Comparison of radiofrequency ablation and ablative external radiotherapy for the treatment of intrahepatic malignancies: A hybrid meta-analysis

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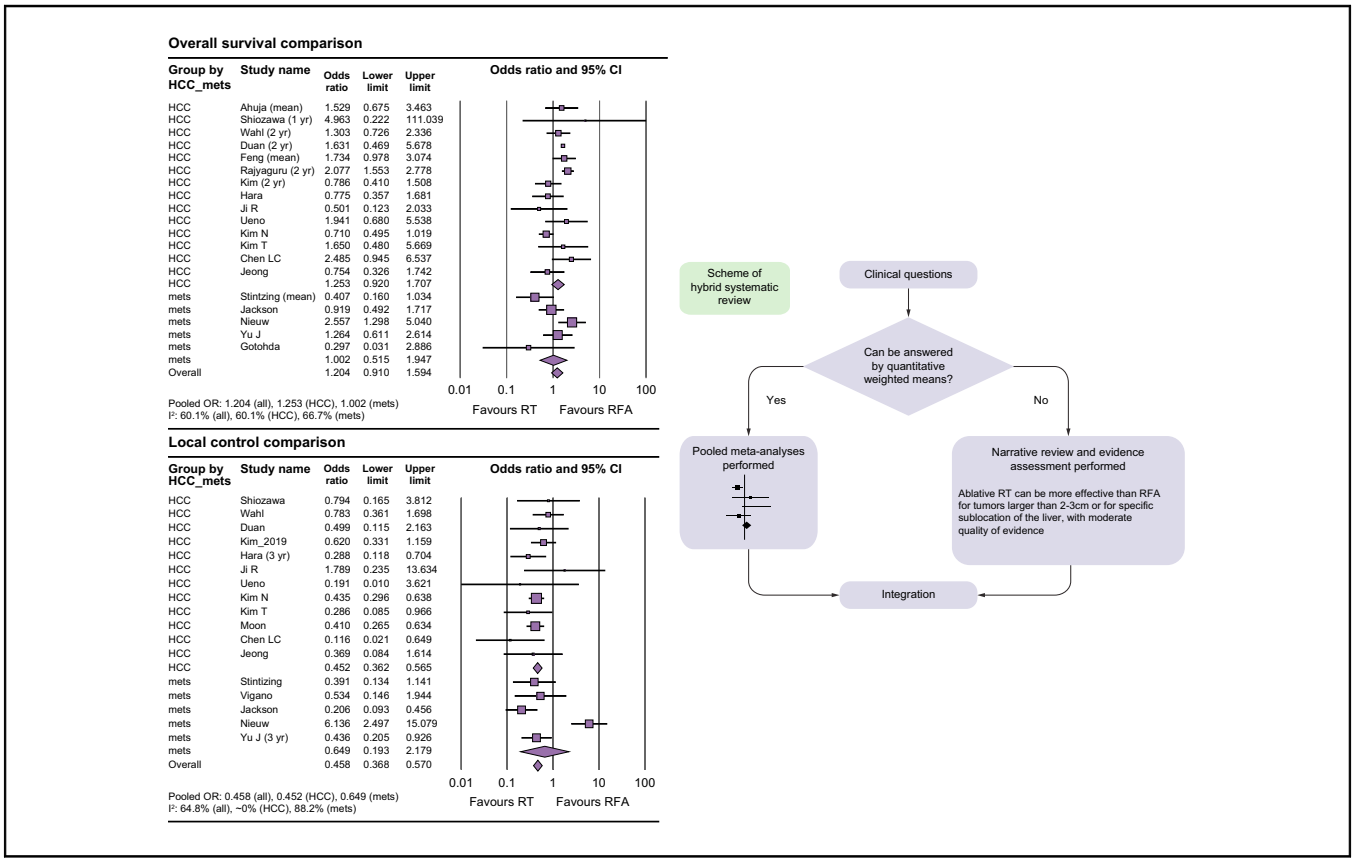
Graphical abstract



Highlights

- RFA is the most widely used non-surgical local modality for the treatment of small intrahepatic malignancies.
- Ablative RT yields a curative effect by focusing high doses on small targets using computerised planning.
- Ablative RT was associated with superior local control and overall survival compared to RFA.
- RT could be more effective than RFA for tumours larger than 2–3 cm or for specific sublocations in the liver.

Impact and implications

Radiofrequency ablation (RFA) and ablative radiotherapy (RT) are non-surgical modalities for the treatment of small intrahepatic malignancies. Ablative RT showed oncologic outcomes at least similar to those of RFA, and was more effective at specific locations (*e.g.* perivascular or subphrenic locations).

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Research article

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Comparison of radiofrequency ablation and ablative external radiotherapy for the treatment of intrahepatic malignancies: A hybrid meta-analysis

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Background & Aims: Radiofrequency ablation (RFA) and ablative external beam radiotherapy (ablative RT) are commonly used to treat small intrahepatic malignancies. We meta-analysed oncologic outcomes and systematically reviewed the clinical consideration of tumour location and size.

Methods: PubMed, Medline, Embase, and Cochrane Library databases were searched on February 24, 2022. Studies comparing RFA and ablative RT, providing one of the endpoints (local control or survival), and encompassing ≥5 patients in each arm were included.

Results: Twenty-one studies involving 4,638 patients were included. Regarding survival, the odds ratio (OR) was 1.204 (p = 0.194, favouring RFA, not statistically significant) among all studies, 1.253 (p = 0.153) among hepatocellular carcinoma (HCC) studies, and 1.002 (p = 0.996) among colorectal cancer metastasis studies. Regarding local control, the OR was 0.458 (p <0.001, favouring ablative RT) among all studies, 0.452 (p <0.001) among HCC studies, favouring the ablative RT arm, and 0.649 (p = 0.484) among colorectal cancer metastasis studies. Pooled 1- and 2-year survival rates for HCC studies were 91.8% and 77.7% after RFA, and 89.0% and 76.0% after ablative RT, respectively; and for metastasis studies were 88.2% and 66.4% after RFA and 82.7% and 60.6% after RT, respectively. Literature analysis suggests that ablative RT can be more effective than RFA for tumours larger than 2–3 cm or for specific sublocations in the liver (*e.g.* subphrenic or perivascular sites), with moderate quality of evidence (reference to the grading system of the American Society for Radiation Oncology Primary Liver Cancer Clinical Guidelines). The pooled grade ≥3 complication rates were 2.9% and 2.8% in the RFA and ablative RT arms, respectively (p = 0.952).

Conclusions: Our study shows that ablative RT can yield oncologic outcomes similar to RFA, and suggests that it can be more effective for the treatment of tumours in locations where RFA is difficult to perform or for large-sized tumours.

Systematic Review Registration: This study was registered with PROSPERO (Protocol No: CRD42022332997).

Impact and implications: Radiofrequency ablation (RFA) and ablative radiotherapy (RT) are non-surgical modalities for the treatment of small intrahepatic malignancies. Ablative RT showed oncologic outcomes at least similar to those of RFA, and was more effective at specific locations (*e.g.* perivascular or subphrenic locations).

