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ORIGINAL RESEARCH

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

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ABSTRACT

Background: There are limited and discording results on the comparison between stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC). The aim of this meta-analysis was to compare the two treatments in terms of efficacy and safety.
Research design and methods: A bibliographic search was performed on main databases through September 2020. Primary outcome was recurrence-free survival. Overall survival and adverse event rates were the secondary outcomes. Results were expressed as odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI)
Results: Nine studies enrolling 6545 patients were included. Recurrence-free survival at 1-year was similar between the two treatments (OR 2.11, 0.67–6.63); recurrence-free survival at 2- and 3-year was significantly in favor of SBRT as compared to RFA (OR 2.06, 1.48–2.88 and 1.86, 1.07–3.26, respectively). In a meta-analysis of plotted HRs, SBRT significantly outperformed RFA (HR 0.50, 0.33–0.76, $p = 0.001$). Overall survival was similar between the two treatments (HR 1.03, 0.72–1.47). No significant difference in terms of severe adverse event rate was observed (OR 1.38, 0.28–6.71).
Conclusions: SBRT prolongs recurrence-free survival as compared to RFA in HCC patients, although no significant survival benefit was demonstrated.

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KEYWORDS
Liver cancer; HCC; RFA; recurrence; SBRT; survival

Q3 1. Introduction

Hepatocellular carcinoma (HCC) represents the fifth most common kind of cancer and the most important cause of mortality in cirrhotic subjects [1].

Although an increasing number of HCC patients in the developed countries are currently amenable of curative therapies at the time of diagnosis [2], tumor recurrence and long-term survival still remain an unsolved issue.

In the last years, imaging-guided ablative therapies such as radiofrequency ablation (RFA) have garnered an important role in the treatment of HCC, due to their safety and efficacy to lead to complete necrosis of the tumoral nodule; in particular, RFA was found to be competitive with surgery in patients with a single nodule <3 cm [3]. However, the significant incidence of local and distant recurrences pushed to test other competitive therapies, among them stereotactic body radiotherapy (SBRT).

SBRT is a form of image-guided robotic radiosurgery using a radiation delivery platform that can detect and correct for intrafraction tumor motion, and it represents an alternative to RFA for patients with tumors in 'at-risk' locations such as adjacent to anatomical structures or major vessels, where the heat-sink effect might decrease the efficacy of RFA.

Despite the increasing number of studies testing this new technique [4], there is still limited evidence on the comparison between SBRT and RFA in unresectable HCC patients.

A recent meta-analysis compared the two treatments in several kinds of liver malignancies showing discordant results, in particular better local control with SBRT but higher survival rates in patients treated with RFA [5]; therefore, given the publication of several recent studies in this field, we decided to conduct an updated meta-analysis focused on HCC patients.

2. Material and methods

2.1. Search strategy and selection criteria

Studies included in this meta-analysis were prospective or case–control studies that met the following inclusion criteria: (a) Patients: adult HCC patients treated with (b) Interventions: SBRT or (c) Comparator: percutaneous RFA, and reported (d) Outcome: complete ablation of the treated nodules, overall survival, recurrence-free survival (RFS).

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Supplemental data for this article can be accessed here.

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We excluded (a) single cohort non-comparative studies, (b) studies conducted in patients with residual tumor after previous loco-regional treatment.

The search strategy was conducted in main databases through September 2020, based on the following search string: (radiofrequency ablation OR RFA) AND (stereotactic OR SBRT OR SABR OR CyberKnife) AND (HCC OR hepatic cell OR liver cell cancer OR hepatocellular OR liver cancer OR hepatic cancer). An updated literature search of conference proceedings of main international liver meetings was performed on 20 September 2020 to identify additional studies.

2.2. Data abstraction and quality assessment

Data on several baseline characteristics and outcomes were abstracted onto a standardized form, by two authors independently (AF, AC).

The risk of bias of individual studies was assessed independently by two authors (AF, IC) in the context of the primary outcome, based on the Newcastle Ottawa scale [6]. Eventual disagreements were solved following a third opinion (RS).

