Refined Estimates of Local Recurrence Risks and the Impact of the DCIS Score Adjusting for Clinico-pathological Features: Meta-Analysis of E5194 and Ontario DCIS Cohort Studies

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Background

- Breast-conserving surgery (BCS; lumpectomy) alone, without radiation, is one local treatment option for low risk DCIS (ductal carcinoma in situ) of the breast
- Better tools are needed to estimate the risk of local recurrence (LR) after BCS alone to inform treatment decisions
- The Oncotype DX® Breast DCIS Score™ test has been validated as a predictor of 10-year LR risk after BCS alone in the ECOG-ACRIN E5194 prospective study[1] and the Ontario DCIS population-based study[2]
- On multivariate analyses, in addition to the DCIS Score, tumor size and age at diagnosis were significant predictors of LR

Objective

- To provide refined estimates of LR risk after BCS alone, combining data from these two studies and integrating the effect of age and tumor size

Methods

- Local recurrence data from E5194[1] and Ontario DCIS[2] cohorts
  - E5194 (n=327). Protocol required patients to have negative margins (3 mm or greater).
  - Ontario DCIS Cohort (n=571 with negative margins). 114 patients with known multifocality and 11 patients with missing tumor size or age were excluded, leaving 446 patients for analysis. Missing tumor sizes imputed based on tumor block data[3]
- Meta-analysis cohort includes 773 patients treated by BCS alone
- Identical Cox proportional hazards regression models were fit for each study
- Covariates for any local recurrence were pre-specified (significant covariates from prior analyses)
  - Age at diagnosis (< 50 years, ≥ 50 years)
  - DCIS Score result
  - Tumor size category (≤ 1 *cm*, > 1-2.5 *cm*, > 2.5 *cm*)
  - Year of diagnosis (before year 2000, year 2000 or later)
- Covariate for invasive local recurrence were limited by number of events. Included significant covariates and those with strong hazard ratios (HR):
  - DCIS Score result
  - Tumor size (≤ 2.5 *cm*, > 2.5 *cm*)
  - Year of diagnosis (before year 2000, year 2000 or later)

Methods

Patient-specific meta-analysis

- Risk estimates were produced for individual patients (from each cohort) based on patient covariate values
- Risk information was combined across cohorts using patient-specific meta-analysis[4]
- Precision-weighted estimates of 10 year risk of LR and invasive LR were calculated
- The study with the more precise estimate (inverse variance) for the individual patient received higher weight
- This method allows for risk estimates of populations unique to one study (e.g. patients with tumor size > 2.5 *cm* were only included in the Ontario DCIS Cohort)

Results

Table 1. Patient Characteristics

	E5194 (n=327)	Ontario DCIS Cohort (n=446)
DCIS Score		
Median (10th-90th %ile)	25 (8-58)	30 (5-63)
Low risk	232 (70.9%)	288 (64.6%)
Intermediate risk	53 (16.2%)	72 (16.1%)
High risk	42 (12.8%)	86 (19.3%)
Age at diagnosis		
Median (10th-90th %ile)	61 (45-77)	62 (45-79)
< 50 years	66 (20.2%)	92 (20.6%)
≥ 50 years	261 (79.8%)	354 (79.4%)

	E5194 (n=327)	Ontario DCIS Cohort (n=446)
Tumor size		
≤ 1 *cm*	260 (79.5%)	181 (40.6%)
> 1-2.5 *cm*	67 (20.5%)	238 (53.4%)
> 2.5 *cm*	0	27 (6.1%)
Diagnosis in 2000 or later	180 (55.0%)	191 (42.8%)
Tamoxifen use	110 (33.6%)	—*

*17% of Ontario DCIS Cohort patients > 65 years of age used tamoxifen.

- Median follow-up time was 11.5 years for E5194 and 9.8 years for Ontario DCIS Cohort

Table 2. Multivariable Cox Models for Any Local Recurrence

	E5194 (n=327; 53 local recurrences)			Ontario DCIS Cohort (n=446; 65 local recurrences)		
Effect	Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
DCIS Score / 50	2.48	(1.29, 4.75)	.006	1.95	(1.14, 3.32)	.014
Tumor size > 1-2.5 *cm* vs. ≤ 1 *cm*	1.45	(0.78, 2.69)	.24	1.47	(0.82, 2.64)	.19
Tumor size > 2.5 *cm* vs. ≤ 1 *cm*	—	—	—	2.99	(1.32, 6.76)	.009
Age ≥ 50 y	0.61	(0.33, 1.11)	.10	0.84	(0.48, 1.49)	.55
Diagnosis in 2000 or later	0.67	(0.38, 1.17)	.16	0.49	(0.28, 0.87)	.016

