

Supplementary Material

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I. Supplementary Materials and Methods

1. Search strategy and results

(1) Summary of search results

No.	DB	Results	Duplication
1	Ovid-MEDLINE	94	
2	Ovid-EMBASE	1159	
3	CENTRAL	113	
4	KoreaMed	53	497
5	KMBASE	34	
6	KISS	313	
Number of Search Results (including duplication)		1766	
Number of Search Results (without duplication)		1269	

(2) Keywords

(A) International database

1) Ovid-MEDLINE

PICO	No.	Searches
Patients (HCC)	1	exp Carcinoma, Hepatocellular/co, dt, et, mo, rt, su, th [Complications, Drug Therapy, Etiology, Mortality, Radiotherapy, Surgery, Therapy]
	2	((hepat* or liver) adj5 (neoplas* or cancer* or carcin* or tumo?r* or malignan*)).ti,ab.
	3	1 or 2
Patients (elderly)	4	exp Aged/
	5	(advanced years or ageing or aging or aged or elder* or old* or frail* or geriatric* or gerontolog* or oncogeriat* or senior adult* or senium or octogenarian).ti,ab.
	6	4 or 5
Patients	7	3 and 6
Intervention	8	exp Hepatectomy/
	9	(liver or hepat* or segment*) adj5 (surgical or surger* or resect* or trans?ection* or operat* or excis* or extirpate* or segmentectom*).ti,ab.
	10	hepatectom*.ti,ab.
	11	or/8-10
Patients &	12	7 and 11

Intervention		
Patients & Intervention (Human study)	13	Animals/
	14	Human/
	15	13 not 14
	16	12 not 15
SD(RCT) *SIGN filter	17	(Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or randomized controlled trial.pt. or multicenter study.pt. or clinical trial.pt. or exp Clinical Trials as topic/ or (clinical adj trial\$.tw. or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. or PLACEBOS/ or placebo\$.tw. or randomly allocated.tw. or (allocated adj2 random\$.tw.) not (case report.tw. or letter/ or historical article/)
SD (Observational study) *SIGN filter	18	Epidemiologic Studies/ or exp Case Control Studies/ or exp Cohort Studies/ or Case-control.tw. or (cohort adj (study or studies)).tw. or Cohort analy\$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/
SD total	19	17 or 18
P & I (human study) & SD(RCT, cohort)	20	16 and 19
SD (exclusion study design)	21	Case Study/ or case report.tw. or letter/ or Editorial.pt. or review.pt.
Total	22	20 not 21

2) Ovid-EMBASE

	No.	Searches
	1	exp liver cancer/co, dm, dr, dt, et, rt, si, su, th [Complication, Disease Management, Drug Resistance, Drug Therapy, Etiology, Radiotherapy, Side Effect, Surgery, Therapy]
Patients (HCC)	2	exp liver cell carcinoma/co, dm, dr, dt, et, rt, si, su, th [Complication, Disease Management, Drug Resistance, Drug Therapy, Etiology, Radiotherapy, Side Effect, Surgery, Therapy]

	3	((hepat* or liver) adj5 (neoplas* or cancer* or carcin* or tumo?r* or malignan*)).ti,ab.
	4	1 or 2 or 3
	5	exp aged/
Patients (elderly)	6	(advanced years or ageing or aging or aged or elder* or old* or frail* or geriatric* or gerontolog* or oncogeriat* or senior adult* or senium or octogenarian).ti,ab.
	7	5 or 6
Patients	8	4 and 7
Intervention	9	exp liver resection/
	10	exp segmentectomy/
	11	(liver or hepat* or segment*) adj5 (surgical or surger* or resect* or trans?ection* or operat* or excis* or extirpate* or segmentectom*).ti,ab.
	12	hepatectom*.ti,ab.
	13	or/9-12
Patients & Intervention	14	8 and 13
Patients & Intervention (Human study)	15	Animals/
	16	Human/
	17	15 not 16
	18	14 not 17
SD(RCT) *SIGN RCT filter	19	(Clinical Trial/ OR Randomized Controlled Trial/ OR controlled clinical trial/ OR multicenter study/ OR Phase 3 clinical trial/ OR Phase 4 clinical trial/ OR exp RANDOMIZATION/ OR Single Blind Procedure/ OR Double Blind Procedure/ OR Crossover Procedure/ OR PLACEBO/ OR randomi?ed controlled trial\$.tw. OR rct.tw. OR (random\$ adj2 allocat\$).tw. OR single blind\$.tw. OR double blind\$.tw. OR ((treble or triple) adj blind\$).tw. OR placebo\$.tw. OR Prospective Study/) not (Case Study/ OR case report.tw. OR abstract report/ or letter/ OR Conference proceeding.pt. OR Conference abstract.pt. OR Editorial.pt. OR Letter.pt. OR Note.pt.)
SD (Observational study) *SIGN filter	20	Clinical study/ OR Case control study OR Family study/ OR Longitudinal study/ OR Retrospective study OR (Prospective study/ not Randomized controlled trials/) OR Cohort analysis/ OR (Cohort adj (study or studies)).mp. OR (Case control adj (study or studies)).tw. OR (follow up adj (study or studies)).tw. OR (observational adj (study or studies)).tw. OR (epidemiologic\$ adj (study or studies)).tw. OR (cross sectional adj (study or studies)).tw.
SD total	21	19 or 20
P & I (human study) & SD(RCT, observational)	22	18 and 21

