Therapeutic Advances in Gastroenterology

Survival benefits from adjuvant transcatheter arterial chemoembolization in patients undergoing liver resection for hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract

Background: Although adjuvant transcatheter arterial chemoembolization (TACE) has been used to prevent recurrence after surgery in patients with hepatocellular carcinoma (HCC), the survival benefits from adjuvant TACE remain controversial. We sought to systematically evaluate the data on the effectiveness of adjuvant TACE for HCC, as well as identify patient populations that might benefit from adjuvant TACE.

Methods: The PubMed, Embase, Medline and Cochrane library were systematically searched for studies published before July 2019 that compared adjuvant TACE *versus* surgery alone for HCC. The study endpoints were overall survival (OS) and disease-free survival (DFS). Patients with large HCC (⩾5 cm), multinodular HCC, microvascular invasion (MVI), or portal vein tumor thrombosis (PVTT) were analyzed in subgroup analyses.

Results: Twenty-four studies with 6977 patients were included in the analytic cohort. The pooled analysis demonstrated that adjuvant TACE was associated with a better OS and DFS [hazard ratio (HR): 0.67 and 0.67, both $p < 0.01$]. In subgroup analyses, pooled results revealed that adjuvant TACE was associated with an improved OS and DFS in patients with multinodular HCC (HR: 0.79 and 0.31, both $p < 0.01$), MVI (HR: 0.62 and 0.67, both $p < 0.01$), or PVTT (HR: 0.49 and 0.58, both $p < 0.01$), but not among patients with large HCC (⩾5 cm).

Conclusion: Postoperative adjuvant TACE may be effective to improve OS and DFS in patients with multinodular HCC, or HCC with MVI or PVTT. Future randomized controlled trials are needed to better define the benefit of adjuvant TACE in subset patients with HCC.

Keywords: adjuvant therapy, disease-free survival, hepatocellular carcinoma, overall survival, transcatheter arterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related mortality worldwide.[1] Surgical resection, liver transplantation and tumor ablation are the three curative modalities used to treat HCC.[2] Surgical resection remains the primary curative treatment option due to limited donor availability for liver transplantation and technical limitations associated with tumor ablation. Even after curative surgery, the prognosis for patients with HCC is still, however, poor due to the high incidence of postoperative recurrence that is a major cause of subsequent mortality.[3–5] Factors associated with HCC

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recurrence include large tumor size (⩾5 cm), multi-nodularity, microvascular vascular invasion (MVI), and the presence of portal vein tumor thrombosis (PVTT).[6,7] Various adjuvant therapies have been used at several centers especially among patients with a high risk of HCC recurrence in an attempt to reduce the possibility of recurrence after surgery. Adjuvant therapeutic approaches have included interferon, sorafenib, immunotherapy, and systemic chemotherapy.[8–14] None of these therapies have, however, been determined to be an effective regimen to international authoritative guidelines.[15–17]

Postoperative transcatheter arterial chemoembolization (TACE), which can be performed 1–2 months after curative resection of HCC, is also a proposed adjuvant therapy to prevent postoperative recurrence.[18–21] Adjuvant TACE has been proposed to theoretically eliminate intrahepatic micro-metastases or residual tumor foci, thus preventing recurrence and improving patient survival after resection of HCC.[18–21] The role of adjuvant TACE remains controversial, with several studies reporting no survival benefit or even a decrease in overall survival (OS) and disease-free survival (DFS).[22,23] Specifically, postoperative TACE may impair hepatic and immunological functions and thus have an unintended adverse effect. The role of adjuvant TACE among patients after resection of HCC remains debated, with some investigators suggesting that adjuvant TACE may only benefit specific subsets of patients.[24,25] A comprehensive review of current data on adjuvant TACE may provide an evidence-based approach to identifying which patients might benefit from adjuvant TACE after surgical resection of HCC.

As such, the aim of this study was to perform a systematic review and meta-analysis of pooled published results on long-term outcomes of HCC patients who underwent adjuvant TACE after surgery. In addition to assessing outcomes among patients who did *versus* did not receive adjuvant TACE, subgroup analyses were performed to identify specific cohorts of patients who might benefit the most from adjuvant TACE.

Methods

A systematic review and meta-analysis on existing published medical literature was conducted following the Cochrane Collaboration guidelines.[26]

Literature search strategy

The PubMed, Embase and Cochrane Library were searched for studies published before July 2019 using the following terms and search strategy to identify relevant studies: ("Hepatocellular Carcinoma [MeSH]" OR "Liver Cancer" OR "Hepatic Cancer" OR "Primary Hepatic Carcinoma" OR "PHC" OR "Hepatocellular Cancer" OR "HCC") AND ("Chemoembolization [MeSH]" OR "Transarterial Chemoembolization" OR "Transcatheter Arterial Chemoembolization" OR "TACE" OR "Chemotherapy") AND ("Hepatectomy [MeSH]" OR "Surgical [MeSH]" OR "Surgical Resection" OR "Surgery" OR "Hepatic Resection" OR "Liver Resection"). The references of the included studies, relevant reviews and meta-analysis were manually screened to identify other eligible studies. Only studies written in English, regardless of patient population, were included.

Eligibility criteria

The inclusion criteria for eligible studies were: (1) Studies that reported patients undergoing surgical resection for HCC; (2) Surgical resection with or without adjuvant TACE was compared; (3) Information on long-term survival was provided. Studies that met any one of the following criteria were excluded: (1) Studies on patients with recurrent or metastatic HCC; (2) Patients received any preoperative/neoadjuvant treatments; (3) No survival comparison of patients who did *versus* did not receive adjuvant TACE; (4) Replicated data reported by the same authors; (5) Abstracts, reviews, case reports, letters to the editor, and articles written in languages other than English.

Data extraction

Two reviewers (L.L. and C.L.) independently performed data extraction and a third author (T.Y.) cross-checked the data. Any disagreement was resolved through discussion. The data extracted included the surname of the first author, year of publication, study type, period of patient inclusion, number of patients, mean tumor size (cm), number of patients with Child–Pugh (A/B), number of patients with cirrhosis, number of patients with HBsAg (+), number of patients with multiple tumor numbers (⩾2), median OS (months), and median DFS (months). The hazard ratios (HRs) associated with the OS curves were extracted to assess prognosis. The methods

for data extraction and calculation, especially the data in the Kaplan–Meier curves, were adopted from methods described in detail by Tierney *et al.*[27] and Parmar *et al.*[28] A calculation spreadsheet in Microsoft Excel was developed to obtain the observed minus expected events (O-E), the variance (V), the HR, the log (HR), and its standard error (SE) for each of the individual trials.

