DCISionRT®

San Antonio Breast Cancer Symposium 2022

Title: 7-gene predictive biosignature improves risk stratification for breast ductal carcinoma in situ patients compared to clinicopathologic criteria, identifying a low risk group not clinically benefiting from adjuvant radiotherapy

Background: Prognostic and predictive tools are needed to optimize treatment for women diagnosed with ductal carcinoma in situ (DCIS). While radiotherapy (RT) is standard of care for DCIS after breast conserving surgery (BCS), those at low-risk for ipsilateral breast recurrence (IBR) risk may be treated without RT. Low-risk has been defined as the absence of high risk clinicopathologic (CP) factors, including larger (>2 cm), palpable, or high nuclear grade (NG) tumors, and younger age (< 50 yrs). However, prospective trials have failed to identify low risk patients (pts) who do not clinically benefit from RT after BCS (RTOG 9804). DCISionRT® (PreludeDxTM, CA) is a 7-gene predictive biosignature providing a validated score (DS) to assess the 10-yr IBR risk and RT benefit, using individual tumor biology and CP factors. This study assessed total 10-yr IBR rates, RT benefit, and number needed to treat (NNT) for risk groups defined by biosignature and CP criteria.

Methods: DCIS patients (n=926) from four international cohorts (median follow up 8.5 yrs, 1-3rd quartile 5.8 –10.2 yrs) treated with BCS (negative margins), with (n=641) and without RT (n=335), had formalin-fixed paraffin-embedded tissues analyzed at a CLIA lab (PreludeDx, Laguna Hills, CA) for DCISionRT with a Residual Risk subtype (RRt). A biosignature Low Risk group (DS≤2.8 without RRt) was contrasted to a High Risk group comprising Elevated Risk (DS>2.8 without RRt) and Residual Risk (DS>2.8 with RRt) groups. Low-risk CP groups were RTOG 9804-like (NG1-2, non-palpable, negative margins, screening detected) or (age >50 and NG 1-2). Total 10-yr IBR rates were evaluated using Cox Proportional Hazards and Kaplan Meier analysis by treatment, biosignature and CP risk groups. NNT was determined with 10-yr IBR rate differences with RT.

Results: The biosignature classified 37% (n=338) of women as Low Risk and 63% (n=588) as High Risk. Among women who did not receive RT, biosignature Low Risk pts had lower IBR than biosignature High Risk pts (5.6% vs. 25.7%, p<.001). About half of pts defined as CP low-risk by 9804-like (51%) or favorable Age/NG (58%) criteria were reclassified by the biosignature to High Risk. These pts had significant RT benefit: 9804-like group - HR 0.3, p=.007, absolute 10-yr IBR reduction of 12.7%, and for favorable Age/NG group - HR .34,p=0.012, absolute 10-yr IBR reduction of 11.2%. The corresponding NNTs were ~8-9. Overall, RT significantly reduced IBR for biosignature High Risk patients (p<.001, n=588), with an absolute 17.7% reduction and a NNT of ~6. For patients in CP high risk groups, 23% of not-9804-like and 31% of (age< 50 or NG 3) pts were reclassified as biosignature Low Risk. RT did not significantly reduce IBR in any Low Risk Biosignature group, including those in CP high-risk groups. IBR for not-9804-like group was 5.9% vs 3.0% without and with RT, p=.52, and for (age< 50 or NG 3) pts was 4.4% vs 3% without and with RT, p=.70. For CP low-risk and biosignature Low Risk groups, RT reduced IBR by 0%. Overall, RT did not significantly reduce IBR rate for biosignature Low Risk patients (p=.71, n=338), with a 0.8% absolute 10-yr IBR rate difference and a NNT of~100.

Conclusions: In a large multicenter population, DCISionRT was a better predictor of 10-yr prognosis and RT benefit than CP criteria alone. Pts with biosignature Low Risk disease, comprising about 1/3 of CP high-risk pts, had no significant RT benefit. Whereas pts with biosignature High Risk disease, comprising about 1/2 of CP low-risk pts, significantly benefited from RT, highlighting the lack of accuracy of these CP factors in assessing RT benefit.

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Table 1. Ten-Year Risk of Ipsilateral Breast Recurrence (IBR)

	Biosignature Low Risk group (DS≤2.8 without RRT)					Biosignature High Risk group Combined Elevated/Residual Risk, DS>2.8 without or with RRt)				
		10-year IBR risk					10-year IBR risk			
Clinical-Pathologic Groups	**n (%)**	**No RT (95%CI)**	**RT (95%CI)**	**HR (95%CI)**	**p**	**n (%)**	**No RT (95%CI)**	**RT (95%CI)**	**HR (95%CI)**	**p**
Overall	338 (37%)	5.6% (3, 12%)	4.8% (3, 9%)	0.8 (0.3, 2.3)	.71	588 (63%)	25.7% (14, 30%)	8.0% (3, 9%)	0.2 (0.1, 0.5)	<.001
RTOG 9804-like* 'good-risk' (low-risk)	232 (49%)	5.5% (2, 14%)	5.5% (3, 11%)	0.96 (0.3, 3.3)	.96	240 (51%)	19.5% (11, 34%)	6.8% (4, 13%)	0.3 (0.1, 0.7)	.007
Not RTOG 9804-like* (high-risk)	106 (23%)	5.9% (2, 22%)	3.0% (1, 12%)	0.5 (0.1, 3.8)	.52	348 (77%)	30.5% (21, 43%)	8.7% (6, 14%)	0.23 (0.1, 04)	<.001
Age ≥50 and Grade 1 or 2 (low-risk)	190 (42%)	6.3% (2, 16%)	6.3% (3, 14%)	0.9 (0.3, 3.0)	.88	263 (58%)	18.4% (11, 30%)	7.2% (4, 13%)	0.34 (0.2, 0.8)	.012
Age <50 or Grade 3 (high-risk)	148 (31%)	4.4% (1, 17%)	3.0% (1, 9%)	0.7 (0.1, 4.0)	.70	325 (69%)	34.3% (26, 48%)	8.5% (5, 14%)	0.2 (0.1, 0.4)	<.001
(*RTOG 9804-like criteria (Nuclear Grade 1 or 2, Non-Palpable, Screening Detected, Negative Margins)										

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