Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma

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Key words
doxorubicin eluting bead, hepatocellular carcinoma, objective tumor response, survival.

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Abstract
Background and Aim: Doxorubicin-eluting bead transarterial chemoembolization (DEB-TACE) is a novel locoregional treatment for unresectable hepatocellular carcinoma (HCC). However, to date, the benefits of DEB-TACE versus conventional transarterial chemoembolization (TACE) remain unclear. This meta-analysis was conducted to evaluate the efficacy and safety of the two treatments for patients with unresectable HCC.

Methods: We searched for relevant articles by means of computerized bibliographic search and complementary manual search. Objective tumor response, overall survival, and adverse events were then calculated and analyzed.

Results: A total of seven clinical studies with 700 participants were included in the current meta-analysis. Significantly better objective tumor response was found for DEB-TACE than for conventional TACE (OR = 1.92, 95% CI [1.34, 2.77]; P = 0.0004), with relative risk difference of 0.15 [0.07, 0.24] (P = 0.0003). One-year and 2-year survival rates were statistically significantly higher for DEB-TACE compared with conventional TACE (Peto OR, 95% CI: 0.64 [0.46, 0.89], P = 0.007; 0.61 [0.47, 0.80], P = 0.0003, respectively). Peto ORs of 6-month and 3-year survival were 0.72 [0.46, 1.14] (P = 0.16) and 0.77 [0.55, 1.06] (P = 0.11), respectively, showing no difference statistically. However, we could still find a tendency favoring DEB-TACE. Adverse side effects were similar in both groups, with postembolization syndrome occurring most commonly.

Conclusions: This meta-analysis shows that DEB-TACE provides significantly better tumor response compared with conventional TACE. One-year and 2-year survival are better with DEB-TACE. In addition, DEB-TACE is as safe as conventional TACE. Therefore, DEB-TACE is a better choice for HCC patients for whom curative treatments like liver transplantation and liver resection are not suitable.

Introduction
Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide. Despite the widespread use of surveillance programs, curative treatments like liver transplantation, liver resection, and radiofrequency ablation are not suitable for a great number of HCC patients because of the advanced stage of their HCC.1,2

Transarterial chemoembolization (TACE) is now considered the first-line treatment for advanced HCC.4 Two randomized studies6,7 and a systematic review8 have confirmed that patients who receive TACE treatment receive significantly better survival benefit. The mechanism of action of TACE is the obstruction of the hepatic artery, which supplies most of the blood flow to the tumor, by periodic injection of chemotherapeutic drugs like cisplatin or doxorubicin, mixed with a viscous emulsion such as lipiodol, selectively into the artery.9 With TACE, higher intratumor drug concentration can be obtained, resulting in an ischemic effect on the tumor, as well as a strong cytotoxic effect.10 However, there is still little consensus regarding optimal chemotherapeutic agents and treatment intervals for TACE.11,12 Also, some potential post-TACE complications, like acute liver or renal failure and upper gastrointestinal bleeding, are severe.11

Recently, a novel drug delivery embozization system, drag-eluting beads, has been introduced into TACE. Drug-eluting bead transarterial chemoembolization (DEB-TACE) uses microspheres as embolic agents; these are loaded with chemotherapeutic drugs (usually doxorubicin) and will gradually release them into the target tumor.13,14 The use of drug-eluting beads loaded with doxorubicin has been shown to result in lower systemic doxorubicin concentration and higher tumor concentration compared with conventional lipiodol-based TACE.
regimens, significantly reducing systemic drug-related adverse effects.15–18 Despite the benefits of DEB-TACE, little is known about the survival benefit compared with conventional TACE. It is still controversial whether DEB-TACE or conventional TACE is a better choice for advanced HCC patients. In an attempt to address this dilemma, we performed this meta-analysis of all available studies to compare tumor response and patient survival between patients treated with DEB-TACE and patients treated with conventional TACE.

**Methods**

**Search strategy and selection criteria.** Computerized bibliographic searches were performed in the PubMed/EMBASE, Embase, Google Scholar, CancerLit, and Cochrane Library databases using the following key words: “drug-eluting bead,” “transarterial chemotherapy,” “hepatocellular carcinoma,” “HCC,” and “liver cell carcinoma.” Complementary manual searches were conducted by searching reference lists for all available review articles, primary studies, and books to identify other studies that were not found in the computer search.

