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EPIDEMIOLOGY

Can we select individuals with low risk ductal carcinoma in situ (DCIS)? A population-based outcomes analysis

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Abstract Ductal carcinoma in situ (DCIS), a non-invasive breast cancer, is usually treated by breast-conserving surgery (BCS). Randomized trials prove that the addition of radiotherapy (XRT) leads to lower rates of recurrence. Despite the evidence, half of women do not receive XRT after BCS. It is unknown how well clinicians identify women with low risk DCIS for treatment by BCS alone or to what extent women with DCIS develop recurrent cancer due to the omission of radiotherapy. We report the outcomes of a population of women with DCIS treated with BCS, alone or with radiotherapy, and evaluate the effectiveness of each therapeutic approach. All women diagnosed with DCIS and treated with BCS, alone or with radiotherapy in Ontario from 1994 to 2003 were identified. Treatments and outcomes were validated by chart review. Survival analyses were used to study the development of local recurrence (LR) in relation to patient and tumor characteristics and the use of radiotherapy. The cohort included 3,762 women treated with breast-conserving therapy; 1,895 of whom (50 %) also received radiation. At 10 years median follow-up, LR developed in 233 (12 %) women who received radiotherapy and in 363 (19 %) of women who did not ($p < 0.0001$). The 10-year actuarial LR rate for women who did and did not receive radiotherapy was 12.7 and 20.0 % ($p < 0.0001$). Differences were significant for both for invasive LR (7.0 vs. 10.0 %, $p < 0.0001$) and for DCIS recurrence (6.1 vs. 10.8 %, $p < 0.0001$). We estimate that 22 % of recurrences diagnosed in Ontario women treated for DCIS between 1994 and 2003 would have been prevented if all patients had received radiotherapy. The omission of radiotherapy after BCS for DCIS resulted in substantive recurrences that might have been avoided with treatment. Additional markers are needed to identify a low risk group in whom radiation can be safely omitted.

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Introduction

Ductal carcinoma in situ (DCIS), a non-invasive form of breast cancer, comprises up to 25 % of mammographically detected breast cancers [1]. Up to 20 % of DCIS patients may later develop invasive breast cancer which is associated with an increased risk of breast cancer mortality [2, 3]. The aims of treatment of DCIS are to minimize the risk of local recurrence (LR) and invasive breast cancer with optimal breast preservation.

Most women diagnosed with DCIS will be candidates for breast-conserving surgery (BCS). Four randomized clinical trials have proven that breast radiation can significantly reduce the risk of subsequent invasive breast cancer by 8.6 % at 10 years ($p < 0.001$), and of DCIS recurrence by 8.4 % at 10 years ($p < 0.001$), following BCS for DCIS [2, 4–7]. In response, treatment guidelines on the management of DCIS now recommend that women treated by BCS should be offered radiotherapy [8–10].

Despite its proven efficacy, treatment pattern studies report that only one-half of women treated by BCS for DCIS receive radiotherapy [11–13]. The reasons for the omission of radiotherapy are unclear but may reflect clinicians' assumption that women at low risk of recurrence (i.e., <10 % at 10 years) following treatment by BCS alone can be identified such that radiotherapy can be safely avoided [14–17]. Studies reporting low rates of recurrence following BCS alone are based on institutional case series or cohort studies of highly selected patients (e.g., small tumors, low/intermediate grade, and wide negative resection margins) and may not reflect the outcomes achieved in a general population of women with DCIS treated by this approach. For example, in one population-based study of 1,036 women treated by BCS alone, 20 % developed a LR after a median follow-up interval of 78 months [18]. In another population-based study of 460 women treated by BCS alone, 18 % developed LR after a median follow-up of 9.4 years [11, 19]. It is unclear to what extent treatment guidelines enable clinicians to identify individuals with DCIS in whom BCS alone is associated with low rates of recurrent breast cancer [8, 13].

We established a large ($N = 5{,}800$) population-based cohort of women diagnosed with pure DCIS with median follow-up interval of 10 years. We identified all women diagnosed with DCIS in the province of Ontario from 1994 to 2003. Ontario is the largest province in Canada with a health care system of universal access and universal health coverage. We report the rates of LR (DCIS and invasive) among women selected for treatment by BCS alone or BCS and radiation and report the long-term rates of breast preservation following each therapeutic approach.

