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Critical Review

Genomically Guided Breast Radiation Therapy: A Review of the Current Data and Future Directions

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Abstract

Purpose: To highlight the current evidence and the limitations in data to support a personalized approach in breast oncology radiation therapy management and define steps needed for clinical implementation.

Methods and Materials: A critical review of the current literature on the use of genomics in breast radiation therapy was undertaken by a group of breast radiation oncologists to discuss current data, future directions, and challenges.

Results: A summary of the existing data, ongoing clinical trials, and future directions is provided. The authors note many groups have developed radiation-specific genomic assays, which demonstrate promise in prediction of local control and benefit from radiation therapy; however, prospective validation of their utility is needed. Limitations continue to exist in our understanding of tumor biology and how it can be integrated into clinical practice.

Conclusions: Given the relative ubiquity of breast radiation therapy, the variety of dose and fractionation approaches, and the current data to support a personalized approach, it is our belief that the delivery of breast radiation therapy is uniquely poised for a genomically personalized radiation therapy approach. Prospective clinical trials implementing genomic signatures are needed at this time to advance the field.

Introduction

Adjuvant radiation therapy is integral in the locoregional management of breast cancer. Whole breast radiation therapy significantly reduces the rate of local recurrence after breast conserving therapy, which has translated to an improvement in breast cancer mortality.[1] Similarly, postmastectomy radiation therapy significantly

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reduces the risk of locoregional recurrence (LRR) and improves overall survival in patients with lymph node (LN) positive (+) breast cancer.[2] Advancements in treatment planning and image guidance techniques have improved the ability of radiation oncologists to deliver conformal doses of radiation to target volumes accurately while avoiding dose to normal tissues, improving the therapeutic ratio. Still, for early stage patients, benefits versus toxicity must be considered carefully and to date there are no personalized tools in routine practice to inform these decisions.

It is well-established that breast cancer is a heterogeneous disease comprised of multiple subtypes with differing response to treatment.[3-5] Despite this, radiation oncologists still largely prescribe to uniform doses in practice. Breast cancer is uniquely suited to the development of personalized strategies, as it is one of the disease sites most commonly treated with radiation therapy.

In this article, we will review the current evidence for genomic risk stratification for local recurrence and prediction of radiation therapy benefit. We then will discuss ongoing clinical trials using biological parameters to guide radiation therapy treatment decisions. Finally, we will discuss next steps in moving the field of precision genomic breast radiation therapy forward.

Search and Review Methodology

Original preclinical and clinical scientific articles were identified within a literature search using Google Scholar and PubMed. No date restrictions were applied. An English language restriction was applied. The search was initially performed in October 2020. Additional relevant studies were identified by manually searching reference lists and citing articles of identified papers or by direct input from the authors of this review. After an initial redundancy check, the identified scientific articles were screened for suitability by experts in the field. An inclusion criterion required articles to sufficiently detail methodology, patient cohorts, and clinical endpoints. Articles were stratified by a focus on invasive or preinvasive (DCIS) disease.

Radiation Therapy Biomarkers in Breast Cancer

It is increasingly apparent that breast tumor biology can be reliably measured and applied to clinical context to inform prognosis and treatment selection. The trial assigning individualized options for treatment (TAILORx) and microarray in node-negative and 1 to 3 positive lymph node disease may avoid chemotherapy (MINDACT) trials showed that hormone therapy alone is noninferior to chemotherapy plus hormone therapy in women with early stage, hormone receptor positive (HR+), node negative breast cancer with favorable biology determined by the Oncotype DX Recurrence Score (RS) and Mammaprint 70-Gene Signature, respectively.[6,7] Similarly, and perhaps more dramatically, the randomized clinical trial of standard adjuvant endocrine therapy +/- chemotherapy in patients with 1-3 positive nodes, hormone receptor-positive and HeR2-negative breast cancer with recurrence score (RS) of 25 or Less (RxPONDER) trial recently demonstrated that postmenopausal women with 1 to 3 positive nodes in HR+ and Her2- breast cancer and Recurrence Score results of 0 to 25 can forgo adjuvant chemotherapy regardless of clinical pathologic parameters (results presented at San Antonio Breast Cancer Symposium December 10, 2020; clinicaltrials.gov identifier: NCT01272037). These groundbreaking clinical trials define a role for genomic assays in the adjuvant management of breast cancer and illustrate the feasibility of such biomarkers in delivering personalized treatment, in which metrics of tumor biology outperform clinical factors to estimate prognosis and guide therapeutic decision making.

