

Stereotactic body radiotherapy vs radiofrequency ablation in the treatment of hepatocellular carcinoma: a meta-analysis

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Abstract

Background Both stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) are effective local treatments for hepatocellular carcinoma (HCC), but whether RFA is superior to SBRT is still controversial. Therefore, we performed a meta-analysis to compare the treatment outcomes of SBRT with RFA as curable or bridge intention.

Methods We searched online databases for studies that compared treatment outcome for SBRT and RFA. Eligibility criteria included evaluation of local control, overall survival (OS), transplant rate, and post-transplant pathological necrosis.

Results 10 retrospective studies with a total of 2732 patients were included. 2 studies were in favor of SBRT in local control, 2 studies preferred RFA in OS and others reported comparable outcomes for both. SBRT demonstrated significantly higher 1- and 3-year local control than RFA (OR 0.42, 95% CI 0.24 to 0.74, $P = 0.003$; OR 0.54, 95% CI 0.37 to 0.80, $P = 0.002$, respectively). However, SBRT reported significantly shorter 1- and 2-year OS (OR 1.52, 95% CI 1.21 to 1.90, $P = 0.0003$; OR 1.66, 95% CI 1.38 to 2.01, $P < 0.00001$, respectively). As bridge treatment, no significant difference was shown in transplant rate and post-transplant pathological necrosis rate (OR 0.57, 95% CI 0.32 to 1.03, $P = 0.060$; OR 0.49, 95% CI 0.13 to 1.82, $P = 0.290$, respectively).

Conclusions This study demonstrates SBRT is able to complete a better local control for HCC than RFA, though the OS is inferior to RFA because of tumor burden or liver profiles of the enrolled studies. Well-designed, randomized, multicenter trials will be required to further investigate the conclusion.

Background

Liver transplantation is the most beneficial therapy for early hepatocellular carcinoma (HCC) patients, as it removes both the tumor and the cirrhotic liver(1). However, given organ availability limitation, a number of patients that may benefit from this treatment have to stay on the waiting list for a long time. Therefore, stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) are offered as potentially alternative local control modalities for patients in the waiting list(2,3).

RFA induces coagulative necrosis of tumor through thermal effect and is the first-line treatment for small HCC (≤ 3 cm), providing comparable long-term outcome with resection(4). However, RFA has several contraindications, including large tumor size, lesions adjacent to major vessels or close to the liver hilum. As the above circumstances may result in incomplete ablation, which potentially leads to worse prognosis(5–9).

SBRT is an advanced technology that delivers ablative radiation doses to tumors in a few fractions while minimizing the dose to normal liver tissue. Early results with SBRT have shown considerable local control even for large tumors or HCC ineligible for surgery(10). Moreover, SBRT has been frequently used as an alternative to RFA for small HCC patients with tumors near critical anatomical structures or major vessels due to the heatsink effect that can occur with RFA(11).

Recent publications have reported either comparable outcomes between the two treatment modalities or favorable outcomes for one to the other(3,10,12–19). However, the efficacy of these two treatments regarding disease control and long-term survival are ununified. The aim of this meta-analysis is mainly to compare the benefits of SBRT and RFA in the local progression control and overall survival (OS) in the treatment for HCC.

Methods

Study selection

The inclusion criteria of this meta-analysis were: (1) diagnosed primary liver cancer definitively. Patients diagnosed with HCC based on pathological evidence from fine needle aspiration (FNA) or in the absence of biopsy evidence, based on imaging techniques including contrast-enhanced ultrasonography (CEUS), computed tomography (CT), and magnetic resonance imaging (MRI) accompanied with alpha-fetoprotein elevation; (2) no evidence of invasion into the major portal/hepatic vein branches or extrahepatic metastasis based on radiologic imagine; (3) patients without previous treatment of transcatheter arterial chemoembolization (TACE), surgery, chemotherapy, or other anti-tumor treatment; (4) documented indications for SBRT and RFA clearly; (5) either randomized controlled trials or retrospective studies were candidates; (6) patients of two groups with comparable basic clinical characters; (7) studies with outcome information regarding local progression (LP) rates, OS rates, and/or transplant rates.

Studies with following characteristics were excluded: (1) studies that did not report original data, including abstracts, case reports, expert opinions, editorials, reviews or letters; (2) either group in the studies combined other therapies; (3) studies based on the same cohort.

Search strategy

A systematic online databases search of PubMed Central, Embase, Cochrane Library and Google Scholar was separately conducted by two reviewers to identify all relevant availability of studies until August 26th 2019.

