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EDITORIAL

The Elusive Prize of Radiation Therapy Predictive Assays in Breast Cancer

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The introduction of clinical genomic assays and other molecular biomarkers into radiation therapy (RT) decision-making for breast cancer has lagged behind breast medical oncology by at least a decade. Today, however, studies are ongoing to define the value of existing genomic assays used for systemic therapy recommendations in RT decisions and, perhaps more importantly, to define novel biomarkers explicitly for radiation patients.[1] Vicini et al report on a novel biosignature prognostic for in-breast recurrence after breast conserving surgery for ductal carcinoma in situ (DCIS) with and without radiation.[2] Numerous randomized studies have reported a benefit for breast RT after breast conserving surgery for DCIS, remarkably with similar relative risk reduction of ~50% across even clinically low-risk groups.[3] An ideal prognostic assay would predict both durable low risk of in-breast recurrence with surgery alone and also the robust absence of radation benefit. Such an assay would allow patients and their physicians confidence that RT could be omitted without risk of loss of even a small benefit. Herein, the authors find their biosignature score can identify patients with a 10-year total in breast recurrence risk of 5.6% without RT. The 10-year risk after radiation among low-risk patients, 4.6%, is not statistically improved compared with this result. The question to be addressed is whether this biosignature is ready for clinical use to inform prognosis and predict the value of radiation and dictate who it should be offered to.

Several publications outline the robust steps needed to report and lock down a biomarker and the threshold for its use.[4] Exploratory analyses in training data sets are used to generate a hypothesis for validation in independent, also called "uncontaminated," data sets. In Vicini et al, the authors newly redefine the cut-offs of a previously described biomarker signature score that is currently commercially available, the DCISionRT assay (PreludeDx, Inc., Laguna Hills, CA). The commercial report has been updated to the current cut-offs. The test is an immunohistochemical assay of 7 proteins (COX-2, FOXA1, p16/Ink4a, SIAH2, HER2, PR, and Ki67) integrated with 4 clinical variables. The initial assay was trained and cross-validated previously in retrospective data sets.[5,6] This work includes 1 cohort that predates hormone therapy for DCIS and includes about 10% of patients with a palpable DCIS. The previously published DCISionRT assay was prognostic, with high-risk scores (>3.0) having significantly higher risk of recurrence after lumpectomy without radiation than low-risk scores.[5,6] Confidence intervals overlapped among low-risk scored patients with and without radiation,[5,6] and on multivariable analysis excluding margin-positive patients, benefit of RT was restricted to the high-risk cohort. This prompted the promising hypothesis that the assay was predictive for RT benefit.

Validation with a data set where radiation was randomized would be critical to ensure that the lack of significant difference between radiation and no radiation in low-risk patients was not due to imbalances in the unrandomized arms. Further, with small differences between arms, the question of power should be addressed to say the nonsignificant difference is indicative of a noninferior result. If

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validated though, this would represent a holy grail of sorts, a predictive assay for radiation benefit in patients with DCIS undergoing breast conserving surgery. Unfortunately, the published validation of the prior locked down cut-off (elevated risk >3.0) using the data from the randomized SweDCIS trial was not prognostic among those without radiation or predictive of radiation benefit.[7] As a continuous variable, the score was prognostic among those not receiving radiation for total in-breast events, including recurrence of DCIS. However, it was not prognostic for invasive in-breast recurrences, suggesting a possible signal for a different cut-off.[7] This was a departure from the positive results presented at the San Antonio Breast Cancer Symposium in 2017.[8] In the ultimate publication, the cut-point for the assay was retrained in the randomized data set according to the prespecified statistical plan.[7] After testing cut-offs between 1.0 and 3.0, a new cut-off of 2.8 was selected based on a significant multiplicative radiation and score interaction *P* value of .035 for invasive events (interaction for total events was not significant at this threshold). This became the new baseline to be validated ideally in an uncontaminated data set.