The need for similar biomarkers to guide patient selection for adjuvant radiation therapy for breast cancer is illustrated by the CALGB 9343 and PRIME II trials, in which HR+/HER2− patients thought to be at the lowest risk for recurrence still derived significant benefit from adjuvant radiation in terms of local control, although their absolute risk for recurrence was low even with the omission of whole breast radiation.[8,9] Similarly, modern series showed that patients with T1-T2 tumors and low volume axillary nodal metastases treated with modified radical mastectomy and systemic therapy have low absolute rates of LRR, putting into question their need for adjuvant radiation therapy.[10-12] Although it is understood that addition of adjuvant radiation decreases the risk for recurrence in these populations, current guidelines suggest radiation may not be recommended in all cases.[13] Thus, these populations represent an ideal group to evaluate the feasibility of radiation therapy de-escalation based on biomarker status. On the other hand, some patients will experience recurrence despite adjuvant radiation therapy,[1,2] and strategies are needed to identify patients who would benefit from treatment intensification with an increased prescription dose.

Current Landscape for RT Dose and Fractionation in Breast Cancer

Multiple trials have been completed or are ongoing evaluating various radiation fractionation schedules in the management of early stage breast cancer, largely revealing low risks of recurrence and equivalence of both

recurrence and toxicity across dose and fractionation schemes. Conventionally fractionated regimens of 45 to 50 Gy in 25 fractions of 1.8 to 2.0 Gy to the whole breast plus a boost to the lumpectomy cavity have traditionally been the standard of care after lumpectomy. Long-term results of the START A/B and Canadian trials of hypofractionated whole breast radiation therapy (40-42 Gy in 15-16 fractions) demonstrated equivalence in toxicity, cosmesis, and disease control to conventionally fractionated regimens.[14,15] These trials have made hypofractionated whole breast irradiation the standard of care after lumpectomy in LN− patients.[16] An additional course of radiation, a boost, may be added to the end to the highest risk targets based on randomized trials showing increased local control in postlumpectomy patients with both invasive[17,18] and noninvasive breast cancer.[19] The 10-year results from the FAST trial suggest 28.5 Gy delivered in 5 once-weekly fractions of 5.7 Gy to the whole breast has similar rates of normal tissue effects to conventional whole breast radiation to 50 Gy in 25 fractions, and 30 Gy in 6.0 Gy fractions resulted in significantly higher rates of normal tissue effects.[20]

A number of early trials assessing partial breast irradiation techniques demonstrate similar local control and cosmetic outcomes compared with conventional whole breast radiation for carefully selected patients. The partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (IMPORT-LOW) trial was a 3-arm study that demonstrated noninferiority between 40 Gy to the whole breast, 40 Gy to the partial breast, and 36 Gy to the partial breast, each in 15 once daily fractions.[21] Long-term results of the Florence Trial showed no difference in local recurrence and decreased toxicity for 30 Gy in 5 daily fractions to the partial breast compared with 50 Gy in 25 fractions to the whole breast.[22] Similarly, the RAPID trial showed that delivery of 38.5 Gy in 10 twice daily fractions to the partial breast is noninferior to 50 Gy in 25 fractions or 42.5 Gy in 16 fractions to the whole breast in terms of local control, has lower rates of acute skin toxicity but more commonly resulted in moderate late toxicity and adverse cosmesis.[23] In contrast, NSABP B-39/RTOG 0413 showed minimally higher rates of local recurrence (0.7% at 10 years) with APBI delivered as 34 Gy via brachytherapy or 38.5 Gy via external beam in 10 fractions for 5 treatment days compared with conventionally fractionated whole breast radiation.[24] The FAST-Forward trial compared 40 Gy in 15 fractions to 27 Gy or 26 Gy in 5 fractions to either the breast or the chest wall, showing noninferior local control and similar rates of toxicity at 5 years of follow-up with 26 Gy in 5 fractions.[25]

Hypofractionation studies have taken place in the postmastectomy setting. There is good long-term data from the British Columbia randomized trial of post mastectomy radiation using a dose of 37.5 Gy in 16 fractions.[26] The results of a phase 3 study conducted in China of hypofractionation (43.5 Gy in 15 daily fractions) versus conventional fractionation (50 Gy in 25 daily fractions) in the postmastectomy, unreconstructed setting delivered with electrons revealed no differences in LRR with a similar toxicity profile with approximately 5 years of follow-up.[27] A phase 2 trial of a shorter course of radiation therapy of 36.63 Gy in 11 fractions revealed low rates of toxicity and high local control with 5 years of follow-up.[28,29] The ongoing RT-CHARM (Alliance A221505, NCT03414970) and FABREC studies (NCT03422003) randomizes women treated with mastectomy and either immediate reconstruction or plans to undergo reconstruction within 18 months after radiation, with the primary endpoint of reconstruction complications. Given the preponderance of available data pointing to the effectiveness of various fractionation schedules, a biologically informed approach to dose and fractionation schedule could help identify a personalized optimal fractionation schedule for each patient.