This meta-analysis was performed in consistent with the Preferred Reporting In Systematic Reviews and Meta-Analysis (PRISMA) statement checklist. The subject headings (MeSH) search and text word search were used, including “radiofrequency ablation”, “stereotactic body radiation therapy” and “hepatocellular carcinoma”. These terms were used in different combinations. Only human beings and English language studies were included. A manual research was performed by browsing all references of all identified studies. This progressed research was repeated to ensure to include the whole relevant studies. The research was completed by two reviewers before the data analysis independently (Y-X. Pan and M. X). If a study was controversial, the corresponding author was asked to judge (Y-J. Zhang).

Data collection

Data were extracted from the included studies, including: number of patients in the SBRT and RFA groups, age, gender, primary tumor size, number of tumors, median dose of SBRT, Child-Pugh class, median follow-up time, 1-, 2- and 3-LP rates, 1-, 2-, 3- and 5-year OS, post-transplant necrosis rate and time to liver transplant.

Definitions

Local progression was defined as the recurrence of lesion in the treatment area by imaging studies. And LP time was the period from the initial treatment to the discovery of LP or last follow-up. The OS was defined the period from the date of initial treatment of the HCC to the date of death related to any cause. Transplant rate was the proportion of patients who received liver transplantation after SBRT or RFA therapies. Post-transplant pathological necrosis was evaluated by post-transplant pathology.

Statistical analysis and synthesis

All analyses were performed with the help of statistical software, named Review Manager, version 5.3 (Nordic Cochrane Centre; Oxford, England). For data evaluation, patients were assigned into two groups: the SBRT-treated group and the RFA-treated group. The odds ratio (OR) and/or hazard ratios (HR) accompanying 95% confidence intervals (95% CI) were calculated for dichotomous and univariable analysis outcomes in terms of LP, OS and prognostic factor on treatment allocation, respectively. Meanwhile, we assessed the heterogeneity among trials according to the Chi-squared (χ^2) test including the inconsistency factor (I^2). The heterogeneity was defined as a *P* value of less than 0.05 or an I^2 greater than 40%. A random-effect model was applied when the heterogeneity ($I^2 < 40\%$) was absent or low, or we use a fixed-effect model if the heterogeneity ($I^2 > 40\%$) was moderate or high(20). A potential publication bias was assessed by visually inspecting the Begg's funnel plots in which the standard error (SE) of log OR or log HR was plotted against the OR or HR, respectively.

Results

Search results and quality assessment

A total of 440 studies were identified for the first time from PubMed by the search strategy previously established and 269 studies were identified via other sources or review. Subsequently, 11 studies were deleted for duplication with the help of Mendeley (Elsevier Inc.; Atlanta, GA, USA). The titles and abstracts of 270 studies were then screened for inclusion. The full texts of 36 studies were read and, finally, we included 10 non-randomized controlled trial (Non-RCT) studies that met the present meta-analysis criteria(3,10,13–16,18,19,21,22). The details of PRISMA flow diagram of the literature for meta-analysis is shown in Supplementary Figure S1(23).

In present analysis, 3 studies were based on already existed database(13,15,19) and the remaining 7 studies were based on retrospective studies(3,10,16–18,21,22). 2 studies conducted SBRT or RFA for

transplant intent. 5 studies were performed in USA(10,13,15,18,19), 2 in Japan(12,16), 1 in Canada(3), 1 in South Korea(17), and 1 in China(22). Out of 2732 patients from the 10 included studies 859 patients were classified into the SBRT group, and the rest 1873 patients were classified into the RFA group. The Newcastle Ottawa Scale (NOS)(24) were used to assess the quality of non-randomized studies. Among all studies included, over 50% of which were medium-score studies because of inconsistent comparability, although the sections of selection and outcomes were relatively appropriate qualities. Therefore, we believed that the present meta-analysis possesses a medium-class of quality (Supplementary Table S1).

Among included studies, 2 studies were in favor of SBRT on local control(10,21), 2 studies preferred to RFA on OS(15,19) and others reported comparable outcomes between groups(3,13,16–18,22). Notably, according to baseline characteristics, several studies enrolled patients in SBRT group were prone to suffer from larger tumor diameter(3,10,16,19) and higher proportion of Child-Pugh C patients(18) (Table 1). These groups were evaluated for therapeutic efficacy in treating HCC patients. The details of the studies included in the present meta-analysis are listed in Table 1.

