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Prognosis for intrahepatic cholangiocarcinoma patients treated with postoperative adjuvant transcatheter hepatic artery chemoembolization

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ABSTRACT

Objective: We used meta-analysis to evaluate the efficacy of transcatheter hepatic arterial chemoembolization (TACE) for the treatment of intrahepatic cholangiocarcinoma (ICC). Methods: We performed the meta-analysis using the R 3.12 software and the quality evaluation of data using the Newcastle-Ottawa Scale. The

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main outcomes were recorded as 1-year overall survival (OS), 3-year OS, 5-year OS, and hazard ratio (HR) of TACE treatment or non-TACE treatment. The heterogeneity test was performed using the Q-test based on chi-square and I^2 statistics. Egger's test was used to test the publication bias. The odds ratio or HR and 95% confidence interval (CI) were used to represent the effect index. Results: Nine controlled clinical trials involving 1724 participants were included in this study; patients came mainly from China, Italy, South Korea, and Germany. In the OS meta-analysis, the 1-year and 3-year OS showed significant heterogeneity, but not the 5-year OS. TACE increased the 1-year OS (odds ratio = 2.66, 95% CI: 1.10-6.46) of the patients with ICC, but the 3- and 5-year OS rates were not significantly increased. The results had no publication bias, but the stability was weak. The HR had significant heterogeneity ($I^2 = 0\%$, $P = 0.54$). TACE significantly decreased the HR of ICC patients (HR = 0.59, 95% CI: 0.48-0.73). The results had no publication bias, and the stability was good. Conclusions: Treatment with TACE is effective for patients with ICC. Regular updating and further research and analysis still need to be carried out.

ARTICLE INFO

Keywords: Meta-analysis; Intrahepatic cholangiocarcinoma; Transcatheter hepatic artery chemoembolization

Introduction

Intrahepatic cholangiocarcinoma (ICC), a disease distinct from hepatocellular carcinoma (HCC),[1-3] is the second most common primary malignancy in the liver. It is derived from bile duct epithelial cells and belongs to the group of cholangiocarcinoma diseases, constituting about 5%-15% of the cases.[4-7] The incidence of ICC is only about 10% but is on the rise.[8-11] The seriousness of the situation is shown by the cumulative mortality rate having increased by 39% between 1979 and 2004.[12-15] Although there has been some progress in the study of ICC in recent years, therapy and prognosis for the disease are still far from satisfactory.[16-18] An important reason for the slow progress is that the early symptoms of ICC are not visible, and there is a lack of adequate diagnostic methods. By the time it has been diagnosed, ICC has often reached an advanced stage, and the opportunity for surgery has been lost. [19-22]

Transcatheter hepatic artery chemoembolization (TACE), a palliative local treatment method, is widely used in the treatment of unresectable primary and metastatic liver cancer.[23-25] Compared with systemic chemotherapy, TACE can provide higher local drug concentration with less systemic toxicity.[26-28] TACE induces ischemic necrosis of the tumor by embolizing the artery that supplies it with blood. TACE has been demonstrated to improve the overall survival (OS) of patients with ICC.[29-32] However, there is no consensus in the literature as to the efficacy of TACE for ICC, possibly because of the small sample sizes in these studies.

A recent retrospective study reported that ICC patients treated with conventional TACE showed prolonged survival compared to the control group.[33] Whereas patients undergoing surgery had a median OS of only 5 months, in those receiving adjuvant TACE, the OS increased to a median of 12 months. Despite this, TACE did not prolong the recurrence-free survival compared with non-TACE groups but could prolong the short-term OS of patients with ICC.[33] Also, Lu et al[34] suggested that only patients with elevated serum gamma-glutamyl transferase levels would benefit from TACE treatment following curative liver resection for ICC. Thus, the results from studies on the efficacy of TACE are somewhat contradictory. However, there is still a lack of meta-analysis on the TACE treatment following exairesis for ICC.

In this review, a meta-analysis was performed to investigate the prognosis of TACE treatment following exairesis for ICC to better understand the effect of TACE on ICC. We hope that this work will serve as a reference for clinical practice and as a foundation for further studies.

Table 1
The search strategy of the publications included.

