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EPIDEMIOLOGY

The time-varying effect of radiotherapy after breast-conserving surgery for DCIS

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Abstract

Background A better understanding underlying radiation (RT) response after breast-conserving surgery (BCS) is needed to mitigate over-treatment of DCIS. The hazard ratio (HR) measures the effect of RT but assumes the effect is constant over time. We examined the hazard function adjusted for adherence to surveillance mammography to examine variations in LR risk and the effect of RT over time.

Methods Crude hazard estimates for the development of LR in a population cohort of DCIS treated by BCS ± RT were computed. Multivariable extended Cox models and hazard plots were used to examine the association between receipt of RT and risk of each outcome adjusted for baseline covariates and adherence to mammography.

Results Population cohort includes 3262 women treated by BCS; 1635 received RT. Median follow-up was 13 years. LR developed in 364 women treated by BCS alone and 274 treated with RT. LR risk peaked at 2 years, declined until year 7, and then remained steady. The peak hazard of LR was associated with adverse features of DCIS. Early LR risk was attenuated in patients treated with RT but late annual risks of LR and invasive LR were similar among the two treatment groups. On multivariate analysis, RT was associated with a reduction in early LR risk (HR = 0.52, 95% CI 0.43–0.63, $p < 0.0001$) but did not reduce the risk of late LR (HR = 0.89, 95% CI: 0.67, 1.19, $p = 0.44$) (interaction, $p = 0.002$).

Conclusions The effect of RT is not uniform over time and greatest in the first 7 years after BCS for DCIS, which can guide future research to understand mechanisms underlying RT response and optimize future management of DCIS.

Keywords Ductal carcinoma in situ · DCIS · Hazards · Local recurrence · Radiation

Background

Ductal carcinoma in situ (DCIS) is a non-invasive form of breast cancer that DCIS now represents 20% of newly diagnosed breast cancers. Most women with DCIS will be treated with breast-conserving surgery (BCS) followed by whole breast RT which is proven to lower the risk of Local Recurrence (LR) and invasive LR [1]. However, this therapeutic approach leads to over-treatment of women with low risk, indolent disease or inadequate treatment of those with radiation-resistant disease who develop LR despite receiving RT. To this end, extensive research efforts are underway to better

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understand the underlying mechanisms of radiation response after BCS, to guide future research efforts to target RT more effectively to those most likely to benefit and mitigate the impact of overdiagnosis and over-treatment of DCIS [2–4].

The main measure of the effect of RT (after breast-conserving surgery) on outcomes such as the risk of LR is the hazard ratio (HR), which represents the probability (hazard) of an event in the intervention group relative to the hazard of the event in those who did not receive treatment [5]. The HR represents the average effect of RT over an entire study period and as such the HR alone provides no indication of variations in LR risk over time nor does it provide information on variations in the magnitude of the effect of RT over time. Therefore, the HR will only be an accurate representation of the effect of RT if its effect is constant over time.

The hazard function on the other hand represents the rate of recurrence within a very short (or instantaneous) time frame (given that an individual has survived up to time *t*), and is a useful measure to examine variations of recurrence risk and variations in the magnitude of the effect of RT over time [5, 6]. Analyses of the temporal variations of local recurrence risk are helpful to guide follow-up strategies [6, 7] but in addition, they may also shed insight into the mechanisms of treatment effects. Moreover, past studies evaluating the risks of LR risks in patients treated with or without RT after BCS have not accounted for the impact of adherence to surveillance mammography, which can influence the detection of a LR [8–10]. Improved understanding of temporal variations in the effect of RT can shed insight into the mechanisms of the effect of RT in DCIS and can guide future research initiatives aimed at discovering biomarkers predictive of RT response.

Methods

Cohort

The population cohort includes all individuals diagnosed with pure DCIS treated by BCS, with or without radiotherapy, in Ontario from 1994 to 2003. Identification of the population cohort has been previously described [3, 11]. Cases with prior history of cancer ($N=3036$), those who developed invasive breast cancer within 6 months of DCIS ($N=191$), died within 2 months ($N=2$), had microinvasion or pure LCIS without DCIS on pathology review ($N=2332$), or were treated with mastectomy ($N=1774$) were excluded. The cohort includes 3262 cases of pure DCIS treated by breast-conserving surgery with or without RT.

Outcomes

LR was defined as the development of invasive breast cancer or further DCIS in the ipsilateral breast at least 6 months following the initial diagnosis of DCIS. Invasive LR was defined as the first invasive breast cancer that developed in the ipsilateral breast 6 months or more after the initial diagnosis of DCIS. Contralateral breast cancer was defined as the first invasive or DCIS breast cancer that developed in the contralateral breast 6 months or more after the initial diagnosis of DCIS. For this endpoint, cases were not censored if the initial ipsilateral LR was DCIS. The last date of follow-up is March 31, 2014.

