Meta-analysis: preoperative transcatheter arterial chemoembolization does not improve prognosis of patients with resectable hepatocellular carcinoma

Yanming Zhou†, Xiaofeng Zhang†, Lupeng Wu†, Feng Ye†, Xu Su†, Lehua Shi‡ and Bin Li*†

Abstract

Background: Long-term outcomes of partial liver resection of hepatocellular carcinoma (HCC) remain satisfactory due to high incidences of recurrence. This study was intended to see whether preoperative transcatheter arterial chemoembolization (TACE) reduces postoperative tumor recurrences and prolongs survival of patients with resectable HCC.

Methods: A computerized literature search was performed to identify relevant articles. The quality of nonrandomized comparative studies (NRCTs) was assessed using the methodological index for nonrandomized studies (MINORS). Data synthesis was performed using Review Manager 5.0 software.

Results: Twenty-one studies (4 randomized controlled trials and 17 NRCTs) with a total of 3,210 participants were suitable for analysis. There was no significant difference in disease-free and overall survival at 5-year (32.1% vs. 30.0% and 40.2% vs. 45.2%), and intra- and extra-hepatic recurrence (51.2% vs. 53.6% and 12.9% vs. 10.3%) between patients with and without preoperative TACE. Postoperative morbidity (28.9% vs. 26.8%) and in-hospital mortality (4.1% vs. 3.1%) were also similar between the two groups.

Conclusions: Preoperative TACE does not seem to improve prognosis and therefore it is prudent to recommend it as a preoperative routine procedure for resectable HCC.

Keywords: Hepatocellular carcinoma, Transcatheter arterial chemoembolization, Prognosis

Background

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, and ranks the third leading cause of cancer-related death [1]. Hepatectomy is considered the main curative treatment for HC with a 5-year survival of 23.8–54.8% as reported in the most recent series [2-5]. Tumor recurrence even after radical surgery affects 75-100% HC patients, accounting for the major cause of death of HC patients [6]. The development of appropriate strategies to prevent tumor recurrence is therefore critical for improving long-term outcomes of HC patients after surgical resection.

Transcatheter arterial chemoembolization (TACE), which induces tumor ischemic necrosis by arterial injection of chemotherapeutic drugs and embolizing agents, is recommended as the first-line palliative treatment for inoperable HCC in the 2005 practice guidelines issued by the American Association for the Study of Liver Diseases [7]. Some researchers believed that it may reduce the viability of HCC cells before surgery and reduce postoperative tumor recurrence [8]. Although several studies have demonstrated the survival benefits of preoperative TACE for patients with HCC [9,10], others have failed to show any significant survival benefit [11-16]. Therefore, the role of preoperative TACE for HCC remains a contradictory issue. A recent review of three randomized...
controlled trials (RCTs) showed that preoperative TACE did not significantly improve survival [17]. However, their study only involved 257 participants, and therefore may not be convincing enough to confirm the effect conclusively [18]. To produce more reliable evidence for clinical decision-making, meta-analytic techniques could be applied to nonrandomized comparative studies (NRCTs) to ensure both the number and sample size of RCTs [19], knowing that meta-analysis of well-designed NRCTs is feasible and the results are remarkably similar to those of contemporaneous RCTs [20]. The present meta-analysis should be able to provide an updated evaluation on preoperative TACE for resectable HCC by taking into account all the currently evidence from RCTs and well-designed NRCTs.

Methods

Inclusion and exclusion criteria

The present meta-analysis was performed by following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Primary studies that evaluated the efficacy of preoperative TACE vs. no-preoperative TACE for resectable HCC were considered for inclusion. For duplicate publications reported by the same authors, either the one of higher quality or the most recent publication was selected. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and uncontrolled studies were excluded. Study populations including recurrent HCC or unresectable diseases were also excluded.

Study selection

A computerized search of the literature was performed by searching Medline, EMBASE, OVID, and Cochrane database from the time of inception to June 2012. The following medical subject heading (MeSH) terms were used: “hepatectomy,” “hepatocellular carcinoma,” and “transarterial chemoembolization”. Only studies on humans and in the English language were considered for inclusion. Reference lists of all identified articles were manually searched for additional studies. Publication bias was assessed visually using a funnel plot.

Data extraction

Two reviewers (LW and YZ) independently extracted the following parameters from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, the number of subjects in each arm, survival, recurrence, morbidity and mortality. All relevant texts, tables and figures were reviewed for data extraction.

Qualitative analysis

The RCTs were scored using the Jadad composite scale [21], which evaluates studies based on appropriate randomization, double blinding, and an adequate description of withdrawals and drop-outs. For evaluation of NRCTs, the methodological index for nonrandomized studies (MINORS) with some modifications were applied [22]. The following 12 items were evaluated for each study: a clearly stated aim, consecutive patients, prospective data collection, reported endpoints, unbiased outcome evaluation, adequate length of follow-up, loss to follow up <5%, ≥ 20 patients in each arm, adequate control group, contemporary groups, controls equivalent to cases, and adequate statistical analyses. Studies achieving more than 16 points (maximum 24) were defined as well-designed and were included in the meta-analysis [20]. Those with less than 16 points were excluded.

Outcomes of interests

Items for assessing long-term outcomes included disease-free and overall survival rate at 5 year, total recurrence, hepatic recurrence, and extrahepatic recurrence.

Items for assessing short-term outcomes included postoperative morbidity and in-hospital mortality.

