

Adjuvant Transarterial Chemoembolization for Patients with Intrahepatic Cholangiocarcinoma after Surgical Resection: A Systematic Review and Meta-analysis

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ABSTRACT

Aim: To investigate the efficacy of postoperative adjuvant transarterial chemoembolization (TACE) in patients with intrahepatic cholangiocarcinoma (ICC) after resection.

Methods: Studies were systematically searched until August 2021 in the following databases: MEDLINE, EMBASE, PUBMED, Web of Science, Cochrane Library, Science Direct, and Springer Link. Overall survival (OS) and recurrence-free survival (RFS) were considered as the main outcomes. Pooled hazard ratio (HR) with 95% confidence interval (95%CI) was reported as results for the survival data. Subgroup analysis was conducted on the outcomes stratified by early-stage ICC and intra-arterial chemotherapeutic regimen.

Results: Eleven studies with 2,757 patients were finally included in the study. The pooled HR of OS was 0.68 (95%CI: 0.50-0.87, $P=83.7\%$). The pooled HR of RFS was 1.00 (95%CI: 0.69-1.31, $P=88\%$). Receipt of postoperative adjuvant TACE improved the OS in the early-stage ICC subgroup (HR=0.68, 95%CI: 0.50-0.86, $P=54\%$). Addition of carboplatin could slightly improve the OS (HR=0.6, 95%CI: 0.35-0.85, $P=48\%$). But receipt of postoperative adjuvant TACE (HR=1.06, 95%CI: 0.83-1.29, $P=41.2\%$) or use of carboplatin (HR=1.30, 95%CI: 0.93-1.67, $P=0\%$) caused no significant improvement in the RFS in the early-stage ICC subgroup.

Conclusions: Postoperative adjuvant TACE could improve the OS in ICC patients after hepatectomy but could not prevent late recurrence. Survival benefit was also found in early-stage ICC patients undergoing postoperative adjuvant TACE after hepatectomy. Addition or non-addition of carboplatin in chemoembolization showed a similar OS outcome.

Key words: intrahepatic cholangiocarcinoma – transarterial chemoembolization – hepatectomy – systematic review – meta-analysis.

Abbreviations: CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; ICC: intrahepatic cholangiocarcinoma; LNM: lymph node metastases; MVI: microvascular invasion; NOS: Newcastle-Ottawa Scale; OS: overall survival; RFS: recurrence-free survival; TACE: transarterial chemoembolization.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC), which originates from the biliary epithelium of the peripheral or distal intrahepatic bile duct branches, is the second most frequently diagnosed primary hepatic cancer, and it accounts for approximately 10% of all cholangiocarcinoma. Many patients are confirmed to have an unresectable malignancy and they lose the chance of surgical resection after the detection of

ICC [1, 2]. Hepatectomy remains the best option to achieve a curative treatment; however, the overall survival (OS) and recurrence-free survival (RFS) have not been satisfactory in patients with ICC who had underwent complete surgical resection. The prognosis is discouraging due to the recurrence of ICCs after initial hepatectomy [3-5]. Hence, it is essential to decrease the incidence of postoperative recurrence in order to improve the long-term survival of patients with resectable ICC.

Multiple adjuvant therapies, such as systemic intravenous chemotherapy, radiotherapy, chemoradiotherapy, and transarterial chemoembolization (TACE), have been used in postoperative supplementary treatment of patients with ICC who underwent curative hepatectomy to prevent recurrence [6-10]. Postoperative adjuvant TACE was proved to have a beneficial effect on survival improvement, and it has been widely used for liver malignancies after surgical

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resection, such as hepatocellular carcinoma (HCC), ICC, and combined HCC and cholangiocarcinoma [10-13]. It was considered a potential adjuvant therapy to exterminate residual micrometastases, tumor satellites, or microvascular invasion (MVI) [14]. However, due to the methodological limitation and small number of enrolled patients in the postoperative adjuvant TACE subgroup in the previously published meta-analysis [10, 11], the long-term survival outcome remains unclear. In addition, the survival benefit of postoperative adjuvant therapies compared to hepatectomy alone in patients with early-stages ICC (especially in stage I disease) is still controversial [15].