Statistics

Characteristics of the cohort were described using counts and proportions for categorical variables, stratified by receipt of RT. The survivor functions for any LR and invasive LR were estimated and illustrated using the Kaplan–Meier method, and log-rank tests were used to assess for differences in the survival estimates between women who did and did not receive RT. To gain an understanding of the instantaneous rate of any LR and invasive LR at various points after diagnosis, the crude hazard estimates for each outcome were computed using the life table method and plotted under a kernel smoothing function [12]. Multivariable extended Cox regression models were used to examine the association between the receipt of RT and the risk of each outcome [13]. Baseline covariates included in the model were receipt of radiation, age at diagnosis, tumor size, high nuclear grade, multifocality, subtype, and margin status.

Most local recurrences are detected by surveillance mammography; therefore, differences in adherence patterns to surveillance mammography could lead to calculated differences in LR risk over time (detection bias). In order to account for potential detection bias, we ascertained the use of mammography for each individual in the cohort from the date of diagnosis to last follow-up. We created a time-varying covariate representing mammography adherence. Each woman in the cohort was considered adherent at baseline and was considered adherent for 12 months after each mammogram. If she did not have a mammogram 12 months following her most recent mammogram, she was considered non-adherent at that time. This covariate was updated continuously until the last date of follow-up for each individual in the cohort. For individuals who developed a LR, the follow-up period for mammography adherence was terminated 3 months prior to the date of LR, as we were interested in capturing surveillance

mammograms patterns unrelated to the diagnostic work-up of LR. The cox models and the calculations of hazards of LR risk and invasive LR were adjusted for differences in mammography adherence accordingly. The effect of RT over time was explored by plotting the hazards of LR in women treated with or without RT and an extended cox model was used to explore an interaction between the effect of radiation and time to local recurrence.

Results

Cohort

The population cohort includes 3262 women treated by BCS; 1627 women were treated by BCS alone and 1635 received RT. Most cases who received RT were treated with conventional fractionation (59%). Boost RT was administered in 29% ($N=481$) cases. Median follow-up interval was 13 years (range 10.3–20.2 years). Patient characteristics are presented in Table 1. Most women were older than 50 years at diagnosis. Patients treated with RT were more likely to have lesions > 10 mm, with high nuclear grade and comedo necrosis. The majority of patients (68.4%) had negative resection margins. Local recurrence (DCIS or invasive) developed in 364 (22.4%) women treated by BCS alone and in 274 (16.8%) women treated with BCS + RT. An ipsilateral invasive LR (either as a first event or subsequent to an initial DCIS LR) developed in 217 (13.3%) women treated by BCS alone and 178 (10.9%) of those treated by BCS + RT. The 15-year local recurrence-free survival risks (LRFS) were 75% for patients treated by BCS alone 80% for those treated with conventional RT and 84.5% for those treated with hypofractionation RT ($p<0.0001$). Invasive LRFS risks were 85.5%, 87.2%, and 87.4%, respectively ($p=0.04$) (Fig. 1).

The hazards for developing LR after treatment by BCS alone or BCS + RT over a 15-year time period is illustrated in Fig. 2. Among women treated by BCS alone, the hazard of LR peaked within the first 2 years following treatment and then steadily declined until year 7. Thereafter, the risk of LR remained stable throughout the remaining years of study (years 7–15 following diagnosis). We then more closely evaluated the hazard of LR in subgroups of women with (or without) adverse prognostic features of DCIS. As depicted in Fig. 3, the highest hazards of LR at 2 years were observed in cases with positive resection margins (defined as DCIS at the margin), tumor size > 2.5 cm, multifocal DCIS, age < 50 years at diagnosis, or those with high nuclear grade.

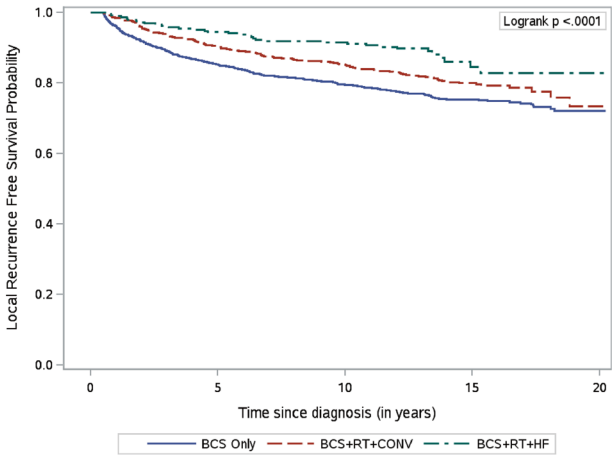
We observed a similar pattern in the hazard of LR among women treated with RT, with an increasing risk of LR for the first 2 years following treatment, although the peak in LR risk was attenuated compared to those treated by BCS alone without RT. By year 7, the hazards of LR were similar among the two treatment groups (Fig. 2).

