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Validation of a multi-omic biosignature to predict locoregional recurrence risk and the benefit of adjuvant radiation therapy in women with early-stage invasive breast cancer treated with breast-conserving surgery and endocrine therapy

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Background

- Randomized clinical trials demonstrate that radiotherapy (RT) after breast conserving surgery (BCS) significantly reduces the risk of invasive loco-regional recurrences (LRR) in women with early-stage hormone receptor positive (HR+) HER2 negative (HER2–) invasive breast cancer (IBC).
- However, several RT de-escalation trials have demonstrated that certain patients, particularly those with favorable clinicopathologic features, may safely omit RT without compromising survival outcomes. These findings highlight the heterogeneity of RT benefit across HR+ HER2– IBC populations.
- A Multi-Omic test combining next generation sequencing, multiplex proteomics, and spatial biology was previously developed and cross-validated to predict invasive LRR risk and RT benefit in HR+ HER2– early-stage IBC (n=922).
- In this independent analysis, we evaluated the performance of this previously validated test in a retrospective non-randomized cohort of HR+ HER2– IBC patients identified at the Royal Melbourne Hospital (RMH), Australia.

Methods

- Women with HR+HER2– T1/2N0/XM0 invasive breast cancer (IBC) identified at the Royal Melbourne Hospital (RMH) with definitive breast-conserving surgery (BCS) between 2006–2017 were included (n=426). Patients received adjuvant therapy consisting of ±RT, ±endocrine therapy (ET), and ±chemotherapy (CT) according to institutional standards.
- Treatment and outcome data were collected by RMH and transferred to an independent third-party biostatistics group (MCG, Australia). Following central pathology review at RMH, FFPE tumor samples were sent to a CLIA-certified laboratory (Laguna Hills, CA) for biomarker analysis.
- RNA expression was measured using targeted next generation sequencing and protein expression was quantified by multiplex immunofluorescence. All assays were performed blinded to treatment and outcome. The test integrates Multi-Omic assay data to derive two biosignatures: Decision Score (DS) predicts overall risk of locoregional recurrence (LRR) and Radio-Resistance Index (RRI): predicts individualized benefit from RT.
- Test results were transferred to and independently analyzed by MCG to validate the test using a pre-specified analysis plan.

Results

- Complete biomarker and clinical information were available in 426 women treated with ET of whom 319 patients received RT. (Table 1)
- The study demonstrated that the test was prognostic for LRR risk, where increasing continuous DS was associated with higher invasive LRR risk (LRR HR=2.4 per 5 units, p<.001) adjusted for clinicopathologic risk factors and treatment. (Figure 1)
- The test was also predictive for RT benefit. Overall, patients substantially benefited from RT (HR=0.1, p<.001) but RT treated patients with higher RRI had higher LRR risk (HR=6.0 per 5 units, RRI:RT interaction p<.001) adjusted for clinicopathologic risk factors and treatment. (Figure 1)

- The assay identified patients treated without radiotherapy (RT) with low 10-year locoregional recurrence risk (LRR) who had no to minimal benefit from RT.
- The assay identified patients with elevated 10-year LRR risk who had significant therapeutic benefit (STB) from RT, and others who had minimal therapeutic benefit (MTB) from RT.
- This independent validation confirmed the results reported in a prior validation.

Figure 1. Multivariable analysis of CP factors and adjuvant treatment in patients treated with BCS

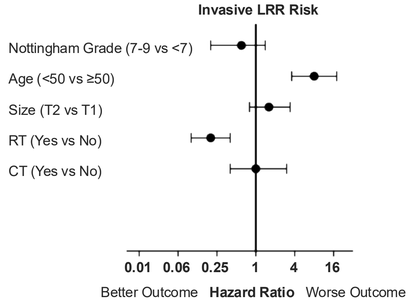


Figure 2. Multivariable analysis of biosignature, adjusted for CP factors and adjuvant treatment in patients treated with BCS

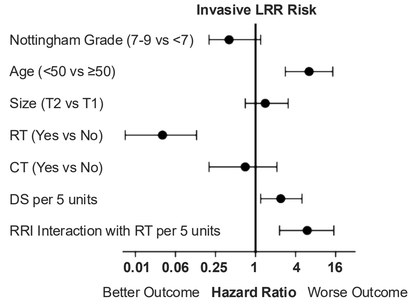


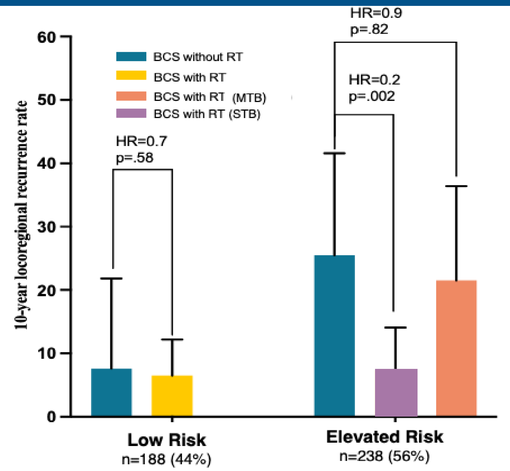
Table 1: Clinicopathologic feature distribution by RT treatment for all eligible patients

	All Patients	No RT after BCS; n(%)	RT after BCS; n (%)
All Patients	426	107 (25%)	319 (75%)
Age			
<50 years	63 (15%)	0 (0.0%)	63 (20%)
≥50 years	363 (85%)	107 (100%)	256 (80%)
Tumor Grade			
<7	333 (78%)	85 (80%)	248 (78%)
7 to 9	93 (22%)	22 (20%)	71 (22%)
Tumor Size			
T1	350 (82%)	101 (94%)	249 (78%)
T2	76 (18%)	6 (6%)	70 (22%)
RT Boost			
No	183 (46%)	107 (100%)	76 (26%)
Yes	213 (54%)	0 (0%)	213 (74%)
Chemotherapy			
No	373 (88%)	107 (100%)	266 (83%)
Yes	53 (12%)	0 (0%)	53 (17%)

Results (*continued*)

- In a categorical analysis, RT had no significant association with LRR (HR=0.7, p=.58) in a Low Risk group (DS≤5, n=188), where mean 10-yr LRR was 8% without RT and 7% with RT. (Figure 3)
- The mean 10-year LRR was 26% without RT in the Elevated Risk group (DS>5, n=238). Among these patients, those with RRI≤5 had significant therapeutic benefit (STB) from radiotherapy (HR=0.2, p=0.001), with an 18% absolute reduction in 10-year LRR risk. (Figure 3)
- In contrast, patients with RRI>5 had minimal therapeutic benefit (MTB) from RT (HR=0.9, p=0.8), and their 10-year LRR risk remained 22% despite RT. (Figure 3)

Figure 3. Comparison of 10-yr local regional risk (LRR) by categorical biosignature risk groups (No RT versus RT ± boost)



Conclusions

- In this external, independent validation, the Multi-Omic test reliably stratified women with early-stage HR+ HER2– IBC into clinically meaningful low and elevated risk groups.
- The test identified patients with low 10-year LRR risk who derived no significant benefit from RT, as well as elevated-risk groups, one with significant therapeutic benefit from RT and another with minimal therapeutic benefit from RT.
- This prognostic and predictive test may help to prevent over- and under-treatment with RT.

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