Introduction

Surgical resection is the most reliable curative treatment for small-sized, localised hepatic malignancies.[1,2] Compared with surgery, radiofrequency ablation (RFA) is a simpler modality that inflicts less damage to the liver. Therefore, it has been used as a surrogate radical modality for localised liver malignancies.[1–3] However, external beam radiation therapy (EBRT) has gained popularity in the treatment of intrahepatic malignancies, especially with the advent of CT-based computerised planning, which enables precise targeting and normal liver sparing.[4] Recent comparative studies have reported that the local control rate of stereotactic body radiotherapy (SBRT) for intrahepatic malignancies is comparable to that of RFA.[5] To make clinical decisions pertaining to the most suitable treatment modality, consideration of the tumour location and size is necessary. RFA has been most efficient in treating small tumours (<2–3 cm),[6,7] but has difficulty in treating specific sublocations (*e.g.* subphrenic or perivascular sites).[8,9] EBRT is able to deliver a prescribed dose efficiently to relatively large tumours, and can be less affected by locational difficulties.[10] Therefore we have systematically reviewed the literature on clinical considerations of tumour location and size to aid in clinical decision-making; we have also performed a comparative meta-analysis of the

Keywords: Intrahepatic malignancy; Liver cancer; External beam radiation therapy; Radiofrequency ablation.

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oncologic outcomes of RFA and ablative EBRT in the treatment of intrahepatic malignancies.

Materials and methods

Study design

We conducted our systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[11] and also referred to the Cochrane Handbook for methodological aspects. We used patient, intervention, comparison, outcomes (PICO) to frame the main hypothetical question, 'Does ablative radiotherapy (RT) have oncologic outcomes (*e.g.* survival and local control) and toxicity profiles comparable to RFA for the treatment of patients with localised liver malignancies?' We then conducted a systematic review with formal meta-analyses. The auxiliary hypothetical question was 'Is ablative RT more efficient than RFA for the treatment of large-sized (>2–3 cm) liver malignancies present in locations that are difficult to access (*e.g.* perivascular, liver dome)?' A narrative review with evidence grading was performed on the auxiliary question because the criteria for tumour size and difficult locations varied in different studies, and it was necessary to subjectively evaluate the details of the treatment (*i.e.* a hybrid systematic review, Fig. 1). The primary endpoint was local control (LC) and the secondary endpoint was overall survival (OS). Grade ≥3 complications were investigated as the secondary endpoints. This study was registered with PROSPERO (Protocol No: CRD42022332997).

Study inclusion and data collection

Four databases, including PubMed, MEDLINE, Embase, and Cochrane Library, were searched until February 24, 2022. The studies that fulfilled the following inclusion criteria were included: (1) clinical studies comparing RFA and ablative RT for treatment of liver malignancies; (2) data for at least 1 endpoint (LC or OS); and (3) each arm (RFA and ablative RT) should encompass 5 or more patients with hepatocellular carcinoma (HCC) or liver metastases. Studies regarding thermal ablation which include cases of both RFA and microwave ablation (MWA) were also included. The reference lists of the included studies were also checked to identify potentially missing studies. Language restrictions were not applied, and external consultation was performed when language translation was necessary. Conference abstracts were included if they met the inclusion criteria. Multiple studies from a single institution were included if they did not have overlapping patient data. Otherwise, the study was selected using the following criteria prioritised in numerical order: (1) larger sample size; (2) data on more endpoints; and (3) time elapsed since publication. Two independent reviewers searched the literature, and any disagreement was resolved through mutual discussion and re-investigation. Search terms and strategies according to the databases are shown in Supplementary Data 1. We used pre-designed sheets including (1) general information, including author name, publication source, patient recruitment period, affiliation, type of study, and study design and (2) clinical information including number of patients, target patients, follow-up periods, LC rates, overall survival rates, rate and detail of grade ≥3 complications, and differential clinical outcomes according to tumour size and location. OS and LC data were acquired from a descriptive graph in the absence of numerical data.

Quality assessment

According to a preliminary search, the majority of candidate studies were observational studies. We used the Newcastle–Ottawa scale,[12] as recommended in the *Cochrane Handbook for the Assessment of Observational Studies*.[13] A study with a score of 8–9 was evaluated as high quality, that with a score of 6–7 as medium quality, and a study with a score of 5 or less as low quality. As observational studies with a high risk of bias are not recommended for meta-analysis, as referenced by the Cochrane handbook,[14] we excluded low-quality studies from the present systematic review, if the authors agreed.

Effect measures and data synthesis

The main effect measure to assess the primary and secondary endpoints was the pooled odds ratio (OR) of OS and LC rates, in comparison of RFA and SBRT. Considering the possible

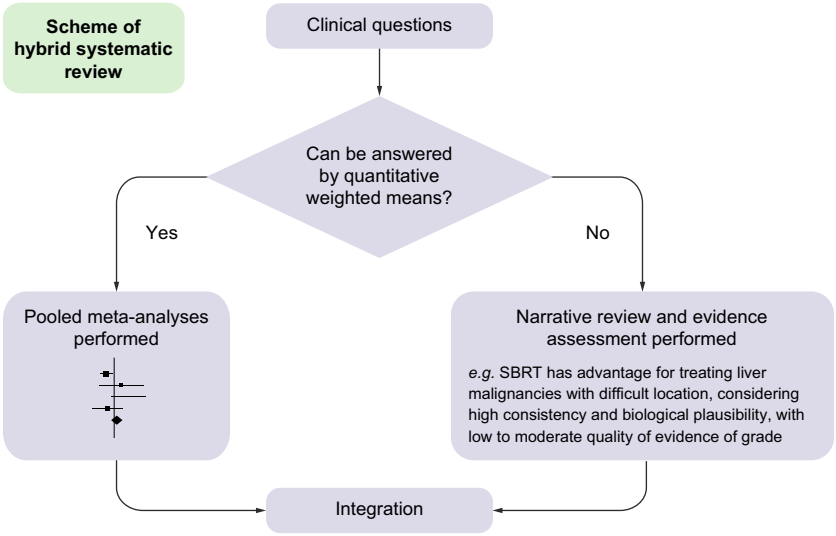

Fig. 1. Flow diagram of a hybrid systematic review. SBRT, stereotactic body radiotherapy.

heterogeneity in response evaluation (*e.g.* complete or partial response), LC was set as an endpoint and acquired either reported LC rate or non-local failure rate. Pooled analyses of OS were weighted using the number of patients, and those of LC were based on the patient or tumour number as reported by individual studies. The pooled percentiles of LC and OS were also calculated for clinical reference. Regarding complications, the pooled percentile rate of grade ≥3 complications was calculated and subjectively reviewed. Because the vast majority of candidate studies were observational studies from different institutions, there would be a possible heterogeneity with regard to treatment detail and clinical characteristics; thus, a random-effects model was used for the pooled analysis of the endpoints, in accordance with the Cochrane handbook.[14]

Subgroup analyses were also performed for comparability. The studies were regarded as having reliable comparability if they were randomised studies, performed intentional statistical matching (*e.g.* propensity scoring matching, inverse-probability weighting), or reported no significant difference regarding known clinical factors (including but not limited to age, tumour size, Child–Pugh class, and tumour location). Studies without available comparative information or those with SBRT arms having inferior clinical profiles (*e.g.* p <0.05, or >20% difference) were regarded as not having reliable comparability. The stepwise-hierarchical pooled analysis by Shin *et al.*[15] was referred to for the stepwise analysis methods and interpretation of the subject owing to scarce randomised literature. Subgroup analyses were also performed according to the disease, including HCC and colorectal cancer (CRC) with liver metastases.

We performed the Cochran Q test[16] and I^2 statistics[17] to assess heterogeneity in the pooled analyses, and I^2 values of 25%, 50%, and 75% were regarded as low, moderate, and high heterogeneity, respectively. Publication bias assessments for pooled analyses involving >10 studies were performed using a visual funnel plot assessment and quantitative Egger's test.[18] Possible publication bias was considered to exist if the funnel plots showed asymmetry and the 2-tailed p value was <0.1 in the Egger's test. Duval and Tweedie's trim-and-fill method[19] was used for analyses with possible publication bias to yield the adjusted reference values. All statistical analyses were performed using the Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA).