Methods

Cohort identification

To identity the population of women diagnosed with DCIS in Ontario, we obtained full text electronic copies of all breast pathology reports held at the Ontario Cancer Registry (OCR) including reports with invasive breast cancer (ICD code 174), DCIS (ICD 233), or benign diagnoses. All patient identifiers were removed and each case was assigned a study ID. We reviewed and abstracted pathology data by a method of automated text extraction to ensure appropriate inclusion of cases of DCIS. Cases with a final diagnosis of invasive breast cancer or benign disease were excluded ($N = 118{,}905$). We excluded women who were diagnosed with DCIS with microinvasion or invasive breast cancer within 6 months of diagnosis of DCIS ($N = 141$).

During the period from January 1994 to December 2003, we received 129,140 breast pathology reports. We identified 7,282 cases of pure DCIS and 2,953 cases of DCIS with microinvasion. We linked these cases with the OCR database to exclude cases with previous invasive breast cancer ($N = 3{,}036$) or DCIS with microinvasion ($N = 1{,}447$). The population cohort includes 5,752 women with pure DCIS.

Pathology

For 2,138 (57 %) cases, a centralized pathology review of all diagnostic slides was performed by an expert breast pathologist. For the remaining cases, we electronically abstracted data from the original pathology reports [20]. We validated the accuracy of the data mining algorithm in a subset of 1,000 cases of DCIS. The data algorithm achieved >95 % accuracy. Tumor size and margin width were not consistently reported during the time interval of this study and therefore, these variables were not abstracted. We abstracted the following data elements: nuclear grade (low, intermediate, high, unreported), comedo necrosis (present, absent, unreported), multifocality (present, absent, unreported), and

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margin status (positive, negative, unreported). Margin status was defined as "positive" if there were tumor cells identified at the inked resection margin.

Treatment

To obtain data on treatment, we linked the study database to administrative databases held at the Institute for Clinical Evaluative Sciences (ICES) by deterministic linkage using encrypted health card number and unique OCR number as identifiers. We performed linkage with the Canadian Institute for Health Information (CIHI) database of hospital discharge summaries, the Ontario Health Insurance Plan (OHIP) database of physician billings, the Registered Persons Database (RPDB) and the OCR database [21]. For each case, we identified all surgical procedures performed on the breast or regional lymph nodes within 6 months of diagnosis. All surgical treatments were validated by chart review and for each case final breast surgery (mastectomy vs. BCS) was determined. The date of definitive diagnosis is the date of the initial breast cancer surgery associated with a pathological diagnosis of DCIS. Postoperative radiation (XRT) was scored for patients receiving XRT within 12 months of the date of diagnosis to allow for possible multiple surgical procedures prior to radiotherapy consultation. All radiation data were obtained by primary chart abstraction. All patients who received radiation were treated with whole breast radiation. The majority of individuals ($N = 1{,}062$, 56 %) received a dose of 50 Gy/25 fractions delivered over 5 weeks. 744 (36 %) women received a hypofractionated regimen (40–44 Gy/16 fractions). Tamoxifen usage in women over 65 years of age was identified through linkage with the Ontario Drug Benefit database. We were unable to determine tamoxifen usage in women <65 years of age.

Outcomes

We identified outcomes by deterministic linkage of administrative databases held at ICES with validation by primary review of the operative reports and pathology reports. All outcomes were determined from the date of diagnosis of DCIS. The last date of follow-up is March 31, 2010. Local (invasive or DCIS) recurrence is defined by the detection of invasive breast cancer or DCIS that developed in the ipsilateral breast 12 months or more beyond the initial diagnosis of DCIS. Contralateral breast cancer is defined by the presence of DCIS or invasive breast cancer that developed in the opposite breast beyond the diagnosis of DCIS. We identified the surgical treatment of any LR or contralateral breast cancer using CIHI and calculated the rate of any mastectomy at 10 years. Overall mortality is estimated from the date of diagnosis of DCIS to the date of death from any cause. The date of death was determined from the RPDB and cause of death from the OCR. To adjust for the presence of co-morbid illnesses, we identified all diagnoses during the 12 months prior to that of DCIS as recorded in CIHI using Deyo's method [22].

