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EPIDEMIOLOGY

Multiple foci of microinvasion is associated with an increased risk of invasive local recurrence in women with ductal carcinoma in situ treated with breast-conserving surgery

Eileen Rakovitch[1,2,4,6] · Rinku Sutradhar[2,4] · Nafisha Lalani[1,4] · Sharon Nofech-Mozes[3,4] · Sumei Gu[2] · Mira Goldberg[5] · Wedad Hanna[3,4] · Cindy Fong[2] · Lawrence Paszat[1]

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Abstract

Purpose The impact of Ductal Carcinoma in Situ (DCIS) with multiple foci of microinvasion (MI) (≤ 1 mm) on the risks of local recurrence (LR) and invasive LR is unknown, leading to uncertainty if DCIS with multiple foci of MI requires more aggressive treatment. We report a population-based analysis of the impact of multiple foci of MI, confirmed by pathology review, on the 15-year risks of LR and invasive LR treated with breast-conserving surgery (BCS) ± radiotherapy (RT).

Methods Cohort includes all women diagnosed with DCIS ± MI from 1994 to 2003 treated with BCS ± RT. Cox proportional hazards model was used to evaluate the impact of multiple foci of MI on the risks of LR and invasive LR, adjusting for covariates. The 15-year local and invasive local recurrence-free survival rates were calculated using the Kaplan–Meier method with differences compared by log-rank test.

Results The cohort includes 2988 women treated by BCS; 2721 had pure DCIS (51% received RT), 267 had DCIS with one or more foci of MI (58% had RT). Median follow-up was 13 years. Median age at diagnosis was 58 years. On multivariable analyses, the presence of multiple foci of MI was associated with an increased risk of invasive LR (HR = 1.59, 95% CI 1.01–2.49, p = 0.04) but not DCIS LR (HR = 0.89, 95% CI 0.46, 1.76, $p = 0.7$). The 15-year invasive LRFS risks for cases with pure DCIS, with 1 focus or multiple foci of MI were 85.7%, 85.6%, 74.7% following treatment by BCS alone, 87.2%, 89.9%, and 77% for those treated with BCS + RT without boost and 89.2%, 91.3%, and 95% for women treated with BCS + RT and boost.

Conclusions The presence of multiple foci of MI in DCIS is associated with higher 15-year risks of invasive LR after breast-conserving therapy compared to women with pure DCIS but treatment with whole breast and boost RT can mitigate this risk.

Keywords Ductal carcinoma in situ · DCIS · Microinvasion · Radiotherapy · Local recurrence

✉ Eileen Rakovitch
eileen.rakovitch@sunnybrook.ca

[1] Department of Radiation Oncology, Toronto, ON, Canada

[2] ICES, Toronto, ON, Canada

[3] Department of Pathology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

[4] Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

[5] Department of Oncology, McMaster University, Hamilton, ON, Canada

[6] LC Campbell Chair in Breast Cancer Research, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

Introduction

Ductal carcinoma in situ (DCIS) with microinvasion (MI) comprises approximately 5–10% of DCIS cases and 1–2% of all breast cancer cases [1, 2]. Most women will be treated with breast-conserving surgery (BCS) followed by whole breast radiation, yet the optimal management of DCIS with MI remains elusive. This is in part because the current AJCC definition of microinvasion is based on the depth of invasion not exceeding 1 mm [3], and as such includes a diverse spectrum of disease ranging from cases with a single focus of MI to those with more extensive MI. DCIS with MI is associated with other established adverse features of DCIS including high grade, larger tumor size and younger age [4–7]. Past studies are limited by inclusion of small numbers of patients or those with nodal metastases [4–10]. Therefore, the impact of multiple foci of MI on the risks of local recurrence or invasive LR remains unclear, particularly among women with negative nodes who have an excellent prognosis [5]. As a result, there is uncertainty if women with DCIS with multiple foci of MI require more aggressive treatment such as higher doses of radiation or mastectomy compared to those with a single focus of MI or pure DCIS. We examined the impact of multiple foci of MI, confirmed by expert pathology review, on the 15-year risks of LR and invasive LR in a population cohort of DCIS (± MI) treated with breast-conserving surgery (BCS) with or without radiation (RT).