Therefore, the aim of this present study was to identify the OS and RFS benefit of postoperative adjuvant TACE in ICC patients and to use further subgroup analyses to determine the risk factors that might affect the adjuvant TACE efficacy.

METHODS

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [16]. This research protocol was registered in the PROSPERO: International prospective register of systematic reviews (CRD42021271140). All the data were based on published articles; hence, there was no need of obtaining ethical approval or informed consent.

Literature Search and Selection

Related studies about postoperative adjuvant TACE for ICC patients after surgical resection were systematically searched until August 2021 in the following databases: MEDLINE, EMBASE, PUBMED, Web of Science, Cochrane Library, Science Direct, and Springer Link. The search terms were as follows: [(intrahepatic cholangiocarcinoma) OR (cholangiocarcinoma) OR (ICC)] AND [(adjuvant transarterial chemoembolization) OR (chemoembolization) OR (TACE)]. Identification of the related studies was performed by screening the references of searched literatures. Records of literature were also identified by a manually expanded search. No study design restriction or language limitation was considered in this systematic review and meta-analysis. Literature search and selection was individually conducted by two reviewers. Any divergence between the two reviewers was determined by discussion with a third reviewer in order to reach an agreement.

Eligibility Criteria

The inclusion criteria were: (1) patients with ICC who had underwent surgical resection and were confirmed by pathology; (2) the postoperative adjuvant TACE group and the non-TACE group were included; (3) full-text article with long-term survival outcomes, such as OS or RFS. The exclusion criteria were as follows: (1) palliative resection, recurrence, or metastatic tumor; (2) neoadjuvant therapy before surgical resection; (3) patients received other postoperative adjuvant therapies before or after TACE; (4) non-availability of information or insufficient data; (5) poor methodological quality; (6) case report, comments, reviews, letters, or conference abstract. If the authors of different studies belonged to the same institution at overlapping times, those studies were

not excluded immediately but conscious comparison of the methods and results was needed.

Data Extraction and Quality Assessment

Data extraction and quality assessment was individually conducted by two reviewers. Any divergence between the two reviewers was determined by discussion with a third reviewer in order to reach an agreement. The modified Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of included studies, and a score of ≥ 6 , 6~4, and < 4 was considered to indicate high, moderate, and low quality, respectively [17]. Name of the first author, year of publication, language, study period (until the censored time) and design, simple size, male ratio, age, MVI, lymph node metastases (LNM), multifocal tumor, resection margin, TNM stage, chemotherapeutic regimen, interval between hepatectomy and adjuvant TACE, supplementary treatment after ICC recurrence, median follow-up duration, and hazard ratio (HR) with 95% confidence interval (CI) of OS or RFS were extracted and assessed. The HR result of OS or RFS with 95%CI was extracted directly from the original data or from the Kaplan-Meier curves by using the Engauge Digitizer software [18-19].

Data Synthesis and Statistical Analysis

Pooled HRs and 95%CIs were reported as the results of survival data. When propensity score matching analysis was performed, the non-adjusted HR was extracted. Forest plots were used to show meta-analysis results. The I^2 statistic test was used to evaluate heterogeneity, and significant study heterogeneity was considered when the I^2 value was higher than 0.5 [20]. Considering potential clinical heterogeneity among the enrolled studies, the random-effect model was used for all outcomes. Random effects models were used weighted by the Inverse-Variance heterogeneity method. Statistical significance was considered when the p-value was less than 0.05. Subgroup analysis was performed on the outcomes stratified by early-stage ICC (percentage of stage I ICC $> 50\%$ or not) and intra-arterial chemotherapeutic regimen (combined with or without carboplatin) to reveal the source of heterogeneity, and to investigate the factors that might affect the survival benefit of adjuvant TACE [21]. Sensitivity analysis was also performed to assess the stability of the pooled results [22]. Publication bias was assessed by the Funnel plot with Egger test [6]. Statistical analysis was conducted by using the Stata software (version 13.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study Selection and Clinical Characteristics