Search	Query	Items found
#1	Search TACE	4480
#2	Search "transarterial chemoembolization"	2582
#3	Search "Transcatheter arterial chemoembolization"	1740
#4	Search "transcatheter hepatic arterial chemoembolization"	64
#5	Search #1 OR #2 OR #3 OR #4	6063
#6	Search ICC	19288
#7	Search "intrahepatic cholangiocarcinoma"	2171
#8	Search "intrahepatic bile duct carcinoma"	49
#9	Search #6 OR #7 OR #8	20556
#10	Search #5 AND #9	67

Materials and methods

Search strategy

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[35] A systematic literature search was conducted to search the clinical studies in English electronic literature databases, including Embase, the Cochrane Library, and PubMed. The following search terms were used: "TACE" (OR "transarterial chemoembolization" OR "transcatheter arterial chemoembolization" OR "transcatheter hepatic arterial chemoembolization") AND "ICC" OR ("intrahepatic cholangiocarcinoma" OR "intrahepatic bile duct carcinoma") (Table 1). The deadline for the literature search was June 18, 2018.

Inclusion and exclusion criteria

Strict inclusion and exclusion criteria for the literature for this meta-analysis were developed. Studies were enrolled if they (1) were reported on ICC (case group: ICC patients treated with TACE; control group: ICC patients treated without using TACE), (2) were published in the English literature, and (3) could provide or aid in computation of prognostic data in both the postoperative case and control groups, including 1-, 3-, and 5-year OS and hazard ratio (HR).

Studies were excluded if they met the following criteria (1) they lacked complete data and could not be used for statistical analysis, (2) they were nonoriginal articles, such as reviews, letters, and overviews, and (3) they were repeated publications on the same data. In those cases, only the latest reports or the articles with the complete information were included.

Data extraction and Quality assessment

Two authors independently extracted relevant data from the included publications. The contents of the extraction included the first authors of the publications, the year of publication, the country and time of the study, the study groups, the number of case and control groups, gender ratios, age range, and the data on follow-up time and prognosis. All the selected publications were assessed by quality evaluation criteria for cohort study provided by the Newcastle-Ottawa Scale, including Exposed selection, Comparability, and Outcome, with a full score of 9.[36] If the opinions of the 2 authors on data extraction and quality evaluation differed, their viewpoints were reconciled through group discussions with a third investigator.

Statistical analysis

Meta-analysis was performed using R v3.12 software (R Foundation for Statistical Computing, Beijing, China, Meta package); the odds ratio (OR) or the HR and 95% confidence interval (CI) were used to represent the effect index.

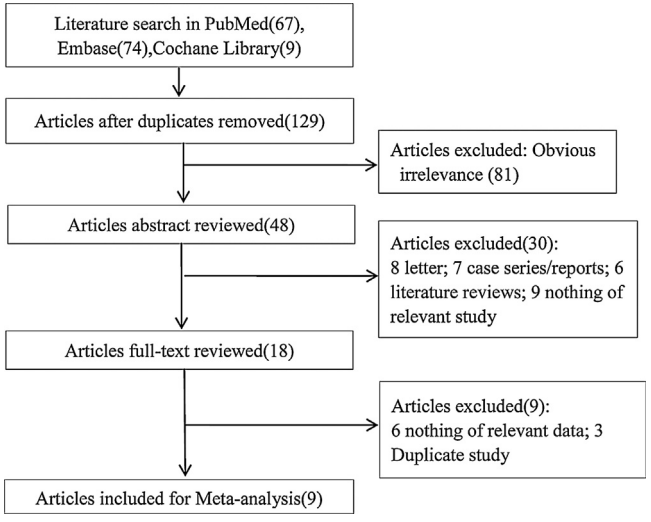

Fig. 1. Flow diagram showing the selection process for the literature.