Statistical analysis and synthesis

Dichotomous variables were tested by odds ratio (OR) with a 95% confidence interval (95% CI), and continuous variables were tested by the weighted mean difference (WMD) with a 95% CI. Between-study heterogeneity was evaluated by $\chi^2$ and $I^2$. Data that were not significantly heterogeneous ($P > 0.1$) were calculated using a fixed effects model, and heterogeneous data ($P < 0.1$) were calculated using a random-effects model. Sensitivity analysis was undertaken by using the following subgroups: (1) RCTs, (2) NRCTs, and (3) studies with matched clinicopathological parameters. Statistical analyses were performed with Review Manager version 5.0 (The Cochrane Collaboration, Software Update, Oxford). A value of $P < 0.05$ was considered statistically significant.

Results

Eligible studies

Twenty-six studies that matched the selection criteria were retrieved from the electronic databases [9-16,23-41]. Of these studies, one study was excluded due to overlap of authors and nonrandomized nature [23], and therefore the most recent RCT was included [24]. Four NRCTs with fewer than 16 points were excluded [9,25-27]. Finally, 21 articles, including four RCTs [14-16,24] and 17 NRCTs [10-13,28-40], met the inclusion criteria.

The characteristics of the 21 studies are summarized in Table 1. A total of 3,210 patients were included in the meta-analysis, of whom 1,431 received preoperative TACE...
| Reference | Year       | Inclusion Period | Country | Group       | No. of patients | M/F | Mean age (years) | Mean AFP (ng/ml) | Child-Pugh A/B/C | LB N/H/C | Tumor size (cm) | Matching | Not matching | Score |
|------------|------------|------------------|---------|-------------|----------------|-----|------------------|------------------|-----------------|-----------|----------------|----------|--------------|-------|
| Wu [14]    | 1995       | 1983-1991        | Taiwan | TACE (+) TACE (−) | 24/28          | 23/1 | 51.8 ± 12.4      | ≥ 400 (n = 15)   | 22/2/0          |        | 14.3 ± 4.2       | 1-3,5-15 | 17            | 2     |
| Yamasaki [15] | 1996     | 1987-1989        | Japan   | TACE (+) TACE (−) | 50/47          | 50/0 | 54.9 ± 6.4       | 332 ± 11.5       | 24/4/0          |        | 14.5 ± 3.3       | 3-5-12   |              | 2     |
| Zhou [16]   | 2009       | 2001-2003        | China   | TACE (+) TACE (−) | 52/56          | 49/7 | 45.3 ± 9.8       | ≥ 400 (n = 16)   | 44/8/0          |        | 3.1 ± 0.8        | 12,4-9,12 |              | 2     |
| Kaibori [24] | 2012      | 2004-2007        | Japan   | TACE (+) TACE (−) | 42/43          | 35/7 | 68.1 ± 5.7       | ≥ 400 (n = 17)   | 37/5/0          | 1/27/14 | 10-10,13,15    | 11-12    | 10-12        | 3     |
| Nagasue [12] | 1989     | 1980-1986        | Japan   | TACE (+) TACE (−) | 31/107         | 25/6 | 56.5 ± 9.1       | >20 (n = 18)     | 17/13/1         |       | >3 (n = 17)      | 1-3,5,6  | 8-11,14       | 19    |
| Adachi [13] | 1993       | 1981-1991        | Japan   | TACE (+) TACE (−) | 46/26          | 39/7 | 55.9 ± 7.1       | >20 (n = 24)     | >20 (n = 24)    |        | >3 (n = 25)      | 3-6,10-12 | 2-4,6,8,11        | 18    |
| Harada [28] | 1996       | 1992-1994        | Japan   | TACE (+) TACE (−) | 105/35         | 90/15 | 57.6 ± 9.7       | >20 (n = 27)     | 37/18/5         |       | >3 (n = 36)      | 1-3,5-7,12,14 | 13-18       | 18    |
| Uchida [29] | 1996       | 1986-1991        | Japan   | TACE (+) TACE (−) | 60/68          | 50/10 | 59.0 ± 9.9       | >20 (n = 45)     | 43/6/0          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Majno [10]  | 1997       | 1985-1995        | France  | TACE (+) TACE (−) | 49/27          | 44/5 | 59.2 ± 7.1       | >20 (n = 27)     | 37/18/5         |       | >3 (n = 31)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Di Carlo [11] | 1998       | 1989-1997        | Italy   | TACE (+) TACE (−) | 55/45          | 49/6 | 63.0 ± 6.0       | >10 (n = 13)     | 43/6/0          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Paye [30]   | 1998       | 1986-1992        | France  | TACE (+) TACE (−) | 24/24          | 21/3 | 57 ± 7           | >10 (n = 13)     | 43/6/0          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Lu [31]     | 1999       | 1988-1994        | China,  | TACE (+) TACE (−) | 44/76          | 36/8 | 51.5 ± 9.5       | >100 (n = 6)     | 17/10/0         |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Ochiai [32] | 2003       | 1978-1994        | Japan   | TACE (+) TACE (−) | 100/48         | 78/22 | 59.6 ± 8         | >400 (n = 74)    | 22/2/2          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Sugo [33]   | 2003       | 1997-2000        | Japan   | TACE (+) TACE (−) | 146/81         | 122/24 | 57.6 ± 9.4       | >400 (n = 30)    | 118/27/1        |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Sasaki [34] | 2006       | 1982-2003        | Japan   | TACE (+) TACE (−) | 109/126        | 85/24 | 43/5             | >65 (n = 38)     | 12/2/0          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Chen [35]   | 2007       | 1990-2004        | China   | TACE (+) TACE (−) | 89/157         | 71/18 | 45.5 ± 6.3       | >65 (n = 68)     | 7/11/0          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Choi [36]   | 2007       | 1998-2005        | Korea   | TACE (+) TACE (−) | 120/153        | 93/27 | 52.4 ± 9.6       | >100 (n = 40)    | 117/0/0         |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Kim [37]    | 2008       | 1995-2000        | Korea   | TACE (+) TACE (−) | 97/237         | 80/17 | 48.8 ± 9.2       | >1000 (n = 70)   | 97/237          |       | >3 (n = 32)      | 1-3,5,7,12,14 | 13-18       | 18    |
| Study          | Year  | Start-End | Country   | TACE (+) | TACE (−) | Age | Gender | AFP Level | ICG R15 (%) | Child-Pugh Grade | Viral Status | Operative Procedures | Tumor Size | Tumor Number | Histologic Grade | Vascular invasion | Tumor Encapsulation | Intrahepatic Metastasis or Satellite Nodules | Pathological Stage | Capsular Invasion | Adjacent Organ Invasion |
|---------------|-------|-----------|-----------|----------|----------|-----|--------|-----------|-------------|------------------|-------------|---------------------|------------|--------------|------------------|-------------------|-------------------|-----------------------------|-------------------|----------------|---------------------|
| Lee [38]      | 2009  | 2000-2006 | Taiwan    | 114      | 236      | 89/25| 173/63| 57.9 ± 11.3| 2265.88 ± 8438.55| 110/4/0          | —/—/79      | —/—/152              | —/—/—/—    | 2265.88 ± 8438.55| 110/4/0      | 11/18         | 1-3,5,7-10, 12,15 | 11/18             |
| Kang [39]     | 2010  | 1997-2007 | Korea     | 32       | 64       | 25/7 | 51/13 | 52.4 ± 9.8 | 9584.4 ± 26238.5 | 30/2/0          | —/—/—       | —/—/—                | —/—/—/—    | —/—/—/—                | 30/2/0      | 64/0/0        | 1-3,5,6,9,10,15 | —/—/—/—           |
| Yamashita [40]| 2012  | 1995-2008 | Japan     | 42       | 95       | 36/7 | 77/18 | 58 ± 12     | 1527 ± 4415    | 31/—/—           | —/—/7       | —/—/—               | —/—/—/—    | 1527 ± 4415            | 31/—/—     | 88/—/—       | 2-4,7-11     | 1,5,6             |