SD(exclusion study design)	23	Case Study/ or case report.tw. or conference abstract.pt. or abstract report/ or letter/ or Editorial.pt. or review.pt.
Total	24	22 not 23

3) CENTRAL (Cochrane Central Register of Controlled Trials)

	No.	Searches
Patients (HCC)	1	MeSH descriptor: [Liver Neoplasms] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT, etiology - ET, mortality - MO, radiotherapy - RT, surgery - SU, therapy - TH]
	2	((hepat* or liver) near/5 (neoplas* or cancer* or carcin* or tumor* or malignan*)):ti,ab
	3	[1-#2-#2]
Patients (elderly)	4	MeSH descriptor: [Aged] explode all trees
	5	(advanced years or ageing or aging or aged or elder* or old* or frail* or geriatric* or gerontolog* or oncogeriat* or senior adult* or senium or octogenarian):ti,ab
	6	#4 or #5
Patients	7	#3 and #6
Intervention	8	MeSH descriptor: [Hepatectomy] explode all trees
	9	(liver or hepat* or segment*) near/5 (surgical or surger* or resect* or trans?ection* or operat* or excis* or extirpate* or segmentectom*):ti,ab
	10	hepatectom*:ti,ab
	11	[1-#10-#10]
Patients & Intervention	12	#7 and #11
Patients & Intervention (Human study)	13	MeSH descriptor: [Animals] this term only
	14	MeSH descriptor: [Humans] this term only
	15	#13 not #14
	16	#12 not #15
Total		Trials results

(B) Local database

1) KoreaMed

	No	Searches
Patients	1	((("liver cancer"[ALL])) OR ("hepatocellular carcinoma"[ALL]))
	2	((("hepatic"[ALL])) OR ("liver"[ALL]))
	3	((("cancer"[ALL]) OR ("neoplasms"[ALL]) OR ("tumor"[ALL]) OR ("carcinoma"[ALL]) OR ("malignant"[ALL]))
	4	2 AND 3
	5	1 OR 4
Patients	6	("ageing"[ALL]) OR ("aging"[ALL]) OR ("aged"[ALL]) OR ("elder"[ALL]) OR ("older"[ALL]) OR ("frail"[ALL]) OR

		("geriatric"[ALL]) OR ("gerontology"[ALL]) OR ("senior adult"[ALL]) OR ("senium"[ALL]) OR ("octogenarian"[ALL])
Intervention	7	("surgical"[ALL]) OR ("surgery"[ALL]) OR ("resection"[ALL]) OR ("operation"[ALL]) OR ("excise"[ALL]) OR ("extirpate"[ALL]) OR ("segmentectomy"[ALL]) OR ("hepatectomy"[ALL])
P&I	8	5 AND 6 AND 7

