META ANALYSIS

Radiofrequency ablation combined with transcatheter arterial chemoembolization therapy versus surgical resection for Barcelona-Clinic Liver Cancer (BCLC) A hepatocellular carcinoma: a meta-analysis

Weidong Wang, Sinan Hou, Zelong Zhong, JiaYan Ni, Xiongying Jiang, Dong Chen, Yaoting Chen, Jianghong Luo, Hongliang Sun, Linfeng Xu

ABSTRACT

Purpose: The objective of our study was to compare the effectiveness of the combination of transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) with that of surgical resection (SR) in Barcelona-Clinic Liver Cancer (BCLC) A hepatocellular carcinoma.

Materials and Methods: PubMed, Medline, Embase, and Cochrane Library were searched for comparisons of the two therapies from January 2006 to December 2017. Overall survival rate (OS), recurrence-free survival rate (RFS), complications, and the average length of hospital stay were compared and analyzed. Review Manager v. 5.2 from the Cochrane Collaboration was used for statistical analyses.

Results: Seven case-control studies and one randomized controlled trial were identified, of which 717 were treated with a combination of TACE and RFA and 785 were treated with SR. Meta-analysis data revealed that TACE plus RFA had significantly better effectiveness on 1.0-y OS (OR = 0.50, p = .009). The major complications (ORcomplications = 1.88, p = .02) after the combined therapy were significantly lower than those after SR. There were three studies that reported the average length of hospital stay. The hospital stay for the SR group vs the combined therapy group was 19.8 ± 8.4 d vs 7.4 ± 2.2 d, respectively (p < .0001); 18.7 ± 4.9 d vs 11.5 ± 6.9 d, respectively (p < .0001); and 16.6 ± 6.7 d vs 8.5 ± 4.1 d, respectively (p < .0001). There was no significant difference in 3.0- or 5.0-y OS and 1.0-, 3.0-, or 5.0-y RFS.

Conclusion: The combination of TACE and RFA has advantages in improving 1.0-y OS, reducing complications, and shortening the length of hospital stay over that of SR in the treatment of patients with BCLC A HCC.

Keywords: radiofrequency ablation; transarterial chemoembolization; surgical resection; hepatocellular carcinoma;meta-analysis

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ÌNTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common of all malignant tumors, with more than 700,000 new cases every year worldwide. HCC is the sixth most common cancer and the third most frequent cause of cancer deaths (1, 2). Asian patients account for 80.0% of HCC victims worldwide (3). According to the Barcelona-Clinic Liver Cancer (BCLC) staging system, curative therapy, such as surgical resection (SR) and radiofrequency ablation (RFA), are the mainstays of treatment for BCLC A hepatocellular carcinoma (defined as one HCC nodule <5.0 cm or a maximum of three nodules <3.0 cm). SR might improve the patient's survival benefit (5.0-y survival >70.0%) (4), but only 15–20% of patients with HCC are candidates for surgery because of either underlying chronic liver disease resulting in poor hepatic reserve or a multifocal distribution of tumor nodules (5, 6). RFA is considered a viable alternative to SR in patients with early HCC, especially those with impaired liver function (7). For patients with a tumor <3.0 cm in diameter, ablation is an efficient and safe treatment that provides overall survival rates (OS) similar to those achieved with SA; however, with increasing tumor size (3.0–5.0 cm), local tumor progression from incomplete ablation is a negative prognostic factor in patients with HCC treated with RFA (8-10).

Transarterial chemoembolization (TACE) as a palliative therapy that has been widely accepted for the treatment for HCC. Some studies (11, 12) have shown that TACE can increase the therapeutic effect of RFA, especially in large HCCs. The data from a previous meta-analysis indicate that the combination of TACE and RFA is more effective than RFA monotherapy in the treatment of patients with HCC

(13, 14); however, whether the combination treatment of TACE plus RFA can achieve better results compared with SA for BCLC A HCC is still uncertain.

Some studies have suggested that the effectiveness of TACE plus RFA was associated with better recurrence-free survival rate (RFS) and OS than SR in HCC (15), while other studies reported opposite results (16, 17). Still other studies found that TACE plus RFA is safe and as effective as SR for patients with HCC (18-22). To determine whether TACE plus RFA is more effective than SR for patients with BCLC A HCC, we performed this meta-analysis to comprehensively compare the effectiveness of the two therapies. This comparison could demonstrate a more effective choice for the treatment of patients with BCLC A HCC.

MATERIALS AND METHODS

Retrieval of published studies

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. To identify relevant studies, we comprehensively searched PubMed, Embase, Web of Science, and Cochrane library from January 2006 to December 2017. We used a combination of the terms “hepatocellular carcinoma” or “liver cancer”, and “surgical resection” or “hepatectomy” and “radiofrequency ablation” and “transarterial chemoembolization”. A limit was set on randomized controlled trials (RCTs), cohort studies, or case-control studies that were designed to the compare clinical efficacy and safety of TACE plus RFA with those of SR for BCLC A HCC. Language restrictions were not imposed in this search.