LB liver background; N/H/C normal/hepatitis/cirrhosis; 1, Age; 2, Gender; 3, AFP level; 4, ICG R15 (%); 5, Child-Pugh grade; 6, Viral status; 7, Operative procedures; 8, LB; 9, Tumor size; 10 Tumor number; 11, Histologic grade; 12, Vascular invasion; 13, Tumor encapsulation; 14, Intrahepatic metastasis or satellite nodules; 15, Pathological stage; 16, Capsular invasion; 17, Adjacent organ invasion.
and 1,779 were allocated to a control group. The number of patients in each study varied from 40 to 350 patients. In the enrolled patients, the percentage of men ranged from 76.9% to 100% and the mean age ranged from 45.3 ± 9.8 to 68.1 ± 5.7 years. Eight studies were completely matched with respect to the reported clinicopathological parameters \[12,15,16,28,30,32,35,39\]. One trial was conducted to compare outcomes of whole-liver TACE, selective TACE, and without preoperative TACE \[24\]. Only selective TACE arm was considered in the present meta-analysis.

The data regarding the effects of TACE on tumor responses were available in 18 studies \[10-16,24,28,30-38\], in which histological examination on surgical specimens revealed that a total of 260 patients (20.1%) of 1,292 patients had complete tumor necrosis ranging from 0 to 53.6%.

The funnel plot (Figure 1) for 5-year disease-free survival in the included studies demonstrated asymmetry, indicating an insignificant sign of publication bias.

### Overall meta-analysis

The results from overall meta-analysis are summarized in Table 2.

#### Long-term outcomes

The 5-year disease-free survival was 7.0–57% for preoperative TACE and 8.0–48.8% for control in 18 studies \[10,11,13-16,24,28,31-40\]. The 5-year overall survival was 15.4–62.7% for preoperative TACE and 19.0–62.5% for control in 16 studies \[11,12,14-16,24,28,29,31,34-40\]. Pooled analyses showed that preoperative TACE use was not associated with significant improvement in disease-free and 5-year overall survival (32.1% vs. 30.0%, \(P = 0.17\); 40.2% vs. 45.2%, \(P = 0.37\), respectively). There was significant heterogeneity between studies reporting these two outcomes (\(P = 0.02\), \(P < 0.01\)); respectively) (Figures 2, 3).

Eleven studies reported on total recurrence after surgery: 411 (61.0%) of 673 with preoperative TACE vs. 536 (58.4%) of 917 without TACE \[10,14,16,24,30,32,35,36,38-40\].