Table 1
Characteristics of
include studies

Author	Design	Group	Number of patients	Number of tumor (1/≥2)	Age (years)	Sex (M/F)	Tumor size (cm)	Median dose (Gy)	Child-Pugh Class (A/B/C)	Median follow up (months)
Mohamed et al., 2016 (American)	Non-RCT	SBRT	23	14/9	57.5 (44-70.2)	20/3	NR	50 (45-60)	17/0/5	41 (7.3-77.9)
		RFA	9	8/1	57.5 (44-70.2)	8/1	NR		9/0/0	41 (7.3-77.9)
Wahl et al., 2016 (American)	Non-RCT	SBRT	63	49/14*	62 (35-85)	54/9*	2.2 (0-10)	50 (27-60)	43/18/2*	27 (0.5-86.5)*
		RFA	161	109/52*	60 (31-81)	117/44*	1.8 (0.6-7.0)		80/68/13*	50.9 (3.5-112.8)*
Sapisochin et al., 2017 (Canada)	Non-RCT	SBRT	36	17/19*	60.4 (56.4-64.8)	30/5	4.5 (2.9-5.8)*	36 (30-40)	22/14/0*	28.1 (14.9-64.7)*
		RFA	244	156/88*	57.8 (53.5-62)	208/36	2.5 (1.9-3)*		158/68/8*	52.2 (21-90.7)*
Hara et al., 2019 (Japan)	Non-RCT	SBRT	106	94/12	74 (48-93)	71/35	1.8 (1.0-3.0)	37.5 (35-40)	104/2/0	33.7 (0.5-75.0)
		RFA	106	93/13	75 (47-88)	76/30	1.7 (0.7-2.8)		105/1/0	29.9 (6.0-72.8)
Berger et al., 2017 (American)	Non-RCT	SBRT	157	NR	68.61 (11.74)	113/44	4.8 (4.8)	NR	NR	NR
		RFA	627	NR	68.21 (10.00)	454/173	4.2 (4.6)		NR	NR
Duan et al., 2016 (China)	Non-RCT	SBRT	37	NR	NR	NR	1-5	NR	NR	NR
		RFA	40	NR	NR	NR	1-5		NR	NR
Kim et al., 2019 (Korea)	Non-RCT	SBRT	95	95/0	63.0 (35.0-85.0)	80/15	2.4 (0.7-5.5)	60 (52-60)	90/5/0	21.9 (11.8-31.2)
		RFA	95	95/0	67.0 (40.0-86.0)	83/12	2.1 (0.8-4.6)		90/5/0	21.6 (11.1-37.3)
Rajyaguru et al., 2018 (American)	Non-RCT	SBRT	275	190/85	65 (55-75)	194/81	2.5 (2.5-3.5)	45 (45-55)	NR	25.3 (14.1-41.0)
		RFA	521	349/172	65 (55-75)	381/140	2.5 (2.5-3.5)		NR	25.3 (14.1-41.0)
Shiozawa et al., 2015 (Japan)	Non-RCT	SBRT	35	35/0	75.1 (67-83)*	24/11	2.86 (1.2-5)*	50.6 (7.8)	28/7/0	12.6 (6.8-35.5)*
		RFA	38	38/0	68.7 (42-86)*	27/11	1.75 (0.7-2.9)*		31/7/0	18.7 (7.4-40.8)*
Parikh et al., 2018	Non-RCT	SBRT	32	NR	77 (72-81.25)	20/12	NR	NR	NR	NR

(American)	RFA	32	NR	79 (76-82)	22/10	NR	NR	NR
Total	SBRT	859						
	RFA	1873						

SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; NR, not reported. *Statistically significant ($P < 0.05$).

Local progression rates

6 out of the 10 studies illustrated 1-, 2- and 3-year LP rates(10,16–18,21,22). Our pooled results showed that the SBRT group had significantly better 1- and 3-year local control rates than the RFA group (OR 0.42, 95% CI 0.24 to 0.74, $P = 0.003$; OR 0.54, 95% CI 0.37 to 0.80, $P = 0.002$, respectively). However, the 2-year LP rate showed marginal benefit of SBRT group than RFA group (OR 0.67, 95% CI 0.43 to 1.05, $P = 0.080$). No heterogeneity was shown among the studies of 1-, 2- and 3-year local progression rates ($\chi^2 = 2.93$, $I^2 = 0\%$; $\chi^2 = 0.33$, $I^2 = 0\%$; $\chi^2 = 2.66$, $I^2 = 0\%$, respectively), so the fixed effect model was used to pool the outcomes (Figure 1).

Overall Survival

9 studies with 2700 patients compared OS rates of SBRT group with RFA group(3,10,13,15–17,19,21,22), 1 study with 280 patients were excluded as both SBRT and RFA were applied as bridge therapies before transplantation and thus the actual OS rates of SBRT or RFA might be affected by subsequent transplantation(3). Heterogeneity was low for the studies that reported 1- and 2-year OS rates ($\chi^2 = 10.47$, $I^2 = 33\%$; $\chi^2 = 7.93$, $I^2 = 24\%$, respectively), so the fixed effect model was used to pool the outcomes. However, high heterogeneities were observed in the studies that reported 3- and 5-year OS rates ($\chi^2 = 20.54$, $I^2 = 76\%$; $\chi^2 = 12.88$, $I^2 = 77\%$, respectively), so the random effect model was used to pool the outcomes (Figure 2). The pool results showed that 1- and 2-year OS rates of RFA group were better than SBRT group (OR 1.52, 95% CI 1.21 to 1.90, $P = 0.0003$; OR 1.66, 95% CI 1.38 to 2.01, $P < 0.00001$, respectively). Whereas, there were no differences for 3- and 5-year OS rates in both groups (OR 1.44, 95% CI 0.90 to 2.33, $P = 0.130$; OR 1.35, 95% CI 0.81 to 2.26, $P = 0.250$, respectively).