Current Landscape of RT Genomic Biomarkers

Invasive breast cancer

Tools initially designed to assess distant disease and systemic therapy benefit

The Oncotype DX RS was developed as prognostic tool to determine the rate of distant disease recurrence and has an established role in determining the magnitude of benefit to chemotherapy delivery in HR+/HER2− breast cancer.[30] Several studies have demonstrated that this tool can also discriminate between groups who have various LRR risks after standard local therapy. Retrospective analyses of patients treated on multiple clinical trials demonstrated that the Oncotype DX RS can stratify the risk of LRR in patients with both LN negative (LN−) and LN+ disease. Mamounas et al showed that in HR +, LN− patients treated on the NSABP B14 and B20 clinical trials, RS was significantly associated with LRR and this association was independent of other clinical factors.[31] Because B14 and B20 asked systemic therapy questions, all patients were treated with standard local therapy (mastectomy or lumpectomy with radiation therapy) the analysis could discriminate groups at highest risk of LRR after standard treatment, but not specifically address who benefited from breast radiation therapy. The Oncotype DX RS was also used to assess outcomes in LN+ patients from the NSABP B-28 study of HR+ patients treated with doxorubicin and cyclophosphamide for 4 cycles with or without paclitaxel. The RS was a statistically significant predictor of LRR on univariate analyses (10-year cumulative incidence of LRR 3.3%, 7.2%, and 12.2% for low, intermediate, and high RS,

respectively, $P < .001$) and the score remained significant on multivariate analysis. However, when assessing the 21 gene RS by number of positive nodes, only patients with ≥4 positive nodes and not 1 to 3 positive nodes significantly benefited.[32]

Woodward et al demonstrated similar results in their analysis of patients with HR+, LN+ tumors treated on the SWOG 8814 trial.[33] A multivariable model controlling for randomized treatment, number of positive nodes, and surgical type showed a higher RS was prognostic for LRR. These studies suggest that patients with low volume axillary nodal metastases and low RS have low absolute risk for LRR, and thus may be candidates for omission of adjuvant regional nodal irradiation. In this population, in which the benefit of postmastectomy radiation has recently been called into question,[13] the Oncotype DX RS represents a potential solution for improved patient selection. The use of the Oncotype DX RS to guide decision making in this setting is being assessed with the ongoing TAILOR RT trial, which will be discussed here later. The Mammaprint 70-gene signature was also shown to be an independent predictor for LRR in 1053 patients with breast cancer at the Netherlands Cancer Institute. The study population included both LN− and LN+ patients treated with either breast conserving surgery and adjuvant radiation therapy or mastectomy with or without radiation therapy. When incorporated with clinicopathologic factors, the discrimination of the gene signature was nonsignificantly improved.[34]

Tools specifically designed for local-regional recurrence and benefit from RT

Several groups have developed radiation-specific genomic classifiers to stratify local recurrence risk and identify patients who benefit from radiation therapy. These studies are summarized in Table 1. The Danish Breast Cancer Cooperative Group developed and validated a 7 gene signature in high-risk patients treated with mastectomy from the Danish 82b and 82c trials, which identified a low risk group that did not benefit from postmastectomy radiation therapy.[35] The group at the Netherlands Cancer Institute identified a signature of 111 genes associated with local recurrence in young patients treated with lumpectomy and radiation therapy; however, the signature did not perform well in an independent validation cohort.[36,37] Speers et al at the University of Michigan developed a 51-gene radiosensitivity signature (RSS) using clonogenic survival assays to predict the radiosensitivity of breast cancer cell lines, and further refined the signature in a cohort of patients treated with lumpectomy and radiation. The signature dichotomizes patients into high or low risk for local recurrence with 84% sensitivity and 89% negative predictive value for LRR at 10 years, outperforming all clinical and pathologic variables in 2 independent datasets of patients undergoing breast conserving therapy. The signature was also independently associated with overall survival (HR = 1.8, $P < .05$). The RSS could not be validated as a predictive biomarker as there was no control group of patients who did not receive radiation therapy.[38] The Michigan group later used the same cohorts to develop a 41-gene classifier which differentiated patients at risk for early versus late recurrence. Notably, the signature correctly identified a group at risk for early recurrence with 100% specificity, signifying a group who may benefit from upfront treatment intensification.[39]