### Table 2 Results of overall meta-analysis

| Outcomes                          | No. of studies | No. of patients | Results | OR (95% CI) | \(P\) value | HG p value |
|-----------------------------------|----------------|----------------|---------|-------------|-------------|------------|
| **Long-term outcomes**            |                |                |         |             |             |            |
| 5-years disease-free survival     | 18 \[10,11,13-16,24,28,31-40\] | 1275 | 1567 | 32.1% | 30.0% | 1.19 (0.93, 1.53) | 0.17 | 0.02 |
| 5-years overall survival          | 16 \[11,12,14-16,24,28,29,31,34-40\] | 1038 | 1463 | 40.2% | 45.2% | 0.85 (0.59, 1.22) | 0.37 | <0.01 |
| Total recurrence                  | 11 \[10,14,16,24,30,32,35,36,38-40\] | 673 | 917 | 61.0% | 58.4% | 0.99 (0.72, 1.36) | 0.95 | 0.08 |
| Intrahepatic recurrence           | 12 \[10-12,14,16,24,29,30,32,35,36,39\] | 660 | 797 | 51.2% | 53.6% | 0.84 (0.67, 1.05) | 0.12 | 0.23 |
| Extrapancreatic recurrence        | 9 \[10,14,16,24,30,32,35,36,39\] | 519 | 591 | 12.9% | 10.3% | 1.30 (0.88, 1.92) | 0.19 | 0.33 |
| **Short-term outcomes**           |                |                |         |             |             |            |
| Overall morbidity                 | 11 \[10-12,14,16,24,29,30,35,36,40\] | 583 | 803 | 28.9% | 26.8% | 1.02 (0.80, 1.32) | 0.85 | 0.42 |
| Liver failure                     | 6 \[11,12,14,16,29,36\] | 337 | 457 | 5.9% | 6.3% | 1.06 (0.57, 1.96) | 0.86 | 0.31 |
| Bile leakage                      | 6 \[12,14,16,29,35,36\] | 371 | 569 | 3.5% | 2.8% | 1.12 (0.53, 2.35) | 0.77 | 0.80 |
| Pleural effusion                  | 4 \[12,29,35,36\] | 300 | 485 | 7.0% | 8.0% | 0.93 (0.53, 1.65) | 0.24 | 0.26 |
| Ascites                           | 3 \[29,35,36\] | 269 | 378 | 6.3% | 6.1% | 0.98 (0.51, 1.89) | 0.96 | 0.16 |
| Intra-abdominal abscess           | 5 \[11,14,29,35,36\] | 348 | 451 | 2.5% | 1.3% | 1.66 (0.63, 4.40) | 0.31 | 0.58 |
| Wound infection                   | 5 \[12,14,16,35,36\] | 311 | 501 | 3.2% | 2.5% | 1.11 (0.48, 2.53) | 0.81 | 0.35 |
| Postoperative bleeding            | 3 \[11,12,36\] | 206 | 305 | 3.3% | 2.9% | 1.25 (0.41, 3.81) | 0.69 | 0.63 |
| Stress ulcer bleeding             | 3 \[12,29,35\] | 180 | 332 | 1.1% | 1.2% | 1.31 (0.29, 5.92) | 0.73 | 0.74 |
| Pneumonia                         | 4 \[11,12,14,35\] | 199 | 337 | 4.0% | 2.1% | 1.64 (0.60, 4.46) | 0.33 | 0.23 |
| Mortality                         | 16 \[10-12,14-16,24,28-30,33-36,38,40\] | 1100 | 1325 | 4.1% | 3.1% | 1.25 (0.80, 1.97) | 0.33 | 0.85 |

HG heterogeneity.
Pooled analyses showed that the difference was insignificant between the two groups ($P = 0.95$). There was moderate heterogeneity between studies ($P = 0.08$).

Further pooled analysis of studies providing information found that the percentages of both intra- and extrahepatic recurrence were also similar in the two groups (51.2% vs. 53.6%, $P = 0.12$; 12.9% vs. 10.3%, $P = 0.19$, respectively). No significant heterogeneity was detected between the groups in reporting these two outcomes (Figures 4, 5).

Short-term outcomes

Eleven studies reported on overall morbidity: 169 (28.9%) of 583 with preoperative TACE vs. 216 (26.8%) of 803 without TACE [10-12,14,16,24,29,30,35,36,40]. Pooled analyses showed that the difference was insignificant between the two groups ($P = 0.85$) without significant heterogeneity (Figure 6). Further subanalysis showed that the risk was comparable between patients in both study groups with respect to liver failure (5.9% vs. 6.3%, $P = 0.86$), bile leakage (3.5% vs. 2.8%, $P = 0.77$), pleural effusion (7.0% vs. 8.0%, $P = 0.24$), ascites (6.3% vs. 6.1%, $P = 0.96$), intra-abdominal abscess (2.5% vs. 1.3%, $P = 0.31$), wound infection (3.2% vs. 2.5%, $P = 0.81$), postoperative bleeding (3.3% vs. 2.9%, $P = 0.69$), stress ulcer bleeding (1.1% vs. 1.2%, $P = 0.73$), and pneumonia (4.0% vs. 2.1%, $P = 0.33$).

Sixteen studies reported on in-hospital mortality [10-12,14,16,24,28,30,33-36,38,40], showing that 87 patients died: 46 in the preoperative TACE group and 41 in the control group. Pooled analyses showed that there was no statistical difference between the two groups ($P = 0.33$) (Figure 7).

Sensitivity analysis

As Table 3 shows, the results of sensitivity analysis derived from three subgroups were all consistent with those derived from overall meta-analysis.