Additionally, a secondary analysis was performed to control the potential report bias, and we enrolled the studies that reported outcomes of both LP and OS. As result, the 1-, 2-, 3- and 5-year OS rates indicated no significant difference between both groups (OR 0.96, 95% CI 0.59 to 1.57, $P = 0.870$; OR 1.35, 95% CI 0.89 to 2.03, $P = 0.160$; OR 0.97, 95% CI 0.28 to 3.36, $P = 0.960$; OR 0.65, 95% CI 0.37 to 1.16, $P = 0.150$, respectively) (Supplementary Figure S2).

Prognosis for treatment allocation

3 and 5 studies evaluated the results of treatment allocation as a prognostic factor for LP(10,16,17) and OS(13,15,17,19,21), respectively. The treatment allocation was not a prognostic factor for LP [HR 0.80, 95%

IC 0.58 to 1.09, $P = 0.160$]. However, RFA group was more favorable than SBRT group for OS benefits (HR 1.43, 95% IC 1.23 to 1.80, $P < 0.00001$). Heterogeneity did not exist among the studies ($\chi^2 = 5.39$, $I^2 = 63\%$; $\chi^2 = 3.64$, $I^2 = 0\%$, respectively), so the fixed effect model was applied to pool the outcomes (Figure 3).

Transplant and post-transplant pathological necrosis rate

3 and 2 studies reported the transplant rate and post-transplant pathological necrosis rate, respectively (3,10,18). There were no significant differences in transplant rate and post-transplant pathological necrosis rate for both SBRT and RFA (OR 0.57, 95% CI 0.32 to 1.03, $P = 0.060$; OR 0.49, 95% CI 0.13 to 1.82, $P = 0.290$, respectively). No significant heterogeneity was observed when the transplant and post-transplant pathological necrosis rates were evaluated ($\chi^2 = 4.55$, $I^2 = 56\%$; $\chi^2 = 1.03$, $I^2 = 3\%$, respectively) and the fixed-effect model was used (Figure 4).

Publication bias

The Begg's funnel plot was used to evaluate the reliability of publication bias in our meta-analysis (25). The shape of 11 funnel plots was basically inverted and bilateral symmetry. Therefore, these results indicated that there was little publication bias among all comparisons in this meta-analysis (Supplementary Figure S3).

Discussion

The main finding of this meta-analysis is that SBRT showed a better local control than RFA for patients with HCC, though the 1- and 2-year OS rates of SBRT were inferior because of the tumor burden and liver profiles. Recently, RFA, as a traditional curable treatment, was challenged by SBRT (15,21,22). With the development of imaging technique, such as four-dimensional computed tomography (4DCT), SBRT is able to provide a more precise picture of HCC for treatment design (26). This improvement of SBRT effectively fixed the deficiencies of the high incomplete ablation rate of RFA under several specific conditions (7).

In 2006, Romero *et al.* firstly applied the radiational technique of SBRT as a salvage treatment to control the primary and metastatic liver tumors (27). Although only 25 patients with 45 lesions that were unfit for other local control treatment were included in this study, the results indicated that SBRT was feasible with acceptable toxicity and local control efficacy. They also pointed out that for patients with Child B accompanied by high toxicity risks, the optimal dose-fractionation schemes had to be found. Inspired by Romero *et al.*, other investigators mainly focused on the application of SBRT on unresectable HCC or its effect in combination with other therapies (28–30). All these studies proved that SBRT was safe and provided satisfying local control for HCC, which encouraged the temptation of expanding the indications of SBRT from a salvage or bridge treatment to curable intention.

RFA has long been applied as the first-line treatment for small HCC according to several clinical practice guidelines, including European Society for Medical Oncology (ESMO) and American Association for the

Study of Liver Disease (AASLD)(31,32). However, RFA still suffers from high incidence of local incomplete ablation because of technical limitations (varies from 2% to 60%(5–9)) and it required additional or combination therapies(33). As an advanced technique that shows reliable local control on HCC, SBRT have been considered as a potentially alternative therapy to RFA.