Based on the literature search strategy, 1,684 records of study were identified. After duplicate removal, title and abstract review, and full-text reading, a total of eleven studies [23-33] with 2,757 patients were finally included in the study. A flow diagram of the study search and selection process is shown in Fig. 1. The clinical characteristics and survival outcome of the included studies are summarized in Tables I and II. Most of the included studies were designed as single-center retrospective studies [23-28, 31-33]. Almost all included studies were published in English and only one study was published

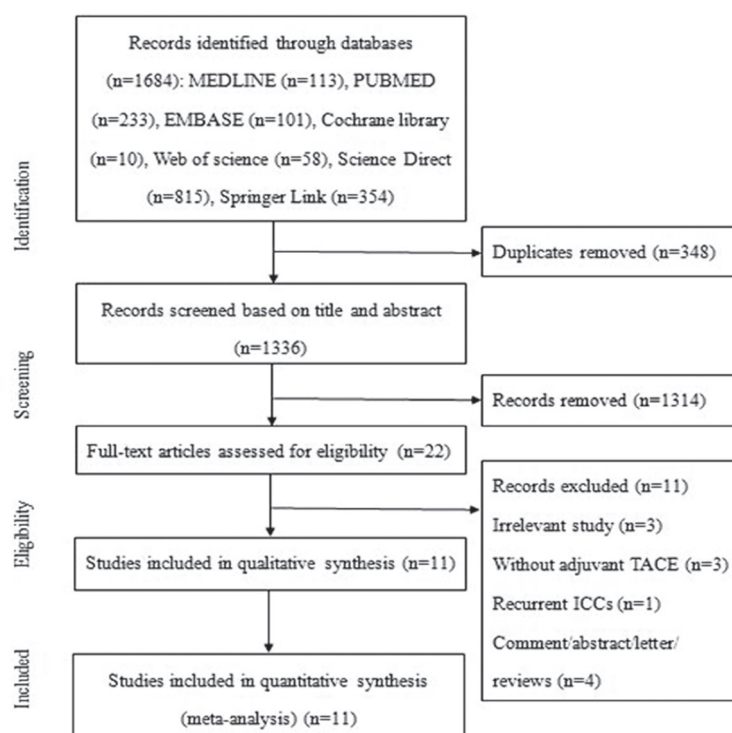


Fig. 1. Flow diagram of the study search and selection process.

in Chinese [23]. Six studies [24, 26, 28-30, 33] considered the effect of MVI on ICC, and one of the studies [33] only performed postoperative adjuvant TACE after hepatectomy in ICC patients with MVI. Ten studies [23-30, 32, 33] and seven

studies [23, 24, 26, 29, 30, 32, 33] reported LNM and multifocal ICC tumor, respectively. Nine studies [24-27, 29-33] considered the TNM stage of ICC and two studies [26, 31] included cases of mostly stage I disease. Nine studies only performed