Inclusion and exclusion criteria

To be enrolled in this meta-analysis, clinical studies were required to fulfill the following inclusion criteria: (1) study design: the trials had to have comparative data on clinical efficacy or safety of TACE plus RFA treatment with SR in the treatment of BCLC A HCC (defined as one HCC nodule <5.0 cm or a maximum of three nodules <3.0 cm); (2) characteristics of patients: trials were required to have relatively integrated basic characteristics of enrolled patients, such as age, percentage of males, trial design, tumor size, tumor number, Child-Pugh class, and electrocorticography performance status; (3) outcomes: reported at least one item of the results of OS or RFS or the average length of hospital stay or major complications (which was defined as an event that led to substantial morbidity and disability, increased the level of care, hospital admission, or substantially lengthened hospital stay); (4) year of publication: from January 2006 to December 2017. The exclusion criteria were reviews without original data, expert opinions, abstracts, editorials, letters, case reports, and studies lacking control groups.

Data extraction

Data extraction was independently conducted by two reviewers and using a standardized approach, with any disagreements settled by a discussion of the respective study data and adjudicated by a third reviewer (Lin-feng Xu). From each study, the following data were extracted: publication details (name of the first author, year of publication, and country) and study characteristics (study design, average age, percentage of men, treatment, tumor size, Child-Pugh grade, OS, RFS, and major complications).

Statistical analyses

To obtain an overall comparison of the efficacy of TACE plus RFA versus that of SR, standard meta-analysis techniques were used. All analyses were performed on dichotomous outcomes. We analyzed dichotomous variables using the estimation of odds ratios (OR) with a 95.0% confidence interval (95%CI). Pooled OR with 95%CI were calculated using either the fixed-effects model or random-effects model. For each meta-analysis, the chi-squared (χ^2) and I^2 tests were first calculated to assess the heterogeneity of the included trials. $P < .05$ or $I^2 > 50.0\%$ were considered significant. For $P > .05$ or $I^2 < 50.0\%$, the assumption of homogeneity was deemed invalid and the random-effects model was used; otherwise, data were assessed using the fixed-effects model. The risk of bias of the included trials was assessed using funnel plots, and an asymmetric funnel plot suggests possible publication bias. Statistical analysis was performed using Review Manager (v 5.2) from the Cochrane Collaboration. Results were deemed significant at a $P < .05$.

RESULTS

Our search yielded 64 studies. After reviewing each abstract or original publication and extracting data from the publications, seven case-control studies and one RCT were included in our meta-analysis (Yamakado et al., 2008; Kagawa et al., 2010; Takuma et al., 2013; Kim et al., 2013; Li et al., 2015; Liu et al., 2016; Lee et al., 2017; and Bholee et al., 2017) that comprised 1,502 patients, of which 785 were treated with SR and 717 with TACE plus RFA. The baseline characteristics of the trials included in the meta-analysis are listed in Table 1. The OS, RFS, and major complications of the patients in all included trials are summarized in Tables 2 and 3.

Study quality

The quality of the case-control studies was evaluated according to the Newcastle-Ottawa scales. The quality of the RCTs was evaluated according to the revised Jadad’s scale (23, 24). All seven case-control studies had five to seven points; the RCT had four points.

Overall survival rate

Eight studies reported data on the 1.0-y OS and there was no significant heterogeneity among these six studies ($\chi^2_{1\text{-year}} = 3.43$, $I^2_{1\text{-year}} = 0.0\%$, $P_{1\text{-year}} = .84$); thus, the fixed-effects model was used to pool the results. Meta-analysis showed that the combination of TACE plus RFA was associated with a higher 1.0-y OS compared with that of SR (OR 1.0-y = 0.50, 95% CI: 0.30–0.84, p = .009) (Fig. 1).

There were eight and seven studies that reported data for 3.0- and 5.0-y OS, respectively, and based on the results of tests for heterogeneity among the trials ($\chi^2_{3\text{-year}} = 18.62$, $I^2_{3\text{-year}} = 62.0\%$, $P_{3\text{-year}} = .009$; $\chi^2_{5\text{-year}} = 22.48$, $I^2_{5\text{-year}} = 73.0\ \%$, $P_{5\text{-year}}$

= .0001), the random-effects model was used to pool the results. Meta-analysis showed that there was no significant difference between the TACE plus RFA and SR on 3.0- and 5.0-y OS ($OR_{3\text{-year}}$ = 0.95, 95%CI: 0.59–1.52, p = 0.82; $OR_{5\text{-year}}$ = 0.91, 95%CI: 0.58–1.43, p = .68) (Fig. 2, 3).

Table 1. Baseline characteristics of included clinical trials.