The advantages of a specific modality according to tumour location and size were assessed with reference to the grading system outlined in the liver cancer practice guidelines of the American Society of Radiation Oncology (ASTRO).[20] The evidence grading system is summarised in Table S1.

Results

Study selection and characteristics

A total of 1,438 studies were initially searched. Those duplicated among databases and having irrelevant formats (*e.g.* reviews, letters, conference abstracts, editorials, case reports, trial protocols, and lab studies) were machine-filtered. Eventually, 544 studies were screened using the abstracts and citations. After excluding 500 articles for various reasons, 44 studies underwent full-text review, and 21 studies involving 4638 patients (RFA 2807, ablative RT 1831) that met all inclusion criteria were finally included.[21–41] The inclusion process is illustrated in Fig. 2.

Among the 21 studies, 16 had full text and 5 were conference abstracts. Fourteen studies involved patients with HCC, and 7 studies involved patients with CRC and liver metastases. With regard to radiation modalities, 18 studies investigated the results of SBRT, 2 of CyberKnife®, and 1 of proton therapy. The majority (17 of 21) were observational studies that were retrospectively designed, 2 were studies based on the US National Cancer Database, and there was 1 prospective observational study and 1 randomised study. General information regarding these studies is summarised in Table 1.

Among HCC studies, the median 2-year OS rates were 78.5% (range: 52.9–92.9) in the RFA arm and 77.6% (range: 46.3–90.2) in the ablative RT arm; the median 2-year LC rates were 84.5% (63.8–94.7) in the RFA arm and 91.7% (74.9–100) in the ablative RT arm. Regarding CRC studies, the median 2-year OS rates were 64.3% (50.2–80) in the RFA arm and 65.4% (52.3–80) in the ablative RT arm; the median 2-year LC rates were 60.8% (56.4–93.3) in the RFA arm and 77.0% (71.5–88.2) in the ablative RT arm. Regarding comparability analysis methods, 9 studies used intentional patient-matching methods (*e.g.* propensity score matching; inverse probability of weighting). Eight studies performed statistical comparisons; 6 of them showed that the ablative RT arm had inferior clinical factors (*e.g.* p <0.05, or >20% numeral difference), and 2 of them reported no statistically significant difference between the RT and the RFA arms regarding clinical factors. Clinical factors included, but were not limited to, age, Child–Pugh score, tumour size, and difficult location to be treated. Three studies did not provide relevant information. One study performed a randomised allocation. Table S2 provides information regarding the clinical characteristics of the included studies.

Quality and bias assessments

According to the Newcastle–Ottawa scale, 10 of the 21 studies were regarded as having high quality (8–9 points) and 8 studies had medium quality (6 or 7 points). None of the studies were assessed as having low quality. Therefore, all studies that fulfilled the inclusion criteria were included in the present systematic review. Details of scoring and the reasons according to each scoring category are shown in Table S3.

Synthesis of clinical endpoints

With regard to OS, the OR was 1.204 (95% CI: 0.910–1.594, p = 0.194) among all studies, 1.253 (95% CI: 0.920–1.707, p = 0.153) among HCC studies, and 1.002 (95% CI: 0.515–1.947, p = 0.996) among CRC metastases studies. Among studies with reliable comparability, the OR was 1.149 (95% CI: 0.821–1.610, p = 0.417) for all studies, 1.201 (95% CI: 0.844–1.710, p = 0.309) among HCC studies, and 0.746 (95% CI: 0.247–2.258, p = 0.64) among CRC metastases studies. These results are summarised in Table 2 and are shown in Fig. 3 as forest plots. With regard to LC, the OR was 0.458 (95% CI: 0.368–0.570, p <0.001) among all studies and 0.452 (95% CI: 0.362–0.565, p <0.001) among HCC studies, favouring the ablative RT arm, and 0.649 (95% CI: 0.193–2.179, p = 0.484) among CRC metastasis studies. Among studies with reliable comparability (*e.g.* randomised studies, studies performed with intentional statistical matching, no significant differences in known clinical factors), the OR was 0.466 (95% CI: 0.357–0.609, p <0.001) among all studies, 0.421 (95% CI: 0.227–0.779, p <0.001) among HCC studies, and 0.459 (95% CI: 0.359–0.586, p = 0.006) among CRC metastases studies, all favouring the ablative RT arm.

Pooled analyses of the LC percentile included all studies, and pooled analyses of the OS percentile included HCC and CRC metastasis studies separately. Among HCC studies, the pooled 1-,

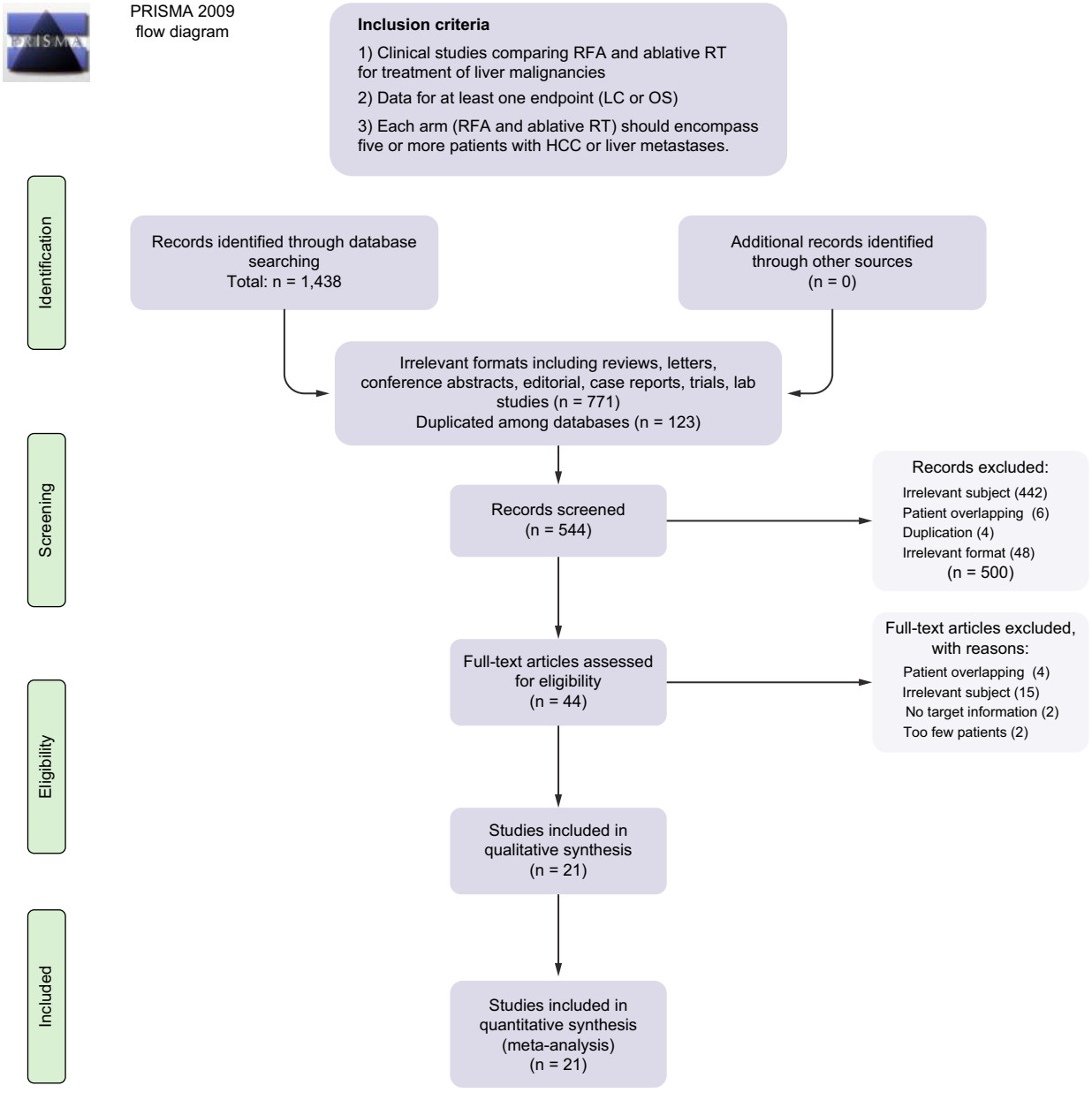

Fig. 2. Study inclusion plot. HCC, hepatocellular carcinoma; LC, local control; OS, overall survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RFA, radiofrequency ablation; RT, radiotherapy.

