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

Frank Vicini[1], Chirag Shah[2], Steven Shivers[3], Per Karlsson[4], Erik Holmberg[4] Michael C Leo[5], Sheila Weinmann[5], Fredrik Warnberg[6] and Troy Bremer[3]

[1]21st Century Oncology, Farmington Hills, MI; [2]Cleveland Clinic, Cleveland, OH; [3]PreludeDx, Laguna Hills, CA;

[4]University of Gothenburg, Gothenburg, Sweden; [5]Kaiser Permanente Northwest Center for Health Research, Portland, OR; [6]University of Gothenburg, Uppsala, Sweden

Background

- The goal of therapy for DCIS is to prevent local invasive breast cancer recurrences.
- 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 'good risk' clinico-pathologic features have not identified a group of patients who do not benefit significantly from RT after BCS with respect to local control.
- 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 'good 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 535 women meeting 'good risk' clinico-pathologic RTOG 9804-like criteria (negative margins vs wide margins) and for 660 women meeting ECOG E5194 grade 1 or 2 criteria. In this subset, there were 38 invasive breast cancer events within 10 years of diagnosis for RTOG 9804-like patients and 49 for patients meeting ECOG E5194 criteria.
- 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 criteria (See Table 2).
- However, in the biosignature Elevated Risk group, RT significantly reduced invasive cancer risk (p<.002) for patients with RTOG9804 (HR=0.16, 95%CI[0.05,0.47]) or ECOG 5194 Grade 1 or 2 criteria (HR=0.27, 95%CI[0.12,0.64]). This corresponds to a 10-year invasive relative risk reduction of 84% for RTOG 9804, 73% for ECOG 5194 Grade 1 or 2. The 10-year absolute invasive benefit from RT was 15% for RTOG 9804, 8% for ECOG E5194 Grade 1 and 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.

Outcomes in clinicopathological low-risk DCIS women after breast cancer surgery (BCS):

- DCISionRT Elevated Risk patients had substantial risk of 10-year invasive occurrence
- DS Elevated Risk patients (>3) had significant RT benefit (8-15% absolute difference)
- DS Low Risk patients (≤3) had minimal RT benefit (1-2% absolute difference)

Figure 1. Absolute Risk in 'Good' Risk Patients Reclassified by DCISionRT with and without RT

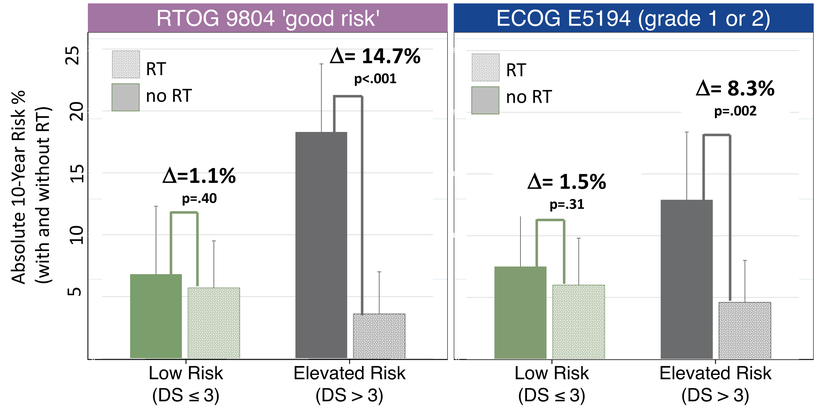

Table 1. Patient Clinicopathologic Characteristics and DS Group of 'Good Risk' Patients

	RTOG 9804		ECOG E5194 (grade 1 or 2)	
	Low Risk	Elevated Risk	Low Risk	Elevated Risk
Age				
50 or Under	84 (64%)	47 (36%)	106 (59%)	73 (41%)
Over 50	212 (52%)	192 (48%)	238 (49%)	243 (51%)
Size*				
≤ 10mm	218 (58%)	156 (42%)	246 (57%)	188 (43%)
10-25mm	60 (45%)	74 (55%)	78 (40%)	119 (60%)
Grade*				
Low	112 (58%)	81 (42%)	142 (55%)	116 (45%)
Intermediate	184 (54%)	156 (46%)	202 (51%)	197 (49%)
Radiation Therapy				
BCS alone	113 (60%)	76 (40%)	138 (56%)	109 (44%)
BCS + RT	183 (53%)	163 (47%)	206 (50%)	207 (50%)
Endocrine Therapy				
No ET	233 (55%)	188 (45%)	271 (52%)	253 (48%)
+ ET	63 (55%)	51 (45%)	73 (54%)	63 (46%)

* Size and/or grade was unkown for some patients.

Table 2. 10-Year Risk of Invasive Cancer in 'Good Risk' Patients

Criteria	Patients	Events	10-Year Invasive Cancer Risk		Absolute Risk Difference
Low Risk Biosignature (DS≤3)			No RT	RT	RT benefit
RTOG 9804	296	23	6.8% (0.6 – 12.3)	5.7% (1.3 – 9.5)	1.1%
ECOG E5194	344	26	7.5% (1.2 – 12.9)	6.0% (1.8 - 9.7)	1.5%
Elevated Risk Biosignature (DS>3)			No RT	RT	RT benefit
RTOG 9804	239	15	18.3% (1.0 – 30.0)	3.6% (0.0 – 7.0)	14.7%
ECOG E5194	316	23	12.9% (2.7 – 20.6)	4.6% (1.1 – 7.8)	8.3%

Conclusions

- The DCIS biosignature identified patients from four cohorts that met 'good 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.

1) Bremer, Clin Cancer Res Dec 2018; 2) Wärnberg, Cancer Res Feb 2018; 3) Weinman, Clin Cancer Res Aug 2020