Guiding de-escalation of treatment for patients with DCIS using a predictive 7-gene biosignature: Identification of a clinically low-risk patient group

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BACKGROUND: NCCN treatment guidelines support de-escalation of radiotherapy (RT) for "low risk" patients with ductal carcinoma in situ (DCIS) treated with breast conserving surgery (BCS) for which improved specificity in identifying patients with low in-breast recurrence (IBR) rates who are unlikely to benefit from RT is needed. "low risk" has been defined as the absence of "high risk" clinicopathological (CP) factors, which include younger age (<50 yrs) or tumors that are 2 cm or larger, palpable, or high nuclear grade. However, these CP factors have failed to identify a patient group with lower recurrence risk that do not clinically benefit from RT after BCS. Thus, the clinical utility of a Low Risk group identified by the predictive 7-gene biosignature was characterized overall and for patient subsets meeting "low risk" or "high risk" CP criteria.

METHODS: DCIS patients (n=926) from four international cohorts treated with BCS (negative margins) with (n=641) and without RT (n=335) were evaluated for CP criteria (age<50 or grade 3, and RTOG 9804 like) and clinical outcomes. Formalin-fixed paraffin-embedded tissue samples for each patient were analyzed at a CLIA lab (PreludeDx, Laguna Hills, CA) for the predictive 7-gene biosignature with a Residual Risk subtype (RRt). The biosignature reported a decision score (DS) of 0-10 and presence/absence of the RRt subtype. A Low Risk group (DS≤2.8 without RRt) was compared with the combined Elevated Risk (DS>2.8 without RRt) and Residual Risk groups (DS>2.8 with RRt), where 10-yr total IBR rates were evaluated using Cox Proportional Hazards and Kaplan Meier analysis by treatment, biosignature Risk group, and CP criteria.

RESULTS: The biosignature classified 37% of women treated with BCS as Low Risk (n=338) and 63% (n=588) were classified into the combined Elevated/Residual Risk group. Among patients who did not receive RT, those in the Elevated/Residual Risk group had higher IBR rates (p<.001) than those in the Low Risk group, with corresponding 10-yr IBR rates of 25.7% (95% CI: 18.8%, 34.4%) vs 5.6% (95% CI: 2.5%, 12.1%), respectively. RT did not reduce the IBR rate in the Low Risk group (p=0.71), where the 10-yr IBR rate was 4.8% (95% CI: 2.5%, 9.1%) after RT, corresponding to a number needed to treat (NNT) of ~100. However, the Elevated/Residual Risk group benefited from RT (p<0.001), with a 17.7% (95% CI: 9.4%, 26%) absolute 10-year IBR rate reduction, corresponding to a NNT of 6. The biosignature reclassified 35-40% of patients with "high risk" CP criteria into the Low Risk group. IBR rates in the Low Risk group for patients with "high risk" CP were not significantly different than those with "low risk" CP criteria.

CONCLUSION: The 7-gene biosignature was a better predictor of prognosis and RT benefit than standard CP risk stratification, identifying a low risk group with no significant benefit from RT. The 10-yr IBR rate with or without RT remained consistent in the biosignature Low Risk group independent of CP criteria, further supporting identification of a true low risk group who may forgo RT.