- Multivariate test for equality of hazard ratios between studies: Chi-square (4 d.f.) = 1.34, p=.86
- Test for equality of baseline log cumulative hazard at 10 years: p=.49
- HRs from E5194 and Ontario cohorts were similar for tumor size (≤ 2.5 *cm*), age and year of diagnosis after 2000
- Nuclear grade did not add significant prognostic value to the model (meta-analysis p=.40)
- Non-randomized tamoxifen use was not significantly associated with LR (p=.33, E5194). A sensitivity analysis adjusting for tamoxifen use showed very little effect on the HRs for DCIS Score, tumor size, or age.

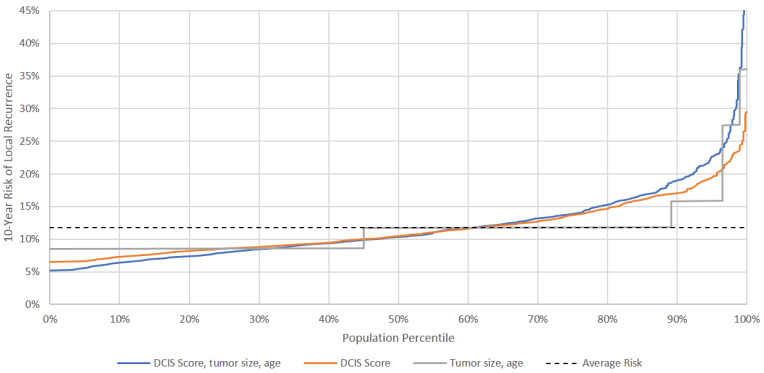
> The DCIS Score results and the clinico-pathologic covariates (tumor size, age at diagnosis, and year of diagnosis) both contribute significantly to the prognostic value of the 10-year risk of local recurrence estimates

- DCIS Score with clin-path vs. clin-path alone: meta-analysis likelihood ratio chi-square 12.9 (2 d.f.), p=.002
- DCIS Score with clin-path vs. DCIS Score alone: meta-analysis likelihood ratio chi-square 18.8 (7 d.f.), p=.009

Results

Figure 1. Meta-analysis Predictiveness Curves for 10-year LR Risk Adjusted for Diagnosis Year 2000 or Later

Estimated 10-year LR risk plotted against the percentage of patients in the E5194 and the Ontario DCIS cohorts with that risk or lower



Predictors	Percentage of Patients		
	Risk ≤ 8%	Risk ≤ 10%	Risk > 15%
DCIS Score,tumor, size, age	25.9%	47.0%	21.1%
DCIS Score	17.7%	45.1%	18.4%
Tumor size, age	0	44.1%	10.9%

- Improved prediction of LR risk with combined DCIS Score results, tumor size, age than either DCIS Score result alone or tumor size and age.
- Using DCIS Score results with tumor size and age, more women at higher risk are identified
- Using DCIS Score results with tumor size and age, more women with very low LR risk are identified

Table 3. Average 10-year LR Risks by Combinations of Age, Tumor Size, and DCIS Score Group

10-year risk of local recurrence[a] (range[b]) by DCIS Score group (%)				
Tumor Size (*cm*)	Age (yr)	Low DCIS Score (0-38)	Intermediate DCIS Score (39-54)	High DCIS Score (55-100)
≤ 1	≥ 50	7.2 (5.3-10.0)	11.3 (10.2-12.7)	14.6 (12.9-23.1)
	< 50	10.2 (7.4-13.9)	15.8 (14.1-17.4)	19.6 (17.7-30.7)
1.1-2.5	≥ 50	10.1 (7.3-12.6)	13.9 (12.8-15.6)	19.5 (15.8-28.7)
	< 50	14.5 (10.1-17.2)	18.9 (17.4-21.1)	23.2 (21.4-37.2)
> 2.5	≥ 50	20.4 (14.9-27.0)	29.1 (27.4-33.3)	41.1 (33.8-54.4)
	< 50	30.2 (20.6-36.1)	39.5 (36.6-43.6)	48.6 (44.1-66.5)

[a]Average risk for E5194 and Ontario DCIS Cohort patients in DCIS Score groups.
[b]Risks at boundaries of DCIS Score groups.