The hazard plots suggest a time-dependent effect of RT on the recurrence risk. The greatest effect of RT was in the reduction of recurrence risk within the first 7 years following BCS. Beyond 7 years, recurrence risks in patients treated with or without RT were relatively similar and constant. To further examine the temporal effect of RT, we used a Cox proportional hazards model to explore the presence of a significant interaction between the effect of RT and time to LR. On multivariate analysis adjusted for adherence to mammography, pathological covariates, age, and year of diagnosis, there was a significant interaction between the effect of RT and time to LR ($p=0.002$). The administration of RT was

Table 1 Patient characteristics

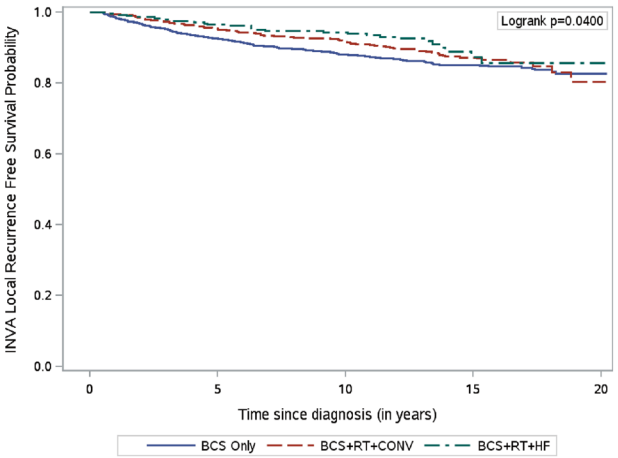
	BCS only $N=1627$	BCS + RT $N=1635$	p value
Age at diagnosis			0.002
< 50	328 (20.2%)	404 (24.7%)	
≥ 50	1299 (79.8%)	1231 (75.3%)	
Tumor size (mm)			< 0.001
≤ 10	538 (33.1%)	449 (27.5%)	
10.1–25	494 (30.4%)	643 (39.3%)	
> 25 mm	150 (9.2%)	178 (10.9%)	
Unknown	445 (27.4%)	365 (22.3%)	
Necrosis			< 0.001
Absent/unknown	799 (49.1%)	630 (38.5%)	
Present	828 (50.9%)	1005 (61.5%)	
High nuclear grade			< 0.001
Yes	477 (29.3%)	622 (38.0%)	
No	1150 (70.7%)	1013 (62.0%)	
Multifocality			0.013
Present	296 (18.2%)	354 (21.7%)	
Absent	1331 (81.8%)	1281 (78.3%)	
Subtype			< 0.001
Solid	944 (58.0%)	1133 (69.3%)	
Cribriform	466 (28.6%)	353 (21.6%)	
Other	217 (13.3%)	149 (9.1%)	
Margin status			< 0.001
Negative	1066 (65.5%)	1168 (71.4%)	
Positive	136 (8.4%)	139 (8.5%)	
Unknown	425 (26.1%)	328 (20.1%)	
Radiation dose			
Conventional fractionation		965 (59%)	
Hypofractionation		632 (39%)	
Unknown		38 (2%)	
Boost			
Yes		481 (29%)	
No		1154 (71%)	

(a) Any Local Recurrence



	5 yr	10 yr	15 yr
BCS alone (N=1622)			
No. of LR	232	81	42
No. at risk	1266	1051	434
BCS + Conventional RT (N=825)			
No. of LR	78	118	148
No. at risk	715	644	253
BCS + Hypofractionated RT (N=291)			
No. of LR	16	24	33
No. at risk	263	236	53

(b) Invasive Local Recurrence



	5 yr	10 yr	15 yr
BCS alone (N=1622)			
No. of LR	116	64	30
No. at risk	1376	1166	500
BCS + Conventional RT (N=825)			
No. of LR	38	64	91
No. at risk	754	696	278
BCS + Hypofractionated RT (N=291)			
No. of LR	10	16	25
No. at risk	269	243	55

Fig. 1 Kaplan–Meier plots for the development of **a** Any local recurrence and **b** invasive local recurrence following treatment by BCS alone or BCS + RT

associated with a significant reduction in the risk of LR within the first 7 years from diagnosis (HR = 0.52, 95% CI 0.43–0.63, $p < 0.0001$) but was not associated with a reduced risk of LR beyond 7 years (HR = 0.89, 95% CI: 0.67, 1.19, $p = 0.44$) (Table 2).

Other factors independently associated with an increased risk of LR include age at diagnosis < 50 years (HR = 1.50, 95% CI: 1.26, 1.78, $p < 0.0001$), tumor size 1.1–2.5 cm (HR = 1.31, 95% CI: 1.06, 1.62, $p = 0.014$), 2.6–4.0 cm (HR = 2.01, 95% CI: 1.49, 2.72, $p < 0.0001$), tumor size ≥ 4.0 cm (HR = 2.52, 95% CI: 1.73, 3.67, $p < 0.0001$), high nuclear grade (HR = 1.28, 95% CI: 1.08, 1.52, $p = 0.005$), and multifocality (HR = 1.34, 95% CI: 1.11, 1.61, $p = 0.002$) (Table 2).

We found a similar pattern in the hazards of invasive LR and also found a statistically significant interaction between the effect of RT and time to invasive LR ($p = 0.0012$) (Fig. 2). The administration of RT reduced the risk of invasive LR risk within the first 7 years of diagnosis (HR = 0.55, 95% CI: 0.42, 0.71, $p < 0.0001$) but had no significant effect on the development of late invasive LRs (HR = 1.07, 95% CI: 0.78, 1.48, $p = 0.67$).