2-, and 3-year OS rates were 91.8% (95% CI: 87.2–94.9), 77.7% (70.7–83.4), and 76.0% (64.4–84.7) in the RFA arm, respectively; the corresponding rates for the ablative RT arm were 89.0% (95% CI: 83.6–92.7), 76.0% (64.4–84.7), and 65.9% (53.7–76.3), respectively. Among CRC metastases studies, pooled 1-, 2-, and 3-year OS rates were 88.2% (95% CI: 77.9–94.0), 66.4% (50.9–79.0), and 52.1% (41.1–62.8) in RFA arm; the corresponding rates for the ablative RT arm were 82.7% (95% CI: 61.6–93.4), 60.6% (50.7–69.6), and 43.6% (26.6–62.1), respectively. Pooled 1-, 2-, and 3-year LC percentile rates were 82.3% (95% CI: 77.2–86.4), 80.1% (72.7–85.8), and 92.4% (89.2–94.7) in RFA arms, and 92.4% (95% CI: 89.2–94.7), 86.5% (81.7–90.2), 83.9% (77.7–88.7) in ablative RT arms, respectively.

Pooled results of OS and LC percentiles are summarised in Table 3.

Heterogeneity analyses and publication bias assessment

Heterogeneity in the pooled analyses of LC was moderate to high (I^2=64.8%), very low (I^2=~0%), and high (I^2=88.2%), including all studies, HCC studies, and CRC metastases studies. In the subgroup analyses, including studies with reliable comparability, heterogeneity was very low in pooled analyses of all HCC and CRC metastasis studies. With regard to OS, heterogeneity was moderate to high in all pooled analyses (Table 2). No publication bias was identified in the pooled analyses of local control (p = 0.824) and overall survival (p = 0.468). The funnel plots are shown in Fig. S1.

Table 1. General information of included studies.

Author	Year of publication	Years of patients recruit	Affiliation	Country	Study type	Source	No. of patients	Study design	Subject of study
Ahuja	2014		Louisiana State Univ.	US	Conference abstract	CIRSE	TACE and RFA 32 TACE and SBRT 32	R	HCC
Shiozawa	2015	2011–2014	Toho Univ.	Japan	Full article	World J Gastroenterol	RFA 38, CyberKnife 35 (all solitary tumour)	R	HCC
Wahl	2016	2004–2012	Univ. of Michigan	US	Full article	J Clin Oncol	RFA 161, SBRT 63 (tumours: RFA 249, SBRT 83)	P	HCC
Duan	2016	2011–2012	Beijing 302 hospital	China	Conference abstract	Hepatol	RFA 40, SBRT 37	R	HCC
Feng	2016	2004–2011	Univ. of Michigan	US	Conference abstract	ASCO	RFA 78, SBRT 78 (after PSM)	NCDB	HCC
Rajyaguru	2018	2004–2013	Gundersen Health System	US	Full article	J Clin Oncol	RFA 521, SBRT 296 (after PSM)	NCDB	HCC
Kim	2019	2012–2016	Yonsei Cancer Center	Korea	Full article	Radiother Oncol	RFA 95, SBRT 95 (after PSM) (tumour n = patient n)	R	HCC
Hara	2019	2012–2016	Yokohama City Univ., Ofuno Chao Univ.	Japan	Full article	Hepatology	RFA 106, SBRT-HFRT 106 (after PSM)	R	HCC
Ji R	2022	2008–2021	Univ. of Hong Kong	HK SAR, China	Full article	Medicine	RFA 38 SBRT 22	R	HCC
Ueno	2021	2014–2019	Kurashiki Central Hospital	Japan	Full article	J Gastrointestinal Oncol	RFA 62 SBRT 31 (after PSM)	R	HCC
Kim N	2020	2010–2016	East Asian Multicentres	China, Japan, HK SAR, Taiwan, and Korea	Full article	J Hepatol	RFA 313 SBRT 313 (after PSM)	R	HCC
Kim T	2021	2013–2017	National Cancer Center	Korea	Full article	J Hepatol	RFA 56 PBT 80	RCT	HCC
Moon	2019	2006–2018	Multicentres of US	US	Conference abstract	AASLD	RFA 529 (include 123 MWA) SBRT 387 lesions	R	HCC
Chen LC	2019	2014–2017	Dalin Tzu Chi Hosp.	Taiwan	Conference abstract	ASTRO	RFA 84 SBRT 24	R	HCC
Stintzing	2013	2005–2011	Comprehensive Cancer Centre	Germany	Full article	Acta Oncol	RFA 30, CyberKnife 30 (tumours: RFA 35, CyberKnife 35)	R	CRC liver mets
Viganò	2018	2004–2013	Humanitas Univ.	Italy	Full article	World J Surg	RFA 19, SBRT 14	R	CRC liver only mets
Jackson	2018	2000–2015	Univ. of Michigan	US	Full article	Int J Radiat Oncol Biol Phys	RFA 69, SBRT 92	R	CRC and other liver mets
Nieuwenhuizen S	2021	from 2007	Amsterdam registry	Netherland	Full article	Cancers	RFA 144 (include 81 MWA) SBRT 55	R	CRC liver mets
Jeong	2021	2013	Asan hospital	Korea	Full article	J Gastroenterol Hepatol	RFA 172 SBRT 87 (after IPTW)	R	CRC liver mets
Yu J	2021	2007–2014	Asan hospital	Korea	Full article	Cancer Res Treat	RFA 178 SBRT 44 (after IPTW)	R	CRC liver mets
Gotohda	2020	2010–2016	Seven centres from Japan	Japan	Full article	JGH open	RFA 42 SBRT 5	R	CRC liver mets

ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; CIRSE, cardiovascular and interventional radiological society of Europe; HCC, hepatocellular carcinoma; LT, liver transplantation; NCDB, national cancer database; P, prospective; R, retrospective; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolisation.

Complications

Thirteen studies provided comparative complication data.[22,23,28,29,31–35,38–40,42] The Common Terminology Criteria for Adverse Events by the National Cancer Institute of the US was used in most studies except the study by Ji *et al.*[32] of which used the Clavien–Dindo classification. Pooled grade ≥3 complication rates were 2.9% (95% CI: 1.4–6.1) and 2.8% (1.6–4.9) in the RFA and ablative RT arms, respectively (p = 0.952 for difference). The vast majority of complications in RFA arms were as a result of mechanical damage from the procedures (*e.g.* bleeding, perforation, and pneumothorax). Among 20 grade ≥3 complication events from the ablative RT arms of 13 studies, 55% were hepatic damage (*e.g.* ascites, biliary stricture, liver function worsening), whereas 45% were gastrointestinal damage (*e.g.* bleeding or ulcer). Table 4 summarises the reported complications.

