Radiofrequency Ablation versus Liver Resection for Colorectal Cancer Liver Metastasis: An Updated Systematic Review and Meta-analysis

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Abstract

Background: Controversial results about the therapeutic value of radiofrequency ablation (RFA) and liver resection (LR) in the treatment of colorectal cancer liver metastasis (CRCLM) have been reported. Thus, we performed the present meta-analysis to summarize the related clinical evidences.

Methods: A systematic literature search was conducted using PubMed (Medline), EMBASE, Cochrane Library, and Web of Science, for all years up to April 2016. Pooled analyses of the overall survival (OS), progression-free survival (PFS), and morbidity rates were performed.

Results: A total of 14 studies were finally enrolled in the meta-analysis. Patients treated by LR gained a longer OS and PFS than those of patients treated by RFA. Patients in the RFA group had lower morbidity rates than those of patients in the LR group. Publication bias analysis revealed that there was no significant publication bias in the meta-analysis.

Conclusions: Patients with CRCLM gained much more survival benefits from LR than that from RFA. RFA rendered lower rates of morbidities. More well-designed randomized controlled trails comparing the therapeutic value of LR and RFA are warranted.

Key words: Colorectal Liver Metastasis; Liver Resection; Meta-analysis; Radiofrequency Ablation

Introduction

Colorectal carcinoma (CRC) is the fourth most common malignancy worldwide, and the disease burden of CRC continues to increase.[1] Around 40% of the patients presented with colorectal liver metastasis (CRCLM) at their initial diagnosis. Surgical resection is considered the golden standard in the treatment of CRCLM, with 5-year overall survival (OS) rate ranging from 27% to 58%.[2,3] Nevertheless, only 10–25% of patients with CRCLM are eligible for surgical resection in terms of the extent location of the disease and concurrent medical conditions.[2,3] Several alternative locoregional therapies including the radiofrequency ablation (RFA), percutaneous ethanol injection, acetic acid injection, microwave coagulation, and transcatheter arterial chemoembolization have been developed. Among these alternative treatments, RFA, which is featured with simplicity, safety, and minimally invasive, is frequently used.

The therapeutic role of RFA gains has been well established in the management of hepatocellular carcinoma (HCC) at early or intermediate stages. Controversial results comparing the therapeutic value of RFA and liver resection (LR) in colorectal cancer liver metastasis (CRCLM) have been reported. Despite the large number of patients treated by RFA worldwide, a randomized study comparing this approach with surgery has not been performed yet. Weng et al.[4] and Wu et al.[5] have reported their meta-analysis results that

Access this article online	
Quick Response Code:	**Website:** www.cmj.org
	DOI: 10.4103/0366-6999.195470

LR was superior to RFA in the treatment of patients with CRCLM. In recent years, several new comparative studies have been reported. The relevant clinical evidences have increased. Therefore, it is essential for us to search the available articles and perform the updated meta-analysis comparing the efficacy and safety of LR and RFA in the management of CRCLM.

METHODS

Literature search
A literature search of the online databases including PubMed (Medline), EMBASE, Cochrane Library, and Web of Science was performed for all studies up to April 2016. The search algorithm included the following words: "Radiofrequency ablation" (e.g., "radio frequency ablation," "radio-frequency ablation" "RFA"), "'resection" (e.g., "hepatectomy"), "colorectal" (e.g., "colon" and "rectal"), "cancer" (e.g., "tumor"), and liver metastasis (e.g., "liver metastases"). Only studies published in English were selected. Reference lists of all the retrieved articles were manually searched for potentially related articles.

Inclusion criteria
The following criteria were fulfilled for the studies included in the meta-analysis: (1) the studies comparing the clinical outcomes of RFA and LR in the treatment of colorectal cancer liver metastases; (2) the studies reporting at least 3- or 5-year OS and (or) 3- or 5-year disease-free survival (DFS) of each treatment group; and (3) if more than one studies were reported by the same research, only the most recent one with the most comprehensive information was included.

Exclusion criteria
The following studies (cohorts) were excluded from the study: (1) the original studies which did not report the comparative results about the therapeutic value of RFA and LR; (2) those published in the form of review articles, letters, comments, and case reports.

Quality assessment
The quality assessment of the primary studies was carried out using the Newcastle-Ottawa Scale (NOS). Two authors (Yue Han and Dong Yan) performed the study quality assessment independently. When discrepancy occurred, a third author (Xiao Li) was referred. Studies with NOS ≥6 were considered to be of high quality.

