Risk after local excision alone for DCIS patients: the importance of margin status

Rakovitch E,[1] Nofech-Mozes S,[1,2] Hanna W,[1] Baehner FL,[3,4] Saskin R,[5] Miller D,[3] Tuck A,[6] Sengupta S,[7] Elavathil L,[8] Jani PA,[9] Bonin M,[10] Chang MC,[3,11] Robertson S,[12] Slodkowska E,[1] Fong CH,[5] Anderson JA,[3] Cherbavaz DB,[3] Shak S,[3] Paszat L[1]

[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]Genomic Health, Inc., Redwood City, CA, United States; [4]University of California, San Francisco, San Francisco, CA, United States; [5]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [6]London Health Sciences Centre, London, ON, Canada; [7]Kingston General Hospital, Kingston, ON, Canada; [8]Henderson General Hospital, Hamilton, ON, Canada; [9]Thunder Bay Regional Health Sciences Centre, Thunder Bay, ON, Canada; [10]Northern Ontario School of Medicine, Thunder Bay, ON, Canada; [11]Health Sciences North Sudbury, Sudbury, ON, Canada; [12]Mount Sinai Hospital, Toronto, ON, Canada

Background

- DCIS is associated with high survival but treatment is recommended due to risk of recurrence (DCIS or invasive cancer).[1]
  - Many individuals will be treated by breast-conserving surgery (BCS), often followed by radiation.[2]
- Clinical and pathologic factors such as tumor size, nuclear grade and margin status are currently used to estimate local recurrence risk and guide treatment recommendations.
- These factors do not reliably identify individuals at low risk of recurrence after BCS.
- Biomarkers may improve risk assessment of individuals with DCIS treated by BCS.

Figure 1. Oncotype DX® DCIS Score™ Assay[3]

Proliferation Group	Hormone Receptor Group	Reference Group
Ki67	*PR*	*ACTB (β-actin)*
STK15		*GAPDH*
Survivin		*RPLPO*
CCNB1 (cyclin B1)		*GUS*
MYBL2	*GSTM1*	*TFRC*
Seven cancer-related genes		Five reference genes

- Multigene expression assay
- 12 of 21 genes from Oncotype DX Recurence Score assay
- DCIS Score Result:
  - Continuous score (0–100)
  - Three pre-specified risk groups:
    - Low <39
    - Intermediate 39–54
    - High ≥55
- Provides individualized estimates of the 10-year risk of local recurrence (LR) in patients with DCIS treated by BCS alone

- The DCIS Score assay was initially validated in a cohort of patients from the ECOG 5194 study who were selected for observation after surgical excision and provides individualized estimates of the 10-year risk of LR in patients with DCIS treated by BCS alone.[3]
- These results were recently validated in an established population-based cohort diagnosed with pure DCIS from 1994–2003, treated with BCS alone, and with clear resection margins (no ink on tumor).[4]
  - The DCIS Score result was shown to be significantly associated with LR in patients with clear margins.
  - The impact of the score as a predictor of LR in patients with positive/unknown resection margins remains unclear and is the focus of these analyses and presentation.

Present Study Objectives

Primary Objective

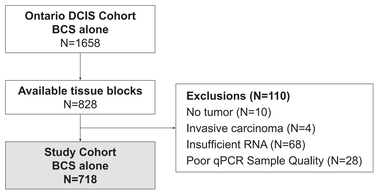
- To evaluate if the DCIS Score result is associated with the risk of **LR** (DCIS or invasive) in patients treated with **BCS alone**
  - In patients with positive / unknown resection margins
  - All patients regardless of margin status

Secondary Objectives

- To evaluate if the DCIS Score result is associated with the risk of **Invasive LR** and **DCIS LR**
  - In patients with positive / unknown resection margins
  - All patients regardless of margin status

Methods

Figure 2. Patient Population*



Central pathology review performed for all cases

Statistical Methods

- The primary outcome analyzed was local ipsilateral recurrence.
  - LR was defined as DCIS or invasive breast cancer in the same breast six months or more after diagnosis of DCIS.
- The secondary outcomes were invasive LR and DCIS LR.
- All subgroup analyses were pre-specified.
- Cox proportional hazards models were used to estimate univariable and multivariable hazard ratios.
- Kaplan-Meier (KM) estimates were used to evaluate 10-year risk of recurrence by DCIS risk group (log rank tests were used to compare risk groups).

Results

Table 1. Patient Characteristics

	Clear Margins (N=571)	Positive/unknown Margins (N=147)
Age ≥50 years	459 (81%)	118 (80%)
Nuclear Grade		
Low	55 (10%)	11 (7%)
Intermediate	332 (58%)	86 (59%)
High	184 (32%)	50 (34%)
Comedo Necrosis	350 (61%)	89 (61%)
Solid Subtype	358 (63%)	93 (63%)
Tumor Size		
≤10 mm	150 (26%)	29 (20%)
>10 mm	140 (25%)	32 (22%)
Missing	281 (49%)	86 (59%)
Multifocality*	114 (20%)	39 (27%)
ER-positive by RT-PCR	541 (95%)	135 (92%)
HER2-positive by RT-PCR	100 (18%)	25 (17%)

*Presence of at least 2 foci of DCIS in the same quadrant at least 5 mm apart.[5]

Table 2. Factors Associated with LR: Multivariable Analysis (All Patients)

Characteristic	N	HR (95% C.I.)	P value^
DCIS Score /50	718	**2.11 (1.43, 3.09)**	**<0.001**
Age at diagnosis# (yr)			0.003
<50	139	**1.83 (1.21, 2.70)**	
≥50	577	1.0	
Tumor size**			0.041
<10 mm	172	**1.72 (1.03, 2.93)**	
≥10 mm	179	1.0	
Subtype			0.55
Solid	451	**1.14 (0.75, 1.80)**	
Cribriform	219	1.0	
Multifocality*			<0.001
Present	153	**1.98 (1.36, 2.85)**	
Absent	565	1.0	
Margins			0.054
Positive/Unknown	147	**1.46 (0.98, 2.12)**	
Clear	571	1.0	