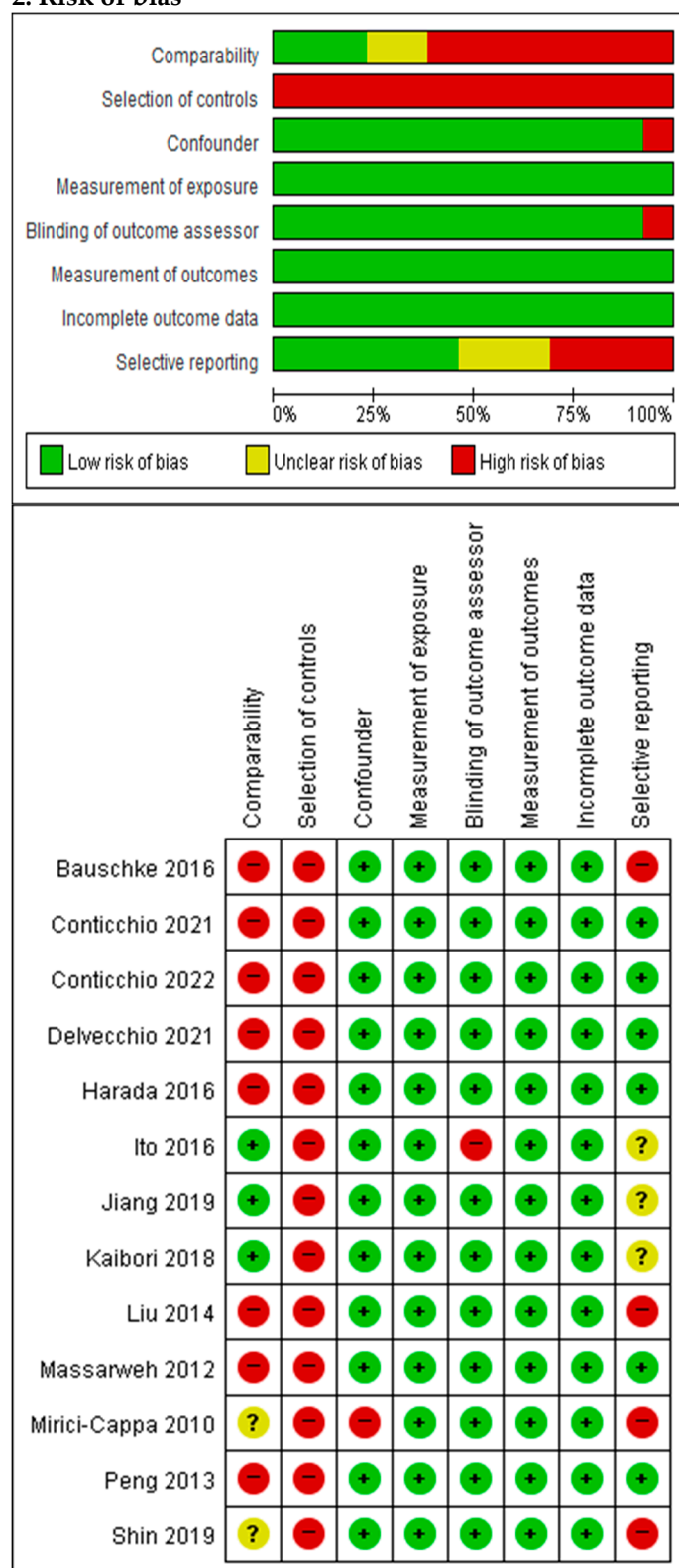
2) KMBASE

	No	Searches
Patients	1	([ALL=hepatocellular carcinoma] OR [ALL=liver cancer])
Patients	2	((([ALL=aged] OR [ALL=aging]) OR [ALL=elderly]) OR [ALL=older])
Intervention	3	((([ALL=surgery] OR [ALL=resection]) OR [ALL=operation]) OR [ALL=hepatectomy])
P&I	4	1 and 2 and 3
Patients	5	[ALL=간암] OR [ALL=간세포암종]
Patients	6	((([ALL=노인] OR [ALL=노령]) OR [ALL=고령]) OR [ALL=초고령])
Intervention	7	[ALL=간절제]
P&I	8	5 and 6 and 7
	9	4 OR 8

3) KISS

	No	Searches
Patients	1	전체 = liver cancer hepatocellular carcinoma 간암 간세포암종
Patients	2	전체 = aging aged elderly
	3	전체 = 노인 노령 고령 초고령
Intervention	4	전체 = surgery resection operation hepatectomy 간절제
P&I	5	1 AND 2 AND 4
	6	1 AND 3 AND 4
	7	5 + 6

2. Risk of bias



II. Supplementary Tables

Supplementary Table S1. Detailed characteristics of studies included in the systematic review and meta-analysis

Study	RFA									Surgery								
	Intervention	n	Age	Male (%)	BCLC 0/A stage (%)	Child Pugh class A (%)	Tumor size >3cm (%)	Multiple tumors (%)	cirrhosis (%)	Control	n	Age	Male (%)	BCLC 0/A stage (%)	Child Pugh class A (%)	Tumor size >3cm (%)	Multiple tumors (%)	cirrhosis (%)
Conticchio 2022[2]	RFA	58	74	64	NA	90	2.0cm	0	100	LLR	58	75.4	76	NA	86	median 3.0cm	0	100
Conticchio 2021[3]	RFA	136	75	72	100	84	(>2cm) 74	14	100	LR	136	74.7	76	100	85	(>2cm) 79	12	100
Delvecchio 2021[4]	RFA	26	75	65	NA	100	2.05cm	0	100	LR	26	74.26	62	NA	81	median 2.3cm	0	100
Shin 2019[5]	RFA	139	NR	NR	100	NR	NR	NR		SR	131	NR	NR	100	NR	NR	NR	
Jiang 2019[6]	RFA	956	NR	65.6	NR	NR	42	17.7	21.5	LR	956	NR	66.3	NR	NR	45.7	17.2	severe fibrosis or LC 18.9
Kaibori 2018[7]	RFA	461	77	62	NR	89	0	6	NR	LR	461	77	61	NR	89	0	5	NR
Harada 2016[8]	RFA	20	73	55	100	mean 5.5	1.6	mean 1.1	NR	LLR/OLR	20/48	74/70	45/54	100	mean 5.2/5.6	mean 1.8/2.3	mean 1.1/1.3	NR
Bauschke 2016[1]	RFA	64	NR	NR	NA	78	NR	38	77	LR	63	NR	NR	NA	95	NR	22	17
Ito 2016[9]	RFA	27	71	55.6	UICC stage I-II 100	96.3	0	22.2	NR	LR	27	69	59.3	UICC stage I-II 100	96.3	0	7.4	NR
Liu 2014[10]	RFA	139	79.6	67	69.1	64	vol mean 14 cm3	17.3	NR	SR	118	78.9	85	66.7	78.8	vol mean 171 cm3	17.8	NR
Peng 2013[11]	RFA	89	70.4	84.3	NR	87.6	39.2	6.7	100	LR	91	68.7	84.6	NR	94.5	34.1	14.3	100