Discussion

The design of TACE is based on the principle that primary HCC is supplied almost exclusively (90%) by the hepatic arteries. The obstruction of the feeding

---

### Table 2: Sensitivity analysis results

| Study/Anal Subgroup | TACE (+) Events | TACE (-) Events | Odds Ratio MMR Random 95% CI | Odds Ratio MMR Random 95% CI |
|---------------------|----------------|----------------|-----------------------------|-----------------------------|
| Chen 2010           | 41             | 89             | 1.11 (0.74, 1.67)           | 0.80 (0.52, 1.23)           |
| Di Carlo 1998       | 21             | 55             | 2.47 (0.90, 6.41)           | 1.29 (0.89, 1.89)           |
| Hirota 1996         | 52             | 98             | 1.28 (0.96, 1.70)           | 0.92 (0.65, 1.30)           |
| Kalbiri 2012        | 7              | 42             | 0.89 (0.66, 1.20)           | 0.96 (0.67, 1.38)           |
| Kang 2010           | 8              | 32             | 0.40 (0.16, 1.03)           | 0.49 (0.20, 0.89)           |
| Lee 2009            | 54             | 114            | 0.62 (0.39, 0.97)           | 0.81 (0.49, 1.30)           |
| Lu 1999             | 14             | 44             | 1.09 (0.89, 1.34)           | 0.98 (0.71, 1.43)           |
| Nagasue 1989        | 5              | 31             | 0.54 (0.14, 1.95)           | 0.51 (0.15, 1.61)           |
| Ochiai 2003         | 10             | 45             | 1.56 (0.97, 2.51)           | 0.87 (0.51, 1.51)           |
| Uchida 1996         | 15             | 60             | 0.21 (0.10, 0.44)           | 0.22 (0.11, 0.43)           |
| Wu 1995             | 7              | 23             | 0.82 (0.29, 2.59)           | 0.69 (0.29, 1.68)           |
| Yamashita 1996      | 31             | 108            | 1.01 (0.65, 1.58)           | 0.83 (0.50, 1.39)           |
| Yamashita 2012      | 24             | 42             | 1.75 (0.84, 3.68)           | 1.53 (0.72, 3.25)           |
| Zhou 2009           | 16             | 52             | 1.83 (0.75, 4.40)           | 0.85 (0.59, 1.23)           |

Total events 418 / 683

Heterogeneity: $Q = 4.70, df = 15 (P = 0.99), I^2 = 75$

Test for overall effect: $Z = 0.89 (P = 0.37)$

---

Figure 2 Results of the meta-analysis on 5-year disease-free survival.

Figure 3 Results of the meta-analysis on 5-year overall survival.
arteries can induce tumor ischemic necrosis. A combination of chemotherapy can drastically increase the local concentration of the chemotherapeutic agent and may improve the benefit of therapy. In 2003, a review of 7 RCTs showed that TACE significantly improved 2-year overall survival compared with nonactive treatment in patients with unresectable HCC [41]. In 2005, this therapy was recommended as standard intervention for unresectable patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread [7]. In contrast, the results of present pooled analysis of 21 trials do not support the use of preoperative TACE in the management of patients with resectable HCC.

Although TACE is effective for main tumors, intrahepatic metastases, tumor thrombi in the portal veins, and capsular invasion, which are considered risk factors contributing to HCC recurrence, are more unresponsive to TACE because of collateral and portal vein blood supply [8,13,16]. In addition, TACE mainly affects well-differentiated HCC without completely killing poorly differentiated cells [42], which harbour a high grade of malignancy and ready spread within the portal venous system [43]. Furthermore, hematogeneous and lymphatic spread dissemination of cancer cells can precede TACE treatment. It is therefore reasonable to conclude that TACE is unable to reduce the risk of postoperative recurrence, or confer a survival advantage.

Adachi et al. [13] and Harada et al. [28] reported that the TACE subgroup with complete tumor necrosis had a better survival rate than the group without TACE. This is partly due to residual confounding, because tumors with complete necrosis are strongly associated with favorable tumor-related factors, such as smaller tumor size and tumor encapsulation or less portal involvement. On the other hand, several other reports failed to make the same conclusion [15,28,30,31]. It was found in the present study that approximately 20.1% of HCC tumors responded completely to TACE, suggesting that most of the HCC tumor cells were viable even when treated with TACE. The labeling index of proliferating cell nuclear antigen (a most widely used proliferation-associated marker) was significantly higher in the TACE group, indicating that residual HCC cells following preoperative TACE exhibit more aggressive behavior [44]. In support of this observation, Liou et al. [45] indicated that incomplete HCC necrosis after TACE (especially combined with necrotic area >50% main tumor size) was associated with the development of lung metastasis that has a strong adverse impact on patient survival. Adachi et al. [13] and Kim et al. [37] found that subjects with partial tumor necrosis had the lowest disease-free survival rate among the TACE subgroups and tended to have a lower survival rate than the group without TACE. Zhou et al. [16] noted that five patients lost the chance of potentially curative liver resection because of progression of disease with metastases.

**Figure 4** Results of the meta-analysis on intrahepatic recurrence.

**Figure 5** Results of the meta-analysis on extrahepatic recurrence.
and liver failure \( n = 1 \) during intervals between last TACE hepatic resection. The mechanism underlying accelerated tumor progression by TACE is unclear. Intratumoral necrosis was found to weaken the adhesive potential of the tumor and subsequently facilitate the release of cancer cells from the primary tumor and dislodgement into the bloodstream [46]. Xiao et al. [47] reported that mutated p53 could enhance the proliferation of HCC cells and suppress the apoptosis of HCC cells after TACE. In addition, vascular endothelial growth factor (VEGF), the most specific known angiogenic factor that plays a critical role in tumor growth, invasion, and metastasis, was up-regulated by tumor tissue ischemia and hypoxia after TACE [48].

