CORRESPONDENCE

RE: Test of Four Colon Cancer Risk-Scores in Formalin Fixed Paraffin Embedded Microarray Gene Expression Data

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We read with interest the recent analysis by Di Narzo et al. (1) regarding four prognostic assays designed to identify patients with resected colorectal cancer (CRC) at high risk of recurrence, of which two were developed exclusively in patients with stage II disease (2,3). The potential utility of these tools lies in the ability to identify a high-risk population among those with stage II CRC where standard clinicopathological variables are poor predictors of recurrence risk. In this patient population there remains clinical equipoise regarding management, because of a small but statistically significant improvement in overall survival with the addition of chemotherapy, but the absence of benefit in the majority of patients with exposure to treatment-associated toxicity (4). This study examined four prognostic scores using samples obtained during the PETACC-3 trial of adjuvant 5-fluorouracil/leucovorin chemotherapy alone or in combination with irinotecan (5). The authors concluded that the risk scores only marginally improved current prognostic models, and while this analysis is timely and important, a number of factors must be taken into account when we consider its clinical relevance.

First, we question the clinical utility of applying a prognostic assay to a population where treatment has been administered, given the potential modification of outcome by this intervention. We believe that these scores are optimally used to prospectively aid decisions regarding use of adjuvant chemotherapy.

Second, the PETACC-3 dataset consists of samples from 688 patients, of which only 16% are stage II (5). The prognostic assays included in this study demonstrate optimal performance in appropriate patient populations. For example, the Almac 634 transcript ColDx signature (2) has been further validated in a cohort of 393 patients with stage II disease who had not received cytotoxic chemotherapy (6). In this setting the performance was equivalent to that of the initial study, with univariate hazard ratio for relapse-free interval for the high-risk subgroup of 2.0 (95% confidence interval = 1.3 to 3.3, P < .01), remaining statistically significant after adjustment for prognostic factors.

Finally, the methodology applied across the assays was to split each continuous score at its median in order to divide the samples into equally sized low- and high-risk groups. However, in each assay predefined dichotomization thresholds for risk and the number of risk classes determine the proportion of patients in each group. For example, for the ColDx assay 34% and 66% of patients in the training set were classed as high and low risk, respectively (2). We propose that the predefined biomarker cut-offs for each assay should be utilized for comparisons.

In conclusion, prognostic RNA-based assays have previously been shown to have considerable clinical utility. This has been clearly demonstrated in breast cancer where the 21-gene Oncotype Dx signature has been validated for use in clinical practice as a prognostic tool (7). Our comments are not intended to diminish the efforts of this group in carrying out this analysis, but we believe that the use of these assays for investigational purposes should be in the appropriate clinical setting, with the use of their predefined thresholds.

Notes

The authors have no conflicts of interest to disclose.

References