Eligible studies included randomized controlled trials (RCTs) and prospective or retrospective cohort studies comparing DEB-TACE and conventional TACE in human patients that were published from January 2000 to January 2013. Articles in all languages were searched for. Studies were excluded if they reported neither tumor response nor overall survival. Case-report studies and studies with insufficient data were also excluded. The included studies were selected independently by two investigators (Donghui Cheng and Rong Wang). Disagreements were solved by discussion.

**Data collection and study quality assessment.** Data concerning patient characteristics, trial characteristics, and study outcomes were extracted by two investigators (Qian Zhou and Kaijun Huang) independently. Disagreements were solved by discussion. The quality of the trials was assessed using a modified version of the Newcastle–Ottawa scale.21 Data collection and study quality assessment followed the Quality of Reporting of Meta-Analyses standards.

**Statistical analysis.** Statistical analysis was performed following the guidelines published by the Cochrane Collaboration in the Cochrane Reviewer’s Handbook. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate tumor response in different groups, using fixed-effects or random-effects models. We calculated observed minus expected events and variance in 6-month, 1-year, 2-year and 3-year survival from Kaplan–Meier curves in accordance with Tierney et al.’s methods,22 then combined the results using a fixed-effect model. All calculations for the current meta-analysis were performed using Review Manager (version 5.0 for Windows; Cochrane Collaboration, Oxford, UK).

**Assessment of publication bias and heterogeneity.** Publication biases were assessed visually using funnel plots. Statistical heterogeneity was evaluated with a forest plot and by determining the inconsistency ($I^2, P \leq 0.1$).

**Results**

**Literature search.** As the flow diagram (Fig. 1) shows, bibliographic search yielded 18 relevant articles after exclusion of articles that did not deal with DEB-TACE versus conventional TACE or did not report the specific results being evaluated in this review; no relevant studies were found through manual search. From these 18 articles, we retrieved 10 articles for further review23–32 and excluded eight articles because of insufficient data.17,33–39 As three articles (Vogl et al.,30 Lammer et al.,31 and Lencioni et al.25) were focused on the same group of patients, these articles were analyzed as one study (the PRECISION V study). Two of the retrospective studies (Song et al. 201123 and Song et al. 201224) had the same authors, and it was not clear that these studies involved separate patients; as the authors were the same, the time period for recruitment overlapped, and the eligibility criteria appeared the same, Song et al. 201123 was eliminated. Finally, seven clinical studies with 700 participants were included in the current meta-analysis.

**Included trials and study characteristics.** As shown in Table 1, all studies were designed to compare DEB-TACE with conventional TACE in HCC patients as the primary aim (more information in Supporting Information Table 1). Only the PRECISION V study (Vogl et al.,30 Lammer et al.,31 and Lencioni et al.25) was multicenter, while the others were single-center studies. Only two studies (Sacco et al.26 and the PRECISION V study) were randomized. Patients selected in most of the studies were in Child–Pugh class A or B, except the study conducted by Dhanasekaran et al.,28 who selected patients regardless of Child–Pugh class, and the study conducted by Wiggermann et al.,28 who only selected patients in Child–Pugh class A. The etiology of cirrhosis in patients in the selected studies was related to HBV, HCV, alcohol abuse or other factors. In Table 1 we summarize the characteristics of the included studies. None of the studies report statistically significant differences in baseline characteristics between the two groups with regard to demographics, etiology of underlying chronic liver disease, liver function, tumor stage, or serum
### Study Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Study design</th>
<th>Region</th>
<th>Patient selection criteria</th>
<th>Child–Pugh class</th>
<th>BCLC stage</th>
<th>Etiology, n (HBV/HCV/others)</th>
<th>n (A/B/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Song et al. 2012</td>
<td>60</td>
<td>Retrospective cohort analysis</td>
<td>Korea</td>
<td>Child–Pugh Class A or B</td>
<td>56/4/0</td>
<td>27/230</td>
<td>NA</td>
<td>9/7/0</td>
</tr>
<tr>
<td>Recchia et al. 2012</td>
<td>35</td>
<td>Prospective</td>
<td>Italy</td>
<td>Unresectable HCC</td>
<td>12/6/0</td>
<td>28/204</td>
<td>NA</td>
<td>7/6/15</td>
</tr>
<tr>
<td>Sacco et al. 2011</td>
<td>33</td>
<td>Prospective, randomized</td>
<td>Spain</td>
<td>Confirmed HCC; Child–Pugh class A or B</td>
<td>25/6/0</td>
<td>29/4/7</td>
<td>NA</td>
<td>4/2/8</td>
</tr>
<tr>
<td>Ferrer et al. 2011</td>
<td>34</td>
<td>1999–2009</td>
<td>Spain</td>
<td>Child–Pugh Class A or B</td>
<td>22/6/0</td>
<td>25/4/5</td>
<td>NA</td>
<td>17/5/2</td>
</tr>
<tr>
<td>Wiggermann et al. 2010</td>
<td>47</td>
<td>1999–2008</td>
<td>Germany</td>
<td>Child–Pugh class A or B</td>
<td>25/9/0</td>
<td>25/4/5</td>
<td>NA</td>
<td>17/5/2</td>
</tr>
<tr>
<td>Dhanasekaran et al. 2010</td>
<td>45</td>
<td>1998–2008</td>
<td>USA</td>
<td>Child–Pugh class A or B</td>
<td>25/9/0</td>
<td>25/4/5</td>
<td>NA</td>
<td>17/5/2</td>
</tr>
<tr>
<td>Vogl et al. 2011</td>
<td>22</td>
<td>2006–2008</td>
<td>France, Germany, Switzerland, Greece</td>
<td>Child–Pugh class A or B</td>
<td>22/6/0</td>
<td>28/204</td>
<td>29/16/0</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Odds ratios of survival over different lengths of time