In the present meta-analysis, in-hospital mortality did not differ significantly between TACE group patients and non-TACE group patients. However, Gerunda et al. [25] reported that three patients died of liver failure during 2–5 months after surgery in the TACE group. Sasaki et al. [34] and Uchida et al. [29] reported that late death due to liver failure was significantly higher in the TACE group than that in the non-TACE group. Uchida et al. [29] considered that hepatic function impairment induced by TACE could be repaired easily in the noncirrhotic liver, but hepatic function may gradually and progressively deteriorate due to TACE in some cirrhotic patients.

This study has several limitations. First, much of the evidence comes from NRCTs that could either exaggerate or underestimate the measured magnitude of effect size [20]. To minimize this effect, we limited the analysis to well-designed studies. As a matter of fact, the estimates from overall meta-analysis were consistent with those derived from RCTs, suggesting that the magnitude of the effect was not affected by the inclusion of NRCTs. Second, significant heterogeneity was present in some outcomes. Variability in the surgeon experience and the chemoembolization schedule may have introduced potential bias. In addition, clinicopathological factors associated with recurrence, such as hepatitis status, cirrhotic liver, and tumor staging, might be another source of potential heterogeneity. The use of random-effects models partially mitigates this concern. Third, although 21 studies involving more than 3,000 patients were enrolled for analysis, funnel plot analysis revealed the sign of publication bias. This may relate to the use of published English data only. Fourth, it is important to note that 18 of the 21 studies were from

| TACE (+) | TACE (-) | Odds Ratio M-H Pool, 95% CI |
|----------|----------|--------------------------|
| Chen 2007 | 31 89 | 38 157 | 14.81 | 1.61 [0.95, 2.89] |
| Choi 2007 | 20 120 | 38 157 | 21.11 | 0.92 [0.53, 1.61] |
| Di Carlo 1998 | 16 55 | 15 45 | 9.81 | 0.92 [0.35, 3.1] |
| Halkon 2012 | 3 42 | 8 42 | 6.06 | 0.34 [0.06, 1.37] |
| Majo 1997 | 25 49 | 19 27 | 18.41 | 0.52 [0.20, 1.38] |
| Nageo 1989 | 8 31 | 31 107 | 0.51 | 0.85 [0.34, 2.11] |
| Paye 1986 | 15 24 | 10 24 | 4.96 | 0.63 [0.25, 2.23] |
| Uchida 1998 | 14 60 | 11 60 | 0.55 | 1.39 [0.06, 3.08] |
| Wu 1995 | 5 24 | 7 28 | 4.21 | 0.79 [0.21, 2.91] |
| Yamashita 2012 | 9 42 | 22 95 | 6.78 | 0.89 [0.36, 2.18] |
| Zhou 2009 | 15 47 | 12 56 | 6.11 | 1.72 [0.71, 4.17] |

Total (95% CI) 563 863 100% 1.02 [0.80, 1.32]
Table 3 Results of sensitivity analysis

| Outcome                        | No. of studies | No. of patients | Results | OR (95% CI) | P value | HG p value |
|--------------------------------|----------------|-----------------|---------|-------------|---------|------------|
|                                |                | TACE (+)        | TACE (+) |              |         |            |
|                                |                | TACE (+)        | TACE (+) |              |         |            |
| RCTs                           |                |                 |         |             |         |            |
| 5-years disease-free survival  | 4[14-16,24]    | 167             | 172     | 29.3%       | 31.9%   | 0.85 (0.53, 1.39) | 0.52 | 0.16 |
| 5-years overall survival       | 4[14-16,24]    | 167             | 172     | 36.5%       | 38.3%   | 0.89 (0.56, 1.41) | 0.61 | 0.11 |
| Total recurrence               | 3[14,16,24]    | 116             | 124     | 74.1%       | 74.2%   | 1.03 (0.36, 2.90) | 0.96 | 0.07 |
| Intrahepatic recurrence        | 3[14,16,24]    | 116             | 124     | 50.0%       | 46.7%   | 1.32 (0.47, 3.70) | 0.59 | 0.02 |
| Extrahepatic recurrence        | 3[14,16,24]    | 116             | 124     | 28.4%       | 22.5%   | 1.37 (0.42, 4.43) | 0.60 | 0.04 |
| Overall morbidity              | 3[14,16,24]    | 113             | 127     | 20.3%       | 21.2%   | 0.97 (0.52, 1.82) | 0.93 | 0.14 |
| Mortality                      | 4[14-16,24]    | 163             | 174     | 3.1%        | 4.0%    | 0.70 (0.22, 2.30) | 0.56 | 0.95 |
| NRCTs                          |                |                 |         |             |         |            |
| 5-years disease-free survival  | 14[10,11,13,28,31-40] | 1108         | 1395    | 32.4%       | 29.8%   | 1.28 (0.98, 1.67) | 0.07 | 0.04 |
| 5-years overall survival       | 12[11,12,28,29,31-40] | 871          | 1291    | 40.9%       | 46.1%   | 0.86 (0.55, 1.32) | 0.48 | <0.01 |
| Total recurrence               | 8[10,30,32,35,36,38-40] | 559          | 795     | 58.1%       | 55.8%   | 0.98 (0.77, 1.25) | 0.86 | 0.11 |
| Intrahepatic recurrence        | 9[10-12,29,30,32,35,36,39] | 546          | 675     | 51.2%       | 56.5%   | 0.79 (0.62, 1.01) | 0.06 | 0.84 |
| Extrahepatic recurrence        | 6[10,30,32,35,36,39] | 403          | 467     | 8.4%        | 7.0%    | 1.22 (0.73, 2.06) | 0.44 | 0.74 |
| Overall morbidity              | 8[10-12,29,30,35,36,40] | 470          | 676     | 31.0%       | 27.9%   | 1.03 (0.79, 1.36) | 0.81 | 0.50 |
| Mortality                      | 12[10-12,28-30,33-36,38,40] | 937          | 1151    | 4.3%        | 2.9%    | 1.39 (0.85, 2.28) | 0.19 | 0.74 |
| Studies with complete matched clinicopathological parameters |                |                 |         |             |         |            |
| 5-years disease-free survival  | 6[15,16,28,32,35,39] | 421          | 404     | 26.8%       | 22.0%   | 1.13 (0.62, 2.05) | 0.69 | 0.02 |
| 5-years overall survival       | 7[12,15,16,28,32,35,39] | 452          | 511     | 44.6%       | 35.2%   | 1.15 (0.76, 1.74) | 0.50 | 0.08 |
| Total recurrence               | 5[16,30,32,35,39] | 297           | 349     | 73.7%       | 76.5%   | 0.91 (0.62, 1.33) | 0.64 | 0.15 |
| Intrahepatic recurrence        | 6[12,16,30,32,35,39] | 328          | 456     | 56.4%       | 60.1%   | 0.81 (0.59, 1.11) | 0.20 | 0.69 |
| Extrahepatic recurrence        | 5[16,30,32,35,39] | 297           | 349     | 13.1%       | 9.4%    | 1.40 (0.83, 2.38) | 0.21 | 0.80 |
| Overall morbidity              | 4[12,16,30,35] | 191           | 344     | 36.1%       | 28.2%   | 1.36 (0.91, 2.01) | 0.13 | 0.48 |
| Mortality                      | 6[12,15,16,28,30,35] | 339          | 423     | 4.4%        | 3.7%    | 1.16 (0.52, 2.57) | 0.71 | 0.50 |

