


Figure 3. Overall survival rates according to tumor size (A), region (B), Child-Pugh (CP) score (C), and Barcelona Clinic Liver Cancer (BCLC) stage (D)

Table 1. Hepatocellular carcinoma stereotactic body radiotherapy study details and patient characteristics

Author	Year	Location	Time of study	Study type	N	Males (%)	Median-age (range)	Initially Dx (%)	Txnaïve (%)	Viral etiology (%)	CP class A/B/C (%)	ALBI grade 1/2/3 (%)
Shin[17]	2022	Korea	2011-2017	R	72	64	Mean 62.75 ± 10.84	100	47	69	82/18/0	NR
Roquette[18]	2022	France	2007-2018	R	318	85	69 (43-93)	NR	65	12	86/13/1	NR
Rordlamool[19]	2022	Thailand	2013-2019	R	27	89	64 (57-69)	NR	44	70	85/15/0	NR
Ueno[20]	2021	Japan	2014-2019	R	44	73	78 (70-82)	75	0	68	84/16/0	21/77/2
Kibe[21]	2020	Japan	2005-2017	R	144	67	73 (40-89)	NR	0	84	90/10/0	NR
Mathew[22]	2020	Canada and USA	2003-2016	R	297	74	69.3 (22-94)	NR	40	52	76/20/2	31/59/9
Fu[23]	2020	China	2011-2018	R	32	97	59.5 (29-80)	NR	0	75	100/0/0	NR
Park[24]	2020	Korea	2007-2013	R	290	79	61 (36-90)	NR	3	87	86/14/0	NR
Yoon[25]	2020	Korea	2013-2016	P2	50	80	64 (41-74)	NR	4	90	100/0/0	NR
Su[26]	2020	China	2009-	R	167	84	56 (47-	NR	100	87	82/18/0	44/53/3

			2017				65)					
Sun[27]	2020	China	2011-2015	R	122	74	Mean 54.31 ± 9.35	100	100	100	91/9/0	26/67/7
Shen[28]	2019	Taiwan	2008-2017	R	46	76	64 (37-86)	35	35	85	87/13/0	52/44/4
Lee[29]	2019	Taiwan	2008-2016	R	32	75	67 (42-91)	NR	59	100	94/6/0	NR
Kimura[30]	2018	Japan	2008-2017	R	28	61	77 (58-90)	46	NR	79	82/18/0	NR
Hijazi[31]	2016	Saudi Arabia	2009-2015	R	23	NR	71 (27-89)	NR	NR	NR	52/39/9	NR
Que[32]	2016	Taiwan	2008-2012	R	115	77	66 (31-91)	NR	55	90	90/10/0	NR
Jang[33]	2013	Korea	2003-2011	R	82	73	60 (39-79)	34	0	76	90/10/0	NR

Abbreviations: N = number; Dx = diagnosis; Tx = treatment; CP = Child-Pugh; ALBI = Albumin-Bilirubin; R = retrospective study; P2 = prospective phase 2 study; NR = not reported.

Table 2. Hepatocellular carcinoma stereotactic body radiotherapy (SBRT) treatment outcomes