The heterogeneity test was based on the chi-square Q test[37] and I^2 statistics. For statistical heterogeneity ($P < 0.05$ or $I^2 > 50\%$), the combined effect value was calculated by a random effects model; otherwise, a fixed effect model was used to compute the pooled effect size.[38] The publication bias test was performed by Egger's method.[39] Finally, the sensitivity was analyzed by the "leave one out" method.[40]

Results

Literature search

The publication search and selection process are shown in a flowchart (Fig 1). Altogether, 150 potentially eligible papers were retrieved from the PubMed, Embase, and Cochrane Library database in the initial search using pre-designed retrieval strategies. According to the inclusion criteria, 141 articles (21 that were repetitive, 81 that had no relationship with questions addressed in our study, 30 that were omitted after browsing the titles and abstracts, and nine that were disregarded after reading the full text) were excluded.[34-36,41-46]

Study characteristics and quality assessment

In this meta-analysis, a total of 1724 patients with ICC were included. The general features of the selected literature are detailed in Table 2. As shown in Table 2, publication year of the selected literature ranged from 2008 and 2016, with the clinical studies reported in these papers performed between 1997 and 2013; the patients were mainly from China, Italy, South Korea, and Germany. The gender distribution was uneven, with more males than females included. Most patients were of middle age or elderly, with an average age of about 50-year old; the follow-up time was 1-125 months, usually being after about 24 months (Table 2). The results showed that the quality scores of the nine articles included were above 5-7 points, higher than those of the excluded ones (Table 2).

Table 2
The characteristics of the publications included.

Author	Study Year	Study Location	Study Year	NOS	Group	N	Age	Gender (M/F:)	Follow-up (months)	1-year OS	3-year OS	5-year OS	HR (95CI%)
Aliberti C	2008	Italy	2006 .2-2007. 9	5	TACE	11	68.5 (60-82)	NA	NA	8	NA	NA	NA
					Palliative care	9		NA	NA	2	NA	NA	NA
Li A	2016	China	2007.1-2013.10	6	TACE	87	53 (45–61)	78/9	≥24	NA	NA	NA	0.40 (0.12-1.27)
					Resection					NA	NA	NA	1
Li J	2015	China	2008.1-2011.2	6	TACE	122	54 (35-74)	97/25	25.3 (2.2-76.2)	97	58	47	NA
					Resection	431	54 (36-76)	271/160		272	157	128	NA
Li T	2013	China	2000.1-2011.12	5	TACE	283	55 (18-79)	174/109	17 (1-98)	NA	NA	NA	0.56 (0.37-0.87)
					Resection					NA	NA	NA	1
Lu ZF	2016	China	2000.1-2011.12	7	TACE	75	56 ± 11	NA	NA	NA	NA	NA	0.69 (0.51-0.95)
					Resection	150	58 ± 11	NA	NA	NA	NA	NA	1
Park SY	2011	Korea	1996.1-2009.4	5	TACE	72	64 ± 10	47/52	NA	37	NA	NA	NA
					Supportive treatment	83	65 ± 11	51/32	NA	4	NA	NA	NA
Scheuermann U	2013	Germany	1997.9-2012.2	6	TACE	32	64 (44-87)	17/15	1-125	13	5	3	NA
					Resection	130	65 (33-79)	65/65		79	46	29	NA
Shen WF	2011	China	2002.7-2003.12	5	TACE	53	NA	45/8	18 (3-96)	37	20	15	NA
					Resection	72	NA	43/29		39	18	15	NA
Wu ZF	2012	China	2005.1-2006.12	6	TACE	57	Median 56	88/26	24	41	21	11	0.49 (0.32-0.76)
					Resection	57				31	9	6	1

TACE, transcatheter arterial chemoembolization; NOS, Newcastle-Ottawa Scale; OS, overall survival; HR, hazard ratio; CI, confidence interval; M/F, Male/Female.