Many observational or retrospective studies in recent years have indicated that SBRT showed a non-inferior local control rate compared to RFA(10,16–18,22). Shiozawa *et al.* first compared the clinical outcomes between SBRT and RFA for HCC patients in a pilot study in 2015 and reported that SBRT was likely to become an important option for local treatment of early HCC(16). The subsequent studies indicated that SBRT appeared to be a reasonable alternative treatment of inoperable HCC in 2016(10,22). Subsequently, several large volume validation studies based on online database had also proved comparable outcomes between SBRT and RFA regarding local control(13,19). Moreover, in 2019, Kim *et al.* retrospectively reviewed the institutional database for RFA and SBRT with curative intent, and they revealed that SBRT appears to be an effective alternative treatment for HCC when RFA is not feasible due to tumor location or size(17). However, another database validation from the American national cancer database revealed better OS of RFA than SBRT(15). A meta-analysis is needed to attain definitive proof to solve these debates. Thus, we performed this meta-analysis to help identify the advantages and disadvantages of SBRT and RFA in HCC.

In the present meta-analysis, with respect to local control, SBRT showed significantly lower 1- and 3-year LP rates, which indicated that SBRT achieved superior local control to RFA in treating HCC. In detail, there were 5 and 4 studies enrolled the 1- and 3-year LP rate analysis, respectively. Among these studies, studies from Wahl *et al.* and Duan *et al.* were based on patients with inoperable HCC(10,22), studies of Hara *et al.* and Shiozawa *et al.* were based on patients with early-stage HCC(16,21) and studies from Kim *et al.* and Mohamed *et al.* did not specify patients characteristics(17,18). Most of the enrolled studies tended to draw the conclusions with respect to local control that supported SBRT. Moreover, Wahl *et al.* and Hara *et al.* reached significantly favorable results for SBRT in treating inoperable and early-stage HCC, respectively(10,21). However, only Kim *et al.* clarified the information of HCC location(17), others did not refer this critical factor which might influence the local control of RFA in our previous study(34). Additionally, treatment allocation was not a significance prognostic factor based on prognostic analysis. Therefore, further studies are needed to guarantee the appropriate individual treatment allocation.

Although, SBRT enjoyed higher local control rates than RFA in the present study, the 1- and 2-year OS rates of SBRT were significantly lower than RFA. Notably, Berger *et al.*(19) and Rajyaguru *et al.*(15) who reported favorable OS rates of RFA with large sample volume did not illustrate the LP rates correspondingly. There were two main reasons to the contradictory results between OS rates and LP rates. Firstly, there might be report bias when analyzing LP rates for both groups which might result in inconsistent outcomes between LP rates and OS rates because of unreported LP. Therefore, we conducted the secondary analysis on OS rates that included the studies that reported both LP rates and OS rates, and found that the 1-, 2-, 3- and 5-year OS rates were comparable between SBRT and RFA. Secondly, as the first-line treatment, RFA is more likely to be assigned to patients with better conditions. Patients underwent SBRT were prone to suffer from larger tumor size and worse liver function, which indicated worse prognosis and decreased OS. Interestingly, the 3- and 5-year OS rates showed no significance in both groups, indicating that patients who

did not die of tumor burden or liver functions in a short time might finally benefit from both treatments similarly. Meanwhile, RFA showed significant survival benefit for prognostic analysis on treatment allocation, which also could be explained by the reasons above. Therefore, we believed that the real effects of SBRT and RFA on long-term survival need to be further validated by high-level evidence, including randomized clinical trial (RCT).

As for bridge therapies to transplant, both SBRT and RFA provided a similar effect on patients waiting for transplantation. And the post-transplant pathological necrosis rate was comparable between both groups. These outcomes indicated that SBRT can be safely utilized as a bridge treatment to patients in the waiting list for transplantation with HCC, as an alternative to conventional bridging therapies. However, only 3 studies and 536 patients in total compared these parameters and more solid studies were needed to be enrolled in future.

This meta-analysis suffered from several limitations. First of all, only retrospective studies were available, resulting in relatively low quality of the evidence for the whole pooled results. Secondly, there are a total of 10 studies with 2732 participants, but the sample sizes of 4 studies were relatively small. A further sensitivity analysis on the factors affecting outcomes could not be applied. Therefore, some well-designed, large, prospective, and multi-center studies are desperately needed to obtain more solid evidence.

Conclusion

In sum, our meta-analysis shows that SBRT provided better local control than RFA, and it could be used as a potentially alternative local control treatment for HCC.

Abbreviations

SBRT = stereotactic body radiotherapy

RFA = radiofrequency ablation

HCC = hepatocellular carcinoma

OS = overall survival

FNA = fine needle aspiration

CEUS = contrast-enhanced ultrasonography

CT = computed tomography

MRI = magnetic resonance imaging

TACE = transcatheter arterial chemoembolization

PRISMA = Preferred Reporting In Systematic Reviews and Meta-Analysis

OR = odds ratio

HR = hazard ratios

SE = standard error

Non-RCT = non-randomized controlled trial

NOS = Newcastle Ottawa Scale

4DCT = four-dimensional computed tomography

ESMO = European Society for Medical Oncology

AASLD = American Association for the Study of Liver Disease

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YXP, QL and DDH designed experiments and drafted the manuscript. YZF, JCW and MX were responsible for data collection and statistical analysis. SLL, LX and MZL helped revise the manuscript. MSC and YJZ approved the final version.

