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Title: A DCIS biosignature with a novel residual risk subtype identifies patients with varying risk and RT benefit among younger and high grade DCIS patients

Background: High nuclear grade and young age (<50 years) are two clinicopathologic factors commonly used to make treatment decisions in patients with DCIS. However, randomized studies have failed to identify low-risk patients who did not benefit from radiation therapy (RT) after breast-conserving surgery (BCS) and those at elevated-risk despite RT, potentially leading to over- or under-treatment of DCIS. Here we validated DCISionRT and our novel integrated residual risk subtype (RRt) biosignature (PreludeDx, Laguna Hills, CA) to assess 10-year risk of ipsilateral breast recurrences (IBR) in patients with grade 3 disease and/or young age (<50 years) treated with definitive BCS with or without RT.

Methods: The integrated DCISionRT+RRt biosignature was evaluated in women diagnosed with DCIS (no microinvasive disease) from 4 multinational cohorts: Uppsala University Hospital, Sweden (1986-2004), University of Massachusetts, Worcester, MA (1999-2008), Kaiser Permanente Northwest, Portland, OR (1990-2007), and Royal Melbourne Hospital, Australia (2006-2011). Patients were treated with BCS with and without RT. A central pathology review and biosignature testing was performed on formalin-fixed paraffin embedded tissue at a CLIA-certified lab (Laguna Hills, CA). The biosignature reported a “decision score” (DS+) and RRt status. Individual patient outcome and biosignature results were analyzed independently (McCloud Consulting). The clinical utility of the integrated biosignature was assessed in three groups of patients: a) Low Risk (DS+≤2.8), b) Elevated Risk (DS+>2.8 without RRt) and c) Residual Risk (RR) (DS+>2.8 with RRt).

Results: Of 926 patients, 471 were either grade 3 and/or young (<50 years) and were the focus of this analysis. For this subgroup, the integrated biosignature classified patients into Low Risk (n=150, 32%), Elevated Risk (n=165, 35%), and Residual Risk (n=156, 33%) groups, Table 1. The 10-year total IBR risk for women in the Low Risk group without RT (all Grade 3 and/or <50 years) was only 2.2% and there was no significant improvement with adjuvant RT (D=-0.8%, p=0.334). In contrast, the Elevated Risk group had elevated 10-yearIBR risk (27.6%) and benefited significantly from RT (D=23.80%, p<0.001). Both the Elevated Risk and the Residual Risk groups benefited significantly from RT (p<0.001), but there was higher IBR risk after RT in the Residual Risk group (13.2% vs. 3.8, p=0.01).

Results: The integrated biosignature demonstrated prognostic and predictive RT response among women with grade3 disease and/or young age (<50) and reclassified them into three distinct groups: (1) Low Risk with a 10-year total IBR risk of only 2.2% with BCS alone with no significant RT benefit; (2) Elevated Risk with a 10-year IBR risk of 27.6% without RT, reduced to 3.8% with RT; and (3) Residual Risk with the highest risk without RT and elevated residual 10-year risk of 13.2% after RT. When using grade or age alone, one-third of patients were over treated with RT. These findings are consistent with the results from the whole cohort analysis (n=926), illustrating that neither high-grade DCIS nor young age were significant risk factors after accounting for biosignature results.

Table 1. 10-Year IBR Rates in Patients Treated with BCS with and without Adjuvant RT

	Grade 3 and/or Age Under 50 n=471			All Patients n=926		
	Low Risk Group DS+ ≤ 2.8	**Elevated Risk Group** DS+ > 2.8 without RRt	**Residual Risk Group** DS+ > 2.8 with RRt	**Low Risk Group** DS+ ≤ 2.8	**Elevated Risk Group** DS+ > 2.8 without RRt	**Residual Risk Group** DS+ > 2.8 with RRt
Number of Patients	150	165	156	342	395	189
% Nuclear Grade 3	51%	74%	93%	22%	31%	77%
% Age <50	59%	45%	31%	26%	19%	26%
No Radiation	2.2% (0.3-14.5%)	27.6% (16.6-43.8%)	55.1% (33.5-79.2%)	4.8% (2.0-11.4%)	21.0% (14.2-30.4%)	52.1% (33.2-73.9%)
Radiation	3.0% (1.0-9.0%)	3.8% (1.4-9.8%)	13.2% (7.7-22.1%)	4.7% (2.5-9.0%)	5.0% (2.9-8.7%)	13.7% (8.3-22.2%)
Absolute Risk Reduction	-0.8% (-6.2-4.6%)	23.8% (9.9-37.8%)	41.9% (17.6-66.2%)	0.1% (-5.0-5.2%)	16.0% (7.6-24.4%)	38.4% (17.1-59.7%)
p-value	0.33	<0.001	<0.001	0.78	<0.001	<0.001

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