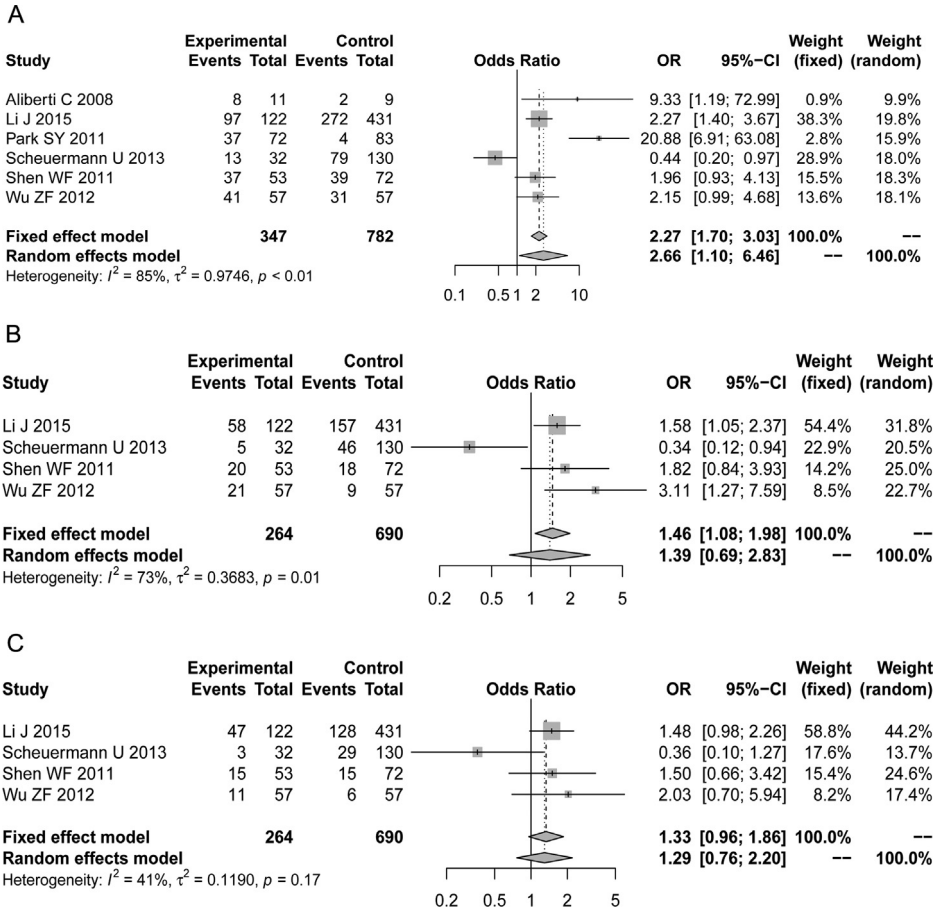

Fig. 2. Forest plot comparing the OS of the TACE and non-TACE groups. (A) 1-year OS; (B) 3-year OS; (C) 5-year OS. CI, confidence interval; OR, odds ratio.

A Meta-analysis of pooled quantitative OS

Because of the significant heterogeneity of results from studies of 1-year OS ($I^2 = 85.30\%$, $P < 0.01$) and 3-year OS ($I^2 = 73.00\%$, $P = 0.01$), we applied the random effects model (Fig 2A and B; Table 3) to calculate the pooled effect size. The result indicated that TACE treatment significantly increased the 1-year OS (OR = 2.66, 95% CI: 1.10-6.46) of the patients with ICC compared with those who underwent non-TACE treatment ($P = 0.03$, Fig 2A and Table 3). However, the 3-year OS (OR = 1.39, 95% CI: 0.69-2.83,) in the TACE group was not significantly changed compared with that in the group which did not undergo TACE ($P = 0.36$, Fig 2B and Table 3).

There was no significant heterogeneity ($I^2 = 40.90\%$, $P = 0.17$) between the studies on 5-year OS (Fig 2C and Table 3); thus the fixed-effects model was used to calculate the pooled OR and 95% CIs. The pooled result showed that although the 5-year OS of patients treated with TACE was higher than that of the untreated group, (OR = 1.33, 95% CI: 0.96-1.86, $P = 0.09$) the difference between the 2 groups was not significant (Fig 2C and Table 3).

The publication bias was evaluated by Egger's method, and no publication bias was identified (1-year OS, $t = 0.23$, $P = 0.83$; 3-year OS, $t = 0.29$, $P = 0.80$; and 5-year OS, $t = 0.57$, $P = 0.63$; Table 3), indicating that the results were stable and reliable. In addition, the "leave one out" method was used to determine the sensitivity across the study.

Table 3
The results of meta-analysis.