Study(year)	Design	Country	Treatment	NO. of patients	Age	Sex (M/F)	Tumor size (cm)	Child-Pugh class (A/B/C)	Follow-up (month)	Hospitalization (days)
Yamakado K etal(2008)	CS	Japan	SR	62	64.5± 9.6	51/11	2.7 ± 2.1	62/0/0	38 ± 20	---
			TACE+RFA	104	66.5 ± 8.7	79/25	2.5 ± 0.8	104/0/0	37 ± 18	---
Kagawa T et al (2010)	CS	Japan	SR	55	66.1± 8.4	40/15	2.8(1-5)	---	49(1-102)	---
			TACE+RFA	62	67.5 ± 8.4	39/23	2.4(0.8-5)	---	50(9-95)	---
Takuma Y et al (2013)	CS	Japan	SR	176	67.0(61.3–73.0)	128/48	2.5(2–3.3)	167/9/0	45(28-61)	---
			TACE+RFA	154	71.0(65.0–75.5)	107/47	2 (1.6–2.5)	114/40/0	52(34-84)	---
Kim JW et al (2013)	CS	Korea	SR	47	58.8 ± 10.7	36/11	3.66 ± 0.76	45/2/0	31.7±10	19.8± 8.4
			TACE+RFA	37	61.7 ± 11.1	31/6	3.46 ± 0.75	31/0/0	29.9±7.8	7.4 ±2.2
Li S et al(2015)	CS	China	SR	148	54(23–75)	133/15	3.9 ± 1.8	140/8/0	43.4 ± 25.9	18.7 ± 4.9
			TACE+RFA	137	51(23–74)	129/8	3.7 ± 1.8	124/13/0	43.4 ± 25.9	11.5 ± 6.9
Liu H et al(2016)	RCT	China	SR	100	49 (30–76)	94 /6	3.0 (0.6–5.0)	98/2/0	56 (5-85)	---
			TACE+RFA	100	52 (31–80)	86 /14	2.8 (0.6–5.0)	96/4/0	56 (5-85)	---
A. K. Bholee (2017)	CS	China	SR	148	52.2 ± 11.2	136 /12	3.0 ± 1.1	144/4/0	50.2 ± 32.3	---
			TACE+RFA	74	54.9 ± 10.8	68 /6	2.9 ± 1.1	70/4/0	56.9 ± 33.5	---
Hyo-jae Lee (2017)	CS	Korea	SR	49	60.8 ± 8.2	37 /12	2.5 ± 0.3	49/0/0	41.0 (3.6–87.4)	16.6 ± 6.7
			TACE+RFA	49	61.7 ± 9.8	37 /12	2.6 ± 0.3	49/0/0	34.3 (6.3–72.9)	8.5 ± 4.1

RCT, randomized controlled trial; CS, cohort study; SR, surgical resection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; M, male; F, female. Data*: total data of the relative study. NA, not applicable; SD, standard deviation.

Recurrence-free survival rate

There were eight, eight, and seven studies that reported data on 1.0-, 3.0-, and 5.0-y RFS, and based on the results of tests for heterogeneity between trials ($\chi^2_{1\text{-year}}$ = 34.50, $I^2_{1\text{-year}}$ = 80.0%, $P_{1\text{-year}}$ < .001;$\chi^2_{3\text{-year}}$ = 21.65, $I^2_{3\text{-year}}$ = 68.0%, $P_{3\text{-year}}$ = .0003;$\chi^2_{5\text{-year}}$ = 62.25, $I^2_{5\text{-year}}$ = 93.0%, $P_{5\text{-year}}$ < .00001), the random-effects model was used to pool the results. The meta-analysis showed that there was no significant difference between the TACE plus RFA and SR on 1.0-, 3.0-, and 5.0-y RFS ($OR_{1\text{-year}}$ = 0.85, 95%CI: 0.43–1.67, p = .63; $OR_{3\text{-year}}$ = 1.22, 95%CI: 0.83–1.79, p = .32; $OR_{5\text{-year}}$ = 1.00, 95%CI: 0.47–2.12, p = 1.00) (Fig. 4, 5, 6).

Major complications

Major complications were defined as an event that led to substantial morbidity and disability, increased the level of care required, resulted in hospital admission, or substantially lengthened the hospital stay. All other complications were considered minor. There were seven studies that reported the comparative data for major complications. Based on the results of test for heterogeneity between trials (χ^2 = 5.94, I^2 = 0.0%, P = .43), the fixed-effects model was used to pool the results in the analysis of major complications. Meta-analysis data and forest plots indicated that SR was associated with significantly higher complications than TACE plus RFA therapy (OR = 1.88, 95%CI: 1.10–3.22, P = .02) (Fig. 7).

Average length of hospital stay

Three studies reported the average length of hospital stay as follows for the SR group vs the combined therapy group: 19.8 ± 8.4 d vs 7.4 ± 2.2 d (p < .0001); 18.7 ± 4.9 vs 11.5 ± 6.9 d (p < .0001); and 16.6 ± 6.7 vs 8.5 ± 4.1 d (p < .0001), respectively.