Massarweh 2012[12]	RFA	206	74.7	63.1	NR	NR	49	44.7	81.6	LR	209	75.7	61.2	NR	NR	80.9	34	49.8
Mirici- Cappa 2010[13]	RFA	119	74.4	68.9	NR	58.8	NR	NR	97.5	LR	32	73.8	71.9	NR	71.9	NR	NR	100

Supplementary Table S2. Comparison of overall survival, disease free survival between surgery and RFA group

Overall survival						
	Overall survival (months)		3-year survival rate		5-year survival rate	
	RFA group	Surgery group	RFA group	Surgery group	RFA group	Surgery group
median	60	60	65.0%	70.0%	53.8%	57.5%
range	15.5-85	35.5-88.8	28.8%-78.5%	47.5-80.2%	8.5%-65.5%	37.3%-76.6%
Disease free survival						
	Disease free survival (months)		3-year disease free survival rate		5-year disease free survival rate	
	RFA group	Surgery group	RFA group	Surgery group	RFA group	Surgery group
median	26.3	31.0	62.7%	60.6%	30.3%	38.9%
range	20.4-42.3	28.0-57.2	35.7%-75.3%	39.3%-82.0%	16.3%-64.7%	33.1%-77.4%

Abbreviations: RFA: radio frequency ablation

Supplementary Table S3. A meta-analysis of overall survival in the surgical group vs. RFA

Group	No. of studies	Univariable analysis	
		Pooled HR (95% CI) (random model)	I ²
Overall estimate	10	1.44 (1.22-1.70)	81%
Using data			
Calculated data	5	1.41 (1.09-1.82)	84%
Reported data	5	1.49 (1.21-1.84)	66%
Definition of elderly			
≥ 65-70 years	9	1.43 (1.20-1.71)	83%
≥ 75 years	1	1.57 (1.12-2.20)	NA
Publication year			
2016-2022	7	1.62 (1.32-1.98)	64%
2010-2015	3	1.19 (0.94-1.50)	85%
Country			
Asia	3	1.26 (0.86-1.87)	84%
Non-Asia	7	1.54 (1.26-1.90)	82%
Risk of bias: comparability			
Low risk	4	1.49 (1.14-1.94)	74%
High or unclear risk	6	1.41 (1.14-1.75)	81%

Abbreviations: No., number; NA, non-available; HR, hazard ratio; CI, confidence interval

Supplementary Table S4. Comparison of recurrence in RFA and surgical group

Outcomes	No of studies	No. of patients, RFA/surgery	Pooled OR	95% CI	I ²	P of Chi ²
All						
Total recurrence	2	115/117	0.79	0.47-1.32	0%	0.42
Local recurrence	3	174/176	4.90	2.16-11.08	0%	0.43
Intra-hepatic recurrence	2	147/149	0.62	0.38-1.00	0%	0.64
Extra-hepatic recurrence	2	147/149	0.67	0.11-4.21	0%	0.70
Sensitivity analysis: HCC size ≤ 3cm						
Total recurrence	1	26/26	1.17	0.39-3.50	NA	NA
Local recurrence	2	85/85	5.96	1.91-18.64	13%	0.28
Intra-hepatic recurrence	1	58/58	0.52	0.22-1.23	NA	NA
Extra-hepatic recurrence	1	58/58	0.49	0.04-5.57	NA	NA

Abbreviations: HCC, hepatocellular carcinoma; No., number; NA, non-available; OR, odds ratio; CI, confidence interval