Table I. Clinical characteristics of included studies

Study	Year	Period	Design	Simple size (TACE vs. non-TACE)	Gender, male (%)	Age (years)	MVI, %	LNM, %	Multi-focal, %	STAGE I, %	R0 resection
Wang C., [23]	2009	2005-2008	RS	80 (36:44)	80	82.5% ≤60yr	NA	20	5	NA	NA
Shen W.F., [24]	2011	2002-2010	RS	125 (53:72)	70.4	46.4% <54yr	30.4	8	34.4	33.4	Yes
Wu Z.F., [25]	2012	2005-2011	RS	114 (57:57)	77.19	56	NA	9.6	NA	57	Yes
Li T., [26]	2014	2000-2011	RS	211 (68:143)	80	55	26.1	25.4	25.1	99	Yes
Li J., [27]	2015	2008-2014	RS	553 (122:431)	66.5	54	NA	18.8	NA	51.2	Yes
Lu Z.F., [28]	2017	2000-2014	RS	272 (89:183)	NA	58	4.78	78.7	NA	NA	Yes
Wang L., [29]	2020	2012-2020	RM	367 (32:335)	63.1	56	9.7	12.9	28.2	58.74	Yes
Wang L., [30]	2020	2014-2018	RM	335 (39:296)	63.3	62.1% <60yr	9	12.2	30.4	57.6	Yes
Liu G.F., [31]	2021	2012-2020	RS	269 (35:234)	65.4	60	NA	NA	NA	100	Yes
Tang Y.Y., [32]	2021	2012-2020	RS	208 (80:128)	33.2	59.6% ≤60yr	NA	14.9	31.2	36.5	No
Cheng Z.J., [33]	2021	2002-2019	RS	223 (68:155)	75.8	51.4	100	66.4	25.1	39.5	Yes

RS: retrospective single-center; RM: retrospective multicenter; MVI: microvascular invasion; LNM: lymph node metastasis; NA: not available; TACE: transarterial chemoembolization.

Table II. Survival outcome and quality assessment results of included studies

Study	Year	Follow-up	median OS (TACE vs. non-TACE, mo)	HR of OS (95%CI)	median RFS (TACE vs. non-TACE, mo)	HR of RFS (95%CI)	NOS
Wang C., [23]	2009	at last 41 mo	15:12.8	0.89 (0.57-1.38)	NA	NA	5
Shen W.F., [24]	2011	median 18 mo	12:5	0.75 (0.51-1.10)	13:18	1.28 (0.91-1.80)	8
Wu Z.F., [25]	2012	NA	26:25	0.49 (0.32-0.76)	12.7:24.8	1.35 (0.85-2.16)	7
Li T., [26]	2014	median 17 mo	20:9	0.55 (0.36-0.83)	11:2	1.61 (1.03-2.50)	6
Li J., [27]	2015	median 25.3 mo	27.6:20.4	0.78 (0.61-0.99)	22:14.3	0.93 (0.74-1.16)	7
Lu Z.F., [28]	2017	at last 36 mo	17:8.5	0.69 (0.51-0.95)	NA	NA	6
Wang L., [29]	2020	median 22 mo	63:21	1.49 (0.94-2.36)	58.8:21.2	0.98 (0.64-1.49)	5
Wang L., [30]	2020	median 21.5 mo	63:18	0.60 (0.36-0.99)	50:10	0.78 (0.51-1.19)	8
Liu G.F., [31]	2021	median 48.2 mo	59.9:66.8	0.90 (0.51-1.57)	20.8:29.5	1.59 (1.03-2.43)	8
Tang Y.Y., [32]	2021	median 26.8 mo	15.7	0.24 (0.16-0.35)	12.1	0.31 (0.21-0.45)	4
Cheng Z.J., [33]	2021	median 80.9 mo	17.2:12.0	0.81 (0.58-1.12)	9.4:6.8	0.79 (0.56-1.11)	8

OS: overall survival; RFS: recurrence-free survival; HR: hazard ratio; CI: confidence interval; NOS: Newcastle-Ottawa Scale; NA: not available; TACE: transarterial chemoembolization.

postoperative adjuvant TACE for R0 resection of ICC [24-31, 33]. The interval between hepatectomy and adjuvant TACE ranged from 3 to 8 weeks. The embolization and chemotherapy regimen included iodized oil with 5-fluorouracil, epirubicin, and hydroxycamptothecin. Two studies also used carboplatin for intra-arterial chemotherapeutic regimen [24, 25]. Five studies [23-27] reported supplementary treatment after ICC recurrence and these were mainly as follows: TACE, radiotherapy, supportive therapy, systemic chemotherapy, re-resection, and percutaneous ablation. Although two studies [29, 30] were reported by the same institution at overlapping periods with potential patient duplication, the main outcomes of OS showed a significant difference according to the extracted data, which concluded a contrary efficacy of postoperative adjuvant TACE. Then we reserved these two studies and performed sensitive analysis to investigate the possible effect of patient duplication on pooled results. The results of NOS were shown in Table II and all of the included studies were considered to be of high or moderate quality.