Assessment of publication bias

The publication bias in this meta-analysis was determined using a funnel plot. In the analysis of the effect of 1.0-y OS and complications, the symmetry of the funnel plot's shape suggested that there was no obvious publication bias in this meta-analysis (Fig. 8, 9).

Table 2 Overall survival rates of patients in the included trials.

Study(year)	NO. of patients	1-year overall survival rate (%)	2-year overall survival rate (%)	3-year overall survival rate (%)	4-year overall survival rate (%)	5-year overall survival rate (%)	Major Complications
Yamakado K etal (2008)			NA		NA		
SR	62	97(60/62)		93(58/62)		81(50/62)	3.2(2/62)
TACE+RFA	104	98(102/104)		94(98/104)		75(78/104)	2.2(3/104)
Kagawa T et al (2010)			NA		NA		NA
SR	55	92.5(51/55)		82.7(45/55)		76.9(42/55)	
TACE+RFA	62	100(62/62)		94.8(59/62)		64.6(40/62)	
Takuma Y et al (2013)			NA		NA		
SR	176	97(171/176)		87(153/176)		74(91/176)	0.6(1/176)
TACE+RFA	154	99(152/154)		83(128/154)		58(89/154)	1.1(2/154)
Kim JW et al (2013)						NA	
SR	47	95.7(45/47)	89.4(42/47)	84.3(40/47)	80.3(38/47)		14.9(7/47)
TACE+RFA	37	97.3(36/37)	86.5(32/37)	78.4(29/37)	78.4(29/37)		2.7(1/37)
Li S et al(2015)			NA		NA		
SR	148	88(130/148)		66(98/148)		47(69/148)	2(3/148)
TACE+RFA	137	95(130/137)		74(101/137)		67(92/137)	1.5(2/137)
Liu H et al(2016)			NA		NA		
SR	100	97.0(97/100)		83.7(84/100)		61.9(62/100)	23.0(23/100)
TACE+RFA	100	96.0(96/100)		67.2(67/100)		45.7(46/100)	11.0(11/100)
A. K. Bholee(2017)			NA		NA		
SR	148	91.2(135/148)		64.4(95/148)		47.7(71/148)	4.1(6/148)
TACE+RFA	74	94.6(70/74)		75.1(56/74)		55.3(41/74)	1.4(1/74)
Hyo-jae Lee(2017)			NA		NA		
SR	49	93.9(46/49)		86.7(42/49)		74.6(37/49)	2.0(1/49)
TACE+RFA	49	95.9(47/49)		87.4(43/49)		87.4(43/49)	6.1(3/49)

TACE, transarterial chemoembolization; RFA, percutaneous radiofrequency ablation; SR, surgical resection; NA, not applicable.

Table 3 Recurrence-free survival rates of patients in included trials.

Study(year)	NO. of patients	1-year Recurrence-free Survival rates(%)	2-year Recurrence-free Survival rates(%)	3-year Recurrence-free Survival rates(%)	4-year Recurrence-free Survival rates(%)	5-year Recurrence-free Survival rates(%)
Yamakado K et al(2008)			NA		NA	
SR	62	89(55/62)		69(43/62)		26(16/62)
TACE+RFA	104	92(96/104)		64(67/104)		27(28/104)
Kagawa T et al (2010)			NA		NA	
SR	55	64.5(35/55)		40.1(22/55)		18.0(10/55)
TACE+RFA	62	75.6(47/62)		41.1(25/62)		36.4(23/62)
Takuma Y et al (2013)			NA		NA	
SR	176	84(148/176)		56(98/176)		40(91/176)
TACE+RFA	154	85(131/154)		37(57/154)		15(23/154)
Kim JW et al (2013)						NA
SR	47	81.8(38/47)	68.5(32/47)	68.5(32/47)	65(31/47)	
TACE+RFA	37	89.2(33/37)	75.2(28/37)	69.4(25/37)	69.4(25/37)	
Li S et al(2015)			NA		NA	
SR	148	75(111/148)		58(86/148)		44(65/148)
TACE+RFA	137	92(126/137)		69(95/137)		61(84/137)
Liu H et al(2016)			NA		NA	
SR	100	94.0(94/100)		68.2(68/100)		48.4(48/100)
TACE+RFA	100	83.0(83/100)		44.9(45/100)		35.5(36/100)
A. K. Bholee (2017)			NA		NA	
SR	148	87.8(130/148)		48.3(71/148)		33.5(50/148)
TACE+RFA	74	68.9(51/74)		49.2(36/74)		40.9(30/74)
Hyo-jae Lee(2017)			NA		NA	
SR	49	83.7(41/49)		63.4(31/49)		45.4(22/49)
TACE+RFA	49	91.7(45/49)		63.1(31/49)		55.2(27/49)

TACE, transarterial chemoembolization; RFA, percutaneous radiofrequency ablation; SR, surgical resection; NA, not applicable.