2.3. Outcomes assessed

The primary outcome was recurrence-free survival, defined as the time from treatment to tumor recurrence or death from any cause. Secondary outcomes were overall survival, complete response, defined as complete ablation of the treated nodules (i.e. complete necrosis at the post-treatment imaging), adverse event rate. Survival outcomes (namely, RFS and overall survival) were analyzed as survival rates at different time-points (1-, 2-, and 3-year), and as median survival.

In the case of propensity score matched studies, only data after matching were considered.

2.4. Statistical analysis

The two treatment groups were compared by means of a random-effects model based on DerSimonian and Laird test [7] and results were expressed in terms of odds ratio (OR) along with the relevant 95% confidence intervals (CIs).

Presence of heterogeneity was measured in terms of I2 tests with I2 < 20% interpreted as low-level heterogeneity and I^2 between 20% and 50% as moderate heterogeneity. Any potential publication bias was verified through visual assessment of funnel plots.

Sensitivity analyses in the context of the primary outcome were based on a) study location (East versus West), b) study quality (high versus low), c) treatment endpoint (ablation of the nodule vs achievement of a 5-mm ablation margin surrounding the tumor).

With the aim to take into account properly the different follow-up length among the studies and, within each study, between the two study groups and to include in the analysis not only the number of patients at risk but also when events occurred and their censoring, hazard ratios (HRs) from Kaplan Meier curves were plotted in accordance with the methods described by Tierney et al. [8].

In order to evaluate the impact of mean nodule size and proportion of hepatitis B virus (HBV) patients on the primary outcome (RFS) and to explore eventual sources of heterogeneity, a meta-regression analysis based on the aforementioned variables was conducted.

All statistical analyses were conducted using RevMan version 5 from the Cochrane collaboration and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), *metafor* package [9].

For all calculations, a two-tailed p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Literature search and characteristics of included studies

Figure 1 shows the flow chart of the search strategy conducted in this meta-analysis.

Out of 725 studies initially identified, after exclusion of reviews, case reports, single cohort studies, and animal models, 13 potentially relevant studies were extracted. After exclusion of overlap series and of a study conducted in patients with residual tumor after previous RFA [10], 9 retrospective studies [11–19] were finally included in the meta-analysis.

Table 1 reports the main characteristics of the included studies.

The recruitment period ranged from 2004 to 2016. Four studies [11,12,16,18] were conducted in Asia, whereas the other studies were conducted in the USA [13–15,17,19]. Globally, 1250 patients were treated with SBRT and 5295 with RFA.

Overall, the two arms were well balanced in terms of clinical and tumoral parameters in the included studies. Patients were mainly in Child Pugh stage A and viral etiology was the predominant cause of the underlying liver disease. The mean tumor size ranged from 1.75 cm to 3.7 cm and mean age of recruited patients was between 57 and 77 years. The majority of treated patients were male and with performance status 0. Three studies clearly reported the ablation of the tumoral nodule plus a 5-mm margin surrounding the nodule as tumor response [11,12,15].

Quality assessment of the included trials is depicted in the Supplementary Table 1. Three studies were deemed at higher risk of bias [14,18,19] due to inadequacy of follow-up of cohorts [14,19] or because published only as conference abstract [18].

3.2. Recurrence-free survival

Recurrence-free survival rates at different time points are reported in Table 2.

Based on five studies [14–16,18,19], OR for RFS at 1-year was non-significantly in favor of SBRT (OR 2.11, 0.67–6.63), with moderate evidence of heterogeneity (I^2 = 52%). As the time elapsed from the initial treatment, a significantly greater magnitude of recurrence-free survival benefit was observed in patients treated with SBRT (OR 2.06, 1.48–2.88 at 2-year and OR 1.86, 1.07–3.26 at 3-year), with low to moderate evidence of heterogeneity (I^2 = 0% and 37%, respectively; Table 2).