Statistical analyses

We studied the development of any LR (DCIS or invasive) and invasive LR in relation to patient characteristics, tumor characteristics, and treatment. The outcomes of LR, invasive and DCIS recurrence, and overall survival were measured from the time of initial treatment of DCIS adjusted for year of diagnosis. Univariate survival distributions were estimated using the Kaplan–Meier method and compared using the log rank test. Multivariate analyses employing Cox proportional hazards regression models were used to evaluate the relationship between the outcome and independent variables. The proportional hazards assumption was tested and proven valid for individual factors and overall model using time-dependent covariates. Comedo necrosis and nuclear grade were not entered into the multivariable model simultaneously because they are highly correlated. The median follow-up interval of the cohort is 10 years; therefore, 10-year actuarial LR rates and crude rates were similar.

Results

The cohort includes 3,762 individuals treated by breast-conserving therapy; 1,867 patients (50 %) received breast-conserving therapy alone and 1,895 (50 %) received radiation. The women treated by breast-conserving therapy alone were, on average, 4 years older than the women treated with radiation (61 vs. 57 years; $p < 0.01$; Table 1). Women with high grade DCIS, DCIS with comedo necrosis, multifocality, solid subtype, or positive resection margins were more likely to receive radiotherapy compared to those without these features ($p < 0.0001$, Table 1).

After a median follow-up interval of 10 years (10.12 in women who received BCS alone and 10.04 in women who received BCS and radiation, $p = 0.13$), the 10-year actuarial rate of LR was 20.0 % (crude rate: 363/1,867 = 19.5 %) for women selected for BCS alone and 12.7 % (crude rate: 233/1,895 = 12.3 %) for those who received radiotherapy ($p < 0.0001$). The 5- and 10-year actuarial LR-free survival rates (LRFS) among individuals treated by BCS alone were 85.4 and 80.0 %, compared to 91.7 and 87.3 % for those who received radiotherapy ($p < 0.0001$, Table 2; Fig. 1). The differences were significant for both invasive LR and DCIS recurrence. The 5- and 10-year actuarial invasive LR rates were 3.7 and 7.0 % for those who received radiation compared to 6.7 and 10.0 % for women who did not ($p < 0.0001$) (crude rate: 10 vs. 6 %; $p < 0.001$). The 5- and

Table 1 Patient characteristics in those who received BCS alone and those who received BCS and whole breast irradiation (XRT)

	BCS alone $N = 1,867$	BCS + XRT $N = 1,895$	p value
Age			
Mean (range)	61.03 (23–95)	56.88 (20–85)	<0.001
Charlson's co-morbidity index			
High	7 (0.4 %)	6 (0.3 %)	0.934
Low	53 (2.8 %)	56 (3.0 %)	
None	1,807 (96.8 %)	1,833 (96.7 %)	
Span of DCIS (mm)			
Mean (range)	13.45 (1–105)	13.57 (1–72)	0.768
Unreported (including zero)	855	766	
Necrosis			
Present	854 (45.7 %)	1,060 (55.9 %)	<0.001
Absent	465 (24.9 %)	389 (20.5 %)	
Unreported	548 (29.4 %)	446 (23.5 %)	
Nuclear grade			
High	486 (26.0 %)	657 (34.7 %)	<0.001
Moderate	696 (37.3 %)	729 (38.5 %)	
Low	216 (11.6 %)	128 (6.8 %)	
Unreported	469 (25.1 %)	381 (20.1 %)	
Multifocality			
Present	323 (17.3 %)	387 (20.4 %)	0.014
Absent/unreported	1,544 (82.7 %)	1,508 (79.6 %)	
Architectural subtype			
Solid	1,009 (54.0 %)	1,197 (63.2 %)	<0.001
Cribriform	486 (26.0 %)	387 (20.4 %)	
Micropapillary	27 (1.4 %)	23 (1.2 %)	
Other	97 (5.2 %)	64 (3.4 %)	
Unreported	248 (13.3 %)	224 (11.8 %)	
Margin status			
Positive	241 (12.9 %)	283 (14.9 %)	<0.001
Negative	1,003 (53.7 %)	1,093 (57.7 %)	
Unreported	623 (33.4 %)	519 (27.4 %)	
Tamoxifen			
Yes	113 (6.1 %)	94 (5.0 %)	<0.001
No/unknown	1,754 (93.9 %)	1,801 (95.0 %	

10-year actuarial DCIS LRFS rates were 4.8 and 6.1 % versus 8.4 and 10.8 % for women who did and did not receive radiation ($p < 0.0001$) (crude rate: 10 vs. 6 %; $p < 0.001$) (Table 2). The effect of radiation was significant in women with low, moderate and high grade disease and in women with multiple low risk factors (Figs. 2, 3).

