Evaluating the Potential Benefits of Using Sustained Response as a Prognostic Factor in Intermediate Hepatocellular Carcinoma Following Treatment With Conventional Chemoembolization

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Zhang and colleagues address the question of whether there is an accurate predictor of overall survival (OS) after conventional transarterial chemoembolization (cTACE) for intermediate hepatocellular carcinoma (HCC). A valid predictor could act as an early surrogate outcome measure that would allow early adjustments to patient management to strike an appropriate balance between tumor control and quality of life. Specifically, they evaluated the utility of sustained response duration (SRD) as a prognostic factor for OS after cTACE for intermediate HCC. They used data from a multicenter cohort study that enrolled 2403 consecutive patients with naive intermediate HCC from 2 cancer centers in China from 2000 to 2008 (primary cohort) and 2011 to 2012, with the second center providing a validation of SRD as a surrogate, using a modified version of the Response Evaluation Criteria in Solid Tumors to define tumor response. The authors defined SRD as the time between achieving a complete response, partial response, or stable disease and when progressive disease occurred. In their primary cohort, SRD of 6 months or more was associated with 5-year OS after cTACE. The time-dependent area under the receiver operating characteristic curve (AUC) for SRD was 0.913, where a value of 0.5 is equivalent to guessing and 1.0 indicates perfect prediction of the clinical outcome. Patients with SRD of 6 months or more had the longest median OS (67.7 months). The hazard ratio (HR) for SRD of 6 months or more vs less than 6 months was 0.145 (95% CI, 0.124-0.170). The significance of the association between SRD and OS was confirmed in the validation cohort. Their conclusion was that SRD of 6 months or more may serve as an early surrogate end point after cTACE for intermediate HCC.

Quantitatively, these results are compelling. In more than 30 years as a statistician and epidemiologist, I have only very rarely seen HRs and AUCs of such a large magnitude. (The HR of 0.145 represents a nearly 7-fold improvement in OS for those with SRD ≥ 6 months compared with those without.) One implication of the study findings is that SRD of 6 months or more can potentially be used as a surrogate end point for OS in clinical trials. However, the prognostic value of SRD is not enough to justify its use as a surrogate end point. We would have to see that a treatment effect on SRD at the trial level, which might be the HR comparing cTACE with some novel treatment, is reflected by a similar treatment effect on OS. That association between SRD treatment effect and OS treatment effect would need to be replicated across several trials.

A related point of interest from a methodological perspective is immortal time bias. The authors handled this potential problem well, which avoided 1 source of bias and is reassuring about the magnitude of the association they observed. The current study counted follow-up time from the time of diagnosis of HCC. The potential challenge is that someone has to survive long enough to achieve SRD of 6 months or more. If a patient who eventually achieves the SRD threshold is defined from the start of follow-up as having SRD of 6 months or more, then, by definition, they cannot have failed during those 6 months (plus whatever prior time it took to achieve response). That would then be time that is counted in the time at risk for the group with SRD of 6 months or more, but that should not be attributed to the SRD group because in reality it is not time at risk. To avoid this issue, the authors treated SRD as a time-dependent covariate when they did the analysis. (This is implied by their use of the time-dependent AUC, although not mentioned specifically in the Methods section.)

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This method treats the initial follow-up time, prior to achieving SRD of 6 months or more, as non-SRD time, and the value changes when that same patient achieves SRD of 6 months or more. During the review process, I learned that the authors did one other thing to address this methodological problem. In a sensitivity analysis, they excluded patients who survived less than 6 months and redid the analysis with similar results.

Returning to the clinical interpretation, why might the further requirement for SRD not be satisfied? There was a similar question for the use of circulating tumor cells (CTCs) in metastatic breast cancer. Patients were randomized to continuing current care vs changing treatment on the basis of the CTC results. (People with poor prognosis had their therapy changed.) The trial showed that CTC was very strongly prognostic for treatment response and subsequent survival. However, there was no clinical benefit to modifying treatment because there were no effective treatments to which patients could be switched. The situation is potentially similar in the current study. There is a factor (SRD) that, assuming the result is valid, is strongly associated with the outcome of interest, OS. The question is whether basing clinical decisions on SRD truly leads to better outcomes or whether SRD might simply be identifying patients with more indolent disease. The authors note the possibility that using SRD "would allow new strategies to be discarded early and enable testing new therapies." In other words, patients for whom 1 drug is not effective could be switched to another drug, which might be an investigational drug. One conclusion from the earlier clinical trial was that CTCs could serve to identify patients for inclusion in randomized trials of new therapies.

In this study, the authors note that cTACE for intermediate HCC can cause liver function damage, which can lead to treatment discontinuation and potentially serious harm. Gastrointestinal bleeding is another potential adverse effect. What they propose is that when SRD of 6 months or more is reached, it might be reasonable to adopt a wait-and-see approach in the interest of avoiding future toxic effects. Operationally, this means waiting those 6 months (plus the time required to achieve the response). Conversely, when progressive disease occurs, a new treatment regimen could be indicated. As the authors note, the current study provides only indirect support for this type of treatment model. Definitive evidence, as in the CTC example, would need to come from a randomized clinical trial, eg, comparing a treatment algorithm based on SRD with treatment administered "on schedule" (using the authors’ words). That requires, strictly speaking, at least 6 months of treatment (plus the time taken to achieve the response). In this context, although avoiding toxic effects is a benefit, if cTACE is only administered once or twice after SR is achieved and a patient has already tolerated earlier administration of cTACE, how much benefit could be realized is an open question. A randomized trial could test an algorithm that is more aggressive, eg, stop treatment once CR is reached, continue if only partial response or stable disease are achieved, and switch treatments if disease progresses.

An important question in the context of this analysis is the relevance of data from 2012 to the current environment. The most recent treatment guidelines are still similar to what they were in 2012. In particular, cTACE is still recommended for intermediate HCC. Although drug-eluting beads to deliver TACE have been developed, there is no difference in efficacy between cTACE and TACE using drug-eluting beads. An additional question is what the optimal regimen for follow-up would be. For example, might more intense frequency of follow-up, say once every 2 months, be more appropriate than what is done currently?

In summary, this article provides preliminary evidence for a treatment strategy that could reduce the exposure to potential harms related to cTACE without substantially increasing the risk of death.

ARTICLE INFORMATION
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Conflict of Interest Disclosures: None reported.

REFERENCES


