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Title: A multi-marker test for invasive risk post DCIS treated with BCS +/- RT

Background: Breast ductal carcinoma in situ (DCIS) is a heterogeneous disease associated with a spectrum of ipsilateral breast event (IBE) risk, but has excellent survival that appears to be independent of local treatment. Reducing overtreatment is an important unmet need for DCIS patients. Individualized patient treatment relies on limited clinical and pathologic information. 10-Year invasive recurrence risk (10yIRR) was assessed using Size and Grade identified by ECOG 9804 and a biomarker based risk assessment. The prognostic biomarker based risk assessment was developed using cross-validation modeling within two large patient cohorts treated with and without RT after BCS.

Material and Methods: Patients were from Uppsala University Hospital (UUH), diagnosed 1986 - 2004, and University of Massachusetts (UMass), diagnosed 1999 - 2008, treated with BCS with (56%) or without (44%) RT. Biomarkers (p16/INK4A, Ki-67, COX-2, PgR, HER2, FOXA1, SIAH2 via IHC/ISH) from FFPE tissue were assessed by board certified pathologists. Pathology and clinical data were collected from medical records.

The biomarker based risk assessment was developed, targeting 5% 10yIRR for the “low risk” group. Parameters and biomarker thresholds were determined by multiple cross-validation on the combined patient sets (n=600, 8.1 year median follow-up). Each partition divided patients into independent training and testing subsets. The consensus risk scores were generated on a continuous scale, and thresholds stratified them into two risk groups for statistical analysis. Elevated Size-Grade risk was defined as (Tumor Size >2.5 cm or Grade 3). 10yIRR by biomarker based assessment and Size-Grade risk groups were evaluated for patients with DCIS diagnosed by mammography and treated with definitive Breast Conserving Surgery (n=379) using Kaplan-Meier analysis and Cox proportional hazards analysis.

Results: Independent of the Size-Grade risk group, patients treated with RT had lower 10yIRR than those not treated with RT. However, 10yIRR was substantially lower for patients with low biomarker assessed risk ($p<.001$), but not low Size-Grade based risk. In patients with low biomarker assessed risks, 10yIRR were similar regardless of RT. Patients whose biomarker assessed risk were not low, and who had RT, had less than half the 10yIRR of those without RT.

Conclusions: The biomarker based risk stratification identified patients at risk for invasive IBEs in cross-validation. The biomarker based risk prognostic is being evaluated in multiple independent validation studies. Patients with low biomarker based risk had 10yIRR without RT that is low and similar to that with RT.

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10-YEAR IPSILATERAL RISK						
	BCS, No RT			BCS, RT		
	Risk±95% CI	Prevalence	N	Risk±95% CI	Prevalence	N
Baseline Invasive Risk	11%±5%	39%	150	6%±4%	56%	229
Size-Grade Signature ***"Low"***	**10%**±6%	66%	99	**4%**±5%	44%	102
Size-Grade Signature ***not "Low"***	**15%**±11%	34%	51	**7%**±5%	56%	127
Biomarker Assessment ***"Low"***	**5%**±5%	73%	110	**6%**±5%	73%	168
Biomarker Assessment ***not "Low"***	**28%**±13%	27%	40	**6%**±7%	27%	61

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