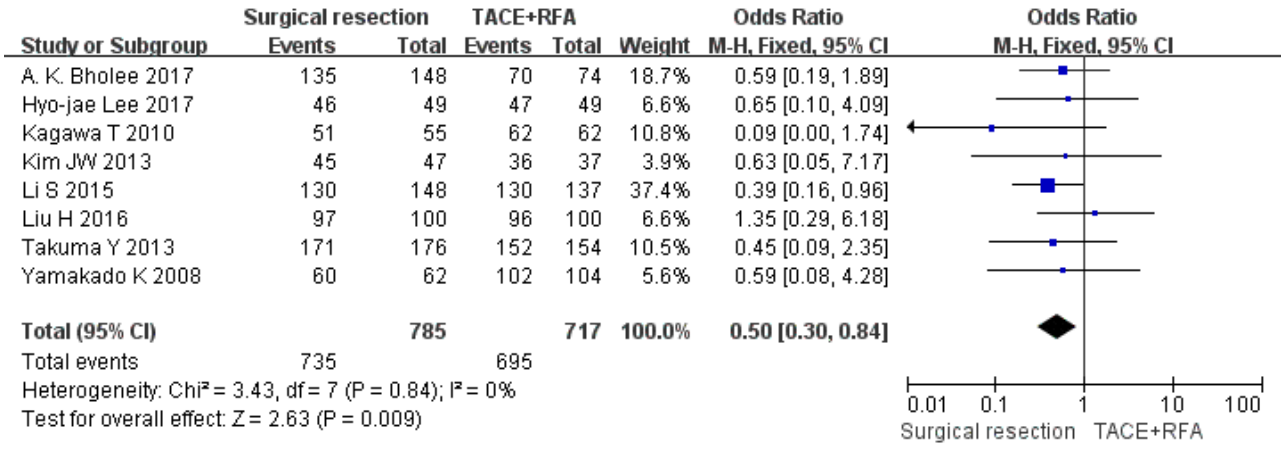

Figure 1. Meta-analysis of 1.0-y overall survival rate.

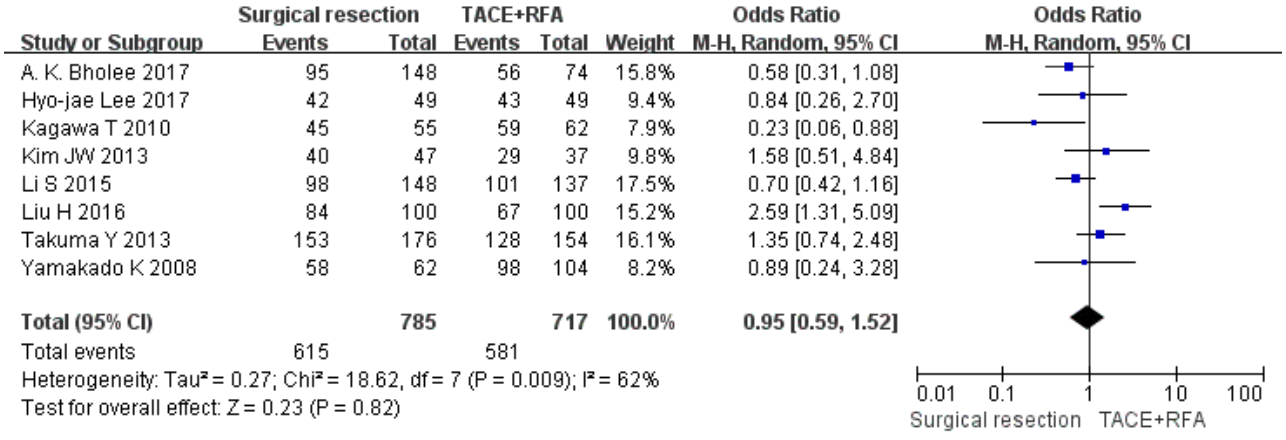

Figure 2. Meta-analysis of 3.0-y overall survival rate.

