

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

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Supplementary data 1. Draft of search strategy

Search strategy in Embase and Medline

#1 ((rfa OR 'radiofrequency'/exp OR radiofrequency) AND ('sbrt'/exp OR sbrt OR stereotactic OR proton OR cyberknife) AND (hcc OR hepatocellular OR 'liver'/exp OR liver))

#2 AND ('article'/it OR 'conference abstract'/it)

*#1 is our basic strategy using Emtree; #2 is to filter studies with irrelevant formats (e.g. reviews, editorials, letters, conference abstracts)

Search terms used in Pubmed and Cochrane library

Pubmed: ((rfa OR 'radiofrequency'/exp OR radiofrequency) AND ('sbrt'/exp OR sbrt OR stereotactic OR proton OR cyberknife) AND (hcc OR hepatocellular OR 'liver'/exp OR liver)) NOT review[PT]

Cochrane library: ((rfa OR 'radiofrequency'/exp OR radiofrequency) AND ('sbrt'/exp OR sbrt OR stereotactic OR proton OR cyberknife) AND (hcc OR hepatocellular OR 'liver'/exp OR liver))

Fig. S1. Funnel plots of pooled analyses of primary endpoints (odd ratio in comparison of RFA vs SBRT arms). No significant publication bias was noted regarding pooled comparative analyses of local control ($p=0.824$) and overall survival ($p=0.468$).

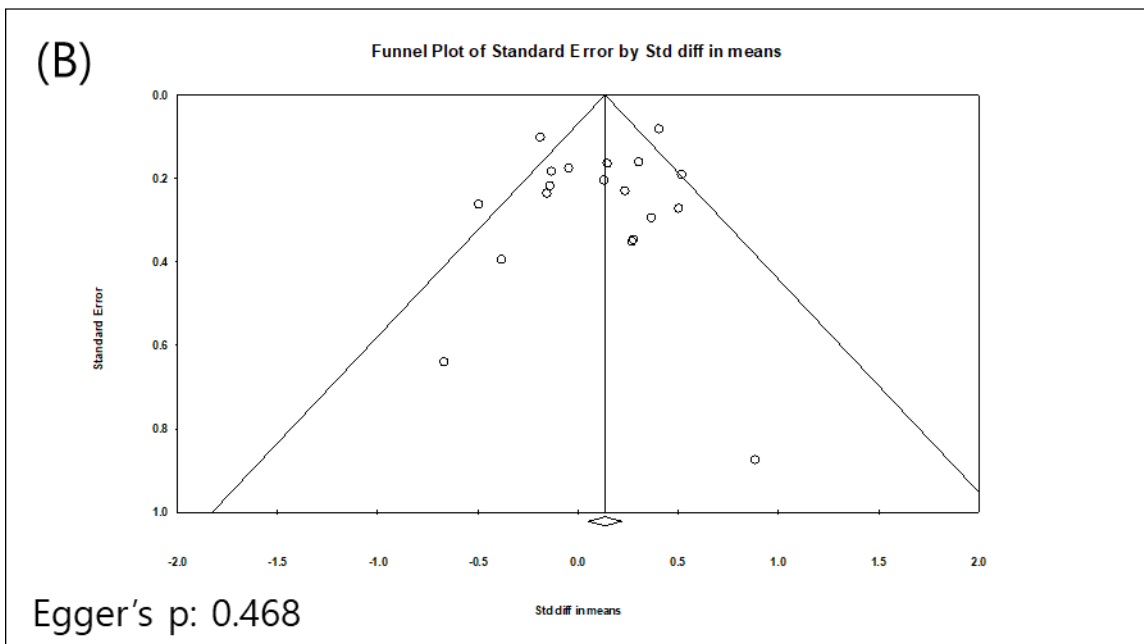
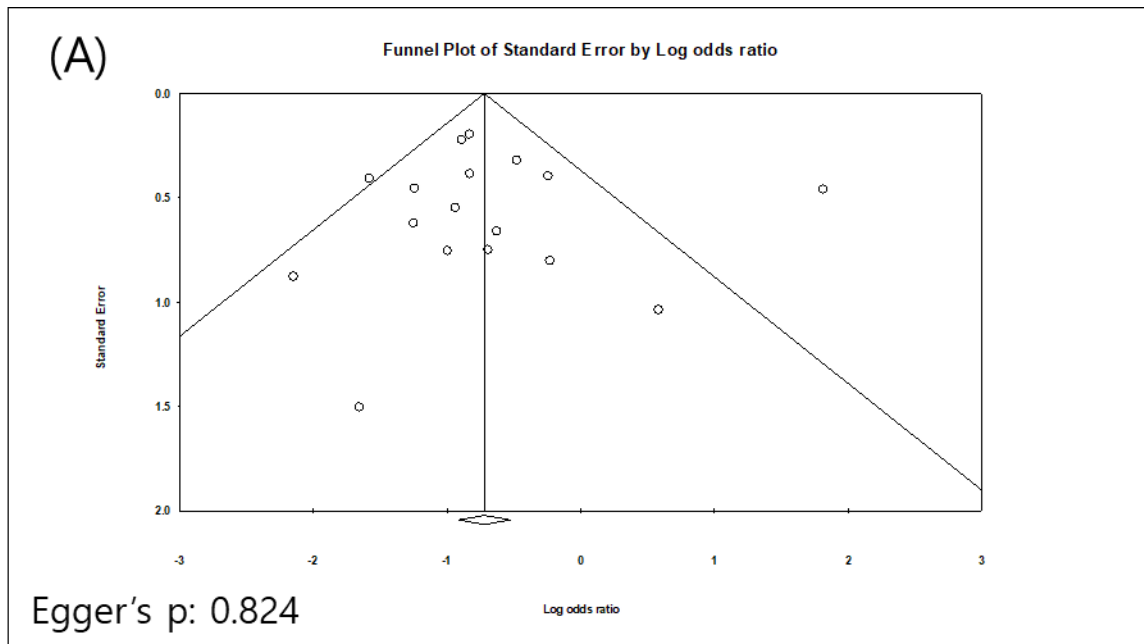