Quality assessment

Cochrane Handbook for Systematic Reviews of Interventions was used to assess the quality of the randomized controlled trials (RCTs) included in the meta-analysis. Sequence generation of randomization, allocation concealment, blinding of patients and personnel and blinding of outcome assessment were evaluated. The bias within and across the studies was further assessed based on the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I)[29] by the Cochrane Bias Methods Group (BMG). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) System was used to assess the quality of the evidence and the strength of the recommendations.[30]

Data analysis

The Review Manager (RevMan, the Cochrane Collaboration, Oxford, UK) version 5.3 was used for data pooling. The primary endpoint of the meta-analysis was OS and DFS. The effect measures for OS and DFS were expressed as HR. If adjusted ratios are reported in some studies, such as using propensity score matching analysis, adjusted HRs are used in the analysis. The effect measures for survival rates (at 1-, 3- and 5-year) and DFS rates (at 1-, 2- and 3-year) were expressed as odds ratio (OR). The pooled HR, OR and 95% confidence interval (95% CI) associated with the various outcomes were calculated. Statistical method of Exp(O-E)/Var was adopted to calculate pooled HR and Mantel–Haenszel was adopted to calculate pooled OR. According to the updating Cochrane handbook, random-effects model was chosen as a priority for all analyses, and then the alternative test was performed as a sensitivity test. The results of data pooling in the meta-analysis were presented as "forest plots." Generally, heterogeneity among studies was assessed using the I^2 statistic and the chi-square (X^2)-based Q test. A $p < 0.1$ or $I^2 > 50$ indicated significant heterogeneity.[31] The 95% CI of the pooled ratio was provided for analysis of statistically significant, as well as the effect range estimate.

Results

Included studies

Through searches of PubMed ($n = 564$), Embase ($n = 346$) and Cochrane library ($n = 14$) databases, 924 articles were identified. Some 282 duplicate references were excluded. After abstract reviewing, 580 of the 642 original articles were eliminated for failure to meet the inclusion criteria. In addition, of the remaining 62 studies, 38 were excluded after reviewing the full text due to incomplete data or non-English language. Eventually, 24 studies [nine RCTs[20,23,32–38] and 15 non-randomized controlled trials (NRCTs)[18,19,21,22,39–49]] were included in the systematic review. The search and screening processes of the medical literature review are summarized in Figure 1.

Quality assessment

Methodological quality was unknown risk of bias in four RCTs[20,36–38] and high risk of bias in the remaining five RCTs[23,32–35] (Supplement Table 1). Nine NRCTs[18,21,22,39,42–44,48,49] were of relatively moderate risk of bias; six NRCTs[19,40,41,45–47] were of relatively serious risk of bias (Supplement Table 2).

Baseline characteristics

Twenty-four studies including nine RCTs[20,23,32–38] and 15 NRCTs[18,19,21,22,39–49] including 6912 patients were published between 1994 and 2019. Among the entire cohort, 5627 (81%) patients were male. TACE was performed 1–2 months after curative resection of HCC by using lipiodol-based regimens, including the administration of an anticancer-in-oil emulsion followed by embolic agents. Mean tumor size was reported in 11 studies,[18,19,21,23,36,37,40,41,44,46,48] involving 1948 (30%) patients with a median size of 7 cm (range 3–10). Some 743 (18%) patients with multiple tumors ($\geqslant 2$) were reported in 13 studies[18–23,34,35,37,42,44,46,49] involving 3980 patients. In addition, 3492 (74%) patients with HBsAg (+) were reported in 17 studies[18–23,32,34–37,39,40,42,44,46,49] involving 4720 patients. The detailed baseline characteristics of

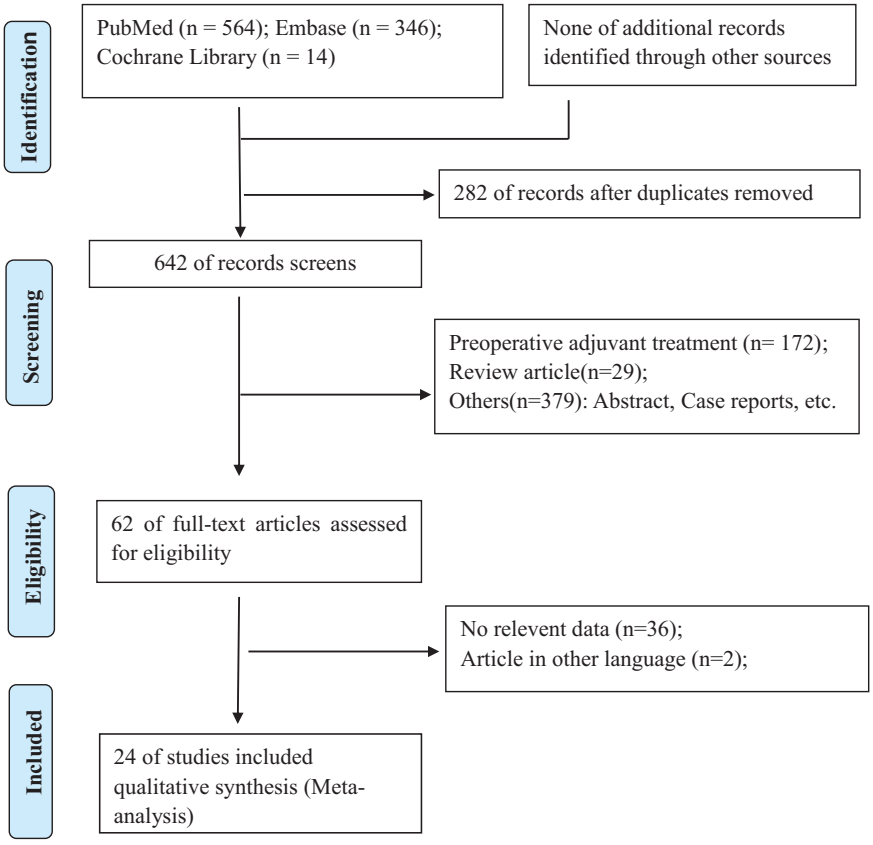


Figure 1. PRISMA flow diagram showing selection of articles for review.

the enrolled studies and patients are shown in Table 1.

Overall survival

The OS was calculated based on the six RCTs[20,32,33,36–38] and 15 NRCTs[18,19,21,22,39–46,48,49] that incorporated 6573 patients ($n = 2572$, 39% for surgery followed by adjuvant TACE *versus* n = 4001, 61% for surgery alone). The pooled HR for OS among all studies was 0.67 (95% CI 0.60–0.76, $p < 0.001$; $I^2 = 0\%$, $p = 0.58$), which was in favor of the surgery followed by adjuvant TACE group (Figure 2A). No significant publication bias was noted in the funnel plot (Supplement Figure 1). Furthermore, the pooled analysis of all studies demonstrated that patients who underwent surgery followed by adjuvant TACE had better 1-, 3-, and 5-year survival *versus* patients who had surgery only (Figure 2B). Of note, the survival benefit was consistent among RCTs and NRCTs. While there was a heterogeneity at 3 years in RCT studies ($I^2 = 67\%$, $p = 0.01$), other studies demonstrated no significant heterogeneity. The pooled effect was estimated by using the random-effect model as demonstrated in a forest plot (Supplement Figure 2A–C). No significant publication bias was noted in the funnel plot (Supplement Figure 3A–C).

