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EDITORIAL

SUNRISE-DI study. The daily sunrise is easier to predict than the benefit of adjuvant treatment in colon cancer

Making decisions regarding adjuvant treatment is a nuanced process for the oncologist, fraught with uncertainty, and entails tremendous emotional impact for patients.[1] In the case of stage II colorectal cancer, the benefit derived from adjuvant chemotherapy (CT) remains unknown and, while it is recommended for all patients with stage III tumors, it will be of no benefit for half of them.[2] Therefore, having prognostic and predictive factors aids in deciding on the advisability of adjuvant therapy. Gene expression profiling was proposed more than a decade ago as a potential biomarker. Nevertheless, none of its versions have yielded sufficient evidence thus far for its use in adjuvancy.[3,4]

The SUNRISE-DI study by Oki et al.[5] explores how the information derived from the 12-gene Recurrence Score (12-RS) affects decision making in patients with stages II and III adenocarcinoma of the colon, comparing the decisions made before (without bearing the 12-RS in mind) and after (in light of the 12-RS). In short, the results reveal that availing oneself of the 12-RS leads to a change in the decision made in 40% of the cases (45% in stage III and 30% in stage II). Likewise, it illustrates that the percentage of physicians who feel confident in their decision rose from 51% to 81% in stage II and from 65% to 83% in stage III. Consequently, this study reports on the interpretation of molecular analyses and how it affects decision making in a given clinical setting, in addition to bringing to light some of the weaknesses of the argumentative background of gene signatures.

The lack of results regarding overall survival, adverse effects, or quality of life is certainly among the most conspicuous limitations of the study. This precludes the acquisition of any kind of insight about the magnitude of the clinical benefit/harm associated with implementing the method. Gene expression profiling has proven marginal prognostic value with respect to traditional histopathological variables,[6] without any evidence of interaction with the type of treatment. All of this is relevant, inasmuch as two-thirds of the individuals recruited for this study had stage III tumors and, of them, approximately one-third were pT4 or pN2. The European Society for Medical Oncology[7] and National Comprehensive Cancer Network[8] clinical guidelines recommend CT with oxaliplatin in all of them and consider that, to date, the jury is still out with respect to the clinical usefulness of gene expression profiling.

In contrast to this feeble rationale, the 12-RS was used in the SUNRISE-DI study to curtail adjuvant therapy in 38% of the participants with stage III tumors that were deemed to be high risk on the basis of pathological criteria. Moreover, some of the recommendations for treatment change after the 12-RS do not appear to obey any consistent pattern, while others are arguable in the context of current clinical evidence. For instance, in individuals with stage IIIA/B, the step-back from 'any CT' to 'no CT' in five of the participants in the 'IDEA high-risk' group after 12-RS is worthy of note, as is the step-up from 'oxaliplatin-no' to 'oxaliplatin-yes' in four cases after receiving a 'high-risk' 12-RS score in the 'IDEA low-risk' group. This points toward an apparent skepticism on the part of the participating physicians as to the proven efficacy of adding oxaliplatin,[9] in contrast to the recommendations published in the clinical guidelines. Other decisions could, in fact, be more readily defensible, particularly in stages II, where there is far less proof of the role of CT in general, and of oxaliplatin, in particular. Thus, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial, the 12-RS accounted for some of the heterogeneity within each stage. While the gene panel was not predictive of benefit with oxaliplatin, the marginal risk depended on prognosis.[10] That said, the differences based on the 12-RS were small and the uncertainty surrounding the estimates was quite vast. Furthermore, Oki et al. stress the value of more accurate stratification using the 12-RS in the 'post-IDEA collaboration' era. Nevertheless, the conclusion of the IDEA study is founded on a pooled analysis of six randomized trials that failed to attain their primary objective, with a non-negligible risk of 3 months of CAPOX 3 being inferior in the presence of high-risk pathological factors.[11] As with genetic signatures, the IDEA study also has its limitations, particularly the randomization into two (3 versus 6) instead of four groups (FOLFOXx3, FOLFOXx6, CAPOXx3, CAPOXx6) and the decision to accept high- and low-risk groups as valid outcomes, despite a negative interaction test and its *post hoc* nature.[11] These limitations, in addition to those of the 12-RS assay, call into question the relevance of the SUNRISE-DI study design and its outcomes, which contribute nothing new regarding the usefulness of the IDEA or the 12-RS strategy.

The credibility of the SUNRISE-DI study is compromised by another methodological flaw, as the unit of study to conduct the analyses should be the physicians who make recommendations about groups of patients along the same lines in all their patients who display the same characteristics. If there had been 2 physicians who factored in the

12-RS and who included 40 patients each and 6 physicians who included 2 patients each and who did not bear the 12-RS in mind, the 12-RS would have modified the decision in 80 versus 12 patients and in 2 versus 6 physicians. The variability in the decisions across the physicians could have been determined by means of a mixed-effect model. We wonder if, perhaps, the sample size needed should have been calculated on the basis of the number of physicians instead of the number of patients.

Finally, the authors justify some of their recommendations in favor of de-escalation by labeling some patients, unwilling to trade the risks for the benefits of the adjuvant CT as fatalistic, using a definition based on data quoted, but never published.[12] Despite the obvious emotional impact of the diagnosis in the patients,[1] it may not be the patients' fatalism but the researchers' overconfidence in the predictive capacity of the 12-RS that determined their recommendations.

The evidence that 12-RS influences decision making does not make it a better biomarker now than before the publication of the SUNRISE-DI study. Still, these results are valuable in that they fire the debate apropos of the reasoning behind clinical decisions in the results of controversial studies, which occurs very frequently because there are few absolute, unarguable truths. One of these truths is that the sun rises every day and that it gives us life and warmth. The rest is debatable. At the end of the day, the SUNRISE-DI study reveals the influence of the 12-RS assay diagnostic test on clinical decisions, but does not prove that it improves them.

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