Characteristics distinguishing women who recur early vs late

We compared the pathological characteristics of women who developed an ipsilateral LR within 7 years of diagnosis to those who developed LR beyond 7 years. Women who developed an early LR were significantly more likely to have high-grade DCIS than those who developed LR beyond 7 years. No other features distinguished those who recurred early from those who recurred beyond 7 years (Table 3). None of the features distinguished those who developed an early invasive LR from those who developed an invasive LR beyond 7 years (data not shown). In a subgroup of 1564 patients, the Oncotype DX DCIS Score was measured; 718 cases were treated by BCS alone and 846 were treated with BCS + RT [3]. We found no difference in the time to LR by Oncotype DX DCIS Score risk group and there was no significant interaction between the effect of RT, the Oncotype DX DCIS score risk group, and time to LR ($p = 0.26$).

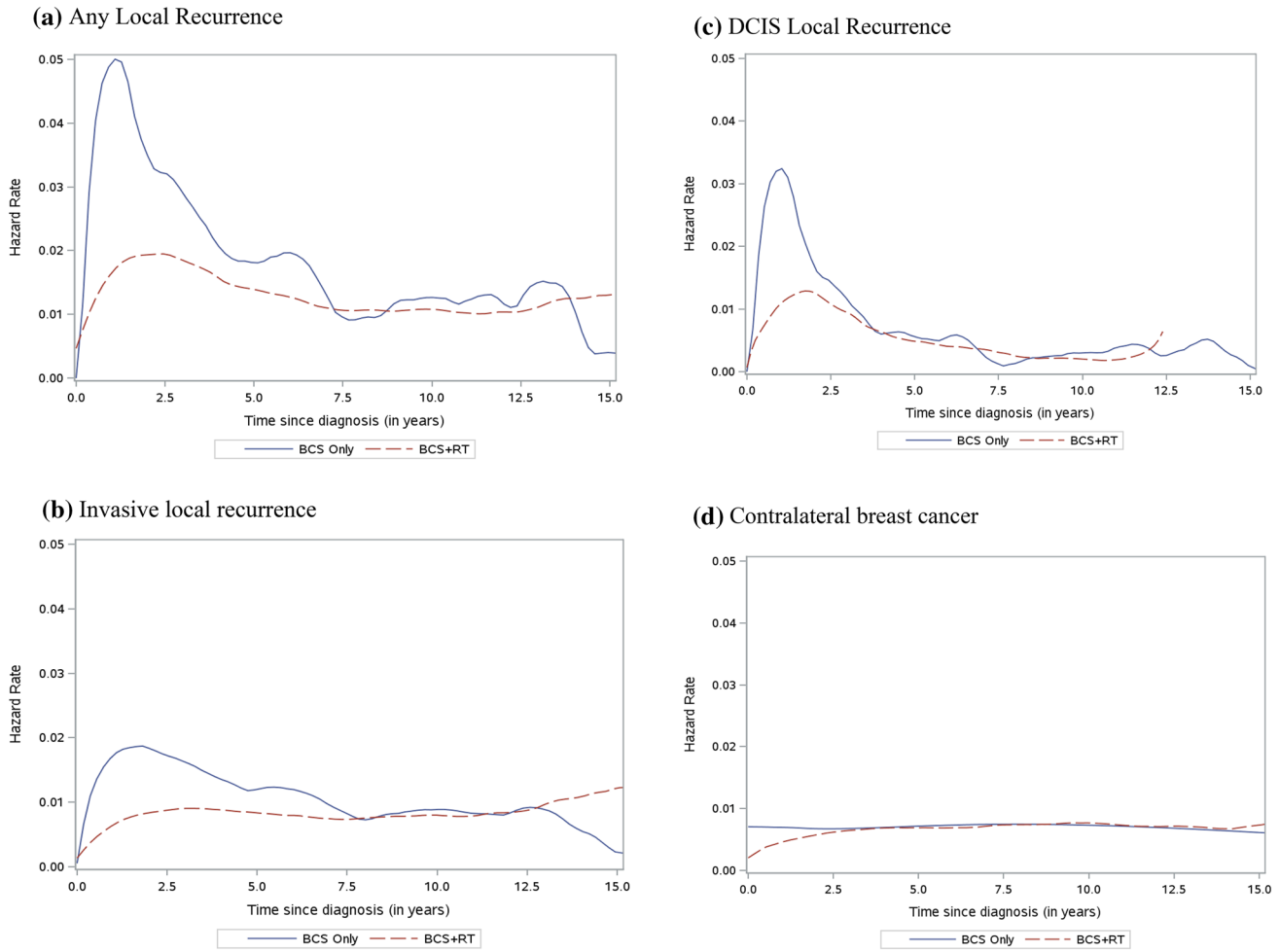


Fig. 2 Smoothed Hazard Functions for the annual risks of developing **a** local recurrence, **b** invasive local recurrence, **c** DCIS local recurrence, and **d** contralateral breast cancer following BCS alone or BCS + RT. Following BCS, the hazard of LR increases and reaches a peak 2 years and then declines. The hazard of LR is reduced in cases treated with RT. Beyond year 7, the hazards of LR are similar in women treated by BCS alone or BCS + RT