Supplementary Table S5. Comparison of hospital stay in RFA and surgical group

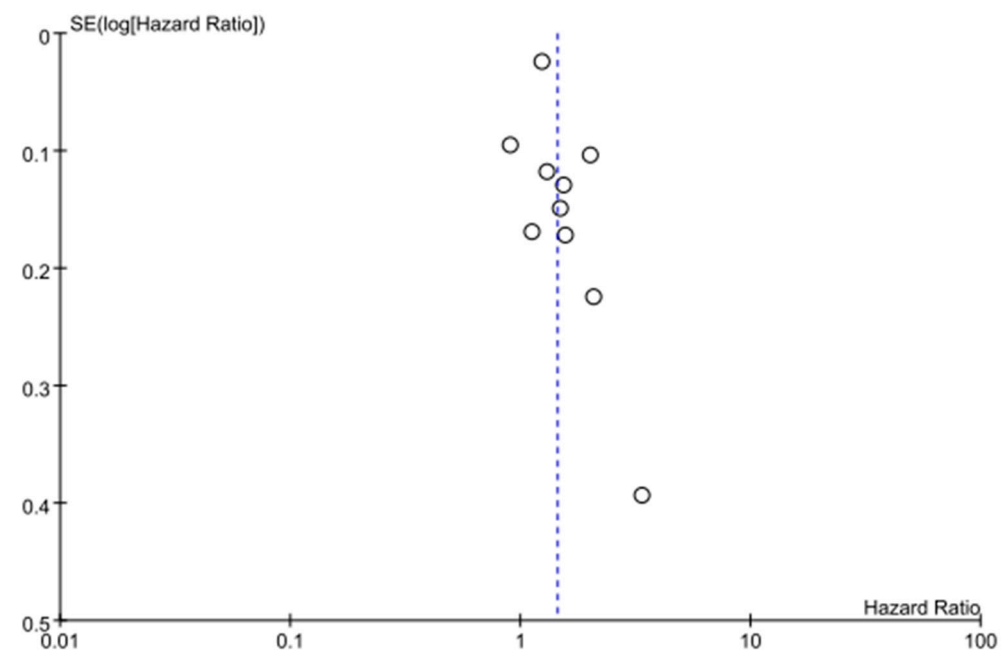
Study	Country	Elderly definition	No. RFA/surgery	RFA Median (range), days	Surgery Median (range), days	P
Conticchio, 2022[2]	Europe	70	58/58 (LLR)	3 (1-15)	5 (2-25)	0.001
Conticchio, 2021[3]	Europe	70	136/136 (OLR)	2 (1-23)	7 (1-203)	<0.001
Harada, 2016[8]	Japan	NA	20/20 (LLR)		9 (7-14)	not sig
			20/48 (OLR)	8 (2-14)	15 (7-66)	<0.0001
Ito, 2016[9]	Japan	NA	27/27 (LR)	mean 7.6 (95% CI 6.8-8.4)	mean 12.6 (95% CI 11.0-14.2)	<0.00003
Peng, 2013[11]	China	65	89/91 (LR)	mean 8.01, SD 2.70	mean 13.5, SD 4.05	<0.001

Abbreviations: LLR, laparoscopic liver resection. OLR, open liver resection; RFA, radiofrequency ablation; No., number; NA, non-available; CI, confidence interval; SD, standard deviation