Table 4. Multivariable Cox Models for Invasive Local Recurrence

	E5194 (n=327; 27 invasive LRs)			Ontario DCIS Cohort (n=446; 38 invasive LRs)		
Effect	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
DCIS Score / 50	3.02	(1.28, 7.14)	.012	2.18	(1.12, 4.27)	.023
Tumor size > 2.5 *cm* vs. ≤ 2.5 *cm*	—	—	—	2.20	(0.85, 5.65)	.10
Diagnosis in 2000 or later	0.92	(0.42, 2.00)	.83	0.57	(0.28, 1.20)	.14

- Multivariate test for equality of hazard ratios between studies: Chi-square (2 d.f.) =.98, p=.63
- Test for equality of baseline log cumulative hazard at 10 years: p=.88
- Age and nuclear grade were not significant although the number of events limited statistical power
- Large tumor size and diagnosis year had strong hazard ratios.

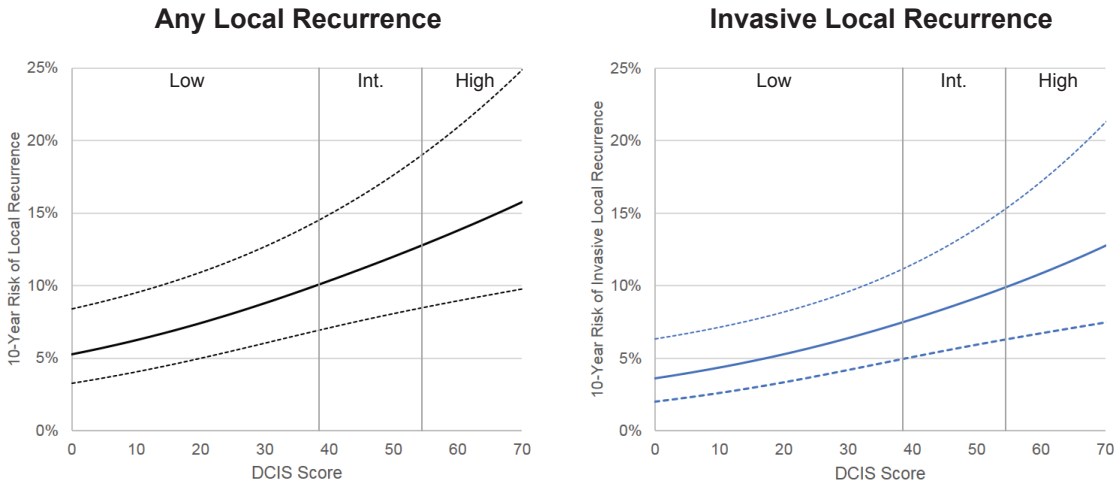
Table 5. Average 10-year Invasive LR Risks by Tumor Size, and DCIS Score Group

10-year risk of local recurrence[a] (range[b]) by DCIS Score group (%)			
Tumor size (*cm*)	Low DCIS Score (0-38)	Intermediate DCIS Score (39-54)	High DCIS Score (55-100)
≤ 2.5	5.3 (3.6-7.4)	8.5 (7.5-9.8)	12.1 (10.0-20.5)
> 2.5	11.6 (7.7-15.5)	17.1 (15.8-20.3)	26.2 (20.6-40.0)

[a]Average risk for E5194 and Ontario DCIS Cohort patients in DCIS Score groups.
[b]Risks at boundaries of DCIS Score groups.

Results

Figure 2. Example Patient-specific Meta-analysis Local Recurrence Risk Estimates for Patients With Diagnosis in Year 2000 or Later, Age ≥ 50 y, Tumor Size ≤ 1 *cm*



Strengths & Limitations

Strengths

- Refined 10-year estimates of LR risk incorporating the effect of clinical, pathologic, and molecular factors
- Large numbers of annotated DCIS patients with known DCIS Score results
- Known central expert pathology assessment

Limitations

- Limited patient numbers in some subsets
- Tamoxifen used by some patients (not randomized)
- Two different types of study populations (prospective protocol vs population based cohort) combined for analysis

Conclusions

- The DCIS Score result provides individualized 10-year risk of LR for women with DCIS treated with BCS alone, without radiation
- This meta-analysis provides refined 10-year risk of LR by DCIS Score result adjusting for the effects of age, tumor size, and year of diagnosis
- These results aid in individualizing the treatment decision-making process for women with DCIS after BCS
  - For lower risk DCIS, BCS alone may be adequate
  - For higher risk DCIS, adding treatment after BCS should be considered

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