Discussion

It is well established that RT reduces the risk of local recurrence and invasive local recurrence after BCS for DCIS [1]. Our analysis demonstrates that the risks of LR and invasive LR vary over time. We found that established adverse prognostic features of DCIS (such as young age, tumor size) are associated with an increased risk of early LR and invasive LR (< 7 years) and that the effect of RT is in the reduction of early events. The annual risk of late recurrences (> 7 years after BCS) is similar irrespective of baseline prognostic features or treatment with RT. Recognition of these time-dependent effects can inform future research to identify molecular alterations underlying early versus late recurrences and to optimize therapeutic interventions aimed at reducing future recurrence risks for women with DCIS.

The effect of RT has traditionally been measured by calculations of the cumulative risks of LR or the hazard ratios of individuals treated with or without RT, which do not measure variations in recurrence risk or variations in the effect of treatment over time. We found that an individual's risk of LR after resection of DCIS is not uniform over time. The hazards of LR peak at 2 years following BCS, declines until year 7, and then remains constant thereafter. Moreover, we observed that the magnitude of the effect of RT on the reduction of LR (and invasive LR) risk is also not uniform over time. There was a significant interaction between the effect of RT and time to LR. That is, the administration of RT is associated with a reduction in the risk of an early LR (within first 7 years) but thereafter the persistent annual risks of recurrence are similar among women treated with or without RT. The time-varying patterns of recurrence and the effect of RT lead to several plausible explanations for the

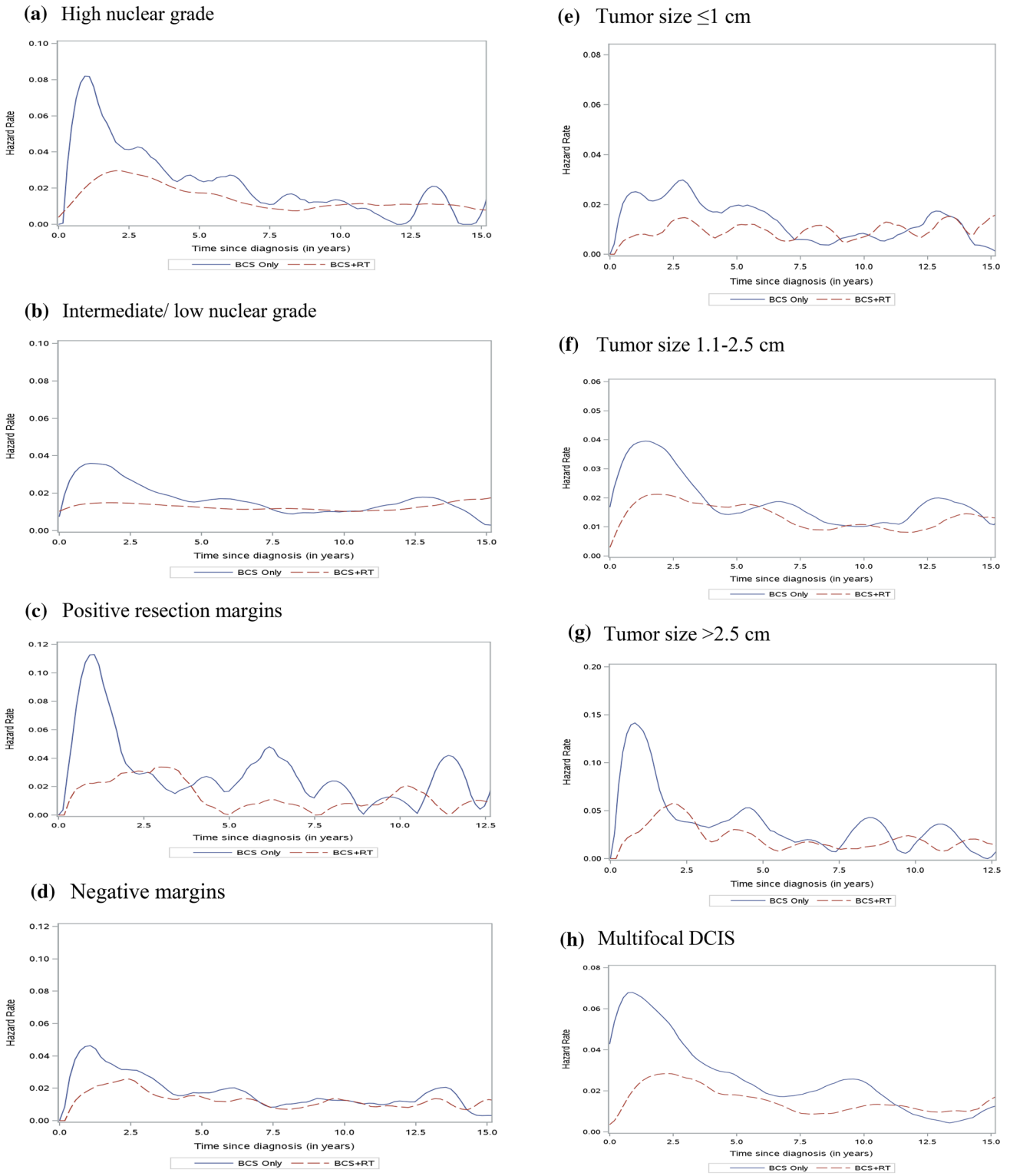
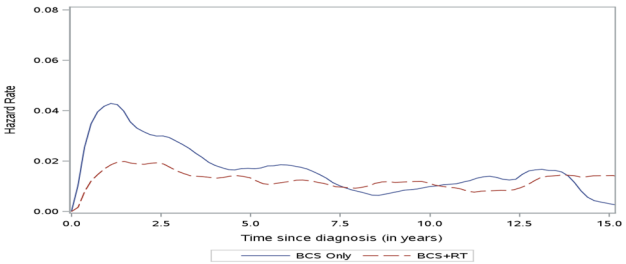
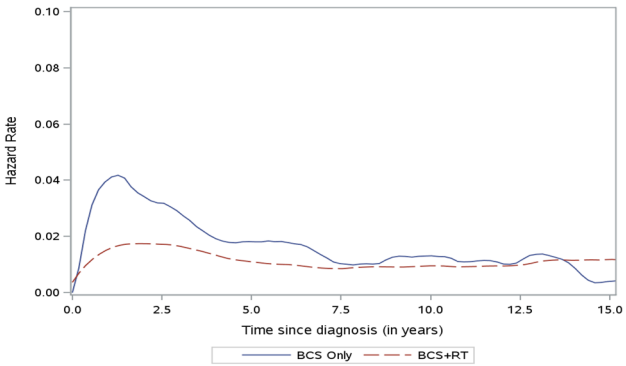