Data extraction
Data extraction was performed independently by Yue Han and Dong Yan, and in the case of discrepancy, the decision was made by discussion with a third author (Xiao Li). The main extracted data included: (1) the first author, the year of publication, sample size, study location, and study design; (2) the baseline oncological characteristics of patients including the tumor number, tumor size, and lymph node metastasis; and (3) the outcome of the trials including the OS and DFS at 3 and 5 years as well as the mortality and/or morbidity.

Statistical analysis
Calculation for dichotomous variables was carried out using the risk ratio (RR) and their 95% confidence interval (CI) as the summary statistic. Interstudy heterogeneity among the included studies was evaluated by the I^2 statistics.[6] Time-to-event data including the 3-year OS, 3-year progression-free survival (PFS), 5-year OS, and the 5-year PFS were extracted from individual trials. Pooled categorical comparisons were made by Chi-squared test. If the I^2 was larger than 50%, implying significant statistical heterogeneity between studies, the random effects (DerSimonian-Laird method) model was adopted; in the presence of no observable interstudy heterogeneity ($I^2 < 50\%$), the fixed-effect model was applied. Two-sided $P < 0.05$ was considered statistically significant. Sensitivity analysis was performed to evaluate the stability of the results. Each study involved in the meta-analysis was removed each time to reflect the influence of the individual data set on the pooled effects. Evidence of publication bias was evaluated using the Begg's test[7] and Egger's test.[8] All analyses were performed using STATA statistical software package version 12.0 (STATA Corp., College Station, Texas, USA).

RESULTS

Description of the enrolled studies
Three studies[9-11] were from the same medical center, the latest one with the most comprehensive information[11] was enrolled. Thus, a total of 14 studies[3,11-23] with sample size ranging from 29 to 455 have been enrolled [Figure 1]. Of them, 1466 patients underwent LR and 739 patients underwent RFA. The detailed information of the included studies was summarized in Table 1. NOS was not less than 6 in 12 of the studies.

Overall survival
With observable interstudy heterogeneity, patients in the RFA group had inferior 3-year OS (RR: 1.466, 95% CI: 1.218–1.765, P < 0.001, P value of Q-test for
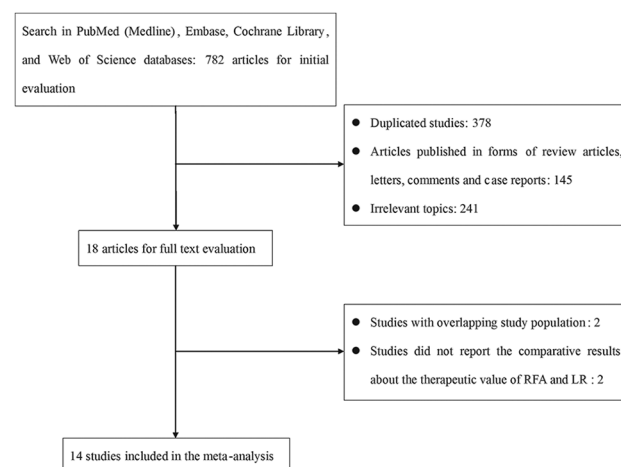
Figure 1: The flowchart describing the selection of the literature. RFA: Radiofrequency ablation; LR: Liver resection.