On multivariable analysis performed on the entire population, the hazards ratio for radiation versus no radiation was 0.52 (CI = 0.45, 0.63, $p < 0.0001$). Other predictors of LR were age at diagnosis less than or equal to 50 years (HR = 1.6, 95 % CI 1.3, 1.9, $p < 0.0001$), high nuclear grade (HR = 1.9, 95 % CI 1.3, 2.7, $p = 0.0003$), intermediate nuclear grade (HR = 1.4, 95 % CI 1.0, 2.0, $p = 0.04$), positive resection margin (HR = 1.5, 95 % CI 1.2, 1.9, $p = 0.0002$), and unreported margin status (HR = 1.3, 95 % CI 1.1, 1.6, $p = 0.01$). The hazards ratios stratified by initial treatment (BCS alone or BCS and radiation) are shown in Table 3.

The population cohort includes 755 women with high grade DCIS and a negative resection margin. In this subgroup, the 10-year actuarial rate of LR was 23 % for women treated with BCS alone and was 12 % for those who received radiotherapy ($p = 0.0003$). Among 1,169 women with low or intermediate grade DCIS and negative resection margins treated with BCS alone, the 10-year actuarial rate of LR was 17 % for women who did not receive radiation and was 11 % for women who received radiation ($p = 0.0026$). Among 439 women with

Table 2 Population-based outcomes following breast-conserving therapy for DCIS

	BCS alone	BCS + XRT	*p* value
Median follow-up (years)	10.12	10.04	0.128
Any local recurrence (LR)	363 (19.5 %)	233 (12.3 %)	<0.0001
5-year actuarial LR-free survival rate	85.4 %	91.7 %	<0.0001
10-year actuarial LR-free survival rate	80.0 %	87.3 %	
DCIS recurrence	179 (9.6 %)	121 (6.4 %)	<0.0001
5-year actuarial LR-free survival rate	91.6 %	95.2 %	<0.0001
10-year actuarial LR-free survival rate	89.2 %	93.9 %	
Invasive recurrence	184 (9.9 %)	112 (5.9 %)	<0.0001
5-year actuarial LR-free survival rate	93.3 %	96.3 %	<0.0001
10-year actuarial LR-free survival rate	89.7 %	93.0 %	
Contralateral breast cancer	89 (4.8 %)	97 (5.1 %)	0.81
DCIS	36 (1.9 %)	28 (1.5 %)	0.43
Invasive	53 (2.8 %)	69 (3.6 %)	0.14
Breast cancer mortality	47 (2.5 %)	62 (3.3 %)	0.39

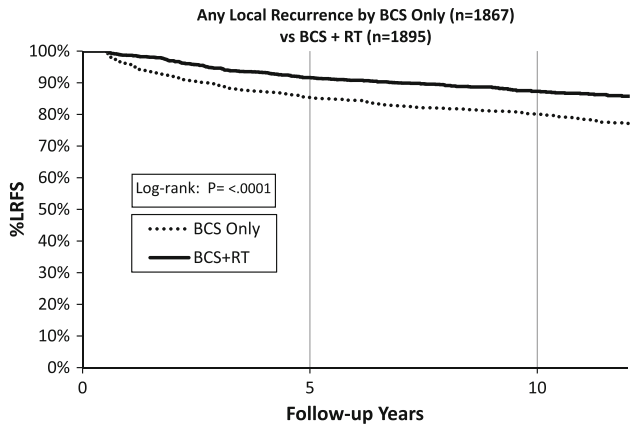

Fig. 1 Local recurrence-free survival rates in women selected for treatment by BCS with or without radiotherapy

multifocal DCIS, the 10-year actuarial rate of LR was 29 % for those who treated by BCS alone and 14 % for those who received radiation ($p < 0.0001$, Table 4).

