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CORRESPONDENCE

Optimal Lesion Number for Evaluation of Tumor Response in Response Evaluation Criteria in Solid Tumors

TO THE EDITOR: We read with interest the article by Hillman et al[1] on the use of limited tumor selection for reporting imaging-based response assessment in clinical oncology trials. We applaud the authors for their attention to this very important question of how best to use imaging information to determine patient responses to anticancer therapies. We agree with the authors' suggestion that one of the original recommendations[2] of the Response Evaluation Criteria in Solid Tumors (RECIST) panel (namely the measurement of up to 10 target lesions) was likely excessive, noting that the most recent revision to the RECIST recommendations[3] has reduced this number to five lesions. In their recent article, Hillman et al[1] suggest that this number could be further reduced to two lesions without significantly affecting the outcome of clinical trials. However, the authors' methodology raises several questions and concerns that cast doubt about the validity of this conclusion that measurement of two tumors alone will suffice to describe the global radiologic response of the patient.

The data presented in the article indicate that in approximately 75% of the reported cases in the North Central Cancer Treatment Trials databank, the site reported only one or two target lesions at baseline. In the ensuing analysis—namely, the comparison of response assessment category obtained using only the largest two target lesions versus that obtained by using "all reported" target lesions—it is clear that in these cases, concordance in response assessment by the two methods will be 100% by definition. Therefore, given the small number of cases where three or more target lesions were selected for measurement and reporting, it is clear that the database used for the evaluation does not allow one to determine the optimal number of target lesions to report, negating the authors' primary conclusions.

The authors also indicate that roughly three fourths of progression events are due to either nonradiographic (ie, symptomatic) progression or the appearance of new lesions on imaging. Clearly in these cases as well, the determination of progression versus nonprogression status will be independent of the number of target lesions used for reporting. That the number of tumors measured does not significantly affect response classification in the current study appears simply therefore to be a function of the authors' methodology and data set chosen for analysis. Indeed, careful analysis of the data presented in Table 2 indicates that when three or more target lesions were reported by the site, the concordance for response assessment using only the two largest target lesions does decline noticeably.

It appears that the more important scientific question to pursue is how the number of selected target lesions measured may influence the assessment of radiographic response, a topic that can be difficult to evaluate from clinical trial databases alone, but should instead be studied through retrospective image evaluation. This issue has been evaluated in several theoretic and experimental models. Schwartz et al[4] have suggested that a larger number of lesions may be required to accurately define imaging response. Theoretic and statistical work has also been undertaken to better understand the influence that number and choice of tumor lesions has on determining radiologic response to treatment.[5,6]

In the current era of targeted and biologic therapies, it appears that the effectiveness of imaging to document tumor response needs greater attention, as evidenced by the difficulties in using standard RECIST guidelines to accurately reflect tumor status in patients treated with certain targeted therapies, such as gastrointestinal stromal tumor response to imantinib[7,8] or hepatocellular carcinoma response to sorafenib.[9] As more complex combination therapies are introduced, the potential for intertumor response heterogeneity may increase, necessitating a more comprehensive, rather than reductionist, approach in the evaluation of imaging response methods.

In summary, we believe that the optimum methodology for reporting radiographic response in clinical trials remains an important area of scientific study. However, comprehensive evaluation of this question should be undertaken in data sets where the complete radiographic scans are available for centralized review and analysis. The more limited methodology applied by Hillman et al[1] in the current study risks obscuring, rather than revealing, the truth regarding how imaging responses may be most accurately and reproducibly reported in clinical trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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