<table>
<thead>
<tr>
<th>Time</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>OR [95% CI]</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>6</td>
<td>488</td>
<td>0.72 [0.46, 1.14]</td>
<td>0</td>
</tr>
<tr>
<td>1 year</td>
<td>6</td>
<td>488</td>
<td>0.64 [0.46, 0.89]</td>
<td>0</td>
</tr>
<tr>
<td>2 years</td>
<td>6</td>
<td>488</td>
<td>0.61 [0.47, 0.80]</td>
<td>0</td>
</tr>
<tr>
<td>3 years</td>
<td>4</td>
<td>373</td>
<td>0.77 [0.55, 1.06]</td>
<td>50</td>
</tr>
</tbody>
</table>

*Values of Mantel–Haenszel estimates. CI, confidence interval; OR, odds ratio.

### Meta-analysis of objective tumor response

Five studies (513 participants) assessed tumor response. Tumor response was classified according to the Modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST) or the European Association for the Study of the Liver (EASL) criteria. Objective tumor response rate was defined as complete plus partial response. The meta-analysis using a fixed-effects model showed significantly better objective tumor response rate for DEB-TACE compared with conventional TACE (OR = 1.92, 95% CI [1.34, 2.77]; P = 0.0004), with a relative risk difference of 0.15 [0.07, 0.24] (P = 0.0003). As moderate heterogeneity was found (heterogeneity: $\chi^2 = 0.15, df = 4$ [P = 0.14]; $I^2 = 42\%$), a random-effects model was used, and the result changed little (OR = 1.95, 95% CI [1.16, 3.28]; P = 0.01) (Fig. 2). No significant publication bias with regard to objective tumor response was found using the funnel plot (Fig. 3).

As two of the included studies were RCTs, subgroup analysis dividing the included studies into RCTs and non-RCTs was performed. No statistically significant difference was found between the groups (ORs = 1.55 [0.95, 2.53] and 2.17 [0.87, 5.40], respectively).

### Meta-analysis of overall survival

Six studies (488 participants) estimated overall survival using Kaplan–Meier curves. As shown in Table 2, 1-year and 2-year survival rates were statistically significantly higher for DEB-TACE (Peto OR = 0.64, 95% CI [0.46, 0.89]; P = 0.007) compared with conventional TACE (Peto OR = 0.61 [0.47, 0.80]; P = 0.0003). Peto ORs for 6-month and 3-year survival were 0.72 [0.46, 1.14] (P = 0.16) and 0.77 [0.55, 1.06] (P = 0.11), respectively, showing no difference statistically. However, we could still find a tendency favoring DEB-TACE. No heterogeneity was found in 6-month, 1-year, or 2-year survival ($I^2 = 0\%$, 0%, 20%, respectively). No significant publication bias with regard to objective tumor response was found using the funnel plot. More detailed forest and funnel plots of overall survival are given in Supporting Information Figures S1–S6.

