

RE: Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

Treasure et al

495 words

The CLOCC trial analysis reports a significant overall survival benefit from radio-frequency ablation (RFA) treatment of liver metastases from colorectal cancer.(1) There was no difference in overall survival at five years and at nearly 10 years the conclusion relies on 11 patients at risk. We noted the asymmetry of the CONSORT diagram and were unable to reconcile it with the log-rank and Kaplan-Meier analyses. In the combined arm (CONSORT diagram left) nine patients were excluded as either 'ineligible' or not receiving adjuvant chemotherapy, leaving 51 patients and 39 deaths. In the systemic treatment alone arm no patients were excluded, despite 10 patients being deemed 'ineligible', resected or having a 'major protocol violation' giving 53 deaths out of a population of 59 patients (right). The Kaplan-Meier plot for overall survival is based on denominators of 60 and 59 (combined arm and systemic alone respectively) suggesting an intention to treat analysis. However, if the deaths among the nine excluded patient were omitted, with the denominator of 60 retained, the two arms of the trial have been treated differently in the survival analysis, potentially creating a false impression of a survival benefit.

The authors report a difference in the number of liver metastases, a major determinant of survival (2), in the two randomised arms. Nevertheless, their supplemental material reports identical estimated treatment effects (HR=0.62) in the ( $\leq 4$ ) and ( $>4$ ) metastases group. In contrast, a simple analysis of survival proportions, from data provided in Supplementary Figure I of (1), generates very different estimated odds ratio effects of 0.41 (63% versus 81% survival) and 0.07 (68% versus 97% survival) in the two groups, the latter being significant at the 5% level. This suggests that the HRs are not constant over time and investigation of the time varying effect of RFA is of interest. This would help to quantify the authors' implicit claim that overall survival benefit is only apparent with long-term follow-up.

The CLOCC trial report opens with 'Surgery is the gold standard of treatment in patients with resectable colorectal liver metastases'(1) but a systematic review and meta-analysis of treatment of advanced colorectal cancer, while lauding the diligence of oncologists in doing randomised trials of systemic treatments, contrasts this with the absence of controlled trials of metastasectomy.(3) The paper suggests that longer survival due to RCT proven systemic treatments presents more opportunities for metastasectomy to be performed.(3) It may be an example of reverse causation: the association between increased numbers of metastasectomies is the result, not the cause, of more long term surviving patients. Policies of more intensive monitoring after primary resection have consistently brought forward the identification of metastases suitable for metastasectomy, but no survival benefit was evident in randomised controlled trials.(4) CLOCC is a small randomised Phase II trial which is already being taken as definitive evidence that treating CRC metastases confers survival benefit.(5-7) This makes clarification of discrepancies in the arms of the trial, and a more detailed examination of the reported overall survival effect, urgently needed.

Reference List

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