The group led by Torres-Roca et al developed the 10-gene radiosensitivity index (RSI) and related GARD (genomically adjusted radiation dose) score by using a systems-based biology approach to identify genes associated with the surviving fraction of cells at 2 Gy in various cancer cell lines.[40,41] They identified a broad range of GARD scores among 2487 breast cancer samples, demonstrating the wide genetic variability in breast cancer with regard to radiation sensitivity. Validation studies showed RSI is correlated with clinical outcomes and benefit of radiation therapy in multiple disease sites (head and neck, rectal, esophageal, glioblastoma, pancreas, endometrium, lung, and prostate) as well as breast cancer.[42-50] In 2 separate cohorts of patients with breast cancer, RSI was found to predict outcomes in patients treated with radiation therapy after breast conserving therapy, but not in patients who did not receive radiation therapy, demonstrating its potential as a predictive biomarker specifically for radiation therapy benefit.[49] RSI may differ according to breast cancer subtype. Differences in breast tumor biology which are recognized to carry ramifications for systemic therapy treatment selection may similarly be useful for selection of patients needing intensified radiation treatment strategies.[51] Integration of RSI with molecular subtype showed that radioresistant, triple negative tumors have worse local control despite radiation therapy and suggests the prognostic effect of RSI varies with biologic subtype.[48,52]

The group at Lund University led by Sjöström proposed a single sample predictor (SSP) classifier incorporating genes based on their association with the interaction between LRR and radiation therapy. This pragmatic approach allowed the SSP model to stratify patients into clinically relevant groups: those with sufficiently low risk of recurrence to be spared radiation therapy, those who have low risk of recurrence with the addition of radiation therapy and thus should be given radiation therapy, and those who remain at high risk of recurrence even with radiation therapy and thus would benefit from treatment intensification.[53] The group also applied the RSI and RSS in their cohort and found mixed results depending on ER and radiation therapy status.

Table 1 Summary of breast radiation therapy gene signatures

First author	Journal	Year published	Institution	Signature name	No. of genes	Training cohort characteristics	Validation cohort characteristics
Tramm[35]	Clinical Cancer Research	2014	Danish Breast Cancer Group, Denmark	DBCG-RT Profile	7	191 patients treated with mastectomy from Danish 82bc cohort, with 26.7% rate of LRR, median age 55, 72% ER+, 94% LN+	112 patients treated from Danish 82bc cohort
Kreike[36]	Clinical Cancer Research	2009	Netherlands Cancer Institute, Netherlands	111-gene signature	111	165 patients treated with BCS + RT at multiple European centers, age <51 with tumors <5 cm, 20% positive margins, 44% LN+, 71% ER+	295 patients treated with BCS + RT from the Netherlands Cancer Institute (originally published by van de Vijver), age <52 with tumors <5 cm, 49% LN+, 77% ER+
Servant[37]	Clinical Cancer Research	2012	Institut Curie, France	N/A	N/A	N/A	A total of 343 patients, including 148 patients from the Netherlands Cancer Institute (same population as Kreike) and 195 patients from Institut Curie in France treated with BCS + RT, all age <50 with tumors <5 cm, 11% positive margins, 36% LN+, 78% ER+
Speers[38]	Clinical Cancer Research	2015	University of Michigan, US	Radiosensitivity Signature	51	343 patients from the Servant dataset	228 of the 295 patients from the Netherlands Cancer Institute (van de Vijver) dataset (67 overlapping patients with the Servant dataset were removed)
Eschrich[49]	Clinical Cancer Research	2012	Moffitt Cancer Center, US	Radiosensitivity Index	10	N/A	344 lymph node negative patients treated at Erasmus medical center in the Netherlands, median age 52, 80% received BCS + RT and 20% mastectomy alone, 97% T1-T2, 73% ER+ and 159 patients treated at Karolinska University in Sweden with median age 58, 38% LN+

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Table 1 (*Continued*)

First author	Journal	Year published	Institution	Signature name	No. of genes	Training cohort characteristics	Validation cohort characteristics
Sjöström[53]	Breast Cancer Research	2018	Lund University, Sweden	Single Sample Predictor	248	172 patients treated with BCS at 6 centers in Sweden with negative margins, 22% LN +, 71% ER+, 69% received RT	164 patients treated with BCS at 6 centers in Sweden with negative margins, 22% LN+, 85% ER+, 86% received RT, as well as patients from the Servant and van de Vijver datasets
Sjöström[57]	Journal of Clinical Oncology	2019	Lund University, Sweden	ARTIC		Patients from the Sjostrom, Servant, and van de Vijver datasets	748 patients with node-negative, stage I-IIA breast cancer treated with BCS and randomized to RT vs no RT on the SweBCG91-RT dataset, median age 60, 81% ER+
Speers[39]	Red Journal	2020	University of Michigan, US	Early vs late recurrence signature	41	343 patients from the Servant dataset	112 patients from the van de Vijver dataset who were treated with BCS and adjuvant radiation
Cui[55]	Clinical Cancer Research	2018	Stanford University, US	Radiosensitivity Signature, Immune Signature	34 and 4, respectively	343 patients from the Servant dataset (radiosensitivity signature) and 66 patients from the University of California, San Francisco	van de Vijver dataset, 286 patients from Erasmus medical center, 1981 patients from the METABRIC cohort

Abbreviations: ER = estrogen receptor; BCS = breast conservation surgery; LN =lymph node; LRR = locoregional recurrence; RT = radiation therapy.

