

## Letters to the Editor

---

### Meta-analysis of Transarterial Embolization in Patients with Unresectable Hepatocellular Carcinoma [letter]

**From:**

Robert P. Myers, MD  
 Liver Unit, University of Calgary  
 3350 Hospital Drive NW, Rm G126, Calgary, Alberta,  
 Canada T2N 4N1  
 e-mail: [drrobmyers@hotmail.com](mailto:drrobmyers@hotmail.com)

Supported by grants from the Canadian Institutes for Health Research and the Alberta Heritage Foundation for Medical Research.

**Editor:**

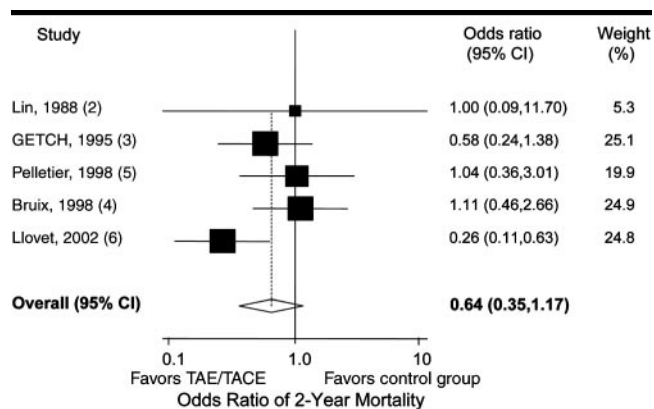
Transarterial embolization performed alone or in combination with chemotherapy is a controversial treatment strategy for patients with unresectable hepatocellular carcinoma. In the July 2002 issue of *Radiology*, Dr Cammà and colleagues attempted to clarify this issue by using meta-analytic techniques (1). On the basis of results in five randomized controlled trials involving comparison of transarterial embolization alone or in combination with chemotherapy versus nonactive treatment (control group) (2–6), the authors concluded that (chemo)embolization reduces overall 2-year mortality significantly (odds ratio, 0.54; 95% CI: 0.33, 0.89). However, several methodologic issues raise questions about the validity of these results.

First, as conceded by the authors, there was considerable intertrial heterogeneity that raises questions about the appropriateness of combining these randomized controlled trials in a meta-analysis. Although results of statistical tests to assess the heterogeneity of treatment effects were not significant, the baseline characteristics of the patients and the treatment regimens differed substantially. Discrepancies between transarterial embolization methods, the frequency of repetition of the procedure (from never to monthly), intraarterial chemotherapeutic agents administered (none, doxorubicin, or cisplatin), and cointerventions (eg, intravenous 5-fluorouracil and tamoxifen administration) were marked.

Second, the authors erred in their handling of two trials that included multiple intervention arms and a control group (2,6). In calculating the effect sizes of these trials for their summary estimate of 2-year mortality (figure 1 in the article), Dr Cammà and colleagues included the 56 control subjects (in the 424 total patients) twice. This error exaggerates the relative effectiveness of (chemo)embolization, since results in both of these trials suggested a benefit (which was statistically significant in one [6] of therapy). The appropriate means of dealing with this data is to combine results of the (chemo)embolization arms and make a single pairwise comparison with the control group (7). When this analysis is performed by using a random-effects model, as was used by the authors, the effect of (chemo)embolization is not statistically significant (odds ratio, 0.62; 95% CI: 0.35, 1.08;  $\chi^2$  test for heterogeneity,  $P = .17$ ).

Finally, the authors stated that they performed an intention-to-treat analysis. However, in the trial of Lin et al (2), one-third of the randomized patients (transarterial embolization, eight of 21; transarterial embolization with administration of intravenous 5-fluorouracil, eight of 21; control group, five of 21) were withdrawn prior to 24 months. Therefore, the true 2-year mortality of these patients is unclear from the published data; this fact was not considered by Dr Cammà and colleagues in their analysis. By considering these patients treatment failures (ie, deaths) according to the intention-to-treat principle, the potential benefit of (chemo)embolization remains statistically nonsignificant (odds ratio, 0.64; 95% CI: 0.35, 1.17; Figure). Exclusion of this trial (2), which is reasonable considering its methodologic weaknesses, has a minimal effect on the results (odds ratio, 0.63; 95% CI: 0.32, 1.23).

The question remains: Does transarterial (chemo)emboli-



Graph represents a random-effects intention-to-treat meta-analysis to compare transarterial embolization alone (*TAE*) or in combination with chemotherapy (*TACE*) versus nonactive treatment (*control group*) in patients with unresectable hepatocellular carcinoma. Data are shown on a logarithmic scale.

zation improve survival when administered to unselected patients with unresectable hepatocellular carcinoma? The totality of the current evidence based on data from randomized controlled trials suggests that it does not. However, the most recent high-quality trial showed a survival benefit in a selected subgroup of patients (6). Only additional trials of sound methodologic quality in well-defined patient populations will clarify the role of this therapy definitively.