Overall Survival and Recurrence-free Survival

All included studies considered the OS outcome and nine out of these 11 studies [24-27, 29-33] considered the RFS outcome. The pooled HR of OS was 0.68 (95%CI: 0.50-0.87, $I^2=83.7\%$) (Fig. 2). For this part, the funnel plot showed approximately symmetric distributions and Egger's test revealed no significant publication bias ($p=0.887$) among included studies (Fig. 3). The pooled HR of RFS was 1.00 (95%CI: 0.69-1.31, $I^2=88\%$) (Fig. 4). For this part, the funnel plot showed approximately symmetric distributions and Egger's test revealed no significant publication bias ($p=0.702$) among the included studies (Fig. 5). There was significant heterogeneity in the HRs of OS and RFS among the included studies, and further subgroup analysis and sensitivity analysis were performed.

Subgroup Analyses and Sensitivity Analysis

For OS of ICC patients after hepatectomy, receipt of postoperative adjuvant TACE showed a survival benefit in the early stage ICC subgroup (HR=0.68, 95%CI: 0.50-0.86,

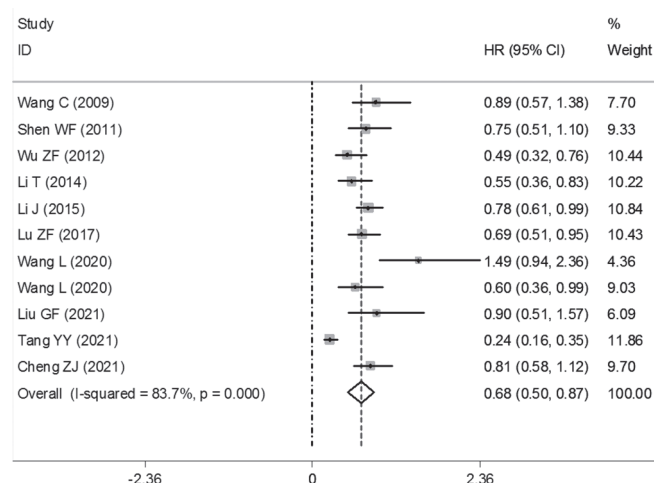


Fig. 2. The forest plot of pooled HR of OS for patients with ICC after resection (postoperative adjuvant TACE group vs. non-TACE group).

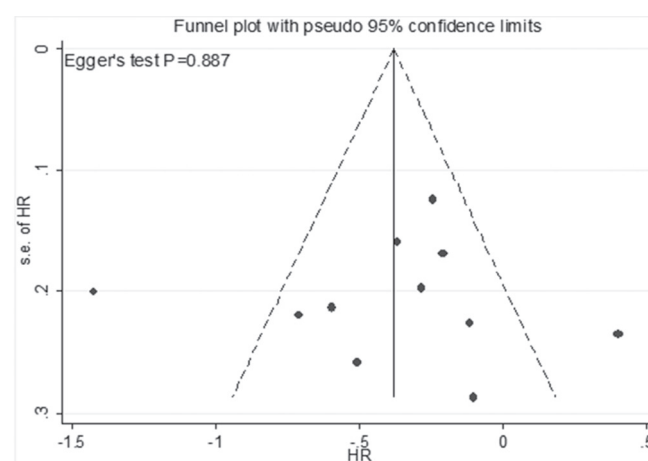


Fig. 3. The funnel plot with Egger's test result of OS outcome.