Evidence grading review considering tumour location

Seven studies reported treatment efficacy related to tumour location in comparison with the 2 arms. Among them, 2 studies[28,39]

Table 2. Pooled rate of odds ratio regarding local control and survival.

Studies (subject)	No. of studies	No. of cases	Heterogeneity p	I^2 (%)	Heterogeneity assessment	OR (95% CI)	RFA *vs.* SBRT (*p* value)
All studies (local control)							
All	17	3,670	<0.001	64.8	Moderate to high	0.458 (0.368-0.570)	<0.001
HCC	11	2,974	0.555	~0	Very low	0.452 (0.362-0.565)	<0.001
CRC mets	6	696	<0.001	88.2	High	0.649 (0.193-2.179)	0.484
Studies with reliable comparability (local control)							
All	10	2,109	0.838	~0	Very low	0.466 (0.357-0.609)	<0.001
HCC	8	1,817	0.68	~0	Very low	0.421 (0.227-0.779)	<0.001
CRC mets	2	292	0.87	~0	Very low	0.459 (0.359-0.586)	0.006
All studies (overall survival)							
All	19	3,504	<0.001	60.10%	Moderate to high	1.204 (0.910-1.594)	0.194
HCC	14	2,875	0.002	60.1	Moderate to high	1.253 (0.920-1.707)	0.153
CRC mets	5	629	0.017	66.7	Moderate to high	1.002 (0.515-1.947)	0.996
Studies with reliable comparability (overall survival)							
All	12	2,856	<0.001	67.5	Moderate to high	1.149 (0.821-1.610)	0.417
HCC	10	2,634	0.001	68.1	Moderate to high	1.201 (0.844-1.710)	0.309
CRC mets	2	222	0.06	71.7	Moderate to high	0.746 (0.247-2.258)	0.604

CRC, colorectal cancer; HCC, hepatocellular carcinoma; LC, local control; OR, odds ratio; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

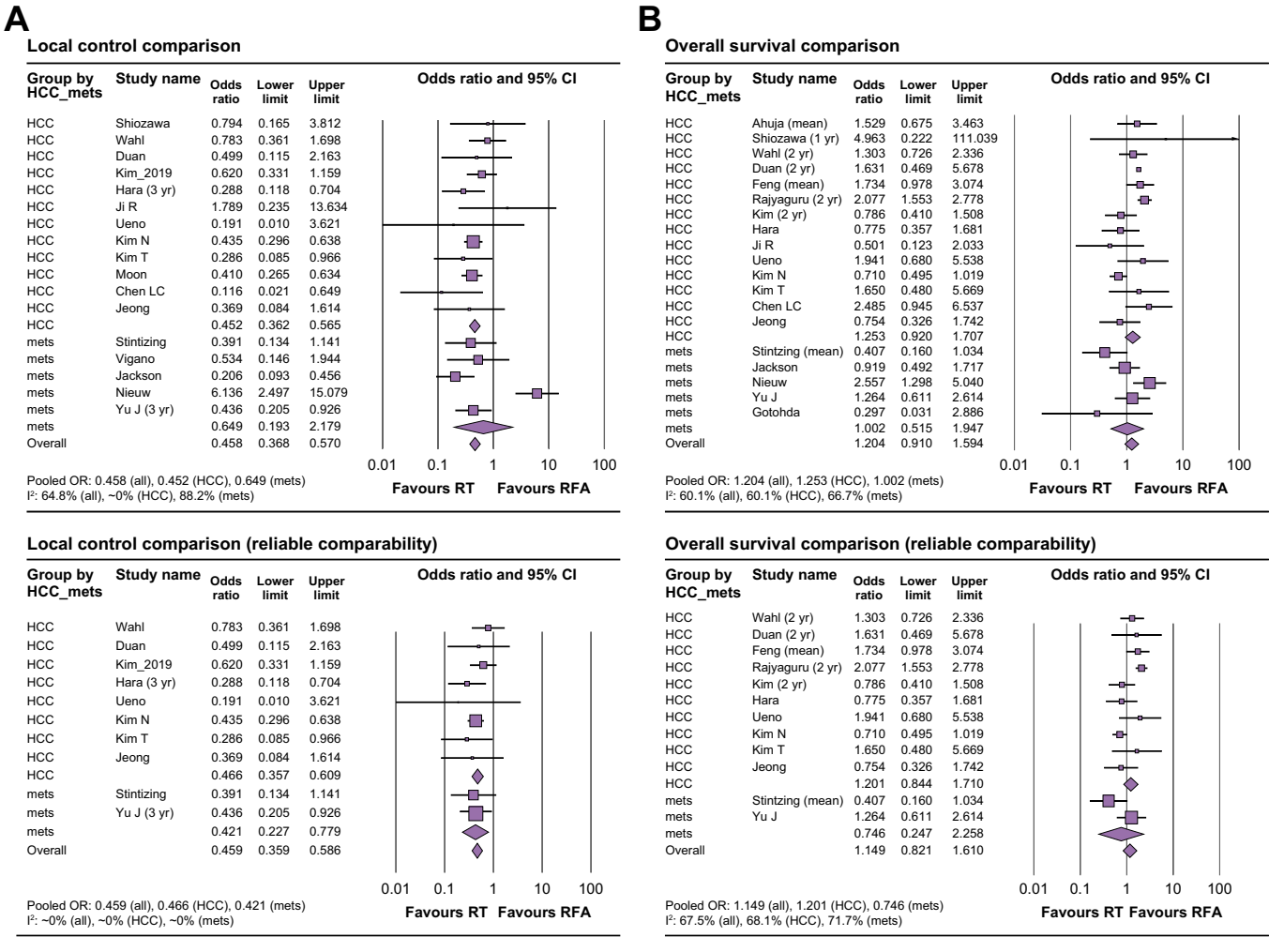

Fig. 3. Forest plots of local control and overall survival. (A) local control comparison of all included studies (upper) and of studies with reliable comparability (lower); (B) overall survival comparison of all included studies (upper) and of studies with reliable comparability (lower). HCC, hepatocellular carcinoma; OR, odds ratio; RFA, radiofrequency ablation; RT, radiotherapy.

Table 3. Pooled percentile of clinical endpoints.

