

# Comment on a meta-analysis comparing hepatic resection or transarterial chemoembolization as initial treatment for hepatocellular carcinoma

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## Dear editor

We read with great interest the meta-analysis by Tian et al<sup>1</sup> comparing the efficacy of initial hepatic resection (HR) or transarterial chemoembolization (TACE) for patients with primary hepatocellular carcinoma (HCC). The results from this analysis of eleven cohort studies involving 6,297 patients suggested similar overall survival (OS) and recurrence rate for the two techniques. We believe this conclusion should be treated with caution because it conflicts with much larger original studies<sup>2,3</sup> and large systematic reviews.<sup>4,5</sup>

Potential problems with patient heterogeneity weaken the validity of the meta-analysis by Tian et al. Those authors did not mention explicitly that they selected only studies examining HR or TACE as initial therapy, yet all except one study focused on initial therapy. That one study,<sup>6</sup> involving 1,296 patients, compared preoperative TACE plus HR with HR alone. This may have introduced significant clinical heterogeneity into the study population, since preoperative TACE plus HR, HR alone, and TACE alone are associated with substantially different OS. In addition, this meta-analysis included patients with early,<sup>7</sup> intermediate,<sup>8,9</sup> and advanced HCC.<sup>10</sup> This may have introduced additional heterogeneity, since recommended HCC treatments depend on tumor stage.<sup>11</sup> Unfortunately, it is impossible to assess tumor stage in this meta-analysis because essential information, including tumor number and incidence of macrovascular invasion, is not reported.

For reasons that are unclear, this meta-analysis failed to include several studies comparing initial HR and TACE to treat primary HCC. These include large, propensity score-matched studies;<sup>2,12</sup> a large, well-designed retrospective study;<sup>13</sup> and a randomized trial.<sup>14</sup> All four of these studies reported that initial HR was associated with significantly longer short- and long-term OS in patients with intermediate or advanced HCC. A meta-analysis<sup>15</sup> with similar goals to Tian et al but much larger – bringing together 50 studies involving 14,673 patients with primary HCC – found significantly higher 1-, 3-, and 5-year OS after initial HR than initial TACE. Subgroup analyses in that study showed similar results for patients in Barcelona Clinic Liver Cancer (BCLC) stage A, patients in BCLC stage B, and patients with portal vein tumor thrombus.

Several methodological issues in the meta-analysis by Tian et al further weaken their conclusions. First, although those authors did acknowledge that HR is considered curative while TACE is only palliative, they nevertheless calculated a recurrence rate for TACE and compared it with recurrence after HR. This may not be valid, since it

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is unclear whether tumors completely disappear after one or more cycles of TACE. Second, although most studies in this meta-analysis were “high quality” based on the Newcastle–Ottawa Scale, all were low quality based on Cochrane quality assessment standards. Third, those authors did not report intention-to-treat analyses, which meant, among other things, that the same total number of patients in each study was used to calculate survival at 1, 2, 3, 4, and 5 years. The reality is that patients die during follow-up, which intention-to-treat analysis would capture. Fourth,  $I^2$  in most studies in the meta-analysis was  $>80\%$ , indicating significant heterogeneity and suggesting that meta-analysis may be inappropriate.

Though we compliment Tian et al on their effort, and studies like this meta-analysis are necessary to gain a definitive picture of optimal initial treatment, which remains controversial for certain types of HCC patients,<sup>11,16</sup> such studies should be conducted in a way that controls for patient heterogeneity.

## Disclosure

The authors report no conflicts of interest in this communication.

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