Fig. 3 Hazard functions of the annual risks of developing Local Recurrence over time following treatment by BCS alone or BCS + RT: Subgroup analysis. Plot of the annual risks of LR following treatment by BCS alone or BCS + RT in subgroup of patients with **a** high nuclear grade, **b** intermediate/low nuclear grade, **c** positive resection margins, **d** negative margins, **e** tumor size ≤ 1 cm, **f** tumor size 1.1–2.5 cm, **g** tumor size > 2.5 cm, **h** multifocal DCIS, **i** unifocal DCIS, **j** age > 50 years at diagnosis, **k** age ≤ 50 years at diagnosis. The early hazards of LR are highest in cases with established adverse prognostic features of DCIS

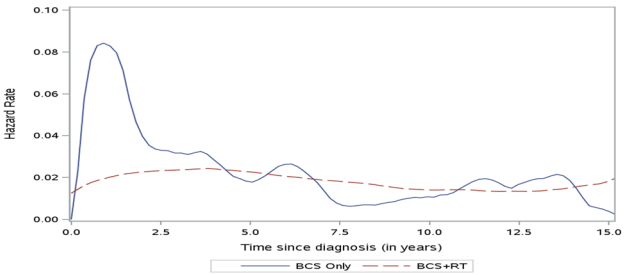
(i) Unifocal



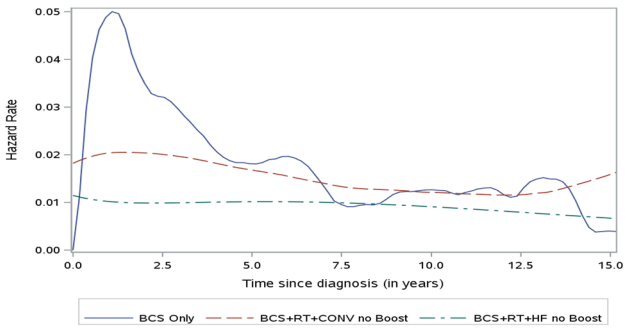
(j) Age > 50 years at diagnosis



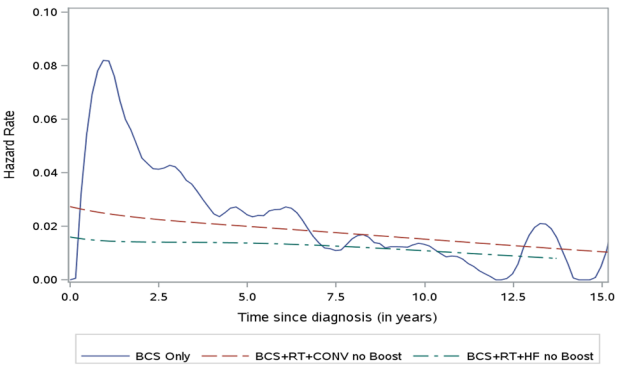
(k) Age ≤50 years at diagnosis



(l) Conventional vs. Hypofractionation



(m) Conventional vs. Hypofractionation in patients with High Grade DCIS



(n) Conventional vs. Hypofractionation in patients with tumor size >2.5cm

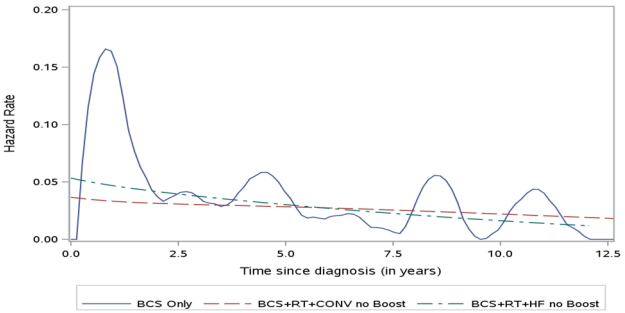


Fig. 3 (continued)