Subject Modality	No. of cohorts	No. of cases	Effect size % (95% CI)	RFA *vs.* ablative RT (*p* value)	Heterogeneity p	I^2(%)
One-year LC rate (HCC and CRC mets)						
All	32	3,687	87.2 (84.2–89.7)		<0.001	83.3
RFA	16	2,172	82.3 (77.2–86.4)		<0.001	80.0
RT	16	1,515	92.4 (89.2–94.7)	<0.001	<0.001	63.9
Two-year LC rate						
All	28	2,549	84 (80.0–87.3)		<0.001	84.8
RFA	14	1,464	80.1 (72.7–85.8)		<0.001	88.2
RT	14	1,084	86.5 (81.7–90.2)	0.094	<0.001	66.4
Three-year LC rate						
All	26	2,809	79.6 (74.9–83.6)		<0.001	87.4
RFA	13	1,649	75.7 (68.6–81.7)		<0.001	88.7
RT	13	1,160	83.9 (77.7–88.7)	0.062	<0.001	80.4
One-year OS (HCC)						
All	24	2,875	90.3 (87.0–92.9)		<0.001	81.8
RFA	12	1,686	91.8 (87.2–94.9)		<0.001	85.6
RT	12	1,189	89.0 (83.6–92.7)	0.333	<0.001	79.7
Two-year OS (HCC)						
All	22	2,802	77.2 (71.4–82.2)		<0.001	90.6
RFA	11	1,648	77.7 (70.7–83.4)		<0.001	88.2
RT	11	1,154	76.0 (64.4–84.7)	0.775	<0.001	92.7
Three-year OS (HCC)						
All	18	2,518	67.5 (60.3–74.0)		<0.001	91.1
RFA	9	1,449	68.5 (59.3–76.5)		<0.001	90.7
RT	9	1,069	65.9 (53.7–76.3)	0.718	<0.001	92.4
One-year OS (CRC mets)						
All	8	629	86.6 (77.7–92.3)		<0.001	86.0
RFA	4	433	88.2 (77.9–94.0)		0.001	81.8
RT	4	196	82.7 (61.6–93.4)	0.507	0.001	81.1
Two-year OS (CRC mets)						
All	8	629	62.2 (54.0–69.8)		<0.001	80.8
RFA	4	433	66.4 (50.9–79.0)		<0.001	88.2
RT	4	196	60.6 (50.7–69.6)	0.517	0.195	36.3
Three-year OS (CRC mets)						
All	8	629	49.9 (40.5–59.3)		<0.001	83.7
RFA	4	433	52.1 (41.1–62.8)		0.003	78.5
RT	4	196	43.6 (26.6–62.1)	0.444	0.002	79.5
Grade ≥3 complication						
All	26	4,698	2.9 (1.9–4.4)		<0.001	72.5
RFA	13	3,415	2.9 (1.4–6.1)		<0.001	73.0
RT	13	1,283	2.8 (1.6–4.9)	0.952	<0.001	73.2

CRC, colorectal cancer; HCC, hepatocellular carcinoma; LC, local control; OS, overall survival; RFA, radiofrequency ablation; RT, radiotherapy.

reported that difficult location was a factor affecting inferior LC in RFA arms, whereas it was not a factor in ablative RT arms. Kim *et al.*[34] reported that SBRT showed better LC in the treatment of subphrenic and segment 8 tumours. Two studies[40,42] reported that LC was higher in the SBRT arm, although the SBRT arm included more tumours in difficult locations. Two studies[32,33] reported that although the majority of the SBRT arm included tumours in difficult locations, as different from the RFA arm, LC was higher or non-inferior. To summarise, all the above studies[28,32–34,39,40,42] consistently reported that SBRT could be more effective in the treatment of tumours in difficult locations, and 4 studies[33,34,40,42] reported better LC with SBRT (Table 5) than with RFA. This corresponds to a moderate quality of evidence based on the grading system proposed by ASTRO (Table S1).

Evidence grading review considering tumour size

Eleven studies reported treatment efficacy related to size consideration in the 2 arms. In 4 studies, LC did not differ between the arms in the treatment of tumours <2 cm in size, but SBRT was preferred with regard to LC in the treatment of tumours >2 cm in size.[23,28,31,40] Two studies reported that tumour size >3 cm was related to inferior LC in RFA arm but not in the SBRT arm.[34,38] Four studies included only patients with tumours ≤3 cm in size, and 2 of them reported no difference between the arms, while the other 2 reported better LC rates in SBRT arms.[33,35,39,42] Moon *et al.*[36] showed that the 1-year LC rates were 87% *vs.* 93.4% for tumours ≤2 cm and 71.4% *vs.* 84.8% for tumours >2 cm (RFA *vs.* SBRT). In summary, 5 studies[23,28,31,36,40] consistently suggested more efficient LC of SBRT compared with RFA for larger tumours (>2–3 cm), and 9 studies[23,28,31,34–36,38,40,42] consistently suggested at least non-inferior LC of SBRT compared with RFA for smaller tumours (<2–3 cm) (Table 5). This corresponds to a moderate quality of evidence in the grading system judging the literature on HCC by ASTRO (Table S1).

Discussion

Brief review of literature

According to a recent meta-analysis, the survival outcomes of RFA were comparable to that of surgical resection among HCC patients within the Milan criteria.[43] For liver metastases, RFA has been used in the treatment of patients with adverse clinical conditions as a lesser invasive surrogate with fewer complications.[3] Regarding EBRT, the ablative role by precisely targeting and delivering a high dose of external radiation to localised lesions has emerged. SBRT, which delivers a high-dose of X-ray beams (70–100 Gy in equivalent dose, 2 Gy per fraction scheme

Table 4. Complications according to treatment modalities.

Author	Source	Subject of study	No. of patients (no. of tumours)	Complications of grade ≥3
Shiozawa, 2015	World J Gastroenterol	HCC	RFA 38, CyberKnife 35	No late adverse effect in RFA 11.4% (4 cases of ascites, 2 of them liver-related death) in SBRT 1-yr CP score in SBRT higher than RFA group (p = 0.003)
Wahl, 2016	J Clin Oncol	HCC	RFA 161, SBRT 63	≥G3 complication: RFA 11% *vs.* SBRT 5%. (p = 0.31) 2 G5 bleeding in RFA arms
Kim, 2019	Radiother Oncol	HCC	RFA 668, SBRT 105 (before PSM)	3.7% in RFA group had grade 3 or 4 toxicities no G ≥3 toxicity in SBRT arm, however RILD in 7 cases (6.7%)
Hara, 2019	Hepatology	HCC	RFA 231, SBRT-HFRT 143 (before PSM)	One G5 peritonitis and 1 G5 gastric haemorrhage in RFA
Ji R, 2022	Medicine	HCC	RFA 38 SBRT 22	No severe (Clavien–Dindo ≥III) complication in both arms
Ueno, 2021	J Gastrointestinal Oncol	HCC	RFA 62 SBRT 31 (after PSM)	No serious complication noted in both arms
Kim N, 2020	J Hepatol	HCC	RFA 1568 SBRT 496 (before PSM)	No difference in grade 3–4 toxicity (2.6% *vs.* 1.6%, p = 0.268) CP score change of >2 points was higher in SBRT arm at 3 months (4.7 *vs.* 11.2%, p <0.001) but restored at 6 months (8.1% *vs.* 6.3%, p = 0.278)
Kim T, 2021	J Hepatol	HCC	RFA 56 PBT 80	G3 LFT increase (14.3%) and G3 bleeding (1.8%) in RFA arm No grade 3/4 Cx in PBT arm
Jeong, 2021	HCC	HCC	RFA 172 SBRT 87 (after IPTW)	G4 haemorrhage in RFA arm (0.6%); G3 biliary stricture in SBRT arm (1.1%)
Stintzing, 2013	Acta Oncol	CRC liver mets	RFA 30, CyberKnife 30	No ≥G3 complication in both arms
Jackson, 2018	Int J Radiat Oncol Biol Phys	CRC and other liver mets	RFA 69, SBRT 92	≥G3 complication: RFA 4.3% *vs.* SBRT 4.3% (p = ns)
Nieuwenhuizen, 2021	Cancers	CRC liver mets	RFA 144, SBRT 55	6.3% in RFA arm (all procedure related damage) *vs.* 0 cases
Yu J, 2021	Cancer Res Treat	CRC liver mets	RFA 178, SBRT 44 (after IPTW)	No G3 or higher complication in both arms

CP, Child-Pugh; CRC, colorectal cancer; HCC, hepatocellular carcinoma; HFRT, hypofractionated radiotherapy; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LFT, liver function test; LT, liver transplantation; PSM, propensity score matching; RFA, radiofrequency ablation; RILD, radiation-induced liver disease; SBRT, stereotactic body radiotherapy.