### Safety

Four included studies reported that the most common adverse event in both groups was postembolization syndrome (i.e., transient fever, fatigue, abdominal pain, nausea), with no statistical difference between the two groups. Sacco et al. reported tumor markers. Quality assessments of each study are presented in Supporting Information Table 2.
and sensitivity analysis was performed. No reverse result was reported two cases of major complications, cholecystitis and liver failure (with conventional TACE and DEB-TACE, respectively).

Four included studies reported results of laboratory tests of liver function. Compared with baseline, AST, bilirubin, serum albumin, and prothrombin levels were significantly increased after procedure in both groups. Only increases in ASL level after procedure were found to be significantly less frequent with DEB-TACE than with conventional TACE.24,26,31

**Sensitivity analysis.** In order to assess the effect of low-quality articles on the results (Supporting Information Table 2), articles found to be of lower quality in the quality assessment (total score < 4; Wiggermann et al and Ferrer et al. 27) were eliminated, and sensitivity analysis was performed. No reverse result was found after the process, while heterogeneity in objective tumor response was found ($\chi^2 = 5.77$, d.f. = 2 [P = 0.06]; $I^2 = 65$%). In addition, 3-year survival rate became statistically significantly higher for DEB-TACE compared with conventional TACE (Peto OR = 0.67, 95% CI [0.45, 0.99]; P = 0.04).

**Discussion**

In this meta-analysis, computerized bibliographic search and manual search were performed to find studies comparing the efficacy and safety of DEB-TACE and conventional TACE in patients with HCC. A total of seven controlled clinical studies with 700 participants were included. DEB-TACE was found to provide better objective tumor response than conventional TACE. Moreover, meta-analysis of overall survival showed significantly increased 1-year and 2-year survival rates for DEB-TACE compared with conventional TACE. However, 6-month and 3-year survival rates show no significant difference, implying that DEB-TACE may not truly be better. At present, the choice between conventional TACE and DEB-TACE for treating patients with advanced HCC is hotly debated. TACE is considered the standard treatment option for unresectable HCC with reserve liver function.5,7 DEB-TACE, a novel drug delivery system, uses microspheres as embolic agents; these are loaded with chemotherapeutic drugs (usually doxorubicin) and deliver the drugs arterially.9 Unlike conventional TACE, DEBs can sequester doxorubicin hydrochloride from solution and release it sustainedly. Varela et al.17 and Poon et al.18 reported that DEB-TACE could substantially diminish systemic chemotherapeutic drug concentrations as well as significantly reduce drug-related adverse effects. Burrel et al. demonstrated that DEB-TACE has

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DEB-TACE</th>
<th>cTACE</th>
<th>Odds Ratio</th>
<th>M-H, Random [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.1 RCT</td>
<td>PRECISION V study</td>
<td>48 93</td>
<td>47 108</td>
<td>31.5%</td>
</tr>
<tr>
<td>Sacco et al. 2011</td>
<td>24 34</td>
<td>17 33</td>
<td>17.3%</td>
<td>2.26 [0.83, 6.17]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>127 141</td>
<td>48.8%</td>
<td>1.55 [0.95, 2.53]</td>
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</tr>
<tr>
<td>Total events</td>
<td>72 64</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.70$, d.f. = 1 (P = 0.40); $I^2 = 0.0%$</td>
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<tr>
<td>Test for overall effect: $Z = 1.77$ (P = 0.08)</td>
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</table>