The RSS showed association with local recurrence in the full cohort, but when stratified for ER and radiation therapy status remained significant for LRR only in the ER+ radiation therapy treated group and was not found to be predictive of radiation therapy benefit. The RSI was not associated with LRR in the overall cohort but performed well in the ER− radiation therapy treated subgroup, consistent with prior results.[52] RSI was predictive of radiation therapy benefit, as a Cox regression model, including radiation therapy, RSI, and the interaction term was significantly predictive of LRR in the full cohort.[53]

The group at Stanford led by Cui et al developed 2 gene expression–based signatures including a radiosensitivity signature and an immune signature.[54] The radiosensitivity signature was developed as a prognostic classifier by selecting genes associated with local-recurrence free survival after radiation therapy, and the immune signature was developed as a predictive model with feature selection on the basis of their association with the interaction between radiation therapy and clinical outcome. Both signatures were found to be prognostic in validation cohorts, and after selecting a cohort with 1:1 matching between patients treated with and without radiation therapy based on clinical characteristics, both signatures demonstrated predictive association with radiation therapy benefit due to statistically significant interaction terms. When the 2 signatures were integrated to form 3 groups (radiosensitive/immune-effective, radioresistant/immune-defective, and discordant groups), this classification also resulted in a significant interaction term with radiation therapy, indicative of a predictive biomarker.[54]

The linear quadratic model is commonly used by radiation oncologists to estimate the biologic effects of radiation dose on diseased and normal tissues, considering the total dose of radiation, the radiation fraction size, and the sensitivity of the tissues receiving radiation.[55,56] Because both the linear quadratic model and RSI are based on the cellular radiation survival curve, Scott et al further hypothesized that RSI could be integrated into the linear quadratic model as a method to predict an individual tumor's unique response to a given radiation therapy dose.[46] The prognostic utility of the resulting metric, the GARD, has been validated in multiple disease sites including breast cancers treated with radiation therapy. In breast cancer, a high GARD was a significant predictor for distant metastasis-free survival in 2 independent cohorts of patients treated with adjuvant radiation.[46] The effect of GARD also was assessed in 2 datasets of triple negative breast cancer treated with adjuvant radiation therapy and found that GARD was an independent predictor of local control in both cohorts.[49] At a uniform dose of 40 Gy, 60 Gy, or 70 Gy, the cumulative proportion of patients achieving the optimized GARD was 40%, 78%, and 91%, respectively. Sjöström et al later developed the clinicogenomic Adjuvant Radiation therapy Intensification Classifier (ARTIC), which combines patient age with the expression of 27 genes. In a landmark study, they found the interaction between ARTIC score and radiation therapy to be an independent predictor of LRR in patients with early stage breast cancer treated on the SweBCG91-RT trial, representing the first genomic classifier to be validated as predictive of radiation therapy benefit in the context of a phase 3 clinical trial in which patients were randomized to receive or not receive radiation therapy.[57] Eight previously published gene expression signatures, including the RSS, RSI, 70-gene signature, and 21-gene signature failed to predict radiation therapy benefit in this group of patients, highlighting the importance of establishing generalizability for the utility of biomarkers. One of the primary reasons for this finding may be that ARTIC selected genes that had good technical characteristics in both formalin fixed paraffin embedded and fresh frozen tissue which may explain its improved performance over the other signatures.

Ductal Carcinoma in Situ

Similar to invasive breast cancer, every prospective trial evaluating breast radiation therapy for DCIS demonstrates a significant local-control benefit. Yet many women do well without radiation therapy and adjuvant treatment has not been shown to effect survival prospectively. Patient selection for adjuvant radiation therapy for DCIS therefore remains an area of active investigation. Prospective observational data suggests that even in the groups considered to be at the lowest clinical risk, the rate of recurrence approaches 1% to 2% per year without adjuvant radiation therapy after breast conserving surgery.[58,59] RTOG 9804 evaluated the role of radiation therapy in a low risk population and showed that the addition of adjuvant radiation decreases the risk of both invasive and noninvasive recurrences but does not improve overall survival.[60] Thus, patient selection for omission of adjuvant radiation therapy remains difficult and DCIS-specific genomic signatures of recurrence risk have been developed to improve risk stratification and aid decision-making.