Group	Sample size			Test of association			Model	Test of heterogeneity[a,b]			Egger's test for publication bias[c]	
	K	Cases	Control	*OR (95%CI)*	*Z*	*P*		*Q*	*P*	I^2 (%)	*t*	*P*
1-year OS	6	347	782	2.6611 [1.0956; 6.4637]	2.16	0.0307	Random	34.00	<0.01	85.3	0.2332	0.8270
3-year OS	4	264	690	1.3928 [0.6856; 2.8293]	0.92	0.3596	Random	11.12	0.01	73.0	0.2921	0.7977
5-year OS	4	264	690	1.3336 [0.9571; 1.8582]	1.70	0.0890	Fixed	5.08	0.17	40.9	0.5700	0.6262

[a] Random-effects model was used when the p for heterogeneity test <0.05, otherwise the fixed-effect model was used.
[b] $P < 0.05$ is considered statistically significant for Q statistics.
[c] Egger's test to evaluate publication bias, $P < 0.05$ is considered statistically significant. OR: Odds ratio; CI: confidence interval.

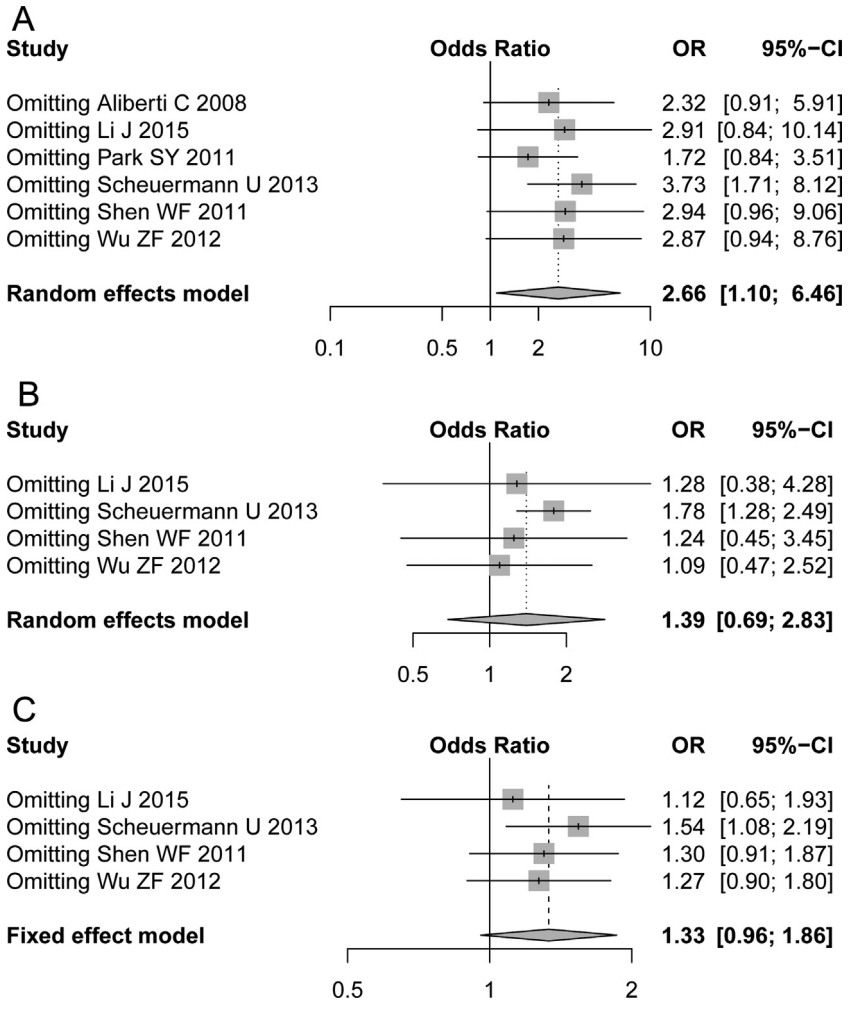

Fig. 3. Sensitivity analysis by the "leave one out" method for the OS of ICC patients treated with TACE. (A) 1-year OS, (B) 3-year OS, and (C) 5-year OS. CI, confidence interval. OR, odds ratio.

