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Concept and design: Rombouts, Hugen, Nagtegaal, de Wilt.
Acquisition, analysis, or interpretation of data: All authors.
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COMMENT & RESPONSE

Inappropriate Grading of Adverse Events in Cancer Clinical Trials

To the Editor Consideration of toxic effects is a critical part of cancer treatment. Therefore, the grading and reporting of all grades of adverse events, especially high-grade adverse events, must be standardized to allow for consistency and comparison across trials. The Common Terminology Criteria for Adverse Events (CTCAE) has been widely used for reporting of adverse events in oncology journals and at meetings.[1]

The recent study by Cristina et al[2] demonstrated that women with colorectal cancer receiving chemotherapy had a clinically relevant greater risk of nonhematologic and objectively measureable hematologic adverse events compared with men. The authors reported that, in 2974 patients receiving chemotherapy, 18 women (1.4%) vs 6 men (0.4%) had grade 3 or 4 alopecia ($P < .003$).[2] However, in the CTCAE, which was also used for grading adverse events in this important trial, the maximum grade for alopecia is grade 2. Thus, this is one example of the misuse of CTCAE and should be corrected immediately.[1]

In our previous study, we found that a substantial proportion of contemporary cancer clinical trials use inappropriate grading and reporting of adverse events that does not conform to CTCAE.[1,3] This situation is more urgent for trials evaluating toxic effects data, such as the study by Cristina et al.

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In Reply We thank Dr Zhang and colleagues for their comment regarding the grading of adverse events in the phase 3 PETACC-3 trial, which compared biweekly infusional fluorouracil/leucovorin alone or in combination with irinotecan as adjuvant treatment of stage 3 colon cancer.[1] We agree with Dr Zhang that the quality of adverse event grading is a critical issue in clinical trials, especially when evaluating factors influencing toxic effects. However, in contrast to what Zhang and colleagues assume, the investigators of the PETACC-3 trial[1] graded alopecia correctly as mentioned in our article[2]; adverse events were graded according to the National Cancer Institute of Canada Common Toxicity Grading expanded common toxicity criteria (version revised in May 1991, which was detailed in the PETACC-3 protocol but is no longer available for reference). In this version, alopecia is graded from grade 1 (mild hair loss) to grade 3 (total body hair loss). Therefore, no correction is needed; in 2974 patients receiving chemotherapy, 1.4% of women vs 0.4% of men presented with an alopecia grade greater than 2.[2] It is in the Common Toxicity Criteria version 2.0 and later that alopecia was graded as either grade 1 (mild hair loss) or grade 2 (pronounced hair loss).[3] Moreover, we would like to mention that, regardless of the number of categories in which alopecia is graded, a bias in the comparative assessment of the severity of alopecia between men and women is likely to be introduced by differences in baseline condition, with men more often having alopecia at baseline. Furthermore, sex differences in the subjective perception of the

severity of alopecia might also contribute to a bias because women might pay more attention to their hair loss. However, the significant differences in neutropenia described in our article clearly indicate that significant sex differences are present in chemotherapy toxic effects, including objectively measurable toxic effects.

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Assessing the Prognostic Value of the Automated Bone Scan Index for Prostate Cancer

To the Editor Armstrong and colleagues[1] conducted an important study to assess the use of the automated Bone Scan Index (aBSI) as a tool in predicting, among other outcomes, overall survival (OS) in patients with metastatic prostate cancer. As a continuous prediction score, the aBSI's hazard ratio (HR) for OS was statistically significant, with a lower aBSI associated with better survival. However, evaluations based on HRs are difficult to interpret clinically.[2-4] Moreover, the concordance index for the discriminative ability of the aBSI was only 0.63, which suggests that the continuous aBSI score may not be an effective prediction tool at the individual patient level. In practice, one may use the aBSI to stratify patients into several ordered categories. When stratifying by quartiles of the aBSI score, Armstrong and colleagues[1] reported observed median OS times (lowest to highest aBSI quartiles) of 34.7, 27.3, 21.7, and 13.3 months, respectively. These values appear to demonstrate the clinically interpretable discriminative ability of the stratified aBSI. Unfortunately, statistical inference for median times across strata was not provided. To further investigate, we generated 95% CIs of median OS times for patients in quartile 1 to quartile 4 using reconstructed data from the Kaplan-Meier curves in Figure 2A.[1] Some CIs (quartile 2 and quartile 3) overlapped. That is, the true median OS times of patients in quartile 2 and quartile 3 may be identical, suggesting that the stratified aBSI may lack discriminative capability. The wide, overlapping CIs likely resulted from unstable median time estimates.

An alternative assessment method for the discriminative ability of aBSI may be based on restricted mean survival times (RMST).[2-4] The RMSTs for 36-month follow-up are 26.4, 24.7, 21.9, and 16.0 months. The difference between quartile 1 and quartile 4 is 10.4 months (95% CI, 8.0-12.8 months; $P < .001$); the difference between quartile 2 and quartile 4 is 8.8 months (95% CI, 6.3-11.2 months; $P < .001$); and the difference between quartile 3 and quartile 4 is 6.0 months (95% CI, 3.5-8.4 months; $P < .001$). Over a 36-month follow-up period, a patient with an aBSI in quartile 1 would live for 26.4 months on average. Moreover, a patient with an aBSI in quartile 1 would, on average, live for 10.4 more months than a patient with an aBSI in quartile 4. The RMST provides a clinically and statistically informative assessment of the stratified aBSI.

In predictive medicine, one usually generates several categories/strata from a continuous score system to construct a stratification procedure. A desirable stratification scheme would possess small intrastratum variation and clinically meaningful discriminatory capability across strata. The usual practice of using score quartiles to group patients may be suboptimal. This issue has been discussed and alternatives have been proposed in a recently published study.[5]

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In Reply We thank Sun and colleagues for their interest and comments regarding our work.[1] We agree that restricted mean survival time (RMST) analysis is a recent and valuable