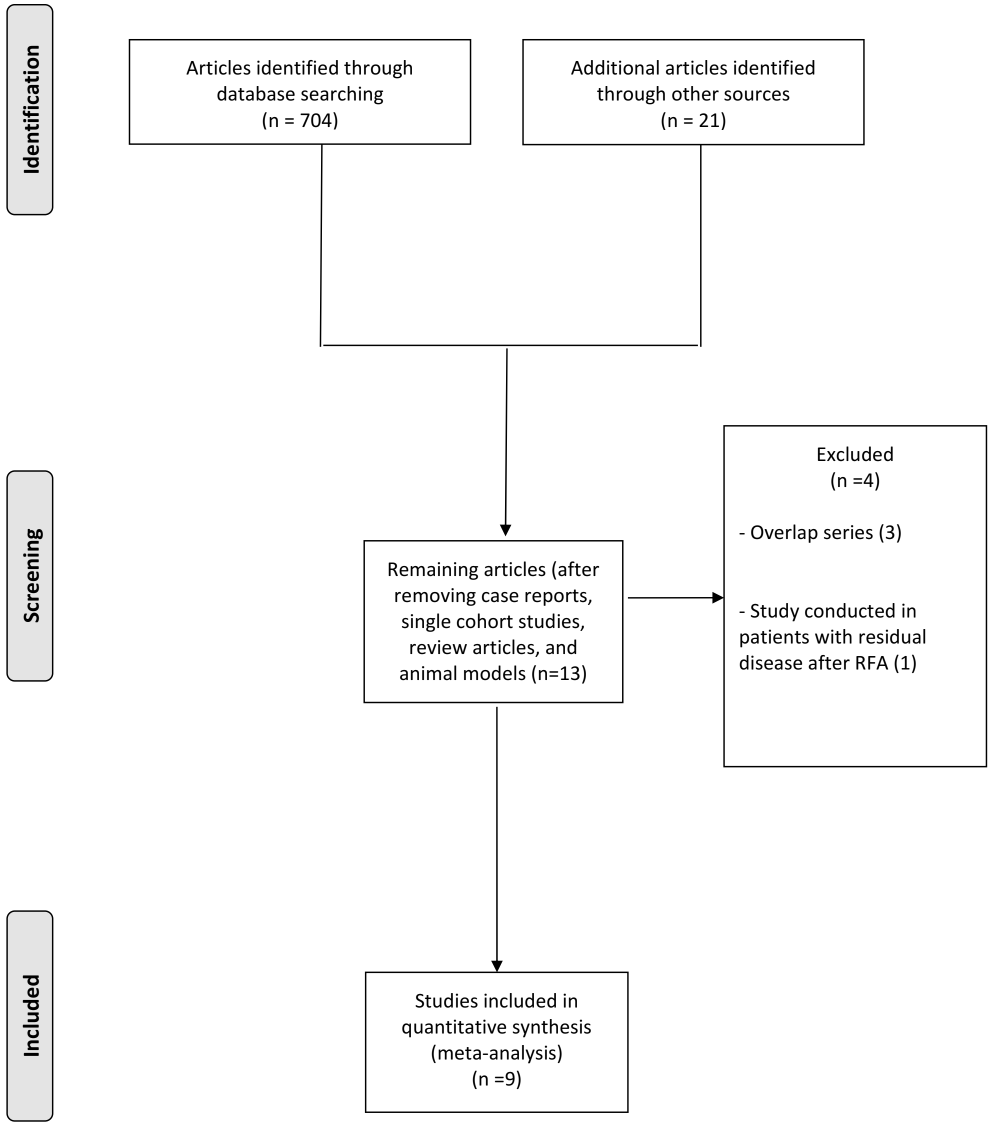

Figure 1. Flow chart of the search strategy.

Meta-analysis of plotted HRs is reported in Figure 2. Based on six studies [11,12,14–16,18], SBRT significantly outperformed RFA in terms of RFS (HR 0.50, 0.33–0.76, p = 0.001), with moderate evidence of heterogeneity (I^2 = 32%).

No significant publication bias was found by means of visual examination of funnel plot (data not shown).

In order to further confirm these findings, sensitivity analysis was performed with three different subgroups analyses, as reported in Supplementary Table 2. The superiority of SBRT over RFA was confirmed in all of the subsets tested, based on study location (East versus West), quality (high versus low), and definition of treatment response (nodule ablation versus ablation of a safety margin surrounding the tumor). Heterogeneity was mainly low or moderate in all of the comparisons (I^2 = 0% to 18%).

Meta-regression confirmed the lack of correlation between mean nodule size (Figure 3a) and the proportion of HBV patients (Figure 3b) and the HRs for recurrence free survival.

