A novel biosignature identifies DCIS patients with a poor biologic subtype with unacceptably high rates of local recurrence after breast conserving surgery and radiotherapy

Frank Vicini, MD[1]; Chirag Shah, MD [2]; Pat Whitworth, MD[3]; Steven C Shivers, PhD[4]; Fredrik Wärnberg , MD PhD[5]; G Bruce Mann, MD PhD[6]; Troy Bremer, PhD[4]

[1]NRG Oncology, and GenesisCare, Pontiac, MI; [2]Cleveland Clinic, Cleveland, OH; [3]Nashville Breast Center, Nashville, TN; [4]PreludeDx, Laguna Hills, CA;
[5]Dept of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden; [6]The Royal Melbourne and Royal Women's Hospital, Parkville, Australia

Background

- There is an unmet need to identify women diagnosed with DCIS who have a low recurrence risk and could omit radiotherapy (RT) after breast conserving surgery (BCS), or an elevated recurrence risk after treatment with BCS plus RT
- DCISionRT® and its response subtype (Rst) biosignature were evaluated in a contemporary cohort treated with BCS with or without RT to identify these risk groups.

Methods

- Pathology, clinical data, and FFPE tissue samples were evaluable for 485 women diagnosed with DCIS at centers in Sweden (1996-2004), the USA (1999-2008), and Australia (2006-2011)
- Patients were treated with BCS (negative margins) with or without whole breast RT. Ipsilateral breast tumor recurrence (IBTR) included DCIS or Invasive Breast Cancer (IBC) that was local, regional, or metastatic
- The patients were classified into Low and Elevated risk groups to assess IBTR and IBC rates
- Patients in the Elevated risk group were categorized by two subtypes: a good response subtype (good Rst) or a poor response subtype (poor Rst) after BCS plus RT
- Biosignatures were calculated using biomarkers (p16/INK4A, Ki-67, COX-2, PgR, HER2, FOXA1, SIAH2) assayed using IHC on FFPE tissue
- Hazard ratios and 10-year risks were calculated using Cox proportional hazards (CPH) and Kaplan-Meier analyses.

Results

- In the DCISionRT elevated risk group, RT was associated with significantly reduced recurrence rates, but only for those patients with a good Rst (Table 1, IBTR HR=0.18, p<0.001, IBC HR=0.15, p=0.003, n=241)
- For elevated risk group patients with a poor Rst, no benefit to RT was noted (Table 1)
- Irrespective of RT, patients with a poor Rst had 10-year IBTR/IBC rates of 25%/16%, which were much higher than good Rst rates of 6.6%/4.5% (IBE HR=3.6, p=0.02, IBC HR=4.4, p=0.04, n=190)
- For patients in the low-risk group, there was no significant difference in 10-year IBTR/IBC rates with and without RT (Table 1, IBTR p=0.4, IBC p=0.9, n=177)
- The distribution of clinicopathologic risk factors (age <50 years, grade 3, size >2.5 cm) did not identify poor vs. good response subtypes
- Multivariable analysis (n=485) indicated these traditional clinicopathologic factors and endocrine therapy were not significantly associated with IBTR (p≥0.22) or IBC (p≥0.34).

- A novel biologic subtype identified patients who had unacceptably high 10-year recurrence rates after standard breast conserving surgery and radiotherapy
- Patients were identified who had low 10-yr recurrence rates and may be candidates for omitting adjuvant RT

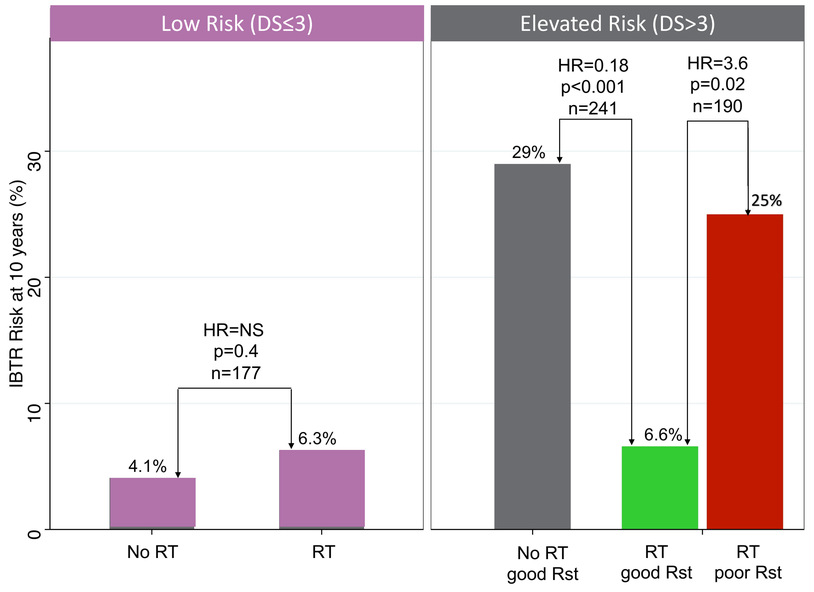

Table 1. 10-Year Rates of IBTR/IBC by Patient Groups

	Patients n	%10-year Rate IBTR/IBC
Low Risk Group (DS ≤ 3)		
BCS without RT	91	4.1 / 2.9
BCS plus RT	86	6.3 / 2.7
Elevated Risk Group (DS > 3)		
BCS without RT, all	118	29 / 18
BCS without RT, good Rst	100	29 / 19
BCS plus RT; good Rst	141	6.6 / 4.5
BCS plus RT; poor Rst	49	25 / 16

Table 2: Clinicopathology of Patient Groups

DS Risk Group	Elevated Risk (DS > 3)	
Treatment	BCS + RT	
Biosignature	Good Rst	Poor Rst
Age		
50 and under	39 (71%)	16 (29%)
Over 50	102 (76%)	33 (24%)
Size		
≤ 10 mm	51 (78%)	14 (22%)
> 10 mm	76 (71%)	31 (29%)
Grade		
Grade 1 or 2	67 (86%)	11 (14%)
Grade 3	67 (64%)	38 (36%)
Necrosis		
Absent	26 (87%)	4 (13%)
Present	87 (71%)	36 (29%)
Her-2 IHC		
0-2+	111 (100%)	0 (0%)
3+	30 (38%)	49 (62%)

Conclusions

- Biosignature identified a Low risk patient group with low 10-year recurrence rates with or without RT who may be candidates for omitting adjuvant RT
- Biosignature also identified an Elevated risk group receiving BCS plus RT with a poor response subtype (Rst) that had unacceptably high recurrence rates, warranting potential intensified or alternate therapy