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Figures

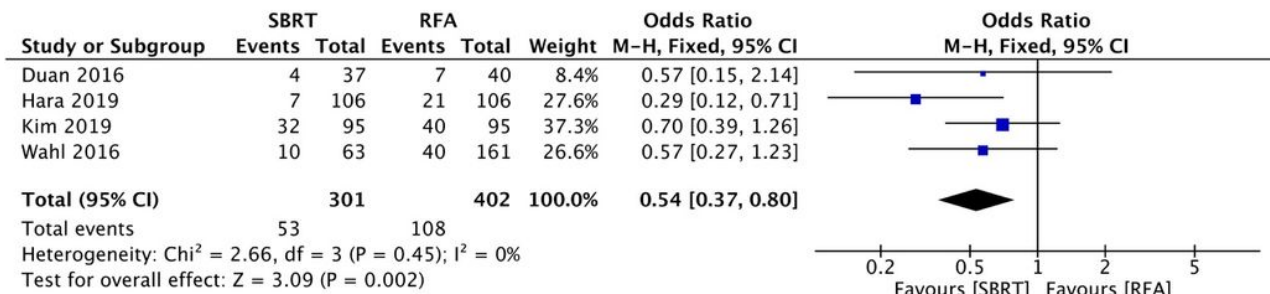
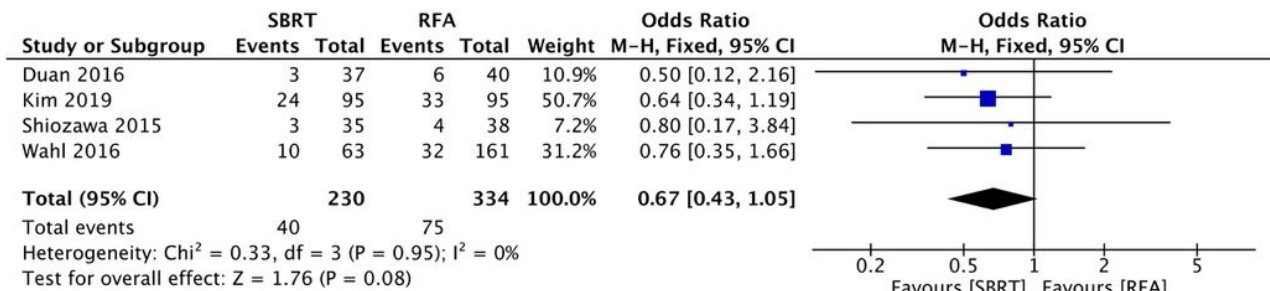
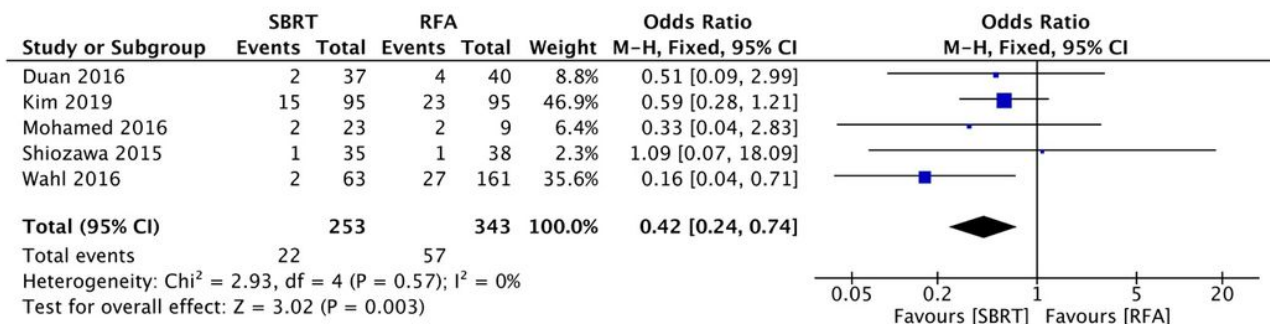