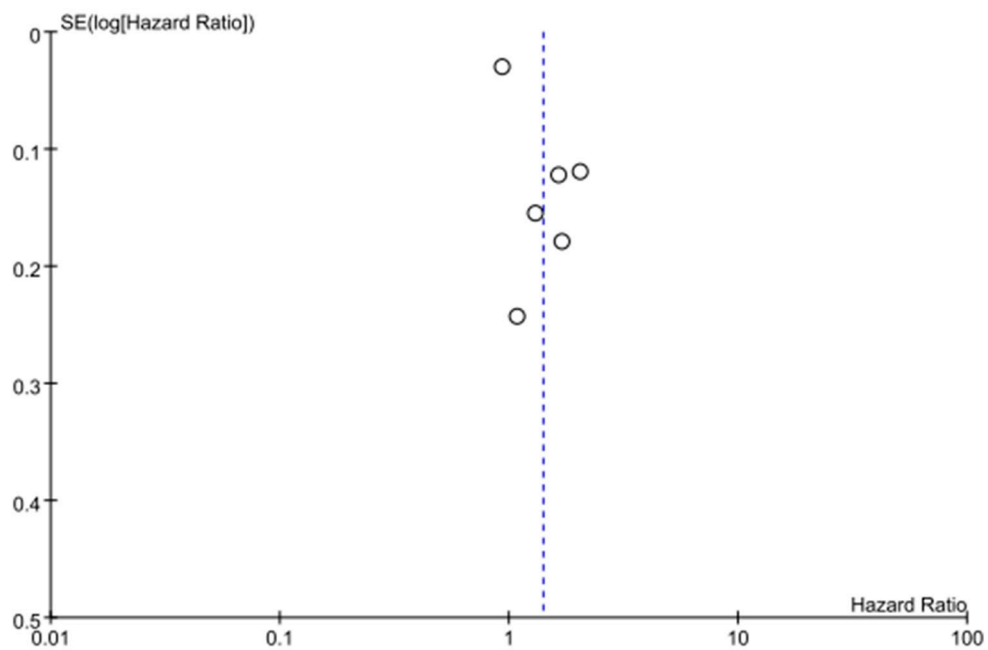
III. Supplementary Figures

Supplementary Figure S1. Funnel plots

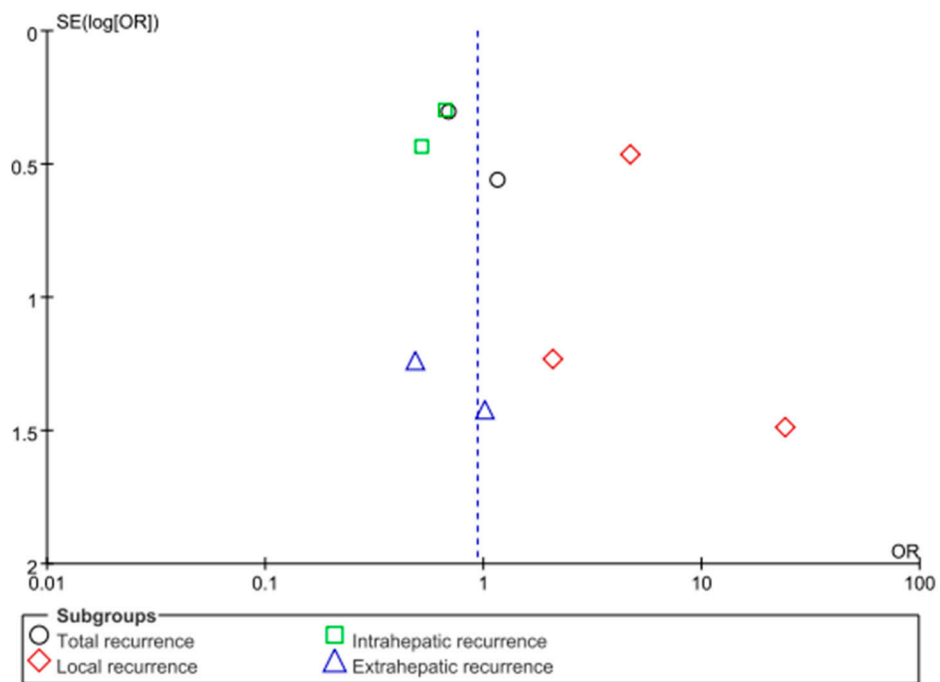
(A) overall survival



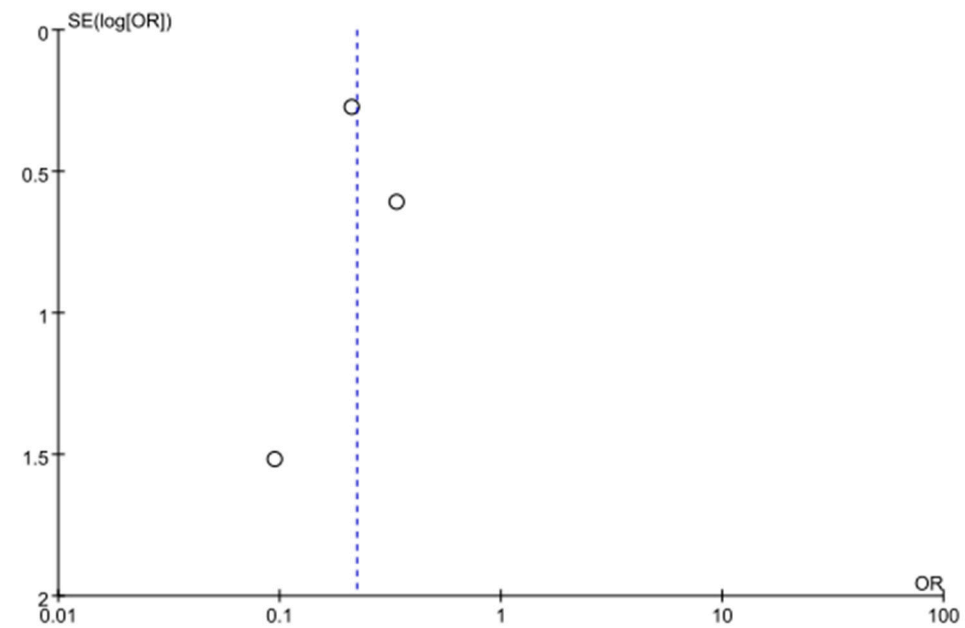
(B) disease free survival



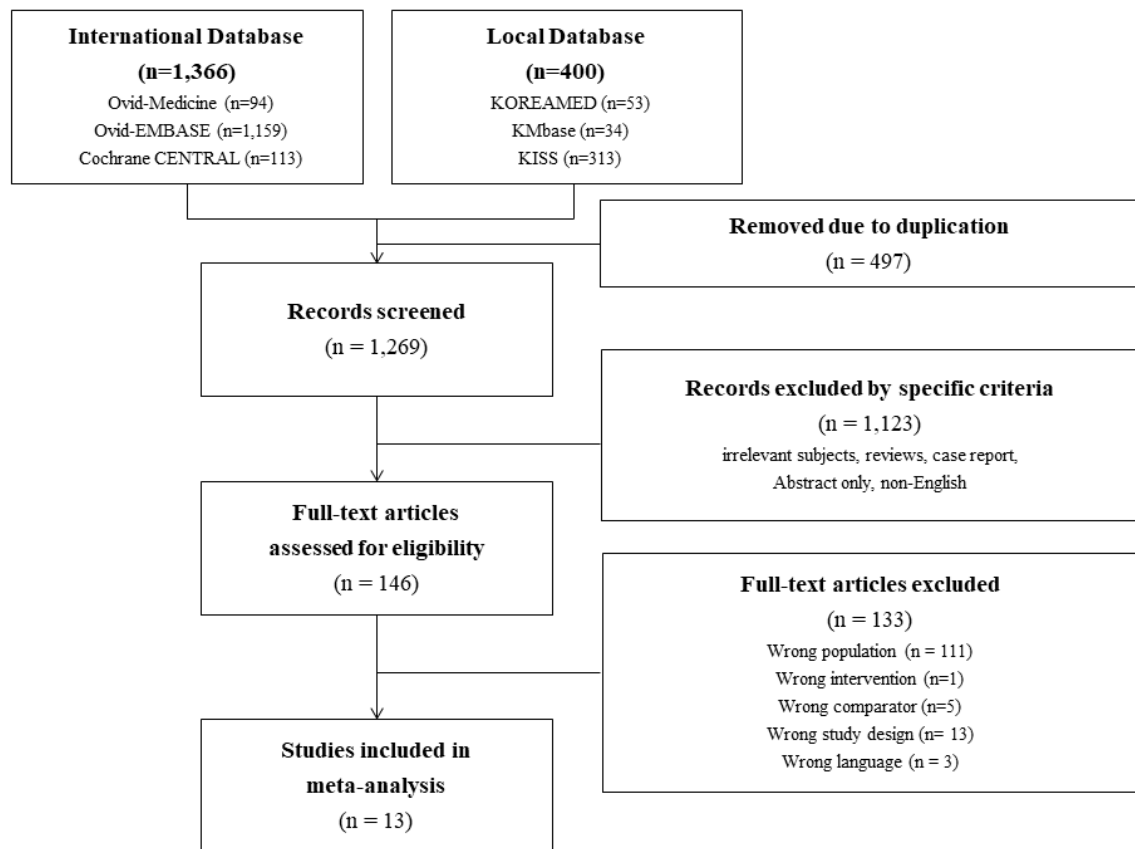
(C) recurrence



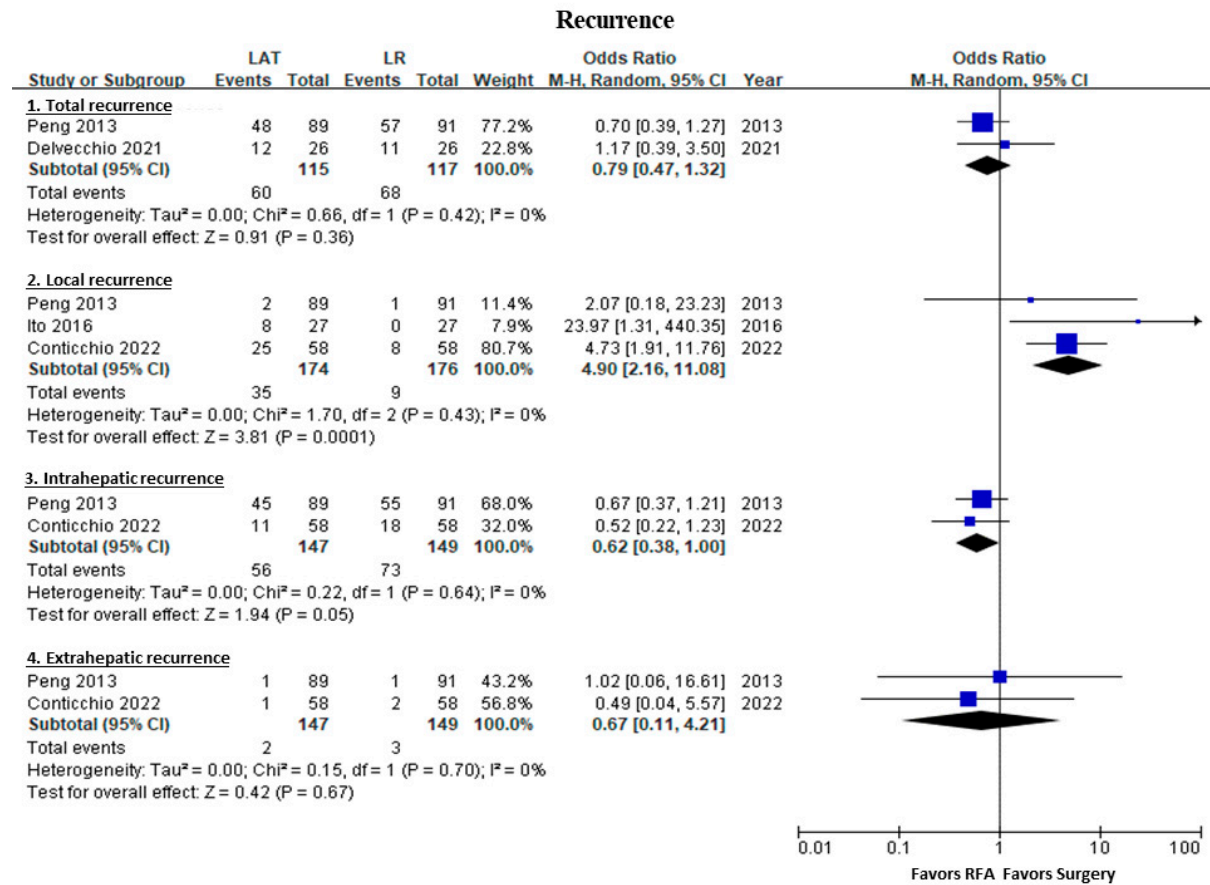
(D) adverse events



Supplementary Figure S2. Flow chart



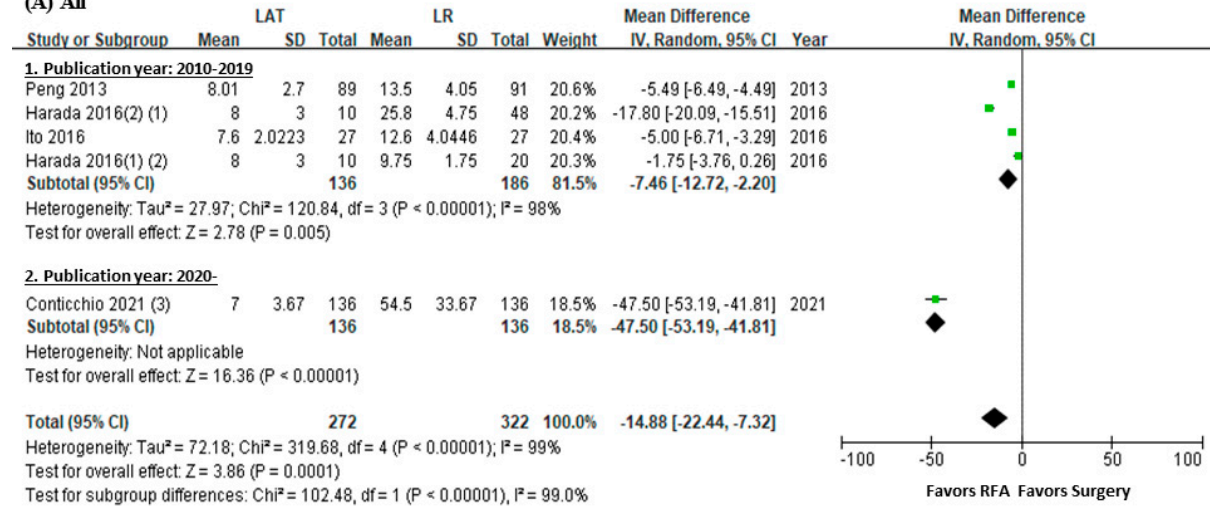
Supplementary Figure S3. Forest plot of recurrence rate
