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Title: DCIS biological risk profile predicts risk of recurrence after breast conserving surgery in a Kaiser Permanente NW population

Background: Patients with DCIS and their physicians need tools that provide better information about the individual patient's biological risk profile to help make treatment decisions. Prelude and the Kaiser Permanente Northwest Center for Health Research (KPCHR) validated a biological risk signature based test to assess ipsilateral breast event (IBE) risk after breast conserving surgery (BCS) with radiation (+RT) or without radiation therapy (-RT).

Material and Methods: The Prelude DCIS test was independently validated in a retrospective cohort from the Kaiser Permanente Northwest (KPNW) integrated healthcare system in patients diagnosed with DCIS from 1990- 2007 and treated with BCS±RT(n=608). KPCHR performed central pathology review to identify patients meeting study eligibility criteria with formalin fixed paraffin embedded (FFPE) tissue samples (n=475); KPCHR also reviewed medical records to collect patient, treatment, and outcome data. FFPE patient samples were provided to Prelude for testing. REMARK guidelines were followed.

A panel of biomarkers (HER2, PR, Ki-67, COX2, p16/INK4A, FOXA1 and SIAH2) were assayed by the Prelude CLIA lab and scored by board-certified pathologists (n=455). Prelude's DCIS test was executed independently using biomarker and clinicopathologic data while blinded to patient outcome data. The risk results were provided to KPCHR under a Data Transfer Authority. KPCHR biostatisticians executed a predefined and co-developed statistical analysis plan. IBE rates were assessed using Kaplan-Meier survival analysis. Hazard ratios (HR) were determined using Cox proportional hazards analysis, with RT as a covariate.

Results: The Prelude DCIS test score was statistically associated with total IBE as a continuous linear variable (0-10 unit scale) on a per unit basis, HR of 1.12, 95% CI [1.03,1.23], p=0.01. The DCIS test score (0-10) corresponded to recurrence risks ranging from 10% to 42% (≤2, >7) for patients treated with BCS-RT and ranging from 4% to 11% (≤2, >7) for patients treated with BCS+RT. Patients treated with BCS ±RT with an elevated test score (≤3 vs >3) had a higher recurrence risk, n=455, HR=1.87 [1.03 - 3.38], p=0.04. In patients treated with BCS-RT in this sample, patients with a higher DCIS signature had an elevated recurrence risk, n=78, HR=2.37, 95% CI [0.82, 6.85], p=0.11. The 10-year contralateral breast event rate was 4%, 95% CI [2%, 6%]. Median follow-up time was 10.4 years.

Discussion: Patients diagnosed with DCIS and treated with BCS ±RT, were stratified into clinically relevant low and elevated risk groups (≤3 vs >3) in an independent validation of the Prelude DCIS test. Patients in the elevated risk group had substantially higher likelihood of 10-year total IBE. The number of patients treated with BCS -RT was limited and while the stratification by risk group for BCS -RT was in the expected direction, it did not reach statistical significance. Two additional validation studies are scheduled to be completed in 2016.

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10-YEAR IBE RISK						
	BCS –RT			BCS +RT		
	Risk, [95% CI]	Prevalence	N	Risk, [95% CI]	Prevalence	N
Baseline Total Risk	20%, [12%, 32%]	100%	78	8%, [5%, 11%]	100%	377
Low Risk Group (≤3)	**10% [3%, 29%]**	53%	41	**5%, [2%, 10%]**	40%	149
Elevated Risk Group (>3)	**30%, [17%, 51%]**	47%	37	**10%, [6%, 15%]**	60%	228

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