HG heterogeneity.
Asia. This may raise a question regarding the validity of the results and applicability to other areas. Finally, although some authors have reported the efficacy of preoperative TACE for patients with advanced HCC [33] and large HCC [31,40], the results are not further estimable for subgroup analysis given the absence of data in this respect in the other studies.

Conclusions

The updated meta-analysis represents the largest body of information currently available for assessing the role of preoperative TACE for HCC. This study demonstrates that preoperative TACE does not seem to improve the prognosis and therefore it should be prudent to recommend it as a preoperative routine procedure for resectable HCC.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

YZ participated in the design and coordination of the study, carried out the critical appraisal of studies and wrote the manuscript. LW, FY, XZ, and XS developed the literature search, carried out the extraction of data, assisted in the critical appraisal of included studies and assisted in writing up. LS, YZ, and BL carried out the statistical analysis of studies. All authors read and approved the final manuscript.

Acknowledgements

We thank Doctor Yanfang Zhao (Department of Health Statistics, Second Military Medical University, Shanghai, China) for her critical revision of the manuscript. The authors thank the Editorial Office of BMC Gastroenterology for their careful language editing and manuscript preparation.

References

1. Forner A, Hessheimer AJ, Isabel Real M, et al. Treatment of hepatocellular carcinoma. Crit Rev Oncol Hematol. 2006, 60:89–98.
2. Katz SC, Shia J, Liau KH, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg 2009, 249:617–623.
3. Fan ST, Mao LQ, Poon RT, et al. Continuous improvement of surgical outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg 2011, 253:745–756.
4. Zhou Y, Su C, Li B, et al. Safety and efficacy of trisectionectomy for hepatocellular carcinoma. ANZ J Surg 2011, 81:895–899.
5. Shragger B, Jibara G, Schwartz M, et al. Resection of hepatocellular carcinoma without cirrhosis. Ann Surg 2012, 255:1135–1143.
6. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000, 232:10–24.
7. Braux J, Sherman M. Practice guidelines committee. American association for the study of liver diseases. Management of hepatocellular carcinoma. Hepatology 2005, 42:1208–1236.
8. Higuchi T, Kikuchi M, Okazaki M. Hepatocellular carcinoma after transcatheter hepatic arterial embolization. A histopathologic study of 84 resected cases. Cancer 1994, 73:2259–2267.
9. Imacka S, Sasaki Y, Shibata T, et al. A pre-operative chemoembolization therapy using lipiodol, cisplatin and gelatin sponge for hepatocellular carcinoma. Cancer Chemother Pharmacol 1989, 23:516–521.
10. Majno PE, Adam R, Bismuth H, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997, 226:688–701.
11. Di Carlo V, Ferrari G, Castoldi R, et al. Pre-operative chemoembolization of hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterology 1998, 45:1950–1954.
12. Nagasue N, Galizia G, Kohno H, et al. Adverse effects of preoperative hepatic artery chemoembolization for resectable hepatocellular carcinoma: a retrospective comparison of 138 liver resections. Surgery 1989, 106:81–86.
13. Adachi E, Matsumata T, Nishizaki T, et al. Effects of preoperative transarterial hepatic arterial chemoembolization for hepatocellular carcinoma. The relationship between postoperative course and tumor necrosis. Cancer 1993, 72:3593–3598.
14. Wu CC, Ho YZ, Ho WL, et al. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. Br J Surg 1995, 82:122–126.
15. Yamasaki S, Hasegawa H, Kinoshita H, et al. A prospective randomized trial of the preventive effect of preoperative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res 1996, 87:205–211.
16. Zhou WP, Lai EC, Lui AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg 2009, 249:195–202.
17. Wang X, Li J, Peng Y, et al. Influence of preoperative transarterial chemoembolization on the prognosis for patients with resectable hepatocellular carcinoma: a meta-analysis of randomized trials. Hepatogastroenterology 2011, 58:869–874.
18. Rorskam K, Rothwell PM. Meta-analysis of small randomized controlled trials in surgery may be unreliable. Br J Surg 2010, 97:466–469.
19. Mathurin P, Raynard B, Dharnay S, et al. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. Aliment Pharmacol Ther 2005, 17:247–1261.
20. Abraham NS, Byrne CJ, Young JM, et al. Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures is as good as randomized controlled trials. J Clin Epidemiol 2010, 63:238–245.