Methods

Study population

The development of this population cohort has been described [11, 12]. We reviewed all breast pathology reports held by the Ontario Cancer Registry (OCR) from January 1, 1994 to December 31, 2003. We excluded patients with a final diagnosis of invasive breast cancer > 5 mm, benign breast disease and those presenting with bilateral lesions or initial laterality unknown. Patients with positive lymph nodes were also excluded. We used deterministic linkage with the Canadian Institute for Health Information (CIHI) database for hospital admissions to identify breast surgical treatments (breast-conserving surgery or mastectomy) for each case in the cohort. The date of diagnosis was defined as the procedure date leading to definitive histologic confirmation of DCIS. All surgical and radiation data were validated by primary chart abstraction. For each case, we abstracted the total radiation dose and number of fractions delivered, beam energy (MV), and the administration of supplemental radiation to the tumor cavity ("boost" radiation). Data on endocrine therapy prescription were available for women 65 years of age or older from the Ontario Drug Benefits database. Patients treated by mastectomy were excluded from the analysis.

Pathologic assessment

We identified all individuals treated by BCS with a final diagnosis of pure DCIS or with DCIS with microinvasion (defined as ≤ 1 mm) (N = 3827). Of these, 2988 had systematic pathology review (78%) and these cases are included in this analysis where the presence of MI, the number of foci of MI and baseline pathological characteristics including nuclear grade (high grade/non-high), presence of multifocality (foci of DCIS at least 5 mm apart: present/absent), histological subtype (solid or cribriform/other), tumor size/extent (< 10 mm/≥ 10 mm/missing), and margin status (negative/positive or unknown) were systematically ascertained. For cases where the presence of MI was equivocal on H&E, smooth muscle myosin and or p63 immunohistochemistry was used to evaluate the myoepithelial cell layer.

Outcomes

Outcomes were ascertained by deterministic linkage of administrative databases held at the ICES (CIHI, OHIP, OCR). All outcomes were determined from the date of diagnosis of DCIS. The last date of follow-up was March 31, 2014. Patients were censored at the time of recurrence or death, or at the last date of contact as determined by one of the administrative databases at ICES. Local recurrence was defined as diagnosis of DCIS or invasive breast cancer in the same breast 6 months or more following the initial diagnosis of DCIS. Invasive LR was defined as the development of invasive breast cancer in the same breast 6 months beyond the date of diagnosis, regardless of an initial DCIS LR. To identify a secondary breast event, we linked the cohort with CIHI database to identify breast surgical procedures performed beyond 6 months from diagnosis. The corresponding histological diagnoses were determined by CIHI or OCR databases (ICD 174 or C50 for invasive breast cancer, ICD code 233 or D05 as DCIS) or from review of the corresponding pathology reports. For 52 cases (8.6%), the laterality of the secondary breast event was unavailable. As such, we modeled parameters associated with laterality using the remaining cohort with complete data and imputed laterality for the 52 cases accordingly. The results of the analyses were similar with or without the 52 cases and as such complete data are provided. The date of death was determined from the Registered Persons Database.