Author	Median size (cm) (range)	BCLC stage 0/A/B/C/D (%)	PVI (%)	Median SBRT dose (Gy) (range)	No. of fx	Median BED$_{10}$ Gy	Median f/u (mo)	LC at 1/3/5 years (%)			PFS at 1/3/5 years (%)			OS at 1/3/5 years (%)		
Shin[17]	Mean 1.71 ± 0.643	100*/0/0/0	0	55 (40-60)	3-5	NR	NR	96	73	68	85	61	40	97	80	80
Roquette[18]	(0.5-10.5)	12/48/12/20/8	17	45 (21-54)	3-6	112.5	70	97	94	94	62	21	13	72	29	11
Rordlamool[19]	3 (2-6)	0/4/4/92/0	NR	40 (30-50)	5-7	72 (48-100)	12	80	80	80	52	36	NR	59	28	21
Ueno[20]	1.4 (1-2.3)	69/39/0/0/0	0	40	5	72	23	98	98	98	NR	NR	NR	86	67	41
Kibe[21]	2.3 (1.0-6.2)	23/48/1/28/0	NR	40 (35-40)	5	72 (59.5-72)	37	97	89	89	NR	NR	NR	96	66	40
Mathew[22]	2.7 (0.5-18.1)	27/18/53†	0	40 (27-60)	3-6	79.2 (45-180)	20	94	86	86	47	15	NR	77	39	24
Fu[23]	2.8 (1.4-6.9)	NR	NR	42 (30-54)	6	71.4 (45-91.8)	24	87	73	73	70	54	54	86	67	67
Park[24]	1.7 (0.7-6)	NR	NR	45 (30-60)	3-4	112.5 (60-180)	38	98	94	91	NR	NR	NR	93	64	45
Yoon[25]	1.3 (0.7-	NR	0	45	3	112.5	48	100	100	97	60	31	27	96	87	78

	3.1)															
Su[26]	3.4 (1-19.5)	0/100/0/0/0	0	42 (28-50)	1-5	100.8	35	85	63	59	66	38	27	86	65	57
Sun[27]	NR	NR	0	(48-54)	5-8	NR	60	95	92	92	82	56	46	92	77	63
Shen[28]	5.3 (3.0-7.9)	0/20/28/48/4	NR	45 (28-60)	4-5	85.5 (43.7-132)	17	91	73	73	NR	NR	NR	73	47	22
Lee[29]	Mean 4.7± 2.3	0/0/0/100/0	59	48 (30-60)	3-6	86 (45-120)	18	82	63	43	42	28	NR	79	42	14
Kimura[30]	1.85 (0.8-5.5)	61/39/0/0/0	0	(40-48)	4-5	(72-105.6)	16	95	95	95	74	42	42	100	69	34
Hijazi[31]	5 (2-9)	NR	NR	45 (16-50)	2-6	85.5	12	85	32	32	56	NR	NR	47	37	18
Que[32]	NR (1.8-18)	0/10/20/70/0	30	(26-40)	3-5	(48.36-89.7)	16	85	81	81	43	40	31	64	37	27
Jang[33]	3 (1-7)	0/53/29/18/0	10	51 (33-60)	3	137.7 (69.3-180)	30	91	80	80	52	40	32	83	55	39

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; PVI = portal vein invasion; BED = biologically effective dose which was calculated using the α/β ratio of 10; LC = local control; PFS = progression-free survival; OS = overall survival; NR = not reported.

*means patients with BCLC stage 0 and A.

†divides into three groups: BCLC stage 0 and A vs. B vs. C and D.

Table 3. Pooled rates of local control (LC) and overall survival (OS)

Group	Cohorts	Patients (n)	*P*, Heterogeneity	I^2	Egger's test, *P*	Fixed Event rate (95% CI)	Random Event rate (95% CI)	*P* (between groups)
1-year LC								
ALL	17	1889	< .0001	77.87 %	.1124	0.95 (0.94 - 0.96)	0.93 (0.90-0.96)	
Size <3 cm	8	957	.0349	53.61 %	.8826	0.97 (0.95 - 0.98)	0.97 (0.94-0.99)	.0088
Size ≥3 cm	7	695	< .0001	81.67 %	.0846	0.93 (0.91 - 0.95)	0.89 (0.82-0.95)	
mBED <100 Gy_{10}	8	645	.0047	65.76 %	.0819	0.94 (0.92 - 0.96)	0.92 (0.87-0.96)	.1748
mBED ≥100 Gy_{10}	6	935	< .0001	86.17 %	.7902	0.96 (0.94 - 0.97)	0.96 (0.91-0.99)	
Eastern	15	1274	< .0001	78.72 %	.1903	0.94 (0.93 - 0.95)	0.93 (0.89-0.96)	.1944
Western	2	615	.0585	72.06 %	-	0.95 (0.94 - 0.97)	0.95 (0.92-0.98)	
3-year LC								
ALL	17	1889	< .0001	91.76 %	.1361	0.87 (0.86 - 0.89)	0.84 (0.77-0.90)	
Size <3 cm	8	957	< .0001	86.09 %	.9657	0.91 (0.89 - 0.92)	0.91 (0.84-0.96)	.0162
Size ≥3 cm	7	695	< .0001	94.71	.1077	0.82	0.71	