$P=54\%$). Addition of carboplatin in intra-arterial chemotherapy could slightly improve the efficacy of postoperative adjuvant TACE (HR=0.60, 95%CI: 0.35-0.85, $I^2=48\%$) compared with the non-carboplatin regimen (HR=0.74, 95%CI: 0.62-0.86,

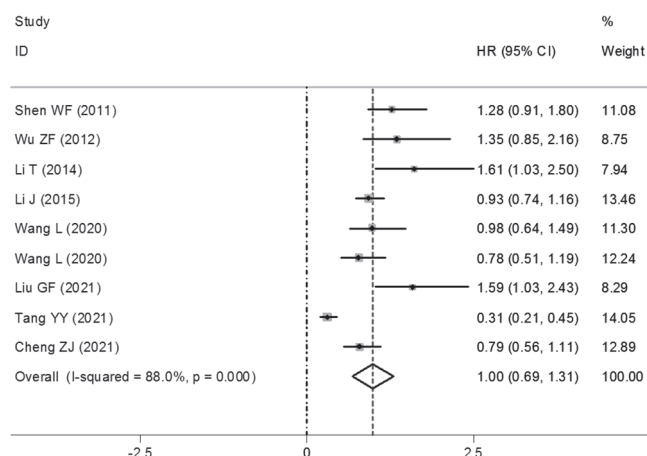


Fig. 4. The forest plot of pooled HR of RFS for patients with ICC after resection (postoperative adjuvant TACE group vs. non-TACE group).

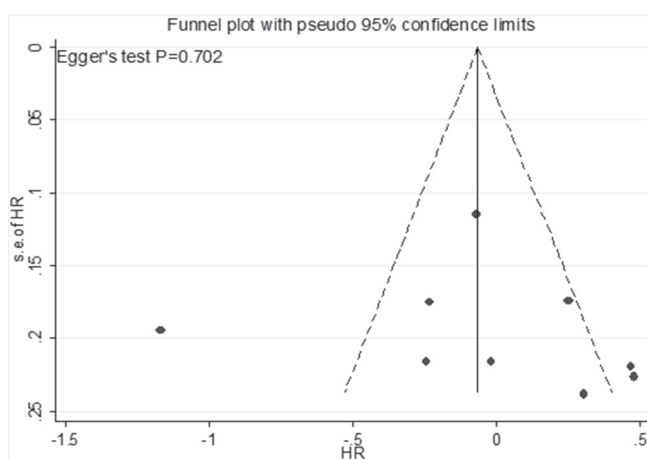


Fig. 5. The funnel plot with Egger's test result of RFS outcome.

$I^2=22.5\%$). For RFS of ICC patients after hepatectomy, receipt of postoperative adjuvant TACE (HR=1.06, 95%CI: 0.83-1.29, $I^2=41.2\%$) or addition of carboplatin (HR=1.30, 95%CI: 0.93-1.67, $I^2=0\%$) caused no significant survival improvement in the early stage ICC subgroup (Table III). We proved that early-stage ICC and addition of carboplatin were the potential sources of heterogeneity in pooled HRs of OS and RFS outcomes. Then a sensitivity analysis showed that the pooled results did not

change the stability after removal of studies one by one, which revealed the robustness of the effect models (Figs. 6-7).

DISCUSSION

This systematic evaluation and meta-analysis showed a survival benefit of postoperative adjuvant TACE in patients with ICC after surgical resection compared with hepatectomy alone. To our best knowledge, postoperative adjuvant TACE after ICC resection was very widely used in China. This procedure always used few iodized oil with chemotherapeutic agent, but gelfoam or permanent particles was not needed. We found that the OS outcome was improved after receipt of adjuvant TACE. However, the improvement in RFS was not significant. This result was different from the systematic evaluation reported by Ke et al. [11]. In their subgroup analysis, adjuvant TACE for ICC showed a RFS benefit versus surgery alone. Because of the small number of included studies in the subgroup, we considered that the results need be viewed with caution. Compared with systematic chemotherapy, intra-arterial chemotherapy had a higher local concentration of the chemotherapeutic agent in the target hepatic tissue and could yield residual micrometastases or tumor cells with less systematic toxicity [12, 34]. Nevertheless, vascular endothelial growth factor was released from the tumor tissue due to hypoxia caused by intra-arterial embolization, which had a potential effect on local recurrence [35]. In addition, the processing time of postoperative adjuvant TACE was shorter than the recurrence time. According to our study, the interval between hepatectomy and adjuvant TACE was at most 8 weeks, which revealed that therapeutic efficacy might not overlap with the follow-up in the long term. Therefore, we agreed that adjuvant TACE could prolong the OS because this approach can suppress early recurrence, but TACE showed no efficacy in preventing late tumor recurrence [24].