<table>
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<th>DEB-TACE</th>
<th>cTACE</th>
<th>Odds Ratio</th>
<th>M-H, Random [95% CI]</th>
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</thead>
<tbody>
<tr>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.2 Not RCT</td>
<td>Ferrer et al. 2011</td>
<td>26 47</td>
<td>11 25</td>
<td>18.0%</td>
</tr>
<tr>
<td>Song et al. 2012</td>
<td>49 60</td>
<td>34 69</td>
<td>22.5%</td>
<td>4.59 [2.05, 10.27]</td>
</tr>
<tr>
<td>Wiggermann et al. 2011</td>
<td>5 22</td>
<td>5 22</td>
<td>10.7%</td>
<td>1.00 [0.24, 4.10]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>129 116</td>
<td>51.2%</td>
<td>2.17 [0.87, 5.40]</td>
<td></td>
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<tr>
<td>Total events</td>
<td>80 50</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.37; \chi^2 = 4.65$, d.f. = 2 (P = 0.10); $I^2 = 57%$</td>
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<td>Test for overall effect: $Z = 1.67$ (P = 0.10)</td>
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</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DEB-TACE</th>
<th>cTACE</th>
<th>Odds Ratio</th>
<th>M-H, Random [95% CI]</th>
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</thead>
<tbody>
<tr>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>256 257</td>
<td>100.0%</td>
<td>1.95 [1.16, 3.28]</td>
<td></td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.14; \chi^2 = 6.88$, d.f. = 4 (P = 0.14); $I^2 = 42%$</td>
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<td>Test for overall effect: $Z = 2.52$ (P = 0.01)</td>
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</table>
an adequate safety profile, although it may increase the incidence of hepatic abscess.28 Postembolization syndrome (i.e., transient fever, fatigue, abdominal pain, nausea) was the most common complication in both DEB-TACE and conventional TACE patients, and no differences between groups were found.24 Liver injury was observed with both treatments; AST, bilirubin, serum albumin, and prothrombin levels were significantly increased after procedure for both treatments compared with baseline. The multicenter PRECISION V study26–32 reported that no statistically significant difference in treatment-related complications and treatment-emergent adverse effects was found between groups. We can conclude that DEB-TACE is at least as safe as conventional TACE.

Little is known about the survival benefit of DEB-TACE compared with conventional TACE. Burrel et al., using appropriate selection criteria and state-of-the-art techniques, showed that the survival expectancy of patients treated with DEB-TACE was higher than previously reported.20 Sacco et al.26 and Ferrer et al.27 found no statistically significant differences between the two groups due to small sample size. After statistical analysis, we found significant increases in 1-year and 2-year survival for patients treated with DEB-TACE. Because only four studies reported 3-year survival, no statistically significant differences in 3-year survival were found between the two treatments. These data imply that DEB-TACE may not truly be better; a long follow-up RCT to evaluate the survival benefit of DEB-TACE is needed.

This meta-analysis provides powerful and comprehensive evidence showing the benefits of DEB-TACE over conventional TACE for treating unresectable HCC. However, there are still some limitations in our study. First, we included both prospective and retrospective studies with no standard randomization, which may have introduced patient selection bias. In addition, none of the studies included in the meta-analysis were designed for evaluating overall survival. Also, the mRECIST and EASL criteria for evaluating tumor response are different; this may have led to different interpretations. Physicians should interpret our results carefully when applying them in clinical work. In addition, despite the many RCTs that have been done to identify the optimal chemoembolization procedure, lack of standardization affects some aspects of treatment, including embolization technique and treatment schedules. Moreover, whether patients should receive repeated courses of TACE at fixed intervals until the planned number of courses is reached or until a complete radiological response is achieved remains unclear. Physicians should be aware of this situation in clinical work.

In conclusion, this meta-analysis shows that DEB-TACE provides significantly better tumor response as compared with conventional TACE. One-year and 2-year survival are better with DEB-TACE. In addition, DEB-TACE is as safe as conventional TACE. DEB-TACE is a better choice for HCC patients for whom curative treatments like liver transplantation, liver resection, and radiofrequency ablation are not suitable.

Acknowledgments

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Author contributions. Kaijun Huang designed and organized the study protocol. Donghui Cheng and Rong Wang reviewed and selected the articles. Qian Zhou and Kaijun Huang extracted and analyzed the data and wrote the paper. All authors had access to the data and statistical analyses. Each author approved the final article and attested to the validity of the results.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Supporting Information Table S1 Characteristics of studies included in the meta-analysis.

Supporting Information Table S2 Quality assessment of trials included in the meta-analysis.

Supporting Information Table S3 Odds ratio of overall survival over different lengths of time.

Supporting Information Figure S1 Forest plot of 6-month overall survival.

Supporting Information Figure S2 Forest plot of 1-year overall survival.

Supporting Information Figure S3 Forest plot of 2-year overall survival.

Supporting Information Figure S4 Forest plot of 3-year overall survival.

Supporting Information Figure S5 Funnel plot of 6-month, 1-year, and 2-year overall survival.

Supporting Information Figure S6 Funnel plot of 3-year overall survival.