Table 1: Baseline characteristics of included studies

Author	Year	Design	Study period	Study location	Treatment	Sample size (male/female)	Age (years)	Tumor size (cm)	Tumor number	Tumor stage (I and II versus III and IV)	LN (+/−)	NOS
Oshowo	2003	Retro	Not reported	UK	LR	10/10	63 (52–77)*	4 (2–7)*	1			5
					RFA Perc	11/14	57 (34–80)*	3 (1–10)*	1			
Evrard	2004	Retro	2000–2002	France	LR	10/7	57 (25–88)*	2.2	1 (1–5)*			5
					RFA Open	19/14	66 (21–82)*	1	3 (1–8)*			
Abdalla	2006	Retro	1992–2002	USA	LR	190	60 (23–88)*	2.5				7
					RFA Open	57	60 (23–88)*	2.5	1 (1–8)*			
White	2007	Retro	1992–2002	USA	LR	20/10	62 (42–81)*	2.7 ± 1.1‡	1		17/13	6
					RFA Perc	8/15	62 (48–77)*	2.4 ± 1.0‡	1		11/11	
Gleisner	2008	Retro	1999–2006	USA	LR	121/71	61	3.5 (2.0–5.0)*	1.0–2.5	28/164	122/70	6
					RFA Perc	7/4	60	2.5 (1.9–4.0)*	1	0/11	7/4	
Berber	2008	Retro	1996–2007	USA	LR	57/33	64	3.8 ± 0.2‡	1			6
					RFA Open	43/25	64	3.7 ± 0.2‡	1			
Her	2009	Retro	1999–2005	Korea	LR	27/15		2.6 (0.6–8.0)*	1	2/40	26/16	6
					RFA Open/ Perc	15/10		2.5 (0.8–3.6)*	1	1/24	18/7	
Reuter	2009	Retro	1995–2007	USA	LR	69/57	61.9	5.3	Mean: 2.1	26/100		6
					RFA	46/20	63.5	3.2	2.8	14/52		
Mckay	2009	Retro	1998–2007	Canada	LR	29/29	67 (28–83)*	4.1 (1.5–14.5)*	1 (1–7)*			6
					RFA Open/ Perc	25/18	67 (37–83)*	3.0 (1–7.5)*	2 (1–6)*			
Otto	2009	Prosp	2002–2008	Germany	LR	49/33	62 (38–80)*	5 (1–15)*	2 (1–11)*	11/71	11/71	7
					RFA Perc	20/8	64 (42–78)*	2 (1–5)*	2 (1–5)*	4/24	22/60	
Kim	2011	Retro	1995–2009	Korea	LR	168/110	57.1	2.6 ± 2.0‡	1.5			6
					RFA Open/ Perc	121/56	60.4	2.1 ± 1.0‡	1.6			
Ko	2014	Retro	2004–2009	Korea	LR	7/10	≤65:4 >65:8	3.59 (1.60– 4.90)†		I–III: 8 IV: 4	9/3	6
					RFA	4/8	≤65:12 >65:5	2.02 (0.80– 4.60)†		I–III: 13 IV: 4	11/6	
Tanis	2014	Retro	2000–2006	Europe	LR	58/23	61 (29–77)*		1 (1–4)*			6
					RFA	33/22	64 (39–79)*	3.0 (1.0–3.9)*	4 (1–9)*			
Lee	2015	Retro	2000–2009	Korea	LR	73/29	60 (3–79)*	1.7 (0.2–3.0)*	Single: 63 Multiple: 39		30/72	6
					RFA Open	35/16	58.5 (35.0– 79.0)*	1.8 (1.0–3.0)*	Single: 29 Multiple: 22		13/38	

*Median (range); †Mean (range); ‡Mean ± SD. SD: Standard deviation; Retro: Retrospective study; Prosp: Prospective study not random; LR: Hepatic resection; RFA: Radiofrequency ablation; Perc: Percutaneous; Open/Perc: Contains data from both open and percutaneous surgery; LN: Lymph node metastasis; NOS: Newcastle–Ottawa Scale.

heterogeneity test [P_h]: 0.013) [Figure 2a and Table 2] and 5-year OS (*RR*: 1.361, 95% *CI*: 1.163–1.593, $P < 0.001$, $P_h < 0.001$) [Figure 2c and Table 2] when compared with patients in the LR group. Moreover, majority of the subgroup analyses showed that the LR group had better long-term survival than RFA group in terms of 3-year OS [Table 2].

Disease-free survival
Patients in the RFA group gained significantly shorter 3-year PFS (*RR*: 1.344, 95% *CI*: 1.196–1.510, $P < 0.001$, $P_h = 0.005$) [Figure 2b and Table 2] and 5-year PFS (*RR*: 1.396, 95% *CI*: 1.230–1.584, $P < 0.001$, $P_h < 0.001$) [Figure 2d and Table 2] than those of patients in the LR group. The significantly higher DFS rates in LR group were also observed in majority of the subgroups [Table 2].

Safety
Nine of the included studies compared the morbidities between the RFA group and LR group. The incidence of postoperative morbidity was significantly lower in the RFA group than that in the LR group (odds ratio: 0.494, 95% *CI*: 0.280–0.873, $P = 0.015$, $P_h < 0.001$) [Figure 3 and Table 2].

Sensitivity analyses
A single primary study was removed at a time to test its influence on the overall results. The pooled analyses of the rest studies agreed with the overall results [Figure 4].