Potential differences in OS among patients who underwent surgery followed by adjuvant TACE *versus* patients who underwent surgery alone were further examined by stratifying patients according to several risk factors (Figure 3). Specifically, among patients with tumor diameter ⩾5 cm, the pooled HR demonstrated there were no difference among patients who underwent surgery followed by adjuvant TACE *versus* surgery alone (HR 0.84, 95% CI 0.51–1.37, $p = 0.49$; $I^2 = 30\%$, $p = 0.24$). In contrast, among patients with multinodular HCC (⩾2), as well as patients who had HCC with MVI or PVTT, the pooled HRs were in favor of surgery followed by adjuvant TACE (HR 0.79, 95% CI 0.64–0.98, $p = 0.03$; HR 0.62, 95% CI 0.52–0.74, $p < 0.001$; $I^2 = 0\%$, $p = 0.67$ and HR 0.49, 95% CI 0.34–0.69, $p < 0.001$; $I^2 = 19\%$, $p = 0.27$, respectively). No significant

Table 1. Baseline characters of studies and patients.

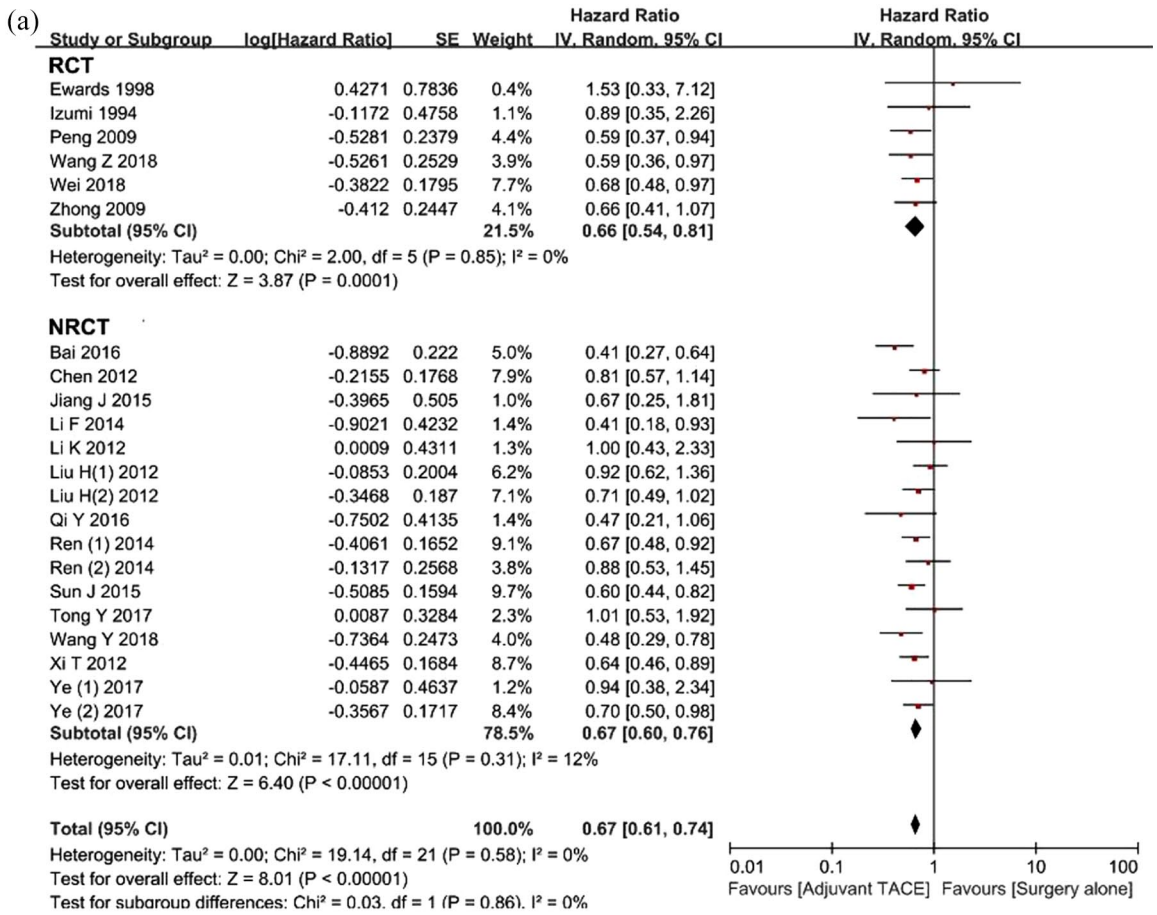
Name	Study	Period	Group	Number	Tumor size	Child (A/B)	Cirrhosis (%)	HBsAg (+ %)	Tumors (⩾2, %)	Median OS	Median DFS
Izumi *et al.*[32]	RCT	1987–1992	S-TACE	23	NA	NA	NA	6 (26)	NA	49	28
			Surgery	27	NA	NA	NA	2 (7)	NA	41	19
Li *et al.*[33]	RCT	1990–1993	S-TACE	70	NA	NA	NA	NA	NA	NA	NA
			Surgery	70	NA	NA	NA	NA	NA	NA	NA
Ewards *et al.*[23]	RCT	1991–1995	S-TACE	30	9	NA	17 (57)	25 (83)	11 (37)	NA	NA
			Surgery	36	10	NA	19 (53)	31 (86)	15 (42)	NA	NA
Li *et al.*[34]	RCT	1998–2001	S-TACE	39	NA	23/16	NA	32 (82)	6 (15)	NA	NA
			Surgery	45	NA	22/23	NA	37 (82)	9 20)	NA	NA
Li *et al.*[35]	RCT	1998–2001	S-TACE	35	NA	18/17	NA	29 (83)	19 (54)	NA	NA
			Surgery	37	NA	15/22	NA	34 (92)	17 (46)	NA	NA
Peng *et al.*[36]	RCT	1996–2004	S-TACE	51	9	44/7	42 (82)	31 (61)	NA	13	NA
			Surgery	53	8	46/7	37 (70)	40 (75)	NA	9	NA
Zhong *et al.*[37]	RCT	2001–2004	S-TACE	57	10	56/1	NA	53 (93)	44 (77)	23	6
			Surgery	58	10	58/0	NA	52 (90)	42 (72)	14	4
Wei *et al.*[38]	RCT	2009–2012	S-TACE	116	NA	116/0	50 (43)	NA	NA	44	17
			Surgery	118	NA	116/2	42 (36)	NA	NA	NA	NA
Wang *et al.*[20]	RCT	2011–2014	S-TACE	140	NA	NA	72 (51)	29 (21)	38 (27)	22	26
			Surgery	140	NA	NA	66 (47)	39 (28)	31 (22)	9	24
Tanaka *et al.*[38]	NRCT	NA	S-TACE	24	NA	NA	6 (25)	6 (25)	6 (25)	NA	NA
			Surgery	41	NA	NA	26 (63)	9 (22)	8 (20)	NA	NA
Ren *et al.*[39] (1)	NRCT	1995–1998	S-TACE	108	NA	106/2	84 (78)	27 (25)	NA	NA	NA
			Surgery	190	NA	187/3	149 (78)	47 (25)	NA	NA	NA
Ren *et al.*[39] (2)	NRCT	1995–1998	S-TACE	77	NA	77/0	71 (92)	11 (14)	NA	NA	NA
			Surgery	174	NA	165/5	152 (87)	43 (25)	NA	NA	NA
Xi *et al.*[40]	NRCT	1996–2001	S-TACE	145	7	145/0	NA	117 (81)	NA	NA	NA
			Surgery	576	7	560/16	NA	450 (78)	NA	NA	NA
Li *et al.*[41]	NRCT	2005–2010	S-TACE	35	6	34/1	32 (91)	NA	NA	NA	NA
			Surgery	41	7	39/2	36 (88)	NA	NA	NA	NA
Chen *et al.*[42]	NRCT	2001–2007	S-TACE	766	NA	754/12	NA	668 (86)	120 (16)	NA	NA
			Surgery	1158	NA	1133/25	NA	1005 (87)	128 (11)	NA	NA