Treatment by BCS alone

Among women treated by BCS alone ($N = 1{,}867$), age <50 years at diagnosis (HR = 1.4, 95 % CI 1.1, 1.8, $p = 0.003$), high nuclear grade (HR = 1.6, 95 % CI 1.1, 2.4, $p = 0.013$), positive resection margins (HR = 1.4, 95 % CI 1.0, 1.9, $p = 0.025$), and the presence of multifocality (HR = 1.6, 95 % CI 1.3, 2.1, $p = 0.0001$) were significant predictors of LR (Table 3). We reviewed the women who did not receive radiotherapy with regards to these characteristics to see if we could define a subgroup for whom the risk of recurrence was low (<10 % at 10 years). The 10-year actuarial rates of any LR were 18 % for ages 61 and above, 20 % for ages 51–60, and 25 % for ages 50 and below ($p = 0.01$). The 10-year actuarial LRs rates were 19 % for those with a negative margin, 26 % for those with a positive margin, and 20 % for those with unreported margins ($p = 0.015$). The 10-year actuarial rates were 16 % for those with low/intermediate grade, 26 % for those with high grade, and 20 % for those with unreported nuclear grade ($p = 0.005$). The 10-year actuarial rates were 29 % for women with multifocal DCIS, compared to 18 % for those without ($p < 0.0001$).

We then excluded individuals with positive or unknown margin status and evaluated the outcomes achieved in women with reported negative resection margins. For women with low grade DCIS, the 10-year actuarial rate of LR was 15 %, for women with intermediate grade DCIS, the rate of recurrence was 17 %, and for those with unreported nuclear grade the recurrence rate was 18 %. Among women with low or intermediate grade DCIS, the 10-year actuarial recurrence rate was 17 % for women 50 and below and was 17 % for women older than 50 years ($p = 0.59$). The 10-year actuarial LR rate of women with multifocal DCIS treated by BCS alone was 33 and 16 % for those without multifocality (Table 4).

We then considered these factors in combination for women with known negative resection margins. We excluded individuals age <50 years at diagnosis, with positive resection margins and those with high nuclear grade. The 10-year actuarial LR rate was 17 %. We further evaluated the outcomes of individuals with complete pathological data. The population cohort included 741 individuals age >50 with unifocal DCIS, reported low/intermediate nuclear grade and reported negative resection margins. The 10-year actuarial rate of LR was 14 %. Therefore, based on age, grade, multifocality, and margin