According to our results, postoperative adjuvant TACE in patients with early-stage ICC significantly improved the OS after hepatectomy but could not improve the RFS. Postoperative adjuvant TACE did not promote early recurrence after R0 resection in patients with stage I-ICC. This result was different from those of related published studies [25, 26, 31]. We concluded that the effect of growth factor release from tumor tissue due to hypoxia caused by intra-arterial

Table III. Subgroup analysis on postoperative adjuvant TACE stratified by TNM stage of ICC

			Number of studies	HR (95%CI)	Subtotal I^2 (p)
OS	Early stage ICC	YES	6	0.68 (0.50-0.86)	54% (0.054)
		NO	3	0.58 (0.16-1.01)	91.4% (<0.001)
	Carboplatin	YES	2	0.60 (0.35-0.85)	48% (0.165)
		NO	8	0.74 (0.62-0.86)	22.5% (0.250)
RFS	Early stage ICC	YES	6	1.06 (0.83-1.29)	41.2% (0.131)
		NO	3	0.76 (0.23-1.28)	91.8% (<0.001)
	Carboplatin	YES	2	1.30 (0.93-1.67)	0% (0.862)
		NO	6	0.96 (0.76-1.16)	41.1% (0.131)

CI: confidence interval; HR: hazard ratio; ICC: intrahepatic cholangiocarcinoma; OS: overall survival; RFS: recurrence-free survival.

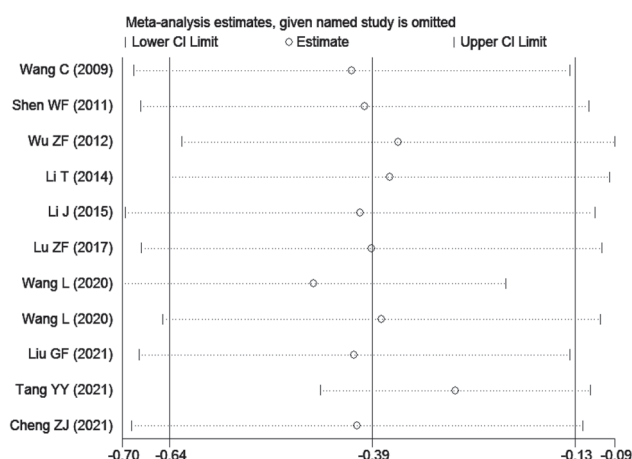


Fig. 6. Sensitivity analysis result of OS outcome

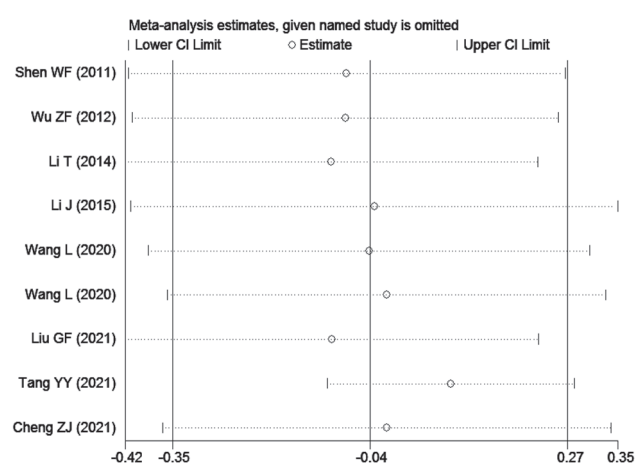


Fig. 7. Sensitivity analysis result of RFS outcome.

