Editorial

Precision medicine in early breast cancer—can this apply to radiotherapy?

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Our understanding of breast cancer has improved by leaps and bounds over the past 5 decades. The Early Breast Cancer Trialists' Collaborative Group has provided Level 1 evidence on the survival benefits of multi-modality management after surgery with polychemotherapy, radiotherapy and endocrine therapy in early breast cancer (1,2). While advancements in treatment has led to an improvement in disease-free and overall survival, we now increasingly realise that a one-size-fits-all strategy does not apply to all breast cancer patients. Un-informed use of systemic therapy can potentially cause additional toxicities with no clinical benefit in low risk cancers, or be grossly inadequate for patients who are at high risk and futile in refractory patients. Identification of predictive biomarkers such as estrogen receptor and HER2 status, as well as prognostication tools such as Adjuvant! Online has allowed us to tailor the use of systemic treatment (3). Genomic profiling has also revealed at least five biological subtypes of breast cancer with marked difference in prognosis, and major efforts have been made to incorporate this in the decision-making process (4).

Much progress has been made in the field of precision medicine in early breast cancer, particularly with regard to the use of adjuvant chemotherapy. Gene expression profiling technologies such as OncoType Dx and MammaPrint have been retrospectively validated in distinguishing early breast cancer patients with low versus high risk of distant recurrence (5,6). More recently, the TAILORx and MINDACT studies have provided preliminary prospective data that these tools can identify patients with good prognostic cancers who do not need adjuvant chemotherapy (7,8). As a testament to its potential utility, the American Society of Clinical Oncology has already shown support in using these biomarker assays to guide decisions in systemic therapy use in the clinical setting (9).

But can this level of precision be applied to the use of adjuvant radiotherapy in early breast cancer? Adjuvant radiotherapy is particularly important for locoregional control in patients undergoing breast conservation surgery, but a large cohort study has already shown that the risk differs by biological subtype (defined by immunohistochemistry), with HER2-enriched and basal subtypes having higher risk of regional recurrence despite radiotherapy. While there is an unmet need for greater precision in prescribing radiotherapy, various groups have tried with limited success to identify a predictive and prognostic tool similar to that for systemic therapy.

Speers *et al.* published their work "*Development and Validation of a Novel Radiosensitivity Signature in Human Breast Cancer*" in *Clinical Cancer Research* in April 2014, to help answer this critical question (10). Unlike previous research, Speers *et al.* formulated a breast cancer-specific molecular signature of radiation response from *in vitro* studies in 16 different breast cancer cell lines. Interestingly, they found that radiosensitivity was independent of biological subtype. A training dataset of 343 early breast cancer patients treated with breast conserving surgery and adjuvant radiotherapy was used to develop the radiosensitivity signature (RSS) which comprised of 51 genes involved in cell cycle regulation, DNA damage, and DNA repair. This was subsequently validated in an independent cohort of 228 breast cancer patients, and was found to predict patients who would develop

locoregional recurrence at 10 years with a sensitivity of 84% and negative predictive value of 89%.

The RSS was a culmination of comprehensive preclinical work and rigorous statistical analysis, resulting in the translation from bench to bedside. Novel genes (*TACC1* and *RND3*) were found to be upregulated in radioresistant cell lines, and confirmed to confer significant radiosensitisation with single gene knockdown. Impressively, the RSS was found to outperform traditional clinic-pathological predictors such as grade, tumor size, and nodal status, in predicting local recurrence and overall survival. The 10-year ROC AUC of 0.72 is also comparable to the performance of existing prognostic signatures such as OncoType Dx (11).

While this is the first time that a RSS has performed well on validation in a breast cancer cohort, the results are far from conclusive. The training and validation work were performed on non-randomised datasets of early breast cancer patients who were mostly treated with breast conservation surgery and radiotherapy (12,13). This adds an additional layer of complexity in interpreting the results due to the presence of confounders that may not be entirely accounted for. Even though multivariate analysis using Cox regression was performed, more robust techniques such as propensity scores could have been adopted to control for potential confounders. Also, the patient cohorts were treated more than a decade ago, in a pre-modern era of radiotherapy, and before more commonplace use of third generation systemic therapy and trastuzumab, all of which have impact on risk of recurrence.

What is most puzzling, and interesting, is the fact that biological subtype did not impact on the risk of recurrence when RSS was included in the analysis. This is contrary to present knowledge from other groups who have done similar work in developing radiation-specific assays, the most prominent being the radiosensitivity index (RSI) (14). The RSI is a validated ten-gene expression signature which has been shown to be predictive of distant metastasis-free survival in breast cancer patients treated with radiotherapy (15). When integrated with biological subtype, the ability to predict local recurrence was enhanced in triple negative breast cancer subtypes (16). In addition, RSI was able to predict a benefit of radiation dose escalation in the luminal/RSI-resistant subgroup. Why is there a difference? The RSI was developed from 48 different cancer cell lines and validated across a variety of tumour groups. Hence, it likely represents generic cancer pathways involved in cellular response to radiation, and would not reflect the biological heterogeneity of breast cancer. On the contrary, because the RSS was generated from breast cancer specific cell lines, the genetic signature may incorporate intrinsic aspects of the biological subtypes. Furthermore, the hazard ratios for local recurrence for HER2 versus Luminal A subtypes in the validation dataset for RSS was clinically meaningful (HR 1.87) but the P value (0.43) may not be significant due to small numbers on stratification (the third supplementary table in Speers *et al.*). To further support their proposed RSS, the authors also applied the RSI to the study validation dataset, and found that RSS was superior in differentiating prognostic subgroups.

So are we ready for greater precision in prescribing radiotherapy in early breast cancer? Is RSS positioned for prime time use by radiation oncologists? Unfortunately, there remains much to be understood and studied. RSS needs to be further validated, preferably using more modern breast cancer cohorts. The gold standard to ascertain the validity of the RSS would be to conduct a prospective randomised controlled trial in the same vein as TAILORx and MINDACT. Its counterpart RSI is already being developed as a commercial assay in conjunction with National Cancer Institute's Clinical Assay Development Program (17). If these radiation-specific assays do come to fruition in the clinic, they must meet one or more of the following requirements: (I) identify breast cancer patients with sufficiently good prognosis who can be spared radiotherapy; (II) tailor the radiation dose for early breast cancer patients of different prognosis; (III) highlight patients with radioresistant cancers who will not benefit from radiotherapy who may then require intensified systemic therapy or other novel therapies. Having prognostic impact is no longer novel; adding predictive power will be more beneficial to the practising clinician.

Another important question that remains unanswered is—how can radiation-specific assays be integrated with the myriad of existing genomic-based decision making tools? Of note, OncoType Dx has been shown to be able to predict the risk of local recurrence in breast cancer patients who underwent mastectomy, but is less useful in those treated with breast conservation and adjuvant radiotherapy (18). Clearly, the current prognostication assays in use are not equipped for personalisation of radiotherapy, but we do not want to end up with the costly situation of having to resort to multiple tests to formulate a multi-disciplinary management plan. The ultimate vision would be to streamline and unify platforms to allow for concerted testing.

Alas, we are still in the infancy of discovering how best

to personalise the usage of radiotherapy in early breast cancer. There is still a long road ahead before we can truly tailor the post-operative management for patients in the real world, but Speers *et al.* has shown us early evidence that this is feasible. Now that we have bolstered the treatment options for early stage breast cancer, the next decade will hopefully see oncologists focus on bringing precision medicine to the forefront of multidisciplinary management, to improve survival outcomes and reduce treatment-related morbidity.

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Footnote

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