(Continued)

Table 1. (Continued)

Name	Study	Period	Group	Number	Tumor size	Child (A/B)	Cirrhosis (%)	HBsAg (+ %)	Tumors (⩾2, %)	Median OS	Median DFS
Liu *et al.*[43] (1)	NRCT	1998–2006	S-TACE	112	NA	NA	NA	NA	NA	NA	NA
			Surgery	138	NA	NA	NA	NA	NA	NA	NA
Liu *et al.*[43] (2)	NRCT	1998–2006	S-TACE	66	NA	NA	NA	NA	NA	NA	NA
			Surgery	112	NA	NA	NA	NA	NA	NA	NA
Li *et al.*[19]	NRCT	2006–2009	S-TACE	26	5	12/14	17 (65)	13 (50)	4 (15)	35	NA
			Surgery	34	5	16/18	21 (62)	17 (50)	8 (24)	15	NA
Sun *et al.*[18]	NRCT	2004–2013	S-TACE	137	7	135/2	88 (64)	121 (88)	11 (8)	NA	NA
			Surgery	185	7	182/3	109 (59)	163 (88)	17 (9)	NA	NA
Jiang *et al.*[44]	NRCT	2007–2010	S-TACE	61	6	NA	51 (84)	50 (82)	17 (28)	32	NA
			Surgery	61	6	NA	51 (84)	52 (85)	15 (25)	28	NA
Liu *et al.*[45]	NRCT	2005–2013	S-TACE	162	NA	NA	NA	NA	NA	56	23
			Surgery	205	NA	NA	NA	NA	NA	35	21
Qi *et al.*[22]	NRCT	2012–2014	S-TACE	91	NA	NA	79 (87)	77 (85)	23 (25)	NA	NA
			Surgery	109	NA	NA	89 (82)	96 (88)	25 (23)	NA	NA
Bai *et al.*[46]	NRCT	2009–2010	S-TACE	31	12	31/1	28 (90)	6 (19)	6 (19)	22	14
			Surgery	51	10	47/4	47 (92)	11 (22)	9 (18)	9	7
Liu *et al.*[47]	NRCT	2010–2014	S-TACE	62	NA	59/3	NA	NA	NA	NA	NA
			Surgery	55	NA	54/1	NA	NA	NA	NA	NA
Tong *et al.*[48]	NRCT	2010–2014	S-TACE	83	4	81/2	35 (42)	NA	NA	38	NA
			Surgery	83	3	80/3	36 (43)	NA	NA	31	NA
Ye *et al.*[49] (1)	NRCT	2012–2015	S-TACE	72	NA	70/2	63 (88)	66 (92)	10 (14)	NA	NA
			Surgery	187	NA	180/7	156 (83)	168 (90)	32 (17)	NA	NA
Ye *et al.*[49] (2)	NRCT	2012–2015	S-TACE	86	NA	84/2	72 (84)	72 (84)	13 (15)	NA	37
			Surgery	174	NA	172/2	143 (82)	156 (90)	37 (21)	NA	13
Wang *et al.*[21]	NRCT	2004–2015	S-TACE	57	6	54/3	49 (86)	47 (82)	11 (19)	NA	NA
			Surgery	57	6	54/3	46 (81)	51 (89)	11 (19)	NA	NA

Ren (1) and (2) was divided into two group by without or with risk factors for residual tumor; Liu H (1) and (2) was divided into two group by serum γ-glutamyl transpeptidase (GGT) ⩽80 U/L or GGT >80 U/L; Ye (1) and (2) was divided into two group by without or with microvascular invasion. DFS, disease-free survival; NA, not available; NRCT, non-randomized controlled trial; OS, overall survival; RCT, randomized controlled trial; S-TACE, surgery followed by adjuvant transcatheter arterial chemoembolization.



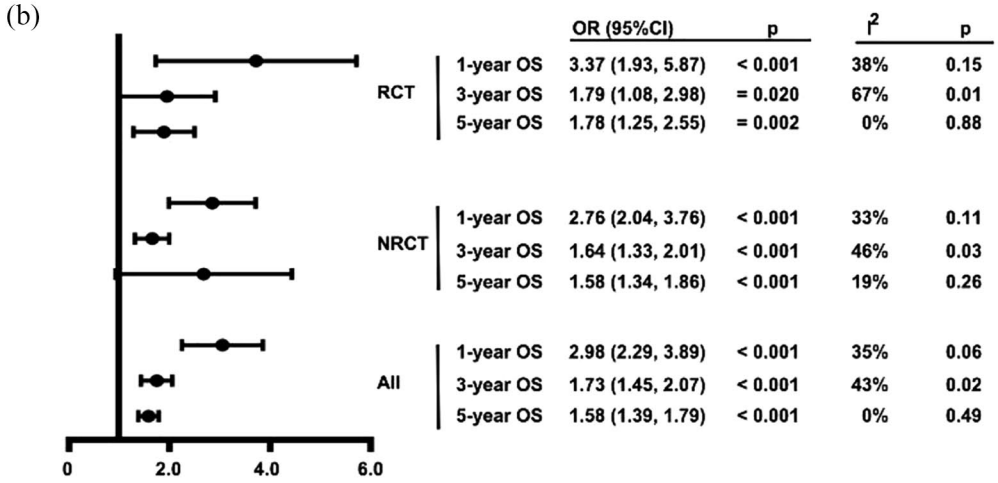


Figure 2. Forest plots comparing the overall survival between surgery followed by adjuvant TACE and surgery alone.
NRCT, non-randomized controlled trial; RCT, randomized controlled trial; TACE, transcatheter arterial chemoembolization