#### References

1. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002; 224:47–54.
2. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Gastroenterology* 1988; 94:453–456.
3. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. *N Engl J Med* 1995; 332:1256–1261.
4. 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.
5. Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. *J Hepatol* 1998; 29: 129–134.
6. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:1734–1739.
7. Clarke M, Oxman AD. *Cochrane Reviewers' Handbook 4.1* [updated June 2000]. In: Review Manager (RevMan) [computer program]. Version 4.1. Oxford, England: The Cochrane Collaboration, 2000.

#### Dr Cammà and colleagues respond:

In response to the letter of Dr Myers, we believe that it is correct to test for quantitative but also for qualitative heterogeneity. If there is substantial qualitative heterogeneity, it is

preferable not to pool the studies. If there is not substantial qualitative heterogeneity, the random-effects model should take care of the quantitative heterogeneity. Those who perform meta-analysis should choose a random-effects model if they think the studies are different from one another in a way too complex to capture with a few simple study characteristics. We need not view heterogeneity of treatment effect as an argument against the pooling of clinical trial data. When heterogeneity does not arise because of inadequate design or incomplete publication of results, we should welcome it as an opportunity to optimize treatment benefit. Meta-regression analysis provides a useful tool to explore such heterogeneity (1).

The second question arises about the statistical analysis and interpretation of results of trials that compare multiple variants of a treatment against a common control. Studies of this kind are called multiple-treatment studies. Because of the common control group, our units are not independent, and we need to account for this correlation. One approach to obtaining a single estimate is to discard effect size estimate for all but one treatment in a study. Another possibility is to treat correlated effect as an independent and then adjust the significance level. Finally, the most natural method is to combine correlated data by using multivariate techniques. In most cases, however, the gain in efficiency that results from pooling of correlated estimates does not justify the effort required. Little information is lost by choosing one variant of the treatment against the control. The analysis can then proceed by using only independent estimators of effect size. The advantage of such an approach is simplicity (2).

In our analysis, the exclusion of the transarterial embolization arms of Lin et al (3) and Llovet et al (4) makes no difference. For example, the reduction in the odds of death, including all comparisons, is 0.54 (95% CI: 0.33, 0.89) and 0.69 (95% CI: 0.44, 1.06) when the arms of Lin et al (3) and Llovet et al (4) are excluded. To simply emphasize the statistical significance of one or other group is likely to be misleading. The statistical significance of one group and not another more likely results from the number of patients included in each group than to a differential effect of treatment.

With regard to the last question, in the trial of Lin et al (3), one-third of the patients were withdrawals but not losses from observation. Withdrawals are patients who are still alive who must be excluded from the study because the length of time they have been in the study is shorter than the interval for which survival is being calculated. Losses from observation are instead patients who were excluded from the study because the follow-up procedures failed to determine their status, not because that they had reached the limits of the time for observation. We do not understand why withdrawals should be considered treatment failures (5).

Finally, results of sensitivity analysis in our article clearly show that pooling of the four remaining trials after the omission of the study by Llovet et al (4) results in a loss of significance for the overall mortality. Thus, we agree that future trials are needed in which results of transarterial embolization used in

combination with chemotherapy are compared with results of no treatment.

#### References

1. Lau J, Ioannidis JPA, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1988; 351:123-127.
2. Gleser LJ, Olkin I. Stochastically dependent effect sizes. In: Cooper H, Hedges LV, eds. *The handbook of research synthesis*. New York, NY: Russell Sage Foundation, 1984; 340-355.
3. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Gastroenterology* 1988; 94:453-456.
4. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:1734-1739.
5. Lee ET. Introduction. In: Lee ET, ed. *Statistical methods for survival data analysis*. 2nd ed. New York, NY: Wiley, 1992; 1-7.

Calogero Cammà, MD,\* Filippo Schepis, MD,† Mario Cottone, MD,‡ and Antonio Craxì, MD§  
National Council of Research

Via Ugo La Malfa 153, 90146 Palermo, Italy\*

e-mail: [camma@ismeda.pa.cnr.it](mailto:camma@ismeda.pa.cnr.it)

Department of Experimental Medicine, Clinica G.

Salvatore, University of Catanzaro, Italy†

Department of General Medicine and Pneumology‡ and

Department of Gastroenterology, Section of Clinical Medicine,§ University of Palermo, Italy