Statistical analysis

Descriptive statistics were used to report the distribution of all baseline covariates among our cohort of women. Differences in baseline covariates between women with microinvasion and those with pure DCIS were calculated using t tests for continuous variables and χ^2 test for categorical variables. Cox proportional hazards regression models were used to determine the hazard of the outcome against the main exposure, adjusting for other covariates. In order to account for systematic differences between women treated with and without radiotherapy, a propensity score was calculated for each patient. There was no difference in the hazards of local recurrence with or without propensity score adjustment and therefore it was not included in the final Cox regression model. Local recurrence-free survival (LRFS) and invasive LRFS were calculated using the Kaplan–Meier method and differences between groups (pure, 1 focus of

MI, multiple foci of MI) tested using the log-rank test. All statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Study population

The cohort includes 2988 cases treated with breast-conserving surgery with complete pathology review: 2721 had pure DCIS and 267 had DCIS with MI (1 focus, $N = 156$; multiple foci, $N = 111$). Overall, 1376 (51%) of cases with pure DCIS and 154 (58%) cases with MI received RT. Median follow-up was 13 years (range 11–16) and median age at diagnosis was 58 years. Endocrine therapy was prescribed to 7.1% ($N = 19$) of women with MI and 5.3% ($N = 144$) of women with pure DCIS ($p = 0.22$). Women with MI were more likely to have high nuclear grade (66% versus 37%; $p < 0.001$), tumor size ≥ 10 mm (54% vs. 34%; $p < 0.001$), comedo necrosis (82.4% vs. 61.1%, $p < 0.001$), and multifocal disease (26.2% vs. 21.3%, $p = 0.06$) compared to those without MI (Table 1).

Local recurrence

Local recurrence (LR) (DCIS or invasive) developed in 571 cases (21%) with pure DCIS, 33 cases (21%) with 1 focus of MI and 23 cases (27%) with multiple foci of MI. We performed univariate and multivariate analyses evaluating the impact of multiple foci of MI on the development of any LR (DCIS or invasive) and on the development

Table 1 Patient characteristics

Variable	Pure DCIS $N = 2721$	DCIS + MI $N = 267$	Whole Cohort $N = 2988$	p value
Age				
Median (IQR)	58 (50–68)	57 (50–68)	58 (50–68)	0.17
< 50	613 (22.5%)	65 (24.3%)	678 (22.7%)	0.50
≥ 50	2108 (77.5%)	202 (75.7%)	2310 (77.3%)	
Local treatment				
BCS alone	1345 (49.4%)	113 (42.3%)	1458 (48.8%)	0.03
BCS + breast RT	1376 (50.6%)	154 (57.7%)	1530 (51.2%)	
Hormone therapy	145 (5.3%)	19 (7.1%)	164 (5.5%)	0.22
Nuclear grade				
High	1012 (37.2%)	176 (65.9%)	1188 (39.8%)	< 0.001
Low/intermediate/unknown	1709 (62.8%)	91 (34.1%)	1800 (60.2%)	
Necrosis				
Absent/unknown	1059 (38.9%)	47 (17.6%)	1106 (37.0%)	< 0.001
Present	1662 (61.1%)	220 (82.4%)	1882 (63.0%)	
Multifocality				
Present	580 (21.3%)	70 (26.2%)	650 (21.8%)	0.06
Absent/unknown	2141 (78.7%)	197 (73.8%)	2338 (78.2%)	
Margin status				
Negative	2099 (77.1%)	220 (82.4%)	2319 (77.6%)	0.05
Positive/unknown	622 (22.9%)	47 (17.6%)	669 (22.4%)	
Histological subtype				
Solid	1814 (66.7%)	218 (81.6%)	2032 (68.0%)	< 0.001
Cribriform	722 (26.5%)	39 (14.6%)	761 (25.5%)	
Other	185 (6.8%)	10 (3.7%)	195 (6.5%)	
Tumor size/extent (mm)				
< 10	509 (18.7%)	25 (9.4%)	534 (17.9%)	< 0.001
≥ 10	913 (33.6%)	143 (53.6%)	1056 (35.3%)	
Unable to determine	1299 (47.7%)	99 (37.1%)	1398 (46.8%)	
Number of foci of microinvasion				
0 (pure DCIS)	2721 (100%)	–	2721 (100%)	
1	–	156 (58.4%)	156 (58.4%)	
≥ 2	–	111 (41.6%)	111 (41.6%)	