21. Jadad AR, Moore RA, Carroll D, et al. Assessment the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996, 17:1–12.
22. Slim K, Nini E, Foretter D, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003, 73:712–716.
23. Kalsbø T, Tanigawa N, Matsui Y, et al. Influence of transcatheter arterial chemoembolization on the prognosis after hepatectomy for hepatocellular carcinoma in patients with severe liver dysfunction. Anticancer Res 2006, 26:5385–5392.
24. Kalsbø T, Tanigawa N, Karlia S, et al. A prospective randomized controlled trial of preoperative whole-liver chemolipiodolization for hepatocellular carcinoma. Dig Dis Sci 2012, 57:1404–1412.
25. Gerunda GE, Neri D, Merenda R, et al. Transcatheter hepatic arterial oily chemoembolization for resectable hepatocellular carcinoma. Abstract. Surgery 2000, 128:467–468.
26. Zhang Z, Liu Q, He J, et al. Safety and efficacy of transarterial hepatic arterial oily chemoembolization for hepatocellular carcinoma. Br J Surg 2000, 87:1135–1136.
27. Harada T, Matsuo K, Inoue T, et al. Preoperative transcatheter arterial chemoembolization for hepatocellular carcinoma after hepatectomy: A retrospective review. Hepatogastroenterology 2012, 59:36–38.
28. Uchida M, Kohno H, Kubota H, et al. Role of preoperative transcatheter arterial oily chemoembolization for resectable hepatocellular carcinoma. World J Surg 2012, 36:2066–2073.
31. Lu CD, Peng SY, Jiang XC, et al. Preoperative transcatheter arterial chemoembolization and prognosis of patients with hepatocellular carcinomas: retrospective analysis of 120 cases. World J Surg 1999, 23:293–300.
32. Ochiai T, Sonoyama T, Hironaka T, et al. Hepatectomy with chemoembolization for treatment of hepatocellular carcinoma. Hepatogastroenterology 2003, 50:750–755.
33. Sugo H, Futagawa S, Beppu T, et al. Role of preoperative transcatheter arterial chemoembolization for resectable hepatocellular carcinoma: relation between postoperative course and the pattern of tumor recurrence. World J Surg 2003, 27:1295–1299.
34. Sasaki A, Iwashita Y, Shibata K, et al. Preoperative transcatheter arterial chemoembolization reduces long-term survival rate after hepatic resection for resectable hepatocellular carcinoma. Eur J Surg Oncol 2006, 32:773–779.
35. Chen XP, Hu DY, Zhang ZW, et al. Role of meshepatectomy with or without transcatheter arterial chemoembolization for large centrally located hepatocellular carcinoma. Dig Surg 2007, 24:208–213.
36. Choi GH, Kim DH, Kang CM, et al. Is preoperative transarterial chemoembolization needed for a resectable hepatocellular carcinoma? World J Surg 2007, 31:2370–2377.
37. Kim S, Lim YS, Lee HC, et al. Pre-operative transarterial chemoembolization for resectable hepatocellular carcinoma adversely affects post-operative patient outcome. Aliment Pharmacol Ther 2008, 27:339–345.
38. Lee KT, Lu YW, Wang SN, et al. The effect of preoperative transarterial chemoembolization of resectable hepatocellular carcinoma on clinical and economic outcomes. J Surg Oncol 2009, 99:343–350.
39. Kang JY, Choi MS, Kim SJ, et al. Long-term outcome of preoperative transarterial chemoembolization and hepatic resection in patients with hepatocellular carcinoma. Korean J Hepatol 2010, 16:383–388.
40. Yamashita Y, Takeishi K, Tsujita E, et al. Beneficial effects of preoperative lipiodolization for resectable large hepatocellular carcinoma (≥5 cm in diameter). J Surg Oncol 2012, 106:498–503.
41. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003, 37:429–442.
42. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 1998, 27:1578–1583.
43. Ikeda K, Saijo T, Tsujiota A, et al. Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. Cancer 1993, 71:19–25.
44. Huang J, He X, Lin X, et al. Effect of preoperative transcatheter arterial chemoembolization on tumor cell activity in hepatocellular carcinoma. Chin Med J 2000, 113:446–448.
45. Liou TC, Shih SC, Kao CR, et al. Pulmonary metastasis of hepatocellular carcinoma associated with transarterial chemoembolization. J Hepatol 1995, 23:563–568.
46. Bonfill RD, Bustuabad OD, Ruggiero RA, et al. Tumor necrosis can facilitate the appearance of metastases. Clin Exp Metastasis 1988, 6:121–129.
47. Xiao EH, Li JQ, Huang JF. Effects of p53 on apoptosis and proliferation of hepatocellular carcinoma cells treated with transcatheter arterial chemoembolization. World J Gastroenterol 2004, 10:190–194.
48. Xiao EH, Guo D, Bian DJ. Effect of preoperative transcatheter arterial chemoembolization on angiogenesis of hepatocellular carcinoma cells. World J Gastroenterol 2009, 15:4582–4586.