underlying mechanisms of local recurrence and the effect of RT.

The peak hazards of LR were most pronounced in cases with established adverse prognostic features of DCIS including tumor size > 2.5 cm, positive resection margins, age < 50 years at diagnosis, multifocal DCIS, or high nuclear grade. These features are more likely to be associated with residual DCIS on re-excision lumpectomy or completion

Table 2 Multivariate analysis: factors associated with the development of local recurrence

	HR (95% CI)	*p* value
Age at diagnosis < 50 years	1.51 (1.27, 1.79)	< 0.0001
Tumor size		
> 10–≤ 25 mm	1.31 (1.06, 1.62)	0.014
> 25 mm	2.16 (1.66, 2.82)	< 0.0001
High nuclear grade	1.28 (1.08, 1.52)	0.005
Multifocality	1.33 (1.10, 1.61)	0.002
Subtype		
Solid	0.98 (0.75, 1.28)	0.88
Cribriform	0.90 (0.67, 1.21)	0.47
Margin status		
Positive	1.07 (0.82, 1.40)	0.61
Unknown	0.97 (0.76, 1.23)	0.78
Radiation*Time to local recurrence	.	0.002
≤ 7 years	0.52 (0.43, 0.63)	< 0.0001
> 7 years	0.89 (0.67, 1.19)	0.45

mastectomy specimens suggesting that the early rise in LR risk may be due to the regrowth of residual cancer cells or undetected DCIS [14]. Our findings corroborate but also extend prior trial data. In the EORTC 10,853 randomized trial, administration of RT was associated with a decrease in the hazards of invasive and DCIS LR but after 5 years the risk of invasive LR was similar between the two treatment groups [9]. In the SweDCIS randomized clinical trial [8], the hazard for in situ LR increased within the first 10 years following BCS (hazard = 0.05) and then declined to zero beyond year 10. However, neither analysis adjusted for the effect of adherence to surveillance mammography. In the SweDCIS study, 40% of the study population was older than 70 years and outside the screening program age range. Since most LRs are detected through mammography, variations in the rates of surveillance mammography between treatment groups could influence the calculated annual risks of local recurrence. In our analysis, we accounted for potential detection bias (of local recurrence) related to differential rates of adherence to surveillance mammography between the two treatment groups over time. For each individual in

Table 3 Characteristics of cases who developed an early vs. late local recurrence

	BCS alone		*p* value	BCS + RT		*p* value
	≤ 7 years	> 7 years		≤ 7 years	> 7 years	
	N = 276	*N* = 88		*N* = 171	*N* = 103	
Age at diagnosis			0.54			0.80
< 50	75 (27.2%)	21 (23.9%)		59 (34.5%)	34 (33.0%)	
≥ 50	201 (72.8%)	67 (76.1%)		112 (65.5%)	69 (67.0%)	
Tumor size (mm)			0.82			0.10
≤ 10	68 (24.6%)	23 (26.1%)		28 (16.4%)	29 (28.2%)	
10.1–25	79 (28.6%)	27 (30.7%)		76 (44.4%)	35 (34.0%)	
> 25	46 (16.7%)	11 (12.5%)		30 (17.5&)	16 (15.5%)	
Unknown	83 (30.1%)	27 (30.7%)		37 (21.6%)	23 (22.3%)	
Necrosis			0.30			0.20
No	122 (44.2%)	46 (52.3%)		55 (32.2%)	41 (39.8%)	
Present	154 (55.8%)	42 (47.7%)		116 (67.8%)	62 (60.2%)	
Nuclear grade			0.02			0.009
High	108 (39.1%)	20 (22.7%)		84 (49.1%)	34 (33.0%)	
Other	168 (60.9%)	68 (77.3%)		87 (50.9%)	69 (67.0%)	
Multifocality			0.57			0.21
Present	71 (25.7%)	20 (22.7%)		50 (29.2%)	23 (22.3%)	
Absent	205 (74.3%)	68 (77.3%)		121 (70.8%)	80 (77.7%)	
Subtype			0.53			0.69
Solid	175 (63.4%)	51 (58.0%)		123 (71.9%)	71 (68.9%)	
Cribriform	66 (23.9%)	22 (25.0%)		31 (18.1%)	23 (22.3%)	
Other	35 (12.7%)	15 (17.0%)		17 (9.9%)	9 (8.7%)	
Margin status			0.28			0.58
Negative	169 (61.2%)	62 (70.5%)		123 (71.9%)	68 (66.0%)	
Positive	33 (12.0%)	7 (8.0%)		16 (9.4%)	11 (10.7%)	
Unknown	74 (26.8%)	19 (21.6%)		32 (18.7%)	24 (23.3%)	
Boost administered				44 (25.7%)	36 (35.0%)	0.10