[EQD2]) within 1–2 weeks, and precise radiotherapy which delivers particle beams at doses within the ablative range, have both yielded local control comparable to that of other ablative modalities.[5,35,44] As 2 modalities have overlapping roles in treating localised intrahepatic malignancies, several researchers reported comparative oncologic outcomes.[5,10] Notably, Kim *et al.*[35] reported non-inferior local control in the treatment of small HCCs by delivery of proton beam therapy in ablative doses (91.3 Gy in EQD2) in a phase III randomised study. Certain studies based on a national database reported that RFA yields favourable survival outcomes compared with those of SBRT[26]; whereas no significant difference was noted in studies with matched cohorts.[23,34] RFA is most efficient in treating tumours <2 cm in size[6,7]; however, it is less efficient in the treatment of tumours larger than 2–3 cm or for specific sublocation of the liver (*e.g.* subphrenic or perivascular sites), and may even pose a risk of complications.[8,9] EBRT is less affected by the location of the tumour, and it is possible to deliver a sufficient radiation dose covering tumours >2–3 cm with clinical margins.[10] Several investigators reported that SBRT showed higher local control when treating tumours >2–3 cm in matched cohort studies, and can be advantageous for treating tumours in difficult locations.[34,40,42]

Local control and survival

Our study reported that ablative RT has a better efficacy with regard to LC than RFA. Comparative OR was significant in the pooled analyses of all studies (OR: 0.458, p <0.001) and HCC studies (OR: 0.452, p <0.001). Similarly, the comparative OR was significant in the pooled analyses of all studies (OR: 0.466, p <0.001), HCC studies (OR: 0.421, p <0.001), and CRC metastasis studies (OR: 0.459, p = 0.006) with very low heterogeneity (I^2: ∼0% in all above analyses), among studies with reliable comparability. Although not as rigid as the pooled analysis of randomised controlled trials, the pooled results of studies with reliable comparability have very low heterogeneity and are consistently valid, increasing the reliability of hypothesis testing.[15] Although both RFA and ablative RT confer a high LC probability for small intrahepatic malignancies, RFA might yield suboptimal LC for tumours near major vessels or the diaphragm, or those exceeding 2–3 cm in size.[9,45–47] However, ablative RT is less limited by tumour location because it does not cause mechanical damage and can provide a prescribed dose within a relatively wide range.[10,48] In clinical practice, ablative RT is considered less preferred than RFA and is applied more often in recurrent settings.[23,33,37,39] In some studies, patients who underwent ablative RT had less favourable clinical parameters than those who underwent RFA.[22,31,32,36–38] Considering the above, we assume that the difference in LC between modalities was a result of the characteristics of the modalities rather than clinical differences.

Controversy has existed on the effect on survival, of selection between RFA and ablative RT. A study based on a national database reported favourable OS in the RFA arm.[26] However, it had a limitation – the data of liver fibrosis were missing in nearly 70% of patients; furthermore, many of the factors used for propensity

Table 5. Complications and size considerations in treatment efficacy.

Author	Subject of study	No. of patients (no. of tumours)	Consideration of size in treatment efficacy
Wahl, 2016	HCC	RFA 161, SBRT 63 (tumours: RFA 249, SBRT 83)	Favouring SBRT with tumours > 2 cm (HR 3.35, $p = 0.025$), no difference in LC with tumours <2 cm (HR 2.50, $p = 0.15$)
Kim, 2019	HCC	RFA 668, SBRT 105	Favouring SBRT with tumours > 2 cm (HR 2.18, $p = 0.012$), no difference in LC with tumours ≤2 cm (HR 2.25, $p = 0.061$) (before PSM)
Jackson, 2018	CRC and other liver mets	RFA 69, SBRT 92 (tumours: RFA 122, SBRT: 170)	Favouring SBRT with tumours > 2 cm (HR 3.54, $p < 0.01$), no difference in LC with tumours <2 cm (HR 2.18, $p = 0.4$)
Yu J, 2021	CRC liver mets	RFA 178 SBRT 44	Favouring SBRT with tumours > 2 cm (HR 0.153, $p < 0.001$), no difference in LC with tumours <2 cm (HR 0.648, $p = 0.1$) (IPTW cohort)
Kim N, 2020	HCC	RFA 1568 SBRT 496	>3 cm size related to inferior LC with RFA (HR 1.26, $p = 0.030$) of which was not related with SBRT (HR 1.01, $p = 0.960$) (before PSM)
Nieuwenhuizen, 2021	CRC liver mets	RFA 144 SBRT 55	>3 cm size related to inferior LC with RFA ($p < 0.001$) of which was not related with SBRT ($p = 0.361$)
Kim T, 2021	HCC	RFA 56 PBT 80	All ≤3 cm in size LC 83.9/77.6% *vs.* 94.8/88.3% (RFA *vs.* SBRT) at 2/3 years ($p = 0.123$)
Hara, 2019	HCC	RFA 106 SBRT-HFRT 106	All ≤3 cm in size LC: 79.8% *vs.* 93.2% (RFA *vs.* SBRT) at 3 years ($p < 0.01$) (PSM cohort)
Ueno, 2021	HCC	RFA 62 SBRT 31	All ≤3 cm in size LC 93/87% *vs.* 100/100% (RFA *vs.* SBRT) at 2/3 years ($p = 0.024$) (PSM cohort)
Jeong, 2021	HCC	RFA 172 SBRT 87	All ≤3 cm in size LC 90.6% *vs.* 96.3% (RFA *vs.* SBRT) at 4 years ($p = 0.167$) (IPTW cohort)
Moon, 2019	HCC	RFA 529 SBRT 387 lesions	For ≤2 cm tumours, 1-year LC was 87 *vs.* 93.4%; for >2 cm tumours, 1-year LC was 71.4 *vs.* 84.8% (RFA *vs.* SBRT)
			Location consideration in treatment efficacy
Kim, 2019	HCC	RFA 668, SBRT 105	Subphrenic location related to inferior LC with RFA (HR 1.53, $p = 0.003$), which was not related with SBRT (HR 1.00, $p = 0.996$) (before PSM)
Jeong, 2021	HCC	RFA 172 SBRT 87	Perivascular location related to inferior LC with RFA (4-year LC: 72% *vs.* 97%, <0.001), which was not related with SBRT (4-year LC: 94.7% *vs.* 95.5%, $p = 0.872$) (IPTW cohort)
Kim N, 2020	HCC	RFA 1568 SBRT 496	Favouring SBRT with subphrenic tumours (2-year LC 77% *vs.* 84.7%, $p = 0.005$ Favouring SBRT with segment 8 tumours (2-year LC 77.4% *vs.* 85.5% $p = 0.014$) (before PSM)
Hara, 2019	HCC	RFA 106 SBRT-HFRT 106	More tumours in difficult location (attaching organs) in SBRT arm (42% *vs.* 100%) LC: 79.8% *vs.* 93.2% (RFA *vs.* SBRT) at 3 years ($p < 0.01$) (PSM cohorts)
Yu J, 2021	CRC liver mets	RFA 178 SBRT 44	More tumours in difficult location in SBRT arm (60.7% *vs.* 90.9%, $p = 0.001$) LC 58% *vs.* 76% (RFA *vs.* SBRT) at 3 years (IPTW cohort)
Ueno, 2021	HCC	RFA 62 SBRT 31	Vast majority of SBRT arm had difficult location compared with few difficult locations in RFA arm ($p < 0.001$) Cumulative LC 90.3 *vs.* 100% (RFA *vs.* SBRT) ($p = 0.024$) (PSM cohort)
Ji R, 2022	HCC	RFA 38 SBRT 22	Majority in SBRT arm had difficult locations whereas there were no difficult locations for patients in RFA arm LC (overall): 94.7 *vs.* 90.6 ($p = 0.566$)