of invasive LR compared to cases with a single focus of MI or those with pure DCIS. On multivariable analysis, the presence of multiple foci of MI was associated with a significantly increased risk of invasive LR (HR = 1.59, 95% CI 1.01–2.49, $p = 0.04$) but not DCIS LR (HR = 0.89, 95% CI 0.46–1.76, $p = 0.7$) or any LR (HR = 1.30, 95% CI 0.89–1.88, $p = 0.17$). Factors –1.84, $p < 0.0001$), administration of RT (HR = 0.62, 95% CI 0.53–0.73, $p < 0.0001$), the presence of multifocal DCIS (HR = 1.38, 95% CI 1.15–1.65, $p = 0.0004$) and high nuclear grade (HR = 1.31, 95% CI 1.11–1.55, $p = 0.002$). In addition to the presence of multiple foci of MI, factors associated with the development of invasive LR were: age < 50 years at diagnosis (HR = 1.44, 95% CI 1.15–1.81; $p = 0.002$), administration of RT (HR = 0.79, 95% CI 0.64–0.97; $p = 0.03$), and the presence of multifocality (HR = 1.44, 95% CI 1.14–01.81; $p = 0.002$). The presence of 1 focus of MI was not associated with an increased risk of any LR (HR = 0.88, 95% CI 0.62–1.26, $p = 0.49$), invasive LR (HR = 0.83, 95% CI 0.50, 1.35, $p = 0.44$) or DCIS LR (HR = 0.89, 95% CI 0.52–1.53) compared to cases with pure DCIS treated with breast-conserving therapy (Table 2).

Treatment with RT after BCS was associated with a similar relative reduction in LR risk (interaction, p = 0.15) and invasive LR among individuals with or without MI (interaction, $p = 0.67$). However, for women with multiple foci of MI, RT was associated with a greater absolute reduction in LR risk and invasive LR. Among women with multiple foci of MI, the 15-year LRFS risk was 62.3% following treatment by BCS alone, 70.3% for those treated with BCS + RT without boost (absolute benefit from RT = 8%, $p = 0.10$) and 90.0% for those treated with BCS + RT with boost (absolute benefit of boost = 19.7%). Among women with DCIS and 1 focus of MI, the 15-year LRFS risks were 67.7% among those treated by BCS alone, 81.8% for those treated by BCS + RT without boost (absolute benefit from RT = 14.1%, $p = 0.026$) and 91.3% for those treated with boost (absolute benefit of boost = 9.5%). Among women with pure DCIS, the 15-year LRFS risks were 73.7% following treatment by

Table 2 Multivariable analysis

Variable	Any local recurrence			Invasive local recurrence		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Number of foci of microinvasion						
1 Focus	0.88	0.62, 1.26	0.49	0.83	0.50, 1.35	0.44
≥ 2 Foci	1.30	0.89, 1.88	0.17	1.59	1.01, 2.49	0.04
None	1.0					
Age at diagnosis (years)						
< 50	1.55	1.31, 1.84	< 0.0001	1.44	1.15, 1.80	0.002
≥ 50	1.0			1.0		
Nuclear grade						
High	1.31	1.11, 1.55	0.002	1.24	0.99, 1.55	0.06
Low/intermediate/unknown	1.0			1.0		
Multifocality						
Present	1.38	1.15, 1.65		1.40	1.09, 1.79	0.004
Absent	1.0			1.0		
Subtype						
Solid	0.91	0.66, 1.25	0.55	0.92	0.60, 1.40	0.69
Cribriform	0.81	0.57, 1.14	0.23	0.79	0.50, 1.25	0.32
Other	1.0			1.0		
Margin status						
Negative	0.85	0.71, 1.02	0.08	0.83	0.65, 1.06	0.14
Positive/unknown	1.0			1.0		
Tumor Size						
≥ 10 mm	1.21	0.95, 1.56	0.13	1.11	0.80, 1.56	0.53
Unknown	1.26	0.99, 1.59	0.06	1.36	0.99, 1.86	0.06
< 10 mm	1.0			1.0		
Local treatment						
BCS + RT	0.62	0.53, 0.73	< 0.0001	0.79	0.64, .097	0.04
BCS alone	1.0			1.0		