Table S1. Grading classification system recommended by American Society of Radiation Oncology (Ref. Apisarnthanarax et al., Practical Radiation Oncology (2021) 000, 1–24 [1])

Quality of evidence grade	Study types and quality	Evidence interpretation
High	2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	1 well-conducted and highly generalizable RCT or a meta-analysis of such trials OR 2 or more RCTs with some weaknesses of procedure or generalizability OR 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	1 RCT with some weaknesses of procedure or generalizability OR 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes OR 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert opinion	Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus ($\geq 90\%$) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Table S2. Full table of clinical information of included studies

Author	Subject of study	No. of patients (No. of tumors)	RT profile	Target patients	% of prior liver-directed Tx	Propensity matching	Imaging criteria, Definition of local control	Local control		p value	Overall survival		p value
								RFA (1/2/3 years)	Ablative RT (1/2/3 years)		RFA (1/2/3 years)	Ablative RT (1/2/3 years)	
Ahuja, 2014	HCC	TACE & RFA 32 TACE & SBRT 32				NA		PFS mean 48.5 months Vs 26.1 months		0.026	mean survival period 54.2 Vs 36.2 months		0.31
Shiozawa, 2015	HCC	RFA 38, Cyberknife 35 (patients n = tumor n)	60 Gy (3-5F)	RFA: solitary HCC <=3cm, unfeasible for surgery SBRT: solitary HCC <=5cm, CPC <=8		No; SBRT arm had negative factors	recurrence of <2cm of the treated lesion	97.4/89.4/76.3 %	97.1/91.4/74.3%	0.71	100% (1 year)	95.2% (1 year)	0.075
Wahl, 2016	HCC	RFA 161, SBRT 63 (tumors: RFA 249, SBRT 83)	27-60 Gy (3-5F)	localized HCC	RFA M0 (0-7); SBRT M2 (0-7)	Yes (IPTW)	RECIST, absence of progressive disease	83.6/80.2/75.1 % (tumors)	97.4/83.8/83.8% (tumors)	0.016	69.6/52.9% (1,2 years)	74.1, 46.3% (1,2 years)	NS
Duan, 2016	HCC	RFA 40, SBRT 37 (patients n = tumor n)		inoperable, single HCC <5cm		No; no statistical differences		90.0/85.0/82.5 %	94.6/91.9/89.2%	0.394	97.5/87.5/82.5 %	94.6/81.1/70.3 %	0.209
Feng, 2016	HCC	RFA 78, SBRT 78	na	T1-2N0, >65 yrs old		Yes (PSM)		na	na		mean OS 2.25 yrs	mean OS 2.04 yrs	0.06
Rajyaguru, 2018	HCC	RFA 521, SBRT 296	na	T1-2N0		Yes (PSM)		na	na		85.9/65.0/47.5 %	76.3/47.2/34.4 %	<0.001
Kim, 2019	HCC	RFA 95, SBRT 95 (patients n = tumor n)	mostly 60Gy/4 F or 52Gy/4 F	localized HCC ≤3 in number and <5cm in max. diameter	RFA 87.4% SBRT 92.6%	Yes (PSM)	mRECIST, without progression in PTV or adjacent to ablation zone	76.1/64.9/60.9 %	83.7/74.9/66.8%	0.243	87.1/71.8/55.5 %	86.9/76.4/69.0 %	0.667