*Presence of at least two foci of DCIS in the same quadrant at least 5 mm apart[5]

^Profile likelihood C.I., likelihood ratio P value

#Two patients missing age

**Missing tumor size was included as an additional indicator variable in the model to prevent data loss

Results

Figure 3. 10 Year Risk of LR in Patients by DCIS Score Risk Group, Regardless of Margin Status

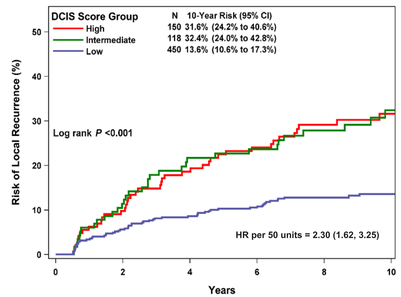


Figure 4. Risk of Invasive and DCIS LR, Regardless of Margin Status

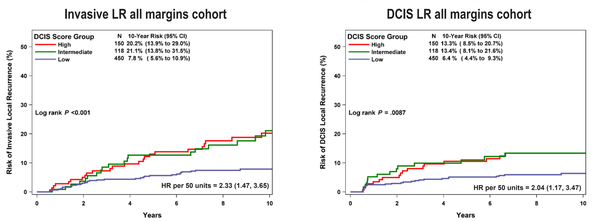
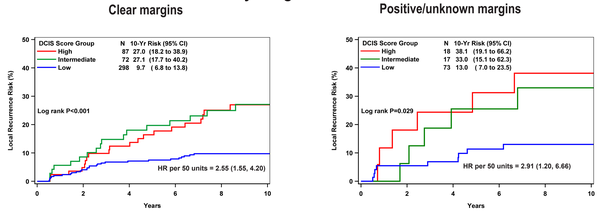


Table 3. Local Recurrence by Margin Status

Resection margin status	N	# local recurrences	10 yr KM risk of LR (%) and 95% CI	P value*
Clear	571	100	19.2 (15.9, 22.9)	
Unknown	86	18	21.7 (14.1, 32.7)	0.047
Positive	61	18	28.2 (18.2, 42.0)	

*P-value based on log rank test

Figure 5. 10 Year Risk of LR by DCIS Score Risk Group in Patients Without Multifocality, by Margin Status



Results

Figure 6. 10 Year LR Event Rates by Margin Status and Focality

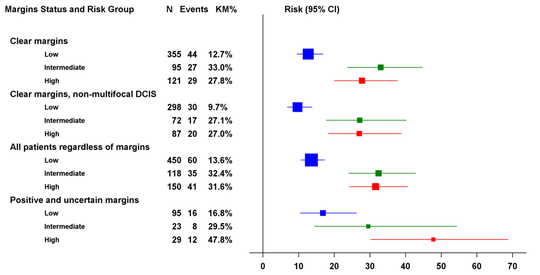


Table 4. 10 Year Risk of LR by DCIS Score Risk Group by Margin Status

		Clear margins		Clear margins & non-multifocal DCIS		Positive/unknown margins		All patients regardless of margins	
		N	95% CI	N	95% CI	N	95% CI	N	95% CI
Risk Group	Low (<39)	355	12.7% (9.5%, 16.9%)	298	9.7% (6.8%, 13.8%)	95	16.8% (10.4%, 26.3%)	450	13.6% (10.6%, 17.3%)
	Intermediate (39–54)	95	33.0% (23.6%, 44.8%)	72	27.1% (17.7%, 40.2%)	23	29.5% (14.4%, 54.4%)	118	32.4% (24.0%, 42.8%)
	High (≥55)	121	27.8% (20.0%, 37.8%)	87	27.0% (18.2%, 38.9%)	29	47.8% (30.4%, 68.8%)	150	31.6% (24.2%, 40.6%)
	Log rank P-value	571	<0.001	457	<0.001	147	0.004	718	<0.001

Conclusions

- The presence of positive/unknown margins is associated with a higher risk of LR compared to patients with clear margins.
- The DCIS Score result effectively risk stratifies patients with or without clear margins.
- Individuals with no multifocality and a low risk DCIS Score result have the lowest risk of LR (10 year LR = 9.7%).
- The DCIS Score result can improve decision making and the management of DCIS, by
  - helping clinicians / patients weigh risk of recurrence with benefits of treatment,
  - reducing over-treatment of individuals at low risk of recurrence, and
  - reducing under-treatment of individuals at higher risk of recurrence.

References

1. Allegra CJ, Aberle DR, Ganschow P, et al. National Institutes of Health State-of-the-Science Conference statement: Diagnosis and Management of Ductal Carcinoma In Situ September 22-24, 2009. J Natl Cancer Inst. 2010;102(3):161-9.
2. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer v1.2015.
3. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst. 2013;105(10):701-10.
4. Rakovitch E, Nofech-Mozes S, Hanna W, et al. A large prospectively-designed study of the DCIS score: Predicting recurrence risk after local excision for ductal carcinoma in situ patients with and without irradiation. Presented at the annual San Antonio Breast Cancer Symposium; San Antonio, TX; December, 2014.
5. Sikand K, Lee AH, Pinder SE, Elston CW, Ellis IO. Sections of the nipple and quadrants in mastectomy specimens for carcinoma are of limited value. J Clin Pathol. 2005;58(5):543-5.

Funding provided by the Canadian Cancer Society Research Institute

The authors thank Emily Burke and Kevin Chew for their contributions.