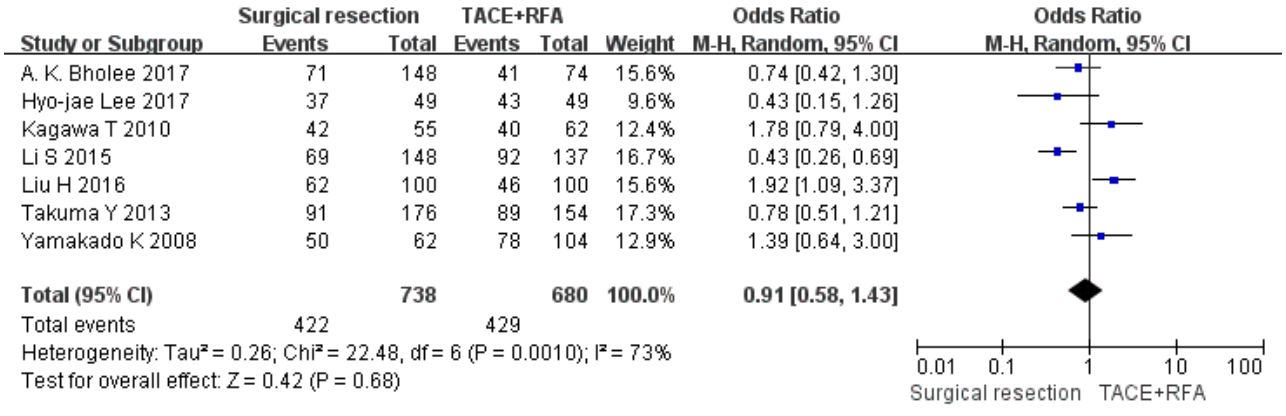

Figure 3. Meta-analysis of 5.0-y overall survival rate.

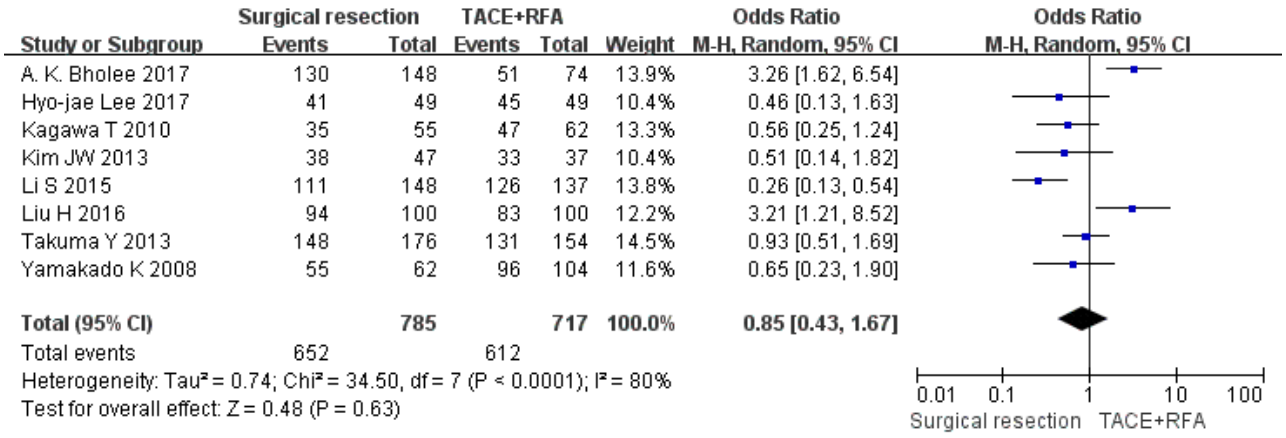

Figure 4. Meta-analysis of 1.0-y recurrence-free survival rate.

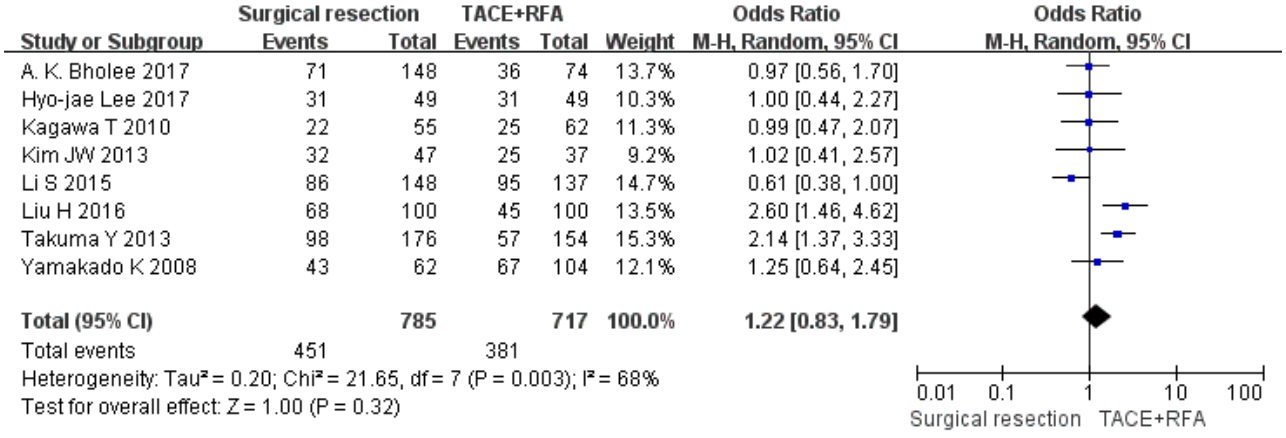

Figure 5. Meta-analysis of 3.0-yrecurrence-free survival rate.