By omitting the studies of Scheuerman et al,[46] Li et al,[43] and Park et al[31] (Fig 2A), the OR values in the 1-year OS were reversed (Fig 3A). Also, by omitting the study of Scheuerman et al,[46] the OR values in the 3- and 5-year OS were all appreciably changed (Figs 2B and C, 3B and C). Thus, more studies of sufficient relevance are needed to confirm the results.

Meta-analysis quantitative data merging- HR

According to the significant heterogeneity ($I^2 = 0\%$, $P = 0.54$), a fixed effect model was used to calculate the pooled effect size of HR. The meta-analysis revealed that there were differences between the groups treated with or without TACE (HR = 0.59, 95% CI: 0.48-0.73), and the mortality rate of people treated with TACE was 0.59 times that of patients subjected to non-TACE surgery, a result that was statistically significant (HR = 0.59, 95% CI: 0.48-0.73; Fig 4A).

No publication bias was found by Egger's test ($t = 1.59$, $P = 0.25$), suggesting that the result was stable.[47] The sensitivity was analyzed by the "leave one out" method, and the results

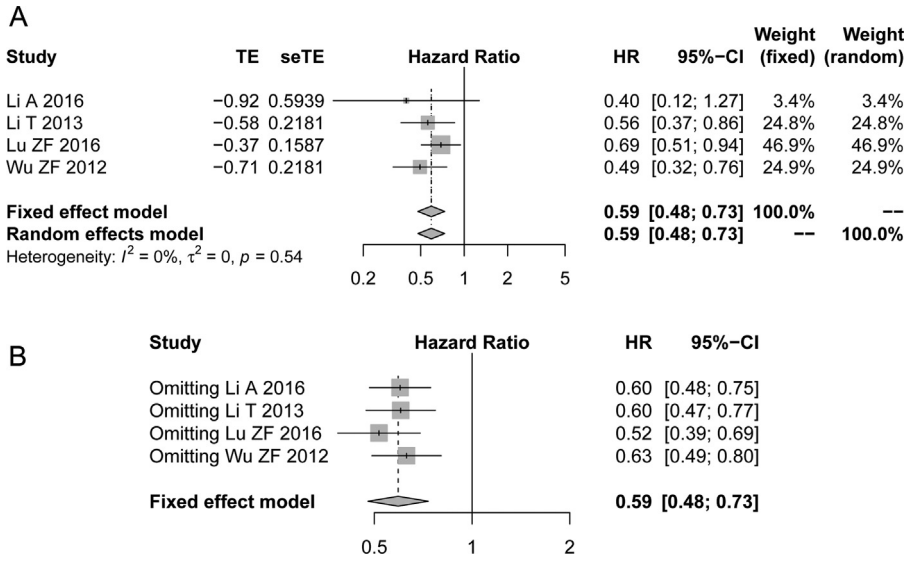

Fig. 4. Meta-analysis quantitative data merging-HR. (A) Forest plot comparing the hazard ratio (HR) of Experimental TACE-treated and non-TACE-treated groups; TE, logarithm of the corresponding utility value; seTE, Standard error, corresponding to the utility value; CI, confidence interval. (B) Sensitivity analysis by meta-analysis for the HR of ICC patients treated with TACE. CI, confidence interval. HR, hazard ratio.

showed that the HR value of each model was not reversed, indicating that the results were stable (Fig 4B).[48]

Discussion

Currently, it remains unresolved whether treatment with TACE is safe and efficacious in prolonging the patient's survival time.[49-52] In the meta-analysis presented here, we included nine studies comparing survival outcomes in terms of 1-, 3-, and 5-year OS and HR between TACE and non-TACE surgery in ICC patients. Our results revealed that TACE treatment achieved a significantly higher 1-year OS and a distinctly lower HR in ICC patients compared with non-TACE treatment. Furthermore, TACE prolonged the 3- and 5- year OS, but without statistical significance.

TACE may be able to extend the short-term OS of ICC patient.[53-55] In the present study, the 1-, 3-, and 5-year OS were all upregulated by TACE treatment, although the 1-year OS is significantly increased by TACE treatment, and there is no significant difference in the upregulation of 3- and 5-year OS.