(a) all, (b) sensitivity analysis ($\leq 3\text{cm}$)



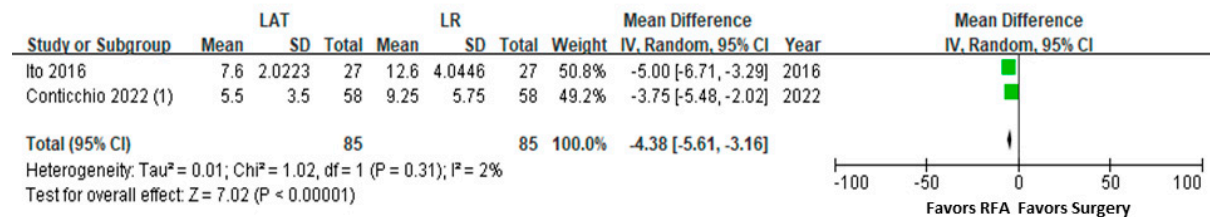
Supplementary Figure S4. Forest plot of hospital stay
(a) all, (b) sensitivity analysis ($\leq 3\text{cm}$)

Length of hospital stay

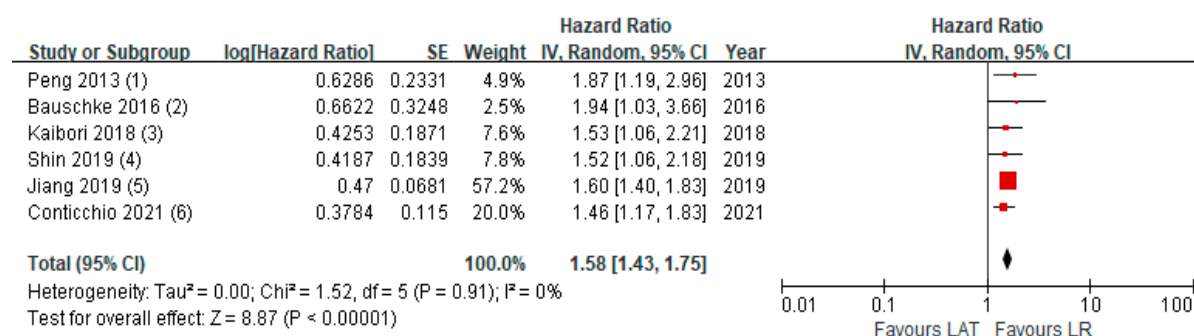
(A) All



(B) HCC $\leq 3\text{cm}$



Supplementary Figure S5. Multivariate meta-analysis of overall mortality risk



Footnotes

(1) Covariates : Tumor size, prothrombin activity

(2) Covariates : Charlson index, AFP, cirrhosis, Child's stage, Diameter of lesions, Number of lesions

(3) Covariates : age, sex, HBsAg, HCVAb, Child-Pugh class, serum albumin, total bilirubin, prothrombin activity, platelet, a-fetoprotein and...

(4) Covariates : Age, BMI, Albumin, Bilirubin, PT, Creatinine, Tumor number, tumor size, BCLC stages

(5) Covariates : Age, Tumor size, AFP, Fibrosis

(6) Covariates : INR, Multiple nodule, MELD

IV. References

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