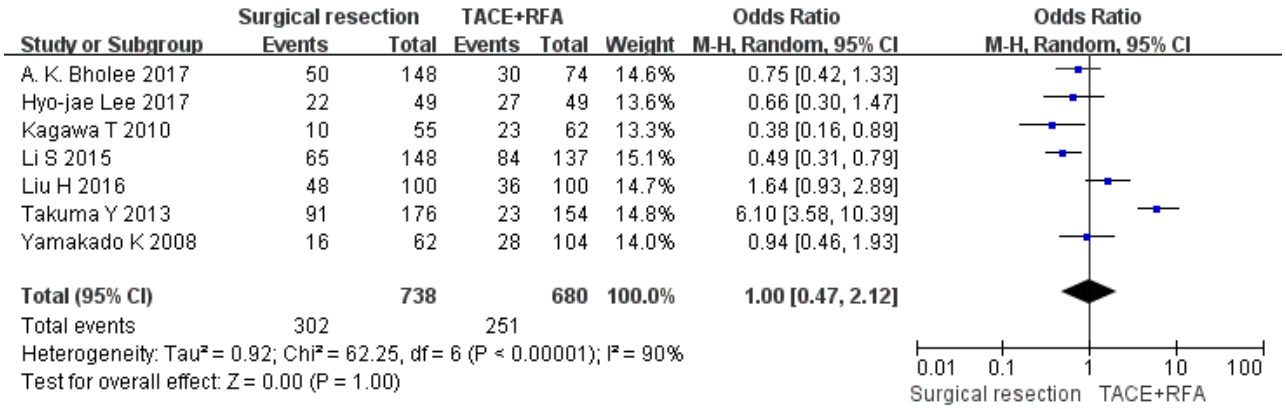

Figure 6. Meta-analysis of 5.0-yrecurrence-free survival rate.

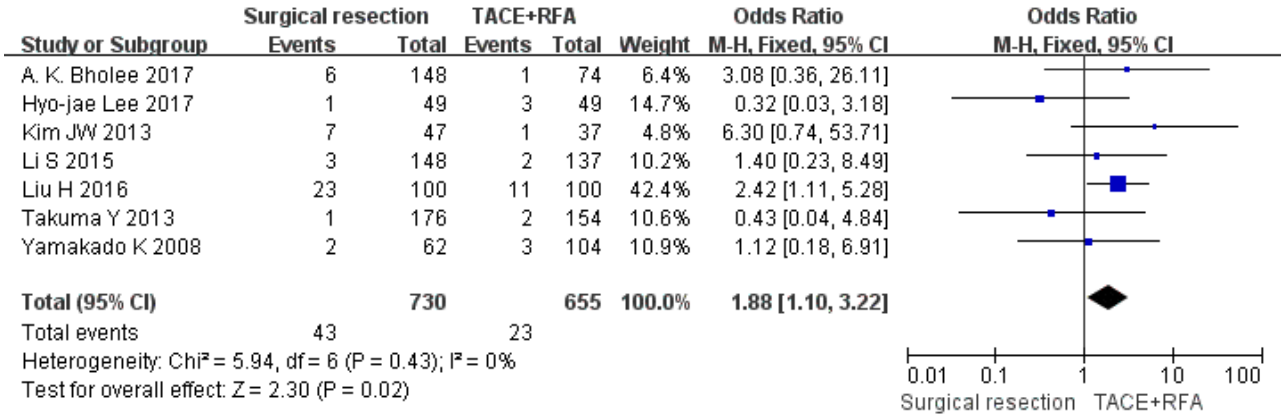

Figure 7. Meta-analysis of major complications.

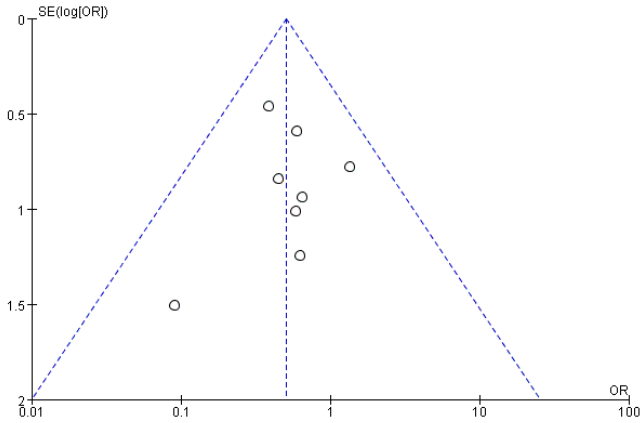

Figure 8. Funnel plot of 1.0-year overall survival rate.