Publication bias
The funnel plot did not show significant asymmetry by Begg's test in 3-year survival [$P_r > |z| = 0.945$,
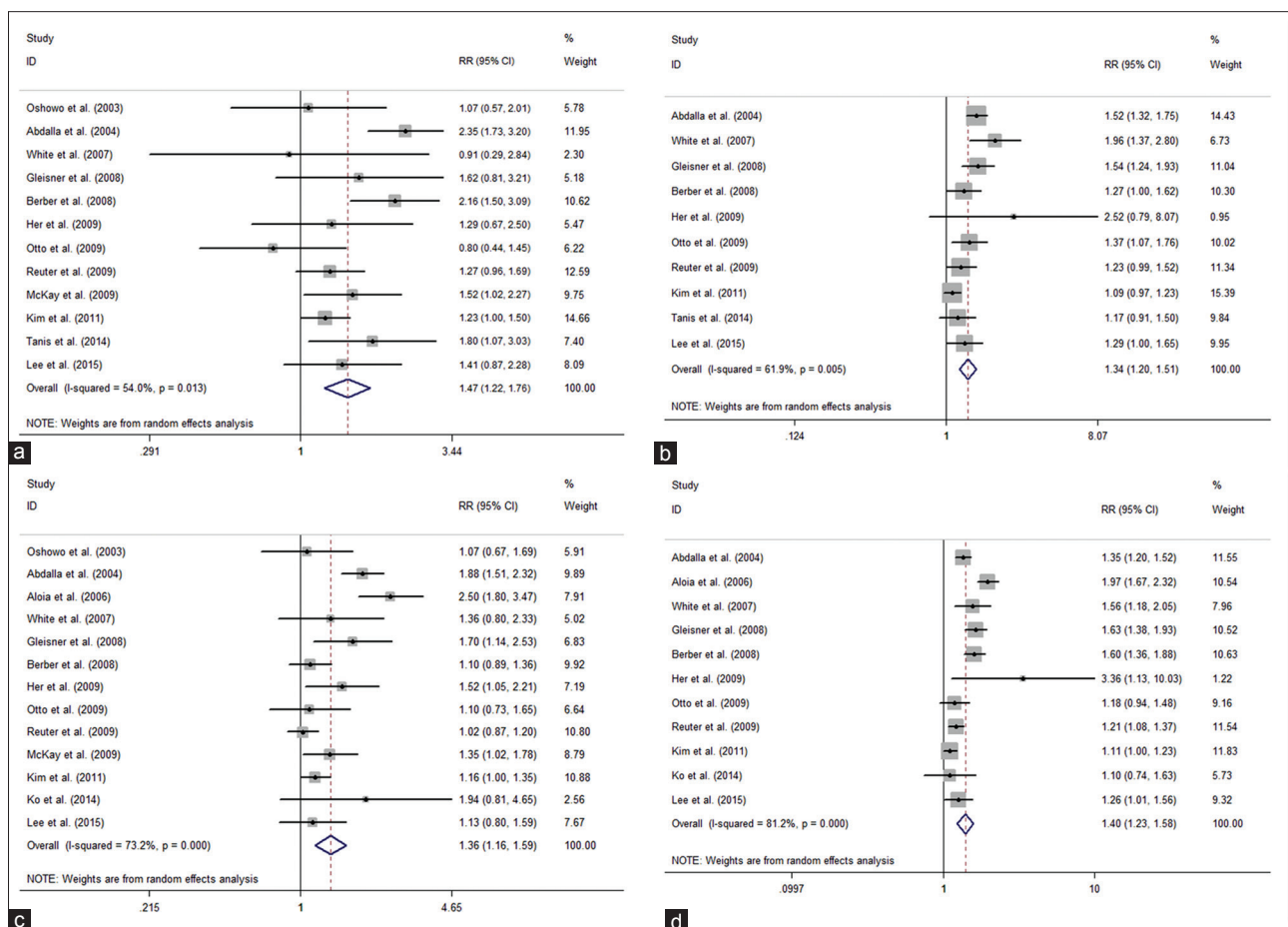
Figure 2: Pooled analysis comparing the survival rate between patients in the liver resection and radiofrequency ablation groups. (a) Pooled analysis comparing the 3-year overall survival rate. (b) Pooled analysis comparing the 3-year progression-free survival rate. (c) Pooled analysis comparing the 5-year overall survival rate. (d) Pooled analysis comparing the 5-year progression-free survival rate. Horizontal lines correspond to the study-specific risk ratio and 95% CI, respectively. The size of the squares reflects the study-specific weight. The diamond represents the results for the pooled risk ratio and 95% CI. RR: Risk ratio; CI: Confidence interval.
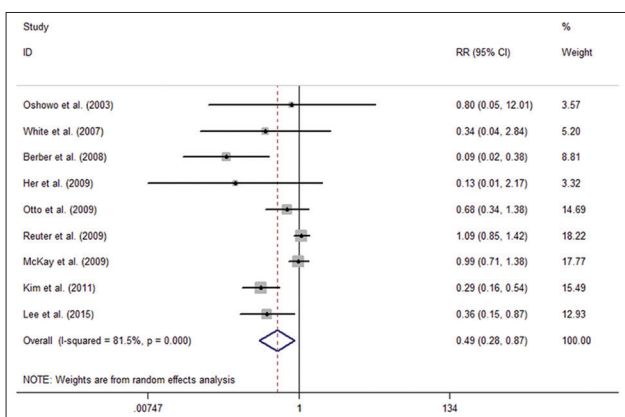
Figure 3: Pooled analysis comparing the morbidity rate of patients in the liver resection and radiofrequency ablation groups. Random effects model was used. Horizontal lines correspond to the study-specific hazard ratio and 95% CI, respectively. The size of the squares reflects the study-specific weight. The diamond represents the results for the pooled risk ratio and 95% CI. RR: Risk ratio; CI: Confidence interval.