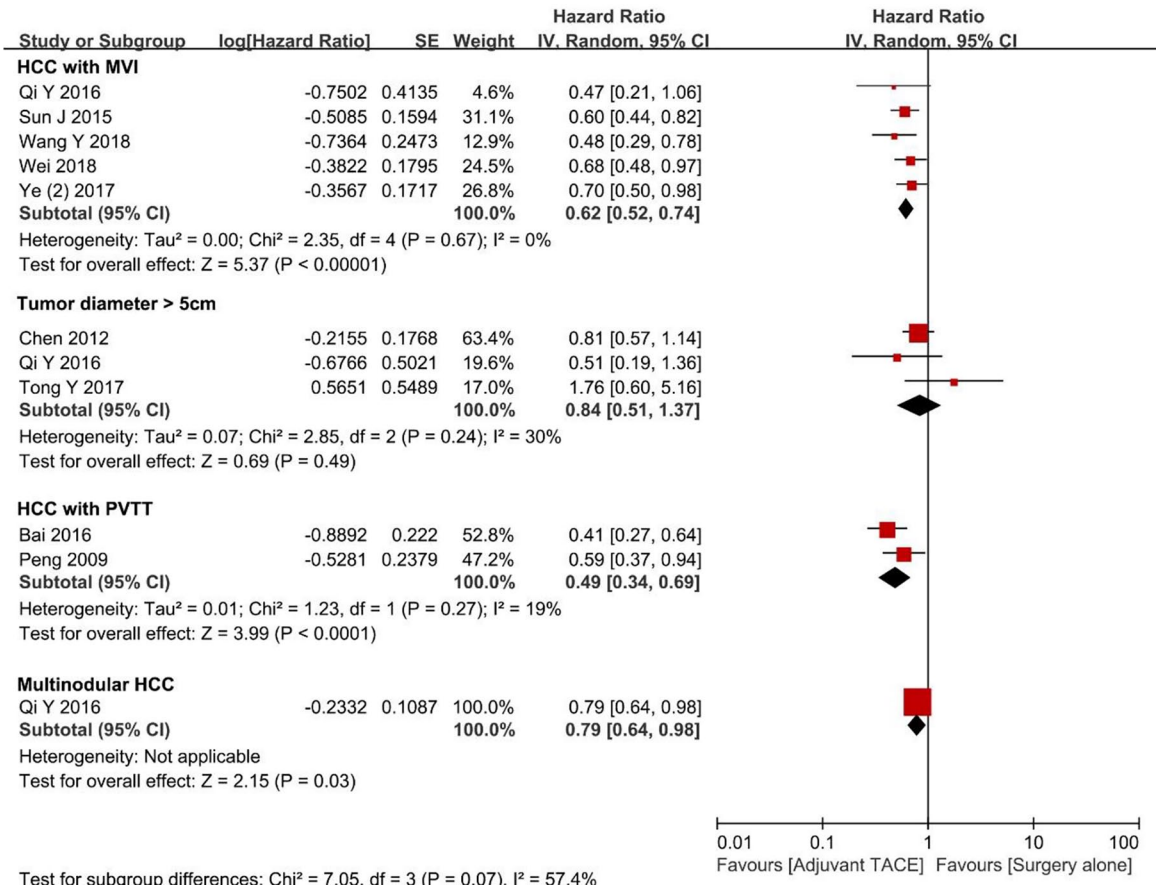


Figure 3. Forest plots comparing the overall survival stratified by different risk factors.
HCC, hepatocellular carcinoma; MVI, microvascular vascular invasion; PVTT, portal vein tumor thrombosis; TACE, transcatheter arterial chemoembolization

publication bias was noted in the funnel plot (Supplement Figure 3D).

Disease-free survival

The pooled DFS was calculated based on the seven RCTs[20,23,32,34,35,37,38] and six NRCTs[21,22,40,41,46,48] that comprised 2260 patients (n = 882, 39% for surgery followed by adjuvant TACE *versus* n = 1378, 61% for surgery alone). The pooled HR of DFS for all studies was 0.71 (95% CI 0.61–0.84, $p < 0.001$; $I^2 = 60\%$, $p = 0.003$), which was in favor of adjuvant TACE after surgical resection. The potential reason for the heterogeneity may have been due to the inclusion of the study by Edward *et al.*;[23] when this study was excluded, there were no significant heterogeneity ($I^2 = 18\%$, $p = 0.27$) (Figure 4A). No significant publication bias was demonstrated in the funnel plot (Supplement Figure 4). At the same time, the pooled analysis of all studies demonstrated that patients who underwent surgery followed by adjuvant TACE had a better 1-, 2-, and 3-year DFS than patients who had surgery only (Figure 4B). Though there were no statistical differences in 3-year DFS in the RCT subgroup and 2-year DFS in the NRCT subgroup, patients who underwent surgery followed by adjuvant TACE still had a better survival than patients who had surgery only. In addition, there was good consistency in the reported survival benefit in all included studies. The pooled effect was estimated by using the random-effect model as shown in forest plots (Supplement Figure 5A–C). No significant publication bias was noted in the funnel plot (Supplement Figure 6A–C).

Potential differences in DFS among patients who underwent surgery followed by adjuvant TACE *versus* surgery alone were examined by stratifying patients according to several risk