the cohort, we determined annual adherence to mammography from the year of diagnosis until the date of recurrence or last follow-up and created a time-dependent covariate for inclusion into the cox model. On multivariate analysis (adjusting for adherence), there was a statistically significant interaction between the effect of RT and time to LR. That is, the administration of RT was associated with a significant reduction in early LR risk within the first 7 years from diagnosis (HR = 0.52, 95% CI: 0.43–0.63, $p < 0.0001$) but was not associated with a reduced risk of LR after year 7 (HR = 0.89, 95% CI: 0.67, 1.19, $p = 0.44$; interaction term, $p = 0.002$). Overall, the attenuated (but persistent) early LR risk in patients treated with RT suggests that RT does not completely eradicate all residual malignancy. The differential amplitude in the early hazards of LR among women treated by BCS with or without RT (represented by the hazards ratio) may reflect the proportion of radio-resistant subpopulations of residual neoplastic cells.

Another observational study of 1252 women diagnosed with DCIS from 1994 to 2012 reported cumulative risks among women treated with BCS with or without RT in 5-year time intervals [15]. They reported that the risks of a secondary breast event diminish over time for patients treated by BCS alone but increased for those treated with RT [15]. However, the increased risk of a secondary breast event was due to a higher risk of contralateral breast cancers among women treated with RT. Selection may have occurred to treat younger women or those at higher risk of a secondary breast event with RT. The risks of an ipsilateral breast event (DCIS or invasive) were lower for women treated with RT (compared to those treated by BCS alone) for the first 10 years of follow-up, but beyond 10 years the risks of an ipsilateral event was similar among the two groups corroborating our findings that the impact of RT is in reducing the early risk of local recurrence. Furthermore, the median follow-up was 7.8 years for the whole cohort and 6.2 years for those treated by BCS alone. In our analysis, the median follow-up time for the cohort exceeded 13 years with over 1000 patients still at risk at 10 years following diagnosis. In addition, in our analysis, time points were data-driven based on the function form of the crude instantaneous hazard, as opposed to an arbitrarily categorization of follow-up time into 5-year intervals, and showed convergence of the annual hazards of recurrence near the 7-year mark.

Beyond 7 years, we observed a persistent annual risk of LR, which was similar among women treated by BCS alone or BCS + RT irrespective of age at diagnosis or tumor size, the presence of multifocality, nuclear grade, or margin status of the index lesion. There are several plausible explanations for the persistent late LR risk. One possibility may be explained by the presence of two distinct subpopulations of residual cells. Over time the more aggressive subpopulations recur, leaving an increasing proportion of more indolent tumor cells (selection bias) in the surviving individuals. Since indolent DCIS will have a lower hazard of LR, the apparent overall hazard will decrease. Alternatively, late LR risks may be due to de novo malignant transformation of 'normal' epithelium to DCIS. A study by Enderling et al. modeled the time to LR following treatment with BCS and RT for DCIS [16]. The model predicted that following treatment with RT, the time to LR would be 30–35 years if the surrounding epithelium were completely normal, in the absence of any putative genetic mutations. One limitation of their model is the assumption that all residual cancer cells would be eradicated by RT. They predicted the time to LR would be reduced to 10–25 years if the surrounding normal tissue contained some of the putative genetic mutations required for carcinogenesis and to 5–7 years if in addition the surrounding cells were also genetically unstable (enabling more rapid acquisition of the remaining putative mutations required for carcinogenesis).

The study has several potential limitations. Treatment was not randomized but was determined based on clinicopathologic features and patient preference. During the time interval of this study, many pathology reports lacked information on tumor size and resection margin information. Furthermore, we were unable to evaluate the effect of tamoxifen on the temporal risks of recurrence because few (< 15%) cases in the cohort received endocrine therapy. The impact of hormone receptor status and adjuvant endocrine therapy on temporal pattern of recurrence could not be evaluated.

In summary, the magnitude of the effect of RT after BCS for DCIS varies over time. The administration of RT reduces the early hazard of LR and invasive LR but a persistent late risk of LR and invasive LR remain irrespective of the administration of RT. There was no difference in the hazards of LR or invasive LR among cases treated with conventional versus hypofractionated radiotherapy. Additional research is needed to identify putative genomic alterations within DCIS lesions and the surrounding stroma, to understand their influence on recurrence risk and RT response, in an effort to optimize future management of DCIS.

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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

Conflicts of interest ERakovitch has received research grant funding from Genomic Health Inc. A Thompson has received lecture honoraria from Pfizer outside of this work. T Whelan has received other research grant funding from Genomic Health Inc. All other authors declare no conflict of interest.

Ethical approval Ethical approval was obtained from Sunnybrook Health Sciences Centre.

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