Figure 5a], 5-year OS [$P_r > |z| = 0.360$, Figure 5b], 3-year DFS [$P_r > |z| = 0.592$, Figure 5c], 5-year DFS

[$P_r > |z| = 0.533$, Figure 5d], and morbidity rates [$P_r > |z| = 0.466$, Figure 5e].

DISCUSSION

In the present meta-analysis, we found that patients with CRCLM who were treated by LR gained better survival outcomes than those who were treated by RFA. However, RFA outperformed LR in terms of fewer perioperative morbidity rates.

Surgical resection is considered to be the first-line treatment for the local control of CRCLM. However, hepatectomy is not always possible due to large tumor size, anatomic location, and poor health status. RFA, which has the advantages of minimal invasiveness, might be favorable for the local control of CRCLM.[24] Besides, with the advances in the imaging-guided location, artificial hydrothorax, and the probes, the indications for RFA have been greatly expanded. Nevertheless, there has been no consensus on whether RFA can get the similar therapeutic value as that of LR.

Table 2: Main results of the meta-analysis

Analysis	OS						PFS					
	n	HR (95% CI)	P	I²	Ph	Pr	n	HR (95% CI)	P	I²	Ph	Pr
3-year	12	1.466 (1.218–1.765)	<0.001	54.0	0.013		10	1.344 (1.196–1.510)	<0.001	61.9	0.005	
Subgroup 1												
Intraoperative	5	1.733 (1.306–2.300)	<0.001	62.1	0.032	0.415	5	1.347 (1.223–1.485)	<0.001	25.3	0.253	0.023
Percutaneous	3	0.900 (0.597–1.357)	0.616	0	0.807		2	1.601 (1.133–2.262)	0.008	61.2	0.108	
Both	4	1.338 (1.133–1.580)	0.001	0	0.498		3	1.127 (1.011–1.257)	0.031	10.4	0.328	
Subgroup 2												
Size of liver metastasis <3 cm	3	1.380 (0.886–2.149)	0.154	0	0.957		3	1.365 (1.065–1.750)	0.014	0	0.590	
Size of liver metastasis <5 cm	3	1.492 (1.066–2.089)	0.020	0	0.527		3	1.393 (1.061–1.830)	0.017	64.2	0.061	
Subgroup 3												
Asian	1	1.407 (0.870–2.277)	0.164	–	–	0.909	1	1.286 (1.002–1.650)	0.048	–	–	0.813
Caucasian	11	1.468 (1.200–1.796)	<0.001	58.2	0.008		9	1.354 (1.189–1.541)	<0.001	66.2	0.003	
Subgroup 4												
Sample size ≥100	9	1.529 (1.238–1.887)	<0.001	63.7	0.005	0.287	8	1.298 (1.162–1.451)	<0.001	60.0	0.014	0.065
Sample size <100	3	1.123 (0.732–1.722)	0.596	0	0.847		2	2.060 (1.423–2.983)	<0.001	0	0.658	
5-year	13	1.361 (1.163–1.593)	<0.001	73.2	<0.001		11	1.396 (1.230–1.584)	<0.001	81.2	<0.001	
Subgroup 1												
Intraoperative	5	1.309 (1.005–1.706)	0.046	83.3	<0.001	0.347	5	1.395 (1.239–1.571)	<0.001	67.6	0.015	0.395
Percutaneous	4	1.229 (0.951–1.588)	0.115	0	0.605		3	1.276 (1.089–1.497)	0.003	32.6	0.227	
Both	4	1.534 (1.107–2.126)	0.010	83.0	0.001		3	1.669 (0.981–2.841)	0.059	94.5	<0.001	
Subgroup 2												
Size of liver metastasis <3 cm	5	1.395 (0.884–2.201)	0.153	76.8	0.002		5	1.282 (0.896–1.834)	0.174	66.8	0.017	
Size of liver metastasis <5 cm	4	1.638 (1.035–2.591)	0.035	74.4	0.008		4	1.468 (1.108–1.945)	0.008	80.8	0.001	
Subgroup 3												
Asian	2	1.238 (0.899–1.705)	0.191	22.3	0.257	0.851	2	1.226 (1.012–1.484)	0.037	0	0.552	0.345
Caucasian	11	1.370 (1.154–1.626)	<0.001	77.0	<0.001		9	1.437 (1.245–1.658)	<0.001	84.5	<0.001	
Subgroup 4												
Sample size ≥100	9	1.359 (1.125–1.640)	0.001	81.1	<0.001	0.937	8	1.387 (1.206–1.595)	<0.001	85.8	<0.001	0.825
Sample size <100	4	1.390 (1.083–1.785)	0.010	0	0.564		3	1.489 (0.968–2.290)	0.070	60.5	0.079	
Morbidity of all studies	9	0.494 (0.280–0.873)ᵃ	0.015	81.5	<0.001							