3.3. Survival

As reported in Table 2, survival rates at all of the tested time-points resulted comparable between the two treatments. In particular, OR at 1 year was 0.78 (0.45–1.34), at 2 years 0.77 (0.41–1.45), at 3 years 0.74 (0.49–1.23), with moderate to high evidence of heterogeneity (I^2 = 26% to 85%).

As depicted in Figure 4, meta-analysis of pooled HRs for survival showed similar results between the two treatments (HR 1.03, 0.72–1.47; p = 0.87), with moderate evidence of heterogeneity (I^2 = 46%).

No evidence of publication bias was found (data not shown).

3.4. Other secondary outcomes

Tumor response was evaluated in three studies [15,18,19]. As reported in Supplementary Figure 1, no significant difference

Table 1. Baseline data.

Study (year)	Country	Publication type	Treatment	Number of patients	Age (years)	Gender (male)	Child-Pugh (A/B/C)	Etiology (HBV/HCV/Other)	AFP	Tumor size (cm)
Hara (2019)	Japan	Full article retrospective	RFA	106	75 (47–88)	76 (71.7%)	105 (99.1%)/1 (0.9%)/0	13 (12.3%)/70 (66%)/24 (22.7%)	NR	1.7 (0.7–2.8)
			SBRT	106	74 (48–93)	71 (67%)	104 (98.1%)/2 (1.9%)/0	9 (8.5%)/79 (74.5%)/18 (17%)	NR	1.8 (1–3)
Kim (2020)	Korea	Full article retrospective	RFA	313	67.3 (59.4–74)	236 (75.4%)	273 (87.2%)/40 (12.8%) (B + C)	166 (53%)/99 (31.6%)/48 (15.3%)	10.4 (4.4–60)	2.2 (1.6–3.2)
			SBRT	313	65.8 (58.7–75)	238 (76%)	277 (88.5%)/36 (11.5%) (B + C)	180 (57.5%)/88 (28.1%)/45 (14.4%)	14.7 (4.8–95.5)	2.1 (1.5–3.1)
Mohamed (2016)	USA	Full article retrospective	RFA	9	NR	NR	9 (A + B) (100%)/0	NR	NR	NR
			SBRT	24	NR	NR	24 (A + B) (100%)/0	NR	NR	NR
Parikh (2018)	USA	Full article retrospective	RFA	32	79 (76–82)	22 (68.7%)	NR	NR	NR	NR
			SBRT	32	77 (72–81)	20 (62.5%)	NR	NR	NR	NR
Rajyaguru (2018)	USA	Full article retrospective	RFA	521	NR	381 (73.1%)	NR	NR	Elevated in 240	109/412 (<2/≥2)
			SBRT	275	NR	194 (70.5%)	NR	NR	Elevated in 143	49/231 (<2/≥2)
Sapisochin (2017)	USA	Full article retrospective	RFA	244	57.8 (53.6–62)	208 (85.2%)	159 (65.2%)/68 (27.9%)/8 (3.3%) (>B8)	51 (20.9%)/147 (60.2%)/46 (18.9%)	12 (5–41.5)	2.5 (1.9–3)
			SBRT	36	60.4 (56.4–64.8)	31 (86.1%)	22 (61.1%)/14 (38.9)/0 (>B8)	6 (16.7%)/17 (47.2%)/13 (36.1%)	20 (6–48)	4.5 (2.9–5.8)
Wahl (2015)	USA	Full article retrospective	RFA	161	60 (31–81)	117 72.7%)	49.6%/42.2%/8.2%	9.6%/59.8%/30.6%	8.8 (1.4–42,630)	1.8 (0.6–7)
			SBRT	63	62 (35–85)	54 (85.7%)	68.7%/28.9%/2.4%	3.6%/53%/16.8%	18.6 (1.4–6,256)	2.2 (0–10)
Shiozawa (2015)	Japan	Full article retrospective	RFA	38	68.7 (42–86)	27 (71%)	31 (81.6%)/7 (18.4%)/0	9 (23.7%)/18 (47.4%)/11 (28.9%)	NR	1.75 (0.7–2.9)
			SBRT	35	75.1 (55–89)	24 (68.6%)	28 (80%)/7 (20%)/0	4 (11.4%)/23 (65.7%)/8 (22.9%)	NR	2.86 (1.2–5)
Duan (2016)	China	Abstract retrospective	RFA	40	NR	NR	NR	NR	NR	NR
			SBRT	37	NR	NR	NR	NR	NR	NR

Abbreviations: RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; AFP, alpha-feto protein; NR, non-reported.