Hara, 2019	HCC	RFA 106, SBRT-HFRT 106	35-40Gy/5 For 36-45GY/1 2-15F	localized HCC ≤3cm, 3 or less in numbers, curative intent	RFA 52%, SBRT 54%	Yes	mRECIST	79.8% (3 years)	93.2% (3 years)	<0.01	93/84.2/69.1%	95.2/87.3/70.4 %	0.86
Ji R, 2022	HCC	RFA 38 SBRT 22	27.5-50Gy in 5F	≤5cm in size ≤3 in number CPC A or B	All received prior TACE	No; SBRT arm had negative factors	mRECIST, not PD	94.7% (overall)	90.9% (overall)	0.566	100/75% (1,2 years)	88.2/85.7% (1,2 years)	0.576
Ueno, 2021	HCC	RFA 62 SBRT 31 (after PSM)	40Gy in 5F	single HCC ≤3cm	RFA 1.7% SBRT 65.2%	Yes	RECIST	100/93/87%	100/100/100 %	0.024	95.2/84.2/70.9	90.3/73.3/67.3	0.401
Kim N, 2020	HCC	RFA 313 SBRT 313 (after PSM)	MEQD 2 72Gy (IQR 65.6-88.0)	maximum ≤6 cm for a single tumor sum of diameters ≤6 cm for up to 3 lesions.	RFA 82.1% SBRT 84.3%	Yes	mRECIST	73.8/68.9/65.7 %	90.2/83.6/82 %	<0.00 1	87.6/71.1/58.5 %	88.4/77.6/62.6 %	
Kim T, 2021	HCC	RFA 56 PBT 80	66GyE in 10 F	HCCs ≤3cm in size, ≤2 in numbers	RFA 46.4% PBT 47.5%	RCT	RECIST, no recurrence within 1cm margin of PTV or ablation zone	85.6/83.9/77.6	97.6/94.8/88.3	0.123	98.4/92.9/87.2	96.1/88.8/79.0	0.6
Moon, 2019	HCC	RFA 529 SBRT 387 lesions				No; SBRT arm had negative factors		82.9% (1 year, tumors)	92.2% (1 year, tumors)	<0.00 1			
Chen LC, 2019	HCC	RFA 84 SBRT 24	40-54Gy in 5-6F		RFA m0.07 SBRT m1.96 times	No; SBRT arm had negative factors		77.8/63.8/59.4 %	93.8/93.8/93.8%	0.03	90.5/78.5/67,7	74.4/59.5/59.5	0.022
Jeong, 2021	HCC	RFA 172 SBRT 87 (after IPTW)	M45 Gy in 3F	≤3cm in size, ≤3 in numbers	RFA 52% SBRT 95.4%	Yes (IPTW)	no recurrence in edge of RFA zone, tumor increase in targeted area	99.4/93.5/92	97.8/97.5/96	0.167	98.8/87.4/77.8	96/90.2/77.2	0.786