Figure 1

Forest plots demonstrating 1-, 2- and 3-years LP in SBRT and RFA for HCC

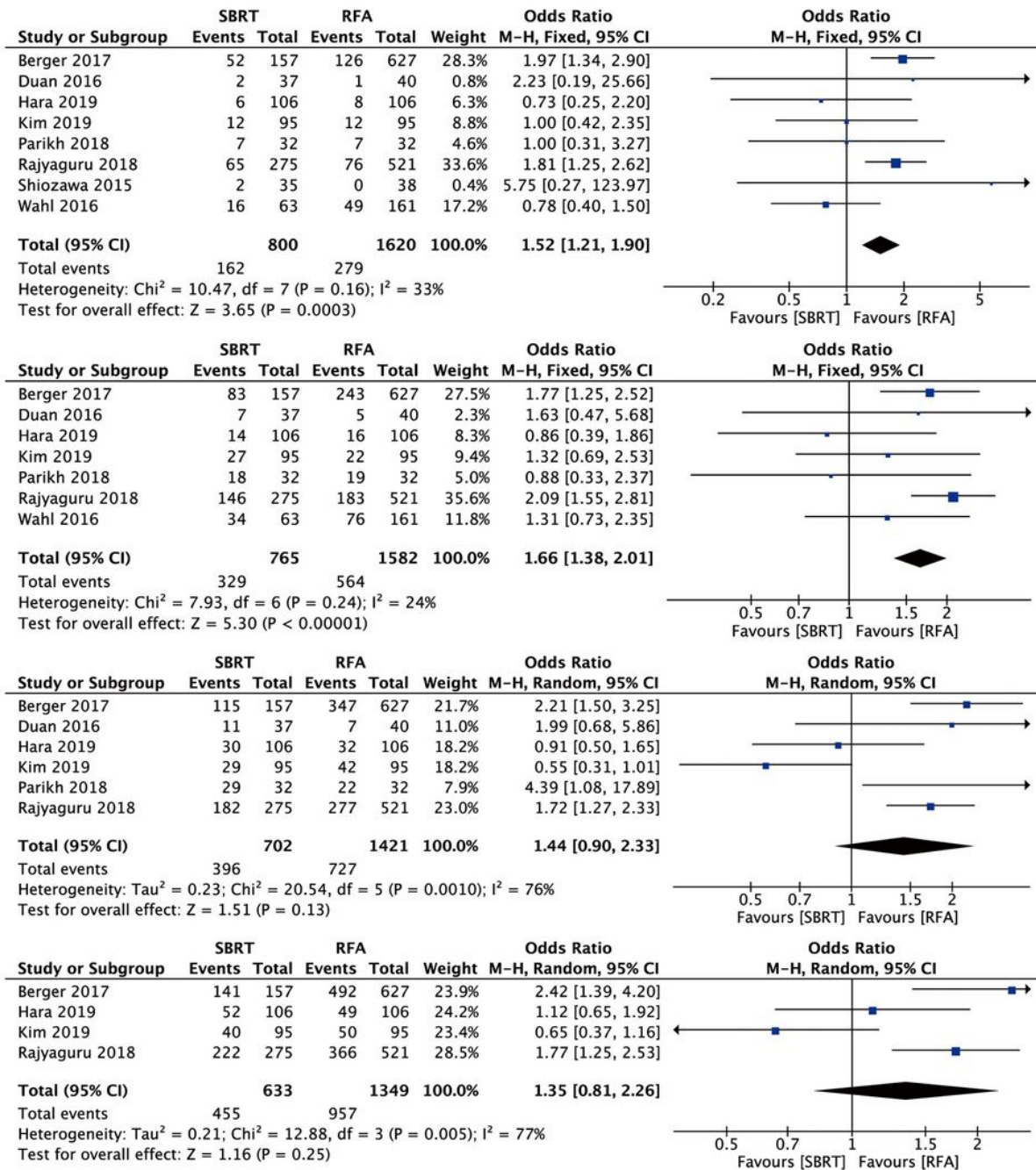


Figure 2

Forest plots demonstrating 1-, 2-, 3- and 5-years LP in SBRT and RFA for HCC

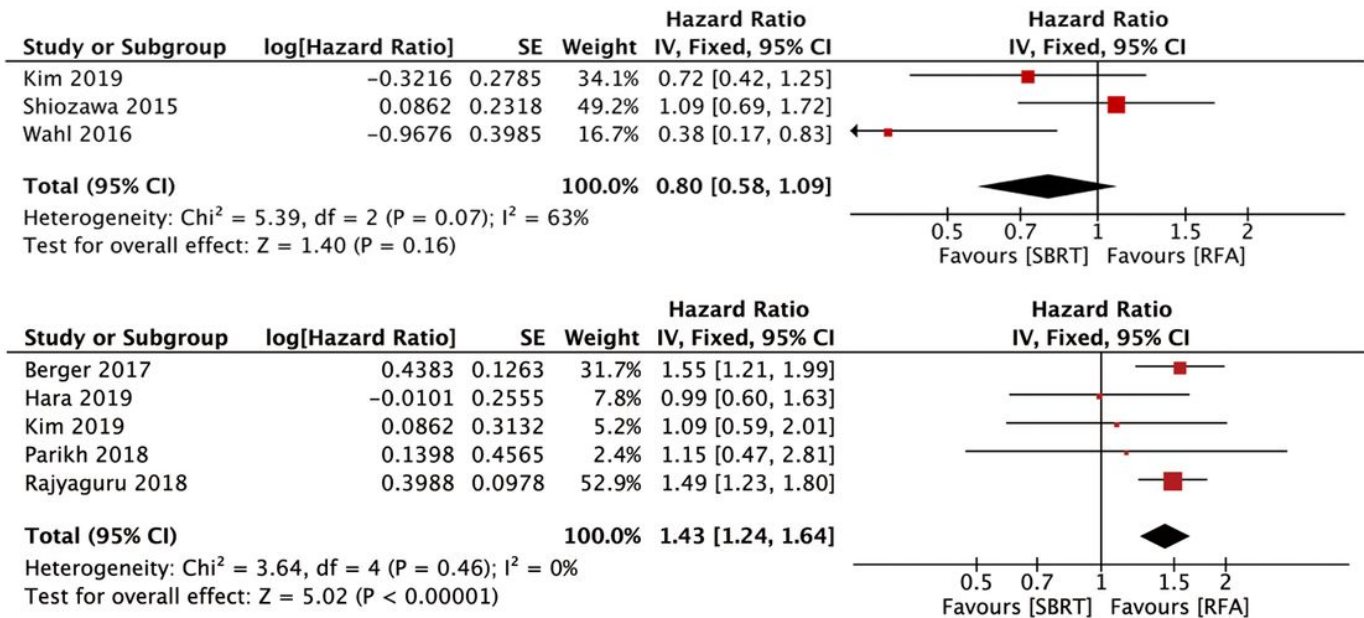


Figure 3