HR hazard ratio, *95% CI* 95% confidence intervals, *BCS* breast-conserving surgery

BCS alone, 80.3% for those treated by BCS + RT without boost (absolute benefit from RT = 6.6%, p < 0.0001)) and 82.3% for those treated with boost (absolute benefit of boost = 2%). (Table 3).

Furthermore, individuals with DCIS and multiple foci of MI treated by BCS alone (without RT) had lower 15-year invasive LRFS risks compared to those with a single focus of MI or those with pure DCIS. However, high 15-year invasive LRFS rates were achieved among cases treated with RT although the low event rate limited statistical power. Among women with multiple foci of MI the 15-year invasive LRFS risks were 74.7% after treatment by BCS alone, 77.0% after treatment with RT without boost (absolute benefit 2.3%) and 95.0% after BCS + RT with boost (20.3% benefit). By comparison the 15-year invasive LRFS rates for cases with 1 focus of MI were 86.5%, 89.5% and 91.3% and 85.7%, 87.2% and 89.2% for those with pure DCIS following treatment by BCS alone, BCS + RT without boost and BCS + RT with boost, respectively (Table 3).

Figure 1 illustrates the LRFS and invasive LRFS risks achieved in women with pure DCIS, one focus or multiple foci of MI following treatment with BCS alone, BCS + RT with or without boost.

There were 32 women with low risk features of DCIS (age ≥ 65 years at diagnosis with nuclear grade 1 or 2 and clear margins) and microinvasion; 19 patients had 1 focus of MI and 13 had ≥ 1 focus. We examined the risks of local recurrence following breast-conserving surgery with or without RT to determine if this subgroup would be potential candidates for the omission of RT after BCS. The 5-year risk of LR among those treated with BCS alone was 84.4% and 91.7% for those treated with BCS + RT ($p = 0.08$). Although the power was limited to achieve statistical significance, the data suggests that the omission of RT is associated with a significant LR risk that can be reduced with breast RT.

Discussion

We report a large population-based analysis with complete pathology review describing the outcomes achieved in women with DCIS with or without microinvasion with negative nodes treated by breast-conserving therapy. We found that the presence of multiple foci of MI is associated with an increased risk of invasive LR compared to cases with pure DCIS or those with DCIS and 1 focus of MI. However, high long-term rates of local recurrence-free survival and invasive local recurrence-free survival can be achieved by treatment with breast-conserving surgery followed by whole breast RT with boost.

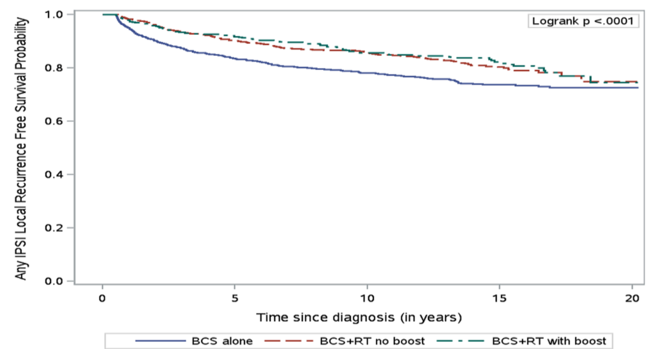
Our analysis complements and extends the findings or prior studies [6, 8–10, 13–15]. Our study is based on a large population cohort with complete standardized pathology review to systematically quantify the presence and extent of MI with long-term data on the development of local recurrence and invasive LR. Wang et al. published an eloquent analysis of 8863 cases diagnosed with DCIS with MI and 87,695 cases of pure DCIS identified from the SEER database. The median follow-up time was 91 months [5]. On multivariate analysis, adjusted for competing risk and treatment propensity, they found that cases with DCIS and MI had worse cause-specific survival (HR = 1.9; 95% CI 1.643–2.240; $p < 0.001$) and overall survival (HR = 1.18; 95% CI 1.085–1.291; p < 0.001) compared to cases with pure DCIS. The cancer-specific survival was 4.1% at 10 years and 9.65% at 20 years among cases with DCIS with MI compared to 1.49% and 4.0% for those with pure DCIS ($p < 0.001$). However, this analysis includes cases with positive lymph node metastases (including N2, N3 disease) and cases treated with chemotherapy. In this analysis, we excluded cases with positive lymph nodes (which carry a worse prognosis [5, 16]) and those treated with chemotherapy to limit the impact of competing risks and the confounding effects of systemic chemotherapy on the risks of local recurrence.