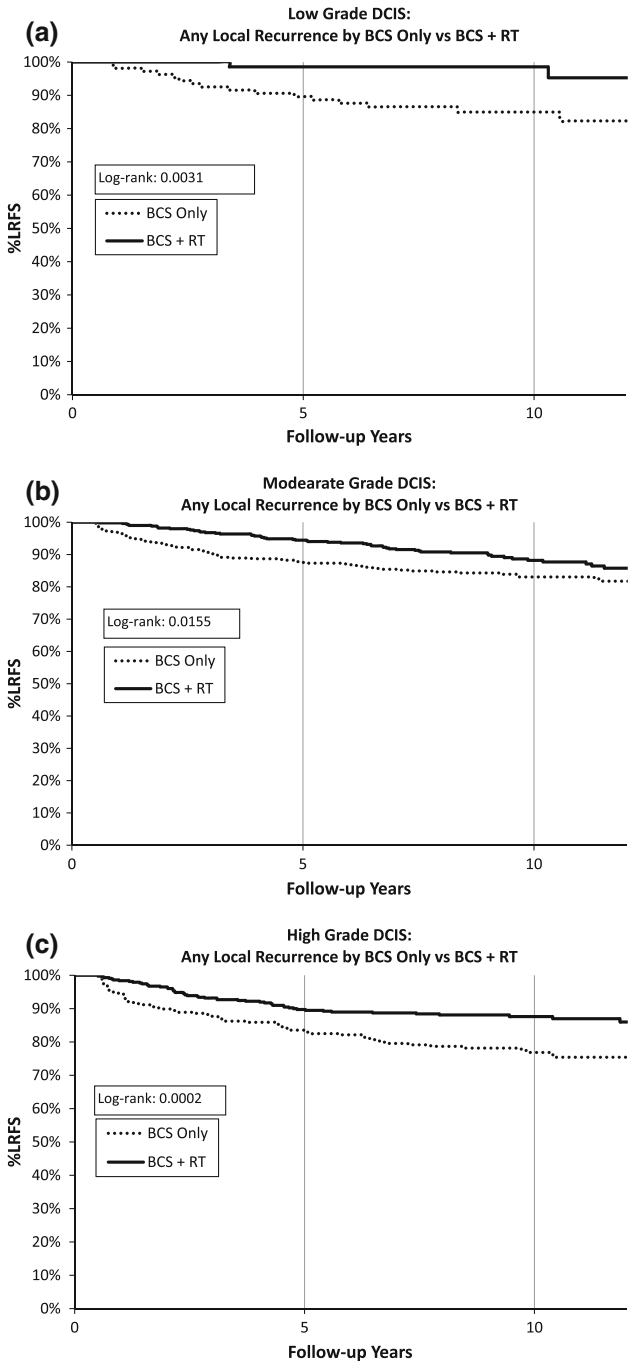

Fig. 2 Local recurrence-free survival rates in women selected for treatment by BCS with or without radiotherapy with low (**a**), moderate (**b**), and high (**c**) grade DCIS in women with negative margins

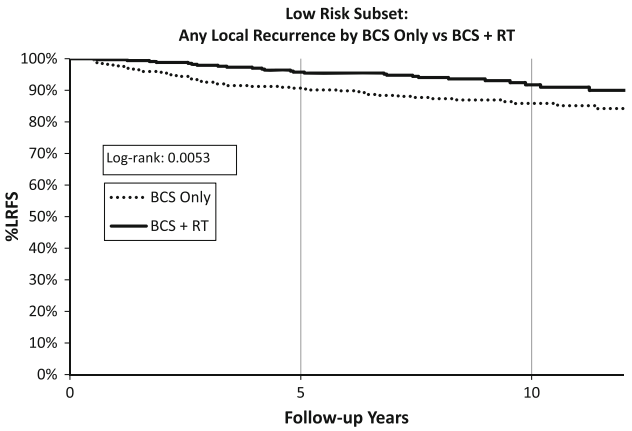

Fig. 3 Local recurrence-free survival rates in women selected for treatment by BCS with or without radiotherapy in women under 50 years, with low/intermediate nuclear grade, negative margins, and unifocal DCIS

status, we were unable to identify a subgroup of women for whom treatment by BCS alone was associated with a sufficiently low rate of LR (e.g., 10 %) such that radiotherapy might be avoided (Table 4).

There were 596 incident cases of LR in the entire cohort of 3,762 women with DCIS (including 300 cases of invasive cancer). 363 of 596 (61 %) LRs occurred among women who did not receive radiotherapy; of these, 179 of 363 (49 %) were invasive cancers. If the 1,867 women in the cohort who did not receive radiotherapy had received treatment, and we assume that the incidence of LR among women who did not have radiotherapy would be reduced to the rate among women who were treated (12 %), then the total number of recurrences in the cohort would decline from 596 to 463 if all women had received radiotherapy (a decline of 22 %) and the total number of local invasive recurrences would decline from 300 to 222 (a decline of 26 %).

Long-term breast preservation and survival

In the population cohort, 363 women developed a LR after BCS alone and 233 developed a LR after treatment with BCS and radiation. Among women initially treated by BCS alone who developed LR 232 (64 %) received salvage mastectomy. Among women whose initial treatment was BCS and radiation who developed LR 173 (74 %) received salvage mastectomy. At 10 years, the actuarial mastectomy rate was 18 % among women initially treated by BCS alone compared to 14 % for those who received radiation ($p = 0.0007$). At 10 years of follow-up, there were no significant differences in the rates of contralateral breast cancer (DCIS or invasive) or breast cancer-specific mortality (Table 2).

Discussion

Several guidelines have been published providing a framework for the management of DCIS [23–26]. Treatment guidelines recommend that most women treated by

Table 3 Factors associated with local recurrence: multivariable analyses

	HR	(95 % CI)	*p* value
Breast-conserving surgery (BCS) alone			
Age < 50 years (reference > 50 years)	1.4	(1.1, 1.8)	0.003
Nuclear grade (reference = low)			
High	1.6	(1.1, 2.4)	0.013
Moderate	1.2	(0.8, 1.7)	0.46
Unreported	1.1	(0.8, 1.7)	0.54
Margin status (reference = negative)			
Positive	1.4	(1.0, 1.9)	0.025
Unreported	1.2	(0.9, 1.6)	0.23
Multifocality (reference = absent)			
Present	1.6	(1.3, 2.1)	0.0001
BCS + whole breast irradiation (XRT)			
Age < 50 years (reference > 50 years)	1.9	(1.5, 2.5)	<0.0001
Nuclear grade (reference = low)			
High	3.0	(1.3, 6.8)	0.009
Moderate	2.5	(1.1, 5.7)	0.03
Unreported	1.8	(0.7, 4.2)	0.20
Margin status (reference = negative)			
Positive	1.7	(1.2, 2.4)	0.002
Unreported	1.5	(1.1, 2.1)	0.02
Multifocality (reference = absent)			
Present	1.2	(0.9, 1.6)	0.31