CRC, colorectal cancer; HCC, hepatocellular carcinoma; HFRT, hypofractionated radiotherapy; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LC, local control; PBT, proton beam therapy; PSM, propensity score matching; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

matching were social but not clinical factors (*e.g.* race, location of treatment facility, etc.). In a randomised study by Kim *et al.*,[35] no difference in OS was reported between ablative proton therapy and RFA. There was no difference in OS between the RFA and SBRT arms in a study that involved propensity matching in approximately 2,000 patients from 5 countries.[34] In the present study, pooled analyses did not reveal a comparative difference in the overall and subgroup analyses according to the primary disease (Table 2). The survival of HCC patients is affected by several clinical factors including liver function, biological profile, previous treatment, and local control.[26,34,40] In addition, both treatment methods were effective, with a 2-year LC rate >80% in the pooled analyses (Table 3). Therefore, investigating OS differences based only on the selection of local modalities might be difficult. Although the pooled analyses and the majority of individual studies reported no significant difference, future randomised studies are needed to define the effect of selection between the 2 modalities on OS.

Feasibility considering tumour location and size

Overall grade ≥3 complication rates in the pooled analyses were <3% in both modalities (RFA 2.9%; ablative RT 2.8%, $p = 0.952$), indicating their feasibility. The characteristics of the complications were different between the 2 methods: most of the toxicities caused by RFA were caused by mechanical damage, whereas ablative RT mainly caused hepatic or gastrointestinal damage.

Because RFA mainly causes mechanical complications, tumour location significantly affects treatment safety and efficacy. Cao *et al.*[49] reported a major complication rate of 10.7% after RFA for periportal HCCs, which was higher than that of non-periportal controls (5.1%). Kang *et al.*[9] reported that aggressive intrasegmental recurrence occurred in 15% of periportal tumours after RFA because of thermal damage to the intrahepatic vessels. Song *et al.*[50] reported 9.5% of peritoneal seeding after RFA for subphrenic tumours and a local tumour progression rate of 37.8% at 3 years. Lee *et al.*[45] reported that the local recurrence risk was significantly higher after RFA for HCCs in the periportal location (hazard ratio [HR]: 2.29) and subphrenic location (HR: 2.25). The higher recurrence risk related to difficult locations and could be owing to suboptimal ablation to avoid possible complications or the heat-sink effect for perivascular tumours (*i.e.* ineffective thermal ablation hindered by blood flow).[46,49,51]

Ablative RT uses X-ray beams from multiple directions, which penetrate the body and accumulate in the target tumour.[52] Because cell death by X-rays is biological death caused by DNA damage, direct mechanical or thermal damage does not occur.[52,53] Normal organs have various radiation tolerances; the major vessel can tolerate radiation doses as high as ≥90 Gy in EQD2 clinically, and partial fibrosis does not alter blood flow.[54–56] Application of ablative RT to subphrenic tumours rarely induces pulmonary plural toxicities because radiation can cause partial fibrosis or atrophy but not rupture[34,40,57]; therefore, organ functions can be maintained. Therefore, ablative RT is often administered to tumours in locations where it is difficult to perform RFA. Several studies have reported that SBRT arms showed higher[33,34,40,42] or similar LC[32] although they had more target tumours in difficult locations. Similarly, Kim *et al.*[28] and Jeong *et al.*[39] reported that difficult locations (*e.g.* subphrenic or perivascular) were related to inferior LC after RFA, but not after SBRT.

As tumour size increases, it might have a biologically aggressive profile, and the presence of microinvasion or subclinical satellite nodules is frequent.[58,59] For large tumours, it is difficult to secure sufficient ablative margins because of the possible risk of damage to the heat-sink effects in adjacent organs.[58,60] For HCCs ≥3 cm in size, the local recurrence rate of RFA has been reported to be 30–50%.[47] When ablative RT is applied to liver tumours, the blood vessels or bile ducts can tolerate the radiation dose required for treatment.[44] Therefore, ablative RT could be performed with clinical margins covering subclinical disease for patients with preserved liver function and tumours with a distance of 1–2 cm from the small bowel, which is less affected by tumour size. Accordingly, in our systematic review, SBRT showed better LC for treatment of intrahepatic tumours >2 cm in size[23,28,31,40]; however, tumour size >3 cm showed inferior LC with RFA but not with SBRT.[34,38] LC being similar between modalities for treatment of small tumours (<2–3 cm) was shown as well.[33,35,36,39,42]

In summary, ablative RT could be more effective than RFA for treatment of tumours in difficult locations or with relatively large sizes. However, ablative RT should be cautiously applied to tumours near the small bowel or in patients with impaired liver function.

Limitations and future perspectives

Because most of the included studies were non-randomised, heterogeneity in clinical and methodological aspects could not be entirely overcome. For example, when analysing the effectiveness of treatment modalities according to tumour size, the reference size was not constant among studies, and the statistical methods and effect measures were also different. The definition of difficult location was subjective, and only 1 study[34] provided values of oncologic outcome according to specific location. In addition, heterogeneity in treatment outcomes could exist between previously treated and treatment-naïve tumours. Although most studies did not report segregated results, future studies are expected to report separate results to enable subgroup analyses. Regarding RFA arms, we included the studies with subject of thermal ablation including both RFA and MWA. Although the 2 modalities are similar in applying thermal damage to the tissue using a needle, MWA is reported to be effective for relatively larger tumours and is less affected by the heat-sink effect.[61] MWA cases must be separated into subgroups and evaluated if the relevant literature increases.

Many clinical decisions inevitably rely on information obtained from observational studies, particularly in the field of oncology. To the best possible extent, we performed an evidence-grading review for possible subjective outcomes, quantitative analyses for major oncologic outcomes, subgroup analyses, and formal heterogeneity assessments. As sufficient information from randomised studies is lacking, integration of clinical outcomes through quantitative and qualitative meta-analysis could be an alternative route to help in clinical decision-making.[62,63]

Our study suggests that ablative RT can yield oncologic outcomes similar to that with RFA and that ablative RT can be more effective for tumours in locations where it is difficult to perform RFA or in cases of large-sized tumours. However, no standardised guidance exists to clarify the indications for RFA and ablative RT. Therefore, it is necessary to establish decision criteria for selecting an optimum modality between the 2, considering the efficacy and feasibility according to specific location, tumour size, and other clinical circumstances. As ablative RT has been commonly applied as salvage therapy, further studies are needed to compare the efficacy of the 2 modalities in recurrent and primary treatment settings. As a randomised study has been limited to only 1 that compared proton therapy and RFA, future randomised trials involving SBRT and RFA arms are warranted to obtain more robust conclusions.

Abbreviations

ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; CIRSE, cardiovascular and interventional radiological society of Europe; CRC, colorectal cancer; EBRT, external beam radiation therapy; EQD2, Equivalent dose, 2 Gy per Fraction; HCC, hepatocellular carcinoma; HFRT, hypofractionated radiotherapy; IPTW, inverse probability of treatment weighting; LC, local control; LT, liver transplantation; MWA, microwave ablation; NCDB, national cancer database; OS, overall survival; P, prospective; PBT, proton beam therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSM, propensity score matching; R, retrospective; RCT, randomised controlled trial; RFA, radiofrequency ablation; RT, radiotherapy; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolisation.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception and study design: JS. Data collection: CHR, JSL, SYK. Analysis: CHR. Drafting: CHR. Editing and supervision: JS. Final approval: all authors. The authors are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

Data are available within the article or the Supplementary materials.

Supplementary data

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