DCISionRT®

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Title: DCIS biosignature reclassified patients who met RTOG 9804 or ECOG-ACRIN E5194 'low-risk' clinicopathologic criteria into an elevated invasive risk group who benefited significantly from radiation therapy

Background: The goal of therapy for DCIS is to prevent invasive breast cancer. Randomized clinical trials for DCIS demonstrated that patients benefited from adjuvant radiation therapy (RT) after breast conserving surgery (BCS). However, treatment selection for patients with DCIS remains a challenge. Studies evaluating 'low-risk' clinicopathologic features have not identified a group of patients who do not benefit significantly from RT after BCS. Recently, a biosignature, DCISionRT (PreludeDx, Laguna Hills, CA), has been validated in multiple cohorts. The test provides a continuous 10-year breast event risk for patients treated with and without RT after BCS. In this study, we examined the utility of the biosignature to identify patients who met RTOG 9804 or ECOG 5194 'low-risk' criteria but remained at elevated invasive risk after BCS and benefited from RT.

Methods: The analysis was performed in a combined cohort made up of four studies. FFPE tissue samples and patient outcomes were obtained from Uppsala University Hospital and Västmanland County Hospital, Sweden (UUH) between 1986 and 2004, the University of Massachusetts, Worcester (UMass) from 1999 to 2008, from Kaiser Permanente Northwest (KPNW) from 1990-2007, and from the SweDCIS trial cohort (1987-2000). Patients were treated with or without RT after BCS. Treatment decisions were neither randomized nor strictly rules-based, except for the randomized SweDCIS trial for RT. Individual patient outcome and biosignature results were analyzed independently at University of South Florida. Hazard ratios (HR) were determined using Cox proportional hazards analyses, and 10-year risks were assessed with survival analysis.

Results: Complete biomarker and clinical data was available for 660 women meeting a 'low-risk' clinico-pathologic criteria like ECOG 5194 grade 1 or 2 and for 535 women meeting RTOG 9804 like criteria. In this subset, there were 49 invasive breast cancer events for ECOG 5194 and 38 for RTOG 9804 within 10 years of diagnosis. In the biosignature low risk group there was no significant reduction from RT ($p>0.15$), where the 10-year absolute invasive benefit from RT varied from 1% to 2% for patients meeting RTOG 9804 or ECOG 5194, Table 1. However, in the biosignature elevated risk group, RT significantly reduced invasive cancer risk ($p<.0022$) for RTOG9804 or ECOG 5194 Grade 1 or 2 criteria. The 10-year absolute invasive benefit from RT was 15% for RTOG 9804, 12% for ECOG 5194 Grade 1 and 2. This corresponded to a 10-year invasive relative risk reduction of 84% for RTOG 9804, 74% for ECOG 5194 Grade 1 or 2. The number needed to treat (NNT) in the biosignature low risk group was > 100 for RTOG 9804 like criteria, while the NNT was 7 in the biosignature elevated risk group.

Conclusions: The DCIS biosignature identified patients from four cohorts that met 'low-risk' clinicopathologic criteria like RTOG 9804 or ECOG 5194 grade 1 or 2, and had elevated 10-year risk after BCS but had a substantial 84% relative benefit from RT. In contrast, the biosignature also identified a low risk group of patients with who had minimal (1-2%) risk reduction from RT. In comparison with traditional clinicopathologic features used to make RT recommendations, the DCISionRT score was dramatically associated with RT therapy benefit.

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TABLE 1 – Biosignature low risk group (DS<=3)

	patients, n	events, n	10-year invasive risk difference, %	10-year Invasive Cancer Risk, %	
	+/- RT	+/- RT	no RT - RT	No RT	RT
RTOG9804	296	23	0.6	6.9	6.3
ECOG 5194 (Grade 1-2)	344	26	1.4	7.6	6.2

TABLE 2 – Biosignature elevated risk group (DS>3)

	patients, n	events, n	10-year invasive risk difference, %	10-year Invasive Cancer Risk, %	
	+/- RT	+/- RT	no RT - RT	No RT	RT
RTOG9804	239	15	15.0	17.9	2.9
ECOG 5194 (Grade 1-2)	316	23	11.8	15.9	4.2

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