The Oncotype DCIS score was evaluated in 327 patients from the ECOG E5194 trial, which was designed to assess the risk of local recurrence after lumpectomy alone in a group of highly selected patients considered to be at low risk of recurrence. The DCIS score was found to be an independent predictor of both invasive and noninvasive recurrences in this population.[61] Rakovitch et al confirmed the prognostic utility of the Oncotype DCIS score in patients from the Ontario population-based DCIS cohort study, demonstrating that patients with high-risk score benefited from adjuvant radiation therapy more than those with low risk score.[62,63] Because the Oncotype DCIS score was developed on a dataset of

patients treated without radiation therapy, it is strictly a prognostic tool, which when paired with clinical factors, can help identify a woman at an acceptably low risk of 10-year local recurrence, for whom both patient and clinician may feel omission of radiation therapy is acceptable. This tool does not provide predictive information regarding the relative benefit of radiation therapy. A recent study has revealed that the Oncotype DX RS can predict breast cancer mortality in DCIS when assessed in patients ≤50.[64] For women with a high RS, treatment with radiation therapy was associated with a 71% relative and a 5% absolute reduction in the 20-year cumulative risk of death from BC thus identifying high-risk cohorts in which breast radiation therapy should not be withheld.

The DCISionRT score (PreludeDx, Laguna Hills, CA) builds upon this model, and is both a prognostic and predictive tool, similar to Oncotype in invasive breast cancer. In one study by Bremer et al, it was associated independently with both invasive and noninvasive in-breast recurrences (prognostic). An interaction analysis between the risk score and radiation therapy reached significance, suggestive of a treatment-predictive effect.[65] Although nearly every randomized trial has demonstrated a ~50% relative reduction in local control with radiation therapy for DCIS, DCISionRT discriminated between low and high-risk groups which derived small (HR = 0.7) and large (0.3) relative benefit from radiation therapy, respectively. In a later study, Weinmann et al validated these findings in an external cohort, demonstrating that DCISionRT is independently associated with the risk for any recurrence, but was underpowered to test the interaction between the risk score and radiation therapy.[66]

As summarized here, gene expression classifiers have consistently demonstrated the ability to outperform traditional clinicopathologic methods of risk assessment and treatment selection. Despite this, no radiation-specific biomarker has formed the primary basis for a prospective clinical trial as of this writing. This may be due to varying generalizability in external cohorts, possibly due to technical differences in sample quality, method of gene expression assessment, tissue processing or storage techniques, and cohort composition. For example, models trained in populations that were selected to have an artificially high rate of local recurrence may generalize poorly to more clinically representative populations. Furthermore, the performance of RSI, RSS, and SSP may vary by HR status and biologic subtype, highlighting the importance of clearly defining the most appropriate populations for additional study.[38,49,53] The ARTIC score is the first example of a radiation therapy-specific biomarker that successfully translated into the context of patients treated on a randomized trial, a necessary step toward incorporation into the framework for development of biomarker-based radiation trials.

An additional consideration in the development of genomic radiosensitivity classifiers is that the focus to date has been on the development of predictive biomarkers, in which patients are placed into discrete, often dichotomous groups based on an optimal cutpoint to discriminate between patients who should or should not receive radiation therapy. Although this approach simplifies statistical analyses and provides a conceptual framework to study the clinical utility of a given biomarker, it results in significant loss of biological information, may reduce statistical power, and can lead to significant confounding and measurement biases.[67-69] The continuous spectrum of underlying tumor biology and radiosensitivity is diminished when patients are dichotomized with this approach. Similarly, the clinical paradigm used with this approach is for treatment with or without radiation therapy, which neglects that a spectrum of dose may be appropriate to match the corresponding spectrum of radiosensitivity. RSI and GARD are unique exceptions, but prospective trials have not yet tested its ability to determine radiation therapy dose ranges for specific tumors and scores. Therefore, evaluation of biomarkers on a continuous spectrum and association with radiation therapy dose effect should be a central focus in future studies of personalized breast radiation therapy. Additionally, it should be recognized that the sample sizes required to prospectively test hypotheses using biomarkers on a continuous spectrum may be large, which may necessitate support in multi-institutional or cooperative group settings.

Ongoing Clinical Trials Incorporating Biological Parameters

Although previous randomized trials have failed to identify a group of women at such low clinical risk that they do not benefit from adjuvant whole breast radiation therapy,[8,9,70,71] integration with genomic biomarkers may reveal a group in whom adjuvant hormone therapy alone may be sufficient to prevent the majority of local recurrences after breast conserving surgery.[31,72,73] Thus, several clinical trials are currently ongoing which omit postlumpectomy radiation therapy in patients with low clinical and low genomic risk. These ongoing trials are summarized in Table 2.