a: Odds ratio; OS: Overall survival; PFS: Progression–free survival; *N*: Number; *HR*: Hazard ratio; *Ph*: *P* value of Q test for heterogeneity test; *Pr*: *P* value of meta regression analysis.

The inferior survival outcomes of RFA could be explained in several aspects. First, RFA patients were more likely to recur near the RFA site due to incomplete ablation of lesion size, heat sink effect, or limitations of the technique.[25,26] The underlying molecular mechanism explaining the higher recurrence rates and inferior survival outcome remains to be resolved. Yoshida *et al*.[26] found that sublethal heat treatment skewed HCC cells toward epithelial-mesenchymal transition and transformed them to a progenitor-like, highly proliferative cellular phenotype *in vitro* and *in vivo*, which was driven significantly by p46-Src homology and collagen and downstream extracellular signal-related kinase 1/2. Second, in many medical institutions, the patients who underwent RFA were those who were not eligible for surgery because of poor health condition, inadequate liver function reserve, or extensive tumor burden. Third, the resection allows in-depth intraoperative exploration and pathological evaluation as well. More comprehensive evaluation of the tumor status may be beneficial for the design of treatment strategies.

Subgroup analyses showed that in patients with tumor size <3 cm, the survival outcomes of RFA and LR were identical. Recently, the American Society of Clinical Oncology performed an evidence review for RFA on both resectable and unresectable CRCLMs.[15] They found that patients with liver lesion measuring <3 cm had a high ablation success rate and the best outcome. For larger tumors, to achieve the safe margin, the RFA needle needs to be repositioned for multiple ablation zones, which will increase the chance of an incomplete ablation and the risk for a local recurrence.