							of SBRT						
Stintzing, 2013	CRC liver mets	RFA 30, cyberknife 30 (tumors: RFA 35, cyberknife 35)	24-26Gy (1F)	unresectable mets., all mets. were curatively treated	RFA 67% CK 47%	No; no statistical differences	no recurrence in the treated margin	65/61% (1, 2 years, tumors)	85/80% (1,2 yrs, tumors)	0.20 (at 2 year)	MS 34.4mo	MS 52.3mo	0.06
Vigano, 2018	CRC liver only mets	RFA 19, SBRT 8 (tumors: RFA 27, SBRT 17)	75Gy (3F)	liver only mets of CRC		NA		63.0/56.4% (1, 2 years, tumors)	70.8/70.8% (1, 2 years, tumors)	0.261			
Jackson, 2018	CRC and other liver mets	RFA 69, SBRT 92 (tumors: RFA 112, SBRT: 170)	24-61Gy (M50)/3-5F	unresectable mets. with limited or stable extraphepatic mets	RFA M1 (0-6), SBRT M1 (0-8)	No; SBRT arm had negative factors	RECIST	74.7/60.6/60.6 %	96.0/88.2/82.2 %	0.057	75.0/50.2/43.3 %	63.1/52.3/26.9 %	0.6
Nieuwenhuizen, 2021	CRC liver mets	RFA 144 SBRT 55	60Gy/3-12F	colorectal liver metastases, not locally treated in prior	previously untreated	No; SBRT arm had negative factors		95.6/93.3/91.5	81.2/71.5/58.2	<0.0001	94/80/65%	84/61/37%	p<0.001
Yu J, 2021	CRC liver mets	RFA 178 SBRT 44 (after IPTW)	36-60Gy in 3-5 F	CRC liver mets <5 in numbers	NA	Yes (IPTW)	RECIST	72/ /58%	90/ /76%	NS	91/74.5/56	96/69.8/58	NS
Gotohda, 2020	CRC liver mets	RFA 42 SBRT 5		CRC live rmets (M2.4cm)	NA	NA					87.1/54/38.6	80/80/80%	

Abbreviations: RT, radiotherapy; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; NA, not assessbile; PFS, progression free survival; IPTW, inverse-probability treatment weighting; PSM, propensity-score matching; OS, overall survival; HFRT, hypofractionated radiotherapy; PBT, proton beam therapy; CRC, colorectal cancer; CK, cyberknife
Heading of upper case M denoted median values and lower case m denoted mean values.

Table S3. Scoring sheet according to New-Castle Ottawa scale

	Selection				Comparability	Outcome			Overall score (9 to be full)
	1	2	3	4	1	1	2	3	
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Ahuja	1	1	1	1	0	1	0	1	7
Shiozawa	1	1	1	1	0	1	1	1	7
Wahl	1	1	1	1	2	1	1	1	9
Duan	1	1	1	1	0	1	1	1	7
Feng	1	1	1	1	2	1	1	1	9
Rajyaguru	1	1	1	1	2	1	1	1	9
Kim	1	1	1	1	2	1	1	1	9
Stintzing	1	1	1	1	0	1	1	1	8
Viganò	1	1	1	1	0	1	1	1	8
Jackson	1	1	1	1	0	1	1	1	8
Hara	1	1	1	1	2	1	1	1	9
Ji R	1	1	1	1	0	1	1	1	7
Ueno	1	1	1	1	2	1	1	1	9
Kim N	1	1	1	1	2	1	1	1	9
Kim T	1	1	1	1	2	1	1	1	9
Moon	1	1	1	1	0	1	0	1	7
Chen LC	1	1	1	1	0	1	0	1	7
Jeong	1	1	1	1	2	1	1	1	9
Nieuwenhuizen S	1	1	1	1	0	1	1	1	7

Yu J	1	1	1	1	2	1	1	1	9
Gotohda	1	1	1	1	0	1	0	1	6

Scoring note:

Selection criteria: The representativeness (Category 1) was high in that all studies were conducted on patients with a highly specific clinical category who received local treatment (RFA or SBRT) for small intrahepatic malignancies. Most of the treatment was performed in a tertiary hospital, and ascertainment of exposure (Category 3) was also satisfied because all information was obtained from secure medical records. Regarding outcomes of interest (Category 4), since the main outcomes of interest are survival and tumor control, they cannot present before treatment; hence, the category is satisfied in all studies. Considering that SBRT is the modality of interest, non-exposed cohort is drawn from very similar population of which has common clinical indication; therefore all studies scored one point (Category 2).

Comparability: Full score (2 points) was given if the study compared two arms in regard of ≥ 2 known clinical factors (including but not limited to, age, Child-Pugh score, tumor size, tumor location); 0 points were assigned for studies without statistical comparison between arms.

Outcome: All studies had data from secure medical records; hence, all studies had one point in Category 6. Considering the life expectancy of small HCC or liver metastases patients, only studies without follow-up period information or with median follow-up period less than 1 year scored 0 point, and all other studies (having 1 year or longer follow-up) scored 1 point. All studies were conducted in a tertiary hospital targeting cancer patients, and since follow-up loss was minimal and did not impair the reliability of the study results, all studies scored 1 point in Category 8.

Supplementary reference

1. Apisarnthanarax, Smith, et al. External beam radiation therapy for primary liver cancers: An ASTRO clinical practice guideline. *Practical radiation oncology*, 2022, 12.1: 28-51.