Table 3 Kaplan–Meier estimates of local recurrence-free and invasive local recurrence-free survival

	BCS Alone	BCS + RT-no boost	BCS + RT-with boost	*p* value
15-year LRFS				
Pure DCIS (*N* = 272)	73.7	80.3	82.3	< 0.0001
1 Focus (*N* = 156)	67.7	81.8	91.3	0.026
≥ 2 Foci (*N* = 111)	62.3	70.3	90.0	0.10
15-year invasive LRFS				
Pure DCIS (*N* = 272)	85.7	87.2	89.2	0.29
1 Focus (*N* = 156)	86.5	89.9	91.3	0.67
≥ 2 Foci (*N* = 111)	74.7	77.0	95.0	0.2

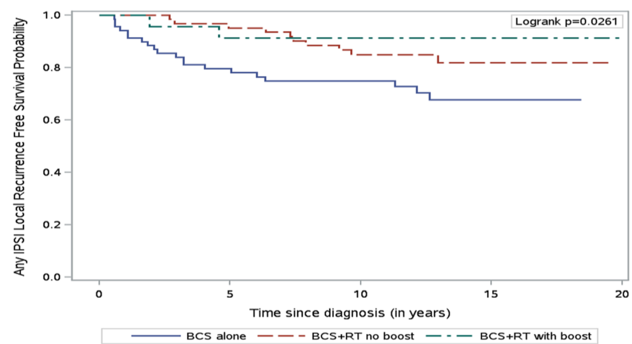
Fig. 1 Local recurrence-free survival risks following breast-conserving surgery with or without Radiation for **a** Pure DCIS, **b** DCIS with 1 focus of Microinvasion and **c** DCIS with Multiple Foci of Microinvasion

(a) Pure DCIS



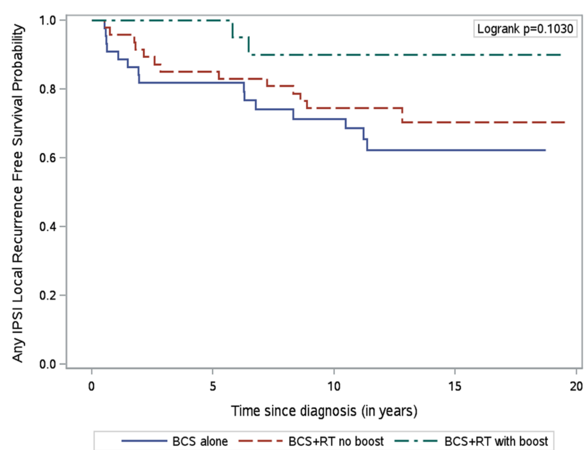
# at risk	5 year	10 year	15 year
BCS alone (N=1269)	1051	883	341
BCS+RT no boost (N=968)	859	778	239
BCS+RT with boost (N=382)	347	297	162