Table 2. Survival and recurrence-free survival rates at different time points and safety outcomes.

Variable	Time Point	No. of Studies	No. of patients	OR (95% CI)	Within-group heterogeneity (I^2)
Survival Rate	1-year	5	SBRT: 442 RFA: 792	0.78 (0.45–1.34)	39%
	2-year	4	SBRT: 688 RFA: 1035	0.77 (0.41–1.45)	85%
	3-year	4	SBRT: 731 RFA: 980	0.74 (0.49–1.23)	26%
Recurrence-free survival Rate	1-year	5	SBRT: 195 RFA: 492	2.11 (0.67–6.63)	52%
	2-year	3	SBRT: 413 RFA: 514	2.06 (1.48–2.88)	0%
	3-year	3	SBRT: 456 RFA: 459	1.86 (1.07–3.26)	37%
Adverse events	Adverse Event Rate	6	SBRT: 885 RFA: 2163	1.63 (1.01–2.64)	33%
	Severe Adverse Event Rate	5	SBRT: 389 RFA: 595	1.38 (0.28–6.71)	36%

Abbreviation: CI, confidence interval; OR, odds ratio; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy

in terms of complete response was observed (OR 1.30, 0.17–-9.95), with high evidence of heterogeneity (I^2 = 71%).

Pooled rates of complications were 23.2% (95% CI 5.9%-40.5%) and 17% (3.5%-30.5%) with SBRT and RFA, respectively (OR 1.63, 1.01–2.64, I^2 = 37%; Supplementary Figure 2 and Table 2). Severe adverse event rate was similar between the two groups (OR 1.38, 0.28–6.71, I^2 = 36%; Table 2), with a pooled rate of severe complications of 7.8% (1.5%-14.1%) with SBRT and 6.9% (0.9%-12.8%) with RFA.

The detailed list of adverse events registered in the included trials is reported in Supplementary Table 3. Most frequent complications were impaired liver function and fatigue.

4. Discussion

Locoregional treatments constitute a valuable treatment option in patients with early HCC, namely those with single nodule <5 cm or up to 3 nodules <3 cm, particularly when not suitable to surgical therapies.

Although percutaneous ethanol injection (PEI) was proved to be as effective as RFA in the case of single nodules <2 cm, the higher recurrence rate observed with PEI fostered the widespread use of RFA even if PEI might represent still an option in nodules located in 'at risk' segments, such as those adjacent to the abdominal wall or to other organs [20].

While microwave ablation (MWA) and laser ablation can be considered as valuable options in unresectable HCC patients, SBRT has been recently developed and tested in an increasing number of studies [21,22].

Whilst HCC is a radiosensitive tumor, the uncertain ability to precisely deliver adequate doses and the consequent risk of developing radiation-induced liver disease (RILD) have limited the use of external body radiation in cirrhotic patients. Moreover, the proximity of other radiosensitive organs such as the stomach and bowel represent additional challenges [22]. SBRT implies several novel advancements in the field, in particular the highly sophisticated treatment planning allowing selectivity of the procedure with the aim to spare the surrounding non-tumoral liver parenchyma, the ability to accurately assess and control for respiratory induced liver motion, CT-based verification of the position of the tumor and adjacent organs thus decreasing the risk of irradiating other organs or remnant hepatic parenchyma [23].

Based on the aforementioned properties, SBRT can deliver much higher doses in fewer treatments, usually over 3 to 5 outpatient sessions [24,25].

There is currently limited evidence on the comparison between SBRT and RFA in unresectable HCC patients; given the recent publication of several series comparing the two techniques, we decided to address this unsolved issue through a meta-analysis of nine studies in order to provide definitive data able to inform the guidelines.