				%		(0.79 - 0.85)	(0.54-0.86)	
mBED <100 Gy_{10}	8	645	< .0001	88.01 %	.1148	0.84 (0.81 - 0.87)	0.77 (0.66-0.87)	.0803
mBED جي10 0 Gy_{10}	6	935	< .0001	95.36 %	.9423	0.90 (0.88 - 0.92)	0.90 (0.79-0.98)	
Eastern	15	1274	< .0001	91.79 %	.2800	0.85 (0.83 - 0.87)	0.82 (0.74-0.90)	.1347
Western	2	615	.0010	90.76 %	-	0.91 (0.88 - 0.93)	0.90 (0.82-0.97)	
5-year LC								
ALL	17	1889	< .0001	92.34 %	.1108	0.86 (0.84 - 0.88)	0.82 (0.74-0.88)	
Size <3 cm	8	957	< .0001	83.40 %	.9971	0.89 (0.87 - 0.91)	0.89 (0.83-0.94)	.0216
Size جي3 cm	7	695	< .0001	95.67 %	.1078	0.81 (0.78 - 0.84)	0.68 (0.49-0.85)	
mBED <100 Gy_{10}	8	645	< .0001	90.54 %	.1035	0.83 (0.80 - 0.86)	0.75 (0.62-0.86)	.1067
mBED جي10 0 Gy_{10}	6	935	< .0001	95.30 %	.9039	0.88 (0.86 - 0.90)	0.88 (0.76-0.97)	
Eastern	15	1274	< .0001	92.02 %	.2987	0.83 (0.81 - 0.85)	0.80 (0.71-0.88)	.0671
Western	2	615	.0010	90.76 %	-	0.91 (0.88 -	0.90 (0.82-0.97)	

						0.93)		
1-year OS								
ALL	17	1889	< .0001	91.09 %	.9814	0.85 (0.83 - 0.86)	0.84 (0.78-0.90)	
Size <3 cm	8	957	< .0001	88.80 %	.3794	0.90 (0.88 - 0.92)	0.93 (0.86-0.97)	.0005
Size ≥3 cm	7	695	< .0001	78.58 %	.4922	0.77 (0.73 - 0.80)	0.74 (0.66-0.82)	
mBED <100 Gy_{10}	8	645	< .0001	87.51 %	.4173	0.82 (0.79 - 0.85)	0.78 (0.67-0.88)	.0835
mBED ≥100 Gy_{10}	6	935	< .0001	93.00 %	.3641	0.86 (0.84 - 0.88)	0.90 (0.80-0.96)	
Eastern	15	1274	< .0001	89.03 %	.1611	0.89 (0.87 - 0.90)	0.86 (0.79-0.91)	.0168
Western	2	615	.1228	58.00 %		0.75 (0.71 - 0.78)	0.75 (0.69-0.80)	
3-year OS								
ALL	17	1889	< .0001	93.74 %	.2657	0.53 (0.51 - 0.56)	0.57 (0.47-0.66)	
Size <3 cm	8	957	< .0001	92.64 %	.1109	0.60 (0.57 - 0.63)	0.68 (0.55-0.79)	.0114
Size ≥3 cm	7	695	< .0001	91.13 %	.7209	0.42 (0.39 - 0.46)	0.44 (0.30-0.58)	
mBED <100 Gy_{10}	8	645	< .0001	84.95 %	.7376	0.49 (0.45 - 0.52)	0.50 (0.38-0.61)	.2521

