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Title: A Novel Biosignature to Predict Radiation Therapy Response in Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Surgery

Background: Radiation therapy (RT) is a standard component of treatment for most patients with early-stage, hormone receptor-positive, invasive breast cancer (BC) following breast-conserving surgery (BCS). RT recommendations are primarily based on clinicopathologic (CP) factors, such as tumor size, nodal status, and histological grade. While these factors provide prognostic information, their ability to accurately identify patients at a higher risk of ipsilateral breast recurrence (IBR) or those who will significantly benefit from RT is unclear. Therefore, incorporation of additional predictive markers beyond CP factors is warranted and there remains a need to refine the selection criteria for patients who will derive the greatest benefit from RT. In this study, we aimed to explore the role of immune and metabolic signaling axes as potential predictive markers for RT response in hormone receptor-positive breast cancer patients.

Methods: A cohort of 939 women from Sweden were diagnosed with BC between 1987 and 2004. A subset of 471 patients was diagnosed with T1-T2N0M0 BC and underwent BCS with negative margins. Patients were treated with BCS plus/minus RT (median dose 50Gy) based upon physician preference. Biomarkers were assayed in formalin-fixed paraffin-embedded tissue micro arrays using multiplex immunofluorescence and multi-spectral imaging in a CLIA lab (Laguna Hills, CA). Immune and metabolic axes were defined employing biomarkers and used to classify patients into three risk groups: 1) Low Risk (lower baseline risk and no RT benefit), 2) Elevated Risk (higher baseline risk and significant RT benefit), and 3) Residual Risk (higher baseline risk and suboptimal RT benefit). Risk groups were analyzed for IBR rate using Kaplan-Meier and Cox proportional hazards analyses. Risk group prognosis and RT prediction was assessed for RT-risk group interaction in multivariable analysis, adjusting for CP factors.

Results: Among the patients with complete biomarker data, 261 were hormone receptor-positive, and had a median follow-up of 140 months. Median age was 62 years (28-88 years), and median tumor size was 1.1 cm (0.1-4 cm). Some patients (21%) received endocrine therapy (ET), and most (76%) received RT, with 79% of patients who received ET also receiving RT. In the overall population, RT following BCS was associated with a reduction in HR for recurrence (HR=0.3, 95%CI [0.1, 0.5], p< 0.001). Patients classified as Low Risk (41%) did not have a significant benefit from RT (HR=0.9, 95%CI [0.1, 8.3], p=0.95) in multivariable analysis adjusted for CP factors. For patients who were classified as Elevated Risk (31%), multivariable analysis showed a higher IBR rate without RT (HR=5.7, 95%CI [1.3, 25.1], p< 0.021) relative to the Low Risk group who had a significant benefit from RT (HR=0.1, 95%CI [0.02, 0.2], p< 0.001). Patients classified into the Residual Risk group (28%) had no significant reduction from RT (HR=0.7, 95%CI [0.2, 2.0], p=0.61). However, in multivariable analysis adjusted for CP factors, patients treated with RT in the Residual Risk group had higher IBR rates (HR=3.7, 95%CI [1.6, 8.7], p=0.0026) compared to RT-treated patients in other risk groups. The biosignature was predictive for RT benefit in multivariable analysis adjusted for CP factors (p-interaction < 0.001).

Conclusion: The biosignature used in this study demonstrated the potential to identify patients who may derive limited benefit from RT, allowing for tailored therapeutic approaches. These findings underscore the importance of individualized treatment decisions based on risk stratification. Further clinical validation and refinement of risk stratification strategies are warranted to optimize outcomes in hormone receptor-positive, BC patients undergoing BCS.

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