BCS be offered radiotherapy; but suggest that the omission of radiotherapy might be considered in selected women with small, low, or intermediate grade lesions and wide resection margins. Despite the proven efficacy of radiotherapy and guideline recommendations, half of women treated by local excision for DCIS do not receive radiation [11, 13, 21, 27, 28]. For example, in the surveillance, epidemiology, and end results database (SEER) of women diagnosed with DCIS in the United States, 46 % of women treated by lumpectomy did not receive radiation therapy [13, 27, 28]. Studies from other populations report similar patterns but did not report the corresponding outcomes; therefore, it is unknown to what extent individuals in these populations treated by BCS alone experienced low rates of recurrence [13, 27, 28]. We found that women treated by local excision alone were more likely to have lower risk features of DCIS compared to women treated with radiation. Despite this difference, they experienced higher rates of LR and invasive cancer compared to those who received radiotherapy.

It is not clear why radiotherapy is omitted in individual cases. Possible reasons include patient preference, access to therapy and the physicians' interpretation of the risks and benefits of radiotherapy. In some cases, the omission of radiation is due to suboptimal compliance with treatment guidelines. For example, many pathology reports lack pertinent pathological information (such as resection margin width, nuclear grade, or tumor size) needed to facilitate adherence to guidelines, to identify women with low risk DCIS who can be treated by BCS alone. The lack of complete pathological reporting in DCIS is well documented [29, 30]. Improved adherence to synoptic reporting may help clinicians identify women with low risk DCIS in whom radiation may be omitted.

Treatment guidelines suggest that individuals with high grade DCIS are not good candidates for treatment by BCS alone [23, 24]. Nevertheless, one-third of women with high grade DCIS do not receive radiation treatment [13, 21]. We found that 22 % of all women with high grade DCIS treated by BCS alone and 29 % of those with high grade disease under the age of 50 developed a LR. Individuals with high grade DCIS who develop a LR have an increased risk of developing subsequent distant metastases [3, 31]. We did not observe a difference in breast cancer-related mortality after a median follow-up interval of 10 years from initial diagnosis, but extended follow-up is needed.

There have been several published reports of low rates of LR in selected women with DCIS treated by BCS alone [14–16]. The Eastern Cooperative Oncology Group studied women with favorable DCIS who were treated by local excision alone [14]. Women included in this study had high grade DCIS ≤1 cm or low or intermediate nuclear grade less than 2.5 cm, and a minimum negative resection margin width of 3 mm. After a median follow-up interval of

Table 4 Outcomes of subset of patients with DCIS treated by BCS with and without radiation

Subset	BCS alone 10 year actuarial LR rate (*n*/*N*)	BCS + XRT 10 year actuarial LR rate (*n*/*N*)	*p* value
Low grade (all ages)	14 % (18/109)	3 % (2/74)	0.003
Age $\leq$ 50	15 % (3/20)	5 % (1/14)	0.48
Age > 50	14 % (15/89)	3 % (1/60)	0.003
Intermediate grade (all ages)	18 % (77/484)	12 % (56/502)	0.03
Age $\leq$ 50	19 % (14/98)	18 % (22/141)	0.7
Age > 50	18 % (63/386)	10 % (34/361)	0.005
High grade (all ages)	26 % (70/322)	15 % (52/433)	0.0003
Age $\leq$ 50	35 % (20/70)	21 % (22/137)	0.03
Age > 50	23 % (50/252)	13 % (30/296)	0.0004
Unreported grade (all ages)	20 (15/84)	12 % (5/83)	0.019
Multifocality			
Present	29 % (55/179)	14 % (34/261)	<0.0001
Absent/unreported	19 % (125/824)	12 % (81/832)	0.0008
Age > 50			
Unifocal DCIS			
Low/intermediate/unreported grade			
Negative/unreported margins (N = 1,452)			
Local recurrence	15 % (116/793)	8 % (50/659)	<0.0001
DCIS local recurrence	7 % (53/793)	4 % (22/659)	0.004
Invasive local recurrence	8 % (63/793)	5 % (28/659)	0.004
Age > 50			
Unifocal DCIS			
Low/intermediate grade			
Negative resection margins (N = 741)			
Local recurrence	14 % (55/400)	8 % (26/341)	0.01
DCIS local recurrence	7 % (28/400)	4 % (12/341)	0.04
Invasive local recurrence	7 % (27/400)	5 % (14/341)	0.12