Heterogeneity remained to be a concern in our meta-analysis. We conducted the meta-regression analysis based on the RFA method, sample size, and study region. These factors failed to explain the source of heterogeneity. Only in the pooled analysis for 5-year PFS, RFA method accounted for part of the heterogeneity. We surmised that the heterogeneity of the included studies might be caused by the heterogeneity in the study design, patients' baseline characteristics, follow-up duration, and so on. Further,
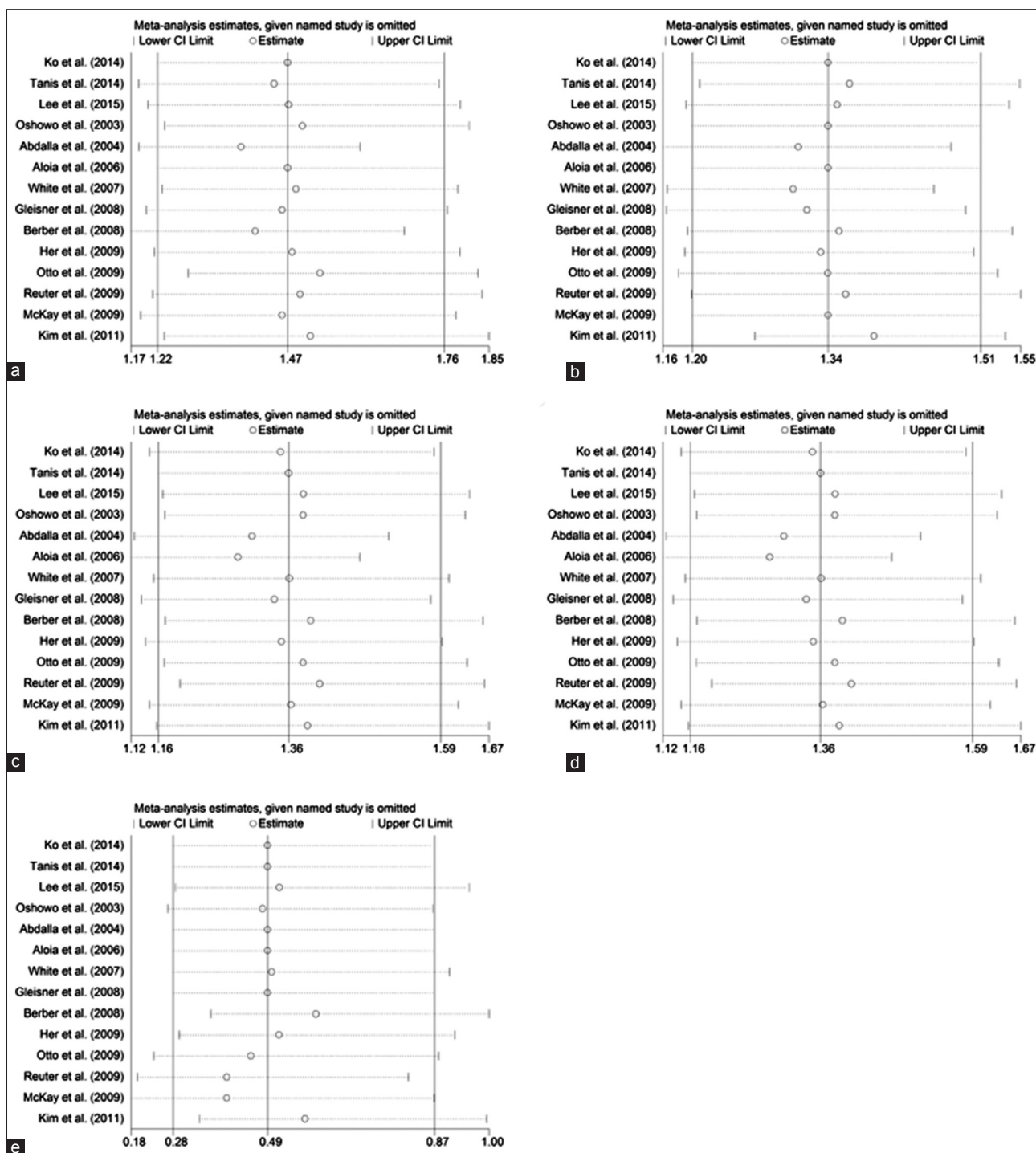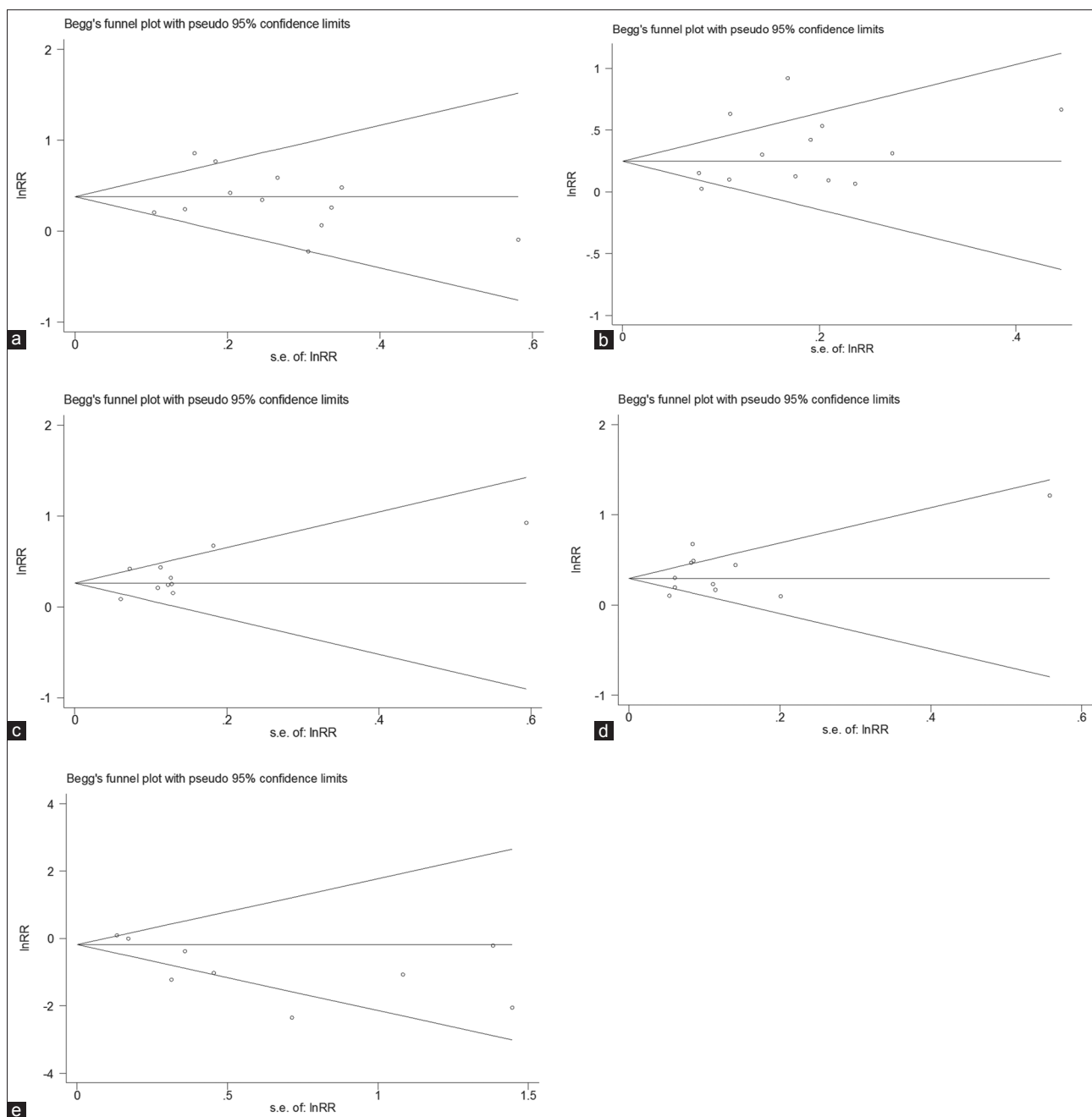
Figure 4: Sensitivity analyses of the survival and morbidity rate comparisons between patients in the liver resection and radiofrequency ablation groups. (a) Sensitivity analysis of the 3-year overall survival rate comparison. (b) Sensitivity analysis of the 3-year progression-free survival rate comparison. (c) Sensitivity analysis of the 5-year overall survival rate comparison. (d) Sensitivity analysis of the 5-year progression-free survival rate comparison. (e) Sensitivity analysis of the morbidity rate comparison. A single study was removed at a time, and the pooled estimation of the remaining studies was performed. *CI*: Confidence interval.