In the current report, the new cut-off of 2.8 was not validated as a new dichotomous cut-point. Instead, it was hypothesized that recurrences would be driven by k-ras gatekeeping through 1 of the assayed proteins SIAH2 (Seven In Absentia Homolog) assessed here in a proprietary way, along with HER2 (Human Epidermal growth Factor Receptor 2). In addition to the previously established low-risk and high-risk groups, a new third group was proposed, called "residual risk," encompassing patients with high risk of recurrence not completely abated with radiation. This completely new score using all 3 groups is tested for validation in the current report. It is noted that the risk inferred by k-ras signaling surrogates was a prespecified hypothesis that would enhance the evaluation of the robustness of this new category, but details on how this cohort was developed and trained and to what extent the developer of the residual risk hypothesis had seen the prior data (and association of events with the related marker) are unclear. This retrained scoring with the new residual risk group was thus examined in an overall cohort, which included the 3 previously studied cohorts (Kaiser, UMass, and Uppsala), as well as patients from a new Australian cohort. The results are presented from all 4 cohorts combined, as well as from the Australian/Kaiser patients combined, and proposed as an uncontaminated true validation cohort. Limitations of retrospective research apply, of course. Namely, the use of RT was not randomized in these studies and patients in the final cohorts represent the ~50% of cases for which adequate blocks and clinical information were available. No comparison of the cases included in the study to the case population from which they were drawn is presented (those without blocks or with incomplete clinical data), so it is unclear if these cases are representative of the populations as a whole.

Reported in Vicini et al, the residual risk group is enriched for larger tumors, HER2 3+ tumors, and high-grade tumors. The 3 risk group classification was prognostic for total ipsilateral breast events in both the analysis of all patients and the new cohort not previously examined. Regarding invasive in-breast recurrence, the score was not prognostic for elevated versus low risk in the full or independent cohort. The same is true for residual versus elevated. Although the absolute risk increases in each risk group, the confidence intervals overlap. Thus, the new 3 group scoring using the 2.8 cut-off and residual risk category is validated in the independent cohort for total in-breast events but not invasive in-breast recurrence. On multivariable analysis for total in-breast events, the score is independently prognostic. Considering the potential that the score predicts RT benefit among low-risk patients, the authors note a hazard ratio of .87 and .76 for reduction in total and invasive in-breast recurrence, respectively, are not statistically significant. Given the nonrandomized nature of the data set, small numbers in the low-risk subgroup of the validation cohort (n = 230), and low number of events in each arm, this seems to remain in the realm of hypothesis generation regarding prediction of RT benefit. Meanwhile, 15 year follow-up of the Radiation Therapy Oncology Group (RTOG) 9804 randomized trial assessing the benefit of radiation in low-risk patients with DCIS was recently published, showing a low in-breast recurrence risk of 1% per year without radiation.[9] Invasive recurrences were reduced from 9.5% to 5.4% with use of radiation; however, there was no overall, disease-free, or mastectomy-free survival advantage, suggesting patients who meet RTOG 9804 eligibility criteria had sufficiently low risk to permit RT omission.

What are the risks of using a test that has not been robustly validated for treatment decisions? The commercial availability of the test implies it is in use currently for clinical decision-making. Indeed, in 1 study the test changed clinical recommendations in ~40% of patients, with 20% of them forgoing radiation.[10] Of note, nearly 50% of the patients in the study met eligibility for the recently published and randomized study of radiation in DCIS, RTOG 9804. Of these patients, 54% were recommended for radiation before DCISionRT testing, suggesting that the randomized data for low-risk disease are not guiding practice. Furthermore, the current report highlights that among those with score ≤3.0 were some patients with what would now be called "residual risk," as well as those from 2.8 to 3.0 who will now be reclassified into the high-risk group. These patients, however, may have been offered observation based on the use of the report before the retraining. This highlights the risk of implementing a single clinical tool in decision-making that has not been tested in a prospective randomized trial. It may still provide meaningful additional information similar to the consideration of lymph-vascular space invasion in the risk/benefit assessment for patients with invasive disease. In that sense, the independent prognostic value of the biosignature score herein may add value as an additional variable to be considered along with traditional variables. At this time, however, it should be considered that the newly locked categorization has only been validated

regarding prediction in the independent subset of 230 low-risk patients reported here, and it remains promising but investigational for prognosis and hypothesis-generating for prediction.

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