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Title: A Biosignature Integrating Immune and Metabolic Signaling Axes To Assess Limited Radiation Therapy Response in Early Stage Breast Cancer From a Low-Risk Cohort

Background: Radiation therapy (RT) post breast-conserving surgery (BCS) reduces in-breast recurrence (IBR) rate in early-stage invasive breast cancer (BC) patients. RT treatment recommendation is often driven by clinicopathological (CP) factors; however, CP factors alone have limited ability to identify which women significantly benefit from RT, or those with higher IBR risk after BCS plus RT. Biologic factors driving unique phenotypes, in addition to CP, may improve the prediction of RT response. In this study, we evaluated the role of immune and metabolic signaling axes in predicting RT response in hormone receptor-positive, HER2-negative, early-stage BC patients.

Material and Methods: Biomarkers from immune and metabolic signaling axes were studied in a cohort of 939 women from Sweden, at a CLIA certified lab (Laguna Hills, CA). Formalin fixed paraffin embedded tissues were assayed for protein expression using multiplex immunofluorescence and multi-spectral imaging. Immune and metabolic axes were assessed using biomarkers combined with a non-linear model, adjusting for patient age. RT prediction by the model was assessed along and adjusted for CP factors and also among patients over 50 years. The model defined patient risk groups that were analyzed for IBR rate using Kaplan Meier analyses and Cox proportional hazards to test for RT-risk group interaction.

Results: Within the cohort, 440 patients had hormone receptor-positive, HER2-negative BC treated with BCS (negative margins) and +/- RT without chemotherapy, where 296 patients had complete biomarker data. CP factors individually were not predictive for RT benefit, but grade was prognostic for IBR rate (p=0.02) after BCS without RT. In multivariable analysis, adjusting for CP factors (grade, palpability, continuous size, and age), the model was predictive for RT benefit (p-interaction = 0.046), identifying patients (n=129) with worse RT benefit (HR=7.8) compared to baseline RT benefit. The model was not prognostic for IBR rate in patients treated with BCS without RT (16% 10-yr IBR rate) but identified patients with increased IBR rates after BCS plus RT (HR=3.9, p<0.001), where corresponding 10-yr IBR rates increased from 3% to 15%. The model was also predictive for RT benefit in women over 50 years (p-interaction=0.05). The model identified 28% of women over 50 years who had increased IBR rates after BCS plus RT (HR=4.0, p=0.004), where corresponding 10-yr IBR rates increased from 3% to 12%.

Conclusion: The model incorporating metabolic and immune signaling axes assessed in the study was predictive for RT benefit among women with early-stage hormone receptor-positive, HER2-negative BC. While CP factors were not predictive of RT benefit, the inclusion of metabolic and immune signaling axes improved identification of patients with high residual risk after BCS plus RT and can potentially aid in personalized treatment of early-stage breast cancer based on individualized risk.

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