embolization was limited after R0 resection for stage I ICC. However, our subgroup analysis showed no survival benefit for ICC patients after hepatectomy at advanced stages. According to our inclusion criteria, our subgroup analysis only included 3 studies of non-early-stage ICC and detailed information of the TNM stage was not available in some studies, which might have led to bias in that part. In addition, advanced stage ICCs were more unresectable lesions, and it was preferable to receive TACE, intravenous chemotherapy, or radiotherapy instead of hepatectomy [36-38]. In our subgroup analysis of the chemotherapeutic regimen, addition of carboplatin showed a similar OS result. 5-Fluorouracil based chemotherapy has been widely used in TACE for hepatic malignancies, and other chemotherapeutic agents, such as doxorubicin and platinum, have also been usually used [39, 40]. Different types of intra-arterial chemotherapeutic strategies showed similar effects on the survival benefit [6, 21, 39]. However, all published meta-analyses (including our present study) included few studies in these subgroups regarding the chemotherapeutic regimen using different chemotherapeutic strategies. Further high-quality studies are required to investigate the efficacy of postoperative adjuvant TACE combined with carboplatin after ICC resection.

Other prognostic factors, such as MVI, LNM, multifocal tumor, and resection margin, also played important roles in tumor recurrence after ICC resection [41]. Positive resection

margin was identified as one of the high-risk prognostic factors, and adjuvant therapy after hepatectomy was related with lower mortality in these patients [15]. In our meta-analysis, R0 resection was performed in most of the included studies, excluding the study by Tang et al. [32]. Within about 20% of the positive margin after ICC resection, they found a significant survival benefit in their patients. Postoperative supplementary treatment of TACE could suppress the residual tumor recurrence or progression. It tended to cause LNM and multifocal tumor, which might lead to postoperative recurrence and poor prognosis after surgical resection for ICC [42-44]. In our meta-analysis, the incidence of LNM and multifocal tumor was in the range of 8-78.7% and 5-34.4%, respectively. Due to insufficient data and the small number of included studies, a further subgroup analysis or meta-regression was not performed. However, we only focused on the survival benefit between early and advanced stages of ICC, which could be indirectly affected by these two factors. As a common poor prognostic factor in ICC, MVI might lead to recurrence after hepatectomy [45]. It was proved that postoperative adjuvant TACE could improve the survival outcomes in HCC [39], but its effect is still controversial in ICC. Based on the results presented by Cheng et al. [33], postoperative adjuvant TACE only showed a survival benefit in ICC patients who did not undergo lymphadenectomy or who had a higher CA19-9 level. Due to the complexity of ICC recurrence, use of adjuvant TACE should be considered in combination with various prognostic factors.

There are several limitations to this study. Firstly, most of the studies included in this meta-analysis were designed as a retrospective single-center; hence, bias of population selection was likely. Secondly, insufficient data of risk factors of ICC recurrence, such as tumor satellites and MVI, were reported in some studies, which led to limited subgroup analysis for efficacy evaluation. Thirdly, only two studies [24, 25] used the chemotherapeutic regimen combined with carboplatin, which might have potentially affected the subgroup analysis results. Finally, all included studies were performed in China; hence, further international multicenter trials are required.

CONCLUSIONS

Postoperative adjuvant TACE could improve the OS in ICC patients after hepatectomy, but it could not improve the RFS. In the early-stage ICC subgroup after hepatectomy, postoperative adjuvant TACE also showed an OS benefit. Addition or non-addition of carboplatin in chemoembolization showed a similar OS outcome. However, considering the limitations of this present study, further high-quality clinical trials are required to prove these results.

Conflicts of interest: None to declare.

Authors' contribution: J.S. conceived and designed the study. X.W., L.Z., K.F. performed the literature search and selection, and assessed the quality of the included papers. L.W. synthesized the data and performed the statistical analysis. L.W. and J.S. wrote the paper and edited the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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