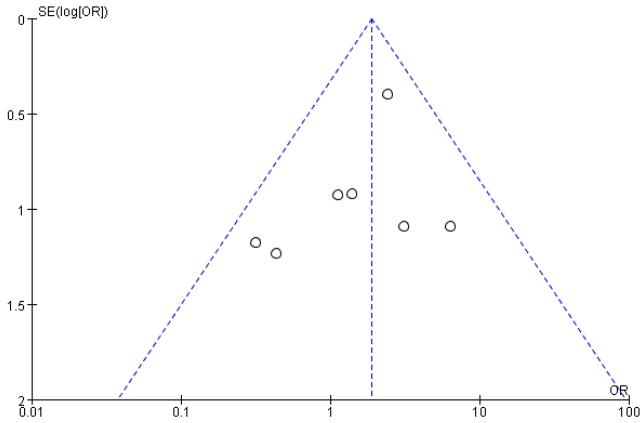

Figure 9. Funnel plot of major complications.

DISCUSSION

SR remains the best treatment choice for patients with early stage HCC. As new imaging techniques and technology advance, imaging-guided therapies for liver cancer have undergone rapid developments because of their efficacy and minimal invasiveness. RFA is considered a viable alternative to SR in patients with early HCC; however, whether SR or RFA is the better alternative treatment for small HCC is still controversial (25-28). Incomplete ablation is one of the main obstacles that greatly hinders the effectiveness of RFA for HCC, the reasons of which are, first, for the tumor with a large size or irregular shape, it is often difficult to determine the ideal ablated margin. Second, the mechanical limits of RFA and the target temperature for ablation cannot be easily reached because of the “heat sink” effect of blood vessels, especially large vessels, within or around the tumor. There could exist microscopic vascular invasion and satellites around the HCC. Local tumor progression caused by incomplete ablation is a negative prognostic factor (29-32) for achieving a larger ablated zone and complete necrosis of HCC; therefore, the combination of interventional therapies was designed for clinical practice. One such strategy is TACE plus RFA. TACE is regional therapy that treats HCC by obstructing tumor vessels and providing regional chemotherapy. TACE might reduce the heat-sink effect of large vessels adjacent to HCC, resulting in a considerable increase in the ablation zone. TACE might also be effective in treating undetected micrometastasis adjacent to the main tumor. In addition, edematous changes in the tumor and its surrounding area induced by ischemia and inflammation after TACE is expected to enlarge the tumor necrosis area during the RFA procedure (33-35). Thus, combining TACE with RFA is expected to reduce local progression; however, some studies consider that TACE is not necessary when RFA can completely ablate the tumor, and it might increase the occurrence of adverse events (36, 37). Whether sequential treatment of TACE plus RFA can achieve therapeutic effects better or similar to SR is still uncertain (15-22). A meta-analysis is a suitable method by which to resolve this conflict.

Guo’s (38) meta-analysis on this topic showed that TACE plus RFA is safe and as effective as SR for patients with early stage HCC; however, that

meta-analysis comprised only four studies. Hence, we created this meta-analysis to include more new studies to further compare the effectiveness of the two therapies and reach a more valid conclusion. Our meta-analysis data revealed that TACE plus RFA had significantly better effectiveness on 1.0-y OS (OR 1.0-y = 0.47, 95 %CI: 0.26–0.85, p = .01). The major complications (OR = 2.07, 95%CI: 1.15–3.75, p = .02) after the combined therapy were significantly lower than those after SR. There was no significant difference between the combined therapy and SR on the 3.0- and 5.0-y OS and the 1.0-, 3.0-, and 5.0-y RFS. In addition, TACE plus RFA therapy might shorten the length of the hospital stay. Thus, we believe that TACE plus RFA has shown to be minimally invasive and safe in treating patients with BCLC A HCC, that that it is a viable choice of treatment. With further research on the topic and the progress in technology, scholars have reached new conclusions. In particular, Liu's (16) RCS, which is regarded as the most efficient and high-level evidence for clinical research, contributes quite a bit to the final result. For these reasons, we draw a conclusion different from that reached in Guo's study.

The risk of bias in this meta-analysis was assessed by the review manager from the Cochrane Collaboration. Publication bias of this study was evaluated using funnel plot symmetry (39, 40). In the analysis of the effect of 1.0-y OS and major complications, the symmetry of the funnel plot's shape suggested that there was no obvious bias in this meta-analysis. The quality of the case-control studies was evaluated according to the Newcastle-Ottawa scales. The overall quality of the studies included in this meta-analysis was detected and judged to be high; therefore, we can conclude that the studies included in the meta-analysis are strong evidence to support our results.

Conclusions

The combination of TACE and RFA has greater advantages of improving 1.0-y OSR, reducing complications, and shortening the length of hospital stay than SR in the treatment of patients with BCLC A HCC.

Study Limitations

This study had several limitations. The included studies were mostly case-control studies with only one RCS, which could lead to selection bias. In addition, because of the lack of sufficient data, we were unable to perform subgroup analyses to compare the effect of TACE plus RFA and SR on patients with different disease statuses (such as <3.0 cm HCC or 3.0–5.0 cm HCC). The inclusion criteria bias of the included studies might also affect the obvious consistency of the effects, cause between-study heterogeneity, and finally influence the entire quality of our study. In the future, more RCTs should be enrolled to provide additional evidence.

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