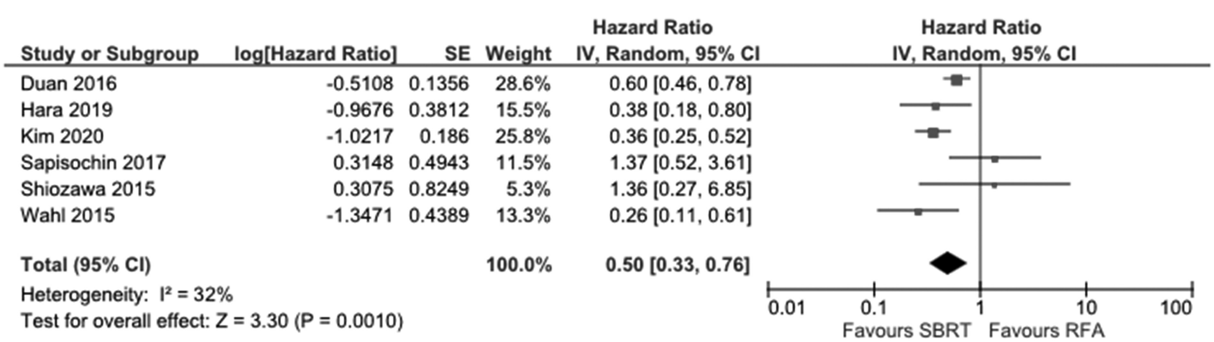

Figure 2. Stereotactic body radiotherapy significantly outperformed radiofrequency ablation in terms of recurrence-free survival (hazard ratio 0.50, 0.33–0.76, p = 0.001), with moderate evidence of heterogeneity (I^2 = 32%).

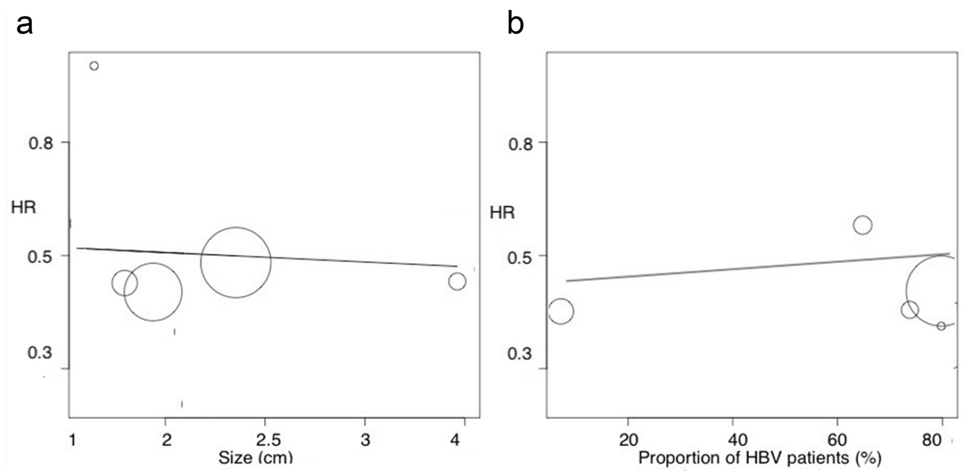

Figure 3. Meta-regression confirmed the lack of correlation between mean nodule size (Figure 3a) and the proportion of HBV patients (Figure 3b) and the hazard ratio for recurrence free survival.

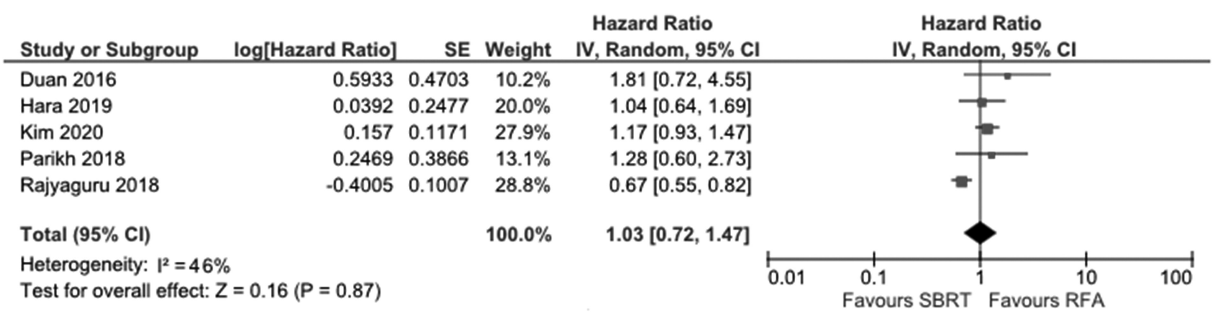

Figure 4. Meta-analysis of pooled hazard ratios for survival showed similar results between stereotactic body radiotherapy and radiofrequency ablation (hazard ratio 1.03, 0.72–1.47; p = 0.87), with moderate evidence of heterogeneity (I^2 = 46%).