The University of Michigan initiated the multi-institutional IDEA trial (NCT02400190), in which women aged 50 to 69 with stage I, ER+, PR+, HER2− breast cancer and Oncotype DX RS of ≤18 will receive adjuvant hormone therapy alone after lumpectomy. Similarly, the Dana Farber Cancer Institute initiated the PRECISION trial (NCT02653755), in which women age 50 to 75 with ER+ or PR+ and HER2- tumors ≤2 cm and low risk PAM-50 score will receive hormone therapy alone after lumpectomy. Patients who elect to undergo radiation therapy independent of the PAM50 score are also

Table 2 Summary of Ongoing De-escalation Breast Radiation therapy Trials

Trial name	NCT identifier	Sponsor	Trial design	Inclusion criteria	Standard of care arm	Experimental arm	Primary endpoint
IDEA (Individualized Decisions for Hormone therapy Alone)	NCT02400190	University of Michigan Rogel Cancer Institute	Single arm phase 2	Postmenopausal with pT1N0, ER +/PR +/HER2−, Oncotype Dx ≤18	N/A	Hormone therapy alone without radiation therapy after BCS	5-y locoregional recurrence
LUMINA (A Prospective Cohort Study Evaluating Risk of Local Recurrence Following Breast Conserving Surgery and Hormone therapy in Low Risk Luminal A Breast Cancer)	NCT01791829	Ontario Clinical Oncology Group	Single arm phase 2	Age ≥55, ER+/PR +/HER2−, Luminal A subtype	N/A	Hormone therapy alone without radiation therapy after BCS	5-y ipsilateral breast tumor recurrence
PRECISION (Profiling Early Breast Cancer for Radiation therapy Omission)	NCT02653755	Dana Farber Cancer Institute	Nonrandomized phase 2	Age 50-75, pT1N0, ER + or PR + and HER2−, grade 1-2	PAM50 intermediate or high-risk receive standard RT and hormone therapy	PAM50 low risk receive hormone therapy with omission of RT after BCS	5-y locoregional recurrence
TAILOR RT (Regional Radiation therapy in Biomarker Low Risk Node Positive Breast Cancer)	NCT03488693	Canadian Cancer Trials Group	Randomized phase 3	Age ≥40, pT1-2 with 1-3 + lymph nodes after BCS or mastectomy with, 1-2 + ALND lymph nodes after BCS with SLNB, or 1 + lymph node after mastectomy with SLNB, ER +/HER2−, Oncotype Dx ≤18	Whole breast irradiation with regional nodal irradiation after BCS, postmastectomy radiation to the chest wall and regional lymph nodes after mastectomy	Whole breast irradiation without regional lymph node irradiation after BCS, no postmastectomy radiation after mastectomy	9.5-y breast cancer recurrence free interval

Abbreviations: ALND = axillary lymph node dissection; BCS = breast conservation surgery; ER = estrogen receptor; NCT = national clinical trial identifier; PR = progesterone receptor; RT = radiation therapy; SLNB = sentinel lymph node biopsy.

followed on this trial. Both the IDEA and PRECISION trials have met their target accrual and have closed. The LUMINA trial (NCT01791829) is a single arm study of women age ≥55 with T1 luminal A tumors who will receive hormone therapy alone after lumpectomy. As these trials do not include an arm with radiation, the goal is to evaluate whether patients with low risk biology have sufficiently low absolute risk of local recurrence that they can be managed with hormone therapy alone.

The ongoing TAILOR RT trial (NCT03488693) is based on the previously described findings that patients with HR+, pN1 disease and low risk Oncotype DX RS have sufficiently low risk for recurrence that their axillary disease can effectively be managed with systemic therapy alone.[32,33] The trial includes patients with HR+, pN1 tumors treated either with breast conserving therapy or mastectomy with sentinel LN biopsy or axillary dissection. Patients who receive lumpectomy are randomized to whole breast radiation plus regional nodal irradiation versus whole breast radiation alone, and patients who receive mastectomy are randomized to chest wall and regional nodal irradiation versus no radiation. Thus, in keeping with these trials, TAILOR RT hypothesizes that there is a subset of tumors with indolent biology that may not benefit from adjuvant radiation, even among a limited LN+ HR+ cohort. It should be noted that TAILOR RT does not mandate the use of chemotherapy, and patients are allowed to receive hormone therapy alone. In the context of the previously discussed RxPONDER study, the result is that a postmenopausal patient with pN1 disease enrolled on the TAILOR RT trial could receive adjuvant hormone therapy alone without receiving chemotherapy or radiation therapy: a powerful illustration of how genomic risk stratification has altered the field of breast oncology.

Future Directions

Although the ongoing trials discussed represent an important step toward de-escalation of breast RT, one reasonable criticism against them is that they use an all or nothing approach to radiation therapy delivery. As discussed, this approach does not consider that even within specific breast cancer subgroups, there may exist a wide spectrum of radiosensitivity, where many patients could miss out on the opportunity to receive therapy that is tailored to their unique tumor biology. Furthermore, studies of radiation specific classifiers that have attempted to place patients into groups who do or do not benefit from adjuvant radiation, with the assumption that currently used radiation doses have already been optimized at the individual patient level.[38,39,49,53,57] Based on this assumption, these classifiers are unable to account for the spectrum of radiosensitivity that may exist even within low or high-risk subgroups. For example, in patients predicted to be at high risk of recurrence despite adjuvant radiation and thus requiring treatment intensification, the classifiers are unable to specify how many additional Gy would be needed to overcome the intrinsic radioresistance of those tumors, or which tumors may be so resistant that delivery of sufficient dose would not be feasible and thus alternative methods of treatment intensification would be needed. Similarly, tumors classified as radiosensitive and thus benefiting from radiation therapy may still be overtreated with standard doses of radiation. We propose that in addition to classifiers that identify patients who benefit from radiation therapy, novel strategies are needed to predict the radiation therapy doses needed to achieve optimal clinical outcomes for individual patients.