6 years, the rate of LR was 10.5 % [14]. The RTOG 98-04 clinical trial randomized women with low risk DCIS to receive radiation or observation; 62 % received tamoxifen. At 5 years, the addition of radiation lead to significantly lower rate of LR, 0.4 % for women who received radiation and 3.2 % for those who did not (HR = 0.14, 95 % CI 0.03–0.61, p = 0.002) [17]. We were unable to identify a subset of women with similar low rates of LR following treatment by BCS alone. During the time interval of this study, many pathology reports lack information such as tumor size and resection margin width. For example, we identified 97 cases with unifocal DCIS and reported tumor size <3 cm, low or intermediate nuclear grade and resection margin width >3 mm treated by BCS alone. The 10-year actuarial rate of LR was 7 % [cumulative incidence rate = 9.3 % (95 % CI 4.3–16.9 %)]. This represents a small proportion of the entire cohort. Further research with more complete pathological data is needed to identify a low risk subset of patients with DCIS.

The omission of radiotherapy in half of women treated by BCS, in our population cohort and other populations, suggests that BCS alone is offered to individuals with higher risk DCIS, who do not meet the eligibility criteria of the ECOG or RTOG clinical trials. In our study, women with unifocal disease, aged >50 years with low/intermediate grade DCIS and known negative resection margins had a 10-year actuarial rate of LR of 14 %.

Although the study cohort represents a large population of women with DCIS, there are several limitations. Data on clinical presentation, family history of breast cancer, BRCA mutation status, and data on breast imaging were not available. Data on tamoxifen usage was not available for women younger than 65 years of age; however, tamoxifen utilization was limited in women diagnosed with DCIS during the time period of this study (1994–2003). Among women older than 65 years, only 17 % received tamoxifen. In addition, data on exact tumor size, margin width estrogen receptor (ER), and progesterone receptor

(PR) status were not routinely reported during the time period of this study.

In summary, the omission of radiotherapy after BCS for DCIS resulted in a substantial number of recurrences, including invasive recurrences that might have been avoided with treatment. Women selected for treatment by BCS alone are more likely to have favorable features such as low/intermediate grade, older age at diagnosis and unifocal disease. Despite this difference, patients treated with radiation had a 7 % lower absolute risk of LR compared to those treated by surgery alone. Therefore, 14 patients require radiotherapy to prevent one LR and 25 would need to be treated to prevent one mastectomy. Radiation lowered the risk of LR in all subgroups. Younger women (<50 years) with high grade DCIS had the highest risk of LR with a 10-year rate of LR of 22 % following treatment by BCS and radiation. Most individuals received conventional doses of radiation; therefore, the impact of higher doses of radiation (vs. mastectomy) requires further evaluation. The Institute of Medicine recommends research evaluating the comparative effectiveness of therapeutic radiation, comparing the benefits of radiation with its potential risks [32]. We found that radiation is as effective in preventing LR as reported in clinical trials (HR = 0.52, 95 % CI 0.45–0.62). Furthermore, individuals who received radiation had higher long-term rates of breast preservation because many women receive salvage mastectomy as treatment of LR. Additional follow-up continues to determine the ultimate fate of these patients in terms of breast cancer mortality. Currently, it is challenging to identify a low risk group based on clinical and pathological grounds alone, but it is possible, that in the future, additional markers will be developed which will enable clinicians to identify patients who may be good candidates for the avoidance of radiotherapy.

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Conflict of interest No conflict of interest to report.

Ethics Ethics approval for this study was obtained by Sunnybrook Ethics Board, Sunnybrook Health Science Centre.

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