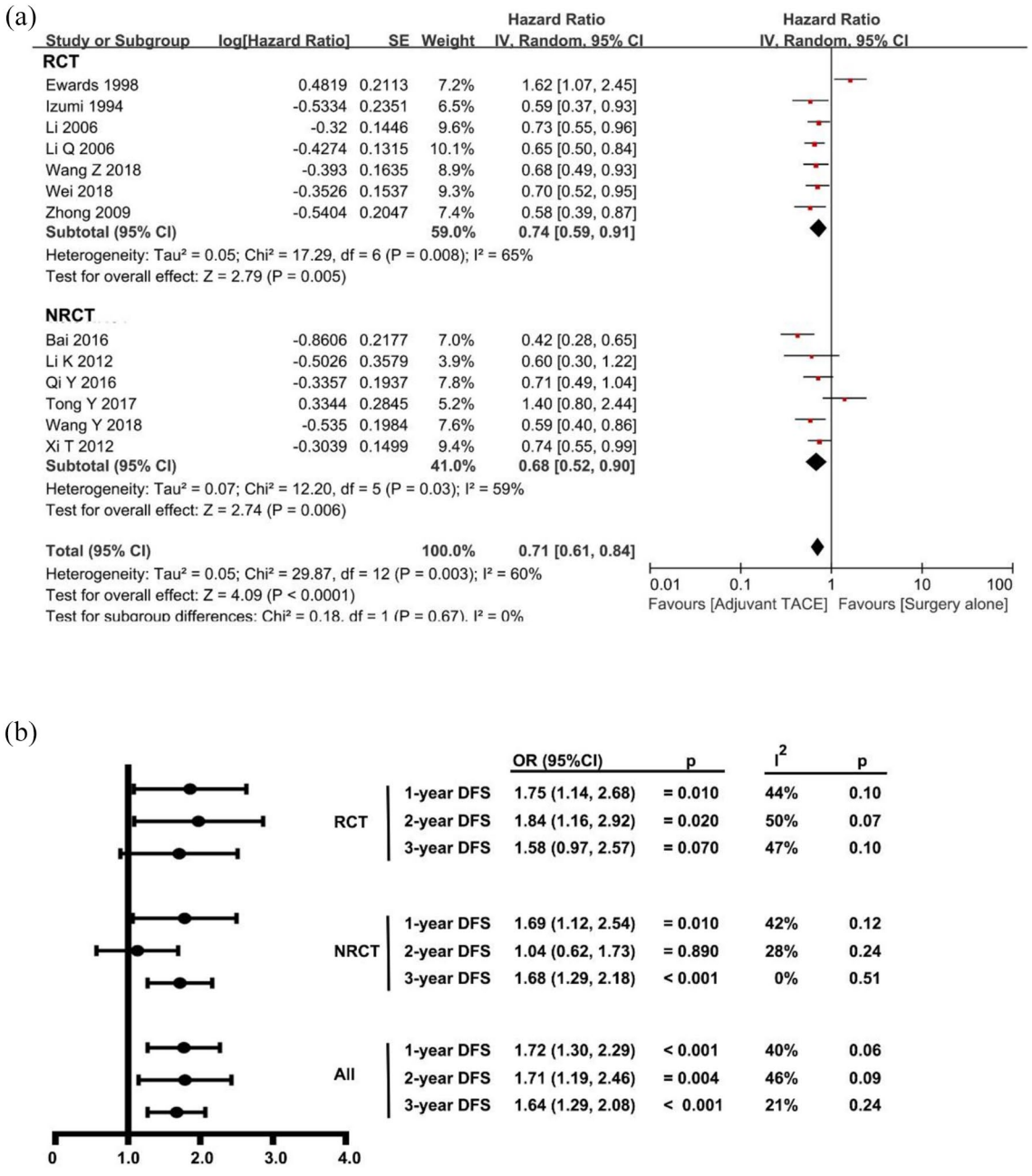


Figure 4. Forest plots comparing the disease-free survival between surgery followed by adjuvant TACE and surgery alone.
NRCT, non-randomized controlled trial; RCT, randomized controlled trial; TACE, transcatheter arterial chemoembolization

factors (Figure 5). For patients with tumor diameter ⩾5 cm, the pooled HR demonstrated no significant difference between surgery followed by adjuvant TACE *versus* surgery alone (HR 1.51, 95% CI 0.33–6.99, $p = 0.60$; $I^2 = 92\%$, $p < 0.001$). In contrast, among patients with multinodular HCC (⩾2), or HCC with MVI or PVTT, the pooled HRs were in favor of a survival benefit for patients undergoing surgery followed by adjuvant TACE (HR 0.31, 95% CI 0.15–0.64, $p = 0.002$; $I^2 = 0\%$, $p = 0.62$; HR 0.67, 95% CI 0.55–0.82, $p < 0.001$; $I^2 = 0\%$, $p = 0.72$ and HR 0.54, 95% CI 0.36–0.83, $p = 0.004$; $I^2 = 66\%$, $p = 0.09$, respectively). No significant publication bias was noted in the funnel plot (Supplement Figure 6D).

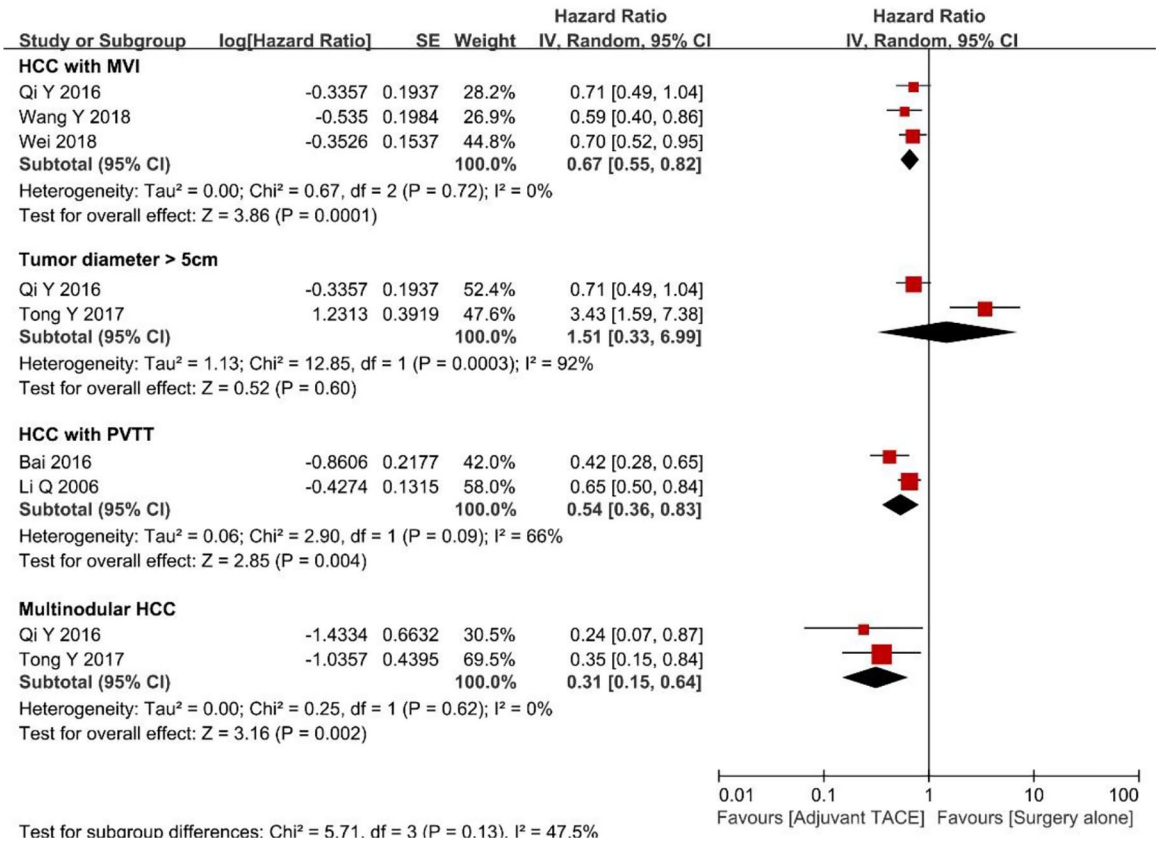


Figure 5. Forest plots comparing the disease-free survival stratified by different risk factors.
HCC, hepatocellular carcinoma; MVI, microvascular vascular invasion; PVTT, portal vein tumor thrombosis

Sensitivity analysis

A sensitivity analysis was performed, in which one study at a time was removed and the others analyzed to estimate whether the results could have been affected markedly by a single study. Apart from 3-year in RCTs and 2-year in NRCTs for DFS (Figure 4B), the sensitivity analysis demonstrated the results were well stable.

Discussion

This meta-analysis aimed to evaluate the effectiveness of adjuvant TACE after surgery for HCC using the latest published data. In addition, we sought to identify patient populations who might benefit the most from this adjuvant therapy. To this end, 24 studies (nine RCTs and 15 NRCTs) comprising 6912 patients were included in the meta-analysis. Of note, adjuvant TACE following resection of HCC was noted to be associated with an improvement in both OS and DFS. In particular, certain subgroups of patients benefited the most from adjuvant TACE such as HCC patients with multinodular HCC, as well as patients with HCC who had MVI or PVTT. In contrast, there appeared not to be benefit of adjuvant TACE when assessing only tumor size (⩾5 cm) alone.