We made several key observations. First, SBRT led to a significant improvement in terms of recurrence-free survival, in particular at mid-long term (from 2 years from the treatment onwards). This finding was independent on nodule size and etiology of the underlying liver disease, as confirmed in meta-regression analysis. Second, the aforementioned lower rates of tumor recurrence did not turn to a clear survival benefit given the comparability of the two treatments in terms of overall survival (HR 1.03, 0.72–1.47). Probably, there are several liver-related causes of mortality in cirrhotic patients that could not be taken into account properly in the meta-analysis due to lack of data and this aspect might explain the apparent discrepancy between recurrence and survival findings. Third, the two therapies were equivalent also in terms of severe adverse events and complete response rate, although this finding should be interpreted with caution due to the limited evidence supporting this comparison. The very low evidence supporting the tumor response analysis, based on only three studies and weakened by high heterogeneity, did not enable us to address the apparent discrepancy between the response rate and the recurrence outcomes between the two treatments. However, even in response analysis, SBRT showed a non-significant favorable trend (RR 1.30) and it can be postulated that with a larger sample size and a higher number of studies this finding could be strengthened thus reaching the significance threshold. Unfortunately, current evidence does not allow to draw definitive conclusions in this regard.

Although SBRT led to a significantly increased rate of overall complications, severe adverse events, namely those able to impact on patient outcomes, were similar between the two therapies (OR 1.38, 0.28–6.71). Overall, the rate of severe adverse events was low in the included studies, thus confirming that both the techniques are safe with a low incidence of major complications. Of note, the vast majority of recruited patients were in Child-Pugh stage A or B, which represent the limit within a curative therapy can be offered to HCC patients.

However, it should be noted that four patients treated with SBRT in the study by Hara et al. [11] died due to post-treatment liver failure. This complication may be due to a marginal detrimental effect of SBRT on liver function. In fact, while RFA-induced ablation is limited to the target nodule and to an adequate ablative margin of 5 mm, thus sparing the surrounding liver parenchyma, the focal liver reaction area following SBRT seems to be larger, particularly in patients with severe liver cirrhosis [26]. Therefore, although this seems a rare event, larger numbers of patients and more uniform studies in a prospective manner are needed to properly explore this aspect.

There are some limitations to our study. First, the lack of randomized-controlled trials and the relatively limited number of recruited patients, which did not allow to conduct specific subgroup analyses. However, all of the main outcomes could be analyzed and a rigorous meta-regression was conducted in order to find potential confounders in our analysis. Second, the impact of several variables on final outcomes could not be investigated due to lack of data, for example advanced fibrosis and AFP. Third, the insufficient and uneven follow-up time may have overestimated the clinical outcomes and should be expanded in future studies. However, we performed a further meta-analysis of pooled HRs with the aim to overcome any potential bias related to different follow-up length in the included studies. Furthermore, a different analysis according to the recurrence location (local versus distant) was not feasible due to the lack of data. Fourth, moderate heterogeneity was found in several comparisons, although at least part of this heterogeneity could be explained in sensitivity analysis. Finally, the analysis of the costs was beyond the scope of the manuscript, therefore we cannot make definitive assumptions in this regard.

5. Conclusions

The current meta-analysis shows that SBRT prolongs recurrence-free survival as compared to RFA in HCC patients, although this result does not translate to a significant survival benefit. Further trials reporting long-term outcomes are needed to confirm these findings.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Antonio Facciorusso, Andrea Chierici, Ivan Cincione, Christian Cotsoglou were involved in the conception and design

Antonio Facciorusso and Andrea Chierici were involved in the analysis and interpretation of the data

Antonio Facciorusso and Babu P Mohan were involved in the drafting of the paper

Rodolfo Sacco, Daryl Ramai, Babu P Mohan, Saurabh Chandan, and Andrew Ofosu revised the manuscript critically for intellectual content

All of the authors approved the final version to be published and agree to be accountable for all aspects of the work.

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