high-quality randomized controlled trails (RCTs) are needed to resolve this problem.

A well-designed RCT may provide more convincing data about the strengths and shortcomings of RFA and LR in the treatments of CRCLM. Nevertheless, no results from the RCT have been published yet. This issue can be explained by

several reasons. One factor may be the reluctance of patients to be randomly assigned. Some patients prefer to undergo surgical operation rather than RFA. Another factor is surely the objective difficulty in balancing the clinicopathological features, including stage of disease, size, and number of liver metastasis, presence or absence of extrahepatic disease,

Figure 5: Funnel plot describing the comparative analysis of survival and morbidity rates between patients in the liver resection and radiofrequency ablation groups. (a) Funnel plot describing the comparative analysis of 3-year overall survival rate. (b) Funnel plot describing the comparative analysis of 3-year progression-free survival rate. (c) Funnel plot describing the comparative analysis of 5-year overall survival rate. (d) Funnel plot describing the comparative analysis of 5-year progression-free survival rate. (e) Funnel plot describing the comparative analysis of morbidity rate. *RR*: Risk ratio.

types of previous, concomitant, or salvage chemotherapies, and primary and secondary end points between the two arms. Moreover, many clinicians may be reluctant to enroll patients into trials because they are convinced that the currently available data from highly selected patient series provide sufficient evidence. Finally, the huge economic costs of performing the RCT may represent a further obstacle.

Admittedly, there are several limitations in our study. First of all, majority of the enrolled studies were retrospectively performed, which were susceptible to several biases. Second, heterogeneity was remarkable in our meta-analysis. Heterogeneity might exist in the age, sample size, study region, tumor stage, liver function reserve, and history of previous treatments of the patients. Moreover, the clinicopathological features of patients in the RFA groups might not be comparable to that of patients in the LR group. Third, it is indeed quite important to analyze the influence of chemotherapy and some other therapies on the prognosis. To our regret, only one study provided us with

the survival outcome with respect to whether the patients underwent chemotherapies. Moreover, the detailed cycles, regiments, and the other therapies were not homogeneous. We hope that future randomized controlled studies may resolve this problem and provide us with much more sound clinical evidences. Finally, publication bias remains to be a main concern. Articles with negative results were much more difficult to be favored.[8] Thus, the present results may be overvalued to some extent.[8] In addition, although we tried our best to identify as more relevant articles as possible, we only searched articles written in English in a limited number of online databases. The included number of studies may be somehow insufficient.

In conclusion, CRCLM patients who underwent LR gained better clinical outcomes compared with those of patients who underwent RFA. Meanwhile, the advantages of RFA including lower morbidity should be noted. More well-designed RCTs should be performed before we finally arrive at a rational comprehension about the therapeutic value of the two treatment options.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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