Adjuvant TACE has been most often used as a means to prevent postoperative recurrence in a few Eastern countries. The proposed mechanism of adjuvant TACE is the elimination of intrahepatic micro-metastases, residual small foci or dissociated cancer cells due to extrusion at the time of surgery.[18,19,50] While some studies have reported no benefit of adjuvant TACE after HCC resection, other studies have demonstrated a survival benefit, especially among patients at a high recurrence risk. In 2010, Zhong *et al.* performed a meta-analysis of six RCTs involving 659 HCC patients to evaluate the efficacy of postoperative TACE.[14] The authors reported that adjuvant TACE decreased the 1- and 3-year incidences of death among patients undergoing HCC resection. In 2014, Cheng *et al.* performed a meta-analysis of six RCTs to assess the beneficial effects

of adjuvant TACE after HCC resection.[51] These authors reported that adjuvant TACE offered potential benefits after curative HCC resection among patients who had a mean tumor size >5 cm, which was different than the results of the current study. In 2015, Qi *et al.* published a meta-analysis including 19 RCT and NRCT studies, which suggested that adjuvant TACE improved DFS among patients with HCC.[52] In this study, however, the difference in OS was not statistically significant (HR = 0.85, 95% CI 0.72–1.00, $p = 0.06$), and the heterogeneity among studies was statistically significant ($I^2 = 70\%$, $p < 0.001$).

Compared with previous meta-analyses,[14,51,52] the current review was much more extensive as it included 24 studies (nine RCTs and 15 NRCTs) comprising 6912 patients. In addition, the method of data extraction and calculation was more robust as it was adopted in detail from Tierney *et al.*[27] and Parmar *et al.*[28] Data included in the Kaplan–Meier curve analyses, in particular, were more extensive than previous analyses. Of note, the pooled HR in the current study demonstrated significant improvements in OS and DFS among patients who received adjuvant TACE. Importantly, there was no significant heterogeneity. In addition, the survival benefit of adjuvant TACE had a good consistency among RCTs and NRCTs. Pooled OR analyses at 1-, 3- and 5-year for OS, as well as DFS 1-, 2- and 3-year were consistent with previous results of pooled HR.

Another strength of the current study was the subset analyses we performed to identify patient populations who might benefit the most from adjuvant TACE. Specifically, patients who had adjuvant TACE *versus* surgery alone were examined relative to such risk factors as tumor size ⩾5 cm, multinodular HCC, MVI and PVTT. In subgroup analyses, the pooled results indicated that adjuvant TACE was associated with improved OS and DFS among patients with multinodular HCC, as well as HCC with MVI or PVTT. In contrast, there was no differential survival benefit to adjuvant TACE relative to tumor size of ⩾5 cm.

Several limitations should be considered when interpreting data from the current study. The usage of gelatin sponge and/or related material may difference in each patient, though TACE were performed 1–2 months after curative resection of HCC by using lipiodol-based regimens. Lack of standardized technique of intra-arterial therapy was the major limitation. Then, the consistency and representativeness of patients included was also suboptimal. This heterogeneity in the selection of patients may have led to selection bias. In addition, not all RCTs were high-quality studies and many NRCTs were predominantly retrospective in nature. As such there may be inherent selection bias from some of the studies. Moreover, many studies did not disclose some factors, such as median OS, DFS or the value of HR, which led to the pooling results of some factors only from a few articles. Finally, as all studies were performed in Asia, the results of this meta-analysis might not be applicable to patients in Western countries.

In conclusion, this systematic review and meta-analysis provides updated evidence to support adjuvant TACE as a possible treatment to improve the long-term oncological prognosis for patients undergoing curative resection for HCC, especially in those patients with multinodular HCC, MVI or PVTT. Future RCTs are still needed to better define the benefit of adjuvant TACE in subset patients with HCC.

Author contributions

Lei Liang, Chao Li and Yong-Kang Diao contributed equally to this work. Lei Liang, Chao Li, Feng Shen, Dong-Sheng Huang, Cheng-Wu Zhang and Tian Yang conceived and designed the study. Lei Liang and Chao Li searched the literature and extracted the data. Lei Liang, Chao Li, Yong-Kang Diao, Hang-Dong Jia and Hao Xing wrote the manuscript. Feng Shen and Tian Yang proofread the manuscript. Timothy M. Pawlik, Wan Yee Lau and Dong-Sheng Huang made critical revision of the manuscript. Tian Yang obtained funding. All authors approved the final version of the manuscript. The authors declare no competing financial interests.

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Supplemental material

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References

1. Torre LA, Bray F, Siegel RL, *et al.* Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.
2. Vitale A, Peck-Radosavljevic M, Giannini EG, *et al.* Personalized treatment of patients with very early hepatocellular carcinoma. *J Hepatol* 2017; 66: 412–423.
3. Tabrizian P, Jibara G, Shrager B, *et al.* Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. *Ann Surg* 2015; 261: 947–955.
4. Cucchetti A, Piscaglia F, Cescon M, *et al.* Conditional survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. *Clin Cancer Res* 2012; 18: 4397–4405.
5. Tsai TJ, Chau GY, Lui WY, *et al.* Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. *Surgery* 2000; 127: 603–608.
6. Imamura H, Matsuyama Y, Tanaka E, *et al.* Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003; 38: 200–207.
7. Wu JC, Huang YH, Chau GY, *et al.* Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. *J Hepatol* 2009; 51: 890–897.
8. Sun HC, Tang Z-Y, Wang L, *et al.* Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. *J Cancer Res Clin Oncol* 2006; 132: 458–465.
9. Wang S-N, Chuang S-C and Lee K-T. Efficacy of sorafenib as adjuvant therapy to prevent early recurrence of hepatocellular carcinoma after curative surgery: a pilot study. *Hepatol Res* 2014; 44: 523–531.
10. Lee JH, Lee JH, Lim YS, *et al.* Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. *Gastroenterology* 2015; 148: 1383–1391.e6.
11. Kohno H, Nagasue N, Hayashi T, *et al.* Postoperative adjuvant chemotherapy after radical hepatic resection for hepatocellular carcinoma (HCC). *Hepatogastroenterology* 1996; 43: 1405–1409.
12. Liu CJ, Lee PH, Lin DY, *et al.* Heparanase inhibitor PI-88 as adjuvant therapy for hepatocellular carcinoma after curative resection: a randomized phase II trial for safety and optimal dosage. *J Hepatol* 2009; 50: 958–968.
13. Chua TC, Saxena A, Chu F, *et al.* Hepatic resection with or without adjuvant iodine-131-lipiodol for hepatocellular carcinoma: a comparative analysis. *Int J Clin Oncol* 2011; 16: 125–132.
14. Zhong J-H, Li H, Li L-Q, *et al.* Adjuvant therapy options following curative treatment of hepatocellular carcinoma: a systematic review of randomized trials. *Eur J Surg Oncol* 2012; 38: 286–295.
15. Bruix J, Sherman M and American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53: 1020–1022.
16. Verslype C, Rosmorduc O, Rougier P, *et al.* Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23(Suppl. 7): vii41–vii48.
17. European Association for the Study of the Liver and European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908–943.
18. Sun JJ, Wang K, Zhang CZ, *et al.* Postoperative adjuvant transcatheter arterial chemoembolization after R0 hepatectomy improves outcomes of patients who have hepatocellular carcinoma with microvascular invasion. *Ann Surg Oncol* 2016; 23: 1344–1351.
19. Li F, Guo Z, Zhang Y, *et al.* Postoperative adjuvant arterial chemoembolization improves the survival of hepatitis B virus-related hepatocellular carcinoma: a retrospective control study. *Ir J Med Sci* 2015; 184: 753–759.
20. Wang Z, Ren Z, Chen Y, *et al.* Adjuvant transarterial chemoembolization for HBV-related hepatocellular carcinoma after resection: a randomized controlled study. *Clin Cancer Res* 2018; 24: 2074–2081.