Survival rates in patients after 6-month, 1-year, and 2-year treatment with TACE were improved compared to those receiving supportive therapy.[56-59] Studies by Li et al[43] and Shen et al[33] also supported our meta-analysis results that the 1-year OS was increased by TACE treatment compared with the non-TACE group. More recently, no significant differences were found in the 3- and 5-year OS between TACE and non-TACE treatment for HCC patients after liver transplantation[60]. Thus, all of the results point to the TACE treatment efficaciously prolonging the short-term (<2 years) survival of ICC patients.

Because local structural or periductal invasion can be completely resected together with the primary tumor or after careful lymph node dissection to remove all locally involved lymph nodes, some patients with ICC at stage III or IV can still obtain a fair prognosis by surgical resection. It is well known that TACE increases the local drug concentration available to kill tumor cells effectively and induces ischemic necrosis of tumors by embolizing the artery supply-

ing blood to the tumor.[26,61-64] However, there was no significant difference between the groups treated with or without TACE in both 3- and 5-year OS in the present meta-analysis. Similarly, Li T et al[44] suggested that TACE treatment may have no significant impact on the 3- and 5-year OS compared to the non-TACE treatment group. Nevertheless, the study of Li et al[43] showed that the 3- and 5-year OS in patients treated with TACE was significantly higher than in the group untreated by TACE. The source of these differences may be the significant heterogeneity observed in the 3-year OS, and the low sensitivity of the 3- and 5-year OS.

Patients included in this study had different ages and genders, and come from different countries and regions (China, Italy, South Korea, and Germany), which may account for the differences in the results. It was reported that highest incidence rates of ICC were found mostly among Asians (non-white, non-black ethnic backgrounds),[16] indicating that the ethnic differences should be taken into consideration in the study of ICC patients with TACE. Besides, it was reported that ICC with an abundant blood supply might respond better to treatment with TACE.[62-64] However, the blood supply type of ICC in this study is unclear; this aspect needs further review and meta-analysis. Thus, the function and molecular mechanism of TACE need more research, and a meta-analysis with a larger sample size and complete patient information to characterize the effectiveness of TACE on ICC patients is also required.[65-68]

The HR in this study is defined as the ratio of the risk of death in patients treated by TACE and that in patients treated by other methods. These results found that the heterogeneity of the 2 HRs was not significant. More importantly, compared with the control group, the risk of death in the group treated with TACE was significantly decreased. Our results are consistent with the studies of Li et al[44] in which the HR was 0.62, Wu et al[45] (HR 0.49), and Lu et al[34] (HR 0.44) in the TACE treatment group, with significant differences. Although it was reported that postoperative TACE failed to delay tumor recurrence,[29] Gusani et al[69] showed TACE to be beneficial for patients with advanced and unresectable ICCs, which is consistent with our meta-analysis results. All these results suggested that the results on HR analysis were stable, and consequently, the conclusions reliable.

There are several limitations to the meta-analysis presented here. Firstly, unknown sources of heterogeneity may affect the meta-analysis results. Second, because of the incomplete demographic data in the works of literature that were included, no further subgroup meta-analysis and regression analysis on age and race have been done. Thirdly, a sensitivity analysis (1- and 3-year OS) showed that if some of the publications were excluded; the combined HR values were reversed, indicating that the results were unstable. Finally, the studies analyzed here were based on controlled clinical trials, not qualified randomized controlled trials (RCTs). Since the quality of evidence from controlled clinical trial trials is not as high as from RCTs, the conclusions reached here still require a confirmation from high-quality RCTs.

Conclusion

This study demonstrated that TACE increased the 1-year OS of patients with ICC and decreased the risk of death in ICC patients. TACE is an effective short-term treatment for ICC. Further research and updating are necessary to verify the conclusions.

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution

JBL, YSM, GRW and DF designed the study. JBL, KJC, CCL, TMW, HMW, YS, ZZL, JHW, ZJW, XQJ, GRW, YSM, and DF performed the statistical analyses and interpreted the data. JBL, YSM, GRW, and DF wrote the manuscript. JBL, KJC, CCL, and TMW contributed equally to this work. All authors contributed to the final version of the manuscript and approved the final manuscript.

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