mBED جي10 0 Gy_{10}	6	935	< .0001	96.34 %	.2700	0.53 (0.50 - 0.56)	0.62 (0.44-0.79)	
Eastern	15	1274	< .0001	86.71 %	.4643	0.63 (0.60 - 0.66)	0.61 (0.53-0.69)	< .0001
Western	2	615	.0081	85.75 %	-	0.34 (0.30 - 0.38)	0.34 (0.24-0.44)	
5-year OS								
ALL	17	1889	< .0001	95.45 %	.3078	0.36 (0.34 - 0.38)	0.40 (0.29-0.51)	
Size <3 cm	8	957	< .0001	94.46 %	.1394	0.42 (0.39 - 0.45)	0.51 (0.37-0.66)	.0309
Size جي3 cm	7	695	< .0001	95.38 %	.8090	0.25 (0.21 - 0.28)	0.25 (0.10-0.44)	
mBED <100 Gy_{10}	8	645	< .0001	82.45 %	.7866	0.29 (0.26 - 0.33)	0.30 (0.21-0.40)	.2697
mBED جي10 0 Gy_{10}	6	935	< .0001	97.45 %	.3571	0.35 (0.32 - 0.38)	0.43 (0.23-0.65)	
Eastern	15	1274	< .0001	91.02 %	.4692	0.46 (0.44 - 0.49)	0.43 (0.34-0.53)	.0035
Western	2	615	< .0001	94.74 %	-	0.17 (0.14 - 0.20)	0.17 (0.06-0.32)	

Abbreviations: mBED = median biologically effective dose which was calculated using the α/β ratio of 10.

Table 4. Hepatic toxicity

	Acute hepatic toxicity			Late toxicity	
Author	Hepatic toxicity* ≥ grade 3 (%)	Classic RILD (%)	Nonclassic RILD (%)	Type of Hepatic toxicity ≥ grade 3	%
Shin			13		
Roquette	2		18	0	0
Rordlamool	30	4	7		
Ueno					
Kibe		0		LC progression	1
Mathew	25†	0	16	Biliary toxicity	1
Fu	0	0	0		
Park	3	0	6	Biliary toxicity	9
Yoon	0	0	2	0	0
Su	1‡		10		
Sun	0	3	5	0	0
Shen		4§	20§		
Lee	0	16	25	0	0
Kimura	7			0	0
Hijazi	0	0	4	0	0
Que	16†	0	3		
Jang	4	0	5	0	0

Abbreviations: RILD = radiation-induced liver disease; LC = liver cirrhosis.

*was defined according to Common Terminology Criteria for Adverse Events.

†some patients had more than one kind of hepatic toxicity.

‡this study reported only hepatic toxicity of grade 5.

§two patients had both classic RILD and nonclassic RILD.

Table 5. Key opinions for stereotactic body radiotherapy (SBRT) to hepatocellular carcinoma (HCC)

Recommendations on
Patient Selection
1. Patients with HCC <3cm can be considered for SBRT with favorable local control and survival outcomes. SBRT to HCC ≥3 cm can be performed with the expectation of durable long-term local control. 2. SBRT can be performed when the pretreatment liver function is Child-Pugh (CP) class A or B7. SBRT to patients with CP class ≧B8 should be delivered with caution, particularly CP class C patients.
Treatment
1. SBRT with 1-9 fractions is recommended for patients with liver-confined HCC. No specific recommendation for the optimal dose fractionation can be made.
Treatment outcome
1. Considering worse overall survival rates in patients from western regions as compared to those from eastern regions, in spite of similar local control rates, different follow-up strategies according to the etiology of HCC may be needed. 2. Classic radiation-induced liver disease (RILD) is a rare event following SBRT to HCC with proper patient selection. 3. The incidence of classic RILD and non-classic RILD should be separately recorded in order to facilitate comparisons with historical SBRT studies. The use of Common Terminology of Criteria for Adverse Events criteria is recommended in order to facilitate comparisons to other treatment modalities.