Although it is clear there is a rich body of evidence supporting the testing of genomic signatures in adjuvant breast cancer management, identifying the challenges and potential solutions to clinical trial implementation is essential. Genomic signatures have shown clear potential utility in the setting of radiation therapy decision making and are primed for clinical validation. Efforts in the radiation oncology community to deliver genomically guided radiation therapy will need to be developed in collaboration with our colleagues in breast surgical and medical oncology. The delivery of neoadjuvant systemic therapy is becoming increasingly common in the management of high-risk breast cancer patients.[74,75] Given the number of signatures which have been developed using tissue unexposed to neoadjuvant therapy,[35,36,38,39,49,53,54,57] trials may require pretreatment tissue biopsies before receipt of neoadjuvant therapy. This may require consultation and discussion of adjuvant radiation therapy at initial diagnosis and collaboration with colleagues to ensure patients are not enrolled in competing trials or to optimize clinical trial design to incorporate both a systemic therapy and radiation therapy hypothesis. Moving forward it will also be critically important to determine how genomic signatures such as RSI, the RSS, and Oncotype DX among others are affected by receipt of neoadjuvant therapy to reflect this evolving treatment paradigm. Current efforts to determine the value of preoperative radiation therapy may also be key in validating genomic signatures for radiation therapy. Similarly, collaboration with surgical oncologists will remain important, as breast cancer management is also trending toward less aggressive surgical management, evidenced by the ongoing ALLIANCE A011202 trial (NCT01901094), which randomizes clinically lymph node positive patients who do not achieve a complete pathologic response on sentinel lymph biopsy after neoadjuvant chemotherapy to completion axillary dissection versus axillary radiation alone. In the theoretical example of a clinically node-positive patient with residual disease on sentinel lymph node biopsy after neoadjuvant chemotherapy, omission of axillary radiation on the basis of favorable genomic risk could result in suboptimal outcomes. Therefore, in the era of increasing use of neoadjuvant systemic therapy and de-escalation of surgical management,

the extent of potential residual disease should be accounted for when attempting to stratify radiation therapy based on tumor biology in this population.

In addition, to move these signatures forward will require collaborative efforts between institutions and cooperative groups. Given the collective strength of cooperative groups as well as the clearly rich history of landmark breast cancer trials run through these groups, this serves as an obvious platform to elevate genomic biomarkers to the forefront of clinical trial evaluation. In addition to using cooperative groups for prospective evaluation, improved collaboration across institutions will be key. Examples of successful research consortia across institutions include the Oncology Research Information Exchange Network[76] and the Radiogenomics Consortium.[77] Given the scarcity of tumor tissue linked to clinical outcomes and the unique expertise needed to conduct such clinical trials the importance of institutional collaborations is obvious. These cooperative groups and research consortia not only serve as a rich source of data and expertise but also as a potential source of research funding. Leveraging the strength of these networks is critical to allocate funds for this important area of research in which radiation therapy trials are significantly underfunded.[78] Breast radiation therapy is a uniquely poised disease site to take advantage of the strength of research consortia given the relative abundance of data and genomic signatures to support the use of prospective validation. These trials may lay the foundation for other disease sites to follow in the radiation oncology community for the study of genomically guided RT.

Conclusions

Available data suggests that there is a spectrum of tumor biology within breast cancer which can be measured and translated into actionable metrics to guide treatment. To an extent, this spectrum has become a part of the routine treatment paradigm in the systemic management of breast cancer with prospective data validating the use of the Oncotype DX and Mammaprint 70 Gene Signatures. Radiation oncology has trailed behind the medical oncology community with adoption of gene signatures into routine clinical practice. Given the number of ongoing trials that exclude radiation for low-risk patient populations and trials altering RT dose and fractionation schedules, the breast radiation oncology landscape is ideally poised to prospectively assess the use of genomic tools for informed decision making.

We assert that rather than using a one-size-fits all approach, the continuous spectrum of tumor biology should ideally be matched with a corresponding spectrum of radiation dose prescription, allowing radiation oncologists to maximize clinical efficacy and simultaneously minimizing unnecessary treatment. Using the collective strength of cooperative groups and research consortia will be critical to assessing current data in the prospective setting.

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