Forest plots demonstrating prognostic factor for LP and OS regarding to treatment allocation.

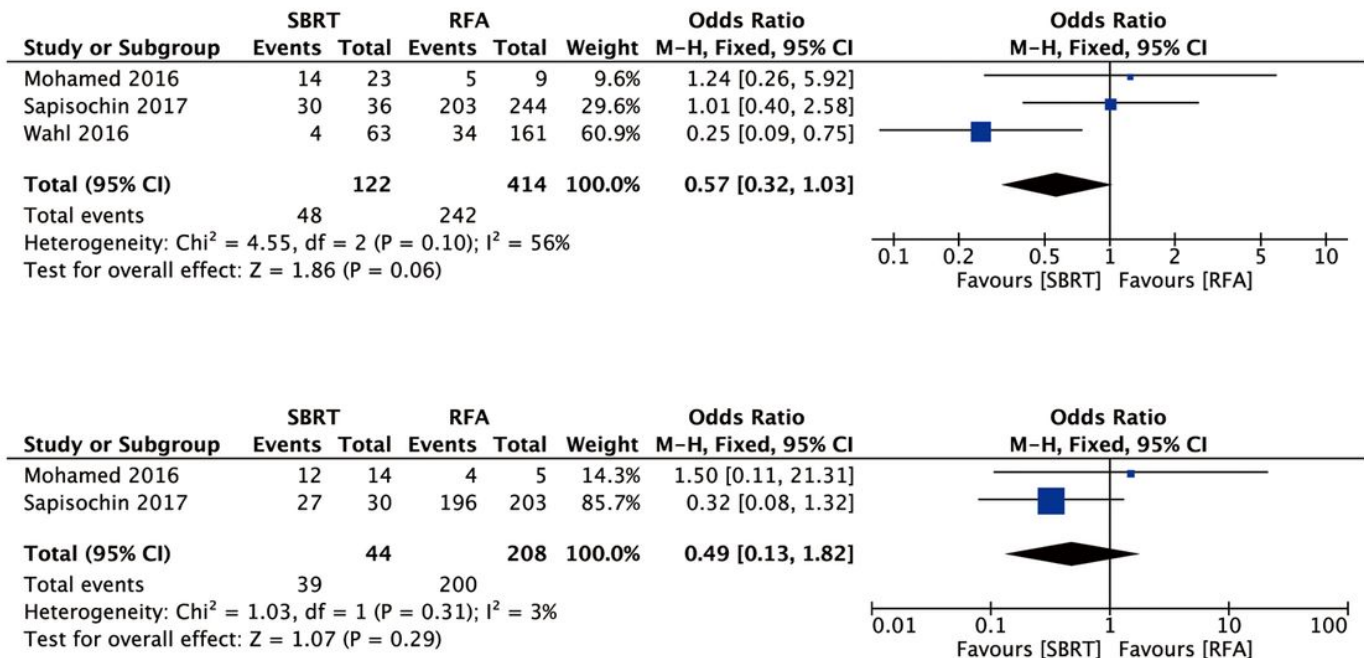


Figure 4

Forest plot demonstrating transplant rate and post-transplant pathologic necrosis in SBRT and RFA for HCC.

Supplementary Files

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