(b) 1 focus of Microinvasion



No. at risk	5 year	10 year	15 year
BCS alone (N=69)	53	40	10
BCS+RT no boost (N=62)	59	48	19
BCS+RT with boost (N=24)	21	19	13

(c) Multiple Foci of Microinvasion



	5 year	10 year	15 year
BCS alone (N=42)	34	27	≤5
BCS+RT no boost (N=45)	40	34	7
BCS+RT with boost (N=20)	20	17	8

Our findings corroborate other reports that DCIS with MI is more likely to harbor established adverse features of DCIS such as higher nuclear grade, comedo or solid subtype, necrosis compared to cases of pure DCIS [6] but in addition, we found that the presence of multiple foci of MI was associated with an increased risk of invasive LR (HR = 1.59, 95% CI 1.01–2.49, $p = 0.04$) but was not associated with an increased risk of DCIS LR (HR = 0.89, 95% CI 0.46, 1.76, $p = 0.7$) following breast-conserving treatment. Women with multiple foci of MI treated by BCS alone without RT experienced the highest risk of LR and invasive LR (15-year LRFS was 62.3% and the 15 year invasive LRFS was 74.7%). By comparison, the presence of a single focus of MI was not associated with an increased risk of LR (HR = 0.88, 95% CI 0.62, 1.26, $p = 0.49$) or invasive LR (HR = 0.83, 95% CI 0.50, 1.35, $p = 0.44$) compared to cases with pure DCIS.

The administration of RT was associated with a similar proportional reduction in the risk of LR and invasive LR for cases with pure DCIS, 1 focus of MI or those with multiple foci of MI but those with multiple foci of MI derived the greatest absolute benefit from whole breast RT and boost RT. Women with DCIS and multiple foci of MI treated by BCS alone had a 15-year LRFS risk of 62.3% and a 15-year invasive LRFS risk of 74.7% while those treated with BCS followed by whole breast and boost RT had 15-year LRFS and invasive LRFS risks of 90.0% and 95.0%, respectively (Table 3). The administration of boost RT was at the discretion of the radiation oncologist. Although the differences in 15-year LRFS risks were large, the low event rate limited statistical power.

The reasons why the presence of multiple foci of MI is associated with a higher risk of invasive LR are not clear. DCIS with MI is more likely to be estrogen and progesterone receptor negative, exhibit basal-like phenotype or Her2/neu overexpression compared to pure DCIS lesions [5, 9, 17, 18]. Both triple negative and Her2/neu positive phenotypes have been reported to be associated with a higher risk of LR following treatment of invasive breast cancer [19–21]. We were unable to evaluate the impact of systemic therapy on the risks of LR and invasive LR because most cases in the population cohort did not receive systemic therapy. Among women > 65 years of age at diagnosis (for whom complete information on systemic therapy is available), anti-estrogen therapy was prescribed to 13.1% of those with pure DCIS, 12. % of cases with 1 focus of MI and 16.2% of those with multiple foci of MI and chemotherapy was administered to < 3% of cases with MI. Further research is needed to determine the role of ER, PR and Her2/neu overexpression and the impact of systemic therapy on the risks of LR and invasive LR following breast-conserving therapy for cases with DCIS and multiple foci of MI.

In summary, the presence of multiple foci of MI in DCIS is associated with higher 15-year risks of invasive LR compared to women with pure DCIS. However, treatment with whole breast and boost RT can mitigate this risk leading to high 15-year local recurrence and invasive local recurrence-free survival rates.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest ERakovitch has received research grant funding from Genomic Health Inc. All other authors declare no conflict of interest.

Ethical approval This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board. It is an observational analysis, and no procedures or interventions were performed.

Informed consent This is a population-based retrospective analysis. All personal identifiers for each case in this population cohort were removed. This study was facilitated through ICES which is named as a prescribed entity in Section 45 of PHIPA (Regulation 329/04, Section 18) which allows access and utilization of administrative data for research purposes with a waived requirement for consent.

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