21. Wang YY, Wang LJ, Xu D, *et al*. Postoperative adjuvant transcatheter arterial chemoembolization should be considered selectively in patients who have hepatocellular carcinoma with microvascular invasion. *HPB (Oxford)*. Epub ahead of print 22 September 2018. DOI: 10.1016/j.hpb.2018.08.001.
22. Qi Y-P, Zhong J-H, Liang Z-Y, *et al*. Adjuvant transarterial chemoembolization for patients with hepatocellular carcinoma involving microvascular invasion. *Am J Surg*. Epub ahead of print 6 August 2018. DOI: 10.1016/j.amjsurg.2018.07.054.
23. Lai EC, Lo CM, Fan ST, *et al*. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. *Arch Surg* 1998; 133: 183–188.
24. Zhong J-H and Li L-Q. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: a meta-analysis. *Hepatol Res* 2010; 40: 943–953.
25. Zhong J-H, Ma L and Li L-Q. Postoperative therapy options for hepatocellular carcinoma. *Scand J Gastroenterol* 2014; 49: 649–661.
26. Panic N, Leoncini E, de Belvis G, *et al*. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One* 2013; 8: e83138.
27. Tierney JF, Stewart LA, Ghersi D, *et al*. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; 8: 16.
28. Parmar MK, Torri V and Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998; 17: 2815–2834.
29. Sterne JA, Hernan MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919.
30. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–926.
31. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
32. Izumi R, Shimizu K, Iyobe T, *et al*. Postoperative adjuvant hepatic arterial infusion of lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. *Hepatology* 1994; 20: 295–301.
33. Li JQ, Zhang YQ, Zhang WZ, *et al*. Randomized study of chemoembolization as an adjuvant therapy for primary liver carcinoma after hepatectomy. *J Cancer Res Clin Oncol* 1995; 121: 364–366.
34. Li Q, Wang J, Sun Y, *et al*. Postoperative transhepatic arterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma: a randomized study with 131 cases. *Dig Surg* 2006; 23: 235–240.
35. Li Q, Wang J, Sun Y, *et al*. Efficacy of postoperative transarterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma complicated by portal vein tumor thrombosis–a randomized study. *World J Surg* 2006; 30: 2004–2011; discussion 2012–2013.
36. Peng B-G, He Q, Li J-P, *et al*. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. *Am J Surg* 2009; 198: 313–318.
37. Zhong C, Guo RP, Li JQ, *et al*. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for stage III A hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2009; 135: 1437–1445.
38. Wei W, Jian P-E, Li S-H, *et al*. Adjuvant transcatheter arterial chemoembolization after curative resection for hepatocellular carcinoma patients with solitary tumor and microvascular invasion: a randomized clinical trial of efficacy and safety. *Cancer Commun (Lond)* 2018; 38: 61.
39. Ren Z-G, Lin Z-Y, Xia J-L, *et al*. Postoperative adjuvant arterial chemoembolization improves survival of hepatocellular carcinoma patients with risk factors for residual tumor: a retrospective control study. *World J Gastroenterol* 2004; 10: 2791–2794.
40. Xi T, Lai EC, Min AR, *et al*. Adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma: a non-randomized comparative study. *Hepatogastroenterology* 2012; 59: 1198–1203.
41. Li KW, Wen TF, Li X, *et al*. The effect of postoperative TACE on prognosis of HCC with microscopic venous invasion. *Hepatogastroenterology* 2012; 59: 1944–1946.
42. Chen X, Zhang B, Yin X, *et al*. Lipiodolized transarterial chemoembolization in hepatocellular carcinoma patients after curative resection. *J Cancer Res Clin Oncol* 2013; 139: 773–781.

43. Liu H, Zhang A, Qian N, *et al*. Postoperative transarterial chemoembolization benefits patients with high γ-glutamyl transferase levels after curative hepatectomy for hepatocellular carcinoma: a survival stratification analysis. *Tohoku J Exp Med* 2012; 227: 269–280.

44. Jiang JH, Guo Z, Lu HF, *et al*. Adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma: propensity score analysis. *World J Gastroenterol* 2015; 21: 4627–4634.

45. Liu W, Wang K, Bao Q, *et al*. Hepatic resection provided long-term survival for patients with intermediate and advanced-stage resectable hepatocellular carcinoma. *World J Surg Oncol* 2016; 14: 62.

46. Bai T, Chen J, Xie Z-B, *et al*. The efficacy and safety of postoperative adjuvant transarterial embolization and radiotherapy in hepatocellular carcinoma patients with portal vein tumor thrombus. *OncoTargets Ther* 2016; 9: 3841–3848.

47. Liu C, Sun L, Xu J, *et al*. Clinical efficacy of postoperative adjuvant transcatheter arterial chemoembolization on hepatocellular carcinoma. *World J Surg Oncol* 2016; 14: 100.

48. Tong Y, Li Z, Liang Y, *et al*. Postoperative adjuvant TACE for patients of hepatocellular carcinoma in AJCC stage I: friend or foe? A propensity score analysis. *Oncotarget* 2017; 8: 26671–26678.

49. Ye JZ, Chen JZ, Li ZH, *et al*. Efficacy of postoperative adjuvant transcatheter arterial chemoembolization in hepatocellular carcinoma patients with microvascular invasion. *World J Gastroenterol* 2017; 23: 7415–7424.

50. Kubo S, Takemura S, Sakata C, *et al*. Adjuvant therapy after curative resection for hepatocellular carcinoma associated with hepatitis virus. *Liver Cancer* 2013; 2: 40–46.

51. Cheng X, Sun P, Hu Q-G, *et al*. Transarterial (chemo)embolization for curative resection of hepatocellular carcinoma: a systematic review and meta-analyses. *J Cancer Res Clin Oncol* 2014; 140: 1159–1170.

52. Qi X, Liu L, Wang D, *et al*. Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Oncotarget* 2015; 6: 36838–36859.